

ROR gamma (ROR γ) modulators.

The present invention relates to modulators of ROR γ , to pharmaceutical compositions comprising the same and to the use of said compounds for the treatment of ROR γ -mediated diseases or conditions, in particular autoimmune diseases and inflammatory diseases.

T helper (T_H) cells play a crucial role in the adaptive immune system as they coordinate defense against specific pathogens. The interleukin 17 (IL-17) producing lineages of T_H cells, amongst which T_H17 cells, have been directly implicated in the pathology of a multitude of autoimmune and inflammatory diseases, including, but not limited to, psoriasis, multiple sclerosis, rheumatoid arthritis, Crohn's disease, asthma, chronic obstructive pulmonary disease, and irritable bowel disease (Harrington *et al*, Nature Immunology 6, 1123-1132, 2005; Park *et al*, Nature Immunology 6, 1133-1141, 2005; Weaver *et al*, Annual Reviews Immunology 25, 821-852, 2007; Littman *et al*, Cell 140, 845-858, 2010).

Interleukin 17 and interleukin 23 (IL-23) are two pivotal cytokines in T_H17 biology. IL-17 is secreted by T_H17 cells and is a potent inducer of tissue inflammation; IL-23 has been shown to be a key participant in amplifying and stabilizing the proliferation of the T_H17 cell type via the IL-23 receptor (IL-23R) (Cua *et al*, Nature 421, 744-748, 2003; Aggarwal *et al*, J Biol Chem 278, 1910-1914, 2003). These findings highlight the therapeutic potential of targeting the IL-17/IL-23 axis.

The retinoic-acid-receptor-related orphan receptor γ t (ROR γ t) acts as a master regulator of the development of T_H17 cells (Ivanov *et al*, Cell 126, 1121-1133, 2006), but also as a critical component in non-T_H17 IL-17 producing cells, such as for example $\gamma\delta$ T-cells. The ROR gene family is part of the nuclear hormone receptor superfamily, and consists of three members (ROR α , ROR β , and ROR γ). Each gene is expressed in different isoforms, differing foremost in their N-terminal sequence (Jetten, Nuclear Receptor Signaling 7, e003, 2009). Two isoforms of ROR γ have been identified: ROR γ 1 and ROR γ 2 (also known as ROR γ t). The term ROR γ is used here to describe both ROR γ 1 and/or ROR γ 2.

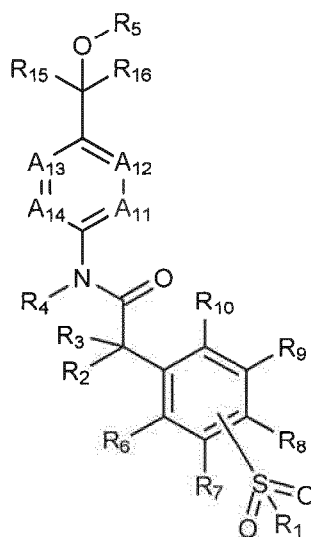
Deficiency in, or inhibition of, ROR γ t results in, for example, decreased levels of IL-17 and IL-23R gene expression and amelioration of disease score in an experimental autoimmune encephalomyelitis (EAE) mouse model, highlighting the critical role of

ROR γ t in IL-17/IL-23 mediated pathogenic responses (Ivanov *et al*, Cell 126, 1121-1133, 2006; Solt *et al*, Nature 472, 491-494, 2011).

Given the important role of ROR γ in immune and inflammatory disorders it is desirable to prepare modulators of ROR γ (as for example described in WO2011115892A1, WO2013029338A1 and WO2013171729A2), which can be used in the treatment of

The present invention provides such novel ROR γ modulator compounds.

The present invention relates to novel compounds according to Formula I



Meta or para

(Formula I)

or a pharmaceutically acceptable salt thereof wherein

A₁₁ – A₁₄ are N or CR₁₁, CR₁₂, CR₁₃, CR₁₄, respectively, with the proviso that no more than two of the four positions A can be simultaneously N;

R₁ is C(1-6)alkyl, C(3-6)cycloalkyl, C(3-6)cycloalkylC(1-3)alkyl, (di)C(1-6)alkylamino, (di)C(3-6)cycloalkylamino or (di)(C(3-6)cycloalkylC(1-3)alkyl)amino, with all carbon atoms of alkyl groups optionally substituted with one or more F and all carbon atoms of cycloalkyl groups optionally substituted with one or more F or methyl;

R₂ and R₃ are independently H, F, methyl, ethyl, hydroxy, methoxy or R₂ and R₃ together is carbonyl, all alkyl groups, if present, optionally being substituted with one or more F;

R₄ is H or C(1-6)alkyl;

R₅ is H, hydroxyethyl, methoxyethyl, C(1-6)alkyl, C(6-10)aryl, C(6-10)arylC(1-3)alkyl, C(1-9)heteroaryl, C(1-9)heteroarylC(1-3)alkyl, C(3-6)cycloalkyl, C(3-6)cycloalkylC(1-3)alkyl, C(2-5)heterocycloalkyl or C(2-5)heterocycloalkyl-

5 C(1-3)alkyl, all groups optionally substituted with one or more F, Cl, C(1-2)alkyl, C(1-2)alkoxy or cyano ;

the sulfonyl group with R₁ is represented by one of R₇, R₈ or R₉;

the remaining R₆-R₁₄ are independently H, halogen, C(1-3)alkoxy, (di)C(1-3)alkylamino or C(1-6)alkyl, all of the alkyl groups optionally being substituted with one or more F;

10 and R₁₅ and R₁₆ are independently H, C(1-6)alkyl, C(3-6)cycloalkyl, C(3-6)cycloalkylC(1-3)alkyl, C(6-10)aryl, C(6-10)arylC(1-3)alkyl, C(1-9)heteroaryl, C(1-9)heteroarylC(1-3)alkyl, C(2-5)heterocycloalkyl or C(2-5)heterocycloalkyl-C(1-3)alkyl, all groups optionally substituted with one or more F, Cl, C(1-2)alkyl, C(1-2)alkoxy or cyano.

15

The term C(1-6)alkyl as used herein means a branched or unbranched alkyl group having 1-6 carbon atoms, for example methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, n-pentyl and n-hexyl. All carbon atoms may optionally be substituted with one or more halogen.

20 The term C(1-4)alkyl as used herein means an alkyl group having 1-4 carbon atoms, i.e. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, or tert-butyl. All carbon atoms may optionally be substituted with one or more halogen.

The term C(1-3)alkyl as used herein means an alkyl group having 1-3 carbon atoms, i.e. methyl, ethyl, propyl or isopropyl. All carbon atoms may optionally be substituted
25 with one or more halogen.

The term C(1-2)alkyl as used herein means an alkyl group having 1-2 carbon atoms i.e. methyl or ethyl. All carbon atoms may optionally be substituted with one or more halogen.

30 The term C(6-10)aryl as used herein means an aromatic hydrocarbon group having 6-10 carbon atoms, for example phenyl or naphthyl. The preferred aromatic hydrocarbon group is phenyl. All carbon atoms may optionally be substituted with one or more halogen.

The term C(6-10)arylC(1-3)alkyl as used herein means an C(6-10)aryl group attached to a C(1-3)alkyl group, both with the same meaning as previously defined.

The term C(6)aryl as used herein means an aromatic hydrocarbon group having 6 carbon atoms, i.e. phenyl. All carbon atoms may optionally be substituted with one or more halogen.

The term C(6)arylC(1-3)alkyl as used herein means an C(6)aryl group attached to a C(1-3)alkyl group, both with the same meaning as previously defined.

The term heteroatom as used herein refers to a nitrogen, sulphur or oxygen atom.

The term C(1-9)heteroaryl as used herein means an aromatic group having 1-9 carbon atoms and 1-4 heteroatoms, which may be attached via a nitrogen atom if feasible, or a carbon atom. Examples include imidazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, furyl, pyrazolyl, isoxazolyl, tetrazolyl and quinolyl. All carbon atoms may optionally be substituted with one or more halogen or methyl.

The term C(1-9)heteroarylC(1-3)alkyl as used herein means an C(1-9)heteroaryl group attached to a C(1-3)alkyl group, both with the same meaning as previously defined.

The term C(3-6)cycloalkyl as used herein means a saturated cyclic hydrocarbon having 3-6 carbon atoms, i.e. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. All carbon atoms may optionally be substituted with one or more halogen or methyl.

The term C(3-5)cycloalkyl as used herein means a saturated cyclic hydrocarbon having 3-5 carbon atoms, i.e. cyclopropyl, cyclobutyl or cyclopentyl. All carbon atoms may optionally be substituted with one or more halogen or methyl.

The term C(3-4)cycloalkyl as used herein means a saturated cyclic hydrocarbon having 3-4 carbon atoms, i.e. cyclopropyl or cyclobutyl. All carbon atoms may optionally be substituted with one or more halogen or methyl.

The term C(3-6)cycloalkylC(1-3)alkyl as used herein means an C(3-6)cycloalkyl group attached to an C(1-3)alkyl group, both with the same meaning as previously defined. An example is cyclopropylmethyl.

The term C(3-5)cycloalkylC(1-3)alkyl as used herein means an C(3-5)cycloalkyl group attached to an C(1-3)alkyl group, both with the same meaning as previously defined.

The term cyclopropylmethyl as used herein means a methyl group substituted with cyclopropyl. All carbon atoms are optionally substituted with one or more halogen or methyl.

The term C(2-5)heterocycloalkyl as used herein means a saturated cyclic hydrocarbon having 2-5 carbon atoms and 1-3 heteroatoms, which may be attached via a nitrogen

atom if feasible, or a carbon atom. Examples include piperazinyl, pyrazolidinyl, piperidinyl, morpholinyl and pyrrolidinyl. All carbon atoms may optionally be substituted with one or more halogen or methyl.

5 The term C(2-5)heterocycloalkylC(1-3)alkyl as used herein means an C(2-5)heterocycloalkyl group attached to an C(1-3)alkyl group, both with the same meaning as previously defined.

The term (di)C(1-6)alkylamino as used herein means an amino group, which is monosubstituted or disubstituted independently with C(1-6)alkyl group(s), having the same meaning as previously defined.

10 It is to be understood that in the (di)C(1-6)alkylamino groups containing two C(1-6)alkyl groups, one of the C(1-6)alkyl groups can be replaced by a C(3-6)cycloalkyl group as previously defined.

The term (di)C(1-2)alkylamino as used herein means an amino group, which is monosubstituted or disubstituted independently with C(1-2)alkyl group(s), having the same meaning as previously defined.

The term (di)C(3-6)cycloalkylamino as used herein means an amino group, which is monosubstituted or disubstituted independently with C(3-6)cycloalkyl group(s), having the same meaning as previously defined. An example is cyclopropylamino.

20 It is to be understood that in the (di)C(3-6)cycloalkylamino groups containing two C(3-6)cycloalkyl groups, one of the C(3-6)cycloalkyl groups can be replaced by a C(1-6)alkyl group as previously defined.

The term (di)C(3-4)cycloalkylamino as used herein means an amino group, which is monosubstituted or disubstituted independently with C(3-4)cycloalkyl group(s), having the same meaning as previously defined.

25 It is to be understood that in the (di)C(3-4)cycloalkylamino groups containing two C(3-4)cycloalkyl groups, one of the C(3-4)cycloalkyl groups can be replaced by a C(1-6)alkyl group as previously defined.

The term cyclopropylamino means an amino group substituted with cyclopropyl. All carbon atoms may optionally be substituted with one or more halogen or methyl.

30 The term (di)(C(3-6)cycloalkylC(1-3)alkyl)amino as used herein means an amino group, which is monosubstituted or disubstituted independently with C(3-6)cycloalkylC(1-3)alkyl group(s) as previously defined.

It is to be understood that in the (di)C(3-6)cycloalkylC(1-3)alkylamino groups containing two C(3-6)cycloalkylC(1-3)alkyl groups, one of the C(3-6)cycloalkylC(1-3)alkyl groups can be replaced by a C(1-6)alkyl or a C(3-6)cycloalkyl group, both as previously defined.

- 5 The term (di)C(1-3)alkylamino as used herein means an amino group, which is monosubstituted or disubstituted independently with C(1-3)alkyl group(s), having the same meaning as previously defined.

The term C(1-3)alkoxy means an alkoxy group having 1-3 carbon atoms, the alkyl moiety being branched or unbranched. All carbon atoms are optionally substituted with
10 one or more F.

The term C(1-2)alkoxy means an alkoxy group having 1-2 carbon atoms. Preferred is methoxy. All carbon atoms may optionally be substituted with one or more F.

The term halogen as used herein means Cl or F.

In the above definitions with multifunctional groups, the attachment point is at the last
15 group.

When, in the definition of a substituent, is indicated that "all of the alkyl groups" of said substituent are optionally substituted, this also includes the alkyl moiety of an alkoxy group.

The term "substituted" means that one or more hydrogens on the designated
20 atom/atoms is/are replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. "Stable compound" or "stable structure" is defined as a compound or structure that is
25 sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

The term pharmaceutically acceptable salt represents those salts which are, within the
30 scope of medical judgment, suitable for use in contact for the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. They may be obtained during the final isolation and

purification of the compounds of the invention, or separately by reacting the free base function with a suitable mineral acid such as hydrochloric acid, phosphoric acid, or sulfuric acid, or with an organic acid such as for example ascorbic acid, citric acid, tartaric acid, lactic acid, maleic acid, malonic acid, fumaric acid, glycolic acid, succinic acid, propionic acid, acetic acid, methanesulfonic acid, and the like. The acid function
 5 can be reacted with an organic or a mineral base, like sodium hydroxide, potassium hydroxide or lithium hydroxide.

In one embodiment the invention also relates to a compound according to Formula I wherein R₁ is C(1-4)alkyl, C(3-5)cycloalkyl, C(3-5)cycloalkylC(1-3)alkyl,
 10 (di)C(1-2)alkylamino or (di)C(3-4)cycloalkylamino.

In another embodiment the invention relates to a compound according to Formula I wherein R₁ is C(1-2)alkyl, C(3-4)cycloalkylC(1-3)alkyl, cyclopropyl, methylamino or C(3-4)cycloalkylamino.

In another embodiment the invention relates to a compound according to Formula I
 15 wherein R₁ is ethyl, cyclopropylamino or cyclopropylmethyl.

In another embodiment the invention relates to a compound according to Formula I wherein R₁ is ethyl.

In yet another embodiment the invention relates to a compound according to Formula I wherein R₁ is cyclopropylamino.

20 In again another embodiment the invention relates to a compound according to Formula I wherein R₁ is cyclopropylmethyl.

In yet another embodiment the invention relates to a compound according to Formula I wherein R₂ and R₃ independently are H, methyl or hydroxy, H being the most preferred.

The invention also relates to a compound according to Formula I wherein R₄ is H or C(1-2)alkyl, H being the most preferred.
 25

In yet another embodiment R₅ is H, hydroxyethyl, methoxyethyl or C(1-6)alkyl, all alkyl groups optionally being substituted with one or more F.

In again another embodiment R₅ in Formula I is H or C(1-3)alkyl, H being the most preferred.

30 In another embodiment R₅ in Formula I is C(6-10)arylC(1-3)alkyl or C(3-6)cycloalkylC(1-3)alkyl.

In again another embodiment R_5 in Formula I is C(6)arylC(1-3)alkyl or C(3-6)cycloalkylC(1-3)alkyl.

In again another embodiment R_5 in Formula I is benzyl.

In another embodiment the invention relates to a compound according to Formula I
 5 wherein R_6 - R_{10} are H. In this case, however, one of the groups R_7 , R_8 or R_9 is the sulfonyl group with R_1 attached to it.

In yet another embodiment the sulfonyl group is represented by R_8 , i.e. the sulfonyl group is attached at the para position of the aryl ring.

In yet another embodiment the sulfonyl group is represented by R_8 , i.e. the sulfonyl
 10 group is attached at the para position of the aryl ring, R_{10} is methyl and the remaining R_6 - R_9 are H.

In yet another embodiment the sulfonyl group is represented by R_7 or R_9 , i.e. the sulfonyl group is attached at the meta position of the aryl ring.

In yet another embodiment the invention relates to a compound according to Formula I
 15 wherein R_{11} - R_{14} are independently H, halogen, methyl or methoxy, H being preferred.

In yet another embodiment the invention relates to a compound according to Formula I wherein A_{11} - A_{14} are carbon atoms.

In yet another embodiment the invention relates to a compound according to Formula I wherein A_{11} is nitrogen.

20 In yet another embodiment the invention relates to a compound according to Formula I wherein A_{12} is nitrogen.

In one embodiment the invention relates to a compound according to Formula I wherein R_{15} and R_{16} are independently C(1-6)alkyl, C(3-6)cycloalkyl, C(3-6)cycloalkylC(1-3)alkyl, C(6-10)aryl, C(6-10)arylC(1-3)alkyl, C(1-9)heteroaryl, C(1-9)heteroarylC(1-3)alkyl, C(2-5)heterocycloalkyl or C(2-5)heterocycloalkyl-
 25 C(1-3)alkyl, all groups optionally substituted with one or more F, Cl, C(1-2)alkyl, C(1-2)alkoxy or cyano.

In one embodiment the invention relates to a compound according to Formula I wherein either R_{15} or R_{16} is CF_3 .

In another embodiment the invention relates to a compound according to Formula I wherein R_{15} is CF_3 and R_{16} is C(1-6)alkyl, C(3-6)cycloalkyl, C(3-6)cycloalkylC(1-3)alkyl, C(6)aryl or C(6)arylC(1-3)alkyl.

5 In another embodiment the invention relates to a compound according to Formula I wherein R_{15} is CF_3 and R_{16} is H, C(1-6)alkyl, C(3-6)cycloalkyl or C(3-6)cycloalkylC(1-3)alkyl, C(1-6)alkyl being the most preferred.

In another embodiment the invention relates to a compound according to Formula I wherein R_{15} is CF_3 and R_{16} is C(1-6)alkyl, C(3-6)cycloalkyl or C(3-6)cycloalkylC(1-3)alkyl, C(1-6)alkyl being the most preferred.

10 In yet another embodiment the invention relates to a compound according to Formula I wherein R_{15} is CF_3 and R_{16} is cyclopropyl, cyclopentyl or cyclohexylmethyl.

In yet another embodiment the invention also relates to a compound according to Formula I wherein R_{15} is CF_3 and R_{16} is CF_3 , propyl, isopropyl, 2-methylpropyl or 2,2-dimethylpropyl.

15 In another embodiment the invention also relates to a compound according to Formula I wherein both R_{15} and R_{16} are CF_3 .

In yet another embodiment the invention also relates to a compound according to Formula I wherein both R_{15} and R_{16} are cyclopropyl.

20 The invention also relates to those compounds wherein all specific definitions for A_{11} through A_{14} , R_1 through R_{16} , and all substituent groups in the various aspects of the inventions defined here above occur in any combination within the definition of the compound of Formula I.

25 In another aspect the invention relates to compounds of Formula I which have a pIC50 of 5 or higher. In yet another aspect the invention relates to compounds according to Formula I with a pIC50 of more than 6. In yet another aspect the invention relates to compounds according to Formula I with a pIC50 of more than 7. In yet another aspect the invention relates to compounds according to Formula I with a pIC50 of more than 8.

In yet another aspect the invention resides in the compounds according to Formula I selected as described in examples 1 - 114.

30 In yet another aspect the invention resides in the compounds according to Formula I selected as described in examples 1 - 41 and example 112.

The compounds of Formula I can form salts, which are also within the scope of this invention. Reference to a compound of Formula I herein is understood to include reference to salts thereof, unless otherwise indicated.

5 The compounds of Formula I may contain asymmetric or chiral centers and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of Formula I as well as mixtures thereof, including racemic mixtures, form part of the present invention.

10 Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g. chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g. hydrolyzing) the individual diastereomers to the
15 corresponding pure enantiomers. Enantiomers can also be separated by use of chiral HPLC column.

The compounds of the invention may form hydrates or solvates. It is known to those of skill in the art that charged compounds form hydrated species when lyophilized with water, or form solvated species when concentrated in a solution with an appropriate
20 organic solvent. The compounds of this invention include the prodrugs, hydrates or solvates of the compounds.

The skilled artisan will recognize that desirable IC₅₀ values are dependent on the compound tested. For example, a compound with an IC₅₀ value less than 10⁻⁵ M is
25 generally considered a candidate for drug selection. Preferably, this value is lower than 10⁻⁶ M. However, a compound which has a higher IC₅₀ value, but is selective for the particular receptor, may be even a better candidate.

30 The compounds of the invention inhibit ROR γ activity. Modulation of ROR γ activity can be measured using for example biophysical (natural) ligand displacement studies, biochemical AlphaScreen or FRET assays, cellular GAL4 reporter gene assays, cellular IL-17 promotor reporter assay or functional IL-17 ELISA assays using for example mouse splenocytes or human peripheral blood mononuclear cells (PBMCs) cultured under T_H17 polarizing conditions (Solt et al, Nature 472, 491-494, 2011).

In such assays, the interaction of a ligand with ROR γ can be determined by measuring, for example, the ligand modulated interaction of cofactor-derived peptides with the ROR γ ligand binding domain, or measuring the gene products of ligand modulated ROR γ mediated transcription using, for example, luciferase reporter assays or IL-17
5 ELISA assays.

The present invention also relates to a pharmaceutical composition comprising compounds or pharmaceutically acceptable salts thereof having the general Formula I in admixture with pharmaceutically acceptable auxiliaries and optionally other therapeutic agents. The auxiliaries must be "acceptable" in the sense of being
10 compatible with the other ingredients of the composition and not deleterious to the recipients thereof.

The invention further includes a compound of Formula I in combination with one or more other drug(s).

Compositions include e.g. those suitable for oral, sublingual, subcutaneous,
15 intravenous, intramuscular, nasal, local, or rectal administration, and the like, all in unit dosage forms for administration.

For oral administration, the active ingredient may be presented as discrete units, such as tablets, capsules, powders, granulates, solutions, suspensions, and the like.

For parenteral administration, the pharmaceutical composition of the invention may be
20 presented in unit-dose or multi-dose containers, e.g. injection liquids in predetermined amounts, for example in sealed vials and ampoules, and may also be stored in a freeze dried (lyophilized) condition requiring only the addition of sterile liquid carrier, e.g. water, prior to use.

Mixed with such pharmaceutically acceptable auxiliaries, e.g. as described in the
25 standard reference, Gennaro, A.R. et al., Remington: The Science and Practice of Pharmacy (20th Edition., Lippincott Williams & Wilkins, 2000, see especially Part 5: Pharmaceutical Manufacturing), the active agent may be compressed into solid dosage units, such as pills, tablets, or be processed into capsules or suppositories. By means of pharmaceutically acceptable liquids the active agent can be applied as a fluid
30 composition, e.g. as an injection preparation, in the form of a solution, suspension, emulsion, or as a spray, e.g. a nasal spray.

For making solid dosage units, the use of conventional additives such as fillers, colorants, polymeric binders and the like is contemplated. In general any pharma-

ceutically acceptable additive which does not interfere with the function of the active compounds can be used. Suitable carriers with which the active agent of the invention can be administered as solid compositions include lactose, starch, cellulose derivatives and the like, or mixtures thereof, used in suitable amounts. For parenteral
5 administration, aqueous suspensions, isotonic saline solutions and sterile injectable solutions may be used, containing pharmaceutically acceptable dispersing agents and/or wetting agents, such as propylene glycol or butylene glycol.

The invention further includes a pharmaceutical composition, as hereinbefore described, in combination with packaging material suitable for said composition, said
10 packaging material including instructions for the use of the composition for the use as hereinbefore described.

The exact dose and regimen of administration of the active ingredient, or a pharmaceutical composition thereof, may vary with the particular compound, the route of administration, and the age and condition of the individual subject to whom the
15 medicament is to be administered.

In general parenteral administration requires lower dosages than other methods of administration which are more dependent upon absorption. However, a dosage for humans preferably contains 0.0001-100 mg per kg body weight. The desired dose may be presented as one dose or as multiple sub-doses administered at appropriate
20 intervals throughout the day.

The compounds according to the invention can be used in therapy.

A further aspect of the invention resides in the use of compounds according to the invention or a pharmaceutically acceptable salt thereof for the treatment of ROR γ -
25 mediated diseases or ROR γ mediated conditions.

Another aspect of the invention resides in the use of compounds having the general Formula I or a pharmaceutically acceptable salt thereof for the treatment of autoimmune diseases, in particular those diseases in which Th17 cells and non-Th17 cells, which express Th17 hallmark cytokines play a prominent role. These include, but
30 are not limited to, the treatment of rheumatoid arthritis, psoriasis, inflammatory bowel disease, Crohn's disease and multiple sclerosis.

In another aspect, compounds having the general Formula I or a pharmaceutically acceptable salt thereof can be used for treatment of inflammatory diseases in which

Th17 cells and/or non-Th17 cells, which express Th17 hallmark cytokines play a prominent role such as, but not limited to respiratory diseases, osteoarthritis and asthma. Also, compounds or a pharmaceutically acceptable salt thereof having the general Formula I can be used for treatment of infectious diseases in which Th17 cells and/or non-Th17 cells, which express Th17 hallmark cytokines play a prominent role such as, but not limited to mucosal leishmaniasis.

Compounds having the general Formula I or a pharmaceutically acceptable salt thereof can also be used for treatment of other diseases in which Th17 cells and/or non-Th17 cells, which express Th17 hallmark cytokines play a prominent role such as, but not limited to Kawasaki disease and Hashimoto's thyroiditis.

In yet another aspect the invention resides in the use of compounds having the general Formula I for the treatment of multiple sclerosis, inflammatory bowel disease, Crohn's disease, psoriasis, rheumatoid arthritis, asthma, osteoarthritis, Kawasaki disease, Hashimoto's thyroiditis, cancer and mucosal leishmaniasis.

In another aspect, the compounds according to the invention can be used in therapies to treat or prevent multiple sclerosis, inflammatory bowel disease, Crohn's disease, psoriasis and rheumatoid arthritis, asthma, osteoarthritis, Kawasaki disease, Hashimoto's thyroiditis, cancer and mucosal leishmaniasis.

In another aspect the compounds according to the invention can be used to treat or prevent psoriasis.

In yet another aspect the compounds according to the invention can be used to treat inflammatory bowel disease.

The invention is illustrated by the following examples.

Examples

General methods of preparation.

The compounds described herein, including compounds of general Formula I, building block II and building block III are prepared by the reaction schemes depicted below. Furthermore, in the following schemes, where specific acids, bases, reagents, coupling agents, solvents, etc. are mentioned, it is understood that other suitable acids, bases,

reagents, coupling agents, solvents etc. may be used and are included within the scope of the present invention. Modifications to the reaction conditions, for example, temperature, duration of the reaction or combinations thereof, are envisioned as part of the present invention. The compounds obtained by using the general reaction sequences may be of insufficient purity. The compounds can be purified by using any of the methods for purification of organic compounds, for example, crystallization or silica gel or alumina column chromatography using different solvents in suitable ratios. All possible stereoisomers are envisioned within the scope of the invention.

Chemical names are preferred IUPAC names, generated using ChemBioDraw, version 12.0.

If a chemical compound is referred to using both a chemical structure and a chemical name, and an ambiguity exists between the structure and the name, the structure predominates.

Abbreviations used herein are as follow: **HATU**: 2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; **DMF**: Dimethylformamide;

DiPEA: Diisopropylethylamine; **DMAP**: 4-(dimethylamino)pyridine;

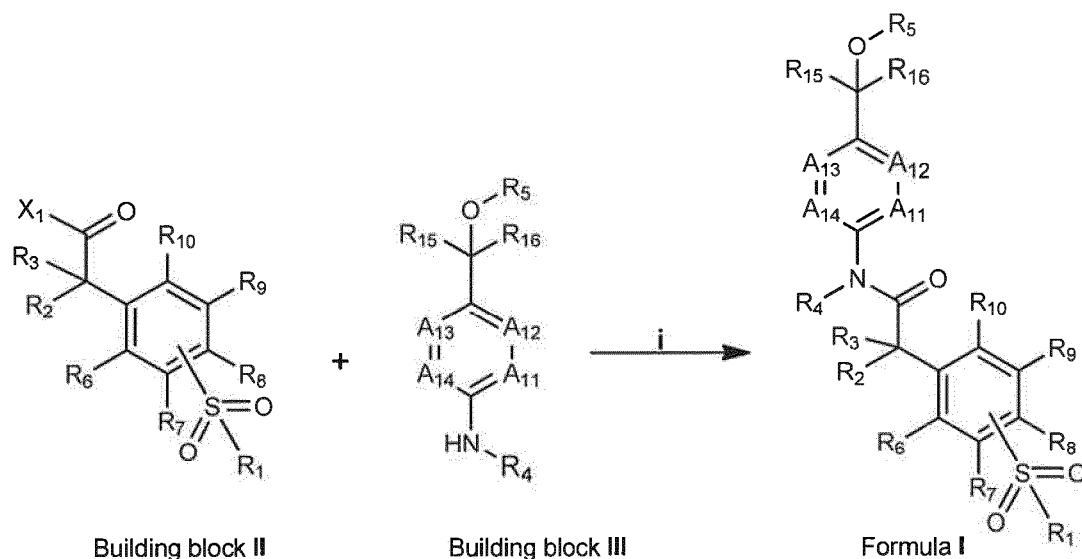
DCC: N,N'-Dicyclohexylcarbodiimide; **mCPBA**: 3-chloroperoxybenzoic acid;

TFA: Trifluoroacetic acid; **TFAA**: Trifluoroacetic anhydride; **THF**: Tetrahydrofuran;

DMSO: Dimethylsulfoxide; **PTSA**: p-Toluenesulfonic acid; **PyBOP**: (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate; **EtOH**: Ethanol; **DIAD**:

Diisopropyl azodicarboxylate; **TLC**: Thin Layer Chromatography; **Pd(dba)₂**: Bis(dibenzylideneacetone)palladium(0); **PPh₃**: Triphenyl phosphine; **NMP**: N-Methyl-2-pyrrolidinone; **EDCI**: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide; **BuLi**: *n*-Butyl lithium; **TBAF**: Tetra-*N*-butylammonium fluoride; **TMS**: Trimethylsilyl.

Scheme 1.



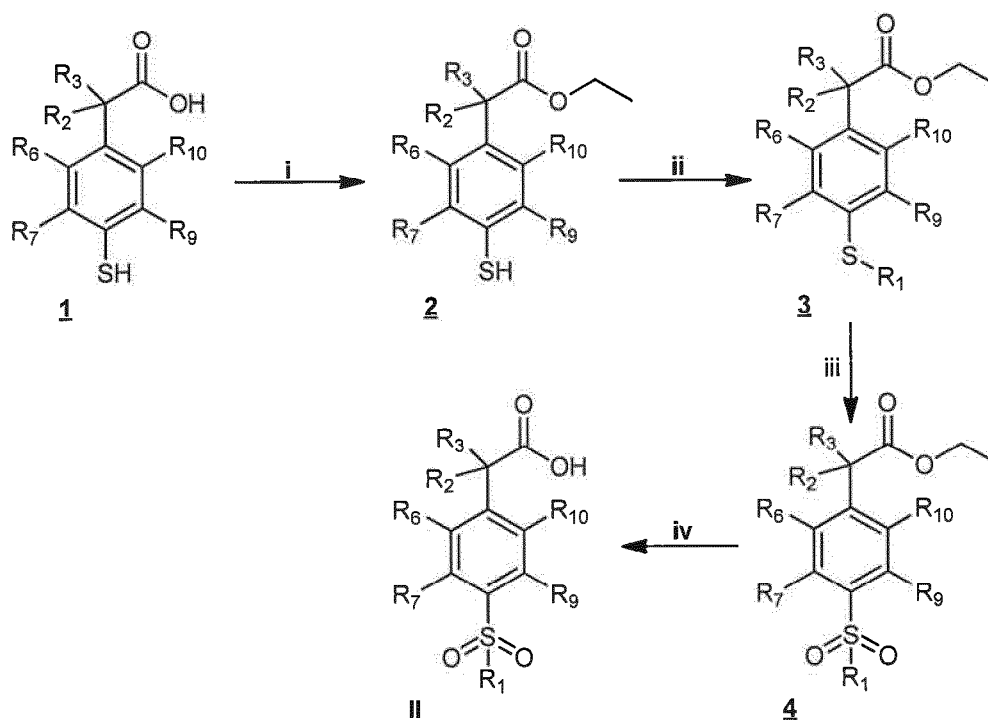
Conditions: i) DCC, DMAP, CH₂Cl₂.

- 5 As depicted in scheme 1, the derivatives of the invention having Formula I can be prepared by methods known in the art of organic chemistry. Compounds of the invention can for example be obtained by an amide coupling reaction between a phenylacetic acid derivative of building block II (X₁ is OH), wherein R₁, R₂, R₃, R₆, R₇, R₈, R₉ and R₁₀ have the meaning as previously described, and an aniline derivative of building block III, wherein R₄, R₅, R₁₅, R₁₆, A₁₁, A₁₂, A₁₃ and A₁₄ have the meaning as previously described, using a coupling reagent such as EDCI, HATU, DCC, or PyBOP or the like, in the presence of a suitable base such as DiPEA or DMAP.

15 Alternatively, the phenylacetic acid derivative of building block II (X₁ = OH) can be converted into an acid chloride derivative of building block II (X₁ = Cl), using for example SOCl₂ or oxalyl chloride. The obtained acid chloride derivative of building block II (X₁ = Cl), wherein R₁, R₂, R₃, R₆, R₇, R₈, R₉ and R₁₀ have the meaning as previously described, can be coupled with an aniline derivative of building block III, wherein R₄, R₅, R₁₅, R₁₆, A₁₁, A₁₂, A₁₃ and A₁₄ have the meaning as previously described in the presence of a suitable base such as Et₃N or the like.

20

Scheme 2



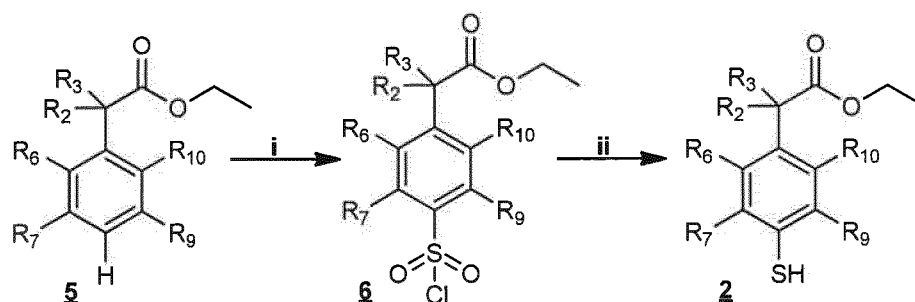
Conditions: i) H_2SO_4 , EtOH; ii) R_1 -halide, K_2CO_3 ; iii) mCPBA; iv) 2N NaOH, EtOH

Scheme 2 illustrates a general method for preparing sulfonylphenylacetic acid derivatives of building block II wherein R_1 , R_2 , R_3 , R_6 , R_7 , R_9 and R_{10} have the meaning as previously described.

Esterification of 4-mercatophenylacetic acid derivatives **1** under acidic conditions, using for example H_2SO_4 in EtOH provides 4-mercaptophenylacetic acid ethylester **2**. Alkylation of the sulfur group using an alkylhalide in the presence of a base, such as K_2CO_3 , gives the corresponding sulfanylphenylacetate derivatives **3** (R_1 = e.g. Alkyl, cycloalkyl, cycloalkyl alkyl). Oxidation, using e.g. mCPBA, gives sulfonylphenylacetate derivatives **4** which after saponification of the ester moiety under basic conditions, e.g. NaOH in EtOH, gives the corresponding phenylacetic acid derivatives of building block II wherein R_1 , R_2 , R_3 , R_6 , R_7 , R_9 and R_{10} have the meaning as previously described.

15

Scheme 3

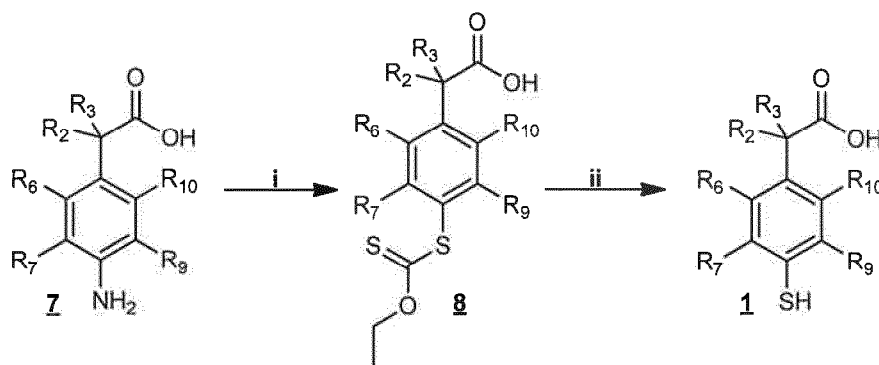


Conditions: i) Chlorosulfonic acid, CH_2Cl_2 ; ii) Tin, 5N HCl in 2-propanol or dioxane.

Scheme 3 illustrates an alternative route for the synthesis of mercaptophenyl acetate derivatives **2** wherein R_2 , R_3 , R_6 , R_7 , R_9 and R_{10} have the meaning as previously described.

Reaction of 2-phenylacetic acid ethylester derivatives **5** with chlorosulfonic acid at $0\text{ }^\circ\text{C}$ to room temperature, provides sulfonylchloride derivatives **6**, (J. Med. Chem., 2009, 52, 19, 6142 – 6152). The chlorosulfone moiety can be reduced by using tin in the presence of HCl in a suitable solvent such as dioxane or 2-propanol to give the desired mercaptophenyl acetate derivatives **2**.

Scheme 4



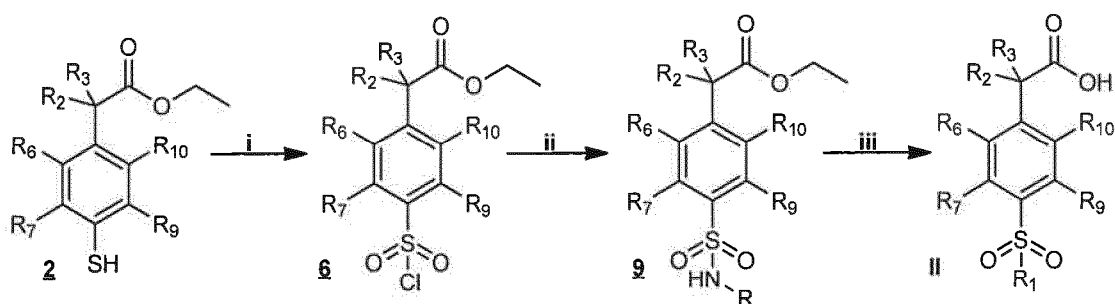
Conditions: i) NaNO_2 , HCl (conc), Potassium ethylxanthate, 2N Na_2CO_3 ; ii) KOH, EtOH

Scheme 4 illustrates a general method for the synthesis of 4-mercatophenylacetic acid derivatives **1** wherein R_2 , R_3 , R_6 , R_7 , R_9 and R_{10} have the meaning as previously described.

Aminophenylacetic acid derivatives **7** can be converted into their corresponding diazonium salts by using methods well known in organic chemistry, which then, after treatment with potassium ethylxanthate in the presence of a base, e.g. Na_2CO_3 , are

converted *in-situ* into the 2-(4-((ethoxymethanethioyl)sulfanyl)phenyl)acetic acid derivatives **8**. Treating compound **8** with for example KOH in EtOH gives the desired 4-mercatophenylacetic acid derivatives **1**.

5 Scheme 5



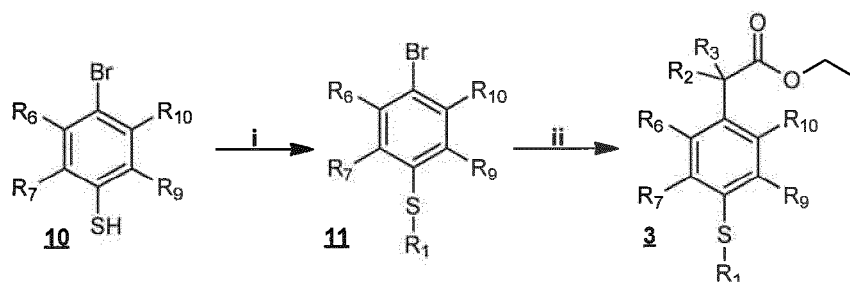
Conditions: i) SOCl_2 , H_2O_2 ii) NH_2R , Et_3N , CH_2Cl_2 iii) 2N NaOH , EtOH .

- 10 Scheme 5 illustrates a general method for the preparation of sulfamoylphenylacetic acid derivatives of building block **II** wherein R_1 , R_2 , R_3 , R_6 , R_7 , R_9 and R_{10} have the meaning as previously described.

Step i shows an alternative method to prepare chlorosulfonyl phenylacetic acid ethylester derivatives **6**. Mercatophenyl acetate derivatives **2** can be converted into chlorosulfonyl phenylacetic acid ethylester derivatives **6** by oxidative chlorination using
 15 a mixture of H_2O_2 and SOCl_2 in a suitable solvent such as CH_3CN , (Bahrami et al., J. Org. Chem. 2009, 74, 9287-9291).

Substitution of the chlorine with a suitable amine, wherein R is e.g. alkyl, cycloalkyl or cycloalkylalkyl, in the presence of a base, e.g. Et_3N , provides the sulfamoylphenylacetic acid ethyl ester derivatives **9**. Saponification of the ethylester under basic conditions, e.g. NaOH in EtOH , gives the desired sulfamoylphenylacetic acid derivatives of building
 20 block **II** wherein R_1 , R_2 , R_3 , R_6 , R_7 , R_9 and R_{10} have the meaning as previously described.

25 Scheme 6:



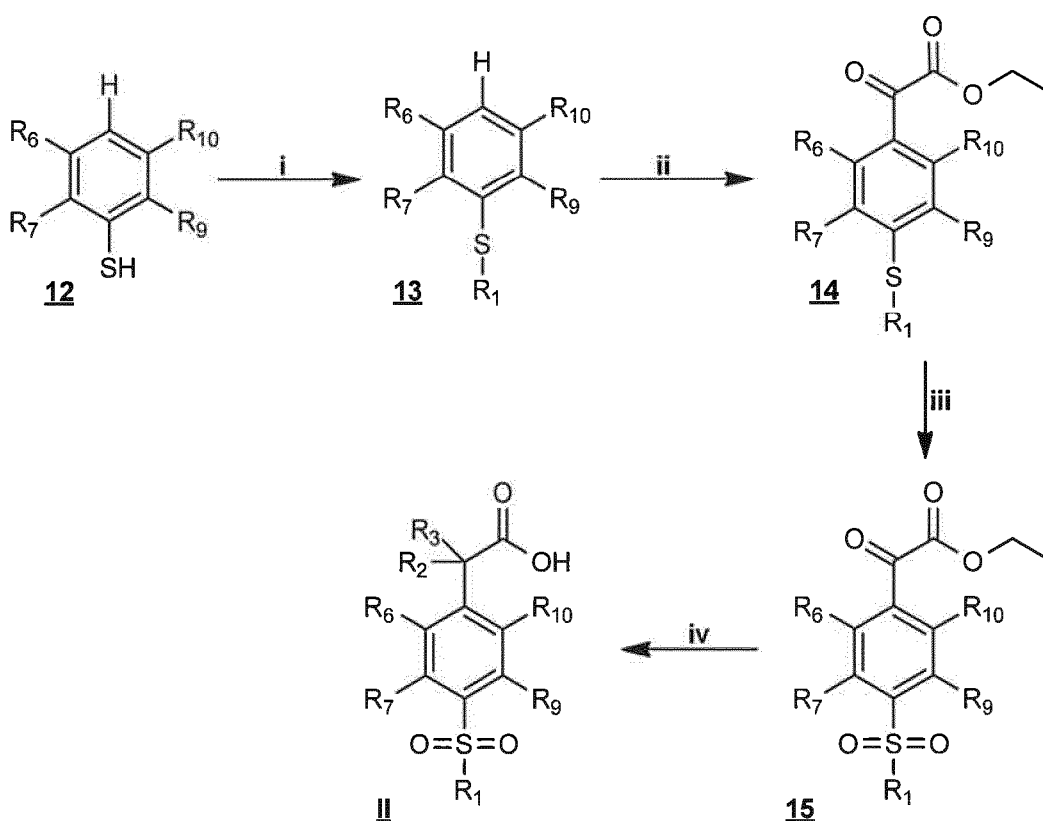
Conditions: i) R₁-halide, K₂CO₃; ii) Diethyl malonate, Pd(dba)₂, 18-crown-6, P(tBu)₃·xHBF₄, K₃PO₄.

- 5 Scheme 6 illustrates an alternative route for the synthesis of sulfanyl acetate derivatives **3** wherein R₁, R₂, R₃, R₆, R₇, R₉ and R₁₀ have the meaning as previously described.

Alkylation of 4-bromophenylthiol derivatives **10**, using an alkylhalide in the presence of a base, such as K₂CO₃, gives the corresponding 4-bromophenylsulfane derivatives **11**
 10 (R₁ = e.g. alkyl, cycloalkyl, cycloalkyl alkyl).

Derivatives **11** can be converted into the corresponding sulfanyl acetate derivatives **3** by a palladium catalyzed coupling with diethyl malonate.

Scheme 7:

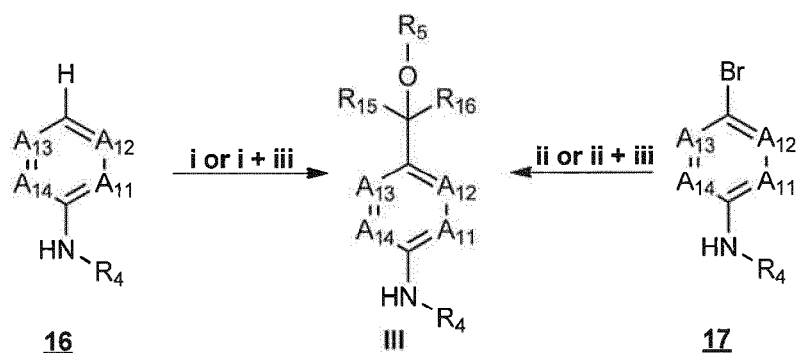


Conditions: (R_2 and R_3 together is carbonyl): i) K_2CO_3 , Alkylhalide, CH_3CN ; ii) ethyl oxalylchloride, $AlCl_3$, CH_2Cl_2 ; iii) mCPBA, CH_2Cl_2 ; iv) 2N NaOH, ethanol.

- 5 Scheme 7 illustrates a route for the synthesis of sulfonylphenyl-2-oxoacetic acid derivatives (R_2 and R_3 together is carbonyl) of building block II wherein R_1 , R_6 , R_7 , R_9 and R_{10} have the meaning as previously described.

Alkylation of thiophenol derivatives **12**, using an alkylhalide in the presence of a base, such as K_2CO_3 , gives the corresponding phenylsulfane derivatives **13** (R_1 = e.g. alkyl, cycloalkyl, cycloalkylalkyl) which, under Friedel-Craft acylation conditions, in the presence of $AlCl_3$ and ethyl oxalylchloride, can be converted to the corresponding ethyl thiophenyl-2-oxoacetate derivatives **14**. Oxidation, using e.g. mCPBA gives ethyl sulfonylphenyl-2-oxopropanoate derivatives **15** which after saponification of the ester moiety under basic conditions, e.g. NaOH in EtOH, give the corresponding sulfonylphenyl-2-oxopropanoic acid derivatives (R_2 and R_3 together is carbonyl) of building block II wherein R_1 , R_6 , R_7 , R_9 and R_{10} have the meaning as previously described.

Scheme 8



Conditions: i) (R₁₅, R₁₆ = CF₃, R₅ = H), Hexafluoroacetone hydrate; ii) BuLi, ketone; iii) DIAD, PPh₃, DMAP, R₅OH.

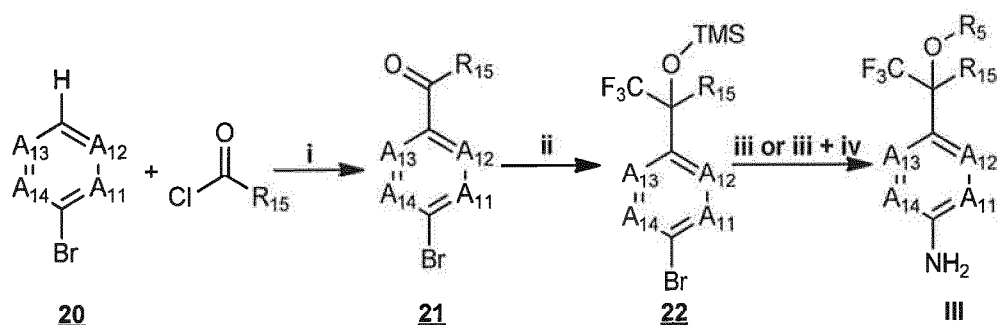
- 5 Scheme 8 shows two general methods for the preparation of (4-aminophenyl) methanol derivatives of building block **III**, wherein R₄, R₅, R₁₅, R₁₆, A₁₁, A₁₂, A₁₃ and A₁₄ have the meaning as previously described.

If R₁₅ and R₁₆ are both CF₃, then heating the aniline derivatives **16** in 1,1,1,3,3,3-hexafluoroacetone hydrate as the solvent in a sealed tube in a microwave, provides in
 10 one step 2-(4-aminophenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol derivatives (R₅ = H) of building block **III**.

Alternatively, the 1,1,1,3,3,3-hexafluoropropan-2-ol moiety can be introduced by treating suitable (*N*-protected)bromoaniline derivatives **17** with *n*-butyl lithium to form the corresponding lithiated intermediate, which then can be converted by treatment with
 15 1,1,1,3,3,3-hexafluoroacetone gas to the desired 2-(4-aminophenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol derivatives (R₅ = H) of building block **III**. This method can also be used for the introduction of other tertiary alcohols, by using e.g. dry acetone, dry dicyclopropylmethanone or the like, as the corresponding ketone.

The alcohol derivatives of building block **III** (R₅ = H) can, for example, be converted
 20 under Mitsunobu conditions, using e.g. DIAD, PPh₃, DMAP and a suitable alcohol, to the corresponding ether derivatives of building block **III** (R₅ = e.g. alkyl, cycloalkyl).

Scheme 9

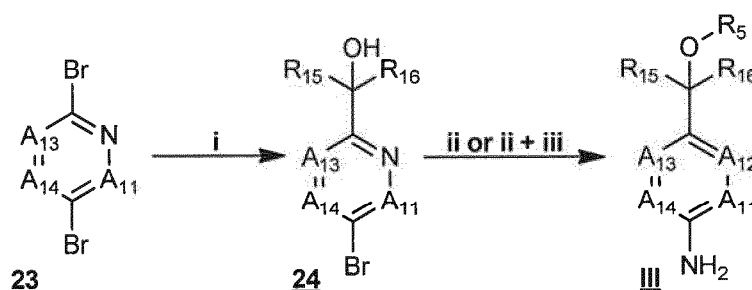


Conditions: i) AlCl_3 , CH_2Cl_2 ; ii) TMSCF_3 , CsF , Toluene/ CH_2Cl_2 ; iii) NH_4OH , Cu_2O , NMP, 80°C , microwave; iv) DIAD, PPh_3 , DMAP, R_5OH .

- 5 Scheme 9 shows a general method for the preparation of 1-(4-aminophenyl)-2,2,2-trifluoroethanol derivatives of building block III, wherein R_5 , R_{15} , A_{11} , A_{12} , A_{13} and A_{14} have the meaning as previously described.

(Hetero)aryl bromides **20** can be converted under Friedel-Crafts acylation conditions, using AlCl_3 and a suitable acid chloride in e.g. CH_2Cl_2 , to the corresponding 1-(4-bromophenyl)ketone derivatives **21**, which can, e.g. via a cesium fluoride or TBAF catalyzed trifluoromethylation, be converted to the corresponding TMS protected 1-(4-aminophenyl)-2,2,2-trifluoroethanol derivatives **22** (Sing et al., J. Org. Chem., 64, p 2873 (1999). Copper catalyzed amination, using Cu_2O in the presence of ammonia (Wolf and Xu, Chem. Comm., p. 3035 (2009), results in the formation of 1-(4-aminophenyl)-2,2,2-trifluoroethanol derivatives III ($\text{R}_5 = \text{H}$). These alcohol derivatives of building block III can, for example, be converted under Mitsunobu conditions, using e.g. DIAD, PPh_3 , DMAP and a suitable alcohol, to the corresponding ether derivatives of building block III ($\text{R}_5 = \text{e.g. alkyl, cycloalkyl}$).

20 Scheme 10



Conditions: ($\text{A}_{12} = \text{N}$): i) BuLi , hexafluoroacetone, toluene; ii) NH_4OH , Cu_2O , NMP, 80°C , microwave; iii) DIAD, PPh_3 , DMAP, R_5OH .

Scheme 10 depicts a general method for the preparation of (5-aminopyridin-2-yl)methanol derivatives of building block III ($A_{12} = N$), wherein R_5 , R_{15} , R_{16} , A_{11} , A_{13} and A_{14} have the meaning as previously described.

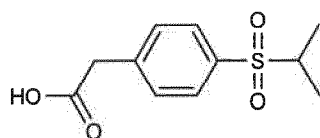
The R_{15}, R_{16} -alcohol moiety can be introduced by treating suitable dibromopyridine derivatives **23** with *n*-butyl lithium to form the corresponding lithiated intermediate, which then can be converted by treatment with the corresponding ketone, e.g. 1,1,1,3,3,3-hexafluoroacetone gas, dry acetone or the like, to the corresponding (5-bromopyridin-2-yl)methanol derivatives **24**. Copper catalyzed amination, using Cu_2O in the presence of ammonia, results in the formation of (5-aminopyridin-2-yl)methanol derivatives of building block III ($A_{12} = N$, $R_5 = H$). These alcohol derivatives of building block III can, for example, be converted under Mitsunobu conditions, using e.g. DIAD, PPh_3 , DMAP and a suitable alcohol, to the corresponding ether derivatives of building block III ($A_{12} = N$, $R_5 =$ e.g. alkyl, cycloalkyl).

15

Synthesis of building blocks II

Building blocks II-1 – II-6

II-1: 2-(4-(isopropylsulfonyl)phenyl)acetic acid.



i) To a solution of 2-(4-mercaptophenyl)acetic acid (10.0 g) in ethanol (120 mL) was added drop wise concentrated sulfuric acid (3.4 mL). The reaction mixture was stirred for 3 hours at 60 °C. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and the remaining oil was neutralized with a saturated aqueous $NaHCO_3$ solution. The product was extracted into ethyl acetate and the combined organic phases were washed with water, brine, dried over magnesium sulfate, and after filtration, concentrated under reduced pressure. The residue was purified on SiO_2 using 10% ethyl acetate in heptane as the eluent to give ethyl 2-(4-mercaptophenyl)acetate (10.2 g) as colourless liquid.

30

ii) To a suspension of the product obtained in the previous step (5.0 g) and potassium carbonate (8.6 g) in acetonitrile (50 mL) was added 2-bromopropane (2.8 mL). After stirring overnight at room temperature, the reaction mixture was filtered and

concentrated under reduced pressure. The residue was purified on SiO₂ using 10% ethyl acetate in heptane as the eluent to give ethyl 2-(4-(isopropylthio)phenyl)acetate (5.34 g) as a colourless liquid.

5 **iii)** To a cooled (0 °C) solution of the product obtained in the previous step (5.3 g) in CH₂Cl₂ (50 mL), was added portion wise mCPBA (11.5 g). After stirring overnight at room temperature, the reaction mixture was filtered and the organic phase was washed with a saturated aqueous NaHCO₃ solution, water, brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified on SiO₂ using 10% ethyl acetate in heptane as the eluent. To give ethyl 2-(4-(isopropylsulfonyl)phenyl)acetate (4.4 g) as a clear oil.

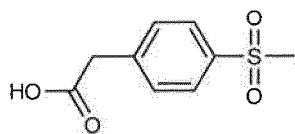
10 **iv)** To a solution of the product obtained in the previous step (4.4 g) in ethanol (50 mL), was added an aqueous 2N NaOH solution. After stirring overnight at room temperature, ethanol was removed under reduced pressure and 100 mL water was added. The aqueous solution was washed with CH₂Cl₂, acidified to pH=1 with an aqueous 6N HCl solution and the product was then extracted into ethyl acetate. The combined organic layers were washed with water, brine, dried over magnesium sulfate and concentrated under reduced pressure to give the title compound 2-(4-(isopropylsulfonyl)phenyl)acetic acid (3.6 g) as a white solid. MS(ES⁺) *m/z* 243.2 [M+H]⁺.

20

Following a procedure analogous to that described for compound **II-1**, using a suitable alkylating reagent (**step ii**), the following compounds were prepared.

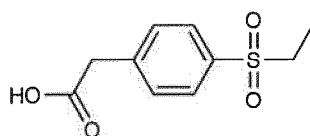
II-2: 2-(4-(methylsulfonyl)phenyl)acetic acid.

25



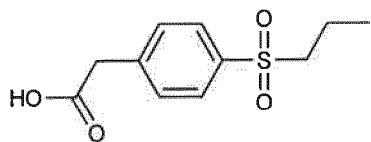
MS(ES⁺) *m/z* 215.2 [M+H]⁺.

II-3: 2-(4-(ethylsulfonyl)phenyl)acetic acid.



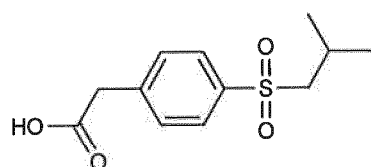
MS(ES⁺) *m/z* 229.1 [M+H]⁺.

II-4: 2-(4-(propylsulfonyl)phenyl)acetic acid.



5 MS(ES⁺) *m/z* 243.2 [M+H]⁺.

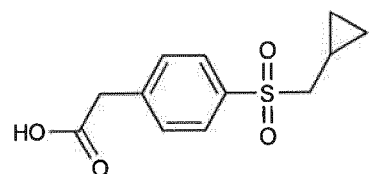
II-5: 2-(4-(isobutylsulfonyl)phenyl)acetic acid.



MS(ES⁺) *m/z* 257.2 [M+H]⁺.

10

II-6: 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)acetic acid.

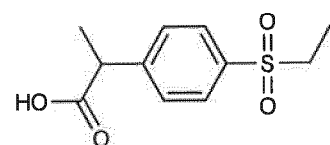


MS(ES⁺) *m/z* 255.2 [M+H]⁺.

15

Building blocks II-7 and II-8

II-7: 2-(4-(ethylsulfonyl)phenyl)propanoic acid.



20 i) Following a procedure described for compound **II-1**, **step i**, 2-phenylpropanoic acid (5.0 g) was converted to ethyl 2-phenylpropanoate (4.4 g).

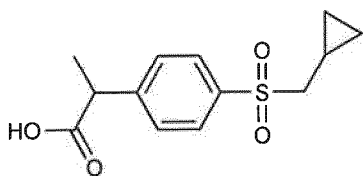
ii) A solution of the product obtained in the previous step (4.4 g) in CH_2Cl_2 (30 mL) was added drop wise at 0 °C to chlorosulfonic acid (21.7 mL). After stirring for 3 hours at room temperature the reaction mixture was quenched by carefully pouring it onto crushed ice. The product was extracted into ethyl acetate and the combined organic layers were washed with water, brine and dried over magnesium sulfate. After filtration, the solvent was removed under reduced pressure to give ethyl 2-(4-(chlorosulfonyl)phenyl)propanoate (5.3 g) as a brown solid. The crude product was used in the next step without purification.

iii) To a suspension of the product obtained in the previous step (5.3 g) and tin powder (12.0 g) in ethanol (50 mL), was added a 4N solution of HCl in dioxane (27 mL). The reaction mixture was stirred at 65°C for 3 hours under a nitrogen atmosphere. The reaction mixture was quenched by pouring it onto crushed ice. The product was extracted into CH_2Cl_2 and the organic layer was washed with water and dried over magnesium sulfate. After filtration, the solvent was removed under reduced pressure. The residue was purified on SiO_2 , using 10% ethyl acetate in heptane as the eluent to give ethyl 2-(4-mercaptophenyl)propanoate (2.8 g) as a colourless liquid.

iv) Following a procedure described for compound **II-1**, **step ii to iv**, the product obtained in the previous step (1.0 g), using iodoethane (0.46 mL) as the alkylating reagent, was converted to the title compound 2-(4-(ethylsulfonyl)phenyl)propanoic acid (0.82 g). MS(ES^+) m/z 243.2 [$\text{M}+\text{H}$] $^+$.

Following a procedure analogous to that described for compound **II-7**, using a suitable alkylating reagent (**step iv**), the following compound was prepared.

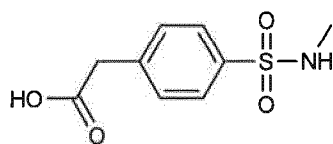
II-8: 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)propanoic acid.



MS(ES^+) m/z 268.1 [$\text{M}+\text{H}$] $^+$.

Building blocks II-9 – II-17

II-9: 2-(4-(*N*-methylsulfonyl)phenyl)acetic acid.



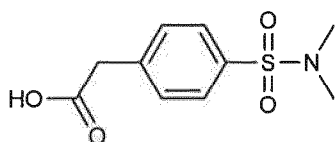
i) Following a procedure described for compound **II-7**, **step ii**, ethyl 2-phenylacetate (1.87 g) was converted to ethyl 2-(4-(chlorosulfonyl)phenyl)acetate.

ii) To a solution of the product obtained in the previous step (1 g) in CH₂Cl₂ was added methylamine hydrochloride (0.31 g mmol). After stirring for 17 hours at room temperature, the reaction mixture was washed with water, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified on SiO₂ using 10% to 20% ethyl acetate in heptane as the eluent to give ethyl 2-(4-(N-methylsulfamoyl)phenyl)acetate as a solid (0.41 g).

iii) Following a procedure described for compound **II-1**, **step iv**, the product obtained in the previous step (0.41 g) was converted to the title compound 2-(4-(N-methylsulfamoyl)phenyl)acetic acid. (0.35 g). MS(ES⁺) *m/z* 230.2 [M+H]⁺.

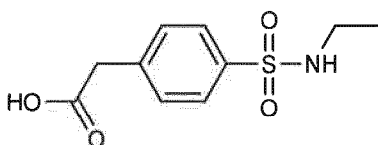
Following a procedure analogous to that described for compound **II-9**, the following compounds were prepared.

II-10: 2-(4-(N,Ndimethylsulfamoyl)phenyl)acetic acid.



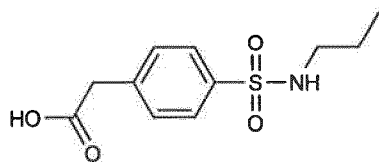
MS(ES⁺) *m/z* 244.1 [M+H]⁺.

II-11: 2-(4-(N-ethylsulfamoyl)phenyl)acetic acid.



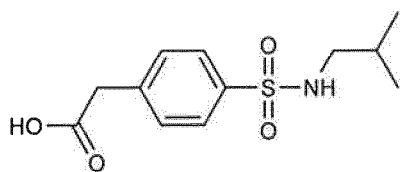
MS(ES⁺) *m/z* 244.1 [M+H]⁺.

II-12: 2-(4-(N-propylsulfamoyl)phenyl)acetic acid.



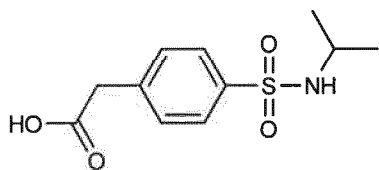
MS(ES⁺) m/z 258.2 [M+H]⁺.

II-13: 2-(4-(*N*-isobutylsulfamoyl)phenyl)acetic acid.



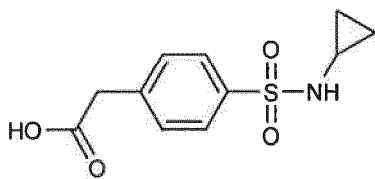
MS(ES⁺) m/z 272.2 [M+H]⁺.

II-14: 2-(4-(*N*-isopropylsulfamoyl)phenyl)acetic acid.



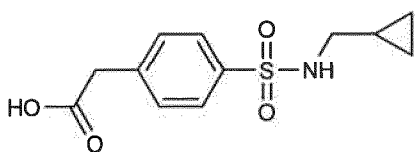
MS(ES⁺) m/z 258.2 [M+H]⁺.

II-15: 2-(4-(*N*-cyclopropylsulfamoyl)phenyl)acetic acid.



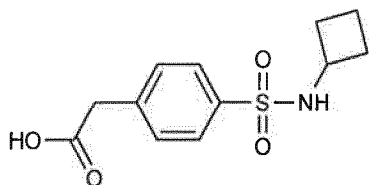
MS(ES⁺) m/z 256.2 [M+H]⁺.

II-16: 2-(4-(*N*-(cyclopropylmethyl)sulfamoyl)phenyl)acetic acid.



MS(ES⁺) m/z 270.2 [M+H]⁺.

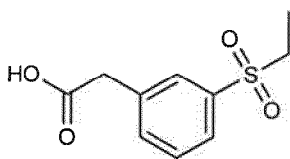
II-17: 2-(4-(*N*-cyclobutylsulfamoyl)phenyl)acetic acid.



5 MS(ES⁺) m/z 270.1 [M+H]⁺.

Building blocks II-18 – II-22

10 **II-18:** 2-(3-(ethylsulfonyl)phenyl)acetic acid.



i) A solution of sodium nitrite (0.916 g) in 20 mL of water was added drop wise to a suspension of 2-(3-aminophenyl)acetic acid (2 g) in 20 mL of water and 2.7 mL of concentrated hydrochloric acid cooled to 0 °C. After the addition was complete, the reaction mixture was stirred at the same temperature for a further 45 minutes. This cold diazonium salt solution was then added drop wise to a mixture of potassium O-ethyl carbonodithioate (2.456 g), 20 mL of water and 10 mL of a 2N Na₂CO₃ solution at room temperature. The reaction mixture was heated at 45 °C until gas evolution stopped. The mixture was subsequently cooled to room temperature, the pH was adjusted to 1 with concentrated HCl. The oily product was extracted into diethyl ether and the organic layer was washed with water, brine, dried over magnesium sulfate and concentrated under reduced pressure to give 2-(3-((ethoxycarbonothioyl)thio)phenyl) acetic acid (4.8 g) as a dark red liquid which was used in the next step without purification.

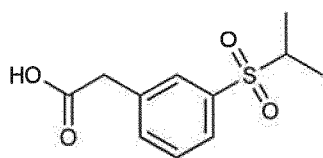
ii) To a solution of the product obtained in the previous step (4.8 g) in ethanol (50 mL) was added an aqueous solution of KOH (1.05 g). The reaction mixture was heated at reflux for 20 hours. The organic solvent was removed under reduced pressure and the remaining aqueous phase was cooled with ice and acidified with concentrated HCl. The product was extracted into diethyl ether and the organic phase was washed with water,

brine, dried over magnesium sulfate and concentrated under reduced pressure to give the 2-(3-mercaptophenyl)acetic acid (3.3 g) as a brown solid which was used in the next step without purification.

iii) Following a procedure described for compound **II-1**, **step i to iv**, the product obtained in the previous step (0.97 g), using iodoethane (0.42 mL) as the alkylating reagent, was converted to the title compound 2-(3-(ethylsulfonyl)phenyl)acetic acid. MS(ES⁺) *m/z* 229.2 [M+H]⁺.

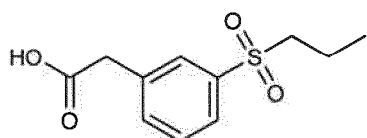
Following a procedure analogous to that described for compound **II-18**, the following compounds were prepared.

II-19: 2-(3-(isopropylsulfonyl)phenyl)acetic acid.



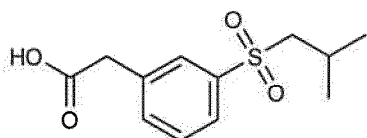
MS(ES⁺) *m/z* 243.2 [M+H]⁺.

II-20: 2-(3-(propylsulfonyl)phenyl)acetic acid.



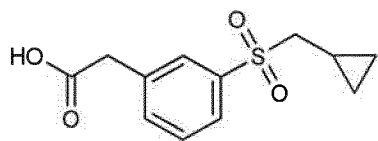
MS(ES⁺) *m/z* 243.1 [M+H]⁺.

II-21: 2-(3-(isobutylsulfonyl)phenyl)acetic acid.



MS(ES⁺) *m/z* 257.2 [M+H]⁺.

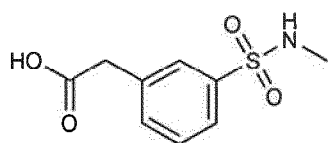
II-22: 2-(3-((cyclopropylmethyl)sulfonyl)phenyl)acetic acid.



MS(ES⁺) m/z 255.2 [M+H]⁺.

5 **Building blocks II-23 – II-29**

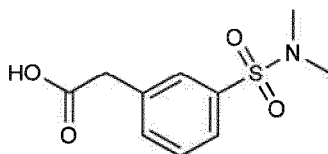
II-23: 2-(3-(*N*-methylsulfamoyl)phenyl)acetic acid.



- i) A mixture of ethyl 2-(3-mercaptophenyl)acetate (compound **II-18**, **step ii**, 0.1 g), 30% H₂O₂ in water (155 μ L) and SOCl₂ (61 μ L) was stirred in CH₃CN at 25 °C for 10 minutes. After completion as indicated by TLC, a solution of methylamine hydrochloride (0.04 g) in pyridine (0.5 ml) was added to the reaction mixture. After stirring for 15 minutes at room temperature, the reaction mixture was acidified with an aqueous 2N HCl solution, and the product was extracted into ethyl acetate. The organic layer was washed with water, brine, dried over magnesium sulfate and concentrated under reduced pressure to give ethyl 2-(3-(*N*-methylsulfamoyl)phenyl) acetate (0.21 g) as a yellow oil which was used in the next step without purification.
- ii) Following a procedure described for compound **II-1**, **step iv**, the product obtained in the previous step (0.2 g) was converted to the title compound 2-(3-(*N*-methylsulfamoyl)phenyl)acetic acid (0.083 g). MS(ES⁺) m/z 230.2 [M+H]⁺.

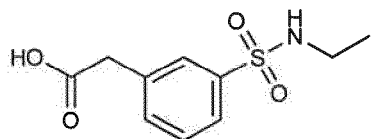
Following a procedure analogous to that described for compound **II-23**, the following compounds were prepared.

II-24: 2-(3-(*N,N*-dimethylsulfamoyl)phenyl)acetic acid.



MS(ES⁺) m/z 244.2 [M+H]⁺.

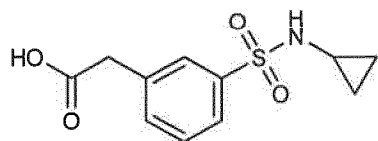
II-25: 2-(3-(*N*-ethylsulfamoyl)phenyl)acetic acid.



MS(ES⁺) *m/z* 244.2 [M+H]⁺.

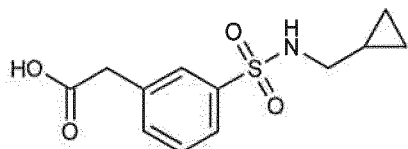
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II-26: 2-(3-(*N*-cyclopropylsulfamoyl)phenyl)acetic acid.



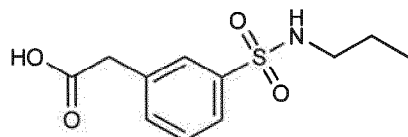
MS(ES⁺) *m/z* 256.1 [M+H]⁺.

10 **II-27:** 2-(3-(*N*-(cyclopropylmethyl)sulfamoyl)phenyl)acetic acid.



MS(ES⁺) *m/z* 270.1 [M+H]⁺.

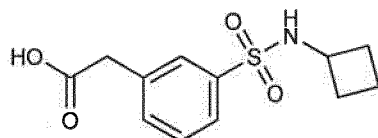
II-28: 2-(3-(*N*-propylsulfamoyl)phenyl)acetic acid.



15

MS(ES⁺) *m/z* 258.1 [M+H]⁺.

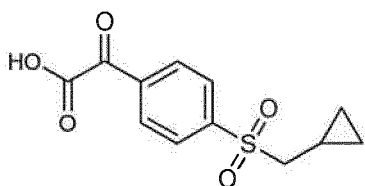
II-29: 2-(3-(*N*-cyclobutylsulfamoyl)phenyl)acetic acid.



20

MS(ES⁺) *m/z* 270.2 [M+H]⁺.

II-30: 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-2-oxoacetic acid.



i) Following a procedure analogous to that described for compound **II-1**, **step ii**, benzenethiol (4.0 g) was converted to (cyclopropylmethyl)(phenyl)sulfane (5.68 g).

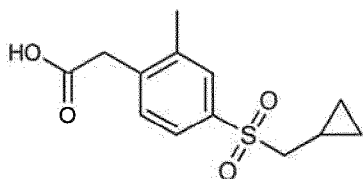
ii) To a cold (0 °C) suspension of AlCl₃ (6.44 g) in CH₂Cl₂ was added drop wise, under a nitrogen atmosphere, ethyl oxalyl chloride (4.25 mL). After stirring for 30 minutes at 0 °C, the product obtained in the previous step (5.68 g), was added drop wise. The purple solution was allowed to warm to room temperature. After stirring for another 2 hours at ambient temperature, the reaction mixture was quenched by pouring it onto ice water. CH₂Cl₂ was added and the layers were separated. The aqueous phase was washed twice with CH₂Cl₂ and the combined organic phases were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified on SiO₂, using 0% to 100% ethyl acetate in heptane as the eluent to give ethyl 2-(4-((cyclopropylmethyl)thio)phenyl)-2-oxoacetate (5.57 g) as a yellow oil.

iii) To a cold solution (0 °C) of the product obtained in the previous step (1.0 g) in CH₂Cl₂ (25 mL) was added portion wise mCPBA (1.95 g). After stirring for 17 hours at room temperature the reaction mixture was filtered. The filtrate was washed with a saturated aqueous NaHCO₃ solution, water, brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified on SiO₂, using 0% to 90% ethyl acetate in heptane as the eluent to give ethyl 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-2-oxoacetate (0.3 g).

iv) To a solution of the product obtained in the previous step (0.3 g) in ethanol (10 mL) was added an aqueous 2N NaOH solution (1.80 mL) and the reaction mixture was stirred for 17 hours at room temperature. The solvent was removed under reduced pressure and water was added (100 mL). The aqueous solution was washed with CH₂Cl₂ and then acidified with an aqueous 6N HCl solution to pH = 1. This aqueous phase was washed with ethyl acetate and the organic phase was washed brine, dried over magnesium sulfate and concentrated under reduced pressure to give the title compound 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-2-oxoacetic acid (0.25 g) as a clear oil.

MS(ES⁺) *m/z* 268.2 [M+H]⁺.

II-31: 2-(4-((cyclopropylmethyl)sulfonyl)-2-methylphenyl)acetic acid.



i) (Bromomethyl)cyclopropane (170 μ L) was added to a mixture of 4-bromo-3-methylbenzenethiol (300 mg) and K_2CO_3 (511 mg) in CH_3CN (15 mL) and the reaction mixture was stirred at room temperature for 3.5 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified on SiO_2 , using 5% ethyl acetate in heptane as the eluent to give 4-bromo-3-methylphenyl)(cyclopropylmethyl)sulfane (95 mg).

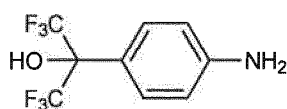
ii) A mixture of the product obtained in the previous step (95 mg), diethylmalonate (390 mg), K_3PO_4 (220 mg) and 18-crown-6 (49 mg) in a microwave tube was purged with nitrogen for 10 minutes. $Pd(dba)_2$ (1 mg) and $P(tBu)_3 \cdot xHBF_4$ (1 mg) were added and the reaction was heated, in a sealed tube, in a microwave for 3 hours at 160 $^{\circ}C$. After cooling to room temperature the reaction mixture was diluted with ethyl acetate and the solution was washed with water. The organic phase was washed with water and the combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified on SiO_2 , using 10% ethyl acetate in heptane as the eluent to give ethyl 2-(4-((cyclopropylmethyl)thio)-2-methylphenyl)acetate (60 mg).

iii) Following a procedure described for compound **II-1**, **step iii to iv**, the product obtained in the previous step (60 mg), was converted to the title compound 2-(4-((cyclopropylmethyl)sulfonyl)-2-methylphenyl)acetic acid (28 mg) as a white solid. $MS(ES^+) m/z$ 296.4 $[M+H]^+$.

25 Synthesis of building blocks III

Building blocks III-1 – III-8

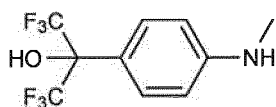
III-1: 2-(4-aminophenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol.



- i) A mixture of aniline (392 μL) and hexafluoroacetone trihydrate (600 μL) were heated, in a sealed tube, in a microwave at 150 $^{\circ}\text{C}$ for 2 hours. The crude product was crystallized from heptane with 20% ethyl acetate to give the title compound 2-(4-aminophenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (490 mg) as a white solid. MS(ES⁺) m/z 260.2 [M+H]⁺.

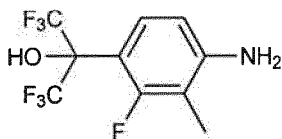
Following a procedure analogous to that described for compound III-1, the following compounds were prepared.

III-2: 1,1,1,3,3,3-hexafluoro-2-(4-(methylamino)phenyl)propan-2-ol.



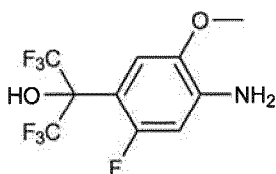
MS(ES⁺) m/z 274.2 [M+H]⁺.

III-3: 2-(4-amino-2-fluoro-3-methylphenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol.



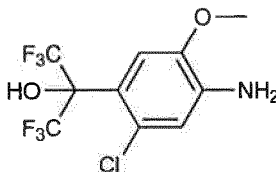
MS(ES⁺) m/z 292.1 [M+H]⁺.

III-4: 2-(4-amino-2-fluoro-5-methoxyphenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol.



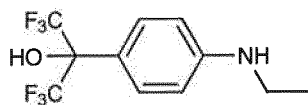
MS(ES⁺) m/z 308.2 [M+H]⁺.

III-5: 2-(4-amino-2-chloro-5-methoxyphenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol.



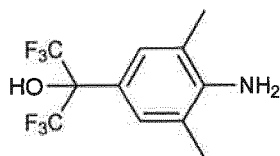
MS(ES⁺) m/z 324.6 [M+H]⁺.

III-6: 2-(4-(ethylamino)phenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol.



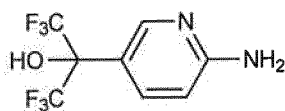
MS(ES⁺) *m/z* 288.2 [M+H]⁺.

5 **III-7:** 2-(4-amino-3,5-dimethylphenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol.



MS(ES⁺) *m/z* 288.2 [M+H]⁺.

III-8: 2-(6-aminopyridin-3-yl)-1,1,1,3,3,3-hexafluoropropan-2-ol.



10

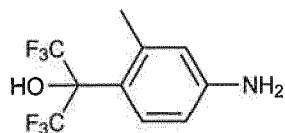
MS(ES⁺) *m/z* 261.2 [M+H]⁺.

Building blocks III-9 – III-12

15

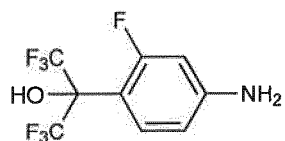
The following compounds were purchased from Parkway Scientific:

III-9: 2-(4-amino-2-methylphenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol.

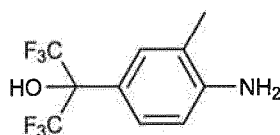


20

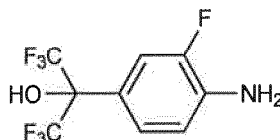
III-10: 2-(4-amino-2-fluorophenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol.



III-11: 2-(4-amino-3-methylphenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol.



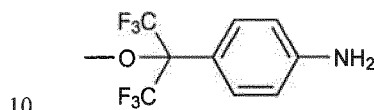
III-12: 2-(4-amino-3-fluorophenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol.



5

Building blocks III-13 – III-19

III-13: 4-(1,1,1,3,3,3-hexafluoro-2-methoxypropan-2-yl)aniline.



10

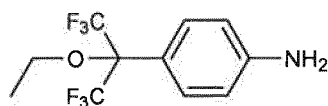
i) A solution of DIAD (141 μ L) in THF (1 mL) was added drop wise to a solution of 2-(4-aminophenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (**III-1**) (100 mg), PPh₃ (152 mg) and methanol (32 μ L) in THF (1 mL) at 0 °C. After stirring for 2 hours at room temperature the solvent was removed under reduced pressure and the remaining yellow oil was purified on a preparative HPLC using 5 to 90 % CH₃CN in water as the eluent to give the title compound 4-(1,1,1,3,3,3-hexafluoro-2-methoxypropan-2-yl)aniline (50 mg) as a white solid. MS(ES⁺) m/z 274.1 [M+H]⁺.

15

Following a procedure analogous to that described for compound **III-13**, the following compounds were prepared.

20

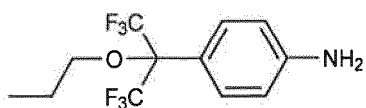
III-14: 4-(2-ethoxy-1,1,1,3,3,3-hexafluoropropan-2-yl)aniline.



MS(ES⁺) m/z 288.1 [M+H]⁺.

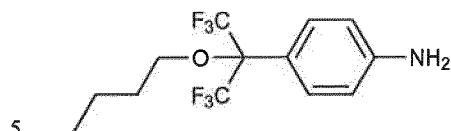
25

III-15: 4-(1,1,1,3,3,3-hexafluoro-2-propoxypropan-2-yl)aniline.



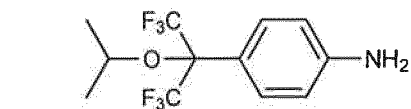
MS(ES⁺) *m/z* 302.1 [M+H]⁺.

III-16: 4-(2-butoxy-1,1,1,3,3,3-hexafluoropropan-2-yl)aniline.



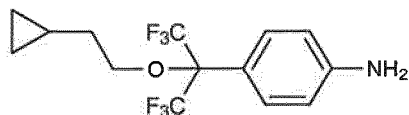
MS(ES⁺) *m/z* 316.2 [M+H]⁺.

III-17: 4-(1,1,1,3,3,3-hexafluoro-2-isopropoxypropan-2-yl)aniline.



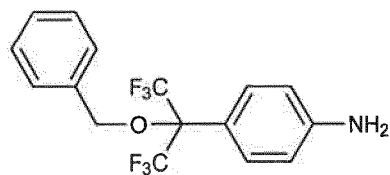
MS(ES⁺) *m/z* 302.1 [M+H]⁺.

III-18: 4-(2-(2-cyclopropylethoxy)-1,1,1,3,3,3-hexafluoropropan-2-yl)aniline.



MS(ES⁺) *m/z* 328.1 [M+H]⁺.

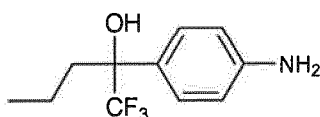
III-19: 4-(2-(benzyloxy)-1,1,1,3,3,3-hexafluoropropan-2-yl)aniline.



MS(ES⁺) *m/z* 350.1 [M+H]⁺.

Building blocks III-20 – III-32

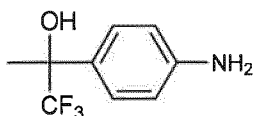
III-20: 2-(4-aminophenyl)-1,1,1-trifluoropentan-2-ol.



- i) To a suspension of AlCl_3 (4.06 g) in bromobenzene (2.72 mL) was added drop wise butyrylchloride (2.66 mL). After addition was complete the reaction mixture was stirred at 50 °C for 2 hours under a nitrogen atmosphere. The reaction mixture was quenched by pouring it onto ice water and the product was extracted into ethyl acetate. The organic phase was washed with water, brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified on SiO_2 , using 0% to 20% ethyl acetate in heptane as the eluent to give 1-(4-bromophenyl)butan-1-one (5.6 g) as a solid.
- ii) To a solution of the product obtained in the previous step (1.0 g) in a mixture of toluene and CH_2Cl_2 (2 ml, 9 : 10) was added (trifluoromethyl)trimethylsilane (0.65 mL). To this suspension CsF (67 mg) was added. After a few minutes an exothermic reaction started and the reaction mixture was stirred for another 30 minutes until completion. The reaction mixture was quenched by the addition of water. The organic layer was washed with water, brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified on SiO_2 , using 0% to 40% ethyl acetate in heptane as the eluent to give ((2-(4-bromophenyl)-1,1,1-trifluoropentan-2-yl)oxy)trimethylsilane (1.5 g) as a solid.
- iii) To a solution of the product obtained in the previous step (1.5 g) in NMP (4 mL) were added Cu_2O (30 mg) and an aqueous NH_4OH solution (4 mL). The reaction mixture was stirred for 15 hours at 80 °C in a microwave. The blue reaction mixture was poured into water and the product was extracted into ethyl acetate. The organic layer was washed with water, brine, dried over magnesium sulfate and concentrated under reduced pressure to give the title compound 2-(4-aminophenyl)-1,1,1-trifluoropentan-2-ol as a brown oil. The crude product was used without further purification. MS(ES^+) m/z 234.1 $[\text{M}+\text{H}]^+$.

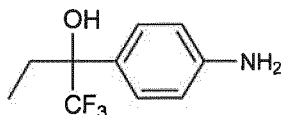
Following a procedure analogous to that described for Example **III-20**, the following compounds were prepared.

III-21: 2-(4-aminophenyl)-1,1,1-trifluoropropan-2-ol.



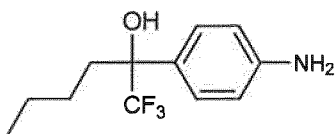
MS(ES⁺) *m/z* 206.1 [M+H]⁺.

III-22: 2-(4-aminophenyl)-1,1,1-trifluorobutan-2-ol.



5 MS(ES⁺) *m/z* 2120.1 [M+H]⁺.

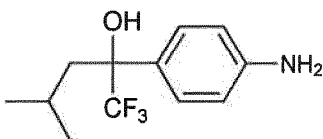
III-23: 2-(4-aminophenyl)-1,1,1-trifluorohexan-2-ol.



MS(ES⁺) *m/z* 248.1 [M+H]⁺.

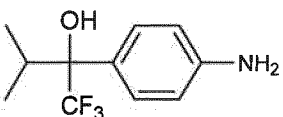
10

III-24: 2-(4-aminophenyl)-1,1,1-trifluoro-4-methylpentan-2-ol.



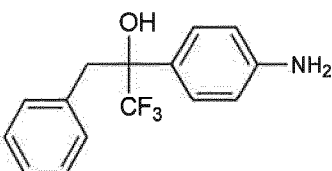
MS(ES⁺) *m/z* 248.1 [M+H]⁺.

15 **III-25:** 2-(4-aminophenyl)-1,1,1-trifluoro-3-methylbutan-2-ol.



MS(ES⁺) *m/z* 234.1 [M+H]⁺.

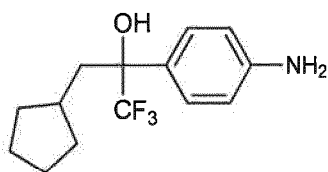
III-26: 2-(4-aminophenyl)-1,1,1-trifluoro-3-phenylpropan-2-ol.



20

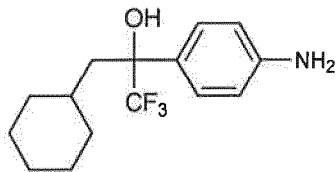
MS(ES⁺) *m/z* 282.1 [M+H]⁺.

III-27: 2-(4-aminophenyl)-3-cyclopentyl-1,1,1-trifluoropropan-2-ol.



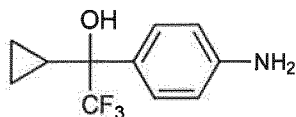
MS(ES⁺) *m/z* 274.1 [M+H]⁺.

III-28: 2-(4-aminophenyl)-3-cyclohexyl-1,1,1-trifluoropropan-2-ol.



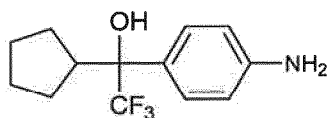
MS(ES⁺) *m/z* 288.1 [M+H]⁺.

III-29: 1-(4-aminophenyl)-1-cyclopropyl-2,2,2-trifluoroethanol.



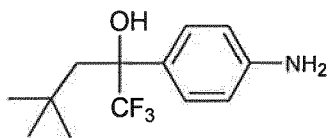
MS(ES⁺) *m/z* 232.1 [M+H]⁺.

III-30: 1-(4-aminophenyl)-1-cyclopentyl-2,2,2-trifluoroethanol.



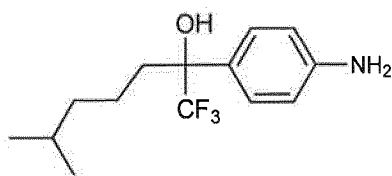
MS(ES⁺) *m/z* 260.1 [M+H]⁺.

III-31: 2-(4-aminophenyl)-1,1,1-trifluoro-4,4-dimethylpentan-2-ol.



MS(ES⁺) *m/z* 262.1 [M+H]⁺.

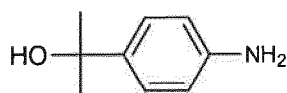
III-32: 2-(4-aminophenyl)-1,1,1-trifluoro-6-methylheptan-2-ol.



MS(ES⁺) m/z 276.1 [M+H]⁺.

5 Building blocks III-33 and III-34

III-33: 2-(4-aminophenyl)propan-2-ol.



i) A solution of 4-bromoanilin (12.46 g) and di-tert-butyl dicarbonate (18.97 g) in THF (500 mL) was stirred at 80 °C for 24 hours. After cooling to room temperature the solvent was removed under reduced pressure and the remaining solid was transferred to a filter and washed with heptane. The filtrate was concentrated under reduced pressure and the remaining solids were washed with heptanes one more time. The combined solids were dried under reduced pressure at 40 °C to give tert-butyl (4-bromophenyl)carbamate (16.73 g) as a white solid.

ii) The product obtained in the previous step (1 g) was dissolved in dry THF (20 mL) in a dried 3-neck flask under a nitrogen atmosphere. The reaction mixture was cooled to -78 °C and BuLi (5.7 mL, 2.5 N in heptane) was added drop wise. After stirring for 1.5 hours at -78 °C, dry acetone (296 uL) was added drop wise. The reaction mixture was allowed to warm to room temperature and stirred for another 17 hours. The reaction mixture was quenched by the addition of a saturated aqueous NH₄Cl solution. The product was extracted into ethyl acetate and the combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified on SiO₂, using 0% to 40% ethyl acetate in heptane as the eluent to give tert-butyl (4-(2-hydroxypropan-2-yl)phenyl)carbamate (210 mg).

iii) To a solution of the product obtained in the previous step (124 mg) in THF (2.5 mL) was added at room temperature a 1 M solution of TBAF in THF (987 uL). The reaction mixture was stirred at 80 °C for 17 hours. The reaction mixture was quenched by the addition of water and the product was extracted into ethyl acetate. The combined organic layers were washed with a saturated aqueous NaHCO₃ solution, brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was

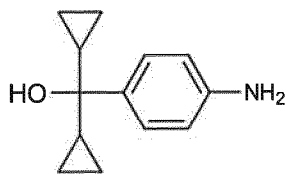
purified on SiO₂, using 0% to 45% ethyl acetate in heptane as the eluent to give title compound 2-(4-aminophenyl)propan-2-ol (44 mg). MS(ES⁺) *m/z* 134.1 [(M-18)+H]⁺.

¹H NMR(500 MHz, DMSO-d₆) : δ 7.12-7.05 (m, 2H), 6.52-6.44 (m, 2H), 4.82 (s, 2H), 4.66 (s, 1H), 1.35 (s, 6H).

5

Following a procedure analogous to that described for compound III-33, the following compound was prepared.

III-34: (4-aminophenyl)dicyclopropylmethanol.



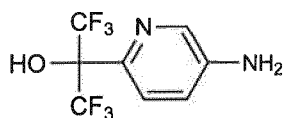
10

MS(ES⁺) *m/z* 186.1 [(M-18)+H]⁺.

¹H NMR(500 MHz, CDCl₃) : δ 7.40-7.34 (m, 2H), 6.67-6.62 (m, 2H), 3.62 (s, 2H), 1.39 (s, 1H), 1.26-1.11 (m, 2H), 0.57-0.45 (m, 4H), 0.39-0.32 (m, 4H).

15

III-35: 2-(5-aminopyridin-2-yl)-1,1,1,3,3,3-hexafluoropropan-2-ol.



i) To a solution of 2,5-dibromopyridine (500 mg) in dry toluene (11 mL) was added dropwise at -78 °C a solution of *n*-BuLi in hexane (1.45 mL, 1.6 M). The reaction mixture was stirred at -78°C for 30 minutes. Hexafluoroacetone gas was bubbled through for about 30 seconds and the reaction mixture was stirred for another 40 minutes at -78°C. After warming up to room temperature, the reaction mixture was washed with an aqueous 5% NH₄Cl solution, water, brine, dried over magnesium sulfate and the solvent was removed under reduced pressure to give 2-(5-bromopyridin-2-yl)-1,1,1,3,3,3-hexafluoropropan-2-ol as a yellow oil (532 mg).

25

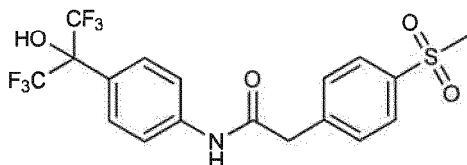
ii) To a solution of the product obtained in the previous step (532 mg) in NMP (2 mL) was added an aqueous 28% NH₄OH solution (2 mL) and Cu₂O (12 mg). The reaction mixture was stirred for 15 hours at 80 °C in a sealed tube. After cooling to room temperature, the blue reaction mixture was poured into water and extracted with ethyl acetate. The combined organic phases were washed with water, brine, dried over magnesium sulfate and concentrated under reduced pressure to give the title

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compound 2-(5-aminopyridin-2-yl)-1,1,1,3,3,3-hexafluoropropan-2-ol (95 mg) as a brown solid. MS(ES⁺) *m/z* 261.1 [M+H]⁺.

5 Examples 1 – 27:

1: *N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-2-(4-(methylsulfonyl)phenyl)acetamide.



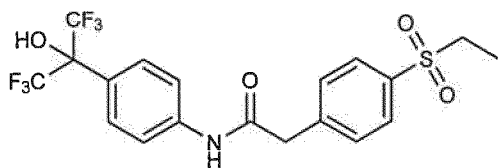
- 10 **i)** To a solution of acid II-2 (47 mg) and HATU (84 mg) in DMF (2 ml), were sequentially added DIPEA (79 μ L) and aniline III-1 (57 mg) at room temperature. The reaction mixture was stirred at 40 °C for 3 hours. After cooling to room temperature, water was added and the product was extracted into ethyl acetate. The combined organic layers were washed with water, brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified on SiO₂, using 1% to 10% methanol in dichloromethane as the eluent, to give the title compound *N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-2-(4-(methylsulfonyl)phenyl)acetamide (70 mg) as a white solid. MS(ES⁺) *m/z* 243.2 [M+H]⁺.

15 ¹H NMR(500 MHz, DMSO-d₆) : δ 10.46 (s, 1H), 8.61 (s, 1H), 7.88-7.86 (m, 2H), 7.71-7.68 (m, 2H), 7.59-7.56 (m, 4H), 3.80 (s, 2H), 3.17 (s, 3H).

Following a procedure analogous to that described for Example 1, using the appropriate building blocks II and III, the following compounds were prepared.

25

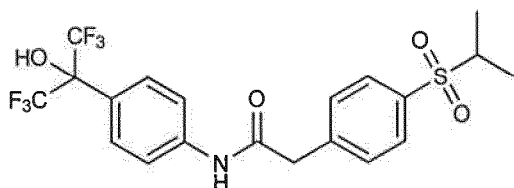
2: 2-(4-(ethylsulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide.



MS(ES⁺) *m/z* 470.2 [M+H]⁺.

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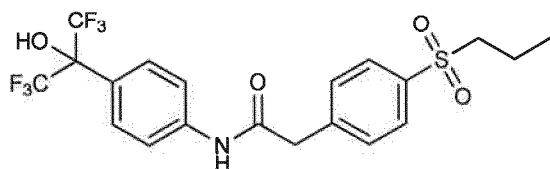
3: *N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-2-(4-(isopropylsulfonyl)phenyl)acetamide.



MS(ES⁺) *m/z* 484.2 [M+H]⁺.

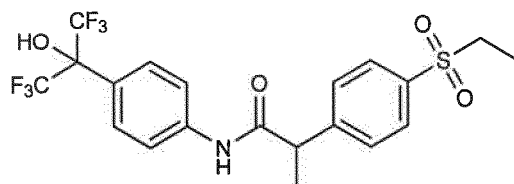
5

4: *N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-2-(4-(propylsulfonyl)phenyl)acetamide.



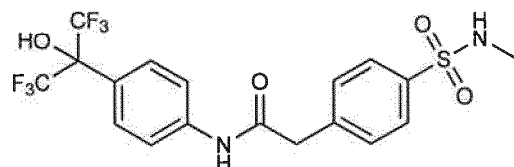
10 MS(ES⁺) *m/z* 484.2 [M+H]⁺.

5: 2-(4-(ethylsulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)propanamide.



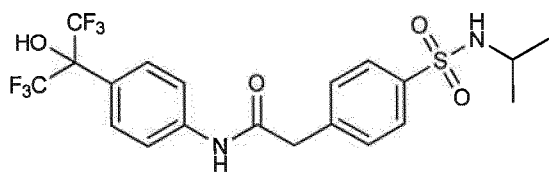
15 MS(ES⁺) *m/z* 484.2 [M+H]⁺.

6: *N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-2-(4-(*N*-methylsulfonyl)phenyl)acetamide.



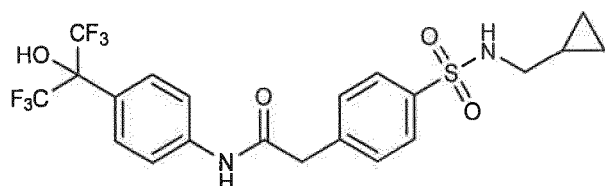
20 MS(ES⁺) *m/z* 471.2 [M+H]⁺.

7: *N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-2-(4-(*N*-isopropylsulfonyl)phenyl)acetamide.



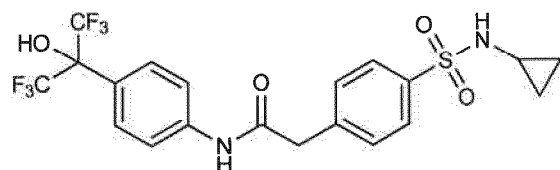
MS(ES⁺) m/z 499.2 [M+H]⁺.

- 5 **8:** 2-(4-(*N*-(cyclopropylmethyl)sulfamoyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide.



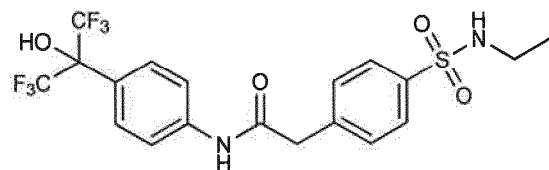
MS(ES⁺) m/z 511.2 [M+H]⁺.

- 10 **9:** 2-(4-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide.



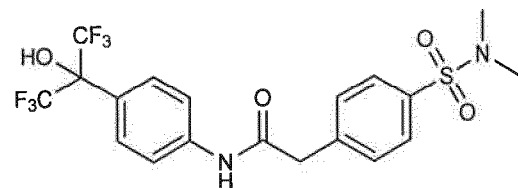
MS(ES⁺) m/z 497.2 [M+H]⁺.

- 15 **10:** 2-(4-(*N*-ethylsulfamoyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide.



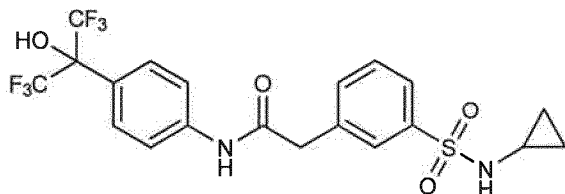
MS(ES⁺) m/z 485.1 [M+H]⁺.

- 20 **11:** 2-(4-(*N,N*-dimethylsulfamoyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide.



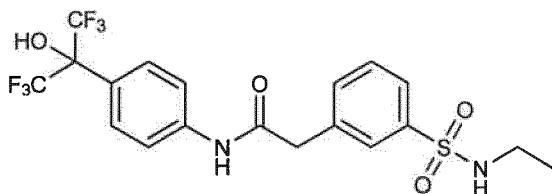
MS(ES⁺) m/z 485.1 [M+H]⁺.

12: 2-(3-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide.



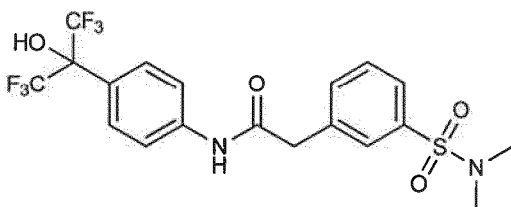
MS(ES⁺) m/z 497.2 [M+H]⁺.

13: 2-(3-(*N*-ethylsulfamoyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide.



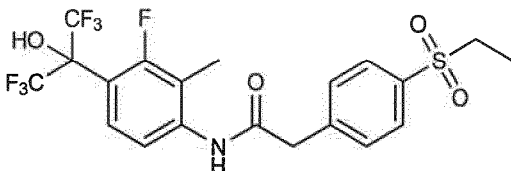
MS(ES⁺) m/z 485.2 [M+H]⁺.

14: 2-(3-(*N,N*-dimethylsulfamoyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide.



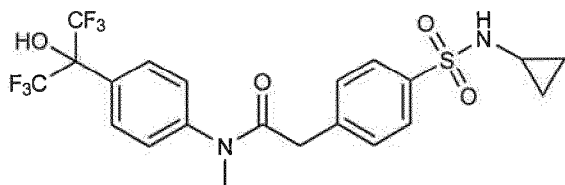
MS(ES⁺) m/z 485.2 [M+H]⁺.

15: 2-(4-(ethylsulfonyl)phenyl)-*N*-(3-fluoro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-methylphenyl)acetamide.



MS(ES⁺) m/z 502.2 [M+H]⁺.

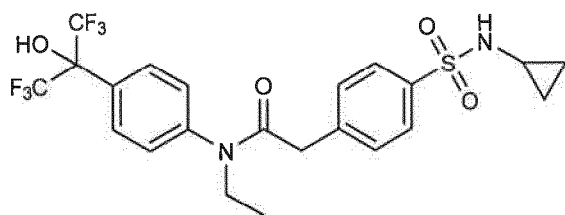
16: 2-(4-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-*N*-methylacetamide.



MS(ES⁺) *m/z* 511.1 [M+H]⁺.

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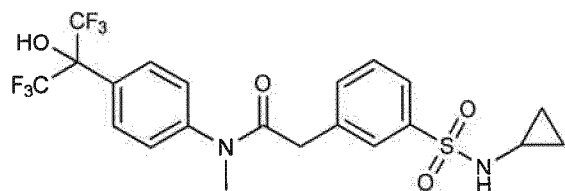
17: 2-(4-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-ethyl-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide.



MS(ES⁺) *m/z* 525.2 [M+H]⁺.

10

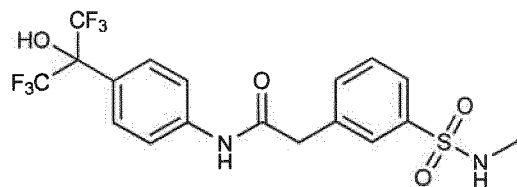
18: 2-(3-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-*N*-methylacetamide.



MS(ES⁺) *m/z* 511.2 [M+H]⁺.

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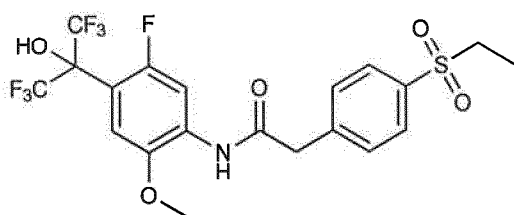
19: *N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-2-(3-(*N*-methylsulfamoyl)phenyl)acetamide.



MS(ES⁺) *m/z* 471.2 [M+H]⁺.

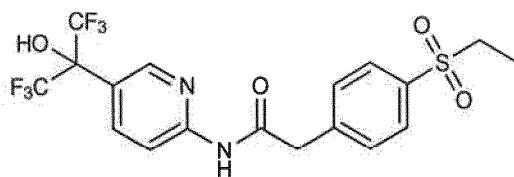
20

20: 2-(4-(ethylsulfonyl)phenyl)-*N*-(5-fluoro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-methoxyphenyl)acetamide.



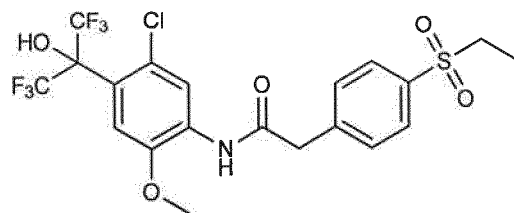
MS(ES⁺) m/z 518.2 [M+H]⁺.

21: 2-(4-(ethylsulfonyl)phenyl)-*N*-(5-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)pyridin-2-yl)acetamide.



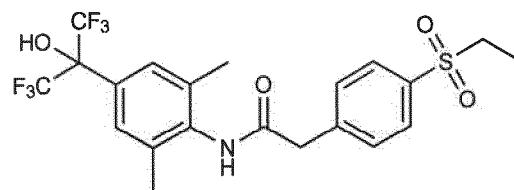
MS(ES⁺) m/z 471.2 [M+H]⁺.

22: *N*-(5-chloro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-methoxyphenyl)-2-(4-(ethylsulfonyl)phenyl)acetamide.



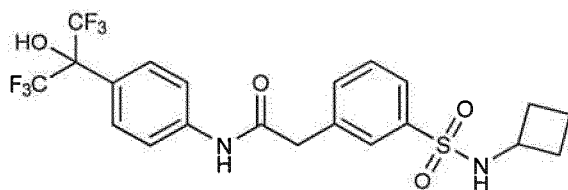
MS(ES⁺) m/z 534.2 [M+H]⁺.

23: 2-(4-(ethylsulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2,6-dimethylphenyl)acetamide.



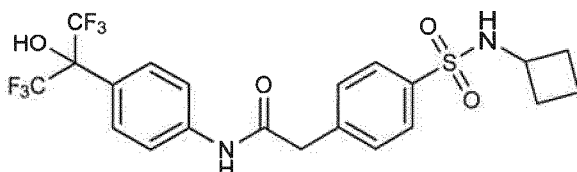
MS(ES⁺) m/z 488.2 [M+H]⁺.

24: 2-(3-(*N*-cyclobutylsulfamoyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide.



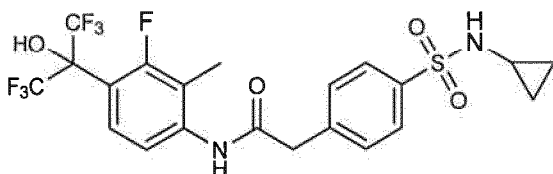
MS(ES⁺) m/z 511.2 [M+H]⁺.

- 5 **25:** 2-(4-(*N*-cyclobutylsulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide.



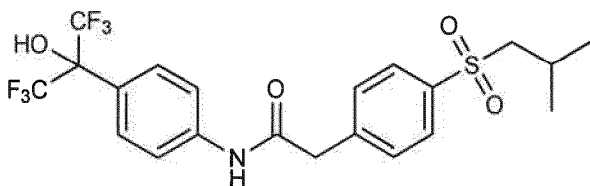
MS(ES⁺) m/z 511.1 [M+H]⁺.

- 10 **26:** 2-(4-(*N*-cyclopropylsulfonyl)phenyl)-*N*-(3-fluoro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-methylphenyl)acetamide.



MS(ES⁺) m/z 529.2 [M+H]⁺.

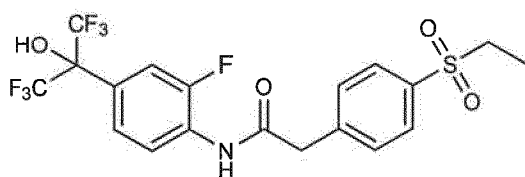
- 15 **27:** *N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-2-(4-(isobutylsulfonyl)phenyl)acetamide.



MS(ES⁺) m/z 498.1 [M+H]⁺.

- 20 **Examples 28 – 41:**

28: 2-(4-(ethylsulfonyl)phenyl)-*N*-(2-fluoro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide.

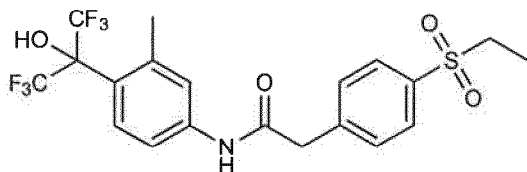


To a solution of 2-(4-amino-3-fluorophenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol, **(III-12)**, 50 mg), 2-(4-(ethanesulfonyl)phenyl)acetic acid, **II-3** (41.7 mg) and DMAP (4.9 mg) in CH_2Cl_2 (2 ml) was added drop wise at 0°C a solution of DCC (45.4 mg) in CH_2Cl_2 (2 ml). After stirring for 17 hours at room temperature, the reaction mixture was filtered and the solvent was removed under reduced pressure. The residue was purified on SiO_2 , using 20% ethyl acetate in heptane as the eluent, to give the title compound **2-(4-(ethanesulfonyl)phenyl)-N-(2-fluoro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide** (62 mg) as a white solid. MS(ES^+) m/z 488 [$\text{M}+\text{H}$] $^+$.

^1H NMR(500 MHz, $\text{DMSO}-d_6$) : δ 10.30 (s, 1H), 8.91 (s, 1H), 8.11 (dd, 1H), 7.86 (d, 2H), 7.62 (d, 2H), 7.46-7.52 (m, 2H), 3.94 (s, 2H), 3.28 (q, 2H), 1.11 (t, 3H).

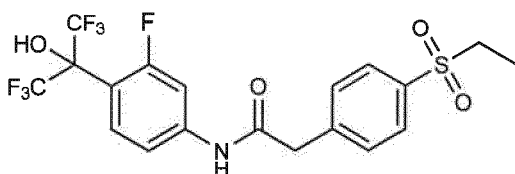
Following a procedure analogous to that described for example **28**, the following compounds were prepared.

29: 2-(4-(ethanesulfonyl)phenyl)-N-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-3-methylphenyl)acetamide.



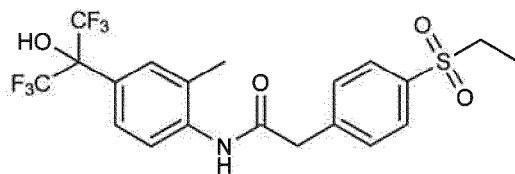
MS(ES^+) m/z 484.2 [$\text{M}+\text{H}$] $^+$.

30: 2-(4-(ethanesulfonyl)phenyl)-N-(3-fluoro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide.



MS(ES^+) m/z 488.2 [$\text{M}+\text{H}$] $^+$.

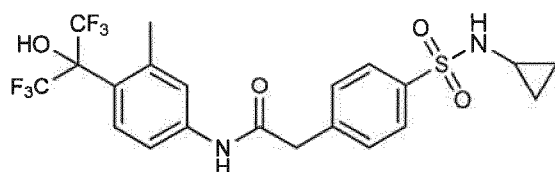
31: 2-(4-(ethylsulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-methylphenyl)acetamide.



MS(ES⁺) *m/z* 484.2 [M+H]⁺.

5

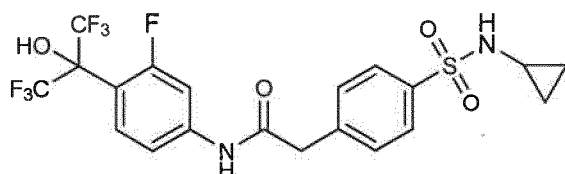
32: 2-(4-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-3-methylphenyl)acetamide.



MS(ES⁺) *m/z* 511.2 [M+H]⁺.

10

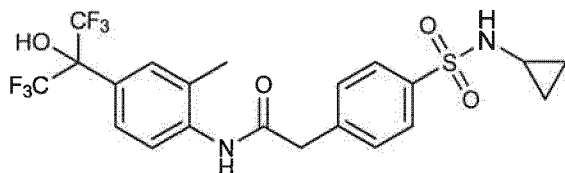
33: 2-(4-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(3-fluoro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide.



MS(ES⁺) *m/z* 515.2 [M+H]⁺.

15

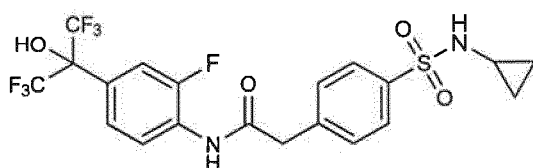
34: 2-(4-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-methylphenyl)acetamide.



MS(ES⁺) *m/z* 511.1 [M+H]⁺.

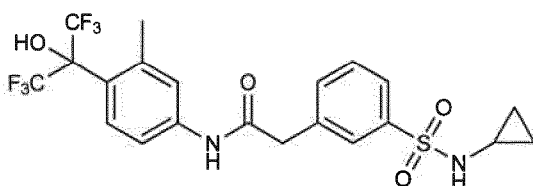
20

35: 2-(4-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(2-fluoro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide.



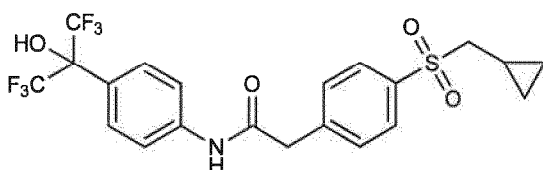
MS(ES⁺) m/z 515.2 [M+H]⁺.

- 5 **36:** 2-(3-(*N*-cyclopropylsulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-3-methylphenyl)acetamide.



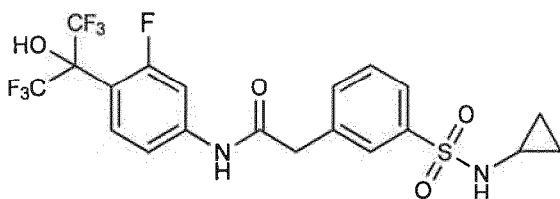
MS(ES⁺) m/z 511.2 [M+H]⁺.

- 10 **37:** 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide.



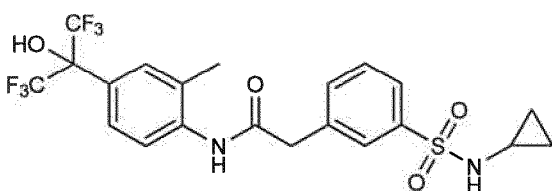
MS(ES⁺) m/z 496.2 [M+H]⁺.

- 15 **38:** 2-(3-(*N*-cyclopropylsulfonyl)phenyl)-*N*-(3-fluoro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide.



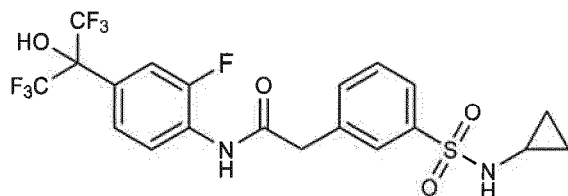
MS(ES⁺) m/z 515.2 [M+H]⁺.

- 20 **39:** 2-(3-(*N*-cyclopropylsulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-methylphenyl)acetamide.



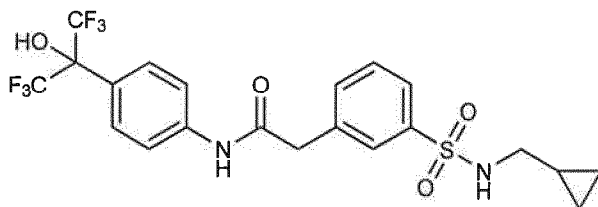
MS(ES⁺) m/z 511.2 [M+H]⁺.

40: 2-(3-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(2-fluoro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide.



MS(ES⁺) m/z 515.2 [M+H]⁺.

41: 2-(3-(*N*-(cyclopropylmethyl)sulfamoyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide.

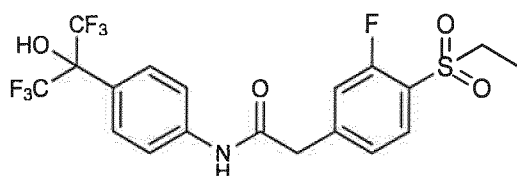


MS(ES⁺) m/z 511.2 [M+H]⁺.

Examples 42 – 111:

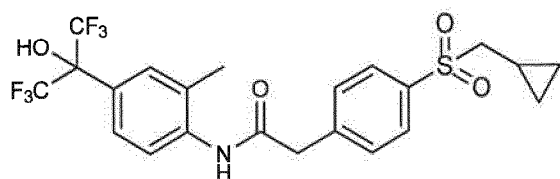
Following a procedure analogous to that described for example **28**, using EDCI instead of DCC, the following compounds were prepared.

42: 2-(4-(ethylsulfonyl)-3-fluorophenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide.



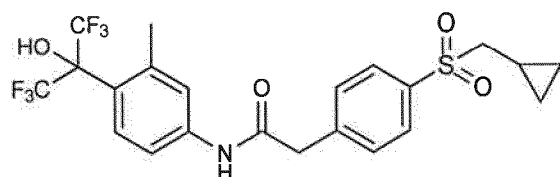
MS(ES⁺) m/z 488.2 [M+H]⁺.

43: 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-methylphenyl)acetamide.



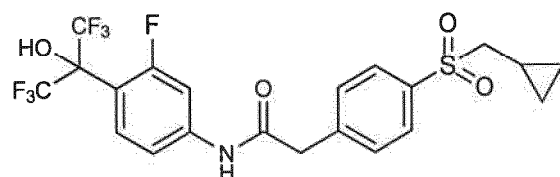
MS(ES⁺) m/z 510.2 [M+H]⁺.

- 44:** 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-3-methylphenyl)acetamide.



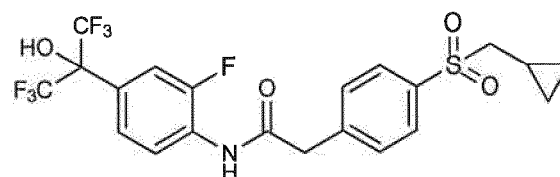
MS(ES⁺) m/z 510.2 [M+H]⁺.

- 45:** 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(3-fluoro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide.



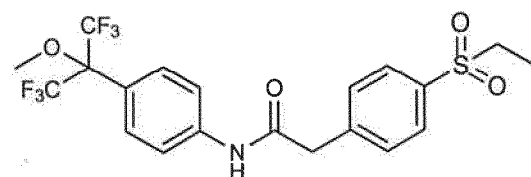
MS(ES⁺) m/z 514.2 [M+H]⁺.

- 46:** 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(2-fluoro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide.



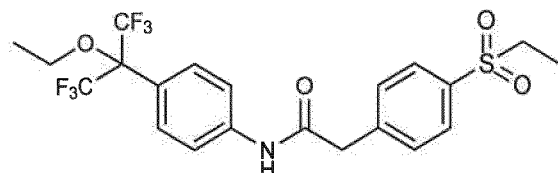
MS(ES⁺) m/z 514.2 [M+H]⁺.

- 47:** 2-(4-(ethylsulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-methoxypropan-2-yl)phenyl)acetamide.



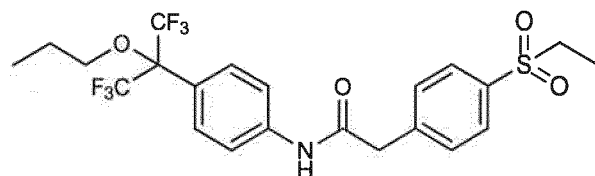
MS(ES⁺) m/z 484.1 [M+H]⁺.

48: *N*-(4-(2-ethoxy-1,1,1,3,3,3-hexafluoropropan-2-yl)phenyl)-2-(4-(ethylsulfonyl)phenyl)acetamide.



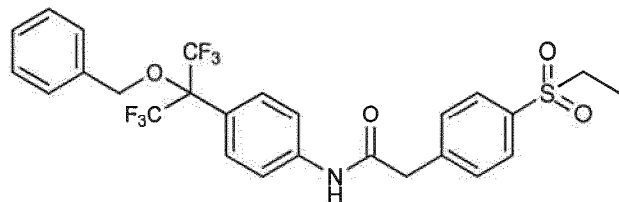
MS(ES⁺) m/z 498.2 [M+H]⁺.

49: 2-(4-(ethylsulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-propoxypropan-2-yl)phenyl)acetamide.



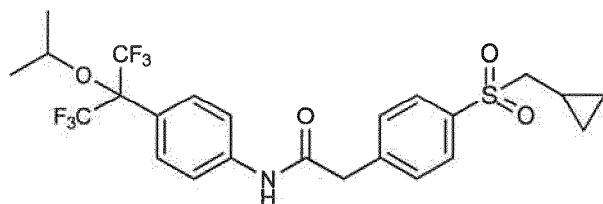
MS(ES⁺) m/z 512.2 [M+H]⁺.

50: *N*-(4-(2-(benzyloxy)-1,1,1,3,3,3-hexafluoropropan-2-yl)phenyl)-2-(4-(ethylsulfonyl)phenyl)acetamide.



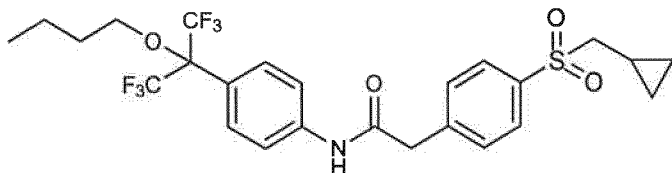
MS(ES⁺) m/z 560.2 [M+H]⁺.

51: 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-isopropoxypropan-2-yl)phenyl)acetamide.



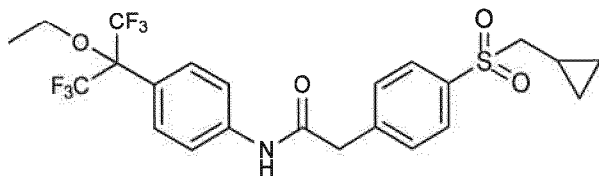
MS(ES⁺) m/z 538.2 [M+H]⁺.

52: *N*-(4-(2-butoxy-1,1,1,3,3,3-hexafluoropropan-2-yl)phenyl)-2-(4-((cyclopropylmethyl)sulfonyl)phenyl)acetamide.



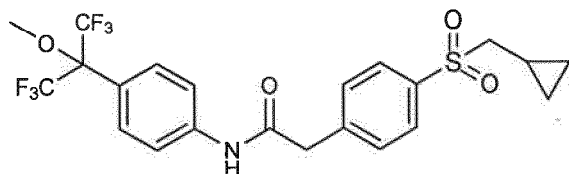
5 MS(ES⁺) *m/z* 552.2 [M+H]⁺.

53: 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(2-ethoxy-1,1,1,3,3,3-hexafluoropropan-2-yl)phenyl)acetamide.



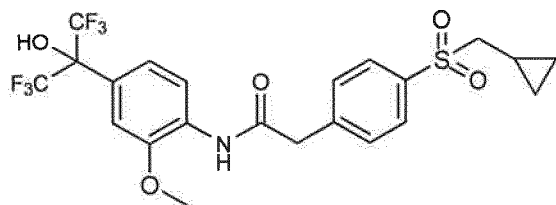
10 MS(ES⁺) *m/z* 524.2 [M+H]⁺.

54: 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-methoxypropan-2-yl)phenyl)acetamide.



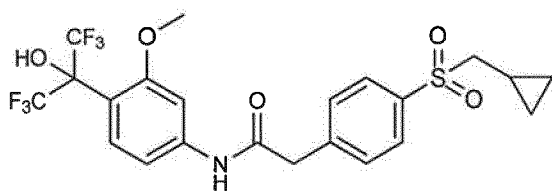
15 MS(ES⁺) *m/z* 510.2 [M+H]⁺.

55: 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-methoxyphenyl)acetamide.



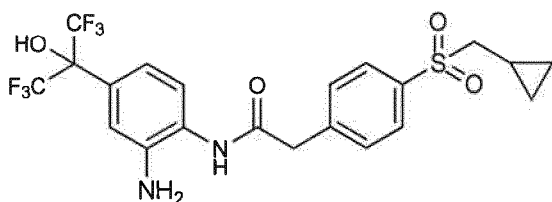
20 MS(ES⁺) *m/z* 526.2 [M+H]⁺.

56: 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-3-methoxyphenyl)acetamide.



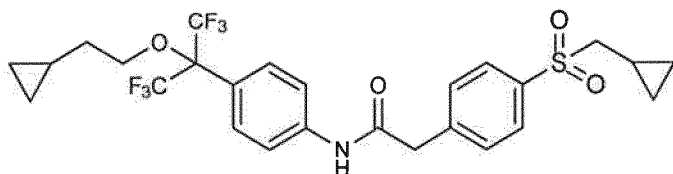
MS(ES⁺) m/z 526.2 [M+H]⁺.

- 5 **57:** *N*-(2-amino-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-2-(4-((cyclopropylmethyl)sulfonyl)phenyl)acetamide.



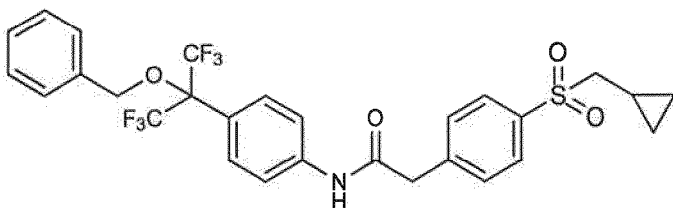
MS(ES⁺) m/z 511.2 [M+H]⁺.

- 10 **58:** *N*-(4-(2-(2-cyclopropylethoxy)-1,1,1,3,3,3-hexafluoropropan-2-yl)phenyl)-2-(4-((cyclopropylmethyl)sulfonyl)phenyl)acetamide.



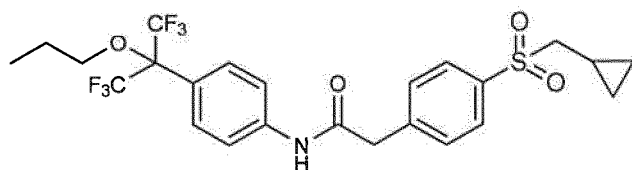
MS(ES⁺) m/z 564.2 [M+H]⁺.

- 15 **59:** *N*-(4-(2-(benzyloxy)-1,1,1,3,3,3-hexafluoropropan-2-yl)phenyl)-2-(4-((cyclopropylmethyl)sulfonyl)phenyl)acetamide.



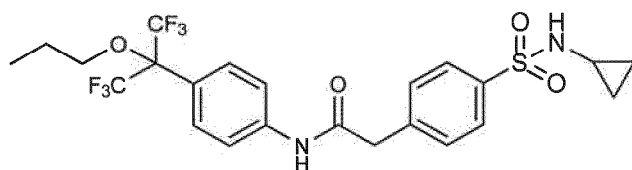
MS(ES⁺) m/z 586.2 [M+H]⁺.

- 20 **60:** 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-propoxypropan-2-yl)phenyl)acetamide.



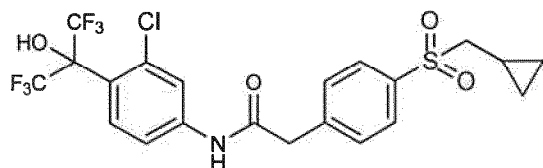
MS(ES⁺) m/z 538.2 [M+H]⁺.

- 5 **61:** 2-(4-(*N*-cyclopropylsulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-propoxypropan-2-yl)phenyl)acetamide.



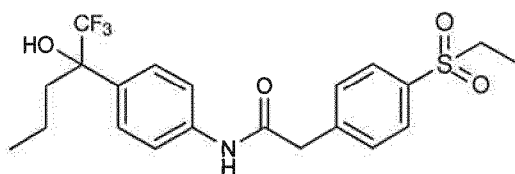
MS(ES⁺) m/z 539.2 [M+H]⁺.

- 10 **62:** *N*-(3-chloro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-2-(4-((cyclopropylmethyl)sulfonyl)phenyl)acetamide.



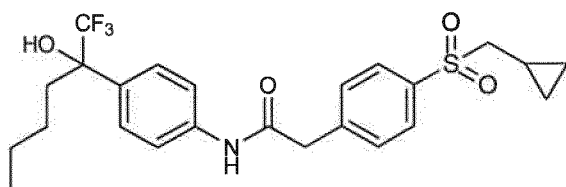
MS(ES⁺) m/z 530.2 [M+H]⁺.

- 15 **63:** 2-(4-(ethylsulfonyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxypentan-2-yl)phenyl)acetamide.



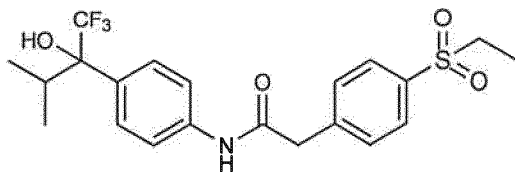
MS(ES⁺) m/z 444.2 [M+H]⁺.

- 20 **64:** 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxyhexan-2-yl)phenyl)acetamide.



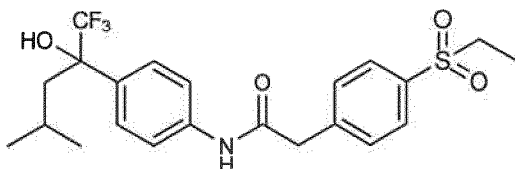
MS(ES⁺) m/z 484.2 [M+H]⁺.

65: 2-(4-(ethylsulfonyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxy-3-methylbutan-2-yl)phenyl)acetamide.



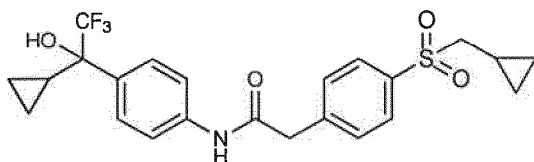
5 MS(ES⁺) *m/z* 444.2 [M+H]⁺.

66: 2-(4-(ethylsulfonyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxy-4-methylpentan-2-yl)phenyl)acetamide.



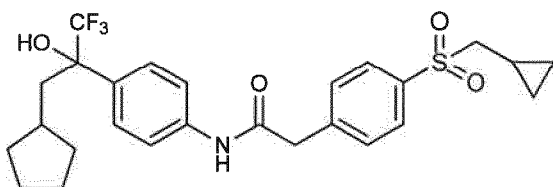
10 MS(ES⁺) *m/z* 458.2 [M+H]⁺.

67: *N*-(4-(1-cyclopropyl-2,2,2-trifluoro-1-hydroxyethyl)phenyl)-2-(4-((cyclopropylmethyl)sulfonyl)phenyl)acetamide.



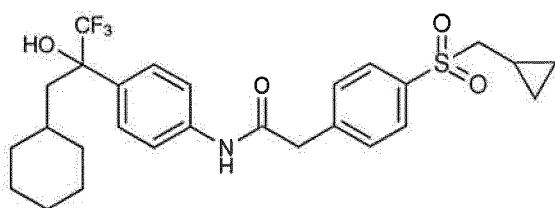
15 MS(ES⁺) *m/z* 468.2 [M+H]⁺.

68: *N*-(4-(3-cyclopentyl-1,1,1-trifluoro-2-hydroxypropan-2-yl)phenyl)-2-(4-((cyclopropylmethyl)sulfonyl)phenyl)acetamide.



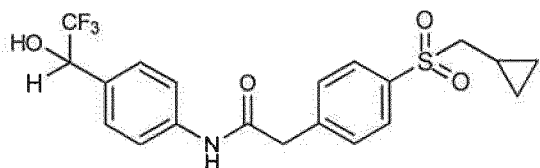
20 MS(ES⁺) *m/z* 510.2 [M+H]⁺.

69: *N*-(4-(3-cyclohexyl-1,1,1-trifluoro-2-hydroxypropan-2-yl)phenyl)-2-(4-((cyclopropylmethyl)sulfonyl)phenyl)acetamide.



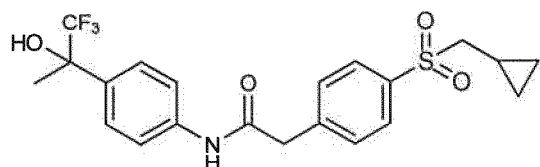
MS(ES⁺) m/z 524.2 [M+H]⁺.

- 5 **70:** 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(2,2,2-trifluoro-1-hydroxyethyl)phenyl)acetamide.



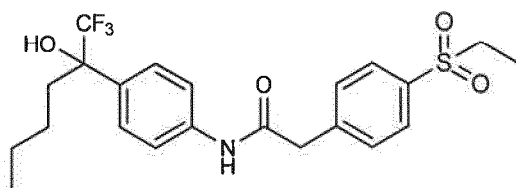
MS(ES⁺) m/z 428.2 [M+H]⁺.

- 10 **71:** 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)phenyl)acetamide.



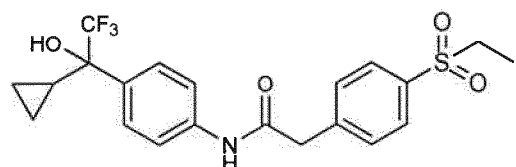
MS(ES⁺) m/z 473.2 [M+H]⁺.

- 15 **72:** 2-(4-(ethylsulfonyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxyhexan-2-yl)phenyl)acetamide.



MS(ES⁺) m/z 458.2 [M+H]⁺.

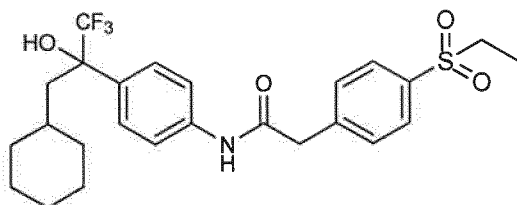
- 20 **73:** *N*-(4-(1-cyclopropyl-2,2,2-trifluoro-1-hydroxyethyl)phenyl)-2-(4-(ethylsulfonyl)phenyl)acetamide.



MS(ES⁺) m/z 442.2 [M+H]⁺.

74: *N*-(4-(3-cyclohexyl-1,1,1-trifluoro-2-hydroxypropan-2-yl)phenyl)-2-(4-(ethylsulfonyl)phenyl)acetamide.

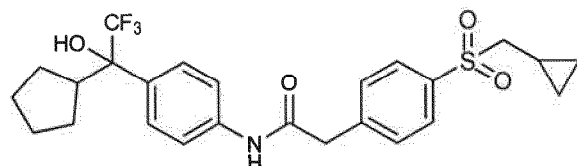
5



MS(ES⁺) m/z 498.2 [M+H]⁺.

75: *N*-(4-(1-cyclopentyl-2,2,2-trifluoro-1-hydroxyethyl)phenyl)-2-(4-((cyclopropylmethyl)sulfonyl)phenyl)acetamide.

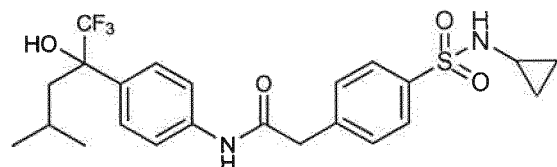
10



MS(ES⁺) m/z 496.2 [M+H]⁺.

76: 2-(4-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxy-4-methylpentan-2-yl)phenyl)acetamide.

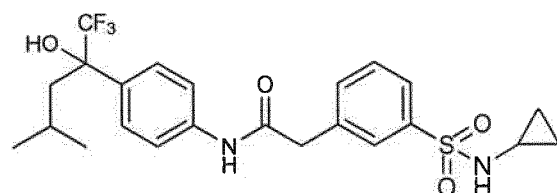
15



MS(ES⁺) m/z 485.2 [M+H]⁺.

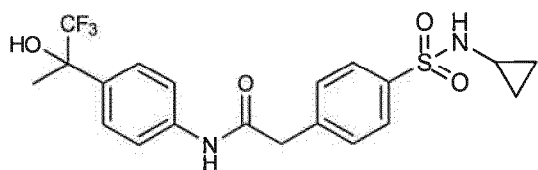
77: 2-(3-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxy-4-methylpentan-2-yl)phenyl)acetamide.

20



MS(ES⁺) m/z 485.2 [M+H]⁺.

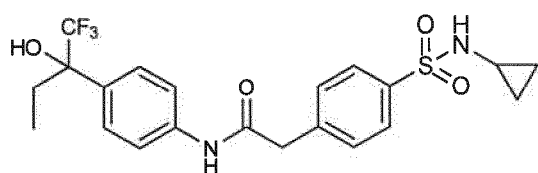
78: 2-(4-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)phenyl)acetamide.



MS(ES⁺) m/z 443.2 [M+H]⁺.

5

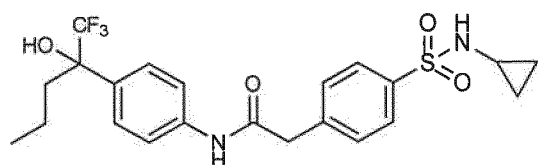
79: 2-(4-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxybutan-2-yl)phenyl)acetamide.



MS(ES⁺) m/z 457.2 [M+H]⁺.

10

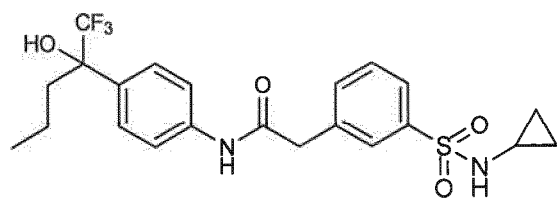
80: 2-(4-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxypentan-2-yl)phenyl)acetamide.



MS(ES⁺) m/z 471.2 [M+H]⁺.

15

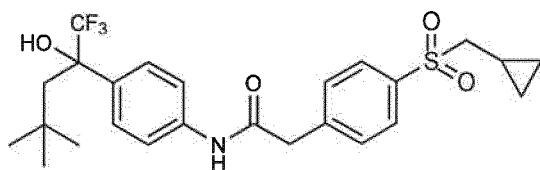
81: 2-(3-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxypentan-2-yl)phenyl)acetamide.



MS(ES⁺) m/z 471.2 [M+H]⁺.

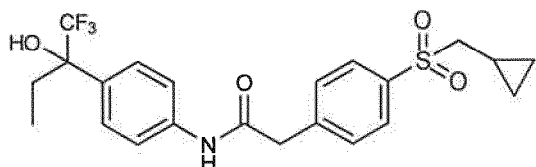
20

82: 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxy-4,4-dimethylpentan-2-yl)phenyl)acetamide.



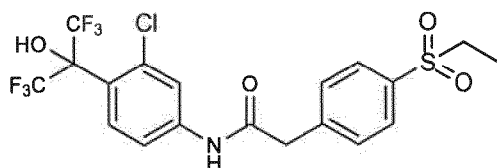
MS(ES⁺) m/z 498.2 [M+H]⁺.

83: 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxybutan-2-yl)phenyl)acetamide.



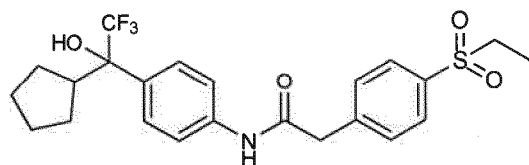
MS(ES⁺) m/z 456.2 [M+H]⁺.

84: *N*-(3-chloro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-2-(4-(ethylsulfonyl)phenyl)acetamide.



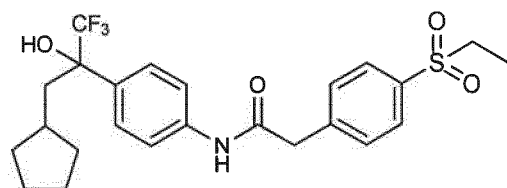
MS(ES⁺) m/z 504.2 [M+H]⁺.

85: *N*-(4-(1-cyclopentyl-2,2,2-trifluoro-1-hydroxyethyl)phenyl)-2-(4-(ethylsulfonyl)phenyl)acetamide.



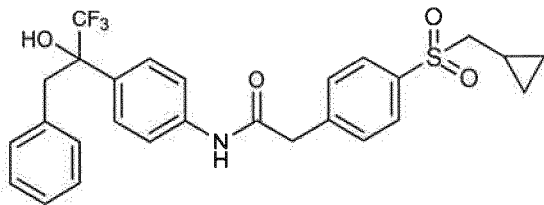
MS(ES⁺) m/z 470.2 [M+H]⁺.

86: *N*-(4-(3-cyclopentyl-1,1,1-trifluoro-2-hydroxypropan-2-yl)phenyl)-2-(4-(ethylsulfonyl)phenyl)acetamide.



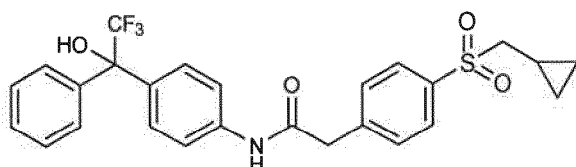
MS(ES⁺) m/z 484.2 [M+H]⁺.

87: 2-(4-cyclopropylmethanesulfonylphenyl)-*N*-[4-(1,1,1-trifluoro-2-hydroxy-3-phenylpropan-2-yl)phenyl]acetamide.



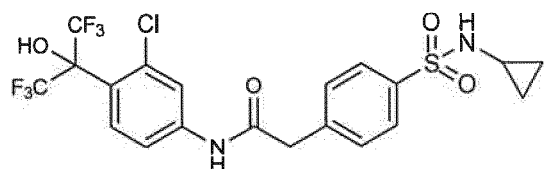
5 MS(ES⁺) *m/z* 518.2 [M+H]⁺.

88: 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(2,2,2-trifluoro-1-hydroxy-1-phenylethyl)phenyl)acetamide.



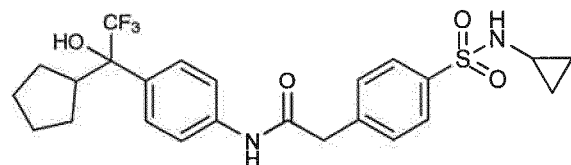
10 MS(ES⁺) *m/z* 504.2 [M+H]⁺.

89: *N*-(3-chloro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-2-(4-(*N*-cyclopropylsulfamoyl)phenyl)acetamide.



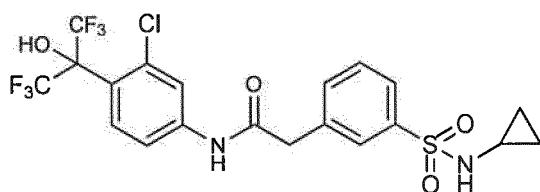
15 MS(ES⁺) *m/z* 531.2 [M+H]⁺.

90: *N*-(4-(1-cyclopentyl-2,2,2-trifluoro-1-hydroxyethyl)phenyl)-2-(4-(*N*-cyclopropylsulfamoyl)phenyl)acetamide.



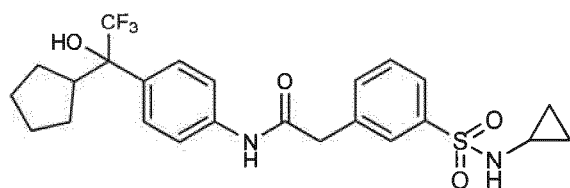
20 MS(ES⁺) *m/z* 597.2 [M+H]⁺.

91: *N*-(3-chloro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-2-(3-(*N*-cyclopropylsulfamoyl)phenyl)acetamide.



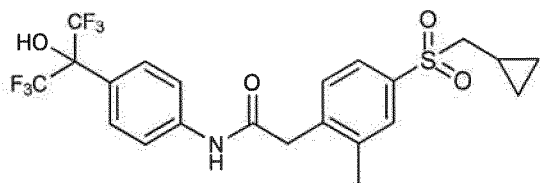
MS(ES⁺) m/z 531.2 [M+H]⁺.

- 5 **92:** *N*-(4-(1-cyclopentyl-2,2,2-trifluoro-1-hydroxyethyl)phenyl)-2-(3-(*N*-cyclopropylsulfamoyl)phenyl)acetamide.



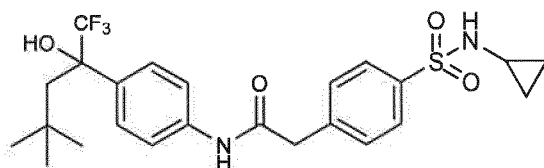
MS(ES⁺) m/z 497.2 [M+H]⁺.

- 10 **93:** 2-(4-((cyclopropylmethyl)sulfonyl)-2-methylphenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide.



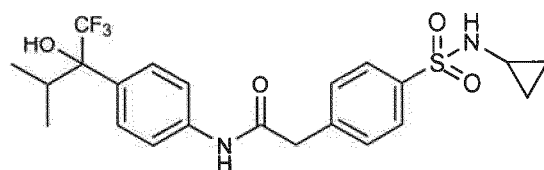
MS(ES⁺) m/z 510.2 [M+H]⁺.

- 15 **94:** 2-(4-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxy-4,4-dimethylpentan-2-yl)phenyl)acetamide.



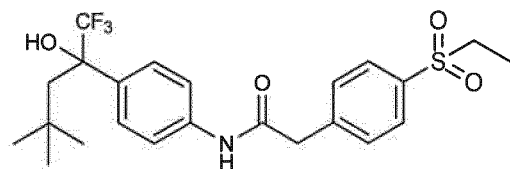
MS(ES⁺) m/z 499.2 [M+H]⁺.

- 20 **95:** 2-(4-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxy-3-methylbutan-2-yl)phenyl)acetamide.



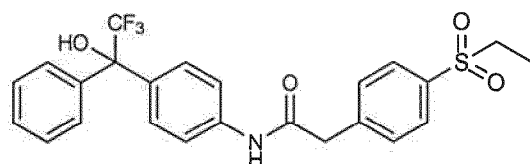
MS(ES⁺) m/z 471.2 [M+H]⁺.

96: 2-(4-(ethylsulfonyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxy-4,4-dimethylpentan-2-yl)phenyl)acetamide.



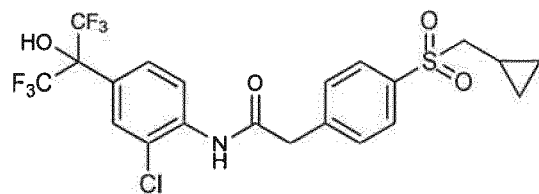
MS(ES⁺) m/z 472.2 [M+H]⁺.

97: 2-(4-(ethylsulfonyl)phenyl)-*N*-(4-(2,2,2-trifluoro-1-hydroxy-1-phenylethyl)phenyl)acetamide.



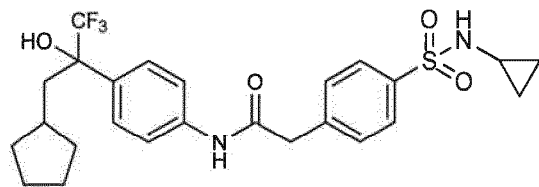
MS(ES⁺) m/z 478.2 [M+H]⁺.

98: *N*-(2-chloro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-2-(4-((cyclopropylmethyl)sulfonyl)phenyl)acetamide.



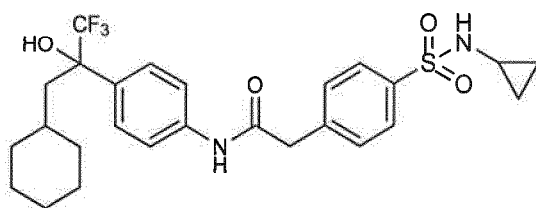
MS(ES⁺) m/z 530.2 [M+H]⁺.

99: *N*-(4-(3-cyclopentyl-1,1,1-trifluoro-2-hydroxypropan-2-yl)phenyl)-2-(4-(*N*-cyclopropylsulfonyl)phenyl)acetamide.



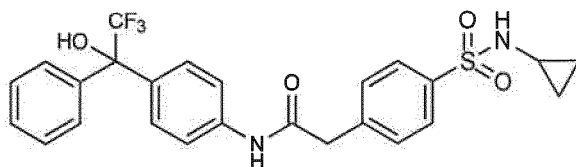
MS(ES⁺) m/z 511.2 [M+H]⁺.

100: *N*-(4-(3-cyclohexyl-1,1,1-trifluoro-2-hydroxypropan-2-yl)phenyl)-2-(4-(*N*-cyclopropylsulfonyl)phenyl)acetamide.



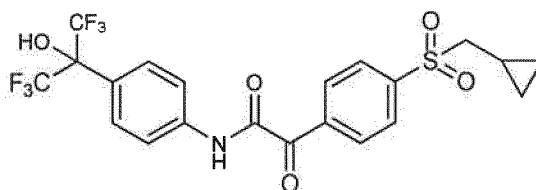
MS(ES⁺) m/z 525.3 [M+H]⁺.

101: 2-(4-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(4-(2,2,2-trifluoro-1-hydroxy-1-phenylethyl)phenyl)acetamide.



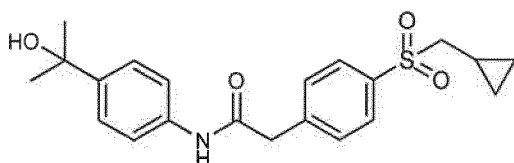
MS(ES⁺) m/z 505.2 [M+H]⁺.

102: 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-2-oxoacetamide.



MS(ES⁺) m/z 510.1 [M+H]⁺.

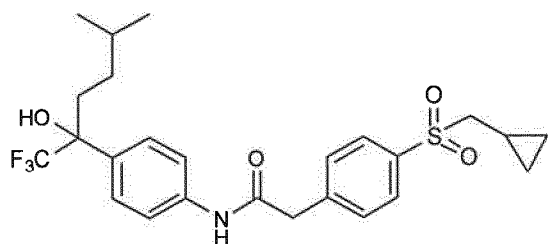
103: 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(2-hydroxypropan-2-yl)phenyl)acetamide.



MS(ES⁺) m/z 370.2 [(M-18)+H]⁺.

¹H NMR(500 MHz, DMSO-d₆) : δ 10.18 (s, 1H), 7.90-7.81 (m, 2H), 7.63-7.56 (m, 2H), 7.52-7.46 (m, 2H), 7.40-7.32 (m, 2H), 4.92 (s, 1H), 3.78 (s, 2H), 3.24 (d, 2H), 1.39 (s, 6H), 0.86-0.78 (m, 1H), 0.48-0.40 (m, 2H), 0.14-0.08 (m, 2H).

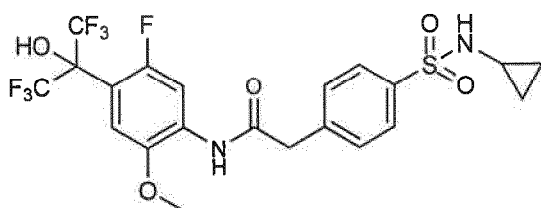
104: 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxy-5-methylhexan-2-yl)phenyl)acetamide.



MS(ES⁺) m/z 498.3 [M+H]⁺.

5

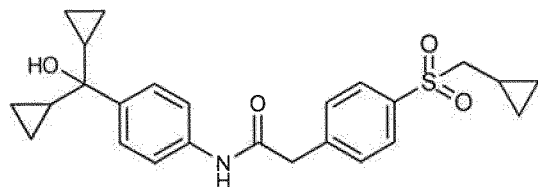
105: 2-(4-(*N*-cyclopropylsulfonyl)phenyl)-*N*-(5-fluoro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-methoxyphenyl)acetamide.



MS(ES⁺) m/z 545.1 [M+H]⁺.

10

106: 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(dicyclopropyl(hydroxy)methyl)phenyl)acetamide.



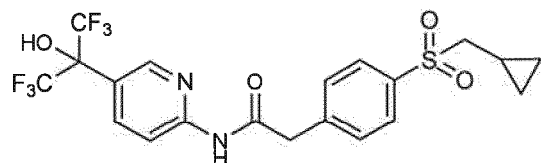
MS(ES⁺) m/z 422.2 [(M-18)+H]⁺.

15

¹H NMR(500 MHz, DMSO-d₆) : δ 10.18 (s, 1H), 7.90-7.80 (m, 2H), 7.65-7.55 (m, 2H), 7.50-7.40 (m, 4H), 4.32 (s, 1H), 3.78 (s, 2H), 3.24 (d, 2H), 1.20-1.09 (m, 2H), 0.86-0.78 (m, 1H), 0.55-0.47 (m, 2H), 0.46-0.41 (m, 2H), 0.38-0.30 (m, 2H), 0.29-0.21 (m, 2H), 0.20-0.14 (m, 2H), 0.13-0.09 (m, 2H).

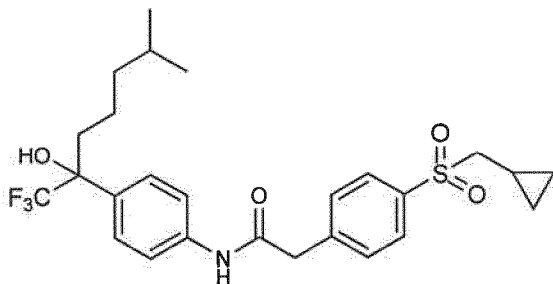
20

107: 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(5-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)pyridin-2-yl)acetamide.



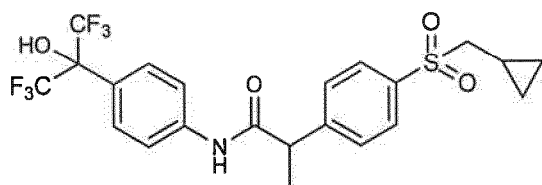
MS(ES⁺) m/z 497.2 [M+H]⁺.

108: 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxy-6-methylheptan-2-yl)phenyl)acetamide.



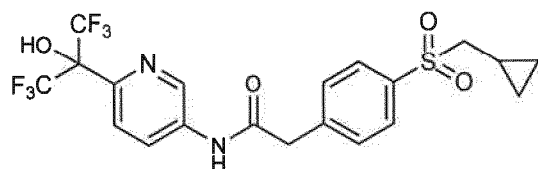
5 MS(ES⁺) *m/z* 512.3 [M+H]⁺.

109: 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)propanamide.



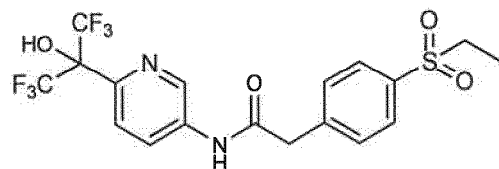
10 MS(ES⁺) *m/z* 510.2 [M+H]⁺.

110: 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(6-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)pyridin-3-yl)acetamide.



15 MS(ES⁺) *m/z* 497.2 [M+H]⁺.

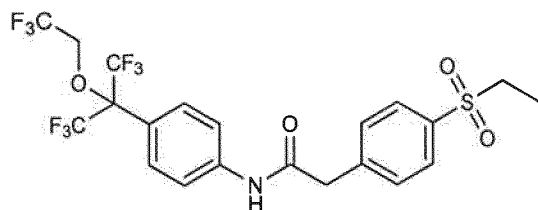
111: 2-(4-(ethylsulfonyl)phenyl)-*N*-(6-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)pyridin-3-yl)acetamide.



20 MS(ES⁺) *m/z* 471.2 [M+H]⁺.

Examples **112** and **113**:

112: 2-(4-(ethylsulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-(2,2,2-trifluoroethoxy)propan-2-yl)phenyl)acetamide.

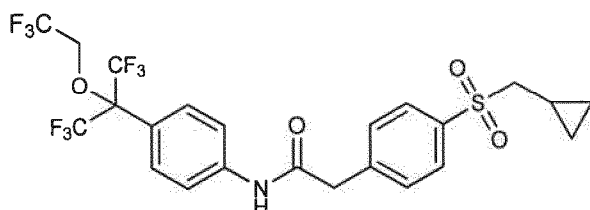


- 5 To a suspension of 2-(4-(ethylsulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide, (example 2) (20 mg) and K₂CO₃ (9 mg) in CH₃CN (1 ml) was added at room temperature 2,2,2-trifluoroethyltrifluoro methanesulfonate (10 mg). After stirring for 17 hours at 80 °C, the reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure.
- 10 The residue was purified on SiO₂, using 20% ethyl acetate in heptane as the eluent, to give the title compound 2-(4-(ethylsulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexa fluoro-2-(2,2,2-trifluoro ethoxy) propan-2-yl)phenyl)acetamide (11 mg) as a white solid. MS(ES⁺) *m/z* 552.2 [M+H]⁺.
- ¹H NMR(500 MHz, DMSO-*d*₆) : δ 10.62 (s, 1H), 7.88-7.86 (m, 2H), 7.84-7.82 (m, 2H), 7.63-7.61 (m, 2H), 7.55-7.53 (m, 2H), 4.27 (q, 2H), 3.85 (s, 2H), 3.28 (q, 2H), 1.10 (t, 3H).
- 15

Following a procedure analogous to that described for example 111, the following compound was prepared.

20

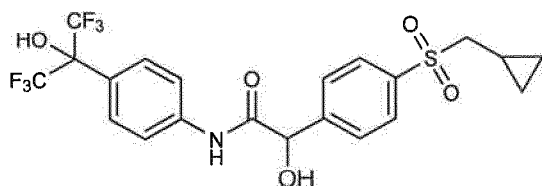
113: 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-(2,2,2-trifluoroethoxy)propan-2-yl)phenyl)acetamide.



MS(ES⁺) *m/z* 578.2 [M+H]⁺.

25

114: 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-2-hydroxyacetamide.



To a solution of 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-2-oxoacetamide, (example **101**) (25 mg) in methanol (2 mL) was added NaBH₄ (4 mg). After stirring for 1 hour at room temperature, the
 5 reaction mixture was concentrated under reduced pressure. To the residue was added an aqueous 1N HCl solution and the product was extracted into ethyl acetate. The combined organic layers were washed with water, brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified on reversed phase semi-prep. HPLC, using 20% to 80% CH₃CN in water, as the eluent, to give the title
 10 compound 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-2-hydroxyacetamide (6 mg) as a white solid. MS(ES⁺) *m/z* 512.1 [M+H]⁺.

Example 115

15 RORy GAL4 reporter gene assay

Example inhibitors 1-114 were tested for their ability to inhibit RORy activity in a RORy GAL4 reporter gene assay. The assay procedure and results are described below.

RORy GAL4 reporter gene assay description

A GAL4 one-hybrid reporter system employing luciferase readout was established to
 20 determine inhibition of RORy in 293FT cells. The RORy ligand-binding domain (LBD) was fused to the yeast GAL4 DNA binding domain (DBD) and placed under the control of the human cytomegalovirus (CMV) immediate early promoter, using expression vector pFN26A (Promega) and standard recombinant DNA cloning methods. To serve as a control in the assay, a similar vector was generated in which the GAL4-DBD was
 25 fused to Herpes simplex virus protein 16 (VP16), a constitutive transcriptional activator.

To monitor the inhibitory effect of compounds on RORy, a transcriptional reporter construct was used. The pGL4.35 vector (Promega) contains nine copies of the GAL4 Upstream Activator Sequence (UAS). This sequence drives the transcription of the luciferase reporter gene *luc2P* in response to binding of a fusion protein containing the
 30 GAL4 DNA binding domain, as for example expressed by the GAL4-RORy-LBD and GAL4-VP16 expression vectors described above. To allow a GAL4 fusion protein to

drive the expression of the luciferase reporter, the pGL4.35 expression vector and the appropriate GAL4 fusion protein expression vector were bulk transfected in the 293FT cells using standard transfection techniques.

5 The day after transfection, cells were plated into 96 well plates, test compound was added and the plates were incubated overnight. Subsequently, the firefly luciferase activity was quantified using luciferase detection reagent and luminescence readout.

Detailed assay description

293FT cells (Invitrogen) were transfected with a GAL4 fusion protein expression vector (as described above) and the transcriptional reporter construct (pGL4.35, Promega). 60
10 μ L of *TransIT*-293 transfection reagent (Mirus Bio) was added drop wise to 1500 μ L Opti-MEM I Reduced Serum Medium (Invitrogen) and incubated at room temperature (RT) for 5 to 20 minutes. 1500 μ L of this reagent mixture was added to 5 μ g of GAL4 fusion protein expression vector and 5 μ g of the transcriptional reporter construct, and incubated at RT for 20 minutes.

15 To harvest 293FT cells from a T75 flask, first the culture medium was taken off the cells. Subsequently, the cells were washed with Phosphate Buffered Saline (PBS) (Lonza), after which the PBS was removed. To dissociate the cells, 1 ml of TrypLE Express (Invitrogen) was added to the flask, followed by incubation at RT until the cells visually started to detach. Cells were collected in 5 mL of assay medium (DMEM
20 culture medium (Lonza), 10% dialyzed FBS (Invitrogen) and Pen/Strep (Lonza)) to achieve a single cell suspension. 10×10^6 cells were spun down and re-suspended in 10 mL of assay medium. Subsequently, the cell suspension was added to the transfection mix tube, and then transferred as a whole to a T75 flask (Greiner), followed by overnight (16-24 hours) incubation at 37°C and 5% CO₂.

25 For compound screening, the cells were harvested (as described above) and counted. 13×10^6 cells were spun down, the supernatant was aspirated and the cells were re-suspended in 17.3 mL of assay medium to obtain a cell suspension of 0.75×10^6 cells/mL. 80 μ L of cell suspension (60,000 cells) was plated per well into a white, flat bottom, tissue culture treated, 96 well screening plates (Greiner).

30 Test compounds were diluted, starting from a 10 mM dimethylsulfoxide (DMSO) stock solution, to serial dilutions in DMSO at 500x the final test concentration. Subsequently, these solutions were diluted to 5x the final test concentration in two 10-fold-dilution steps in assay medium. The final DMSO concentration of the 5x test compound

solution was 1%. 20 μ L of the 5x test compound solution was added to each test well of the 96 well plate previously plated with 80 μ L cell suspension, resulting in the final test concentration with 0.2% DMSO.

The plates were incubated overnight (16-24 hours) at 37°C and 5% CO₂.

- 5 For the luciferase readout, the luciferase reagent (Britelite Plus, Perkin Elmer) was brought to RT. To each test well of the screening plates, 100 μ L of 2.5-fold diluted Britelite Plus reagent was added, followed by incubation at RT for 10 minutes. The luciferase luminescence signal was measured using a Wallac Victor Microplate Reader (Perkin Elmer).
- 10 The half maximum inhibitory concentration (IC₅₀) values for the test compounds were calculated from the luciferase signal using GraphPad Prism software (GraphPad Software).

All exemplified compounds of Formula I (Examples 1 - 114) were found to have mean pIC₅₀ values above 5.

- 15 Examples 2, 4, 5, 6, 9, 10, 12, 15, 19, 21, 22, 23, 26, 28, 29, 31 - 38, 40, 42 - 76, 78 - 80, 82 - 90, 93 - 99, 102, 104, 106 - 110, and 112 - 114 were found to have mean pIC₅₀ values above or equal to 6.

- Examples 2, 9, 29, 32, 33, 35, 37, 43, 44, 45, 46, 49, 51, 52, 53, 54, 55, 59, 60, 61, 62, 64, 66, 67, 68, 69, 71, 75, 76, 82, 83, 87, 88, 93, 94, 96, 98, 104, 106, 107, 108, 109, 113, 114 were found to have mean pIC₅₀ values above or equal to 7.
- 20

Examples 37, 44, 45, 46, 60, 64, 75, 82, 83 were found to have mean pIC₅₀ values above or equal to 8.

Example 116**Peripheral blood mononuclear cell (PBMC) IL-17 assay**

Example inhibitors 2, 9, 32, 33, 35, 37, 43, 44, 45, 46, 51, 53, 54, 59, 60, 67, 71, 83, 107, 113, 114 were tested for their ability to inhibit the IL-17A production in anti-CD3/anti-CD28 stimulated peripheral blood mononuclear cells (PBMCs) isolated from human blood. The assay procedure and results are described below.

PBMC IL-17 assay description

This assay is designed to measure the levels of IL-17A secreted from anti-CD3/anti-CD28 stimulated PBMCs with the aim of measuring ROR γ mediated inhibition of IL-17A production.

The assay medium consists of 90% RPMI 1640 (Lonza), 10% heat inactivated fetal bovin serum (FBS, Lonza) and 100 U/mL penicillin/streptomycin solution.

Assay description

Anti-CD3 antibody (BD Pharmingen) was diluted to 10 μ g/ml in PBS (Lonza). 30 μ L of 10 μ g/ml anti-CD3 solution was added to the inner 60 wells, excluding any negative control wells, of a 96-well cell culture treated U-bottom plate (Greiner). Plates were incubated overnight (16-24 hours) at 37°C and 5% CO₂.

Peripheral blood mononuclear cells were separated from buffy coats (Sanquin) using Ficoll-Paque PREMIUM separation medium (GE Healthcare Life Sciences) according to manufacturer's protocol and re-suspended in assay medium at 37°C.

Test compounds were diluted, starting from a 10 mM dimethylsulfoxide (DMSO) stock solution, to serial dilutions in DMSO at 200x the final test concentration. Subsequently, these solutions were diluted in two dilution steps in assay medium to 10x the final test concentration. The DMSO concentration of the 10x test compound solution was 5%.

Anti-CD28 antibody (BD Pharmingen) was diluted to 20 μ g/mL in PBS. The PBMCs were diluted to a concentration of 2.5×10^6 cells/mL in assay medium at 37°C.

For compound screening, the anti-CD3 coated plates were washed three times with PBS, the wells were subsequently aspirated using vacuum. To each screening well 80 μ L of the PBMC suspension, 10 μ L of the anti-CD28 solution and 10 μ L of the 10x test compound solution was added, resulting in the final test concentration with 0.5%

DMSO. All outer wells were filled with assay medium to prevent evaporation. Plates were incubated for 5 days at 37°C and 5% CO₂.

After incubation the plates were spun down at 1500 rpm for 4 minutes and the supernatant was collected. Subsequently, the IL-17A levels in the supernatants was
5 determined using an IL-17 ELISA kit (human IL-17 DuoSet, R&D systems) according to manufacturer's protocol.

The half maximum inhibitory concentration (IC₅₀) values for the test compounds were calculated from the IL-17A signal using GraphPad Prism software (GraphPad Software).

10

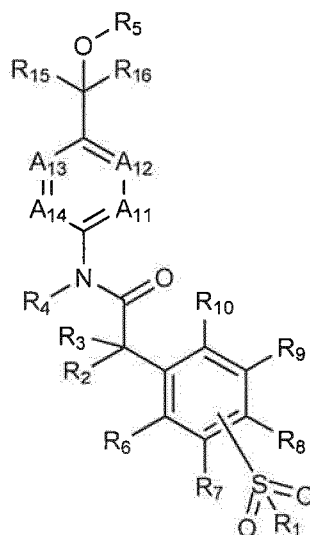
The tested examples 2, 9, 32, 33, 35, 37, 43, 44, 45, 46, 51, 53, 54, 59, 60, 67, 71, 83, 107, 113, 114 were all found to have mean pIC₅₀ values above or equal to 6.

Examples 9, 32, 37, 43, 44, 45, 46, 51, 53, 54, 59, 60, 67, 71, 83, 113, 114 were found to have mean pIC₅₀ values above or equal to 7.

15

Claims

1. A compound according to Formula I



Meta or para

(Formula I)

or a pharmaceutically acceptable salt thereof wherein

A₁₁ – A₁₄ are N or CR₁₁, CR₁₂, CR₁₃, CR₁₄, respectively, with the proviso that no more than two of the four positions A can be simultaneously N;

R₁ is C(1-6)alkyl, C(3-6)cycloalkyl, C(3-6)cycloalkylC(1-3)alkyl, (di)C(1-6)alkylamino, (di)C(3-6)cycloalkylamino or

(di)(C(3-6)cycloalkylC(1-3)alkyl)amino, with all carbon atoms of alkyl groups optionally substituted with one or more F and all carbon atoms of cycloalkyl groups optionally substituted with one or more F or methyl;

R₂ and R₃ are independently H, F, methyl, ethyl, hydroxy, methoxy or R₂ and R₃ together is carbonyl, all alkyl groups, if present, optionally being substituted with one or more F;

R₄ is H or C(1-6)alkyl;

R₅ is H, hydroxyethyl, methoxyethyl, C(1-6)alkyl, C(6-10)aryl, C(6-10)arylC(1-3)alkyl, C(1-9)heteroaryl, C(1-9)heteroarylC(1-3)alkyl, C(3-6)cycloalkyl, C(3-6)cycloalkylC(1-3)alkyl, C(2-5)heterocycloalkyl or C(2-5)heterocycloalkylC(1-3)alkyl, all groups optionally substituted with one or

more F, Cl, C(1-2)alkyl, C(1-2)alkoxy or cyano ;

the sulfonyl group with R₁ is represented by one of R₇, R₈ or R₉;

the remaining R₆-R₁₄ are independently H, halogen, C(1-3)alkoxy, (di)C(1-3)alkylamino or C(1-6)alkyl, all of the alkyl groups optionally being substituted with one or more F; and

R₁₅ and R₁₆ are independently H, C(1-6)alkyl, C(3-6)cycloalkyl,

C(3-6)cycloalkylC(1-3)alkyl, C(6-10)aryl, C(6-10)arylC(1-3)alkyl,

C(1-9)heteroaryl, C(1-9)heteroarylC(1-3)alkyl, C(2-5)heterocycloalkyl or

C(2-5)heterocycloalkylC(1-3)alkyl, all groups optionally substituted with one or more F, Cl, C(1-2)alkyl, C(1-2)alkoxy or cyano.

2. The compound according to claim 1 wherein R₁ is C(1-2)alkyl, cyclopropyl, C(3-4)cycloalkylC(1-3)alkyl, methylamino or C(3-4)cycloalkylamino.

3. The compound according to claim 2 wherein R₁ is ethyl, cyclopropylamino or cyclopropylmethyl.

4. The compound according to claim 3 wherein R₁ is cyclopropylamino or cyclopropylmethyl.

5. The compound according to claim 4 wherein R₁ is cyclopropylmethyl.

6. The compound according to claims 1-5 wherein R₂ and R₃ are independently H, methyl or hydroxy.

7. The compound according to claim 6 wherein R₂ and R₃ are independently H or methyl.

8. The compound according to claims 1-7 wherein R₄ is H or C(1-2)alkyl.

9. The compound according to claims 1-8 where R₅ is H, hydroxyethyl, methoxyethyl or C(1-6)alkyl, all alkyl groups optionally being substituted with one or more F.

10. The compound according to claim 9 wherein R₅ is H or C(1-3)alkyl.

11. The compound according to claims 1-8 wherein R_5 is C(6)arylC(1-3)alkyl or C(3-6)cycloalkylC(1-3)alkyl.
12. The compound according to claim 11 wherein R_5 is benzyl.
13. The compound according to claims 1-12 wherein R_6 - R_{10} are H with the proviso that one of the groups R_7 , R_8 or R_9 is the sulfonyl group with R_1 .
14. The compound according to claim 13 wherein R_8 is the sulfonyl group with R_1 .
15. The compound according to claims 1-12 wherein R_8 is the sulfonyl group with R_1 , and wherein R_{10} is methyl, and the remaining R_6 , R_7 and R_9 are H.
16. The compound according to claims 1-15 wherein A_{11} - A_{14} are CR_{11} , CR_{12} , CR_{13} and CR_{14} , respectively.
17. The compound according to claims 1-15 wherein either:
 A_{11} is nitrogen and A_{12} - A_{14} are CR_{12} , CR_{13} and CR_{14} , respectively; or,
 A_{12} is nitrogen and A_{11} , A_{13} and A_{14} are CR_{11} , CR_{13} and CR_{14} , respectively.
18. The compound according to claims 1-17 wherein R_{11} - R_{14} are independently H, halogen, methyl or methoxy.
19. The compound according to claim 18 wherein R_{11} - R_{14} is H.
20. The compound according to claims 1-19 wherein R_{15} is CF_3 and R_{16} is H, C(1-6)alkyl, C(3-6)cycloalkyl or C(3-6)cycloalkylC(1-3)alkyl.
21. The compound according to claims 1-19 wherein R_{15} is CF_3 and R_{16} is CF_3 , propyl, isopropyl, 2-methylpropyl, 2,2-dimethylpropyl, cyclopropyl, cyclopentyl or cyclohexylmethyl.
22. The compound according to claim 21 wherein both R_{15} and R_{16} are CF_3 .
23. The compound selected from claim 1 which is selected from the group of:

- N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-2-(4-(methylsulfonyl)phenyl)acetamide;
- 2-(4-(ethylsulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide;
- 5 *N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-2-(4-(isopropylsulfonyl)phenyl)acetamide;
- N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-2-(4-(propylsulfonyl)phenyl)acetamide;
- 2-(4-(ethylsulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)propanamide;
- 10 *N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-2-(4-(*N*-methylsulfamoyl)phenyl)acetamide;
- N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-2-(4-(*N*-isopropylsulfamoyl)phenyl)acetamide;
- 15 2-(4-(*N*-(cyclopropylmethyl)sulfamoyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide;
- 2-(4-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide;
- 2-(4-(*N*-ethylsulfamoyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide;
- 20 2-(4-(*N,N*-dimethylsulfamoyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide;
- 2-(3-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide;
- 25 2-(3-(*N*-ethylsulfamoyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide;
- 2-(3-(*N,N*-dimethylsulfamoyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide;
- 30 2-(4-(ethylsulfonyl)phenyl)-*N*-(3-fluoro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-methylphenyl)acetamide;
- 2-(4-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-*N*-methylacetamide;
- 2-(4-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-ethyl-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide;

2-(3-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-*N*-methylacetamide;
N-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-2-(3-(*N*-methylsulfamoyl)phenyl)acetamide;
5 2-(4-(ethylsulfonyl)phenyl)-*N*-(5-fluoro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-methoxyphenyl)acetamide;
2-(4-(ethylsulfonyl)phenyl)-*N*-(5-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)pyridin-2-yl)acetamide;
N-(5-chloro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-methoxyphenyl)-
10 2-(4-(ethylsulfonyl)phenyl)acetamide;
2-(4-(ethylsulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2,6-dimethylphenyl)acetamide;
2-(3-(*N*-cyclobutylsulfamoyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide;
15 2-(4-(*N*-cyclobutylsulfamoyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide;
2-(4-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(3-fluoro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-methylphenyl)acetamide;
N-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-2-(4-(
20 (isobutylsulfonyl)phenyl)acetamide;
2-(4-(ethylsulfonyl)phenyl)-*N*-(2-fluoro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide;
2-(4-(ethylsulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-3-methylphenyl)acetamide;
25 2-(4-(ethylsulfonyl)phenyl)-*N*-(3-fluoro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide;
2-(4-(ethylsulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-methylphenyl)acetamide;
2-(4-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-3-methylphenyl)acetamide;
30 2-(4-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(3-fluoro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide;
2-(4-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-methylphenyl)acetamide;

- 2-(4-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(2-fluoro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide;
- 2-(3-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-3-methylphenyl)acetamide;
- 5 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide;
- 2-(3-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(3-fluoro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide;
- 10 2-(3-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-methylphenyl)acetamide;
- 2-(3-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(2-fluoro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide;
- 2-(3-(*N*-(cyclopropylmethyl)sulfamoyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide;
- 15 2-(4-(ethylsulfonyl)-3-fluorophenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide;
- 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-methylphenyl)acetamide;
- 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-3-methylphenyl)acetamide;
- 20 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(3-fluoro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide;
- 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(2-fluoro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide;
- 25 2-(4-(ethylsulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-methoxypropan-2-yl)phenyl)acetamide;
- N*-(4-(2-ethoxy-1,1,1,3,3,3-hexafluoropropan-2-yl)phenyl)-2-(4-(ethylsulfonyl)phenyl)acetamide;
- 2-(4-(ethylsulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-propoxypropan-2-yl)phenyl)acetamide;
- 30 *N*-(4-(2-(benzyloxy)-1,1,1,3,3,3-hexafluoropropan-2-yl)phenyl)-2-(4-(ethylsulfonyl)phenyl)acetamide;
- 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-isopropoxypropan-2-yl)phenyl)acetamide;

- N*-(4-(2-butoxy-1,1,1,3,3,3-hexafluoropropan-2-yl)phenyl)-2-(4-((cyclopropylmethyl)sulfonyl)phenyl)acetamide;
- 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(2-ethoxy-1,1,1,3,3,3-hexafluoropropan-2-yl)phenyl)acetamide;
- 5 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-methoxypropan-2-yl)phenyl)acetamide;
- 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-methoxyphenyl)acetamide;
- 10 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-3-methoxyphenyl)acetamide;
- N*-(4-(2-(2-cyclopropylethoxy)-1,1,1,3,3,3-hexafluoropropan-2-yl)phenyl)-2-(4-((cyclopropylmethyl)sulfonyl)phenyl)acetamide;
- N*-(4-(2-(benzyloxy)-1,1,1,3,3,3-hexafluoropropan-2-yl)phenyl)-2-(4-((cyclopropylmethyl)sulfonyl)phenyl)acetamide;
- 15 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-propoxypropan-2-yl)phenyl)acetamide;
- 2-(4-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-propoxypropan-2-yl)phenyl)acetamide;
- N*-(3-chloro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-2-(4-((cyclopropylmethyl)sulfonyl)phenyl)acetamide;
- 20 2-(4-(ethylsulfonyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxypentan-2-yl)phenyl)acetamide;
- 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxyhexan-2-yl)phenyl)acetamide;
- 25 2-(4-(ethylsulfonyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxy-3-methylbutan-2-yl)phenyl)acetamide;
- 2-(4-(ethylsulfonyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxy-4-methylpentan-2-yl)phenyl)acetamide;
- 30 *N*-(4-(1-cyclopropyl-2,2,2-trifluoro-1-hydroxyethyl)phenyl)-2-(4-((cyclopropylmethyl)sulfonyl)phenyl)acetamide;
- N*-(4-(3-cyclopentyl-1,1,1-trifluoro-2-hydroxypropan-2-yl)phenyl)-2-(4-((cyclopropylmethyl)sulfonyl)phenyl)acetamide;

- N*-(4-(3-cyclohexyl-1,1,1-trifluoro-2-hydroxypropan-2-yl)phenyl)-2-(4-((cyclopropylmethyl)sulfonyl)phenyl)acetamide;
 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(2,2,2-trifluoro-1-hydroxyethyl)phenyl)acetamide;
- 5 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)phenyl)acetamide;
 2-(4-(ethylsulfonyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxyhexan-2-yl)phenyl)acetamide;
- 10 *N*-(4-(1-cyclopropyl-2,2,2-trifluoro-1-hydroxyethyl)phenyl)-2-(4-(ethylsulfonyl)phenyl)acetamide;
N-(4-(3-cyclohexyl-1,1,1-trifluoro-2-hydroxypropan-2-yl)phenyl)-2-(4-(ethylsulfonyl)phenyl)acetamide;
- 15 *N*-(4-(1-cyclopentyl-2,2,2-trifluoro-1-hydroxyethyl)phenyl)-2-(4-((cyclopropylmethyl)sulfonyl)phenyl)acetamide;
 2-(4-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxy-4-methylpentan-2-yl)phenyl)acetamide;
- 20 2-(3-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxy-4-methylpentan-2-yl)phenyl)acetamide;
 2-(4-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)phenyl)acetamide;
- 25 2-(4-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxybutan-2-yl)phenyl)acetamide;
 2-(4-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxypentan-2-yl)phenyl)acetamide;
- 30 2-(3-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxypentan-2-yl)phenyl)acetamide;
 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxy-4,4-dimethylpentan-2-yl)phenyl)acetamide;
- 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxybutan-2-yl)phenyl)acetamide;
- N*-(3-chloro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-2-(4-(ethylsulfonyl)phenyl)acetamide;
- N*-(4-(1-cyclopentyl-2,2,2-trifluoro-1-hydroxyethyl)phenyl)-2-(4-(ethylsulfonyl)phenyl)acetamide;

- N*-(4-(3-cyclopentyl-1,1,1-trifluoro-2-hydroxypropan-2-yl)phenyl)-2-(4-(ethylsulfonyl)phenyl)acetamide;
- 2-(4-cyclopropylmethanesulfonylphenyl)-*N*-[4-(1,1,1-trifluoro-2-hydroxy-3-phenylpropan-2-yl)phenyl]acetamide;
- 5 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(2,2,2-trifluoro-1-hydroxy-1-phenylethyl)phenyl)acetamide;
- N*-(3-chloro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-2-(4-(*N*-cyclopropylsulfamoyl)phenyl)acetamide;
- N*-(4-(1-cyclopentyl-2,2,2-trifluoro-1-hydroxyethyl)phenyl)-2-(4-(*N*-cyclopropylsulfamoyl)phenyl)acetamide;
- 10 *N*-(3-chloro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-2-(3-(*N*-cyclopropylsulfamoyl)phenyl)acetamide;
- N*-(4-(1-cyclopentyl-2,2,2-trifluoro-1-hydroxyethyl)phenyl)-2-(3-(*N*-cyclopropylsulfamoyl)phenyl)acetamide;
- 15 2-(4-((cyclopropylmethyl)sulfonyl)-2-methylphenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide;
- 2-(4-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxy-4,4-dimethylpentan-2-yl)phenyl)acetamide;
- 2-(4-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxy-3-methylbutan-2-yl)phenyl)acetamide;
- 20 2-(4-(ethylsulfonyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxy-4,4-dimethylpentan-2-yl)phenyl)acetamide;
- 2-(4-(ethylsulfonyl)phenyl)-*N*-(4-(2,2,2-trifluoro-1-hydroxy-1-phenylethyl)phenyl)acetamide;
- 25 *N*-(2-chloro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-2-(4-((cyclopropylmethyl)sulfonyl)phenyl)acetamide;
- N*-(4-(3-cyclopentyl-1,1,1-trifluoro-2-hydroxypropan-2-yl)phenyl)-2-(4-(*N*-cyclopropylsulfamoyl)phenyl)acetamide;
- N*-(4-(3-cyclohexyl-1,1,1-trifluoro-2-hydroxypropan-2-yl)phenyl)-2-(4-(*N*-cyclopropylsulfamoyl)phenyl)acetamide;
- 30 2-(4-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(4-(2,2,2-trifluoro-1-hydroxy-1-phenylethyl)phenyl)acetamide;
- 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-2-oxoacetamide;

2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(2-hydroxypropan-2-yl)phenyl)acetamide;

2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxy-5-methylhexan-2-yl)phenyl)acetamide;

5 2-(4-(*N*-cyclopropylsulfamoyl)phenyl)-*N*-(5-fluoro-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-2-methoxyphenyl)acetamide;

2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(dicyclopropyl(hydroxy)methyl)phenyl)acetamide;

10 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(5-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)pyridin-2-yl)acetamide;

2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1-trifluoro-2-hydroxy-6-methylheptan-2-yl)phenyl)acetamide;

2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)propanamide;

15 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(6-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)pyridin-3-yl)acetamide;

2-(4-(ethylsulfonyl)phenyl)-*N*-(6-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)pyridin-3-yl)acetamide;

20 2-(4-(ethylsulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-(2,2,2-trifluoroethoxy)propan-2-yl)phenyl)acetamide;

2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-(2,2,2-trifluoroethoxy)propan-2-yl)phenyl)acetamide and

2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-2-hydroxyacetamide.

25 24. The compound according to claim 23 which is 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-*N*-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)acetamide.

25. The compound according to anyone of claims 1 to 24 or a pharmaceutically acceptable salt thereof for use in therapy.

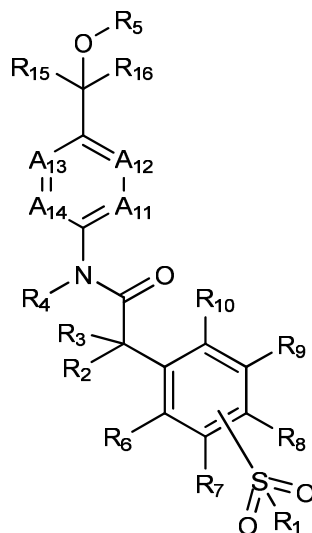
30 26. The compound according to anyone of claims 1 to 24 or a pharmaceutically acceptable salt thereof for use in the treatment of ROR γ -mediated diseases or conditions.

27. A pharmaceutical composition which comprises a compound of Formula I according to any of claims 1 to 24 or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients.

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28. A pharmaceutical composition according to claim 27, which further comprises at least one additional therapeutically active agent.

29. A compound according to Formula I



Meta or para

(Formula I)

or a pharmaceutically acceptable salt thereof wherein

A₁₁ – A₁₄ are N or CR₁₁, CR₁₂, CR₁₃, CR₁₄, respectively, with the proviso that no more than two of the four positions A can be simultaneously N;

R₁ is C(1-6)alkyl, C(3-6)cycloalkyl, C(3-6)cycloalkylC(1-3)alkyl, (di)C(1-6)alkylamino, (di)C(3-6)cycloalkylamino or

(di)(C(3-6)cycloalkylC(1-3)alkyl)amino, with all carbon atoms of alkyl groups optionally substituted with one or more F and all carbon atoms of cycloalkyl groups optionally substituted with one or more F or methyl;

R₂ and R₃ are independently H, F, methyl, ethyl, hydroxy, methoxy or R₂ and R₃ together is carbonyl, all alkyl groups, if present, optionally being substituted with one or more F;

R₄ is H or C(1-6)alkyl;

R₅ is H, hydroxyethyl, methoxyethyl, C(1-6)alkyl, C(6-10)aryl, C(6-10)arylC(1-3)alkyl, C(1-9)heteroaryl, C(1-9)heteroarylC(1-3)alkyl, C(3-6)cycloalkyl, C(3-6)cycloalkylC(1-3)alkyl, C(2-5)heterocycloalkyl or C(2-5)heterocycloalkylC(1-3)alkyl, all groups optionally substituted with one or

more F, Cl, C(1-2)alkyl, C(1-2)alkoxy or cyano ;

the sulfonyl group with R₁ is represented by one of R₇, R₈ or R₉;

the remaining R₆-R₁₄ are independently H, halogen, C(1-3)alkoxy, (di)C(1-3)alkylamino or C(1-6)alkyl, all of the alkyl groups optionally being substituted with one or more F;

R₁₅ and R₁₆ are independently H, C(1-6)alkyl, C(3-6)cycloalkyl,

C(3-6)cycloalkylC(1-3)alkyl, C(6-10)aryl, C(6-10)arylC(1-3)alkyl,

C(1-9)heteroaryl, C(1-9)heteroarylC(1-3)alkyl, C(2-5)heterocycloalkyl or

C(2-5)heterocycloalkylC(1-3)alkyl, all groups optionally substituted with one or

more F, Cl, C(1-2)alkyl, C(1-2)alkoxy or cyano; and

wherein (di)C(1-6)alkylamino is an amino group, which is monosubstituted or disubstituted independently with H or C(1-6)alkyl groups.

30. The compound according to claim 29 which is *N*-(2-amino-4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-2-(4-((cyclopropylmethyl)sulfonyl)phenyl)acetamide.