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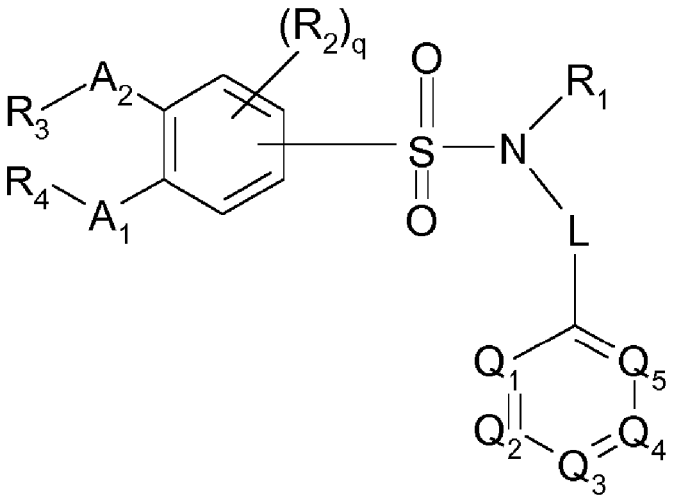
(54) Title : BENZENESULFONAMIDE DERIVATIVES AS INVERSE AGONISTS OF RETINOID-RELATED ORPHAN RECEPTOR GAMMA (ROR GAMMA (T))

(54) Titre : DÉRIVÉS BENZÈNESULFONAMIDES EN TANT QU'AGONISTES INVERSES DU RÉCEPTEUR GAMMA ORPHELIN ASSOCIÉ AUX RÉTINOÏDES ROR GAMMA (T)



(I)

(57) Abstract : The invention relates to benzenesulfonamide derivatives of formula (I), the pharmaceutically acceptable addition salts thereof, the hydrates and/or solvates thereof, and the use of same as inverse agonists of retinoid-related orphan receptor gamma (RORγt). The invention also relates to pharmaceutical compositions comprising such compounds, as well as to the use thereof for the topical and/or oral treatment of RORγt receptor-mediated inflammatory diseases, in particular acne, psoriasis and/or atopic dermatitis.

(57) Abrégé : La présente invention concerne des dérivés benzènesulfonamides de formule (I), leurs sels d'addition pharmaceutiquement acceptables, leurs hydrates et/ou leurs solvates, ainsi que leur utilisation en tant qu'agonistes inverses du récepteur gamma orphelin associé aux rétinoïdes RORγt. L'invention est également relative aux compositions pharmaceutiques comprenant de tels composés, ainsi que leur utilisation pour le traitement par voie topique et/ou orale des maladies inflammatoires médiées par les récepteurs RORγt, notamment l'acné, le psoriasis et/ ou la dermatite atopique.

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Sulfonamide derivatives as inverse agonists of retinoid-related orphan receptor gamma (ROR gamma (t))

The present invention relates to particular sulfonamide derivatives, to the pharmaceutically acceptable addition salts thereof, hydrates thereof and/or solvates thereof, and also to the use thereof as inverse agonist of the retinoid-related orphan receptor gamma RORγt.

The invention also relates to a pharmaceutical composition comprising such compounds and also to the use thereof for the topical and/or oral treatment of inflammatory diseases mediated by the RORγt receptors, especially acne, atopic dermatitis and/or psoriasis.

The nuclear receptors form a large family (known as a superfamily) of transcription factors which correspond to proteins that are capable of being activated by a ligand, of binding to specific DNA sequences and of regulating the transcription of target genes. Thus, these receptors are involved in the regulation of a wide variety of biological functions, including growth, development, reproduction, differentiation and metabolism in a multitude of living organisms.

The first members of this superfamily that were identified and described in the scientific literature are the nuclear receptors of steroid hormones such as the glucocorticoid receptors and the estrogen receptors. This superfamily also comprises among its members many receptors for which no ligand has been identified. These nuclear receptors are known as "orphan receptors".

Retinoid-related orphan receptors thus constitute a subfamily of nuclear receptors. This subfamily is composed of three members each having an intrinsic expression profile: ROR alpha (known as RORα), ROR beta (known as RORβ) and ROR gamma (known as RORγ). Two isoforms of the orphan receptors RORγ have already been identified, namely RORγ1, which is expressed in a variety of tissues such as the thymus, the kidneys, muscles and the liver, and RORγ2 (also known as RORγt), which is expressed exclusively in the cells of the immune system.

In particular, the receptor RORγt plays an important regulating role in cell differentiation of the Th17 lymphocytes which correspond to helper T lymphocytes whose function is to ensure the defense of the body against a large number of extracellular pathogens such as bacteria and fungal infections.

However, it has been demonstrated that the Th17 lymphocytes are also involved in a wide variety of inflammatory disorders, such as acne, and of autoimmune diseases such as psoriasis, rheumatoid arthritis or multiple sclerosis (Peck A, Mellins ED. Precarious balance; Th17 cells in host defense. Infect. Immun. 2010 Jan.; 78(1): 32-8; Suarez-Farinas: J. Allergy Clin. Immunol. 2014; J. Invest. Dermatol. 2008, 128(11), 2625).

Specifically, the Th17 lymphocytes produce numerous cytokines which have distinct profiles, such as interleukin-17A (IL-17A), interleukin-17F (IL-17F), interleukin-26 (IL-26), interleukin-21 (IL-21), interleukin-22 (IL-22) and TNFα, the development, survival and proliferation of which depend on interleukin-23 (IL-23). These cytokines are capable of activating different types of effector cells, such as keratinocytes, thus leading to their hyperproliferation and to the additional production of pro-inflammatory cytokines, chemokines and antimicrobial peptides, which in turn recruit and activate other immune system cells in the inflamed skin, which may lead to amplification of the immune response.

Thus, activation of the Th17 lymphocytes is responsible for the recruitment of cytokines, especially of interleukin-17 (IL17), and of other types of pro-inflammatory cells, which will lead to the mediation of inflammatory disorders such as acne and/or of autoimmune diseases such as psoriasis.

Experiments conducted on mice show that a decrease in the level of expression of the RORγt receptor leads to a decrease in the activity of the Th17 lymphocytes, which consequently makes it possible to greatly reduce the expression of interleukin-17 (IL-17) (Ivanov II, McKenzie BS, Zhou L, Tadokoro CE, Lepelley A, Lafaille JJ, Cua DJ, Littman DR: Cell 2006, 126, 1121-1133) and to efficiently treat inflammatory disorders and autoimmune diseases mediated by these cytokines, especially those for which high levels of interleukin-17 (IL-17) are detected.

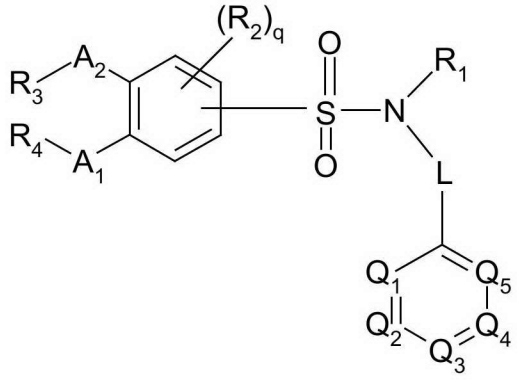
To this end, patent application WO 2013/160 418 describes sulfonamide compounds as inverse agonists of the RORγt receptor in order to be able to treat inflammatory disorders and autoimmune diseases. Similarly, other compounds have also been developed as inverse agonists of the RORγt receptor, such as those

described in patent applications WO 2014/090 712, WO 2014/008 214, WO 2013/169 588, WO 2013/160 419, WO 2013/1 002 027, WO 2013/092 939, WO 2013/092 941, WO 2013/085 890 and WO 2012/100 732.

There is thus a real need to develop novel compounds as inverse agonists of the RORγt receptor in order to be able to efficiently treat diseases mediated by such a receptor, especially inflammatory disorders such as acne, and/or autoimmune diseases such as psoriasis and atopic dermatitis.

This aim is achieved by means of the use of particular sulfonamide derivatives as described below, which make it possible to modulate the activity of the RORγt receptor and consequently to efficiently treat inflammatory disorders and autoimmune diseases of certain pathologies.

One subject of the present invention is thus one or more compounds of formula (I), the pharmaceutically acceptable addition salts thereof, hydrates thereof and/or solvates thereof:



(I)

in which formula (I):

- q denotes zero or a natural integer ranging from 1 to 3,
- L represents a single bond or a methylene group CH_2,
- R^1 represents a linear or branched C_3-C_5 alkyl radical, a C_3-C_5 cycloalkyl radical, a linear or branched C_2-C_5 alkenyl radical, a (C_1)alkyl(C_3-C_5)cycloalkyl radical, a C_4-C_5 heterocycloalkyl radical, a (C_1)alkyl(C_4-C_5)heterocycloalkyl radical,
- R_2 represents a hydrogen atom or a halogen atom, a linear or branched C_1-C_5 alkyl radical, a linear or branched C_2-C_4 alkenyl radical, a C_1-C_4 alkoxy

radical, a cyano group -CN; the alkyl, alkenyl and alkoxy radicals possibly being substituted with one or more halogen atoms,

- R^3 represents a hydrogen atom, a C_1-C_3 alkyl radical or an amino $–NH_2$ radical,
- R^4 represents a hydrogen atom or a group $(CHR^5)_n$-$(Z)_o$-$(CHR'^5)_p$-R^6,
- n, o and p, which may be identical or different, denote zero or a natural integer ranging from 1 to 3,
- Z represents a divalent group chosen from $–CH_2–$, –NH– and –O–,
- R^5 and R'^5, which may be identical or different, represent a hydrogen atom, a methyl radical $-CH_3$, a hydroxyl radical -OH, a C_1 hydroxyalkyl radical, a carboxylic radical -COOH,
- R^6 represents:
  - a hydrogen atom or a halogen atom,
  - a heterocycloalkyl radical optionally substituted with one or more halogen atoms, one or more linear or branched C_1-C_3 alkyl groups, one or more -OH groups, one or more carbonyl functions =O, one or more linear or branched C_1-C_4 hydroxyalkyl groups, a pyrrolidine ring, one or more amino groups, one or more groups $–C(=O)R^7$, one or more groups $S(=O)_2R^7$; R^7 representing a linear or branched C_1-C_3 alkyl radical, a hydroxyl radical -OH, a linear or branched C_1-C_4 alkoxy radical, or an amino radical $N(R^{7a})(R^{7b})$; with R^{7a} and R^{7b}, which may be identical or different, denoting a hydrogen atom, a linear or branched C_1-C_3 alkyl radical or a cyclopropyl radical,
  - a C_3-C_6 cycloalkyl radical optionally substituted with one or more -OH groups,
  - an aromatic or heteroaromatic radical optionally substituted with one or more halogen atoms, one or more linear or branched C_1-C_3 alkyl groups optionally substituted with one or more halogen atoms, one or more C_1-C_3 alkoxy groups, one or more amino groups $–NR^{11}R^{12}$, one or more groups $–COR^{11}$, a carbonyl function (=O), one or more groups $–OR^{11}$, one or more C_1-C_4 hydroxyalkyl groups, one or more groups $–COOR^{11}$, one or more amido groups $–CONR^{11}R^{12}$, one or more groups $–SOR^{11}$, one or more groups $–SO_2R^{11}$, one or more groups $–NHCOR^{11}$, one or more groups $–NHCOOR^{11}$, one or more groups $–SO_2NR^{11}R^{12}$ or one or more -CN groups; R^{11} and R^{12}, which may be identical or different,

representing a hydrogen atom or a linear or branched C_1-C_3 alkyl radical optionally substituted with one or more halogen atoms;

- A_1 represents a divalent group chosen from $–NR^a–$, –O–, –S–, –SO–, $–SO_2–$, $–SO(=NH)–$, $–CH_2–$, –C=C–, $–CH(R^a)–$;
- A_2 represents a single bond or a divalent group chosen from –S–, –SO–, $–SO_2–$, $–SO(=N\text{-}R^b)–$, –CH(OH)–, –C(=O)O–;

given that:

- when A_1 represents one of the divalent groups chosen from: $–NR^a–$, –O–, $–CH_2–$, –C=C– and $–CH(R^a)$, then A_2 does not represent the divalent group –CH(OH)– and –C(=O)O– and R_3 does not represent a hydrogen atom, an amino radical $–NH_2$ or a C_1-C_3 alkyl radical,
- when A_2 represents a single bond and R_3 represents a hydrogen atom, then A_1 represents one of the divalent groups chosen from: –SO– and $–SO(=NH)$-,

- R^a represents a hydrogen atom, a linear or branched C_1-C_3 alkyl radical or an acetyl radical $–C(=O)CH_3$,
- R^b represents a hydrogen atom, a linear or branched C_1-C_3 alkyl radical or a cyclopropyl group,
- Q_1, Q_2, Q_3, Q_4 and Q_5, which may be identical or different, represent a nitrogen atom or a group $–CR'_2$,
- when A_2 represents a divalent group chosen from –S-, –SO, $–SO_2–$ and $–SO(=N\text{-}R^b)–$, then R^a and R^3 can form, together with the carbon atoms to which they are attached, a heterocycloalkyl group which may be optionally substituted with one or more carbonyl functions, one or more C_1-C_3 alkyl radicals,
- when A_1 represents $–NR^a–$, then R^a and R^4 can form, together with the nitrogen atom to which they are attached, a C_2-C_{10} heterocycloalkyl group optionally comprising 1 to 3 heteroatoms chosen from a sulfur atom, a nitrogen atom and an oxygen atom; said heterocycloalkyl group being optionally substituted with at least one radical R^{14},
- R^{14} represents a linear or branched C_1-C_3 alkyl radical, a linear or branched C_1-C_3 alkoxy radical, a halogen atom, a hydroxyl group -OH, a cyano group -CN, a group $–CONR^{15}R^{16}$, a group $–SO_2R^{15}$, a group $–COR^{15}$ or an amino group $–NR^{15}R^{16}$; R^{15} and R^{16}, which may be identical or different, representing a hydrogen atom or a linear or branched C_1-C_3 alkyl radical.

In other words, in accordance with formula (I):

- when A_1 represents one of the following divalent groups: $-NR^a-$, $-O-$, $-CH_2-$, $-C=C-$ or $-CH(R^a)$, then A_2 does not represent a single bond or a divalent group: $-CH(OH)-$ or $-C(=O)O-$,
- when A_2-R_3 represents a hydrogen atom, then A_1 represents one of the following divalent groups: $-SO-$ and $-SO(=NH)$.

The compounds according to the invention correspond to sulfonamide derivatives and preferably to sulfur-based sulfonamide derivatives which comprise in their structure at least one sulfonamide group SO_2-N and at least one sulfur atom.

The compounds according to the invention make it possible to modulate, i.e. to inhibit, the activity of the RORγt receptor.

A subject of the present invention is also the compound(s) as defined previously, as medicament and cosmetic.

Another subject of the invention relates to the compound(s) as defined previously for its use in the treatment of diseases mediated by the RORγt receptor, especially inflammatory disorders and/or autoimmune diseases mediated by the RORγt receptor.

Moreover, the invention also relates to a pharmaceutical composition comprising, in a pharmaceutically acceptable medium, one or more compounds of formula (I) as defined previously, pharmaceutically acceptable addition salts thereof, hydrates thereof and/or solvates thereof.

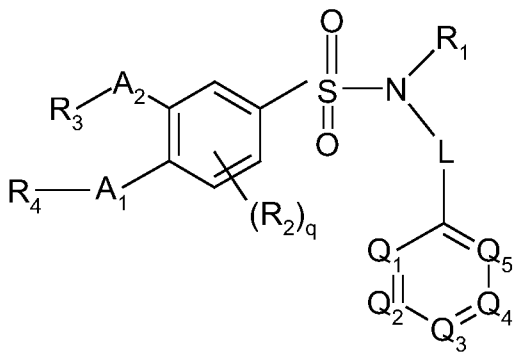
The present invention also relates to the pharmaceutical composition as described previously, for its use for treating diseases mediated by the RORγt receptor, especially inflammatory disorders and/or autoimmune diseases.

Finally, the invention relates to a method for treating diseases mediated by the RORγt receptor, comprising the administration, especially topically or orally, of a therapeutically effective amount of one or more compounds as defined above to a patient.

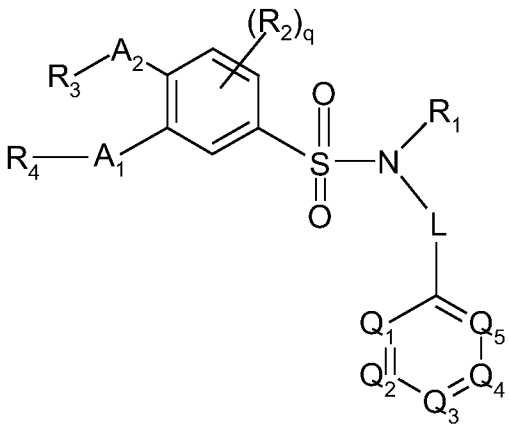
Other subjects, characteristics, aspects and advantages of the invention will emerge even more clearly on reading the description and the examples that follow.

Preferably, the compound(s) of formula (I) are sulfur-based sulfonamides.

Preferably, the compound(s) of formula (I) according to the invention are chosen from the compound(s) of formulae (Ia) and/or (Ib):



(Ia)



(Ib)

in which formulae (Ia) and (Ib) R^1, R_2, R'_2, R^3, R^4, R^5, R'^5, R^6, R^7, R^{7a}, R^{7b}, R^{11}, R^{12}, R^{14}, R^{15}, R^{16}, R^a, R^b, Z, Q_1, Q_2, Q_3, Q_4, Q_5, A_1, A_2, L and the indices q, n, o and p have the same meanings as in formula (I) described previously.

According to one embodiment, in formulae (I), (Ia) and (Ib), L represents a single bond.

According to another embodiment, in formulae (I), (Ia) and (Ib), L represents a methylene group $–CH_2$.

Preferentially, in formulae (I), (Ia) and (Ib), L represents a single bond.

According to one embodiment, in formulae (I), (Ia) and (Ib), R^1 represents a linear or branched C_3-C_5 and especially a branched C_4 alkyl radical.

According to one embodiment, in formulae (I), (Ia) and (Ib), R^1 represents a C_3-C_5 cycloalkyl radical.

According to one embodiment, in formulae (I), (Ia) and (Ib), R^1 represents a linear or branched C_2-C_5 alkenyl radical.

According to one embodiment, in formulae (I), (Ia) and (Ib), R^1 represents a (C_1)alkyl$(C_3$-$C_5)$cycloalkyl radical.

According to one embodiment, in formulae (I), (Ia) and (Ib), R^1 represents a C_4-C_5 heterocycloalkyl radical.

According to one embodiment, in formulae (I), (Ia) and (Ib), R^1 represents a (C_1)alkyl$(C_4$-$C_5)$heterocycloalkyl radical.

Preferentially, R^1 represents a linear or branched C_3-C_5, especially branched, and even more preferentially a branched C_4 alkyl radical.

According to one embodiment, in formulae (I), (Ia) and (Ib), R^3 represents a hydrogen atom.

According to one embodiment, in formulae (I), (Ia) and (Ib), R^3 represents a linear or branched C_1-C_3, and especially C_1, alkyl radical.

According to one embodiment, in formulae (I), (Ia) and (Ib), Q_1, Q_2, Q_4 and Q_5, which may be identical or different, represent a group $-CR'_2-$, with R'_2 possibly representing a hydrogen atom or a linear or branched C_1-C_5 alkyl radical.

Preferably, in formulae (I), (Ia) and (Ib), Q_3 represents a group $-CR'_2-$ with R'_2 representing a linear or branched C_1-C_5 and especially a C_2 alkyl radical.

Preferably, Q_1, Q_2, Q_4 and Q_5, which may be identical or different, represent a group $-CR'_2-$, with R'_2 representing a hydrogen atom.

In accordance with a preferential mode, Q_3 represents a group $-CR'_2-$ with R'_2 representing a linear or branched C_1-C_5 and especially C_2 alkyl radical, and Q_1, Q_2, Q_4 and Q_5, which may be identical or different, represent a group $-CR'_2-$, with R'_2 representing a hydrogen atom.

According to one embodiment, in formulae (I), (Ia) and (Ib), the index q corresponds to zero.

Preferably, in formulae (I), (Ia) and (Ib), A_2 represents a divalent group chosen from –SO–, $-SO_2-$ and $-SO(=N-R^b)-$.

According to one embodiment, in formulae (I), (Ia) and (Ib), A_2 represents the divalent group –SO–.

According to one embodiment, in formulae (I), (Ia) and (Ib), A_2 represents the divalent group $-SO_2-$.

According to one embodiment, in formulae (I), (Ia) and (Ib), A_2 represents the divalent group $-SO(=N-R^b)-$.

According to one embodiment, in formulae (I), (Ia) and (Ib), A_2 represents the divalent group –CH(OH)–.

According to one embodiment, in formulae (I), (Ia) and (Ib), A_2 represents a single bond.

Preferentially, in formulae (I), (Ia) and (Ib), A_2 represents the divalent group $-SO(=N-R^b)-$ with R^b representing a hydrogen atom.

Preferably, in formulae (I), (Ia) and (Ib), A_1 represents a divalent group chosen from the groups $-NR^a-$ and $-CH(R^a)-$.

According to one embodiment, in formulae (I), (Ia) and (Ib), A_1 represents the divalent group $-NR^a-$.

According to one embodiment, in formulae (I), (Ia) and (Ib), A_1 represents the divalent group –O–.

According to one embodiment, in formulae (I), (Ia) and (Ib), A_1 represents the divalent group –SO–.

According to one embodiment, in formulae (I), (Ia) and (Ib), A_1 represents the divalent group –S–.

According to one embodiment, in formulae (I), (Ia) and (Ib), A_1 represents the divalent group $-SO_2-$.

According to one embodiment, in formulae (I), (Ia) and (Ib), A_1 represents the divalent group –SO(=NH)–.

According to one embodiment, in formulae (I), (Ia) and (Ib), A_1 represents the divalent group $-CH_2-$.

According to one embodiment, in formulae (I), (Ia) and (Ib), A_1 represents the divalent group –C=C–.

According to one embodiment, in formulae (I), (Ia) and (Ib), A_1 represents the divalent group $-CH(R^a)-$.

Preferentially, in formulae (I), (Ia) and (Ib), A_1 represents the divalent group –O–, –S– or –SO–, and even more preferentially the divalent group –O–.

According to one embodiment, in formulae (I), (Ia) and (Ib), the indices n, o and p, which may be identical or different, denote zero.

According to one embodiment, in formulae (I), (Ia) and (Ib), the indices n, o and p, which may be identical or different, denote a natural integer ranging from 1 to 3.

According to one embodiment, the indices n and o denote 1 and the index p denotes zero.

According to one embodiment, the indices n and p denote zero and the index o denotes 1.

According to one embodiment, in formulae (I), (Ia) and (Ib), Z represents a methylene group $-CH_2-$.

According to one embodiment, in formulae (I), (Ia) and (Ib), Z represents a divalent group –O–.

According to one embodiment, in formulae (I), (Ia) and (Ib), Z represents a divalent group –NH–.

Preferably, R^4 is other than a hydrogen atom.

According to one embodiment, in formulae (I), (Ia) and (Ib), R^4 represents a group Z-R^6, with Z having the meaning described previously.

According to one embodiment, in formulae (I), (Ia) and (Ib), R^4 represents a group –C_2-R^6.

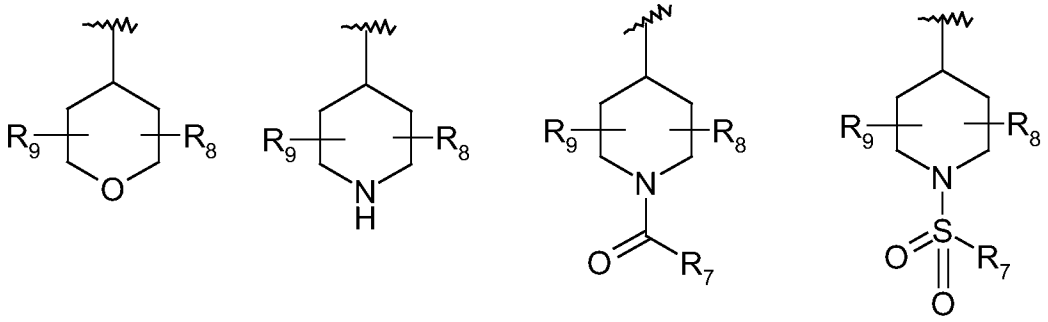
According to one embodiment, in formulae (I), (Ia) and (Ib), R^4 represents a group –O-R^6.

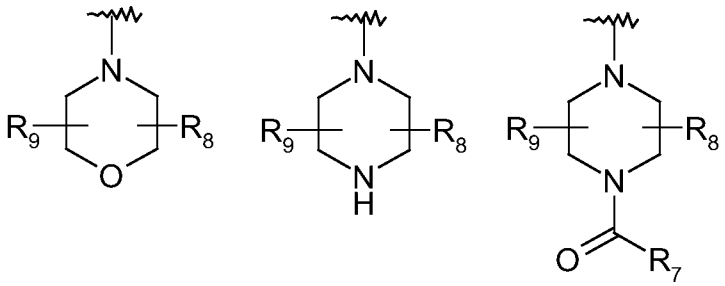
According to one embodiment, in formulae (I), (Ia) and (Ib), R^4 represents a group –NH-R^6.

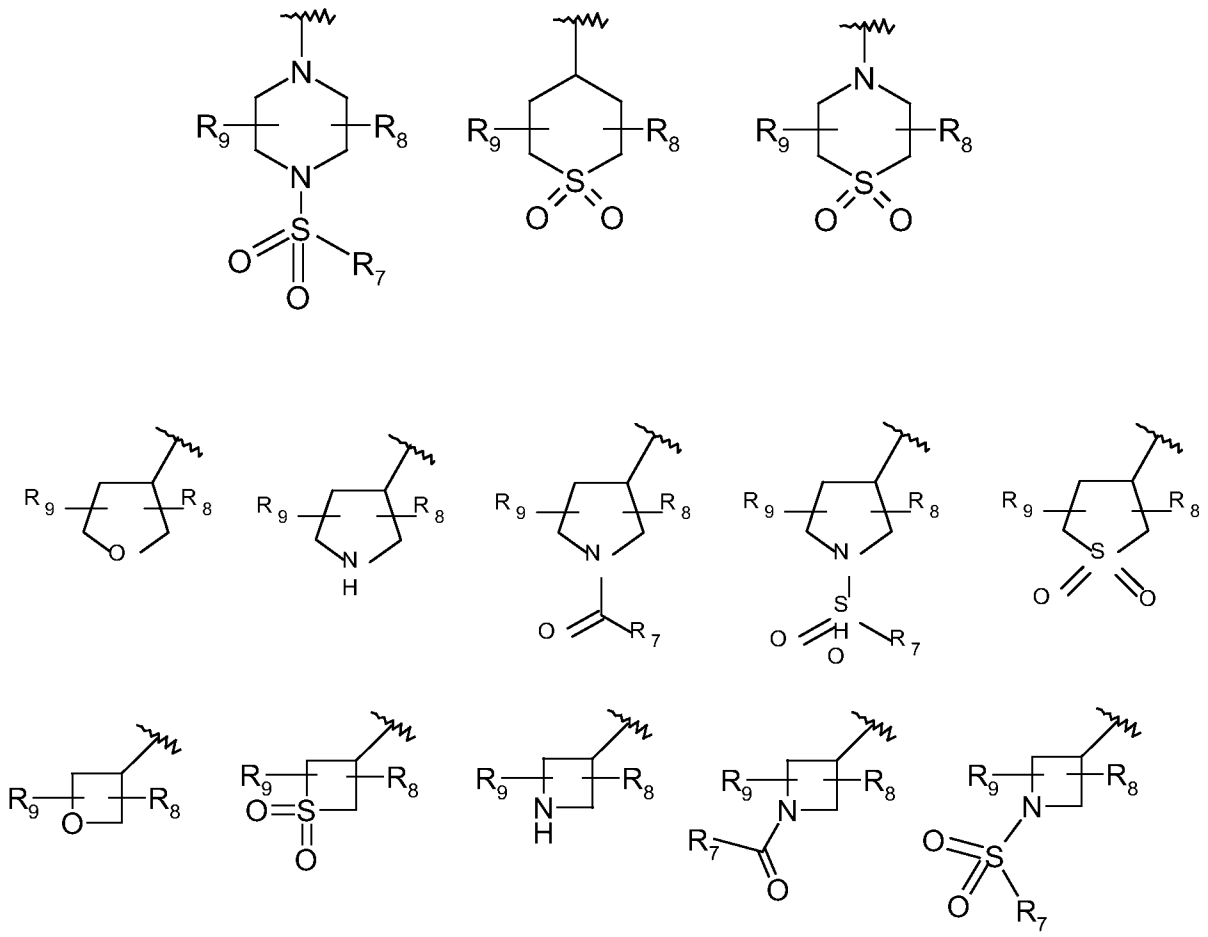
Thus, in formulae (I), (Ia) and (Ib), R^4 is chosen from the groups –CH_2-R^6, –O-R^6 or –NH-R^6.

According to one embodiment, in formulae (I), (Ia) and (Ib), R^6 represents a monocyclic, bicyclic or spiro bicyclic heterocyclic group.

According to one embodiment, R^6 represents a heterocycloalkyl radical, preferably chosen from:



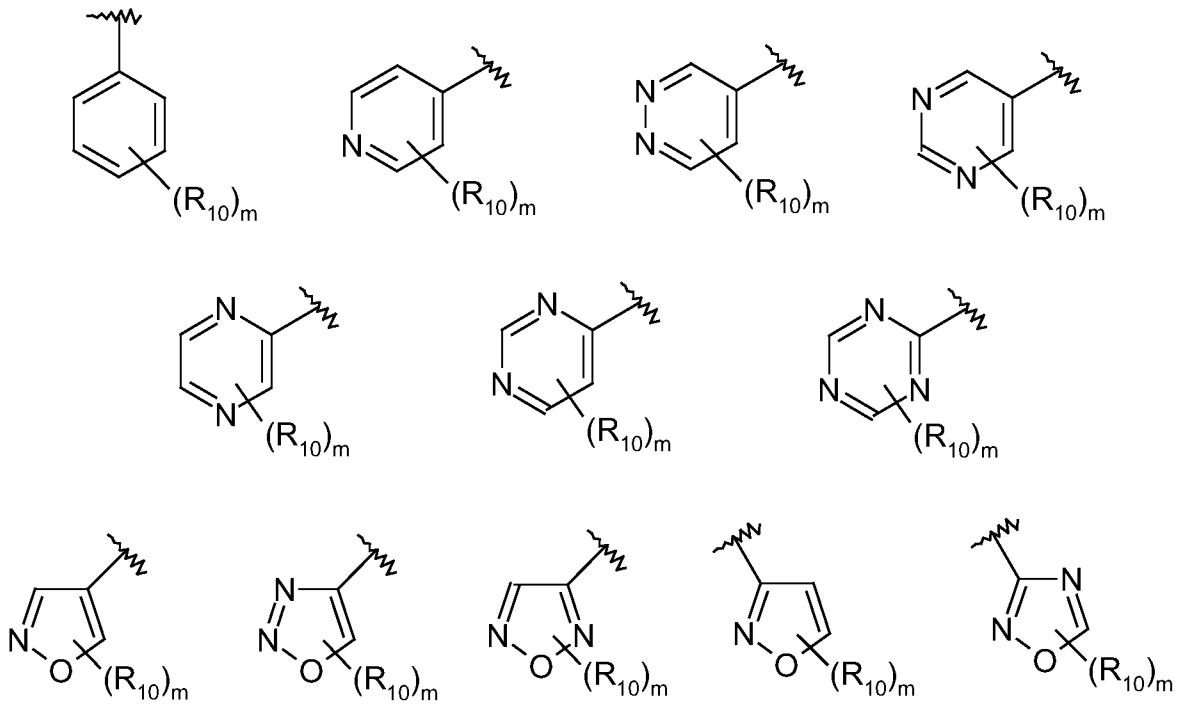




in which:

- R_7 represents a linear or branched C_1-C_3 alkyl radical, a hydroxyl radical -OH, a C_1-C_3 alkoxy radical or an amino radical $N(R^{7a})(R^{7b})$,
- R^{7a} and R^{7b}, which may be identical or different, denote a hydrogen atom, a linear or branched C_1-C_3 alkyl radical or a cyclopropyl radical,
- R_8 and R_9, which may be identical or different, represent a hydrogen atom, a linear or branched C_1-C_3 alkyl radical, a hydroxyl group -OH, a carbonyl group, a (C_1)hydroxyalkyl radical (CH_2OH), an amino group $-NH_2$,
- R_8 and R_9 can form, together with the carbon atoms to which they are attached, a 5- to 7-membered carbocyclic ring.

According to one embodiment, in formulae (I), (Ia) and (Ib), R^6 represents an aromatic or heteroaromatic radical preferably chosen from:



in which:

- R_{10} represents a hydrogen atom or a halogen atom; a linear or branched C_1-C_3 alkyl radical optionally substituted with one or more halogen atoms; a carbonyl function C(=O), a group OR^{11}, a C_1-C_4 hydroxyalkyl group, an amino group $-NR^{11}R^{12}$, a group $-COR^{11}$, a group $-COOR^{11}$, an amido group $-CONR^{11}R^{12}$, a group $-SOR^{11}$, a group $-SO_2R^{11}$, a group $-NHCOR^{11}$, a group $-NHCOOR^{11}$, a group $-SO_2NR^{11}R^{12}$ or a cyano group –CN,
- R^{11} and R^{12}, which may be identical or different, represent a hydrogen atom or a linear or branched C_1-C_3 alkyl radical optionally substituted with one or more halogen atoms,
- m denotes zero or a natural integer ranging from 1 to 3.

Preferentially, R^6 represents an aromatic or heteroaromatic radical as defined previously, optionally substituted with one or more methyl groups $-CH_3$, one or more methoxy groups $-OCH_3$, one or more hydroxyl groups -OH, one or more amino groups $-NH_2$, one or more $-CH_2OH$ groups, one or more cyano groups -CN, one or more halogen atoms, one or more carbonyl functions.

According to one embodiment, R^6 represents a hydrogen atom.

According to one embodiment, R^6 represents a C_3-C_6 cycloalkyl radical.

According to one embodiment, R_8 and R_9 represent a hydrogen atom.

According to one embodiment, R_8 and R_9 represent a linear or branched C_1-C_3 alkyl radical.

According to one embodiment, in formulae (I), (Ia) and (Ib), when A_2 represents a divalent group chosen from –SO, $–SO_2–$, $–SO(=N-R^b)–$, then A_1 represents a divalent group chosen from the groups $–NR^a–$ and $–CH(R^a)$ – and R^a and R_3 form, together with the carbon atoms to which they are attached, a 5- or 6-membered heterocycloalkyl group optionally substituted with one or more carbonyl functions, one or more halogen atoms or one or more C_1-C_2 alkyl radicals.

In accordance with this embodiment, R^a and R_3 form, together with the carbon atoms to which they are attached, an unsubstituted 5- or 6-membered heterocycloalkyl group.

In accordance with this embodiment, A_2 preferentially represents $–SO_2–$.

In accordance with this embodiment, A_2 preferentially represents –SO–.

In accordance with this embodiment, A_2 preferentially represents $SO(=N-R^b)–$ with R^b preferably representing a hydrogen atom or a linear or branched C_1-C_3 alkyl radical.

According to another embodiment, in formulae (I), (Ia) and (Ib), when A_2 represents a divalent group chosen from –SO, $–SO_2–$, $–SO(=N-R^b)–$, then A_1 represents a divalent group chosen from the divalent groups $–NR^a–$, –O–, $–CH_2–$, –C=C– and $–CH(R^a)$.

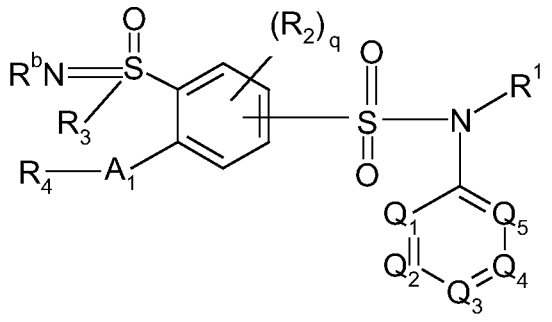
In accordance with this embodiment, R^a and R_3 do not form, together with the carbon atoms to which they are attached, a 5- or 6-membered heterocycloalkyl group.

According to one embodiment, when A_1 represents $–NR^a–$, then R^a and R^4 form, together with the nitrogen atom to which they are attached, a C_2-C_{10} heterocycloalkyl group optionally comprising 1 to 3 heteroatoms chosen from a sulfur atom, a nitrogen atom and an oxygen atom; said heterocycloalkyl group being optionally substituted with at least one radical R^{14} as defined in formula (I) described previously.

In particular, the C_2-C_{10} heterocycloalkyl group may be a monocyclic, bicyclic or spiro bicyclic group.

Preferably, the heterocycloalkyl group is optionally substituted with one, two or three radicals R^{14} as defined previously.

Preferably, the compound(s) according to the invention are chosen from the compounds of formula (II) and also the pharmaceutically acceptable addition salts thereof, hydrates thereof and/or solvates thereof:



(II)

in which formula (II):

- R^3 represents a C_1-C_3 alkyl radical,
- R^1, R_2, R'_2, R^3, R^4, R^5, R'^5, R^6, R^7, R^{7a}, R^{7b}, R_8, R_9, R_{10}, R^{11}, R^{12}, R^a, R^b, Z, Q_1, Q_2, Q_3, Q_4, Q_5, A_1, and the indices q, m, n, o and p have the same meanings as those indicated previously.

Preferably, R^b represents a hydrogen atom or a C_1 alkyl radical.

Preferentially, R^b represents a hydrogen atom.

Preferably, R^3 represents a C_1 alkyl radical.

Preferably, R^1 represents a branched C_3 alkyl radical.

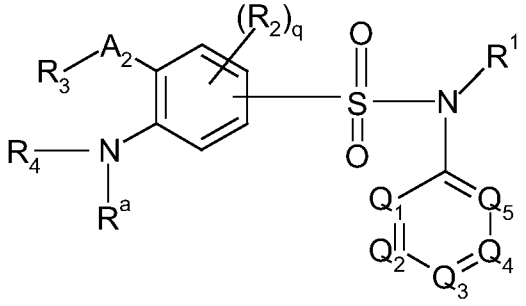
Preferentially, R^4 represents a group $(CHR^5)_n$-$(Z)_o$-$(CHR'^5)_p$-R^6 with R^6 preferably corresponding to an aromatic or heteroaromatic radical, a cycloalkyl radical or a heterocyclic radical as defined above in formula (I) or as previously.

Preferably, Q^1-Q^2 and Q^4-Q^5 correspond to a group $-CR^2$ with R^2 denoting a hydrogen atom and Q^3 corresponds to a group $-CR^2$ with R^2 denoting a linear or branched C_1-C_5 and preferably C_2 alkyl radical.

Preferably, Q^1 and Q^3, which may be identical or different, correspond to a group $-CR'_2$ with R'_2 denoting a hydrogen atom or a linear or branched C_1-C_5 and preferably C_2 alkyl radical.

In accordance with one embodiment, preferably, R^1 represents a linear or branched C_3-C_5 alkyl radical and R^b represents a hydrogen atom.

Preferably, the compound(s) according to the invention are chosen from the compounds of formula (III) and also the pharmaceutically acceptable addition salts thereof, hydrates thereof and/or solvates thereof:



(III)

in which formula (III):

- R^1, R_2, R'_2, R^3, R^b, Q_1, Q_2, Q_3, Q_4, Q_5, A_2 and the index q have the same meanings as in formula (I) described previously,

- R^a and R_4 form, together with the nitrogen atom to which they are attached, a C_2-C_{10} heterocycloalkyl group optionally comprising 1 to 3 heteroatoms chosen from a sulfur atom, a nitrogen atom and an oxygen atom; said heterocycloalkyl group being optionally substituted with at least one radical R^{14},

- R^{14} represents a linear or branched C_1-C_3 alkyl radical, a linear or branched C_1-C_3 alkoxy radical, a halogen atom, a hydroxyl group -OH, a cyano group -CN, a group $-CONR^{15}R^{16}$, a group $-SO_2R^{15}$, a group $-COR^{15}$ or an amino group $-NR^{15}R^{16}$; R^{15} and R^{16}, which may be identical or different, representing a hydrogen atom or a linear or branched C_1-C_3 alkyl radical.

In particular, the C_2-C_{10} heterocycloalkyl group may be a monocyclic, bicyclic or spiro bicyclic group.

The compounds of formulae (I), (II), (III), (Ia) and (Ib) may be in the form of pharmaceutically acceptable salts. Examples of pharmaceutically acceptable salts are described in Berge et al., 1977, "Sels pharmaceutiquement acceptables" [Pharmaceutically acceptable salts], J. Pharm. Sci., Vol. 66, pages 1 -19.

In particular, when the compounds of formula according to the invention are in the form of salts, then the electrical neutrality of said compounds is ensured by an external cationic counterion Y which may be organic or mineral.

Y may be chosen from suitable inorganic cations such as alkali metal ions, especially Na^+, K^+, alkaline-earth metal ions, especially Ca^{2+}, Mg^{2+}, or alternatively other cations such as the aluminum ion Al^{3+}.

Y may be chosen from suitable organic cations such as the ammonium ion NH_4^+, substituted ammonium ions such as NH_3R^+, NHR_2^+, NR_4^+ with R representing a C_1-C_4 alkyl radical.

In particular, the substituted ammonium ions are those chosen from derivatives of ethylamine, diethylamine, dicyclohexylamine, trimethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, melglumine and tromethamine, and amino acids such as lysine and arginine.

An example of a quaternary ammonium ion may be the ion $N^+(CH_3)_4$.

The compound(s) according to the invention may be in the form of the solvates thereof.

For the purposes of the present invention, the term "solvate" means a complex of solute (i.e. the compound according to the invention or the salt of said compound) and of solvent.

If the solvent is water, then the solvate may suitably be considered as a hydrate, for example, a hemihydrate, a monohydrate, a dihydrate, a trihydrate, etc.

For example, the solvates and/or hydrates may be obtained directly at the end of the synthetic process, the target compound being isolated in the form of a hydrate, for example a monohydrate or hemihydrate, or in the form of a solvate of the reaction and/or purification solvent.

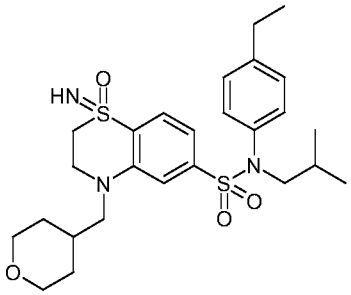
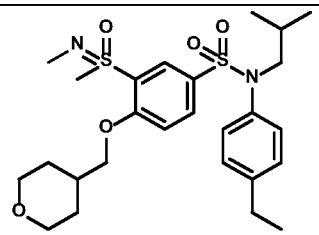
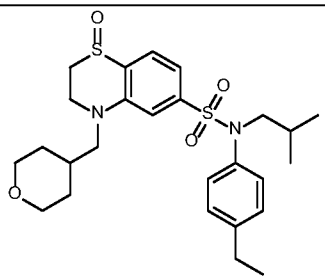
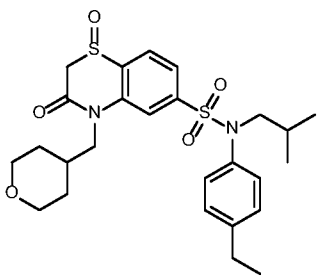
Unless otherwise indicated, any reference to a compound according to the invention also includes the solvate or the hydrate of the corresponding compound.

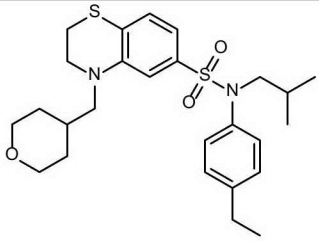
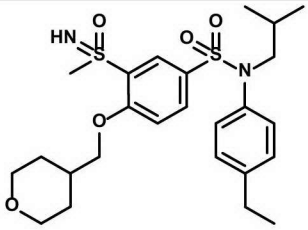
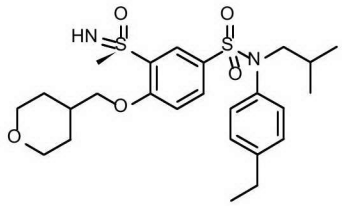
Typical processes for the preparation and identification of hydrates and solvates are well known to those skilled in the art: see, for example, pages 202-209 of KJ Guillory, “Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids” in Polymorphism in Pharmaceutical Solids, edition. Harry G. Britain, Vol. 95, Marcel Dekker, Inc., New York, 1999.

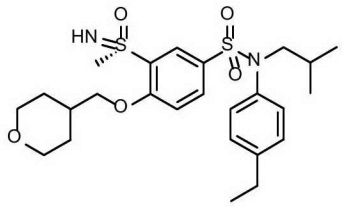
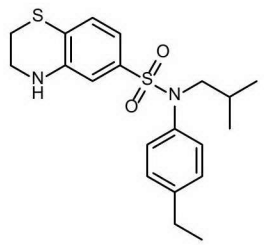
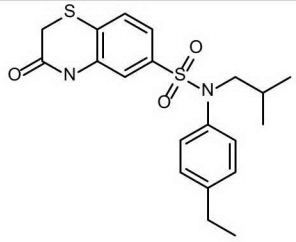
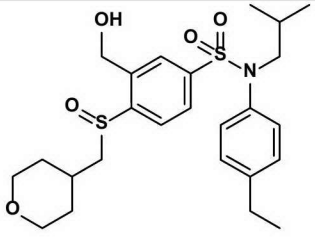
The hydrates and solvates may be isolated and characterized via methods known in the art, such as thermogravimetric analysis (TGA), TGA-mass spectroscopy, TGA-infrared spectroscopy, x-ray powder diffraction, Karl Fischer titration, high-resolution x-ray diffraction, and the like.

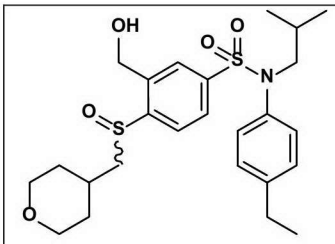
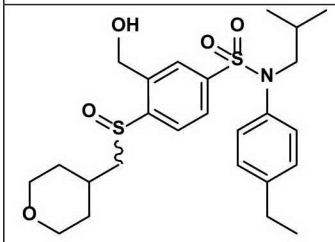
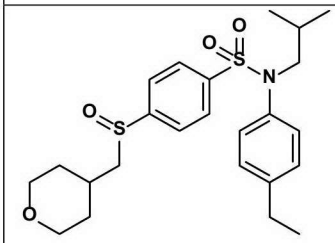
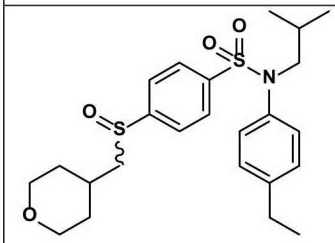
Preferably, the compound(s) of formula (I) are chosen from the following compounds as described in the tables below, and also the pharmaceutically acceptable addition salts thereof, hydrates thereof and/or solvates thereof:

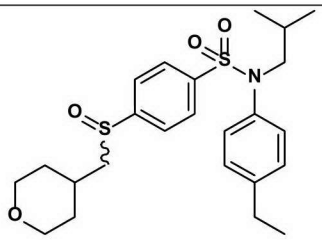
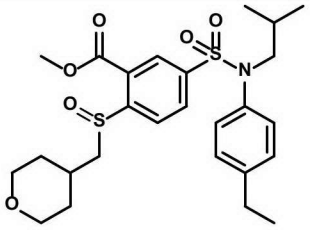
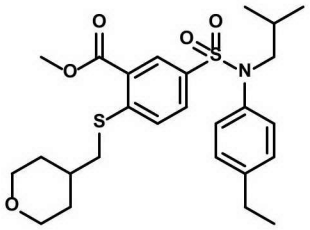
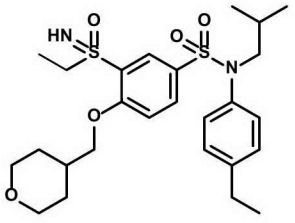
Table 1:

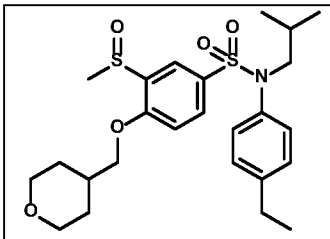
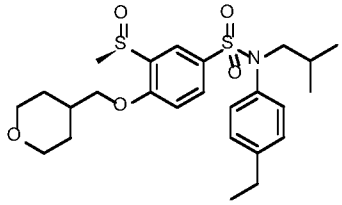
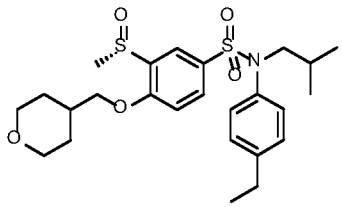
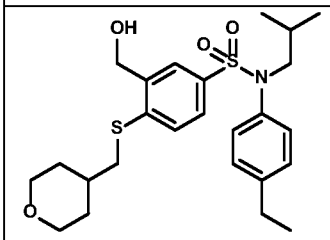
		IC50 hRORg	IC50 hCD4/IL17
	imino-1-oxo-4-(tetrahydropyran-4-ylmethyl)-1,2,3,4-tetrahydro-1λ^6-benzo[1,4]thiazine-7-sulfonic acid (4-ethylphenyl)isobutylamide compound 1	C	ND
	N-(4-ethylphenyl)-N-isobutyl-3-methanesulfinyl-4-(tetrahydropyran-4-ylmethoxy)benzene-N-methylsulfoximine compound 2	B	ND
	1-oxo-4-(tetrahydropyran-4-ylmethyl)-1,2,3,4-tetrahydro-1λ^4-benzo[1,4]thiazine-7-sulfonic acid compound 3	C	ND
	1,3-dioxo-4-(tetrahydropyran-4-ylmethyl)-1,2,3,4-tetrahydro-1 λ^4-benzo[1,4]thiazine-6-sulfonic acid (4-ethylphenyl)isobutylamide	C	ND

	compound 4		
	4-(tetrahydropyran-4-ylmethyl)-3,4-dihydro-2H-benzo[1,4]thiazine-6-sulfonic acid (4-ethylphenyl)isobutylamide compound 6	C	ND
	N-(4-ethylphenyl)-N-isobutyl-3-methanesulfoximino-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide compound 26	A	A
Chiral 	N-(4-ethylphenyl)-N-isobutyl-3-methanesulfoximino-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide compound 7 (enantiomer A of compound 26)	A	A

Chiral 	N-(4-ethylphenyl)-N-isobutyl-3-methanesulfoximino-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide compound 8 (enantiomer B of compound 26)	A	A
	3,4-dihydro-2H-benzo[1,4]thiazine-6-sulfonic acid (4-ethylphenyl)isobutylamide compound 9	C	ND
	3-oxo-3,4-dihydro-2H-benzo[1,4]thiazine-6-sulfonic acid (4-ethylphenyl)isobutylamide compound 10	C	ND
	N-(4-ethylphenyl)-3-hydroxymethyl-N-isobutyl-4-(tetrahydropyran-4-ylmethanesulfinyl)benzenesulfonamide compound 15	B	ND
	N-(4-ethylphenyl)-3-hydroxymethyl-N-isobutyl-	B	ND

	4-(tetrahydropyran-4-ylmethanesulfinyl)benzenesulfonamide compound 11 (enantiomer A of compound 15)		
	N-(4-ethylphenyl)-3-hydroxymethyl-N-isobutyl-4-(tetrahydropyran-4-ylmethanesulfinyl)benzenesulfonamide compound 12 (enantiomer B of compound 15)	B	ND
	N-(4-ethylphenyl)-N-isobutyl-4-(tetrahydropyran-4-ylmethanesulfinyl)benzenesulfonamide compound 29	B	B
	N-(4-ethylphenyl)-N-isobutyl-4-(tetrahydropyran-4-ylmethanesulfinyl)benzenesulfonamide compound 13 (enantiomer A of compound 29)	B	B

	N-(4-ethylphenyl)-N-isobutyl-4-(tetrahydropyran-4-ylmethanesulfinyl)benzenesulfonamide compound 14 (enantiomer B of compound 29)	B	B
	methyl 5-[(4-ethylphenyl)isobutylsulfamoyl]-2-(tetrahydropyran-4-ylmethanesulfinyl)benzoate compound 16	C	ND
	methyl 5-[(4-ethylphenyl)isobutylsulfamoyl]-2-(tetrahydropyran-4-ylmethylsulfanyl)benzoate compound 17	C	ND
	N-(4-ethylphenyl)-N-isobutyl-3-ethanesulfoximino-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide compound 18	A	A

	N-(4-ethylphenyl)-N-isobutyl-3-methanesulfinyl-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide compound 27	A	A
Chiral 	N-(4-ethylphenyl)-N-isobutyl-3-methanesulfinyl-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide compound 19 (enantiomer A of compound 27)	B	A
Chiral 	N-(4-ethylphenyl)-N-isobutyl-3-methanesulfinyl-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide compound 20 (enantiomer B of compound 27)	B	B
	N-(4-ethylphenyl)-3-hydroxymethyl-N-isobutyl-4-(tetrahydropyran-4-ylmethylsulfanyl)benzenesulfonamide	B	A

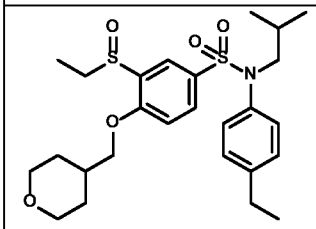
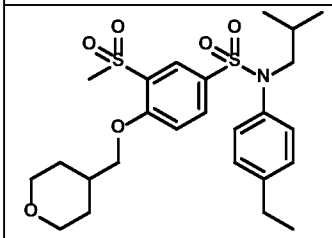
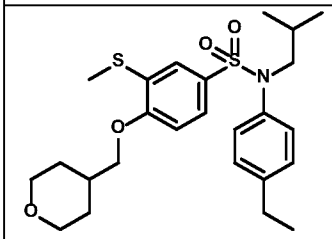
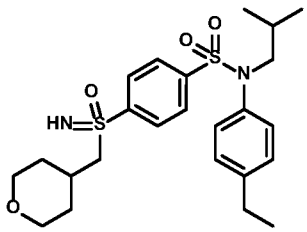
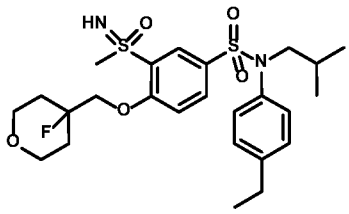
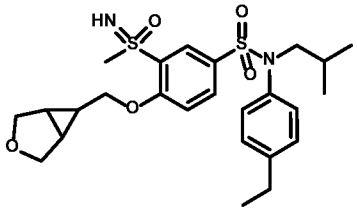
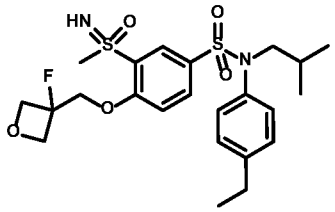
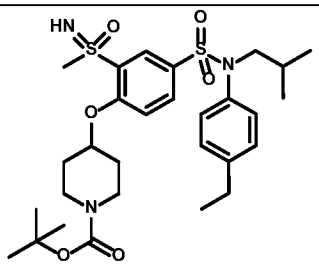
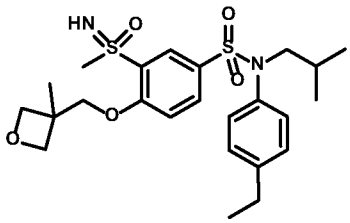
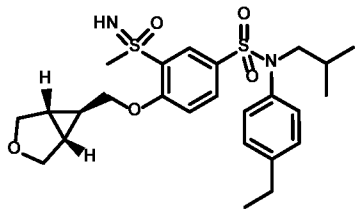
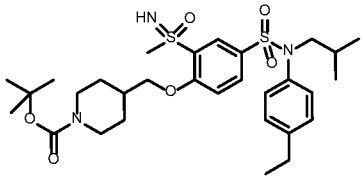
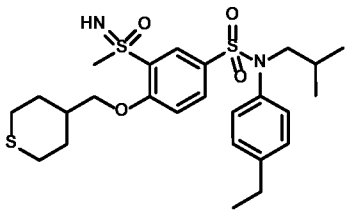
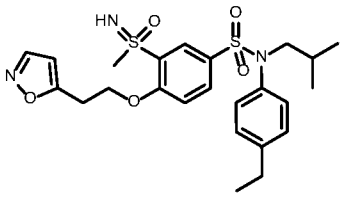
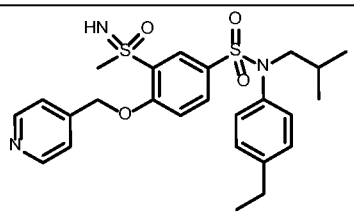
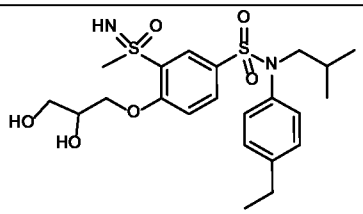
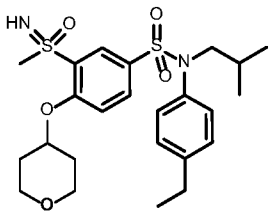
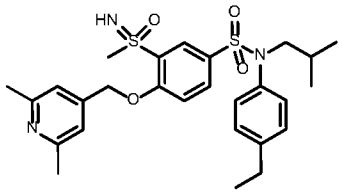
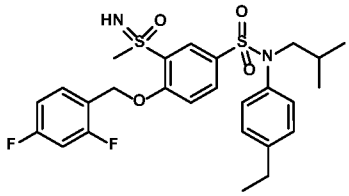
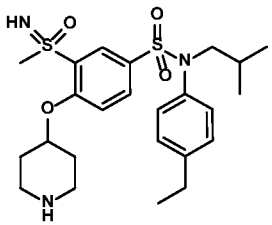
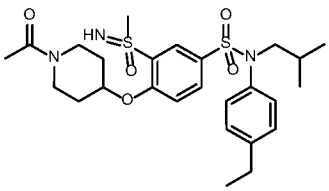
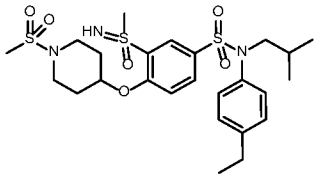
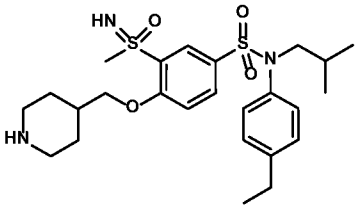
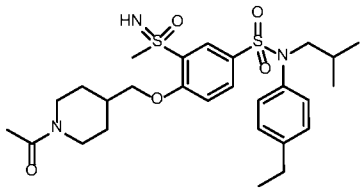
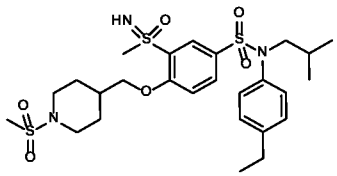
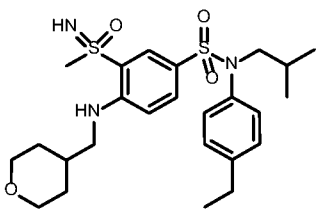
	compound 21		
	ethanesulfinyl-N-(4-ethylphenyl)-N-isobutyl-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide compound 22	B	B
	N-(4-ethylphenyl)-N-isobutyl-3-methanesulfonyl-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide compound 24	B	A
	N-(4-ethylphenyl)-N-isobutyl-3-methylsulfanyl-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide compound 25	B	B
	N-(4-ethylphenyl)-N-isobutyl-4-(tetrahydropyran-4-ylmethanesulfoximinyl)benzenesulfonamide compound 28	C	ND

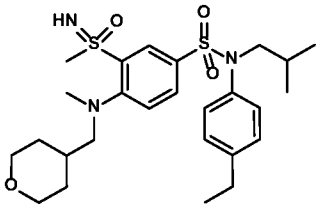
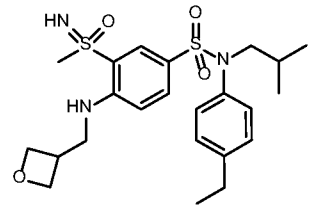
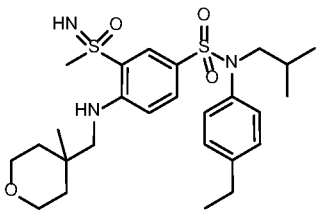
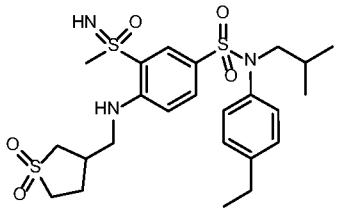
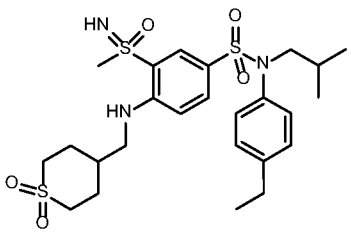
Table 2:

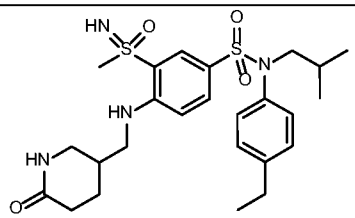
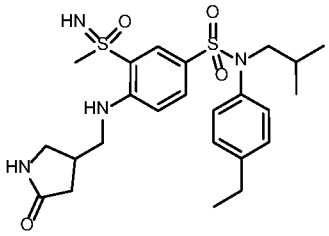
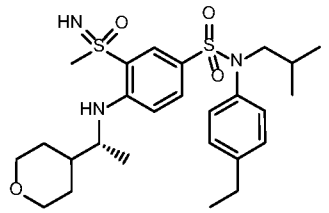
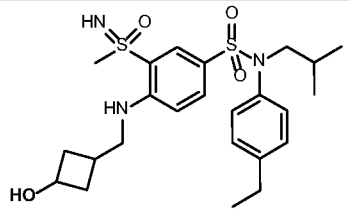
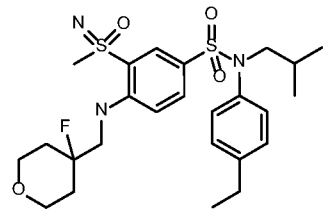
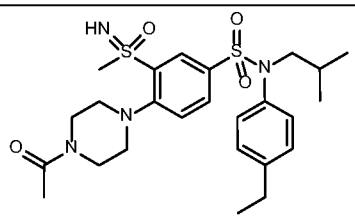
		IC50 hRORg	IC50 hCD4/IL17
	N-(4-ethylphenyl)-4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 30	A	A
	4-((3-oxabicyclo[3.1.0]hexan-6-yl)methoxy)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 31	A	ND
	N-(4-ethylphenyl)-4-((3-fluorooxetan-3-yl)methoxy)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 32	C	ND
	tert-butyl 4-(4-(N-(4-ethylphenyl)-N-isobutylsulfamoyl)-2-(S-methylsulfonimidoyl)phenoxy)piperidine-1-carboxylate compound 33	C	ND
	N-(4-ethylphenyl)-N-isobutyl-4-((3-methyloxetan-3-yl)methoxy)-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 34	C	ND

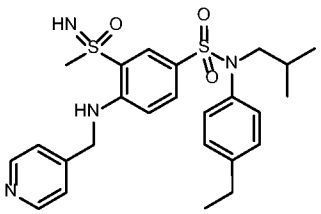
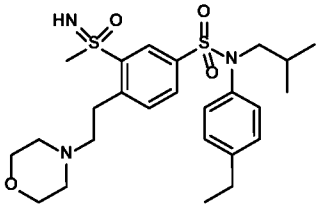
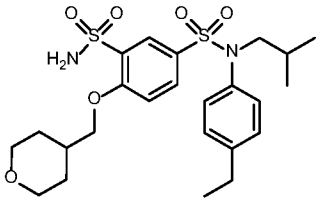
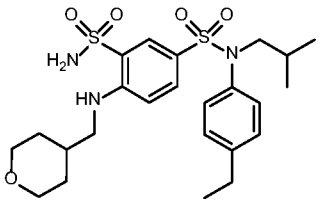
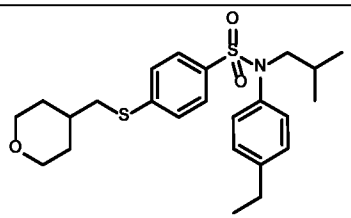
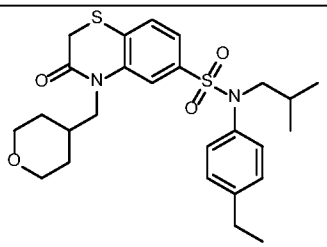
	4-(((1R,5S,6R)-3-oxabicyclo[3.1.0]hexan-6-yl)methoxy)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 35	A	ND
	tert-butyl 4-((4-(N-(4-ethylphenyl)-N-isobutylsulfamoyl)-2-(S-methylsulfonimidoyl)phenoxy)methyl)piperidine-1-carboxylate compound 36	C	ND
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(pyridin-4-ylmethoxy)benzenesulfonamide compound 37	A	ND
	N-(4-ethylphenyl)-N-isobutyl-4-(2-(isoxazol-5-yl)ethoxy)-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 38	C	ND
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(pyridin-4-ylmethoxy)benzenesulfonamide compound 39	C	ND

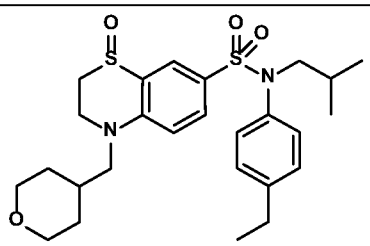
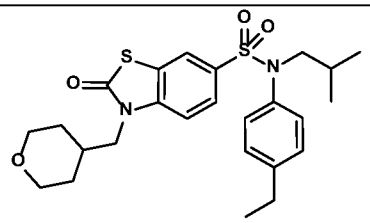
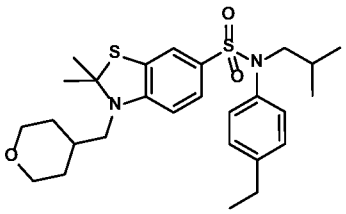
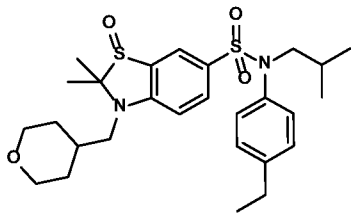
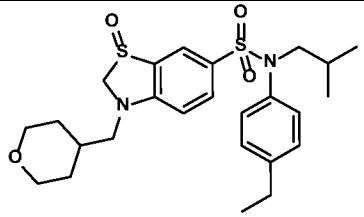
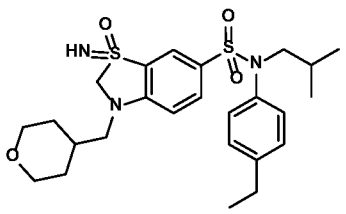
	4-(2,3-dihydroxypropoxy)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 40	C	ND
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((tetrahydro-2H-pyran-4-yl)oxy)benzenesulfonamide compound 42	C	ND
	4-((2,6-dimethylpyridin-4-yl)methoxy)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 43	C	ND
	4-((2,4-difluorobenzyl)oxy)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 45	C	ND
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(piperidin-4-ylmethoxy)benzenesulfonamide N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(piperidin-4-ylmethoxy)benzenesulfonamide compound 46	C	ND

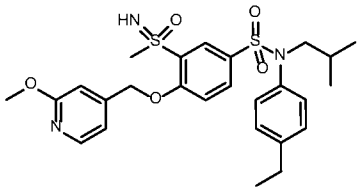
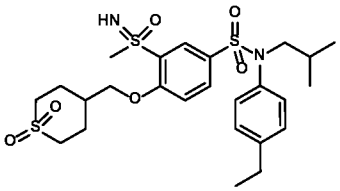
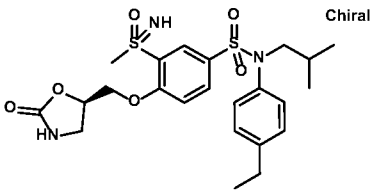
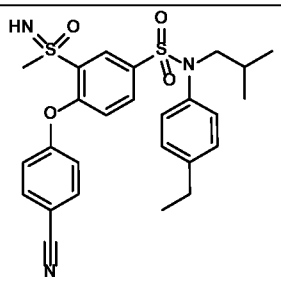
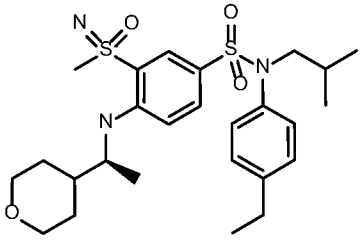
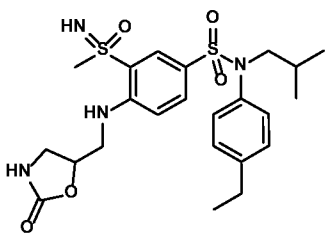
	4-((1-acetylpiperidin-4-yl)oxy)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzene sulfonamide compound 47	C	ND
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((1-(methylsulfonyl)piperidin-4-yl)oxy)benzenesulfonamide compound 48	C	ND
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(piperidin-4-ylmethoxy)benzenesulfonamide compound 49	C	ND
	4-((1-acetylpiperidin-4-yl)methoxy)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 50	C	ND
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((1-(methylsulfonylpiperidin-4-yl)methoxy)benzenesulfonamide compound 51	C	ND
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-[(tetrahydropyran-4-ylmethyl)amino]benzenesulfonamide compound 52	A	A

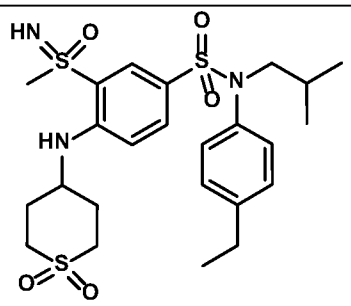
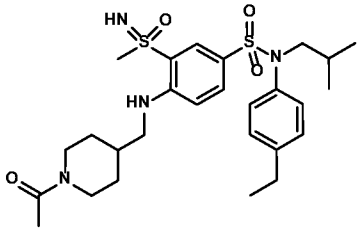
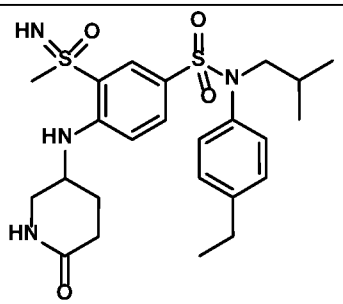
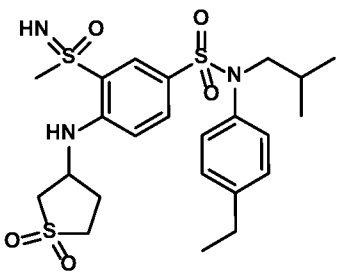
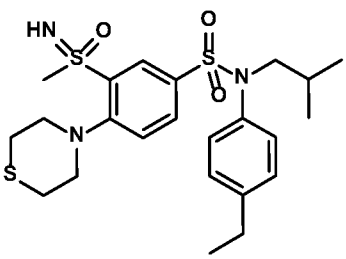
	N-(4-ethylphenyl)-N-isobutyl-4-(methyl((tetrahydro-2H-pyran-4-yl)methyl)amino)-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 53	A	A
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((oxetan-3-ylmethyl)amino)benzenesulfonamide compound 54	B	ND
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(((4-methyltetrahydro-2H-pyran-4-yl)methyl)amino)benzenesulfonamide compound 55	A	A
	4-(((1,1-dioxidotetrahydrothiophen-3-yl)methyl)amino)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 56	B	ND
	4-(((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl)amino)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 57	C	ND

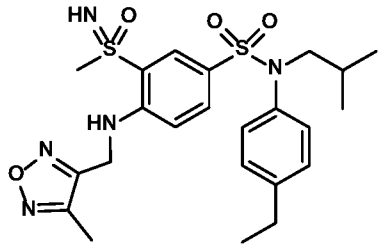
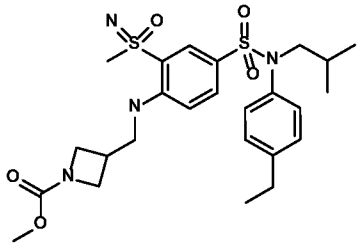
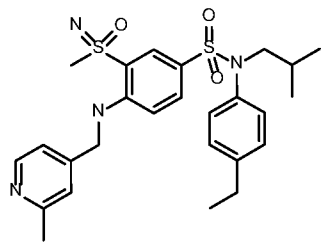
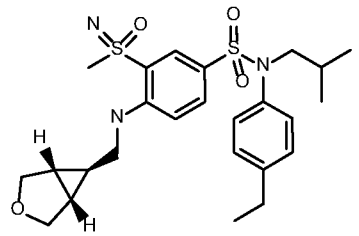
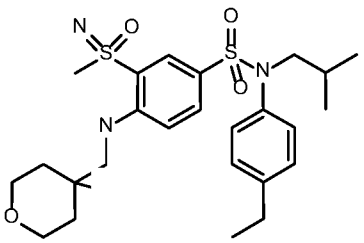
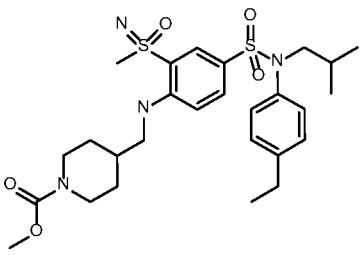
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(((6-oxopiperidin-3-yl)methyl)amino)benzenesulfonamide compound 58	C	ND
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(((5-oxopyrrolidin-3-yl)methyl)amino)benzenesulfonamide compound 59	B	B
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(((R)-1-(tetrahydro-2H-pyran-4-yl)ethyl)amino)benzenesulfonamide compound 60	B	ND
	N-(4-ethylphenyl)-4-(((3-hydroxycyclobutyl)methyl)amino)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 61	A	A
	N-(4-ethylphenyl)-4-(((4-fluorotetrahydro-2H-pyran-4-yl)methyl)amino)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 62	A	A
	4-(4-acetylpiperazin-1-yl)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 63	B	C

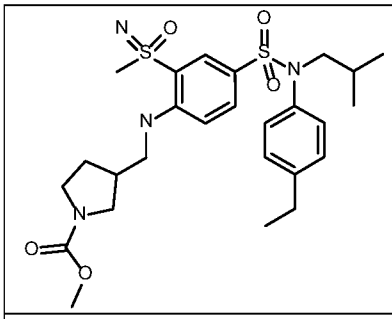
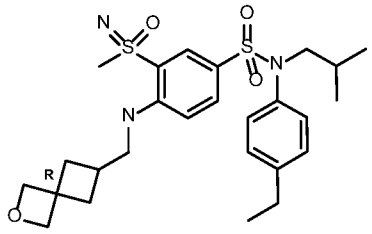
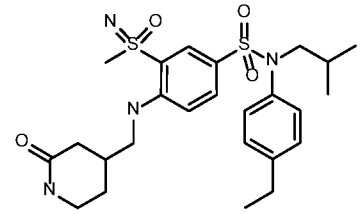
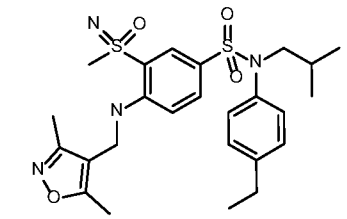
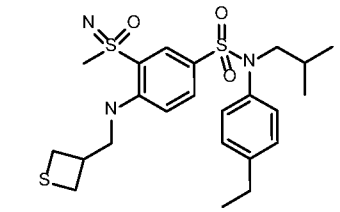
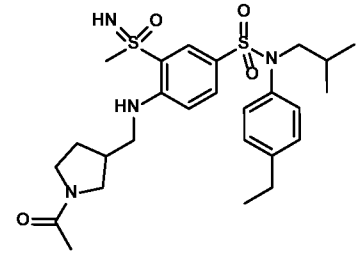
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((pyridin-4-ylmethyl)amino)benzenesulfonamide compound 64	A	A
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(2-morpholinoethyl)benzenesulfonamide compound 65	B	B
	4-(tetrahydropyran-4-ylmethoxy)benzene-1,3-disulfonic acid 3-amide 1-[(4-ethylphenyl)isobutylamide] compound 66	A	A
	4-[(tetrahydropyran-4-ylmethyl)amino]benzene-1,3-disulfonic acid 3-amide 1-[(4-ethylphenyl)isobutylamide] compound 67	B	ND
	N-(4-ethylphenyl)-N-isobutyl-4-(tetrahydropyran-4-ylmethylsulfanyl)benzenesulfonamide compound 68	B	B
	3-oxo-4-(tetrahydropyran-4-ylmethyl)-3,4-dihydro-2H-benzo[1,4]thiazine-7-sulfonic acid (4-ethylphenyl)isobutylamide compound 70	C	ND

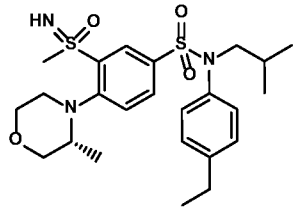
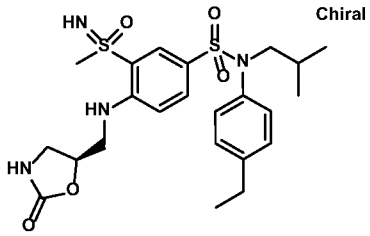
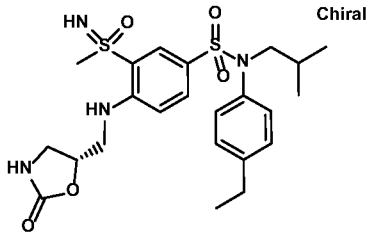
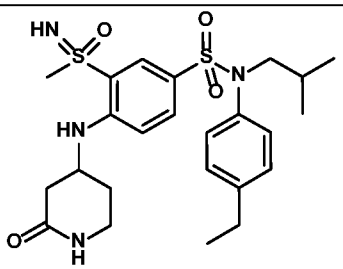
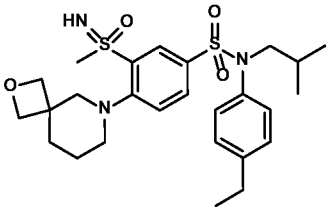
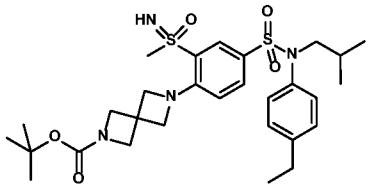
	1-oxo-4-(tetrahydropyran-4-ylmethyl)-1,2,3,4-tetrahydro-1λ^4-benzo[1,4]thiazine-7-sulfonic acid (4-ethylphenyl)isobutylamide compound 71	C	ND
	3-oxo-4-(tetrahydropyran-4-ylmethyl)-3,4-dihydro-2H-benzo[1,4]thiazine-7-sulfonic acid (4-ethylphenyl)isobutylamide compound 72	B	ND
	2,2-dimethyl-3-(tetrahydropyran-4-ylmethyl)-2,3-dihydrobenzothiazole-6-sulfonic acid (4-ethylphenyl)isobutylamide compound 73	C	ND
	2,2-dimethyl-1-oxo-3-(tetrahydropyran-4-ylmethyl)-2,3-dihydro-1H-1λ^4-benzothiazole-6-sulfonic acid (4-ethylphenyl)isobutylamide compound 74	B	ND
	1-oxo-3-(tetrahydropyran-4-ylmethyl)-2,3-dihydro-1H-1λ^4-benzothiazole-6-sulfonic acid (4-ethylphenyl)isobutylamide compound 75	C	ND
	1-imino-1-oxo-3-(tetrahydropyran-4-ylmethyl)-2,3-dihydro-1H-1λ^6-benzothiazole-6-sulfonic acid (4-ethylphenyl)isobutylamide compound 76	C	ND

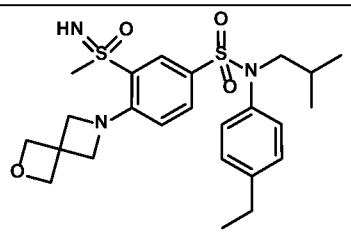
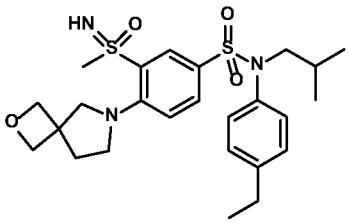
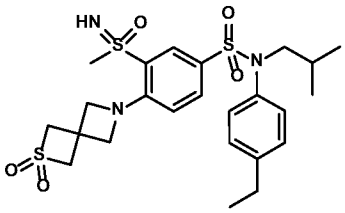
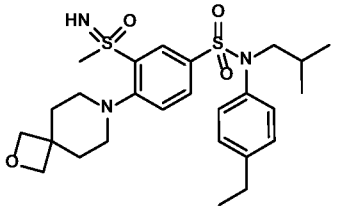
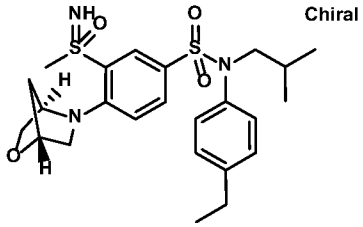
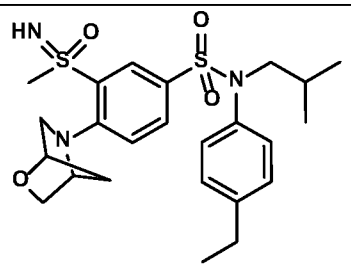
	N-(4-ethylphenyl)-N-isobutyl-4-((2-methoxypyridin-4-yl)methoxy)-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 77	C	ND
	N-(4-ethylphenyl)-N-isobutyl-4-((2-methoxypyridin-4-yl)methoxy)-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 78	C	ND
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(((R)-2-oxooxazolidin-5-yl)methoxy)benzenesulfonamide compound 79	C	ND
	4-(4-cyanophenoxy)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 80	C	ND
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(((S)-1-(tetrahydro-2H-pyran-4-yl)ethyl)amino)benzenesulfonamide compound 81	B	ND
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(((2-oxooxazolidin-5-yl)methyl)amino)benzenesulfonamide	B	ND

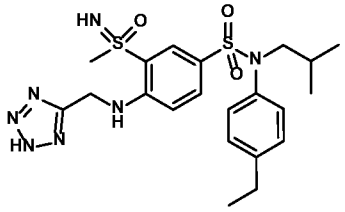
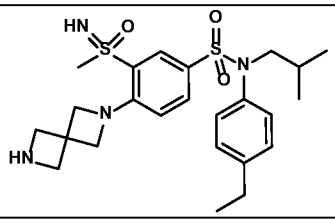
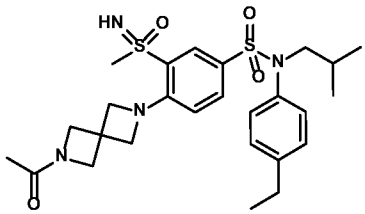
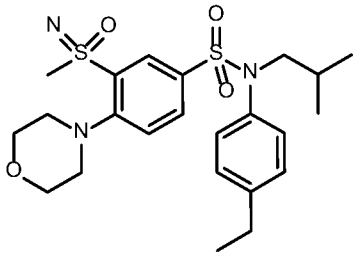
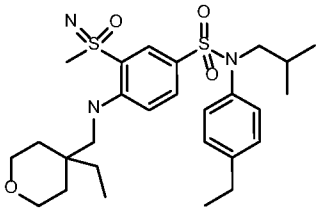
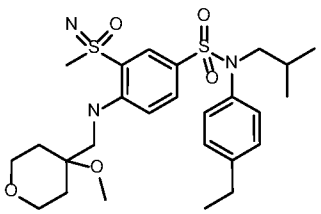
	compound 82		
	4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 83	C	ND
	4-(((1-acetylpiperidin-4-yl)methyl)amino)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 84	C	ND
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((6-oxopiperidin-3-yl)amino)benzenesulfonamide compound 85	C	ND
	4-((1,1-dioxidotetrahydrothiophen-3-yl)amino)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 86	B	ND
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-thiomorpholinobenzenesulfonamide compound 87	A	A

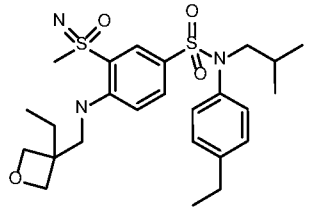
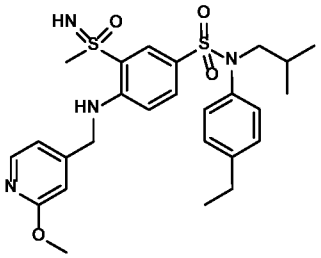
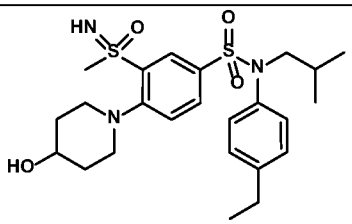
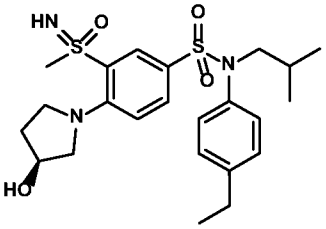
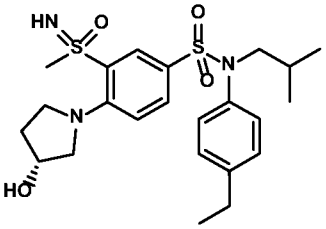
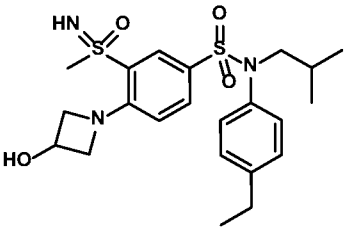
	N-(4-ethylphenyl)-N-isobutyl-4-(((4-methyl-1,2,5-oxadiazol-3-yl)methyl)amino)-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 88	C	ND
	methyl 3-(((4-(N-(4-ethylphenyl)-N-isobutylsulfamoyl)-2-(S-methylsulfonimidoyl)phenyl)amino)methyl)azetidine-1-carboxylate compound 89	C	ND
	N-(4-ethylphenyl)-N-isobutyl-4-(((2-methylpyridin-4-yl)methyl)amino)-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 90	C	ND
	4-((((1R,5S,6S)-3-oxabicyclo[3.1.0]hexan-6-yl)methyl)amino)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 91	A	A
	N-(4-ethylphenyl)-4-(((4-hydroxytetrahydro-2H-pyran-4-yl)methyl)amino)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 92	B	B
	methyl 4-(((4-(N-(4-ethylphenyl)-N-isobutylsulfamoyl)-2-(S-methylsulfonimidoyl)phenyl)amino)methyl)piperidine-1-carboxylate compound 93	C	ND

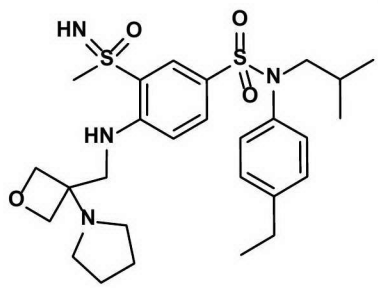
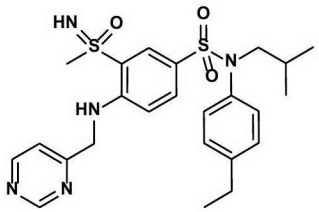
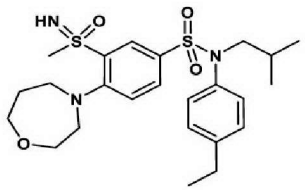
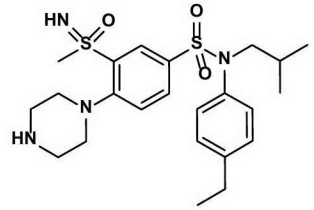
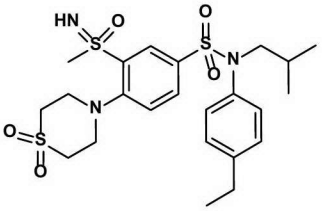
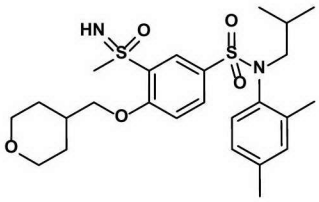
	methyl 3-(((4-(N-(4-ethylphenyl)-N-isobutylsulfamoyl)-2-(S-methylsulfonimidoyl)phenyl)amino)methyl)pyrrolidine-1-carboxylate compound 94	C	ND
	4-(((2-oxaspiro[3.3]heptan-6-yl)methyl)amino)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 95	B	B
	4-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(((2-oxopiperidin-4-yl)methyl)amino)benzenesulfonamide compound 96	C	ND
	4-(((3,5-dimethylisoxazol-4-yl)methyl)amino)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 97	B	ND
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((thietan-3-ylmethyl)amino)benzenesulfonamide compound 99	A	A
	4-(((1-acetylpyrrolidin-3-yl)methyl)amino)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 100	C	ND

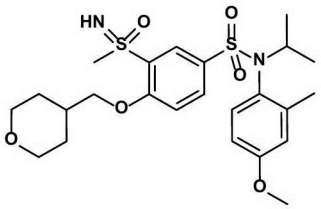
	N-(4-ethylphenyl)-N-isobutyl-4-((R)-3-methylmorpholino)-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 103	C	C
 Chiral	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((((R)-2-oxooxazolidin-5-yl)methyl)amino)benzenesulfonamide compound 105	C	ND
 Chiral	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((((S)-2-oxooxazolidin-5-yl)methyl)amino)benzenesulfonamide compound 106	C	ND
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((2-oxopiperidin-4-yl)amino)benzenesulfonamide compound 107	C	ND
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(2-oxa-6-azaspiro[3.5]nonan-6-yl)benzenesulfonamide compound 109	C	ND
	tert-butyl 6-(4-(N-(4-ethylphenyl)-N-isobutylsulfamoyl)-2-(S-methylsulfonimidoyl)phenyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate compound 110	C	ND

	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)benzenesulfonamide compound 111	A	ND
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(2-oxa-6-azaspiro[3.4]octan-6-yl)benzenesulfonamide compound 112	B	A
	4-(2,2-dioxido-2-thia-6-azaspiro[3.3]heptan-6-yl)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 113	B	B
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(2-oxa-7-azaspiro[3.5]nonan-7-yl)benzenesulfonamide compound 114	B	B
	4-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 115	B	ND
	4-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 117	B	ND

	4-(((2H-tetrazol-5-yl)methyl)amino)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 118	C	ND
	-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(2,6-diazaspiro[3.3]heptan-2-yl)benzenesulfonamide compound 121	C	ND
	4-(6-acetyl-2,6-diazaspiro[3.3]heptan-2-yl)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 122	C	ND
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-morpholinobenzenesulfonamide compound 123	A	A
	N-(4-ethylphenyl)-4-(((4-ethyltetrahydro-2H-pyran-4-yl)methyl)amino)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 124	A	A
	N-(4-ethylphenyl)-N-isobutyl-4-(((4-methoxytetrahydro-2H-pyran-4-yl)methyl)amino)-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 125	B	C

	4-(((3-ethyloxetan-3-yl)methyl)amino)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 126	C	ND
	N-(4-ethylphenyl)-N-isobutyl-4-(((2-methoxypyridin-4-yl)methyl)amino)-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 127	B	B
	N-(4-ethylphenyl)-4-(4-hydroxypiperidin-1-yl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 128	C	C
	N-(4-ethylphenyl)-4-((S)-3-hydroxypyrrolidin-1-yl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 129	C	C
	N-(4-ethylphenyl)-4-((R)-3-hydroxypyrrolidin-1-yl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 130	C	C
	N-(4-ethylphenyl)-4-(3-hydroxyazetidin-1-yl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 131	C	C

	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(((3-(pyrrolidin-1-yl)oxetan-3-yl)methyl)amino)benzenesulfonamide compound 132	C	ND
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((pyrimidin-4-ylmethyl)amino)benzenesulfonamide compound 133	A	A
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(1,4-oxazepan-4-yl)benzenesulfonamide compound 137	B	B
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(piperazin-1-yl)benzenesulfonamide compound 140	C	ND
	N-(4-ethylphenyl)-4-(((3-hydroxycyclobutyl)methyl)amino)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 141	C	ND
	N-(2,4-dimethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide compound 142	A	A

	N-isopropyl-N-(4-methoxy-2-methylphenyl)-3-(S-methylsulfonimidoyl)-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide compound 143	B	B

ND: not determined; A: IC50 < 100 nM.; B: IC50 = 100 nM-1 µM; C: IC50 > 1 µM

In the tables described above, the median inhibitory concentrations IC_{50} for the compounds belonging to formula (I) according to the invention have been given according to the following models:

GAL4-RORγ Transactivation

The RORγ transactivation model was developed from the line HG5LN, which is a HeLa line that stably expresses a luciferase reporter gene controlled by a pentamer of the GAL4 recognition domain of yeast and of a β-globin promoter. The HG5LN line was stably transfected by the DNA-binding domain (DBD) of GAL4 fused to the ROR gamma ligand-binding domain (LBD). Molecules that inhibit the ROR gamma constitutive activity reduce the luciferase expression, thus leading to a reduction in the emitted luminescence.

The cells are seeded in 384-well plates (5000 cells in 45 µL/well of culture medium containing 10% fetal calf serum) and incubated for 4 hours at 37°C, 5% CO_2. 5 µL of the test molecules (compounds described in the tables described above) are then added to each well and the plates are incubated for 18 hours at a temperature of 37°C under 5% of CO_2. 20 µL of luciferase substrate (Promega) are added to each well and the luminescence emitted is read by a microplate reader.

The luminescence units ("RLU") are normalized by positive controls ("POS" containing a saturated concentration of benzenesulfonamide, N-(2,2,2-trifluoroethyl)-*N*-[4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl]) and negative controls ("NEG" containing DMSO): % inhibition = ((RLU-NEG)*100)/(POS-NEG). The IC50 values are calculated from a 4-parameter logistic model using the XLFit software (IDBS).

I L-17A secretion

This model allows measurement of the effect of inhibitors on IL-17A secretion by CD4+ cells. The cells are frozen CD4+ cells (STEMCELL, # 70026), isolated from peripheral human blood and activated with anti-CD3 and anti-CD28 antibodies. The amount of IL-17a secreted is measured by the TR-FRET (kit HTRF® Human Interleukin 17A (Cisbio, #64H17PEC)) technology.

The cells are rapidly thawed, resuspended in their culture medium (RPMI inactivated 10% FCS) supplemented with soluble anti-CD28 antibodies and seeded (100 000 cells/well) in 96-well plates precoated with anti-CD3 antibodies. The cells are then treated with the ranges of inhibitors to be tested (from 1000 nM to 0.05 nM, 0.1% DMSO). After 4 days of incubation, the HTRF signal is measured using a microplate reader (λexcitation = 337 nm, λemission = 620/665 nm). The ratios obtained (665/620) are normalized relative to the positive control (cells activated with anti-CD3 and anti-CD28, 0.1% DMSO). The IC_{50} values are calculated from a 4-parameter logistic model using the XLFit software (IDBS).

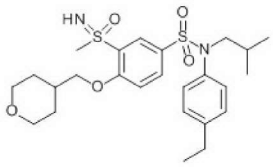
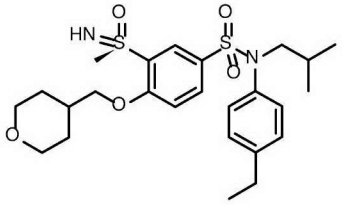
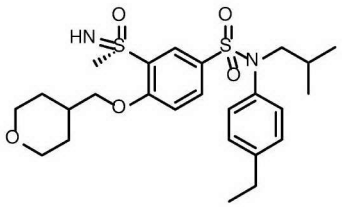
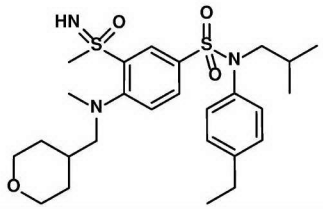
In the table below, the median inhibitory concentrations IC_{50} for the compounds belonging to formula (I) according to the invention have been given in accordance with the hERG test.

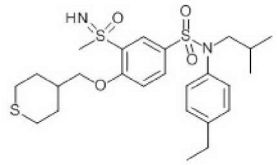
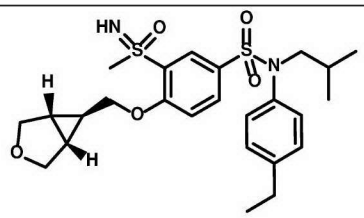
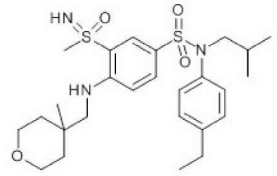
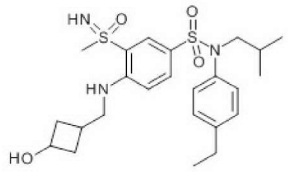
The hERG test makes it possible to study a gene which codes for a protein required for the functioning of heart tissue potassium channels. The patch clamp method on CHO-K1 cells (cells transfected with the hERG gene which has K+ ion activity on the membranes) is used for *in vitro* prediction of the blocking of hERG (human Ether-a-go-go Related).

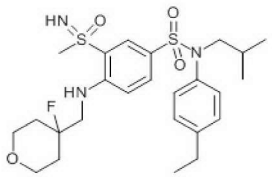
The extracellular solution (control) is applied first. The cells (Chinese hamster ovarian cells expressing the Human Ether-a-go-go Related Gene) are stabilized with the extracellular solution for 5 minutes. The cells are incubated for 5 minutes with the molecules from the weakest to the strongest concentration at 0.6% DMSO final.

The method for calculating the inhibition for each concentration: % inhibition = 100 x (tail current amplitude of the incubated molecule – tail current amplitude of the control vehicle). The result is expressed in the form of an IC_{50} value in μM.

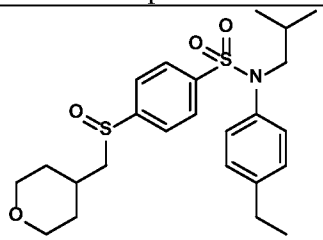
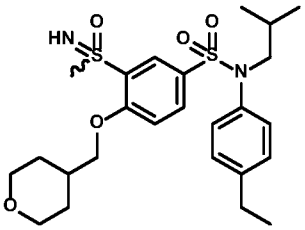
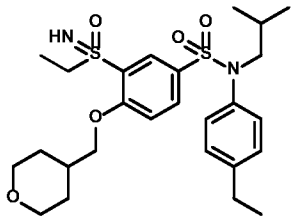
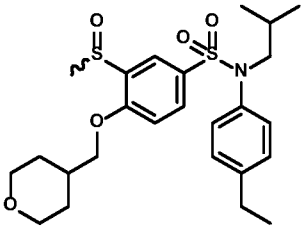
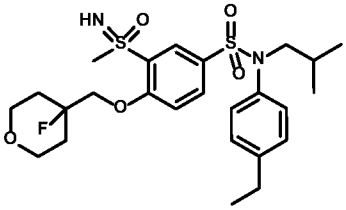
The results are given for the following compounds:

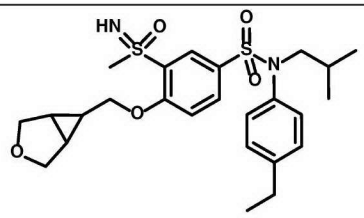
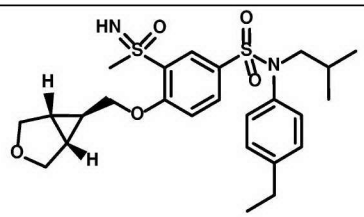
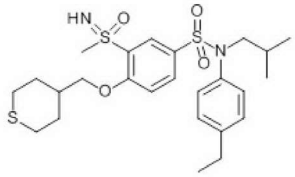
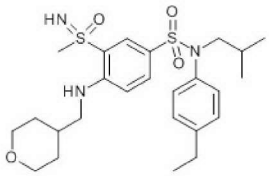
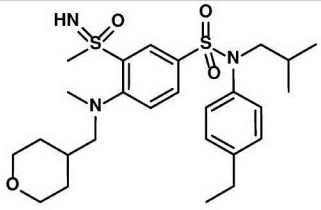
Compounds		hERG IC50
	N-(4-ethylphenyl)-N-isobutyl-3-methanesulfoximino-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide compound 26	> 30
Chiral  enantiomer A	compound 7, enantiomer A of compound 26	> 30
Chiral  enantiomer B	compound 8, enantiomer B of compound 26	> 30
	N-(4-ethylphenyl)-N-isobutyl-4-(methyl((tetrahydro-2H-pyran-4-yl)methyl)amino)-3-(S-	11.8

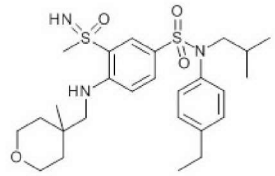
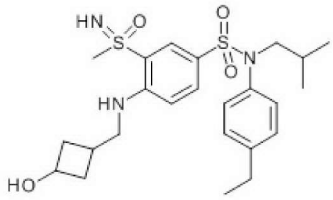
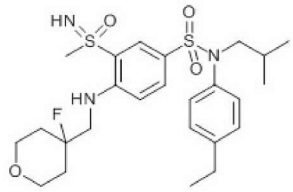
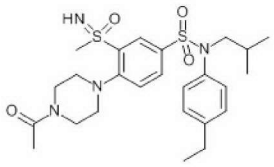
	methylsulfonimidoyl)benzene sulfonamide compound 53	
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(pyridin-4-ylmethoxy)benzenesulfonamide compound 37	11.8
	4-(((1R,5S,6R)-3-oxabicyclo[3.1.0]hexan-6-yl)methoxy)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzene sulfonamide compound 35	> 30
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(((4-methyltetrahydro-2H-pyran-4-yl)methyl)amino)benzenesulfonamide compound 55	14.1
	N-(4-ethylphenyl)-4-(((3-hydroxycyclobutyl)methyl)amino)-N-isobutyl-3-(S-methylsulfonimidoyl)benzene sulfonamide compound 61	25.7
	N-(4-ethylphenyl)-4-(((4-fluorotetrahydro-2H-pyran-4-yl)methyl)amino)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 62	16.4

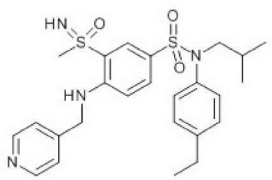
		

Preferentially, the compound(s) of formula (I) according to the invention are chosen from the following compounds:

Compounds	
	N-(4-ethylphenyl)-N-isobutyl-4-(tetrahydropyran-4-ylmethanesulfinyl)benzenesulfonamide compound 29
 enantiomer A	enantiomer A of compound 7
	N-(4-ethylphenyl)-N-isobutyl-3-ethanesulfoximino-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide compound 18
 enantiomer A	N-(4-ethylphenyl)-N-isobutyl-3-methanesulfinyl-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide compound 19
	N-(4-ethylphenyl)-4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 30

	4-((3-oxabicyclo[3.1.0]hexan-6-yl)methoxy)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 31
	4-(((1R,5S,6R)-3-oxabicyclo[3.1.0]hexan-6-yl)methoxy)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 35
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(pyridin-4-ylmethoxy)benzenesulfonamide compound 37
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-[(tetrahydropyran-4-ylmethyl)amino]benzenesulfonamide compound 52
	N-(4-ethylphenyl)-N-isobutyl-4-(methyl((tetrahydro-2H-pyran-4-yl)methyl)amino)-3-(S-methylsulfonimidoyl)benzenesulfonamide

	compound 53
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(((4-methyltetrahydro-2H-pyran-4-yl)methyl)amino)benzenesulfonamide compound 55
	N-(4-ethylphenyl)-4-(((3-hydroxycyclobutyl)methyl)amino)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 61
	N-(4-ethylphenyl)-4-(((4-fluorotetrahydro-2H-pyran-4-yl)methyl)amino)-N-isobutyl-3-(S-methylsulfonimidoyl)benzene sulfonamide compound 62
	:4-(4-acetylpiperazin-1-yl)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide compound 63

	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((pyridin-4-ylmethyl)amino)benzenesulfonamide compound 64

The preferred compound(s) according to the invention have the advantage of having strong biological activity, in particular a median inhibitory concentration IC50 which is less than 100 nM in accordance with the GAL-4 RORγ transactivation test as described previously.

Furthermore, the preferred compound(s) according to the invention have the advantage of having low toxicity.

The invention also relates to the compound(s) as described previously, as medicament and cosmetic.

Preferably, the invention also relates to the compound(s) as described previously, as medicament.

Specifically, the compounds according to the invention have advantageous pharmacological properties, given that said compounds modulate, i.e. inhibit, the activity of the RORγt receptor.

Thus, these properties make the compound(s) of formula (I) as described previously usable as medicament in the treatment of diseases mediated by the RORγt receptor.

Preferably, the compound(s) according to the invention are used in the treatment of inflammatory disorders and/or autoimmune diseases mediated by the RORγt receptor.

More preferentially, the compound(s) according to the invention are used in the treatment of acne, psoriasis and/or atopic dermatitis.

According to one embodiment, compounds (1) to (76) are used in the treatment of acne, psoriasis and/or atopic dermatitis.

Preferably, compounds (7), (8), (18), (19), (26), (30), (31), (35), (37), (52), (53), (55), (61), (62), (63) and (64) are used in the treatment of acne, psoriasis and/or atopic dermatitis.

According to another embodiment, the compounds are used for cosmetic treatment of the skin.

As indicated above, the present invention also relates to a pharmaceutical composition comprising, in a pharmaceutically acceptable medium, one or more compounds of formula (I) as defined previously, pharmaceutically acceptable addition salts thereof, hydrates thereof and/or solvates thereof.

Preferably, the pharmaceutical composition comprises one or more compounds of formula (Ia) and/or (Ib) as defined previously, the pharmaceutically acceptable addition salts thereof, hydrates thereof and/or solvates thereof.

More preferentially, the pharmaceutical composition comprises one or more compounds of formula (Ia) or (Ib) chosen from compounds (1) to (143) defined previously.

Even more preferentially, the pharmaceutical composition comprises one or more compounds of formula (Ia) or (Ib) chosen from compounds (7), (8), (18), (19), (26), (30), (31), (35), (37), (52), (53), (55), (61), (62), (63) and (64).

The pharmaceutical composition according to the invention may be administered orally or topically.

Preferably, the pharmaceutical composition is conditioned in a form that is suitable for topical application.

Via the oral route, the composition may be in the form of tablets, gel capsules, coated tablets, syrups, suspensions, solutions, powders, granules, emulsions, suspensions of microspheres or nanospheres or lipid or polymeric vesicles allowing controlled release.

Via the topical route, the pharmaceutical composition according to the invention is more particularly intended for treating the skin and mucous membranes, and may be in liquid, pasty or solid form, and more particularly in the form of ointments, creams, milks, pomades, powders, impregnated pads, syndets, solutions, gels, sprays, mousses, suspensions, sticks, shampoos or washing bases. It may also be in the form of suspensions of microspheres or nanospheres or lipid or polymeric vesicles or of polymeric or gelled patches allowing controlled release.

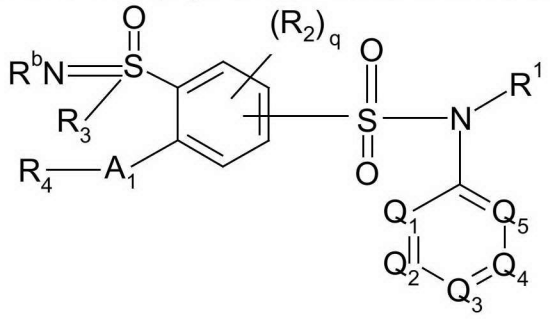
The pharmaceutical composition is used for treating inflammatory disorders and/or autoimmune diseases mediated by the RORγt receptor.

More preferentially, the pharmaceutical composition is used in the treatment of acne, psoriasis or atopic dermatitis.

The invention also relates to a process for treating diseases mediated by the RORγt receptor, comprising the administration, especially topically or orally, of a therapeutically effective amount of the pharmaceutical composition as defined above to a patient.

Preferably, the pharmaceutical composition is applied topically.

In accordance with one embodiment, a subject of the present invention is also one or more compounds of formula (II), and also the pharmaceutically acceptable addition salts thereof, hydrates thereof and/or solvates thereof:



(II)

in which formula (II):

- R_3 represents a C_1-C_3 alkyl radical,
- R^1, R_2, R'_2, R^4, R^5, R'^5, R^6, R^7, R^{7a}, R^{7b}, R_8, R_9, R_{10}, R^{11}, R^{12}, R^a, R^b, Z, Q_1, Q_2, Q_3, Q_4, Q_5, A_1 and the indices q, n, m, o and p have the same meanings as in formula (I) described previously.

Preferably, R^b represents a hydrogen atom or a C_1 alkyl radical.

Preferentially, R^b represents a hydrogen atom.

Preferably, R^3 represents a C_1 alkyl radical.

Preferably, R^1 represents a linear or branched C_3-C_5 alkyl radical.

Preferentially, R^4 represents a group $(CHR^5)_n$-$(Z)_o$-$(CHR'^5)_p$-R^6 with R^6 preferably corresponding to an aromatic or heteroaromatic radical, a cycloalkyl radical or a heterocyclic radical as defined above in formula (I) or as previously.

Preferably, Q^1-Q^2 and Q^4-Q^5 correspond to a group –CR'_2 with R^2 denoting a hydrogen atom and Q^3 corresponds to a group –CR'_2 with R'_2 denoting a linear or branched C_1-C_5 and preferably C_2 alkyl radical.

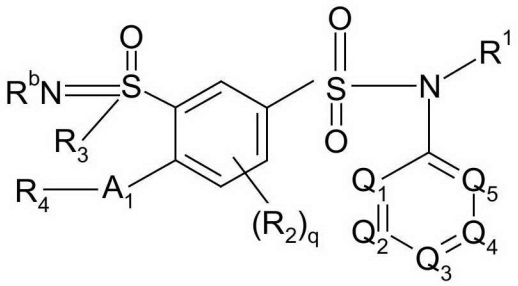
Preferably, Q^1 and Q^3, which may be identical or different, correspond to a group $-CR'_2$ with R'_2 denoting a hydrogen atom or a linear or branched C_1-C_5 and preferably C_2 alkyl radical.

Preferably, the index q is equal to zero.

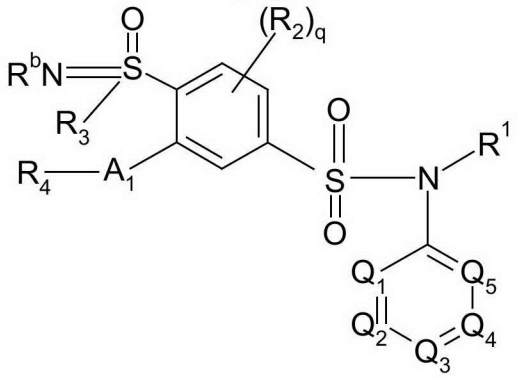
In particular, when the group A_1 represents a divalent group $-NR^a$, then R^a and R_4 do not form, together with the nitrogen atom to which they are attached, a C_2-C_{10} heterocycloalkyl group as defined in formula (I) described previously.

In accordance with one embodiment, preferably, R^1 represents a linear or branched C_3-C_5 alkyl radical and R^b represents a hydrogen atom.

Preferably, the compound(s) of formula (II) are chosen from the compound(s) of formulae (IIa) and (IIb) below:



(IIa)



(IIb)

in which formulae (IIa) and (IIb) R^1, R_2, R'_2, R^3, R^4, R^5, R'^5, R^6, R^7, R^{7a}, R^{7b}, R_8, R_9, R_{10}, R^{11}, R^{12}, R^a, R^b, Z, Q_1, Q_2, Q_3, Q_4, Q_5, A_1 and the indices q, m, n, o and p have the same meanings as in formula (II) described previously.

Preferentially, the compound(s) of formula (III) are chosen from the compound(s) of formulae (IIa).

In accordance with this embodiment, the invention also relates to the compound(s) of formula (II), preferably of formulae (IIa) and (IIb), as medicament and cosmetic.

Preferentially, the invention relates to the compound(s) of formula (II), as medicament and cosmetic.

Preferentially, the invention relates to the compound(s) of formula (IIa), as medicament and cosmetic, especially as medicament.

In particular, the invention relates to the compound(s) of formula (II), preferably of formula (IIa), as medicament in the treatment of diseases mediated by the RORγt receptor, preferably the treatment of inflammatory disorders and/or autoimmune diseases mediated by the RORγt receptor.

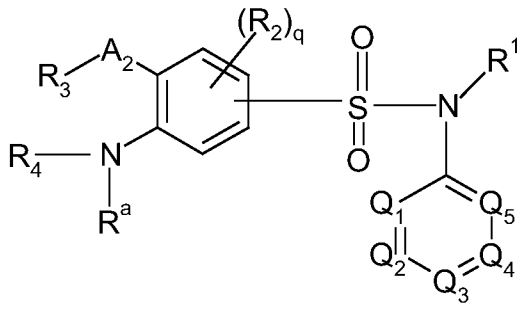
More preferentially, the compound(s) of formula (II) according to the invention, preferably of formula (IIa), are used in the treatment of acne, psoriasis and/or atopic dermatitis.

In accordance with this embodiment, the present invention also relates to a pharmaceutical composition comprising, in a pharmaceutically acceptable medium, one or more compounds of formula (II) as defined previously, pharmaceutically acceptable addition salts thereof, hydrates thereof and/or solvates thereof.

The pharmaceutical composition is used for treating inflammatory disorders and/or autoimmune diseases mediated by the RORγt receptor, preferably for treating acne, psoriasis or atopic dermatitis.

The invention also relates to a process for treating diseases mediated by the RORγt receptor, comprising the administration, especially topically or orally, of a therapeutically effective amount of the pharmaceutical composition as defined above to a patient, in particular topically.

In accordance with another embodiment, a subject of the present invention is also one or more compounds of formula (III), and also the pharmaceutically acceptable addition salts thereof, hydrates thereof and/or solvates thereof:



(III)

in which formula (III):

- R^a and R_4 form, together with the nitrogen atom to which they are attached, a C_2-C_{10} heterocycloalkyl group optionally comprising 1 to 3 heteroatoms chosen from a sulfur atom, a nitrogen atom and an oxygen atom; said heterocycloalkyl group being optionally substituted with at least one radical R^{14},
- R^{14} represents a linear or branched C_1-C_3 alkyl radical, a linear or branched C_1-C_3 alkoxy radical, a halogen atom, a hydroxyl group -OH, a cyano group -CN, a group $-CONR^{15}R^{16}$, a group $-SO_2R^{15}$, a group $-COR^{15}$ or an amino group $-NR^{15}R^{16}$; R^{15} and R^{16}, which may be identical or different, representing a hydrogen atom or a linear or branched C_1-C_3 alkyl radical,
- R^1, R_2, R'_2, R^3, R^b, Q_1, Q_2, Q_3, Q_4, Q_5, A_2 and the index q have the same meanings as in formula (I) described previously.

Thus, A_2 does not represent the divalent group –CH(OH)– and –C(=O)O–.

In other words, in formula (III), A_2 represents a divalent group chosen from the following groups: –S–, –SO–, SO_2–, $-SO(=N-R^b)-$.

Preferably, A_2 represents a divalent group $-SO(=N-R^b)-$.

In particular, R^a and R_4 form, together with the nitrogen atom to which they are attached, a monocyclic, bicyclic or spiro bicyclic C_2-C_{10} heterocycloalkyl group as defined previously.

Preferably, R^a and R_4 form, together with the nitrogen atom to which they are attached, a monocyclic or spiro bicyclic, in particular monocyclic, C_2-C_{10} heterocycloalkyl group.

Preferably, R^a and R_4 form, together with the nitrogen atom to which they are attached, a C_2-C_{10} heterocycloalkyl group, said heterocycloalkyl group being optionally substituted with at least one radical R^{14} as defined previously.

Preferably, the heterocycloalkyl group is optionally substituted with one, two or three radicals R^{14} as defined previously.

In particular, the heterocycloalkyl group is substituted with a radical R^{14}.

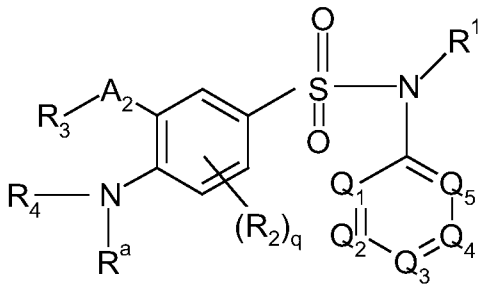
Preferably, Q^1-Q^2 and Q^4-Q^5 correspond to a group $-CR^2$ with R^2 denoting a hydrogen atom and Q^3 corresponds to a group $-CR'_2$ with R'_2 denoting a linear or branched C_1-C_5 and preferably C_2 alkyl radical.

Preferably, Q^1 and Q^3, which may be identical or different, correspond to a group $-CR'_2$ with R'_2 denoting a hydrogen atom or a linear or branched C_1-C_5 and preferably C_2 alkyl radical.

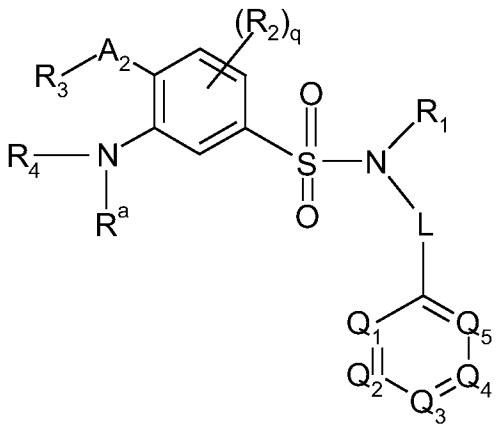
Preferably, the index q is equal to zero.

According to a particular case, A_2 represents a divalent group chosen from –S–, –SO– and SO_2–.

Preferably, the compound(s) of formula (III) are chosen from the compound(s) of formulae (IIIa) and (IIIb) below:



(IIIa)



(IIIb)

in which formulae (IIIa) and (IIIb) R^1, R_2, R'_2, R^3, R_4, R^a, R^b, Q_1, Q_2, Q_3, Q_4, Q_5, A_2 and the index q have the same meanings as in formula (III) described previously.

Preferentially, the compound(s) of formula (III) are chosen from the compound(s) of formulae (IIIa).

Preferably, the invention relates to the compound(s) of formula (III), preferably of formulae (IIIa) and (IIIb), as medicament and cosmetic.

Preferentially, the invention relates to the compound(s) of formula (IIIa), as medicament and cosmetic, especially as medicament.

In particular, the invention relates to the compound(s) of formula (III), preferably of formula (IIIa), as medicament in the treatment of diseases mediated by the RORγt receptor, preferably the treatment of inflammatory disorders and/or autoimmune diseases mediated by the RORγt receptor.

More preferentially, the compound(s) of formula (III), preferably of formula (IIIa), according to the invention are used in the treatment of acne, psoriasis and/or atopic dermatitis.

In accordance with this embodiment, the present invention also relates to a pharmaceutical composition comprising, in a pharmaceutically acceptable medium, one or more compounds of formula (III) as defined previously, pharmaceutically acceptable addition salts thereof, hydrates thereof and/or solvates thereof.

The pharmaceutical composition is used for treating inflammatory disorders and/or autoimmune diseases mediated by the RORγt receptor, preferably for treating acne, psoriasis or atopic dermatitis.

The invention also relates to a process for treating diseases mediated by the RORγt receptor, comprising the administration, especially topically or orally, of a therapeutically effective amount of the pharmaceutical composition as defined above to a patient, in particular topically.

The examples that follow serve to illustrate the invention without, however, being limiting in nature.

Examples:

The standard LCMS method for analyzing the products is as follows: BEH C_{18} standard column (150×2.1 mm, 1.8 μm) solvent: water/acetonitrile 0.1% formic acid.

The preparative HPLC purifications were performed on a C_{18} column using, as eluent: 85% acetonitrile in water/0.1% formic acid.

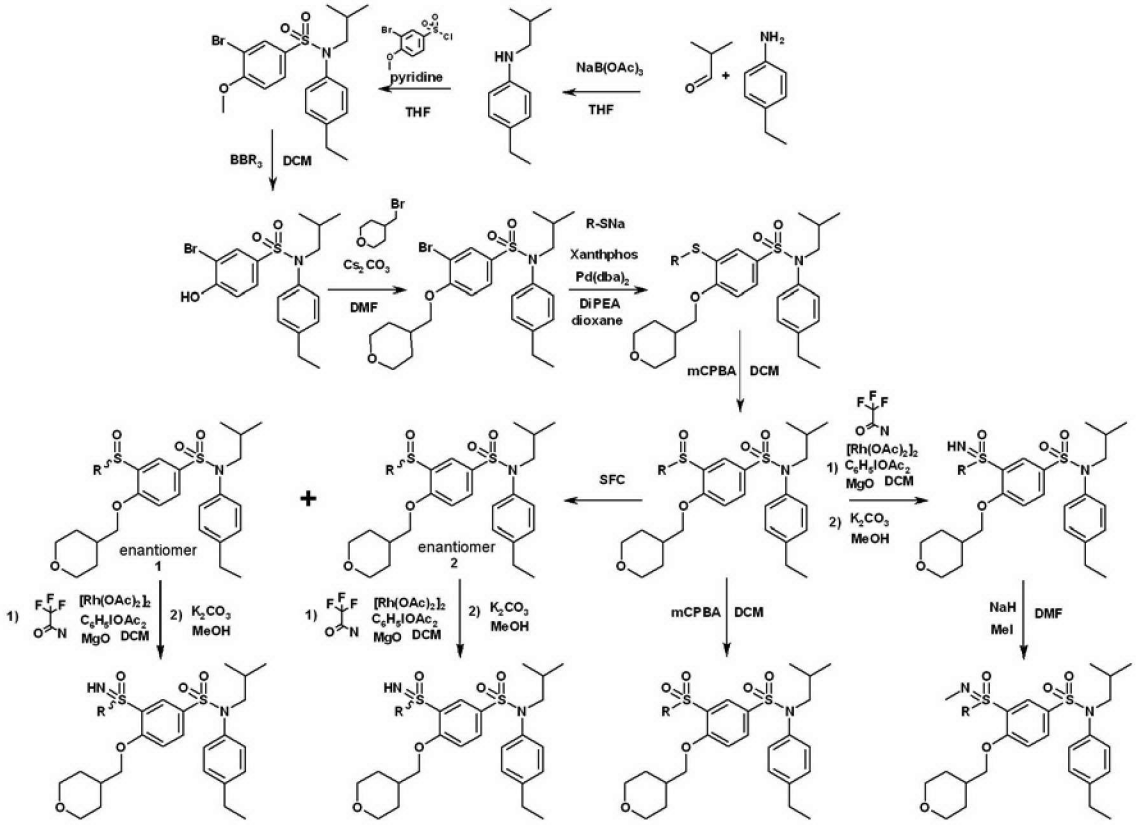
The apparatus used for the chromatography is a 10-20 peak-solution machine, Chiraltechnologie Ic *25x5 micron* column, (eluent phase: supercritical CO_2/methanol, flow rate 4 ml/minute).

The standard LCMS method for analyzing the products is as follows: BEH C18 150×2.1 mm, 1 µm column, solvent: water/acetonitrile 0.1% formic acid.

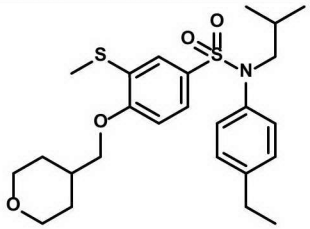
The preparative HPLC purifications were performed on a C18 column using, as eluent: 85% acetonitrile in water/0.1% formic acid.

Part I: Synthesis of the sulfur-based sulfonamides via reaction scheme 1

Reaction scheme 1:

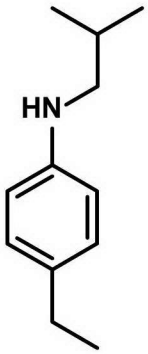


Example 1: Synthesis of N-(4-ethylphenyl)-N-isobutyl-3-methanesulfanyl-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide



Compound 25

1. Synthesis of intermediate 1.1



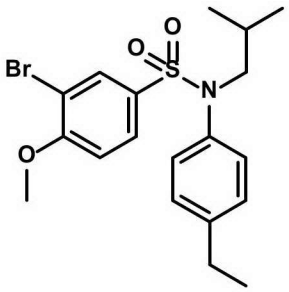
(4-ethylphenyl)isobutylamine

Isobutyraldehyde (6.33 ml; 0.07 mol) in tetrahydrofuran (100 ml) is added to 4-ethylaniline (9.48 ml; 0.08 mol). The mixture is stirred for 2 hours at room temperature. Sodium triacetoxyborohydride (22.04 g; 0.10 mol) is then added. The mixture is stirred overnight at room temperature, water (100 ml) is added and the resulting mixture is extracted with ethyl acetate (2 × 100 ml).

The organic phases are combined, washed with brine (100 ml), dried over Na_2SO_4 and concentrated. The crude product is chromatographed on silica gel (eluent: heptane/dichloromethane from 0 to 50% of dichloromethane). The (4-ethylphenyl)isobutylamine is obtained in the form of an orange oil with a compliant ^1H NMR.

MS : [M+H] = 179

2. Synthesis of intermediate 1.2

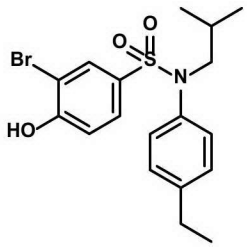


N-(4-ethylphenyl)-N-isobutyl-4-methoxybenzenesulfonamide

3-Bromo-4-methoxybenzenesulfonyl chloride (3.22 g; 11.28 mmol) is added to the (4-ethylphenyl)isobutylamine (2.00 g; 11.28 mmol) and pyridine (5.5 ml; 67.69 mmol) dissolved in tetrahydrofuran (40 ml). The reaction medium is stirred for 4 hours at room temperature, hydrolyzed and extracted with ethyl acetate. The organic phases are combined, washed with saturated NH_4Cl solution and then with brine, dried (Na_2SO_4) and concentrated. The crude product is chromatographed on silica gel (eluent: heptane/ethyl acetate, from 0 to 20% of ethyl acetate). The N-(4-ethylphenyl)-N-isobutyl-4-methoxybenzenesulfonamide (1.63 g; 34%) is obtained in the form of a pale yellow oil with a compliant ^1H NMR.

MS : [M+H] = 426

3. Synthesis of intermediate 1.3



3-Bromo-N-(4-ethylphenyl)-4-hydroxy-N-isobutylbenzenesulfonamide

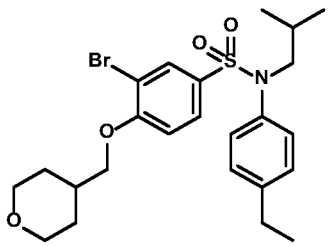
1M boron tribromide in dichloromethane (5.6 ml; 5.63 mmol) is added slowly at a temperature of 0°C to the 3-bromo-N-(4-ethylphenyl)-N-isobutyl-4-methoxybenzenesulfonamide (1.60 g; 3.75 mmol) dissolved in dichloromethane (32 ml). The reaction medium is allowed to return slowly to room temperature, stirred for 16 hours and hydrolyzed at a temperature of 0°C and then extracted with

dichloromethane. The organic phases are combined, washed with brine, dried (Na_2SO_4) and concentrated.

The crude product is chromatographed on silica gel (eluent: heptane/ethyl acetate, from 0 to 30% of ethyl acetate). The 3-bromo-N-(4-ethylphenyl)-4-hydroxy-N-isobutylbenzenesulfonamide (1.41 g; 91%) is obtained in the form of a beige-colored solid with a compliant ^1H NMR.

MS : [M+H] = 414

4. Synthesis of intermediate 1.4



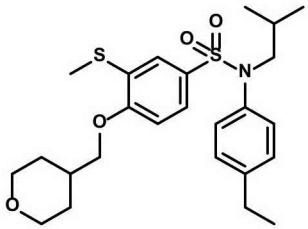
N-(4-ethylphenyl)-N-isobutyl-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide

4-(Bromomethyl)tetrahydropyran (261 mg; 1.46 mmol) and cesium carbonate (790 mg; 2.43 mmol) are added to the 3-bromo-N-(4-ethylphenyl)-4-hydroxy-N-isobutylbenzenesulfonamide (500 mg; 1.21 mmol) dissolved in N,N-dimethylformamide (10 ml). The reaction medium is stirred for 2 hours at a temperature of 80°C, hydrolyzed and extracted with ethyl acetate. The organic phases are combined, washed with brine, dried (Na_2SO_4) and concentrated.

The crude product is chromatographed on silica gel (eluent: heptane/ethyl acetate, from 0 to 30% of ethyl acetate). The N-(4-ethylphenyl)-N-isobutyl-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide (598 mg; 97%) is obtained in the form of a white solid with a compliant ^1H NMR.

MS : [M+H] = 512

Example 1: Synthesis of compound 25 according to the invention



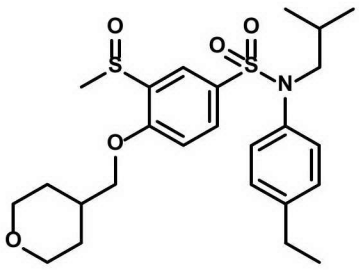
Bis(dibenzylideneacetone)palladium(0) (216 mg; 0.38 mmol) is added to a solution, degassed with argon for 15 minutes, of 3-bromo-N-(4-ethylphenyl)-N-isobutyl-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide (480 mg; 0.94 mmol), N,N-diisopropylethylamine (490 µl; 2.82 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (45 mg; 0.08 mmol) and sodium methanethiolate (264 mg; 3.76 mmol) in 1,4-dioxane (5 ml). The reaction medium is stirred for 3 hours at a temperature of 110°C, hydrolyzed and extracted with ethyl acetate. The organic phases are combined, washed with brine, dried (Na_2SO_4) and concentrated.

The crude product is chromatographed on silica gel (eluent: heptane/ethyl acetate, from 0 to 30% of ethyl acetate). The N-(4-ethylphenyl)-N-isobutyl-3-methylsulfanyl-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide (335 g; 71%) is obtained in the form of a pale yellow solid.

^{1}H NMR (400 MHz, Chloroform-d) δ 7.41 (dd, J = 8.4, 2.1 Hz, 1H), 7.19 – 7.11 (m, 2H), 7.08 (d, J = 2.2 Hz, 1H), 7.04 – 6.95 (m, 2H), 6.83 (d, J = 8.5 Hz, 1H), 4.07 (dt, J = 11.5, 2.8 Hz, 2H), 3.95 (d, J = 6.4 Hz, 2H), 3.49 (td, J = 11.9, 2.1 Hz, 2H), 3.27 (d, J = 7.3 Hz, 2H), 2.66 (q, J = 7.6 Hz, 2H), 2.24 – 2.10 (m, 1H), 1.87 – 1.74 (m, 2H), 1.59 (s, 11H), 1.25 (t, J = 7.6 Hz, 4H), 0.93 (d, J = 6.7 Hz, 7H).

MS : [M+H] = 478

Example 2: Synthesis of N-(4-ethylphenyl)-N-isobutyl-3-methanesulfinyl-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide



Compound 27

3-Chloroperoxybenzoic acid (0.17 g; 0.75 mmol) is added portionwise to a solution of N-(4-ethylphenyl)-N-isobutyl-3-methylsulfanyl-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide (0.40 g; 0.84 mmol) in dichloromethane (8 ml) at 0°C. The reaction medium is stirred for 45 minutes, hydrolyzed with aqueous 10% $Na_2S_2O_3$ solution and extracted with dichloromethane. The organic phase is washed with 1N sodium hydroxide and then dried (Na_2SO_4), filtered and concentrated.

The crude product is chromatographed on silica gel (eluent: heptane/ethyl acetate, from 50 to 100% of ethyl acetate). The N-(4-ethylphenyl)-N-isobutyl-3-methanesulfinyl-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide (0.24 g; 58%) is obtained in the form of a white solid.

^{1}H NMR (DMSO-d_6) δ: 0.85 (t, J = 6.9 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.28 – 1.48 (m, 3H), 1.65 (tdd, J = 11.5, 4.0, 2.1 Hz, 2H), 2.61 (q, J = 7.6 Hz, 2H), 2.74 (s, 3H), 3.21 – 3.40 (m, 5H), 3.90 (ddd, J = 11.5, 4.9, 2.1 Hz, 2H), 4.00 – 4.15 (m, 2H), 6.94 – 7.02 (m, 2H), 7.15 – 7.23 (m, 2H), 7.33 – 7.35 (m, 1H) 7.64 – 7.73 (m, 2H)

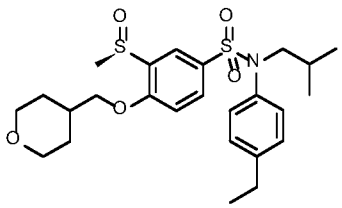
MS : [M+H] = 494

Compound 27: (550 mg; 1.11 mmol) is chromatographed by chiral SFC to separate the two enantiomers (compound 19 and compound 20) below:

Supercritical conditions 100 bar, 70°C; Chiralpak IC 250x4.6 mm 5 µ column]

Example 3: N-(4-ethylphenyl)-N-isobutyl-3-methanesulfinyl-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide (compound 19) - enantiomer A of compound 27

Chiral



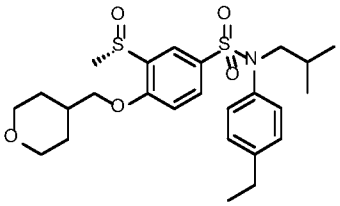
(311 mg; 56%) in the form of a white solid

^{1}H NMR (Chloroform-d) δ: 0.86 – 0.96 (m, 6H), 1.23 (t, J = 7.6 Hz, 3H), 1.40 – 1.65 (m, 7H), 1.65 – 1.87 (m, 2H), 2.11 (s, 1H), 2.63 (q, J = 7.6 Hz, 2H), 2.77 (s, 2H), 3.22 – 3.34 (m, 1H), 3.36 – 3.45 (m, 1H), 3.48 (dd, J = 11.9, 2.2 Hz, 1H), 3.89 – 4.09 (m, 4H), 6.88 (d, J = 8.6 Hz, 1H), 6.94 – 7.01 (m, 2H), 7.09 – 7.16 (m, 2H), 7.57 (dd, J = 8.6, 2.4 Hz, 1H), 8.16 (d, J = 2.3 Hz, 1H)

Retention time (chiral SFC) of 6.0 minutes

Example 4: N-(4-ethylphenyl)-N-isobutyl-3-methanesulfinyl-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide (compound 20) - enantiomer B of compound 27

Chiral

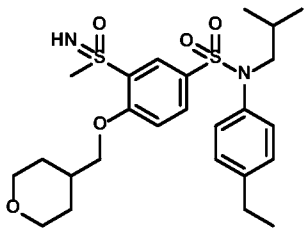


(240 mg; 44%) in the form of a white solid

^{1}H NMR (Chloroform-d) δ: 0.91 (dd, J = 13.3, 6.7 Hz, 6H), 1.23 (t, J = 7.6 Hz, 4H), 1.39 – 1.64 (m, 7H), 1.66 – 1.79 (m, 2H), 2.02 – 2.20 (m, 1H), 2.63 (q, J = 7.7 Hz, 2H), 2.77 (s, 3H), 3.27 (dd, J = 12.9, 6.8 Hz, 1H), 3.36 – 3.52 (m, 3H), 3.87 – 4.10 (m, 4H), 6.88 (d, J = 8.6 Hz, 1H), 6.94 – 7.02 (m, 2H), 7.09 – 7.16 (m, 2H), 7.57 (dd, J = 8.6, 2.3 Hz, 1H), 8.16 (d, J = 2.3 Hz, 1H)

Retention time (chiral SFC) of 9.9 minutes

Example 5: Synthesis of N-(4-ethylphenyl)-N-isobutyl-3-methanesulfoximino-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide



Compound 26

2,2,2-Trifluoroacetamide (0.13 g; 1.16 mmol), magnesium oxide (0.09 g; 2.33 mmol), rhodium(II) acetate dimer (31 mg; 0.07 mmol) and iodobenzene diacetate (0.29 g; 0.89 mmol) are added to a solution, degassed beforehand with argon, of N-(4-ethylphenyl)-N-isobutyl-3-methanesulfinyl-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide (0.23 g; 0.47 mmol) in dichloromethane (8 ml). The

reaction medium is stirred for 4 hours 30 minutes, filtered through Celite and concentrated.

The residue is diluted in methanol (8 ml) and potassium carbonate (0.32 g; 2.33 mmol) is added. The reaction medium is stirred for 30 minutes, hydrolyzed and extracted with ethyl acetate. The organic phases are combined, dried (Na_2SO_4), filtered and concentrated.

The crude product is purified by preparative HPLC. The N-(4-ethylphenyl)-N-isobutyl-3-methanesulfoximino-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide (0.08 g; 34%) is obtained in the form of a white solid.

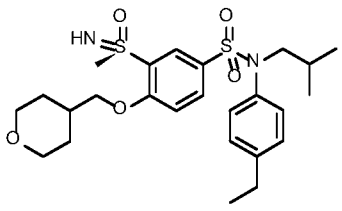
^{1}H NMR (DMSO-d_6) δ: 0.84 (d, J = 4.5 Hz, 3H), 0.86 (d, J = 4.4 Hz, 3H), 1.18 (t, J = 7.6 Hz, 3H), 1.27 – 1.58 (m, 3H), 1.66 – 1.83 (m, 2H), 2.02 – 2.21 (m, 1H), 2.61 (q, J = 7.6 Hz, 2H), 3.19 (d, J = 1.2 Hz, 3H), 3.24-3.39 (m, 4H), 3.83 – 3.96 (m, 2H), 4.11 (dd, J = 6.2, 2.5 Hz, 2H), 4.41 (d, J = 1.5 Hz, 1H), 7.01 (d, J = 8.3 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.8 Hz, 1H), 7.67 (dd, J = 8.8, 2.4 Hz, 1H), 8.00 (d, J = 2.4 Hz, 1H)

MS : [M+H] = 509

A procedure similar to that applied to compound 26 to obtain compounds 19 and 20 is performed so as to obtain compounds 7 and 8 (enantiomers of compound 26).

Example 6: <u>N-(4-ethylphenyl)-N-isobutyl-3-(methanesulfinyl)-4-(tetrahydropyran-4-ylmethoxy)benzenesulfoximine (compound 7) - enantiomer A of compound 26</u>

Chiral



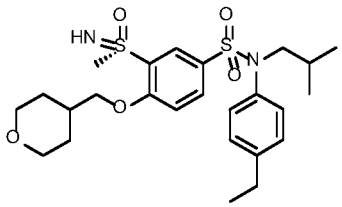
Compound 7

Same procedure as for example 3, on example 4 (213 mg; 0.43 mmol). The N-(4-ethylphenyl)-N-isobutyl-3-((S)-methanesulfinyl)-4-(tetrahydropyran-4-ylmethoxy)benzenesulfoximine (20 mg; 9%) is obtained in the form of a beige-colored solid with a compliant ^{1}H NMR.

MS : [M+H] = 509

Example 7: N-(4-ethylphenyl)-N-isobutyl-3-(methanesulfinyl)-4-(tetrahydropyran-4-ylmethoxy)benzenesulfoximine (compound 8) - enantiomer B of compound 26

Chiral

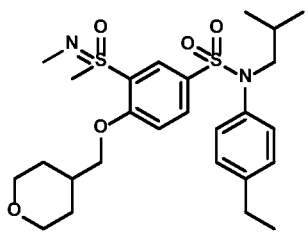


Compound 8

Same procedure as for example 3, on example 5 (132 mg; 0.27 mmol). The N-(4-ethylphenyl)-N-isobutyl-3-((R)-methanesulfinyl)-4-(tetrahydropyran-4-ylmethoxy)benzenesulfoximine (11 mg; 9%) is obtained in the form of an off-white solid with a compliant ^{1}H NMR.

MS : [M+H] = 509

Example 8: Synthesis of N-(4-ethylphenyl)-N-isobutyl-3-methanesulfinyl-4-(tetrahydropyran-4-ylmethoxy)benzene-N-methylsulfoximine



Compound 2

60% sodium hydride (9.2 mg; 0.23 mmol) is added portionwise to a solution at 0°C of N-(4-ethylphenyl)-N-isobutyl-3-(methanesulfinyl)-4-(tetrahydropyran-4-ylmethoxy)benzenesulfoximine (90 mg; 0.18 mmol) in N,N-dimethylformamide (1.8 ml). The reaction medium is stirred for 20 minutes at a temperature of 0°C, and iodomethane (22 µl; 0.35 mmol) is then added dropwise. The reaction medium is stirred for 20 hours at room temperature, hydrolyzed and extracted with ethyl acetate.

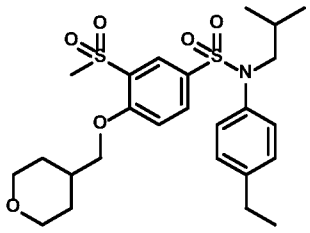
The organic phases are combined, washed with brine, dried (Na_2SO_4) and concentrated, and the crude product is chromatographed on silica gel (eluent: dichloromethane/methanol from 0 to 5% of methanol).

The N-(4-ethylphenyl)-N-isobutyl-3-methanesulfinyl-4-(tetrahydropyran-4-ylmethoxy)benzene-N-methylsulfoximine (59.3 mg; 64%) is obtained in the form of a white solid.

^{1}H NMR (DMSO-d6) δ: 0.85 (t, J = 7.1 Hz, 6H), 1.17 (t, J = 7.6 Hz, 3H), 1.30 – 1.51 (m, 3H), 1.62 – 1.71 (m, 1H), 1.80 (ddd, J = 13.0, 4.1, 2.0 Hz, 1H), 2.08 (s, 1H), 2.34 (s, 3H), 2.59 (q, J = 7.6 Hz, 2H), 3.20 (s, 3H), 3.22 – 3.41 (m, 8H), 3.90 (ddd, J = 11.5, 4.6, 1.9 Hz, 2H), 4.04 (dd, J = 9.5, 6.7 Hz, 1H), 4.17 (dd, J = 9.3, 5.6 Hz, 1H), 6.93 – 7.00 (m, 2H), 7.14 – 7.21 (m, 2H), 7.45 (d, J = 8.8 Hz, 1H), 7.74 (d, J = 2.4 Hz, 1H), 7.86 (dd, J = 8.8, 2.5 Hz, 1H).

MS : [M+H] = 523

Example 9: Synthesis of N-(4-ethylphenyl)-N-isobutyl-3-methanesulfonyl-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide



Compound 24

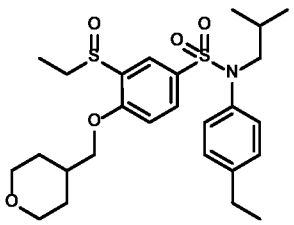
3-Chloroperbenzoic acid (188 mg; 0.84 mmol) is added portionwise at 0°C to N-(4-ethylphenyl)-N-isobutyl-3-methanesulfanyl-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide (200 mg; 0.42 mmol) dissolved in dichloromethane

(2 ml). The reaction medium is stirred for 72 hours, hydrolyzed and extracted with ethyl acetate. The organic phases are combined, washed with brine, dried (Na_2SO_4) and concentrated. The crude product is chromatographed on silica gel (eluent: heptane/ethyl acetate, from 0 to 50% of ethyl acetate). The N-(4-ethylphenyl)-N-isobutyl-3-methanesulfonyl-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide (150 mg; 71%) is obtained in the form of a white solid.

^{1}H NMR (400 MHz, DMSO-d6) δ 7.86 – 7.77 (m, 2H), 7.48 (d, J = 8.7 Hz, 1H), 7.24 – 7.17 (m, 2H), 7.05 – 6.96 (m, 2H), 4.16 (d, J = 6.2 Hz, 2H), 3.95 – 3.86 (m, 2H), 3.32 – 3.25 (m, 6H), 2.61 (q, J = 7.6 Hz, 2H), 2.16 – 2.09 (m, 1H), 1.77 – 1.68 (m, 2H), 1.49 – 1.34 (m, 3H), 1.18 (t, J = 7.6 Hz, 3H), 0.85 (d, J = 6.6 Hz, 6H).

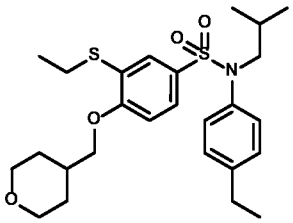
MS : [M+H] = 510

Example 10: Synthesis of ethanesulfinyl-N-(4-ethylphenyl)-N-isobutyl-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide



Compound 22

1. Synthesis of intermediate 10.1



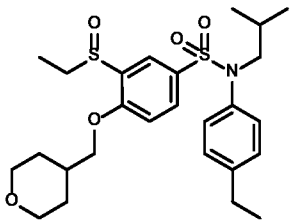
N-(4-ethylphenyl)-3-ethylsulfanyl-N-isobutyl-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide

Bis(dibenzylideneacetone)palladium(0) (225 mg; 0.39 mmol) is added to a solution, degassed with argon for 15 minutes, of 3-bromo-N-(4-ethylphenyl)-N-

isobutyl-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide (500 mg; 0.98 mmol), N,N-diisopropylethylamine (510 µl; 2.94 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (45 mg; 0.08 mmol) and sodium ethanethiolate (91 mg; 1.08 mmol) dissolved in 1,4-dioxane (5 ml). The reaction medium is stirred for 1 hour at 110°C, hydrolyzed and extracted with ethyl acetate. The organic phases are combined, washed with brine, dried (Na_2SO_4) and concentrated. The crude product is purified by preparative HPLC (C18 column, eluent: from 56% to 62% of acetonitrile in water/0.1% of formic acid). The N-(4-ethylphenyl)-3-ethylsulfanyl-N-isobutyl-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide (271 mg; 42%) is obtained in the form of a white solid after trituration in heptane, with a compliant ^{1}H NMR.

MS : [M+H] = 492

2. Synthesis of compound 22 according to the invention



3-Chloroperbenzoic acid (59 mg; 0.26 mmol) is added portionwise at a temperature of 0°C to N-(4-ethylphenyl)-3-ethanesulfanyl-N-isobutyl-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide (260 mg; 0.53 mmol) dissolved in dichloromethane (5 ml). The reaction medium is stirred for 1 hour at room temperature, hydrolyzed with aqueous 10% $Na_2S_2O_3$ solution and then extracted with dichloromethane. The organic phases are combined, washed with 0.1N sodium hydroxide solution and then with brine, dried (Na_2SO_4) and concentrated.

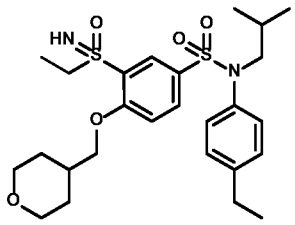
The crude product is chromatographed on silica gel (eluent: heptane/ethyl acetate, from 0 to 100% of ethyl acetate). The 3-ethylsulfinyl-N-(4-ethylphenyl)-N-isobutyl-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide (125 mg; 47%) is obtained in the form of a white solid.

^{1}H NMR (Chloroform-d) δ: 0.84 (dd, J = 13.3, 6.7 Hz, 6H), 1.10 (t, J = 7.4 Hz, 3H), 1.15 (t, J = 7.6 Hz, 3H), 1.33 – 1.55 (m, 2H), 1.58 – 1.72 (m, 2H), 1.94 – 2.12 (m, 1H), 2.56 (q, J = 7.6 Hz, 2H), 2.73 (dq, J = 13.4, 7.4 Hz, 1H), 2.99 (dq, J =

13.5, 7.4 Hz, 1H), 3.21 (dd, J = 12.8, 6.8 Hz, 1H), 3.28 – 3.45 (m, 3H), 3.84 (dd, J = 9.0, 6.3 Hz, 1H), 3.91 (dd, J = 9.0, 6.4 Hz, 1H), 3.98 (ddd, J = 11.6, 4.6, 1.8 Hz, 2H), 6.81 (d, J = 8.7 Hz, 1H), 6.86 – 6.93 (m, 2H), 7.01 – 7.08 (m, 2H), 7.50 (dd, J = 8.6, 2.4 Hz, 1H), 8.02 (d, J = 2.4 Hz, 1H)

MS : [M+H] = 508

Example 11: Synthesis of N-(4-ethylphenyl)-N-isobutyl-3-ethanesulfoximine-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide



Compound 18

2,2,2-Trifluoroacetamide (61 mg; 0.54 mmol), magnesium oxide (44 mg; 1.08 mmol), rhodium(II) acetate (14 mg; 0.03 mmol) and iodobenzene diacetate (133 mg; 0.41 mmol) are added to a solution, degassed beforehand with argon, of 3-ethylsulfinyl-N-(4-ethylphenyl)-N-isobutyl-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide (110 mg; 0.22 mmol) in dichloromethane (8 ml). The reaction medium is stirred for 16 hours at room temperature, filtered through Celite and concentrated. The residue obtained is diluted in methanol (8 ml) and potassium carbonate (150 mg; 1.08 mmol) is added. The reaction medium is stirred for 30 minutes, hydrolyzed and extracted with ethyl acetate. The organic phases are combined, washed with brine, dried (Na_2SO_4) and concentrated.

The crude product is purified by preparative HPLC (C18 column, eluent: from 56% to 62% of acetonitrile in water/0.1% of formic acid). The N-(4-ethylphenyl)-N-isobutyl-3-ethanesulfoximino-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide (23 mg; 20%) is obtained in the form of an off-white solid.

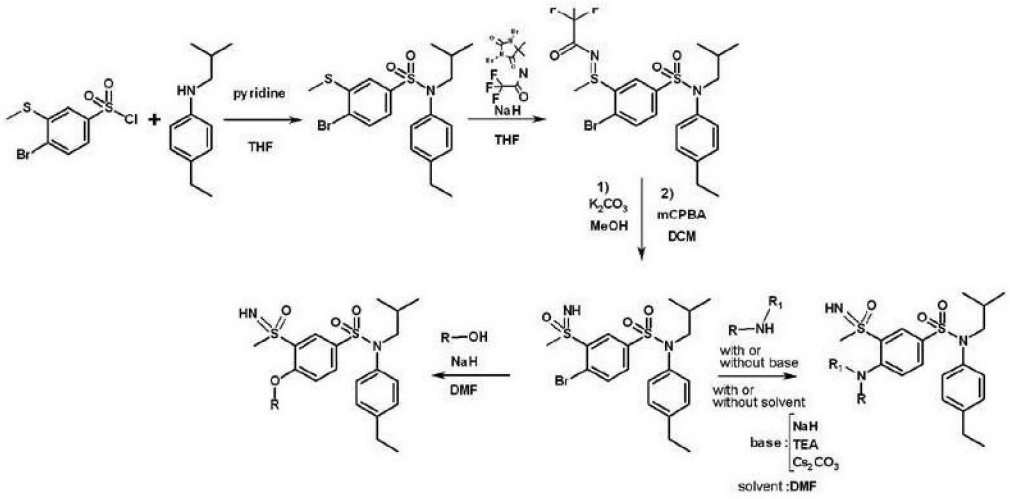
^{1}H NMR (Chloroform-d) δ: 0.93 (dd, J = 8.4, 6.6 Hz, 6H), 1.25 (q, J = 7.4 Hz, 7H), 1.46 – 1.69 (m, 6H), 1.86 (ddq, J = 11.1, 4.5, 2.2 Hz, 2H), 2.14 – 2.30 (m,

1H), 2.67 (q, J = 7.6 Hz, 2H), 2.75 (s, 1H), 3.28 (dd, J = 12.8, 7.0 Hz, 1H), 3.31 – 3.45 (m, 3H), 3.49 (td, J = 11.9, 2.2 Hz, 2H), 4.00 – 4.12 (m, 4H), 6.96 – 7.01 (m, 2H), 7.04 (d, J = 8.8 Hz, 1H), 7.13 – 7.20 (m, 2H), 7.73 (dd, J = 8.7, 2.4 Hz, 1H), 8.12 (d, J = 2.4 Hz, 1H)

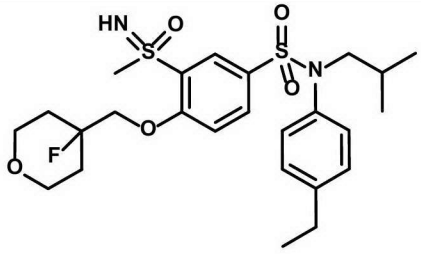
MS : [M+H] = 523

Part II: Synthesis of the sulfur-based sulfonamides via reaction scheme 2

Reaction scheme 2:

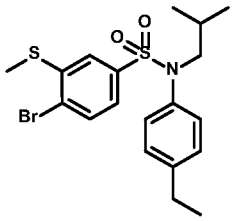


Example 12: Synthesis of N-(4-ethylphenyl)-4-(((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide



Compound 30

1. Synthesis of intermediate 12.1



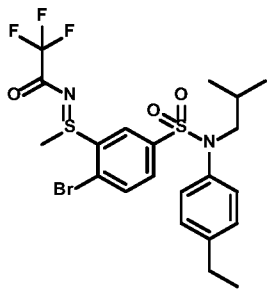
4-bromo-N-(4-ethylphenyl)-N-isobutyl-3-methylsulfanylbenzenesulfonamide

4-Bromo-3-(methylthio)benzene-1-sulfonyl chloride (19.63 g; 61.83 mmol) dissolved in tetrahydrofuran (95 ml) is added to (4-ethylphenyl)isobutylamine (10.96 g; 61.83 mmol) and pyridine (30 ml; 371 mmol) dissolved in tetrahydrofuran (370 ml). The reaction medium is stirred for 16 hours at room temperature and then hydrolyzed and extracted with ethyl acetate. The organic phases are combined, washed with saturated ammonium chloride solution and then with brine, dried (Na_2SO_4) and concentrated. The crude product is taken up in heptane and suction-filtered.

The 4-bromo-N-(4-ethylphenyl)-N-isobutyl-3-methylsulfanylbenzenesulfonamide (21.31 g; 78%) is obtained in the form of a pale yellow solid with a compliant ^1H NMR.

MS : [M+H] = 444

2. Synthesis of intermediate 12.2



(E)-N-((2-bromo-5-(N-(4-ethylphenyl)-N-isobutylsulfamoyl)phenyl)(methyl)-λ^4-sulfanylidene)-2,2,2-trifluoroacetamide

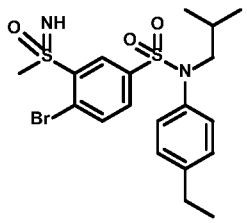
4-Bromo-N-(4-ethylphenyl)-N-isobutyl-3-methylsulfanylbenzenesulfonamide (5.00 g; 11.30 mmol) and 2,2,2-trifluoroacetamide (1.92 g; 16.95 mmol) dissolved in tetrahydrofuran (10 ml) are

added slowly to 60% sodium hydride (0.41 g; 10.17 mmol) suspended in tetrahydrofuran (10 ml) at 0-5°C, and 1,3-dibromo-5,5-dimethylhydantoin (4.85 g; 16.95 mmol) dissolved in tetrahydrofuran (25 ml) is added at a temperature of 0-5°C. The medium is stirred for 1 hour at room temperature. The reaction medium is hydrolyzed with 10% citric acid solution and then extracted with ethyl acetate.

The organic phases are combined, washed with 25% sodium sulfite solution and then with brine, dried (Na_2SO_4) and concentrated. The residue is taken up in ether and suction-filtered. The (E)-N-((2-bromo-5-(N-(4-ethylphenyl)-N-isobutylsulfamoyl)phenyl)(methyl)-λ^4-sulfanylidene)-2,2,2-trifluoroacetamide (4.76 g; 76%) is obtained in the form of a white powder with a compliant ^{1}H NMR.

MS : [M+H] = 554

3. Synthesis of intermediate 12.3



2-bromo-N-(4-ethylphenyl)-N-isobutyl-3-(S-ethylsulfonimidoyl)benzenesulfonamide

Potassium carbonate (2.79 g; 20.16 mmol) is added to (E)-N-((2-bromo-5-(N-(4-ethylphenyl)-N-isobutylsulfamoyl)phenyl)(methyl)-λ^4-sulfanylidene)-2,2,2-trifluoroacetamide (3.72 g; 6.72 mmol) dissolved in methanol (35 ml), and 3-chloroperoxybenzoic acid (2.26 g; 10.08 mmol) is then added slowly at a temperature of 0°C. The reaction medium is stirred for 16 hours at room temperature.

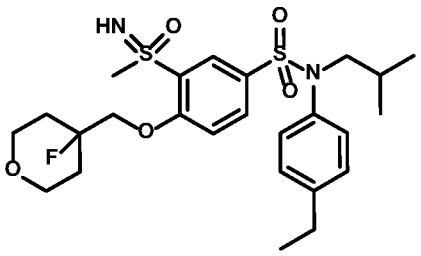
The reaction medium is hydrolyzed and then extracted with ethyl acetate. The organic phases are combined, washed with brine, dried (Na_2SO_4) and concentrated.

The crude product is chromatographed on silica gel (eluent: heptane/ethyl acetate, from 0 to 80% of ethyl acetate). The 4-bromo-N-(4-ethylphenyl)-N-isobutyl-

3-(S-methylsulfonimidoyl)benzenesulfonamide (1.51 g; 47%) is obtained in the form of a white solid with a compliant ^{1}H NMR.

MS : [M+H] = 474

4. Synthesis of compound 30 according to the invention



60% sodium hydride (9 mg; 0.22 mmol) is added slowly to (4-fluorotetrahydropyran-4-yl)methanol (28.33 mg; 0.21 mmol) dissolved in N,N-dimethylformamide (0.5 ml), followed by 4-bromo-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide (50 mg; 0.11 mmol).

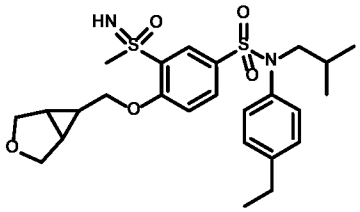
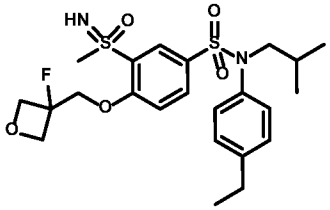
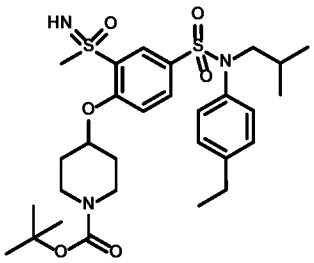
The reaction medium is stirred for 2 hours at room temperature. The reaction medium is hydrolyzed without heating and then extracted with ethyl acetate. The organic phases are combined, washed with brine, dried (Na_2SO_4) and concentrated.

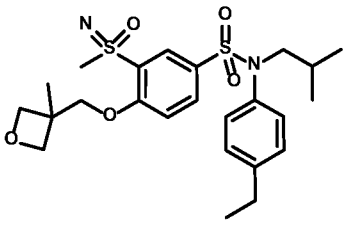
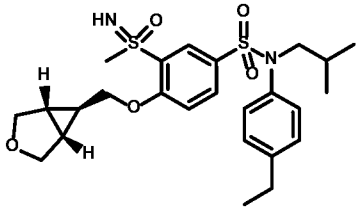
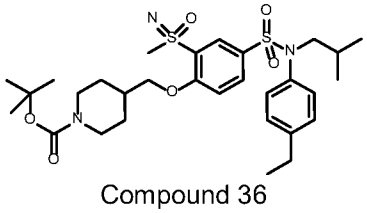
The crude product is purified by preparative HPLC (C18 column, eluent: acetonitrile in water/0.1% of formic acid). N-(4-Ethylphenyl)-4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide (46 mg; 82%) is obtained in the form of a white solid.

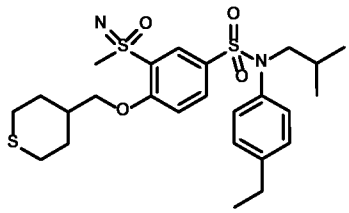
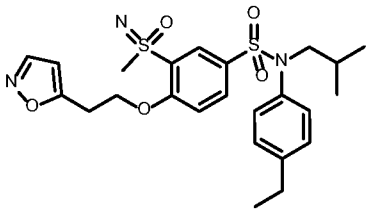
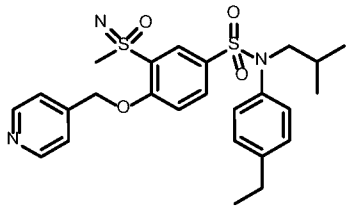
^{1}H NMR (DMSO-d6) δ: 0.86 (dd, J = 6.7, 4.6 Hz, 6H), 1.19 (t, J = 7.6 Hz, 3H), 1.36 – 1.51 (m, 1H), 1.76 – 2.05 (m, 4H), 2.61 (q, J = 7.6 Hz, 2H), 3.19 (d, J = 1.0 Hz, 3H), 3.22 – 3.32 (m, 2H), 3.63 (td, J = 11.2, 3.0 Hz, 2H), 3.80 (dt, J = 11.2, 2.8 Hz, 2H), 4.34 – 4.48 (m, 3H), 6.97 – 7.04 (m, 2H), 7.17 – 7.24 (m, 2H), 7.39 (d, J = 8.8 Hz, 1H), 7.70 (dd, J = 8.7, 2.4 Hz, 1H), 8.01 (d, J = 2.4 Hz, 1H).

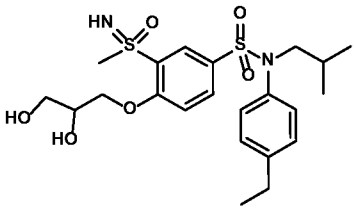
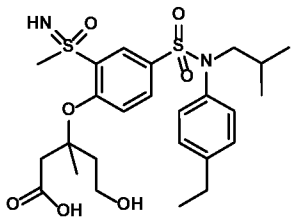
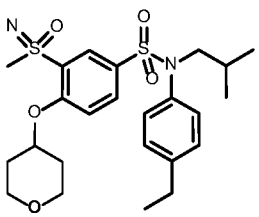
MS : [M+H] = 527

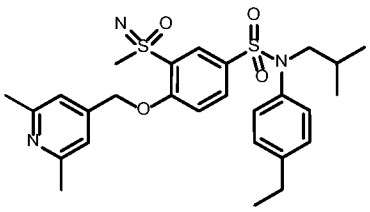
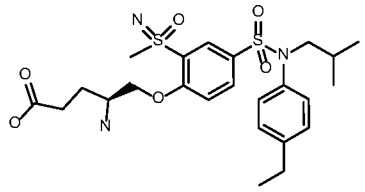
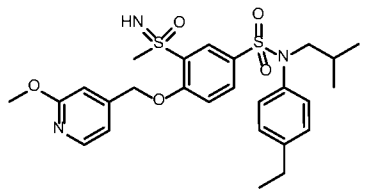
With a procedure similar to that described for example 12, the following are obtained:

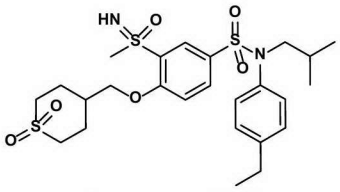
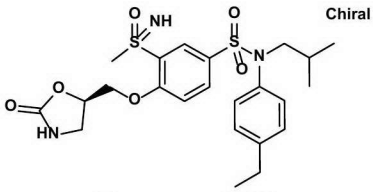
Example 13	 Compound 31	**4-((3-oxabicyclo[3.1.0]hexan-6-yl)methoxy)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.85 (dd, J = 6.7, 4.3 Hz, 6H), 1.12 – 1.23 (m, 4H), 1.43 (dt, J = 13.6, 6.9 Hz, 1H), 1.79 – 1.86 (m, 2H), 2.61 (q, J = 7.6 Hz, 2H), 3.23 (s, 3H), 3.25 – 3.36 (m, 2H), 3.61 (dt, J = 8.3, 1.4 Hz, 2H), 3.78 (d, J = 8.4 Hz, 2H), 4.21 (dd, J = 6.9, 1.9 Hz, 2H), 4.41 (d, J = 1.5 Hz, 1H), 6.96 – 7.03 (m, 2H), 7.17 – 7.24 (m, 2H), 7.34 (d, J = 8.8 Hz, 1H), 7.65 (dd, J = 8.7, 2.4 Hz, 1H), 8.00 (d, J = 2.5 Hz, 1H). MS : [M+H] = 507
Example 14	 Compound 32	**N-(4-ethylphenyl)-4-((3-fluorooxetan-3-yl)methoxy)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.86 (dd, J = 6.6, 4.3 Hz, 6H), 1.19 (t, J = 7.6 Hz, 3H), 1.38 – 1.50 (m, 1H), 2.61 (q, J = 7.6 Hz, 2H), 3.16 (d, J = 1.2 Hz, 3H), 3.22 – 3.41 (m, 2H), 4.46 (d, J = 1.5 Hz, 1H), 4.63 – 4.86 (m, 6H), 6.97 – 7.05 (m, 2H), 7.21 (d, J = 8.3 Hz, 2H), 7.74 (dd, J = 8.7, 2.4 Hz, 1H), 8.00 (d, J = 2.4 Hz, 1H). MS : [M+H] = 499
Example 15	 Compound 33	**tert-butyl 4-(4-(N-(4-ethylphenyl)-N-isobutylsulfamoyl)-2-(S-methylsulfonimidoyl)phenoxy)piperidine-1-carboxylate** ^{1}H NMR (DMSO-d6) δ: 0.85 (dd, J = 6.6, 3.5 Hz, 6H), 1.19 (t, J = 7.6 Hz, 3H), 1.42 (s, 11H), 1.70 – 1.80 (m, 2H), 1.90 (t, J = 10.4 Hz, 2H), 2.61 (q, J = 7.5 Hz, 2H), 3.19 (s, 3H), 3.24 – 3.31 (m, 2H), 3.38 – 3.48 (m, 2H), 3.48 – 3.61 (m, 2H), 4.42 (d, J = 1.4 Hz, 1H), 4.97 – 5.05 (m, 1H), 6.98 – 7.05 (m, 2H), 7.17 – 7.25 (m, 2H), 7.45 (d, J = 9.0 Hz, 1H), 7.64 (dd, J = 8.7, 2.4 Hz, 1H), 8.01 (d, J = 2.3 Hz, 1H). MS : [M+H] = 594

Example 16	 Compound 34	**N-(4-ethylphenyl)-N-isobutyl-4-((3-methyloxetan-3-yl)methoxy)-3-(S-methylsulfonimidoyl)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.86 (dd, J = 6.6, 4.1 Hz, 6H), 1.19 (t, J = 7.6 Hz, 3H), 1.42 (s, 4H), 2.56 – 2.67 (m, 2H), 3.21 (d, J = 1.2 Hz, 3H), 3.24 – 3.32 (m, 2H), 4.30 (d, J = 3.3 Hz, 2H), 4.36 (d, J = 6.0 Hz, 2H), 4.42 (d, J = 1.4 Hz, 1H), 4.62 (dd, J = 5.9, 3.0 Hz, 2H), 6.98 – 7.05 (m, 2H), 7.18 – 7.25 (m, 2H), 7.43 (d, J = 8.8 Hz, 1H), 7.70 (dd, J = 8.7, 2.5 Hz, 1H), 8.02 (d, J = 2.4 Hz, 1H). MS : [M+H] = 495
Example 17	 Compound 35	**4-(((1R,5S,6R)-3-oxabicyclo[3.1.0]hexan-6-yl)methoxy)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.85 (dd, J = 6.7, 4.3 Hz, 6H), 1.18 (t, J = 7.6 Hz, 4H), 1.35 – 1.51 (m, 1H), 1.79 – 1.86 (m, 2H), 2.61 (q, J = 7.6 Hz, 2H), 3.23 (d, J = 1.2 Hz, 3H), 3.25 – 3.31 (m, 2H), 3.61 (dt, J = 8.4, 1.3 Hz, 2H), 3.78 (d, J = 8.3 Hz, 2H), 4.21 (dd, J = 7.0, 1.9 Hz, 2H), 4.41 (d, J = 1.4 Hz, 1H), 6.96 – 7.03 (m, 2H), 7.17 – 7.24 (m, 2H), 7.34 (d, J = 8.8 Hz, 1H), 7.65 (dd, J = 8.7, 2.4 Hz, 1H), 8.00 (d, J = 2.5 Hz, 1H). MS : [M+H] = 507
Example 18	 Compound 36	**tert-butyl 4-((4-(N-(4-ethylphenyl)-N-isobutylsulfamoyl)-2-(S-methylsulfonimidoyl)phenoxy)methyl)piperidine-1-carboxylate** ^{1}H NMR (DMSO-d6) δ: 0.85 (dd, J = 6.6, 4.4 Hz, 6H), 1.14 – 1.31 (m, 5H), 1.41 (s, 10H), 1.82 (s, 2H), 2.04 (s, 1H), 2.53 – 2.66 (m, 3H), 2.77 (s, 2H), 3.17 (d, J = 1.2 Hz, 3H), 3.21 – 3.31 (m, 2H), 3.99 (d, J = 12.8 Hz, 2H), 4.08 – 4.15 (m, 2H), 4.41 (d, J = 1.5 Hz, 1H), 6.97 – 7.04 (m, 2H), 7.17 – 7.24 (m, 2H), 7.37 (d, J = 8.8 Hz, 1H), 7.67 (dd, J = 8.7, 2.5 Hz, 1H), 8.00

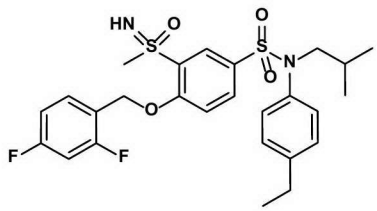
		(d, J = 2.4 Hz, 1H). MS : [M+H] = 608
Example 19	 Compound 37	**N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(pyridin-4-ylmethoxy)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.85 (dd, J = 6.6, 4.5 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.35 – 1.57 (m, 3H), 1.82 – 2.01 (m, 1H), 2.11 – 2.20 (m, 2H), 2.52 – 2.76 (m, 7H), 3.19 (d, J = 1.2 Hz, 3H), 3.32 (s, 8H), 4.05 – 4.12 (m, 2H), 4.40 (d, J = 1.5 Hz, 1H), 6.97 – 7.04 (m, 2H), 7.17 – 7.24 (m, 2H), 7.37 (d, J = 8.9 Hz, 1H), 7.67 (dd, J = 8.8, 2.5 Hz, 1H), 8.00 (d, J = 2.4 Hz, 1H). MS : [M+H] = 525
Example 20	 Compound 38	**N-(4-ethylphenyl)-N-isobutyl-4-(2-(isoxazol-5-yl)ethoxy)-3-(S-methylsulfonimidoyl)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.85 (dd, J = 11.0, 6.7 Hz, 6H), 1.17 (t, J = 7.6 Hz, 3H), 1.43 (t, J = 7.2 Hz, 1H), 2.29 – 2.38 (m, 2H), 2.60 (d, J = 7.6 Hz, 2H), 3.22 – 3.39 (m, 4H), 3.54 (d, J = 2.5 Hz, 3H), 4.64 (s, 1H), 6.83 (s, 1H), 6.94 – 7.04 (m, 2H), 7.22 (d, J = 8.4 Hz, 4H), 7.64 (d, J = 2.3 Hz, 1H), 7.82 (dd, J = 8.9, 2.4 Hz, 1H) MS : [M+H] = 506
Example 21	 Compound 39	**N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(pyridin-4-ylmethoxy)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.86 (dd, J = 6.7, 4.3 Hz, 7H), 1.19 (t, J = 7.6 Hz, 3H), 1.36 – 1.51 (m, 1H), 2.61 (q, J = 7.6 Hz, 2H), 3.15 (d, J = 1.2 Hz, 3H), 3.24 – 3.32 (m, 2H), 4.51 (d, J = 1.5 Hz, 1H), 5.47 (d, J = 2.5 Hz, 2H), 6.97 – 7.04 (m, 2H), 7.17 – 7.24 (m, 2H), 7.44 – 7.54 (m, 2H), 7.73 (dd, J = 8.7, 2.5 Hz, 1H), 8.00 (dt, J = 7.9, 2.0 Hz, 1H), 8.03 (d, J = 2.4 Hz, 1H), 8.59 (dd, J = 4.8, 1.6 Hz, 1H), 8.79 (d, J = 2.5 Hz, 1H). MS : [M+H] = 502

Example 22	 Compound 40	**4-(2,3-dihydroxypropoxy)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.85 (dd, J = 6.6, 3.5 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.37 – 1.49 (m, 1H), 2.61 (q, J = 7.6 Hz, 2H), 3.24 (t, J = 1.4 Hz, 3H), 3.25 – 3.31 (m, 2H), 3.53 (t, J = 5.8 Hz, 2H), 3.89 (dd, J = 10.2, 5.1 Hz, 1H), 4.11 – 4.34 (m, 2H), 4.41 (dd, J = 8.9, 1.4 Hz, 1H), 4.74 (dt, J = 7.7, 5.7 Hz, 1H), 5.08 (d, J = 4.9 Hz, 1H), 6.97 – 7.04 (m, 2H), 7.17 – 7.24 (m, 2H), 7.39 (dd, J = 8.9, 2.1 Hz, 1H), 7.64 – 7.73 (m, 1H), 7.95 – 8.00 (m, 1H). MS : [M+H] = 485
Example 23	 Compound 41	**3-(4-(N-(4-ethylphenyl)-N-isobutylsulfamoyl)-2-(S-methylsulfonimidoyl)phenoxy)-5-hydroxy-3-methylpentanoic acid** ^{1}H NMR (DMSO-d6) δ: 0.85 (t, J = 5.4 Hz, 7H), 1.17 (t, J = 7.6 Hz, 5H), 1.36 – 1.48 (m, 1H), 2.60 (q, J = 7.5 Hz, 2H), 3.14 (d, J = 4.9 Hz, 3H), 3.20 – 3.29 (m, 2H), 4.39 – 4.71 (m, 5H), 5.26 (s, 1H), 6.99 (d, J = 7.2 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 7.40 (dt, J = 8.5, 4.3 Hz, 1H), 7.65 – 7.76 (m, 1H), 7.99 (dd, J = 14.4, 2.4 Hz, 1H). MS : [M+H] = 541
Example 24	 Compound 42	**N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((tetrahydro-2H-pyran-4-yl)oxy)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.85 (dd, J = 6.6, 3.8 Hz, 6H), 1.19 (t, J = 7.6 Hz, 3H), 1.36 – 1.51 (m, 1H), 1.68 – 1.81 (m, 2H), 1.97 – 2.07 (m, 2H), 2.61 (q, J = 7.6 Hz, 2H), 3.21 (d, J = 1.2 Hz, 3H), 3.32 (m,2H, 3.50 – 3.61 (m, 2H), 3.87 – 3.92 (m, 2H), 4.41 (d, J = 1.5 Hz, 1H), 5.00 (dt, J = 7.3, 3.6 Hz, 1H), 6.98 – 7.05 (m, 2H), 7.17 – 7.24 (m, 2H), 7.46 (d, J = 8.9 Hz, 1H), 7.63 (dd, J = 8.8, 2.4 Hz, 1H), 8.02 (d, J = 2.5

		Hz, 1H) MS : [M+H] = 495
Example 25	 Compound 43	**4-((2,6-dimethylpyridin-4-yl)methoxy)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide** 1H NMR (DMSO-d6) δ: 0.85 (dd, J = 6.6, 4.0 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.36 – 1.49 (m, 1H), 2.44 (s, 6H), 2.50 – 2.66 (m, 3H), 3.21 (d, J = 1.1 Hz, 3H), 3.32 (m,2H), 4.55 (d, J = 1.4 Hz, 1H), 5.40 (s, 2H), 6.95 – 7.04 (m, 2H), 7.16 – 7.24 (m, 4H), 7.40 (d, J = 8.8 Hz, 1H), 7.71 (dd, J = 8.7, 2.4 Hz, 1H), 8.04 (d, J = 2.4 Hz, 1H) MS : [M+H] = 530
Example 26	 Compound 44	**((4S)-4-amino-5-(4-(N-(4-ethylphenyl)-N-isobutylsulfamoyl)-2-(S-methylsulfonimidoyl)phenoxy)pentanoic acid** [1]H NMR (DMSO-d6) δ: 0.84 (d, J = 6.4 Hz, 7H), 1.18 (t, J = 7.6 Hz, 3H), 1.42 (dt, J = 13.7, 6.8 Hz, 1H), 1.74 (dd, J = 14.3, 7.3 Hz, 1H), 1.88 (dt, J = 14.3, 6.9 Hz, 1H), 2.30 – 2.41 (m, 2H), 2.61 (q, J = 7.6 Hz, 2H), 3.01 (d, J = 5.9 Hz, 3H), 3.25 (d, J = 7.3 Hz, 3H), 3.50 (s, 2H), 3.68 (s, 1H), 4.67 (d, J = 23.1 Hz, 1H), 4.95 (d, J = 17.8 Hz, 1H), 7.01 (d, J = 8.1 Hz, 3H), 7.20 (d, J = 8.0 Hz, 2H), 7.47 (dd, J = 8.8, 2.9 Hz, 1H), 7.67 – 7.81 (m, 2H), 12.12 (s, 1H) MS : [M+H] = 526
Example 27	 Compound 77	**N-(4-ethylphenyl)-N-isobutyl-4-((2-methoxypyridin-4-yl)methoxy)-3-(S-methylsulfonimidoyl)benzenesulfonamide** [1]H NMR (DMSO-d6) δ: 0.89 (ddd, J = 10.8, 6.5, 3.9 Hz, 6H), 1.23 (t, J = 7.6 Hz,3H), 1.42 – 1.54 (m, 1H), 2.66 (q, J = 7.7 Hz, 2H), 3.25 (s, 3H), 3.28 – 3.35 (m, 2H), 3.92 (s, 3H), 4.61 (s, 1H), 5.50 (s, 2H), 7.05 (d, J = 8.1 Hz, 3H), 7.25 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 8.9 Hz, 1H), 7.57 – 7.73 (m, 2H), 7.76 (dd, J = 8.9, 2.4 Hz, 1H), 8.09 (d, J = 2.6 Hz, 1H), 8.26 (d, J =

		5.3 Hz, 1H). MS : [M+H] = 532
Example 28	 Compound 78	**N-(4-ethylphenyl)-N-isobutyl-4-((2-methoxypyridin-4-yl)methoxy)-3-(S-methylsulfonimidoyl)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.85 (dd, J = 6.6, 4.7 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.36 – 1.50 (m, 1H), 1.88 (t, J = 12.8 Hz, 2H), 2.15 – 2.30 (m, 3H), 2.61 (q, J = 7.6 Hz, 2H), 3.07 – 3.18 (m, 2H), 3.19 (d, J = 1.2 Hz, 3H), 3.20 – 3.32 (m, 4H), 4.18 (dt, J = 6.0, 3.6 Hz, 2H), 4.44 (d, J = 1.5 Hz, 1H), 6.97 – 7.04 (m, 2H), 7.17 – 7.24 (m, 2H), 7.38 (d, J = 8.7 Hz, 1H), 7.68 (dd, J = 8.8, 2.4 Hz, 1H), 8.01 (d, J = 2.4 Hz, 1H). MS : [M+H] = 557
Example 29 CD13325	 Compound 79	**N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(((R)-2-oxooxazolidin-5-yl)methoxy)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.81 – 0.89 (m, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.35 – 1.50 (m, 1H), 2.61 (q, J = 7.6 Hz, 2H), 3.18 (dd, J = 4.2, 1.2 Hz, 3H), 3.22 – 3.32 (m, 2H), 3.59 (dt, J = 32.3, 8.2 Hz, 2H), 4.30 – 4.45 (m, 2H), 4.46 – 4.57 (m, 1H), 5.01 (dt, J = 4.8, 2.3 Hz, 1H), 6.96 – 7.04 (m, 2H), 7.17 – 7.24 (m, 2H), 7.42 (dd, J = 8.8, 2.2 Hz, 1H), 7.65 – 7.75 (m, 2H), 8.00 (dd, J = 10.9, 2.4 Hz, 1H). MS : [M+H] = 510

Example 30: Synthesis of the compound 4-((2,4-difluorobenzyl)oxy)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide



Compound 45

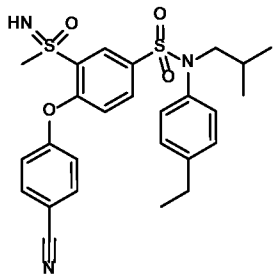
4-Bromo-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide (50.0 mg; 0.11 mmol) is added to a mixture comprising 2,4-difluorobenzyl alcohol (30.5 mg; 0.21 mmol) and cesium carbonate (103.2 mg; 0.32 mmol) dissolved in N,N-dimethylformamide (0.50 ml) after stirring for 20 minutes. The reaction medium is stirred for 20 hours at a temperature of 80°C, hydrolyzed without heating and then extracted with ethyl acetate. The organic phases are combined, washed with saturated sodium chloride solution, dried (sodium sulfate) and concentrated to dryness.

The crude product is purified by preparative HPLC (C18 column, eluent: acetonitrile in water/0.1% of formic acid). The 4-((2,4-difluorobenzyl)oxy)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide (9.4 g; 16%) is obtained in the form of a white solid.

^{1}H NMR (DMSO-d6) δ: 0.86 (dd, J = 6.8, 4.4 Hz, 6H), 1.19 (t, J = 7.6 Hz, 3H), 1.33 – 1.53 (m, 1H), 2.62 (t, J = 7.6 Hz, 2H), 3.12 (s, 3H), 4.47 (s, 1H), 5.42 (s, 2H), 7.01 (d, J = 8.1 Hz, 2H), 7.21 (d, J = 8.0 Hz, 3H), 7.38 (t, J = 9.2 Hz, 1H), 7.55 (d, J = 8.8 Hz, 1H), 7.72 (dd, J = 8.7, 2.5 Hz, 1H), 7.80 (q, J = 8.2 Hz, 1H), 8.03 (d, J = 2.5 Hz, 1H).

MS : [M+H] = 537

Example 31: Synthesis of the compound 4-(4-cyanophenoxy)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide



Compound 80

60% sodium hydride (6.3 mg; 0.16 mmol) is added to (1,1-dioxohexahydro-1λ^6-thiopyran-4-yl)methanol 4-cyanophenol (13.8 mg; 0.12 mmol) dissolved in N,N-dimethylformamide (1.0 ml). The reaction medium is stirred for 20 minutes, followed by addition of 4-bromo-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide (50.0 mg; 0.11 mmol).

The reaction medium is stirred for 1 hour at room temperature and then for 16 hours at a temperature of 80°C. The reaction medium is hydrolyzed by addition of cold water and then extracted with ethyl acetate. The organic phases are combined and then washed with brine, dried (Na_2SO_4) and concentrated.

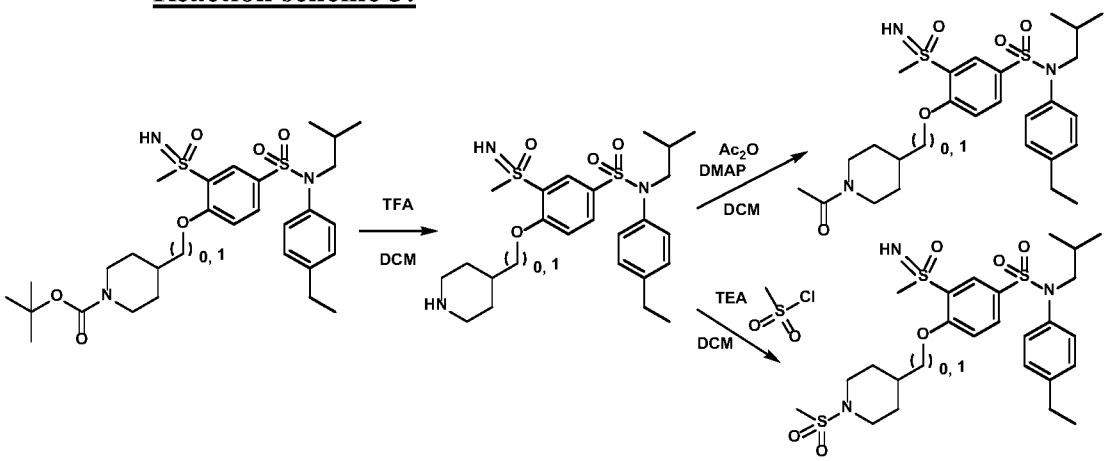
The crude product is chromatographed on silica gel, eluting with heptane/ethyl acetate, from 0 to 100% of ethyl acetate. The 4-(4-cyanophenoxy)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide (14.5 mg; 24%) is obtained in the form of a white solid.

^{1}H NMR (DMSO-d6) δ: 0.87 (dd, J = 6.6, 3.9 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.21 – 1.31 (m, 2H), 1.39 – 1.51 (m, 1H), 2.57 – 2.66 (m, 2H), 3.26 (s, 3H), 3.33 – 3.39 (m, 2H), 4.66 (d, J = 1.5 Hz, 1H), 7.00 – 7.07 (m, 2H), 7.20 – 7.31 (m, 3H), 7.30 – 7.38 (m, 2H), 7.72 (dd, J = 8.6, 2.4 Hz, 1H), 7.93 – 8.00 (m, 2H), 8.09 (d, J = 2.4 Hz, 1H).

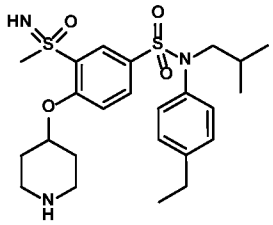
MS : [M+H] = 512

Part III: Synthesis of the sulfur-based sulfonamides via reaction scheme 3

Reaction scheme 3:



Example 32: Synthesis of N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(piperidin-4-ylmethoxy)benzenesulfonamide



Compound 46

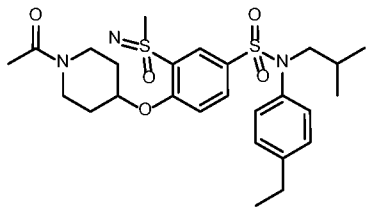
Trifluoroacetic acid (0.2 ml; 2.61 mmol) is added to tert-butyl 4-(4-(N-(4-ethylphenyl)-N-isobutylsulfamoyl)-2-(S-methylsulfonimidoyl)phenoxy)piperidine-1-carboxylate (40.0 mg; 0.07 mmol) dissolved in dichloromethane (1.6 ml). The reaction medium is stirred for 1 hour at room temperature, concentrated, diluted with dichloromethane, washed with saturated sodium hydrogen carbonate solution and then with saturated NaCl solution, and dried (Na_2SO_4). The solvents are evaporated off.

The crude product is purified by preparative HPLC (C18 column, eluent: acetonitrile in water/0.1% of formic acid). The N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(piperidin-4-yloxy)benzenesulfonamide (32.1 mg; 97%) is obtained in the form of a white powder.

Mixture of conformers: ^{1}H NMR (DMSO-d6) δ: 0.86 (dd, J = 6.6, 1.5 Hz, 6H), 1.20 (t, J = 7.6 Hz, 3H), 1.46 – 1.61 (m, 1H), 1.77 – 1.96 (m, 2H), 1.96 – 2.15 (m, 2H), 2.57 – 2.68 (m, 2H), 2.77 – 2.96 (m, 2H), 3.20 (s, 3H), 3.28 – 3.38 (m, 2H), 3.98 – 4.21 (m, 1H), 4.75 – 5.03 (m, 1H), 6.98 – 7.06 (m, 2H), 7.16 – 7.23 (m, 2H), 7.41 (d, J = 8.8 Hz, 1H), 7.64 – 7.72 (m, 1H), 8.05 (d, J = 2.5 Hz, 1H).

MS : [M+H] = 494

Example 33: Synthesis of 4-((1-acetylpiperidin-4-yl)oxy)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide



Compound 47

4-Dimethylaminopyridine (1.6 mg; 0.01 mmol) and acetic anhydride (11.2 µl; 0.12 mmol) are added to a solution of N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(piperidin-4-yloxy)benzenesulfonamide (65.0 mg; 0.13 mmol) in dichloromethane (2 ml) cooled to a temperature of -10°C.

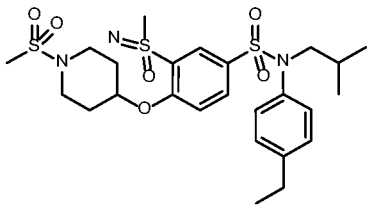
The reaction medium is stirred for 2 hours at room temperature. The reaction medium is hydrolyzed, followed by addition of saturated sodium hydrogen carbonate solution, and then extracted with ethyl acetate. The organic phases are combined, washed with saturated sodium chloride solution, dried (Na_2SO_4) and concentrated to dryness.

The crude product is purified by preparative HPLC (C18 column, eluent: acetonitrile in water/0.1% of formic acid). The 4-((1-acetylpiperidin-4-yl)oxy)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide (34.8 mg; 49%) is obtained in the form of a white solid.

^{1}H NMR (DMSO-d6) δ: 0.86 (dd, J = 6.6, 2.3 Hz, 6H), 1.19 (t, 3H), 1.36 – 1.51 (m, 1H), 1.89 – 2.07 (m, 5H), 2.61 (q, J = 7.6 Hz, 2H), 2.87 (s, 3H), 3.20 (d, J = 1.2 Hz, 3H), 3.23 – 3.31 (m, 5H), 4.47 (d, J = 1.5 Hz, 1H), 5.06 (t, J = 4.1 Hz, 1H), 6.98 – 7.05 (m, 2H), 7.18 – 7.25 (m, 2H), 7.47 (d, J = 9.0 Hz, 1H), 7.67 (dd, J = 8.7, 2.4 Hz, 1H), 8.00 (d, J = 2.4 Hz, 1H).

MS : [M+H] = 536

Example 34: Synthesis of N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((1-(methylsulfonyl)piperidin-4-yl)oxy)benzenesulfonamide



Compound 48

Triethylamine (18.3 µl; 0.13 mmol) and methanesulfonyl chloride (10.2 µl; 0.13 mmol) are added to a solution of N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(piperidin-4-ylmethoxy)benzenesulfonamide (65.0 mg; 0.13 mmol) in dichloromethane (1.3 ml).

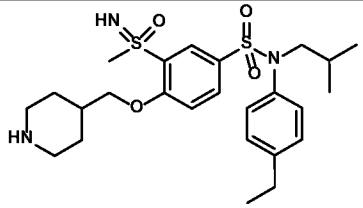
The reaction medium is stirred for 2 hours at room temperature, hydrolyzed by addition of saturated sodium hydrogen carbonate solution, and extracted with ethyl acetate. The organic phases are combined, washed with saturated sodium chloride solution, dried over sodium sulfate and concentrated to dryness.

The crude product is purified by preparative HPLC (C18 column, eluent: acetonitrile in water/0.1% of formic acid). The N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((1-(methylsulfonyl)piperidin-4-yl)oxy)benzenesulfonamide (24.8 mg; 32%) is obtained in the form of a white solid.

^{1}H NMR (DMSO-d6) δ: 0.86 (dd, J = 6.7, 3.4 Hz, 6H), 1.19 (t, J = 7.6 Hz, 3H), 1.36 – 1.51 (m, 1H), 1.81 – 1.88 (m, 2H), 1.99 (d, J = 9.4 Hz, 1H), 2.03 (s, 3H), 2.61 (q, J = 7.6 Hz, 2H), 3.19 (d, J = 1.2 Hz, 3H), 3.22 – 3.31 (m, 2H), 3.43 – 3.52 (m, 1H), 3.53 – 3.74 (m, 3H), 4.42 (dd, J = 3.3, 1.5 Hz, 1H), 5.02 – 5.09 (m, 1H), 6.98 – 7.06 (m, 2H), 7.17 – 7.25 (m, 2H), 7.47 (d, J = 8.9 Hz, 1H), 7.65 (dd, J = 8.8, 2.4 Hz, 1H), 8.02 (d, J = 2.4 Hz, 1H)).

MS : [M+H] = 572

Example 35: Synthesis of N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(piperidin-4-ylmethoxy)benzenesulfonamide



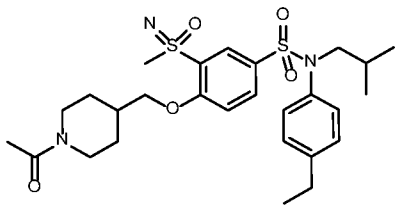
Compound 49

With a procedure similar to that described for example 31, N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(piperidin-4-ylmethoxy)benzenesulfonamide (68.2 mg; 100%) is obtained in the form of a white powder.

^{1}H NMR (DMSO-d6) δ: 0.77 (dd, J = 6.6, 4.4 Hz, 6H), 1.11 (t, J = 7.6 Hz, 3H), 1.14 – 1.24 (m, 2H), 1.24 – 1.43 (m, 1H), 1.70 (d, J = 13.3 Hz, 2H), 1.82 – 1.89 (m, 1H), 2.45 – 2.51 (m, 2H), 2.51 – 2.58 (m, 2H), 2.93 (dt, J = 12.1, 3.3 Hz, 2H), 3.11 (s, 3H), 3.18 (dd, J = 13.0, 7.1 Hz, 3H), 3.99 (dd, J = 6.3, 2.3 Hz, 2H), 4.32 (s, 1H), 6.93 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.8 Hz, 1H), 7.58 (dd, J = 8.8, 2.5 Hz, 1H), 7.92 (d, J = 2.4 Hz, 1H).

MS : [M+H] = 508

Example 36: Synthesis of 4-((1-acetylpiperidin-4-yl)methoxy)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide



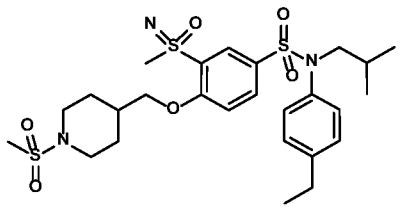
Compound 50

With a procedure similar to that described for example 32, 4-((1-acetylpiperidin-4-yl)methoxy)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide (6.5 mg; 10%) is obtained in the form of a white solid.

^{1}H NMR (DMSO-d6) δ: 0.85 (dd, J = 6.7, 4.2 Hz, 6H), 1.08 – 1.23 (m, 5H), 1.22 – 1.35 (m, 2H), 1.43 (dt, J = 13.4, 6.8 Hz, 1H), 1.88 (d, J = 26.7 Hz, 2H), 2.01 (s, 3H), 2.09 – 2.14 (m, 1H), 2.61 (q, J = 7.6 Hz, 3H), 3.08 (t, J = 12.8 Hz, 1H), 3.18 (s, 3H), 3.22 – 3.30 (m, 2H), 3.87 (d, J = 13.6 Hz, 1H), 4.11 (q, J = 4.4 Hz, 2H), 4.42 (d, J = 11.5 Hz, 2H), 7.01 (d, J = 7.9 Hz, 2H), 7.21 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.8 Hz, 1H), 7.67 (dd, J = 8.8, 2.4 Hz, 1H), 8.00 (d, J = 2.4 Hz, 1H).

MS : [M+H] = 550

Example 37: Synthesis of N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((1-(methylsulfonylpiperidin-4-yl)methoxy)benzenesulfonamide



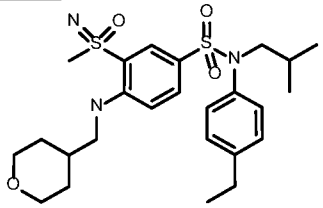
Compound 51

With a procedure similar to that described for example 33, N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((1-(methylsulfonylpiperidin-4-yl)methoxy)benzenesulfonamide (17.2 mg; 25%) is obtained in the form of a white solid.

^{1}H NMR (DMSO-d6) δ: 0.85 (dd, J = 6.7, 4.3 Hz, 6H), 1.19 (t, J = 7.6 Hz, 3H), 1.37 – 1.51 (m, 3H), 1.89 – 2.04 (m, 3H), 2.61 (q, J = 7.7 Hz, 2H), 2.72 – 2.83 (m, 2H), 2.88 (s, 3H), 3.18 (s, 3H), 3.28 (d, J = 7.8 Hz, 2H), 3.62 (d, J = 11.5 Hz, 2H), 4.09 – 4.20 (m, 2H), 4.42 (s, 1H), 7.01 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.1 Hz, 2H), 7.39 (d, J = 8.8 Hz, 1H), 7.68 (dd, J = 8.7, 2.5 Hz, 1H), 8.00 (d, J = 2.5 Hz, 1H).

MS : [M+H] = 586

Example 38: Synthesis of N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-[(tetrahydropyran-4-ylmethyl)amino]benzenesulfonamide



Compound 52

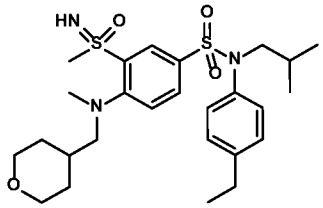
A mixture of 4-bromo-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide (15.0 mg; 0.03 mmol) and 4-aminomethyltetrahydropyran (7.5 µl; 0.06 mmol) is stirred overnight at room temperature.

The crude product is purified by preparative HPLC (C18 column, eluent: acetonitrile in water/0.1% of formic acid). The N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-[(tetrahydropyran-4-ylmethyl)amino]benzenesulfonamide (9.0 mg; 56%) is obtained in the form of a white solid.

^{1}H NMR(DMSO-d6, 400 MHz): δ (ppm) 0.84 (dd, J=6.7, 2.6 Hz, 6H), 1.18 (t, J=7.7 Hz, 3H), 1.28 (dd, J=14.5, 10.3 Hz, 2H), 1.37 – 1.46 (m,1H), 1.66 (d, J=13.3 Hz, 2H), 1.87 (s, 1H), 2.61 (q, J=7.4 Hz, 2H), 3.01 (s, 3H), 3.17 (q, J=6.8, 6.4 Hz, 2H), 3.24 (dd, J=7.4, 3.3 Hz, 2H), 3.89 (dd, J=11.6, 4.0 Hz, 2H), 4.74 (s, 1H), 6.95 (d, J=8.9 Hz, 1H), 7.00 (d, J=7.9 Hz, 2H), 7.20 (d, J=8.1 Hz, 2H), 7.50 (d, J=9.0 Hz, 1H), 7.70 (d, J=2.3 Hz, 1H), 7.84 (t, J=5.5 Hz, 1H).

MS : [M+H] = 508

Example 39: Synthesis of N-(4-ethylphenyl)-N-isobutyl-4-(methyl((tetrahydro-2H-pyran-4-yl)methyl)amino)-3-(S-methylsulfonimidoyl)benzenesulfonamide



Compound 53

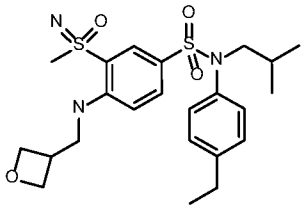
A solution of 4-bromo-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide (15.0 mg; 0.03 mmol) in N,N-dimethylformamide (0.20 ml) is stirred overnight at a temperature of 50°C.

The crude product is purified by preparative HPLC (C18 column, eluent: acetonitrile in water/0.1% of formic acid). The N-(4-ethylphenyl)-N-isobutyl-4-(methyl((tetrahydro-2H-pyran-4-yl)methyl)amino)-3-(S-methylsulfonimidoyl)benzenesulfonamide (9.0 mg; 49%) is obtained in the form of a colorless dry film.

^{1}H NMR (DMSO-d6) δ: 0.85 (dd, J = 6.6, 3.2 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.44 (dt, J = 13.7, 6.8 Hz, 1H), 1.58 (d, J = 13.4 Hz, 2H), 1.93 (s, 1H), 2.61 (q, J = 7.6 Hz, 2H), 2.82 (s, 3H), 2.93 – 3.10 (m, 2H), 3.26 (d, J = 1.3 Hz, 3H), 3.28 – 3.30 (m, 2H), 3.80 – 3.87 (m, 2H), 4.50 (d, J = 1.5 Hz, 1H), 7.00 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.3 Hz, 2H), 7.56 (d, J = 8.6 Hz, 1H), 7.61 (dd, J = 8.6, 2.2 Hz, 1H), 8.13 (d, J = 2.3 Hz, 1H).

MS : [M+H] = 522

Example 40: Synthesis of N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((oxetan-3-ylmethyl)aminobenzenesulfonamide



Compound 54

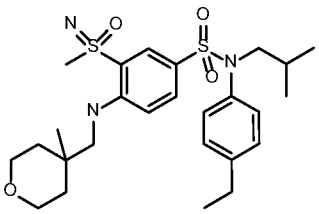
3-Aminomethyloxetane hydrochloride (33 mg; 0.26 mmol) and triethylamine (51 µl; 0.37 mmol) are added to 4-bromo-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide (50.00 mg; 0.11 mmol) dissolved in N,N-dimethylformamide (250 µl). The reaction medium is stirred overnight at 50°C.

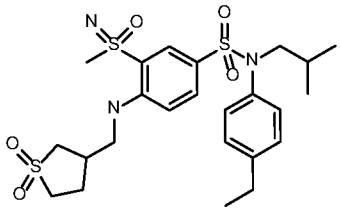
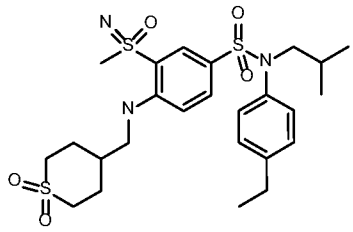
The crude product is purified directly by preparative HPLC (C18 column, eluent: acetonitrile in water/0.1% of formic acid). The N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((oxetan-3-ylmethyl)aminobenzenesulfonamide (14.0 mg; 26%) is obtained in the form of a white solid.

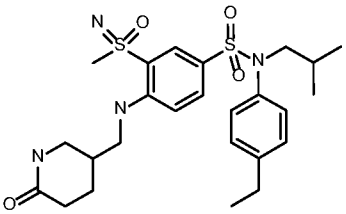
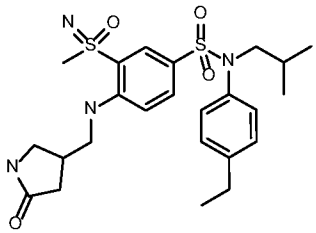
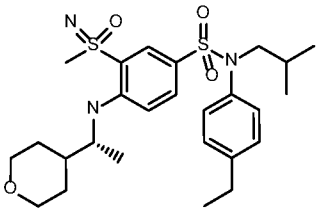
^{1}H NMR (DMSO-d6) δ: 0.84 (dd, J = 6.7, 2.2 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.35 – 1.50 (m, 1H), 2.61 (q, J = 7.7 Hz, 2H), 3.00 (s, 3H), 3.25 (d, J = 6.9 Hz, 2H), 3.58 (dt, J = 14.5, 7.1 Hz, 2H), 4.35 (td, J = 6.0, 2.8 Hz, 2H), 4.70 (td, J = 6.4, 3.3 Hz, 3H), 6.99 (dd, J = 8.5, 5.0 Hz, 3H), 7.20 (d, J = 7.8 Hz, 2H), 7.51 (dd, J = 8.8, 2.5 Hz, 1H), 7.71 (d, J = 2.5 Hz, 1H), 7.82 (t, J = 5.5 Hz, 1H).

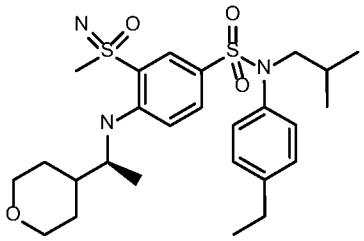
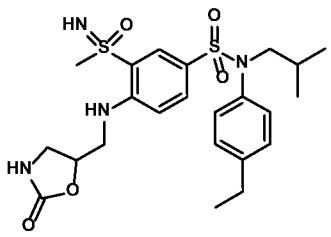
MS : [M+H] = 480

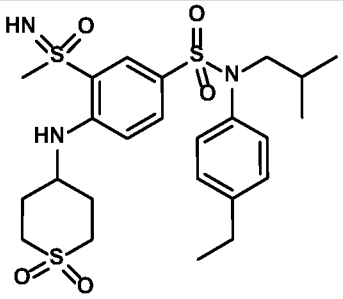
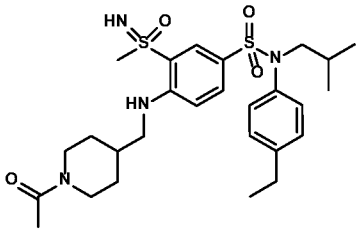
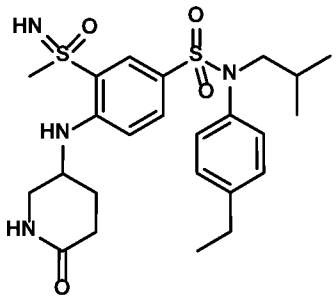
With a procedure similar to that described for example 40, the following are obtained:

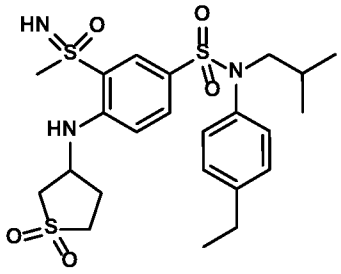
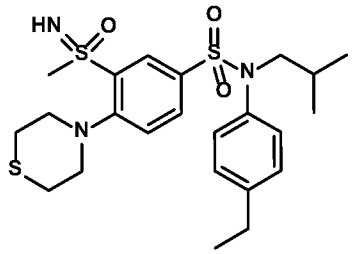
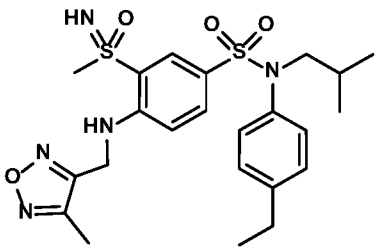
Example 41	 Compound 55	**N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(((4-methyltetrahydro-2H-pyran-4-yl)methyl)amino)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.84 (dd, J = 6.7, 3.3 Hz, 6H), 1.09 (s, 3H), 1.18 (t, J = 7.6 Hz, 3H), 1.31 – 1.38 (m, 2H), 1.38 – 1.47 (m, 1H), 1.54 (ddt, J = 14.2, 9.8, 5.0 Hz, 2H), 2.61 (q, J = 7.7 Hz, 2H),

		3.01 (s, 3H), 3.07 – 3.21 (m, 2H), 3.24 (p, J = 5.6 Hz, 2H), 3.51 – 3.60 (m, 2H), 3.68 (dt, J = 11.8, 4.4 Hz, 2H), 4.84 (s, 1H), 7.00 (d, J = 8.1 Hz, 3H), 7.20 (d, J = 7.9 Hz, 2H), 7.49 (dd, J = 8.9, 2.4 Hz, 1H), 7.69 (d, J = 2.5 Hz, 1H), 7.98 (t, J = 5.1 Hz, 1H). MS : [M+H] = 522
Example 42	 Compound 56	**4-(((1,1-dioxidotetrahydrothiophen-3-yl)methyl)amino)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.84 (dd, J = 6.6, 2.7 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.38 – 1.50 (m, 1H), 1.89 (d, J = 22.1 Hz, 1H), 2.61 (q, J = 7.6 Hz, 2H), 2.90 (t, J = 12.1 Hz, 1H), 3.03 (d, J = 1.5 Hz, 3H), 3.25 (dd, J = 7.5, 3.9 Hz, 2H), 3.44 (t, J = 6.3 Hz, 2H), 4.73 (d, J = 6.3 Hz, 1H), 7.01 (dd, J = 8.6, 5.9 Hz, 3H), 7.20 (d, J = 8.3 Hz, 2H), 7.49 (dd, J = 8.9, 2.4 Hz, 1H), 7.72 (d, J = 2.3 Hz, 1H), 7.85 (s, 1H). MS : [M+H] = 542
Example 43	 Compound 57	**4-(((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl)amino)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.84 (dd, J = 6.7, 2.2 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.42 (dt, J = 13.5, 6.8 Hz, 1H), 1.71 (q, J = 12.2 Hz, 2H), 1.91-1.98 (m, 1H), 2.06-2.14 (m, 2H), 2.61 (q, J = 7.6 Hz, 2H), 3.02 (s, 3H), 3.10 (dd, J = 28.9, 13.4 Hz, 2H), 3.23 – 3.28 (m, 4H), 4.74 (d, J = 1.1 Hz, 1H), 6.97 – 7.02 (m, 3H), 7.20 (d, J = 8.3 Hz, 2H), 7.50 (dd, J = 8.9, 2.4 Hz, 1H), 7.71 (d, J = 2.3 Hz, 1H), 7.84 (t, J = 5.8 Hz, 1H). MS : [M+H] = 556

Example 44	 Compound 58	**N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(((6-oxopiperidin-3-yl)methyl)amino)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.84 (dd, J = 6.6, 2.5 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.42 (dt, J = 13.6, 6.8 Hz, 1H), 1.47 – 1.59 (m, 1H), 1.83-1.93 (m, 1H), 2.02-2.11 (m, 1H), 2.16-2.25 (m, 2H), 2.60 (q, J = 7.7 Hz, 2H), 2.90 – 2.98 (m, 1H), 3.02 (s, 3H), 3.23 – 3.29 (m, 3H), 4.75 (s, 1H), 6.97 – 7.04 (m, 3H), 7.17 – 7.23 (m, 2H), 7.44 – 7.53 (m, 2H), 7.71 (dd, J = 2.3, 1.1 Hz, 1H), 7.83 (s, 1H). MS : [M+H] = 521
Example 45	 Compound 59	**N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(((5-oxopyrrolidin-3-yl)methyl)amino)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.84 (dd, J = 6.6, 2.7 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.42 (dt, J = 13.5, 6.8 Hz, 1H), 2.00 (ddd, J = 16.6, 6.8, 3.6 Hz, 1H), 2.29 (d, J = 8.8 Hz, 1H), 2.60 (q, J = 7.7 Hz, 2H), 2.68 – 2.78 (m, 1H), 3.02 (s, 3H), 3.24 (dd, J = 7.3, 3.6 Hz, 2H), 3.33 – 3.44 (m, 2H), 4.74 (s, 1H), 6.97 (s, 1H), 7.00 (d, J = 8.1 Hz, 2H), 7.16 – 7.23 (m, 2H), 7.50 (dd, J = 8.9, 2.4 Hz, 1H), 7.59 (s, 1H), 7.71 (d, J = 2.3 Hz, 1H), 7.83 (d, J = 5.0 Hz, 1H). MS : [M+H] = 507
Example 46	 Compound 60	**N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(((R)-1-(tetrahydro-2H-pyran-4-yl)ethyl)amino)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.84 (dd, J = 6.7, 3.0 Hz, 6H), 1.10 – 1.23 (m, 6H), 1.26 – 1.40 (m, 1H), 1.42 (p, J = 7.0 Hz, 2H), 1.57 (d, J = 13.1 Hz, 2H), 1.62 – 1.79 (m, 1H), 2.61 (q, J = 7.6 Hz, 2H), 2.99 (dd, J = 4.0, 1.0 Hz, 3H), 3.19 – 3.30 (m, 4H), 3.56 – 3.69 (m, 1H), 3.84

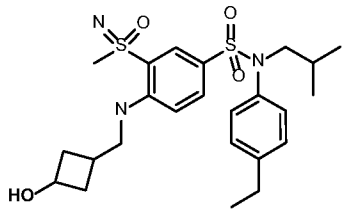
		– 3.95 (m, 2H), 4.78 (d, J = 4.6 Hz, 1H), 6.94 – 7.02 (m, 1H), 7.01 (d, J = 8.4 Hz, 2H), 7.16 – 7.25 (m, 2H), 7.43 – 7.53 (m, 1H), 7.70 (t, J = 2.0 Hz, 1H), 7.80 – 7.90 (m, 1H). MS : [M+H] = 522
Example 47	 Compound 81	**N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(((S)-1-(tetrahydro-2H-pyran-4-yl)ethyl)amino)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.84 (dd, J = 6.7, 3.0 Hz, 6H), 1.10 – 1.23 (m, 6H), 1.24 – 1.48 (m, 2H), 1.57 (d, J = 13.0 Hz, 1H), 1.62 – 1.77 (m, 3H), 2.61 (q, J = 7.6 Hz, 2H), 2.99 (dd, J = 4.0, 1.0 Hz, 3H), 3.21 – 3.30 (m, 4H), 3.60 (d, J = 20.4 Hz, 1H), 3.84 – 3.97 (m, 2H), 4.75 – 4.82 (m, 1H), 6.94 – 7.01 (m, 1H), 7.01 (d, J = 8.4 Hz, 2H), 7.16 – 7.24 (m, 2H), 7.43 – 7.52 (m, 1H), 7.67 – 7.73 (m, 1H), 7.80 – 7.88 (m, 1H). MS : [M+H] = 522
Example 48	 Compound 82	**N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(((2-oxooxazolidin-5-yl)methyl)amino)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.81 – 0.87 (m, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.42 (p, J = 6.6 Hz, 1H), 2.60 (q, J = 7.6 Hz, 2H), 3.02 (t, J = 1.1 Hz, 3H), 3.22 – 3.28 (m, 3H), 3.60 (ddt, J = 11.1, 6.9, 3.9 Hz, 2H), 4.55 (s, 1H), 4.73 (d, J = 11.6 Hz, 1H), 4.82 (s, 1H), 6.94 – 7.04 (m, 2H), 7.06 (d, J = 8.9 Hz, 1H), 7.20 (d, J = 8.2 Hz, 2H), 7.51 (dt, J = 8.9, 2.1 Hz, 1H), 7.60 (s, 1H), 7.72 (dd, J = 3.4, 2.3 Hz, 1H), 7.86 – 8.01 (m, 1H). MS : [M+H] = 509
Example 49		**4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide**

	 Compound 83	^{1}H NMR (Chloroform-d) δ: 0.90 (dd, J = 9.1, 6.6 Hz, 6H), 1.25 (d, J = 8.2 Hz, 4H), 2.31 (s, 2H), 2.44 (s, 2H), 2.58 – 2.66 (m, 2H), 3.04 (s, 3H), 3.07 – 3.23 (m, 4H), 3.24 – 3.37 (m, 2H), 3.75 (s, 1H), 6.67 (d, J = 8.9 Hz, 1H), 7.00 (d, J = 8.3 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 7.58 (dd, J = 8.8, 2.2 Hz, 1H), 8.03 (d, J = 2.2 Hz, 1H). MS : [M+H] = 542
Example 50	 Compound 84	**4-(((1-acetylpiperidin-4-yl)methyl)amino)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide** ^{1}H NMR (Chloroform-d) δ: 0.92 (dd, J = 8.9, 6.7 Hz, 6H), 1.22 – 1.28 (m, 4H), 1.59 (hept, J = 6.8 Hz, 1H), 1.90 (dddd, J = 26.2, 18.2, 8.2, 4.9 Hz, 4H), 2.12 (s, 3H), 2.65 (q, J = 7.8 Hz, 2H), 3.04 (s, 3H), 3.09 – 3.17 (m, 4H), 3.24 (dd, J = 12.8, 6.9 Hz, 1H), 3.34 (dd, J = 12.7, 7.7 Hz, 1H), 3.89 (dd, J = 13.2, 3.5 Hz, 1H), 4.66 – 4.76 (m, 1H), 6.68 (d, J = 9.0 Hz, 1H), 7.01 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 7.55 (dd, J = 8.8, 2.0 Hz, 1H), 7.65 (q, J = 4.4, 3.9 Hz, 1H), 7.99 (d, J = 2.2 Hz, 1H). MS : [M+H] = 549
Example 51	 Compound 85	**N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((6-oxopiperidin-3-yl)amino)benzenesulfonamide** ^{1}H NMR (Chloroform-d) δ: 0.90 (dd, J = 9.2, 6.6 Hz, 6H), 1.19 – 1.27 (m, 5H), 1.58 (hept, J = 7.0 Hz, 1H), 2.55 (s, 2H), 2.64 (d, J = 7.9 Hz, 2H), 3.03 (s, 3H), 3.29 (ddd, J = 39.3, 12.4, 6.9 Hz, 3H), 3.67 (s, 1H), 3.87 – 3.99 (m, 1H), 6.02 (s, 1H), 6.74 (d, J = 8.4 Hz, 1H), 7.00 (d, J = 7.6 Hz, 2H), 7.14 (d, J = 7.6 Hz, 2H), 7.56 (d, J = 7.6 Hz, 1H), 7.92 (s, 1H), 8.02 (d, J = 5.8 Hz, 1H). MS : [M+H] = 507

Example 52	 Compound 86	**4-((1,1-dioxidotetrahydrothiophen-3-yl)amino)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.84 (ddd, J = 6.6, 2.3, 1.0 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.42 (dt, J = 13.6, 6.7 Hz, 1H), 2.12 – 2.24 (m, 1H), 2.61 (q, J = 7.5 Hz, 2H), 3.04 (d, J = 2.6 Hz, 3H), 3.07 – 3.21 (m, 1H), 3.23 – 3.27 (m, 2H), 3.65 (ddd, J = 20.2, 13.3, 7.0 Hz, 1H), 4.44 – 4.56 (m, 1H), 4.74 (s, 1H), 4.80 (s, 1H), 7.00 (d, J = 8.3 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 7.54 (dt, J = 8.3, 1.4 Hz, 1H), 7.73 (dd, J = 4.0, 2.3 Hz, 1H), 7.98 (d, J = 7.1 Hz, 1H), 8.12 (d, J = 6.6 Hz, 1H). MS : [M+H] = 528
Example 53	 Compound 87	**N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-thiomorpholinobenzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.84 (ddd, J = 6.6, 2.3, 1.0 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.42 (dt, J = 13.6, 6.7 Hz, 1H), 2.12 – 2.24 (m, 1H), 2.61 (q, J = 7.5 Hz, 2H), 3.04 (d, J = 2.6 Hz, 3H), 3.07 – 3.21 (m, 1H), 3.23 – 3.27 (m, 2H), 3.65 (ddd, J = 20.2, 13.3, 7.0 Hz, 1H), 4.44 – 4.56 (m, 1H), 4.74 (s, 1H), 4.80 (s, 1H), 7.00 (d, J = 8.3 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 7.54 (dt, J = 8.3, 1.4 Hz, 1H), 7.73 (dd, J = 4.0, 2.3 Hz, 1H), 7.98 (d, J = 7.1 Hz, 1H), 8.12 (d, J = 6.6 Hz, 1H). MS : [M+H] = 528
Example 54	 Compound 88	**N-(4-ethylphenyl)-N-isobutyl-4-(((4-methyl-1,2,5-oxadiazol-3-yl)methyl)amino)-3-(S-methylsulfonimidoyl)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.85 (dd, J = 6.6, 3.5 Hz, 6H), 1.13 – 1.23 (m, 3H), 1.43 (dt, J = 13.6, 6.8 Hz, 1H), 2.61 (q,

		J = 7.6 Hz, 2H), 2.80 (dt, J = 6.8, 3.6 Hz, 4H), 3.25 (q, J = 5.9, 5.3 Hz, 4H), 3.31 (s, 3H), 4.53 – 4.57 (m, 1H), 6.97 – 7.05 (m, 2H), 7.17 – 7.26 (m, 2H), 7.63 (d, J = 8.4 Hz, 1H), 7.71 (dd, J = 8.4, 2.3 Hz, 1H), 8.12 (d, J = 2.3 Hz, 1H). MS : [M+H] = 496

Example 55: Synthesis of N-(4-ethylphenyl)-4-(((3-hydroxycyclobutyl)methyl)amino)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide



Compound 61

3-Aminomethylcyclobutanol hydrochloride (36.33 mg; 0.26 mmol) and cesium carbonate (120.43 mg; 0.37 mmol) are added to 4-bromo-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide (50.00 mg; 0.11 mmol) dissolved in N,N-dimethylformamide (150 µl).

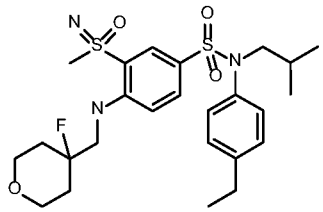
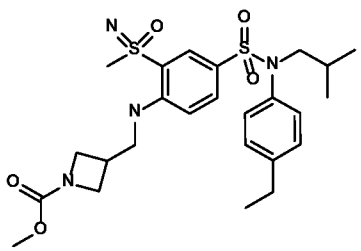
The reaction medium is stirred over the weekend at a temperature of 50°C.

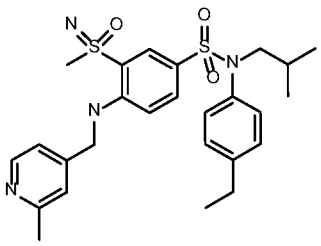
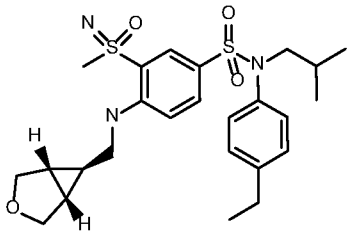
The crude product is purified directly by preparative HPLC (C18 column, eluent: acetonitrile in water/0.1% of formic acid). The N-(4-ethylphenyl)-4-(((3-hydroxycyclobutyl)methyl)amino)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide (20.0 mg; 38%) is obtained in the form of a white solid.

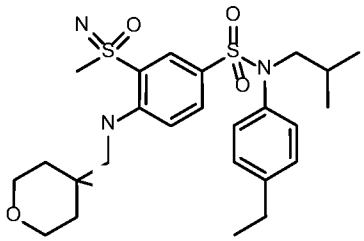
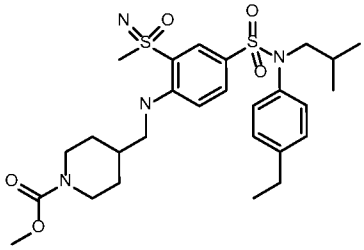
^{1}H NMR (DMSO-d6) δ: 0.84 (dd, J = 6.7, 2.4 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.42 (dt, J = 13.5, 6.7 Hz, 1H), 1.56 (q, J = 8.7 Hz, 1H), 1.94 – 2.07 (m, 2H), 2.27 – 2.36 (m, 2H), 2.60 (q, J = 7.6 Hz, 2H), 2.99 (s, 3H), 3.24 (dd, J = 7.3, 3.5 Hz, 2H), 3.98 (dt, J = 14.2, 7.4 Hz, 1H), 4.70 (d, J = 1.3 Hz, 1H), 5.03 (t, J = 3.1 Hz, 1H), 6.91 (t, J = 8.6 Hz, 1H), 6.99 (dd, J = 8.4, 1.6 Hz, 2H), 7.17 – 7.23 (m, 2H), 7.50 (dt, J = 8.8, 2.9 Hz, 1H), 7.69 (d, J = 2.3 Hz, 1H).

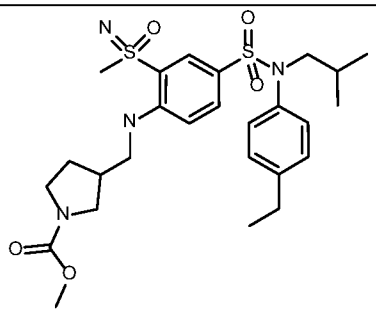
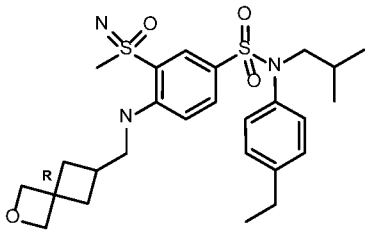
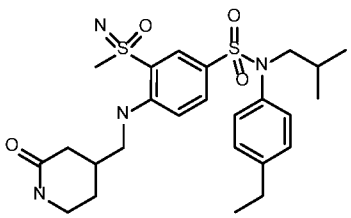
MS : [M+H] = 494

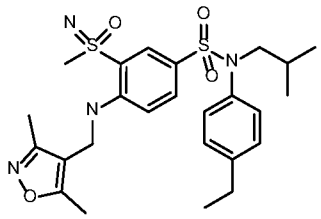
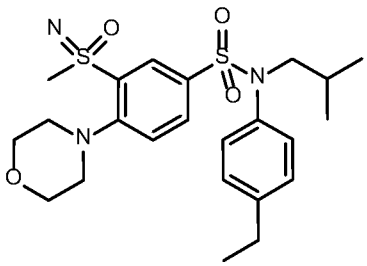
With a procedure similar to that described for example 55, the following are obtained:

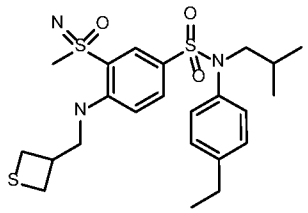
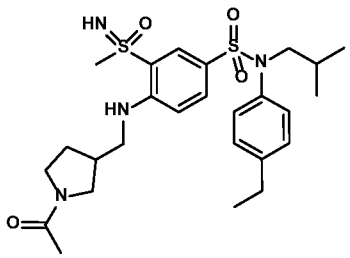
Example 56	 Compound 62	**N-(4-ethylphenyl)-4-(((4-fluorotetrahydro-2H-pyran-4-yl)methyl)amino)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.84 (dd, J = 6.7, 2.4 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.42 (dt, J = 13.6, 6.8 Hz, 1H), 1.81 (tq, J = 19.3, 9.1 Hz, 4H), 2.09 (s, 1H), 2.60 (q, J = 7.6 Hz, 2H), 3.02 (d, J = 0.9 Hz, 3H), 3.25 (dd, J = 7.3, 3.1 Hz, 2H), 3.51 – 3.63 (m, 4H), 3.74 – 3.82 (m, 2H), 4.76 – 4.83 (m, 1H), 7.00 (d, J = 8.3 Hz, 2H), 7.06 (d, J = 8.9 Hz, 1H), 7.17 – 7.22 (m, 2H), 7.50 (dd, J = 8.9, 2.3 Hz, 1H), 7.72 (d, J = 2.3 Hz, 1H), 8.01 (t, J = 5.8 Hz, 1H) MS : [M+H] = 526
Example 57	 Compound 89	**methyl 3-(((4-(N-(4-ethylphenyl)-N-isobutylsulfamoyl)-2-(S-methylsulfonimidoyl)phenyl)amino)methyl)azetidine-1-carboxylate** ^{1}H NMR (DMSO-d6) δ: 0.84 (dd, J = 6.7, 2.3 Hz, 6H), 1.11 – 1.23 (m, 3H), 1.42 (dt, J = 13.6, 6.7 Hz, 1H), 2.55 – 2.66 (m, 2H), 2.99 (s, 3H), 3.25 (ddd, J = 17.8, 9.7, 4.2 Hz, 4H), 3.51 (q, J = 6.5 Hz, 1H), 3.56 (s, 3H), 3.67 (dt, J = 12.1, 6.8 Hz, 2H), 4.00 (p, J = 8.0 Hz, 2H), 4.69 (s, 1H), 6.95 – 7.05 (m, 3H), 7.16 – 7.24 (m, 2H), 7.50 (dd, J = 8.9, 2.3 Hz, 1H), 7.71 (d, J = 2.4 Hz, 1H), 7.81 (t, J = 5.5 Hz, 1H). MS : [M+H] = 537

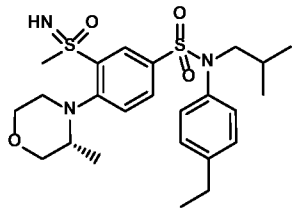
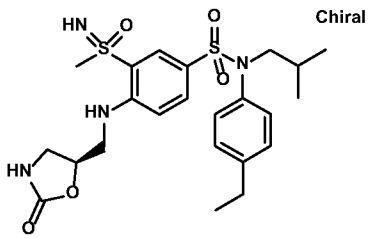
Example 58	 Compound 90	**N-(4-ethylphenyl)-N-isobutyl-4-(((2-methylpyridin-4-yl)methyl)amino)-3-(S-methylsulfonimidoyl)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.83 (dd, J = 6.6, 2.0 Hz, 6H), 1.17 (t, J = 7.6 Hz, 3H), 1.41 (dt, J = 13.6, 6.9 Hz, 1H), 2.45 (s, 3H), 2.59 (q, J = 7.7 Hz, 2H), 3.10 (d, J = 1.0 Hz, 3H), 3.24 (dd, J = 7.4, 2.7 Hz, 2H), 4.58 (d, J = 6.1 Hz, 2H), 4.79 (s, 1H), 6.74 (d, J = 8.9 Hz, 1H), 6.95 – 7.00 (m, 2H), 7.13 – 7.23 (m, 4H), 7.45 (dd, J = 8.8, 2.3 Hz, 1H), 7.76 (d, J = 2.3 Hz, 1H), 8.19 (t, J = 6.0 Hz, 1H), 8.40 (d, J = 5.3 Hz, 1H). MS : [M+H] = 515
Example 59	 Compound 91	**4-((((1R,5S,6S)-3-oxabicyclo[3.1.0]hexan-6-yl)methyl)amino)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.84 (dd, J = 6.7, 2.1 Hz, 6H), 1.00 (dt, J = 7.0, 3.6 Hz, 1H), 1.18 (t, J = 7.6 Hz, 3H), 1.42 (dt, J = 13.6, 6.8 Hz, 1H), 1.69 (hept, J = 3.5 Hz, 2H), 2.56 – 2.66 (m, 2H), 3.02 (d, J = 0.9 Hz, 3H), 3.25 (dd, J = 7.4, 2.5 Hz, 2H), 3.58 (dd, J = 8.2, 2.5 Hz, 2H), 3.74 (dd, J = 8.3, 1.7 Hz, 2H), 4.71 (d, J = 1.3 Hz, 1H), 6.91 (d, J = 9.0 Hz, 1H), 6.95 – 7.01 (m, 2H), 7.15 – 7.25 (m, 2H), 7.50 (dd, J = 8.8, 2.3 Hz, 1H), 7.70 (d, J = 2.3 Hz, 1H), 7.77 (t, J = 5.1 Hz, 1H). MS : [M+H] = 506

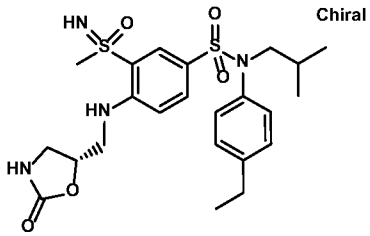
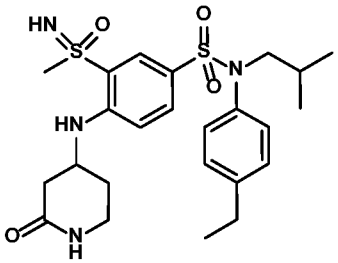
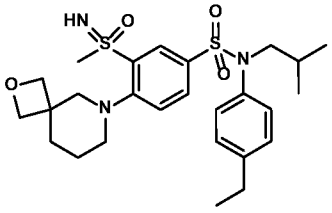
Example 60	 Compound 92	**N-(4-ethylphenyl)-4-(((4-hydroxytetrahydro-2H-pyran-4-yl)methyl)amino)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.84 (dd, J = 6.7, 1.9 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.42 (dt, J = 13.6, 6.8 Hz, 1H), 1.51 (d, J = 13.3 Hz, 2H), 1.62 (dt, J = 15.5, 8.6 Hz, 2H), 2.61 (q, J = 7.6 Hz, 2H), 3.02 (d, J = 0.8 Hz, 3H), 3.20 – 3.30 (m, 2H), 3.59 – 3.70 (m, 2H), 4.69 (d, J = 1.1 Hz, 1H), 4.80 (s, 1H), 6.93 – 7.03 (m, 3H), 7.16 – 7.23 (m, 2H), 7.48 (dd, J = 8.9, 2.4 Hz, 1H), 7.72 (d, J = 2.3 Hz, 1H), 7.88 (t, J = 5.1 Hz, 1H). MS : [M+H] = 524
Example 61	 Compound 93	**methyl 4-(((4-(N-(4-ethylphenyl)-N-isobutylsulfamoyl)-2-(S-methylsulfonimidoyl)phenyl)amino)methyl)piperidine-1-carboxylate** ^{1}H NMR (DMSO-d6) δ: 0.84 (dd, J = 6.7, 2.5 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.41 (dq, J = 13.8, 6.9 Hz, 1H), 1.73 (d, J = 13.3 Hz, 4H), 1.76 – 1.88 (m, 1H), 2.60 (q, J = 7.6 Hz, 2H), 3.01 (d, J = 1.0 Hz, 3H), 3.13 – 3.20 (m, 2H), 3.24 (dd, J = 7.2, 3.3 Hz, 2H), 3.59 (s, 3H), 3.93 – 4.10 (m, 4H), 4.74 (d, J = 1.3 Hz, 1H), 6.95 (d, J = 8.9 Hz, 1H), 6.97 – 7.02 (m, 2H), 7.17 – 7.23 (m, 2H), 7.50 (dd, J = 8.9, 2.4 Hz, 1H), 7.70 (d, J = 2.3 Hz, 1H), 7.83 (t, J = 5.4 Hz, 1H). MS : [M+H] = 565
Example 62		**methyl 3-(((4-(N-(4-ethylphenyl)-N-isobutylsulfamoyl)-2-(S-methylsulfonimidoyl)phenyl)amino)methyl)pyrrolidine-1-carboxylate**

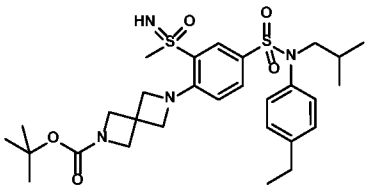
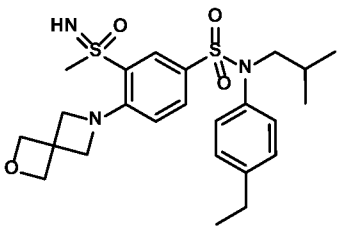
	 Compound 94	^{1}H NMR (DMSO-d6) δ: 0.84 (dd, J = 6.6, 2.5 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.41 (dt, J = 13.5, 6.8 Hz, 1H), 1.58 – 1.76 (m, 1H), 1.93 – 2.08 (m, 2H), 2.60 (q, J = 7.6 Hz, 2H), 3.02 (s, 3H), 3.07 (td, J = 8.5, 7.9, 3.9 Hz, 1H), 3.24 (dd, J = 7.3, 3.2 Hz, 4H), 3.43 (td, J = 9.6, 8.2, 4.3 Hz, 1H), 3.50 (ddd, J = 10.2, 7.3, 2.3 Hz, 1H), 3.58 (s, 3H), 4.75 (s, 1H), 6.96 – 7.03 (m, 3H), 7.17 – 7.23 (m, 2H), 7.50 (ddd, J = 8.9, 2.3, 1.2 Hz, 1H), 7.70 (d, J = 2.2 Hz, 1H), 7.83 (s, 1H). MS : [M+H] = 551
Example 63	 Compound 95	**4-(((2-oxaspiro[3.3]heptan-6-yl)methyl)amino)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.84 (dd, J = 6.6, 2.4 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.40 (dq, J = 13.7, 6.9 Hz, 1H), 1.96 (ddd, J = 10.0, 5.7, 2.0 Hz, 2H), 2.28 – 2.46 (m, 3H), 2.60 (q, J = 7.6 Hz, 2H), 2.99 (d, J = 0.9 Hz, 3H), 3.22 (dtd, J = 14.0, 7.6, 7.0, 5.1 Hz, 4H), 4.49 (s, 2H), 4.59 (s, 2H), 4.71 (d, J = 1.1 Hz, 1H), 6.89 (d, J = 9.0 Hz, 1H), 6.97 – 7.02 (m, 2H), 7.17 – 7.21 (m, 2H), 7.49 (dd, J = 8.9, 2.3 Hz, 1H), 7.69 (d, J = 2.3 Hz, 1H). MS : [M+H] = 520
Example 64	 Compound 96	**4-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(((2-oxopiperidin-4-yl)methyl)amino)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.84 (dd, J = 6.6, 2.7 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.42 (dq, J = 13.9, 7.0 Hz, 2H), 1.86 (d, J = 13.6 Hz, 1H), 1.96 (ddd, J = 16.8, 10.8, 3.4 Hz, 1H), 2.10 –

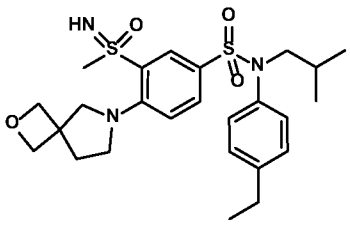
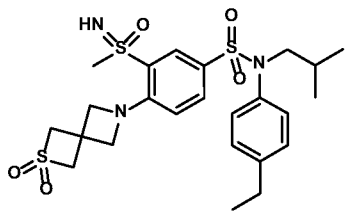
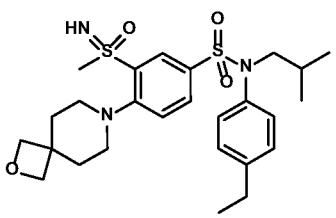
		2.32 (m, 2H), 2.60 (q, J = 7.6 Hz, 2H), 3.02 (s, 3H), 3.13 (td, J = 12.4, 11.2, 6.5 Hz, 2H), 3.14 – 3.30 (m, 4H), 4.77 (s, 1H), 6.96 – 7.03 (m, 2H), 7.16 – 7.24 (m, 2H), 7.47 – 7.55 (m, 1H), 7.54 – 7.66 (m, 1H), 7.70 (dd, J = 2.4, 1.4 Hz, 1H), 7.86 (d, J = 5.9 Hz, 1H). MS : [M+H] = 521
Example 65	 Compound 97	**4-(((3,5-dimethylisoxazol-4-yl)methyl)amino)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.84 (dd, J = 6.7, 2.2 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.41 (dq, J = 13.7, 6.9 Hz, 1H), 2.23 (s, 3H), 2.42 (s, 3H), 2.61 (q, J = 7.6 Hz, 2H), 3.00 (s, 3H), 3.26 (dd, J = 7.3, 2.9 Hz, 2H), 4.28 (t, J = 5.3 Hz, 2H), 4.75 (s, 1H), 6.95 (d, J = 8.8 Hz, 1H), 6.99 (d, J = 8.2 Hz, 2H), 7.20 (d, J = 8.1 Hz, 2H), 7.59 (dd, J = 8.7, 2.4 Hz, 1H), 7.72 (d, J = 2.3 Hz, 1H), 7.80 (t, J = 5.1 Hz, 1H). MS : [M+H] = 519
Example 66	 Compound 123	**N-(4-ethylphenyl)-4-(((4-hydroxycyclohexyl)methyl)amino)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.84 (dd, J = 6.7, 2.8 Hz, 6H), 1.01 – 1.10 (m, 2H), 1.18 (t, J = 7.6 Hz, 3H), 1.42 (dt, J = 13.7, 6.8 Hz, 1H), 1.53 (td, J = 18.2, 15.7, 6.5 Hz, 2H), 1.73 – 1.90 (m, 4H), 2.60 (q, J = 7.5 Hz, 2H), 3.00 (s, 3H), 3.08 (d, J = 6.8 Hz, 2H), 3.24 (dd, J = 7.5, 3.6 Hz, 2H), 4.53

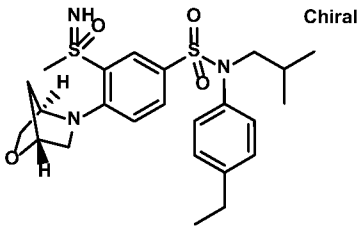
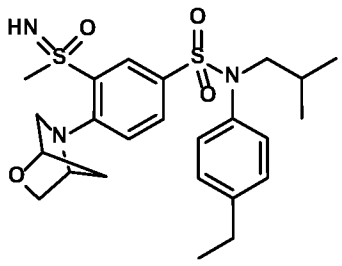
		(d, J = 4.5 Hz, 1H), 4.74 (s, 1H), 6.91 (d, J = 9.0 Hz, 1H), 7.00 (d, J = 8.1 Hz, 2H), 7.20 (d, J = 8.1 Hz, 2H), 7.49 (dd, J = 8.8, 2.5 Hz, 1H), 7.69 (d, J = 2.2 Hz, 1H), 7.81 (t, J = 5.4 Hz, 1H). MS : [M+H] = 522
Example 67	 Compound 99	**N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((thietan-3-ylmethyl)amino)benzenesulfonamide** ^{1}H NMR (Chloroform-d) δ: 0.93 (dd, J = 9.2, 6.8 Hz, 6H), 1.26 (t, J = 7.6 Hz, 3H), 1.62 (dq, J = 13.6, 7.0 Hz, 1H), 2.67 (q, J = 7.6 Hz, 2H), 3.04 (dd, J = 9.4, 6.0 Hz, 2H), 3.11 (s, 3H), 3.26 (dd, J = 12.9, 7.0 Hz, 1H), 3.32 – 3.44 (m, 2H), 3.49 (d, J = 7.0 Hz, 2H), 3.57 (h, J = 6.8, 6.4 Hz, 1H), 6.74 (d, J = 9.0 Hz, 1H), 7.02 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 7.9 Hz, 2H), 7.58 (dd, J = 8.8, 2.3 Hz, 1H), 8.03 (d, J = 2.2 Hz, 1H). MS : [M+H] = 496
Example 68	 Compound 100	**4-(((1-acetylpyrrolidin-3-yl)methyl)amino)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide** ^{1}H 1H NMR (Chloroform-d) δ: 0.89 (dd, J = 8.8, 6.6 Hz, 6H), 1.23 (t, J = 7.9 Hz, 3H), 1.57 (hept, J = 6.8 Hz, 1H), 1.65 – 1.90 (m, 1H), 2.06 (d, J = 2.9 Hz, 3H), 2.21-2.24 (m, 2H), 2.63 (q, J = 7.7 Hz, 2H), 3.03 (d, J = 4.6 Hz, 3H), 3.27 (dtd, J = 20.1, 12.9, 7.5 Hz, 5H), 3.47 (dt, J = 19.3, 9.3 Hz, 1H), 3.55 – 3.83 (m, 2H), 6.60 – 6.72 (m, 1H), 6.98 (d, J = 7.8 Hz, 2H), 7.13 (d, J = 7.8 Hz, 2H), 7.54 (d, J = 8.3 Hz, 1H), 7.69 (s, 1H), 7.98 (dd, J = 4.5, 2.1 Hz, 1H). MS : [M+H] = 535

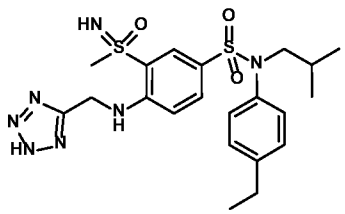
Example 71		**N-(4-ethylphenyl)-N-isobutyl-4-((R)-3-methylmorpholino)-3-(S-methylsulfonimidoyl)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.77 (dd, J = 6.3, 2.6 Hz, 3H), 0.82 – 0.88 (m, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.44 (dt, J = 13.7, 6.8 Hz, 1H), 2.61 (ddt, J = 8.7, 6.3, 3.4 Hz, 2H), 3.40 (dd, J = 17.2, 1.2 Hz, 3H), 3.44 – 3.50 (m, 1H), 3.68 (ddd, J = 11.1, 8.0, 3.0 Hz, 1H), 3.78 (ddt, J = 7.9, 5.2, 2.8 Hz, 1H), 3.87 (dd, J = 10.9, 2.4 Hz, 1H), 4.47 (d, J = 1.5 Hz, 1H), 4.62 (d, J = 1.5 Hz, 1H), 6.92 – 7.05 (m, 2H), 7.19 (dd, J = 8.4, 2.2 Hz, 2H), 7.68 (d, J = 1.3 Hz, 1H), 7.70 – 7.72 (m, 1H), 8.09 (d, J = 1.9 Hz, 1H), 8.25 (t, J = 1.3 Hz, 1H). MS : [M+H] = 494
Example 73		**N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((((R)-2-oxooxazolidin-5-yl)methyl)amino)benzenesulfonamide** ^{1}H NMR (Chloroform-d) δ: 0.90 (dd, J = 9.3, 6.7 Hz, 6H), 1.23 (t, J = 7.6 Hz, 3H), 1.59 (dq, J = 13.8, 6.8 Hz, 1H), 2.64 (q, J = 7.6 Hz, 2H), 3.06 (d, J = 2.6 Hz, 3H), 3.24 (ddd, J = 12.8, 7.0, 2.1 Hz, 1H), 3.34 (ddd, J = 12.9, 7.8, 3.3 Hz, 1H), 3.44 (ddd, J = 8.6, 5.9, 2.4 Hz, 1H), 3.53 – 3.68 (m, 1H), 3.82 (t, J = 8.7 Hz, 1H), 4.93 (qd, J = 6.0, 3.9 Hz, 1H), 5.07 (s, 1H), 6.75 (dd, J = 8.8, 3.0 Hz, 1H), 6.94 – 7.03 (m, 2H), 7.13 – 7.19 (m, 2H), 7.57 (dt, J = 8.8, 2.4 Hz, 1H), 8.01 (dd, J = 5.5, 2.2 Hz, 1H). MS : [M+H] = 509

Example 74	 Compound 106	**N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((((S)-2-oxooxazolidin-5-yl)methyl)amino)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.84 (dd, J = 6.6, 1.9 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.42 (dd, J = 13.7, 7.0 Hz, 1H), 1.52 (td, J = 17.8, 15.2, 7.1 Hz, 2H), 1.94 – 2.09 (m, 2H), 2.60 (q, J = 7.6 Hz, 2H), 3.01 (s, 3H), 3.24 (d, J = 7.4 Hz, 2H), 3.37 – 3.46 (m, 2H), 3.78 (d, J = 11.5 Hz, 2H), 4.69 (s, 1H), 6.99 (d, J = 8.2 Hz, 3H), 7.20 (d, J = 8.4 Hz, 2H), 7.47 (dd, J = 8.9, 2.4 Hz, 1H), 7.70 (d, J = 2.3 Hz, 1H), 7.85 (s, 1H). MS : [M+H] = 509
Example 75	 Compound 107	**N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((2-oxopiperidin-4-yl)amino)benzenesulfonamide** ^{1}H NMR (Chloroform-d) δ: 0.90 (d, J = 7.3 Hz, 6H), 1.17 – 1.27 (m, 3H), 1.45 – 1.68 (m, 2H), 2.57 – 2.68 (m, 2H), 3.01-3.4 (m, 2H), 3.19 – 3.40 (m, 2H), 3.48-3.52 (m, 1H), 3.99 (s, 1H), 6.03 (d, J = 40.9 Hz, 1H), 6.72 (s, 1H), 7.00 (d, J = 7.3 Hz, 2H), 7.15 (d, J = 7.3 Hz, 2H), 7.57 (s, 1H), 8.00 (s, 1H). MS : [M+H] = 508
Example 77	 Compound 109	**N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(2-oxa-6-azaspiro[3.5]nonan-6-yl)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.86 (dd, J = 6.7, 4.1 Hz, 6H), 1.19 (t, J = 7.6 Hz, 3H), 1.44 (dt, J = 13.6, 6.8 Hz, 1H), 1.63 (q, J = 5.6 Hz, 2H), 1.83 (s, 2H), 2.61 (q, J = 7.6 Hz, 2H), 2.92 (d, J = 17.9 Hz, 2H), 3.17 (s, 2H), 3.27 (d, J = 1.2 Hz, 3H), 3.33 (s, 2H), 4.29 (d, J

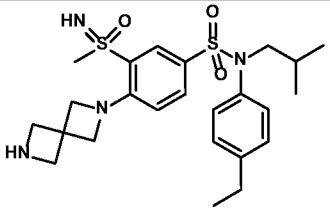
		= 5.6 Hz, 2H), 4.42 – 4.62 (m, 3H), 6.97 – 7.05 (m, 2H), 7.18 – 7.25 (m, 2H), 7.64 – 7.75 (m, 2H), 8.15 (d, J = 2.0 Hz, 1H). MS : [M+H] = 520
Example 78	 Compound 110	**tert-butyl 6-(4-(N-(4-ethylphenyl)-N-isobutylsulfamoyl)-2-(S-methylsulfonimidoyl)phenyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate** ^{1}H NMR (DMSO-d6) δ: 0.83 (dd, J = 6.6, 3.4 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.39 (s, 9H), 2.60 (q, J = 7.6 Hz, 2H), 3.12 (d, J = 1.5 Hz, 3H), 3.23 (dd, J = 7.3, 5.1 Hz, 2H), 4.05 (s, 4H), 4.20 (d, J = 1.7 Hz, 1H), 4.43 (s, 4H), 6.59 (d, J = 8.9 Hz, 1H), 6.94 – 7.01 (m, 2H), 7.15 – 7.23 (m, 2H), 7.42 (dd, J = 8.8, 2.4 Hz, 1H), 7.94 (d, J = 2.3 Hz, 1H). MS : [M+H] = 591
Example 79	 Compound 111	**N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.83 (dd, J = 6.4, 3.3 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.33 – 1.47 (m, 1H), 2.60 (q, J = 7.6 Hz, 2H), 3.12 (s, 3H), 3.24 (h, J = 6.7, 5.8 Hz, 3H), 4.20 (s, 1H), 4.48 (s, 4H), 4.73 (s, 4H), 6.61 (d, J = 8.8 Hz, 1H), 6.98 (d, J = 7.9 Hz, 2H), 7.19 (d, J = 8.2 Hz, 2H), 7.42 (dd, J = 8.8, 2.3 Hz, 1H), 7.93 (d, J = 2.4 Hz, 1H). MS : [M+H] = 493

Example 80	 Compound 112	**N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(2-oxa-6-azaspiro[3.4]octan-6-yl)benzenesulfonamide** ^{1}H 1H NMR (DMSO-d6) δ: 0.90 (dd, J = 6.8, 3.4 Hz, 6H), 1.23 (t, J = 7.6 Hz, 3H), 1.41 – 1.55 (m, 1H), 2.00 (d, J = 5.7 Hz, 4H), 2.66 (q, J = 7.6 Hz, 2H), 2.89 – 3.09 (m, 4H), 3.36 (s, 3H), 4.43 (s, 4H), 4.57 (s, 1H), 7.04 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.1 Hz, 2H), 7.62 (d, J = 8.4 Hz, 1H), 7.72 (dd, J = 8.3, 2.3 Hz, 1H), 8.18 (d, J = 2.3 Hz, 1H). MS : [M+H] = 407
Example 81	 Compound 113	**4-(2,2-dioxido-2-thia-6-azaspiro[3.3]heptan-6-yl)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.84 (dd, J = 6.8, 3.4 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.34 – 1.49 (m, 1H), 2.60 (q, J = 7.6 Hz, 2H), 3.13 (s, 3H), 3.25 (dd, J = 7.4, 5.1 Hz, 2H), 4.28 (s, 1H), 4.52 (d, J = 4.5 Hz, 8H), 6.66 (d, J = 8.9 Hz, 1H), 6.98 (d, J = 8.1 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 7.45 (dd, J = 8.8, 2.3 Hz, 1H), 7.96 (d, J = 2.3 Hz, 1H). MS : [M+H] = 540
Example 82	 Compound 114	**N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(2-oxa-7-azaspiro[3.5]nonan-7-yl)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.84 (d, J = 6.7 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.35 – 1.50 (m, 1H), 2.16 – 2.30 (m, 2H), 2.61 (q, J = 7.5 Hz, 2H), 3.21 (s, 3H), 3.28 (d, J = 7.3 Hz, 2H), 3.42 – 3.62 (m, 2H), 3.68 – 3.83 (m, 2H), 4.21 (s, 1H), 4.54 (dd, J = 6.0, 3.6 Hz, 2H), 4.60 (dd, J = 14.2, 5.9 Hz, 2H), 7.01 (d, J = 7.9 Hz, 2H), 7.19 (dd, J = 8.5, 4.5 Hz, 3H), 7.49 (dd, J

		= 8.8, 2.4 Hz, 1H), 8.05 (d, J = 2.4 Hz, 1H). MS : [M+H] = 520
Example 83	 Compound 115	**4-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide** ^{1}H 1H NMR (DMSO-d6) δ: 0.84 (dd, J = 6.7, 1.5 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.36 – 1.48 (m, 1H), 1.82 – 1.97 (m, 2H), 2.53 – 2.66 (m, 3H), 3.18 (dd, J = 7.4, 1.3 Hz, 3H), 3.28 (dd, J = 7.3, 1.7 Hz, 2H), 3.35 – 3.48 (m, 1H), 3.77 (td, J = 7.6, 1.7 Hz, 1H), 3.81 – 3.97 (m, 2H), 4.11 (d, J = 1.7 Hz, 0.5H), 4.46 (d, J = 1.5 Hz, 0.5H), 4.60 – 4.84 (m, 2H), 6.97 – 7.05 (m, 2H), 7.14 – 7.27 (m, 3H), 7.44 (ddd, J = 8.4, 5.7, 2.4 Hz, 1H), 8.07 (dd, J = 14.5, 2.4 Hz, 1H). MS : [M+H] = 493
Example 85	 Compound 117	**4-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.83 (dt, J = 5.7, 2.8 Hz, 6H), 1.16 (td, J = 7.6, 2.7 Hz, 3H), 1.20 – 1.31 (m, 1H), 1.34 – 1.49 (m, 1H), 1.87 – 1.99 (m, 2H), 2.59 (q, J = 7.6 Hz, 2H), 3.17 – 3.26 (m, 4H), 3.34 (s, 3H), 3.67 – 3.88 (m, 3H), 4.49 (s, 1H), 6.95 – 7.01 (m, 2H), 7.15 – 7.22 (m, 2H), 7.58 – 7.68 (m, 2H), 8.10 (d, J = 2.2 Hz, 1H). MS : [M+H] = 493

Example 86	 Compound 118	**4-(((2H-tetrazol-5-yl)methyl)amino)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.84 (dd, J = 6.7, 1.4 Hz, 7H), 1.18 (t, J = 7.6 Hz, 3H), 1.34 – 1.47 (m, 1H), 2.60 (q, J = 7.6 Hz, 2H), 3.08 (s, 3H), 3.25 (d, J = 7.4 Hz, 4H), 4.86 (d, J = 5.7 Hz, 2H), 6.92 – 7.03 (m, 3H), 7.15 – 7.23 (m, 2H), 7.53 (dd, J = 8.8, 2.3 Hz, 1H), 7.74 (d, J = 2.3 Hz, 1H), 8.20 (t, J = 5.7 Hz, 1H). MS : [M+H] = 494

Example 89: Synthesis of N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(2,6-diazaspiro[3.3]heptan-2-yl)benzenesulfonamide



Compound 121

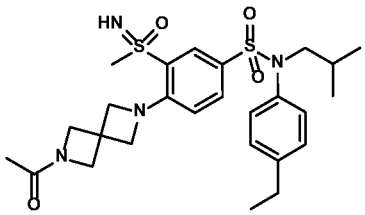
Trifluoroacetic acid (0.28 ml; 3.59 mmol) is added to tert-butyl 6-(4-(N-(4-ethylphenyl)-N-isobutylsulfamoyl)-2-(S-methylsulfonimidoyl)phenyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (55.0 mg; 0.09 mmol) dissolved in dichloromethane (2.75 ml). The reaction medium is stirred for 4 hours at room temperature, concentrated under vacuum, diluted with ethyl acetate, washed with saturated sodium hydrogen carbonate solution and then with saturated sodium chloride solution, dried (Na_2SO_4) and concentrated. The residue is taken up in ether and suction-filtered.

The N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(2,6-diazaspiro[3.3]heptan-2-yl)benzenesulfonamide (44.9 mg; 880%) is obtained in the form of a white solid.

^{1}H NMR (DMSO-d6) δ: 0.83 (dd, J = 6.6, 3.3 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.25 (s, 1H), 1.34 – 1.47 (m, 1H), 2.60 (q, J = 7.6 Hz, 2H), 3.12 (d, J = 1.8 Hz, 3H), 3.23 (dd, J = 7.2, 4.7 Hz, 2H), 3.79 (s, 2H), 4.21 (d, J = 7.3 Hz, 1H), 4.37 (s, 1H), 4.40 (s, 2H), 6.61 (dd, J = 9.1, 3.7 Hz, 1H), 6.94 – 7.01 (m, 2H), 7.15 – 7.23 (m, 2H), 7.41 (dd, J = 8.8, 2.3 Hz, 1H), 7.93 (dd, J = 4.7, 2.3 Hz, 1H).

MS : [M+H] = 492

Example 90: Synthesis of 4-(6-acetyl-2,6-diazaspiro[3.3]heptan-2-yl)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide



Compound 122

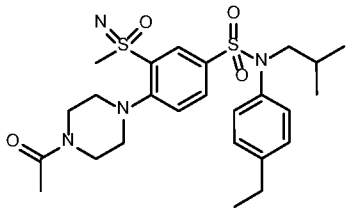
4-Dimethylaminopyridine (0.72 mg; 0.01 mmol) and acetic anhydride (5.6 µl; 0.06 mmol) are added to a solution of 4-oxo-1-piperidin-4-yl-1,2,3,4-tetrahydroquinoline-6-sulfonic acid (4-ethylphenyl)isobutylamide (29.0 mg; 0.06 mmol) in dichloromethane (1.45 ml) cooled to -10°C. The reaction medium is stirred for 30 minutes at room temperature. The reaction medium is hydrolyzed with saturated sodium hydrogen carbonate solution and then extracted with ethyl acetate. The organic phases are combined, washed with brine, dried (Na_2SO_4) and concentrated.

The crude product is purified by preparative HPLC (C18 column, eluent: acetonitrile in water/0.1% of formic acid). The 4-(6-acetyl-2,6-diazaspiro[3.3]heptan-2-yl)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide (23.10 mg; 73%) is obtained in the form of a white solid.

^{1}H NMR (DMSO-d6) δ: 0.84 (dd, J = 6.8, 3.4 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.34 – 1.47 (m, 1H), 1.76 (s, 3H), 2.60 (q, J = 7.6 Hz, 2H), 3.12 (s, 3H), 3.16 – 3.28 (m, 2H), 4.03 (s, 2H), 4.21 (s, 1H), 4.31 (s, 2H), 4.45 (s, 4H), 6.61 (d, J = 8.9 Hz, 1H), 6.98 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 7.43 (dd, J = 8.8, 2.3 Hz, 1H), 7.94 (d, J = 2.3 Hz, 1H).

MS : [M+H] = 533

Example 91: Synthesis of 4-(4-acetylpiperazin-1-yl)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide



Compound 63

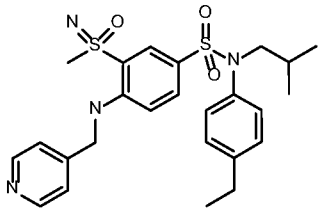
A mixture of 4-bromo-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide (50.0 mg; 0.11 mmol) and 1-piperazin-1-ylethanone (67.68 mg; 0.53 mmol) is stirred over the weekend at 50°C.

The crude product is purified directly by preparative HPLC (C18 column, eluent: acetonitrile in water/0.1% of formic acid). The 4-(4-acetylpiperazin-1-yl)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide (20.0 mg; 36%) is obtained in the form of a white solid.

^{1}H NMR (DMSO-d6) δ: 0.85 (dd, J = 6.7, 3.5 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.44 (dt, J = 13.7, 6.9 Hz, 1H), 2.61 (q, J = 7.6 Hz, 2H), 3.04 (dq, J = 23.9, 5.3 Hz, 4H), 3.34 (d, J = 1.2 Hz, 3H), 3.61 (d, J = 5.4 Hz, 4H), 4.57 (d, J = 1.4 Hz, 1H), 6.97 – 7.05 (m, 2H), 7.17 – 7.25 (m, 2H), 7.62 (d, J = 8.4 Hz, 1H), 7.71 (dd, J = 8.4, 2.3 Hz, 1H), 8.14 (d, J = 2.3 Hz, 1H).

MS : [M+H] = 521

Example 92: Synthesis of N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((pyridin-4-ylmethyl)amino)benzenesulfonamide



Compound 64

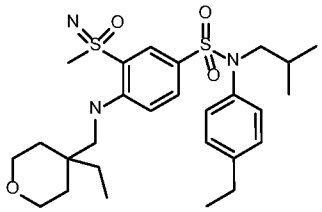
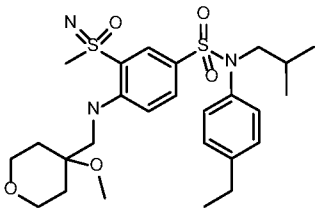
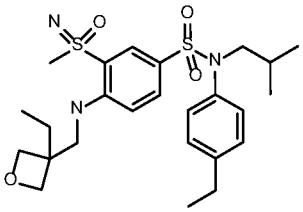
A mixture of 4-bromo-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide (50.0 mg; 0.11 mmol) and 4-picolylamine (53.62 µl; 0.53 mmol) is stirred over the weekend at 50°C.

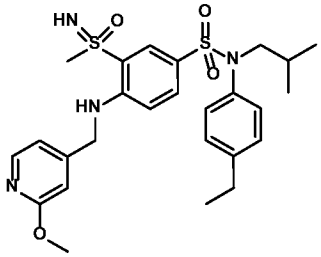
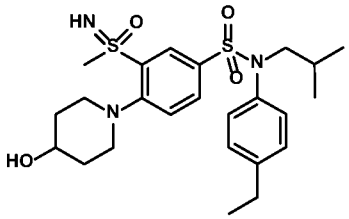
The crude product is purified directly by preparative HPLC (C18 column, eluent: acetonitrile in water/0.1% of formic acid). The N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((pyridin-4-ylmethyl)amino)benzenesulfonamide (26.0 mg; 49%) is obtained in the form of a white solid.

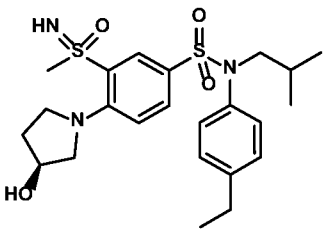
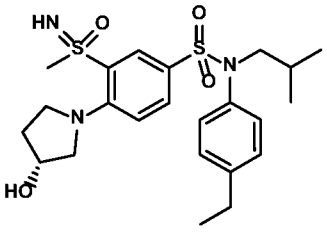
^{1}H NMR (DMSO-d6) δ: 0.83 (d, J = 6.7 Hz, 6H), 1.17 (t, J = 7.6 Hz, 3H), 1.41 (hept, J = 6.7 Hz, 1H), 2.59 (q, J = 7.5 Hz, 2H), 3.11 (s, 3H), 3.23 (dd, J = 7.3, 2.5 Hz, 2H), 4.64 (d, J = 5.9 Hz, 2H), 4.79 (s, 1H), 6.75 (d, J = 8.8 Hz, 1H), 6.97 (d, J = 7.9 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 5.1 Hz, 2H), 7.44 (dd, J = 9.1, 2.4 Hz, 1H), 7.76 (d, J = 2.4 Hz, 1H), 8.21 (t, J = 6.0 Hz, 1H), 8.54 (d, J = 5.2 Hz, 2H).

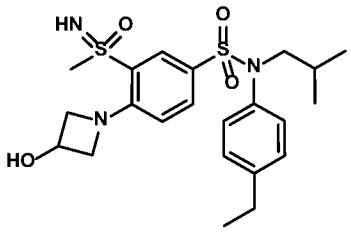
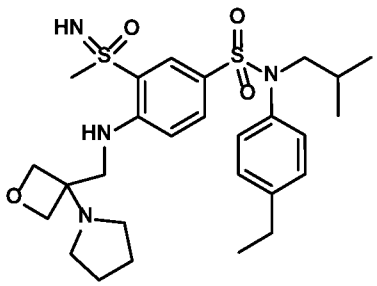
MS : [M+H] = 501

With a procedure similar to that described for example 92, the following are obtained:

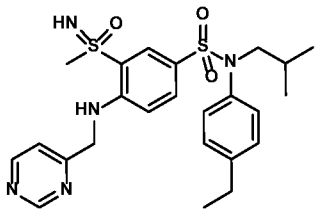
Example 94	 Compound 124	**N-(4-ethylphenyl)-4-(((4-ethyltetrahydro-2H-pyran-4-yl)methyl)amino)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.81 (t, J = 7.6 Hz, 3H), 0.84 (dd, J = 6.7, 3.4 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.38 – 1.57 (m, 7H), 2.61 (q, J = 7.6 Hz, 2H), 3.00 (d, J = 0.8 Hz, 3H), 3.10 – 3.21 (m, 2H), 3.21 – 3.28 (m, 2H), 3.61 (q, J = 6.2 Hz, 4H), 4.85 (s, 1H), 6.99 – 7.04 (m, 3H), 7.16 – 7.24 (m, 2H), 7.51 (dd, J = 8.9, 2.3 Hz, 1H), 7.69 (d, J = 2.3 Hz, 1H), 7.92 (t, J = 4.9 Hz, 1H). MS : [M+H] = 536
Example 95	 Compound 125	**N-(4-ethylphenyl)-N-isobutyl-4-(((4-methoxytetrahydro-2H-pyran-4-yl)methyl)amino)-3-(S-methylsulfonimidoyl)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.84 (dd, J = 6.6, 2.6 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.42 (dt, J = 13.7, 6.9 Hz, 1H), 1.61 (ddd, J = 14.2, 9.0, 4.2 Hz, 2H), 1.75 (t, J = 10.6 Hz, 2H), 2.61 (q, J = 7.6 Hz, 2H), 3.00 (d, J = 0.9 Hz, 3H), 3.13 (s, 3H), 3.19 – 3.32 (m, 4H), 3.57 (ddd, J = 11.1, 8.5, 2.5 Hz, 2H), 3.62 – 3.70 (m, 2H), 4.74 (d, J = 1.1 Hz, 1H), 6.96 (d, J = 9.0 Hz, 1H), 6.99 – 7.04 (m, 2H), 7.16 – 7.22 (m, 2H), 7.51 (dd, J = 8.8, 2.3 Hz, 1H), 7.71 (d, J = 2.2 Hz, 1H), 7.81 (t, J = 4.7 Hz, 1H).
Example 96	 Compound 126	**4-(((3-ethyloxetan-3-yl)methyl)amino)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.85 (dd, J = 6.6, 3.0 Hz, 6H), 0.91 (t, J = 7.4 Hz, 3H), 1.18 (t, J = 7.6 Hz, 3H), 1.42 (dt, J = 13.7, 6.8 Hz, 1H), 1.70 – 1.81 (m, 2H), 2.61 (q, J = 7.6 Hz, 2H), 3.01 (d, J = 0.9 Hz, 3H), 3.21 – 3.30 (m, 2H), 3.37 – 3.56 (m, 2H), 4.36 (d, J = 1.3 Hz, 2H), 4.38 (d, J = 5.0

		Hz, 2H), 4.80 (s, 1H), 6.97 – 7.04 (m, 2H), 7.05 (d, J = 9.0 Hz, 1H), 7.16 – 7.25 (m, 2H), 7.53 (dd, J = 8.8, 2.3 Hz, 1H), 7.71 (d, J = 2.4 Hz, 1H), 7.98 (t, J = 5.1 Hz, 1H). MS : [M+H] = 508
Example 97	 Compound 127	**N-(4-ethylphenyl)-N-isobutyl-4-(((2-methoxypyridin-4-yl)methyl)amino)-3-(S-methylsulfonimidoyl)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.83 (dd, J = 6.6, 1.9 Hz, 6H), 1.17 (t, J = 7.6 Hz, 3H), 1.42 (dq, J = 13.6, 6.7 Hz, 1H), 2.54 – 2.64 (m, 2H), 3.09 (d, J = 0.9 Hz, 3H), 3.24 (dd, J = 7.3, 2.6 Hz, 2H), 3.84 (s, 3H), 4.58 (d, J = 6.0 Hz, 2H), 4.79 (s, 1H), 6.73 – 6.77 (m, 2H), 6.95 – 6.99 (m, 3H), 7.15 – 7.20 (m, 2H), 7.44 (dd, J = 8.8, 2.4 Hz, 1H), 7.76 (d, J = 2.3 Hz, 1H), 8.13 (dd, J = 5.3, 0.7 Hz, 1H), 8.17 (t, J = 6.1 Hz, 1H). MS : [M+H] = 531
Example 98	 Compound 128	**N-(4-ethylphenyl)-4-(4-hydroxypiperidin-1-yl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.85 (dd, J = 6.7, 3.3 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.43 (dt, J = 13.4, 6.6 Hz, 1H), 1.60 (t, J = 9.5 Hz, 2H), 1.82 – 1.91 (m, 2H), 2.61 (q, J = 7.6 Hz, 2H), 2.84 (q, J = 9.2 Hz, 2H), 3.18 – 3.30 (m, 4H), 3.66 (s, 1H), 4.52 (d, J = 1.5 Hz, 1H), 4.71 (d, J = 4.3 Hz, 1H), 6.95 – 7.04 (m, 2H), 7.17 – 7.24 (m, 2H), 7.59 (d, J = 8.4 Hz, 1H), 7.67 (dd, J = 8.4, 2.3 Hz, 1H), 8.12 (d, J = 2.3 Hz, 1H). MS : [M+H] = 494

Example 99	 Compound 129	**N-(4-ethylphenyl)-4-((S)-3-hydroxypyrrolidin-1-yl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.84 (dd, J = 6.6, 1.5 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.42 (dt, J = 13.6, 6.8 Hz, 1H), 1.86 (d, J = 9.6 Hz, 1H), 2.01 (ddd, J = 14.4, 10.7, 4.8 Hz, 1H), 2.60 (q, J = 7.6 Hz, 2H), 3.21 (dd, J = 12.9, 1.3 Hz, 3H), 3.27 – 3.29 (m, 2H), 3.67 (q, J = 8.2 Hz, 1H), 3.73 – 3.85 (m, 1H), 3.91 (dd, J = 10.8, 4.5 Hz, 1H), 4.01 (d, J = 1.8 Hz, 1H), 4.28 (d, J = 1.5 Hz, 1H), 4.39 (s, 1H), 5.01 (dd, J = 19.6, 3.4 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 7.12 (dd, J = 12.6, 8.9 Hz, 1H), 7.20 (d, J = 8.4 Hz, 2H), 7.43 (dd, J = 8.9, 2.4 Hz, 1H), 8.05 (d, J = 2.4 Hz, 1H). MS : [M+H] = 480
Example 100	 Compound 130	**N-(4-ethylphenyl)-4-((R)-3-hydroxypyrrolidin-1-yl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.84 (dd, J = 6.6, 1.5 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.42 (dt, J = 13.6, 6.8 Hz, 1H), 1.86 (d, J = 9.6 Hz, 1H), 2.01 (ddd, J = 14.4, 10.7, 4.8 Hz, 1H), 2.60 (q, J = 7.6 Hz, 2H), 3.21 (dd, J = 12.9, 1.3 Hz, 3H), 3.27 – 3.29 (m, 2H), 3.67 (q, J = 8.2 Hz, 1H), 3.73 – 3.85 (m, 1H), 3.91 (dd, J = 10.8, 4.5 Hz, 1H), 4.01 (d, J = 1.8 Hz, 1H), 4.28 (d, J = 1.5 Hz, 1H), 4.39 (s, 1H), 5.01 (dd, J = 19.6, 3.4 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 7.12 (dd, J = 12.6, 8.9 Hz, 1H), 7.20 (d, J = 8.4 Hz, 2H), 7.43 (dd, J = 8.9, 2.4 Hz, 1H), 8.05 (d, J = 2.4 Hz, 1H). MS : [M+H] = 480

Example 101	 Compound 131	**N-(4-ethylphenyl)-4-(3-hydroxyazetidin-1-yl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.84 (dd, J = 6.6, 3.1 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.41 (dt, J = 14.1, 7.0 Hz, 1H), 2.60 (q, J = 7.7 Hz, 2H), 3.11 (d, J = 1.3 Hz, 3H), 3.24 (dd, J = 7.3, 4.5 Hz, 2H), 4.02 (dd, J = 10.5, 5.7 Hz, 2H), 4.20 (d, J = 1.5 Hz, 1H), 4.50 (s, 2H), 5.71 (s, 1H), 6.63 (d, J = 8.9 Hz, 1H), 6.99 (d, J = 8.4 Hz, 2H), 7.16 – 7.25 (m, 2H), 7.40 (dd, J = 8.8, 2.3 Hz, 1H), 7.94 (d, J = 2.4 Hz, 1H). MS: [M+H] = 466
Example 102	 Compound 132	**N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(((3-(pyrrolidin-1-yl)oxetan-3-yl)methyl)amino)benzenesulfonamide** ^{1}H NMR (DMSO-d6) δ: 0.84 (dd, J = 6.6, 2.0 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.42 (p, J = 6.9 Hz, 1H), 1.76 (d, J = 6.2 Hz, 4H), 2.61 (q, J = 7.6 Hz, 2H), 2.73 (q, J = 5.9 Hz, 4H), 2.96 (d, J = 0.9 Hz, 3H), 3.25 (dd, J = 7.4, 1.6 Hz, 2H), 3.55 – 3.72 (m, 2H), 4.29 (dd, J = 8.5, 6.6 Hz, 2H), 4.59 (s, 1H), 4.78 (d, J = 6.7 Hz, 2H), 6.97 – 7.02 (m, 3H), 7.17 – 7.23 (m, 2H), 7.53 (dd, J = 8.8, 2.4 Hz, 1H), 7.72 (d, J = 2.3 Hz, 1H), 7.85 (t, J = 4.2 Hz, 1H). MS : [M+H] = 549

Example 103: Synthesis of N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((pyrimidin-4-ylmethyl)amino)benzenesulfonamide



Compound 133

4-Bromo-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide (50.0 mg; 0.11 mmol) and 4-(aminomethyl)pyrimidine (34.6 mg; 0.32 mmol) are introduced into a microwave tube. The reaction medium is stirred for 30 minutes at 100°C under microwave irradiation.

The crude product is purified by preparative HPLC (C18 column, eluent: acetonitrile in water/0.1% of formic acid). The N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((pyrimidin-4-ylmethyl)amino)benzenesulfonamide (15.0 mg; 28%) is obtained in the form of a beige-colored solid.

^{1}H NMR (DMSO-d6) δ: 0.83 (dd, J = 6.6, 1.5 Hz, 6H), 1.17 (t, J = 7.6 Hz, 3H), 1.41 (dt, J = 13.7, 6.8 Hz, 1H), 2.60 (q, J = 7.6 Hz, 2H), 3.11 (d, J = 1.0 Hz, 3H), 3.24 (dd, J = 7.4, 1.4 Hz, 2H), 4.72 (dd, J = 5.7, 1.9 Hz, 2H), 4.75 – 4.79 (m, 1H), 6.81 (d, J = 8.9 Hz, 1H), 6.93 – 7.01 (m, 2H), 7.15 – 7.23 (m, 2H), 7.47 (dd, J = 8.8, 2.3 Hz, 1H), 7.50 (dd, J = 5.2, 1.4 Hz, 1H), 7.77 (d, J = 2.3 Hz, 1H), 8.35 (t, J = 5.9 Hz, 1H), 8.77 (d, J = 5.2 Hz, 1H), 9.17 (d, J = 1.4 Hz, 1H).

MS : [M+H] = 502

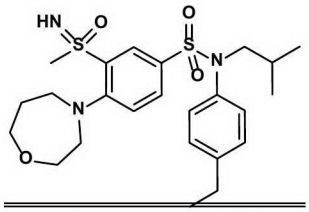
Example 107: Synthesis of N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(1,4-oxazepan-4-yl)benzenesulfonamide

4-Bromo-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide (50.0 mg; 0.11 mmol) is added to 1,4-oxazepane (16.0 mg; 0.16 mmol) and N,N-diisopropylethylamine (0.11 ml; 0.63 mmol) dissolved in dimethyl sulfoxide (2 ml).

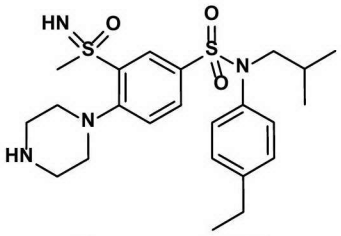
The reaction medium is heated at a temperature of 150°C for 20 minutes with microwave irradiation. The reaction medium is hydrolyzed with 1N hydrochloric acid solution and diluted, and then extracted with ethyl acetate. The organic phases are combined, washed with brine, dried (Na_2SO_4) and concentrated under vacuum.

The crude product is purified directly by preparative HPLC (C18 column, eluent: acetonitrile in water/0.1% of formic acid). The N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(1,4-oxazepan-4-yl)benzenesulfonamide (23.8 mg; 46%) is obtained in the form of a white solid.

^{1}H NMR (Methanol-d4) δ: 0.93 (d, J = 6.7 Hz, 6H), 1.25 (t, J = 7.6 Hz, 3H), 1.49 – 1.64 (m, 1H), 2.09 (p, J = 6.0 Hz, 2H), 2.67 (q, J = 7.6 Hz, 2H), 3.39 (d, J = 7.3 Hz, 2H), 3.48 (s, 3H), 3.90 (dd, J = 6.2, 3.5 Hz, 2H), 3.95 (t, J = 6.1 Hz, 2H), 6.98 – 7.05 (m, 2H), 7.17 – 7.24 (m, 2H), 7.66 (d, J = 8.4 Hz, 1H), 7.74 (dd, J = 8.4, 2.3 Hz, 1H), 8.23 (d, J = 2.2 Hz, 1H).
MS : [M+H] = 494

Example 107	 Compound 137	**N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(1,4-oxazepan-4-yl)benzenesulfonamide** ^{1}H NMR (Methanol-d4) δ: 0.93 (d, J = 6.7 Hz, 6H), 1.25 (t, J = 7.6 Hz, 3H), 1.49 – 1.64 (m, 1H), 2.09 (p, J = 6.0 Hz, 2H), 2.67 (q, J = 7.6 Hz, 2H), 3.39 (d, J = 7.3 Hz, 2H), 3.48 (s, 3H), 3.90 (dd, J = 6.2, 3.5 Hz, 2H), 3.95 (t, J = 6.1 Hz, 2H), 6.98 – 7.05 (m, 2H), 7.17 – 7.24 (m, 2H), 7.66 (d, J = 8.4 Hz, 1H), 7.74 (dd, J = 8.4, 2.3 Hz, 1H), 8.23 (d, J = 2.2 Hz, 1H). MS : [M+H] = 494

<u>Example 110: Synthesis of N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(piperazin-1-yl)benzenesulfonamide</u>


Compound 140

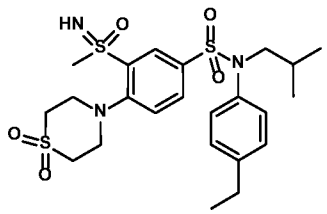
Piperazine (18.2 mg; 0.21 mmol) is added to a solution of 4-bromo-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide (50.00 mg; 0.11 mmol) in N,N-dimethylformamide (0.20 µl). The reaction medium is stirred overnight at 60°C. The crude product is purified by preparative HPLC (C18 column, eluent: acetonitrile in water/0.2% of ammonium carbonate). The N-(4-ethylphenyl)-N-

isobutyl-3-(S-methylsulfonimidoyl)-4-(piperazin-1-yl)benzenesulfonamide (30.0 mg; 53%) is obtained in the form of a white solid.

^{1}H NMR (DMSO-d6) δ: 0.85 (dd, J = 6.6, 3.5 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.43 (dt, J = 13.8, 6.9 Hz, 1H), 2.61 (q, J = 7.6 Hz, 2H), 2.87 (t, J = 4.7 Hz, 4H), 2.99 (d, J = 5.0 Hz, 4H), 3.35 (s, 3H), 4.53 (s, 1H), 6.97 – 7.04 (m, 2H), 7.21 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.5 Hz, 1H), 7.69 (dd, J = 8.4, 2.3 Hz, 1H), 8.14 (d, J = 2.3 Hz, 1H).

MS : [M+H] 479

Example 111: Synthesis of N-(4-ethylphenyl)-4-(((3-hydroxycyclobutyl)methyl)amino)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide



Compound 141

3-Chloroperbenzoic acid (24.4 mg; 0.11 mmol) is added at 0°C to N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-thiomorpholinobenzenesulfonamide (27.0 mg; 0.05 mmol) dissolved in dichloromethane (250 µl). The reaction medium is stirred for 5 hours at room temperature, hydrolyzed with 1N sodium hydroxide solution and extracted with dichloromethane. The organic phases are combined, washed with water, dried ($MgSO_4$) and concentrated under vacuum.

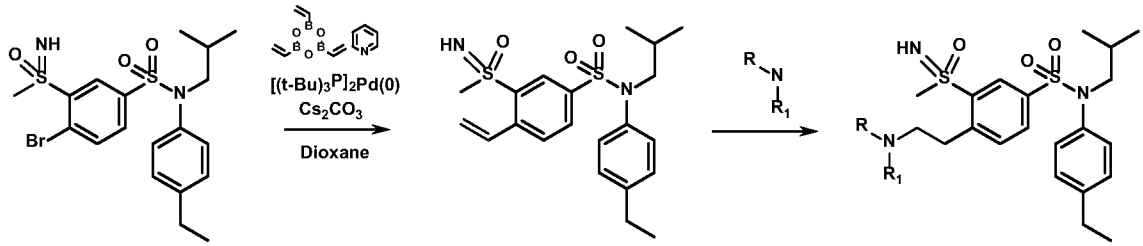
The crude product is purified by preparative HPLC (C18 column, eluent: acetonitrile in water/0.1% of formic acid). The 4-(1,1-dioxidothiomorpholino)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide (8.0 mg; 28%) is obtained in the form of an off-white solid.

^{1}H NMR (DMSO-d6) δ: 0.86 (d, J = 6.6 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.43 (dt, J = 13.5, 6.8 Hz, 1H), 2.61 (q, J = 7.6 Hz, 2H), 3.31 (d, J = 7.8 Hz, 2H), 3.35-3.40 (m, 7H), 3.49 (dd, J = 6.8, 3.4 Hz, 4H), 6.94 – 7.05 (m, 2H), 7.17 – 7.25 (m, 2H), 7.83 – 7.91 (m, 3H).

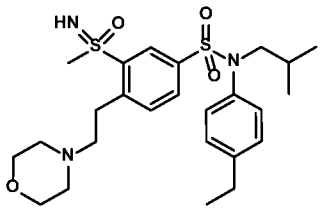
MS : [M+H] 529

Part III: Synthesis of sulfur-based sulfonamides via reaction scheme 3

Reaction scheme 3

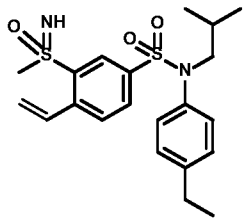


Example 112: Synthesis of N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(2-morpholinoethyl)benzenesulfonamide



Compound 65

1. Synthesis of intermediate 112.1



N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-vinylbenzenesulfonamide

Cesium carbonate (206.45 mg; 0.63 mmol), tert-butyl N-(2-oxiranylmethyl)carbamate (101.66 mg; 0.42 mmol) and water (0.40 ml) are added to a solution of 4-bromo-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide (100.0 mg; 0.21 mmol) in 1,4-dioxane (1.2 ml). The reaction medium is degassed under argon for 10 minutes, followed by addition of bis(tri-tert-butylphosphine)palladium(0) (10.79 mg; 0.02 mmol; 0.10 eq.). The reaction medium is stirred for 2 hours at 90°C, filtered through Celite and rinsed with ethyl acetate. The organic phase is washed with saturated sodium hydrogen carbonate solution and then with water, dried ($MgSO_4$), filtered and concentrated to dryness. The crude product is purified by chromatography on silica gel (eluent: heptane/ethyl acetate, from 0 to 100% of ethyl acetate). The N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-vinylbenzenesulfonamide (70.0 mg; 79%) is obtained in the form of a colorless oil with a compliant ^1H NMR.

MS : [M+H] = 422

2. Synthesis of the compound N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(2-morpholinoethyl)benzenesulfonamide

A mixture of N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-vinylbenzenesulfonamide (70.0 mg; 0.17 mmol; 1.00 eq.) and morpholine (1.0 ml; 11.59 mmol) is stirred for 30 minutes at room temperature.

The crude product is purified by preparative HPLC (C18 column, eluent: acetonitrile in water/0.1% of formic acid). The N-(4-ethylphenyl)-N-isobutyl-3-(S-

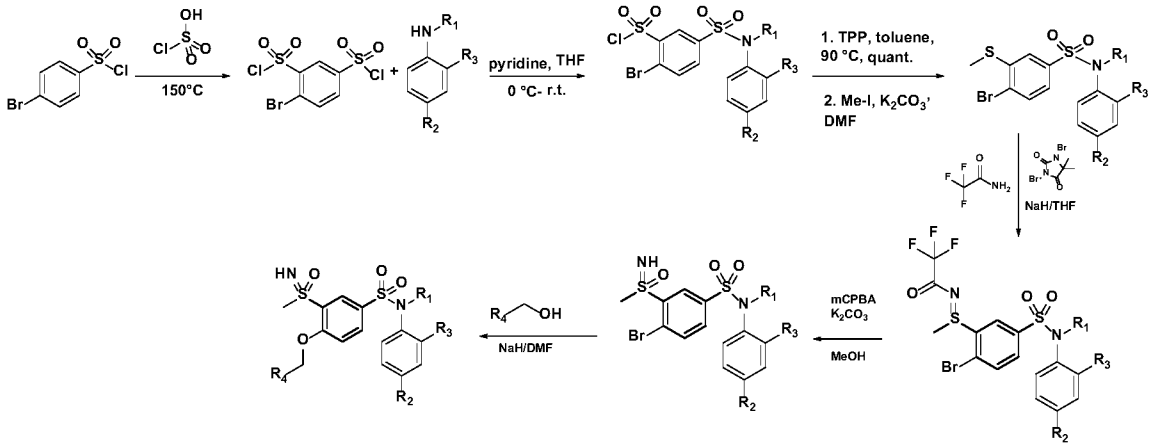
methylsulfonimidoyl)-4-(2-morpholinoethyl)benzenesulfonamide (25.00 mg; 29.59%) is obtained in the form of an ocher-colored powder.

^{1}H NMR (DMSO-d6) δ: 1.10 (d, J = 6.5 Hz, 6H), 1.43 (t, J = 7.6 Hz, 3H), 1.69 (dt, J = 13.4, 6.8 Hz, 1H), 2.71 (d, J = 5.4 Hz, 2H), 2.83 – 2.90 (m, 2H), 3.36 (s, 8H), 3.84 (t, J = 4.5 Hz, 3H), 4.79 (s, 1H), 7.24 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.95 (s, 2H), 8.32 (s, 1H).

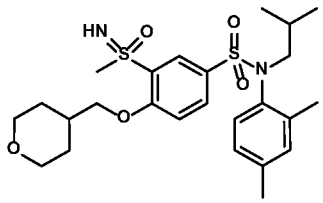
MS : [M+H] = 508

Part IV: Synthesis of sulfur-based sulfonamides via reaction scheme 4

Reaction scheme 4

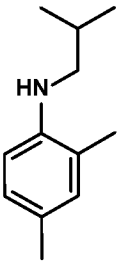


Example 113: Synthesis of N-(2,4-dimethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide



Compound 142

1. Synthesis of intermediate 113.1



(2,4-dimethylphenyl)isobutylamine

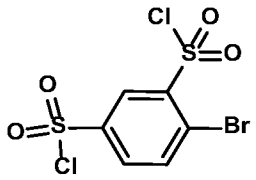
A solution of 2,4-dimethylaniline (30 ml; 0.24 mol) and of isobutyraldehyde (20 ml; 0.22 mol) in tetrahydrofuran (320 ml) is stirred for 30 minutes at room temperature, and sodium triacetoxyborohydride (70 g; 0.33 mol) is then added portionwise. The reaction medium is stirred for 3 hours at room temperature, hydrolyzed and extracted with ethyl acetate. The organic phases are combined, washed with saturated sodium chloride solution and dried ($MgSO_4$).

The solvents are evaporated off. The crude product is chromatographed on silica gel (eluent: heptane/ethyl acetate, from 0 to 10% of ethyl acetate).

The (2,4-dimethylphenyl)isobutylamine (29.9 g; 77%) is obtained in the form of a yellow oil with a compliant NMR.

MS : [M+H] = 177

2. Synthesis of intermediate 113.2

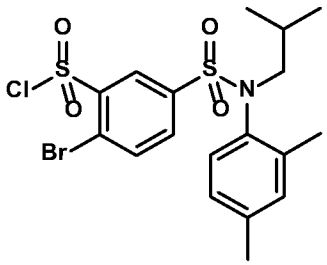


4-bromobenzene-1,3-disulfonyl dichloride

A mixture of 4-bromobenzenesulfonyl chloride (50 g; 0.20 mol) and of chlorosulfonic acid (260 ml; 3.91 mol) is stirred for 6 hours at 150°C. The reaction medium is poured slowly and cautiously onto a mixture of water and ice and is extracted with dichloromethane. The organic phases are combined, dried ($MgSO_4$), filtered and concentrated. The 4-bromobenzene-1,3-disulfonyl dichloride (54 g; 78%) is obtained in the form of a grayish powder with a compliant NMR.

MS : [M+H] = 177

3. Synthesis of intermediate 113.3

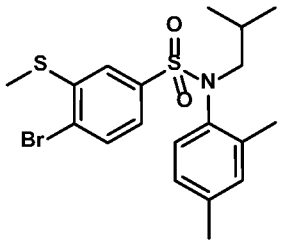


2-bromo-5-[(2,4-dimethylphenyl)isobutylsulfamoyl]benzenesulfonyl chloride

4-Bromobenzene-1,3-disulfonyl dichloride (1.0 g; 2.82 mmol) dissolved in tetrahydrofuran (5 ml) is added to (2,4-dimethylphenyl)isobutylamine (0.50 g; 2.82 mmol) and pyridine (1.4 ml; 17.0 mmol) dissolved in tetrahydrofuran (20 ml). The reaction medium is stirred for 16 hours at room temperature. The reaction medium is hydrolyzed and then extracted with ethyl acetate. The organic phases are combined, washed with aqueous 1M hydrochloric acid solution and then with saturated NaCl solution, dried (Na_2SO_4) and concentrated.

The 2-bromo-5-[(2,4-dimethylphenyl)isobutylsulfamoyl]benzenesulfonyl chloride (1.23 g; 88%) is obtained in the form of a yellow oil with a compliant NMR.

4. Synthesis of intermediate 113.4



4-bromo-N-(4-ethylphenyl)-N-isobutyl-3-methylsulfanylbenzenesulfonamide

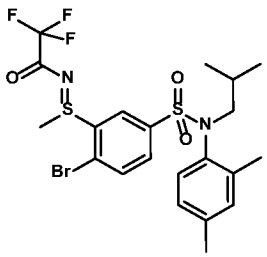
2-Bromo-5-[(2,4-dimethylphenyl)isobutylsulfamoyl]benzenesulfonyl chloride (1.67 g; 3.37 mmol) dissolved in toluene (8 ml) is added slowly to triphenylphosphine (2.66 g; 10.12 mmol) suspended in toluene (17 ml). The reaction medium is stirred for 4 hours at 90°C. The reaction medium is concentrated under vacuum and dissolved in N,N-dimethylformamide (14.5 ml) without purification, and potassium carbonate (0.51 g; 3.72 mmol) and iodomethane (0.32 ml; 5.08 mmol) are then added. The reaction medium is stirred for 20 minutes at room temperature, hydrolyzed and extracted with ethyl acetate. The organic phases are combined, washed with saturated sodium chloride solution and dried (Na_2SO_4).

The solvents are evaporated off. The crude product is chromatographed on silica gel (eluent: heptane/ethyl acetate, from 0 to 10% of ethyl acetate).

The 4-bromo-N-(4-ethylphenyl)-N-isobutyl-3-methylsulfanylbenzenesulfonamide (775.30 mg; 52%) is obtained in the form of a white solid with a compliant NMR.

MS : [M-H] = 441

5. Synthesis of intermediate 113.5



(E)-N-((2-bromo-5-(N-(2,4-dimethylphenyl)-N-isobutylsulfamoyl)phenyl)(methyl)-λ^4-sulfanylidene)-2,2,2-trifluoroacetamide

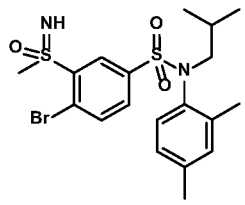
4-Bromo-N-(2,4-dimethylphenyl)-N-isobutyl-3-methylsulfanylbenzenesulfonamide (755.0 mg; 1.71 mmol) and 2,2,2-trifluoroacetamide (289.34 mg; 2.56 mmol) dissolved in tetrahydrofuran (1.51 ml) are added slowly to 60% sodium hydride (61.43 mg; 1.54 mmol) suspended in tetrahydrofuran (3.78 ml) at 0-5°C. 1,3-Dibromo-5,5-dimethylhydantoin (732 mg; 2.56 mmol) dissolved in tetrahydrofuran (1.5 ml) is then added.

The medium is stirred for 1 hour at room temperature, hydrolyzed by addition of saturated sodium hydrogen carbonate solution, and extracted with ethyl acetate. The organic phases are combined and then washed with 25% sodium sulfite solution and then twice with saturated sodium chloride solution and dried (Na_2SO_4). The solvents are evaporated off.

The crude product is chromatographed on silica gel (eluent: heptane/ethyl acetate, from 0 to 50% of ethyl acetate). The (E)-N-((2-bromo-5-(N-(2,4-dimethylphenyl)-N-isobutylsulfamoyl)phenyl)(methyl)-λ4-sulfanylidene)-2,2,2-trifluoroacetamide (233.0 mg; 25%) is obtained in the form of a white powder with a compliant 1H NMR.

MS : [M-H] = 552

6. Synthesis of intermediate 113.6



4-bromo-N-(2,4-dimethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide

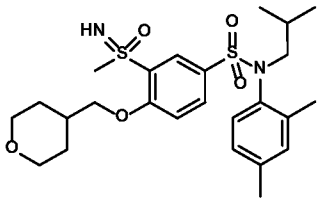
Potassium carbonate (172.30 mg; 1.25 mmol) is added to (E)-N-((2-bromo-5-(N-(4-ethylphenyl)-N-isobutylsulfamoyl)phenyl)(methyl)-λ4-sulfanylidene)-2,2,2-trifluoroacetamide (230.0 mg; 0.42 mmol) dissolved in methanol (2.3 ml), and 3-chloroperoxybenzoic acid (139.7 mg; 0.62 mmol) is then added slowly at 0°C. The

reaction medium is stirred for 3 days at room temperature. The reaction medium is hydrolyzed and then extracted with ethyl acetate. The organic phases are combined, washed with saturated sodium chloride solution and dried (Na_2SO_4). The solvents are evaporated off.

The crude product is chromatographed on silica gel (eluent: heptane/ethyl acetate, from 0 to 80% of ethyl acetate). The 4-bromo-N-(2,4-dimethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide (70.8 mg; 36%) is obtained in the form of a white solid with a compliant NMR.

MS : [M+H] = 475

7. Synthesis of N-(2,4-dimethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide



60% sodium hydride (8.74 mg; 0.22 mmol) is added slowly at a temperature of 0°C to (tetrahydropyran-4-yl)methanol (18.62 mg; 0.16 mmol) dissolved in N,N-dimethylformamide (1.38 ml), followed by 4-bromo-N-(2,4-dimethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide (69.0 mg; 0.15 mmol). The reaction medium is stirred for 2 hours at room temperature and then for 1 hour at 80°C. The reaction medium is hydrolyzed without heating and then extracted with ethyl acetate. The organic phases are combined, washed with saturated sodium chloride solution and dried (Na_2SO_4). The solvents are evaporated off.

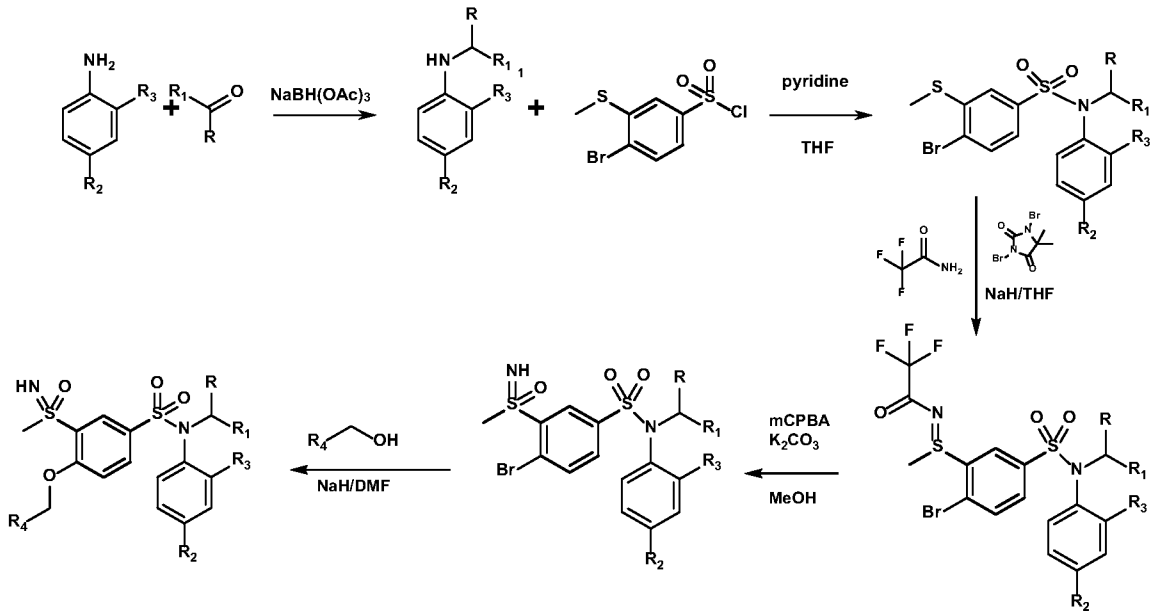
The crude product is purified by preparative HPLC (C18 column, eluent: acetonitrile in water/0.1% of formic acid). The N-(2,4-dimethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide (44.81 mg; 59.54%) is obtained in the form of a white solid.

^{1}H NMR (DMSO-d6) δ: 0.76 (dd, J = 6.8, 3.2 Hz, 3H), 0.82 – 0.91 (m, 1H), 0.95 (t, J = 6.7 Hz, 3H), 1.25 (q, J = 3.6, 2.6 Hz, 1H), 1.40 (p, J = 4.2 Hz, 2H), 1.43 (s, 1H), 1.75 (d, J = 7.5 Hz, 1H), 2.23 – 2.32 (m, 6H), 3.06 (ddd, J = 21.2, 13.1, 4.6 Hz, 1H), 3.20 (dd, J = 2.7, 1.2 Hz, 3H), 3.35 – 3.44 (m, 2H), 3.87 – 3.95 (m, 2H), 4.12 (dd, J = 6.3, 3.6 Hz, 2H), 4.45 (dd, J = 50.6, 1.5 Hz, 1H), 6.58 (dd, J = 16.3, 8.1 Hz, 1H), 6.94 (dd, J = 8.1, 2.0 Hz, 1H), 7.13 (s, 1H), 7.41 (d, J = 8.9 Hz, 1H), 7.74 (td, J = 8.6, 2.5 Hz, 1H), 8.05 (dd, J = 4.9, 2.4 Hz, 1H)

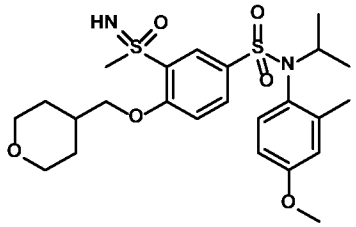
MS : [M+H] = 509

Part V: Synthesis of sulfur-based sulfonamides via reaction scheme 5

Reaction scheme 5

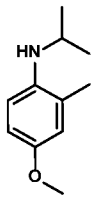

NaBH(OAc)3
pyridine
THF
NaH/THF
mCPBA
K2CO3
MeOH
NaH/DMF

Example 114: Synthesis of N-isopropyl-N-(4-methoxy-2-methylphenyl)-3-(S-methylsulfonimidoyl)-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide



Compound 143

1. Synthesis of intermediate 114.1

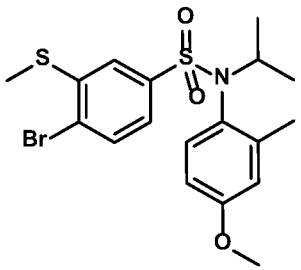


Isopropyl(4-methoxy-2-methylphenyl)amine

Sodium triacetoxyborohydride (4.63 g; 21.9 mmol) is added to a solution of 4-methoxy-2-methylaniline (2.0 g; 14.6 mmol) in acetone (20 ml). The reaction medium is heated for 10 minutes at a temperature of 70°C under microwave irradiation. The reaction medium is poured onto ice and extracted with dichloromethane. The organic phases are combined, washed with saturated sodium chloride solution, dried ($MgSO_4$), filtered and concentrated. The crude product is chromatographed on silica gel (eluent: heptane/ethyl acetate, from 0 to 15% of ethyl acetate). The isopropyl(4-methoxy-2-methylphenyl)amine (1.43 g; 55%) is obtained in the form of a yellow oil with a compliant NMR.

MS : [M+H] = 180

2. Synthesis of intermediate 114.2



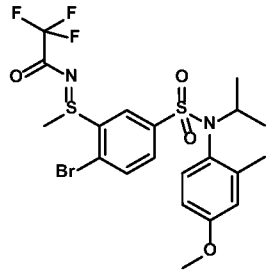
4-bromo-N-isopropyl-N-(4-methoxy-2-methylphenyl)-3-methylsulfanylbenzenesulfonamide

4-Bromo-3-(methylthio)benzene-1-sulfonyl chloride (500 mg; 1.57 mmol) is added to isopropyl(4-methoxy-2-methylphenyl)amine (290 mg; 1.62 mmol) and pyridine (2.4 ml). The reaction medium is heated for 20 minutes at a temperature of 100°C under microwave irradiation, hydrolyzed and extracted with ethyl acetate. The organic phases are combined, washed with 1N hydrochloric acid solution and then with saturated sodium chloride solution and dried ($MgSO_4$). The solvents are evaporated off.

The crude product is chromatographed on silica gel (eluent: heptane/ethyl acetate, from 0 to 40% of ethyl acetate). The 4-bromo-N-isopropyl-N-(4-methoxy-2-methylphenyl)-3-methylsulfanylbenzenesulfonamide (570 mg; 81%) is obtained in the form of a yellow oil with a compliant NMR.

MS : [M+H] = 444

3. Synthesis of intermediate 114.3



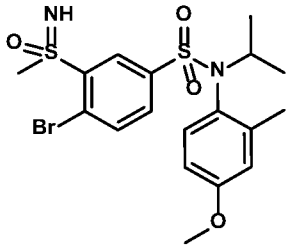
(E)-N-((2-bromo-5-(N-isopropyl-N-(4-methoxy-2-methylphenyl)sulfamoyl)phenyl)(methyl)-λ^4-sulfanylidene)-2,2,2-trifluoroacetamide

4-Bromo-N-isopropyl-N-(4-methoxy-2-methylphenyl)-3-methylsulfanylbenzenesulfonamide (565mg; 1.27 mmol) and 2,2,2-trifluoroacetamide (215.6 mg; 1.91 mmol) dissolved in tetrahydrofuran (1.1 ml) are added slowly to 60% sodium hydride (45.8 mg; 1.14 mmol) suspended in tetrahydrofuran (2.8 ml) at 0-5°C, followed by addition of the solution of 1,3-dibromo-5,5-dimethylhydantoin (545.3 mg; 1.91 mmol) in tetrahydrofuran (1.13 ml). The medium is stirred for 2 hours at room temperature, hydrolyzed by addition of 10% citric acid solution and then extracted with ethyl acetate. The organic phases are combined, then washed with 25% sodium sulfite solution and then twice with saturated sodium chloride solution and dried (Na_2SO_4). The solvents are evaporated off.

The crude product is chromatographed on silica gel (eluent: heptane/ethyl acetate, from 0 to 60% of ethyl acetate). The (E)-N-((2-bromo-5-(N-isopropyl-N-(4-methoxy-2-methylphenyl)sulfamoyl)phenyl)(methyl)-λ^4-sulfanylidene)-2,2,2-trifluoroacetamide (706 mg; 100%) is obtained in the form of a colorless oil with a compliant NMR.

MS : [M-H] = 557

4. Synthesis of intermediate 114.4



4-bromo-N-isopropyl-N-(4-methoxy-2-methylphenyl)-3-(S-methylsulfonimidoyl)benzenesulfonamide

Potassium carbonate (549 mg; 3.97 mmol) is added to (E)-N-((2-bromo-5-(N-isopropyl-N-(4-methoxy-2-methylphenyl)sulfamoyl)phenyl)(methyl)-λ^4-sulfanylidene)-2,2,2-trifluoroacetamide (735 mg; 1.32 mmol) dissolved in methanol (7.4 ml), and 3-chloroperoxybenzoic acid (445 mg; 1.98 mmol) is then added slowly at 0°C. The reaction medium is stirred for 2 hours at room temperature, hydrolyzed and then extracted with ethyl acetate. The organic phases are combined, washed with saturated sodium chloride solution and dried ($MgSO_4$). The solvents are evaporated off.

The crude product is chromatographed on silica gel (heptane/ethyl acetate, from 40 to 80% of ethyl acetate). The 4-bromo-N-isopropyl-N-(4-methoxy-2-methylphenyl)-3-(S-methylsulfonimidoyl)benzenesulfonamide (211.6 mg; 34%) is obtained in the form of a white solid with a compliant NMR.

MS : [M+H] = 477

5. Synthesis of N-isopropyl-N-(4-methoxy-2-methylphenyl)-3-(S-methylsulfonimidoyl)-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide

60% sodium hydride (12.6 mg; 0.32 mmol) is added slowly at 0°C to (tetrahydropyran-4-yl)methanol (26.8 mg; 0.23 mmol) dissolved in N,N-dimethylformamide (2 ml), followed by 4-bromo-N-isopropyl-N-(4-methoxy-2-methylphenyl)-3-(S-methylsulfonimidoyl)benzenesulfonamide (100 mg; 0.21 mmol). The reaction medium is stirred for 1 hour at room temperature and for 90 minutes at a temperature of 60°C, and then hydrolyzed and extracted with ethyl acetate. The

organic phases are combined and then washed with saturated sodium chloride solution and dried (Na_2SO_4). The solvents are evaporated off.

The product is chromatographed on silica gel (eluent: dichloromethane/methanol from 0 to 10% of methanol).

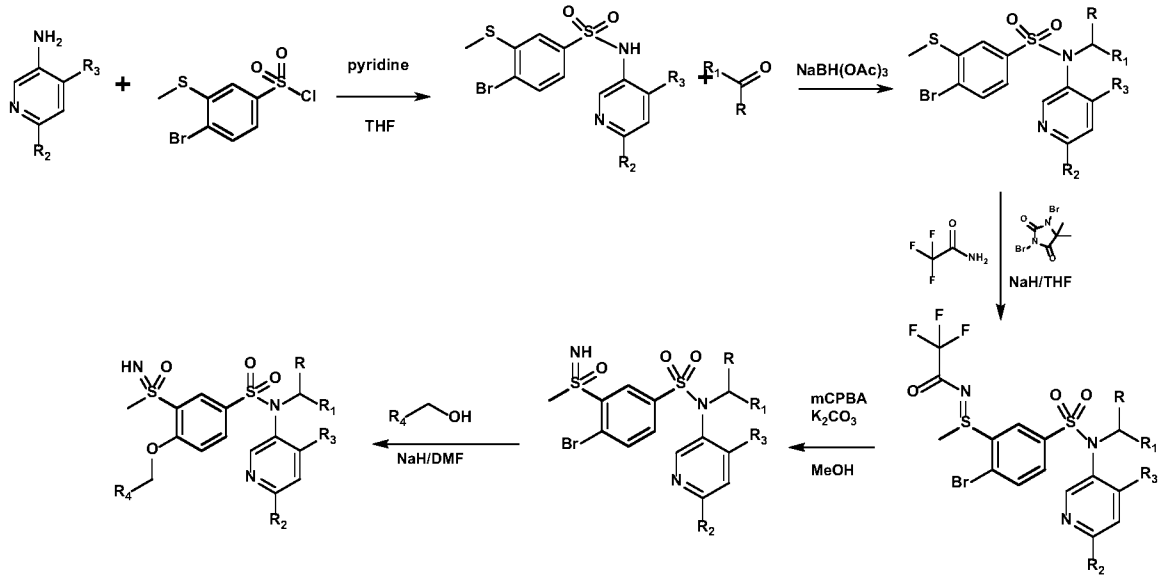
The N-isopropyl-N-(4-methoxy-2-methylphenyl)-3-(S-methylsulfonimidoyl)-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide (76.2 mg; 71%) is obtained in the form of a white solid.

^{1}H NMR (DMSO-d6) δ: 0.79 – 0.93 (m, 4H), 0.98 (dd, J = 6.8, 2.1 Hz, 3H), 1.26 (dd, J = 10.8, 4.6 Hz, 2H), 1.41 (tdd, J = 12.3, 7.6, 4.4 Hz, 2H), 1.75 (t, J = 11.7 Hz, 2H), 2.10 (d, J = 8.7 Hz, 1H), 2.25 (d, J = 8.3 Hz, 3H), 3.19 (d, J = 1.2 Hz, 3H), 3.33 – 3.43 (m, 2H), 3.82 – 3.99 (m, 2H), 4.02 – 4.19 (m, 2H), 4.34 – 4.55 (m, 2H), 6.57 – 6.76 (m, 2H), 6.92 (t, J = 2.2 Hz, 1H), 7.41 (dd, J = 8.8, 2.9 Hz, 1H), 7.84 (dd, J = 8.7, 2.4 Hz, 1H), 8.14 (t, J = 2.7 Hz, 1H)

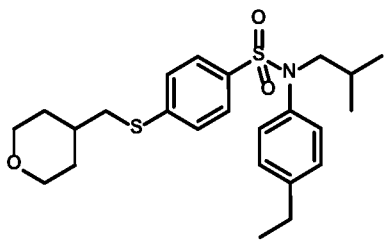
MS : [M+H] = 511

Part VI: Synthesis of sulfur-based sulfonamides via reaction scheme 6

Reaction scheme 6

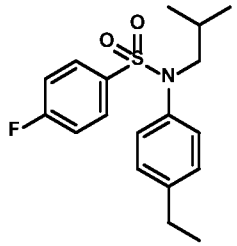


Example 116: Synthesis of N-(4-ethylphenyl)-N-isobutyl-4-(tetrahydropyran-4-ylmethylsulfanyl)benzenesulfonamide



Compound 68

1. Synthesis of intermediate 116.1



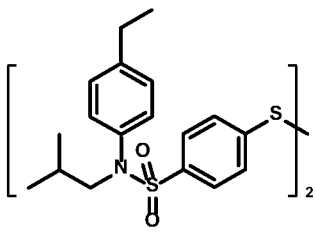
N-(4-ethylphenyl)-4-fluoro-N-isobutylbenzenesulfonamide

4-Fluorobenzenesulfonyl chloride (2.78 g; 14.27 mmol) is added to the (4-ethylphenyl)isobutylamine (2.3 g; 12.28 mmol) and diisopropylamine (5.5 ml; 67.69 mmol) dissolved in tetrahydrofuran (25 ml). The reaction medium is stirred for 16 hours at room temperature, hydrolyzed and extracted with ethyl acetate. The organic phases are combined, washed with saturated ammonium chloride solution and then with brine, dried (Na_2SO_4) and concentrated.

The crude product is chromatographed on silica gel (eluent: heptane/ethyl acetate, from 0 to 10% of ethyl acetate). The N-(4-ethylphenyl)-4-fluoro-N-isobutylbenzenesulfonamide (2.09 g; 48%) is obtained in the form of an orange-yellow solid with a compliant ^1H NMR.

MS : [M+H] = 336

2. Synthesis of intermediate 116.2



Bis[4-[(4-ethylphenyl)isobutylsulfamoyl]thiobenzene] disulfide

A mixture of N-(4-ethylphenyl)-4-fluoro-N-isobutylbenzenesulfonamide (1.0 g; 2.98 mmol) and sodium hydrogen sulfide (2.1 g; 37.26 mmol) in 1-methyl-2-pyrrolidinone (4 ml) is stirred for 2 hours at 80°C and then for 16 hours at room temperature. The reaction medium is diluted with ethyl acetate and acidified by

addition of concentrated HCl and then extracted. The organic phases are combined, washed with water, dried ($MgSO_4$), filtered and concentrated to dryness. The bis[4-[(4-ethylphenyl)isobutylsulfamoyl]thiobenzene] disulfide (1.04 g; 50%) obtained is used directly in the next reaction.

MS : [M+H] = 698

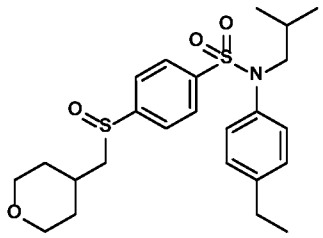
3. Synthesis of N-(4-ethylphenyl)-N-isobutyl-4-(tetrahydropyran-4-ylmethylsulfanyl)benzenesulfonamide

Potassium carbonate (0.41 g; 2.96 mmol) is added to a solution of bis[4-[(4-ethylphenyl)isobutylsulfamoyl]thiobenzene] disulfide (1.03 g; 1.48 mmol) in N,N-dimethylformamide (15 ml). The reaction medium is stirred for 5 minutes, followed by addition of 4-(bromomethyl)tetrahydropyran (0.53 g; 2.96 mmol) and then sodium formaldehyde sulfoxylate (0.60 g; 4.44 mmol) and water (20 µl; 1.10 mmol). The reaction medium is stirred for 1 hour at room temperature, hydrolyzed and extracted with ethyl acetate. The organic phases are combined, washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude product is chromatographed on silica gel, eluting with heptane/ethyl acetate, from 5 to 30% of ethyl acetate. The N-(4-ethylphenyl)-N-isobutyl-4-(tetrahydropyran-4-ylmethylsulfanyl)benzenesulfonamide (1.10 g; 83%) is obtained in the form of a solid.

^{1}H NMR (400 MHz, DMSO-d6) δ 7.55 – 7.34 (m, 4H), 7.23 – 7.15 (m, 2H), 7.02 – 6.93 (m, 2H), 3.90 – 3.81 (m, 2H), 3.30 – 3.21 (m, 3H), 3.02 (d, J = 6.6 Hz, 2H), 2.60 (q, J = 7.6 Hz, 2H), 1.79 – 1.68 (m, 2H), 1.48 – 1.36 (m, 1H), 1.36 – 1.22 (m, 1H), 1.18 (t, J = 7.6 Hz, 3H), 0.84 (d, J = 6.7 Hz, 6H).

MS : [M+H] = 448

Example 117: Synthesis of N-(4-ethylphenyl)-N-isobutyl-4-(tetrahydropyran-4-ylmethylsulfinyl)benzenesulfonamide



Compound 29

3-Chloroperbenzoic acid (414 mg; 1.85 mmol) is added portionwise to a solution of N-(4-ethylphenyl)-N-isobutyl-4-(tetrahydropyran-4-ylmethylsulfanyl)benzenesulfonamide (787 mg; 1.76 mmol) in dichloromethane (20 ml) at 0°C.

The medium is stirred for 3 hours 30 minutes. At 0°C, 13 ml of 1N sodium hydroxide solution are added dropwise, followed by addition of 13 ml of water. The reaction medium is extracted with dichloromethane. The organic phases are washed with aqueous sodium thiosulfate solution, dried over magnesium sulfate, filtered and concentrated. The oil obtained is precipitated from dichloromethane and heptane. The solid is filtered off, rinsed with heptane and dried. The N-(4-ethylphenyl)-N-isobutyl-4-(tetrahydropyran-4-ylmethylsulfinyl)benzenesulfonamide (755 mg; 88%) is obtained in the form of a white solid.

1H NMR (400 MHz, DMSO-d6) δ0.86 (d, J = 6.6 Hz, 7H), 1.18 (t, J = 7.6 Hz, 3H), 1.51 – 1.24 (m, 3H), 1.55 (d, J = 13.3 Hz, 1H), 1.83 (d, J = 13.0 Hz, 1H), 2.16 – 1.98 (m, 1H), 2.60 (q, J = 7.6 Hz, 2H), 2.81 (dd, J = 13.1, 5.0 Hz, 1H), 2.93 (dd, J = 13.2, 8.6 Hz, 1H), 3.38 – 3.28 (m, 4H), 3.95 – 3.70 (m, 2H), 7.08 – 6.85 (m, 2H), 7.27 – 7.14 (m, 2H), 7.80 – 7.66 (m, 2H), 7.95 – 7.81 (m, 2H),

MS : [M+H] = 464

The compound N-(4-ethylphenyl)-N-isobutyl-4-(tetrahydropyran-4-ylmethylsulfinyl)benzenesulfonamide (450 mg; 1.11 mmol) is chromatographed by chiral SFC to separate the two enantiomers (compound 13 and compound 14) below:

[Supercritical conditions: 100 bar, 70°C; Chiralpak IC 250x4.6 mm 5 µ column, eluent: CO_2/ethanol: 30 g of ethanol]

Example 118: N-(4-ethylphenyl)-N-isobutyl-4-(tetrahydropyran-4-ylmethanesulfinyl)benzenesulfoximine (compound 13) - enantiomer A of compound 29

(150 mg; 22%) in the form of a white crystalline solid

^{1}H NMR (400 MHz, DMSO-d6) δ 7.91 – 7.84 (m, 2H), 7.76 – 7.69 (m, 2H), 7.20 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 8.3 Hz, 2H), 3.84 (dd, J = 22.1, 12.3 Hz, 2H), 3.45 – 3.17 (m, 4H), 2.93 (dd, J = 13.2, 8.6 Hz, 1H), 2.81 (dd, J = 13.1, 5.0 Hz, 1H), 2.66 – 2.48 (m, 2H), 2.08 (dddd, J = 19.9, 12.3, 8.7, 4.1 Hz, 1H), 1.89 – 1.79 (m, 1H), 1.60 – 1.25 (m, 4H), 1.18 (t, J = 7.6 Hz, 3H), 0.86 (d, J = 6.7 Hz, 6H).

Retention time (chiral SFC) of 6.92 minutes

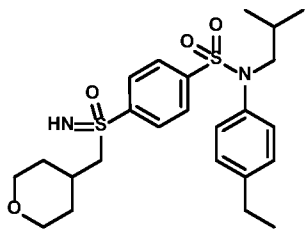
Example 119: N-(4-ethylphenyl)-N-isobutyl-4-(tetrahydropyran-4-ylmethanesulfinyl)benzenesulfonamide (compound 14) - enantiomer B of compound 29

(120 mg; 18%) in the form of a white solid

^{1}H NMR (400 MHz, DMSO-d6) δ 7.92 – 7.80 (m, 2H), 7.80 – 7.64 (m, 2H), 7.28 – 7.11 (m, 2H), 7.04 – 6.92 (m, 2H), 3.85 (ddd, J = 21.3, 10.9, 4.2 Hz, 2H), 3.47 – 3.18 (m, 4H), 2.93 (dd, J = 13.2, 8.6 Hz, 1H), 2.81 (dd, J = 13.1, 5.0 Hz, 1H), 2.61 (q, J = 7.6 Hz, 2H), 2.08 (dtt, J = 19.8, 8.2, 4.1 Hz, 1H), 1.94 – 1.72 (m, 1H), 1.64 – 1.24 (m, 4H), 1.18 (t, J = 7.6 Hz, 3H), 0.86 (d, J = 6.7 Hz, 6H).

Retention time (chiral SFC) of 9.31 minutes

Example 120: Synthesis of N-(4-ethylphenyl)-N-isobutyl-4-(tetrahydropyran-4-ylmethanesulfoximinyl)benzenesulfonamide



Compound 28

2,2,2-Trifluoroacetamide (121 mg; 1.07 mmol), magnesium oxide (87 mg; 2.15 mmol), rhodium(II) acetate dimer (28 mg; 0.06 mmol) and iodobenzene diacetate (263 mg; 0.82 mmol) are added to a solution, degassed beforehand with argon, of N-(4-ethylphenyl)-N-isobutyl-4-(tetrahydropyran-4-ylmethanesulfinyl)benzenesulfonamide (199 mg; 0.43 mmol) in dichloromethane (7 ml). The reaction medium is stirred at room temperature for 20 hours, filtered through Celite and concentrated. The residue obtained is diluted in methanol (7 ml), and potassium carbonate (297 mg; 2.15 mmol) is added.

The medium is stirred for 30 minutes at room temperature, hydrolyzed and extracted with ethyl acetate. The organic phases are combined, washed with brine, dried (Na_2SO_4) and concentrated.

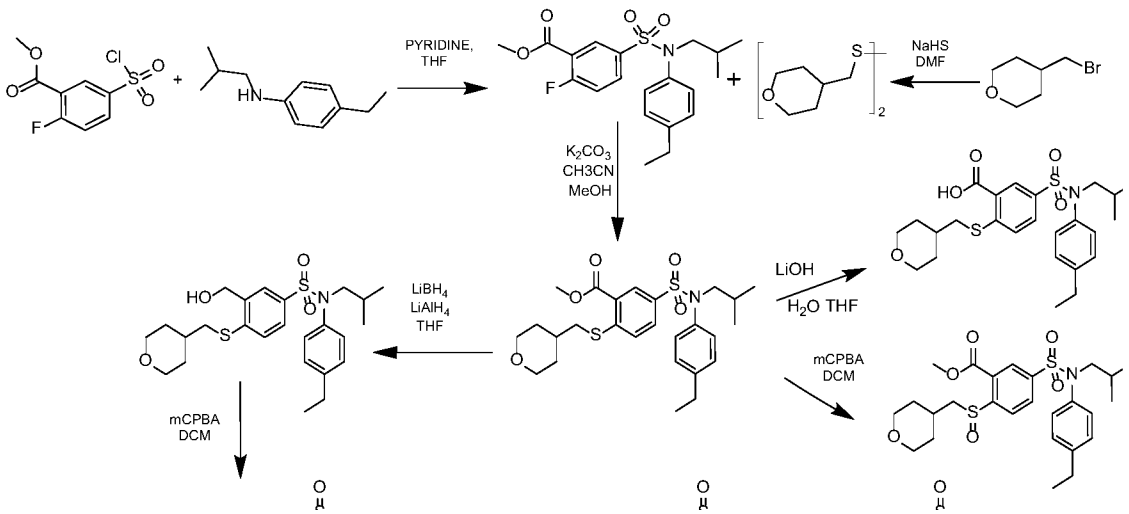
The crude product is chromatographed on silica gel (eluent: 10/90 heptane/ethyl acetate). The N-(4-ethylphenyl)-N-isobutyl-4-(tetrahydropyran-4-ylmethanesulfoximinyl)benzenesulfonamide (87 mg; 41%) is obtained in the form of a cream-colored solid.

^{1}H NMR (400 MHz, DMSO-d6) δ0.86 (dd, J = 6.8, 1.9 Hz, 6H), 1.35 – 1.06 (m, 5H), 1.44 (dt, J = 13.5, 6.9 Hz, 1H), 1.77 – 1.50 (m, 2H), 2.06 (t, J = 9.2 Hz, 1H), 2.61 (d, J = 7.6 Hz, 2H), 3.29 – 3.16 (m, 3H), 3.37 (d, J = 7.2 Hz, 2H), 3.76 (dt, J = 11.7, 3.1 Hz, 2H), 4.55 (s, 1H), 7.07 – 6.84 (m, 2H), 7.19 (dd, J = 8.6, 2.0 Hz, 2H), 7.89 – 7.62 (m, 2H), 8.09 (dd, J = 8.4, 2.0 Hz, 2H).

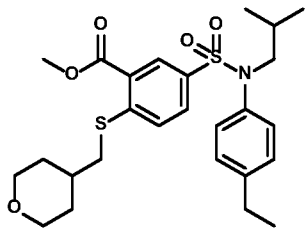
MS : [M+H] = 479

Part VII: Synthesis of sulfur-based sulfonamides via reaction scheme 7

Reaction scheme 7

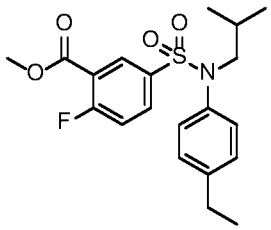


Example 121: Synthesis of methyl 5-[(4-ethylphenyl)isobutylsulfamoyl]-2-(tetrahydropyran-4-ylmethylsulfanyl)benzoate



Compound 17

1. Synthesis of intermediate 121.1



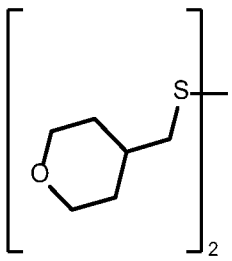
methyl 5-[(4-ethylphenyl)isobutylsulfamoyl]-2-fluorobenzoate

Methyl 5-chlorosulfonyl-2-fluorobenzoate (720 mg; 2.85 mmol) is added to (4-ethylphenyl)isobutylamine (0.95 g; 4.27 mmol) and pyridine (1.38 ml; 0.02 mol; 6.00 eq.) dissolved in tetrahydrofuran (16 ml). The reaction medium is stirred at room temperature for 16 hours, hydrolyzed and extracted with ethyl acetate. The organic phases are combined, washed with brine, dried (Na_2SO_4) and concentrated.

The crude product is chromatographed on silica gel (eluent: heptane/ethyl acetate, from 5 to 20% of ethyl acetate). The methyl 5-[(4-ethylphenyl)isobutylsulfamoyl]-2-fluorobenzoate (800 mg; 71%) is obtained in the form of a beige-colored solid with a compliant ^1H NMR.

MS : [M+H] = 394

2. Synthesis of intermediate 121.2



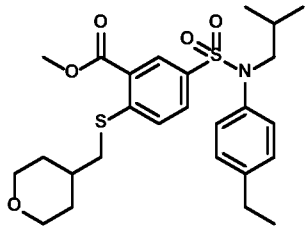
Bis[(tetrahydropyran-4-yl)methane bisulfide

A mixture of 4-(bromomethyl)tetrahydropyran (1.0 g; 5.58 mmol) and sodium hydrogen sulfide (0.44 g; 7.82 mmol) in dimethylformamide (4 ml) is stirred at room temperature for 2 hours. The reaction medium is diluted with ether and acidified by addition of concentrated HCl and then extracted. The organic phases are combined, washed with water, dried over magnesium sulfate, filtered and

concentrated to dryness. The bis[(tetrahydropyran-4-yl)methane bisulfide (565.00 mg; 77%) obtained in the form of a clear oil is used directly in the next reaction.

MS : [M+H] = 263

3. Synthesis of methyl 5-[(4-ethylphenyl)isobutylsulfamoyl]-2-(tetrahydropyran-4-ylmethylsulfanyl)benzoate



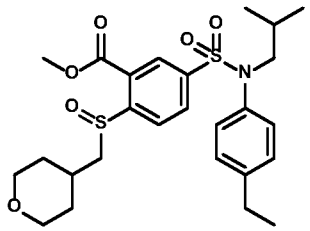
Potassium carbonate (81 mg; 0.59 mmol) is added to methyl 5-[(4-ethylphenyl)isobutylsulfamoyl]-2-fluorobenzoate (200 mg; 0.51 mmol) and bis(tetrahydropyran-4-yl)methane bisulfide (133.39 mg; 0.51 mmol; 1.00 eq.) in acetonitrile (2 ml). The reaction medium is stirred at room temperature for 16 hours, hydrolyzed and extracted with ethyl acetate. The organic phases are combined, washed with brine, dried and concentrated.

The crude product is chromatographed on silica gel, eluting with heptane/ethyl acetate: 5 to 20% of ethyl acetate. The methyl 5-[(4-ethylphenyl)isobutylsulfamoyl]-2-(tetrahydropyran-4-ylmethylsulfanyl)benzoate (214 mg; 83%) is obtained in the form of a white solid.

1H NMR (400 MHz, DMSO-d6) δ 0.85 (d, J = 6.6 Hz, 7H), 1.18 (t, J = 7.6 Hz, 3H), 1.37 (dtd, J = 36.3, 12.9, 12.1, 7.3 Hz, 3H), 1.91 – 1.70 (m, 4H), 2.61 (q, J = 7.6 Hz, 2H), 2.98 (d, J = 6.7 Hz, 2H), 3.35 – 3.24 (m, 4H), 3.91 – 3.80 (m, 5H), 7.05 – 6.98 (m, 2H), 7.23 – 7.17 (m, 2H), 7.66 – 7.59 (m, 2H), 7.89 (d, J = 1.9 Hz, 1H).

MS : [M+H] = 506

Example 122: Synthesis of methyl 5-[(4-ethylphenyl)isobutylsulfamoyl]-2-(tetrahydropyran-4-ylmethanesulfinyl)benzoate



Compound 16

3-Chloroperbenzoic acid (70 mg; 0.31 mmol) is added to a solution of methyl 5-[(4-ethylphenyl)isobutylsulfamoyl]-2-(tetrahydropyran-4-ylmethylsulfanyl)benzoate (150 mg; 0.30 mmol) in dichloromethane (5 ml) at a temperature of 0°C. The reaction medium is stirred for 2 hours. At 0°C, 1N sodium hydroxide is added dropwise, followed by addition of water, and the reaction medium is then extracted with dichloromethane.

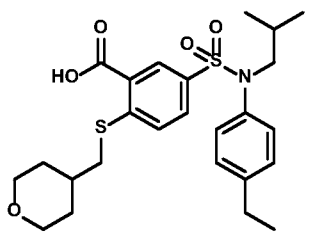
The organic phases are washed with aqueous sodium thiosulfate solution, dried over magnesium sulfate, filtered and evaporated.

The crude product is chromatographed on silica gel (eluent: heptane/ethyl acetate, from 10 to 30% of ethyl). The methyl 5-[(4-ethylphenyl)isobutylsulfamoyl]-2-(tetrahydropyran-4-ylmethanesulfinyl)benzoate (140 mg; 90%) is obtained in the form of a white solid.

1H NMR (400 MHz, DMSO-d6) δ 0.86 (dd, J = 6.7, 4.0 Hz, 6H), 1.19 (t, J = 7.6 Hz, 3H), 1.67 – 1.23 (m, 3H), 1.97 (dd, J = 16.3, 5.1 Hz, 1H), 2.66 – 2.55 (m, 3H), 2.22 (s, 1H), 3.09 (dd, J = 12.8, 9.7 Hz, 1H), 3.44 – 3.31 (m, 4H), 3.89 (s, 5H), 7.07 – 6.97 (m, 2H), 7.22 (d, J = 8.3 Hz, 2H), 8.02 (d, J = 1.9 Hz, 1H), 8.08 (dd, J = 8.3, 2.0 Hz, 1H), 8.30 (d, J = 8.3 Hz, 1H).

MS : [M+H] = 522

Example 123: Synthesis of 5-[(4-ethylphenyl)isobutylsulfamoyl]-2-(tetrahydropyran-4-ylmethylsulfanyl)benzoic acid



Compound 23

A mixture of methyl 5-[(4-ethylphenyl)isobutylsulfamoyl]-2-(tetrahydropyran-4-ylmethanesulfanyl)tetrahydropyran-4-ylbenzoate (277 mg; 0.47 mmol) and lithium hydroxide (0.70 ml; 1.00 M; 0.70 mmol) in tetrahydrofuran (6.93 ml) is stirred at a temperature of 60°C for 24 hours. The reaction medium is hydrolyzed with 1N sodium hydroxide and extracted with ethyl acetate. The organic phases are combined and washed with 1N sodium hydroxide.

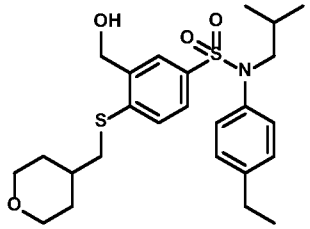
The aqueous phases are combined, acidified with HCl and extracted with ethyl acetate. The organic phases are combined, washed with brine, dried over magnesium sulfate, filtered and concentrated.

The crude product is chromatographed on silica gel, eluting with heptane/ethyl acetate + 1% AcOH, 10 to 50% of ethyl acetate. The 5-[(4-ethylphenyl)isobutylsulfamoyl]-2-(tetrahydropyran-4-ylmethylsulfanyl)benzoic acid (87.00 mg; 36%) is obtained in the form of a solid after crystallization from a mixture of methanol and dichloromethane.

1H NMR (400 MHz,DMSO-d6) δ 0.85 (d, J =6.6 Hz, 6H), 1.18 (t,J = 7.6 Hz, 3H), 1.50 – 1.24 (m, 3H), 1.89 – 1.67 (m, 3H), 2.66 – 2.55 (m,2H), 2.94 (d, J = 6.6Hz, 2H), 3.30 (d, J =7.1 Hz, 3H), 4.03 –3.71 (m, 2H), 7.04 – 6.97 (m, 2H), 7.25 – 7.16 (m, 2H), 7.59 (s,2H), 8.10 – 7.74 (m, 1H), 13.46 (s, 1H).

MS : [M+H] = 492

Example 124: Synthesis of N-(4-ethylphenyl)-3-hydroxymethyl-N-isobutyl-4-(tetrahydropyran-4-ylmethylsulfanyl)benzenesulfonamide



Compound 21

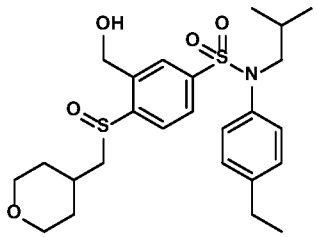
Lithium borohydride (9 mg; 0.40 mmol) is added to methyl 5-[(4-ethylphenyl)isobutylsulfamoyl]-2-(tetrahydropyran-4-ylmethylsulfanyl)benzoate (113 mg; 0.22 mmol) in tetrahydrofuran (3 ml). The reaction medium is stirred at room temperature for 16 hours, hydrolyzed with 5% citric acid for 1 hour and extracted with ethyl acetate. The organic phases are combined, washed with brine, dried over magnesium sulfate, filtered and evaporated.

The crude product is chromatographed on silica gel (eluent: 80/20 heptane/ethyl acetate). The N-(4-ethylphenyl)-3-hydroxymethyl-N-isobutyl-4-(tetrahydropyran-4-ylmethylsulfanyl)benzenesulfonamide (106mg; 96%) is obtained in the form of a white solid.

^{1}H NMR (Chloroform-d) δ: 0.84 (d, J = 6.7 Hz, 6H), 1.16 (t, J = 7.6 Hz, 3H), 1.35 (qd, J = 13.1, 12.4, 3.6 Hz, 2H), 1.50 (hept, J = 6.7 Hz, 1H), 1.73 (d, J = 12.3 Hz, 1H), 2.51 – 2.62 (m, 2H), 2.64 (d, J = 1.7 Hz, 2H), 2.87 (d, J = 6.5 Hz, 2H), 3.22 (d, J = 7.4 Hz, 2H), 3.31 (td, J = 11.8, 1.9 Hz, 2H), 3.92 (ddd, J = 12.5, 4.6, 1.5 Hz, 2H), 4.65 (s, 2H), 6.87 – 6.94 (m, 2H), 7.06 (d, J = 8.3 Hz, 2H), 7.19 (d, J = 8.2 Hz, 1H), 7.33 (dd, J = 8.3, 2.2 Hz, 1H), 7.56 (d, J = 2.1 Hz, 1H)

MS : [M+H] = 478

Example 125: Synthesis of N-(4-ethylphenyl)-3-hydroxymethyl-N-isobutyl-4-(tetrahydropyran-4-ylmethanesulfinyl)benzenesulfonamide



Compound 15

3-Chloroperoxybenzoic acid (302.47 mg; 1.35 mmol) is added to a solution of N-(4-ethylphenyl)-3-hydroxymethyl-N-isobutyl-4-(tetrahydropyran-4-ylmethylsulfanyl)benzenesulfonamide (614.00 mg; 1.29 mmol) in dichloromethane (20.00 ml). The medium is stirred at room temperature for 4 hours. At a temperature of 0°C, the reaction medium is added to water and extracted with ethyl acetate. The

organic phases are washed with brine, dried over magnesium sulfate, filtered and evaporated.

The crude product is chromatographed on silica gel, eluting with heptane/ethyl acetate, from 50 to 100% of ethyl acetate). The N-(4-ethylphenyl)-3-hydroxymethyl-N-isobutyl-4-(tetrahydropyran-4-ylmethanesulfinyl)benzenesulfonamide (455 mg; 71%) is obtained in the form of a white solid.

^{1}H NMR (DMSO-d_6) δ 0.84 (d, J = 6.7 Hz, 6H), 1.16 (t, J = 7.6 Hz, 3H), 1.19 – 1.50 (m, 3H), 1.47 – 1.63 (m, 1H), 1.86 (ddd, J = 13.1, 3.9, 2.1 Hz, 1H), 2.12 (dq, J = 15.5, 5.7, 4.0 Hz, 2H), 2.55 – 2.69 (m, 3H), 2.94 (dd, J = 13.2, 9.4 Hz, 1H), 3.33 (d, J = 3.1 Hz, 3H), 3.74 – 3.95 (m, 2H), 4.60 (dd, J = 5.3, 3.3 Hz, 2H), 5.65 (dd, J = 5.9, 4.8 Hz, 1H), 6.86– 7.07 (m, 2H), 7.10 – 7.30 (m, 2H), 7.57 – 7.76 (m, 2H), 8.01 (d, J = 8.1 Hz, 1H).

MS : [M+H] = 494

Compound 15 (377 mg; 0.76 mmol) is chromatographed by chiral SFC to separate the two enantiomers below

[Supercritical conditions: 100 bar, 70°C; Chiralpak IC 250x4.6 mm 5 µ column, eluent: CO_2/methanol: 45% of methanol]

Example 126: N-(4-ethylphenyl)-3-hydroxymethyl-N-isobutyl-4-(tetrahydropyran-4-ylmethanesulfinyl)benzenesulfonamide (compound 11) - enantiomer A of compound 15

(146 mg; 39%) in the form of a white solid

^{1}H NMR (400 MHz, DMSO-d6) δ 8.01 (d, J = 8.1 Hz, 1H), 7.76 – 7.57 (m, 2H), 7.30 – 7.10 (m, 2H), 7.07 – 6.86 (m, 2H), 5.65 (dd, J = 5.9, 4.8 Hz, 1H), 4.60 (dd, J = 5.3, 3.3 Hz, 2H), 3.95 – 3.74 (m, 1H), 3.33 (d, J = 3.1 Hz, 2H), 2.94 (dd, J = 13.2, 9.4 Hz, 1H), 2.69 – 2.55 (m, 2H), 2.12 (dq, J = 15.5, 5.7, 4.0 Hz, 1H), 1.86 (ddd, J = 13.1, 3.9, 2.1 Hz, 1H), 1.63 – 1.47 (m, 1H), 1.50 – 1.19 (m, 2H), 1.16 (t, J = 7.6 Hz, 3H), 0.84 (d, J = 6.7 Hz, 6H).

Retention time (chiral SFC) of 2.49 minutes

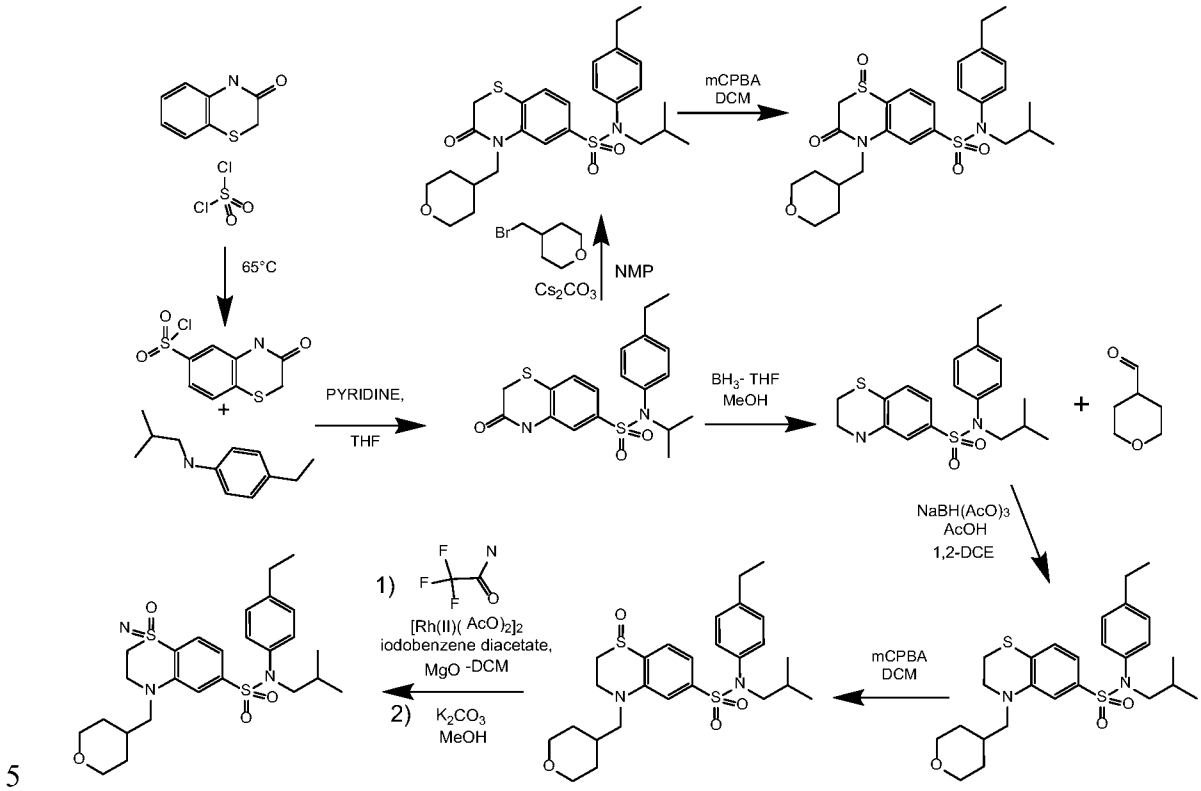
Example 127: N-(4-ethylphenyl)-3-hydroxymethyl-N-isobutyl-4-(tetrahydropyran-4-ylmethanesulfinyl)benzenesulfonamide (compound 12) - enantiomer B of compound 15 (134 mg; 36%) in the form of a white solid

^{1}H NMR (400 MHz, DMSO-d6) δ 8.01 (d, J = 8.1 Hz, 1H), 7.76 – 7.57 (m, 2H), 7.30 – 7.10 (m, 2H), 7.07 – 6.86 (m, 2H), 5.65 (dd, J = 5.9, 4.8 Hz, 1H), 4.60 (dd, J = 5.3, 3.3 Hz, 2H), 3.95 – 3.74 (m, 1H), 3.33 (d, J = 3.1 Hz, 2H), 2.94 (dd, J = 13.2, 9.4 Hz, 1H), 2.69 – 2.55 (m, 2H), 2.12 (dq, J = 15.5, 5.7, 4.0 Hz, 1H), 1.86 (ddd, J = 13.1, 3.9, 2.1 Hz, 1H), 1.63 – 1.47 (m, 1H), 1.50 – 1.19 (m, 2H), 1.16 (t, J = 7.6 Hz, 3H), 0.84 (d, J = 6.7 Hz, 6H).

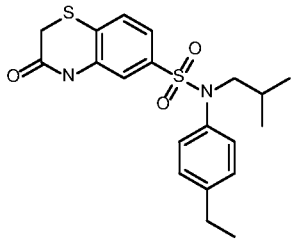
Retention time (chiral SFC) of 2.92 minutes

Part VIII: Synthesis of sulfur-based sulfonamides via reaction scheme 8

Reaction scheme 8

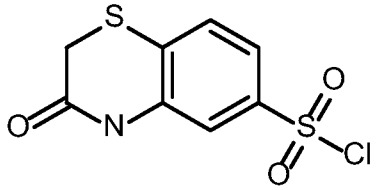


Example 128: Synthesis of 3-oxo-3,4-dihydro-2H-benzo[1,4]thiazine-6-sulfonic acid (4-ethylphenyl)isobutylamide



Compound 10

1. Synthesis of intermediate 128.1



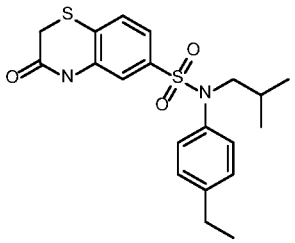
3-oxo-3,4-dihydro-2H-benzo[1,4]thiazine-6-sulfonyl chloride

4H-Benzo[1,4]thiazin-3-one (4.0 g; 24.21 mmol) is added slowly to chlorosulfonic acid (6.5 ml; 96.84 mmol) cooled to 10°C. The temperature is maintained below 20°C. The reaction medium is stirred at room temperature for 1 hour and then heated to a temperature of 65°C, poured slowly onto ice and then extracted with ethyl acetate. The organic phases are combined, washed with brine, dried over sodium sulfate and concentrated. The residue is taken up in ether and suction-filtered.

The 3-oxo-3,4-dihydro-2H-benzo[1,4]thiazine-6-sulfonyl chloride (4.88 g; 76%) is obtained in the form of an ocher-colored powder.

MS : [M+H] = 262

2. Synthesis of compound 10 according to the invention



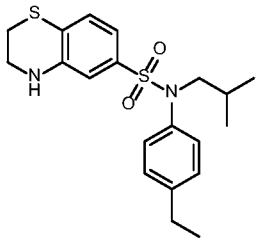
3-Oxo-3,4-dihydro-2H-benzo[1,4]thiazine-6-sulfonyl chloride (3.27 g; 12.41 mmol) is added to (4-ethylphenyl)isobutylamine (2 g; 11.28 mmol) and pyridine (40 ml; 495.56 mmol) dissolved in tetrahydrofuran (5.4 ml). The reaction medium is stirred at room temperature for 2 hours, hydrolyzed and extracted with ethyl acetate. The organic phases are combined, washed with 1N hydrochloric acid solution, with brine, dried over sodium sulfate and concentrated.

The crude product is chromatographed on silica gel (eluent: heptane/ethyl acetate, from 0 to 50% of ethyl acetate). The 3-oxo-3,4-dihydro-2H-benzo[1,4]thiazine-6-sulfonic acid (4-ethylphenyl)isobutylamide (2.53 g; 55%) is obtained in the form of a yellow solid.

^{1}H NMR (Chloroform-d) δ: 0.93 (d, J = 6.7 Hz, 7H), 1.25 (td, J = 7.6, 4.3 Hz, 4H), 1.53 – 1.67 (m, 2H), 2.67 (q, J = 7.6 Hz, 2H), 3.32 (d, J = 7.4 Hz, 2H), 3.50 (s, 2H), 6.94 – 7.04 (m, 2H), 7.07 (d, J = 1.9 Hz, 1H), 7.12 – 7.20 (m, 2H), 7.22 (dd, J = 8.2, 1.8 Hz, 1H), 7.41 (d, J = 8.2 Hz, 1H), 8.28 (s, 1H).

MS : [M+H] = 405

Example 129: Synthesis of 3,4-dihydro-2H-benzo[1,4]thiazine-6-sulfonic acid (4-ethylphenyl)isobutylamide



Compound 9

3-Oxo-3,4-dihydro-2H-benzo[1,4]thiazine-6-sulfonic acid (4-ethylphenyl)isobutylamide (500 mg; 1.28 mmol) is dissolved in the 1M borane-tetrahydrofuran complex with 5 mmol $NaBH_4$ (35 ml). The reaction medium is refluxed for 30 minutes and then cooled to a temperature of 0°C and poured slowly into methanol (35 ml).

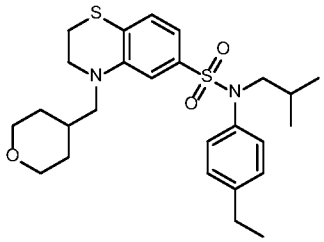
The solvents are concentrated and the residue is chromatographed on silica gel (eluent: heptane/ethyl acetate, from 0 to 40% of ethyl acetate).

The 3,4-dihydro-2H-benzo[1,4]thiazine-6-sulfonic acid (4-ethylphenyl)isobutylamide (437 mg; 86%) is obtained in the form of a white crystalline solid after recrystallization from an ethyl acetate/heptane mixture.

^{1}H NMR (DMSO-d6) δ: 0.82 (d, J = 6.7 Hz, 6H), 1.17 (t, J = 7.6 Hz, 3H), 1.31 – 1.47 (m, 1H), 2.59 (q, J = 7.6 Hz, 2H), 2.97 – 3.05 (m, 2H), 3.25 (d, J = 7.3 Hz, 2H), 3.48 (dt, J = 7.0, 3.0 Hz, 2H), 6.48 – 6.56 (m, 2H), 6.75 (d, J = 2.0 Hz, 1H), 6.95 – 7.04 (m, 3H), 7.14 – 7.21 (m, 2H).

MS : [M+H] = 391

Example 130: Synthesis of 4-(tetrahydropyran-4-ylmethyl)-3,4-dihydro-2H-benzo[1,4]thiazine-6-sulfonic acid (4-ethylphenyl)isobutylamide



Compound 6

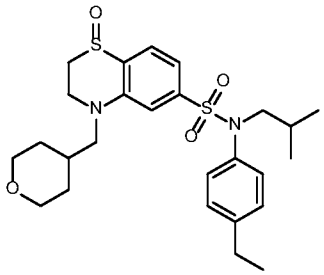
Sodium triacetoxyborohydride (33 mg; 0.15 mmol) is added at a temperature of 0°C to 3,4-dihydro-2H-benzo[1,4]thiazine-6-sulfonic acid (4-ethylphenyl)isobutylamide (20 mg; 0.05 mmol), 4-formyltetrahydropyran (29 mg; 0.26 mmol) and acetic acid (0.15 µl) dissolved in 1,2-dichloroethane. The reaction medium is stirred at room temperature for a period of 24 hours, water is added and the resulting mixture is extracted with ethyl acetate. The organic phases are combined, washed with brine, dried over sodium sulfate and concentrated.

The crude product is chromatographed on silica gel (eluent: heptane/ethyl acetate, from 0 to 50% of ethyl acetate). The 4-(tetrahydropyran-4-ylmethyl)-3,4-dihydro-2H-benzo[1,4]thiazine-6-sulfonic acid (4-ethylphenyl)isobutylamide (15 mg; 59%) is obtained in the form of a beige-colored solid.

1H NMR (DMSO-d6) δ: 0.84 (d, J = 6.6 Hz, 7H), 1.06 – 1.27 (m, 6H), 1.40 – 1.48 (m, 3H), 1.68 – 1.79 (m, 1H), 2.55 – 2.66 (m, 2H), 3.01 (d, J = 6.9 Hz, 2H), 3.08 (t, J = 4.8 Hz, 2H), 3.19 (t, J = 11.5 Hz, 2H), 3.26 (d, J = 7.3 Hz, 2H), 3.62 (t, J = 4.8 Hz, 2H), 3.82 (dd, J = 11.0, 4.2 Hz, 2H), 6.54 (s, 1H), 6.71 (d, J = 7.9 Hz, 1H), 7.02 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.1 Hz, 1H), 7.21 (d, J = 7.9 Hz, 2H).

MS : [M+H] = 489

Example 131: Synthesis of 1-oxo-4-(tetrahydropyran-4-ylmethyl)-1,2,3,4-tetrahydro-1λ^4-benzo[1,4]thiazine-7-sulfonic acid (4-ethylphenyl)isobutylamide



Compound 3

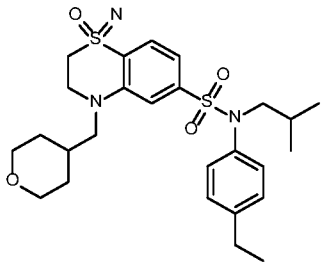
3-Chloroperbenzoic acid (124 mg; 0.55 mmol) is added, at a temperature of 0°C, to 4-(tetrahydropyran-4-ylmethyl)-3,4-dihydro-2H-benzo[1,4]thiazine-7-sulfonic acid (4-ethylphenyl)isobutylamide (300 mg; 0.61 mmol) dissolved in dichloromethane (6 ml). The reaction medium is stirred at room temperature for 30 minutes, hydrolyzed with aqueous 10% $Na_2S_2O_3$ solution and extracted with dichloromethane. The organic phases are combined, washed with 0.1N sodium hydroxide solution, with brine, dried over sodium sulfate and concentrated.

The crude product is chromatographed on silica gel (eluent: dichloromethane/methanol, from 0 to 10% of methanol). The 1-oxo-4-(tetrahydropyran-4-ylmethyl)-1,2,3,4-tetrahydro-1λ^4-benzo[1,4]thiazine-7-sulfonic acid (4-ethylphenyl)isobutylamide (274 mg; 88%) is obtained in the form of a white solid by crystallization from a water/acetone mixture.

1H NMR (DMSO-d6) δ: 0.85 (dd, J = 6.6, 1.3 Hz, 6H), 1.12 – 1.28 (m, 5H), 1.44 (dt, J = 12.8, 9.6 Hz, 3H), 1.71 – 1.88 (m, 1H), 2.61 (q, J = 7.6 Hz, 2H), 2.85 (td, J = 13.6, 3.4 Hz, 1H), 3.09 – 3.36 (m, 12H), 3.64 (dt, J = 14.0, 3.8 Hz, 1H), 3.78 – 3.90 (m, 3H), 6.81 (d, J = 7.3 Hz, 2H), 7.01 – 7.08 (m, 2H), 7.19 – 7.26 (m, 2H), 7.70 (d, J = 8.2 Hz, 1H).

MS : [M+H] = 505

Example 132: Synthesis of 1-imino-1-oxo-4-(tetrahydropyran-4-ylmethyl)-1,2,3,4-tetrahydro-1λ^6-benzo[1,4]thiazine-6-sulfonic acid (4-ethylphenyl)isobutylamide



Compound 1

2,2,2-Trifluoroacetamide (109 mg; 0.97 mmol), rhodium(II) acetate (26 mg; 0.06 mmol), magnesium oxide (78 mg; 1.93 mmol) and iodobenzene diacetate (249 mg; 0.77 mmol) are added to a solution, degassed beforehand with argon, of 1-oxo-4-(tetrahydropyran-4-ylmethyl)-1,2,3,4-tetrahydro-1λ^4-benzo[1,4]thiazine-6-sulfonic acid (4-ethylphenyl)isobutylamide (195.00 mg; 0.39 mmol) in dichloromethane (10 ml). The reaction medium is stirred at room temperature for 16 hours, filtered through Celite and concentrated. The residue obtained is diluted in methanol (10 ml), and potassium carbonate (267 mg; 1.93 mmol) is added.

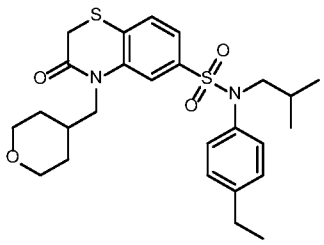
The reaction medium is stirred for 30 minutes and then hydrolyzed and extracted with ethyl acetate. The organic phases are combined, washed with brine and dried over sodium sulfate. The solvents are evaporated off. The crude product is chromatographed on silica gel (eluent: dichloromethane/methanol, from 0 to 5% of methanol).

The 1-imino-1-oxo-4-(tetrahydropyran-4-ylmethyl)-1,2,3,4-tetrahydro-1λ^6-benzo[1,4]thiazine-6-sulfonic acid (4-ethylphenyl)isobutylamide (44.50 mg; 21.97%) is obtained in the form of a white solid.

1H NMR (DMSO-d6) δ: 0.86 (t, J = 4.9 Hz, 8H), 1.09 – 1.33 (m, 9H), 1.36 – 1.49 (m, 3H), 1.75 (qd, J = 8.6, 7.9, 4.2 Hz, 1H), 2.61 (q, J = 7.6 Hz, 2H), 3.17 (dd, J = 15.8, 9.0 Hz, 4H), 3.34 – 3.46 (m, 3H), 3.85 (ddd, J = 23.1, 9.5, 4.1 Hz, 4H), 4.74 (s, 1H), 6.68 (s, 1H), 6.88 (d, J = 8.1 Hz, 1H), 7.05 (d, J = 8.2 Hz, 2H), 7.23 (d, J = 7.9 Hz, 2H), 7.84 (d, J = 8.1 Hz, 1H).

MS : [M+H] = 519

Example 133: Synthesis of 3-oxo-4-(tetrahydropyran-4-ylmethyl)-3,4-dihydro-2H-benzo[1,4]thiazine-7-sulfonic acid (4-ethylphenyl)isobutylamide



Compound 70

4-(Bromomethyl)tetrahydropyran (18 mg; 0.10 mmol) is added to 3-oxo-3,4-dihydro-2H-benzo[1,4]thiazine-7-sulfonic acid (4-ethylphenyl)isobutylamide (20 mg; 0.05 mmol) and cesium carbonate (24 mg; 0.07 mmol) dissolved in 1-methyl-2-pyrrolidone (0.4 ml).

The reaction medium is heated at 80°C for 24 hours, hydrolyzed and then extracted with ethyl acetate. The organic phases are combined, washed with brine and dried over sodium sulfate.

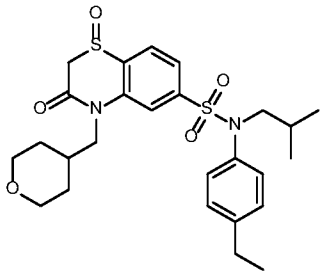
The solvents are evaporated off and the crude product is chromatographed on silica gel (eluent: heptane/ethyl acetate, from 0 to 50% of ethyl acetate).

The 3-oxo-4-(tetrahydropyran-4-ylmethyl)-3,4-dihydro-2H-benzo[1,4]thiazine-7-sulfonic acid (4-ethylphenyl)isobutylamide (10.4 mg; 40%) is obtained in the form of a beige-colored solid.

^{1}H NMR (DMSO-d6) δ: 0.85 (d, J = 6.8 Hz, 7H), 1.17 (t, J = 7.6 Hz, 3H), 1.25 (d, J = 6.5 Hz, 2H), 1.37 – 1.67 (m, 10H), 1.68 – 1.77 (m, 5H), 2.44 (dt, J = 11.1, 4.0 Hz, 10H), 2.60 (q, J = 7.6 Hz, 2H), 3.17 (s, 1H), 3.33 – 3.38 (m, 5H), 3.80 (dt, J = 11.3, 3.7 Hz, 7H), 3.92 (s, 1H), 7.02 (d, J = 7.8 Hz, 2H), 7.18 (dd, J = 18.5, 8.4 Hz, 3H), 7.42 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 2.1 Hz, 1H), 12.17 (s, 2H)

MS : [M+H] = 503

Example 134: Synthesis of 1,3-dioxo-4-(tetrahydropyran-4-ylmethyl)-1,2,3,4-tetrahydro-1λ^4-benzo[1,4]thiazine-6-sulfonic acid (4-ethylphenyl)isobutylamide



Compound 4

3-Chloroperbenzoic acid (161 mg; 0.72 mmol) is added, at 0°C, to 3-oxo-4-(tetrahydropyran-4-ylmethyl)-3,4-dihydro-2H-benzo[1,4]thiazine-6-sulfonic acid (4-ethylphenyl)isobutylamide (400 mg; 0.80 mmol) dissolved in dichloromethane (8 ml).

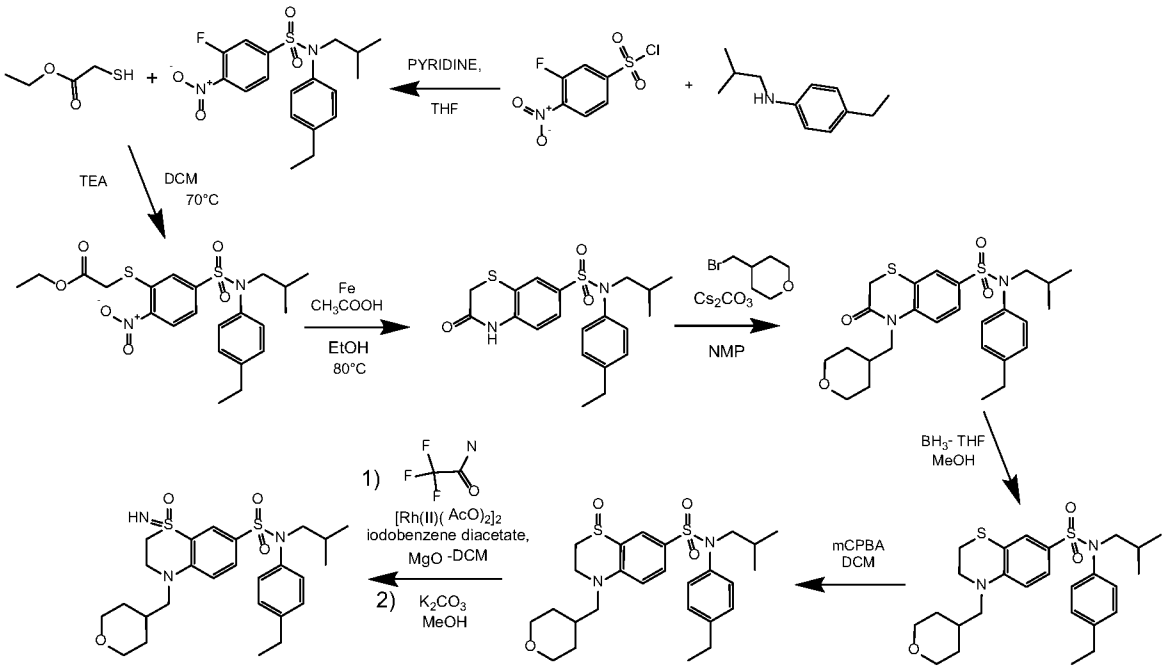
The reaction medium is stirred at room temperature for 1 hour, hydrolyzed with aqueous 10% $Na_2S_2O_3$ solution and extracted with dichloromethane. The organic phases are combined, washed with 0.1N sodium hydroxide solution and then with brine, and dried over sodium sulfate. The solvents are concentrated and the crude product is chromatographed on silica gel (eluent: heptane/ethyl acetate, from 0 to 80% of ethyl acetate). The 1,3-dioxo-4-(tetrahydropyran-4-ylmethyl)-1,2,3,4-tetrahydro-1λ^4-benzo[1,4]thiazine-6-sulfonic acid (4-ethylphenyl)isobutylamide (358 mg; 87%) is obtained in the form of a white solid.

1H NMR (DMSO-d6) δ: 0.87 (d, J = 6.6 Hz, 6H), 1.01 – 1.23 (m, 5H), 1.37 – 1.53 (m, 3H), 1.62 – 1.83 (m, 1H), 2.62 (q, J = 7.6 Hz, 2H), 3.05 – 3.22 (m, 2H), 3.33 – 3.49 (m, 2H), 3.72 – 3.89 (m, 3H), 4.04 (dd, J = 14.8, 8.5 Hz, 1H), 4.29 – 4.39 (m, 2H), 7.01 – 7.08 (m, 2H), 7.21 – 7.28 (m, 2H), 7.43 (dd, J = 7.8, 1.5 Hz, 1H), 7.50 (d, J = 1.6 Hz, 1H), 8.08 (d, J = 7.8 Hz, 1H).

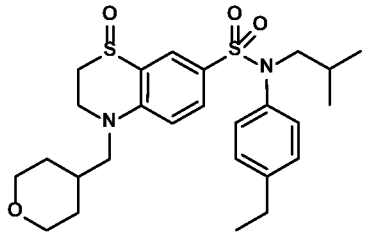
MS : [M+H] = 519

Part IX: Synthesis of sulfur-based sulfonamides via reaction scheme 9

Reaction scheme 9

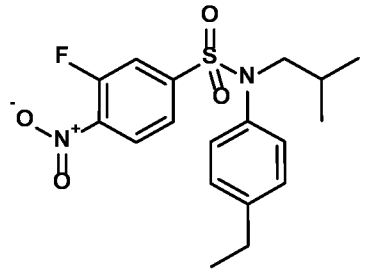

PYRIDINE,
THF
TEA
DCM
70°C
Fe
CH3COOH
EtOH
80°C
Cs2CO3
NMP
BH3- THF
MeOH
mCPBA
DCM
1)
[Rh(II)(AcO)2]2
iodobenzene diacetate,
MgO -DCM
2) K2CO3
MeOH

Example 135: Synthesis of 1-oxo-4-(tetrahydropyran-4-ylmethyl)-1,2,3,4-tetrahydro-1λ^4-benzo[1,4]thiazine-7-sulfonic acid (4-ethylphenyl)isobutylamide



Compound 71

1. Synthesis of intermediate 135.1



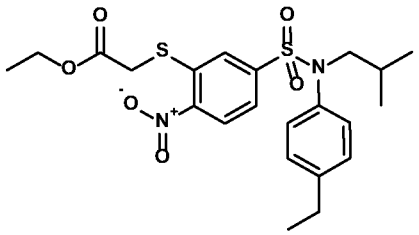
3-bromo-N-(4-ethylphenyl)-N-isobutyl-4-methoxybenzenesulfonamide

3-Fluoro-4-nitrobenzenesulfonyl chloride (5.57 g; 22.56 mmol) is added to a solution of (4-ethylphenyl)isobutylamine (4.0 g; 22.56 mmol) and pyridine (11 ml; 135.37 mmol) in tetrahydrofuran (80 ml). The reaction medium is stirred for 16 hours at room temperature, hydrolyzed and extracted with ethyl acetate. The organic phases are combined, washed with saturated NH_4Cl solution and then with brine, dried (Na_2SO_4) and concentrated.

The crude product is chromatographed on silica gel (eluent: heptane/ethyl acetate, from 0 to 10% of ethyl acetate). The 3-bromo-N-(4-ethylphenyl)-N-isobutyl-4-methoxybenzenesulfonamide (7.02 g; 82%) is obtained in the form of a flaky white solid with a compliant ^{1}H NMR.

MS : [M+H] = 381

2. Synthesis of intermediate 135.2



ethyl {5-[(4-ethylphenyl)isobutylsulfamoyl]-2-nitrophenylsulfanyl}acetate

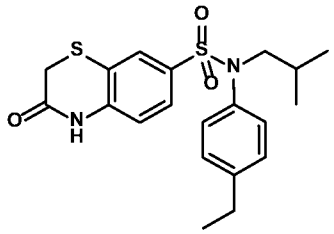
Ethyl thioglycolate (0.86 ml; 7.89 mmol) is added slowly to a solution of N-(4-ethylphenyl)-3-fluoro-N-isobutyl-4-nitrobenzenesulfonamide (3.0 g; 7.89 mmol) and triethylamine (1.31 ml; 9.46 mmol) in tetrahydrofuran (75 ml). The reaction medium is stirred for 16 hours at room temperature.

The crude product is chromatographed on silica gel (eluent: heptane/ethyl acetate, from 0 to 30% of ethyl acetate).

The ethyl {5-[(4-ethylphenyl)isobutylsulfamoyl]-2-nitrophenylsulfanyl}acetate (3.49 g; 92%) is obtained in the form of a bright yellow solid with a compliant ^{1}H NMR.

MS : [M+H] = 481.

3. Synthesis of intermediate 135.3



3-Oxo-3,4-dihydro-2H-benzo[1,4]thiazine-7-sulfonic acid (4-ethylphenyl)isobutylamide

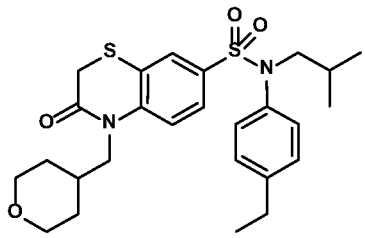
Iron powder (1.16 g; 20.81 mmol) is added to a solution of ethyl {5-[(4-ethylphenyl)isobutylsulfamoyl]-2-nitrophenylsulfanyl}acetate (2.00 g; 4.16 mmol) in ethanol (20 ml) and acetic acid (5 ml).

The reaction medium is stirred for 2 hours at a temperature of 80°C, returned to room temperature, diluted with ethyl acetate and then filtered through Celite. The filtrate is washed with saturated $NaHCO_3$ solution and then with brine, dried (Na_2SO_4) and concentrated.

The crude product is chromatographed on silica gel (eluent: heptane/ethyl acetate, from 0 to 40% of ethyl acetate). The 3-oxo-3,4-dihydro-2H-benzo[1,4]thiazine-7-sulfonic acid (4-ethylphenyl)isobutylamide (0.98 g; 58%) is obtained in the form of a white powder with a compliant ^1H NMR.

MS : [M+H] = 405

4. Synthesis of intermediate 135.4



3-Oxo-4-(tetrahydropyran-4-ylmethyl)-3,4-dihydro-2H-benzo[1,4]thiazine-7-sulfonic acid (4-ethylphenyl)isobutylamide

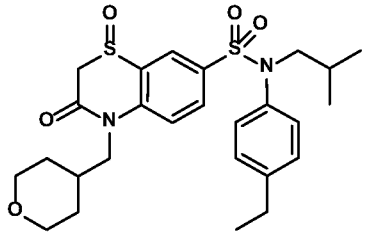
4-(Bromomethyl)tetrahydropyran (797 mg; 4.45 mmol) is added to a mixture of 3-oxo-3,4-dihydro-2H-benzo[1,4]thiazine-7-sulfonic acid (4-ethylphenyl)isobutylamide (900 mg; 2.22 mmol) and cesium carbonate (1.09 g; 3.34 mmol) in 1-methyl-2-pyrrolidone (20 ml).

The reaction medium is stirred for 4 hours at a temperature of 110°C, hydrolyzed and extracted with ethyl acetate. The organic phases are combined, washed with brine, dried (Na_2SO_4) and concentrated.

The crude product is chromatographed on silica gel (eluent: heptane/ethyl acetate, from 0 to 60% of ethyl acetate). The 3-oxo-4-(tetrahydropyran-4-ylmethyl)-3,4-dihydro-2H-benzo[1,4]thiazine-7-sulfonic acid (4-ethylphenyl)isobutylamide (1.11 g; 99%) is obtained in the form of a white solid with a compliant ^1H NMR.

MS : [M+H] = 503

5. Synthesis of intermediate 135.5



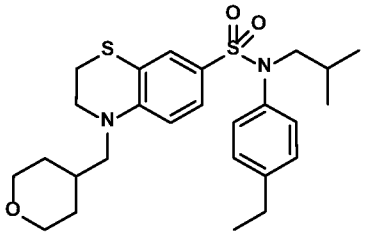
1,3-Dioxo-4-(tetrahydropyran-4-ylmethyl)-1,2,3,4-tetrahydro-1λ^4-benzo[1,4]thiazine-7-sulfonic acid (4-ethylphenyl)isobutylamide

3-Chloroperoxybenzoic acid (223 mg; 0.99 mmol) is added, at a temperature of 0°C, to 3-oxo-4-(tetrahydropyran-4-ylmethyl)-3,4-dihydro-2H-benzo[1,4]thiazine-7-sulfonic acid (4-ethylphenyl)isobutylamide (500 mg; 0.99 mmol) dissolved in dichloromethane (10 ml). The reaction medium is stirred for 30 minutes at room temperature, hydrolyzed with aqueous 10% $Na_2S_2O_3$ solution and extracted with dichloromethane. The organic phases are combined, washed with 0.1N sodium hydroxide solution and with brine, and then dried (Na_2SO_4) and concentrated.

The crude product is chromatographed on silica gel (eluent: heptane/ethyl acetate, from 0 to 80% of ethyl acetate). The 1,3-dioxo-4-(tetrahydropyran-4-ylmethyl)-1,2,3,4-tetrahydro-1λ^4-benzo[1,4]thiazine-7-sulfonic acid (4-ethylphenyl)isobutylamide (310 mg; 60%) is obtained in the form of a white crystalline powder after crystallization from an ethanol/heptane mixture.

MS : [M+H] = 519

6. Synthesis of intermediate 135.6



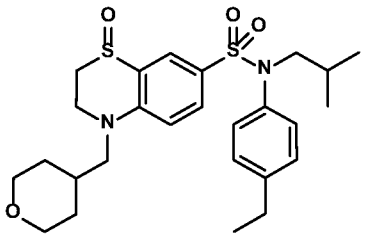
4-(Tetrahydropyran-4-ylmethyl)-3,4-dihydro-2H-benzo[1,4]thiazine-7-sulfonic acid (4-ethylphenyl)isobutylamide

3-Oxo-4-(tetrahydropyran-4-ylmethyl)-3,4-dihydro-2H-benzo[1,4]thiazine-7-sulfonic acid (4-ethylphenyl)isobutylamide (500 mg; 0.99 mmol) is added to a 1M solution of stabilized borane/tetrahydrofuran complex in tetrahydrofuran (35 ml). The reaction medium is stirred at reflux, cooled and poured at 0°C into methanol (35 ml). The solvents are concentrated.

The crude product is chromatographed on silica gel (eluent: heptane/ethyl acetate, from 0 to 50% of ethyl acetate). The 4-(tetrahydropyran-4-ylmethyl)-3,4-dihydro-2H-benzo[1,4]thiazine-7-sulfonic acid (4-ethylphenyl)isobutylamide (466 mg; 95%) is obtained in the form of a white crystalline solid after recrystallization from ether, with a compliant ^{1}H NMR.

MS : [M+H] = 489

7. Synthesis of compound 71 according to the invention



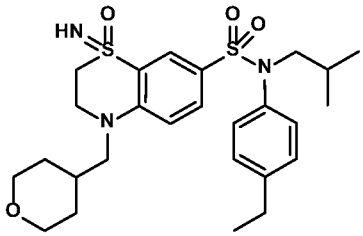
3-Chloroperoxybenzoic acid (175.4 mg; 0.78 mmol) is added, at a temperature of 0°C, to 4-(tetrahydropyran-4-ylmethyl)-3,4-dihydro-2H-benzo[1,4]thiazine-7-sulfonic acid (4-ethylphenyl)isobutylamide (425.0 mg; 0.87 mmol) dissolved in dichloromethane (8.5 ml). The reaction medium is stirred for 15 minutes at room temperature, hydrolyzed with aqueous 10% $Na_2S_2O_3$ solution and then extracted with dichloromethane. The organic phases are combined, washed with 0.1N sodium hydroxide solution and then with brine, dried (Na_2SO_4) and concentrated.

The crude product is chromatographed on silica gel (eluent: heptane/ethyl acetate, from 0 to 100% of ethyl acetate and then dichloromethane/methanol, from 0 to 10% of methanol). The 1-oxo-4-(tetrahydropyran-4-ylmethyl)-1,2,3,4-tetrahydro-1λ^4-benzo[1,4]thiazine-7-sulfonic acid (4-ethylphenyl)isobutylamide (379 mg; 86%) is obtained in the form of a white crystalline powder after crystallization from an ether/heptane mixture.

1H NMR (DMSO-d6) δ: 0.84 (d, J = 6.7 Hz, 6H), 1.19 (t, J = 7.6 Hz, 3H), 1.35 (dddd, J = 34.9, 26.9, 14.1, 8.5 Hz, 3H), 1.53 – 1.61 (m, 2H), 2.02 (ddd, J = 11.6, 7.6, 3.7 Hz, 1H), 2.61 (q, J = 7.6 Hz, 2H), 2.87 (td, J = 13.7, 3.4 Hz, 1H), 3.14 (ddd, J = 13.9, 4.1, 2.3 Hz, 1H), 3.20 – 3.33 (m, 8H), 3.42 – 3.50 (m, 2H), 3.69 (dt, J = 14.1, 3.7 Hz, 1H), 3.82 – 3.98 (m, 3H), 6.97 – 7.04 (m, 2H), 7.09 (d, J = 9.1 Hz, 1H), 7.16 – 7.23 (m, 2H), 7.35 (dd, J = 9.1, 2.3 Hz, 1H), 7.54 (d, J = 2.3 Hz, 1H)

MS : [M+H] = 505

Example 136: Synthesis of 1-imino-1-oxo-4-(tetrahydropyran-4-ylmethyl)-1,2,3,4-tetrahydro-1λ^6-benzo[1,4]thiazine-7-sulfonic acid (4-ethylphenyl)isobutylamide



2,2,2-Trifluoroacetamide (185mg; 1.63 mmol), rhodium(II) acetate dimer (44 mg; 0.10 mmol), magnesium oxide (132 mg; 3.27 mmol) and iodobenzene diacetate (421 mg; 1.31 mmol) are added to a solution, degassed beforehand with argon, of 1-oxo-4-(tetrahydropyran-4-ylmethyl)-1,2,3,4-tetrahydro-1λ^4-benzo[1,4]thiazine-7-sulfonic acid (4-ethylphenyl)isobutylamide (330 mg; 0.65 mmol) in dichloromethane (16.5 ml).

The reaction medium is stirred for 16 hours at room temperature, filtered through Celite and concentrated. The residue is diluted in methanol (16.50 ml) and potassium carbonate (452 mg; 3.27 mmol) is added. The reaction medium is stirred for 30 minutes, hydrolyzed and extracted with ethyl acetate. The organic phases are combined, washed with brine, dried (Na_2SO_4) and concentrated.

The crude product is purified by preparative HPLC (C18 column, eluent: acetonitrile in water/0.1% of formic acid).

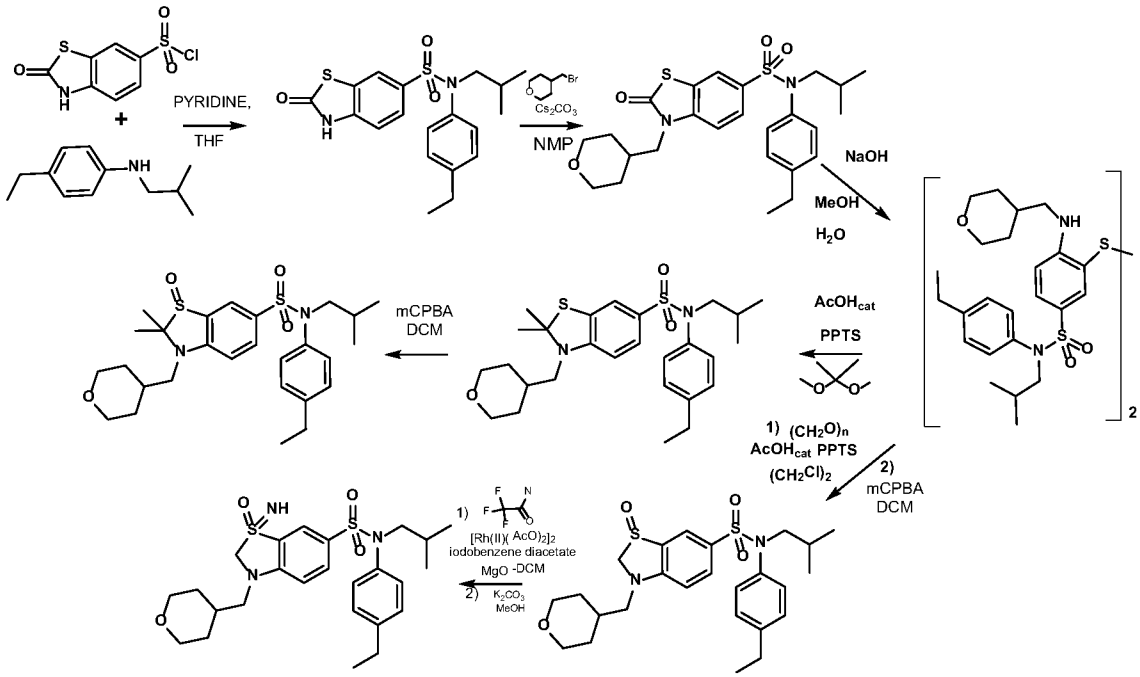
The 1-imino-1-oxo-4-(tetrahydropyran-4-ylmethyl)-1,2,3,4-tetrahydro-1λ^6-benzo[1,4]thiazine-7-sulfonic acid (4-ethylphenyl)isobutylamide (44.5 mg; 13%) is obtained in the form of a cream-colored crystalline powder after recrystallization from a heptane/dichloromethane mixture.

1H NMR (DMSO-d6) δ: 0.73 – 0.94 (m, 7H), 1.19 (t, J = 7.6 Hz, 3H), 1.22 – 1.36 (m, 4H), 1.42 (dt, J = 13.6, 6.8 Hz, 1H), 1.58 (d, J = 13.1 Hz, 2H), 1.85 – 2.10 (m, 1H), 2.61 (q, J = 7.6 Hz, 2H), 3.20 – 3.32 (m, 4H), 3.34 – 3.51 (m, 3H), 3.86 (dd, J = 11.4, 4.0 Hz, 2H), 3.94 (p, J = 3.7 Hz, 2H), 4.68 (s, 1H), 7.00 (dd, J = 15.4, 8.7 Hz, 3H), 7.20 (d, J = 8.1 Hz, 2H), 7.27 (dd, J = 9.2, 2.4 Hz, 1H), 7.86 (d, J = 2.4 Hz, 1H).

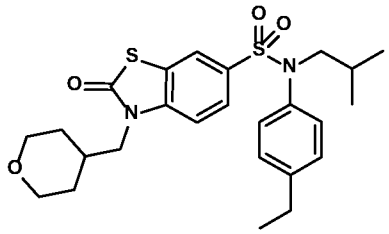
MS : [M+H] = 520

Part X: Synthesis of sulfur-based sulfonamides via reaction scheme 10

Reaction scheme 10

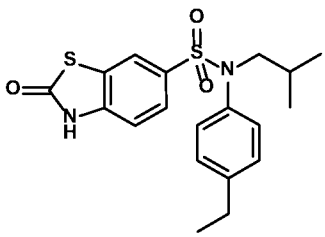

PYRIDINE,
THF
Cs2CO3
NMP
NaOH
MeOH
H2O
mCPBA
DCM
AcOHcat
PPTS
1) (CH2O)n
AcOHcat PPTS
(CH2Cl)2
2)
mCPBA
DCM
1)
[Rh(II)(AcO)2]2
iodobenzene diacetate
MgO -DCM
2)
K2CO3
MeOH

Example 137: Synthesis of 3-oxo-4-(tetrahydropyran-4-ylmethyl)-3,4-dihydro-2H-benzo[1,4]thiazine-7-sulfonic acid (4-ethylphenyl)isobutylamide



Compound 72

1. Synthesis of intermediate 137.1



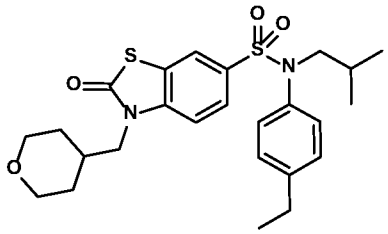
2-Oxo-2,3-dihydrobenzothiazole-6-sulfonic acid (4-ethylphenyl)isobutylamide

2-Oxo-2,3-dihydrobenzothiazole-6-sulfonyl chloride (2.97 g; 11.28 mmol) is added to (4-ethylphenyl)isobutylamine (2.00 g; 11.28 mmol) and pyridine (5.5 ml; 67.69 mmol) dissolved in tetrahydrofuran (40 ml). The reaction medium is stirred for 16 hours at room temperature, hydrolyzed and extracted with ethyl acetate. The organic phases are combined, washed with saturated NH_4Cl solution and then with brine, dried ($MgSO_4$) and concentrated.

The crude product is chromatographed on silica gel (eluent: heptane/ethyl acetate, from 0 to 10% of ethyl acetate). The 2-oxo-2,3-dihydrobenzothiazole-6-sulfonic acid (4-ethylphenyl)isobutylamide (2.67 g; 61%) is obtained in the form of a flaky white solid with a compliant ^1H NMR.

MS : [M+H] = 391

2. Synthesis of compound 72 according to the invention



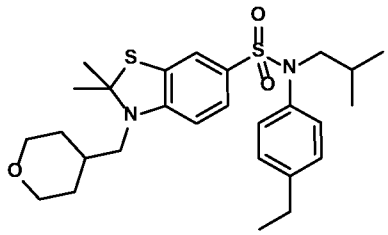
4-(Bromomethyl)tetrahydropyran (2.25 g; 12.55 mmol) is added to 2-oxo-2,3-dihydrobenzothiazole-6-sulfonic acid (4-ethylphenyl)isobutylamide (2.45 g; 6.27 mmol) and cesium carbonate (3.07 g; 9.41 mmol) dissolved in 1-methyl-2-pyrrolidone (50 ml). The reaction medium is stirred for 4 hours at 90°C, hydrolyzed and extracted with ethyl acetate. The organic phases are combined and then washed with brine, dried (Na_2SO_4) and concentrated.

The crude product is chromatographed on silica gel (eluent: heptane/ethyl acetate, from 0 to 60% of ethyl acetate). The 3-oxo-4-(tetrahydropyran-4-ylmethyl)-3,4-dihydro-2H-benzo[1,4]thiazine-7-sulfonic acid (4-ethylphenyl)isobutylamide (2.19 g; 72%) is obtained in the form of a white crystalline solid.

1H NMR (DMSO-d6) δ: 0.85 (d, J = 6.6 Hz, 7H), 1.13 – 1.22 (m, 4H), 1.24 – 1.55 (m, 6H), 2.03 (ddt, J = 10.8, 6.9, 3.4 Hz, 1H), 2.50 – 2.66 (m, 3H), 3.23 (td, J = 11.6, 2.1 Hz, 2H), 3.34 (s, 1H), 3.83 (ddd, J = 11.3, 4.4, 1.9 Hz, 2H), 3.90 (d, J = 7.3 Hz, 2H), 6.96 – 7.04 (m, 2H), 7.14 – 7.22 (m, 2H), 7.42 (dd, J = 8.6, 1.9 Hz, 1H), 7.57 (s, 1H), 8.05 (d, J = 1.9 Hz, 1H)

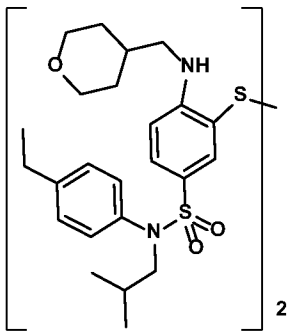
MS : [M+H] = 489

Example 138: Synthesis of 2,2-dimethyl-3-(tetrahydropyran-4-ylmethyl)-2,3-dihydrobenzothiazole-6-sulfonic acid (4-ethylphenyl)isobutylamide



Compound 73

1. Synthesis of intermediate 138.1



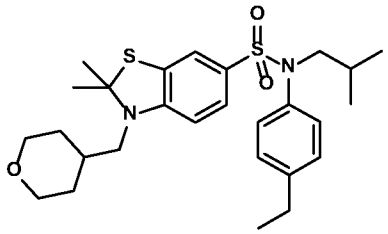
3,3'-disulfanediylbis(N-(4-ethylphenyl)-N-isobutyl-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)benzenesulfonamide

A mixture of 2-oxo-3-(tetrahydropyran-4-ylmethyl)-2,3-dihydrobenzothiazole-6-sulfonic acid (4-ethylphenyl)isobutylamide (500 mg; 1.02 mmol) and sodium hydroxide (410 mg; 10.23 mmol), methanol (6 ml) and water (100 µl) is stirred for 16 hours at a temperature of 80°C. The reaction medium is diluted with 20 ml of ethyl acetate.

The organic phase is washed with 20 ml of saturated NH_4Cl solution, 20 ml of saturated $NaHCO_3$ solution and 20 ml of water, dried ($MgSO_4$), filtered and concentrated to dryness. The 3,3'-disulfanediylbis(N-(4-ethylphenyl)-N-isobutyl-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)benzenesulfonamide (500 mg; 53%) is obtained in the form of a yellow oil with a compliant ^1H NMR.

MS : [M+H] = 923

2. Synthesis of compound 73 according to the invention



2,2-dimethyl-3-(tetrahydropyran-4-ylmethyl)-2,3-dihydrobenzothiazole-6-sulfonic acid (4-ethylphenyl)isobutylamide

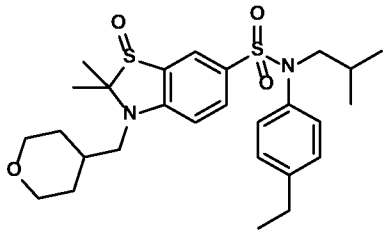
2,2-Dimethoxypropane (1.0 ml; 8.35 mmol) and pyridinium p-toluenesulfonate (245 mg; 0.97 mmol) are added to 3,3'-disulfanediylbis(N-(4-ethylphenyl)-N-isobutyl-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)benzenesulfonamide (300 mg; 0.32 mmol). The reaction medium is stirred for 16 hours at a temperature of 80°C. 3 drops of acetic acid are then added and the reaction medium is stirred for 2 hours at 80°C.

The crude product is purified by preparative HPLC (C18 column, eluent: acetonitrile in water/0.1% of formic acid). The 2,2-dimethyl-3-(tetrahydropyran-4-ylmethyl)-2,3-dihydrobenzothiazole-6-sulfonic acid (4-ethylphenyl)isobutylamide (70 mg; 40%) is obtained in the form of a clear yellow oil.

1H NMR (DMSO-d6) δ: 0.83 (d, J = 6.7 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.21 – 1.33 (m, 2H), 1.31 – 1.47 (m, 1H), 1.63 (s, 8H), 1.80 (s, 1H), 2.60 (q, J = 7.6 Hz, 2H), 3.08 (d, J = 7.2 Hz, 2H), 3.22 – 3.30 (m, 4H), 3.87 (dd, J = 11.5, 3.8 Hz, 2H), 6.47 (d, J = 8.4 Hz, 1H), 6.99 – 7.03 (m, 2H), 7.07 (dq, J = 8.3, 2.1 Hz, 1H), 7.12 (d, J = 2.0 Hz, 1H), 7.16 – 7.21 (m, 2H)

.MS : [M+H] = 503

Example 139: Synthesis of 2,2-dimethyl-1-oxo-3-(tetrahydropyran-4-ylmethyl)-2,3-dihydro-1H-1λ^4-benzothiazole-6-sulfonic acid (4-ethylphenyl)isobutylamide



Compound 74

3-Chloroperoxybenzoic acid (30 mg; 0.15 mmol) is added to a solution of 2,2-dimethyl-3-(tetrahydropyran-4-ylmethyl)-2,3-dihydrobenzothiazole-6-sulfonic acid (4-ethylphenyl)isobutylamide (70 mg; 0.14 mmol) in dichloromethane (2 ml). The reaction medium is stirred for 45 minutes at room temperature, diluted with dichloromethane (10 ml) and water (5 ml), and extracted.

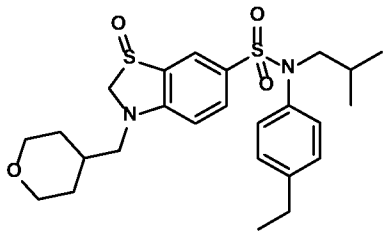
The organic phases are combined, dried ($MgSO_4$), filtered and concentrated.

The crude product is purified by preparative HPLC (C18 column, eluent: acetonitrile in water/0.1% of formic acid). The 2,2-dimethyl-1-oxo-3-(tetrahydropyran-4-ylmethyl)-2,3-dihydro-1H-1λ^4-benzothiazole-6-sulfonic acid (4-ethylphenyl)isobutylamide (20 mg; 28%) is obtained in the form of a pale yellow solid.

1H NMR (DMSO-d6) δ: 0.85 (d, J = 6.7 Hz, 6H), 1.19 (dd, J = 15.7, 8.1 Hz, 6H), 1.25 – 1.49 (m, 3H), 1.56 (d, J = 12.1 Hz, 2H), 1.64 (s, 3H), 1.90 (s, 1H), 2.60 (q, J = 7.6 Hz, 2H), 3.18 – 3.28 (m, 2H), 3.87 (dt, J = 10.6, 4.9 Hz, 2H), 7.00 (t, J = 8.9 Hz, 3H), 7.19 (d, J = 8.1 Hz, 2H), 7.46 (dd, J = 8.5, 2.1 Hz, 1H), 8.00 (d, J = 2.0 Hz, 1H)

.MS : [M+H] = 519

Example 140: Synthesis of the compound 1-oxo-3-(tetrahydropyran-4-ylmethyl)-2,3-dihydro-1H-1λ^4-benzothiazole-6-sulfonic acid (4-ethylphenyl)isobutylamide



Compound 75

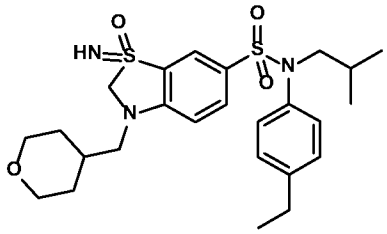
Paraformaldehyde (473 ml; 1.08 mmol), pyridinium p-toluenesulfonate (163 mg; 0.65 mmol) and 1,2-dichloroethane (3 ml) are added to 3,3'-disulfanediylbis(N-(4-ethylphenyl)-N-isobutyl-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)benzenesulfonamide (200 mg; 0.22 mmol).

The reaction medium is stirred for 16 hours at 80°C, filtered, diluted with dichloromethane, dried ($MgSO_4$) and filtered. 3-Chloroperoxybenzoic acid (107 mg; 0.48 mmol) is added to the filtrate. The reaction medium is stirred for 30 minutes at room temperature, diluted with dichloromethane (20 ml) and water (10 ml), and extracted. The organic phase is washed with a sodium sulfite solution (20 ml) and with water (20 ml), dried ($MgSO_4$), filtered and concentrated.

The crude product is purified by preparative HPLC (C18 column, eluent: acetonitrile in water/0.1% of formic acid). The 1-oxo-3-(tetrahydropyran-4-ylmethyl)-2,3-dihydro-1H-1λ^4-benzothiazole-6-sulfonic acid (4-ethylphenyl)isobutylamide (70 mg; 66%) is obtained in the form of a white solid.

1H NMR (DMSO-d6) δ: 0.85 (dd, J = 6.7, 3.5 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.22 – 1.34 (m, 2H), 1.42 (dt, J = 13.6, 6.9 Hz, 1H), 1.55 (t, J = 13.0 Hz, 2H), 1.87 – 2.09 (m, 1H), 2.61 (q, J = 7.5 Hz, 2H), 3.27 (ddt, J = 12.1, 9.7, 6.3 Hz, 4H), 3.40 (dd, J = 14.5, 7.4 Hz, 1H), 3.54 (dd, J = 14.5, 7.2 Hz, 1H), 3.81 – 3.89 (m, 2H), 4.49 (d, J = 13.6 Hz, 1H), 4.76 (d, J = 13.6 Hz, 1H), 6.95 – 7.04 (m, 2H), 7.11 (d, J = 9.0 Hz, 1H), 7.19 (d, J = 8.3 Hz, 2H), 7.43 (dd, J = 8.8, 2.0 Hz, 1H), 8.02 (d, J = 2.0 Hz, 1H).MS : [M+H] = 491

Example 141: Synthesis of 1-imino-1-oxo-3-(tetrahydropyran-4-ylmethyl)-2,3-dihydro-1H-1λ⁶-benzothiazole-6-sulfonic acid (4-ethylphenyl)isobutylamide



Compound 76

2,2,2-Trifluoroacetamide (40.3 mg; 0.36 mmol), rhodium(II) acetate dimer (9.5 mg; 0.02 mmol), magnesium oxide (30 mg; 0.71 mmol) and iodobenzene acetate (92 mg; 0.29 mmol) are added to a solution, degassed beforehand with argon, of 1-oxo-3-(tetrahydropyran-4-ylmethyl)-2,3-dihydro-1H-1λ⁴-benzothiazole-6-sulfonic acid (4-ethylphenyl)isobutylamide (70 mg; 0.14 mmol) in dichloromethane (2 ml). The reaction medium is stirred for 3 days at room temperature, filtered through Celite and concentrated to dryness. The residue is taken up in methanol (1 ml), to which is added potassium carbonate (100 mg; 0.71 mol). The reaction medium is stirred for 1 hour, diluted with ethyl acetate (20 ml) and extracted.

The organic phase is washed with saturated NH_4Cl solution (20 ml), with saturated $NaHCO_3$ solution (20 ml) and with water (20 ml), dried ($MgSO_4$), filtered and concentrated.

The crude product is purified by preparative HPLC (C18 column, eluent: acetonitrile in water/0.1% of formic acid). The 1-imino-1-oxo-3-(tetrahydropyran-4-ylmethyl)-2,3-dihydro-1H-1λ⁶-benzothiazole-6-sulfonic acid (4-ethylphenyl)isobutylamide (25 mg; 33.34%) is obtained in the form of a beige-colored solid.

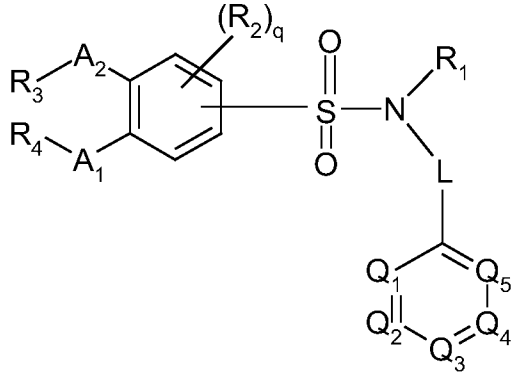
1H NMR (DMSO-d6) δ: 0.84 (d, J = 6.4 Hz, 6H), 1.18 (t, J = 7.6 Hz, 3H), 1.29 (ddd, J = 18.9, 11.8, 7.0 Hz, 2H), 1.42 (p, J = 6.9 Hz, 1H), 1.48 – 1.65 (m, 2H), 1.93 (d, J = 11.7 Hz, 1H), 2.61 (q, J = 7.5 Hz, 2H), 3.25 (m, 4H), 3.46 (t, J = 7.0 Hz, 2H), 3.86 (d, J = 9.7 Hz, 2H), 4.49 (t, J = 4.3 Hz, 2H), 7.01 (d, J = 8.0 Hz, 2H), 7.08

– 7.24 (m, 4H), 7.37 (dd, J = 9.4, 2.3 Hz, 1H), 7.50 (d, J = 2.4 Hz, 1H), 8.23 (d, J = 4.9 Hz, 1H)

.MS : [M+H] = 506

CLAIMS

1. Compound of formula (I), and also the pharmaceutically acceptable addition salts thereof, hydrates thereof and/or solvates thereof:



(I)

in which formula (I):

- q denotes zero or a natural integer ranging from 1 to 3,
- L represents a single bond or a methylene group CH_2,
- R^1 represents a linear or branched C_3-C_5 alkyl radical, a C_3-C_5 cycloalkyl radical, a linear or branched C_2-C_5 alkenyl radical, a (C_1)alkyl(C_3-C_5)cycloalkyl radical, a C_4-C_5 heterocycloalkyl radical, a (C_1)alkyl(C_4-C_5)heterocycloalkyl radical,
- R_2 represents a hydrogen atom or a halogen atom, a linear or branched C_1-C_5 alkyl radical, a linear or branched C_2-C_4 alkenyl radical, a C_1-C_4 alkoxy radical, a cyano group -CN; the alkyl, alkenyl and alkoxy radicals possibly being substituted with one or more halogen atoms,
- R^3 represents a hydrogen atom, a C_1-C_3 alkyl radical or an amino $–NH_2$ radical,
- R^4 represents a hydrogen atom or a group $(CHR^5)_n$-$(Z)_o$-$(CHR'^5)_p$-R^6,
- n, o and p, which may be identical or different, denote zero or a natural integer ranging from 1 to 3,
- Z represents a divalent group chosen from $–CH_2–$, –NH– and –O–,
- R^5 and R'^5, which may be identical or different, represent a hydrogen atom, a methyl radical -CH_3, a hydroxyl radical -OH, a C_1 hydroxyalkyl radical, a carboxylic radical -COOH,
- R^6 represents:

- a hydrogen atom or a halogen atom,
- a heterocycloalkyl radical optionally substituted with one or more halogen atoms, one or more linear or branched C_1-C_3 alkyl groups, one or more -OH groups, one or more carbonyl functions =O, one or more linear or branched C_1-C_4 hydroxyalkyl groups, a pyrrolidine ring, one or more amino groups, one or more groups $–C(=O)R^7$, one or more groups $S(=O)_2R^7$; R^7 representing a linear or branched C_1-C_3 alkyl radical, a hydroxyl radical -OH, a linear or branched C_1-C_4 alkoxy radical, or an amino radical $N(R^{7a})(R^{7b})$; with R^{7a} and R^{7b}, which may be identical or different, denoting a hydrogen atom, a linear or branched C_1-C_3 alkyl radical or a cyclopropyl radical,
- a C_3-C_6 cycloalkyl radical optionally substituted with one or more -OH groups;
- an aromatic or heteroaromatic radical optionally substituted with one or more halogen atoms, one or more linear or branched C_1-C_3 alkyl groups optionally substituted with one or more halogen atoms, one or more C_1-C_3 alkoxy groups, one or more amino groups $–NR^{11}R^{12}$, one or more groups $–COR^{11}$, a carbonyl function (=O), one or more groups $–OR^{11}$, one or more C_1-C_4 hydroxyalkyl groups, one or more groups $–COOR^{11}$, one or more amido groups $–CONR^{11}R^{12}$, one or more groups $–SOR^{11}$, one or more groups $–SO_2R^{11}$, one or more groups $–NHCOR^{11}$, one or more groups $–NHCOOR^{11}$, one or more groups $–SO_2NR^{11}R^{12}$ or one or more -CN groups; R^{11} and R^{12}, which may be identical or different, representing a hydrogen atom or a linear or branched C_1-C_3 alkyl radical optionally substituted with one or more halogen atoms;

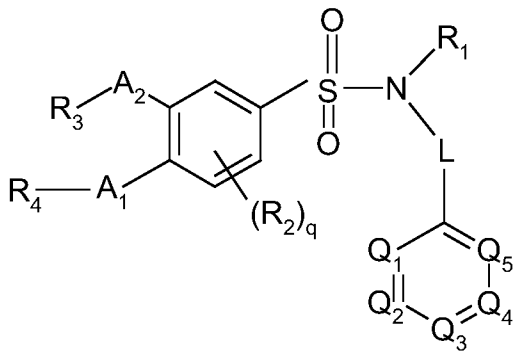
- A_1 represents a divalent group chosen from $–NR^a–$, –O–, –S–, –SO–, $–SO_2–$, $–SO(=NH)–$, $–CH_2–$, –C=C–, $–CH(R^a)–$;
- A_2 represents a single bond or a divalent group chosen from –S–, –SO–, $–SO_2–$, $–SO(=N\text{-}R^b)–$, –CH(OH)–, –C(=O)O–;

given that:

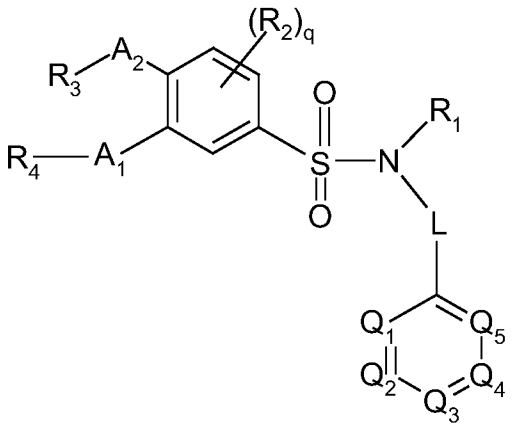
- when A_1 represents one of the divalent groups chosen from: $–NR^a–$, –O–, $–CH_2–$, –C=C– and $–CH(R^a)$, then A_2 does not represent the divalent group –CH(OH)– and –C(=O)O– and R_3 does not represent a hydrogen atom, an amino radical $–NH_2$ or a C_1-C_3 alkyl radical,
- when A_2 represents a single bond and R_3 represents a hydrogen atom, then A_1 represents one of the divalent groups chosen from: –SO– and –SO(=NH)-,

- R^a represents a hydrogen atom, a linear or branched C_1-C_3 alkyl radical or an acetyl radical –C(=O)CH_3,
- R^b represents a hydrogen atom, a linear or branched C_1-C_3 alkyl radical or a cyclopropyl group,
- Q_1, Q_2, Q_3, Q_4 and Q_5, which may be identical or different, represent a nitrogen atom or a group –CR'_2,
- when A_2 represents a divalent group chosen from –S-, –SO, –SO_2– and –SO(=N-R^b)–, then R^a and R^3 can form, together with the carbon atoms to which they are attached, a heterocycloalkyl group which may be optionally substituted with one or more carbonyl functions, one or more C_1-C_3 alkyl radicals,
- when A_1 represents –NR^a–, then R^a and R^4 can form, together with the nitrogen atom to which they are attached, a C_2-C_{10} heterocycloalkyl group optionally comprising 1 to 3 heteroatoms chosen from a sulfur atom, a nitrogen atom and an oxygen atom; said heterocycloalkyl group being optionally substituted with at least one radical R^{14},
- R^{14} represents a linear or branched C_1-C_3 alkyl radical, a linear or branched C_1-C_3 alkoxy radical, a halogen atom, a hydroxyl group -OH, a cyano group -CN, a group –$CONR^{15}R^{16}$, a group –SO_2R^{15}, a group –COR^{15} or an amino group –$NR^{15}R^{16}$; R^{15} and R^{16}, which may be identical or different, representing a hydrogen atom or a linear or branched C_1-C_3 alkyl radical.

2. Compound of formula (I) as claimed in claim 1, chosen from the compounds of formula (Ia) and/or (Ib) below:



(Ia)

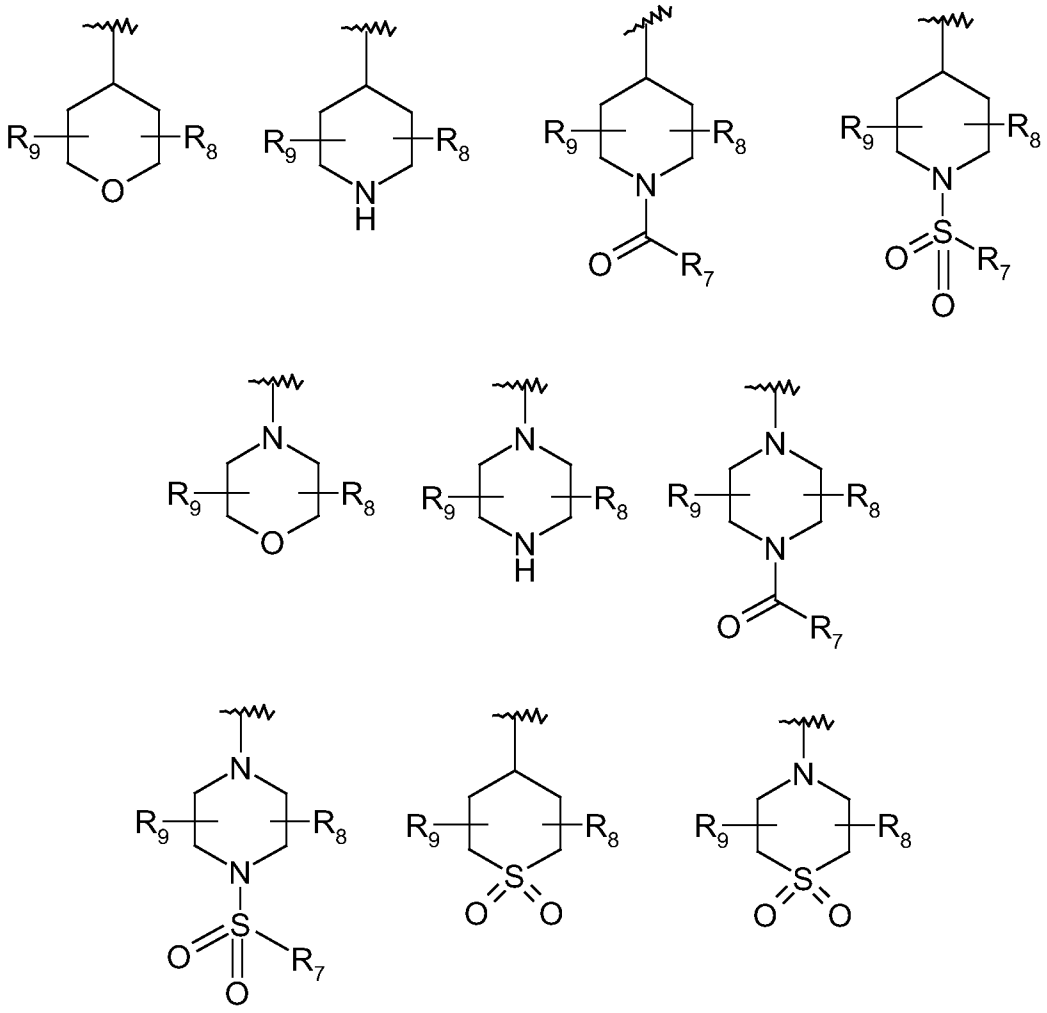


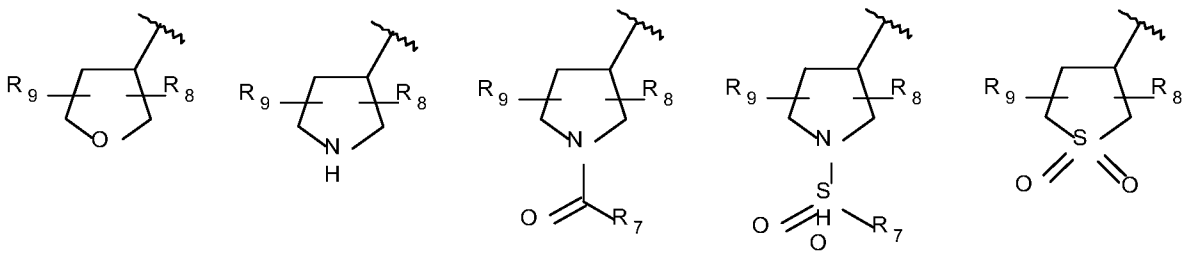
(Ib)

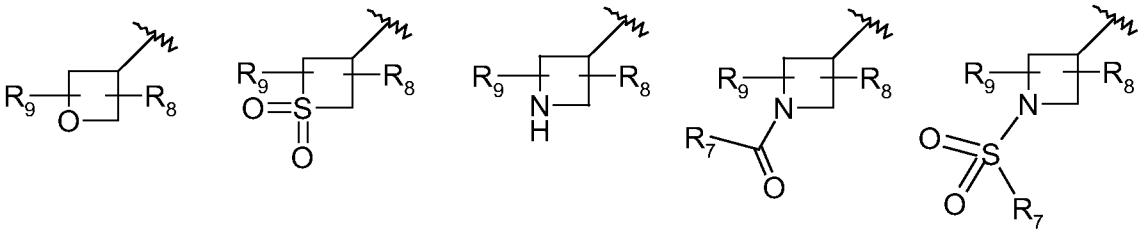
in which formulae (Ia) and (Ib) R^1, R_2, R'_2, R^3, R^4, R^5, R'^5, R^6, R^7, R^{7a}, R^{7b}, R^{11}, R^{12}, R^a, R^b, Z, Q_1, Q_2, Q_3, Q_4, Q_5, A_1, A_2, L and the indices q, n, o and p have the same meanings as in formula (I) as defined in claim 1.

3. Compound as claimed in claim 1 or 2, characterized in that L represents a single bond.

4. Compound of formula (I) as claimed in any one of claims 1 to 3, characterized in that R^6 represents a heterocyclic radical chosen from the following heterocycles:



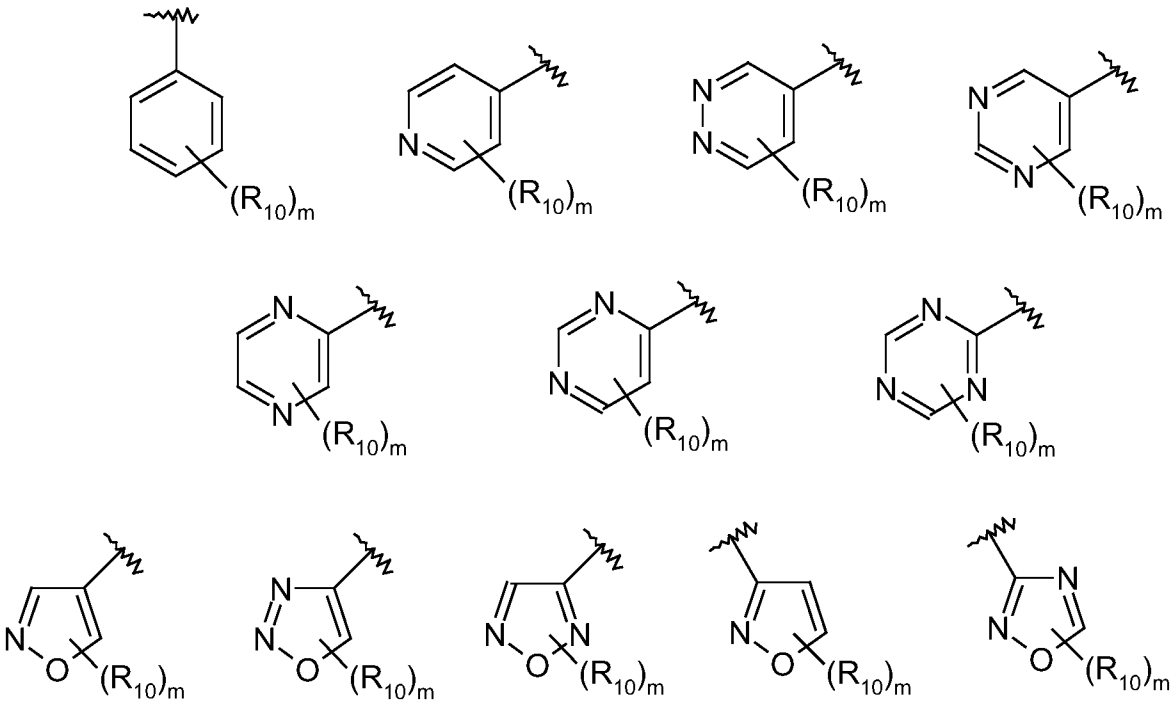




in which:

- R_7 represents a linear or branched C_1-C_3 alkyl radical, a hydroxyl radical -OH, a C_1-C_3 alkoxy radical or an amino radical $N(R^{7a})(R^{7b})$,
- R^{7a} and R^{7b}, which may be identical or different, denote a hydrogen atom, a linear or branched C_1-C_3 alkyl radical or a cyclopropyl radical,
- R_8 and R_9, which may be identical or different, represent a hydrogen atom, a linear or branched C_1-C_3 alkyl radical, a hydroxyl group -OH, a carbonyl group, a (C_1)hydroxyalkyl radical (CH_2OH), an amino group $-NH_2$,
- R_8 and R_9 can form, together with the carbon atoms to which they are attached, a 5- to 7-membered carbocyclic ring.

5. Compound of formula (I) as claimed in any one of claims 1 to 3, characterized in that R^6 represents an aromatic or heteroaromatic radical chosen from:



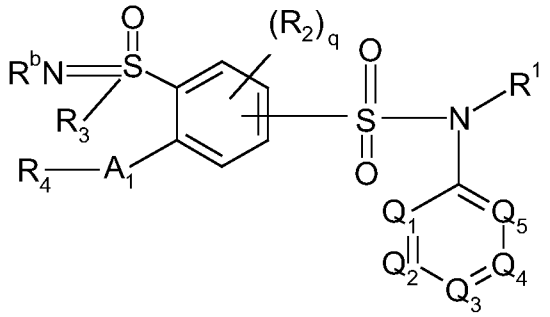
in which:

- R_{10} represents a hydrogen atom or a halogen atom; a linear or branched C_1-C_3 alkyl radical optionally substituted with one or more halogen atoms; a carbonyl function (=O), a group OR^{11}, a C_1-C_4 hydroxyalkyl group, an amino group $-NR^{11}R^{12}$, a group $-COR^{11}$, a group $-COOR^{11}$, an amido group $-CONR^{11}R^{12}$, a group $-SOR^{11}$, a group $-SO_2R^{11}$, a group $-NHCOR^{11}$, a group $-NHCOOR^{11}$, a group $-SO_2NR^{11}R^{12}$ or a cyano group –CN,

- R^{11} and R^{12}, which may be identical or different, represent a hydrogen atom or a linear or branched C_1-C_3 alkyl radical optionally substituted with one or more halogen atoms,

- m denotes zero or a natural integer ranging from 1 to 3 having the same meaning as that indicated in formula (I) defined in claim 1.

6. Compound of formula (I) as claimed in any one of claims 1 to 5, characterized in that it is chosen from the compounds of formula (II) below:



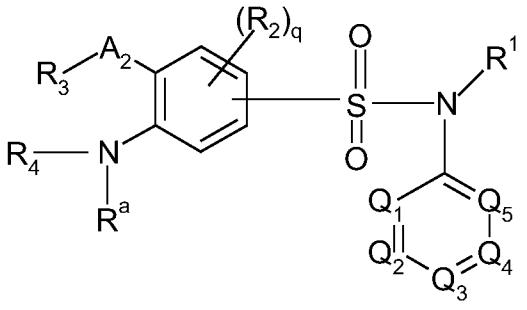
(II)

in which formula (II):

- R^3 represents a C_1-C_3 alkyl radical,

- R^1, R_2, R'_2, R^3, R^4, R^5, R'^5, R^6, R^7, R^{7a}, R^{7b}, R_8, R_9, R_{10}, R^{11}, R^{12}, R^a, R^b, Z, Q_1, Q_2, Q_3, Q_4, Q_5, A_1 and the indices q, m, n, o and p have the same meanings as in formula (I) as defined in any one of claims 1 to 5.

7. The compound of formula (I) as claimed in any one of claims 1 to 5, characterized in that it is chosen from the compounds of formula (III) below:



(III)

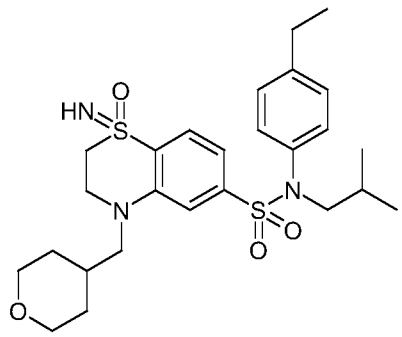
in which formula (III):

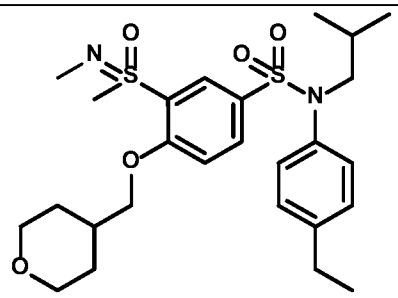
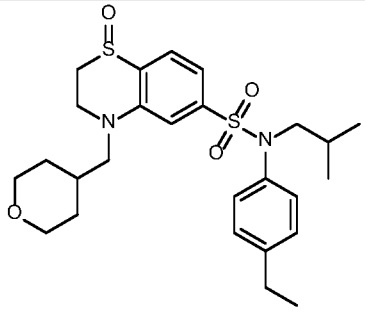
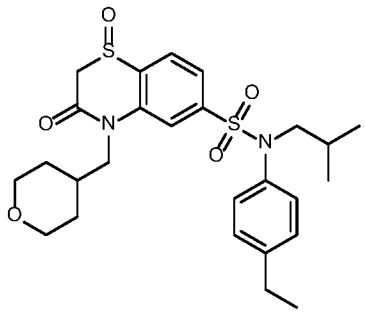
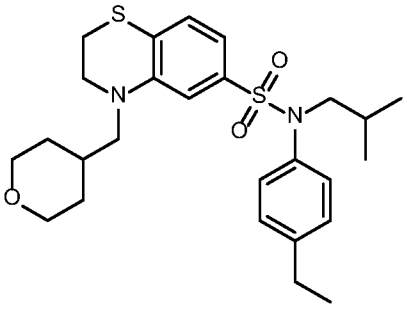
- R^1, R_2, R'_2, R^3, R^b, Q_1, Q_2, Q_3, Q_4, Q_5, A_2 and the index q have the same meanings as in formula (I) as defined in any one of claims 1 to 3,

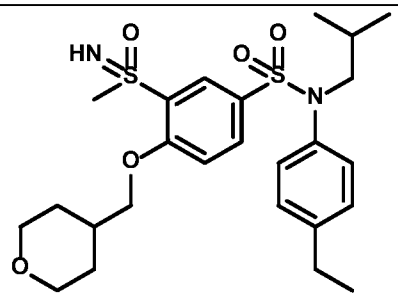
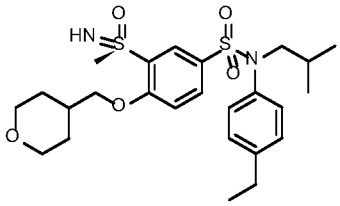
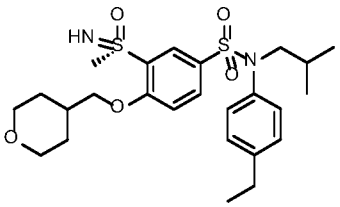
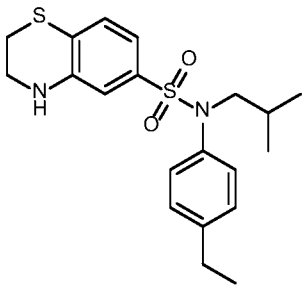
- R^a and R_4 form, together with the nitrogen atom to which they are attached, a C_2-C_{10} heterocycloalkyl group optionally comprising 1 to 3 heteroatoms chosen from a sulfur atom, a nitrogen atom and an oxygen atom; said heterocycloalkyl group being optionally substituted with at least one radical R^{14},

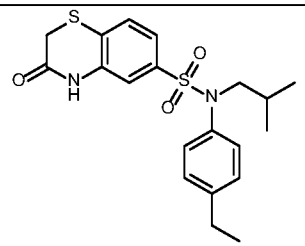
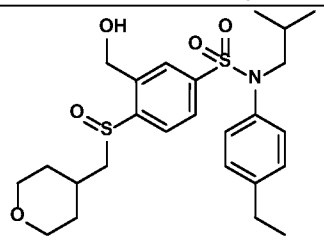
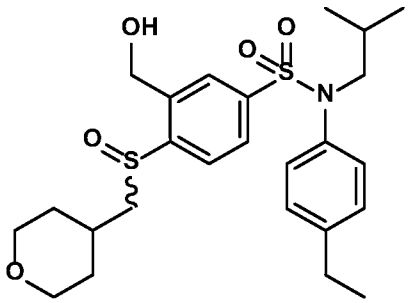
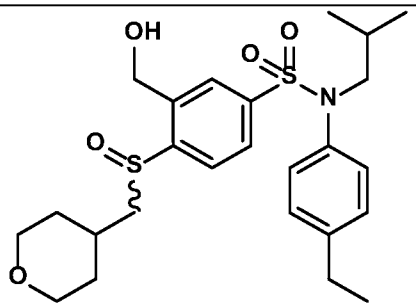
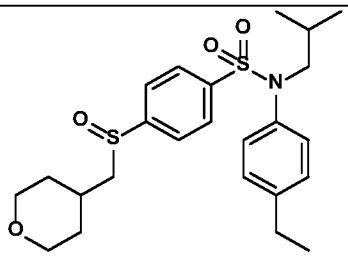
- R^{14} represents a linear or branched C_1-C_3 alkyl radical, a linear or branched C_1-C_3 alkoxy radical, a halogen atom, a hydroxyl group -OH, a cyano group -CN, a group $-CONR^{15}R^{16}$, a group $-SO_2R^{15}$, a group $-COR^{15}$ or an amino group $-NR^{15}R^{16}$; R^{15} and R^{16}, which may be identical or different, representing a hydrogen atom or a linear or branched C_1-C_3 alkyl radical.

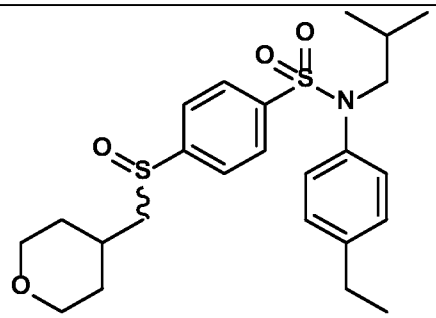
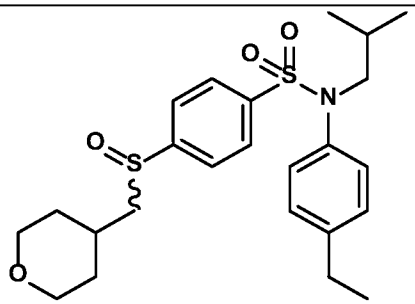
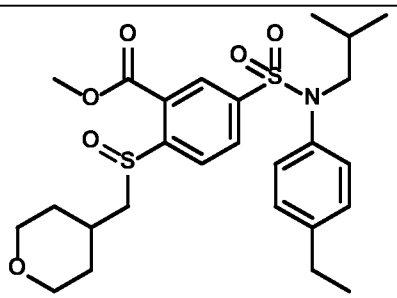
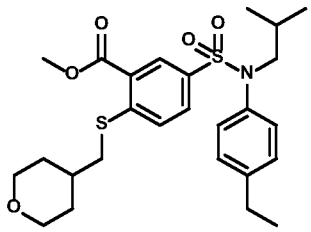
8. Compound as claimed in any one of the preceding claims, characterized in that it is chosen from the following compounds, and also the pharmaceutically acceptable addition salts thereof, hydrates thereof and/or solvates thereof:

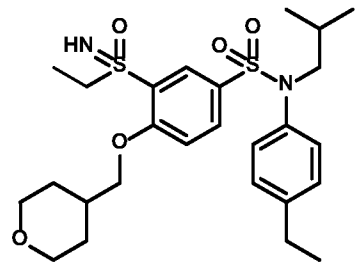
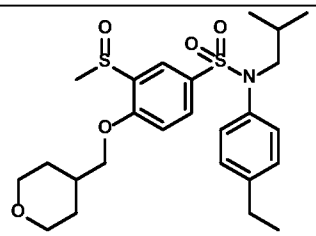
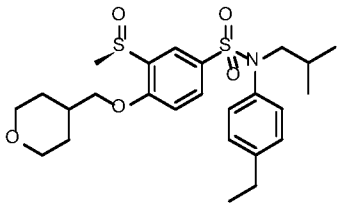
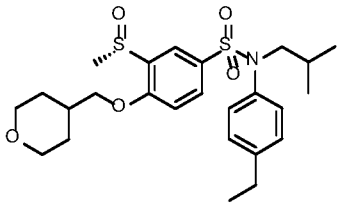
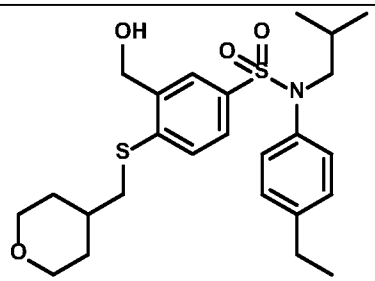
	imino-1-oxo-4-(tetrahydropyran-4-ylmethyl)-1,2,3,4-tetrahydro-1λ⁶-benzo[1,4]thiazine-7-sulfonic acid (4-ethylphenyl)isobutylamide Compound 1
	N-(4-ethylphenyl)-N-isobutyl-3-methanesulfinyl-4-(tetrahydropyran-4-ylmethoxy)benzene-N-methylsulfoximine Compound 2

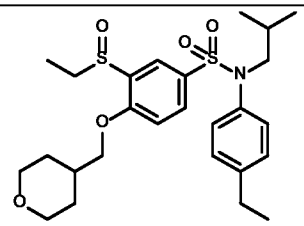
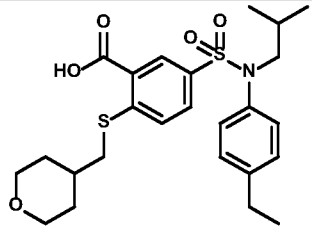
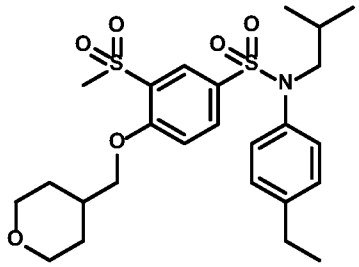
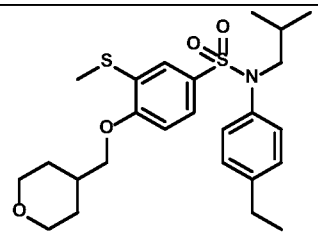
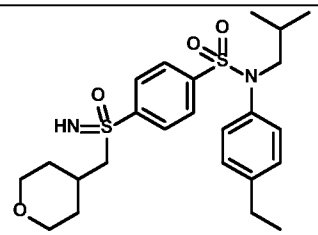
	
	1-oxo-4-(tetrahydropyran-4-ylmethyl)-1,2,3,4-tetrahydro-1λ^4-benzo[1,4]thiazine-7-sulfonic acid Compound 3
	1,3-dioxo-4-(tetrahydropyran-4-ylmethyl)-1,2,3,4-tetrahydro-1 λ^4-benzo[1,4]thiazine-6-sulfonic acid (4-ethylphenyl)isobutylamide Compound 4
	4-(tetrahydropyran-4-ylmethyl)-3,4-dihydro-2H-benzo[1,4]thiazine-6-sulfonic acid (4-ethylphenyl)isobutylamide Compound 6

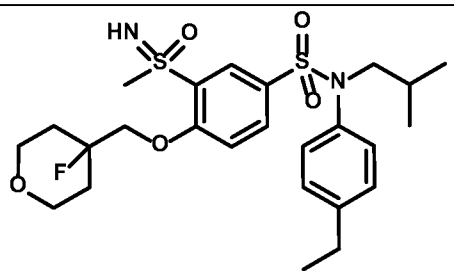
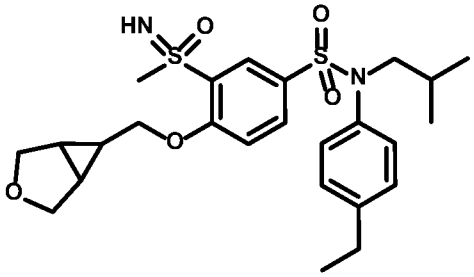
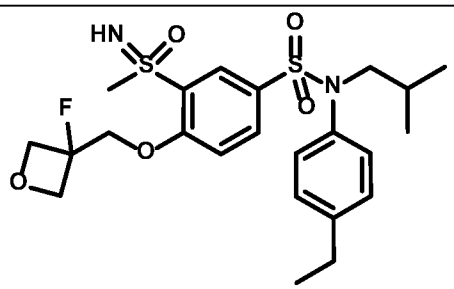
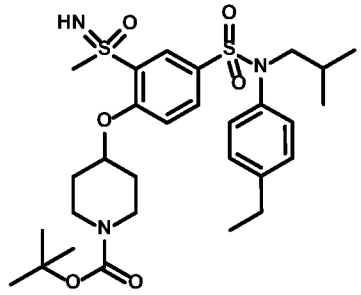
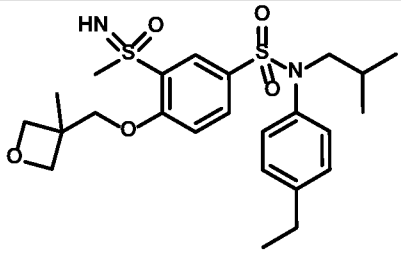
	N-(4-ethylphenyl)-N-isobutyl-3-methanesulfoximino-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide Compound 26
Chiral 	N-(4-ethylphenyl)-N-isobutyl-3-methanesulfoximino-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide compound 7 (enantiomer A)
Chiral 	N-(4-ethylphenyl)-N-isobutyl-3-methanesulfoximino-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide compound 8 (enantiomer B)
	3,4-dihydro-2H-benzo[1,4]thiazine-6-sulfonic acid (4-ethylphenyl)isobutylamide Compound 9

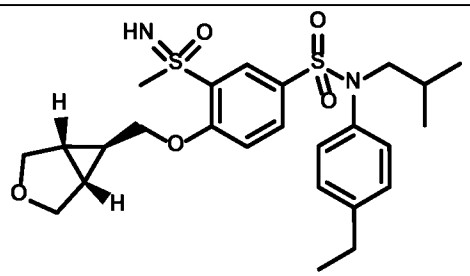
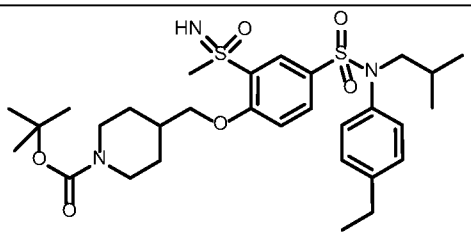
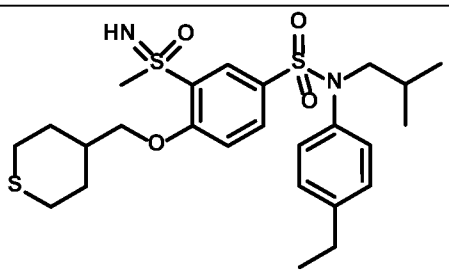
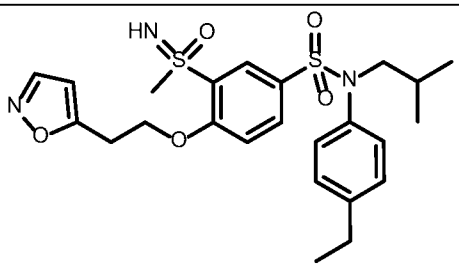
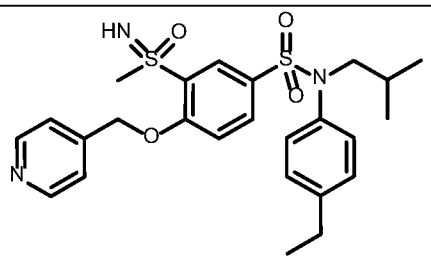
	3-oxo-3,4-dihydro-2H-benzo[1,4]thiazine-6-sulfonic acid (4-ethylphenyl)isobutylamide Compound 10
	N-(4-ethylphenyl)-3-hydroxymethyl-N-isobutyl-4-(tetrahydropyran-4-ylmethanesulfinyl)benzenesulfonamide Compound 15
	N-(4-ethylphenyl)-3-hydroxymethyl-N-isobutyl-4-(tetrahydropyran-4-ylmethanesulfinyl)benzenesulfonamide Compound 11 Enantiomer A
	N-(4-ethylphenyl)-3-hydroxymethyl-N-isobutyl-4-(tetrahydropyran-4-ylmethanesulfinyl)benzenesulfonamide Compound 12 enantiomer B
	N-(4-ethylphenyl)-N-isobutyl-4-(tetrahydropyran-4-ylmethanesulfinyl)benzenesulfonamide Compound 29

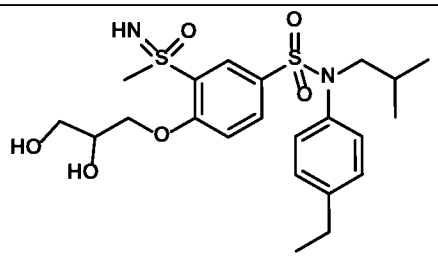
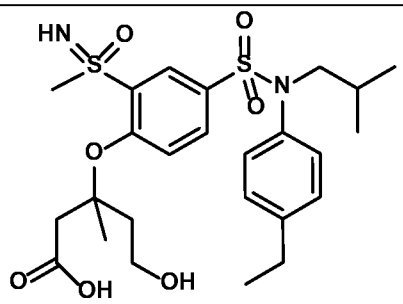
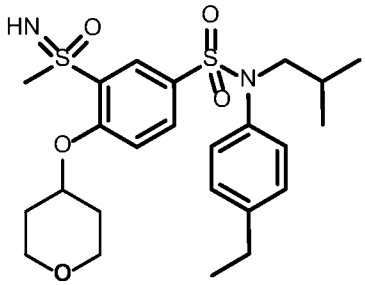
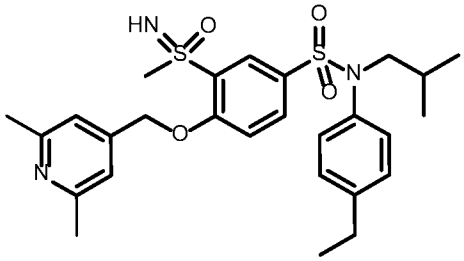
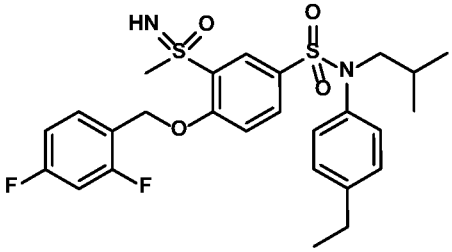
	N-(4-ethylphenyl)-N-isobutyl-4-(tetrahydropyran-4-ylmethanesulfinyl)benzenesulfonamide Compound 13 enantiomer A
	N-(4-ethylphenyl)-N-isobutyl-4-(tetrahydropyran-4-ylmethanesulfinyl)benzenesulfonamide Compound 14 enantiomer B
	methyl 5-[(4-ethylphenyl)isobutylsulfamoyl]-2-(tetrahydropyran-4-ylmethanesulfinyl)benzoate Compound 16
	methyl 5-[(4-ethylphenyl)isobutylsulfamoyl]-2-(tetrahydropyran-4-ylmethylsulfanyl)benzoate Compound 17

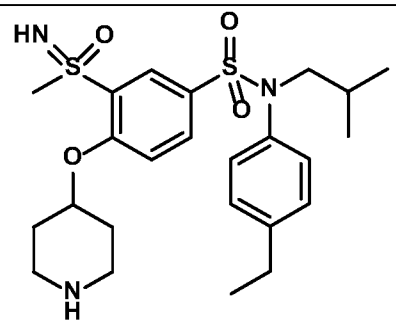
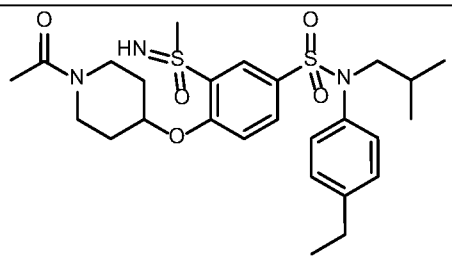
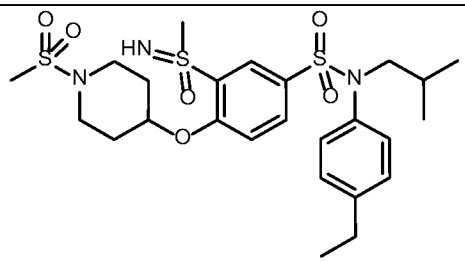
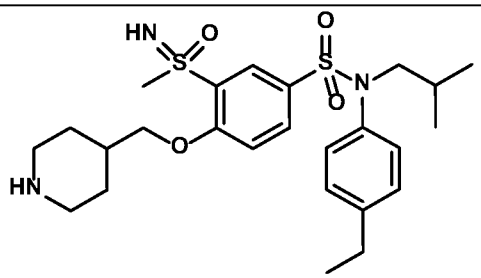
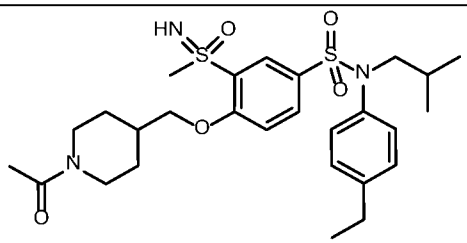
	N-(4-ethylphenyl)-N-isobutyl-3-ethanesulfoximino-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide Compound 18
	N-(4-ethylphenyl)-N-isobutyl-3-methanesulfinyl-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide Compound 27
Chiral 	N-(4-ethylphenyl)-N-isobutyl-3-methanesulfinyl-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide Compound 19 Enantiomer A
Chiral 	N-(4-ethylphenyl)-N-isobutyl-3-methanesulfinyl-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide Compound 20 Enantiomer B
	N-(4-ethylphenyl)-3-hydroxymethyl-N-isobutyl-4-(tetrahydropyran-4-ylmethylsulfanyl)benzenesulfonamide Compound 21

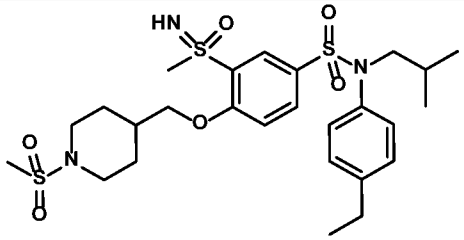
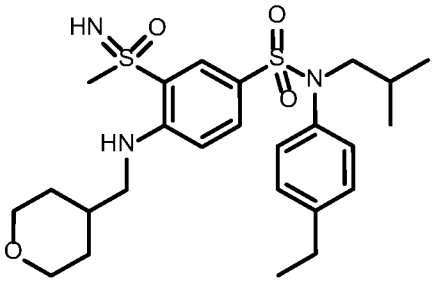
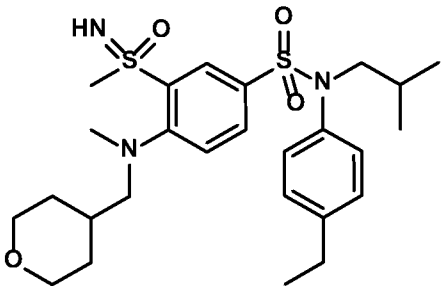
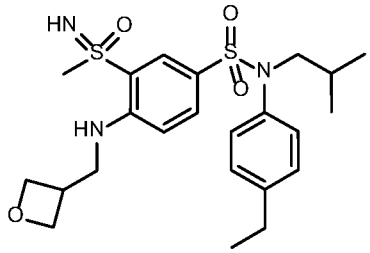
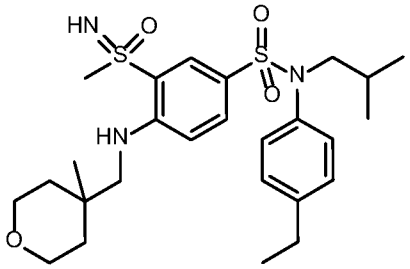
	ethanesulfinyl-N-(4-ethylphenyl)-N-isobutyl-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide Compound 22
	5-[(4-ethylphenyl)isobutylsulfamoyl]-2-(tetrahydropyran-4-ylmethylsulfanyl)benzoic acid Compound 23
	N-(4-ethylphenyl)-N-isobutyl-3-methanesulfonyl-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide Compound 24
	N-(4-ethylphenyl)-N-isobutyl-3-methylsulfanyl-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide Compound 25
	N-(4-ethylphenyl)-N-isobutyl-4-(tetrahydropyran-4-ylmethanesulfoximinyl)benzenesulfonamide Compound 28
	N-(4-ethylphenyl)-4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfona

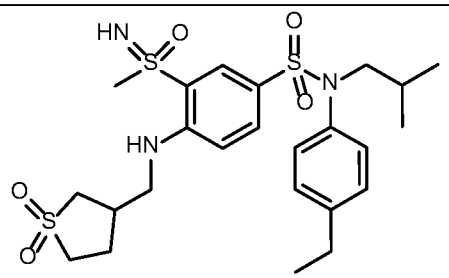
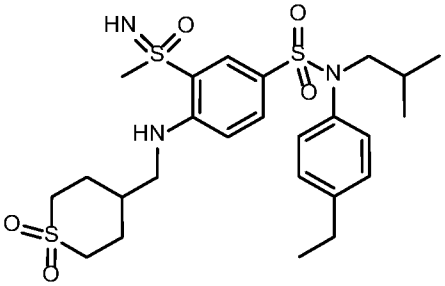
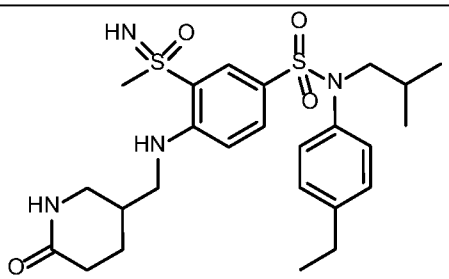
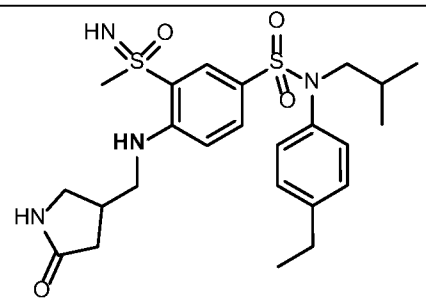
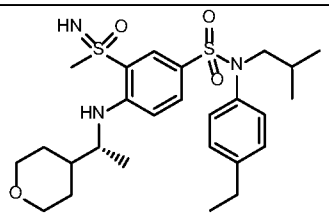
	mide Compound 30
	4-((3-oxabicyclo[3.1.0]hexan-6-yl)methoxy)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 31
	N-(4-ethylphenyl)-4-((3-fluorooxetan-3-yl)methoxy)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 32
	tert-butyl 4-(4-(N-(4-ethylphenyl)-N-isobutylsulfamoyl)-2-(S-methylsulfonimidoyl)phenoxy)piperidine-1-carboxylate Compound 33
	N-(4-ethylphenyl)-N-isobutyl-4-((3-methyloxetan-3-yl)methoxy)-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 34

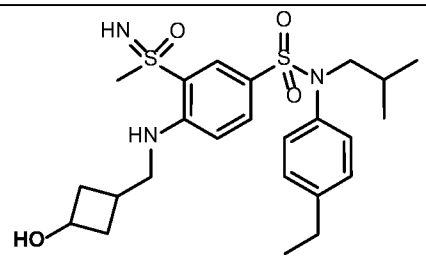
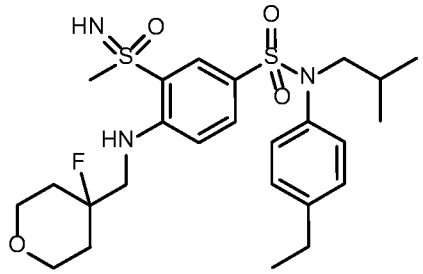
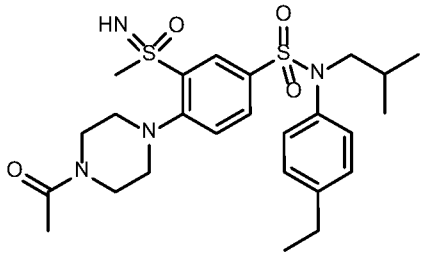
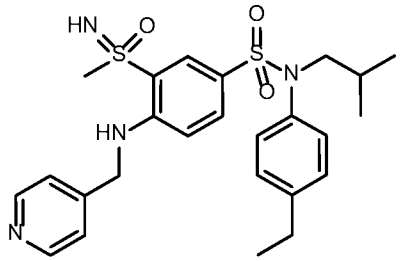
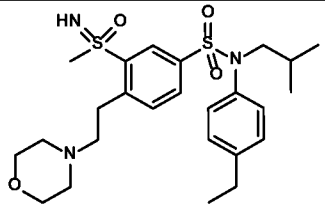
	4-(((1R,5S,6R)-3-oxabicyclo[3.1.0]hexan-6-yl)methoxy)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 35
	tert-butyl 4-((4-(N-(4-ethylphenyl)-N-isobutylsulfamoyl)-2-(S-methylsulfonimidoyl)phenoxy)methyl)piperidine-1-carboxylate Compound 36
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(pyridin-4-ylmethoxy)benzenesulfonamide Compound 37
	N-(4-ethylphenyl)-N-isobutyl-4-(2-(isoxazol-5-yl)ethoxy)-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 38
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(pyridin-4-ylmethoxy)benzenesulfonamide Compound 39

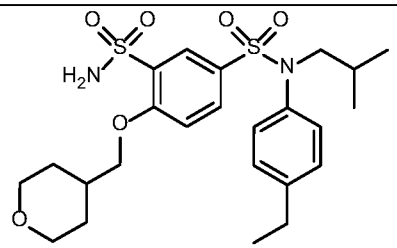
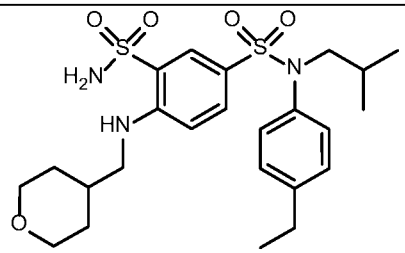
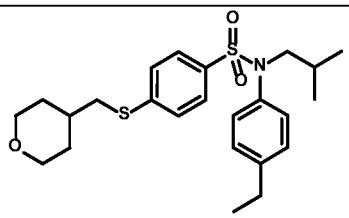
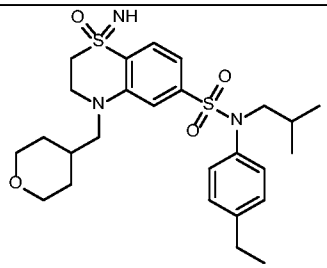
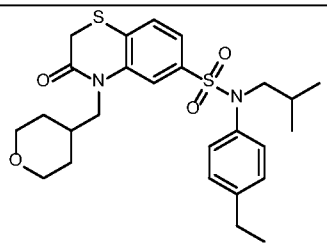
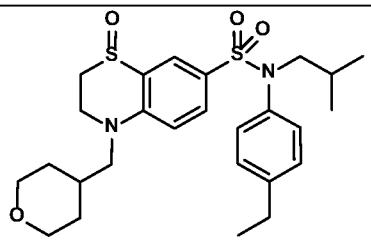
	4-(2,3-dihydroxypropoxy)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 40
	3-(4-(N-(4-ethylphenyl)-N-isobutylsulfamoyl)-2-(S-methylsulfonimidoyl)phenoxy)-5-hydroxy-3-methylpentanoic acid Compound 41
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((tetrahydro-2H-pyran-4-yl)oxy)benzenesulfonamide Compound 42
	4-((2,6-dimethylpyridin-4-yl)methoxy)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 43
	4-((2,4-difluorobenzyl)oxy)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 45

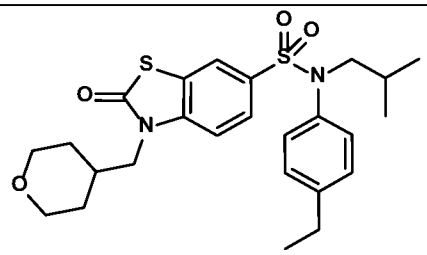
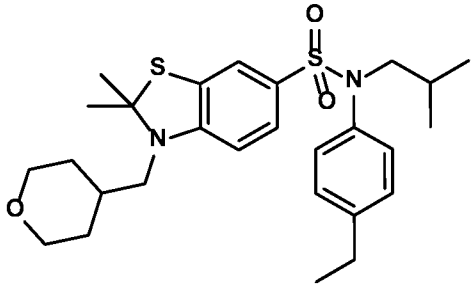
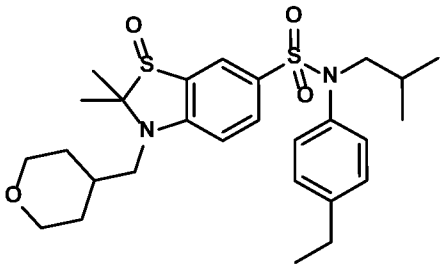
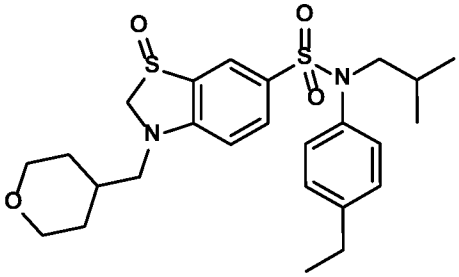
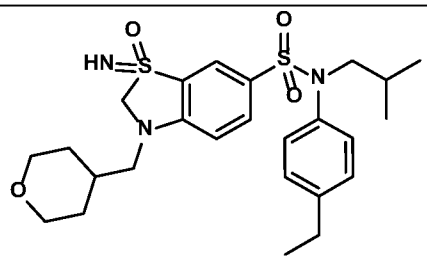
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(piperidin-4-ylmethoxy)benzenesulfonamide N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(piperidin-4-ylmethoxy)benzenesulfonamide Compound 46
	4-((1-acetylpiperidin-4-yl)oxy)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzene sulfonamide Compound 47
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((1-(methylsulfonyl)piperidin-4-yl)oxy)benzenesulfonamide Compound 48
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(piperidin-4-ylmethoxy)benzenesulfonamide Compound 49
	4-((1-acetylpiperidin-4-yl)methoxy)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 50

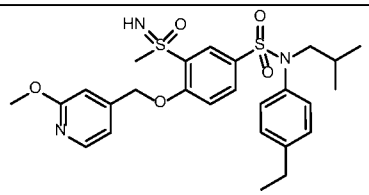
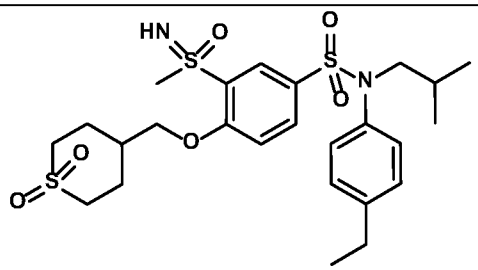
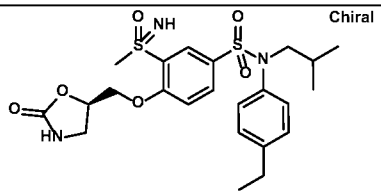
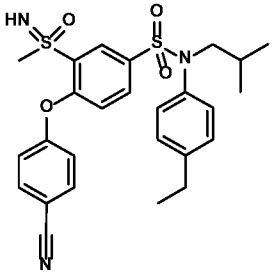
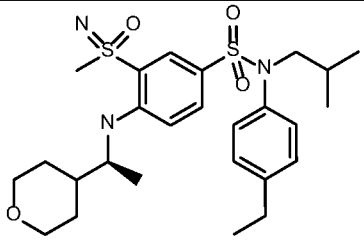
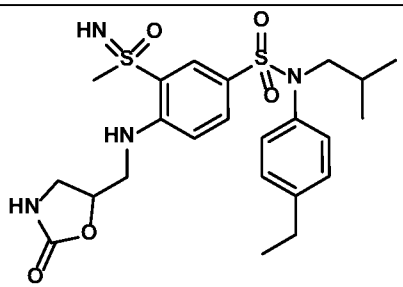
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((1-(methylsulfonylpiperidin-4-yl)methoxy)benzenesulfonamide Compound 51
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-[(tetrahydropyran-4-ylmethyl)amino]benzenesulfonamide Compound 52
	N-(4-ethylphenyl)-N-isobutyl-4-(methyl((tetrahydro-2H-pyran-4-yl)methyl)amino)-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 53
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((oxetan-3-ylmethyl)amino)benzenesulfonamide Compound 54
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(((4-methyltetrahydro-2H-pyran-4-yl)methyl)amino)benzenesulfonamide Compound 55

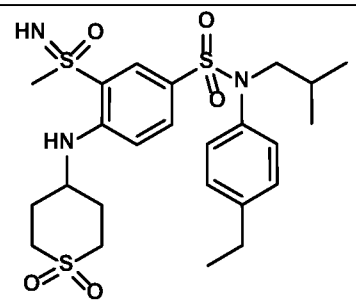
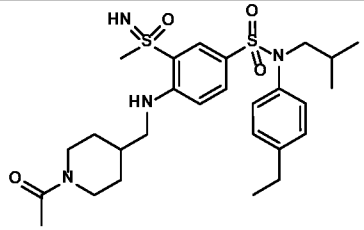
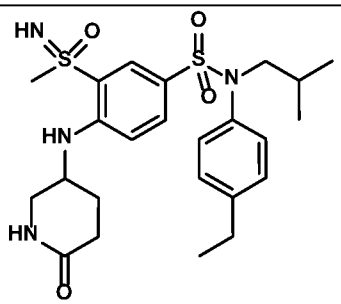
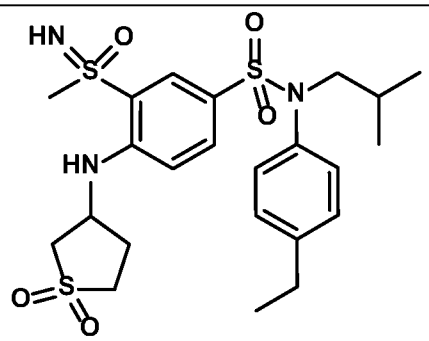
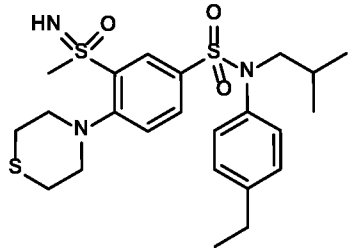
	4-(((1,1-dioxidotetrahydrothiophen-3-yl)methyl)amino)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 56
	4-(((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)methyl)amino)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 57
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(((6-oxopiperidin-3-yl)methyl)amino)benzenesulfonamide Compound 58
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(((5-oxopyrrolidin-3-yl)methyl)amino)benzenesulfonamide Compound 59
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(((R)-1-(tetrahydro-2H-pyran-4-yl)ethyl)amino)benzenesulfonamide Compound 60

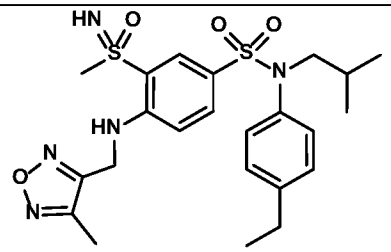
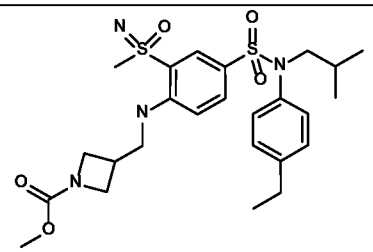
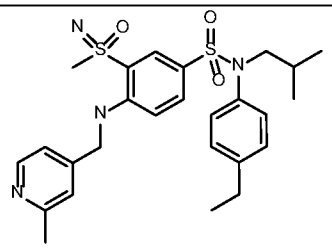
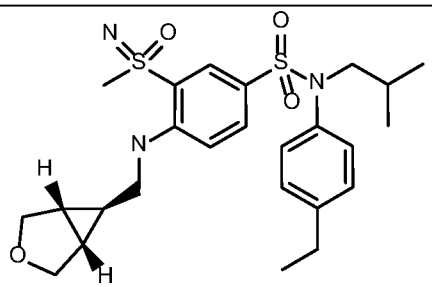
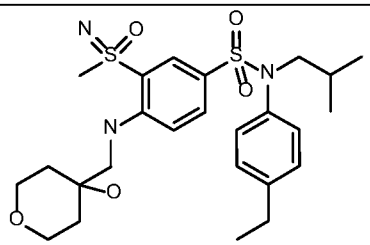
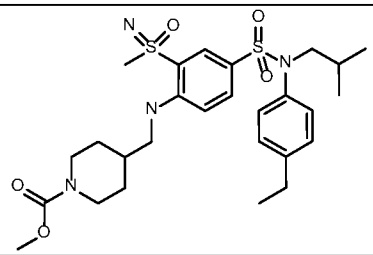
	N-(4-ethylphenyl)-4-(((3-hydroxycyclobutyl)methyl)amino)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 61
	N-(4-ethylphenyl)-4-(((4-fluorotetrahydro-2H-pyran-4-yl)methyl)amino)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 62
	4-(4-acetylpiperazin-1-yl)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 63
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((pyridin-4-ylmethyl)amino)benzenesulfonamide Compound 64
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(2-morpholinoethyl)benzenesulfonamide Compound 65

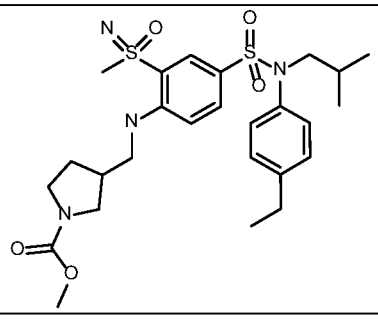
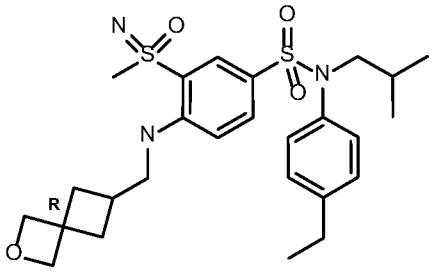
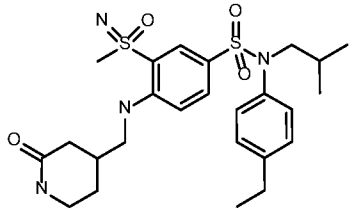
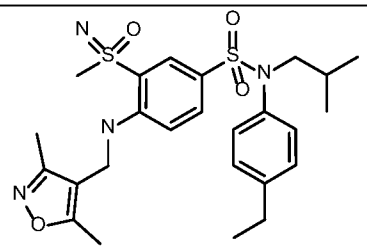
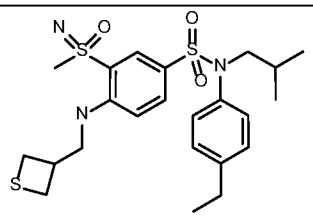
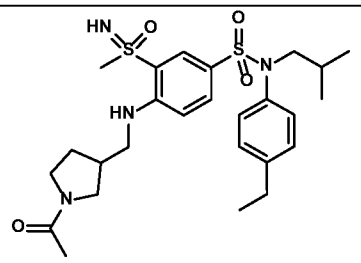
	4-(tetrahydropyran-4-ylmethoxy)benzene-1,3-disulfonic acid 3-amide 1-[(4-ethylphenyl)isobutylamide] Compound 66
	4-[(tetrahydropyran-4-ylmethyl)amino]benzene-1,3-disulfonic acid 3-amide 1-[(4-ethylphenyl)isobutylamide] Compound 67
	N-(4-ethylphenyl)-N-isobutyl-4-(tetrahydropyran-4-ylmethylsulfanyl)benzenesulfonamide Compound 68
	1-imino-1-oxo-4-(tetrahydropyran-4-ylmethyl)-1,2,3,4-tetrahydro-1λ^6-benzo[1,4]thiazine-6-sulfonic acid (4-ethylphenyl)isobutylamide Compound 69
	3-oxo-4-(tetrahydropyran-4-ylmethyl)-3,4-dihydro-2H-benzo[1,4]thiazine-7-sulfonic acid (4-ethylphenyl)isobutylamide Compound 70
	1-oxo-4-(tetrahydropyran-4-ylmethyl)-1,2,3,4-tetrahydro-1λ^4-benzo[1,4]thiazine-7-sulfonic acid (4-ethylphenyl)isobutylamide Compound 71

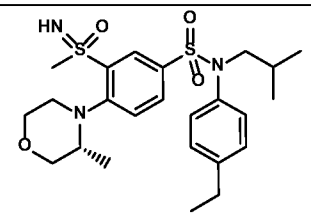
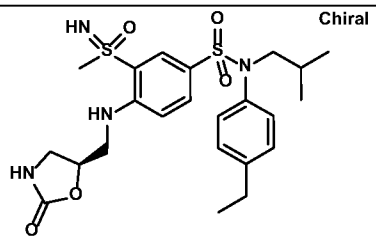
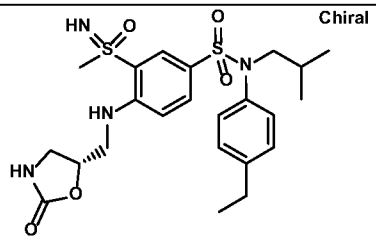
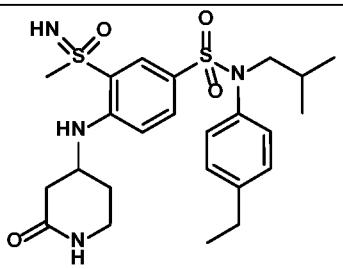
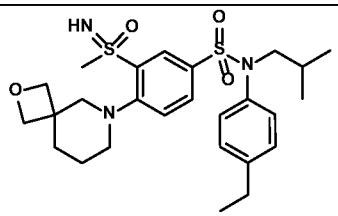
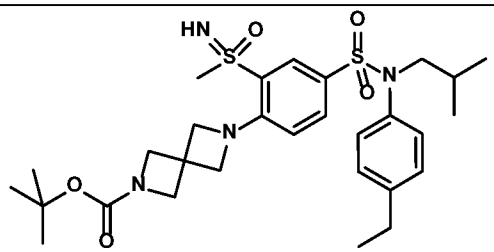
	3-oxo-4-(tetrahydropyran-4-ylmethyl)-3,4-dihydro-2H-benzo[1,4]thiazine-7-sulfonic acid (4-ethylphenyl)isobutylamide Compound 72
	2,2-dimethyl-3-(tetrahydropyran-4-ylmethyl)-2,3-dihydrobenzothiazole-6-sulfonic acid (4-ethylphenyl)isobutylamide Compound 73
	2,2-dimethyl-1-oxo-3-(tetrahydropyran-4-ylmethyl)-2,3-dihydro-1H-1λ^4-benzothiazole-6-sulfonic acid (4-ethylphenyl)isobutylamide Compound 74
	1-oxo-3-(tetrahydropyran-4-ylmethyl)-2,3-dihydro-1H-1λ^4-benzothiazole-6-sulfonic acid (4-ethylphenyl)isobutylamide Compound 75
	1-imino-1-oxo-3-(tetrahydropyran-4-ylmethyl)-2,3-dihydro-1H-1λ^6-benzothiazole-6-sulfonic acid (4-ethylphenyl)isobutylamide Compound 76

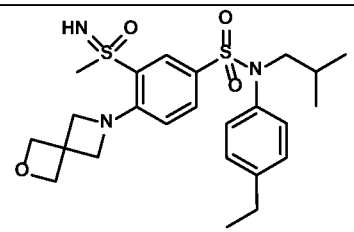
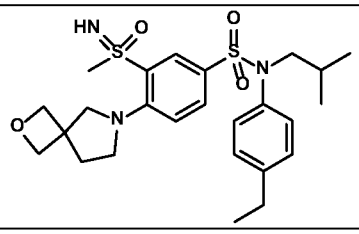
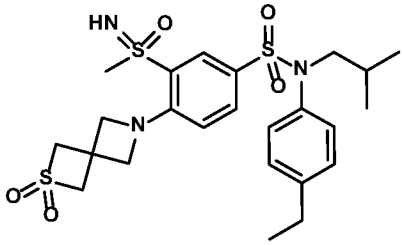
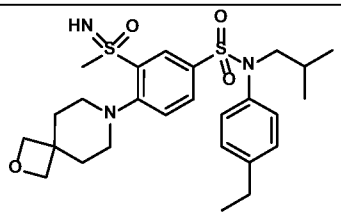
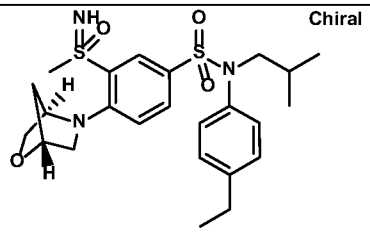
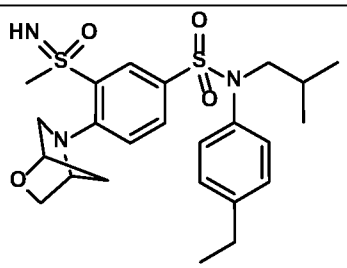
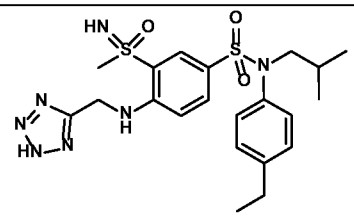
	N-(4-ethylphenyl)-N-isobutyl-4-((2-methoxypyridin-4-yl)methoxy)-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 77
	N-(4-ethylphenyl)-N-isobutyl-4-((2-methoxypyridin-4-yl)methoxy)-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 78
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(((R)-2-oxooxazolidin-5-yl)methoxy)benzenesulfonamide Compound 79
	4-(4-cyanophenoxy)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 80
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(((S)-1-(tetrahydro-2H-pyran-4-yl)ethyl)amino)benzenesulfonamide Compound 81
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(((2-oxooxazolidin-5-yl)methyl)amino)benzenesulfonamide Compound 82

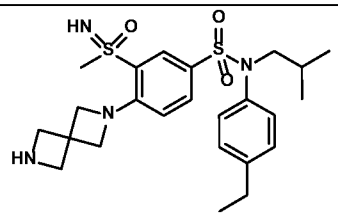
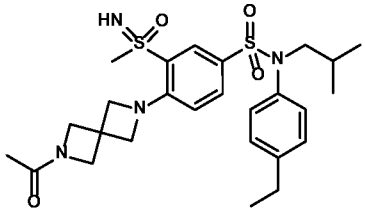
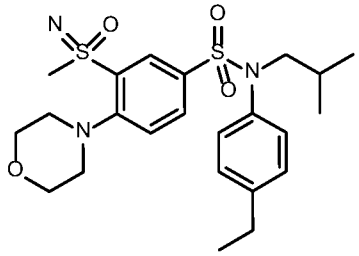
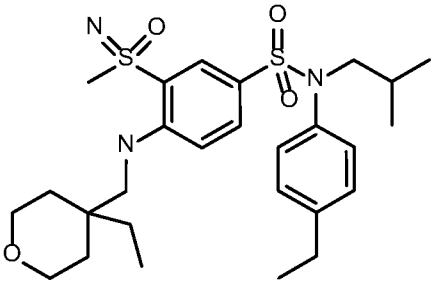
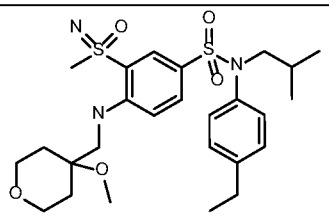
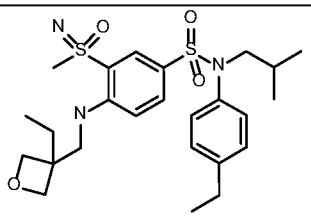
	4-((1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 83
	4-(((1-acetylpiperidin-4-yl)methyl)amino)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 84
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((6-oxopiperidin-3-yl)amino)benzenesulfonamide Compound 85
	4-((1,1-dioxidotetrahydrothiophen-3-yl)amino)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 86
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-thiomorpholinobenzenesulfonamide Compound 87

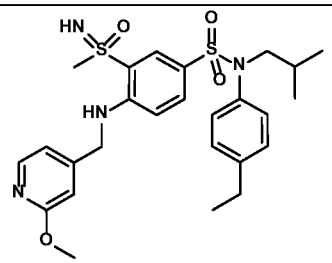
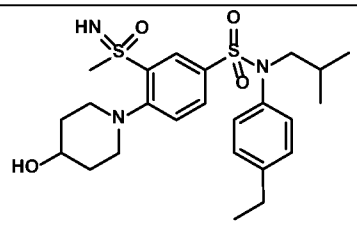
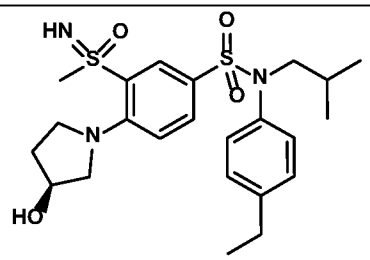
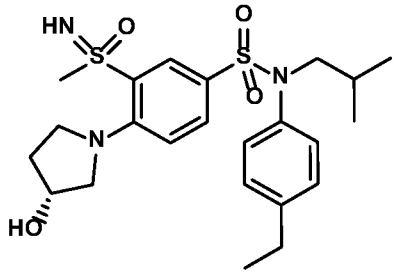
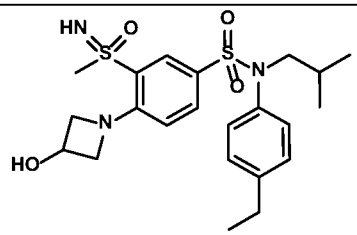
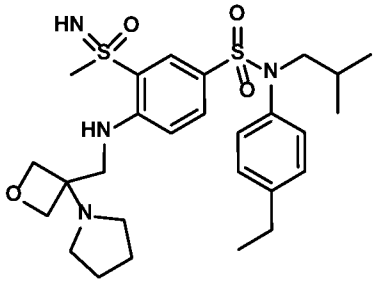
	N-(4-ethylphenyl)-N-isobutyl-4-(((4-methyl-1,2,5-oxadiazol-3-yl)methyl)amino)-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 88
	methyl 3-(((4-(N-(4-ethylphenyl)-N-isobutylsulfamoyl)-2-(S-methylsulfonimidoyl)phenyl)amino)methyl)azetidine-1-carboxylate Compound 89
	N-(4-ethylphenyl)-N-isobutyl-4-(((2-methylpyridin-4-yl)methyl)amino)-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 90
	4-((((1R,5S,6S)-3-oxabicyclo[3.1.0]hexan-6-yl)methyl)amino)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 91
	N-(4-ethylphenyl)-4-(((4-hydroxytetrahydro-2H-pyran-4-yl)methyl)amino)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 92
	methyl 4-(((4-(N-(4-ethylphenyl)-N-isobutylsulfamoyl)-2-(S-methylsulfonimidoyl)phenyl)amino)methyl)piperidine-1-carboxylate Compound 93

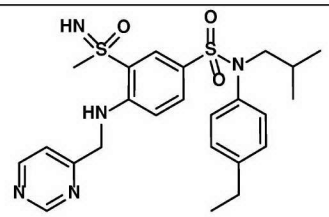
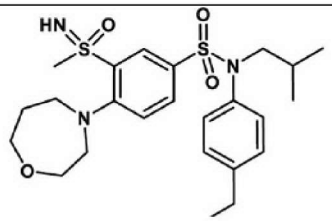
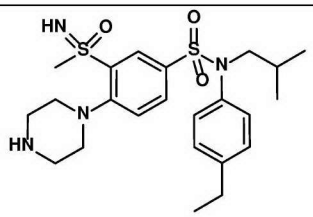
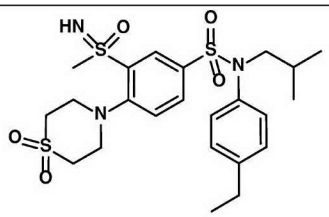
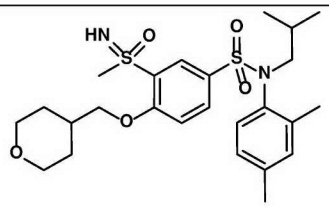
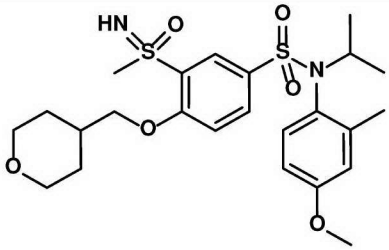
	methyl 3-(((4-(N-(4-ethylphenyl)-N-isobutylsulfamoyl)-2-(S-methylsulfonimidoyl)phenyl)amino)methyl)pyrrolidine-1-carboxylate Compound 94
	4-(((2-oxaspiro[3.3]heptan-6-yl)methyl)amino)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 95
	4-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(((2-oxopiperidin-4-yl)methyl)amino)benzenesulfonamide Compound 96
	4-(((3,5-dimethylisoxazol-4-yl)methyl)amino)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 97
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((thietan-3-ylmethyl)amino)benzenesulfonamide Compound 99
	4-(((1-acetylpyrrolidin-3-yl)methyl)amino)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 100

	N-(4-ethylphenyl)-N-isobutyl-4-((R)-3-methylmorpholino)-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 103
 Chiral	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((((R)-2-oxooxazolidin-5-yl)methyl)amino)benzenesulfonamide Compound 105
 Chiral	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((((S)-2-oxooxazolidin-5-yl)methyl)amino)benzenesulfonamide Compound 106
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((2-oxopiperidin-4-yl)amino)benzenesulfonamide Compound 107
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(2-oxa-6-azaspiro[3.5]nonan-6-yl)benzenesulfonamide Compound 109
	tert-butyl 6-(4-(N-(4-ethylphenyl)-N-isobutylsulfamoyl)-2-(S-methylsulfonimidoyl)phenyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate Compound 110

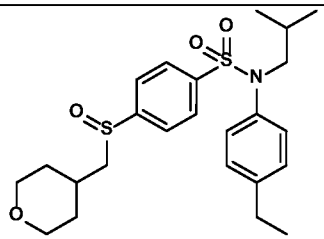
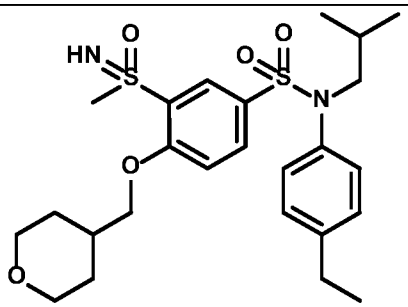
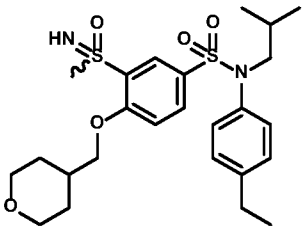
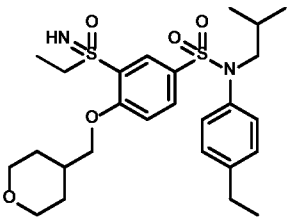
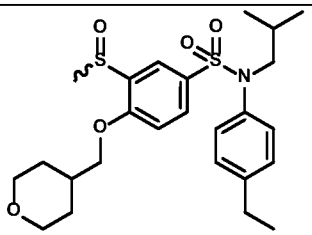
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)benzenesulfonamide Compound 111
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(2-oxa-6-azaspiro[3.4]octan-6-yl)benzenesulfonamide Compound 112
	4-(2,2-dioxido-2-thia-6-azaspiro[3.3]heptan-6-yl)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 113
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(2-oxa-7-azaspiro[3.5]nonan-7-yl)benzenesulfonamide Compound 114
 Chiral	4-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 115
	4-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 117
	4-(((2H-tetrazol-5-yl)methyl)amino)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide

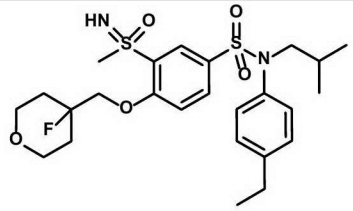
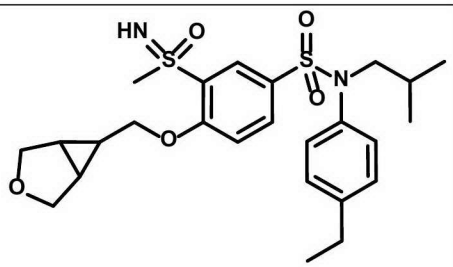
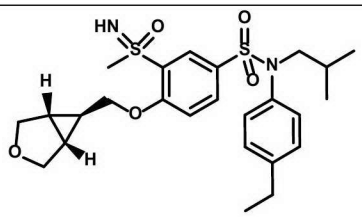
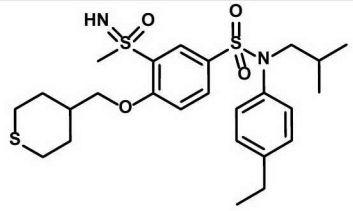
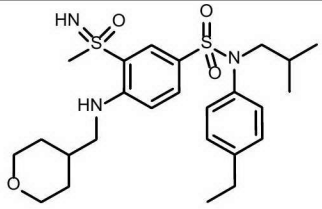
	Compound 118
	-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(2,6-diazaspiro[3.3]heptan-2-yl)benzenesulfonamide Compound 121
	4-(6-acetyl-2,6-diazaspiro[3.3]heptan-2-yl)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 122
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-morpholinobenzenesulfonamide Compound 123
	N-(4-ethylphenyl)-4-(((4-ethyltetrahydro-2H-pyran-4-yl)methyl)amino)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 124
	N-(4-ethylphenyl)-N-isobutyl-4-(((4-methoxytetrahydro-2H-pyran-4-yl)methyl)amino)-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 125
	4-(((3-ethyloxetan-3-yl)methyl)amino)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 126

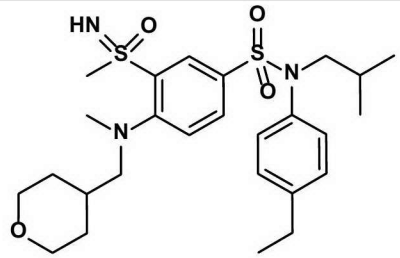
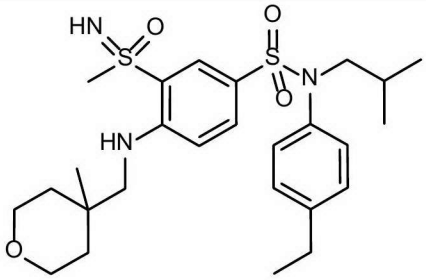
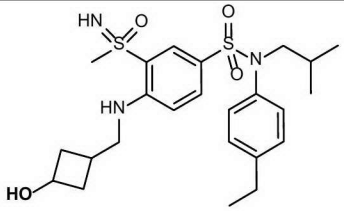
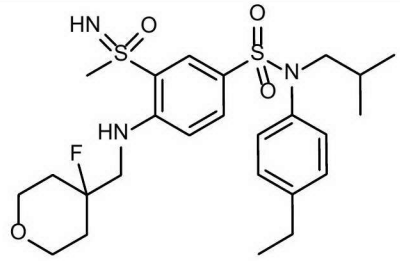
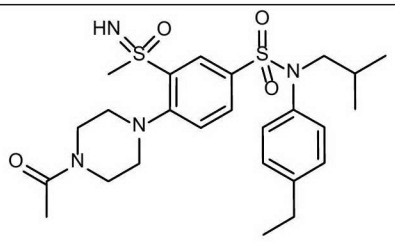
	N-(4-ethylphenyl)-N-isobutyl-4-(((2-methoxypyridin-4-yl)methyl)amino)-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 127
	N-(4-ethylphenyl)-4-(4-hydroxypiperidin-1-yl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 128
	N-(4-ethylphenyl)-4-((S)-3-hydroxypyrrolidin-1-yl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 129
	N-(4-ethylphenyl)-4-((R)-3-hydroxypyrrolidin-1-yl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 130
	N-(4-ethylphenyl)-4-(3-hydroxyazetidin-1-yl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 131
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(((3-(pyrrolidin-1-yl)oxetan-3-yl)methyl)amino)benzenesulfonamide Compound 132

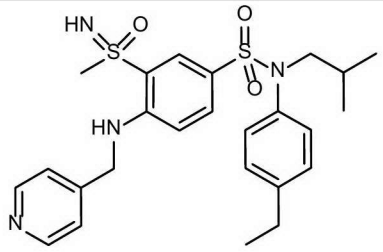
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((pyrimidin-4-ylmethyl)amino)benzenesulfonamide Compound 133
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(1,4-oxazepan-4-yl)benzenesulfonamide Compound 137
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(piperazin-1-yl)benzenesulfonamide Compound 140
	N-(4-ethylphenyl)-4-(((3-hydroxycyclobutyl)methyl)amino)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 141
	N-(2,4-dimethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide Compound 142
	N-isopropyl-N-(4-methoxy-2-methylphenyl)-3-(S-methylsulfonimidoyl)-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide Compound 143

9. Compound as claimed in any one of the preceding claims, characterized in that it is chosen from:

	N-(4-ethylphenyl)-N-isobutyl-4-(tetrahydropyran-4-ylmethanesulfinyl)benzenesulfonamide Compound 29
	N-(4-Ethylphenyl)-N-isobutyl-3-methanesulfoximino-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide Compound 26
 enantiomer A	enantiomer A of compound 7
	N-(4-ethylphenyl)-N-isobutyl-3-ethanesulfoximino-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide Compound 18
	N-(4-ethylphenyl)-N-isobutyl-3-methanesulfinyl-4-(tetrahydropyran-4-ylmethoxy)benzenesulfonamide Compound 19 Enantiomer A

	N-(4-ethylphenyl)-4-((4-fluorotetrahydro-2H-pyran-4-yl)methoxy)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 30
	4-((3-oxabicyclo[3.1.0]hexan-6-yl)methoxy)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 31
	4-(((1R,5S,6R)-3-oxabicyclo[3.1.0]hexan-6-yl)methoxy)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 35
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(pyridin-4-ylmethoxy)benzenesulfonamide Compound 37
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-[(tetrahydropyran-4-ylmethyl)amino]benzenesulfonamide Compound 52

	N-(4-ethylphenyl)-N-isobutyl-4-(methyl((tetrahydro-2H-pyran-4-yl)methyl)amino)-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 53
	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-(((4-methyltetrahydro-2H-pyran-4-yl)methyl)amino)benzenesulfonamide Compound 55
	N-(4-ethylphenyl)-4-(((3-hydroxycyclobutyl)methyl)amino)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 61
	N-(4-ethylphenyl)-4-(((4-fluorotetrahydro-2H-pyran-4-yl)methyl)amino)-N-isobutyl-3-(S-methylsulfonimidoyl)benzene sulfonamide Compound 62
	4-(4-acetylpiperazin-1-yl)-N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)benzenesulfonamide Compound 63

	N-(4-ethylphenyl)-N-isobutyl-3-(S-methylsulfonimidoyl)-4-((pyridin-4-ylmethyl)amino)benzenesulfonamide Compound 64

10. Compound as claimed in any one of the preceding claims, as a medicament.

11. Compound as claimed in any one of the preceding claims, for its use in the treatment of inflammatory disorders and/or autoimmune diseases mediated by the RORγt receptor.

12. Compound as claimed in claim 10, for its use in the treatment of acne.

13. Compound as claimed in claim 10, for its use in the treatment of psoriasis.

14. Pharmaceutical composition comprising one or more compounds as defined in any one of claims 1 to 10.

15. Pharmaceutical composition as claimed in claim 14, characterized for its use for treating inflammatory disorders and/or autoimmune diseases mediated by the RORγt receptor, especially acne, atopic dermatitis and/or psoriasis.