

ALCOHOL DERIVATIVES AS Kv7 POTASSIUM CHANNEL OPENERS**FIELD OF THE INVENTION**

The present invention relates to novel compounds which activate the Kv7 potassium channels. Separate aspects of the invention are directed to pharmaceutical compositions comprising said compounds and uses of the compounds to treat disorders responsive to the activation of Kv7 potassium channels.

BACKGROUND OF THE INVENTION

Voltage-dependent potassium (Kv) channels conduct potassium ions (K^+) across cell membranes in response to changes in the membrane potential and can thereby regulate cellular excitability by modulating (increasing or decreasing) the electrical activity of the cell. Functional Kv channels exist as multimeric structures formed by the association of four alpha and four beta subunits. The alpha subunits comprise six transmembrane domains, a pore-forming loop and a voltage-sensor and are arranged symmetrically around a central pore. The beta or auxiliary subunits interact with the alpha subunits and can modify the properties of the channel complex to include, but not be limited to, alterations in the channel's electrophysiological or biophysical properties, expression levels or expression patterns.

Nine Kv channel alpha subunit families have been identified and are termed Kv1-Kv9. As such, there is an enormous diversity in Kv channel function that arises as a consequence of the multiplicity of sub-families, the

formation of both homomeric and heteromeric subunits within sub-families and the additional effects of association with beta subunits (Christie, 25 *Clinical and Experimental Pharmacology and Physiology*, 1995, 22, 944-951).

The Kv7 channel family consists of at least five members which include one or more of the following mammalian channels: Kv7.1, Kv7.2, Kv7.3, Kv7.4, Kv7.5 and any mammalian or non-mammalian equivalent or variant (including splice variants) thereof. Alternatively, the members of this family are termed by the gene name KCNQ1, KCNQ2, KCNQ3, KCNQ4 and KCNQ5 respectively (Dalby-Brown, et al., *Current Topics in Medicinal Chemistry*, 2006, 6, 9991023).

As mentioned above, the neuronal Kv7 potassium channels play roles in controlling neuronal excitation. Kv7 channels, in particular Kv7.2/Kv7.3 heterodimers, underlie the M-current (Wang et al *Science*. 1998 Dec 4;282(5395):1890-3). The M-current has a characteristic time- and voltage-dependence that results in stabilisation of the membrane potential in response to multiple excitatory stimuli.

In this way, the M-current is involved in controlling neuronal excitability (Delmas & Brown, *Nature*, 2005, 6, 850-862). The M-current is a non-inactivating potassium current found in many neuronal cell types. In each cell type, it is dominant in controlling membrane excitability by being the only sustained current in the

range of action potential initiation (Marrion, Annual Review Physiology 1997, 59, 483-504).

Retigabine (N-(2-amino-4-(4-fluorobenzylamino)-phenyl) carbamic acid ethyl ester) is a compound which binds to the Kv7 potassium channels (Wuttke, et al., Molecular Pharmacology, 2005, 67, 1009-1017). Retigabine activates K⁺ current in neuronal cells and the pharmacology of this induced current displays concordance with the published pharmacology of the M-channel that has been correlated to the Kv7.2/3 K⁺ channel heteromultimer which suggests that activation of Kv7.2/3 channels is responsible for at least some of the anticonvulsant activity of this agent (Wickenden, et al., Molecular Pharmacology 2000, 58, 591-600). Retigabine is effective in reducing the incidence of seizures in epileptic patients (Bialer, et al., Epilepsy Research 2002, 51, 31-71). Retigabine has a broad spectrum and potent anticonvulsant properties. It is active after oral and intraperitoneal administration in rats and mice in a range of anticonvulsant tests (Rostock, et al., Epilepsy Research 1996, 23, 211-223).

The five members of this family of ion channels differ in their expression patterns. The expression of Kv7.1 is restricted to the heart, peripheral epithelial and smooth muscle, whereas the expression of Kv7.2, Kv7.3, Kv7.4 and Kv7.5 appear to be dominant in the nervous system which includes the hippocampus, cortex, ventral tegmental area, and dorsal root ganglion neurons (for a

review see Greene & Hoshi, Cellular and Molecular Life Sciences, 2017, 74(3), 495-508).

The KCNQ2 and KCNQ3 genes appear to be mutated in an inherited form of epilepsy known as benign familial neonatal convulsions (Rogawski, Trends in Neurosciences 2000, 23, 393-398). The proteins encoded by the KCNQ2 and KCNQ3 genes are localised in the pyramidal neurons of the human cortex and hippocampus, regions of the brain associated with seizure generation and propagation (Cooper et al., Proceedings National Academy of Science U S A 2000, 97, 4914-4919).

Furthermore, mRNA for Kv7.3 and 5, in addition to that for Kv7.2, are expressed in astrocytes and glial cells. Thus Kv7.2, Kv7.3 and Kv7.5 channels may help modulate synaptic activity in the CNS and contribute to the neuroprotective effects of KCNQ channel openers (Noda, et al., Society for Neuroscience Abstracts 2003, 53.9), which would be relevant for the treatment of neurodegenerative disorders such as but not limited to Alzheimer's disease, Parkinson's disease and Huntington's chorea.

mRNA for Kv7.2 and Kv7.3 subunits are found in brain regions associated with anxiety and emotional behaviours such as depression and bipolar disorder e.g. hippocampus, ventral tegmental area and amygdala (Saganich, et al. Journal of Neuroscience 2001, 21, 4609-4624; Friedman et al., Nat Commun. 2016; 7: 11671.), and retigabine is reportedly active in animal models of

anxiety-like behaviour (Korsgaard et al J Pharmacol Exp Ther. 2005 Jul;314(1):282-92. Epub 2005 Apr 6.). As such Kv7 channels are relevant for the treatment of emotional related disorders such as but not limited to bipolar depression, major depressive disorder, anxiety, suicide, panic attacks, social phobia.

Kv7.2/3 channels have also been reported to be upregulated in models of neuropathic pain (Wickenden, et al., Society for Neuroscience Abstracts 2002, 454.7), and potassium channel modulators have been hypothesised to be active in both neuropathic pain and epilepsy (Schroder, et al., Neuropharmacology 2001, 40, 888-898). In addition to a role in neuropathic pain, the expression of mRNA for Kv7.2-5 in the trigeminal and dorsal root ganglia and in the trigeminal nucleus caudalis implies that openers of these channels may also affect the sensory processing of migraine pain (Goldstein, et al. Society for Neuroscience Abstracts 2003, 53.8). Taken together, this evidence points to the relevance of KCNQ channel openers for the treatment of chronic pain and neuropathy related disorders.

WO 07/90409 relates to the use of Kv7 channel openers for the treatment of schizophrenia. Kv7 channel openers modulate the function of the dopaminergic system (Friedman et al., Nat Commun. 2016; Scotty et al J Pharmacol Exp Ther. 2009 Mar;328(3):951-62. doi: 10.1124/jpet.108.146944. Epub 2008 Dec 19; Koyama et al., J Neurophysiol. 2006 Aug;96(2):535-43. Epub 2006 Jan 4; Li et al Br J Pharmacol. 2017 Dec;174(23):4277-

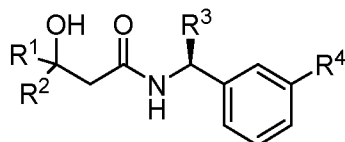
4294. doi: 10.1111/bph.14026. Epub 2017 Oct 19.; Hansen et al J Pharmacol Exp Ther. 2006 Sep;318(3):1006-19. Epub 2006 Jun 14) which would be relevant for the treatment of psychiatric disorders such as but not
5 limited to psychosis, mania, stress-related disorders, acute stress reactions, attention deficit/hyperactivity disorder, posttraumatic stress disorder, obsessive compulsive disorder, impulsivity disorders, personality disorders, schizotypal disorder, aggression, autism
10 spectrum disorders. WO 01/96540 discloses the use of modulators of the M-current formed by expression of KCNQ2 and KCNQ3 genes for insomnia, while WO 01/092526 discloses that modulators of Kv7.5 can be utilized for the treatment of sleep disorders. WO 09/015667 discloses
15 the use of Kv7 openers in the treatment of sexual dysfunction.

Although patients suffering from the above-mentioned disorders may have available treatment options, many of
20 these options lack the desired efficacy and are accompanied by undesired side effects. Therefore, an unmet need exists for novel therapies for the treatment of said disorders.

25 In an attempt to identify new therapies, the inventors have identified a series of novel compounds as represented by Formula I. Accordingly, the present invention provides novel compounds as medicaments for the treatment of disorders which are modulated by the
30 KCNQ potassium channels.

SUMMARY OF THE INVENTION

The present invention relates to a compound of Formula I



Formula I;

wherein

10 R1 is selected from the group consisting of C₁-C₆ alkyl, CF₃, CH₂CF₃, CF₂CHF₂, C₃-C₈ cycloalkyl, wherein said C₃-C₈ cycloalkyl may be substituted with 1 or 2 C₁-C₃ alkyl, F, CHF₂ or CF₃, and

15 R2 is H, C₁-C₆ alkyl or CF₃; or

R1 and R2 combine (together with the carbon atoms they are attached) to form C₃-C₅ cycloalkyl optionally substituted with 1 or 2 F, CHF₂ or CF₃; and

20 R3 is C₁-C₃ alkyl or CH₂O-C₁₋₃ alkyl, said C₁-C₃ alkyl or CH₂O-C₁₋₃ alkyl substituted with C≡N, 3 F or C₃-C₅ cycloalkyl;

25 R4 is selected from the group consisting of OCF₃, or OCHF₂.

According to another aspect of the invention, the invention relates to novel compounds as of present invention.

The invention also concerns a pharmaceutical

5 composition comprising a compound according to the invention and a pharmaceutically acceptable carrier or excipient.

Furthermore, the invention concerns a method of treating
10 a patient as described in the claims and embodiments and includes treatments of patients suffering from epilepsy, a bipolar disorder, migraine and schizophrenia comprising administering to the subject a therapeutically effective amount of the compound
15 according to the invention.

DETAILED DESCRIPTION OF THE INVENTION

According to an embodiment, the compound of Formula I may have an R₄ group which is OCF₃ or OCHF₂.

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According to another embodiment the compound according to Formula I may have an R₃ group is selected from the group comprising CH₂-O-CF₃, CH₂-O-cyclopropyl, CH₂-C≡N.

25 According to a further embodiment, the compound according to Formula I may have an R₁ group which is C₃-C₄ cycloalkyl, optionally substituted with 1 or 2 C₁-C₃ alkyl, F, CHF₂ or CF₃.

30 In yet another embodiment the compound according to any Formula I may have an R₁ group and an R₂ group, which

combine to form cyclobutyl optionally substituted with 1 or 2 F, and R₄ is OCF₃ or OCHF₂.

According to a specific embodiment of the invention the compound according to the invention is selected from the group consisting of:

(S)-N-((R)-2-cyclopropoxy-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-4,4-dimethylpentanamide;

(S)-N-((R)-1-(3-(difluoromethoxy)phenyl)-2-

(trifluoromethoxy)ethyl)-3-hydroxy-4,4-dimethylpentanamide;

(S)-N-((R)-1-(3-(trifluoromethoxy)phenyl)-2-

(trifluoromethoxy)ethyl)-3-hydroxy-4,4-dimethylpentanamide;

(S)-N-((S)-2-cyano-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-hydroxy-4,4-dimethylpentanamide;

(S)-N-((S)-3-cyano-1-(3-(trifluoromethoxy)phenyl)propyl)-3-hydroxy-4,4-dimethylpentanamide;

(R)-N-(2-cyclopropoxy-1-(3-(trifluoromethoxy)

phenyl)ethyl)-2-(3,3-difluoro-1-hydroxycyclobutyl)acetamide;

(R)-N-(2-cyclopropoxy-1-(3-(difluoromethoxy)

phenyl)ethyl)-2-(3,3-difluoro-1-hydroxycyclobutyl)acetamide;

(R)-2-(3,3-difluoro-1-hydroxycyclobutyl)-N-(1-(3-(difluoromethoxy)phenyl)-2-

(trifluoromethoxy)ethyl)acetamide; or

(S)-N-(2-cyano-1-(3-(trifluoromethoxy)phenyl)ethyl)-2-(3,3-difluoro-1-hydroxycyclobutyl)acetamide

or a pharmaceutically acceptable salt of any of these compounds.

Another aspect of the invention relates to a compound

5 selected from the group consisting of:

(R)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-4,4-dimethylpentanamide;

10 (S)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-4,4-dimethylpentanamide;

(S)-3-hydroxy-4,4-dimethyl-N-((S)-1-(3-(2,2,2-trifluoroethoxy)phenyl)ethyl) pentanamide;

15 R)-3-hydroxy-4,4-dimethyl-N-((S)-1-(3-(2,2,2-trifluoroethoxy) phenyl)ethyl)pentanamide;

(R)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-3-(1-(trifluoro-methyl)cyclopropyl)propanamide;

20 (S)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-3-(1-(trifluoro-methyl)cyclopropyl)propanamide;

(R)-N-((R)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-hydroxy-3-(1-(trifluoromethyl)cyclopropyl)propanamide;

25 (S)-N-((R)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl) ethyl)-3-hydroxy-3-(1-(trifluoromethyl)cyclopropyl) propanamide;

(R)-3-(3,3-difluorocyclobutyl)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxypropanamide;

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(S)-3-(3,3-difluorocyclobutyl)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxypropanamide

(R)-3-(3,3-difluorocyclobutyl)-N-((R)-2-

5 (difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-hydroxypropanamide;

(S)-3-(3,3-difluorocyclobutyl)-N-((R)-2-

(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-hydroxypropanamide;

10 (S)-3-(3,3-difluorocyclobutyl)-N-((S)-1-(3-(difluoromethoxy)phenyl)butyl)-3-hydroxypropanamide;

(R)-3-(3,3-difluorocyclobutyl)-N-((S)-1-(3-

(difluoromethoxy)phenyl)butyl)-3-hydroxypropanamide;

(S)-N-((R)-2-(difluoromethoxy)-1-(3-

15 (difluoromethoxy)phenyl)ethyl)-3-(1-ethylcyclopropyl)-3-hydroxypropanamide;

(R)-N-((R)-2-(difluoromethoxy)-1-(3-

(difluoromethoxy)phenyl)ethyl)-3-(1-ethylcyclopropyl)-3-hydroxypropanamide;

20 (S)-N-((S)-1-(3-(difluoromethoxy)phenyl)butyl)-3-hydroxy-4,4-dimethylpentanamide;

(S)-N-((S)-1-(3-(difluoromethoxy)phenyl)-4,4-

difluorobutyl)-3-hydroxy-4,4-dimethylpentanamide;

(S)-N-((S)-1-(3-(difluoromethoxy)phenyl)-3,3-

25 difluoropropyl)-3-hydroxy-4,4-dimethylpentanamide;

(S)-N-((S)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-4,4-dimethylpentanamide;

(R)-2-(3,3-difluoro-1-hydroxycyclobutyl)-N-(2-

(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)

30 ethyl)acetamide;

- (R)-2-(3,3-difluoro-1-hydroxycyclobutyl)-N-(2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)acetamide;
(S)-2-(3,3-difluoro-1-hydroxycyclobutyl)-N-(1-(3-(difluoromethoxy)phenyl)butyl)acetamide;
5 (S)-2-(3,3-difluoro-1-hydroxycyclobutyl)-N-(1-(3-(difluoromethoxy)phenyl)-4,4-difluorobutyl)acetamide;
(S)-2-(3,3-difluoro-1-hydroxycyclobutyl)-N-(1-(3-(trifluoromethoxy)phenyl)propyl)acetamide;
10 (S)-N-(3,3-difluoro-1-(3-(trifluoromethoxy)phenyl)propyl)-2-(3,3-difluoro-1-hydroxycyclobutyl)acetamide;
(S)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-4,4-
15 dimethylpentanamide;
(R)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-(1-fluorocyclopropyl)-3-hydroxybutanamide;
(S)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-(1-
20 fluorocyclopropyl)-3-hydroxybutanamide;
(S)-N-((R)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-(1-fluorocyclopropyl)-3-hydroxybutanamide;
25 (R)-N-((R)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-(1-fluorocyclopropyl)-3-hydroxybutanamide;
(R)-3-cyclopropyl-N-((R)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-hydroxybutanamide;
30 (S)-3-cyclopropyl-N-((R)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-hydroxybutanamide;

(R)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-5,5,5-trifluoro-3-hydroxy-3-methylpentanamide;

5 (S)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-5,5,5-trifluoro-3-hydroxy-3-methylpentanamide;

(R)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-3,5-dimethylhexanamide;

10 (S)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-3,5-dimethylhexanamide;

(S)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-3,4-dimethylpentanamide;

15 (R)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-3,4-dimethylpentanamide;

(S)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-(3,3-dimethylcyclobutyl)-3-hydroxypropanamide;

20 (R)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-(3,3-dimethylcyclobutyl)-3-hydroxypropanamide;

25 (S)-3-cyclopentyl-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxypropanamide;

(R)-3-cyclopentyl-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxypropanamide;

30 (R)-3-(1-fluorocyclopropyl)-3-hydroxy-N-((R)-2-methoxy-1-(3-(trifluoromethoxy)phenyl)ethyl)butanamide;

and (S)-3-(1-fluorocyclopropyl)-3-hydroxy-N-((R)-2-methoxy-1-(3-(trifluoromethoxy)phenyl)ethyl)butanamide

or a pharmaceutically acceptable salt of any of these
5 compounds.

Reference to compounds encompassed by the present invention includes racemic mixtures as well as
10 optically pure isomers of the compounds for which this is relevant, as well as tautomeric forms the compounds for which this is relevant. Furthermore, the compounds of the present invention may potentially exist in polymorphic and amorphous forms, or as unsolvated as
15 well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like.

The present invention also includes isotopelabeled forms of the compounds of the invention, such as
20 Deuterium. The compound may also incorporate positron-emitting isotopes for medical imaging and positron-emitting tomography (PET) studies for determining the distribution of receptors. Suitable positron-emitting isotopes that can be incorporated in compounds of the invention are ^{11}C , ^{13}N , ^{15}O , and ^{18}F . Isotopically-
25 labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples using
30 appropriate isotopically-labeled reagent in place of non-isotopically-labeled reagent.

The compound according to the invention may be in a pharmaceutical composition comprising the compound and a pharmaceutically acceptable excipient or carrier.

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In one embodiment, the invention relates to a compound according to the invention for use in therapy.

10 In another embodiment the invention relates to a method of treating a patient in the need thereof suffering from epilepsy, bipolar disorder, migraine or schizophrenia comprising administering to the subject a therapeutically effective amount of a compound according to the invention

15 In yet another embodiment the invention relates to a method of treating a patient in the need thereof suffering from psychosis, mania, stress-related disorders, acute stress reactions, bipolar depression, major depressive disorder, anxiety, panic attacks, social phobia, sleep
20 disturbances, ADHD, PTSD, OCD, impulsivity disorders, personality disorders, schizotypal disorder, aggression, chronic pain, neuropathy, autism spectrum disorders, Huntington's chorea, sclerosis, multiple sclerosis, Alzheimer's disease comprising administering
25 to the subject a therapeutically effective amount of a compound according to the invention

According to an embodiment the compound of the invention is used in therapy.

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The use of a compound according to the invention is for the treatment of epilepsy, bipolar disorder, migraine or schizophrenia or in another embodiment for the treatment of psychosis, mania, stress-related disorders, acute stress reactions, bipolar depression, major depressive disorder, anxiety, panic attacks, social phobia, sleep disturbances, ADHD, PTSD, OCD, impulsivity disorders, personality disorders, schizotypal disorder, aggression, chronic pain, neuropathy, autism spectrum disorders, Huntington's chorea, sclerosis, multiple sclerosis, Alzheimer's disease.

In another embodiment, the compound of the invention is for the manufacture of a medicament for treating epilepsy, Fragile X syndrome, Angelman syndrome, bipolar disorder, migraine or schizophrenia or in another embodiment for the manufacture of a medicament for treating psychosis, mania, stress-related disorders, acute stress reactions, bipolar depression, major depressive disorder, anxiety, panic attacks, social phobia, sleep disturbances, ADHD, PTSD, OCD, impulsivity disorders, personality disorders, schizotypal disorder, aggression, chronic pain, neuropathy, autism spectrum disorders, Huntington's chorea, sclerosis, multiple sclerosis, Alzheimer's disease.

In the present context, "optionally substituted" means that the indicated moiety may or may not be substituted, and when substituted is mono- or di-substituted. It is understood that where no substituents are indicated for an "optionally

substituted" moiety, then the position is held by a hydrogen atom.

- 5 A given range may interchangeably be indicated with "-
"(dash) or "to", e.g. the term "C₁₋₃ alkyl" is
equivalent to "C₁ to C₃ alkyl".

- 10 The terms "C₁₋₃ alkyl" and "C₁₋₆ alkyl" refer to an
unbranched or branched saturated hydrocarbon having
from one up to six carbon atoms, inclusive. Examples
of such groups include, but are not limited to, methyl,
ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl and t-
butyl.

- 15 The term "C₁₋₃ alkoxy" refers to a moiety of the
formula -OR, wherein R indicates C₁₋₃ alkyl as defined
above.

- 20 The terms "C₃₋₄ cycloalkyl", "C₃₋₅ cycloalkyl", "C₃₋₈
cycloalkyl" or "cyclopropyl" refers to a saturated
monocyclic ring. Examples of such groups includes
cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,
cycloheptyl and cyclooctyl.

- 25 *Administration routes:*

- Pharmaceutical compositions comprising a compound of
the present invention defined above, may be
specifically formulated for administration by any
suitable route such as the oral, rectal, nasal, buccal,
30 sublingual, transdermal and parenteral (e.g.

subcutaneous, intramuscular, and intravenous) route; the oral route being preferred.

It will be appreciated that the route will depend on the general condition and age of the subject to be

5 treated, the nature of the condition to be treated and the active ingredient.

Pharmaceutical formulations and excipients:

In the following, the term, "excipient" or

10 "pharmaceutically acceptable excipient" refers to pharmaceutical excipients including, but not limited to, fillers, antiadherents, binders, coatings, colours, disintegrants, flavours, glidants, lubricants, preservatives, sorbents, sweeteners, solvents, vehicles
15 and adjuvants.

The present invention also provides a pharmaceutical composition comprising a compound according to the invention , such as one of the compounds disclosed in
20 the Experimental Section herein. The present invention also provides a process for making a pharmaceutical composition comprising a compound according to the invention . The pharmaceutical compositions according to the invention may be formulated with

25 pharmaceutically acceptable excipients in accordance with conventional techniques such as those disclosed in Remington, "The Science and Practice of Pharmacy", 22th edition (2012), Edited by Allen, Loyd V., Jr.

30 Pharmaceutical compositions for oral administration include solid oral dosage forms such as tablets,

capsules, powders and granules; and liquid oral dosage forms such as solutions, emulsions, suspensions and syrups as well as powders and granules to be dissolved or suspended in an appropriate liquid.

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Solid oral dosage forms may be presented as discrete units (e.g. tablets or hard or soft capsules), each containing a predetermined amount of the active ingredient, and preferably one or more suitable excipients. Where appropriate, the solid dosage forms may be prepared with coatings such as enteric coatings or they may be formulated so as to provide modified release of the active ingredient such as delayed or extended release according to methods well known in the art. Where appropriate, the solid dosage form may be a dosage form disintegrating in the saliva, such as for example an orodispersible tablet.

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Examples of excipients suitable for solid oral formulation include, but are not limited to, microcrystalline cellulose, corn starch, lactose, mannitol, povidone, croscarmellose sodium, sucrose, cyclodextrin, talcum, gelatin, pectin, magnesium stearate, stearic acid and lower alkyl ethers of cellulose. Similarly, the solid formulation may include excipients for delayed or extended release formulations known in the art, such as glyceryl monostearate or hypromellose. If solid material is used for oral administration, the formulation may for example be prepared by mixing the active ingredient with solid excipients and subsequently compressing the mixture in

a conventional tableting machine; or the formulation may for example be placed in a hard capsule e.g. in powder, pellet or mini tablet form. The amount of solid excipient will vary widely but will typically range
5 from about 25 mg to about 1 g per dosage unit.

Liquid oral dosage forms may be presented as for example elixirs, syrups, oral drops or a liquid filled capsule. Liquid oral dosage forms may also be presented
10 as powders for a solution or suspension in an aqueous or non-aqueous liquid. Examples of excipients suitable for liquid oral formulation include, but are not limited to, ethanol, propylene glycol, glycerol, polyethyleneglycols, poloxamers, sorbitol, poly-sorbate,
15 mono and di-glycerides, cyclodextrins, coconut oil, palm oil, and water. Liquid oral dosage forms may for example be prepared by dissolving or suspending the active ingredient in an aqueous or non-aqueous liquid, or by incorporating the active ingredient into an oil-
20 in-water or water-in-oil liquid emulsion.

Further excipients may be used in solid and liquid oral formulations, such as colourings, flavourings and preservatives etc.

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Pharmaceutical compositions for parenteral administration include sterile aqueous and nonaqueous solutions, dispersions, suspensions or emulsions for injection or infusion, concentrates for injection or
30 infusion as well as sterile powders to be reconstituted in sterile solutions or dispersions for injection or

infusion prior to use. Examples of excipients suitable for parenteral formulation include, but are not limited to water, coconut oil, palm oil and solutions of cyclodextrins. Aqueous formulations should be suitably buffered if necessary and rendered isotonic with sufficient saline or glucose.

Other types of pharmaceutical compositions include suppositories, inhalants, creams, gels, dermal patches, implants and formulations for buccal or sublingual administration.

It is a requisite that the excipients used for any pharmaceutical formulation comply with the intended route of administration and are compatible with the active ingredients.

Doses:

In one embodiment, the compound of the present invention is administered in an amount from about 0.001 mg/kg body weight to about 100 mg/kg body weight per day. In particular, daily dosages may be in the range of 0.01 mg/kg body weight to about 50 mg/kg body weight per day. The exact dosages will depend upon the frequency and mode of administration, the gender, the age, the weight, and the general condition of the subject to be treated, the nature and the severity of the condition to be treated, any concomitant diseases to be treated, the desired effect of the treatment and other factors known to those skilled in the art.

A typical oral dosage for adults will be in the range of 0.1-1000 mg/day of a compound of the present invention, such as 1-500 mg/day, such as 1-100 mg/day or 1-50 mg/day. Conveniently, the compounds of the
5 invention are administered in a unit dosage form containing said compounds in an amount of about 0.1 to 500 mg, such as 10 mg, 50 mg 100 mg, 150 mg, 200 mg or 250 mg of a compound of the present invention.

10 *Isomeric and tautomeric forms:*

When compounds of the present invention contain one or more chiral atoms, reference to the compounds will, unless otherwise specified, cover the enantiomerically or diastereomerically pure compound as
15 well as mixtures of the enantiomers or diastereomers in any ratio.

MDL Enhanced Stereo representation is used to describe unknown stereochemistry of the compounds of the
20 invention. Hence, the label "or1" on a chiral carbon atom is used to indicate that the absolute stereoconformation at this atom is not known; e.g. the stereoconformation at this carbon atom is either (S) or (R).

25 Furthermore, the chiral bond from a carbon atom labelled "or1", using upward wedge or downward wedge, are equal representations; e.g. the two drawings have the same meaning, the meaning being that the absolute
30 stereoconformation at the "or1" labelled carbon atom is not known and can be (S) or (R).

Thus, the use of upward wedge bonds and downward wedge bonds from atoms labelled "or1", are merely intended to provide a visual cue that the drawings represent

5 different stereoisomers, in which the conformation at the "or1" labelled carbon atom is not known.

Furthermore, some of the compounds of the present invention may exist in different tautomeric forms and
10 it is intended that any tautomeric forms that the compounds are able to form are included within the scope of the present invention.

Therapeutically effective amount:

15 In the present context, the term "therapeutically effective amount" of a compound means an amount sufficient to alleviate, arrest, partly arrest, remove or delay the clinical manifestations of a given disease and its complications in a therapeutic intervention
20 comprising the administration of said compound. An amount adequate to accomplish this is defined as "therapeutically effective amount". Effective amounts for each purpose will depend on the severity of the disease or injury as well as the weight and general
25 state of the subject. It will be understood that determining an appropriate dosage may be achieved using routine experimentation, by constructing a matrix of values and testing different points in the matrix, which is all within the ordinary skills of a trained
30 physician.

Treatment and treating:

In the present context, "treatment" or "treating" is intended to indicate the management and care of a patient for the purpose of alleviating, arresting,
5 partly arresting, removing or delaying progress of the clinical manifestation of the disease. The patient to be treated is preferably a mammal, in particular a human being.

10 All references, including publications, patent applications and patents, cited herein are hereby incorporated by reference in their entirety and to the same extent as if each reference were individually and specifically indicated to be incorporated by reference
15 and were set forth in its entirety (to the maximum extent permitted by law).

Use in epilepsy, epileptic syndromes, epileptic symptoms or seizures

20 In another embodiment the invention relates to a method of treating a patient in the need thereof suffering from epilepsy, epileptic syndromes, epileptic symptoms, treatment resistant or refractory epilepsy, or seizures
25 comprising administering to the subject a therapeutically effective amount of a compound according to the invention.

In yet another embodiment the invention relates a method of treating a patient in the need thereof suffering from
30 Focal (partial) epilepsy with simple partial seizures, Focal (partial) epilepsy with complex partial seizures,

Generalized idiopathic epilepsy, Grand mal seizures, Status epilepticus, neonatal seizures, KCNQ epileptic encephalopathy (KCNQ2EE) and Benign Familial Neonatal Convulsions and other epileptic syndromes (such as severe myoclonic epilepsy in infancy, epilepsy with continuous spike waves during slow-wave sleep, West syndrome, Lennox-Gastaut syndrome, Dravet syndrome and Early myoclonic encephalopathy Ohtahara syndrome, or seizures related to stress, hormonal changes, drugs (such as such as amphetamines or cocaine), alcohol, infection, or metabolic disturbances (such as hyponatraemia) or for use in the treatment epileptic symptoms as part of neurogenerative disorders, such as Alzheimer's disease, Lewy body disease, Huntington's disease juvenile form, fronto-temporal lobar degeneration comprising administering to the subject a therapeutically effective amount of a compound of the invention.

The use of a compound according to the invention is for the treatment of epilepsy, including the use in the treatment of Focal (partial) epilepsy with simple partial seizures, Focal (partial) epilepsy with complex partial seizures, Generalized idiopathic epilepsy, Grand mal seizures, Status epilepticus, neonatal seizures, KCNQ epileptic encephalopathy (KCNQ2EE) and Benign Familial Neonatal Convulsions and other epileptic syndromes (such as severe myoclonic epilepsy in infancy, epilepsy with continuous spike waves during slow-wave sleep, West syndrome, Lennox-Gastaut syndrome, Dravet syndrome and Early myoclonic encephalopathy Ohtahara syndrome), or seizures related to stress, hormonal changes, drugs,

alcohol, infection, traumatic brain injury, stroke, brain cancers, autism spectrum disorders or metabolic disturbances (such as hyponatraemia), or for use in the epileptic symptoms as part of neurogenerative disorders, such as Alzheimer's disease, Lewy body disease, Huntington's disease juvenile form, fronto-temporal lobar degeneration.

In another embodiment, the compound of the invention is for the manufacture of a medicament for treating epilepsy, epileptic syndromes, epileptic symptoms, treatment resistant or refractory epilepsy, or seizures including Focal (partial) epilepsy with simple partial seizures, Focal (partial) epilepsy with complex partial seizures, Generalized idiopathic epilepsy, Grand mal seizures, Status epilepticus, neonatal seizures, KCNQ epileptic encephalopathy (KCNQ2EE) and Benign Familial Neonatal Convulsions and other epileptic syndromes (such as severe myoclonic epilepsy in infancy, epilepsy with continuous spike waves during slow-wave sleep, West syndrome, Lennox-Gastaut syndrome, Dravet syndrome and Early myoclonic encephalopathy Ohtahara syndrome, or seizures related to stress, hormonal changes, drugs, alcohol, infection, traumatic brain injury, stroke, brain cancers, autism spectrum disorders or metabolic disturbances (such as hyponatraemia) or for use in the treatment epileptic symptoms as part of neurogenerative disorders, such as Alzheimer's disease, Lewy body disease, Huntington's disease juvenile form, fronto-temporal lobar degeneration.

The classification of epilepsy can be based on ICD-10 (2016, published by WHO) and is described in section G40 and G41, and is included in the treatment of epilepsy according to the invention

- 5 G40.0 Localization-related (focal)(partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset
- G40.1 Localization-related (focal)(partial) symptomatic epilepsy and epileptic syndromes with simple partial
- 10 seizures
- G40.2 Localization-related (focal)(partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures
- G40.3 Generalized idiopathic epilepsy and epileptic
- 15 syndromes
- G40.4 Other generalized epilepsy and epileptic syndromes
- G40.5 Special epileptic syndromes
- G40.6 Grand mal seizures, unspecified (with or without
- 20 petit mal)
- G40.7 Petit mal, unspecified, without grand mal seizures
- G40.8 Other epilepsy
- G40.9 Epilepsy, unspecified
- 25 G41 Status epilepticus

Treatment of Seizures

- A seizure is a sudden, uncontrolled electrical disturbance in the brain. It can cause changes in
- 30 behavior, movements or feelings, and in levels of consciousness. If a person has two or more seizures or

a tendency to have recurrent seizures this is diagnosed as epilepsy.

There are many types of seizures, which range in severity. Seizure types vary by where and how they arise in the brain. Most seizures last from 30 seconds to two minutes.

Focal seizures

10 Focal seizures result from abnormal electrical activity in one area of the brain. Focal seizures can occur with or without loss of consciousness:

- **Focal seizures with impaired awareness.** These seizures involve a change or loss of consciousness or awareness. The person may stare into space and not respond normally to the environment or perform repetitive movements, such as hand rubbing, chewing, swallowing or walking in circles.
- **Focal seizures without loss of consciousness.** These seizures may alter emotions or change the way things look, smell, feel, taste or sound, but the person doesn't lose consciousness. These seizures may also result in the involuntary jerking of a body part, such as an arm or leg, and spontaneous sensory symptoms such as tingling, dizziness and flashing lights.

Generalized seizures

Seizures that appear to involve all areas of the brain are called generalized seizures. Different types of generalized seizures include:

- **Absence seizures.** Absence seizures, previously known as petit mal seizures, often occur in children and are characterized by staring into space or by subtle body movements, such as eye
5 blinking or lip smacking. These seizures may occur in clusters and cause a brief loss of awareness.
- **Tonic seizures.** Tonic seizures cause stiffening of your muscles. These seizures usually affect muscles in the back, arms and legs.
- 10 • **Atonic seizures.** Atonic seizures, also known as drop seizures, cause a loss of muscle control, which may cause suddenly collapse or fall down.
- **Clonic seizures.** Clonic seizures are associated with repeated or rhythmic, jerking muscle
15 movements. These seizures usually affect the neck, face and arms.
- **Myoclonic seizures.** Myoclonic seizures usually appear as sudden brief jerks or twitches of your arms and legs.
- 20 • **Tonic-clonic seizures.** Tonic-clonic seizures, previously known as grand mal seizures, are the most dramatic type of epileptic seizure and can cause an abrupt loss of consciousness, body stiffening and shaking, and sometimes loss of
25 bladder control or biting the tongue.

Many times, seizures may be associated or caused by:

- High fever, which can be associated with an infection
30 such as meningitis
- Lack of sleep

Low blood sodium (hyponatremia), which can happen with diuretic therapy

Medications, such as certain pain relievers, antidepressants or smoking cessation therapies, that

5 lower the seizure threshold

Head trauma that causes an area of bleeding in the brain

Stroke

Brain tumor

10 Drugs, such as amphetamines or cocaine

Alcohol

Headings and sub-headings are used herein for

15 convenience only and should not be construed as limiting the invention in any way.

The use of any and all examples, or exemplary language (including "for instance", "for example", "e.g.", and

20 "as such") in the present specification is intended merely to better illustrate the invention and does not pose a limitation on the scope of invention unless otherwise indicated.

25 The citation and incorporation of patent documents herein is done for convenience only, and does not reflect any view of the validity, patentability and/or enforceability of such patent documents.

The present invention includes all modifications and equivalents of the subject-matter recited in the claims appended hereto, as permitted by applicable law.

5

EXPERIMENTAL SECTION

Biological evaluation:

Cell culture

10 A synthesized cDNA fragment encoding human Kv7.3 and human Kv7.2 separated by a P2A sequence was inserted into the pcDNA5/FRT/TO vector using the BamHI and XhoI restriction sites. The construct was then transfected into HEK Flp-In 293 cells using Lipofectamine2000. The
15 transfected cells were grown for 48 hours in DMEM containing 10% (v/v) FBS and 1% PenStrep and subsequently maintained under selection in DMEM containing 10% (v/v) FBS, 1 % PenStrep and 200 ug/mL Hygromycin B at 37°C in a humidified atmosphere of 5% CO₂. The resultant stable
20 hKv7.2/hKv7.3 cell line (HEK-hKv7.2/hKv7.3) was functionally tested with automated whole cell patch-clamp and displayed a typical Kv7-current which was sensitive to XE991 and potentiated by Retigabine.

25 Thallium influx assay

The thallium influx assay for potassium channel activation was performed analogously to a published procedure (C.D. Weaver, et al., J Biomol Screen 2004, 9, 671-677) using the FLIPR Potassium Assay kit (Molecular
30 Devices). HEK-hKv7.2/hKv7.3 cells were plated onto 96-well, black-walled, clear-bottomed culture plates

(Corning, Acton, MA, USA) at a density of 80,000 cells/well (100 μ l/well) if the cells were assayed the following day, or 40,000 cells/well (100 μ l/well) if the cells were assayed two days after seeding.

- 5 On the assay day, the medium was removed after which 50 μ L/well of test compound diluted to 2x final concentration in HBSS containing 20 mM HEPES, and 50 μ L/well of 2x dye load buffer were added. The cells were then incubated for 60 min at room temperature in
- 10 the dark. Chloride-free stimulation buffer containing Ti^+ and K^+ at 5x final concentration (5x concentration: 5 mM in both cases) and test compound at 1x final concentration, were prepared during the incubation. The cells were then assayed in a FDSS7000EX Functional Drug
- 15 Screening System (Hamamatsu). Following 60 sec of baseline fluorescence signal reading at 0.1 Hz, and 10 sec at 1 Hz, 25 μ L/well of stimulation buffer were added and the fluorescence continuously measured for 50 sec at 1 Hz followed, by 4 min at 0.1 Hz. Compound
- 20 effect was quantified using AUC as readout and normalized to a reference compound, which was included on each plate.

Compound effects

- 25 In the assay described above, the compounds of the invention had the following biological activity:

Example	EC ₅₀ , nM
1a	7600
1b	420
2a	10000

Example	EC ₅₀ , nM
2b	1800
3a	2800
3b	2400
4a	1700
4b	2900
5a	1200
5b	4500
6a	2500
6b	1100
7a	4000
7b	25000
8a	4800
8b	1200
9a	1500
9b	9200
10a	660
10b	4100
11a	5400
11b	1700
12a	1300
12b	6200
13a	960
13b	360
14a	5200
14b	1300
15a	3700
15b	650
16a	2600
16b	430

Example	EC ₅₀ , nM
17	1500
18	950
19	940
20	1500
21	1000
22	4500
23	1500
24	2400
25	1900
26	960
27	2300
28	3200
29	5400
30	1800
31	2600
32	2500
33	2100
34	2500
35	3500
36a	2700
36b	16000

Synthesis of the compounds of the invention:**General Methods:**

- 5 General procedures for synthesis of intermediates and the compounds of general Formula I are described in reaction Scheme 1, and are specifically illustrated in the preparations and Examples. Within the scope of the present invention are variations of the described

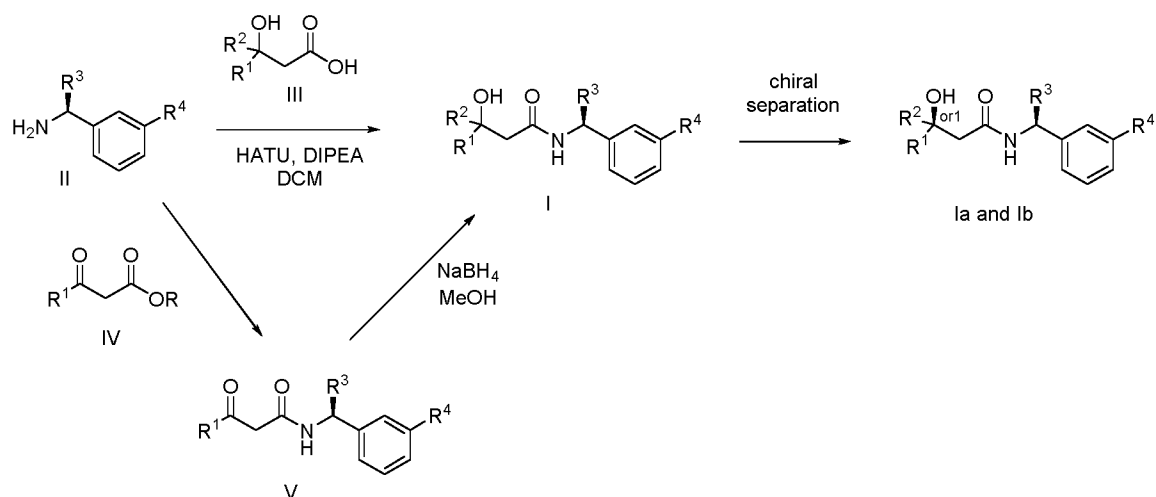
procedures, which are known to a person skilled in the art.

The compounds of the invention are prepared as

- 5 described in Scheme 1. Several of the compounds of general Formula I contain two chiral carbon atoms, and are formed as a mixture of diastereomers. When this is the case, the diastereomers may be separated, to yield the single stereoisomers Ia and Ib.

10

Scheme 1:



- 15 Scheme I depicts the preparation of the compounds of general Formula I by two general routes. The first route is the synthesis of compounds of Formula I by reaction of an enantiomerically pure amine of general Formula II, and an acid of general Formula III, through
 20 methodology well known in the art for the conversion of an acid and an amine into an amide. This methodology includes the formation of reactive derivatives of the acid of Formula III, including, but not limited to,

activated esters and reactive mixed anhydrides,
followed by condensation with amines of general Formula
II. One such methodology is performing the condensation
in the presence of (1-[bis(dimethylamino)methylene]-1H-
5 1,2,3-triazolo[4,5-b]pyridinium 3-oxid
hexafluorophosphate (HATU) and a suitable base such as
diisopropylethylamine (DIPEA), in a solvent such as
dichloromethane (DCM).

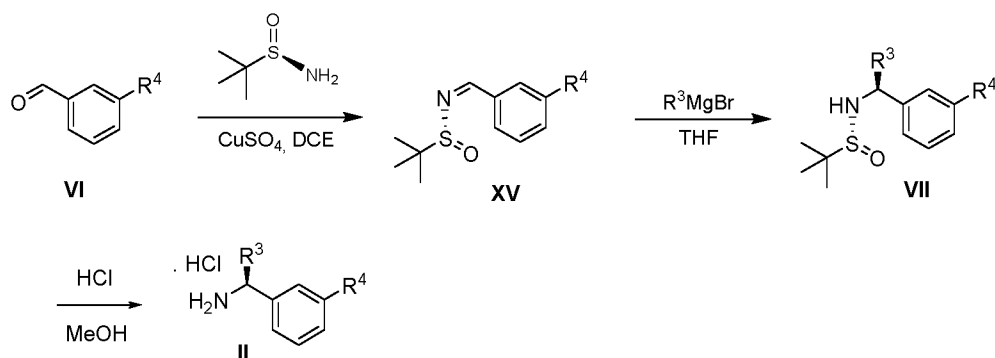
Alternatively, when R^2 is H, the compounds of general

10 Formula I can be prepared via a second general route,
in which intermediates of general Formula V, are
treated with a suitable reducing agent such as NaBH_4 ,
in a suitable solvent such as methanol. The
intermediates of Formula V can be obtained from
15 enantiomerically pure amines of general Formula II, and
a carboxylic acid of general Formula IV ($R = \text{H}$). This
transformation can be effected using similar reaction
conditions as described above for the condensation of
II and III to form I.

20 A variation of this procedure is the direct coupling
reaction between a chiral amine of general Formula II
and a carboxylic acid ester of general Formula IV ($R =$
Me, Et). This reaction can be performed by heating the
reactants to reflux in a suitable solvent such as
25 toluene, in the presence of a suitable base such as
DIPEA, and in the presence of a catalytic amount of a
suitable catalyst such as 4-dimethylamino pyridine
(DMAP).

The optically active amines of general Formula II can
30 be prepared as outlined in Scheme 2a:

Scheme 2a



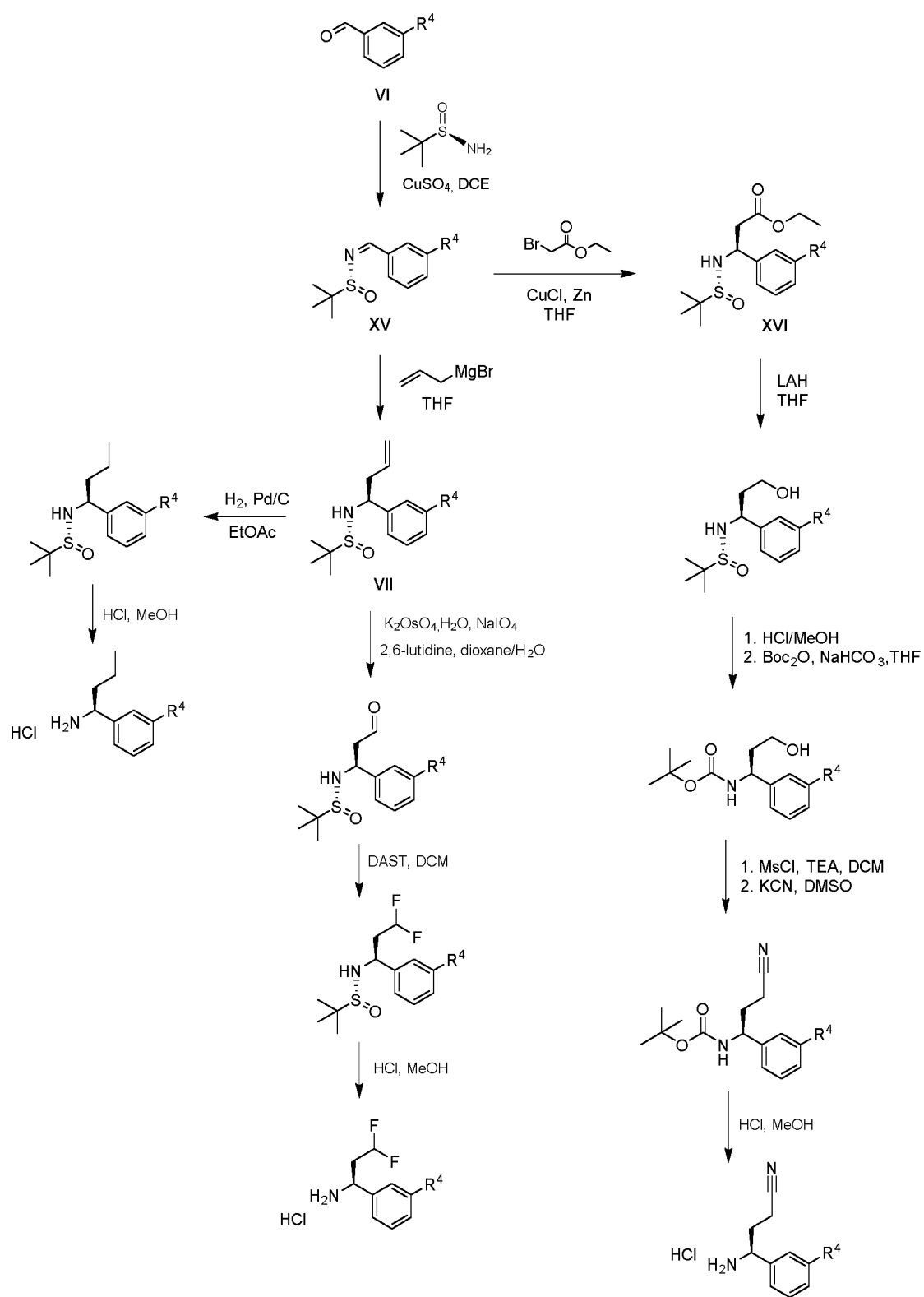
Aldehydes of general Formula VI can be condensed with (R)-2-methylpropane-2-sulfinamide in a suitable solvent such as dichloroethane, in the presence of a drying agent, such as titanium(IV)isopropoxide, or cupric sulfate. The formed sulfinyl imine XV is treated with R³MgBr in a suitable inert solvent such as THF, to yield the corresponding substituted (R)-2-methyl-N-((S)-1-aryl-alkyl)propane-2-sulfinamides VII, which are converted to the compounds of general Formula II by treatment with an appropriate acid in an appropriate solvent, such as HCl in MeOH.

In variations of this procedure, an R³ substituent bearing a functional group can be further modified, by standard functional group conversion methodology known to the chemist skilled in the art. Examples of such manipulations for the preparation of chiral amines are illustrated in Scheme 2b. An intermediate of general Formula VII in which R³ = allyl can be formed from XV and allyl-MgBr, and can undergo catalytic reduction to R³ = n-propyl, using H₂(g) in the presence of a suitable catalyst such as Pd/C, in a suitable solvent such as ethyl acetate. Alternatively, the intermediate

of general Formula VII in which R^3 = allyl can undergo di-hydroxylation followed by oxidative cleavage to yield an intermediate VII in which R^3 = acetaldehyde, by treatment with suitable catalysts such as K_2OsO_4 and
5 $NaIO_4$, in the presence of a suitable base such as 2,6-lutidine, and in a suitable solvent such as dioxane/ H_2O . The obtained aldehyde can undergo additional transformations; for example exchange of oxygen for two fluorine atoms by treatment with a
10 suitable reagent such as (diethylamino)sulfur trifluoride (DAST), in a suitable solvent such as DCM. In a final step, chiral amines can be obtained by hydrolysis as described above.

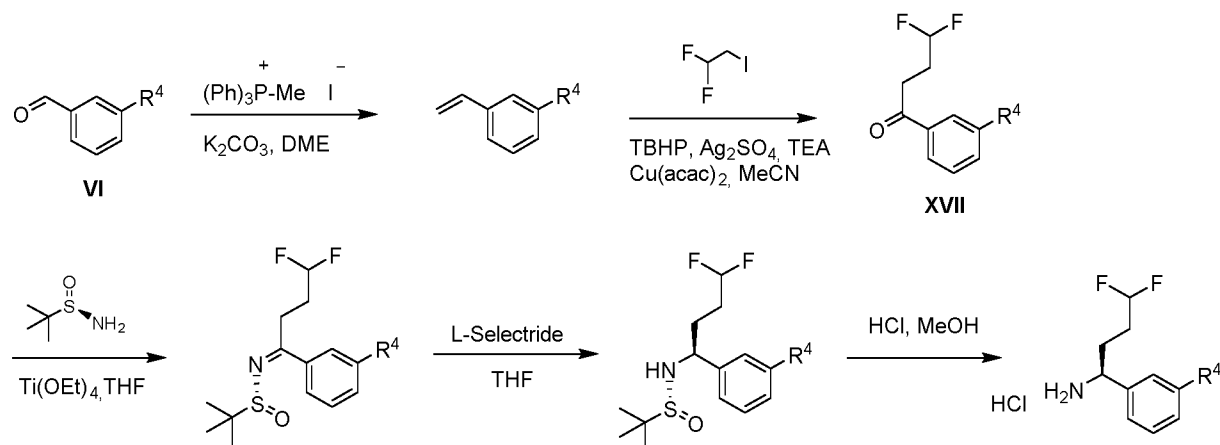
As another example, an intermediate of general Formula
15 XVI in which R^3 is an acetic acid ester, can be formed from XV in a reaction with ethyl 2-bromo acetate, in the presence of $CuCl$ and activated Zn , in a suitable solvent such as THF. The ester group can be further derivatized by transformations known to the skilled
20 chemist. For example, the ester can be reduced to a primary alcohol, by treatment with a suitable reducing agent such as $LiAlH_4$, in a suitable solvent, such as THF. The alcohol obtained may also be further derivatized through transformations known to the
25 skilled practitioner. For example, the alcohol may be transformed into a leaving group through activation with a reagent such as mesyl chloride in the presence of a suitable base such as triethylamine (TEA), in a suitable solvent such as DCM. The resulting mesylates
30 can be reacted with a suitable nucleophile, such as potassium cyanide, in a suitable solvent such as DMSO.

Scheme 2b:



Aldehydes of general Formula VI can also be transformed into chiral amines of general Formula II via an alternative strategy, as illustrated in Scheme 2c:

5 **Scheme 2c:**



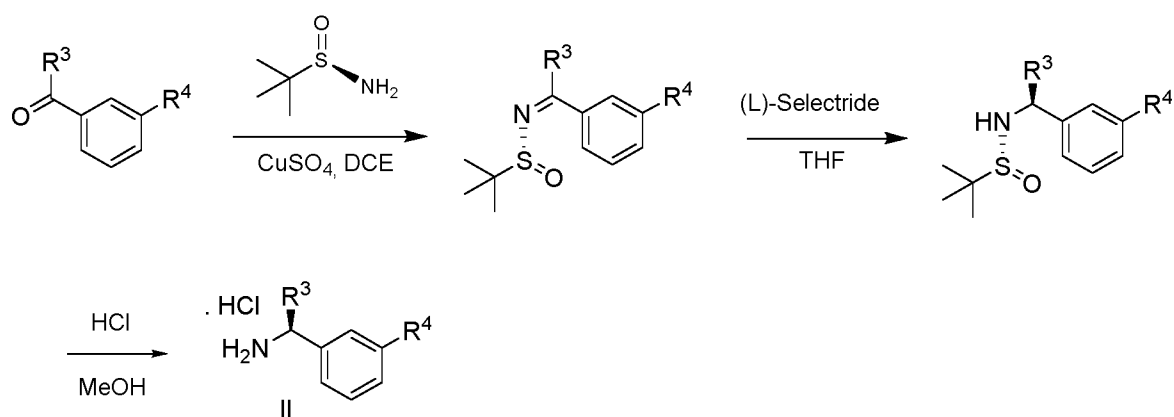
Following this procedure, suitably substituted benzaldehydes VI can be transformed into corresponding suitably substituted styrenes, using Wittig methodology know to the skilled chemist. These intermediates can undergo an alkylation-oxidation reaction to form keto-intermediates XVII. Intermediates of general Formula XVII can be condensed with (R)-2-methylpropane-2-sulfinamide in a suitable solvent such as dichloroethane, in the presence of a suitable drying agent, such as titanium(IV)ethoxide. The formed sulfinyl imine can be reduced with a suitable reducing agent such as L-Selectride, in a suitable inert solvent such as THF, to yield the corresponding suitably substituted (R)-2-methyl-N-((S)-1-aryl-alkyl)propane-2-sulfinamide, which can be converted to chiral amines of general Formula II by treatment with an appropriate acid in an appropriate solvent, such as HCl in MeOH.

The skilled artisan will recognise that other transformations are possible from several of the intermediates; the present invention is intended to include such alternative transformations.

The aldehydes of Formula VI, used to prepare the compounds of the invention, are commercially available, or may be prepared as described in the literature, see Journal of Medicinal Chemistry, 45(18), 3891-3904; 2002.

In another procedure, the chiral amines of Formula II can be obtained from an aryl ketone, through hydride reduction of the intermediate sulfinyl imine obtained from reaction with (*R*)-2-methylpropane-2-sulfinamide, with a reagent such as L-Selectride; as shown in Scheme 3a.

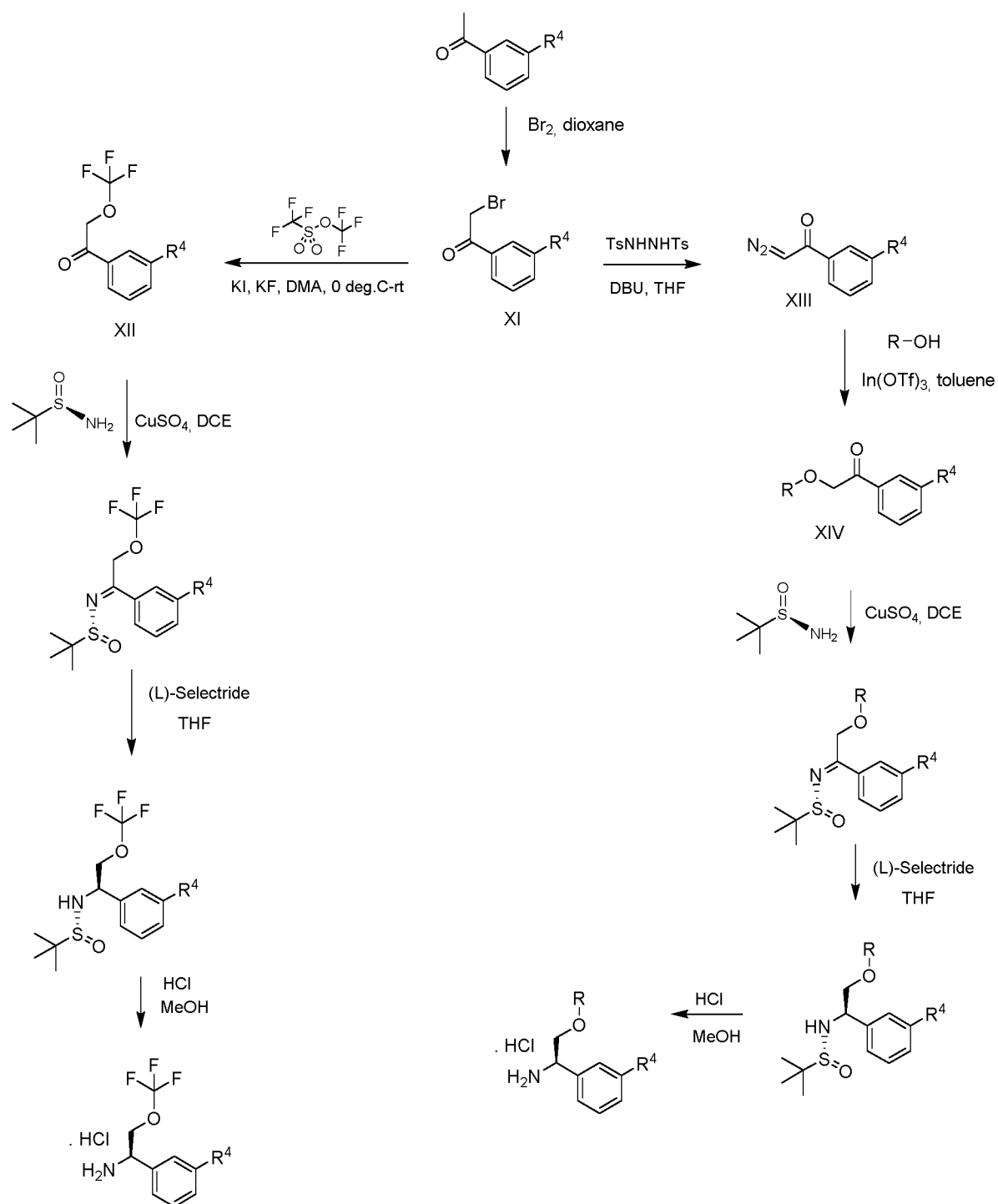
Scheme 3a



A variation of this procedure is illustrated in Scheme 3b. In this procedure, further R³ substituents which are ethers, can be installed from a common alpha

bromoacetophenone intermediate XI, obtained by bromination of a suitably substituted acetophenone. Examples include, but are not limited to introduction of fluoroalkyl methylene ether groups as R³. Thus, using this methodology, suitably substituted bromoacetophenone can be reacted with a fluoroalkoxy donor, such as trifluoromethyl trifluoromethanesulfonate and KF under Finkelstein conditions, in a suitable solvent such as dimethylacetamide (DMA), to give intermediate XII, which can be further transformed into chiral amines as described above. Other examples include, but are not limited to, introduction of alkyl methylene ethers as R³. Thus, suitably substituted bromoacetophenone can be transformed into acyl diazo intermediate XIII, by reaction with 4-methyl-N'-(p-tolylsulfonyl)benzenesulfonohydrazide in the presence of a suitable base, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and in a suitable solvent such as THF. The intermediate XIII can undergo a carbene formation reaction, by treatment with a suitable catalyst such as Indium triflate, in a suitable solvent such as toluene. The formed carbene can be trapped *in situ* by a suitable alcohol, to yield alkoxy keto intermediates XIV. From intermediate XIV, chiral amines of Formula II can be obtained through standard manipulations as described above.

Scheme 3b:



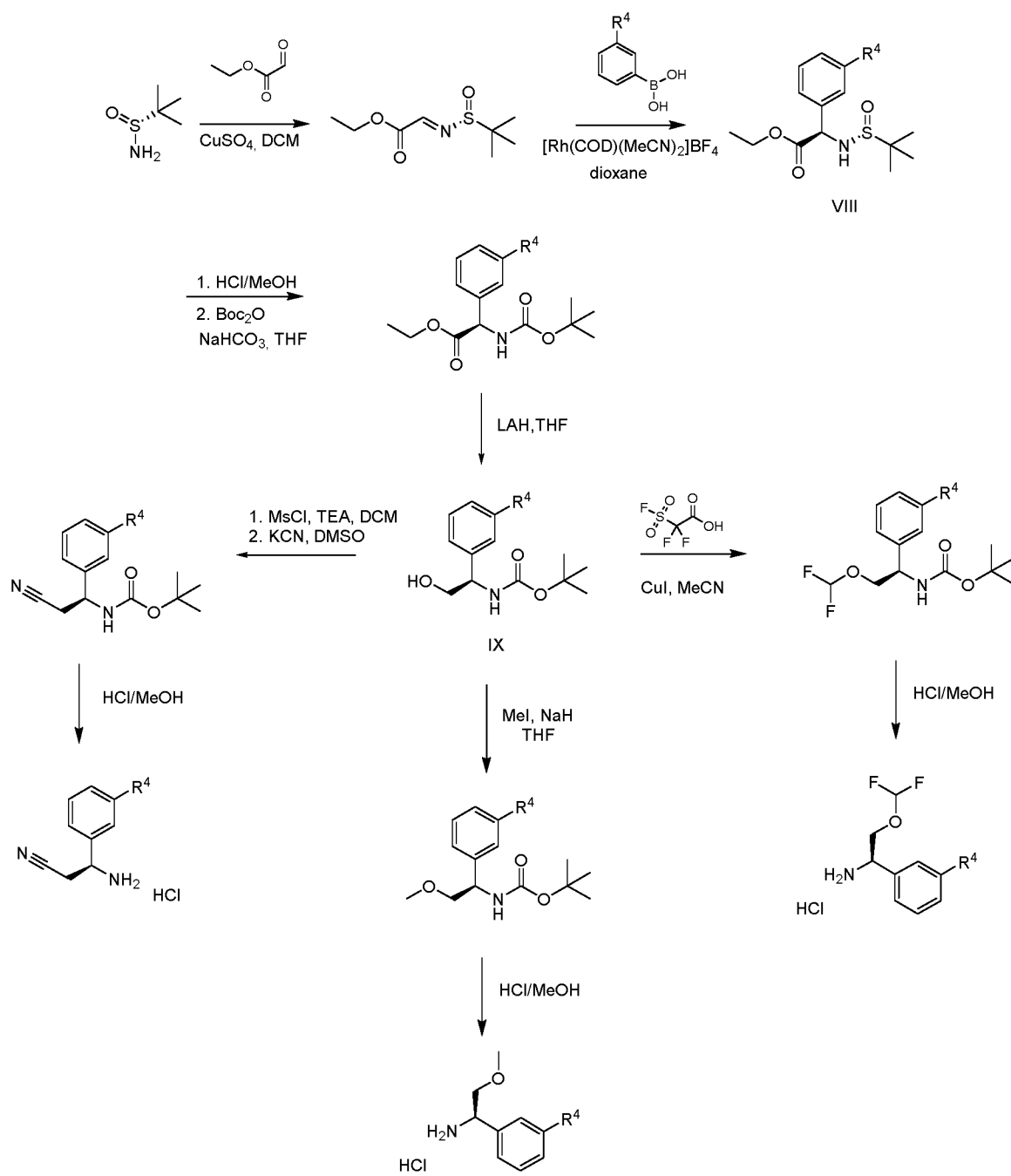
- 5 The suitably substituted ketones or acetophenones used to prepare the compounds of the invention, are

commercially available, or may be prepared by methods known to the person skilled in the art.

The skilled artisan will recognise that other transformations are possible from intermediates of general Formula XI; the present invention is intended to include such alternative transformations.

Another procedure suited for accessing chiral amines of general Formula II, in which R^3 is an ether, is outlined in Scheme 4.

Scheme 4:



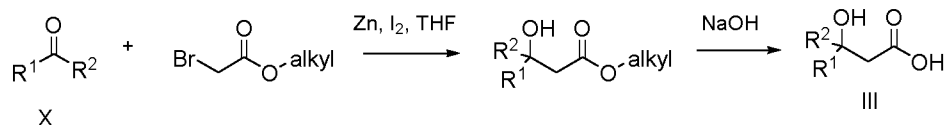
In this procedure, glyoxylate sulfinyl imine, formed in a condensation reaction between a glyoxylic ester and (R)-2-methylpropane-2-sulfinamide, can be reacted with a suitably substituted boronic acid using a suitable catalyst such as bis(acetonitrile)(1,5-cyclooctadiene)rhodium(I) tetra-fluoroborate, in a suitable solvent such as dioxane, as described in JP 2017/095366A. The resulting intermediates VIII can be hydrolysed, re-protected with a suitable protecting group such as Boc under standard conditions, and subjected to ester reduction under suitable conditions such as LiAlH_4 in THF, to yield alcohol intermediates of general Formula IX. Intermediates of Formula IX may be further derivatised to access the desired R^3 substituent. For example, the alcohol group in intermediates IX may be difluoromethylated using a suitable reagent such as 2,2-difluoro-2-(fluorosulfonyl) acetic acid under conditions such as CuI activation, in a suitable solvent such as acetonitrile, or; the alcohol group in IX may be alkylated using simple alkyl halides, such as methyl iodide, in the presence of a suitable base such as NaH in a suitable solvent such as THF. Alternatively, the alcohol of intermediates IX may be transformed into a leaving group through activation with a reagent such as mesyl chloride in the presence of a suitable base such as TEA, in a suitable solvent such as DCM. The resulting mesylates can be reacted with a suitable nucleophile, such as potassium cyanide, in a suitable solvent such as DMSO.

The skilled artisan will recognise that other transformations are possible from intermediates of general Formula IX; the present invention is intended to include such alternative transformations.

5

The carboxylic acids of general Formula III can be prepared as outlined in Scheme 5:

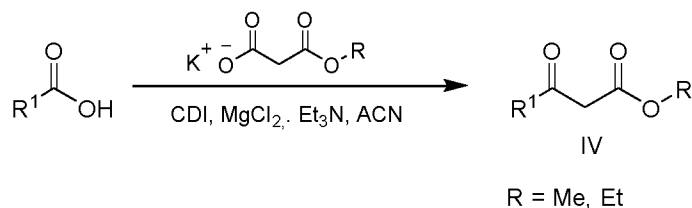
Scheme 5



- 10 Ketones of general Formula X are reacted with an alkyl ester of bromoacetic acid activated with, for example, Zn and iodine, to yield the corresponding aldol adduct. In an alternative procedure, the bromoacetic acid ester can be activated using Zn and TMSCl (trimethylsilyl chloride).
- 15 In a final step, hydrolysis of the alkyl ester is accomplished by treatment with an appropriate base such as NaOH or LiOH in an appropriate solvent, such as water, or an alcohol in water, and followed by acidification with an appropriate acid to yield the
- 20 compounds of Formula III.

Carboxylic acid ester of general Formula IV (R = Me, Et) are commercially available, or may be prepared as outlined in Scheme 6:

25 Scheme 6



Suitably substituted carboxylic acids can be activated using a suitable reagent such as CDI and condensed with potassium 3-ethoxy-3-oxo-propanoate in the presence of
5 MgCl_2 , to yield intermediates of general Formula IV.

^1H NMR spectra were recorded at 400.13 MHz on a Bruker Avance III 400 instrument or at 300.13 MHz on a Bruker Avance 300 instrument. Deuterated dimethyl sulfoxide or
10 deuterated chloroform was used as solvent.

Tetramethylsilane was used as internal reference standard. Chemical shift values are expressed in ppm-values relative to tetramethylsilane. The following abbreviations are used for multiplicity of NMR signals:
15 s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, h = heptet, dd = double doublet, ddd = double double doublet, dt = double triplet, dq = double quartet, tt = triplet of triplets, m = multiplet and
brs = broad singlet.

20

Chromatographic systems and methods to evaluate chemical purity (LCMS methods) and chiral purity (SFC and HPLC methods) are described below.

25 **LCMS Method 1:** Apparatus: Agilent 1200 LCMS system with ELS Detector.

Column	Waters Xbridge-C18, 50×2mm, 5 μm
Flow rate	0.8 mL/min
Run time	4.5 min.
Wavelength	254 nm
Column temp	50 °C

Ion source	ESI		
Solvent A	Water + 0.04% TFA		
Solvent B	MeCN + 0.02% TFA		
Gradient	Time (min)	A%	B%
	0	99	1
	3.4	0	100
	4	0	100
	4.01	99	1
	4.5	99	1

LCMS Method 2: Apparatus: Agilent 1200 LCMS system with ELS Detector

5

Column	Waters XBridge ShieldRP18, 50 x 2.1 mm, 5µm		
Flow rate	0.8 mL/min		
Run time	4.5 min.		
Wavelength	254 nm		
Column temp	40 °C		
Ion source	ESI		
Solvent A	Water + 0.05% NH ₃ .H ₂ O		
Solvent B	MeCN		
Gradient	Time (min)	A%	B%
	0	95	5
	3.4	0	100
	4	0	100
	4.01	95	5
	4.5	95	5

LCMS Method 3: Apparatus Agilent 1200 LCMS system with ELS Detector

Column	Waters Xbridge-C18, 50×2mm, 5μm		
Flow rate	0.8 mL/min		
Run time	4.5 min.		
Wavelength	254 nm		
Column temp	50 °C		
Ion source	ESI		
Solvent A	Water + 0.04% TFA		
Solvent B	MeCN + 0.02% TFA		
Gradient	Time (min)	A%	B%
	0	90	10
	3.4	0	100
	4	0	100
	4.01	90	10
	4.5	90	10

5 LCMS Method 4: Apparatus Shimadzu LC20ADXR LCMS system with ESI Detector

Column	Poroshell HPH-C18, 50×2.7mm, 3μm		
Flow rate	1.2 mL/min		
Run time	3 min.		
Wavelength	190-400 nm		
Column temp	40 °C		
Ion source	ESI		
Solvent A	Water + 0.04% NH ₄ HCO ₃		
Solvent B	MeCN		
Gradient	Time (min)	A%	B%
	0	95	5

	2.2	5	95
	2.8	5	95
	3	95	5

Chiral analytical methods:

5 SFC method 1: Apparatus: Waters UPC2

Column	Chiralpak AD-3 150×4.6mm I.D., 3µm	
Flow rate	2.5 mL/min	
Run time	8 min.	
Wavelength	220 nm	
Column temp	35 °C	
Solvent A	EtOH + 0.05% diethylamine	
Gradient	Time (min)	A%
	0	5
	4.5	40
	7	40
	7.01	5
	8	5

SFC method 2: Apparatus: Agilent 1260

Column	(S,S)Whelk-01 100×4.6mm I.D., 5µm	
Flow rate	2.5 mL/min	
Run time	7 min.	
Wavelength	220 nm	
Column temp	40 °C	
Solvent A	EtOH + 0.05% diethylamine	
Gradient	Time (min)	A%

	0	5
	5.5	40
	5.51	5
	7	5

SFC method 3: Apparatus: Agilent 1260

Column	Chiralpak AS-3 150×4.6mm I.D., 3µm	
Flow rate	2.5 mL/min	
Run time	7 min.	
Wavelength	220 nm	
Column temp	40°C	
Solvent A	EtOH + 0.05% diethylamine	
Gradient	Time	A%
	0	5
	5	40
	5.5	40
	5.51	5
	7	5

5

SFC method 4: Apparatus: Agilent 1260

Column	Chiralpak AD-3 150×4.6mm I.D., 3µm	
Flow rate	2.5 mL/min	
Run time	7 min.	
Wavelength	220 nm	
Column temp	40 °C	
Solvent A	iPrOH + 0.05% diethylamine	
Gradient	Time	A%
	0	5

	5.5	40
	5.51	5
	7	5

SFC Method 5: Apparatus: Agilent 1260

Column	Lux Cellulose-2 150×4.6mm I.D., 3µm	
Flow rate	2.5 mL/min	
Run time	10 min.	
Wavelength	220 nm	
Column temp	40 °C	
Solvent A	MeOH + 0.05% diethylamine	
Gradient	Time	A%
	0	5
	5.5	40
	8.5	40
	8.51	5
	10	5

5

SFC method 6: Apparatus: Agilent 1260

Column	Chiralpak AD-3 150×4.6mm I.D., 3µm	
Flow rate	2.5 mL/min	
Run time	7 min.	
Wavelength	220 nm	
Column temp	35 °C	
Solvent A	EtOH + 0.05% diethylamine	
Gradient	Time (min)	A%
	0	5
	5.5	40

	5.51	5
	7	5

SFC Method 7: Apparatus: Waters UPC2

Column	Chiralpak AS-3 150×4.6mm I.D., 3µm	
Flow rate	2.5 mL/min	
Run time	7 min.	
Wavelength	220 nm	
Column temp	35°C	
Solvent A	EtOH + 0.05% diethylamine	
Gradient	Time (min)	A%
	0	5
	5	40
	5.5	40
	7	5

5 SFC method 8: Apparatus: Waters UPC2

Column	ChiralPak AD-3 150×4.6mm I.D., 3µm	
Flow rate	2.5 mL/min	
Run time	10 min.	
Wavelength	210 nm	
Column temp	35 °C	
Solvent A	EtOH + 0.05% diethylamine	
Gradient	Time	A%
	0	5
	5	40
	7.5	40
	7.51	5
	10	5

SFC method 9: Apparatus: Waters UPC2

Column	Chiralcel OJ-3 150×4.6mm I.D., 3µm	
Flow rate	2.5 mL/min	
Run time	7 min.	
Wavelength	220 nm	
Column temp	35 °C	
Solvent A	MeOH + 0.05% diethylamine	
Gradient	Time	A%
	0	5
	5	40
	5.5	5
	7	5

5 SFC method 10: Apparatus: Agilent 1260

Column	Chiralpak AY-3 150×4.6mm I.D., 3µm	
Flow rate	2.5 mL/min	
Run time	7 min.	
Wavelength	220 nm	
Column temp	40 °C	
Solvent A	EtOH + 0.05% diethylamine	
Gradient	Time	A%
	0	5
	5.5	40
	5.51	5
	7	5

SFC method 11: Apparatus: Agilent 1260

Column	(R,R)Whelk-01 100×4.6mm I.D., 3µm	
Flow rate	2.5 mL/min	
Run time	10 min.	
Wavelength	220 nm	
Column temp	40 °C	
Solvent A	MeOH + 0.05% diethylamine	
Gradient	Time (min)	A%
	0	5
	5.5	40
	8.5	40
	8.51	5
	10	5

SFC method 12: Apparatus: Waters UPC2

Column	(S,S)Whelk-01 100×4.6mm I.D., 3µm	
Flow rate	2.8 mL/min	
Run time	8 min.	
Wavelength	254 nm	
Column temp	35 °C	
Solvent A	iPrOH + 0.05% diethylamine	
Gradient	Time (min)	A%
	0	5
	4	40
	6.5	40
	8.51	5
	8	5

SFC method 13: Apparatus: Waters UPC2

Column	ChiralPak AS-3 150×4.6mm I.D., 3µm	
Flow rate	2.5 mL/min	
Run time	7 min.	
Wavelength	220 nm	
Column temp	35 °C	
Solvent A	iPrOH + 0.05% diethylamine	
Gradient	Time	A%
	0	5
	5	40
	5.5	5
	7	5

SFC method 14: Apparatus: Waters UPC2

Column	ChiralPak IG-3 100×4.6mm I.D., 3µm	
Flow rate	2.8 mL/min	
Run time	8 min.	
Wavelength	220 nm	
Column temp	35 °C	
Solvent A	EtOH + 0.05% diethylamine	
Gradient	Time	A%
	0	5
	4	40
	6.5	40
	6.51	5
	8	5

SFC method 15: Apparatus: Waters UPC2

Column	Cellulose-2 150×4.6mm I.D., 5µm	
Flow rate	2.5 mL/min	
Run time	10 min.	
Wavelength	254 nm	
Column temp	35 °C	
Solvent A	iPrOH + 0.05% diethylamine	
Gradient	Time	A%
	0	5
	5	40
	7.5	40
	7.51	5
	10	5

SFC method 16: Apparatus: Waters UPC2

Column	Cellulose-2 150×4.6mm I.D., 5µm	
Flow rate	2.5 mL/min	
Run time	10 min.	
Wavelength	220 nm	
Column temp	35 °C	
Solvent A	EtOH + 0.05% diethylamine	
Gradient	Time	A%
	0	5
	5	40
	7.5	40
	7.51	5
	10	5

SFC method 17: Apparatus: Waters UPC2

Column	Cellulose-2 150×4.6mm I.D., 5µm	
Flow rate	2.5 mL/min	
Run time	10 min.	
Wavelength	220 nm	
Column temp	35 °C	
Solvent A	MeOH + 0.05% diethylamine	
Gradient	Time	A%
	0	5
	5	40
	7.5	40
	7.51	5
	10	5

SFC Method 18: Apparatus: Agilent

Column	Lux Cellulose-4 100×4.6mm I.D., 3µm	
Flow rate	2 mL/min	
Run time	6.5 min.	
Wavelength	220 nm	
Column temp	35 °C	
Solvent A	EtOH	
Gradient	Time	A%
	0	5
	2	20
	5	20
	6.5	5

SFC Method 19: Apparatus: Agilent

Column	Chiralpak OD-3 150×4.6mm I.D., 3µm	
Flow rate	2.5 mL/min	
Run time	7 min.	
Wavelength	220 nm	
Column temp	40 °C	
Solvent A	EtOH + 0.05% diethylamine	
Gradient	Time	A%
	0	5
	5.5	40
	5.51	5
	7	5

SFC Method 20: Apparatus: Waters UPC2

Column	ChiralPak AD-3 150×4.6mm I.D., 3µm	
Flow rate	2.5 mL/min	
Run time	10 min.	
Wavelength	220 nm	
Column temp	35 °C	
Solvent A	EtOH + 0.05% diethylamine	
Gradient	Time	A%
	0	5
	5	5
	5.5	40
	7.5	40
	7.51	5
	10	5

SFC Method 21: Apparatus: Waters UPC2

Column	Cellulose 2 100×4.6mm I.D., 3µm	
Flow rate	2.8 mL/min	
Run time	8 min.	
Wavelength	220 nm	
Column temp	35 °C	
Solvent A	MeOH + 0.05% diethylamine	
Gradient	Time	A%
	0	5
	4	40
	6.5	40
	6.51	5
	8	5

SFC Method 22: Apparatus: Agilent 1260

Column	Lux Cellulose-2 150×4.6mm I.D., 3µm	
Flow rate	2.5 mL/min	
Run time	7 min.	
Wavelength	220 nm	
Column temp	40 °C	
Solvent A	MeOH + 0.05% diethylamine	
Gradient	Time	A%
	0	5
	5.5	40
	5.51	5
	7	5

Chiral HPLC method 1: Apparatus: SHIMADZU LC-20AB

Column	Chiralpak AS-RH 150*4.6 mm I.D., 5um		
Flow rate	0.8 mL/min		
Run time	25 min.		
Wavelength	220 nm		
Column temp	30 °C		
Solvent A	Water + 0.069% TFA		
Solvent B	MeCN		
Gradient	Time (min)	A%	B%
	0	90	10
	25	20	80

5 Chiral HPLC method 2: Apparatus: SHIMADZU LC-20AB

Column	ChiralCel OD-RH 150×4.6mm I.D., 5um		
Flow rate	0.8 mL/min		
Run time	25 min.		
Wavelength	220 nm		
Column temp	30 °C		
Solvent A	Water + 0.07% TFA		
Solvent B	MeCN		
Gradient	Time	A%	B%
	0	90	10
	14	20	80
	15	90	10
	25	90	10

Chiral HPLC method 3: Apparatus: SHIMADZU LC-20AB

Column	ChiralCel OD-RH 150×4.6mm I.D., 5µm		
Flow rate	0.8 mL/min		
Run time	25 min.		
Wavelength	220 nm		
Column temp	100 °C		
Solvent A	Water + 0.07% TFA		
Solvent B	MeCN		
Gradient	Time	A%	B%
	0	90	10
	14	20	80
	15	90	10
	25	90	10

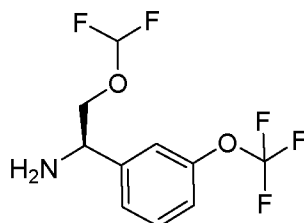
Chiral HPLC method 4: Apparatus: SHIMADZU LC-20AB

Column	ChiralPak AD-RH 150×4.6mm I.D., 5µm		
Flow rate	0.8 mL/min		
Run time	25 min.		
Wavelength	220 nm		
Column temp	30 °C		
Solvent A	Water + 0.07% TFA		
Solvent B	MeCN		
Gradient	Time	A%	B%
	0	90	10
	14	20	80
	15	90	10
	25	90	10

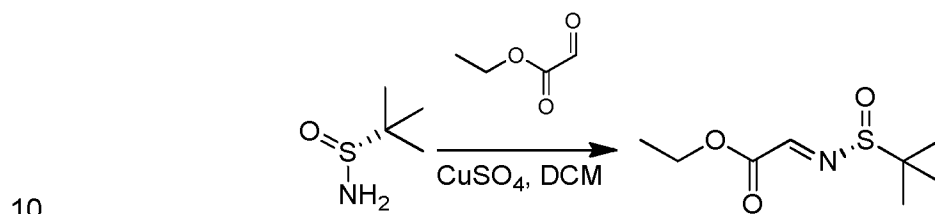
Preparation of intermediates:

I Ib: ((R)-2-(difluoromethoxy)-1-(3-

5 (trifluoromethoxy)phenyl)ethan-1-amine



Step 1: Preparation of ethyl 2-[(R)-tert-butylsulfinyl]imino acetate



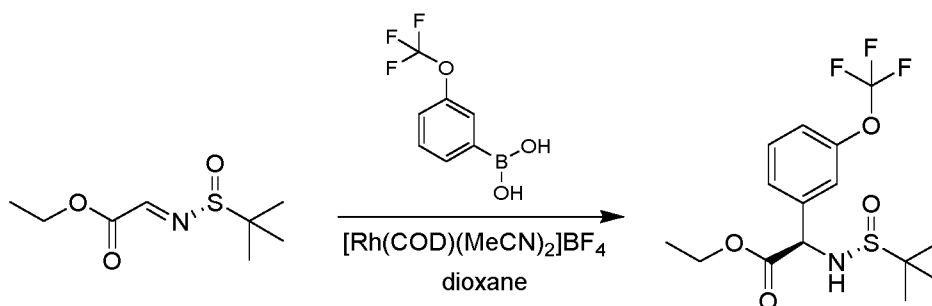
To a solution of ethyl 2-oxoacetate (7.5 g, 36.7 mmol) and (R)-2-methylpropane-2-sulfonamide (4.9 g, 40.4 mmol) in DCM (150 mL) was added CuSO₄ (12.9 g, 80.8 mmol), and the reaction mixture was stirred at 25°C for 24 hours. The solid was filtered off, washed with ethyl acetate (50 mL) and the organic phases were combined and concentrated. The resulting residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate, 5/1) to yield the desired product (5.1 g, 67.6% yield).

15

20

Step 2: Preparation of ethyl (2R)-2-[[(R)-tert-butylsulfinyl] amino]-2-[3-(trifluoromethoxy)phenyl] acetate

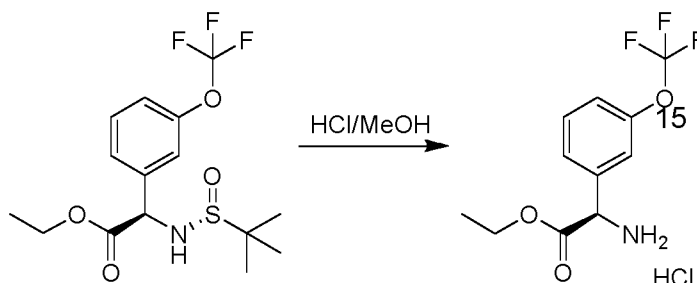
65



To a solution of ethyl-2-[(R)-tert-butylsulfinyl]iminoacetate (7 g, 34.1 mmol) and [3-(trifluoromethoxy)phenyl]boronic acid (8.4 g, 40.9 mmol) in dioxane (100 mL) was added [Rh(COD)(MeCN)₂]BF₄ (1.3 g, 3.4 mmol) and this mixture was stirred at 80°C for 16 hours. The product was purified by silica gel chromatography (petroleum ether: ethyl acetate=5:1) to yield 9.8 g (78%).

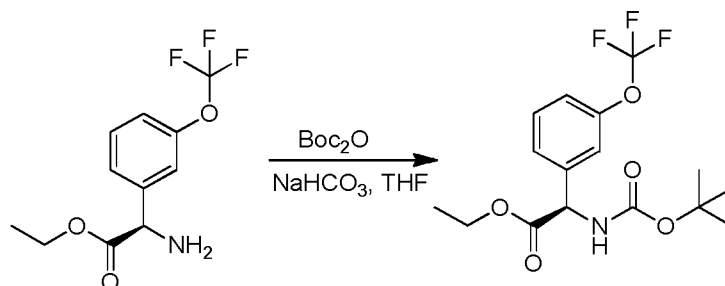
10

Step 3: Preparation of ethyl (2R)-2-amino-2-[3-(trifluoromethoxy)phenyl]acetate hydrochloride



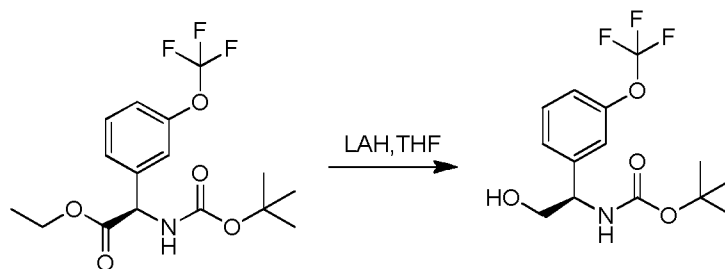
To a solution of ethyl (2R)-2-[[(R)-tert-butylsulfinyl]amino]-2-[3-(trifluoromethoxy)phenyl]acetate (9.8 g, 26.7 mmol) in MeOH (100 mL), was added HCl/MeOH (4 M, 100 mL) and this mixture was stirred at 25°C for 2 hours, and then concentrated to afford ethyl (2R)-2-amino-2-[3-(trifluoromethoxy)phenyl]acetate (7.8 g, crude).

Step 4: Preparation of ethyl (R)-2-((*tert*-butoxycarbonyl)amino)-2-(3-(difluoromethoxy)phenyl)acetate



- 5 To a mixture of ethyl (2R)-2-amino-2-[3-(trifluoromethoxy)phenyl] acetate hydrochloride (6 g) in THF (150 mL), and Boc_2O (8.7 g), NaHCO_3 (1.7 g) was added and stirred at 25°C for 16 hours. The mixture was concentrated and purified by chromatography on
10 silica (petroleum ether:ethyl acetate=10:1) to afford the product (7.2 g).

Step 5: Preparation of *tert*-butyl (R)-(1-(3-(difluoromethoxy)phenyl)-2-hydroxyethyl) carbamate

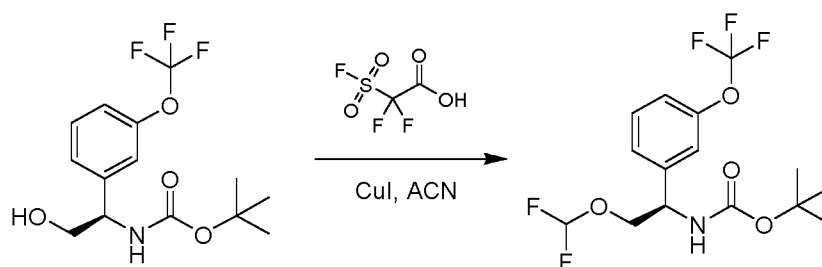


- 15 To a suspension of LiAlH_4 (1.7 g) in THF (200 mL) was added ethyl (R)-2-((*tert*-butoxycarbonyl)amino)-2-(3-(difluoromethoxy)phenyl)acetate (4 g) in THF (25 mL), with ice-cooling. The reaction was allowed to warm to
20 25°C and was stirred for 2 hours. Anhydrous magnesium sulfate was added and then one drop of water and ethyl acetate were successively added. Insoluble substances

were filtered off through a pad of celite. The filtrate was concentrated and purified by chromatography on silica (petroleum ether:ethyl acetate=5:1) (2.1 g).

5

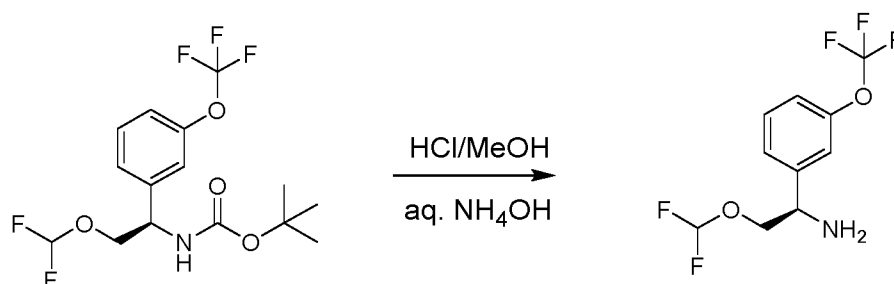
Step 6: Preparation of *tert*-butyl (*R*)-(2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)carbamate



- 10 To a solution of *tert*-butyl (*R*)-(1-(3-(difluoromethoxy)phenyl)-2-hydroxyethyl)carbamate (1.5 g) in MeCN (20 mL), CuI (360 mg) was added and stirred at 25°C under N₂ atmosphere for 30 minutes. A solution of 2,2-difluoro-2-fluorosulfonyl-acetic acid (1.7 g)
- 15 in MeCN (5 mL) was added at 45°C over 30 minutes, and the reaction was stirred at 45°C for 1 hour. The mixture was concentrated and then diluted by ethyl acetate (100 mL), filtered and concentrated to afford the desired product (1.5 g, crude).

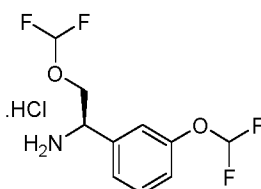
20

Step 7: Preparation of (*R*)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethan-1-amine



To a solution of *tert*-butyl (R)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethan-1-carbamate (1.5 g) in MeOH (15 mL), was added HCl/MeOH (4M in MeOH, 30 mL) at 25°C, and the reaction was stirred at 25°C for 30 minutes. Ammonium hydroxide (30%) was added to pH=9, the solution was concentrated and purified by chromatography on silica (petroleum ether: ethyl acetate = 2:1) to afford (R)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethan-1-amine (700 mg).

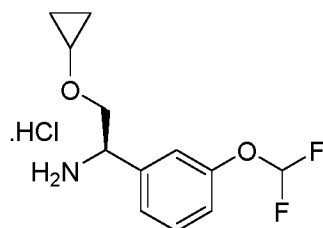
IIa: (R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethan-1-amine hydrochloride



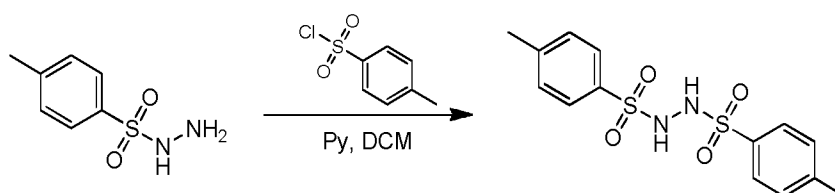
Prepared as described for **IIb** using appropriate reagents

IIc: (R)-2-cyclopropoxy-1-(3-(difluoromethoxy)phenyl)ethan-1-amine hydrochloride

69



Step 1: Preparation of 4-methyl-N'-(p-tolylsulfonyl)benzene sulfonohydrazide

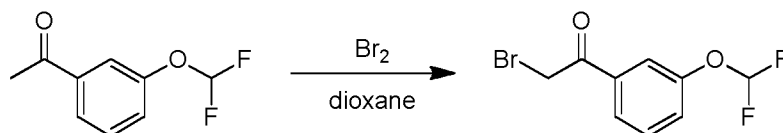


5

To a mixture of 4-methylbenzenesulfonohydrazide (70 g) and 4-methylbenzenesulfonyl chloride (93 g) was added DCM (400 mL). The mixture was cooled to 0°C and pyridine (38.65 g) was added dropwise, and the reaction mixture was stirred at 0°C for 1 hour and 20°C for 7 hours. The mixture was added water (200 mL) and methyl-tert-butyl ether (METB) (200 mL) and filtered. The filter cake was washed with METB (200 mL) and dried to give 4-methyl-N'-(p-tolylsulfonyl)benzenesulfonohydrazide (125 g).

¹H NMR (DMSO-d₆ 400MHz): δ 9.55 (s, 2H), 7.61 (d, 4H), 7.35 (d, 4H), 2.36 (s, 6H).

Step 2: Preparation of 2-bromo-1-(3-(difluoromethoxy)phenyl)ethan-1-one

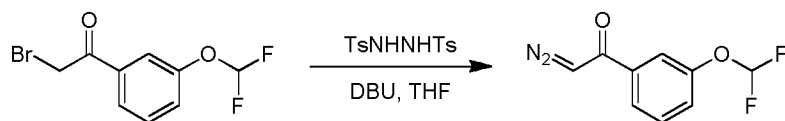


20

To a solution of 1-[3-(difluoromethoxy)phenyl]ethanone (10 g) in dioxane (100 mL) was added a solution of Br₂ (8.58 g) in dioxane (100 mL). The resulting mixture was stirred at 20°C for 2 hours. Sat.aq.NaHCO₃ solution (50 mL) and H₂O (100 mL) was added, and the aqueous phase was extracted with EtOAc (200 mL×2). The organic phase was washed with brine (200 mL), dried over Na₂SO₄ and concentrated to give 2-bromo-1-[3-(difluoromethoxy)phenyl]ethanone (17 g).

¹H NMR (CDCl₃ 400MHz): δ 7.81 (d, 1H), 7.72 (s, 1H), 7.49 (t, 1H), 7.37 (d, 1H), 6.56 (t, 1H), 4.41 (s, 2H).

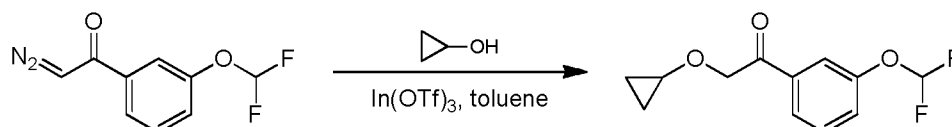
Step 3: Preparation of 1-(3-(difluoromethoxy)phenyl)-2-iminoethan-1-one



To a solution of 2-bromo-1-[3-(difluoromethoxy)phenyl]ethanone (5.6 g) and 4-methyl-N'-(p-tolylsulfonyl)benzenesulfonylhydrazide (11.51 g) in THF (100 mL). DBU (12.87 g) Was added dropwise at 0°C. The reaction mixture was stirred at 0°C for 1 hour and 20°C for 4 hours. The mixture was quenched by sat. aq. NaHCO₃ (200 mL) and diluted with water (200 mL), then extracted with EtOAc (200 mL×2). The organic layer was washed with brine (100 mL), dried over Na₂SO₄ and concentrated. The crude was purified by column chromatograph on silica gel (20% EtOAc in Petroleum ether) to give 1-(3-(difluoromethoxy)phenyl)-2-iminoethan-1-one (6.4 g).

¹H NMR (CDCl₃, 400MHz): δ 7.57 (dt, 1H), 7.55 (s, 1H), 7.46 (t, 1H), 7.31 (dd, 1H), 6.56 (t, 1H), 5.90 (s, 1H).

5 Step 4: Preparation of 2-cyclopropoxy-1-(3-(difluoromethoxy)phenyl)ethan-1-one



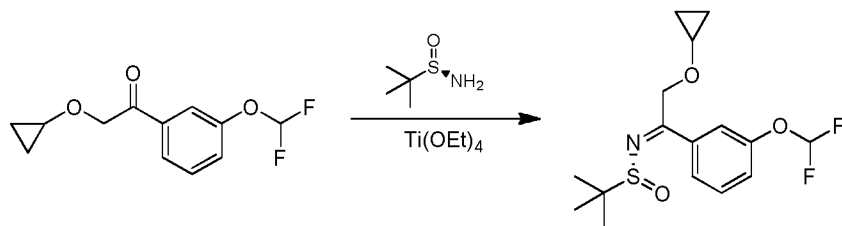
10 To a solution of cyclopropanol (1.75 g) and 2-diazo-1-[3-(difluoromethoxy) phenyl]ethanone (3.2 g) in toluene (50 mL) was added indium(III) triflate (1.7 g) under N₂. The resulting mixture was stirred at 20°C for 16 hours. The mixture was quenched by sat.aq.NaHCO₃ (100 mL) and
 15 diluted with H₂O (50 mL), and then extracted with EtOAc (100 mL×2). The organic layer was washed with brine (200 mL×2), dried over Na₂SO₄ and concentrated. The crude was purified by column chromatograph on silica gel (5% EtOAc in Petroleum ether) to give 2-cyclopropoxy-1-(3-(difluoromethoxy)phenyl)ethan-1-one (6.1 g).

20 ¹H NMR (CDCl₃, 400MHz): δ 7.76 (d, 1H), 7.68 (s, 1H), 7.47 (t, 1H), 7.34 (d, 1H), 6.55 (t, 1H), 4.74 (s, 1H), 3.55-3.50 (m, 1H), 0.70-0.66 (m, 2H), 0.53-0.49 (m, 2H).

25

Step 5: Preparation of (R,Z)-N-(2-cyclopropoxy-1-(3-(difluoromethoxy)phenyl)ethylidene)-2-methylpropane-2-

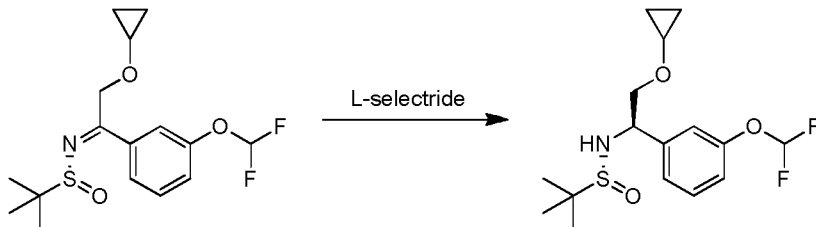
sulfinamide



To a solution of 2-(cyclopropoxy)-1-[3-(
 5 (difluoromethoxy)phenyl]ethanone (6.1 g) and (R)-2-methylpropane-2-sulfinamide (4.6 g) in THF (100 mL) was added $\text{Ti}(\text{OEt})_4$ (11.5 g). The resulting mixture was stirred at 60°C for 8 hours and then used directly in the next step.

10

Step 6: Preparation of (R)-N-((R)-2-cyclopropoxy-1-(3-(difluoromethoxy)phenyl)ethyl)-2-methylpropane-2-sulfinamide

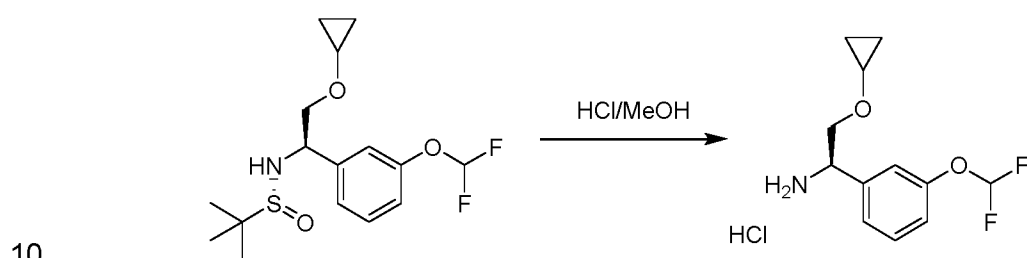


15

To the solution of (R,Z)-N-(2-cyclopropoxy-1-(3-(difluoromethoxy)phenyl)ethylidene)-2-methylpropane-2-sulfinamide in THF (150 mL) from the previous step, was added a solution of L-selectride (1 M in THF, 50.36 mL)
 20 dropwise at -45°C. The mixture was stirred at -45°C for 1 hour, and was quenched by MeOH (100 mL) and H_2O (100 mL), and filtered on celite. The filtrate was extracted with EtOAc (200 mL×2), the organic layer was washed with brine (200 mL×2), dried over Na_2SO_4 and

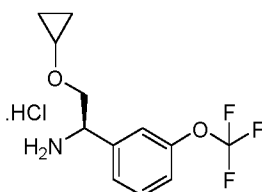
concentrated. The crude was purified by column chromatograph on silica gel (30~50% EtOAc in Petroleum ether) to give (R)-N-((R)-2-cyclopropoxy-1-(3-(difluoromethoxy)phenyl)ethyl)-2-methylpropane-2-sulfinamide (2.4 g).

Step 7: Preparation of (R)-2-cyclopropoxy-1-(3-(difluoromethoxy)phenyl)ethan-1-amine hydrochloride



To a solution of (R)-N-((R)-2-cyclopropoxy-1-(3-(difluoromethoxy)phenyl)ethyl)-2-methylpropane-2-sulfinamide (0.46 g) in MeOH (10 mL) was added HCl/MeOH (10 mL). The resulting mixture was stirred at 20°C for 1 hour and concentrated to give (1R)-2-(cyclopropoxy)-1-[3-(difluoromethoxy)phenyl]ethanamine hydrochloride (0.46 g, crude)

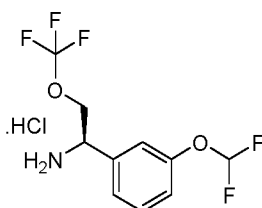
20 **IIId: (R)-2-cyclopropoxy-1-(3-(trifluoromethoxy)phenyl)ethan-1-amine hydrochloride**



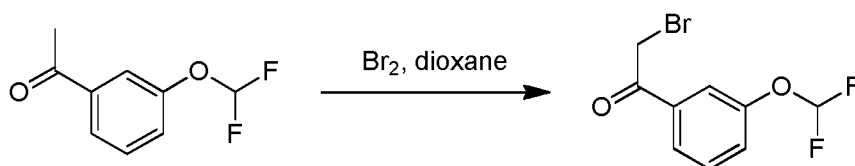
Prepared as described for IIc using 1-[3-(trifluoromethoxy)phenyl] ethanone as starting material.

5

IIe: (R)-1-(3-(difluoromethoxy)phenyl)-2-(trifluoromethoxy)ethan-1-amine hydrochloride



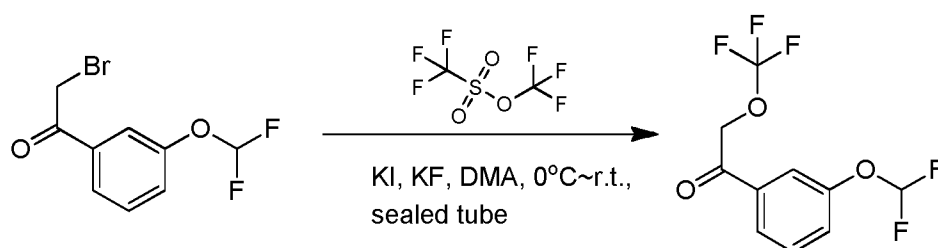
10 Step 1: Preparation of 2-bromo-1-[3-(difluoromethoxy)phenyl]ethanone



15 To a solution of 1-[3-(difluoromethoxy)phenyl]ethanone (5 g) in dioxane (50 mL) was added a solution of Br₂ (4.29 g) in dioxane (50 mL) at 20°C. This mixture was stirred at 20°C for 1 hour, then diluted by EtOAc (200 mL) and washed by water (100 mL×3). The organic phase

20 was dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by column of chromatography on silica gel (Petroleum ether: EtOAc = 10:1) to afford 2-bromo-1-[3-(difluoromethoxy)phenyl]ethanone (5 g).

Step 2: Preparation of 1-(3-(difluoromethoxy)phenyl)-2-(trifluoromethoxy)ethan-1-one

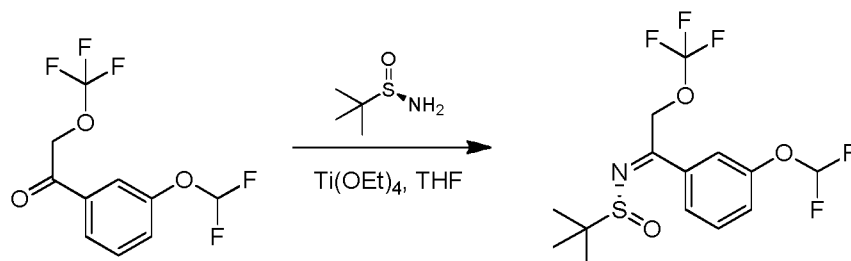


- 5 To a solution of KF (712 mg) in DMA (20 mL) was added trifluoromethyl trifluoromethanesulfonate (4.11 g) at 0°C. The reaction mixture was stirred in a sealed tube for 1 hour, then 2-bromo-1-[3-(difluoromethoxy)phenyl]ethanone (2.5 g, 9.43 mmol) and
- 10 KI (157 mg) were added to this solution at 0°C and was taken to 20°C and stirred for 16 hours. The mixture was diluted with EtAOc (100 mL) and washed with water (50 mL×3). The organic phase was concentrated to yield the product, which was purified by acidic preparative HPLC
- 15 (1.4 g).

¹H NMR (CDCl₃ 400 MHz): δ 7.72 (d, 1H), 7.66 (s, 1H), 7.51 (t, 1H), 7.40 (d, 1H), 6.56 (t, 1H), 5.13 (s, 2H).
¹⁹F NMR (CDCl₃ 400 MHz): δ -61.11, -81.52, -81.71.

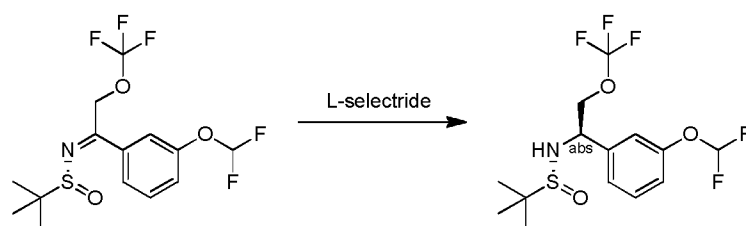
- 20 Step 3: Preparation of (R)-N-(1-(3-(difluoromethoxy)phenyl)-2-(trifluoromethoxy)ethylidene)-2-methylpropane-2-

sulfinamide



A mixture of 1-(3-(difluoromethoxy)phenyl)-2-(trifluoromethoxy)ethan-1-one (900 mg), (R)-2-methylpropane-2-sulfinamide (606 mg) and Ti(OEt)₄ (2.28 g) in THF (50 mL) was stirred at 60°C under N₂ for 16 hours. The product (1.2 g, crude) in THF (70 mL) was obtained and used directly in the next step.

Step 4: Preparation of (R)-N-((R)-1-(3-(difluoromethoxy)phenyl)-2-(trifluoromethoxy)ethyl)-2-methylpropane-2-sulfinamide

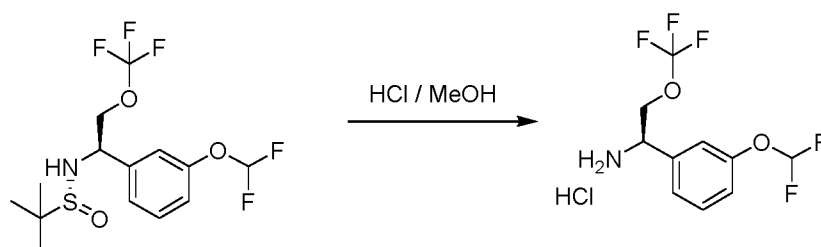


To a solution of (R)-N-((R)-1-(3-(difluoromethoxy)phenyl)-2-(trifluoromethoxy)ethylidene)-2-methylpropane-2-sulfinamide (1.2 g) in THF (70 mL) was added L-selectride (1 M in THF, 3.86 mL) at -60°C. The mixture was stirred at -60°C for 0.5 hour and then diluted with EtOAc (100 mL) and washed with water (50 mL×3). The organic phase was dried, filtered and concentrated. The crude product was purified by chromatography on silica gel (Petroleum ether/Ethyl acetate = 5:1) to afford (R)-N-((R)-1-(3-(difluoromethoxy)phenyl)-2-

(trifluoromethoxy)ethyl)-2-methylpropane-2-sulfinamide
(600 mg).

¹H NMR (CDCl₃ 400 MHz): δ 7.37 (t, 1H), 7.20 (d, 1H),
7.12-7.09 (m, 2H), 6.50 (t, 1H), 4.75-4.72 (m, 1H),
5 4.20-4.16 (m, 1H), 4.14-4.05 (m, 1H), 3.87 (s, 1H),
1.21 (s, 9H).

Step 5: Preparation of (R)-1-(3-
(difluoromethoxy)phenyl)-2-(trifluoromethoxy)ethan-1-
10 amine hydrochloride

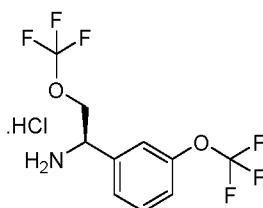


To a solution of (R)-N-((R)-1-(3-
(difluoromethoxy)phenyl)-2-(trifluoromethoxy)ethyl)-2-
15 methylpropane-2-sulfinamide (600 mg) in MeOH (10 mL)
was added HCl/MeOH (4 M in MeOH, 8.0 mL). This mixture
was stirred at 15°C for 1 hour, and then concentrated
to afford ((R)-1-(3-(difluoromethoxy)phenyl)-2-
(trifluoromethoxy)ethan-1-amine hydrochloride

20 (500 mg, crude).

¹H NMR (CDCl₃ 400 MHz): δ 9.17 (s, 3H), 7.40-7.31 (m,
4H), 6.55 (t, 1H), 4.58 (s, 1H), 4.46-4.42 (m, 1H),
4.33-4.29 (m, 1H).

IIf: (R)-2-(trifluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethan-1-amine hydrochloride

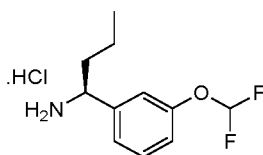


5 Prepared as described for IIe using 1-[3-(trifluoromethoxy)phenyl]ethanone as starting material.

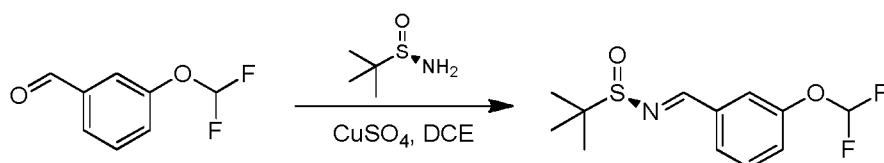
¹H NMR (CDCl₃, 400 MHz): δ 9.18 (s, 3H), 7.19-7.47 (m, 1H), 7.19-7.38 (m, 2H), 7.27 (s, 1H), 4.65 (s, 1H), 4.47-4.42 (m, 1H), 4.32-4.30 (m, 1H).

10

IIg: (S)-1-(3-(difluoromethoxy)phenyl)butan-1-amine hydrochloride



15 Step 1: Preparation of (R)-N-(3-(difluoromethoxy)benzylidene)-2-methylpropane-2-sulfinamide

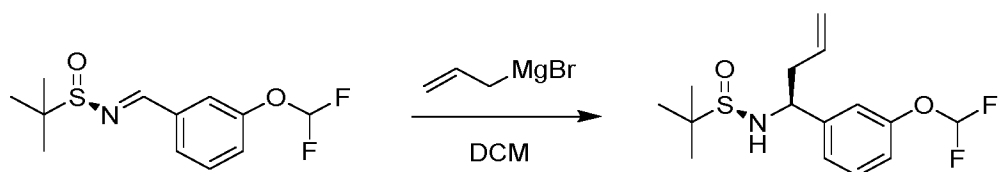


20 To a solution of 3-(difluoromethoxy)benzaldehyde (3 g) and (R)-2-methylpropane-2-sulfinamide (2.54 g) in DCE (120 mL) was added CuSO₄ (13.91 g). The mixture was stirred at 55°C for 16 hours. The reaction mixture was filtered, and the filtrate was concentrated. The residue was purified by column chromatography (SiO₂,

Petroleum ether/Ethyl acetate = 100/1 to 10:1) to afford the product (3 g).

Step 2: Preparation of (R)-N-((S)-1-(3-

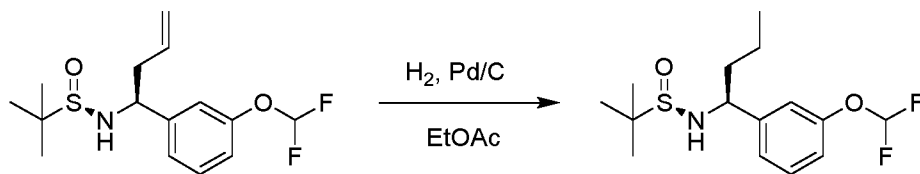
5 (difluoromethoxy)phenyl)but-3-en-1-yl)-2-methylpropane-2-sulfinamide



To a solution of (R)-N-(3-(difluoromethoxy)benzylidene)-2-methylpropane-2-sulfinamide (1 g) in DCM (40 mL) was slowly added allyl(bromo)magnesium (1M solution in THF, 10.9 mL) in THF at 0°C. The resulting mixture was stirred at 0°C for 1 hour and 25°C for 2 hours. The reaction mixture was quenched by addition saturated NH₄Cl (10 mL) at 0°C, then diluted with H₂O (50 mL) and extracted with DCM (40 mL×3). The combined organic phases were washed with H₂O (40 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 100/1 to 1:2) to afford (R)-N-((S)-1-(3-(difluoromethoxy)phenyl)but-3-en-1-yl)-2-methylpropane-2-sulfinamide (580 mg).

¹H NMR (CDCl₃, 400 MHz): δ 7.31 (t, 1H), 7.15 (d, 1H), 7.08 (s, 1H), 7.01 (d, 1H), 6.48 (t, 1H), 5.73-5.66 (m, 1H), 5.19-5.15 (m, 2H), 4.46 (t, 1H), 3.65 (s, 1H), 2.59-2.54 (m, 1H), 2.46-2.38 (m, 1H), 1.19 (s, 9H).

Step 3: Preparation of (*R*)-*N*-((*S*)-1-(3-(difluoromethoxy)phenyl)butyl)-2-methylpropane-2-sulfinamide

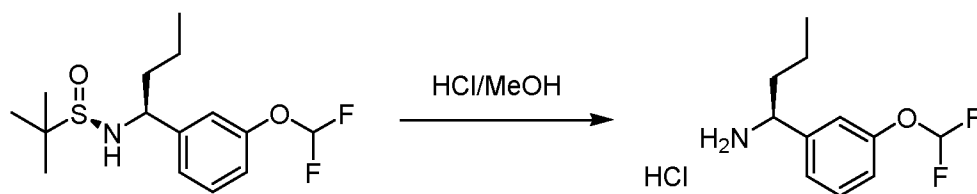


5

To a solution of (*R*)-*N*-((*S*)-1-(3-(difluoromethoxy)phenyl)but-3-en-1-yl)-2-methylpropane-2-sulfinamide (580 mg) in EtOAc (20 mL) was added Pd/C (0.4 g, 10% purity) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (18psi) at 25°C for 0.5 hour. The reaction mixture was filtered and concentrated to afford (*R*)-*N*-((*S*)-1-(3-(difluoromethoxy)phenyl)butyl)-2-methylpropane-2-sulfinamide (560 mg).

10

Step 4: Preparation of (*S*)-1-(3-(difluoromethoxy)phenyl)butan-1-amine hydrochloride

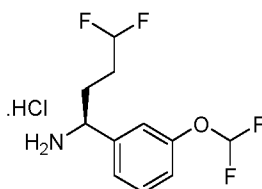


20

To a solution of (*R*)-*N*-((*S*)-1-(3-(difluoromethoxy)phenyl)butyl)-2-methylpropane-2-sulfinamide (580 mg) in MeOH (8 mL) was added HCl/MeOH (4 M, 3.1 mL). The mixture was stirred at 25°C for 3 hours and then concentrated to afford (1*S*)-1-[3-(difluoromethoxy)phenyl] butan-1-amine hydrochloride (250 mg).

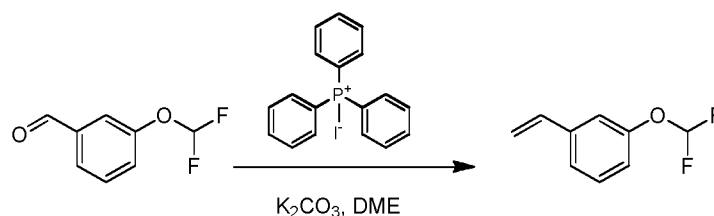
25

IIh: (S)-1-(3-(difluoromethoxy)phenyl)-4,4-difluorobutan-1-amine hydrochloride



5

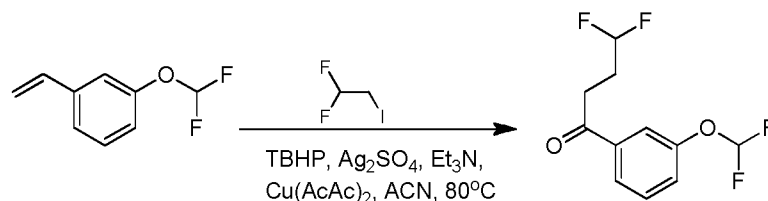
Step 1: Preparation of 1-(difluoromethoxy)-3-vinyl-benzen



- 10 To a solution of methyl triphenylphosphonium iodide (7.05 g) in DME (50 mL) was added K_2CO_3 (2.41 g). The resulting mixture was stirred at 20°C for 1 hour, then 3-(difluoromethoxy)benzaldehyde (1.5 g) was added and stirred continued at 80°C for 15 hours. The mixture was
- 15 filtered, and filtercake was washed with petroleum ether (100 mL). The filtrate was concentrated and purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate = 1/0 to 10/1) to afford 1-(difluoromethoxy)-3-vinylbenzene (1.4 g)
- 20 1H NMR ($CDCl_3$, 400MHz): δ 7.32 (t, 1H), 7.25 (d, 1H), 7.16 (s, 1H), 7.01 (d, 1H), 6.70 (t, 1H), 6.52 (t, 1H), 5.77 (d, 1H), 5.32 (d, 1H).

Step 2: Preparation of 1-(3-(difluoromethoxy)phenyl)-4,4-difluorobutan-1-one

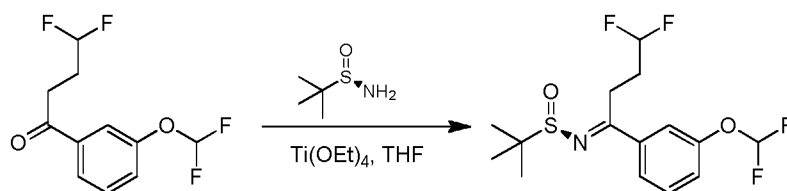
25



To a solution 1,1-difluoro-2-iodo-ethane (1 g), 1-(difluoromethoxy)-3-vinyl- benzene (1.33 g), bis[(Z)-1-methyl-3-oxo-but-1-en-1-yl]copper (273 mg) and Ag₂SO₄ (325 mg) in ACN (20 mL) was added Et₃N (527 mg) and *tert*-butyl hydroperoxide (TBHP) (2.01 g, 70% in water). The resulting mixture was stirred at 80°C for 24 hours. The reaction was quenched with saturated aq. Na₂S₂O₃ and extracted with DCM (10 mL×3). The organic phases were combined, washed with brine (5 mL×2), dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 1/0 to 5/1) to afford 1-(3-(difluoromethoxy)phenyl)-4,4-difluorobutan-1-one (300 mg).

¹H NMR (CDCl₃, 400MHz): δ 7.82 (d, 1H), 7.73 (s, 1H), 7.50 (t, 1H), 7.36 (d, 1H), 6.57 (t, 1H), 6.02 (tt, 1H), 3.18 (t, 2H), 2.35-2.27 (m, 2H).

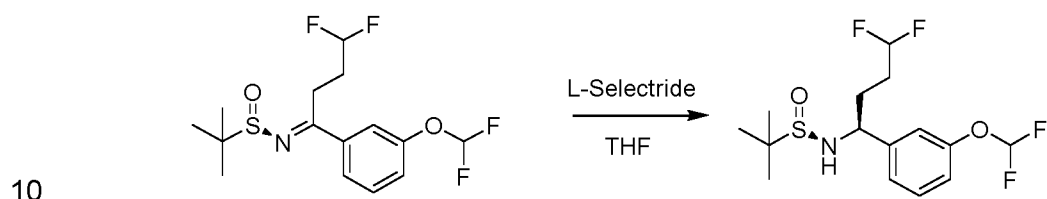
Step 3: Preparation of (*S,E*)-*N*-(1-(3-(difluoromethoxy)phenyl)-4,4-difluorobutylidene)-2-methylpropane-2-sulfinamide



To a solution of 1-(3-(difluoromethoxy)phenyl)-4,4-

5 difluorobutan-1-one (300 mg) and (R)-2-methylpropane-2-sulfinamide (218 mg) in THF (10 mL) was added $\text{Ti}(\text{OEt})_4$ (547 mg). The mixture was stirred at 60°C for 6 hours. The reaction mixture was used directly in the next step.

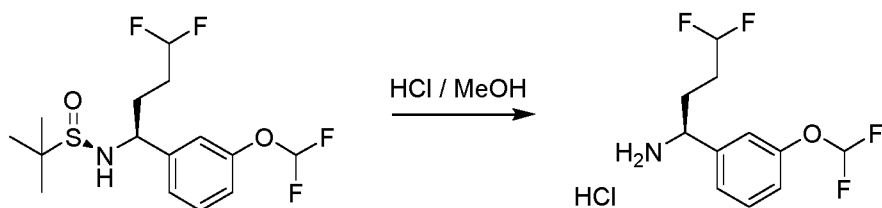
Step 4: Preparation of *N*-[(1*S*)-1-[3-(difluoromethoxy)phenyl]-4,4-difluoro-butyl]-2-methylpropane-2-sulfinamide



L-selectride (1 M in THF, 3.59 mL) was added to a solution of (*S*)-*N*-(1-(3-(difluoromethoxy)phenyl)-4,4-difluorobutylidene)-2-methylpropane-2-sulfinamide (423 mg) in THF at -48°C. The reaction mixture was stirred for 0.5 hour, then it was taken to 0°C and H_2O (~10 mL) was added. The resulting mixture was extracted with EtOAc (35 mL×2). The organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate = 1/0 to 1/1) to afford *N*-[(1*S*)-1-[3-(difluoromethoxy)phenyl]-4,4-difluoro-butyl]-2-methylpropane-2-sulfinamide (140 mg)

25 Step 5: (*S*)-1-(3-(difluoromethoxy)phenyl)-4,4-difluorobutan-1-amine hydrochloride

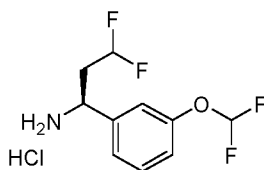
84



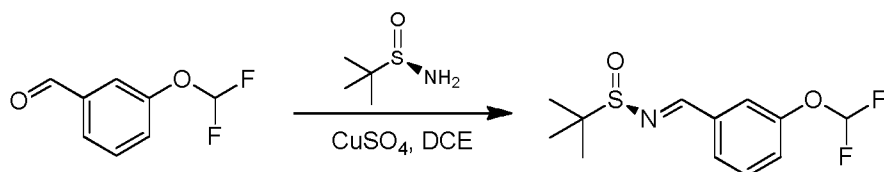
N-[(1S)-1-[3-(difluoromethoxy)phenyl]-4,4-difluorobutyl]-2-methylpropane-2-sulfinamide (140 mg) in MeOH (10 mL) and HCl/MeOH (5 mL, 4M) was stirred at 20°C for 1 hour. The mixture was concentrated to afford (S)-1-(3-(difluoromethoxy)phenyl)-4,4-difluorobutan-1-amine hydrochloride (110 mg)

10

Iii: (S)-1-(3-(difluoromethoxy)phenyl)-3,3-difluoropropan-1-amine hydrochloride



15 Step 1: Preparation of (S,E)-N-(3-(difluoromethoxy)benzylidene)-2-methylpropane-2-sulfinamide



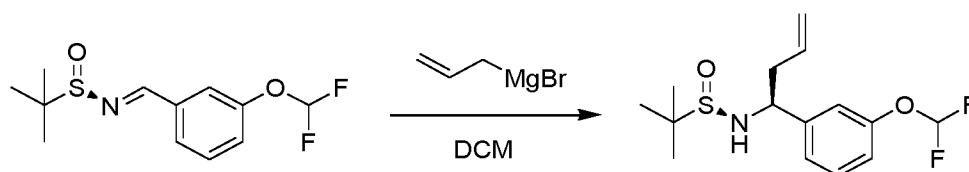
To a solution of 3-(difluoromethoxy)benzaldehyde (5 g) and (R)-2-methylpropane-2-sulfinamide (4.22 g) in DCE (150 mL) was added CuSO₄ (23 g). The reaction mixture was stirred at 55°C for 20 hours, and then filtered and concentrated. The crude product was purified by

chromatography on silica (SiO₂, Petroleum ether/Ethyl acetate = 10/1 to 5/1) to afford (*S,E*)-*N*-(3-(difluoromethoxy)benzylidene)-2-methylpropane-2-sulfinamide (6.9 g).

- 5 ¹H NMR (CDCl₃ 400 MHz): δ 8.55 (s, 1H), 7.65 (d, 1H), 7.62 (s, 1H), 7.47 (t, 1H), 7.25 (d, 1H), 6.55 (t, 1H), 1.25 (s, 9H).

Step 2: Preparation of (*S*)-*N*-((*S*)-1-(3-

- 10 (difluoromethoxy)phenyl)but-3-en-1-yl)-2-methylpropane-2-sulfinamide



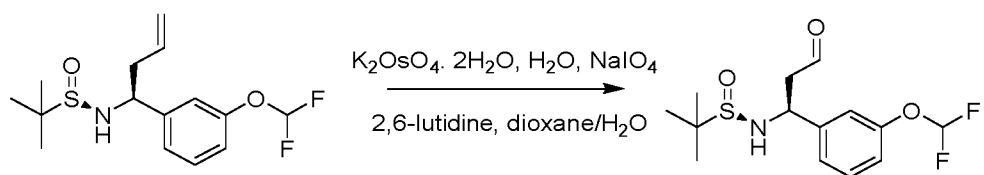
To a solution of (*S,E*)-*N*-(3-

- 15 (difluoromethoxy)benzylidene)-2-methylpropane-2-sulfinamide (2 g) in DCM (60 mL) was slowly added allyl(bromo)magnesium (1 M solution in THF, 21.79 mL) at 0°C. The reaction mixture was stirred at 0°C for 1 hour and 25°C for 2 hours. The reaction was quenched by
- 20 addition of sat.aq.NH₄Cl (10 mL) at 0°C, and then diluted with H₂O (50 mL) and extracted with DCM (40 mL×3). The combined organic phases were washed with H₂O (40 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by chromatography (SiO₂,
- 25 Petroleum ether/Ethyl acetate = 100/1 to 1/2) to afford (*S*)-*N*-((*S*)-1-(3-(difluoromethoxy)phenyl)but-3-en-1-yl)-2-methylpropane-2-sulfinamide (2.3 g).

¹H NMR (CDCl₃ 400 MHz): δ 7.31 (t, 1H), 7.15 (d, 1H), 7.08 (s, 1H), 7.01 (d, 1H), 6.49 (t, 1H), 5.71-5.65 (m,

1H), 5.19–5.15 (m, 2H), 4.48–4.44 (m, 1H), 3.66 (s, 1H), 2.59–2.54 (m, 1H), 2.46–2.40 (m, 1H), 1.18 (s, 9H).

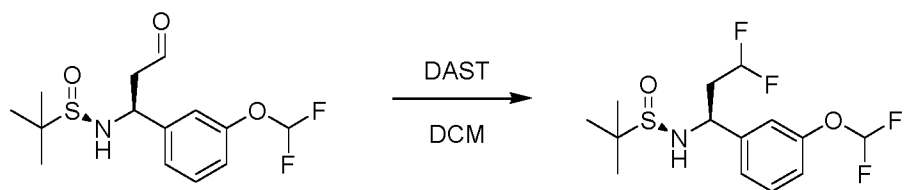
- 5 Step 3: Preparation of (S)-N-((S)-1-(3-(difluoromethoxy)phenyl)-3-oxopropyl)-2-methylpropane-2-sulfinamide



10

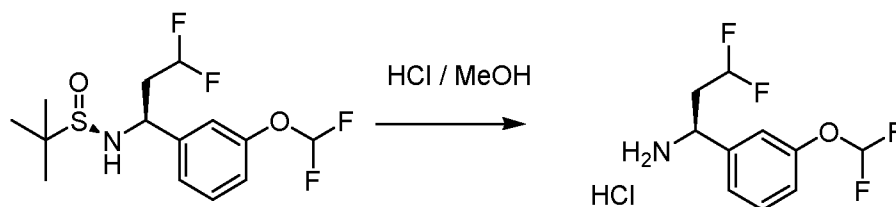
Potassium dioxido(dioxo)osmium hydrate (276 mg) was added in one portion to a stirred solution of (S)-N-((S)-1-(3-(difluoromethoxy)phenyl)but-3-en-1-yl)-2-methylpropane-2-sulfinamide (2.5 g), 2,6-lutidine (1.69 g) and sodium periodate (5.05 g) in a mixture of dioxane (10 mL) and H₂O (3 mL). The reaction mixture was stirred at 20°C for 1 hour and then diluted with DCM (100 mL) and water (20 mL). The aqueous layer was extracted with DCM (25 mL×2). The combined organic extracts were dried over Na₂SO₄. The crude reaction mixture was used directly in the next step.

- 25 Step 4: Preparation of (S)-N-((S)-1-(3-(difluoromethoxy)phenyl)-3,3-difluoropropyl)-2-methylpropane-2-sulfinamide



To a solution of (*S*)-*N*-((*S*)-1-(3-(difluoromethoxy)phenyl)-3-oxopropyl)-2-methylpropane-2-sulfinamide (2 g) in DCM (200 mL) was added dropwise diethylaminosulfur trifluoride (DAST) (3.03 g) at -78°C. The reaction mixture was allowed to come to 20°C and was stirred for 2 hours. The solution was poured into saturated aqueous NaHCO₃ (50 mL) and the organic phase was separated. This solution was dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 5/1 to 1/1) to afford (*S*)-*N*-((*S*)-1-(3-(difluoromethoxy)phenyl)-3,3-difluoropropyl)-2-methylpropane-2-sulfinamide (500 mg).

Step 5: Preparation of (1*S*)-1-[3-(difluoromethoxy)phenyl]-3,3-difluoro-propan-1-amine hydrochloride

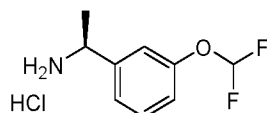


To a solution of (*S*)-*N*-((*S*)-1-(3-(difluoromethoxy)phenyl)-3,3-difluoropropyl)-2-methylpropane-2-sulfinamide (380 mg) in MeOH (15 mL) was added HCl/MeOH (25 mL, 4 M) at 0°C and the reaction was stirred for 0.5 hour, and was allowed to come to 25°C. The reaction mixture was concentrated to afford (1*S*)-1-[3-(difluoromethoxy)phenyl]-3,3-difluoro-propan-1-amine hydrochloride (300 mg, crude, HCl

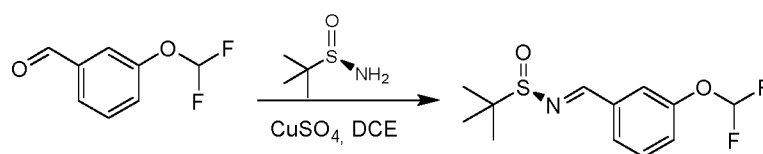
salt). Used directly without further purification.

IIj: (*S*)-1-(3-(difluoromethoxy)phenyl)ethan-1-amine

5 hydrochloride



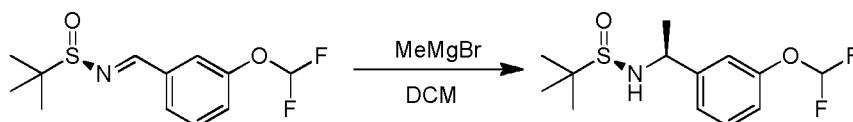
Step 1: Preparation of ((*S,E*)-*N*-(3-(difluoro-
methoxy)benzylidene)-2-methylpropane-2-sulfinamide



10

To a mixture of 3-(difluoromethoxy)benzaldehyde (2 g) and (*R*)-2-methylpropane-2-sulfinamide (1.7 g) in DCE (60 mL) was added CuSO₄ (9.3 g) at 55°C under N₂. The
15 reaction mixture was stirred at 55°C for 12 hours, filtered and the filtrate was concentrated. The crude product was purified by chromatography on silica gel column (Petroleum ether/Ethyl acetate = 20:1-10:1) to give ((*S,E*)-*N*-(3-(difluoro-methoxy)benzylidene)-2-
20 methylpropane-2-sulfinamide (4.5 g).

Step 2: Preparation of (*S*)-*N*-((*S*)-1-(3-(difluoromethoxy)phenyl)ethyl)-2-methylpropane-2-sulfinamide

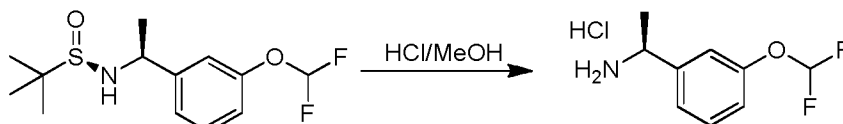


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To a solution of ((*S,E*)-*N*-(3-(difluoro-methoxy)benzylidene)-2-methylpropane-2-sulfinamide (2 g) in DCM (30 mL) was added bromo(methyl)magnesium (3M in Et₂O, 4.8 mL) dropwise at 0°C. The resulting mixture
5 was stirred at 0°C for 1 hour and 20°C for 16 hours. The reaction was quenched by aq. sat. NH₄Cl (10 mL), and the aqueous phase was extracted with ethyl acetate (30 mL×3). The combined organic extracts were washed with brine (40 mL×2), dried with anhydrous Na₂SO₄,
10 filtered, concentrated and purified by chromatography on silica gel (Petroleum ether/Ethyl acetate = 5:1-1:1) to afford (*S*)-*N*-((*S*)-1-(3-(difluoromethoxy)phenyl)ethyl)-2-methylpropane-2-sulfinamide (960 mg).

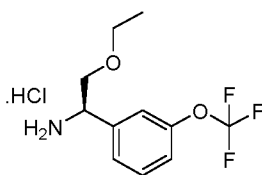
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Step 3: Preparation of (*S*)-1-(3-(difluoromethoxy)phenyl)ethan-1-amine hydrochloride

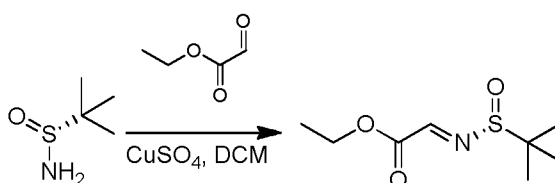


20 To a solution of (*S*)-*N*-((*S*)-1-(3-(difluoromethoxy)phenyl)ethyl)-2-methylpropane-2-sulfinamide (0.8 g) in MeOH (4 mL) was added HCl/MeOH (4 M, 2 mL). The resulting mixture was stirred at 25 °C for 3 hours, and concentrated to afford (*S*)-1-(3-(difluoromethoxy)phenyl)ethan-1-amine hydrochloride
25 (1.6 g, crude).

IIk: (R)-2-ethoxy-1-(3-(trifluoromethoxy)phenyl)ethan-1-amine hydrochloride



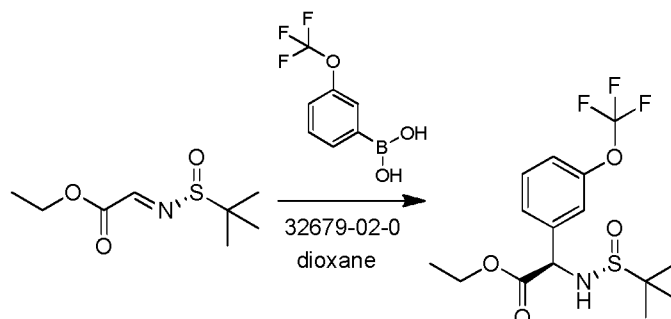
5 Step 1: Preparation of ethyl (R,E)-2-((tert-butylsulfinyl)imino)acetate



10 To a solution of ethyl 2-oxoacetate (7.5 g) and (R)-2-methylpropane-2-sulfinamide (4.90 g) in DCM (150 mL) under N₂ was added CuSO₄ (12.9 g) and the reaction mixture was stirred at 25°C for 24 hours. The solid was filtered off, washed with ethyl acetate (50 mL) and the organic layer was concentrated. The residue was

15 purified by chromatography (SiO₂, hexane/ethyl acetate, 5/1) to yield ethyl (R,E)-2-((tert-butylsulfinyl)imino)acetate (5g).

Step 2: Preparation of ethyl (R)-2-(((S)-tert-butylsulfinyl)amino)-2-(3-(trifluoromethoxy)phenyl)acetate



5

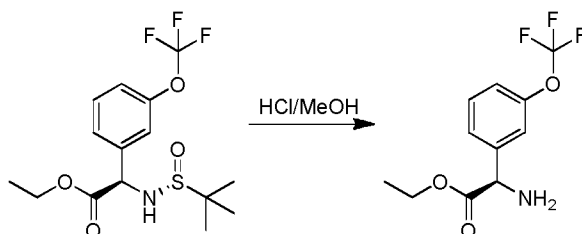
To a solution of ethyl (R,E)-2-(((tert-butylsulfinyl)imino)acetate (5 g) and [3-(trifluoromethoxy)phenyl]boronic acid (6.02 g) in dioxane (80 mL) was added bis(acetonitrile)(1,5-cyclooctadiene)rhodium(I)tetrafluoroborate (CAS:32679-02-0) (1.85 g) and this mixture was stirred at 80°C for 16 hours. The solution was filtered and the organic phase was concentrated. The residue was purified by chromatography (SiO₂, Petroleum Ether:EtOAc=6:1) to afford ethyl (R)-2-(((S)-tert-butylsulfinyl)amino)-2-(3-(trifluoromethoxy)phenyl)acetate (5.1 g).

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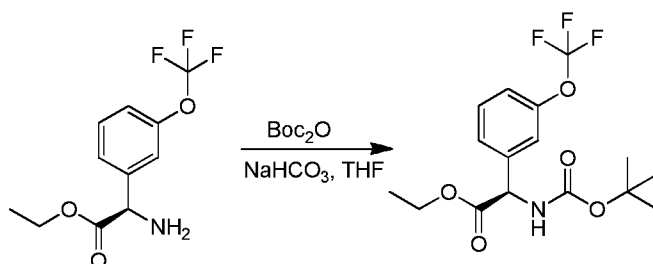
Step 3: Preparation of ethyl (R)-2-amino-2-(3-(trifluoromethoxy)phenyl)acetate

20



To a solution of ethyl (R)-2-(((S)-tert-butylsulfinyl)amino)-2-(3-(trifluoromethoxy)phenyl)acetate (4.6 g) in MeOH (30 mL) was added HCl/MeOH (4 M, 25.04 mL) at 0°C. The reaction mixture was stirred at 25°C for 1 hour and concentrated to afford ethyl (R)-2-amino-2-(3-(trifluoromethoxy)phenyl)acetate as a hydrochloride salt (3.3 g).

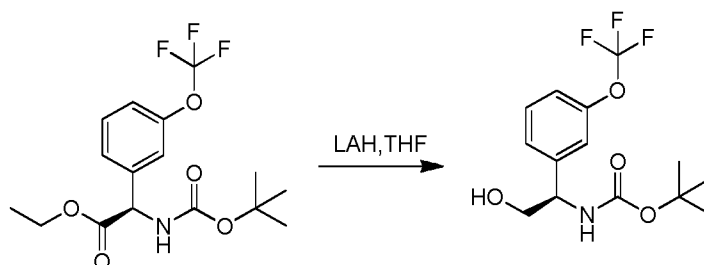
Step 4: Preparation of ethyl (R)-2-((tert-butoxycarbonyl)amino)-2-(3-(trifluoromethoxy)phenyl)acetate



To a mixture of ethyl (R)-2-amino-2-(3-(trifluoromethoxy)phenyl)acetate hydrochloride (3.3 g) in THF (80 mL) was added Boc₂O (4.81 g) and NaHCO₃ (925 mg) and the reaction was stirred at 25°C for 16 hours.

The reaction mixture was concentrated and diluted with EtOAc (20 mL), washed with water (20 mL) and then concentrated. The residue was purified by chromatography (SiO₂; Petroleum Ether:EtOAc=10:1) to afford ethyl (R)-2-((tert-butoxycarbonyl)amino)-2-(3-(trifluoromethoxy)phenyl)acetate (3.8 g).

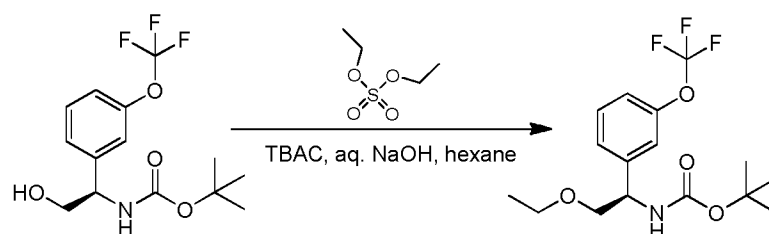
Step 5: Preparation of *tert*-butyl (*R*)-(2-hydroxy-1-(3-(trifluoromethoxy)phenyl)ethyl)carbamate



5

To a suspension of LiAlH_4 (2.1 g) in THF (200 mL) was added ethyl (*R*)-2-((*tert*-butoxycarbonyl)amino)-2-(3-(trifluoromethoxy)phenyl)acetate (5 g) in THF (20 mL) under ice-cooling, and the mixture was stirred at 0°C to 25°C for 2 hours. Anhydrous magnesium sulfate was added and then water (5 mL) and ethyl acetate (100 mL) were successively added, and the insoluble substances was filtered off using celite. The filtrate was concentrated. The crude product was purified by chromatography (SiO_2 , Petroleum Ether:EtOAc =5:1) to afford *tert*-butyl (*R*)-(2-hydroxy-1-(3-(trifluoromethoxy)phenyl)ethyl)carbamate (3.37 g).

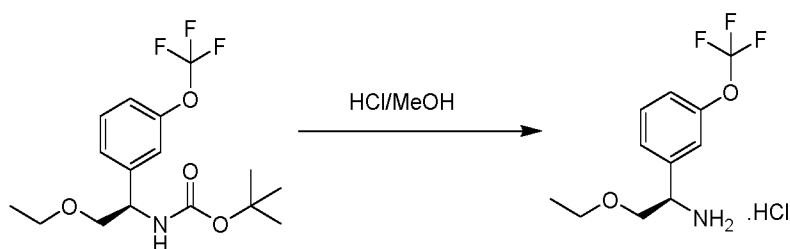
Step 6: Preparation of *tert*-butyl (*R*)-(2-ethoxy-1-(3-(trifluoromethoxy)phenyl)ethyl)carbamate



To a solution of *tert*-butyl (*R*)-(2-hydroxy-1-(3-(trifluoromethoxy)phenyl)ethyl)carbamate

(trifluoromethoxy)phenyl)ethyl)carbamate (1 g) in hexane (15 mL) was added diethyl sulfate (960 mg), tetrabutyl ammonium chloride (TBAC) (87 mg) and a solution of NaOH (324 mg) in H₂O (1.5 mL). The resulting mixture was stirred at 25 °C for 20 hours. The reaction mixture was diluted with EtOAc (200 mL), washed with water (100 mL) and brine (100 mL), dried over Na₂SO₄ and concentrated. The crude was purified by chromatography (SiO₂, 10% EthylAcetate in Petroleum Ether) to give *tert*-butyl (*R*)-(2-ethoxy-1-(3-(trifluoromethoxy)phenyl)ethyl)carbamate (5.9 g).

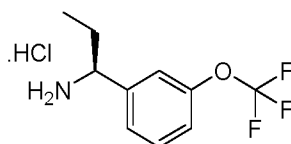
Step 7: Preparation of (*R*)-2-ethoxy-1-(3-(trifluoromethoxy)phenyl)ethan-1-amine hydrochloride



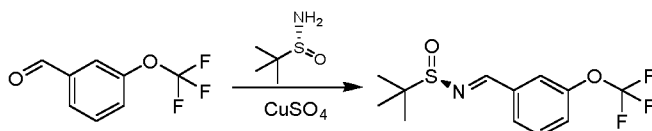
To a solution of *tert*-butyl (*R*)-(2-ethoxy-1-(3-(trifluoromethoxy)phenyl)ethyl)carbamate (5.9 g) in MeOH (100 mL) was added HCl/MeOH (4 M, 63.33 mL) at 25°C and this mixture was stirred at 25°C for 16 hours. The solution was concentrated to afford (*R*)-2-ethoxy-1-(3-(trifluoromethoxy)phenyl)ethan-1-amine hydrochloride (4.5 g).

III: (*S*)-1-(3-(trifluoromethoxy)phenyl)propan-1-amine hydrochloride

95



Step 1: Preparation of (*S,E*)-2-methyl-*N*-(3-(trifluoromethoxy)benzylidene)propane-2-sulfinamide:

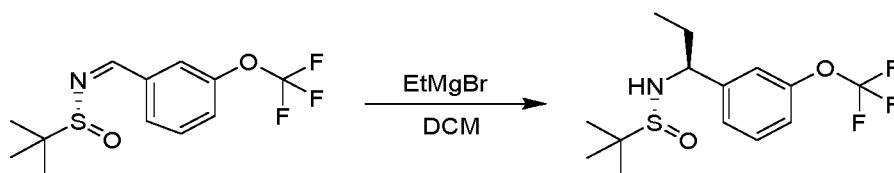


5

A mixture of 3-(trifluoromethoxy)benzaldehyde (10.0 g), (*R*)-2-methylpropane-2-sulfinamide (7.7 g) and CuSO₄ (12.6 g) in DCE (200 mL) was stirred at 55 °C for 16 hours. The mixture was filtered and the filter cake was washed with DCM (200 mL). The filtrate was concentrated. The residue was purified by chromatography (SiO₂, 0-10% Ethylacetate/petroleum ether gradient) to give (*S,E*)-2-methyl-*N*-(3-(trifluoromethoxy)benzylidene)propane-2-sulfinamide (12.6 g).

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Step 2: Preparation of (*S*)-2-methyl-*N*-((*S*)-1-(3-(trifluoromethoxy)phenyl)propyl)propane-2-sulfinamide



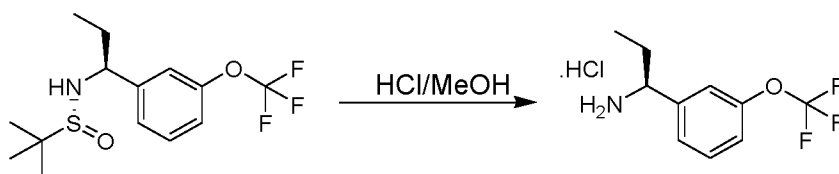
20

To a solution of (*S,E*)-2-methyl-*N*-(3-(trifluoromethoxy)benzylidene)propane-2-sulfinamide (2.0 g) in DCM (40 mL) at 0°C, EtMgBr (3M in Et₂O, 9.1 mL) was added drop-wise. The resulting mixture was stirred at 0°C for 1 hour and 20°C for 3 hours. The mixture was cooled to 0°C and sat.aq NH₄Cl (100 mL) was

25

added. The mixture was extracted with DCM (100 mL × 2), the phases were separated, and the organic layer was washed with brine (200 mL), dried over Na₂SO₄ and concentrated. The residue was purified by chromatography (SiO₂, 0-50% ethyl acetate/petroleum ether gradient) to yield the product (1.4 g).

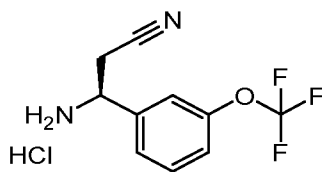
Step 3: Preparation of (*S*)-1-(3-(trifluoromethoxy)phenyl)propan-1-amine hydrochloride



To a solution of (*S*)-2-methyl-*N*-((*S*)-1-(3-(trifluoromethoxy)phenyl)propyl)propane-2-sulfonamide (1.4 g) in MeOH (40 mL) was added HCl/MeOH (4M, 20 mL). The resulting mixture was stirred at 30°C for 12 hours and then concentrated to yield the crude (*S*)-1-(3-(trifluoromethoxy)phenyl)propan-1-amine hydrochloride, which was used without further purification (1 g)

IIIm: (*S*)-3-amino-3-(3-

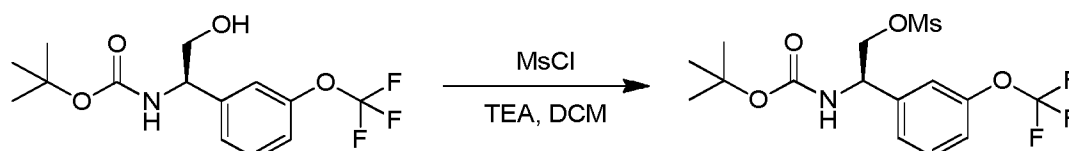
(trifluoromethoxy)phenyl)propanenitrile hydrochloride



Step 1: Preparation of *tert*-butyl (*R*)-(2-hydroxy-1-(3-(trifluoromethoxy)phenyl)ethyl)carbamate

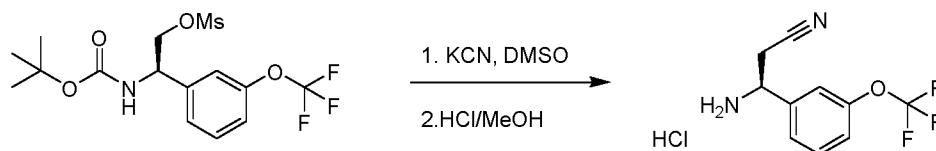
This intermediate was prepared as described for intermediate **IIk**, **Step 1-5**

Step 2: Preparation of (*R*)-2-((*tert*-butoxycarbonyl)amino)-2-(3-(trifluoromethoxy)phenyl)ethyl methanesulfonate



To a solution of *tert*-butyl (*R*)-(2-hydroxy-1-(3-(trifluoromethoxy)phenyl)ethyl)carbamate (2 g) in DCM (20 mL) was added Et₃N (756 mg), then methanesulfonyl chloride (1.75 g) was added at 0 °C. The mixture was stirred at 20 °C for 16 hours. The reaction mixture was washed with saturated aqueous NH₄Cl solution (15 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to afford (*R*)-2-((*tert*-butoxycarbonyl)amino)-2-(3-(trifluoromethoxy)phenyl)ethyl methanesulfonate (2.50 g, crude) which was used in the next step without purification.

Step 3: Preparation of (*S*)-3-amino-3-(3-(trifluoromethoxy)phenyl)propanenitrile hydrochloride



To a solution of (*R*)-2-((*tert*-butoxycarbonyl)amino)-2-(3-(trifluoromethoxy)phenyl)ethyl methanesulfonate (420 mg) in DMSO (5 mL) was added KCN (225 mg) at 20 °C. The

mixture was stirred at 50 °C for 16 hours. The reaction mixture was diluted with 10% Na₂CO₃ solution (40 mL) and extracted with EtOAc (30 mL×3). The combined organic extracts were washed with water (50 mL) and

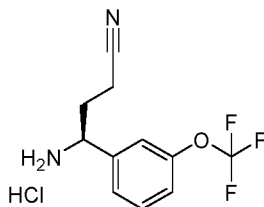
5 brine (50 mL), then dried over Na₂SO₄, filtered and concentrated. The residue was purified by chromatography (SiO₂, Petroleum ether/Ethyl acetate=5/1 to 4/1) to afford *tert*-butyl (S)-(2-cyano-1-(3-(trifluoromethoxy)phenyl)ethyl)carbamate (665 mg).

10 ¹H NMR (400 MHz, CDCl₃): δ 7.46 (t, 1H), 7.33 (d, 1H), 7.24 (m, 2H), 7.04 (d, 1H), 5.31-5.38 (m, 1H), 3.73-3.71 (m, 1H), 3.11-3.05 (m, 1H), 2.84-2.92 (m, 2H), 2.49-2.43 (m, 1H), 2.28-2.37 (m, 1H), 0.93 (s, 9H).

15 To a solution of *tert*-butyl (S)-(2-cyano-1-(3-(trifluoromethoxy)phenyl)ethyl)carbamate (400 mg) in MeOH (8 mL) was added HCl/MeOH (4 M, 4.00 mL) at 0 °C. The mixture was stirred at 25 °C for 16 hours. Then the reaction mixture was concentrated to

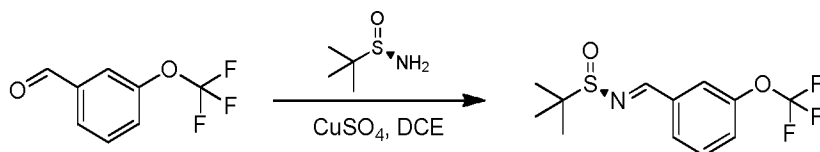
20 afford (S)-3-amino-3-(3-(trifluoromethoxy)phenyl)propanenitrile hydrochloride (280 mg, crude).

IIn: (S)-4-amino-4-(3-(trifluoromethoxy)phenyl)butanenitrile hydrochloride



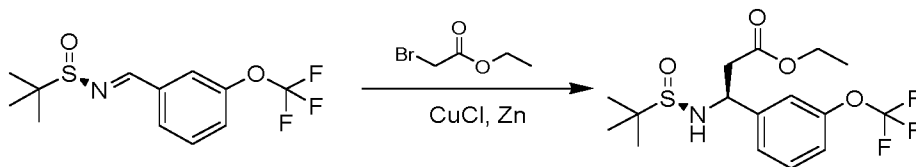
25

Step 1: Preparation of (R,E)-2-methyl-N-(3-(trifluoromethoxy)benzylidene)propane-2-sulfinamide



To a solution of 3-(trifluoromethoxy)benzaldehyde (30 g) and (R)-2-methylpropane-2-sulfinamide (23.0 g) in DCE (600 mL) was added CuSO₄ (37.8 g). The mixture was stirred at 55°C for 24 hours and filtered. The filtercake was washed with DCM (300 mL). The filtrates were combined and concentrated, and the residue was purified by chromatography (SiO₂, Petroleum ether/Ethyl acetate = 0/1 to 5:1) to afford (R,E)-2-methyl-N-(3-(trifluoro-methoxy)benzylidene)propane-2-sulfinamide (41.8 g).

Step 2: Preparation of ethyl (S)-3-(((R)-tert-butylsulfinyl)amino)-3-(3-(trifluoromethoxy)phenyl)propanoate

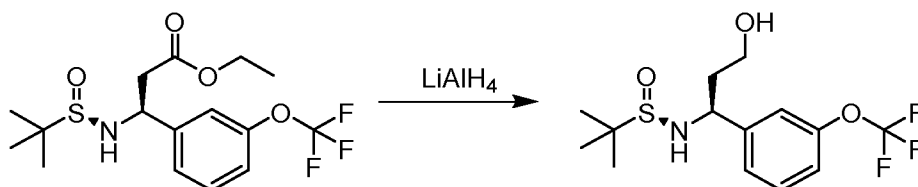


A solution of (R,E)-2-methyl-N-(3-(trifluoromethoxy)benzylidene)propane-2-sulfinamide (5 g) in THF (60 mL) was added to a suspension of activated Zn (11.15 g), CuCl (2.5 g) and ethyl 2-bromoacetate (7.1 g) in THF (60 mL) at 0°C. The reaction mixture was stirred at 50°C for 2 hours, and filtered. The filtercake was washed with DCM (400 mL), the combined organic filtrates were concentrated. The residue was purified by chromatography (SiO₂, Petroleum ether/Ethyl acetate = 1/0 to 5/1) to afford ethyl (S)-3-(((R)-tert-

butylsulfinyl)amino)-3-(3-(trifluoromethoxy)phenyl)propanoate (7 g, crude).

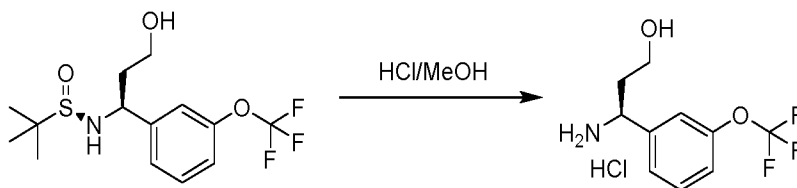
¹H NMR (CDCl₃ 400MHz): δ 7.36 (t, 2H), 7.20 (s, 1H), 7.14 (d, 1H), 5.78 (d, 1H), 5.14-5.10 (m, 1H), 4.14-4.10 (m, 2H), 3.05-2.89 (m, 2H), 1.31 (s, 9H), 1.18 (t, 3H).

Step 3: Preparation of (R)-N-((S)-3-hydroxy-1-(3-(trifluoromethoxy)phenyl)propyl)-2-methylpropane-2-sulfinamide



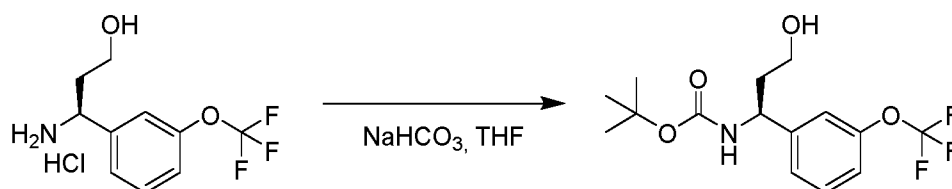
To a solution of ethyl (S)-3-(((R)-tert-butylsulfinyl)amino)-3-(3-(trifluoromethoxy)phenyl)propanoate (7 g) in THF (70 mL) was added LiAlH₄ (696 mg) at 0°C. The resulting mixture was stirred at 0°C for 1 hour, and then quenched by sequential addition of H₂O (0.7 mL), 10% NaOH (0.7 mL) solution and H₂O (2.1 mL) at 0°C. The mixture was filtered. The residue was concentrated to afford the crude (R)-N-((S)-3-hydroxy-1-(3-(trifluoromethoxy)phenyl)propyl)-2-methylpropane-2-sulfinamide (4.2 g).

Step 4: Preparation of (S)-3-amino-3-(3-(trifluoromethoxy)phenyl)propan-1-ol hydrochloride



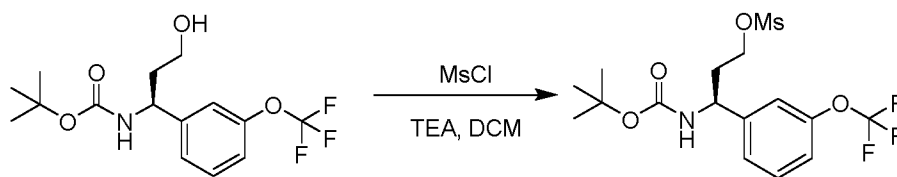
The crude (*R*)-*N*-((*S*)-3-hydroxy-1-(3-(trifluoromethoxy)phenyl)propyl)-2-methylpropane-2-sulfinamide (4 g) from the previous reaction step, was dissolved in MeOH (40 mL) and added HCl/MeOH (4 M, 23.6 mL). The reaction mixture was stirred at 20°C for 16 hours, and was concentrated to afford (*S*)-3-amino-3-(3-(trifluoromethoxy)phenyl)propan-1-ol hydrochloride (3.2 g, crude)

- Step 5: Preparation of *tert*-butyl (*S*)-(3-hydroxy-1-(3-(trifluoromethoxy)phenyl)propyl)carbamate



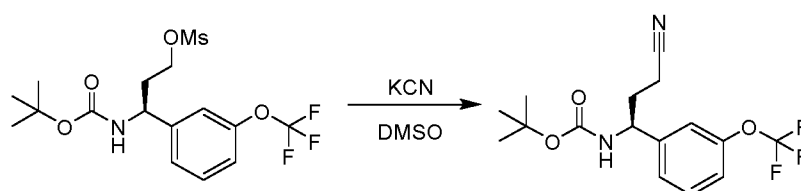
- Crude ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(3-(trifluoromethoxy)phenyl)propanoate from the previous reaction step (3.2 g) was dissolved in THF (35 mL) and added Boc₂O (10.28 g) and NaHCO₃ (2g). The reaction mixture was stirred at 20°C for 16 hours. The mixture was concentrated, and the residue was diluted with water (70 mL), extracted by DCM (100 mL×3), and the combined organic extracts were dried over Na₂SO₄, filtered and concentrated. The residue was purified by chromatography (SiO₂, Petroleum ether/Ethyl acetate = 1/0 to 2/1) to afford *tert*-butyl (*S*)-(3-hydroxy-1-(3-(trifluoromethoxy)phenyl)propyl)carbamate (3.2 g)

Step 6: Preparation of (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(3-(trifluoromethoxy)phenyl)propyl methanesulfonate



To a solution of *tert*-butyl (*S*)-(3-hydroxy-1-(3-(trifluoromethoxy)phenyl)propyl)carbamate (1 g) in DCM (30 mL) was added Et₃N (905 mg) and methanesulfonyl chloride (683 mg) at 0°C. The reaction mixture was stirred at 20°C for 16 hours, and then washed with ice water (15 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to afford ((*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(3-(trifluoromethoxy)phenyl)propyl methanesulfonate (1.2 g)

Step 7: Preparation of *tert*-butyl (*S*)-(3-cyano-1-(3-(trifluoromethoxy)phenyl)propyl)carbamate

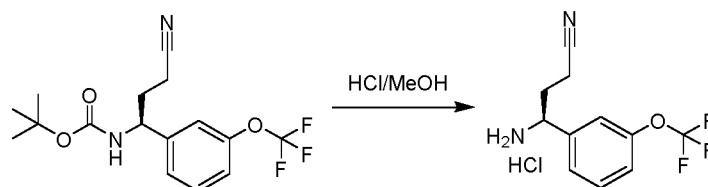


((*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(3-(trifluoromethoxy)phenyl)propyl methanesulfonate obtained in the previous step was dissolved in DMSO (35 mL) and added KCN (661 mg) at 20°C. The reaction mixture was stirred at 50°C for 16 hours, and then diluted with 10% Na₂CO₃ solution (40 mL) and extracted with EtOAc (70 mL×3). The combined organic extracts were washed with water (50 mL) and brine (50 mL), then dried over Na₂SO₄, filtered and concentrated. The residue was purified by chromatography (SiO₂, Petroleum ether/Ethyl acetate = 1/0 to 3/1) to afford *tert*-butyl

(*S*)-(3-cyano-1-(3-(trifluoromethoxy)phenyl)propyl)carbamate (990 mg).

Step 8: Preparation of (*S*)-4-amino-4-(3-

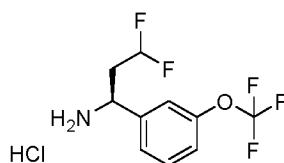
5 (trifluoromethoxy)phenyl)butanenitrile hydrochloride



To a solution of *tert*-butyl (*S*)-(3-cyano-1-(3-(trifluoromethoxy)phenyl)propyl)carbamate (900 mg,) in MeOH (14 mL) was added HCl/MeOH (4 M, 6.53 mL). The mixture was stirred at 20°C for 16 hours and concentrated to afford (*S*)-4-amino-4-(3-(trifluoromethoxy)phenyl)butanenitrile hydrochloride (850 mg).

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IIo: (*S*)-3,3-difluoro-1-(3-(trifluoromethoxy)phenyl)propan-1-amine hydrochloride

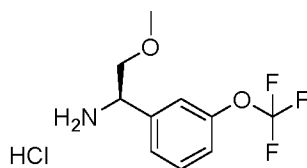


Prepared as described for **IIi** using 3-

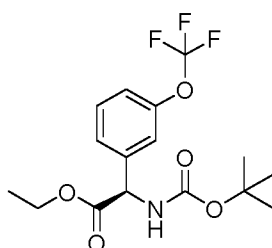
20 (trifluoromethoxy)benzaldehyde as starting material.

IIp: (*R*)-2-methoxy-1-(3-(trifluoromethoxy)phenyl)ethan-1-amine hydrochloride

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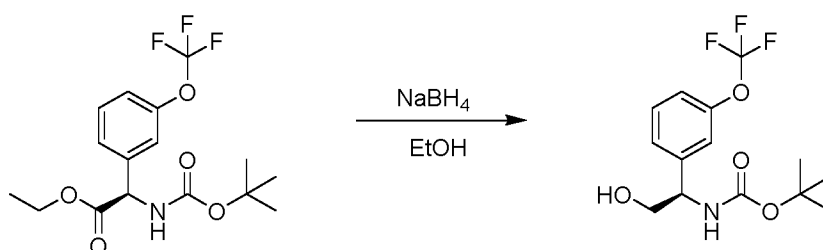


Step 1: Preparation of ethyl (*R*)-2-((*tert*-
butoxycarbonyl)amino)-2-(3-(trifluoromethoxy)phenyl)
5 acetate



This intermediate was prepared as described for **Iik**,
Step 1-4.

10 Step 2: Preparation of *tert*-butyl (*R*)-(2-hydroxy-1-(3-(
(trifluoromethoxy)phenyl)ethyl)carbamate

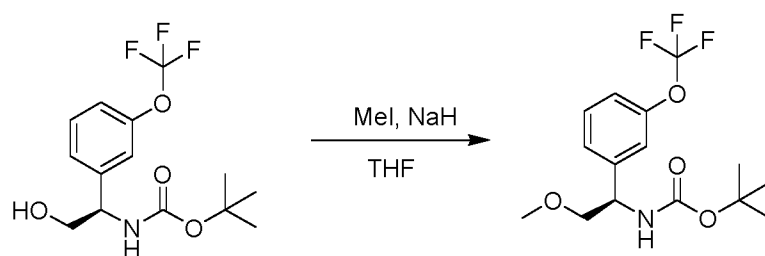


To a solution of ethyl (*R*)-2-((*tert*-
15 butoxycarbonyl)amino)-2-(3-(trifluoromethoxy)phenyl)
acetate(10g) in EtOH (90 mL) was added NaBH₄ (4.17 g)
at 0 °C. The mixture was removed from the cold bath and
stirred for 2 hours. The reaction was quenched with
water (20 mL) and concentrated. The residue was
20 purified by column chromatography (SiO₂, Petroleum

ether/Ethyl acetate = 1/0 to 3/1) to afford the product (13.6 g).

¹H NMR (CDCl₃ 400MHz): δ 7.39 (t, 1H), 7.26 (d, 1H), 7.17-7.15 (m, 2H), 5.34 (s, 1H), 4.80 (s, 1H), 3.93-3.84 (m, 2H), 2.06 (s, 1H), 1.45 (s, 9H).

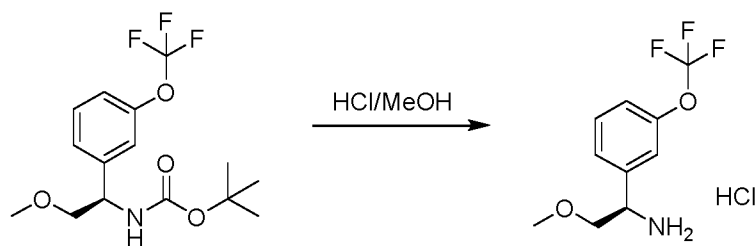
Step 3: Preparation of *tert*-butyl (*R*)-(2-methoxy-1-(3-(trifluoromethoxy)phenyl)ethyl)carbamate



To a solution of *tert*-butyl (*R*)-(2-hydroxy-1-(3-(trifluoromethoxy)phenyl)ethyl)carbamate (1 g) and MeI (4 g) in THF (70 mL) was added NaH (149 mg, 60% in mineral oil) at 0°C. The mixture was stirred at 0°C for 1 hour and stirred at 25 °C for 16 hours. Water (1 mL) was added to quench the reaction. THF was removed and EtOAc (200 mL) was added into the residue. The solution was washed by water (50 mL×3) and concentrated. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 0/1 to 5/1) to afford *tert*-butyl (*R*)-(2-methoxy-1-(3-(trifluoromethoxy)phenyl)ethyl)carbamate (3.2 g).

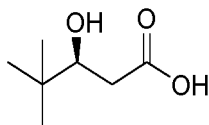
¹H NMR (CDCl₃ 400MHz): δ 7.36 (t, 1H), 7.25 (m, 1H), 7.19 (s, 1H), 7.12 (d, 1H), 5.34 (s, 1H), 4.83 (s, 1H), 3.63-3.56 (m, 2H), 3.35 (s, 3H), 1.43 (s, 9H).

Step 4: Preparation of (R)-2-methoxy-1-(3-(trifluoromethoxy)phenyl)ethan-1-amine hydrochloride



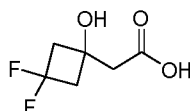
- 5 To a solution of *tert*-butyl (R)-2-methoxy-1-(3-(trifluoromethoxy)phenyl)ethylcarbamate (2.7 g) in MeOH (40 mL) was added HCl/MeOH (4 M, 40 mL) at 25 °C. The mixture was stirred at 25 °C for 16 hours. The mixture was concentrated to afford the desired product
- 10 (1.9 g, crude).

IIIa: (S)-3-hydroxy-4,4-dimethylpentanoic acid



- 15 Prepared according to literature as described in Wang Z. et al: Tetrahedron: Asymmetry 10 (1999) 225-228.

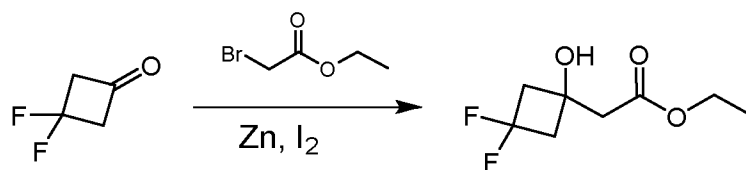
IIIb: 2-(3,3-Difluoro-1-hydroxycyclobutyl)acetic acid



20

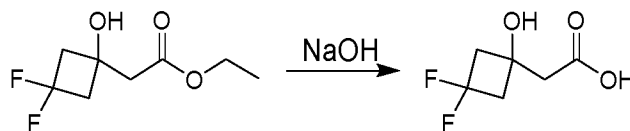
Step 1: Preparation of ethyl 2-(3,3-difluoro-1-hydroxy-cyclobutyl)acetate

107



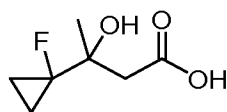
To a solution 3,3-difluorocyclobutanone (0.2 g), Zn (198 mg) and I₂ (10 mg) in THF (13 mL) under N₂, ethyl 2-bromoacetate (378 mg) was added dropwise. The mixture was stirred at 55°C for 6 hours. H₂SO₄ (10%, 10 mL) was carefully added to the reaction mixture at 0°C, and the mixture was extracted with ethyl acetate (20 mL × 3). The organic extract was washed with NaHCO₃ (sat.aq, 10 mL), dried over Na₂SO₄ and concentrated. The crude product (0.26 g) was used directly without further purification.

Step 2: Preparation of 2-(3,3-difluoro-1-hydroxycyclobutyl) acetic acid

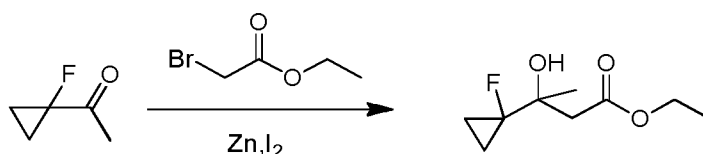


To a solution of ethyl 2-(3,3-difluoro-1-hydroxycyclobutyl) acetate (0.26 g) in MeOH (10 mL) and H₂O (2 mL), NaOH (107 mg) was added at 0° C. The mixture was stirred at 20°C for 8 hours. The reaction solution was cooled to 0°C and 1N HCl was added to the solution until pH reached 1-2. The residue was diluted with brine (10 mL) and extracted with methyl-*tert*-butyl ether (30 mL × 5). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated. The crude product (0.24 g) was used without further purification.

IIIc: 3-(1-fluorocyclopropyl)-3-hydroxybutanoic acid

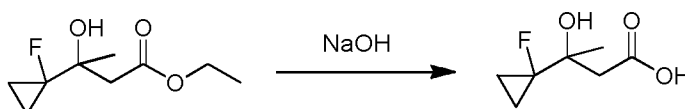


Step 1: Preparation of ethyl 3-(1-fluorocyclopropyl)-3-hydroxy-butanoate



A solution of 1-(1-fluorocyclopropyl)ethanone (0.5 g),
10 Zn (512 mg) and I₂ (62 mg) in THF (30 mL) was stirred at 20°C until the solution changed to colorless and ethyl 2-bromoacetate (981 mg) was added dropwise. The resulting mixture was stirred at 20°C for 0.5 hour and 65°C for 4.5 hours. The reaction was washed with 10% aq.
15 H₂SO₄ (20 mL) and extracted with EtOAc (50 mL×2). The organic extracts were washed with brine (100 mL), dried over Na₂SO₄ and concentrated to afford ethyl 3-(1-fluorocyclopropyl)-3-hydroxy-butanoate (0.83 g, crude).

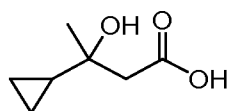
20 Step 2: Preparation of 3-(1-fluorocyclopropyl)-3-hydroxy-butanoic acid



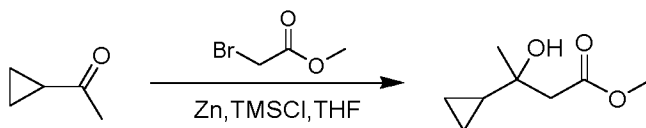
25 To a solution of ethyl 3-(1-fluorocyclopropyl)-3-hydroxy-butanoate (0.83 g) in EtOH (10 mL) was added a

solution of NaOH (350 mg) in H₂O (3 mL). The reaction mixture was stirred at 20 °C for 2 hours and then extracted with EtOAc (50 mL×2). The aqueous layer was acidified by 10% HCl to pH=3 and extracted with EtOAc (50 mL×2). The combined organic extracts were washed with brine (100 mL), dried over Na₂SO₄ and concentrated to afford 3-(1-fluorocyclopropyl)-3-hydroxy-butanoic acid (0.57 g, crude).

10

IIId: 3-Cyclopropyl-3-hydroxybutanoic acid

Step 1: Preparation of methyl 3-cyclopropyl-3-hydroxybutanoate



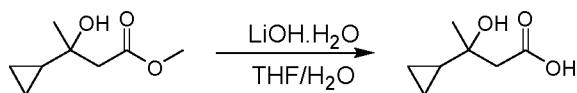
15

Zn (12.4 g) in THF (150 mL) was added TMSCl (1.3 g), and the resulting mixture was stirred at 20 °C for 15 minutes and then heated to 70°C. The heating was stopped, and methyl 2-bromoacetate (21.8 g) was added dropwise at such a rate that the solvent boiled gently. The resulting mixture was stirred at 70°C for 1 hour and 20°C for 1 hour, then a solution of 1-cyclopropylethanone (10 g) in THF (50 mL) was added. The reaction was stirred at 20°C for 16 hours. The mixture was poured onto NH₃·H₂O on ice (100 mL, 28%), and extracted with ethyl acetate (150 mL x2). The organic extract was washed with water (150 mL) and

25

brine (150 mL), dried over Na_2SO_4 and concentrated to give the desired product (8.9 g, crude).

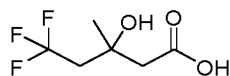
Step 2: Preparation of 3-cyclopropyl-3-hydroxybutanoic acid



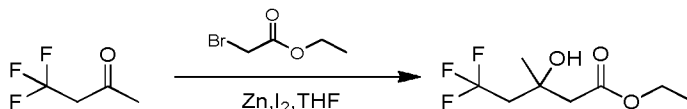
A mixture of crude methyl 3-cyclopropyl-3-hydroxybutanoate (8.9 g) and $\text{LiOH}\cdot\text{H}_2\text{O}$ (11.8 g) in THF (100 mL) and H_2O (50 mL) was stirred at 20°C for 16 hours. H_2O (50 mL) was added and extracted with ethyl acetate (100 mL x2). The organic extracts were discarded. The pH of the aqueous layer was adjusted to ~5 with 2N HCl, extracted with ethyl acetate (100 mL x3) and the combined organic fractions were washed with brine (100 mL x10), dried over Na_2SO_4 , filtered and concentrated to give the desired product in 30% overall yield (5.1 g)

^1H NMR (400 MHz, CDCl_3) δ 2.67–2.51 (m, 2H), 1.25 (s, 3H), 0.90–1.00 (m, 1H), 0.33–0.50 (m, 4H).

IIIe: 5,5,5-Trifluoro-3-hydroxy-3-methylpentanoic acid



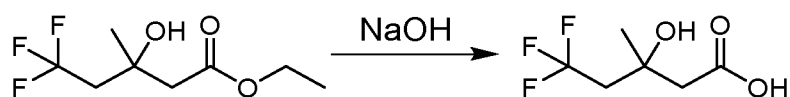
Step 1: Preparation of ethyl 5,5,5-trifluoro-3-hydroxy-3-methylpentanoate



To a mixture of Zn (6.9 g) and I_2 (89 mg) in THF (80 mL) was added 4,4,4-trifluorobutan-2-one (4.4 g) and

ethyl 2-bromoacetate (6.4 g) at 15°C. The mixture was stirred at 60°C for 6 hours. The reaction mixture was cooled to 0°C and quenched with H₂SO₄ (100 mL, 10% aq). The mixture was extracted with ethyl acetate (15 mL × 3). The combined organic extract was washed with brine (15 mL) and dried over Na₂SO₄, filtered and concentrated. The product was obtained (11.00 g, crude) and was used directly without further purification.

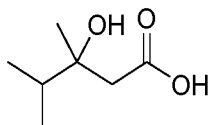
- 10 Step 2: Preparation of 5,5,5-trifluoro-3-hydroxy-3-methylpentanoic acid



- A mixture of ethyl 5,5,5-trifluoro-3-hydroxy-3-methylpentanoate (11 g, crude) and NaOH (4.1 g) in H₂O (150 mL) was stirred at 15°C for 16 hours. The pH was adjusted to ~2 with sat. KHSO₄ at 0°C, and the mixture extracted with ethyl acetate (200 mL × 3). The combined organic extract was washed with brine (300 mL), dried over Na₂SO₄, filtered and concentrated to afford the product (10 g, crude).

- The following were prepared by the same methodology as described for **IIIe**, using the relevant starting materials:

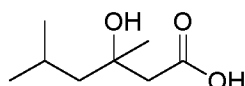
IIIIf: 3-hydroxy-3,4-dimethylpentanoic acid



^1H NMR (CDCl_3 400MHz): δ 2.65-2.46 (m, 2H), 2.09 (s, 1H), 1.85-1.76 (m, 1H), 1.20 (s, 3H), 0.93 (dd, 6H).

5

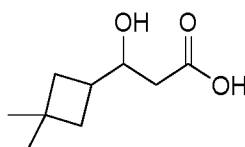
IIIg: 3-Hydroxy-3,5-dimethyl-hexanoic acid



^1H NMR (CDCl_3 400MHz): δ 2.64-2.50 (m, 2H), 1.85-1.79 (m, 1H), 1.49 (d, 2H), 1.32 (s, 3H), 1.03-0.97 (m, 6H).

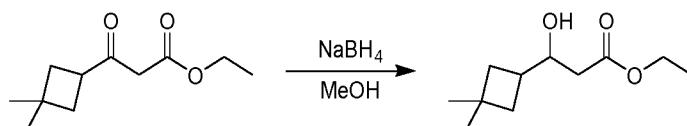
10

IIIh: 3-(3,3-Dimethylcyclobutyl)-3-hydroxy-propanoic acid



15

Step 1: Preparation of ethyl 3-(3,3-dimethylcyclobutyl)-3-hydroxy-propanoate

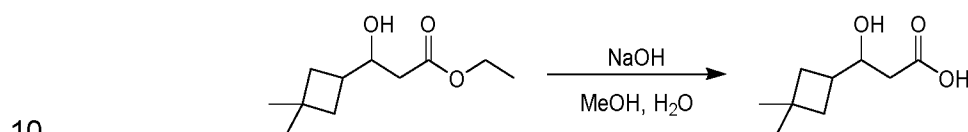


20 To a solution of ethyl 3-(3,3-dimethylcyclobutyl)-3-oxo-propanoate (**IVd**) (1 g) in MeOH (8 mL) was added NaBH_4 (95 mg). The mixture was stirred at 0°C for 10 min. and quenched by addition of H_2O (1 mL), concentrated and then diluted with EtOAc (30 mL), dried
25 over Na_2SO_4 , filtered and evaporated. The residue was purified by chromatography (SiO_2 , Petroleum ether/Ethyl

acetate=5/1 to 4/1) to afford ethyl 3-(3,3-dimethylcyclobutyl)-3-hydroxy-propanoate (907 mg)

¹H NMR (DMSO-d₆ 400MHz): δ 4.70 (d, 1H), 4.06-4.00 (m, 2H), 3.71-3.68 (m, 1H), 2.26-2.23 (m, 1H), 2.15-2.12 (m, 2H), 1.63-1.59 (m, 3H), 1.52-1.49 (m, 1H), 1.17 (t, 3H), 1.09 (s, 3H), 0.99 (s, 3H).

Step 2: Preparation of 3-(3,3-dimethylcyclobutyl)-3-hydroxy-propanoic acid

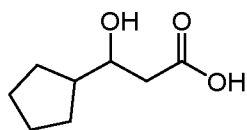


To a solution of ethyl 3-(3,3-dimethylcyclobutyl)-3-hydroxy-propanoate (900 mg) in MeOH (10 mL) was added a solution of NaOH (377 mg) in H₂O (5 mL). The mixture was stirred at 25 °C for 4 hours. The reaction mixture was added 10% HCl solution to adjust pH = 3-4, then diluted with H₂O (30 mL) and extracted with EtOAc (30 mL×2), the combined organic layers were dried over Na₂SO₄, filtered and concentrated to afford 3-(3,3-dimethylcyclobutyl)-3-hydroxy-propanoic acid (760 mg).

¹H NMR (DMSO-d₆ 400MHz): δ 11.96-11.95 (m, 1H), 4.65-4.61 (m, 1H), 3.71-3.66 (m, 1H), 2.19-2.05 (m, 3H), 1.63-1.51 (m, 4H), 1.09 (s, 3H), 1.00 (s, 3H).

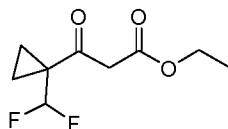
The following was prepared by the same methodology as described for **IIIh**, using the relevant starting materials:

IIIi: 3-cyclopentyl-3-hydroxy-propanoic acid

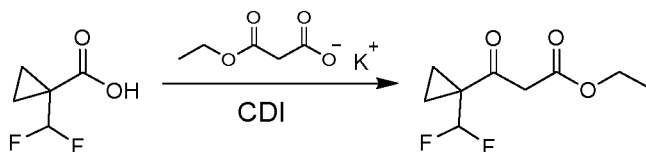


¹H NMR (DMSO-d₆ 400MHz): δ 11.96 (s, 1H), 4.63 (s, 1H),
 5 3.66 (s, 1H), 2.36-2.32 (m, 2H), 1.83-1.75 (m, 1H), 1.62-
 1.35 (m, 8H).

IVa: Ethyl 3-[1-(difluoromethyl)cyclopropyl]-3-oxo-
 10 propanoate



Step 1: Preparation of ethyl 3-[1-(difluoromethyl)
 cyclopropyl]-3-oxo-propanoate

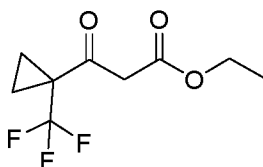


15 Et₃N (2.34 g) and MgCl₂ (1.8 g) was added to a
 suspension of (3-ethoxy-3-oxo-propanoyl)oxy potassium
 salt (2.6 g) in MeCN (30 mL) and stirred at 20°C for 2
 hours. A pre-stirred mixture of carbonyl-diimidazole
 (CDI) (1.4 g) and 1-(difluoromethyl) cyclopropane
 20 carboxylic acid (1 g) in MeCN (20 mL) was added at 0°C
 and stirred at 20°C for 14 hours. The reaction mixture
 was diluted with H₂O (30 mL) and extracted with ethyl
 acetate (80 mL × 2). The combined organic extracts were
 washed with brine (30 mL), dried over Na₂SO₄, filtered
 25 and concentrated. The residue was purified by flash
 chromatography (SiO₂, eluent of 0~10% Ethyl

acetate/petroleum ether gradient). To yield the product (0.98 g)

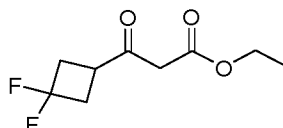
- 5 The following was prepared by the same methodology as described for **IVa**, using the relevant starting materials:

- 10 **IVb: Ethyl 3-oxo-3-[1-(trifluoromethyl)cyclopropyl]propanoate**

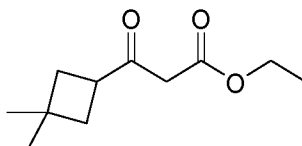


15

- IVc: 3-(3,3-Difluorocyclobutyl)-3-oxopropanoate**



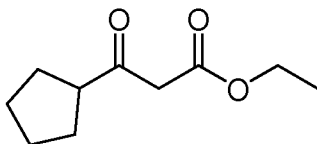
- 20 **IVd: Ethyl 3-(3,3-dimethylcyclobutyl)-3-oxo-propanoate**



¹H NMR (CDCl₃ 400MHz): δ 4.22-4.16 (m, 1H), 3.39 (s, 2H), 3.34-3.25 (m, 1H), 2.08-1.90 (m, 4H), 1.29 (t, 3H), 1.27 (s, 3H), 1.06 (s, 3H).

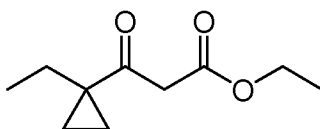
25

IVe: Ethyl 3-cyclopentyl-3-oxo-propanoate



5 $^1\text{H NMR}$ (CDCl_3 400MHz): δ 4.24-4.18 (m, 2H), 3.49 (s, 2H), 3.03-2.95 (m, 1H), 1.84-1.60 (m, 8H), 1.28 (t, 3H).

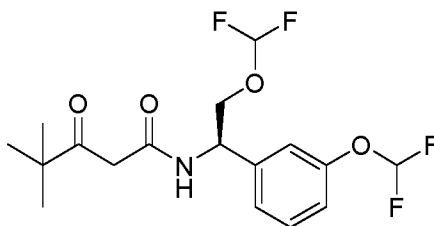
10 IVf: Ethyl 3-(1-ethylcyclopropyl)-3-oxo-propanoate



$^1\text{H NMR}$ (CDCl_3 400MHz): δ 4.22-4.16 (m, 2H), 3.33 (s, 2H), 1.64-1.60 (m, 2H), 1.26-1.20 (m, 6H), 0.94 (t, 3H).

15

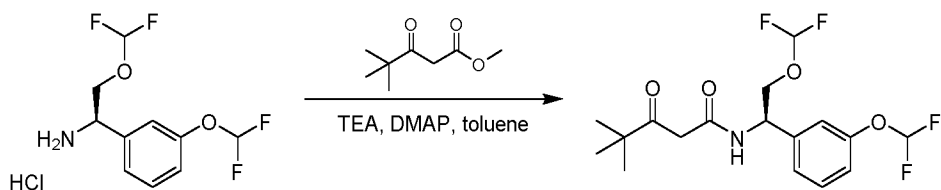
Va: (R)-N-(2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-4,4-dimethyl-3-oxopentanamide



20

Step 1: Preparation of (R)-N-(2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-4,4-dimethyl-3-oxopentanamide

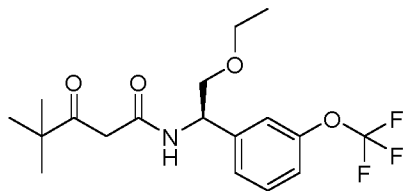
117



A solution of (R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl) ethan-1-amine hydrochloride (IIa) (0.6 g), methyl 4,4-dimethyl-3-oxo-pentanoate (750 mg), TEA (2.40 g) and DMAP (58 mg) in toluene (10 mL) was stirred at 90 °C for 16 hours. The mixture was diluted with EtOAc (50 mL), washed with water (30 mL) and brine (50 mL), dried over Na₂SO₄ and concentrated. The crude was purified by chromatography (SiO₂, 30% EA in Petroleum Ether) to give (R)-N-(2-(difluoromethoxy)-1-(3-(difluoromethoxy) phenyl)ethyl)-4,4-dimethyl-3-oxopentanamide (0.28 g).

The following intermediate was prepared by similar methodology as **Va**, using the relevant intermediates

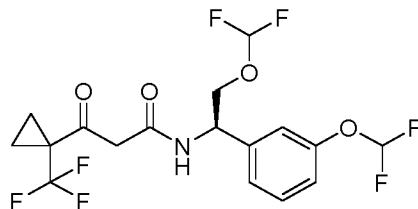
Vb: (R)-N-(2-ethoxy-1-(3-(trifluoromethoxy)phenyl)ethyl)-4,4-dimethyl-3-oxopentanamide



Prepared from **IIk** and 4,4-dimethyl-3-oxo-pentanoic acid.

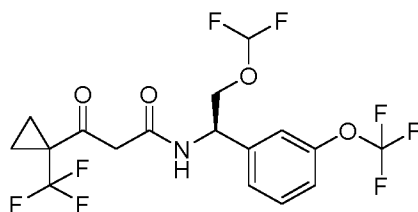
118

Vc: (R)-N-(2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-oxo-3-(1-(trifluoromethyl)cyclopropyl)propanamide



5 Prepared from **IIa** and **IVb**

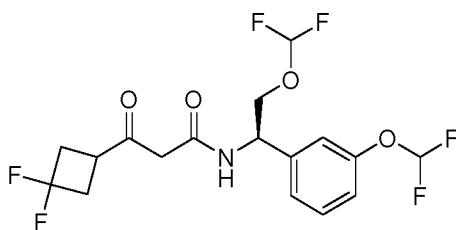
Vd: (R)-N-(2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-oxo-3-(1-trifluoromethyl)cyclopropyl)propanamide



Prepared from **IVb** and **IIb**.

15

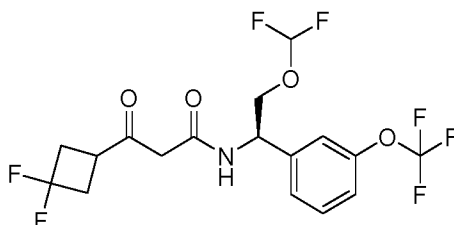
Ve: (R)-3-(3,3-difluorocyclobutyl)-N-(2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-oxopropanamide



20

Prepared from **IVc** and **IIa**

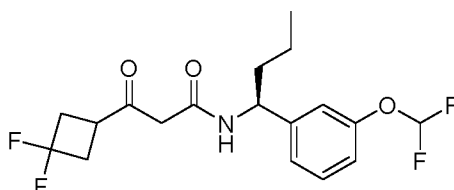
Vf: (R)-3-(3,3-difluorocyclobutyl)-N-(2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-oxopropanamide



Prepared from IVc and IIb

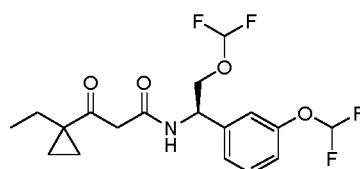
10

Vg: (S)-3-(3,3-difluorocyclobutyl)-N-(1-(3-(difluoromethoxy)phenyl)butyl)-3-oxopropanamide



15 Prepared from IVc and IIg

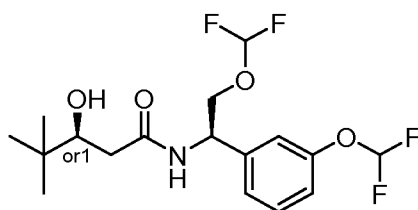
Vh: (R)-N-(2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-(1-ethylcyclopropyl)-3-oxopropanamide



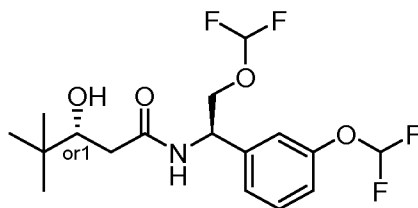
Prepared from IVf and IIa

Examples:

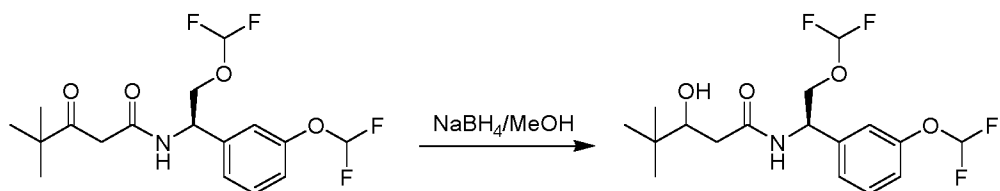
Example 1a: *N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl) ethyl)-3-hydroxy-4,4-dimethylpentanamide



and Example 1b: *N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl) ethyl)-3-hydroxy-4,4-dimethylpentanamide



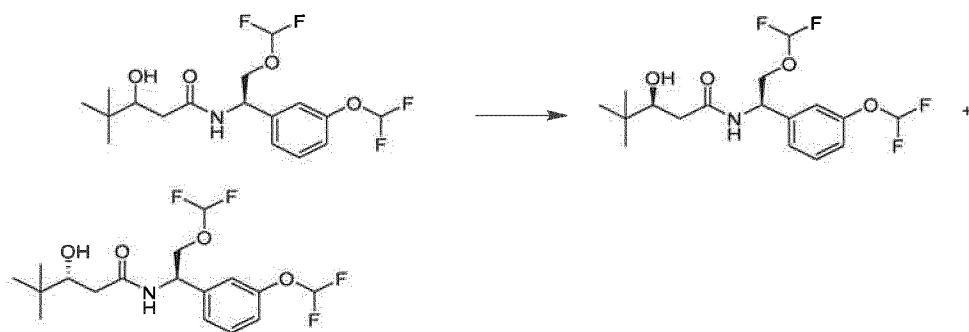
Step 1: Preparation of *N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy) phenyl)ethyl)-3-hydroxy-4,4-dimethylpentanamide



To a solution of (*R*)-*N*-(2-(difluoromethoxy)-1-(3-(difluoromethoxy) phenyl)ethyl)-4,4-dimethyl-3-oxopentanamide (**Va**) (0.28 g) in MeOH (10 mL) was added

NaBH₄ (56 mg) at 0°C. The resulting mixture was stirred at 0°C for 1 hour. The mixture was concentrated and the residue was redissolved in EtOAc (50 mL) and washed with water (50 mL) and brine (50 mL), dried over Na₂SO₄ and concentrated.

Step 2: Separation of (*R*)-*N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-4,4-dimethylpentanamide and (*S*)-*N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-4,4-dimethylpentanamide



N-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-4,4-dimethylpentanamide was separated by chromatography.

Example 1a:

¹H NMR (CDCl₃ 400 MHz): δ 7.34 (t, 1H), 7.16 (d, 1H), 7.09 (s, 1H), 7.04 (d, 1H), 6.59 (d, 1H), 6.50 (t, 1H), 6.20 (t, 1H), 5.30-5.26 (m, 1H), 4.15-4.08 (m, 2H), 3.69-3.66 (m, 1H), 2.90 (d, 1H), 2.43 (dd, 1H), 2.28 (dd, 1H), 0.91 (s, 9H).

LC-MS: t_R = 2.49 min (LC-MS Method 1), m/z = 382.2 [M + H]⁺.

SFC: t_R = 1.94 min (SFC Method 1), ee% = 95.26%.

Example 1b:

¹H NMR (CDCl₃, 400 MHz): δ 7.35 (t, 1H), 7.16 (d, 1H), 7.06-7.04 (m, 2H), 6.60 (d, 1H), 6.50 (t, 1H), 6.20 (t, 1H), 5.28 (m, 1H), 4.10 (m, 2H), 3.67 (m, 1H), 3.04 (d, 1H), 2.45 (dd, 1H), 2.28 (dd, 1H), 0.91 (s, 9H).

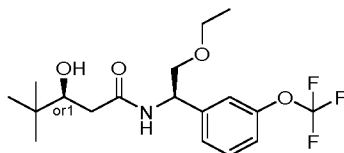
LC-MS: t_R = 2.50 min (LC-MS Method 1), m/z = 382.2 [M + H]⁺.

SFC: t_R = 2.03 min (SFC Method 1), ee% = 95.26%.

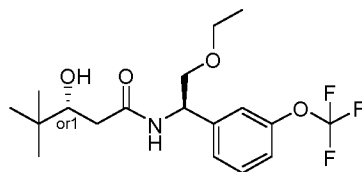
10

The following examples were prepared by similar methodology as described for **1a** and **1b**, using the relevant intermediates:

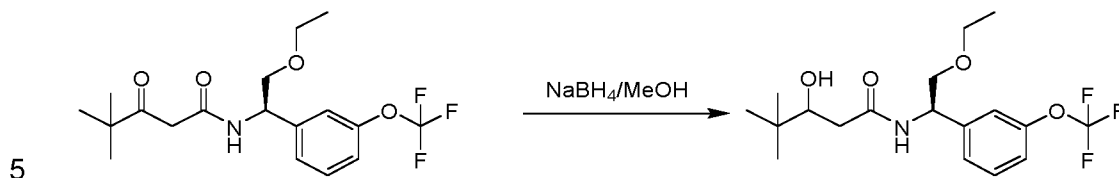
15 **Example 2a:** *N*-((*R*)-2-ethoxy-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-hydroxy-4,4-dimethylpentanamide



20 and **Example 2b:** *N*-((*R*)-2-ethoxy-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-hydroxy-4,4-dimethylpentanamide

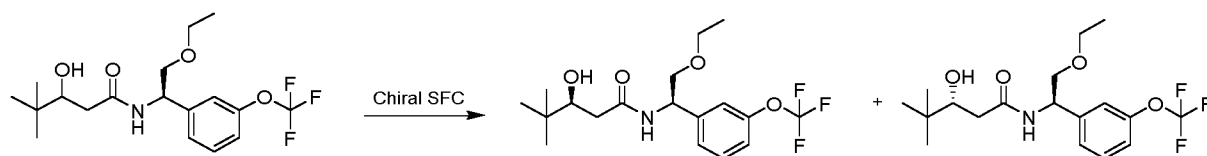


Step 1: Preparation of *N*-((*R*)-2-ethoxy-1-(3-(trifluoromethoxy) phenyl)ethyl)-3-hydroxy-4,4-dimethylpentanamide



Prepared from **Vb**.

Step 2: Separation of (*S*)-3-hydroxy-4,4-dimethyl-*N*-((*S*)-1-(3-(2,2,2-trifluoroethoxy)phenyl)ethyl)pentanamide and (*R*)-3-hydroxy-4,4-dimethyl-*N*-((*S*)-1-(3-(2,2,2-trifluoroethoxy) phenyl)ethyl)pentanamide



15 *N*-((*R*)-2-ethoxy-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-hydroxy-4,4-dimethylpentanamide was separated by chromatography

Example 2a:

20 ¹H NMR (DMSO-d₆ 300MHz): δ 8.34 (d, 1H), 7.48-7.35 (m, 3H), 7.23 (d, 1H), 5.07 (d, 1H), 4.61 (d, 1H), 3.34-3.54 (m, 5H), 2.31-2.20 (m, 1H), 2.17-2.08 (m, 1H), 1.08 (t, 2H), 0.83 (s, 9H).

LC-MS: t_R = 1.87 min (LC-MS Method 4), m/z = 378.2 [M + H]⁺.

25 SFC: t_R = 1.71 min (SFC Method 18), ee% = 96.0%.

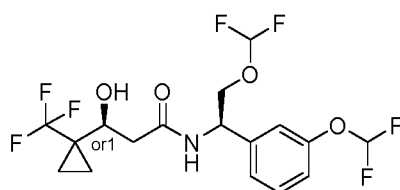
Example 2b:

¹H NMR (DMSO-d₆ 300MHz): δ 8.39 (d, 1H), 7.46 (t, J=7.8 Hz, 5H), 7.35 (t, 2H), 7.23 (d, 3H), 5.06 (d, 1H), 4.63 (d, 1H), 3.56-3.52 (m, 3H), 3.49-3.43 (m, 2H), 2.29-2.25 (m, 1H), 2.19-2.08 (m, 1H), 1.07 (t, , 2H), 0.82 (s, 9H).

LC-MS: t_R = 1.87 min (LC-MS Method 4), m/z =378.2 [M + H]⁺.

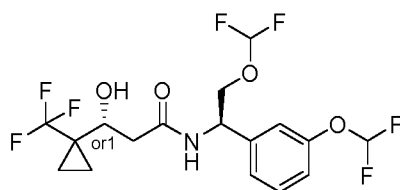
SFC: t_R = 1.82 min (SFC Method 18), ee% = 99.1%.

Example 3a: *N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-3-(1-(trifluoromethyl)cyclopropyl)propanamide



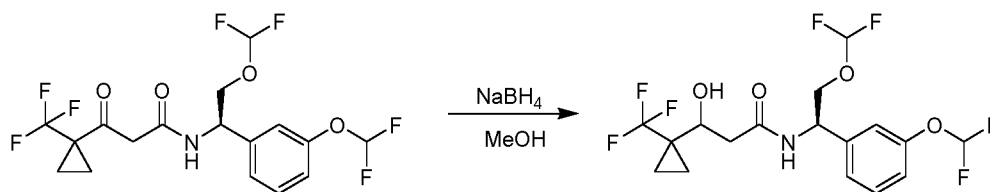
and

Example 3b: *N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-3-(1-(trifluoromethyl)cyclopropyl)propanamide



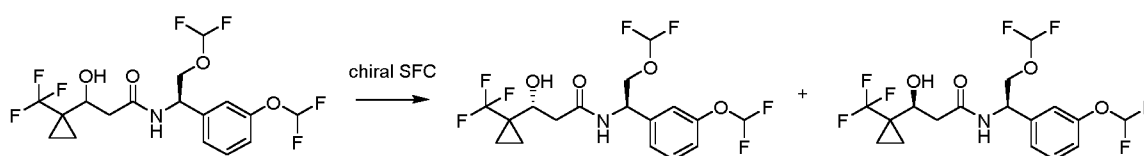
Step 1: Preparation of *N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-3-(1-(trifluoro-methyl)cyclopropyl)propanamide

125



Prepared from **Vc**.

- 5 Step 2: Separation of (R)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-3-(1-(trifluoro-methyl)cyclopropyl)propanamide and (S)- N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-3-(1-(trifluoro-methyl)cyclopropyl)propanamide



- N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl) ethyl)-3-hydroxy-3-(1-(trifluoromethyl)cyclopropyl)propanamide
15 was separated by chiral SFC.

Example 3a:

- ¹H NMR (CDCl₃ 400MHz): δ 7.35 (t, 1H), 7.16 (d, 1H),
20 7.07-7.05 (m, 2H), 6.45 (t, 1H), 6.33 (s, 1H), 6.22 (t, 1H), 5.28-5.24 (m, 1H), 4.17-4.04 (m, 3H), 3.68 (s, 1H), 2.67 (dd, 1H), 2.55 (dd, 1H), 0.92-0.88 (m, 3H), 0.85-0.82 (m, 1H).

- LC-MS: t_R = 2.51 min (LCMS Method 1), m/z = 434.1 [M +
25 H]⁺.

SFC: t_R = 1.95 min (SFC Method 3), ee% = 100%.

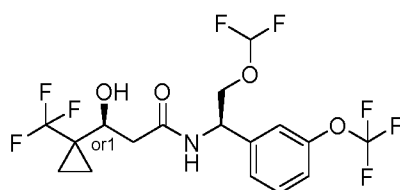
Example 3b:

¹H NMR (CDCl₃ 400MHz): δ 7.36 (t, 1H), 7.16 (d, 1H),
7.06 (m, 2H), 6.50 (t, 1H), 6.38 (d, 1H), 6.21 (t, 1H),
5.27-5.23 (m, 1H), 4.13-4.04 (m, 3H), 3.76 (d, 1H),
2.67-2.56 (m, 2H), 0.98-0.87 (m, 4H).

LC-MS: t_R = 2.51 min (LCMS Method 1), m/z = 434.1 [M + H]⁺.

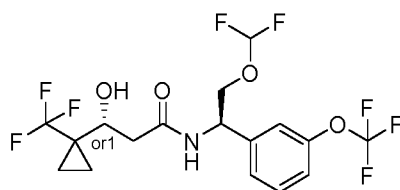
SFC: t_R = 1.58 min (SFC Method 3), ee% = 90,0 %.

Example 4a: *N*-((*R*)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-hydroxy-3-(1-(trifluoromethyl)cyclopropyl)propanamide



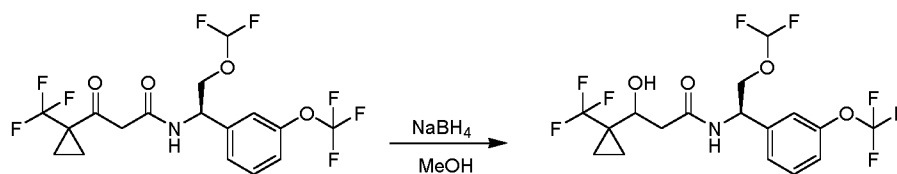
and

Example 4b: *N*-((*R*)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-hydroxy-3-(1-(trifluoromethyl)cyclopropyl)propanamide



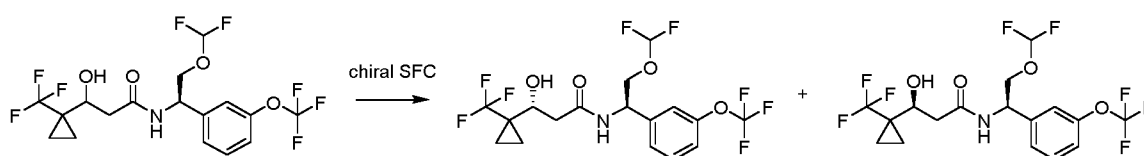
Step 1: Preparation of *N*-((*R*)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-hydroxy-3-(1-(trifluoro-methyl)cyclopropyl)propanamide

127



Prepared from **Vd**.

- 5 Step 2: Separation of (*R*)-*N*-((*R*)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-hydroxy-3-(1-(trifluoromethyl)cyclopropyl)propanamide and (*S*)-*N*-((*R*)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-hydroxy-3-(1-(trifluoromethyl)cyclopropyl)propanamide



- N*-((*R*)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-hydroxy-3-(1-(trifluoromethyl)cyclopropyl)propanamide was separated by chiral SFC.

Example 4a:

- ¹H NMR (CDCl₃ 400MHz): δ 7.41 (t, 1H), 7.27 (s, 1H), 7.18 (m, 2H), 6.41 (s, 1H), 6.23 (t, 1H), 5.30 (s, 1H), 4.16-4.06 (m, 3H), 3.74 (s, 1H), 2.69-2.56 (m, 2H), 1.00-0.90 (m, 4H).

LC-MS: t_R = 2.53 min (LCMS Method 2), m/z = 452.1 [M + H]⁺.

SFC: t_R = 1.21 min (SFC Method 7), ee% = 100%.

Example 4b:

¹H NMR (CDCl₃ 400MHz): δ 7.40 (t, 1H), 7.27 (s, 1H), 7.18

128

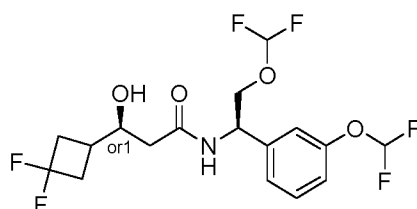
(m, 2H), 6.42 (s, 1H), 6.24 (t, 1H), 5.30 (s, 1H), 4.19-4.05 (m, 3H), 3.69 (s, 1H), 2.71-2.55 (m, 2H), 0.93-0.83 (m, 4H).

LC-MS: t_R = 2.63 min (LCMS Method 1), m/z = 452.1 [M + H]⁺.

SFC: t_R = 1.57 min (SFC Method 7), ee% = 99.8%.

Example 5a: 3-(3,3-difluorocyclobutyl)-N-((R)-2-

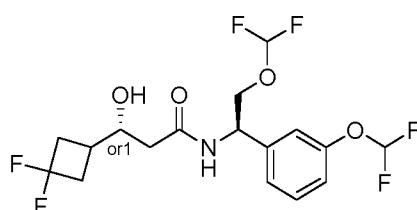
(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxypropanamide



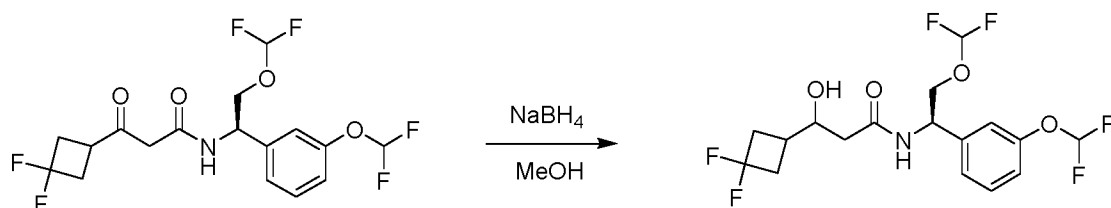
and

Example 5b: 3-(3,3-difluorocyclobutyl)-N-((R)-2-

(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxypropanamide

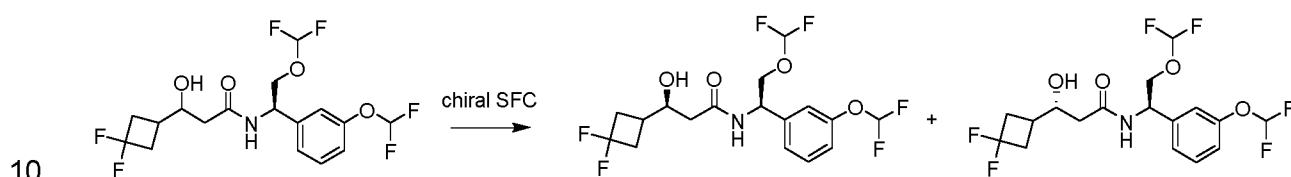


Step 1: Preparation of (R)-3-(3,3-difluorocyclobutyl)-N-(2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-oxopropanamide



Prepared from **Ve**.

Step 2: Separation of (R)-3-(3,3-difluorocyclobutyl)-N-
 ((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxypropanamide and
 (S)-3-(3,3-difluorocyclobutyl)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-
 3-hydroxypropanamide



(R)-3-(3,3-difluorocyclobutyl)-N-(2-(trifluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-oxopropanamide
 was separated by chiral SFC.

15

Example 5a:

¹H NMR (CDCl₃ 400MHz): δ 7.37 (t, 1H), 7.17 (d, 1H),
 7.09-7.07 (m, 2H), 6.51 (t, 1H), 6.32 (m, 1H), 6.13 (t,
 1H), 5.30-5.25 (m, 1H), 4.18-4.14 (m, 1H), 4.10-4.06 (m,
 1H), 4.00-3.96 (m, 1H), 3.64 (d, 1H), 2.59-2.55 (m, 3H),
 2.45-2.35 (m, 2H), 2.34-2.26 (m, 1H), 2.21-2.08 (m, 1H).

20

LC-MS: t_R = 2.74 min (LCMS Method 1), m/z = 416.1 [M + H]⁺.

SFC: t_R = 2.49 min (SFC Method 4), ee% = 97.7%.

25

Example 5b:

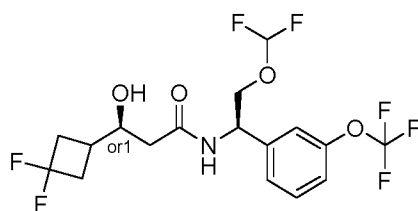
¹H NMR (CDCl₃ 400MHz): δ 7.37 (t, 1H), 7.17 (d, 1H),
 7.08-7.07 (m, 2H), 6.51 (t, 1H), 6.32 (m, 1H), 6.23 (t,
 1H), 5.30-5.26 (m, 1H), 4.18-4.15 (m, 1H), 4.11-4.07 (m,

1H), 4.02-3.98 (m, 1H), 2.64-2.51 (m, 3H), 2.45-2.36 (m, 2H), 2.33-2.25 (m, 1H), 2.21-2.16 (m, 1H).

LC-MS: t_R = 2.73 min (LCMS Method 1), m/z = 416.1 [M + H]⁺.

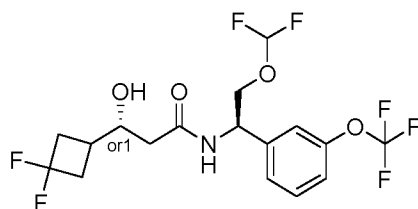
5 **SFC:** t_R = 2.59 min (SFC Method 4), ee% = 96.1%.

Example 6a: 3-(3,3-difluorocyclobutyl)-N-((R)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-hydroxypropanamide

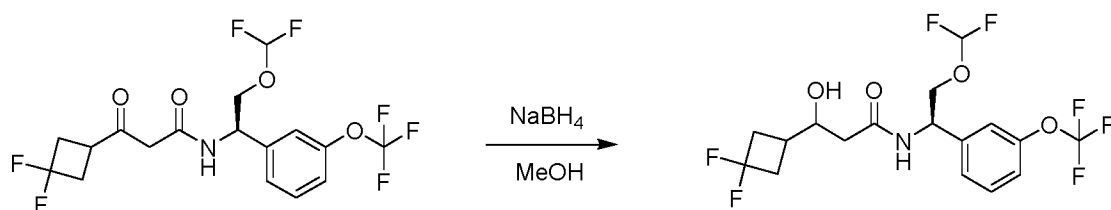


and

Example 6b: 3-(3,3-difluorocyclobutyl)-N-((R)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-hydroxypropanamide

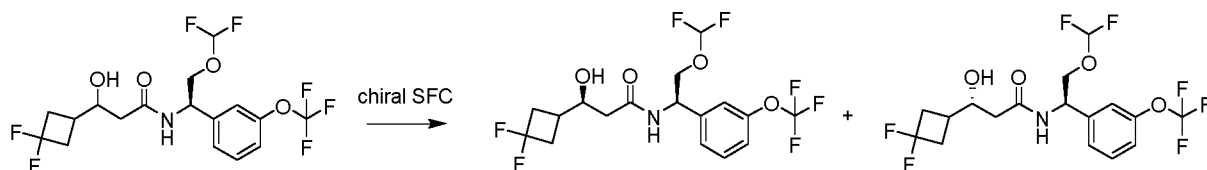


Step 1: Preparation of (R)-3-(3,3-difluorocyclobutyl)-N-(2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-oxopropanamide



Prepared from **Vf**.

Step 2: Separation of (R)-3-(3,3-difluorocyclobutyl)-N-((R)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-hydroxypropanamide and (S)-3-(3,3-difluorocyclobutyl)-N-((R)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-hydroxypropanamide



(R)-3-(3,3-difluorocyclobutyl)-N-((R)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-hydroxypropanamide was separated by chiral SFC.

Example 6a:

¹H NMR (CDCl₃ 400MHz): δ 7.41 (t, 1H), 7.26 (d, 1H), 7.19 (d, 2H), 6.38 (d, 1H), 6.24 (t, 1H), 5.33-5.28 (m, 1H), 4.20-4.16 (m, 1H), 4.13-4.10 (m, 1H), 4.01-4.00 (s, 1H), 3.56 (d, 2H), 2.61-2.54 (m, 3H), 2.44-2.39 (m, 2H), 2.39-2.32 (m, 1H), 2.18 (m, 1H).

LC-MS: t_R = 2.53 min (LCMS Method 1), m/z = 434.0 [M + H]⁺.

SFC: t_R = 1.62 min (SFC Method 5), ee% = 92.9%.

Example 6b:

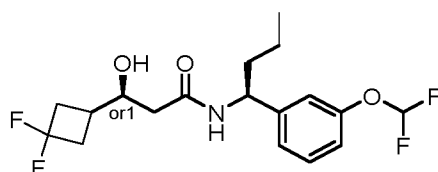
¹H NMR (CDCl₃ 400MHz): δ 7.42 (t, 1H), 7.26 (d, 1H), 7.20-7.18 (m, 2H), 6.34 (d, 1H), 6.24 (t, 1H), 5.33-5.28 (m, 1H), 4.20-4.16 (m, 1H), 4.13-4.00 (m, 1H), 4.00 (m, 1H), 3.61 (s, 1H), 2.61-2.57 (m, 3H), 2.43-2.39 (m, 2H), 2.39-2.32 (m, 1H), 2.20 (m, 1H).

LC-MS: $t_R = 2.54$ min (LCMS Method 1), $m/z = 434.0$ $[M + H]^+$.

SFC: $t_R = 1.71$ min (SFC Method 5), $ee\% = 97.9\%$.

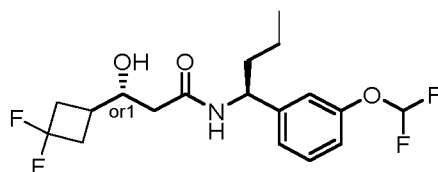
5

Example 7a: 3-(3,3-difluorocyclobutyl)-*N*-((*S*)-1-(3-(difluoromethoxy)phenyl)butyl)-3-hydroxypropanamide

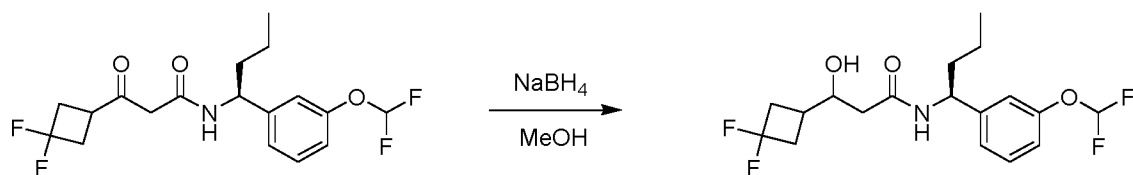


10 and

Example 7b: 3-(3,3-difluorocyclobutyl)-*N*-((*S*)-1-(3-(difluoromethoxy)phenyl)butyl)-3-hydroxypropanamide

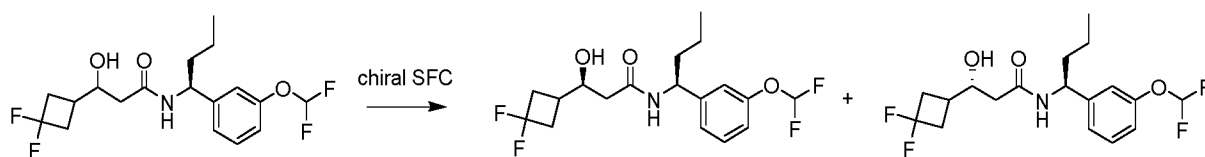


15 **Step 1:** Preparation of 3-(3,3-difluorocyclobutyl)-*N*-((*S*)-1-(3-(difluoromethoxy)phenyl)butyl)-3-hydroxypropanamide

20 Prepared from **Vg**

Step 2: Separation of (*S*)-3-(3,3-difluorocyclobutyl)-*N*-((*S*)-1-(3-(difluoromethoxy)phenyl)butyl)-3-hydroxypropanamide and (*R*)-3-(3,3-difluorocyclobutyl)-

N-((*S*)-1-(3-(difluoromethoxy) phenyl)butyl)-3-hydroxypropanamide



- 5 3-(3,3-difluorocyclobutyl)-*N*-((*S*)-1-(3-(difluoromethoxy) phenyl)butyl)-3-hydroxypropanamide was separated by chiral SFC.

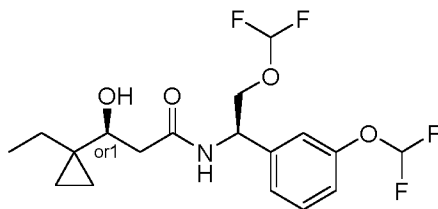
Example 7a:

- 10 ¹H NMR (CDCl₃ 400 MHz): δ 7.32 (t, 1H), 7.11 (d, 1H), 7.01-7.00 (m, 2H), 6.49 (t, 1H), 5.85 (d, 1H), 4.93 (q, 1H), 3.94-3.91 (m, 1H), 3.81 (d, 1H), 2.56-2.21 (m, 7H), 1.74-1.69 (m, 2H), 1.33-1.28 (m, 2H), 0.91 (t, 3H).
- 15 **LC-MS:** *t_R* = 2.41 min (LC-MS Method 1), *m/z* = 378.0 [M + H]⁺.
- SFC:** *t_R* = 2.37 min (SFC method 6), ee% = 92.4%

Example 7b:

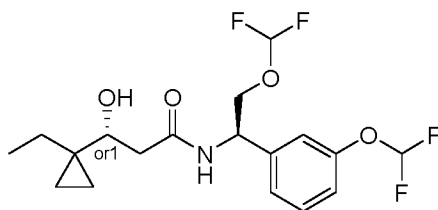
- 20 ¹H NMR (CDCl₃ 400 MHz): δ 7.31 (t, 1H), 7.10 (d, 1H), 7.01-7.00 (m, 2H), 6.49 (t, 1H), 5.86 (d, 1H), 4.93 (q, 1H), 3.96-3.92 (m, 1H), 3.77 (d, 1H), 2.54-2.14 (m, 7H), 1.74-1.70 (m, 2H), 1.33-1.28 (m, 2H), 0.91 (t, 3H).
- LC-MS:** *t_R* = 2.45 min (LC-MS Method 1), *m/z* = 378.0 [M + H]⁺.
- 25 **SFC:** *t_R* = 2.49 min (SFC Method 6), ee% = 99.5%

Example 8a: *N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-(1-ethylcyclopropyl)-3-hydroxypropanamide



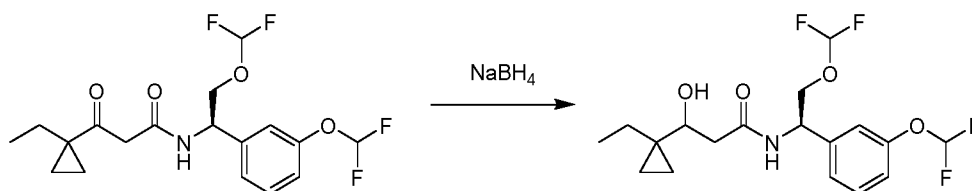
5 and

Example 8b: *N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-(1-ethylcyclopropyl)-3-hydroxypropanamide



10

Step 1: Preparation of *N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-(1-ethylcyclopropyl)-3-hydroxypropanamide

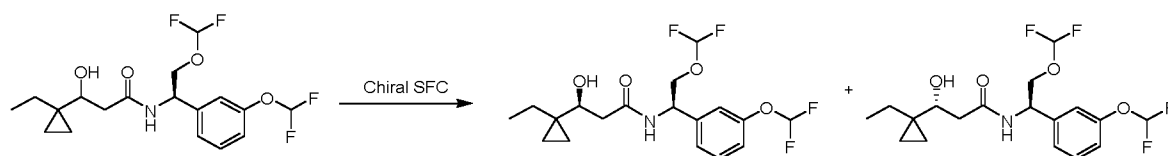


15 Prepared from **Vh**

Step 2: Separation of (*S*)-*N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-(1-ethylcyclopropyl)-3-hydroxypropanamide and (*R*)-*N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-(1-ethylcyclopropyl)-3-hydroxypropanamide

20

135



N-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-(1-ethylcyclopropyl)-3-

5 hydroxypropanamide was separated by chiral SFC

Example 8a:

¹H NMR (CDCl₃ 400MHz): δ 7.28 (t, 1H), 7.11 (d, 1H), 7.03 (s, 1H), 6.98 (d, 1H), 6.66 (d, 1H), 6.44 (t, 1H), 6.14 (t, 1H), 5.24-5.19 (m, 1H), 4.10-4.02 (m, 2H), 3.47-3.44 (m, 1H), 2.57 (d, 1H), 2.50-2.41 (m, 2H), 1.53-1.48 (m, 2H), 1.34-1.31 (m, 1H), 0.83-0.80 (m, 3H), 0.38-0.29 (m, 4H).

15 LC-MS: t_R = 2.38 min (LCMS Method 1), m/z = 394.0 [M + H]⁺.

SFC: t_R = 2.38 min (SFC Method 1), ee% = 99.4%

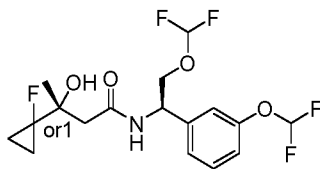
Example 8b:

20 ¹H NMR (CDCl₃ 400MHz): δ 7.29 (t, 1H), 7.11 (d, 1H), 7.01-6.99 (m, 2H), 6.67 (d, 1H), 6.44 (t, 1H), 6.15 (t, 1H), 5.24-5.19 (m, 1H), 4.10-4.00 (m, 2H), 3.49-3.47 (d, 1H), 2.64 (d, 1H), 2.49-2.41 (m, 2H), 1.53-1.48 (m, 2H), 1.34-1.31 (m, 1H), 0.83-0.80 (m, 3H), 0.39-0.29 (m, 4H).

25 LC-MS: t_R = 2.38 min (LCMS Method 1), m/z = 394.0 [M + H]⁺.

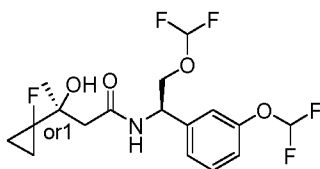
SFC: t = 2.60 min (SFC Method 1), ee% = 98.7 %

Example 9a: *N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-(1-fluorocyclopropyl)-3-hydroxybutanamide



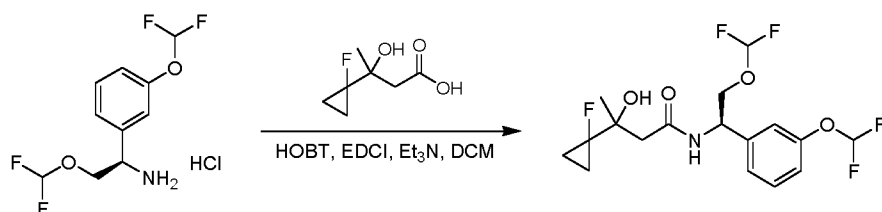
5 and

Example 9b: *N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-(1-fluorocyclopropyl)-3-hydroxybutanamide



10

Step 1: Preparation of *N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-(1-fluorocyclopropyl)-3-hydroxybutanamide

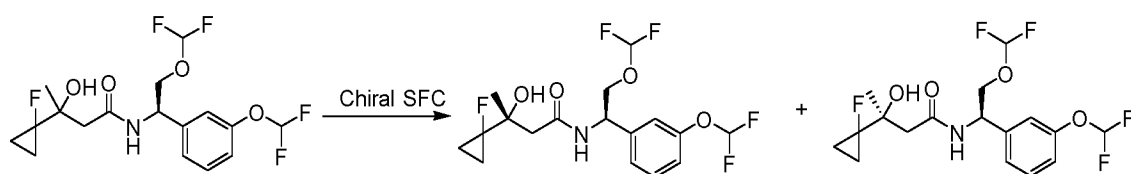


15 To a solution of (*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethan-1-amine hydrochloride (**IIa**) (400 mg) and 3-(1-fluorocyclopropyl)-3-hydroxybutanoic acid (**IIIc**) (307 mg) in DCM (20 mL) was added *N*-hydroxybenzotriazole (HOBt) (213 mg), 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) (363 mg) and

20 Et₃N (320 mg). The mixture was stirred at 25 °C for 16 hours and then diluted with water (10 mL), and extracted with EtOAc (20 mL×3). The combined organic

extracts were dried over Na_2SO_4 , filtered and concentrated. The residue was purified by basic preparative HPLC to afford *N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-(1-fluorocyclopropyl)-3-hydroxybutanamide (250 mg).

Step 2: Separation of (*R*)-*N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-(1-fluorocyclopropyl)-3-hydroxybutanamide and (*S*)-*N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-(1-fluorocyclopropyl)-3-hydroxybutanamide



N-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-(1-fluorocyclopropyl)-3-hydroxybutanamide was separated by chiral SFC.

Example 9a:

^1H NMR (CDCl_3 400MHz): δ 7.38 (t, 1H), 7.20 (d, 1H), 7.10 (m, 2H), 6.52 (t, 1H), 6.39 (d, 1H), 6.25 (t, 1H), 5.31 (m, 1H), 4.80 (s, 1H), 4.15 (m, 2H), 2.71 (dd, 1H), 2.54 (dd, 1H), 1.36 (s, 3H), 0.85-0.55 (m, 4H).

LC-MS: t_R = 2.48 min (LCMS Method 1), m/z = 398.2 $[\text{M} + \text{H}]^+$.

SFC: t_R = 2.46 min (SFC Method 12), ee% = 100%.

Example 9b:

^1H NMR (CDCl_3 400MHz): δ 7.39 (t, 1H), 7.19 (d, 1H), 7.10-7.08 (m, 2H), 6.52 (t, 1H), 6.42 (m, 1H), 6.24 (t,

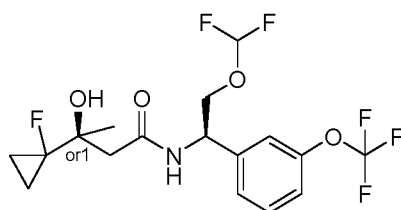
1H), 5.33–5.28 (m, 1H), 4.71 (s, 1H), 4.19–4.10 (m, 2H), 2.72 (d, 1H), 2.52 (d, 1H), 1.36 (s, 3H), 0.99–0.85 (m, 4H).

LC-MS: t_R = 2.47 min (LCMS Method 1), m/z = 398.1 [M + H]⁺.

SFC: t_R = 2.65 min (SFC Method 12), ee% = 98.8%.

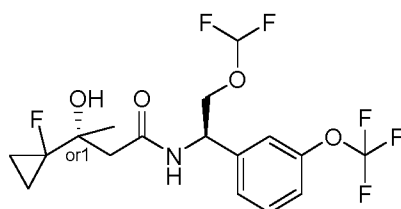
The following examples were prepared by similar methodology as described for Example 9a and Example 9b, using the relevant intermediates:

Example 10a: *N*-((*R*)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-(1-fluorocyclopropyl)-3-hydroxybutanamide

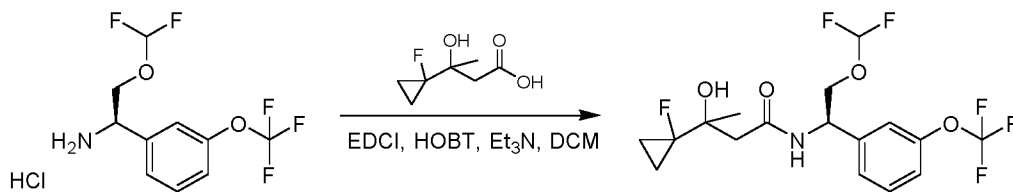


And

Example 10b: *N*-((*R*)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-(1-fluorocyclopropyl)-3-hydroxybutanamide



Step 1: Preparation of *N*-((*R*)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-(1-fluorocyclopropyl)-3-hydroxybutanamide

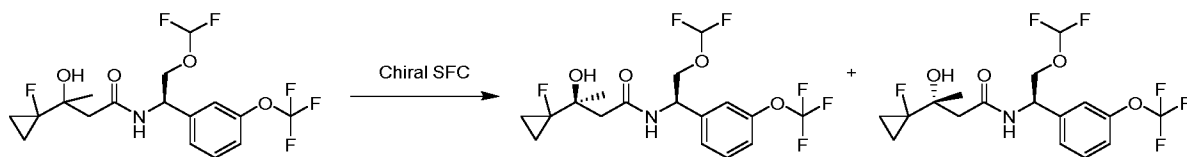


5

Prepared from **I Ib** and **III c**

Step 2: Separation of (*S*)-*N*-((*R*)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-(1-fluorocyclopropyl)-3-hydroxybutanamide and (*R*)-*N*-((*R*)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-(1-fluorocyclopropyl)-3-hydroxybutanamide

10



15

N-((*R*)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-(1-fluorocyclopropyl)-3-hydroxybutanamide was separated using chiral SFC

Example 10a:

20

¹H NMR (CDCl₃ 400MHz): δ 7.48 (t, 1H), 7.35 (d, 1H), 7.27-7.25 (m, 2H), 6.64 (d, 1H), 6.31 (t, 1H), 5.40-5.38 (m, 1H), 4.86 (s, 1H), 4.26-4.18 (m, 2H), 2.78 (d, 1H), 2.60 (d, 1H), 1.42 (s, 3H), 0.86-0.57 (m, 4H).

25

LC-MS: t_R = 2.64 min (LCMS Method 1), m/z = 416.2 [M + H]⁺.

SFC: $t_R = 2.38$ min (SFC Method 2), $ee\% = 100\%$.

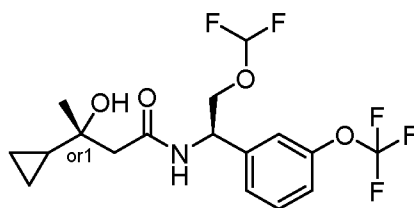
Example 10b:

1H NMR ($CDCl_3$ 400MHz): δ 7.42 (t, 1H), 7.29 (m, 1H),
 5 7.20-7.19 (m, 2H), 6.44-6.06 (m, 2H), 5.35-5.31 (m,
 1H), 4.67 (s, 1H), 4.20-4.12 (m, 2H), 2.73 (dd, 1H),
 2.53 (dd, 1H), 1.36 (s, 3H), 0.99-0.86 (m, 4H).

LC-MS: $t_R = 2.659$ min (LCMS Method 1), $m/z = 416.2$ [M + H] $^+$.

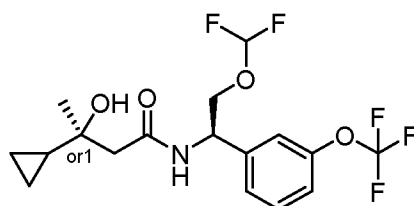
10 SFC: $t_R = 2.561$ min (SFC Method 6), $ee\% = 95.9\%$.

Example 11a: 3-cyclopropyl-N-((R)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl) ethyl)-3-
 15 **hydroxybutanamide**



and

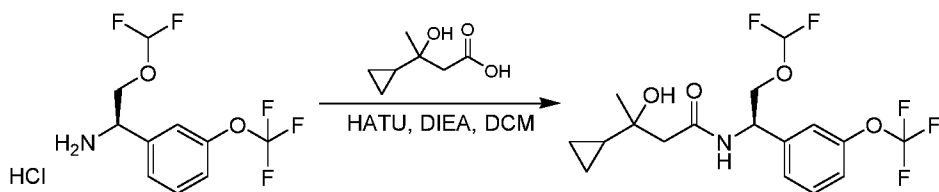
Example 11b: 3-cyclopropyl-N-((R)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl) ethyl)-3-
 20 **hydroxybutanamide**



Step 1: Preparation of 3-cyclopropyl-N-((R)-2-(difluoromethoxy)-1-(3-

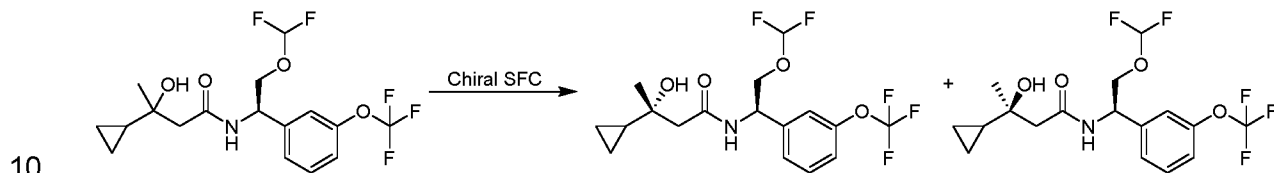
25 (trifluoromethoxy)phenyl) ethyl)-3-hydroxybutanamide

141



Prepared from **IIb** and **IIId**

- 5 Step 2: Separation of (*R*)-3-cyclopropyl-*N*-((*R*)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-hydroxybutanamide and (*S*)-3-cyclopropyl-*N*-((*R*)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-hydroxybutanamide



3-cyclopropyl-*N*-((*R*)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-hydroxybutanamide was separated by chiral SFC

15

Example 11a:

¹H NMR (CDCl₃, 400 MHz): δ 7.38 (t, 1H), 7.26 (d, 1H), 7.17-7.15 (m, 2H), 6.72 (d, 1H), 6.21 (t, 1H), 5.35-5.31 (m, 1H), 4.17-4.09 (m, 2H), 3.36 (s, 1H), 2.52-2.42 (m, 2H), 1.18 (s, 3H), 0.90-0.88 (m, 1H), 0.43-0.34 (m, 4H).

20

LC-MS: *t*_R = 2.42 min (LCMS Method 1), *m/z* = 420.1 [M + Na]⁺.

SFC: *t*_R = 2.17 min (SFC Method 13), ee% = 100%.

25

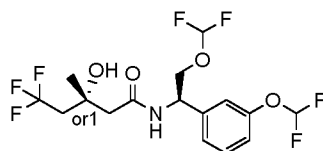
Example 11b:

^1H NMR (CDCl_3 , 400 MHz): δ 7.39 (t, 1H), 7.29–7.20 (m, 1H), 7.21–7.16 (m, 2H), 6.74 (d, 1H), 6.23 (t, 1H), 5.36–5.32 (m, 1H), 4.19–4.10 (m, 2H), 3.40 (s, 1H), 2.49 (s, 2H), 1.18 (s, 3H), 0.90–0.87 (m, 1H), 0.41–0.27 (m, 4H).

5 **LC-MS**: t_R = 2.95 min (LCMS Method 1), m/z = 420.1 $[\text{M} + \text{Na}]^+$.

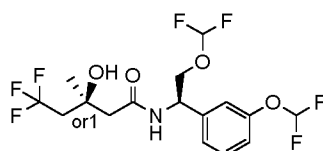
SFC: t_R = 2.48 min (SFC Method 13), ee% = 100%.

10 **Example 12a**: *N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-5,5,5-trifluoro-3-hydroxy-3-methylpentanamide

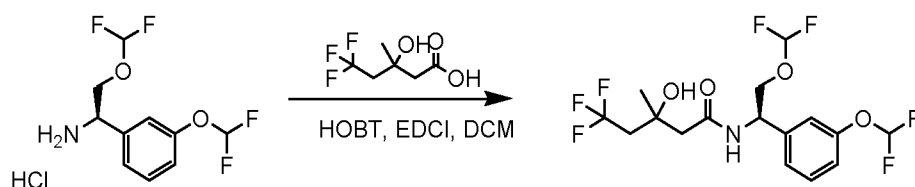


And

15 **Example 12b**: *N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-5,5,5-trifluoro-3-hydroxy-3-methylpentanamide

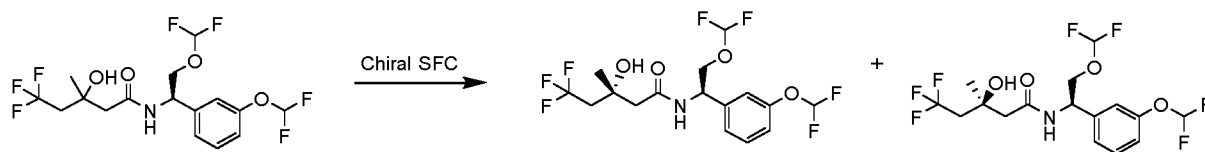


20 **Step 1**: Preparation of *N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-5,5,5-trifluoro-3-hydroxy-3-methylpentanamide



Prepared from **IIa** and **IIIe**

Step 2: Separation of (*R*)-*N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-5,5,5-trifluoro-3-hydroxy-3-methylpentanamide and (*S*)-*N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-5,5,5-trifluoro-3-hydroxy-3-methylpentanamide



10 *N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-5,5,5-trifluoro-3-hydroxy-3-methylpentanamide was separated by chiral SFC

15 Example 12a:

¹H NMR (CDCl₃ 400MHz): δ 7.38 (t, 1H), 7.17 (d, 1H), 7.10-7.08 (m, 2H), 6.51 (t, 1H), 6.37 (d, 1H), 6.25 (t, 1H), 5.32-5.27 (m, 1H), 4.68 (s, 1H), 4.18 (dd, 1H), 2.52 (dd, 1H), 2.61-2.52 (m, 2H), 2.47-2.41 (m, 2H), 1.40 (s, 3H).

LC-MS: t_R = 2.52 min (LCMS Method 1), m/z = 422.1 [M + H]⁺.

SFC: t_R = 1.10 min (SFC Method 14), ee% = 100%.

25 Example 12b:

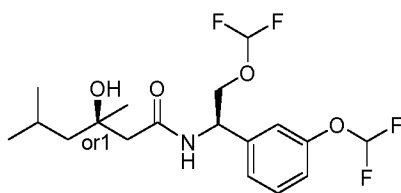
¹H NMR (CDCl₃ 400MHz): δ 7.39 (t, 1H), 7.18 (d, 1H), 7.10-7.08 (m, 2H), 6.52 (t, 1H), 6.36 (d, 1H), 6.24 (t, 1H), 5.33-5.29 (m, 1H), 4.68 (s, 1H), 4.18 (dd, 1H), 2.52 (dd, 1H), 2.61-2.42 (m, 4H), 1.39 (s, 3H).

LC-MS: $t_R = 2.52$ min (LCMS Method 1), $m/z = 422.1$ $[M + H]^+$.

SFC: $t_R = 1.24$ min (SFC Method 14), $ee\% = 95.8\%$.

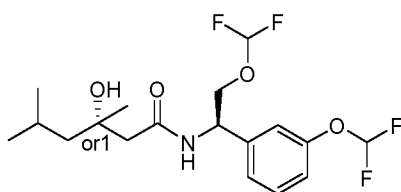
5

Example 13a: *N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-3,5-dimethylhexanamide



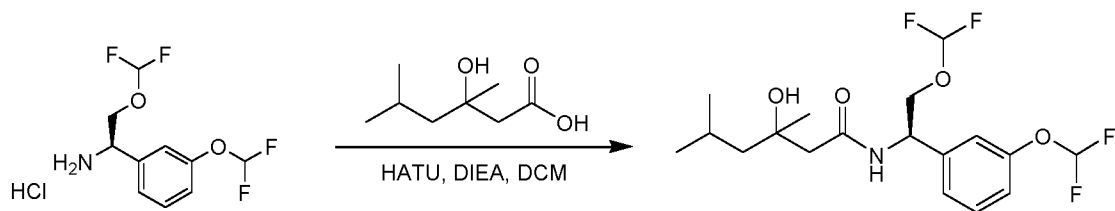
10 And

Example 13b: *N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-3,5-dimethylhexanamide



15

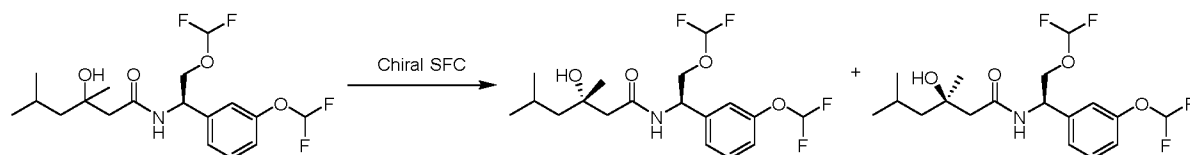
Step 1: Preparation of *N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-3,5-dimethylhexanamide



20

Prepared from **IIa** and **IIIg**

Step 2: Separation of (*R*)-*N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-3,5-dimethylhexanamide and (*S*)-*N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-3,5-



N-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-3,5-dimethylhexanamide was separated by chiral SFC

Example 13a:

¹H NMR (CDCl₃ 400MHz): δ 7.37 (t, 1H), 7.19 (d, 1H), 7.10-7.07 (m, 2H), 6.76 (d, 1H), 6.51 (t, 1H), 6.23 (t, 1H), 5.35-5.30 (m, 1H), 4.19-4.08 (m, 2H), 3.39 (s, 1H), 2.51-2.34 (m, 2H), 1.84-1.76 (m, 1H), 1.43 (d, 2H), 1.27 (s, 3H), 0.98-0.95 (m, 6H).

LC-MS: t_R = 2.54 min (LCMS Method 1), m/z = 396.1 [M + H]⁺.

SFC: t_R = 2.40 min (SFC Method 15), ee% = 99.3 %.

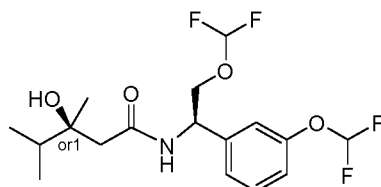
Example 13b:

¹H NMR (CDCl₃ 400MHz): δ 7.37 (t, 1H), 7.19 (d, 1H), 7.10 (s, 1H), 7.07 (d, 1H), 6.73 (d, 1H), 6.51 (t, 1H), 6.23 (t, 1H), 5.35-5.31 (m, 1H), 4.19-4.09 (m, 2H), 3.37 (s, 1H), 2.50-2.34 (m, 2H), 1.85-1.76 (m, 1H), 1.45 (d, 2H), 1.26 (s, 3H), 1.00-0.94 (m, 6H).

LC-MS: t_R = 2.54 min (LC-MS Method 1), m/z = 396.1 [M + H]⁺.

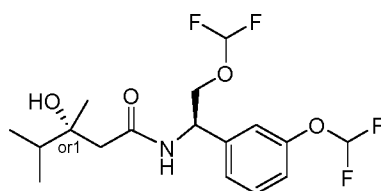
SFC: $t_R = 2.66$ min (SFC Method 15), $ee\% = 98.8\%$.

Example 14a: *N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-3,4-dimethylpentanamide

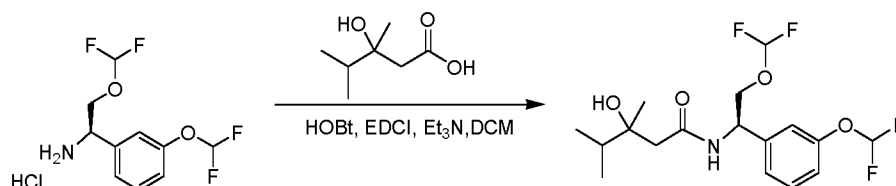


And

Example 14b: *N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-3,4-dimethylpentanamide



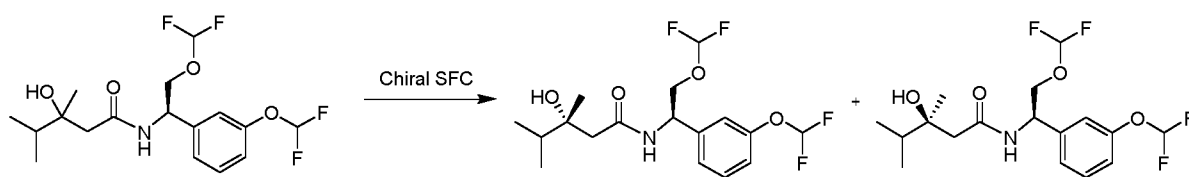
Step 1: Preparation of *N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-3,4-dimethylpentanamide



Prepared from **IIa** and **III f**

Step 2: Separation of (*S*)-*N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-3,4-dimethylpentanamide and (*R*)-*N*-((*R*)-2-

(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-
3-hydroxy-3,4-dimethylpentanamide



- 5 *N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-3,4-dimethylpentanamide was separated using chiral SFC.

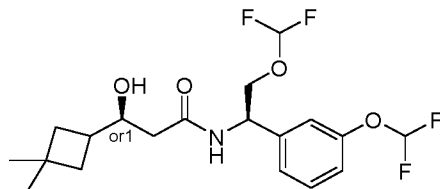
Example 14a:

- 10 ^1H NMR (CDCl_3 400 MHz): δ 7.34 (t, 1H), 7.16 (d, 1H), 7.07 (s, 1H), 7.04 (d, 1H), 6.76 (d, 1H), 6.48 (t, 1H), 6.20 (t, 1H), 5.32-5.27 (m, 1H), 4.16-4.12 (m, 1H), 4.09-4.04 (m, 1H), 3.39 (s, 1H), 2.49-2.28 (m, 2H), 1.77-1.70 (m, 1H), 1.15 (s, 3H), 0.93-0.89 (m, 6H).
- 15 **LC-MS**: t_R = 2.41 min (LCMS Method 1), m/z = 382.0 $[\text{M} + \text{H}]^+$.
SFC: t_R = 2.44 min (SFC Method 15), ee% = 100%.

Example 14b:

- 20 ^1H NMR (CDCl_3 400 MHz): δ 7.35 (t, 1H), 7.16 (d, 1H), 7.08 (s, 1H), 7.04 (d, 1H), 6.79 (d, 1H), 6.48 (t, 1H), 6.19 (t, 1H), 5.31-5.26 (m, 1H), 4.14-4.10 (m, 1H), 4.08-4.04 (m, 1H), 3.43 (s, 1H), 2.48-2.28 (m, 2H), 1.75-1.69 (m, 1H), 1.12 (s, 3H), 0.92-0.88 (m, 6H).
- 25 **LC-MS**: t_R = 2.41 min (LCMS Method 1), m/z = 382.0 $[\text{M} + \text{H}]^+$.
SFC: t_R = 2.68 min (SFC Method 15), ee% = 97.4%.

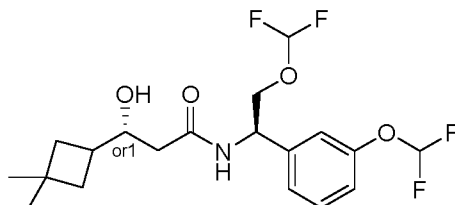
Example 15a: *N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-(3,3-dimethylcyclobutyl)-3-hydroxypropanamide



5

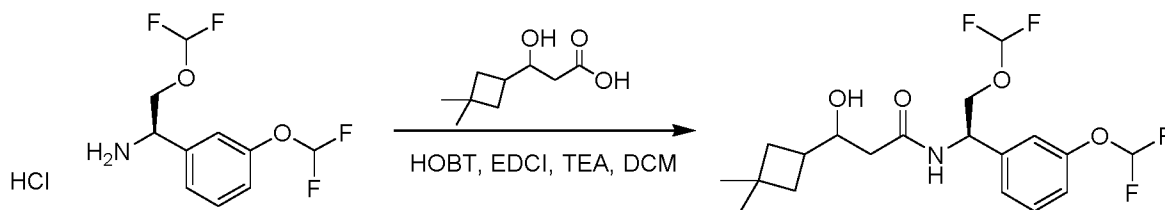
and

Example 15b: *N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-(3,3-dimethylcyclobutyl)-3-hydroxypropanamide



10

Step 1: Preparation of *N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-(3,3-dimethylcyclobutyl)-3-hydroxypropanamide



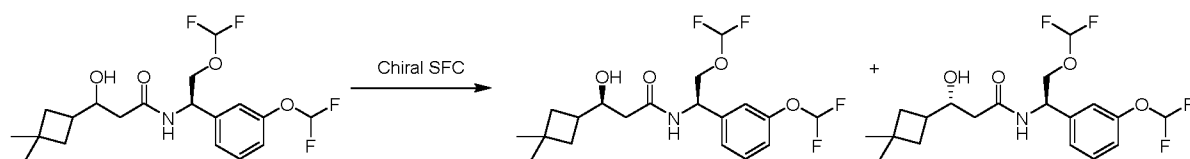
15

Prepared from **IIa** and **IIIh**

Step 2: Separation of (*S*)-*N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-(3,3-dimethylcyclobutyl)-3-hydroxypropanamide and (*R*)-*N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)

20

)phenyl)ethyl)-3-(3,3-dimethylcyclobutyl)-3-hydroxypropanamide



- 5 *N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-(3,3-dimethylcyclobutyl)-3-hydroxypropanamide was separated by chiral SFC

Example 15a:

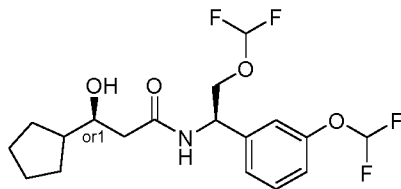
- 10 $^1\text{H NMR}$ (DMSO- d_6 400 MHz): δ 8.41 (d, 1H), 7.40 (t, 1H), 7.26 (d, 1H), 7.21 (t, 1H), 7.20 (s, 1H), 7.09 (d, 1H), 6.67 (t, 1H), 5.17-5.12 (m, 1H), 4.61 (d, 1H), 3.98-3.97 (m, 2H), 3.70-3.67 (m, 1H), 2.16-2.11 (m, 3H), 1.64-1.52 (m, 4H), 1.09 (s, 3H), 0.99 (s, 3H).
- 15 **LC-MS:** t_R = 2.35 min (LC-MS Method 3), m/z = 408.1 [$M + H$] $^+$.
- SFC:** t_R = 2.32 min (SFC Method 16), ee% = 99.7

Example 15b:

- 20 $^1\text{H NMR}$ (DMSO- d_6 400 MHz): δ 8.43 (d, 1H), 7.40 (t, 1H), 7.24 (d, 1H), 7.22 (t, 1H), 7.18 (s, 1H), 7.08 (d, 1H), 6.67 (t, 1H), 5.14-5.10 (m, 1H), 4.63 (d, 1H), 3.99-3.96 (m, 2H), 3.70-3.67 (m, 1H), 2.13-2.08 (m, 3H), 1.64-1.49 (m, 4H), 1.06 (s, 3H), 0.97 (s, 3H).
- 25 **LC-MS:** t_R = 2.34 min (LCMS Method 3), m/z = 408.1 [$M + H$] $^+$.
- SFC:** t_R = 2.64 min (SFC Method 16), ee% = 98.7 %.

150

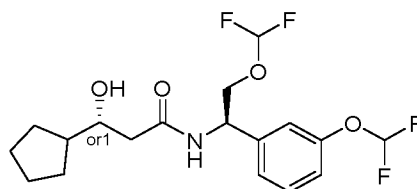
Example 16a: 3-cyclopentyl-*N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxypropanamide



5

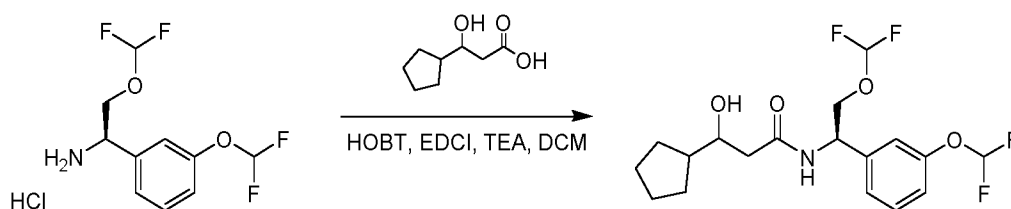
and

Example 16b: 3-cyclopentyl-*N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxypropanamide



10

Step 1: Preparation of 3-cyclopentyl-*N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxypropanamide



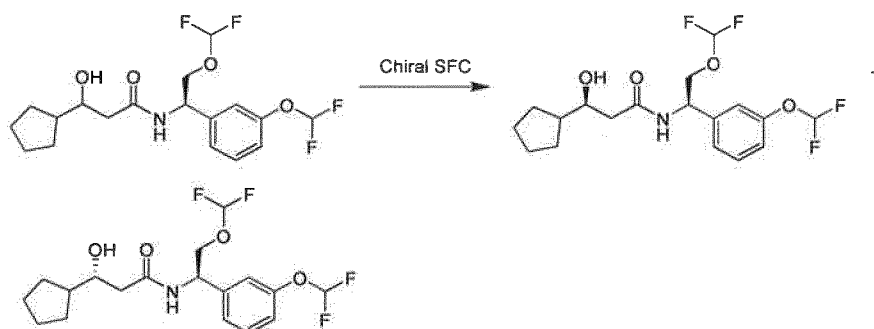
15

Prepared from **IIa** and **IIIi**

Step 2: Separation of (*S*)-3-cyclopentyl-*N*-((*R*)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxypropanamide and (*R*)-3-cyclopentyl-*N*-((*R*)-2-

20

(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-
3-hydroxypropanamide



5

3-cyclopentyl-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxypropanamide
was separated by chiral SFC

10 Example 16a:

¹H NMR (DMSO-d₆ 400 MHz) δ 8.43 (d, 1H), 7.39 (t, 1H), 7.27-7.25 (m, 1H), 7.20 (s, 1H), 7.20 (t, 1H), 7.08 (d, 1H), 6.66 (t, 1H), 5.16-5.14 (m, 1H), 4.61 (d, 1H), 3.99-3.97 (m, 2H), 3.69-3.65 (m, 1H), 2.26-2.25 (m, 2H), 1.80-1.76 (m, 1H), 1.64-1.22 (m, 8H).

LC-MS: t_R = 2.48 min (LC-MS Method 1), m/z = 394.1[M + H]⁺.

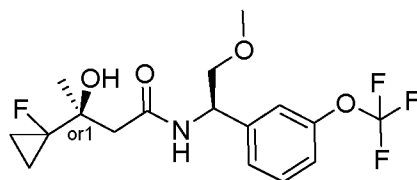
SFC: t_R = 2.64 min (SFC Method 17), ee% = 98.8 %.

20 Example 16b:

¹H NMR (DMSO-d₆ 400 MHz): δ 8.41 (d, 1H), 7.36 (d, 1H), 7.20 (d, 1H), 7.18 (t, 1H), 7.15 (s, 1H), 7.04 (m, 1H), 6.63 (t, 1H), 5.13-5.07 (m, 1H), 4.59 (d, 1H), 3.98-3.91 (m, 2H), 3.66-3.62 (m, 1H), 2.23-2.19 (m, 2H), 1.73-1.69 (m, 1H), 1.60-1.33 (m, 8H).

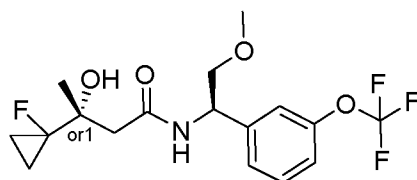
LC-MS: t_R = 2.27 min (LC-MS Method 2), m/z = 394.2[M + H]⁺. **SFC:** t_R = 3.08 min (SFC Method 17), ee% = 100%

Example 36a: 3-(1-fluorocyclopropyl)-3-hydroxy-N-((R)-2-methoxy-1-(3-(trifluoromethoxy)phenyl)ethyl)butanamide



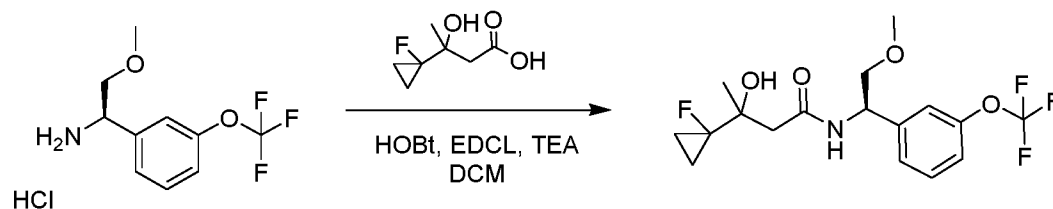
5 and

Example 36b: 3-(1-fluorocyclopropyl)-3-hydroxy-N-((R)-2-methoxy-1-(3-(trifluoromethoxy)phenyl)ethyl)butanamide



10

Step 1: Preparation of 3-(1-fluorocyclopropyl)-3-hydroxy-N-((R)-2-methoxy-1-(3-(trifluoromethoxy)phenyl)ethyl)butanamide



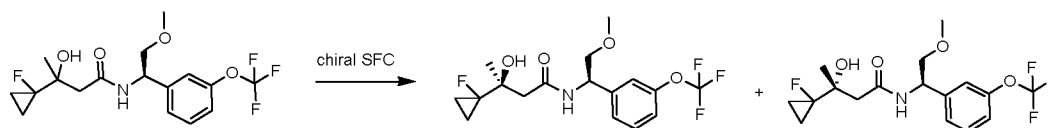
15

Prepared from **IIp** and **IIIc**

Step 2: Separation of (R)-3-(1-fluorocyclopropyl)-3-hydroxy-N-((R)-2-methoxy-1-(3-(trifluoromethoxy)phenyl)ethyl)butanamide and (S)-3-(1-fluorocyclopropyl)-3-hydroxy-N-((R)-2-methoxy-1-(3-(trifluoromethoxy)phenyl)ethyl)butanamide

20

153



3-(1-fluorocyclopropyl)-3-hydroxy-N-((R)-2-methoxy-1-(3-(trifluoromethoxy)phenyl)ethyl)butanamide was separated using chiral SFC.

5

Example 36a:

¹H NMR (CDCl₃ 400MHz): δ 7.38 (t, 1H), 7.29 (d, 1H), 7.22 (s, 1H), 7.16 (d, 1H), 6.58 (d, 1H), 5.18-5.13 (m, 1H), 5.04 (s, 1H), 3.70-3.62 (m, 2H), 3.38 (s, 3H), 2.72-2.68 (m, 1H), 2.54-2.50 (m, 1H), 1.36 (s, 3H), 0.81-0.53 (m, 4H).

10

LC-MS: t_R = 2.43 min (LCMS Method 1), m/z = 380.0 [M + H]⁺.

SFC: t_R = 1.29 min (SFC Method 21), ee% = 99.6%.

15 **Example 36b:**

¹H NMR (CDCl₃ 400MHz): δ 7.38 (t, 1H), 7.28-7.27 (m, 1H), 7.20 (s, 1H), 7.15 (d, 1H), 6.58 (d, 1H), 5.18-5.14 (m, 1H), 4.93 (s, 1H), 3.70-3.62 (m, 2H), 3.38 (s, 3H), 2.71 (dd, 1H), 2.52 (dd, 1H), 1.35 (s, 3H), 1.00-0.86 (m, 4H).

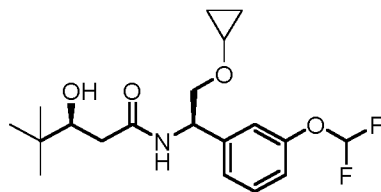
20

LC-MS: t_R = 2.53 min (LCMS Method 1), m/z = 380.0 [M + H]⁺.

SFC: t_R = 1.76 min (SFC Method 22), ee% = 81.4%.

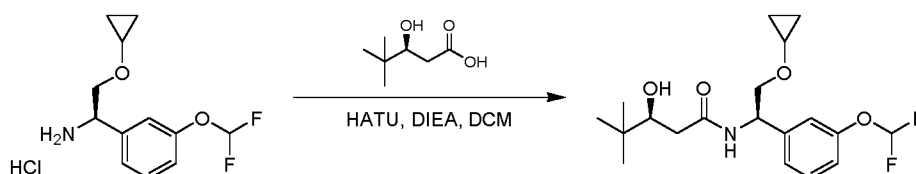
25

Example 17: (*S*)-*N*-((*R*)-2-cyclopropoxy-1-(3-(difluoromethoxy) phenyl)ethyl)-3-hydroxy-4,4-dimethylpentanamide



5

Step 1: Preparation of (*S*)-*N*-((*R*)-2-cyclopropoxy-1-(3-(difluoromethoxy) phenyl)ethyl)-3-hydroxy-4,4-dimethylpentanamide



10

To a solution of (*R*)-2-cyclopropoxy-1-(3-(difluoromethoxy)phenyl)ethan-1-amine hydrochloride (**IIc**) (0.2 g), (*3S*)-3-hydroxy-4,4-dimethyl-pentanoic acid (**IIIa**) (144 mg) and HATU (375 mg) in DCM (10 mL) was added DIEA (319 mg). The mixture was stirred at 20 °C for 16 hours and concentrated. The crude was purified to give (*S*)-*N*-((*R*)-2-cyclopropoxy-1-(3-(difluoromethoxy) phenyl)ethyl)-3-hydroxy-4,4-dimethylpentanamide.

¹H NMR (CDCl₃ 400MHz): δ 7.33 (t, 1H), 7.17 (d, 1H), 7.08 (s, 1H), 7.03 (d, 1H), 6.49 (m, 1H), 6.51 (t, 1H), 5.18-5.14 (m, 1H), 3.80-3.78 (m, 1H), 3.72-3.66 (m, 2H), 3.42 (d, 1H), 3.35-3.25 (m, 1H), 2.44-2.26 (m, 2H), 0.93 (s, 9H), 0.57-0.45 (m, 4H).

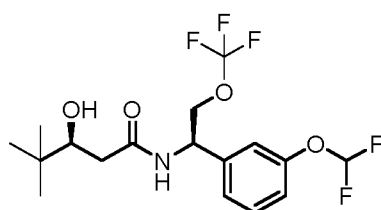
LC-MS: t_R = 2.40 min (LCMS Method 1), m/z = 372.1 [M + H]⁺.

25

SFC: $t_R = 1.988$ min (SFC Method 7), $ee\% = 97.5\%$.

The following examples were prepared by similar methodology as described for example 17, using the relevant intermediates:

Example 18: (S)-N-((R)-1-(3-(difluoromethoxy)phenyl)-2-(trifluoromethoxy)ethyl)-3-hydroxy-4,4-dimethylpentanamide



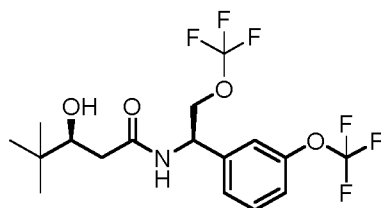
Prepared from **IIe** and **IIIa**

^1H NMR (CDCl_3 , 400 MHz): δ 7.41-7.36 (m, 1H), 7.18 (d, 1H), 7.10-7.08 (m, 2H), 6.67 (d, 1H), 6.52 (t, 1H), 5.37-5.32 (m, 1H), 4.28-4.20 (m, 1H), 3.69 (d, 1H), 2.93 (s, 1H), 2.47-2.43 (m, 1H), 2.36-2.29 (m, 1H), 0.93 (s, 9H).

LC-MS: $t_R = 2.38$ min (LCMS Method 3), $m/z = 400.0$ $[\text{M}+\text{H}]^+$.

SFC: $t_R = 2.11$ min, (SFC Method 4), $ee\% = 96.4\%$.

Example 19: (S)-N-((R)-1-(3-(trifluoromethoxy)phenyl)-2-(trifluoromethoxy)ethyl)-3-hydroxy-4,4-dimethylpentanamide

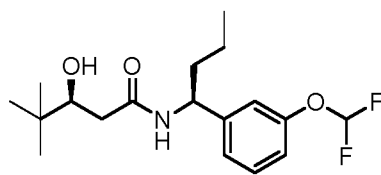


¹H NMR (CDCl₃ 400 MHz): δ 7.35 (t, 1H), 7.21-7.19 (m, 1H), 7.13-7.11 (m, 2H), 6.65 (d, 1H), 5.32-5.27 (m, 1H), 4.21-4.13 (m, 1H), 3.64-3.61 (m, 1H), 2.83 (d, 1H), 2.41-2.36 (m, 1H), 2.29-2.25 (m, 1H), 0.86 (s, 9H).

LC-MS: t_R = 2.56 min (LCMS Method 3), m/z = 418.0 [M+H]⁺.

HPLC: t_R = 13.54 min (HPLC Method 2), ee% = 65.9%

Example 20: (S)-N-((S)-1-(3-(difluoromethoxy)phenyl)butyl)-3-hydroxy-4,4-dimethylpentanamide



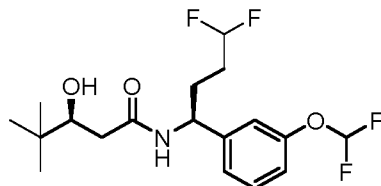
Prepared from IIg and IIIa.

¹H NMR (CDCl₃ 400 MHz): δ 7.33 (t, 1H), 7.14 (d, 1H), 7.03-7.00 (m, 2H), 6.52 (t, 1H), 6.22-6.20 (m, 1H), 4.97 (q, 1H), 3.68-3.64 (m, 1H), 3.31 (d, 1H), 2.39-2.24 (m, 2H), 1.75-1.72 (m, 2H), 1.36-1.29 (m, 2H), 0.95-0.91 (m, 12H).

LC-MS: t_R = 2.30 min (LCMS Method 3), m/z = 344.1 [M + H]⁺.

SFC: t_R = 2.13 min (SFC Method 1), ee% = 98.7%.

Example 21: (*S*)-*N*-((*S*)-1-(3-(difluoromethoxy)phenyl)-4,4-difluorobutyl)-3-hydroxy-4,4-dimethylpentanamide



5 Prepared from **IIh** and **IIIa**.

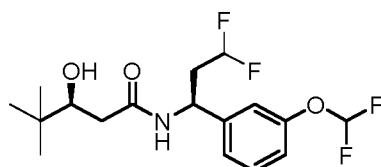
¹H NMR (CDCl₃ 400MHz): δ 7.36 (t, 1H), 7.14 (d, 1H), 7.05 (m, 2H), 6.52 (t, 1H), 6.25 (d, 1H), 5.84 (tt, 1H), 5.03 (q, 1H), 3.68 (m, 1H), 2.97 (d, 1H), 2.40-2.21 (2H),
10 1.98-1.77 (4H), 0.91 (s, 9H).

LC-MS: t_R = 2.43 min (LCMS Method 1), m/z = 380.0 [M + H]⁺.

HPLC: t_R = 14.01 min (HPLC Method 3), ee% = 95.7%.

15

Example 22: (*S*)-*N*-((*S*)-1-(3-(difluoromethoxy)phenyl)-3,3-difluoropropyl)-3-hydroxy-4,4-dimethylpentanamide



20 Prepared from **IIIi** and **IIIa**.

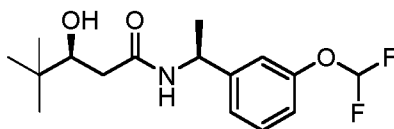
¹H NMR (CDCl₃ 400 MHz): δ 7.35 (t, 1H), 7.14 (d, 1H), 7.05-7.03 (m, 2H), 6.50 (t, 1H), 6.53-6.50 (m, 1H), 5.80 (tt, 1H), 5.30-5.24 (m, 1H), 3.66 (dd, 1H), 2.89 (s, 1H), 2.40-2.22 (m, 4H), 0.89 (s, 9H).
25

LC-MS: t_R = 2.63 min (LCMS Method 1), m/z = 366.2 [M +

H]⁺.

HPLC: t_R = 13.43 min (HPLC Method 1), ee% = 96.7%.

5 **Example 23: (S)-N-((S)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-4,4-dimethylpentanamide**



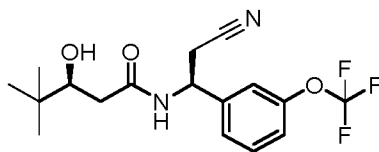
Prepared from **IIj** and **IIIa**.

10 **¹H NMR** (CDCl₃ 400 MHz): δ 7.34-7.30 (m, 1H), 7.16-7.12 (m, 1H), 7.04-6.97 (m, 2 H), 6.31 (t, 1 H), 6.14 (brs, 1 H), 5.12-5.06 (m, 1 H), 3.67-3.62 (m, 1 H), 3.29 (s, 1 H), 2.37-2.31 (m, 1 H), 2.26-2.19 (m, 1 H), 1.47-1.43 (m, 3 H), 0.98 (s, 9 H).

15 **LC-MS:** t_R = 2.155 min (LCMS Method 2), m/z = 316.1 [M + H]⁺.

SFC: t_R = 2.416 min (SFC Method 8), ee% = 100%.

20 **Example 24: (S)-N-((S)-2-cyano-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-hydroxy-4,4-dimethylpentanamide**



Prepared from **IIIm** and **IIIa**.

25

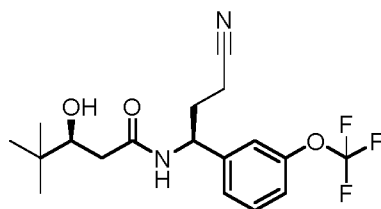
¹H NMR (400 MHz, DMSO-d₆): δ 8.66 (d, 1H), 7.51 (t, 1H), 7.45-7.43 (m, 2H), 7.30 (d, 1H), 5.25-5.23 (m,

1H), 4.62 (d, 1H), 3.57-3.51 (m, 1H), 3.00 (dd, 2H), 2.31-2.11 (m, 2H), 0.81 (s, 9H).

LC-MS: t_R = 2.42 min (LSMS Method 1), m/z = 359.2 [M + H]⁺.

5 **HPLC:** t_R = 12.56 min (HPLC Method 4), ee% = 100%.

Example 25: (S)-N-((S)-3-cyano-1-(3-(trifluoromethoxy)phenyl) propyl)-3-hydroxy-4,4-dimethylpentanamide



Prepared from **IIn** and **IIIa**.

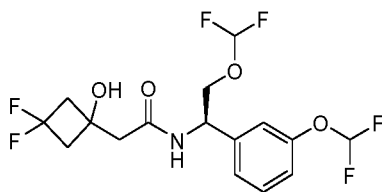
¹H NMR (CDCl₃ 400MHz): δ 7.42 (t, 1H), 7.24 (m, 1H), 7.18 (d, 1H), 7.13 (s, 1H), 6.49 (d, 1H), 5.19-5.13 (m, 1H), 3.75-3.71 (m, 1H), 2.82 (d, 1H), 2.45-2.40 (m, 3H), 2.30-2.27 (m, 1H), 2.23-2.16 (m, 2H), 0.92 (s, 9H).

LC-MS: t_R = 2.44 min (LCMS Method 1), m/z = 373.2 [M + H]⁺.

SFC: t_R = 1.47 min (SFC Method 9), ee% = 95.8%.

Example 26: (R)-2-(3,3-difluoro-1-hydroxycyclobutyl)-N-(2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl) ethyl)acetamide

160



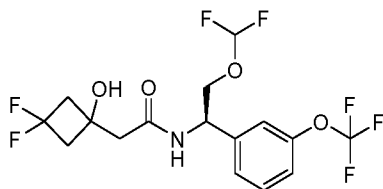
Prepared from **IIa** and **IIIb**.

¹H NMR (CDCl₃ 400 MHz): δ 7.37 (t, 1H), 7.15 (d, 1H),
 5 7.09–7.06 (m, 2H), 6.50 (t, 1H), 6.32 (t, 1H), 6.23 (m,
 1H), 5.29–5.24 (m, 1H), 4.74 (s, 1H), 4.17 (dd, 1H),
 4.08 (dd, 1H), 2.75–2.72 (m, 2H), 2.68 (s, 2H), 2.62–
 2.56 (m, 2H).

LC-MS: t_R = 2.39 min (LCMS Method 1), m/z = 402.1 [M +
 10 H]⁺.

SFC: t_R = 1.87 min (SFC Method 1), ee% = 100%

Example 27: (R)-2-(3,3-difluoro-1-hydroxycyclobutyl)-
 15 **N-(2-(difluoromethoxy)-1-(3-**
(trifluoromethoxy)phenyl)ethyl)acetamide



Prepared from **IIb** and **IIIb**.

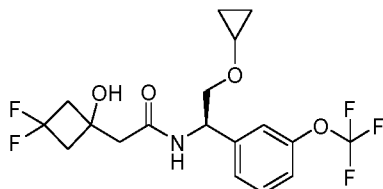
¹H NMR (CDCl₃ 400MHz): δ 7.35 (t, 1H), 7.14–7.09 (m, 3H),
 20 6.18 (t, 1H), 6.21 (d, 1H), 5.23 (m, 1H), 4.66 (br s,
 1H), 4.13 (dd, 1H), 4.04 (dd, 1H), 2.72–2.66 (m, 2H),
 2.64 (s, 2H), 2.56–2.50 (m, 2H).

LC-MS: t_R = 2.53 min (LC-MS Method 1), m/z = 420.2 [M+H]⁺.

HPLC: t_R = 12.77 min (HPLC Method 2), ee% = 86.7%.

25

Example 28: (R)-N-(2-cyclopropoxy-1-(3-(trifluoromethoxy)phenyl)ethyl)-2-(3,3-difluoro-1-hydroxycyclobutyl)acetamide



5

Prepared from **IIId** and **IIIb**.

$^1\text{H NMR}$ (CDCl_3 400MHz): δ 7.37 (t, 1H), 7.22 (d, 1H), 7.15 (m, 2H), 6.40 (d, 1H), 5.13 (m, 1H), 4.92 (s, 1H), 3.81 (m, 1H), 3.69 (m, 1H), 3.29 (m, 1H), 2.78-2.52 (6H), 0.57-0.44 (4H).

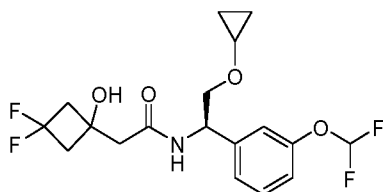
10

LC-MS: t_R = 2.53 min (LC-MS Method 1), m/z = 410.0 $[\text{M} + \text{H}]^+$.

SFC: t_R = 1.50 min (SFC Method 7), ee% = 99.7%

15

Example 29: (R)-N-(2-cyclopropoxy-1-(3-(difluoromethoxy)phenyl)ethyl)-2-(3,3-difluoro-1-hydroxycyclobutyl)acetamide



20

Prepared from **IIe** and **IIIb**.

$^1\text{H NMR}$ (CDCl_3 400 MHz): δ 7.35 (d, 1H), 7.15 (d, 1H), 7.06 (s, 1H), 7.05 (d, 1H), 6.51 (t, 1H), 6.39 (d, 1H), 5.15-5.10 (m, 1H), 4.98 (m, 1H), 3.83-3.67 (m, 2H), 3.31-3.30 (m, 1H), 2.79-2.75 (m, 2H), 2.68 (d, 2H), 2.64-2.52 (m, 2H), 0.60-0.46 (m, 4H).

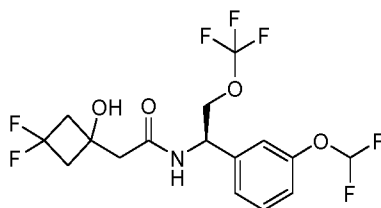
25

LC-MS: $t_R = 2.40$ min (LC-MS Method 1), $m/z = 392.1$ $[M + H]^+$.

SFC: $t_R = 2.32$ min (SFC Method 6), $ee\% = 100.00\%$

5

Example 30: (R)-2-(3,3-difluoro-1-hydroxycyclobutyl)-N-(1-(3-(difluoromethoxy)phenyl)-2-(trifluoromethoxy)ethyl)acetamide



10 Prepared from **IIe** and **IIIb**.

1H NMR ($CDCl_3$ 400MHz): δ 7.39 (t, 1H), 7.15 (d, 1H), 7.08 (m, 2H), 6.51 (t, 1H), 6.30 (m, 1H), 5.32 (m, 1H), 4.63 (s, 1H), 4.23 (m, 2H), 2.76-2.57 (6H).

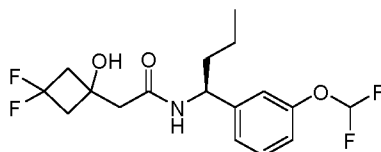
LC-MS: $t_R = 2.48$ min (LC-MS Method 1), $m/z = 420.0$ $[M + H]^+$.

15

SFC: $t_R = 12.96$ min (HPLC Method 2), $ee\% = 75.5\%$

Example 31: (S)-2-(3,3-difluoro-1-hydroxycyclobutyl)-N-(1-(3-(difluoromethoxy)phenyl)butyl)acetamide

20



Prepared from **IIg** and **IIIb**.

1H NMR ($CDCl_3$ 400 MHz): δ 7.35 (t, 1H), 7.13 (d, 1H), 7.04 (m, 2H), 6.52 (t, 1H), 5.91 (m, 1H), 5.04 (s, 1H), 4.96 (q, 1H), 2.78-2.56 (6H), 1.76 (m, 2H), 1.34 (m,

25

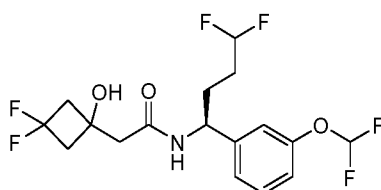
2H), 0.95 (t, 3H).

LC-MS: t_R = 2.44 min (LC-MS Method 1), m/z = 364.0 [M + H]⁺.

SFC: t_R = 1.71 min (SFC Method 10), ee% = 94.8%.

5

Example 32: (S)-2-(3,3-difluoro-1-hydroxycyclobutyl)-N-(1-(3-(difluoromethoxy)phenyl)-4,4-difluorobutyl)acetamide



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Prepared from **IIh** and **IIIb**.

¹H NMR (CDCl₃ 400MHz): δ 7.38 (t, 1H), 7.13 (d, 1H), 7.08 (d, 1H), 7.04 (s, 1H), 6.52 (t, 1H), 5.90 (d, 1H), 5.85 (tt, 1H), 5.00 (q, 1H), 4.82 (s, 1H), 2.78-2.54 (6H), 2.00 (m, 2H), 1.86 (m, 2H).

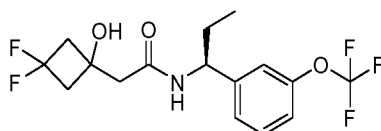
15

LC-MS: t_R = 2.50 min (LCMS Method 1), m/z = 400.1 [M + H]⁺.

HPLC: t_R = 12.48 min (HPLC Method 2), ee% = 98.3%.

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Example 33: (S)-2-(3,3-difluoro-1-hydroxycyclobutyl)-N-(1-(3-(trifluoromethoxy)phenyl)propyl)acetamide



25 Prepared from **III** and **IIIb**.

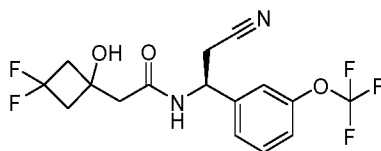
¹H NMR (CDCl₃ 400MHz): δ 7.38 (t, 1H), 7.20 (d, 1H),

7.14 (d, 1H), 7.10 (s, 1H), 5.89 (d, 1H), 4.99 (brs, 1H), 4.89 (q, 1H), 2.77-2.70 (m, 2H), 2.63 (d, 2H), 2.60-2.50 (m, 2H), 1.87-1.80 (m, 2H), 0.92 (t, 3H).

LC-MS: t_R = 2.57 min (LCMS Method 1), m/z = 368.1 [M + H]⁺.

SFC: t_R = 13.09 min (SFC Method 1), ee% = 100%

Example 34: (S)-N-(2-cyano-1-(3-(trifluoromethoxy)phenyl)ethyl)-2-(3,3-difluoro-1-hydroxycyclobutyl)acetamide



Prepared from **IIIm** and **IIIb**.

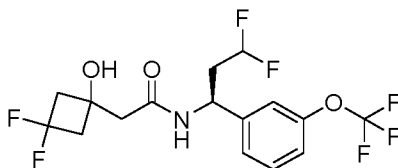
¹H NMR (CDCl₃ 400MHz): δ 7.46 (t, 1H), 7.30 (d, 1H), 7.24 (m, 1H), 7.19 (s, 1H), 6.51 (s, 1H), 5.34-5.29 (m, 1H), 4.44 (s, 1H), 3.09-3.03 (m, 1H), 2.91-2.89 (m, 1H), 2.77-2.73 (m, 2H), 2.70-2.53 (m, 4H).

LC-MS: t_R = 2.257 min (LC-MS Method 1), m/z = 379.0

[M+H]⁺.

SFC: t_R = 2.60 min (SFC Method 11), ee% = 100%.

Example 35: (S)-N-(3,3-difluoro-1-(3-(trifluoromethoxy)phenyl)propyl)-2-(3,3-difluoro-1-hydroxycyclobutyl)acetamide



Prepared from **IIo** and **IIIb**

¹H NMR (CDCl₃ 400 MHz): δ 7.44 (t, 1H), 7.23 (m, 2H),
7.15 (s, 1H), 6.15 (br d, 1H), 5.83 (tt, 1H), 5.32 (m,
5 1H), 4.69 (s, 1H), 2.73 (m, 2H), 2.66 (s, 2H), 2.62-
2.34 (4H).

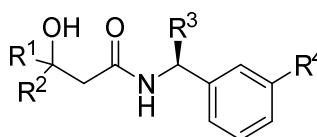
LC-MS: t_R = 2.53 min (LC-MS Method 1), m/z = 404.1 [M +
H]⁺.

SFC: t_R = 1.66 min (SFC Method 19), ee% = 98.5%

CLAIMS

1. A compound of Formula I

5



Formula I;

wherein

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R1 is selected from the group consisting of C₁-C₆ alkyl, CF₃, CH₂CF₃, CF₂CHF₂, C₃-C₈ cycloalkyl, wherein said C₃-C₈ cycloalkyl may be substituted with 1 or 2 substituents selected from the group consisting of C₁-C₃ alkyl, F, CHF₂ and CF₃; and

15

R2 is H, C₁-C₆ alkyl or CF₃; or

R1 and R2 combine to form C₃-C₅ cycloalkyl optionally substituted with 1 or 2 F, CHF₂ or CF₃;

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R3 is C₁-C₃ alkyl or CH₂O-C₁₋₃ alkyl, said C₁-C₃ alkyl or CH₂O-C₁-C₃ is alkyl substituted with C≡N, 3 F or C₃-C₅ cycloalkyl; and

R4 is selected from the group consisting of OCF₃ or OCHF₂,

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or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R4 is OCF₃.

3. The compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R3 is
 5 selected from the group consisting of CH₂-O-CF₃ and CH₂-C≡N.

4. The compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R1 is C₃-C₄ cycloalkyl optionally substituted with 1 or 2 C₁-C₃ alkyl, F, CHF₂
 10 or CF₃.

5. The compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R1 and R2 combine to form cyclobutyl optionally substituted with 1 or 2 F.
 15

6. The compound of claim 1, wherein the compound is selected from the group consisting of:

(S)-N-((R)-1-(3-(difluoromethoxy)phenyl)-2-(trifluoromethoxy)ethyl)-3-hydroxy-4,4-dimethylpentanamide;
 20 (S)-N-((R)-1-(3-(trifluoromethoxy)phenyl)-2-(trifluoromethoxy)ethyl)-3-hydroxy-4,4-dimethylpentanamide;
 (S)-N-((S)-2-cyano-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-hydroxy-4,4-dimethylpentanamide;
 (S)-N-((S)-3-cyano-1-(3-(trifluoromethoxy)phenyl)propyl)-3-
 25 hydroxy-4,4-dimethylpentanamide;
 (R)-2-(3,3-difluoro-1-hydroxycyclobutyl)-N-(1-(3-(difluoromethoxy)phenyl)-2-(trifluoromethoxy)ethyl)acetamide; and
 (S)-N-(2-cyano-1-(3-(trifluoromethoxy)phenyl)ethyl)-2-(3,3-
 30 difluoro-1-hydroxycyclobutyl)acetamide,
 or a pharmaceutically acceptable salt thereof.

7. A compound selected from the group consisting of:

- (R)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-4,4-dimethylpentanamide;
- (R)-N-((R)-2-ethoxy-1-(3-(trifluoromethoxy) phenyl)ethyl)-3-hydroxy-4,4-dimethylpentanamide;
- (S)-N-((R)-2-ethoxy-1-(3-(trifluoromethoxy) phenyl)ethyl)-3-hydroxy-4,4-dimethylpentanamide (R)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-3-(1-(trifluoro-methyl)cyclopropyl)propanamide;
- (S)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-3-(1-(trifluoro-methyl)cyclopropyl)propanamide;
- (R)-N-((R)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-hydroxy-3-(1-(trifluoromethyl)cyclopropyl)propanamide;
- (S)-N-((R)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl) ethyl)-3-hydroxy-3-(1-(trifluoromethyl)cyclopropyl) propanamide;
- (R)-3-(3,3-difluorocyclobutyl)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxypropanamide;
- (S)-3-(3,3-difluorocyclobutyl)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxypropanamide;
- (R)-3-(3,3-difluorocyclobutyl)-N-((R)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl) ethyl)-3-hydroxypropanamide;
- (S)-3-(3,3-difluorocyclobutyl)-N-((R)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-hydroxypropanamide;
- (S)-3-(3,3-difluorocyclobutyl)-N-((S)-1-(3-(difluoromethoxy)phenyl)butyl)-3-hydroxypropanamide;

(R)-3-(3,3-difluorocyclobutyl)-N-((S)-1-(3-(difluoromethoxy) phenyl)butyl)-3-hydroxypropanamide;
 (S)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-(1-ethylcyclopropyl)-3-hydroxypropanamide;
 5 (R)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl) ethyl)-3-(1-ethylcyclopropyl)-3-hydroxypropanamide;
 (S)-N-((S)-1-(3-(difluoromethoxy)phenyl)butyl)-3-hydroxy-4,4-dimethylpentanamide;
 10 (S)-N-((S)-1-(3-(difluoromethoxy)phenyl)-4,4-difluorobutyl)-3-hydroxy-4,4-dimethylpentanamide;
 (S)-N-((S)-1-(3-(difluoromethoxy)phenyl)-3,3-difluoropropyl)-3-hydroxy-4,4-dimethylpentanamide;
 15 (R)-2-(3,3-difluoro-1-hydroxycyclobutyl)-N-(2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)acetamide;
 (R)-2-(3,3-difluoro-1-hydroxycyclobutyl)-N-(2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)acetamide;
 20 (S)-2-(3,3-difluoro-1-hydroxycyclobutyl)-N-(1-(3-(difluoromethoxy)phenyl)butyl)acetamide;
 (S)-2-(3,3-difluoro-1-hydroxycyclobutyl)-N-(1-(3-(difluoromethoxy)phenyl)-4,4-difluorobutyl)acetamide;
 25 (S)-2-(3,3-difluoro-1-hydroxycyclobutyl)-N-(1-(3-(trifluoromethoxy) phenyl)propyl)acetamide;
 (S)-N-(3,3-difluoro-1-(3-(trifluoromethoxy)phenyl)propyl)-2-(3,3-difluoro-1-hydroxycyclobutyl)acetamide;
 (S)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-4,4-dimethylpentanamide;
 30

- (R)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-(1-fluorocyclopropyl)-3-hydroxybutanamide;
- 5 (S)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl) ethyl)-3-(1-fluorocyclopropyl)-3-hydroxybutanamide;
- (S)-N-((R)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl)ethyl)-3-(1-fluorocyclopropyl)-3-hydroxybutanamide;
- 10 (R)-N-((R)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl) ethyl)-3-(1-fluorocyclopropyl)-3-hydroxybutanamide;
- (R)-3-cyclopropyl-N-((R)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy)phenyl) ethyl)-3-hydroxybutanamide;
- 15 (S)-3-cyclopropyl-N-((R)-2-(difluoromethoxy)-1-(3-(trifluoromethoxy) phenyl)ethyl)-3-hydroxybutanamide;
- (R)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-5,5,5-trifluoro-3-hydroxy-3-methylpentanamide;
- 20 (S)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-5,5,5-trifluoro-3-hydroxy-3-methylpentanamide;
- (R)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-3,5-
- 25 dimethylhexanamide;
- (S)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-3,5-dimethylhexanamide;
- (S)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-3,4-
- 30 dimethylpentanamide;

- (R)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxy-3,4-dimethylpentanamide;
- (S)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-(3,3-dimethylcyclobutyl)-3-hydroxypropanamide;
- (R)-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-(3,3-dimethylcyclobutyl)-3-hydroxypropanamide;
- (S)-3-cyclopentyl-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxypropanamide;
- (R)-3-cyclopentyl-N-((R)-2-(difluoromethoxy)-1-(3-(difluoromethoxy)phenyl)ethyl)-3-hydroxypropanamide;
- (R)-3-(1-fluorocyclopropyl)-3-hydroxy-N-((R)-2-methoxy-1-(3-(trifluoromethoxy)phenyl)ethyl)butanamide;
- and (S)-3-(1-fluorocyclopropyl)-3-hydroxy-N-((R)-2-methoxy-1-(3-(trifluoromethoxy)phenyl)ethyl)butanamide, or a pharmaceutically acceptable salt thereof.
8. A pharmaceutical composition comprising a compound according to any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.
9. Use of a compound according to any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treatment of epilepsy, bipolar disorder, migraine, or schizophrenia.
10. Use of a compound according to any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, in the manufacture of a

medicament for treatment of psychosis, mania, stress-related disorders, acute stress reactions, bipolar depression, major depressive disorder, anxiety, panic attacks, social phobia, sleep disturbances, ADHD, PTSD, OCD, impulsivity disorders, personality disorders, schizotypal disorder, aggression, chronic pain, neuropathy, autism spectrum disorders, Huntington's chorea, sclerosis, multiple sclerosis, or Alzheimer's disease.

11. Use of a compound according to any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treatment of epilepsy, epileptic syndromes, epileptic symptoms, treatment resistant or refractory epilepsy, or seizures.

12. Use of a compound according to any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treatment of Focal (partial) epilepsy with simple partial seizures, Focal (partial) epilepsy with complex partial seizures, Generalized idiopathic epilepsy, Grand mal seizures, Status epilepticus, neonatal seizures, KCNQ epileptic encephalopathy (KCNQ2EE), Benign Familial Neonatal Convulsions, severe myoclonic epilepsy in infancy, epilepsy with continuous spike waves during slow-wave sleep, West syndrome, Lennox-Gastaut syndrome, Dravet syndrome and Early myoclonic encephalopathy Ohtahara syndrome, seizures related to stress, hormonal changes, drugs, alcohol, infection, traumatic brain injury, stroke, brain cancers, autism spectrum disorders or metabolic disturbances, or epileptic symptoms as part of neurogenerative disorders.

13. The use according to claim 12, wherein the seizures related to metabolic disturbances is hyponatraemia.

14. The use according to claim 12, wherein the neurodegenerative disorder is Alzheimer's disease, Lewy body disease, Huntington's disease juvenile form, or fronto-temporal lobar degeneration.