

Kv7 modulators

Technical field

The present invention provides novel compounds which modulate 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

Kv7 channels are voltage-dependent potassium channels that conduct potassium ions (K^+) across cell membranes in response to depolarizations of the cell membrane potential. The Kv7 channel family consists of five proteins Kv7.1, Kv7.2, Kv7.3, Kv7.4, Kv7.5 which are encoded by the human genes KCNQ1, KCNQ2, KCNQ3, KCNQ4 and KCNQ5 or the rodent, dog or non-human primate equivalents. The Kv7 proteins have the traditional Kv structure with six transmembrane helices (S1-S6) and with the N and C termini located intracellularly. Functional Kv7 channels exists as homo- or hetero-tetrameric complexes of these subunits surrounding the K^+ conducting transmembrane pore. Functional heteromeric channels described are Kv7.2/Kv7.3, Kv7.4/Kv7.3, Kv7.5/Kv7.3, and Kv7.4/Kv7.5 (for a general Kv7 review, see Soldovieri et al 2011; Physiology, 26, 365-376).

Kv7.2-Kv7.5 has been detected in neurons of the central nervous system (CNS), where especially the Kv7.2/Kv7.3 heteromeric channel plays an important role and underlies the so-called M-current (Brown and Adams, 1980; Nature, 283(5748), 673-676) a sustained and acetylcholine-sensitive K^+ current active in the range of action potential initiation and therefore a dominant conductance controlling neuronal excitability. The specific roles of Kv7.4 and Kv7.5 containing channels in the CNS seems less clear, but their wider expression, also in peripheral tissues such as smooth muscle cells, make especially Kv7.4 a potential off-target for development of Kv7 modulators for neuronal indications (Svaløe et al 2011; Basic & Clinical Pharmacology & Toxicology, 110, 145–153). Kv7 channels are also expressed in primary sensory neurons and are thus targets for treatment of various pain conditions. In contrast to the neuronally expressed Kv7 channels, Kv7.1 is primarily expressed in cardiac cells and in some epithelia, typically in complex with different KCNE β -subunits.

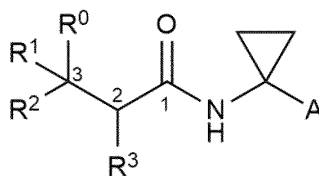
The pivotal role of the $K_v7.2/K_v7.3$ channel in controlling the excitability of CNS neurons is well illustrated by the mutations in both KCNQ2 and KCNQ3, which is strongly linked to neonatal or pediatric epilepsy diseases ranging in severity from relative benign self-limiting cases to serious encephalopathies, whereas such associations are seen much less frequently for $K_v7.5$ and hardly ever for $K_v7.4$ (Maljevic and Lerche, 2014; Progress in Brain Research, 213, 17-53). In line with this, compounds with an activating effect on the neuronal K_v7 channels have for a long time been known as anti-epileptics and analgesics, exemplified by the drugs retigabine, which was registered for the management of treatment resistant focal epilepsies, and flupirtine, which was on the market as an analgesic in some countries including Germany. Retigabine and flupirtine are close chemical analogues and both have now been withdrawn from the market due to long-term toxicities related to their unstable chemical structures (both are anilines) (Bock and Link, 2019; Future Med Chem, 11(4), 337-355). In addition to these chemical problems retigabine also showed adverse effects including both CNS and peripheral tissues of which the risk of causing urinary retention in sensitive patients was probably the most severe (Brickel et al, 2012; Epilepsia, 53(4), 606-612). Retigabine continued in new Ph 3 studies controlled by Xenon Pharmaceuticals under the name Xen496 with children diagnosed with KCNQ2 encephalopathies, but these studies were discontinued in May 2023 for yet unknown reasons.

Since K_v7 activation is a clinically validated concept (with no drugs currently on the market) for both epilepsy and pain, there is great interest in developing new K_v7 activators based on alternative chemical scaffolds. Fortunately, the scientific and patent literature reveals that other chemical classes can also act as K_v7 channel activators, either by interaction with the traditional retigabine activator site in the pore region (S5-6) or with an alternative site in the voltage sensor domains (S1-4). An added benefit of new chemical scaffolds may also be the possibility for better differentiation between K_v7 subtypes and thereby potentially improved efficacy and safety of the medicines. Approximately 1/3 of the epilepsy population is still not adequately treated with the existing medications. Similarly, several chronic pain conditions are poorly managed, which has led to the escalating opioid crisis in the USA. Thus, novel treatment principles are urgently needed for these diseases and improved K_v7 channel activating medicines represent a possible step to resolve these health issues.

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Summary

In one aspect, the present disclosure provides for a compound according to according to formula (I):



formula (I)

or a tautomer, a mesomer, a racemate, an enantiomer or a diastereoisomer thereof, or a mixture thereof; or a pharmaceutically acceptable salt thereof;

wherein,

R^0 is selected from the group consisting of $-OH$, and $-CH_3$;

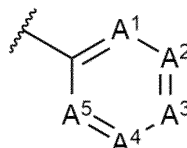
R^1 is aryl optionally substituted with one or more, identical or different, substituents R^4 , or heteroaryl optionally substituted with one or more, identical or different, substituents R^4 ;

R^4 is selected from the group consisting of C_{1-5} alkyl optionally substituted with one or more F, C_{1-5} alkoxy, halogen and CN;

R^2 is selected from the group consisting of $-H$, $-CH_3$, and $-CF_3$;

R^3 is selected from the group consisting of $-H$ and $-OH$;

A is of formula (II):



formula (II)

wherein

A^1 is $C-R^5$ or N;

R^5 is $-H$ or halogen;

A^2 is $C-R^6$;

R^6 is selected from the group consisting of C_{1-5} alkoxy optionally substituted with one or more F; C_{1-5} alkyl optionally substituted with one or more F; halogen; and $N(R^{10})(R^{11})$;

R^{10} is C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^{12} ;

R^{11} is $-H$;

R¹² is selected from the group consisting of halogen, C₃₋₅ cycloalkyl and C₁₋₃ alkyl;

A³ is C-R⁷ or N;

R⁷ is selected from the group consisting of -H, halogen and C₁₋₅ alkyl;

A⁴ is C-R⁸ or N;

- 5 R⁸ is selected from the group consisting of -H, halogen, C₃₋₅ cycloalkyl, C₁₋₅ alkyl optionally substituted with one or more F, C₁₋₅ alkoxy, and -CN;

A⁵ is C-R⁹ or N;

R⁹ is -H or halogen;

with the proviso that the compound is not

- 10 *N*-[1-(3,5-Difluorophenyl)cyclopropyl]-β-methyl-1*H*-imidazole-1-propanamide;
N-[1-(3-Chlorophenyl)cyclopropyl]-β-hydroxybenzenepropanamide;
N-[1-(3-Fluorophenyl)cyclopropyl]-β-hydroxybenzenepropanamide; or
3-Fluoro-N-[1-(3-fluorophenyl)cyclopropyl]-β-hydroxybenzenepropanamide.

- 15 In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound as described herein.

In another aspect, the present disclosure provides a compound as described herein for use as a medicament.

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In another aspect, the present disclosure provides a compound as described herein for use in a method of modulating the activity of a K_v7 channel in a subject, the method comprising administering an effective amount of the compound to the subject.

- 25 In another aspect, the present disclosure provides a compound as described herein for use in a method of modulating the activity of a K_v7.2/ K_v7.3 channel in a subject, the method comprising administering an effective amount of the compound to the subject.

- 30 In another aspect, the present disclosure provides a compound as described herein for use in the treatment of epilepsy or pain.

Definitions

The term “alkyl” as used herein refers to a linear or branched hydrocarbon moiety.

The term "alkoxy" as used herein refers to a group of formula -O- alkyl, wherein alkyl is defined as above. In particular, C₁-C₃ -alkoxy is intended to indicate such hydrocarbon having 1, 2 or 3 carbon atoms. Examples of alkoxy groups include methoxy, ethoxy, n-propoxy, and isopropoxy.

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The term "haloalkyl" as used herein refers to an alkyl group wherein one or more hydrogen atoms have been replaced by a halogen atom, for example one or more hydrogen atoms replace by any of F, Cl, Br or I.

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As used herein the term "cycloalkyl" refers to a monocyclic or polycyclic system. The term "cycloalkyl" also used herein can optionally contain one or more unsaturations or substituents.

The term "heteroatom" refers to sulfur, oxygen or nitrogen.

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The term "heterocyclic" or "heterocycle" as used herein, alone or in combination, refers to saturated or unsaturated aromatic or nonaromatic rings containing from 3 to 20 ring atoms where at least one the ring atoms are heteroatom(s).

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The term "aromatic" or "aryl" refers to a cyclic or polycyclic moiety having a conjugated unsaturated $(4n+2)\pi$ electron system (where n is a positive integer), sometimes referred to as a delocalized π electron system.

The term "heteroaromatic" or "heteroaryl" as used herein, alone or in combination, refers to an aromatic heterocycle containing 5 to 12 atoms of which 1, 2, or 3 ring atoms are heteroatoms. Heteroaryl groups include monocyclic and bicyclic systems. For example, heteroaryl as used herein can be a C₅-C₁₀ monocyclic or C₈-C₁₂ bicyclic aromatic ring system having 1 to 3 heteroatom or heteroatom groups in each ring. Examples of heteroaryl groups include without limitation, pyridinyl, thiazolyl and indolyl.

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The compounds described herein may contain one or more stereocenters. When referring to a chiral carbon or position, the term "stereochemistry configuration" as used herein refers to the absolute configuration of that center, which can be R or S, as determined by the Cahn-Ingold-Prelog priority rules.

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A “heteromeric” channel or protein refers to an ion channel or protein that is composed of multiple different subunits. Some functional K_v7 channels exist in hetero-tetrameric complexes of subunits surrounding the K^+ conducting transmembrane pore, for example the $K_v7.2/K_v7.3$ heteromeric channel.

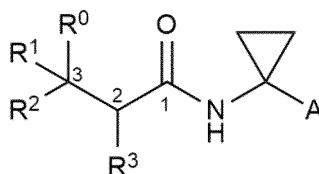
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As used herein, the term “agonism” referring to a K_v7 channel, refers to activating, increasing or enhancing the activity of a K_v7 channel.

Detailed description

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In one aspect, the present disclosure provides for a compound according to formula (I):



formula (I)

or a tautomer, a mesomer, a racemate, an enantiomer or a diastereoisomer thereof,

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or a mixture thereof; or a pharmaceutically acceptable salt thereof;

wherein,

R^0 is selected from the group consisting of $-OH$, and $-CH_3$;

R^1 is aryl optionally substituted with one or more, identical or different, substituents

R^4 , or heteroaryl optionally substituted with one or more, identical or different,

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substituents R^4 ;

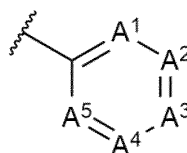
R^4 is selected from the group consisting of C_{1-5} alkyl optionally substituted with one or more F, C_{1-5} alkoxy, halogen and CN;

R^2 is selected from the group consisting of $-H$, $-CH_3$, and $-CF_3$;

R^3 is selected from the group consisting of $-H$ and $-OH$;

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A is of formula (II):



formula (II)

wherein

A^1 is C- R^5 or N;

R⁵ is -H or halogen;

A² is C-R⁶;

R⁶ is selected from the group consisting of C₁₋₅ alkoxy optionally substituted with one or more F; C₁₋₅ alkyl optionally substituted with one or more F; halogen; and

5 N(R¹⁰)(R¹¹);

R¹⁰ is C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R¹²;

R¹¹ is -H;

R¹² is selected from the group consisting of halogen, C₃₋₅ cycloalkyl and C₁₋₃ alkyl;

10 A³ is C-R⁷ or N;

R⁷ is selected from the group consisting of -H, halogen and C₁₋₅ alkyl;

A⁴ is C-R⁸ or N;

R⁸ is selected from the group consisting of -H, halogen, C₃₋₅ cycloalkyl, C₁₋₅ alkyl optionally substituted with one or more F, C₁₋₅ alkoxy, and -CN;

15 A⁵ is C-R⁹ or N;

R⁹ is -H or halogen;

with the proviso that the compound is not

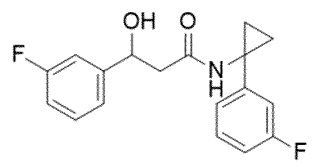
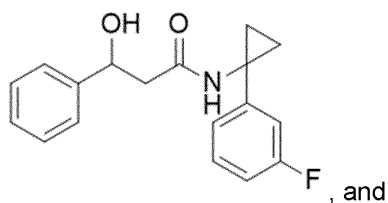
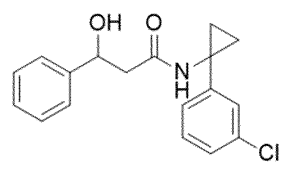
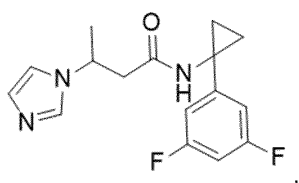
N-[1-(3,5-Difluorophenyl)cyclopropyl]-β-methyl-1*H*-imidazole-1-propanamide;

N-[1-(3-Chlorophenyl)cyclopropyl]-β-hydroxybenzenepropanamide;

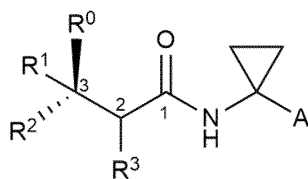
20 N-[1-(3-Fluorophenyl)cyclopropyl]-β-hydroxybenzenepropanamide; or

3-Fluoro-N-[1-(3-fluorophenyl)cyclopropyl]-β-hydroxybenzenepropanamide.

Thus, in one embodiment, the compound is not one of the group consisting of:

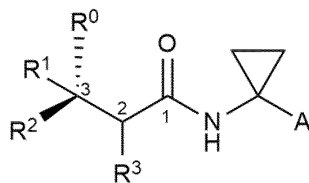


In one embodiment, the compound is of formula (Ia):



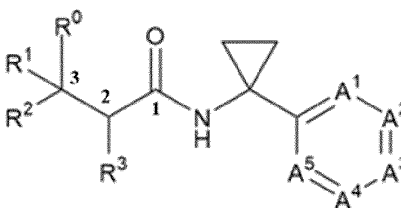
formula (Ia)

5 In one embodiment, the compound is of formula (Ib):



formula (Ib)

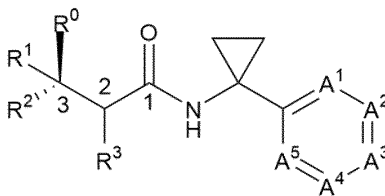
In one embodiment, the compound is of formula (III):



formula (III)

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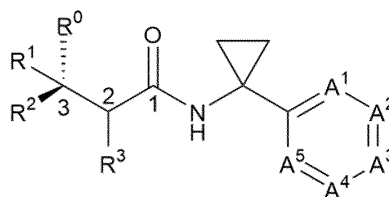
In one embodiment, the compound is of formula (IIIa):



formula (IIIa)

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In one embodiment, the compound is of formula (IIIb):



formula (IIIb)

In one embodiment, R⁰ is -OH. In one embodiment, R⁰ is -CH₃.

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In one embodiment R¹ is aryl, optionally substituted with one or more, identical or different substituents R⁴. In one embodiment R¹ is aryl substituted with one or two, identical or different substituents R⁴. In one embodiment R¹ is phenyl optionally substituted with one or more, identical or different, substituents R⁴. In one embodiment R¹ is phenyl substituted with 0 to 5, identical or different, substituents R⁴, wherein R⁴ is -F, -Cl, -OCH₃, -CH₃, -CN or -CF₃. In one embodiment R¹ is phenyl. In one embodiment R¹ is phenyl substituted with one or more, identical or different, substituents R⁴. In one embodiment R¹ is phenyl substituted with one R⁴. In one embodiment R¹ is phenyl substituted with two, identical or different, substituents R⁴. In one embodiment R¹ is phenyl substituted with three, identical or different, substituents R⁴

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In one embodiment R¹ is heteroaryl, optionally substituted with one or more, identical or different substituents R⁴. In one embodiment R¹ is heteroaryl substituted with one or two, identical or different substituents R⁴. In one embodiment the heteroaryl is pyridinyl. In one embodiment the heteroaryl is pyridin-4-yl. In one embodiment the heteroaryl is pyridin-2-yl. In one embodiment the heteroaryl is pyridin-3-yl. In one embodiment R¹ is pyridinyl optionally substituted with one or more, identical or different, substituents R⁴. In one embodiment R¹ is pyridinyl. In one embodiment R¹ is pyridin-2-yl optionally substituted with one or more, identical or different substituents R⁴. In one embodiment R¹ is pyridin-2-yl substituted with one R⁴. In one embodiment R¹ is pyridin-3-yl optionally substituted with one or more, identical or different substituents R⁴. In one embodiment R¹ is pyridin-3-yl substituted with one R⁴. In one embodiment R¹ is pyridin-4-yl optionally substituted with one or more, identical or different substituents R⁴. In one embodiment R¹ is pyridin-4-yl substituted with one R⁴. In one embodiment R¹ is pyridinyl substituted with 0 to 5, identical or different, substituents R⁴, wherein R⁴ is -F, -Cl, -OCH₃, -CH₃, -CN or -CF₃.

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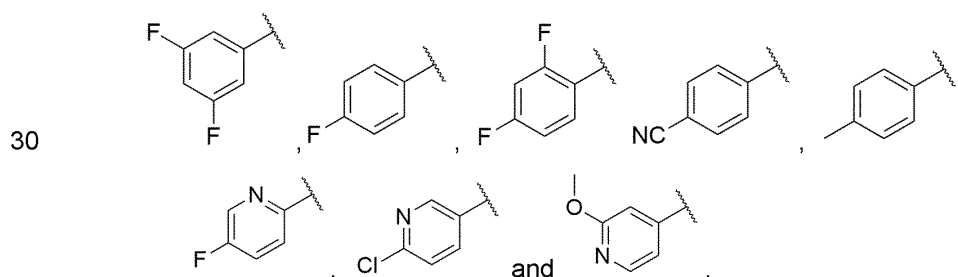
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In one embodiment the heteroaryl is thiazolyl. In one embodiment R¹ is thiazolyl optionally substituted with one or more, identical or different, substituents R⁴. In one embodiment R¹ is thiazol-2-yl optionally substituted with one or more, identical or different, substituents R⁴. In one embodiment R¹ is thiazol-5-yl optionally substituted with one or more, identical or different, substituents R⁴. In one embodiment R¹ is thiazolyl substituted with one or more, identical or different, substituents R⁴, wherein R⁴ is individually halogen, such as Cl, or is C₁₋₃ alkyl, such as -CH₃. In one embodiment the thiazolyl is thiazol-2-yl. In one embodiment the thiazolyl is thiazol-5-yl. In one embodiment R¹ is thiazol-2-yl optionally substituted with one or more, identical or different, substituents R⁴. In one embodiment R¹ is thiazol-5-yl optionally substituted with one or more, identical or different, substituents R⁴. In one embodiment the heteroaryl is indolyl. In one embodiment the heteroaryl is indol-4-yl. In one embodiment R¹ is indolyl optionally substituted with one or more, identical or different, substituents R⁴. In one embodiment R¹ is indol-4-yl optionally substituted with one or more, identical or different, substituents R⁴. In one embodiment R¹ is indolyl optionally substituted with one or more, identical or different, substituents R⁴, wherein R⁴ is C₁₋₃ alkyl, such as -CH₃. In one embodiment R¹ is indol-4-yl optionally substituted with one or more, identical or different, substituents R⁴, wherein R⁴ is C₁₋₃ alkyl, such as -CH₃.

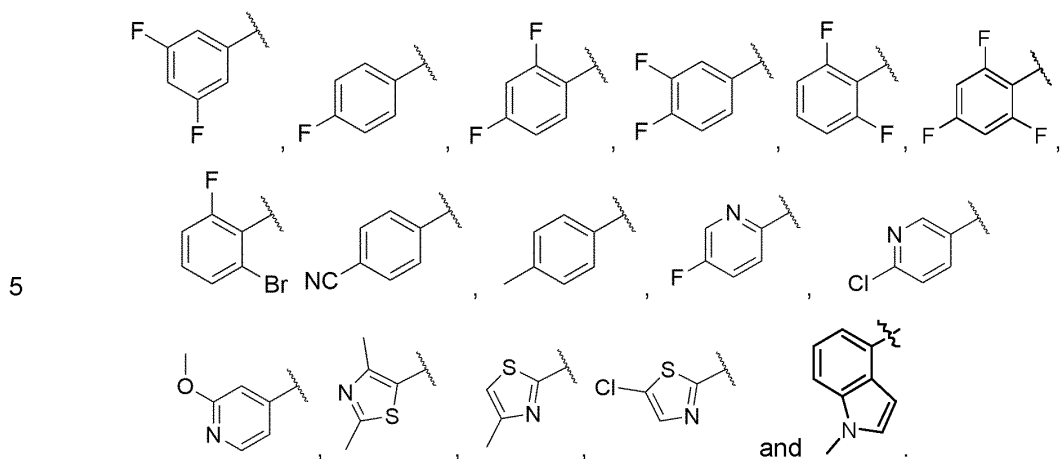
In one embodiment R⁴ is halogen. In one embodiment R⁴ is -F. In one embodiment R⁴ is -Cl. In one embodiment R⁴ is -Br. In one embodiment R⁴ is C₁₋₅ alkoxy. In one embodiment R⁴ is C₁₋₃ alkoxy. In one embodiment R⁴ is -OCH₃. In one embodiment R⁴ is C₁₋₅ alkyl. In one embodiment R⁴ is C₁₋₃ alkyl. In one embodiment R⁴ is -CH₃.

In one embodiment R⁴ is -CN. In one embodiment R⁴ is -CF₃. In one embodiment R⁴ is independently selected from the group consisting of -F, -Cl, -Br, -OCH₃, -CH₃, -CN and CF₃.

In one embodiment R¹ is selected from:



In one embodiment R¹ is selected from:



In one embodiment R¹ is . In one embodiment R¹ is .

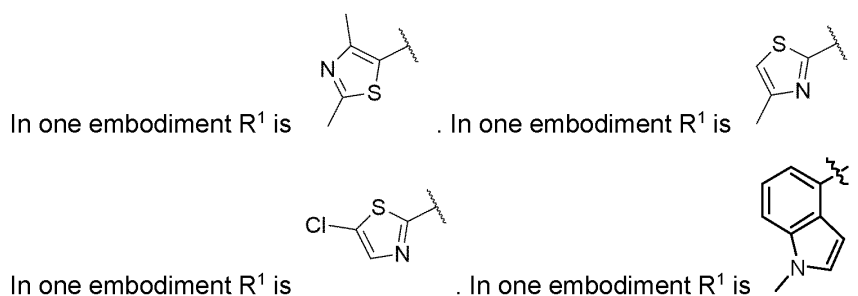
In one embodiment R¹ is . In one embodiment R¹ is .

10 In one embodiment R¹ is . In one embodiment R¹ is .

In one embodiment R¹ is . In one embodiment R¹ is .

In one embodiment R¹ is . In one embodiment R¹ is .

In one embodiment R¹ is . In one embodiment R¹ is .



5 In one embodiment, R² is selected from the group consisting of -H, -CH₃ and -CF₃. In one embodiment R² is not H. In one embodiment, R² is selected from the group consisting of -CH₃ and -CF₃. In one embodiment R² is -CH₃. In one embodiment R² is -CF₃.

10 In one embodiment of the present disclosure when R² is H then then at least one of A¹, A³ and A⁴ is not -CH. In one embodiment R² is H and R⁰ is OH. In one embodiment R² is -CH₃ and R⁰ is OH. In one embodiment, R² is -CF₃ and R⁰ is OH. In one embodiment, R² is H and R⁰ is -CH₃.

15 In one embodiment, R³ is H. In one embodiment, R³ is OH. In one embodiment R⁰ is -OH, R² is -CH₃, and R³ is -H.

20 In one embodiment A is phenyl optionally substituted with one or more substituents R⁵, R⁶, R⁷, R⁸ and/or R⁹. In one embodiment A is phenyl optionally substituted with one substituent R⁵, R⁶, R⁷, R⁸ and/or R⁹. In one embodiment A is phenyl optionally substituted with two substituent R⁵, R⁶, R⁷, R⁸ and/or R⁹.

25 In one embodiment A is pyridinyl optionally substituted with one or more substituents R⁵, R⁶, R⁷, R⁸ and/or R⁹. In one embodiment A is pyridin-2-yl optionally substituted with one or more substituents R⁵, R⁶, R⁷, R⁸ and/or R⁹. In one embodiment A is pyridin-2-yl optionally substituted with one substituent R⁵, R⁶, R⁷, R⁸ and/or R⁹. In one embodiment A is pyridin-2-yl optionally substituted with two substituent R⁵, R⁶, R⁷, R⁸ and/or R⁹.

30 In one embodiment A is pyridin-3-yl optionally substituted with one or more substituents R⁵, R⁶, R⁷, R⁸ and/or R⁹. In one embodiment A is pyridin-3-yl optionally substituted with one substituent R⁵, R⁶, R⁷, R⁸ and/or R⁹. In one embodiment A is pyridin-3-yl optionally substituted with two substituent R⁵, R⁶, R⁷, R⁸ and/or R⁹.

In one embodiment A is pyrimidinyl optionally substituted with one or more substituents R⁵, R⁶, R⁷, R⁸ and/or R⁹. In one embodiment A is pyrimidin-4-yl optionally substituted with one or more, substituents R⁵, R⁶, R⁷, R⁸ and/or R⁹. In one embodiment A is
5 pyrimidin-4-yl optionally substituted with one substituent R⁵, R⁶, R⁷, R⁸ and/or R⁹.

In one embodiment A¹ is C-R⁵; A² is C-R⁶; A³ is C-R⁷; A⁴ is C-R⁸; and A⁵ is C-R⁹.

In one embodiment at least one of A¹, A³ and A⁴ is not -CH. In one embodiment of the
10 present disclosure, at least two of A¹, A², A³ and A⁴ are not -CH.

In one embodiment one of A¹, A³, A⁴, and A⁵ is N. In one embodiment A¹ is N; A² is C-R⁶; A³ is C-R⁷; A⁴ is C-R⁸; and A⁵ is C-R⁹. In one embodiment A¹ is C-R⁵; A² is C-R⁶; A³ is N; A⁴ is C-R⁸; and A⁵ is C-R⁹. In one embodiment A¹ is C-R⁵; A² is C-R⁶; A³ is C-R⁷; A⁴ is N; and A⁵ is C-R⁹. In one embodiment A¹ is N; A² is C-R⁶; A³ is N; A⁴ is C-R⁸; and A⁵ is C-R⁹. In one embodiment A¹ is C-R⁵; A² is C-R⁶; A³ is C-R⁷; A⁴ is C-R⁸; and A⁵ is N.
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In one embodiment A¹ is N. In one embodiment A¹ is C-R⁵. In one embodiment R⁵
20 is -H. In one embodiment A¹ is C(H). In one embodiment R⁵ is halogen. In one embodiment R⁵ is -F. In one embodiment A¹ is C(F).

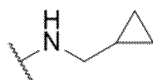
In one embodiment A² is C-R⁶, wherein R⁶ is selected from C₁₋₅ alkoxy optionally substituted with one or more -F, -CF₃, -CF₂H, -Cl, -Br or -CH₃. In one embodiment R⁶ is selected from -CF₃, -Cl, -Br or -CH₃.
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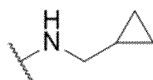
In one embodiment A² is C-R⁶, wherein R⁶ is selected from C₁₋₅ alkoxy optionally substituted with one or more F; C₁₋₅ alkyl optionally substituted with one or more F; halogen and N(R¹⁰)(R¹¹). In one embodiment R⁶ is C₁₋₅ alkoxy optionally substituted with one or more F. In one embodiment R⁶ is C₁₋₄ alkoxy optionally substituted with one or more F. In one embodiment R⁶ is C₁₋₃ alkoxy optionally substituted with one or more F. In one embodiment R⁶ is C₁ alkoxy optionally substituted with one or more F. In one embodiment R⁶ is selected from -OCH₂CF₃, -OCF₃, -OCH₃, -OCH₂CF₂H and -OCF₂H. In one embodiment R⁶ is -OCH₃. In one embodiment R⁶ is -OCF₃. In one embodiment R⁶ is -OCH₂CF₃.
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- In one embodiment R^6 is C_{1-5} alkyl optionally substituted with one or more F. In one embodiment R^6 is C_{1-3} alkyl optionally substituted with one or more F. In one embodiment R^6 is C_1 alkyl optionally substituted with one or more F. In one embodiment R^6 is $-CF_3$.
- 5 In one embodiment R^6 is $-CF_2H$.

In one embodiment R^6 is halogen. In one embodiment R^6 is Br. In one embodiment R^6 is Cl. In one embodiment R^6 is F.

- 10 In one embodiment R^6 $N(R^{10})(R^{11})$, wherein R^{10} is C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^{12} , R^{11} is $-H$, and R^{12} is selected from the group consisting of halogen, C_{3-5} cycloalkyl and C_{1-3} alkyl. In one embodiment R^{10} is C_{1-3} alkyl optionally substituted with one or more, identical or different, substituents R^{12} . In one embodiment R^{12} is halogen. In one embodiment R^{12} is F. In one embodiment R^{10}
- 15 is $-CH_2CF_3$. In one embodiment R^6 is $-N(H)(CH_2CF_3)$. In one embodiment R^{12} is C_{3-5} . In



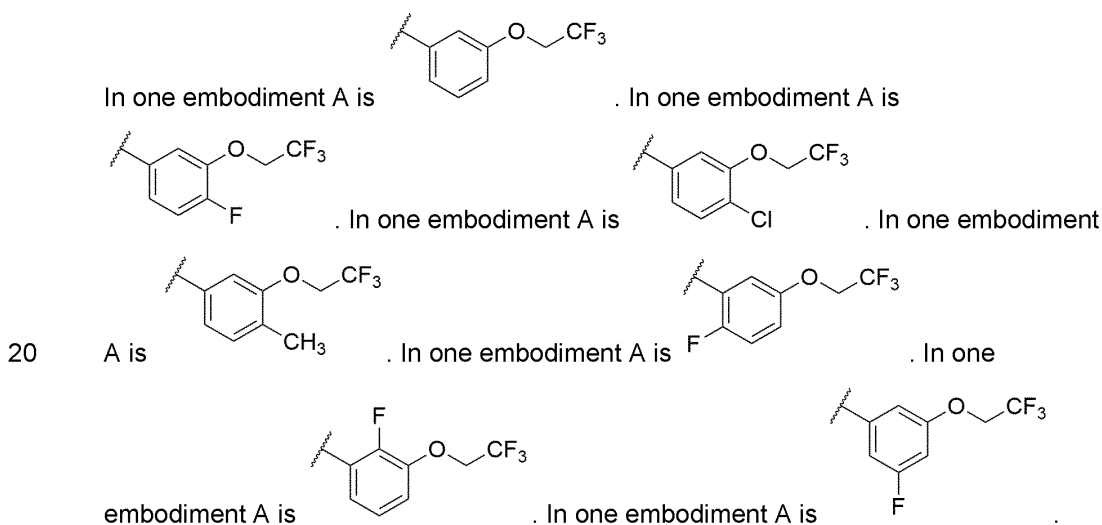
one embodiment R^6 is . In one embodiment R^{12} is C_{1-3} alkyl. In one embodiment R^{12} is CH_3 . In one embodiment R^{10} is $-CH_2C(CH_3)_3$. In one embodiment R^6 is $-N(H)CH_2C(CH_3)_3$. In one embodiment R^{10} is $-C(H)(CH_3)_2$. In one embodiment R^6 is $-N(H)C(H)(CH_3)_2$.

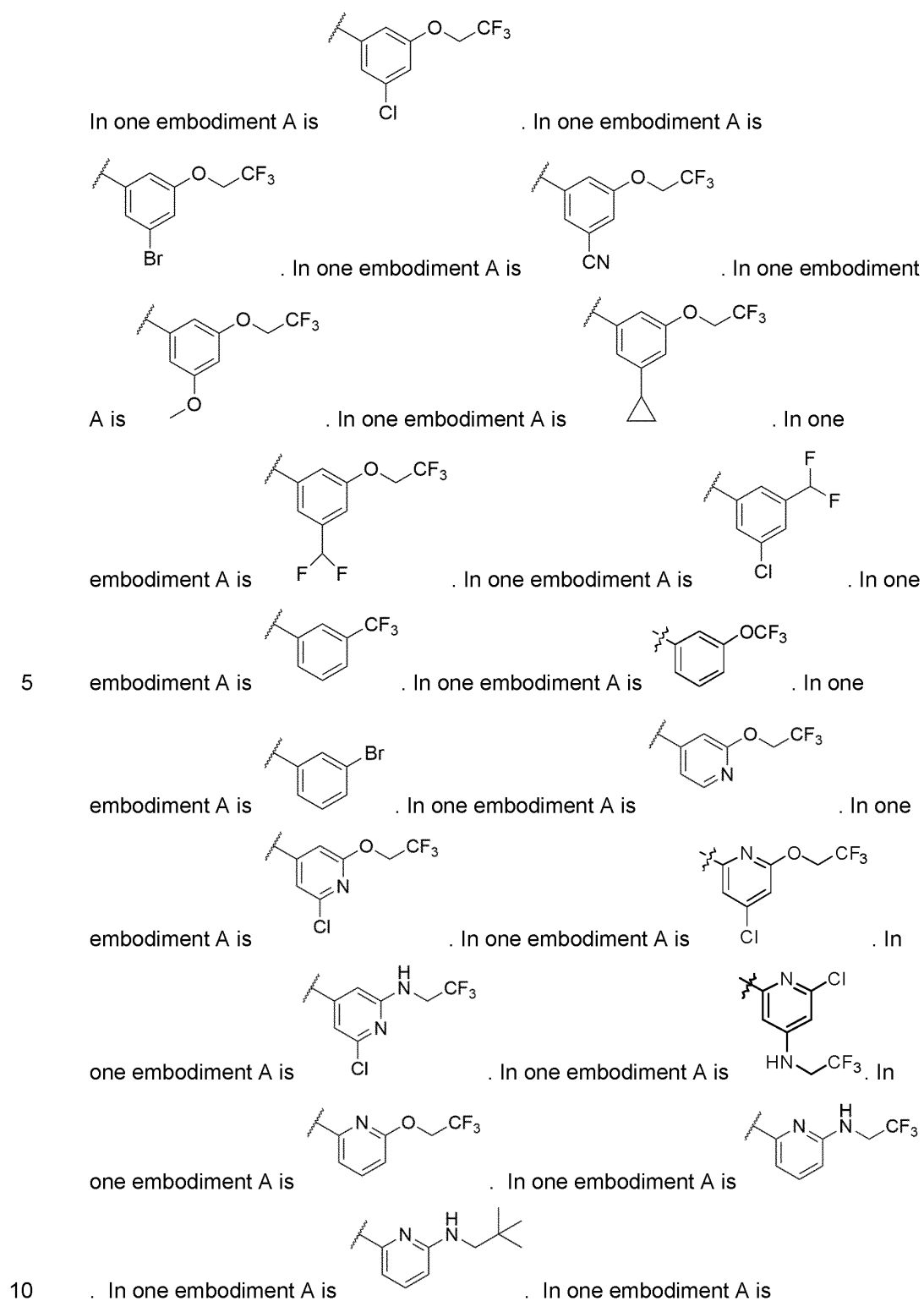
- 20 In one embodiment A^3 is $C-R^7$, wherein R^7 is selected from the group consisting of $-H$, halogen and C_{1-5} alkyl. In one embodiment A^3 is $C-R^7$, wherein R^7 is selected from $-H$, $-F$, $-Cl$, and $-CH_3$. In one embodiment R^7 is $-H$. In one embodiment A^3 is $C(H)$. In one embodiment R^7 is halogen. In one embodiment R^7 is $-F$. In one embodiment R^7 is $-Cl$.
- 25 In one embodiment A^3 is $C(F)$. In one embodiment R^7 is C_{1-5} alkyl. In one embodiment R^7 is C_{1-3} alkyl. In one embodiment R^7 is $-CH_3$. In one embodiment, A^3 is N.

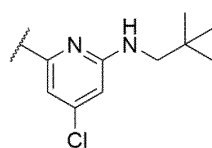
- In one embodiment A^4 is $C-R^8$, wherein R^8 is selected from the group consisting of H, halogen, C_{3-5} cycloalkyl, C_{1-5} alkyl optionally substituted with one or more F, C_{1-5}
- 30 alkoxy, and $-CN$. In one embodiment A^4 is $C-R^8$, wherein R^8 is selected from the group consisting of $-H$, C_{1-5} cycloalkyl, $-CN$, $-F$, $-Cl$, $-Br$ and $-CF_2H$. In one embodiment A^4 is $C-R^8$, wherein R^8 is selected from the group consisting of $-H$, cyclopropyl, methoxy, $-CN$, $-F$, $-Cl$, $-Br$ and $-CF_2H$. In one embodiment R^8 is selected from $-H$, $-F$ and $-Cl$. In one embodiment R^8 is $-H$. In one embodiment A^4 is $C(H)$. In one embodiment R^8 is $-$

CN. In one embodiment A^4 is C(CN). In one embodiment R^8 is halogen. In one embodiment R^8 is F. In one embodiment A^4 is C(F). In one embodiment R^8 is -Br. In one embodiment A^4 is C(Br). In one embodiment R^8 is -Cl. In one embodiment A^4 is C(Cl). In one embodiment R^8 is C_{1-5} alkyl optionally substituted with one or more F. In one embodiment R^8 is C_{1-3} alkyl optionally substituted with one or more F. In one embodiment R^8 is C_1 alkyl optionally substituted with one or more F. In one embodiment R^8 is -CF₂H. In one embodiment A^4 is C(CF₂H). In one embodiment R^8 is -C₃-C₅ cycloalkyl. In one embodiment R^8 is cyclopropyl. In one embodiment A^4 is C(cyclopropyl). In one embodiment R^8 is C_{1-5} alkoxy. In one embodiment R^8 is C_{1-3} alkoxy. In one embodiment R^8 is -OCH₃. In one embodiment A^4 is C(OCH₃). In one embodiment A^4 is N.

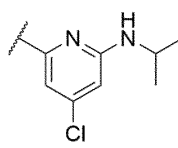
In one embodiment A^5 is C- R^9 , wherein R^9 is -H or halogen. In one embodiment R^9 is -H or -F. In one embodiment R^9 is -H. In one embodiment A^5 is C(H). In one embodiment R^9 is halogen. In one embodiment R^9 is -F. In one embodiment A^5 is C(F). In one embodiment A^5 is N.



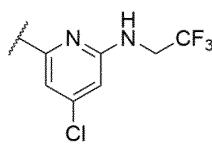




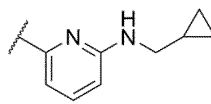
. In one embodiment A is



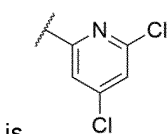
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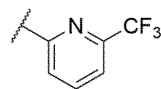
. In one embodiment A is



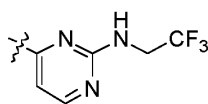
. In one embodiment A



is . In one embodiment A is



. In one embodiment A is

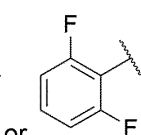
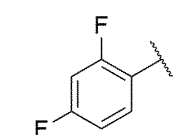
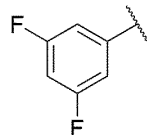


5

In one embodiment R^0 is -OH, R^1 is phenyl substituted with two or three -F, R^2 is -CH₃, R^3 is -H, A^1 is C- R^5 , A^2 is C(OCH₂CF₃), A^3 is C- R^7 , A^4 is C- R^8 , and A^5 is C- R^9 , wherein one of R^5 , R^7 , R^8 , and R^9 is -F, -Cl, -Br, or -CH₃, and the others are -H.

10

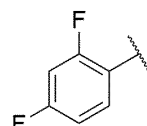
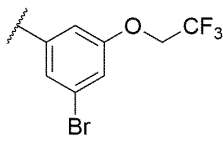
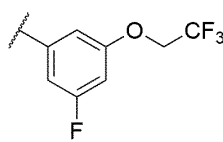
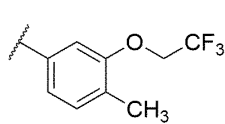
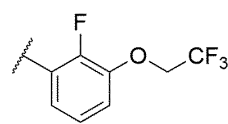
In one embodiment R^0 is -OH, R^1 is



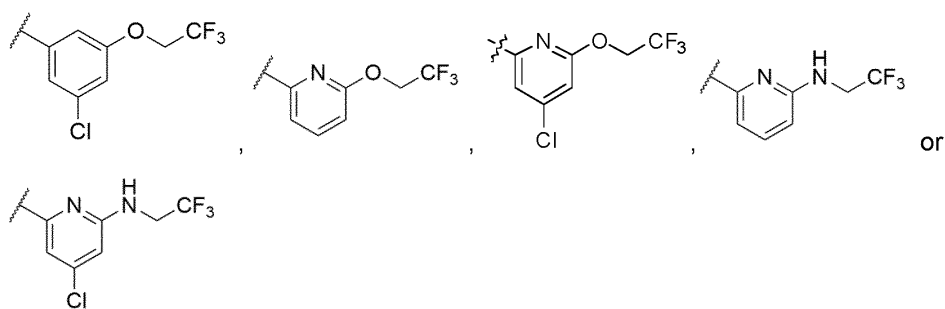
, F or F.

R^2 is -CH₃, R^3 is -H, A^1 is C- R^5 , A^2 is C(OCH₂CF₃), A^3 is C- R^7 , A^4 is C- R^8 , and A^5 is C- R^9 , wherein one of R^5 , R^7 , R^8 , and R^9 is -F, -Cl, -Br, or -CH₃, and the others are -H.

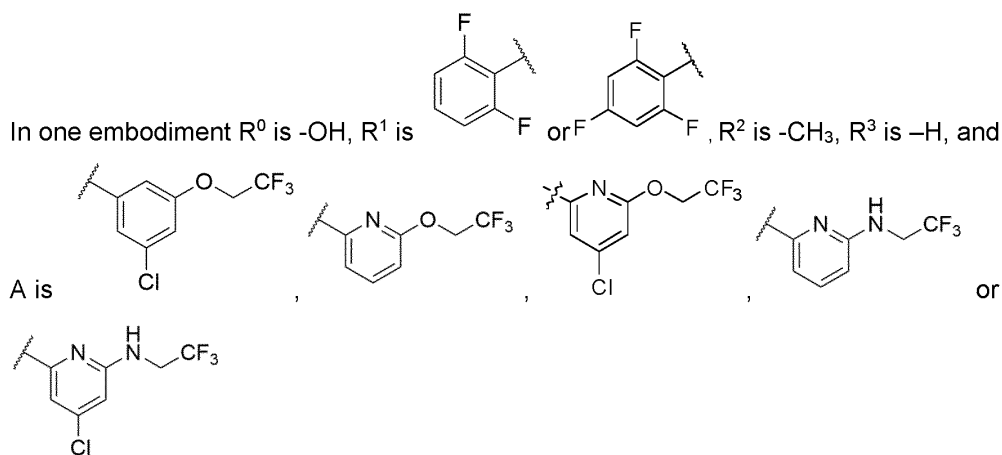
In one embodiment R^0 is -OH, R^1 is

, R^2 is -CH₃, R^3 is -H, and A is

15



5 In one embodiment R^0 is -OH, R^1 is



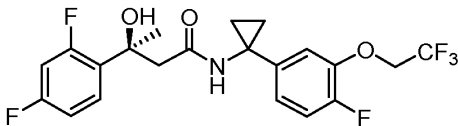
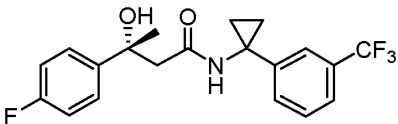
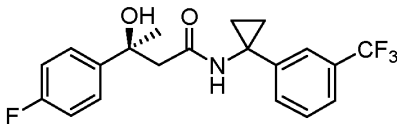
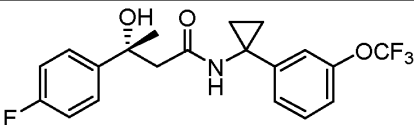
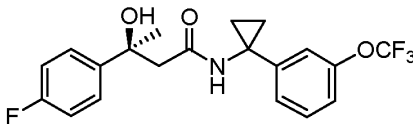
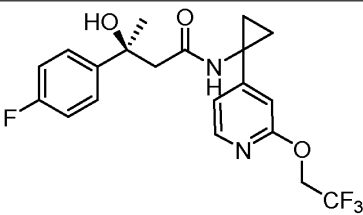
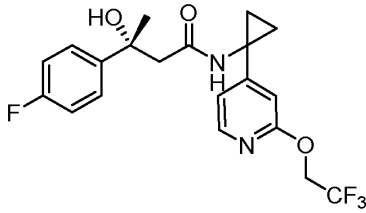
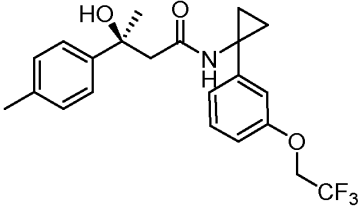
10 In one embodiment the stereochemistry configuration at positions 2 and 3, as defined by formulas (I) and (III), are independently selected from R and S. In one embodiment the stereochemistry configuration at position 3, as defined in formulas (I) and (III), is R. In one embodiment the stereochemistry configuration at position 3, as defined in formulas (I) and (III), is S. In one embodiment the stereochemistry configuration at position 2, as defined in formulas (I) and (III), is R. In one embodiment the stereochemistry configuration at position 2, as defined in formulas (I) and (III), is S.

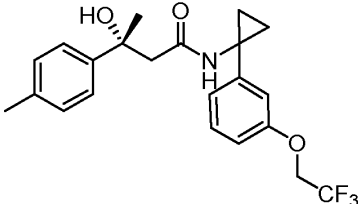
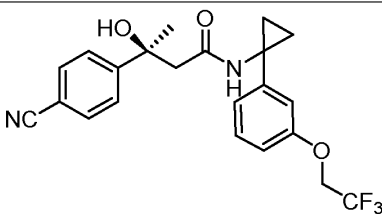
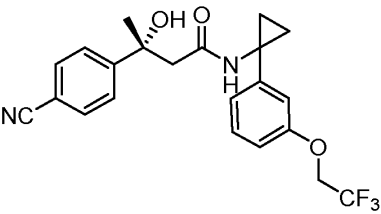
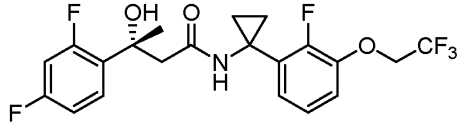
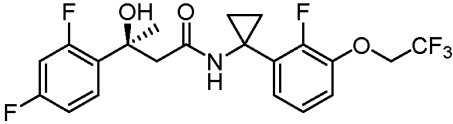
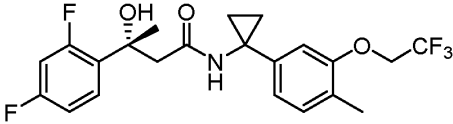
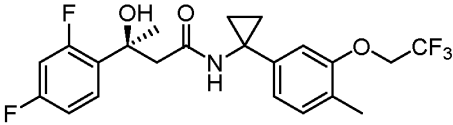
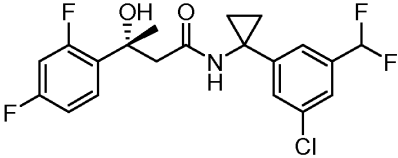
In some embodiments, the compound is as shown in Table A.

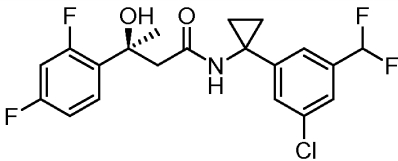
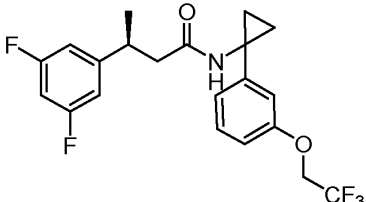
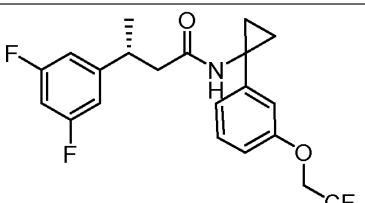
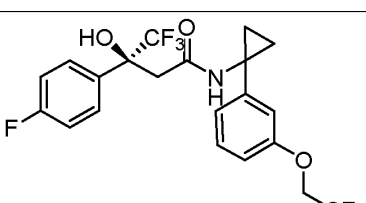
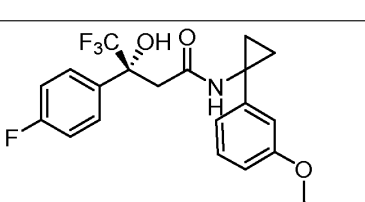
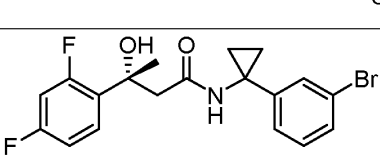
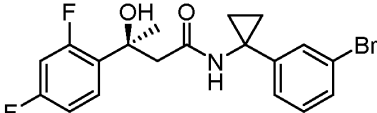
20 In one aspect, the present invention relates to a compound shown in Table A, or a pharmaceutically acceptable salt thereof.

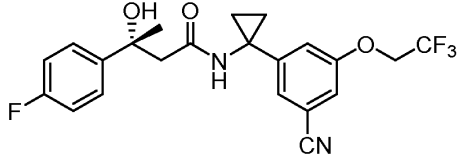
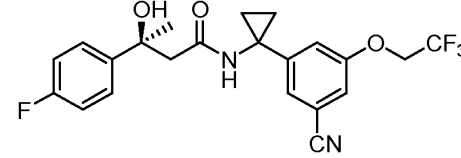
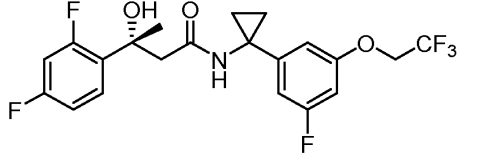
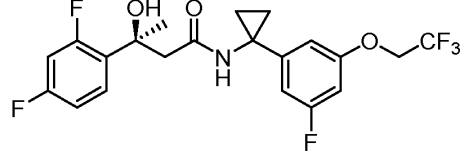
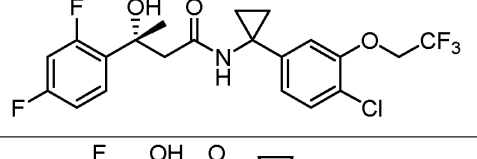
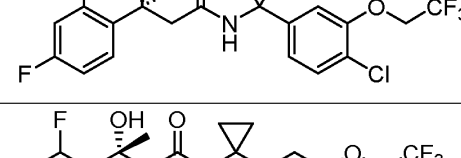
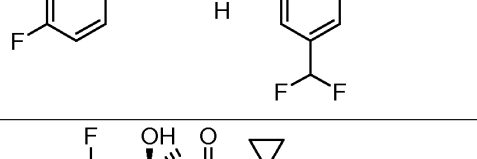
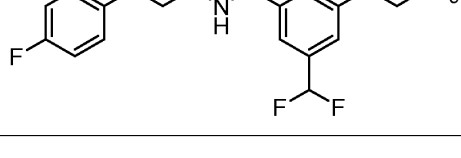
Table A. List of compounds.

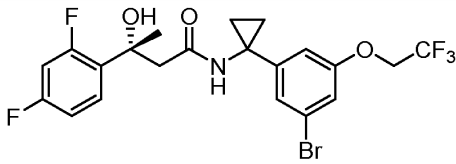
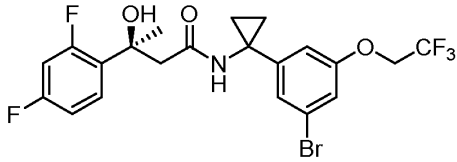
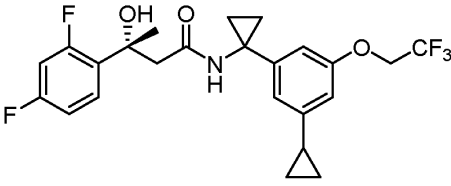
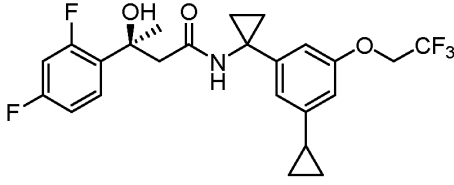
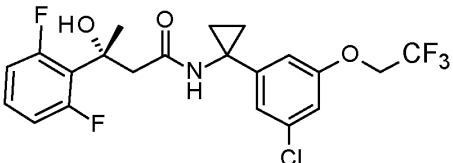
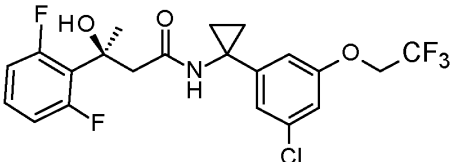
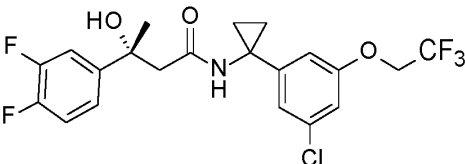
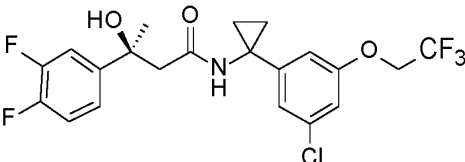
Compound ID.	Structure
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A1b	
A2a	
A2b	
A3a	
A3b	
A4a	
A4b	
A5a	

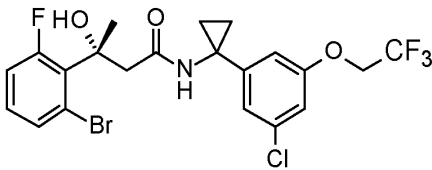
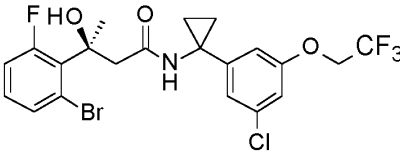
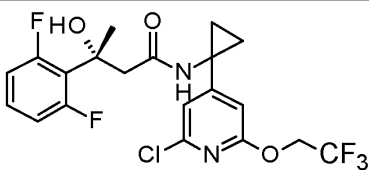
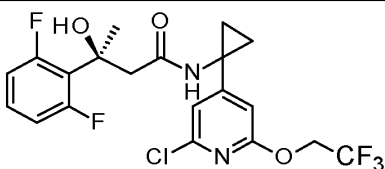
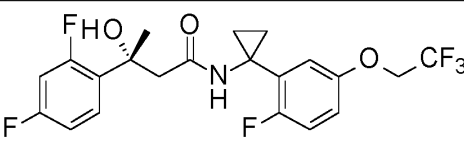
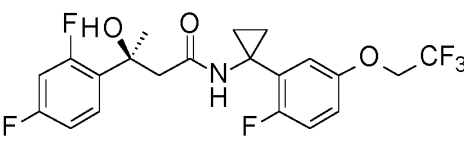
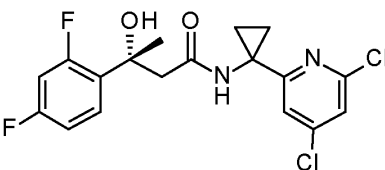
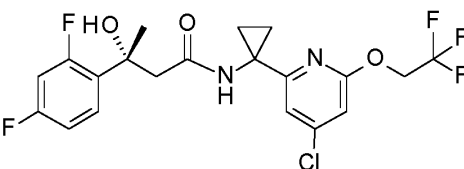
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A6b	
A7a	
A7b	
A8a	
A8b	
A9a	

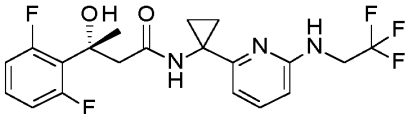
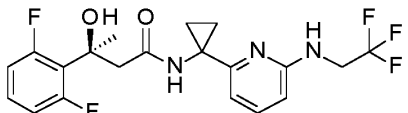
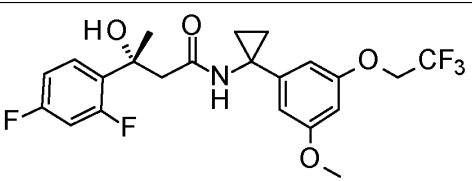
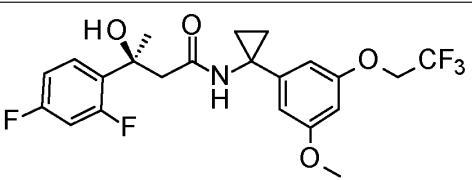
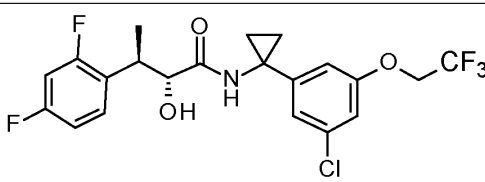
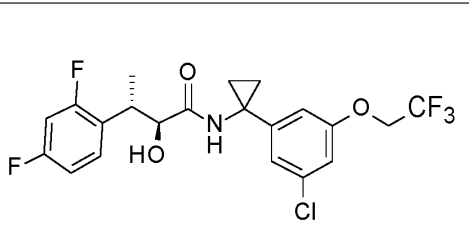
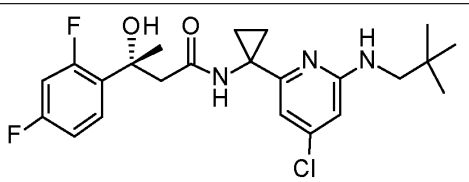
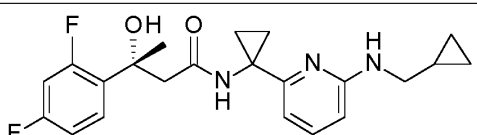
A9b	
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A10b	
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A11b	
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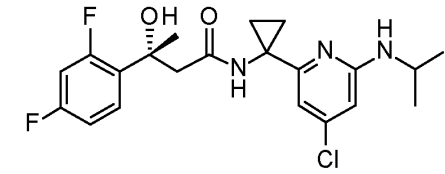
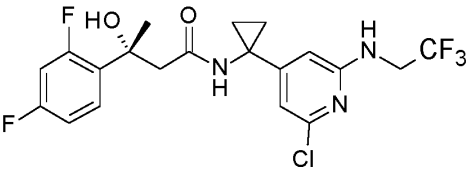
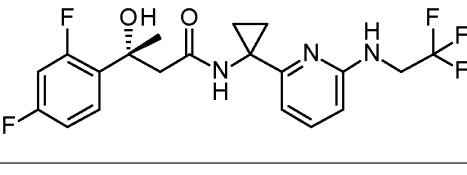
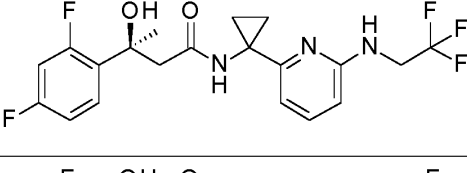
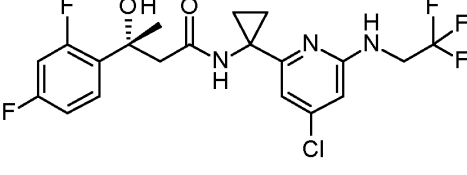
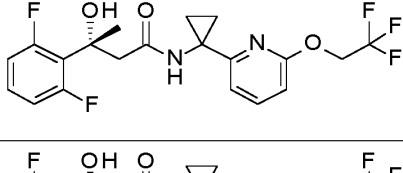
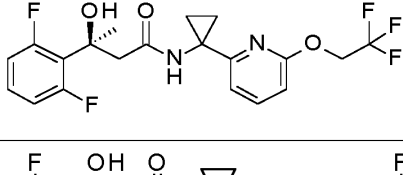
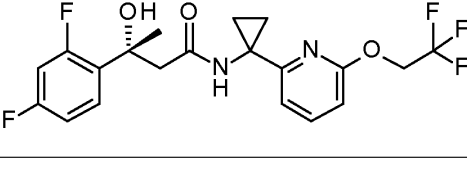
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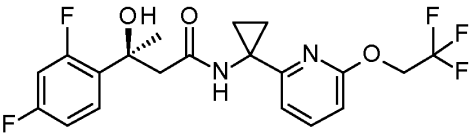
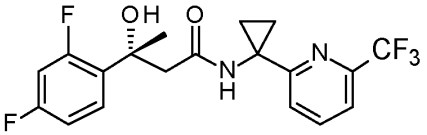
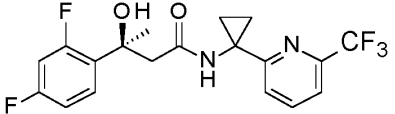
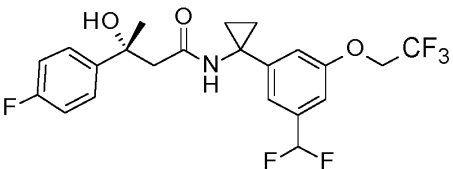
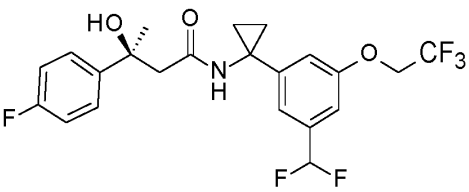
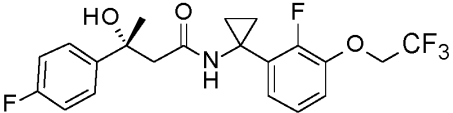
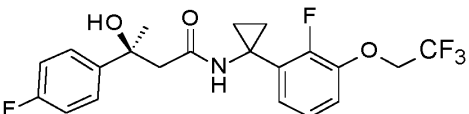
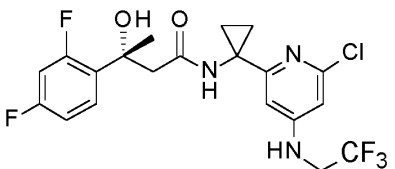
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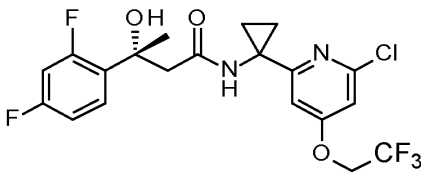
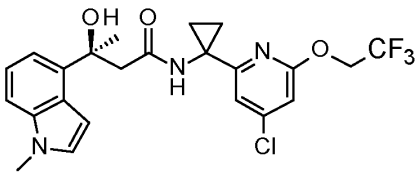
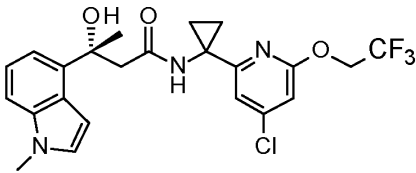
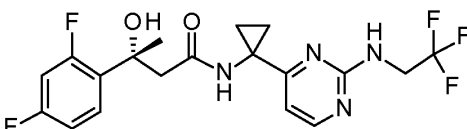
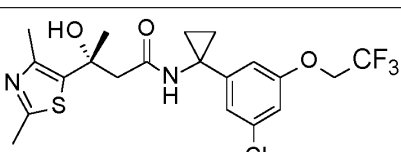
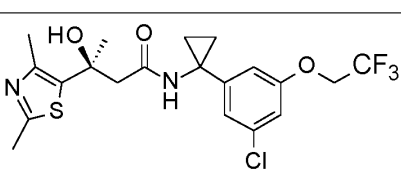
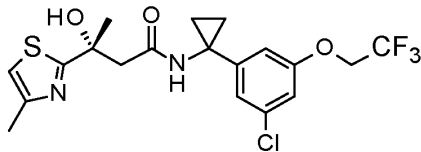
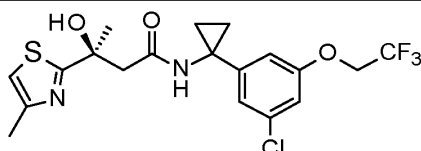
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A50a	
A50b	
A51a	
A51b	

In one embodiment, the compound is selected from the group consisting of:

3-(6-chloropyridin-3-yl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)butanamide,

5 3-(5-fluoropyridin-2-yl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)-cyclopropyl)-butanamide,

3-hydroxy-3-(2-methoxypyridin-4-yl)-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)butanamide,

10 N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,

3-(2,4-difluorophenyl)-N-(1-(4-fluoro-3-(2,2,2-trifluoroethoxy)phenyl)-cyclopropyl)-3-hydroxybutanamide,

3-(4-fluorophenyl)-3-hydroxy-N-(1-(3-(trifluoromethyl)phenyl)cyclopropyl)-butanamide,

15 3-(4-fluorophenyl)-3-hydroxy-N-(1-(3-(trifluoromethoxy)phenyl)cyclopropyl)butanamide,

3-(4-fluorophenyl)-3-hydroxy-N-(1-(2-(2,2,2-trifluoroethoxy)pyridin-4-yl)cyclopropyl)butanamide,

- 3-hydroxy-3-(p-tolyl)-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-
butanamide,
- 3-(4-cyanophenyl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-
butanamide,
- 5 3-(2,4-difluorophenyl)-N-(1-(2-fluoro-3-(2,2,2-trifluoroethoxy)phenyl)-
cyclopropyl)-3-hydroxybutanamide,
- 3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(4-methyl-3-(2,2,2-trifluoroethoxy)phenyl)-
cyclopropyl)butanamide,
- 10 N-(1-(3-chloro-5-(difluoromethyl)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-
hydroxybutanamide,
- 3-(3,5-difluorophenyl)-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-
butanamide,
- 4,4,4-trifluoro-3-(4-fluorophenyl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)-
phenyl)-cyclopropyl)butanamide,
- 15 N-(1-(3-bromophenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- N-(1-(3-cyano-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(4-fluorophenyl)-3-
hydroxybutanamide,
- (3-(2,4-difluorophenyl)-N-(1-(3-fluoro-5-(2,2,2-trifluoroethoxy)phenyl)-
cyclopropyl)-3-hydroxybutanamide,
- 20 N-(1-(4-chloro-3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-
difluorophenyl)-3-hydroxybutanamide,
- N-(1-(3-(difluoromethyl)-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-
difluorophenyl)-3-hydroxybutanamide,
- N-(1-(3-bromo-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-
difluorophenyl)-3-hydroxybutanamide,
- 25 N-(1-(3-cyclopropyl-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-
difluorophenyl)-3-hydroxybutanamide,
- N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,6-
difluorophenyl)-3-hydroxybutanamide,
- 30 N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(3,4-
difluorophenyl)-3-hydroxybutanamide,
- 3-(2-bromo-6-fluorophenyl)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)-
cyclopropyl)-3-hydroxybutanamide,
- N-(1-(2-chloro-6-(2,2,2-trifluoroethoxy)pyridin-4-yl)cyclopropyl)-3-(2,6-
difluorophenyl)-3-hydroxybutanamide,
- 35

- 3-(2,4-difluorophenyl)-N-(1-(2-fluoro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide,
N-(1-(4,6-dichloropyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- 5 N-(1-(4-chloro-6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
3-(2,6-difluorophenyl)-3-hydroxy-N-(1-(6-((2,2,2-trifluoroethyl) amino) pyridin-2-yl)cyclopropyl)butanamide,
- 10 3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(3-methoxy-5-(2,2,2-trifluoroethoxy)phenyl)-cyclopropyl)butanamide,
N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,6-difluorophenyl)-3-hydroxybutanamide,
N-(1-(4-chloro-6-(neopentylamino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- 15 N-(1-(6-((cyclopropylmethyl)amino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
N-(1-(4-chloro-6-(isopropylamino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- 20 N-(1-(2-chloro-6-((2,2,2-trifluoroethyl)amino)pyridin-4-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
N-(1-(6-chloropyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
N-(1-(4-chloro-6-((2,2,2-trifluoroethyl)amino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- 25 3-(2,6-difluorophenyl)-3-hydroxy-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)butanamide,
3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)butanamide,
3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(6-(trifluoromethyl)pyridin-2-yl)cyclopropyl)butanamide,
- 30 N-(1-(3-(difluoromethyl)-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(4-fluorophenyl)-3-hydroxybutanamide,
3-(4-fluorophenyl)-N-(1-(2-fluoro-3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide,

- N-(1-(6-chloro-4-((2,2,2-trifluoroethyl)amino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
N-(1-(6-chloro-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
5 N-(1-(4-chloro-6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-hydroxy-3-(1-methyl-1H-indol-4-yl)butanamide,
3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(2-((2,2,2-trifluoroethyl)amino)pyrimidin-4-yl)cyclopropyl)butanamide,
N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-
10 dimethylthiazol-5-yl)-3-hydroxybutanamide,
N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxy-3-(4-methylthiazol-2-yl)butanamide,
N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(5-chlorothiazol-2-yl)-3-hydroxybutanamide, and
15 3-hydroxy-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-(2,4,6-trifluorophenyl)butanamide,
or a pharmaceutically acceptable salt thereof.

20 In one embodiment the compound of the present invention is selected from the group consisting of:

- (R)-3-(6-chloropyridin-3-yl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)-cyclo-propyl)butanamide,
(R)-3-(5-fluoropyridin-2-yl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)-cyclopropyl)-butanamide,
25 (R)-3-hydroxy-3-(2-methoxypyridin-4-yl)-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)-cyclopropyl)butanamide,
(R)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
(R)-3-(2,4-difluorophenyl)-N-(1-(4-fluoro-3-(2,2,2-trifluoroethoxy)phenyl)-cyclopropyl)-3-hydroxybutanamide,
30 (R)-3-(4-fluorophenyl)-3-hydroxy-N-(1-(3-(trifluoromethyl)phenyl)cyclopropyl)-butanamide,
(R)-3-(4-fluorophenyl)-3-hydroxy-N-(1-(3-(trifluoromethoxy)phenyl)cyclopropyl)butanamide,

- (R)-3-(4-fluorophenyl)-3-hydroxy-N-(1-(2-(2,2,2-trifluoroethoxy)pyridin-4-yl)cyclopropyl)butanamide,
- (R)-3-hydroxy-3-(p-tolyl)-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)-cyclopropyl)butanamide,
- 5 (R)-3-(4-cyanophenyl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)-cyclopropyl)-butanamide,
- (R)-3-(2,4-difluorophenyl)-N-(1-(2-fluoro-3-(2,2,2-trifluoroethoxy)phenyl)-cyclopropyl)-3-hydroxybutanamide,
- (R)-3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(4-methyl-3-(2,2,2-trifluoroethoxy)-phenyl)cyclopropyl)butanamide,
- 10 (R)-N-(1-(3-chloro-5-(difluoromethyl)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (R)-3-(3,5-difluorophenyl)-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-butanamide,
- 15 (R)-4,4,4-trifluoro-3-(4-fluorophenyl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)-phenyl)cyclopropyl)butanamide,
- (R)-N-(1-(3-bromophenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (R)-N-(1-(3-cyano-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(4-fluorophenyl)-3-hydroxybutanamide,
- 20 (R)-3-(2,4-difluorophenyl)-N-(1-(3-fluoro-5-(2,2,2-trifluoroethoxy)-phenyl)cyclopropyl)-3-hydroxybutanamide,
- (R)-N-(1-(4-chloro-3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- 25 (R)-N-(1-(3-(difluoromethyl)-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (R)-N-(1-(3-bromo-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (R)-N-(1-(3-cyclopropyl-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- 30 (R)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,6-difluorophenyl)-3-hydroxybutanamide,
- (R)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(3,4-difluorophenyl)-3-hydroxybutanamide,

- (R)-3-(2-bromo-6-fluorophenyl)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide,
- (R)-N-(1-(2-chloro-6-(2,2,2-trifluoroethoxy)pyridin-4-yl)cyclopropyl)-3-(2,6-difluorophenyl)-3-hydroxybutanamide,
- 5 (R)-3-(2,4-difluorophenyl)-N-(1-(2-fluoro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide,
- (R)-N-(1-(4,6-dichloropyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (R)-N-(1-(4-chloro-6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- 10 (R)-3-(2,6-difluorophenyl)-3-hydroxy-N-(1-(6-((2,2,2-trifluoroethyl) amino)pyridin-2-yl)cyclopropyl)butanamide,
- (R)-3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(3-methoxy-5-(2,2,2-trifluoroethoxy)phenyl)-cyclopropyl)butanamide,
- 15 (R)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,6-difluorophenyl)-3-hydroxybutanamide,
- (R)-N-(1-(4-chloro-6-(neopentylamino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide),
- (R)-N-(1-(6-((cyclopropylmethyl)amino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- 20 (R)-N-(1-(4-chloro-6-(isopropylamino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (R)-N-(1-(2-chloro-6-((2,2,2-trifluoroethyl)amino)pyridin-4-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- 25 (R)-N-(1-(6-chloropyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (R)-N-(1-(4-chloro-6-((2,2,2-trifluoroethyl)amino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (R)-3-(2,6-difluorophenyl)-3-hydroxy-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)butanamide,
- 30 (R)-3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)butanamide,
- (R)-3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(6-(trifluoromethyl)pyridin-2-yl)cyclopropyl)butanamide,

- (R)-N-(1-(3-(difluoromethyl)-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(4-fluorophenyl)-3-hydroxybutanamide,
(R)-3-(4-fluorophenyl)-N-(1-(2-fluoro-3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide,
5 (R)-N-(1-(6-chloro-4-((2,2,2-trifluoroethyl)amino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
(R)-N-(1-(6-chloro-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
(R)-N-(1-(4-chloro-6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-hydroxy-3-(1-methyl-1H-indol-4-yl)butanamide,
10 (R)-3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(2-((2,2,2-trifluoroethyl)amino)pyrimidin-4-yl)cyclopropyl)butanamide,
(R)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-dimethylthiazol-5-yl)-3-hydroxybutanamide,
(R)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxy-3-(4-methylthiazol-2-yl)butanamide,
15 (R)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(5-chlorothiazol-2-yl)-3-hydroxybutanamide, and
(R)-3-hydroxy-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-(2,4,6-trifluorophenyl)butanamide
20 or a pharmaceutically acceptable salt thereof.

In one embodiment the compound is selected from the group consisting of:

- (S)-3-(6-chloropyridin-3-yl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclo-propyl)butanamide,
25 (S)-3-(5-fluoropyridin-2-yl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-butanamide,
(S)-3-hydroxy-3-(2-methoxypyridin-4-yl)-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclo-propyl)butanamide,
30 (S)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
(S)-3-(2,4-difluorophenyl)-N-(1-(4-fluoro-3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide,
(S)-3-(4-fluorophenyl)-3-hydroxy-N-(1-(3-(trifluoromethyl)phenyl)cyclopropyl)-
35 butanamide,

- (S)-3-(4-fluorophenyl)-3-hydroxy-N-(1-(3-(trifluoromethoxy)phenyl)cyclopropyl)butanamide,
- (S)-3-(4-fluorophenyl)-3-hydroxy-N-(1-(2-(2,2,2-trifluoroethoxy)pyridin-4-yl)cyclopropyl)butanamide,
- 5 (S)-3-hydroxy-3-(p-tolyl)-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)butanamide,
- (S)-3-(4-cyanophenyl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-butanamide,
- 10 (S)-3-(2,4-difluorophenyl)-N-(1-(2-fluoro-3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide,
- (S)-3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(4-methyl-3-(2,2,2-trifluoroethoxy)phenyl)-cyclopropyl)butanamide,
- (S)-N-(1-(3-chloro-5-(difluoromethyl)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- 15 (S)-3-(3,5-difluorophenyl)-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-butanamide,
- (S)-4,4,4-trifluoro-3-(4-fluorophenyl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)-cyclopropyl)butanamide,
- (S)-N-(1-(3-bromophenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-
- 20 hydroxybutanamide,
- (S)-N-(1-(3-cyano-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(4-fluorophenyl)-3-hydroxybutanamide,
- (S)-3-(2,4-difluorophenyl)-N-(1-(3-fluoro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide,
- 25 (S)-N-(1-(4-chloro-3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (S)-N-(1-(3-(difluoromethyl)-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- 30 (S)-N-(1-(3-bromo-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (S)-N-(1-(3-cyclopropyl-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (S)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,6-difluorophenyl)-3-hydroxybutanamide,

- (S)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(3,4-difluorophenyl)-3-hydroxybutanamide,
- (S)-3-(2-bromo-6-fluorophenyl)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide,
- 5 (S)-N-(1-(2-chloro-6-(2,2,2-trifluoroethoxy)pyridin-4-yl)cyclopropyl)-3-(2,6-difluorophenyl)-3-hydroxybutanamide,
- (S)-3-(2,4-difluorophenyl)-N-(1-(2-fluoro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide,
- (S)-N-(1-(4,6-dichloropyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- 10 (S)-N-(1-(4-chloro-6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (S)-3-(2,6-difluorophenyl)-3-hydroxy-N-(1-(6-((2,2,2-trifluoroethyl) amino)pyridin-2-yl)cyclopropyl)butanamide,
- 15 (S)-3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(3-methoxy-5-(2,2,2-trifluoroethoxy)phenyl)-cyclopropyl)butanamide,
- (S)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,6-difluorophenyl)-3-hydroxybutanamide,
- (S)-N-(1-(4-chloro-6-(neopentylamino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- 20 (S)-N-(1-(6-((cyclopropylmethyl)amino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (S)-N-(1-(4-chloro-6-(isopropylamino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- 25 (S)-N-(1-(2-chloro-6-((2,2,2-trifluoroethyl)amino)pyridin-4-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (S)-N-(1-(6-chloropyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (S)-N-(1-(4-chloro-6-((2,2,2-trifluoroethyl)amino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- 30 (S)-3-(2,6-difluorophenyl)-3-hydroxy-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)butanamide,
- (S)-3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)butanamide,

- (S)-3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(6-(trifluoromethyl)pyridin-2-yl)cyclopropyl)butanamide,
(S)-N-(1-(3-(difluoromethyl)-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(4-fluorophenyl)-3-hydroxybutanamide,
5 (S)-3-(4-fluorophenyl)-N-(1-(2-fluoro-3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide,
(S)-N-(1-(6-chloro-4-((2,2,2-trifluoroethyl)amino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
(S)-N-(1-(6-chloro-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
10 (S)-N-(1-(4-chloro-6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-hydroxy-3-(1-methyl-1H-indol-4-yl)butanamide,
(S)-3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(2-((2,2,2-trifluoroethyl)amino)pyrimidin-4-yl)cyclopropyl)butanamide,
15 (S)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-dimethylthiazol-5-yl)-3-hydroxybutanamide,
(S)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxy-3-(4-methylthiazol-2-yl)butanamide,
(S)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(5-chlorothiazol-2-yl)-3-hydroxybutanamide, and
20 (S)-3-hydroxy-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-(2,4,6-trifluorophenyl)butanamide,
or a pharmaceutically acceptable salt thereof.

25 **K_v7 modulation**

As demonstrated in the examples, the compounds according to the present invention can produce activating effects of K_v7 channels. Thus, the compounds described herein are useful in the modulation of K_v7 channels, including K_v7 agonism.

- 30 In one embodiment, the compound according to the present disclosure can modulate the activity of a K_v7 channel. In one embodiment, the compound is able to increase the activity of a K_v7.2/K_v7.3 heteromeric channel.

- 35 The activity of a compound on a K_v7 channel may be assessed through different *in vitro* assays in cells as known in the art. For example, fluorescence-based assays of channel

activity assessing ion flux, such as Thallium ion (Tl^+) influx assays, or other fluorescence based assays. The current examples demonstrate an example of a Tl^+ ion flux assay, other types of channel assay will be known to a person of skill in the art.

5 In one embodiment, the compound is able to produce an increase in the activity of the $K_v7.2/K_v7.3$ heteromeric channel, with an EC_{50} of less than 50 μM , such as less than 20 μM , such as less than 10 μM , such as less than 1 μM , such as less than 0.1 μM , such as less than 0.06 μM , such as less than 0.01 μM , such as less than 0.001 μM .

10 In one embodiment, the compound is able to produce an increase in the activity of the $K_v7.2/K_v7.3$ heteromeric channel, with an EC_{50} from about 0.1 nM to about 20 μM , such as from about 0.1 nM to about 10 μM , such as from about 0.1 nM to about 1 μM , such as from about 0.1 nM to about 0.2 μM , such as from 0.1 nM to about 100 nM, such as from about 0.1 nM to about 10 nM.

15 Thus, in one aspect the present disclosure provides a compound as described herein for use in a method of modulating the activity of a K_v7 channel in a subject, the method comprising administering an effective amount of the compound to the subject.

20 In one embodiment, the compound is for use in a method of increasing the activity of a $K_v7.2/K_v7.3$ heteromeric channel in a subject.

In one embodiment the compound is able to increase the activity of a $K_v7.5$ channel. In one embodiment, the compound is able to produce an increase in the activity of the $K_v7.5$ channel, with an EC_{50} from about 0.1 nM to about 20 μM , such as from about 0.1 nM to about 10 μM , such as from about 0.1 nM to about 1 μM , such as from about 0.1 nM to about 0.2 μM , such as from 0.1 nM to about 100 nM, such as from about 0.1 nM to about 10 nM. In one embodiment, the compound is for use in a method of increasing the activity of a $K_v7.5$ channel in a subject. In one embodiment, the compound is for use in a method of increasing the activity of a $K_v7.5$ channel in a subject.

30

Selective K_v7 modulation

In some cases, differentiation between K_v7 subtypes is desired, as this potentially provides for improved efficacy and safety of medicines. In some embodiments, the compound can selectively increase the activity of a $K_v7.2/K_v7.3$ heteromeric channel.

35

In some embodiments, the compound is a subtype-selective Kv7 modulator. In one embodiment the compound is selective for Kv7.2/Kv7.3. In some embodiments, the compound is selective for Kv7.2/Kv7.3 over Kv7.5.

- 5 The selectivity for Kv7.2/Kv7.3 over Kv7.5 of the compounds of the present invention can be observed either in terms of potency selectivity, efficiency selectivity or both.

The term 'potency selectivity' as used herein refers to that the ratio between Kv7.2/Kv7.3 EC₅₀ and Kv7.5 EC₅₀ is larger than 10. In one embodiment, the ratio is calculated
10 according to the formula below:

$$ratio \text{ between EC}_{50} \text{ of Kv7.2/Kv7.3 and EC}_{50} \text{ of Kv7.5} = \frac{EC_{50} \text{ of Kv7.5}}{EC_{50} \text{ of Kv7.2/Kv7.3}}$$

In one embodiment the compound has a ratio between EC₅₀ of Kv7.2/Kv7.3 and EC₅₀ of Kv7.5 of more than 2, such as more than 3, such as more than 5, such as more than 8,
15 such as more than 10, such as more than 15, such as more than 20, such as more than 25, such as more than 30, such as more than 60, such as more than 75, such as more than 100, such as more than 150, such as more than 200, such as more than 230, such as more than 250, such as more than 500. In one embodiment the compound has a ratio between EC₅₀ of Kv7.2/Kv7.3 and EC₅₀ of Kv7.5 of more than 10.
20 In one embodiment, the Kv7.5 EC₅₀ is more than 30 μM. In one embodiment, the compound has an EC₅₀ for Kv7.2/Kv7.3 of less than 10 μM and an EC₅₀ for Kv7.5 of more than 30 μM.

In one embodiment the EC₅₀ is measured in an *in vitro* cell-based assay of ion flux,
25 such as a Thallium ion (Tl⁺) assay.

The term 'efficacy selectivity' as used refers to that the efficacy is larger than 50% at Kv7.2/Kv7.3 and less than 25% at Kv7.5, relative to 10 μM retigabine.

30 In one embodiment the compound has an efficacy for Kv7.2/Kv7.3 larger than 50%, such as larger than 60%, such as larger than 70%, such as larger than 75%, such as larger than 80%, such as larger than 85%, such as larger than 90%, such as larger than 95%, such as larger than 100%, such as larger than 110%. In one embodiment the compound has an efficacy for Kv7.5 of less than 60%, such as less than 50%, such

as less than 40%, such as less than 30%, such as less than 20%, such as 0%. In one embodiment the compound has an efficacy for $K_v7.5$ of less than 25%. In one embodiment the compound has an efficacy for $K_v7.2/K_v7.3$ larger than 50%, and an efficacy for $K_v7.5$ of less than 25%.

5

In one embodiment the compound is potency selective. In one embodiment the compound is efficacy selective. In one embodiment the compound is potency selective and efficacy selective.

10 **Preparation of compounds**

Compounds according to the present invention may be prepared according to any conventional methods of chemical synthesis known by the skilled person, e.g. those described in the working examples. The starting materials for the processes described in the present application are known or may readily be prepared by conventional methods known by the skilled artisan from commercially available chemicals.

15

The end products of the reactions described herein may be isolated by conventional technique such as extraction, crystallisation, distillation, chromatography etc. Moreover the compounds according to the present invention may be separated into different stereoisomers, respectively (R) and (S), using chiral chromatography, such as chiral preparative HPLC.

20

The compounds of this invention may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

25

Pharmaceutically Acceptable Salts

The chemical compound of the invention may be provided in any form suitable for the intended administration, including pharmaceutically (i.e. physiologically) acceptable salts. Such salts may be formed by procedures well known and described in the art.

30

Pharmaceutical compositions

The present invention also relates to a pharmaceutical composition comprising, for example as an active ingredient, a pharmaceutically effective amount of a compound of Formula (I) as defined above. In one embodiment, said pharmaceutical composition comprises a therapeutically effective amount of the compound of Formula (I) or a

35

pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, excipient, or diluent.

5 While the compound of Formula (I) of the present invention for use in therapy may be administered in the form of the raw chemical compound, it is preferred to introduce the active ingredient, optionally in the form of a physiologically acceptable salt, in a pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

10 In a preferred embodiment, the invention provides pharmaceutical compositions comprising the chemical compound of the invention, or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable carriers, and, optionally, other therapeutic and/or prophylactic ingredients, known and used in the art. The carrier(s) should be "acceptable" in the sense of being compatible with the other
15 ingredients of the formulation and not harmful to the recipient thereof.

A therapeutically effective dose refers to that amount of active ingredient, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity, e.g. ED₅₀, may be determined by standard pharmacological procedures in cell cultures or
20 experimental animals. The dose ratio between therapeutic and toxic effects is the therapeutic index and may be expressed by ratio between plasma levels resulting in therapeutic effects and plasma ratios resulting in toxic effects. Pharmaceutical compositions exhibiting large therapeutic indexes are preferred.

25 The dose administered may be adjusted to the age, weight and condition of the individual being treated, as well as the route of administration, dosage form and regimen, and the result desired, and the exact dosage can be determined by the practitioner.

30 **Medical use**

Given the activity of the compounds in K_v7 channels, the compounds according to the present disclosure may be useful in treatment of conditions associated with K_v7 modulation. The examples demonstrate that compounds according to the present disclosure produce similar effects to the compound retigabine in K_v7 channels. Thus, in
35 one aspect, the present disclosure provides a pharmaceutical composition comprising a

compound as described herein. For example, the pharmaceutical composition may comprise one or more excipients as known in the art.

5 In another aspect, the present disclosure provides a compound as described herein for use as a medicament.

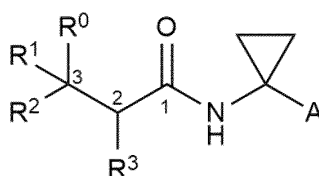
In another aspect, the present disclosure provides a compound as described herein for use in a method of treatment of one selected from epilepsy or pain in a subject, said method comprising administering a therapeutically effective amount of a compound as described herein to the subject.

In another aspect, the present disclosure provides for a method of treatment of epilepsy or pain in a subject in need thereof, said method comprising administering a therapeutically effective amount of a compound as described herein to the subject.

15 In another aspect, the present disclosure provides for a use of a compound as described herein in the manufacture of a medicament for the treatment of epilepsy or pain in a subject in need thereof.

Items

20 1. A compound according to formula (I):



formula (I)

or a tautomer, a mesomer, a racemate, an enantiomer or a diastereoisomer thereof, or a mixture thereof; or a pharmaceutically acceptable salt thereof;

25 wherein,

R⁰ is selected from the group consisting of -OH, and -CH₃;

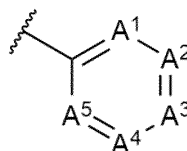
R¹ is aryl optionally substituted with one or more, identical or different, substituents R⁴, or heteroaryl optionally substituted with one or more, identical or different, substituents R⁴;

30 R⁴ is selected from the group consisting of C₁₋₅ alkyl optionally substituted with one or more F, C₁₋₅ alkoxy, halogen and CN;

R² is selected from the group consisting of -H, -CH₃, and -CF₃;

R³ is selected from the group consisting of -H and -OH;

A is of formula (II):



formula (II)

5 wherein

A¹ is C-R⁵ or N;

R⁵ is -H or halogen;

A² is C-R⁶;

10 R⁶ is selected from the group consisting of C₁₋₅ alkoxy optionally substituted with one or more F; C₁₋₅ alkyl optionally substituted with one or more F; halogen; and N(R¹⁰)(R¹¹);

R¹⁰ is C₁₋₅ alkyl optionally substituted with one or more, identical or different, substituents R¹²;

R¹¹ is -H;

15 R¹² is selected from the group consisting of halogen, C₃₋₅ cycloalkyl and C₁₋₃ alkyl;

A³ is C-R⁷ or N;

R⁷ is selected from the group consisting of -H, halogen and C₁₋₅ alkyl;

A⁴ is C-R⁸ or N;

20 R⁸ is selected from the group consisting of -H, halogen, C₃₋₅ cycloalkyl, C₁₋₅ alkyl optionally substituted with one or more F, C₁₋₅ alkoxy, and -CN;

A⁵ is C-R⁹ or N;

R⁹ is -H or halogen;

with the proviso that the compound is not

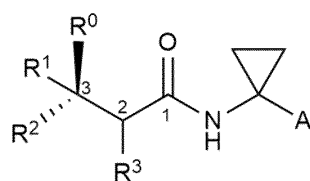
N-[1-(3,5-Difluorophenyl)cyclopropyl]-β-methyl-1*H*-imidazole-1-propanamide;

25 *N*-[1-(3-Chlorophenyl)cyclopropyl]-β-hydroxybenzenepropanamide; or

N-[1-(3-Fluorophenyl)cyclopropyl]-β-hydroxybenzenepropanamide; or

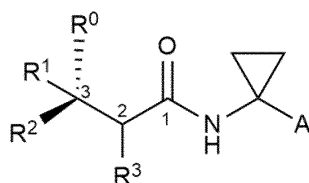
3-Fluoro-*N*-[1-(3-fluorophenyl)cyclopropyl]-β-hydroxybenzenepropanamide.

2. The compound according to item 1, wherein the compound is of formula (Ia):



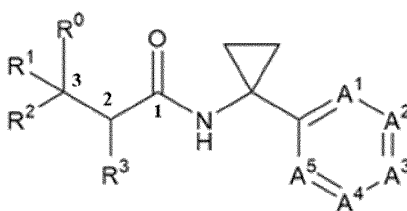
formula (Ia)

3. The compound according to item 1, wherein the compound is of formula (Ib):



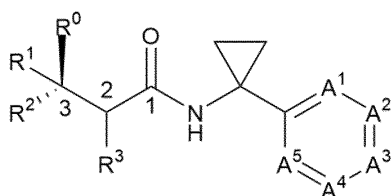
formula (Ib)

4. The compound according to item 1, wherein the compound is of formula (III):



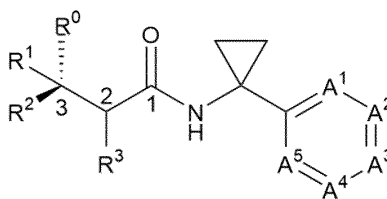
formula (III)

5. The compound according to item 1, wherein the compound is of formula (IIIa):



formula (IIIa)

6. The compound according to item 1, wherein the compound is of formula (IIIb):



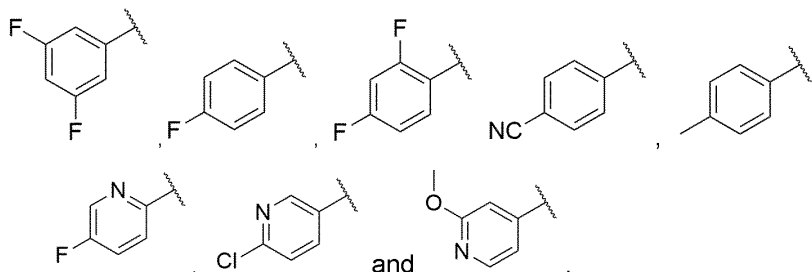
formula (IIIb)

7. The compound according to any one of the preceding items, wherein R⁰ is -OH.
- 5 8. The compound according to any one of the preceding items, wherein R⁰ is -CH₃.
9. The compound according to any one of the preceding items, wherein R¹ is aryl, optionally substituted with one or more, identical or different substituents R⁴.
10. The compound according to any one of the preceding items, wherein R¹ is aryl substituted with one or two, identical or different substituents R⁴.
- 10 11. The compound according to any one of the preceding items, wherein R¹ is phenyl optionally substituted with one or more, identical or different, substituents R⁴.
12. The compound according to any one of the preceding items, wherein R¹ is phenyl.
- 15 13. The compound according to any one of the preceding items, wherein R¹ is phenyl substituted with one or more, identical or different, substituents R⁴.
14. The compound according to any one of the preceding items, wherein R¹ is phenyl substituted with one R⁴.
- 20 15. The compound according to any one of the preceding items, wherein R¹ is phenyl substituted with two, identical or different, substituents R⁴.
16. The compound according to any one of the preceding items, wherein R¹ is phenyl substituted with three, identical or different, substituents R⁴.
17. The compound according to any one of the preceding items, wherein R¹ is heteroaryl, optionally substituted with one or more, identical or different substituents R⁴.
- 25 18. The compound according to any one of the preceding items, wherein R¹ is heteroaryl substituted with one or two, identical or different substituents R⁴.
19. The compound according to any one of the preceding items, wherein the heteroaryl is pyridinyl.
- 30

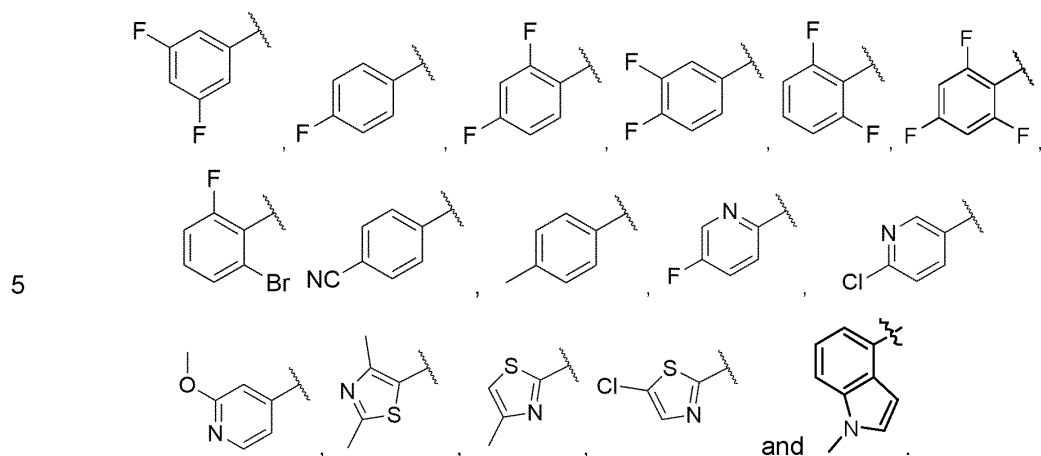
20. The compound according to any one of the preceding items, wherein the heteroaryl is pyridin-4-yl.
21. The compound according to any one of the preceding items, wherein the heteroaryl is pyridin-2-yl.
- 5 22. The compound according to any one of the preceding items, wherein the heteroaryl is pyridin-3-yl.
23. The compound according to any one of the preceding items, wherein R¹ is pyridinyl optionally substituted with one or more, identical or different, substituents R⁴.
- 10 24. The compound according to any one of the preceding items, wherein R¹ is pyridinyl.
25. The compound according to any one of the preceding items, wherein R¹ is pyridin-2-yl optionally substituted with one or more, identical or different substituents R⁴.
- 15 26. The compound according to any one of the preceding items, wherein R¹ is pyridin-2-yl substituted with one R⁴.
27. The compound according to any one of the preceding items, wherein R¹ is pyridin-3-yl optionally substituted with one or more, identical or different substituents R⁴.
- 20 28. The compound according to any one of the preceding items, wherein R¹ is pyridin-3-yl substituted with one R⁴.
29. The compound according to any one of the preceding items, wherein R¹ is pyridin-4-yl optionally substituted with one or more, identical or different substituents R⁴.
- 25 30. The compound according to any one of the preceding items, wherein R¹ is pyridin-4-yl substituted with one R⁴.
31. The compound according to any one of the preceding items, wherein the heteroaryl is thiazolyl.
- 30 32. The compound according to any one of the preceding items, wherein R¹ is thiazolyl optionally substituted with one or more, identical or different, substituents R⁴.
33. The compound according to any one of the preceding items, wherein R¹ is thiazol-2-yl optionally substituted with one or more, identical or different, substituents R⁴.

34. The compound according to any one of the preceding items, wherein R¹ is thiazol-5-yl optionally substituted with one or more, identical or different, substituents R⁴.
- 5 35. The compound according to any one of the preceding items, wherein R¹ is thiazolyl substituted with one or more, identical or different, substituents R⁴, wherein R⁴ is individually halogen, such as Cl, or is C₁₋₃ alkyl, such as -CH₃.
36. The compound according to any one of the preceding items, wherein the thiazolyl is thiazol-2-yl.
- 10 37. The compound according to any one of the preceding items, wherein the thiazolyl is thiazol-5-yl.
38. The compound according to any one of the preceding items, wherein R¹ is thiazol-2-yl optionally substituted with one or more, identical or different, substituents R⁴.
- 15 39. The compound according to any one of the preceding items, wherein R¹ is thiazol-5-yl optionally substituted with one or more, identical or different, substituents R⁴.
40. The compound according to any one of the preceding items, wherein the heteroaryl is indolyl.
- 20 41. The compound according to any one of the preceding items, wherein the heteroaryl is indol-4-yl.
42. The compound according to any one of the preceding items, wherein R¹ is indolyl optionally substituted with one or more, identical or different, substituents R⁴.
- 25 43. The compound according to any one of the preceding items, wherein R¹ is indol-4-yl optionally substituted with one or more, identical or different, substituents R⁴.
44. The compound according to any one of the preceding items, wherein R¹ is indolyl optionally substituted with one or more, identical or different, substituents R⁴, wherein R⁴ is C₁₋₃ alkyl, such as -CH₃.
- 30 45. The compound according to any one of the preceding items, wherein R¹ is indol-4-yl optionally substituted with one or more, identical or different, substituents R⁴, wherein R⁴ is C₁₋₃ alkyl, such as -CH₃.
- 35 46. The compound according to any one of the preceding items, wherein one or more R⁴ is halogen.

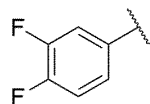
47. The compound according to any one of the preceding items, wherein one or more R^4 is -F.
48. The compound according to any one of the preceding items, wherein one or more R^4 is -Cl.
- 5 49. The compound according to any one of the preceding items, wherein one or more R^4 is -Br.
50. The compound according to any one of the preceding items, wherein one or more R^4 is C_{1-5} alkoxy.
51. The compound according to any one of the preceding items, wherein one or more R^4 is C_{1-3} alkoxy.
- 10 52. The compound according to any one of the preceding items, wherein one or more R^4 is -OCH₃.
53. The compound according to any one of the preceding items, wherein one or more R^4 is C_{1-5} alkyl.
- 15 54. The compound according to any one of the preceding items, wherein one or more R^4 is C_{1-3} alkyl.
55. The compound according to any one of the preceding items, wherein one or more R^4 is -CH₃.
56. The compound according to any one of the preceding items, wherein one or more R^4 is -CN.
- 20 57. The compound according to any one of the preceding items, wherein one or more R^4 is -CF₃.
58. The compound according to any one of the preceding items, wherein R^4 is independently selected from the group consisting of -F, -Cl, -Br, -OCH₃, -CH₃, -CN and CF₃.
- 25 59. The compound according to any one of the preceding items, wherein R^1 is selected from:



60. The compound according to any one of the preceding items, wherein R^1 is selected from:

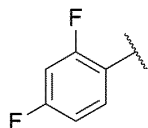


61. The compound according to any one of the preceding items, wherein R^1 is

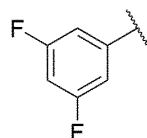


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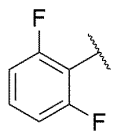
62. The compound according to any one of the preceding items, wherein R^1 is



63. The compound according to any one of the preceding items, wherein R^1 is

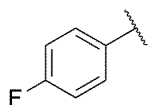


64. The compound according to any one of the preceding items, wherein R^1 is



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65. The compound according to any one of the preceding items, wherein R¹ is

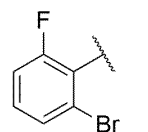


66. The compound according to any one of the preceding items, wherein R¹ is

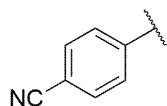


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67. The compound according to any one of the preceding items, wherein R¹ is

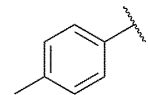


68. The compound according to any one of the preceding items, wherein R¹ is

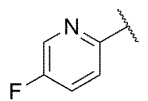


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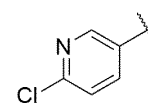
69. The compound according to any one of the preceding items, wherein R¹ is



70. The compound according to any one of the preceding items, wherein R¹ is

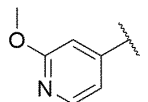


71. The compound according to any one of the preceding items, wherein R¹ is

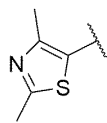


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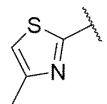
72. The compound according to any one of the preceding items, wherein R¹ is



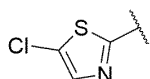
73. The compound according to any one of the preceding items, wherein R¹ is



74. The compound according to any one of the preceding items, wherein R^1 is

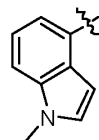


75. The compound according to any one of the preceding items, wherein R^1 is



5

76. The compound according to any one of the preceding items, wherein R^1 is



77. The compound according to any one of the preceding items, wherein R^2 is selected from the group consisting of -H, -CH₃ and -CF₃.

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78. The compound according to any one of the preceding items, wherein R^2 is not H.

79. The compound according to any one of the preceding items, wherein R^2 is selected from -CH₃ and -CF₃.

15

80. The compound according to any one of the preceding items, wherein R^2 is -CH₃.

81. The compound according to any one of the preceding items, wherein R^2 is -CF₃.

20

82. The compound according to any one of the preceding items, wherein when R^2 is H then at least one of A^1 , A^3 and A^4 is not -CH.

83. The compound according to any one of the preceding items, wherein R^2 is -CH₃ and R^0 is OH.

25

84. The compound according to any one of the preceding items, wherein R^2 is $-\text{CF}_3$ and R^0 is OH.
85. The compound according to any one of the preceding items, wherein R^2 is H and R^0 is OH.
- 5 86. The compound according to any one of the preceding items, wherein R^2 is H and R^0 is $-\text{CH}_3$.
87. The compound according to any one of the preceding items, wherein R^3 is H.
88. The compound according to any one of the preceding items, wherein R^3 is OH.
- 10 89. The compound according to any one of the preceding items, wherein R^0 is $-\text{OH}$, R^2 is $-\text{CH}_3$, and R^3 is $-\text{H}$.
90. The compound according to any one of the preceding items, wherein A is phenyl optionally substituted with one or more substituents R^5 , R^6 , R^7 , R^8 and/or R^9 .
- 15 91. The compound according to any one of the preceding items, wherein A is phenyl optionally substituted with one substituent R^5 , R^6 , R^7 , R^8 and/or R^9 .
92. The compound according to any one of the preceding items, wherein A is phenyl optionally substituted with two substituent R^5 , R^6 , R^7 , R^8 and/or R^9 .
- 20 93. The compound according to any one of the preceding items, wherein A is pyridinyl optionally substituted with one or more substituents R^5 , R^6 , R^7 , R^8 and/or R^9 .
94. The compound according to any one of the preceding items, wherein A is pyridin-2-yl optionally substituted with one or more substituents R^5 , R^6 , R^7 , R^8 and/or R^9 .
- 25 95. The compound according to any one of the preceding items, wherein A is pyridin-2-yl optionally substituted with one substituent R^5 , R^6 , R^7 , R^8 and/or R^9 .
96. The compound according to any one of the preceding items, wherein A is pyridin-2-yl optionally substituted with two substituent R^5 , R^6 , R^7 , R^8 and/or R^9 .
- 30 97. The compound according to any one of the preceding items, wherein A is pyridin-3-yl optionally substituted with one or more substituents R^5 , R^6 , R^7 , R^8 and/or R^9 .
98. The compound according to any one of the preceding items, wherein A is pyridin-3-yl optionally substituted with one substituent R^5 , R^6 , R^7 , R^8 and/or R^9 .
- 35 99. The compound according to any one of the preceding items, wherein A is pyridin-3-yl optionally substituted with two substituent R^5 , R^6 , R^7 , R^8 and/or R^9 .

100. The compound according to any one of the preceding items, wherein A is pyrimidinyl optionally substituted with one or more substituents R⁵, R⁶, R⁷, R⁸ and/or R⁹.
101. The compound according to any one of the preceding items, wherein A is pyrimidin-4-yl optionally substituted with one or more, substituents R⁵, R⁶, R⁷, R⁸ and/or R⁹.
102. The compound according to any one of the preceding items, wherein A is pyrimidin-4-yl optionally substituted with one substituent R⁵, R⁶, R⁷, R⁸ and/or R⁹.
103. The compound according to any one of the preceding items, wherein A¹ is C-R⁵; A² is C-R⁶; A³ is C-R⁷; A⁴ is C-R⁸; and A⁵ is C-R⁹.
104. The compound according to any one of the preceding items, wherein at least one of A¹, A³ and A⁴ is not -CH.
105. The compound according to any one of the preceding items, wherein one of A¹, A³, A⁴, and A⁵ is N.
106. The compound according to any one of the preceding items, wherein A¹ is N; A² is C-R⁶; A³ is C-R⁷; A⁴ is C-R⁸; and A⁵ is C-R⁹.
107. The compound according to any one of the preceding items, wherein A¹ is C-R⁵; A² is C-R⁶; A³ is N; A⁴ is C-R⁸; and A⁵ is C-R⁹.
108. The compound according to any one of the preceding items, wherein A¹ is C-R⁵; A² is C-R⁶; A³ is C-R⁷; A⁴ is N; and A⁵ is C-R⁹.
109. The compound according to any one of the preceding items, wherein A¹ is N; A² is C-R⁶; A³ is N; A⁴ is C-R⁸; and A⁵ is C-R⁹.
110. The compound according to any one of the preceding items, wherein A¹ is C-R⁵; A² is C-R⁶; A³ is C-R⁷; A⁴ is C-R⁸; and A⁵ is N.
111. The compound according to any one of the preceding items, wherein A¹ is N.
112. The compound according to any one of the preceding items, wherein A¹ is C-R⁵.
113. The compound according to any one of the preceding items, wherein R⁵ is -H.
114. The compound according to any one of the preceding items, wherein A¹ is C(H).

115. The compound according to any one of the preceding items, wherein R^5 is halogen.
116. The compound according to any one of the preceding items, wherein R^5 is -F.
- 5 117. The compound according to any one of the preceding items, wherein A^1 is C(F).
118. The compound according to any one of the preceding items, wherein A^2 is C- R^6 , wherein R^6 is selected from C_{1-5} alkoxy optionally substituted with one or more F, -CF₃, -CF₂H, -Cl, -Br or -CH₃. The compound according to any one of items 1 to 10, wherein R^6 is selected from -CF₃, -Cl, -Br or -CH₃.
- 10 119. The compound according to any one of the preceding items, wherein A^2 is C- R^6 , wherein R^6 is selected from C_{1-5} alkoxy optionally substituted with one or more F; C_{1-5} alkyl optionally substituted with one or more F; halogen and N(R^{10})(R^{11}).
- 15 120. The compound according to any one of the preceding items, wherein R^6 is C_{1-5} alkoxy optionally substituted with one or more F.
121. The compound according to any one of the preceding items, wherein R^6 is C_{1-4} alkoxy optionally substituted with one or more F.
- 20 122. The compound according to any one of the preceding items, wherein R^6 is C_{1-3} alkoxy optionally substituted with one or more F.
123. The compound according to any one of the preceding items, wherein R^6 is C_1 alkoxy optionally substituted with one or more F.
- 25 124. The compound according to any one of the preceding items, wherein R^6 is selected from -OCH₂CF₃, -OCF₃, -OCH₃, -OCH₂CF₂H and -OCF₂H.
125. The compound according to any one of the preceding items, wherein R^6 is -O-CH₂-CF₃.
126. The compound according to any one of the preceding items, wherein R^6 is -OCH₃.
- 30 127. The compound according to any one of the preceding items, wherein R^{12} is -CF₃.
128. The compound according to any one of the preceding items, wherein R^6 is C_{1-5} alkyl optionally substituted with one or more F.

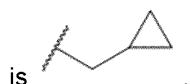
129. The compound according to any one of the preceding items, wherein R^6 is C_{1-3} alkyl optionally substituted with one or more F.
130. The compound according to any one of the preceding items, wherein R^6 is C_1 alkyl optionally substituted with one or more F.
- 5 131. The compound according to any one of the preceding items, wherein R^6 is $-CF_3$.
132. The compound according to any one of the preceding items, wherein R^6 is $-CF_2H$.
133. The compound according to any one of the preceding items, wherein R^6 is halogen.
- 10 134. The compound according to any one of the preceding items, wherein R^6 is Br.
135. The compound according to any one of the preceding items, wherein R^6 is Cl.
- 15 136. The compound according to any one of the preceding items, wherein R^6 is F.
137. The compound according to any one of the preceding items, wherein R^6 is $-OCF_3$.
- 20 138. The compound according to any one of the preceding items, wherein R^6 is $-OCH_2CF_3$.
139. The compound according to any one of the preceding items, wherein R^6 is $N(R^{10})(R^{11})$, wherein R^{10} is C_{1-5} alkyl optionally substituted with one or more, identical or different, substituents R^{12} , R^{11} is $-H$, and R^{12} is selected from the group consisting of halogen, C_{3-5} cycloalkyl and C_{1-3} alkyl.
- 25 140. The compound according to any one of the preceding items, wherein R^{10} is C_{1-3} alkyl optionally substituted with one or more, identical or different, substituents R^{12} .
141. The compound according to any one of the preceding items, wherein R^{12} is halogen.
- 30 142. The compound according to any one of the preceding items, wherein R^{12} is F.
143. The compound according to any one of the preceding items, wherein R^{10} is $-CH_2CF_3$.

144. The compound according to any one of the preceding items, wherein R^6 is $-N(H)(CH_2CF_3)$.

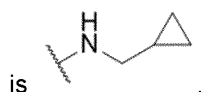
145. The compound according to any one of the preceding items, wherein R^{12} is C_{3-5} cycloalkyl.

5 146. The compound according to any one of the preceding items, wherein R^{12} is cyclopropyl.

147. The compound according to any one of the preceding items, wherein R^{10}



148. The compound according to any one of the preceding items, wherein R^6



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149. The compound according to any one of the preceding items, wherein R^{12} is C_{1-3} alkyl.

150. The compound according to any one of the preceding items, wherein R^{12} is CH_3 .

15 151. The compound according to any one of the preceding items, wherein R^{10} is $-CH_2C(CH_3)_3$.

152. The compound according to any one of the preceding items, wherein R^6 is $-N(H)CH_2C(CH_3)_3$.

20 153. The compound according to any one of the preceding items, wherein R^{10} is $-C(H)(CH_3)_2$.

154. The compound according to any one of the preceding items, wherein R^6 is $-N(H)C(H)(CH_3)_2$.

25 155. The compound according to any one of the preceding items, wherein A^3 is $C-R^7$, and wherein R^7 is selected from the group consisting of $-H$, halogen and C_{1-5} alkyl.

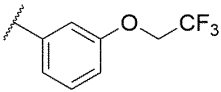
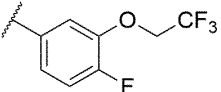
156. The compound according to any one of the preceding items, wherein A^3 is $C-R^7$, wherein R^7 is selected from $-H$, $-F$, $-Cl$, and $-CH_3$.

157. The compound according to any one of the preceding items, wherein R^7 is $-H$.

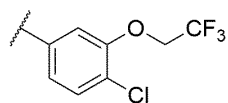
30 158. The compound according to any one of the preceding items, wherein A^3 is $C(H)$.

159. The compound according to any one of the preceding items, wherein R^7 is halogen.
160. The compound according to any one of the preceding items, wherein R^7 is -F.
- 5 161. The compound according to any one of the preceding items, wherein R^7 is -Cl.
162. The compound according to any one of the preceding items, wherein A^3 is C(F).
- 10 163. The compound according to any one of the preceding items, wherein R^7 is C_{1-5} alkyl.
164. The compound according to any one of the preceding items, wherein R^7 is C_{1-3} alkyl.
165. The compound according to any one of the preceding items, wherein R^7 is $-CH_3$.
- 15 166. The compound according to any one of the preceding items, wherein A^3 is N.
167. The compound according to any one of the preceding items, wherein A^4 is $C-R^8$; wherein R^8 is selected from the group consisting of H, halogen, C_{3-5} cycloalkyl, C_{1-5} alkyl optionally substituted with one or more F, C_{1-5} alkoxy, and -
- 20 CN.
168. The compound according to any one of the preceding items, wherein A^4 is $C-R^8$; wherein R^8 is selected from the group consisting of -H, C_1-C_5 cycloalkyl, -CN, -F, -Cl, -Br and $-CF_2H$.
169. The compound according to any one of the preceding items, wherein A^4 is $C-R^8$; wherein R^8 is selected from the group consisting of -H, cyclopropyl, methoxy, -CN, -F, -Cl, -Br and $-CF_2H$.
- 25 170. The compound according to any one of the preceding items, wherein R^8 is selected from -H, -F and -Cl.
171. The compound according to any one of the preceding items, wherein R^8 is -H.
- 30 172. The compound according to any one of the preceding items, wherein A^4 is C(H).
173. The compound according to any one of the preceding items, wherein R^8 is $-CN$.

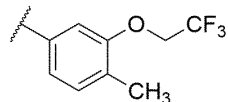
174. The compound according to any one of the preceding items, wherein A⁴ is C(CN).
175. The compound according to any one of the preceding items, wherein R⁸ is halogen.
- 5 176. The compound according to any one of the preceding items, wherein R⁸ is F.
177. The compound according to any one of the preceding items, wherein A⁴ is C(F).
178. The compound according to any one of the preceding items, wherein R⁸ is -Br.
- 10 179. The compound according to any one of the preceding items, wherein A⁴ is C(Br).
180. The compound according to any one of the preceding items, wherein R⁸ is -Cl.
- 15 181. The compound according to any one of the preceding items, wherein A⁴ is C(Cl).
182. The compound according to any one of the preceding items, wherein R⁸ is C₁₋₅ alkyl optionally substituted with one or more F.
183. The compound according to any one of the preceding items, wherein R⁸ is C₁₋₃ alkyl optionally substituted with one or more F.
- 20 184. The compound according to any one of the preceding items, wherein R⁸ is C₁ alkyl optionally substituted with one or more F.
185. The compound according to any one of the preceding items, wherein R⁸ is -CF₂H.
- 25 186. The compound according to any one of the preceding items, wherein A⁴ is C(CF₂H).
187. The compound according to any one of the preceding items, wherein R⁸ is -C₃-C₅ cycloalkyl.
188. The compound according to any one of the preceding items, wherein R⁸ is cyclopropyl.
- 30 189. The compound according to any one of the preceding items, wherein A⁴ is C(cyclopropyl).
190. The compound according to any one of the preceding items, wherein R⁸ is C₁₋₅ alkoxy.

191. The compound according to any one of the preceding items, wherein R^8 is C_{1-3} alkoxy.
192. The compound according to any one of the preceding items, wherein R^8 is $-OCH_3$.
- 5 193. The compound according to any one of the preceding items, wherein A^4 is $C(OCH_3)$.
194. The compound according to any one of the preceding items, wherein A^4 is N.
195. The compound according to any one of the preceding items, wherein A^5 is $C-R^9$, and wherein R^9 is -H or -halogen.
- 10 196. The compound according to any one of the preceding items, wherein A^5 is $C-R^9$, and wherein R^9 is -H or -F.
197. The compound according to any one of the preceding items, wherein R^9 is -H.
- 15 198. The compound according to any one of the preceding items, wherein A^5 is $C(H)$.
199. The according to any one of the preceding items, wherein R^9 is -halogen.
- 20 200. The compound according to any one of the preceding items, wherein R^9 is -F.
201. The compound according to any one of the preceding items, wherein A^5 is $C(F)$.
202. The compound according to any one of the preceding items, wherein A^5 is N.
- 25 203. The compound according to any one of the preceding items, wherein A is .
204. The compound according to any one of the preceding items, wherein A is .

205. The compound according to any one of the preceding items, wherein A is

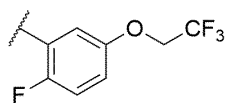


206. The compound according to any one of the preceding items, wherein A is

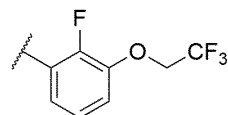


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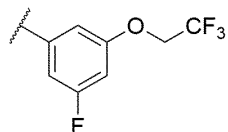
207. The compound according to any one of the preceding items, wherein A is



208. The compound according to any one of the preceding items, wherein A is

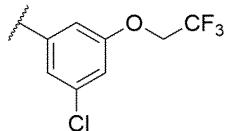


209. The compound according to any one of the preceding items, wherein A is

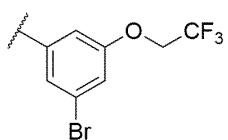


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210. The compound according to any one of the preceding items, wherein A is

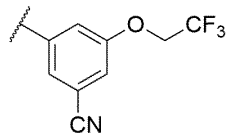


211. The compound according to any one of the preceding items, wherein A is

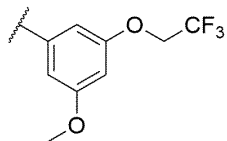


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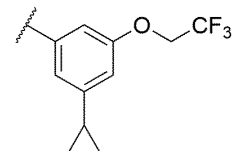
212. The compound according to any one of the preceding items, wherein A is



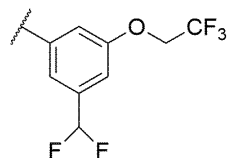
213. The compound according to any one of the preceding items, wherein A is



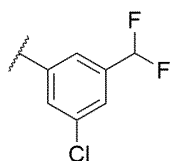
214. The compound according to any one of the preceding items, wherein A is



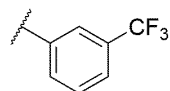
- 5 215. The compound according to any one of the preceding items, wherein A is



216. The compound according to any one of the preceding items, wherein A is

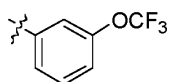


217. The compound according to any one of the preceding items, wherein A is

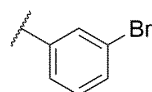


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218. The compound according to any one of the preceding items, wherein A is

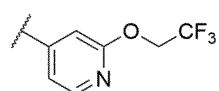


219. The compound according to any one of the preceding items, wherein A is

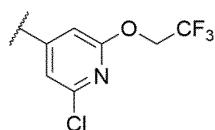


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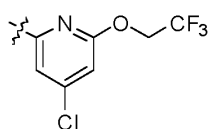
220. The compound according to any one of the preceding items, wherein A is



221. The compound according to any one of the preceding items, wherein A is

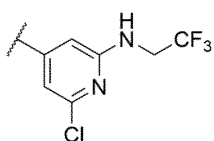


222. The compound according to any one of the preceding items, wherein A is

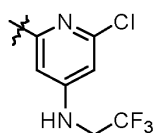


5

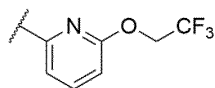
223. The compound according to any one of the preceding items, wherein A is



224. The compound according to any one of the preceding items, wherein A is

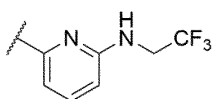


225. The compound according to any one of the preceding items, wherein A is

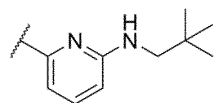


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226. The compound according to any one of the preceding items, wherein A is

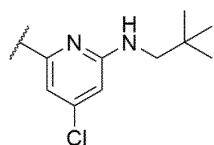


227. The compound according to any one of the preceding items, wherein A is

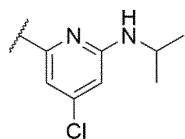


15

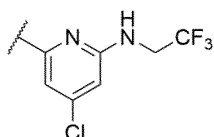
228. The compound according to any one of the preceding items, wherein A is



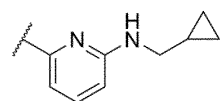
229. The compound according to any one of the preceding items, wherein A is



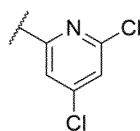
230. The compound according to any one of the preceding items, wherein A is



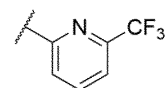
- 5 231. The compound according to any one of the preceding items, wherein A is



232. The compound according to any one of the preceding items, wherein A is

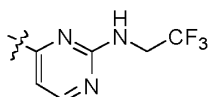


233. The compound according to any one of the preceding items, wherein A is



10

234. The compound according to any one of the preceding items, wherein A is



235. The compound according to item 1, wherein

15

R^0 is -OH,

R^1 is phenyl substituted with two or three -F,

R^2 is -CH₃,

R^3 is -H,

A^1 is C- R^5 ,

A^2 is C(OCH₂CF₃),

20

A^3 is C- R^7 ,

A^4 is C- R^8 , and

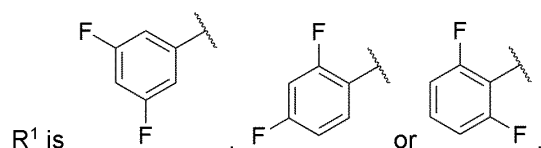
A^5 is C- R^9 ,

wherein one of R^5 , R^7 , R^8 , and R^9 is -F, -Cl, -Br, or -CH₃, and the others are -H.

25

236. The compound according to item 1, wherein

R^0 is -OH,



R^2 is $-\text{CH}_3$,

R^3 is $-\text{H}$,

A^1 is $\text{C}-R^5$,

A^2 is $\text{C}(\text{OCH}_2\text{CF}_3)$,

A^3 is $\text{C}-R^7$,

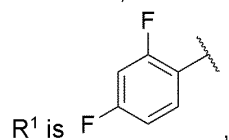
A^4 is $\text{C}-R^8$, and

A^5 is $\text{C}-R^9$,

wherein one of R^5 , R^7 , R^8 , and R^9 is $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, or $-\text{CH}_3$, and the others are $-\text{H}$.

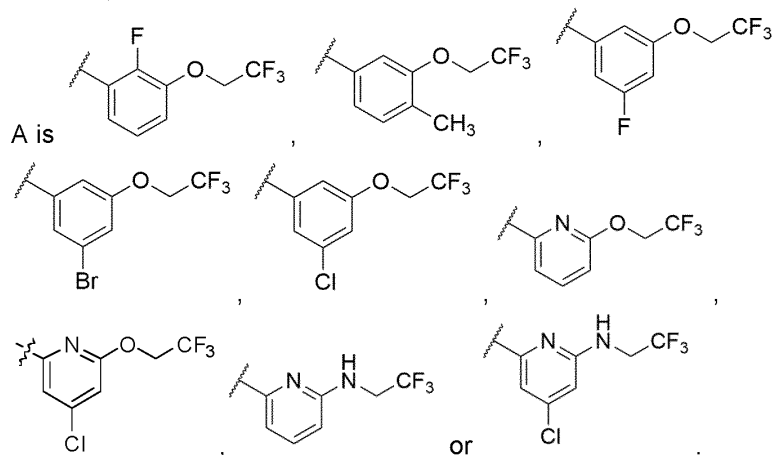
237. The compound according to item 1, wherein

R^0 is $-\text{OH}$,



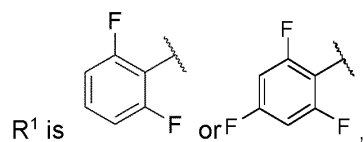
R^2 is $-\text{CH}_3$, and

R^3 is $-\text{H}$,



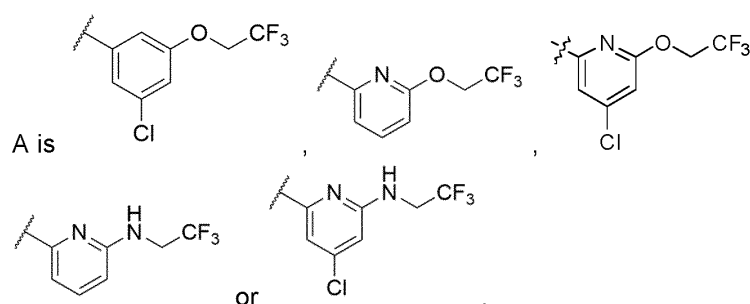
238. The compound according to item 1, wherein

R^0 is $-\text{OH}$,



R^2 is $-\text{CH}_3$,

R^3 is $-\text{H}$, and



239. The compound according to any one of the preceding items, wherein the stereochemistry configuration at positions 2 and 3, as defined by formulas (I) and (III), are independently selected from R and S.
240. The compound according to any one of the preceding items, wherein the stereochemistry configuration at position 3, as defined in formulas (I) and (III), is R.
241. The compound according to any one of the preceding items, wherein the stereochemistry configuration at position 3, as defined in formulas (I) and (III), is S.
242. The compound according to any one of the preceding items, wherein the compound is selected from the group consisting of:
- 3-(6-chloropyridin-3-yl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)butanamide,
 - 3-(5-fluoropyridin-2-yl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)-cyclopropyl)-butanamide,
 - 3-hydroxy-3-(2-methoxypyridin-4-yl)-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)butanamide,
 - N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
 - 3-(2,4-difluorophenyl)-N-(1-(4-fluoro-3-(2,2,2-trifluoroethoxy)phenyl)-cyclopropyl)-3-hydroxybutanamide,
 - 3-(4-fluorophenyl)-3-hydroxy-N-(1-(3-(trifluoromethyl)phenyl)cyclopropyl)-butanamide,
 - 3-(4-fluorophenyl)-3-hydroxy-N-(1-(3-(trifluoromethoxy)phenyl)cyclopropyl)butanamide,
 - 3-(4-fluorophenyl)-3-hydroxy-N-(1-(2-(2,2,2-trifluoroethoxy)pyridin-4-yl)cyclopropyl)butanamide,

- 3-hydroxy-3-(p-tolyl)-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-
butanamide,
- 3-(4-cyanophenyl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-
butanamide,
- 5 3-(2,4-difluorophenyl)-N-(1-(2-fluoro-3-(2,2,2-trifluoroethoxy)phenyl)-
cyclopropyl)-3-hydroxybutanamide,
- 3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(4-methyl-3-(2,2,2-trifluoroethoxy)phenyl)-
cyclopropyl)butanamide,
- 10 N-(1-(3-chloro-5-(difluoromethyl)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-
hydroxybutanamide,
- 3-(3,5-difluorophenyl)-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-
butanamide,
- 4,4,4-trifluoro-3-(4-fluorophenyl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)-
phenyl)-cyclopropyl)butanamide,
- 15 N-(1-(3-bromophenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- N-(1-(3-cyano-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(4-fluorophenyl)-3-
hydroxybutanamide,
- (3-(2,4-difluorophenyl)-N-(1-(3-fluoro-5-(2,2,2-trifluoroethoxy)phenyl)-
cyclopropyl)-3-hydroxybutanamide,
- 20 N-(1-(4-chloro-3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-
difluorophenyl)-3-hydroxybutanamide,
- N-(1-(3-(difluoromethyl)-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-
difluorophenyl)-3-hydroxybutanamide,
- N-(1-(3-bromo-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-
25 difluorophenyl)-3-hydroxybutanamide,
- N-(1-(3-cyclopropyl-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-
difluorophenyl)-3-hydroxybutanamide,
- N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,6-
difluorophenyl)-3-hydroxybutanamide,
- 30 N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(3,4-
difluorophenyl)-3-hydroxybutanamide,
- 3-(2-bromo-6-fluorophenyl)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)
cyclopropyl)-3-hydroxybutanamide,
- N-(1-(2-chloro-6-(2,2,2-trifluoroethoxy)pyridin-4-yl)cyclopropyl)-3-(2,6-
35 difluorophenyl)-3-hydroxybutanamide,

- 3-(2,4-difluorophenyl)-N-(1-(2-fluoro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide,
N-(1-(4,6-dichloropyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- 5 N-(1-(4-chloro-6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
3-(2,6-difluorophenyl)-3-hydroxy-N-(1-(6-((2,2,2-trifluoroethyl) amino) pyridin-2-yl)cyclopropyl)butanamide,
- 10 3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(3-methoxy-5-(2,2,2-trifluoroethoxy)phenyl)-cyclopropyl)butanamide,
N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,6-difluorophenyl)-3-hydroxybutanamide,
N-(1-(4-chloro-6-(neopentylamino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- 15 N-(1-(6-((cyclopropylmethyl)amino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
N-(1-(4-chloro-6-(isopropylamino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- 20 N-(1-(2-chloro-6-((2,2,2-trifluoroethyl)amino)pyridin-4-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
N-(1-(6-chloropyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
N-(1-(4-chloro-6-((2,2,2-trifluoroethyl)amino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- 25 3-(2,6-difluorophenyl)-3-hydroxy-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)butanamide,
3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)butanamide,
3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(6-(trifluoromethyl)pyridin-2-yl)cyclopropyl)butanamide,
- 30 N-(1-(3-(difluoromethyl)-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(4-fluorophenyl)-3-hydroxybutanamide,
3-(4-fluorophenyl)-N-(1-(2-fluoro-3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide,

- N-(1-(6-chloro-4-((2,2,2-trifluoroethyl)amino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
 N-(1-(6-chloro-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
 5 N-(1-(4-chloro-6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-hydroxy-3-(1-methyl-1H-indol-4-yl)butanamide,
 3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(2-((2,2,2-trifluoroethyl)amino)pyrimidin-4-yl)cyclopropyl)butanamide,
 N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-dimethylthiazol-5-yl)-3-hydroxybutanamide,
 10 N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxy-3-(4-methylthiazol-2-yl)butanamide,
 N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(5-chlorothiazol-2-yl)-3-hydroxybutanamide and
 15 3-hydroxy-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-(2,4,6-trifluorophenyl)butanamide
 or a pharmaceutically acceptable salt thereof.

243. The compound according to any one of the preceding items, wherein the
 20 compound is selected from the group consisting of:
 (R)-3-(6-chloropyridin-3-yl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)-cyclo-propyl)butanamide,
 (R)-3-(5-fluoropyridin-2-yl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)-cyclopropyl)-butanamide,
 25 (R)-3-hydroxy-3-(2-methoxypyridin-4-yl)-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)-cyclopropyl)butanamide,
 (R)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
 (R)-3-(2,4-difluorophenyl)-N-(1-(4-fluoro-3-(2,2,2-trifluoroethoxy)phenyl)-cyclopropyl)-3-hydroxybutanamide,
 30 (R)-3-(4-fluorophenyl)-3-hydroxy-N-(1-(3-(trifluoromethyl)phenyl)cyclopropyl)-butanamide,
 (R)-3-(4-fluorophenyl)-3-hydroxy-N-(1-(3-(trifluoromethoxy)phenyl)cyclopropyl)butanamide,

- (R)-3-(4-fluorophenyl)-3-hydroxy-N-(1-(2-(2,2,2-trifluoroethoxy)pyridin-4-yl)cyclopropyl)butanamide,
- (R)-3-hydroxy-3-(p-tolyl)-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)-cyclopropyl)butanamide,
- 5 (R)-3-(4-cyanophenyl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)-cyclopropyl)-butanamide,
- (R)-3-(2,4-difluorophenyl)-N-(1-(2-fluoro-3-(2,2,2-trifluoroethoxy)phenyl)-cyclopropyl)-3-hydroxybutanamide,
- (R)-3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(4-methyl-3-(2,2,2-trifluoroethoxy)-phenyl)cyclopropyl)butanamide,
- 10 (R)-N-(1-(3-chloro-5-(difluoromethyl)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (R)-3-(3,5-difluorophenyl)-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-butanamide,
- 15 (R)-4,4,4-trifluoro-3-(4-fluorophenyl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)-phenyl)cyclopropyl)butanamide,
- (R)-N-(1-(3-bromophenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (R)-N-(1-(3-cyano-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(4-fluorophenyl)-3-hydroxybutanamide,
- 20 (R)-3-(2,4-difluorophenyl)-N-(1-(3-fluoro-5-(2,2,2-trifluoroethoxy)-phenyl)cyclopropyl)-3-hydroxybutanamide,
- (R)-N-(1-(4-chloro-3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- 25 (R)-N-(1-(3-(difluoromethyl)-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (R)-N-(1-(3-bromo-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (R)-N-(1-(3-cyclopropyl-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- 30 (R)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,6-difluorophenyl)-3-hydroxybutanamide,
- (R)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(3,4-difluorophenyl)-3-hydroxybutanamide,

- (R)-3-(2-bromo-6-fluorophenyl)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide,
- (R)-N-(1-(2-chloro-6-(2,2,2-trifluoroethoxy)pyridin-4-yl)cyclopropyl)-3-(2,6-difluorophenyl)-3-hydroxybutanamide,
- 5 (R)-3-(2,4-difluorophenyl)-N-(1-(2-fluoro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide,
- (R)-N-(1-(4,6-dichloropyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (R)-N-(1-(4-chloro-6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- 10 (R)-3-(2,6-difluorophenyl)-3-hydroxy-N-(1-(6-((2,2,2-trifluoroethyl) amino)pyridin-2-yl)cyclopropyl)butanamide,
- (R)-3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(3-methoxy-5-(2,2,2-trifluoroethoxy)phenyl)-cyclopropyl)butanamide,
- 15 (R)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,6-difluorophenyl)-3-hydroxybutanamide,
- (R)-N-(1-(4-chloro-6-(neopentylamino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (R)-N-(1-(6-((cyclopropylmethyl)amino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- 20 (R)-N-(1-(4-chloro-6-(isopropylamino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (R)-N-(1-(2-chloro-6-((2,2,2-trifluoroethyl)amino)pyridin-4-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- 25 (R)-N-(1-(6-chloropyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (R)-N-(1-(4-chloro-6-((2,2,2-trifluoroethyl)amino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (R)-3-(2,6-difluorophenyl)-3-hydroxy-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)butanamide,
- 30 (R)-3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)butanamide,
- (R)-3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(6-(trifluoromethyl)pyridin-2-yl)cyclopropyl)butanamide,

- (R)-N-(1-(3-(difluoromethyl)-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(4-fluorophenyl)-3-hydroxybutanamide,
 (R)-3-(4-fluorophenyl)-N-(1-(2-fluoro-3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide,
 5 (R)-N-(1-(6-chloro-4-((2,2,2-trifluoroethyl)amino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
 (R)-N-(1-(6-chloro-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
 10 (R)-N-(1-(4-chloro-6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-hydroxy-3-(1-methyl-1H-indol-4-yl)butanamide,
 (R)-3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(2-((2,2,2-trifluoroethyl)amino)pyrimidin-4-yl)cyclopropyl)butanamide,
 (R)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-dimethylthiazol-5-yl)-3-hydroxybutanamide,
 15 (R)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxy-3-(4-methylthiazol-2-yl)butanamide,
 (R)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(5-chlorothiazol-2-yl)-3-hydroxybutanamide and
 (R)-3-hydroxy-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-(2,4,6-trifluorophenyl)butanamide
 20 or a pharmaceutically acceptable salt thereof.

244. The compound according to anyone of the preceding items, wherein the compound is selected from the group consisting of:
 25 (S)-3-(6-chloropyridin-3-yl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclo-propyl)butanamide,
 (S)-3-(5-fluoropyridin-2-yl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-butanamide,
 30 (S)-3-hydroxy-3-(2-methoxypyridin-4-yl)-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclo-propyl)butanamide,
 (S)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
 (S)-3-(2,4-difluorophenyl)-N-(1-(4-fluoro-3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide,

- (S)-3-(4-fluorophenyl)-3-hydroxy-N-(1-(3-(trifluoromethyl)phenyl)cyclopropyl)-butanamide,
- (S)-3-(4-fluorophenyl)-3-hydroxy-N-(1-(3-(trifluoromethoxy)phenyl)cyclopropyl)butanamide,
- 5 (S)-3-(4-fluorophenyl)-3-hydroxy-N-(1-(2-(2,2,2-trifluoroethoxy)pyridin-4-yl)cyclopropyl)butanamide,
- (S)-3-hydroxy-3-(p-tolyl)-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)butanamide,
- (S)-3-(4-cyanophenyl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-butanamide,
- 10 (S)-3-(2,4-difluorophenyl)-N-(1-(2-fluoro-3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide,
- (S)-3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(4-methyl-3-(2,2,2-trifluoroethoxy)phenyl)-cyclopropyl)butanamide,
- 15 (S)-N-(1-(3-chloro-5-(difluoromethyl)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (S)-3-(3,5-difluorophenyl)-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-butanamide,
- (S)-4,4,4-trifluoro-3-(4-fluorophenyl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)-cyclopropyl)butanamide,
- 20 (S)-N-(1-(3-bromophenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (S)-N-(1-(3-cyano-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(4-fluorophenyl)-3-hydroxybutanamide,
- 25 (S)-3-(2,4-difluorophenyl)-N-(1-(3-fluoro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide,
- (S)-N-(1-(4-chloro-3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (S)-N-(1-(3-(difluoromethyl)-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- 30 (S)-N-(1-(3-bromo-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (S)-N-(1-(3-cyclopropyl-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,

- (S)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,6-difluorophenyl)-3-hydroxybutanamide,
- (S)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(3,4-difluorophenyl)-3-hydroxybutanamide,
- 5 (S)-3-(2-bromo-6-fluorophenyl)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide,
- (S)-N-(1-(2-chloro-6-(2,2,2-trifluoroethoxy)pyridin-4-yl)cyclopropyl)-3-(2,6-difluorophenyl)-3-hydroxybutanamide,
- (S)-3-(2,4-difluorophenyl)-N-(1-(2-fluoro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide,
- 10 (S)-N-(1-(4,6-dichloropyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (S)-N-(1-(4-chloro-6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- 15 (S)-3-(2,6-difluorophenyl)-3-hydroxy-N-(1-(6-((2,2,2-trifluoroethyl) amino)pyridin-2-yl)cyclopropyl)butanamide,
- (S)-3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(3-methoxy-5-(2,2,2-trifluoroethoxy)phenyl)-cyclopropyl)butanamide,
- (S)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,6-difluorophenyl)-3-hydroxybutanamide,
- 20 (S)-N-(1-(4-chloro-6-(neopentylamino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (S)-N-(1-(6-((cyclopropylmethyl)amino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- 25 (S)-N-(1-(4-chloro-6-(isopropylamino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (S)-N-(1-(2-chloro-6-((2,2,2-trifluoroethyl)amino)pyridin-4-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (S)-N-(1-(6-chloropyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- 30 (S)-N-(1-(4-chloro-6-((2,2,2-trifluoroethyl)amino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (S)-3-(2,6-difluorophenyl)-3-hydroxy-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)butanamide,

- (S)-3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)butanamide,
(S)-3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(6-(trifluoromethyl)pyridin-2-yl)cyclopropyl)butanamide,
5 (S)-N-(1-(3-(difluoromethyl)-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(4-fluorophenyl)-3-hydroxybutanamide,
(S)-3-(4-fluorophenyl)-N-(1-(2-fluoro-3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide,
(S)-N-(1-(6-chloro-4-((2,2,2-trifluoroethyl)amino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
10 (S)-N-(1-(6-chloro-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
(S)-N-(1-(4-chloro-6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-hydroxy-3-(1-methyl-1H-indol-4-yl)butanamide,
15 (S)-3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(2-((2,2,2-trifluoroethyl)amino)pyrimidin-4-yl)cyclopropyl)butanamide,
(S)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-dimethylthiazol-5-yl)-3-hydroxybutanamide,
(S)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxy-3-(4-methylthiazol-2-yl)butanamide,
20 (S)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(5-chlorothiazol-2-yl)-3-hydroxybutanamide and
(S)-3-hydroxy-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-(2,4,6-trifluorophenyl)butanamide
25 or a pharmaceutically acceptable salt thereof.

245. The compound according to any one of the preceding items, wherein the compound is able to modulate the activity of a K_v7 channel.
246. The compound according to any one of the preceding items, wherein the
30 compound is an agonist of a K_v7 channel.
247. The compound according to any one of the preceding items, wherein the compound is able to increase the activity of a $K_v7.2/K_v7.3$ heteromeric channel
248. The compound according to any one of the preceding items, wherein the compound is able to produce an increase in the activity of the $K_v7.2/K_v7.3$
35 heteromeric channel, with an EC_{50} of less than 50 μM , such as less than 20 μM ,

such as less than 10 μM , such as less than 1 μM , such as less than 0.1 μM , such as less than 0.06 μM , such as less than 0.01 μM , such as less than 0.001 μM .

249. The compound according to any one of the preceding items, wherein the compound is able to produce an increase in the activity of the $\text{K}_{\text{v}}7.2/\text{K}_{\text{v}}7.3$ heteromeric channel, with an EC_{50} from about 0.1 nM to about 20 μM , such as from about 0.1 nM to about 10 μM , such as from about 0.1 nM to about 1 μM , such as from about 0.1 nM to about 0.2 μM , such as from 0.1 nM to about 100 nM, such as from about 0.1 nM to about 10 nM.
250. The compound according to any one of the preceding items, wherein the compound is able to increase the activity of a $\text{K}_{\text{v}}7.5$ channel.
251. The compound according to any one of the preceding items, wherein the $\text{K}_{\text{v}}7.5$ EC_{50} is more than 30 μM .
252. The compound according to any one of the preceding items, wherein the compound is able to produce an increase in the activity of the $\text{K}_{\text{v}}7.5$ channel, with an EC_{50} from about 0.1 nM to about 20 μM , such as from about 0.1 nM to about 10 μM , such as from about 0.1 nM to about 1 μM , such as from about 0.1 nM to about 0.2 μM , such as from 0.1 nM to about 100 nM, such as from about 0.1 nM to about 10 nM.
253. The compound according to any one of the preceding items, wherein the compound is a subtype-selective $\text{K}_{\text{v}}7$ modulator.
254. The compound according to any one of the preceding items, wherein the compound is selective for $\text{K}_{\text{v}}7.2/\text{K}_{\text{v}}7.3$.
255. The compound according to any one of the preceding items, wherein the compound is selective for $\text{K}_{\text{v}}7.2/\text{K}_{\text{v}}7.3$ over $\text{K}_{\text{v}}7.5$.
256. The compound according to any one of the preceding items, wherein the compound can selectively increase the activity of a $\text{K}_{\text{v}}7.2/\text{K}_{\text{v}}7.3$ heteromeric channel.
257. The compound according to any one of the preceding items, wherein the compound has an EC_{50} for $\text{K}_{\text{v}}7.2/\text{K}_{\text{v}}7.3$ of less than 10 μM and an EC_{50} for $\text{K}_{\text{v}}7.5$ of more than 30 μM .
258. The compound according to any one of the preceding items, wherein the compound has a ratio between EC_{50} of $\text{K}_{\text{v}}7.2/\text{K}_{\text{v}}7.3$ and EC_{50} of $\text{K}_{\text{v}}7.5$ of more than 2, such as more than 3, such as more than 5, such as more than 8, such as more than 10, such as more than 15, such as more than 20, such as more than 25, such as more than 30, such as more than 60, such as more than 75, such as

more than 100, such as more than 150, such as more than 200, such as more than 230, such as more than 250, such as more than 500.

- 5 259. The compound according to any one of the preceding items, wherein the compound has a ratio between EC₅₀ of K_v7.2/K_v7.3 and EC₅₀ of K_v7.5 of more than 10.
260. The compound according to any one of the preceding items, wherein the compound has a ratio between EC₅₀ of K_v7.2/K_v7.3 and EC₅₀ of K_v7.5 of more than 100.
- 10 261. The compound according to items 257 to 260, wherein the ratio is calculated according to the formula below:
- $$\text{ratio between EC}_{50} \text{ of K}_{v7.2}/\text{K}_{v7.3} \text{ and EC}_{50} \text{ of K}_{v7.5} = \frac{\text{EC}_{50} \text{ of K}_{v7.5}}{\text{EC}_{50} \text{ of K}_{v7.2}/\text{K}_{v7.3}}$$
262. The compound according to any one of the preceding items, wherein the compound is potency selective.
- 15 263. The compound according to any one of the preceding items, wherein the compound has an efficacy for K_v7.2/K_v7.3 larger than 50%, such as larger than 60%, such as larger than 70%, such as larger than 75%, such as larger than 80%, such as larger than 85%, such as larger than 90%, such as larger than 95%, such as larger than 100%, such as larger than 110%.
- 20 264. The compound according to any one of the preceding items, wherein the compound has an efficacy for K_v7.5 of less than 60%, such as less than 50%, such as less than 40%, such as less than 30%, such as less than 20%, such as 0%.
265. The compound according to any one of the preceding items, wherein the compound has an efficacy for K_v7.5 of less than 25%.
- 25 266. The compound according to any one of the preceding items, wherein the compound has an efficacy for K_v7.2/K_v7.3 larger than 50%, and an efficacy for K_v7.5 of less than 25%.
267. The compound according to any one of the preceding items, wherein the compound is efficacy selective.
- 30 268. The compound according to any one of the preceding items, wherein the compound is potency selective and efficacy selective.
269. The compound according to any one of the preceding items, wherein the EC₅₀ is measured in an *in vitro* cell-based assay of ion flux, such as a Thallium ion (Tl⁺) assay.

270. A pharmaceutical composition comprising the compound according to any one of items 1 to 269.

271. A compound according to any one of items 1 to 269, or a pharmaceutical composition according to item 270, for use as a medicament.

5 272. Use of a compound according to any one of items 1 to 269, or a pharmaceutical composition according to item 270, for the manufacture of a medicament for a disease or condition.

273. A method of treatment of a disease or condition in a subject, the method comprising administering an effective amount of a compound according to any one of items 1 to 269, or a pharmaceutical composition according to item 270 to the subject.

10 274. A compound according to any one of items 1 to 269, or a pharmaceutical composition according to item 270, for use in a method of modulating the activity of a K_v7 channel in a subject, the method comprising administering an effective amount of the compound to the subject.

15 275. The compound or the pharmaceutical composition for use according to item 274, wherein the method is a method of increasing the activity of a $K_v7.2/K_v7.3$ heteromeric channel.

20 276. A compound according to any one of items one of items 1 to 269, or a pharmaceutical composition according to item 270, for use in an method of treatment, prevention or alleviation of epilepsy or pain in a subject, the method comprising administering an effective amount of the compound to the subject.

25 277. Use of a compound according to any one of items 1 to 269, or a pharmaceutical composition according to item 270, for the manufacture of a medicament for the treatment, prevention or alleviation of epilepsy or pain.

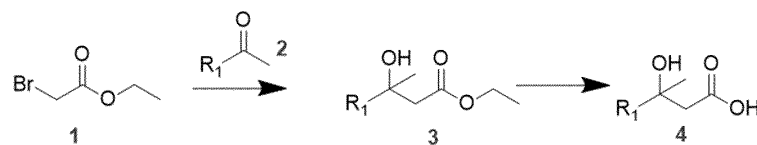
30 278. A method of treatment, prevention or alleviation of epilepsy or pain in a subject, the method comprising administering an effective amount of a compound according to any one of items 1 to 269, or a pharmaceutical composition according to item 270 to the subject.

Examples

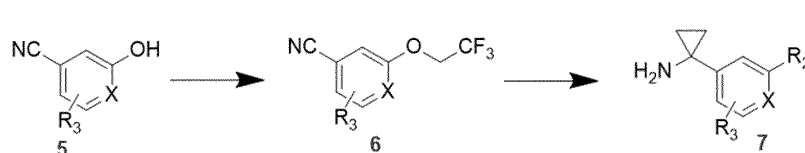
General procedure for preparation of compounds according to the present disclosure:

35 The compounds of the present disclosure were prepared according to the below synthetic scheme 1.

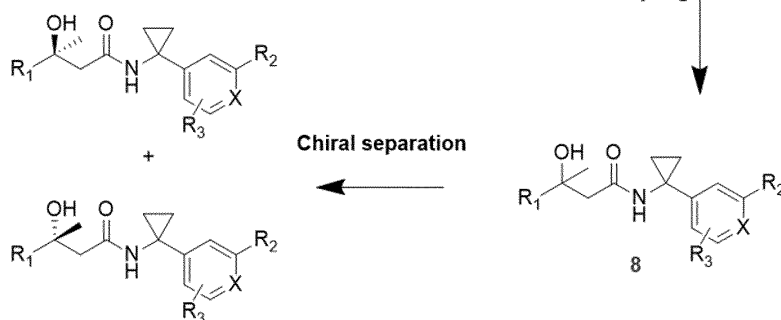
Acid preparation



Amine preparation



Coupling



Scheme 1.

General procedures for compound-3:

Procedure A: To a stirred solution of compound-2 (1 eq) in THF (10 vol) added Zn (1.5 eq), I₂ (0.02 eq) followed by dropwise addition of ethyl bromoacetate (1 eq). Resulting reaction mixture heated on preheated oil bath at 55 °C for 10 to 30 min. Resulting reaction mixture stirred under argon overnight. Reaction mixture was quenched using sat. NH₄Cl solution, filtered and extracted with EtOAc (3 x 20 vol) to get crude compound-3. Crude compound-3 was purified using combiflash chromatography (EtOAc in hexane as eluent) to get compound-3 in 35 to 80% yield.

Procedure B: A combined solution of ethyl bromoacetate (1 eq), Zn (1.5 eq), Br₂ (0.2 eq) in anhydrous THF heated in preheated bath for 30 min. The generated reagent supernatant solution added to a solution of compound-2 (1 eq) in anhydrous THF. Resulting reaction mixture stirred at rt for 1 h to overnight. Reaction mixture was quenched using sat. NH₄Cl solution, filtered and extracted with EtOAc (3 x 20 vol) to get crude compound-3. Crude compound-3 was purified using combiflash chromatography (EtOAc in hexane as eluent) to get compound-3 in 35 to 80% yield.

General procedure for compound-4: To a stirred solution of compound-3 in THF : water : MeOH (10 vol, 3:2:1) added LiOH (1.5 eq). Reaction was monitored by TLC, quenched with water, extracted with EtOAc. Organic layer dried over anhydrous Na₂SO₄ to get crude compound-4. Crude compound-4 obtained further purified using combiflash chromatography.

General procedure for compound-6: To a stirred solution of compound-5 (1 eq) in DMF (10 vol) added Cs₂CO₃ (3 eq) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (1 eq). Resulting reaction mixture stirred at rt overnight and quenched with water. Reaction mixture was extracted with EtOAc (3 x 20 vol). Organic layer dried over anhydrous Na₂SO₄ and concentrated under high *vacuo* to get compound-6 which was purified using combiflash chromatography (5 to 10% EtOAc in hexane) to get pure enough compound-6.

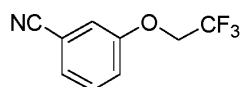
General procedure for compound-7: To a solution of compound-6 (1 eq) in Et₂O added Ti(OiPr)₄ (1 eq), at -78 °C followed by dropwise addition of EtMgBr (3 M in Et₂O, 2 eq). Resulting reaction stirred for 2 h and quenched using BF₃:Et₂O (2 eq). After overnight stirring added 1 N HCl and extracted reaction mixture with Et₂O. Aq. layer basified and extracted with Et₂O. Organic layer obtained after basification given brine wash, dried over anhydrous Na₂SO₄ and concentrated under *vacuo* to get crude compound-7. Crude compound-7 was purified using combiflash chromatography (20 to 60% EtOAc in hexane) to get pure enough compound-7.

General procedure for compound-8: To a stirred solution of compound-4 (1 eq) in DMF (10 vol) added HATU (1.5 eq), DIPEA (3 eq). Resulting reaction mixture stirred for 15 min then added compound-7 (1 eq). The reaction mixture was diluted with cold water and extracted with EtOAc (2 x 10 vol). Combined organic layer given brine wash, dried over anhydrous Na₂SO₄ and concentrated under *vacuo*.

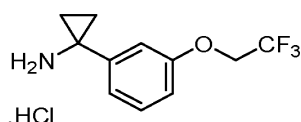
Chiral separation: The compounds according to the present disclosure were separated into different stereoisomers using Chiral preparative HPLC. Thus, for each example, two peaks are obtained: Peak-1 and Peak-2, each peak corresponding to a different stereoisomer. Each peak is isolated, characterized and tested for biological evaluation as described below.

Example 1: Synthesis of 3-(6-chloropyridin-3-yl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)butanamide

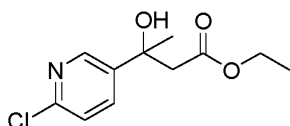
Synthesis of 3-(2,2,2-trifluoroethoxy)benzonitrile (6a): 3-Hydroxybenzonitrile (20 g, 168.01 mmol) converted to compound-6a (27.5 g, 83%) using general procedure for compound-6, H-NMR (DMSO-d₆, 300 MHz): δ 7.60-7.53 (m, 3 H), 7.39-7.45 (m, 1 H), 4.87 (q, J = 9 Hz, 2 H).

**6a**

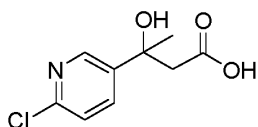
Synthesis of 1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropan-1-amine hydrochloride (7a): Compound-6a (20 g, 99.43 mmol) converted to 7a (7.5 g, 34%) using general procedure for compound-7. After acidification during work up compound-7a extracted as HCl salt in diethyl ether, H-NMR (DMSO-d₆, 300 MHz): δ 8.78 (bs, 3 H), 7.38-7.42 (m, 1 H), 7.02 -7.10 (m, 3 H), 4.80 (q, J = 8.7 Hz, 2 H), 1.24-1.34 (m, 4 H).

**7a**

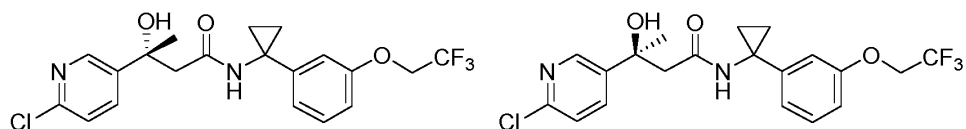
Synthesis of ethyl 3-(6-chloropyridin-3-yl)-3-hydroxybutanoate (3a): 1-(6-Chloropyridin-3-yl)ethan-1-one (0.932 g, 5.99 mmol) converted to compound-3a (0.68 g, 47%) using general procedure A for compound-3, m/z (LC-MS): 243.95 [M+H]⁺.



Synthesis of 3-(6-chloropyridin-3-yl)-3-hydroxybutanoic acid (4a): Compound-3a (0.68 g, 2.79 mmol) converted to compound-4a (0.51 g, 85%) as yellow gummy using general procedure for compound-4, H-NMR (DMSO-d₆, 300 MHz): δ 1.51 (s, 3 H), 2.73 (dd, J = 14.7 Hz, 2 H), 5.51 (bs, 1 H), 7.42 (d, J = 8.7 Hz, 1 H), 7.87 (dd, J = 2.7 Hz, 8.7 Hz, 1 H), 8.46 (d, J = 2.7 Hz, 1 H).



Example 1: Synthesis of 3-(6-chloropyridin-3-yl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)butanamide (Example 1 peak-1 & Example 1 peak-2):



5

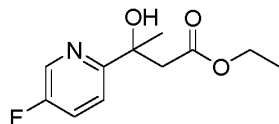
Following general procedure for compound-8, compound-4a (0.2 g, 0.927 mmol) converted to **Example 1** (290 mg, 73%) using compound-7a. The enantiomers were separated using Chiral prep HPLC, Column: (Chiralpak IG, 250mmX21 mm, 5 μ m), Eluent: n-Hexane(A) and EtOH:MeOH 1:1 (B), Flow: 10 mL/min, Isocratic: 70(A):30(B), diluent EtOH:DCM, 3:1, 10 mL, Injection vol, 0.5 mL, run time 20 min, to get Peak-1 (104.9 mg), Peak-2: (101.3 mg); H-NMR (DMSO-d₆, 300 MHz): δ 0.89-0.96 (m, 2 H), 1.05-1.12 (m, 2 H), 1.46 (s, 3H), 2.60 (dd, J = 13.8 Hz, 2 H), 4.67 (q, J = 9 Hz, 2 H), 5.79 (s, 1 H), 6.43 (d, J = 8.1 Hz, 1 H), 6.59 (s, 1 H), 6.78 (dd, J = 2.1 Hz, 8.1 Hz, 1 H), 7.03-7.09 (m 1 H), 7.43 (d, J = 8.4 Hz, 1 H), 7.84 (dd, J = 2.7 Hz, 8.1 Hz, 1 H), = 2.7 Hz, 1 H), 8.52 (s, 1 H), HRMS calculated for: [C₂₀H₂₀ClF₃N₂O₃+H]⁺ 429.1187; found: 429.1195 (**Example 1 peak-1**), 429.1198 (**Example 1 peak-2**). Analytical Chiral HPLC: CHIRALPAK-IG (150X4.6mmX5 μ m) Mobile Phase : (A) n-HEXANE (B) 0.1% HCOOH IN EtOH : MeOH (80:20) Isocratic : 80:20 (A:B) Flow : 1.0ml/min Diluent : EtOH, Column Temp : 25°C, Inj. volume: 5.000, Acq. method: IG_8020_1_B_30MIN.amx. Peak-1 (Rt: 4.961, 100% ee) Peak-2: (Rt: 11.357, 100% ee)

20

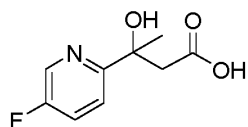
Example 2: Synthesis of 3-(5-fluoropyridin-2-yl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)butanamide

Synthesis of ethyl 3-(5-fluoropyridin-2-yl)-3-hydroxybutanoate (3b): 1-(5-

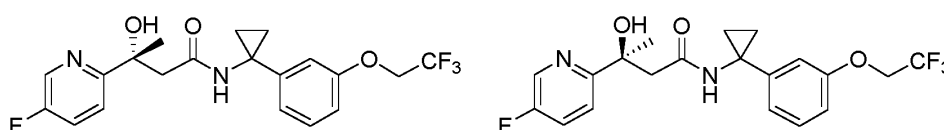
25 Fluoropyridin-2-yl)ethan-1-one (0.25 g, 1.797 mmol) converted to compound-3b (80 mg, 20%) as yellow oil using general procedure A for compound-3, m/z (LC-MS): 228.1 [M+H]⁺.



Synthesis of 3-(5-fluoropyridin-2-yl)-3-hydroxybutanoic acid (4b): Compound-3b (80 mg, 0.352 mmol) converted to compound-4b (60 mg, 75%) as yellow solid using general procedure for compound-4, m/z (LC-MS): 199.95 [M+H]⁺.



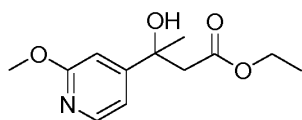
5 **Example 2: Synthesis of 3-(5-fluoropyridin-2-yl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)butanamide (Example 2 peak-1 & Example 2 peak-2):**



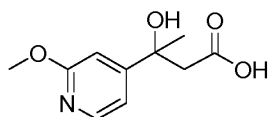
Following general procedure for compound-8, compound-4b (60 mg, 0.301 mmol)
 10 converted to **Example 2** (50 mg, 40%) using compound-7a. The enantiomers were separated using Chiral prep HPLC, Column: (Chiralpak IH, 150x4.6mm, 5μm), Eluent: n-Hexane(A) and IPA:MeOH 1:1 (B), Flow: 1 mL/min, Isocratic: 85(A):15(B), diluent EtOH, to get Peak-1 (20.3 mg), Peak-2: (24.9 mg); H-NMR (DMSO-d₆, 400 MHz): δ 0.98-1.09 (m, 2 H), 1.10-1.18 (m, 2 H), 1.42 (s, 3H), 2.58 (d, J = 14.4 Hz, 1 H), 2.87 (d, J = 14.4 Hz, 1 H), 4.68 (q, J = 9 Hz, 2 H), 5.91 (s, 1 H), 6.51 (d, J = 8.8 Hz, 1 H), 6.60-6.61 (m, 1 H), 6.80 (dd, J = 2 Hz, 8.2 Hz, 1 H), 7.06-7.11 (m, 1 H), 7.68 (dd, J = 2 Hz, 8 Hz, 2 H), 8.48 (s, 1 H), 8.61 (s, 1 H), HRMS calculated for: [C₂₀H₂₀F₄N₂O₃+H]⁺ 413.1483; found: 413.1492 (**Example 2 peak-1**), 413.1551 (**Example 2 peak-2**).
 Analytical Chiral HPLC: CHIRALPAK-IH (150X4.6mmX5μm) Mobile Phase : (A) n-
 20 HEXANE (B) IPA: MeOH (50:50) Isocratic : 85:15(A:B) Flow : 1.0ml/min Diluent : EtOH, Column Temp : 25°C, Inj. volume: 10.000, Acq. method: IH_8515_7_C-30min.amx. Peak-1 (Rt: 3.053, 100% ee) Peak-2: (Rt: 4.84, 100% ee).

Example 3: Synthesis of 3-hydroxy-3-(2-methoxypyridin-4-yl)-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)butanamide

25 **Synthesis of ethyl 3-hydroxy-3-(2-methoxypyridin-4-yl)butanoate (3c):** 1-(2-Methoxypyridin-4-yl)ethan-1-one (0.55 g, 0.992 mmol) converted to compound-3c (240 mg, 28%) as colourless liquid using general procedure A for compound-3, m/z (LC-MS): 239.90 [M+H]⁺.

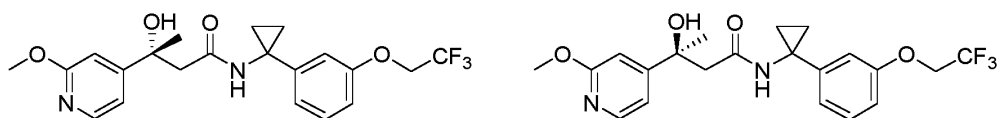


Synthesis of 3-hydroxy-3-(2-methoxypyridin-4-yl)butanoic acid (4c): Compound-3c (240 mg, 1.0031 mmol) converted to compound-4c (98 mg, 46%) as off white solid using general procedure for compound-4, m/z (LC-MS): 212.10 [M+H]⁺.



5

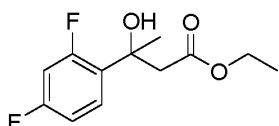
Example 3: Synthesis of 3-hydroxy-3-(2-methoxypyridin-4-yl)-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)butanamide (Example 3 peak-1 & Example 3 peak-2):



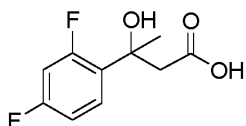
- 10 Following general procedure for compound-8, compound-4c (0.2 g, 0.947 mmol) converted to **Example 3** using compound-7a and purified by prep HPLC, Column: LUNA Phenomenex (250x21.2mm, 5.0μ), Eluent: 0.1% HCOOH in water (A) and acetonitrile (B), Flow: 18 mL/min, Time: % B, 0/50, 2/60, 6/85 to get pure enough **Example 3a/b** (75 mg, 19%) which was separated using Chiral prep HPLC, Column:
- 15 (Chiralpak IG, 250x21mm, 5μm), Eluent: n-Hexane(A) and EtOH (B), Flow: 15 mL/min, Isocratic: 90(A):10(B), to get Peak-1 (27 mg), Peak-2: (23 mg) as colourless gummy oil; H-NMR (DMSO-d₆, 400 MHz): δ 0.97-1.02 (m, 2 H), 1.05-1.25 (m, 2 H), 1.43 (s, 3H), 2.59 (d, J = 14.1 Hz, 1 H), 2.69 (d, J= 14.1 Hz, 1 H), 3.84 (s, 3 H), 4.68 (q, J = 8.6 Hz, 2 H), 5.75 (s, 1 H), 6.48 (d, J = 8 Hz, 1 H), 6.60 (s, 1 H), 6.78-6.82 (m, 2 H), 7.00-7.07
- 20 (m, 2 H), 8.09 (d, J = 8 Hz, 1 H), 8.54 (bs, 1 H), HRMS calculated for: [C₂₁H₂₃F₃N₂O₄+H]⁺ 425.1683; found: 425.1698 (**Example 3 peak-1**), 425.1697 (**Example 3 peak-2**). Analytical Chiral HPLC: CHIRALPAK-IG (150X4.6mmX5μm) Mobile Phase : (A) n-HEXANE (B) 0.1% HCOOH IN EtOH:MeOH (80:20) Isocratic : 70:30 (A:B) Flow : 1.0ml/min Diluent : EtOH, Column Temp : 25°C, Inj. volume: 5.000,
- 25 Acq. method: IG_7030_1_B_30MIN.amx. Peak-1 (Rt: 3.097, 100% ee) Peak-2: (Rt: 3.607, 100% ee)

Example 4: Synthesis of N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide

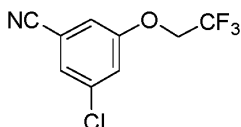
Synthesis of ethyl 3-(2,4-difluorophenyl)-3-hydroxybutanoate (3d): 1-(2,4-Difluorophenyl)ethan-1-one (1 g, 6.405 mmol) converted to compound-**3d** (1 g, 64%) as off white solid using general procedure **A** for compound-**3**; H-NMR (DMSO- d_6 , 400 MHz): δ 0.96 (t, J = 6.9 Hz, 3 H), 1.53 (s, 3 H), 2.76 (dd, J = 13.8 Hz, 2 H), 3.89 (q, J = 6.6 Hz, 2 H), 6.99-7.05 (m, 1 H), 7.08-7.16 (m, 1 H), 7.54-7.62 (m, 1 H).



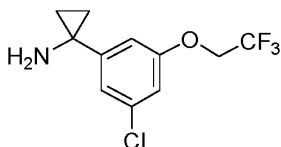
Synthesis of 3-(2,4-difluorophenyl)-3-hydroxybutanoic acid (4d): Compound-**3d** (1 g, 4.409 mmol) converted to compound-**4d** (800 mg, 90%) as colourless liquid using general procedure for compound-**4**; H-NMR (DMSO- d_6 , 400 MHz): δ 1.51 (s, 3 H), 2.69-2.78 (m, 2 H), 5.53 (bs, 1 H), 6.99-7.16 (m, 2 H), 7.56-7.65 (m, 1 H).



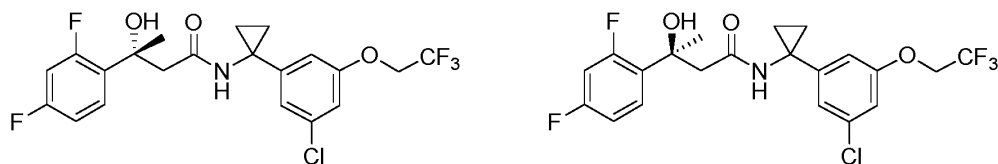
Synthesis of 3-chloro-5-(2,2,2-trifluoroethoxy)benzonitrile (6b): 3-Chloro-5-hydroxybenzonitrile (6 g, 39.07 mmol) converted to **6b** (7.5 g, 82%) using general procedure for compound-**6**; H-NMR (DMSO- d_6 , 400 MHz): δ 4.92 (q, J = 9 Hz, 2 H), 7.60-7.62 (m, 1 H), 7.63-7.64 (m, 1 H), 7.71-7.73 (m, 1H).



Synthesis of 1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropan-1-amine hydrochloride (7b): Compound-**6b** (9 g, 38.20 mmol) converted to compound-**7b** (5 g, 43%) as off white solid using general procedure for compound-**7**. After acidification solids obtained washed with hexane to get desired compound as HCl salt, m/z (LC-MS): 265.90 [M+H]⁺.



Example 4: Synthesis of N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide (Example 4 peak-1 & Example 4 peak-2):

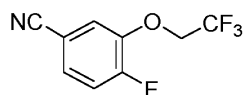


- 5 Following general procedure for compound-8, compound-4d (100 mg, 0.462 mmol) converted to **Example 4** (103 mg, 43%) as off white solid using compound-7b. The enantiomers were separated using Chiral prep HPLC, Column: (Chiralpak IH, 250x21mm, 5µm), Eluent: n-Hexane(A) and EtOH : IPA 1:1 (B), Flow: 15 mL/min, Isocratic: 80(A):20(B), diluent EtOH : DCM (3:1, 5 mL), Injection volume-0.2 mL, run
- 10 time 15 min, to get Peak-1 (34.8 mg), Peak-2: (38.7 mg) as colourless gummy oil; H-NMR (DMSO-d₆, 400 MHz): δ 0.88-0.99 (m, 2 H), 1.15-1.20 (m, 2 H), 1.49 (s, 3 H), 2.63 (d, J = 14 Hz, 1 H), 2.75 (d, J = 14 Hz, 1 H), 4.75 (q, J = 8.8 Hz, 2 H), 5.96 (s, 1 H), 6.55 (s, 1 H), 6.70 (s, 1 H), 6.94 (s, 1 H), 6.98-7.02 (m, 1 H), 7.10-7.16 (m, 1 H), 7.58-7.64 (m, 1 H), 8.59 (s, 1 H), HRMS calculated for: [C₂₁H₁₉ClF₅NO₃+H-H₂O]⁺ 446.0941; found: 446.0956 (**Example 4 peak-1**), 446.0954 (**Example 4 peak-2**). Analytical Chiral HPLC: CHIRALPAK-IH (150X4.6mmX5µm) Mobile Phase : (A) n-HEXANE (B) IPA :MeOH(50:50) Isocratic : 85:15(A:B) Flow : 1.0ml/min Diluent : EtOH, Column Temp : 25°C, Inj. volume: 5.000, Acq. method: IH_8515_7_C-30min.amx. Peak-1 (Rt: 2.68, 92%) Peak-2: (Rt: 3.46, 100%)

20

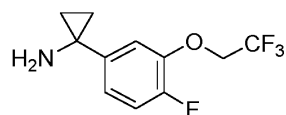
Example 5: Synthesis of 3-(2,4-difluorophenyl)-N-(1-(4-fluoro-3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide

- Synthesis of 4-fluoro-3-(2,2,2-trifluoroethoxy)benzonitrile (6c):** 4-Fluoro-3-hydroxybenzonitrile (1 g, 7.298 mmol) converted to compound-6c (1 g, 63%) as white solid using general procedure for compound-6, H-NMR (DMSO-d₆, 300 MHz): δ 4.90 (q, J = 8.8 Hz, 2 H), 7.50-7.64 (m, 2 H), 7.88-7.92 (m, 1 H).

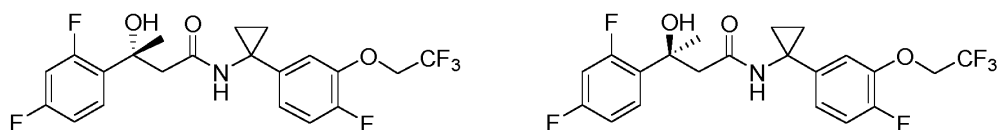


Synthesis of 1-(4-fluoro-3-(2,2,2-trifluoroethoxy)phenyl)cyclopropan-1-amine (7c): Compound-6c (600 mg, 2.738 mmol) converted to compound-7c (250 mg, 36%)

as off white solid using general procedure for compound-7, m/z (LC-MS): 250.35
[M+H]⁺.



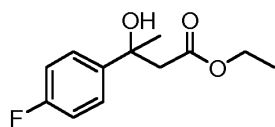
Example 5: Synthesis of 3-(2,4-difluorophenyl)-N-(1-(4-fluoro-3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide (Example 5 peak-1 & Example 5 peak-2):



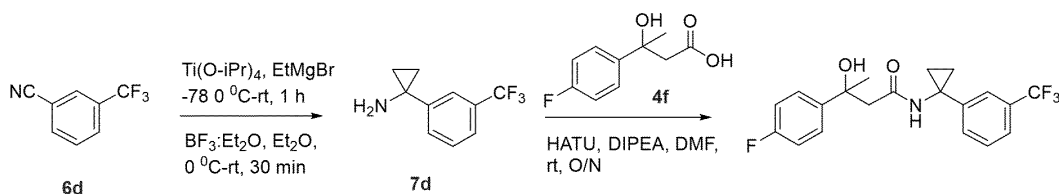
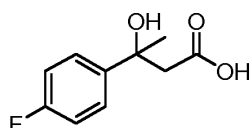
Following general procedure for compound-8, compound-4d (0.093 g, 0.432 mmol) converted to **Example 5** (40 mg, 20%) using compound-7c. The enantiomers were separated using Chiral prep HPLC, Column: (Chiralpak IH, 250x21mm, 5μm), Eluent: n-Hexane(A) and IPA : MeOH (1:1) (B), Flow: 15 mL/min, Isocratic: 90(A):10(B), diluent EtOH : DCM (1:1, 3 mL), Injection volume-0.5 mL, run time 14 min, to get Peak-1 (12 mg,) Peak-2: (9 mg) as off white solid; H-NMR (DMSO-d₆, 300 MHz): δ 0.87-0.99 (m, 2 H), 1.12-1.20 (m, 2 H), 1.48 (s, 3 H), 2.60 (d, J = 14.1 Hz, 1 H), 2.74 (d, J = 14.1 Hz, 1 H), 4.76 (q, J = 8.7 Hz, 2 H), 6.04 (bs, 1 H), 6.48-6.54 (m, 1 H), 6.79 (d, J = 6.6 Hz, 1 H), 6.92-7.07 (m, 2 H), 7.13-7.20 (m, 1 H), 7.54-7.62 (m, 1 H), 8.63 (bs, 1 H), HRMS calculated for: [C₂₁H₁₉F₆NO₃+H-H₂O]⁺ 430.1236; found: 430.1246 (**Example 5 peak-1**), 430.1250 (**Example 5 peak-2**). Analytical Chiral HPLC: CHIRALPAK-IH (150X4.6mmX5μm) Mobile Phase: (A) n-HEXANE (B) IPA : MeOH (50:50) Isocratic : 85:15 (A:B) Flow : 1.0ml/min Diluent : EtOH Column Temp : 25°C, Inj. volume: 5.000, Acq. method: IH_8515_7_C-15min.amx. Peak-1 (Rt: 2.63, 100% ee) Peak-2: (Rt: 3.81, 100% ee)

Example 6: Synthesis of 3-(4-fluorophenyl)-3-hydroxy-N-(1-(3-(trifluoromethyl)phenyl)cyclopropyl)butanamide

Synthesis of ethyl 3-(4-fluorophenyl)-3-hydroxybutanoate (3e): 1-(4-Fluorophenyl)ethan-1-one (2 g, 14.478 mmol) converted to compound-3e (3 g, 94%) using general procedure A for compound-3, H-NMR (DMSO-d₆, 300 MHz): δ 1.00 (t, J = 6.9 Hz, 3 H), 1.5 (s, 3 H), 2.51-2.70 (m, 2 H), 3.90 (q, J = 6 Hz, 2 H), 5.30 (s, 1 H), 7.04-7.11 (m, 2 H), 7.42-7.47 (m, 2 H).

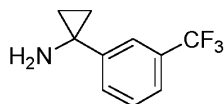


Synthesis of 3-(4-fluorophenyl)-3-hydroxybutanoic acid (4e): Compound-3e (3 g, 13.27 mmol) converted to compound-4e (1.1 g, 42%) as off white solid using general procedure for compound-4, H-NMR (DMSO-d₆, 300 MHz): δ 1.49 (s, 3 H), 2.65 (s, 2 H), 5.25-5.30 (bs, 1 H), 7.05-7.11 (m, 2 H), 7.42-7.48 (m, 2 H).

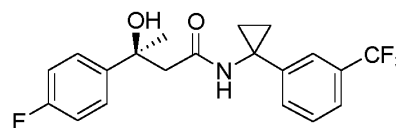
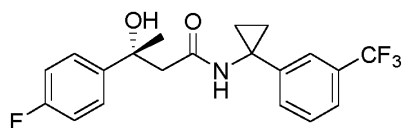


Synthesis of 1-(3-(trifluoromethyl)phenyl)cyclopropan-1-amine (7d): 3-

(Trifluoromethyl)benzonitrile (2 g, 11.688 mmol) converted to compound-7d (350 mg, 15%) using general procedure for compound-7. After basification using NaHCO₃, compound extracted as free base, m/z (LC-MS): 202.40 [M+H]⁺.



Example 6: Synthesis of 3-(4-fluorophenyl)-3-hydroxy-N-(1-(3-(trifluoromethyl)phenyl)cyclopropyl)butanamide (Example 6 peak-1 & Example 6 peak-2):



Following general procedure for compound-8, compound-4e (0.15 g, 0.757 mmol) converted to **Example 6** (110 mg, 38%) using compound-7d. The enantiomers were separated using Chiral prep HPLC, Column: (Chiralpak IH, 150mmX4.6 mm, 5 μ m), Eluent: n-Hexane(A) and IPA : MeOH 1:1 (B), Flow: 1.0 mL/min, Isocratic: 85(A):15(B) to get Peak-1 (37.9 mg) Peak-2: (42.8 mg). H-NMR (DMSO-d₆, 400 MHz): δ 0.98-1.03 (m, 2 H), 1.05-1.24 (m, 2 H), 1.46 (s, 3H), 2.55 (d, J = 14.1 Hz, 1 H), 2.67 (d, J = 14.1 Hz, 1 H), 4.92 (q, J = 8.6 Hz, 2 H), 5.64 (s, 1 H), 7.08-7.13 (m, 3 H), 7.30-7.31 (m, 1 H),

7.33-7.37 (m, 1 H), 7.44-7.48 (m, 3 H), 8.60 (s, 1 H), HRMS calculated for:

$[C_{20}H_{19}F_4NO_2+H-H_2O]^+$ 364.1319; found: 364.1329 (**Example 6 peak-1**), 364.1331

(**Example 6 peak-2**). Analytical Chiral HPLC : CHIRALPAK-IH (150X4.6mmX5 μ m)

Mobile Phase: (A) n-HEXANE (B) IPA : MeOH(50:50) Isocratic: 93:07 (A:B) Flow:

5 1.0ml/min Diluent: EtOH Column Temp : 25°C, Inj. volume: 10.000, Acq. method:

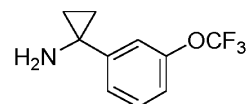
IH_9307_7_C_30MIN.amx. Peak-1 (Rt: 7.293, 100% ee) Peak-2: (Rt: 7.286, 100% ee).

Example 7: Synthesis of 3-(4-fluorophenyl)-3-hydroxy-N-(1-(3-(trifluoromethoxy)phenyl)cyclopropyl) butanamide

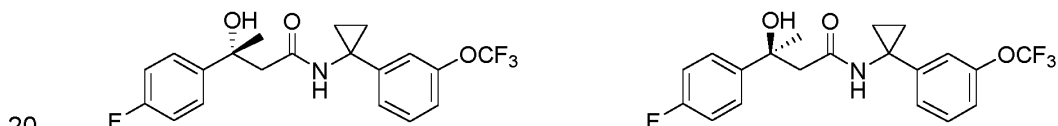
10 **Synthesis of 1-(3-(trifluoromethoxy)phenyl)cyclopropan-1-amine hydrochloride**

(**7e**): 3-(Trifluoromethoxy)benzonitrile (200 mg, 1.06 mmol) converted to **7e** (160 g, crude) using general procedure for compound-**7**. After acidification during work up compound-**7e** extracted as HCl salt in diethyl ether, H-NMR (DMSO- d_6 , 400 MHz): δ 0.97-0.94 (m, 2H), 1.03-1.00 (m, 2 H), 7.11 -7.09 (m, 1 H), 7.22-7.20 (m, 1 H), 7.39-

15 7.30 (m, 2 H).



Example 7: Synthesis of 3-(4-fluorophenyl)-3-hydroxy-N-(1-(3-(trifluoromethoxy)phenyl)cyclopropyl) butanamide (Example 7 peak-1 & Example 7 peak-2):



Following general procedure for compound-**8**, compound-**4e** (100 mg, 0.460 mmol) converted to **Example 7** (135 mg, 74%) using compound-**7e**. The enantiomers were separated using Chiral prep HPLC, Column: (Chiralpak IH, 250mmX21mm, 5 μ m), Eluent: n-Hexane(A) and IPA : MeOH 1:1 (B), Flow: 15 mL/min, Isocratic: 90(A):10(B),

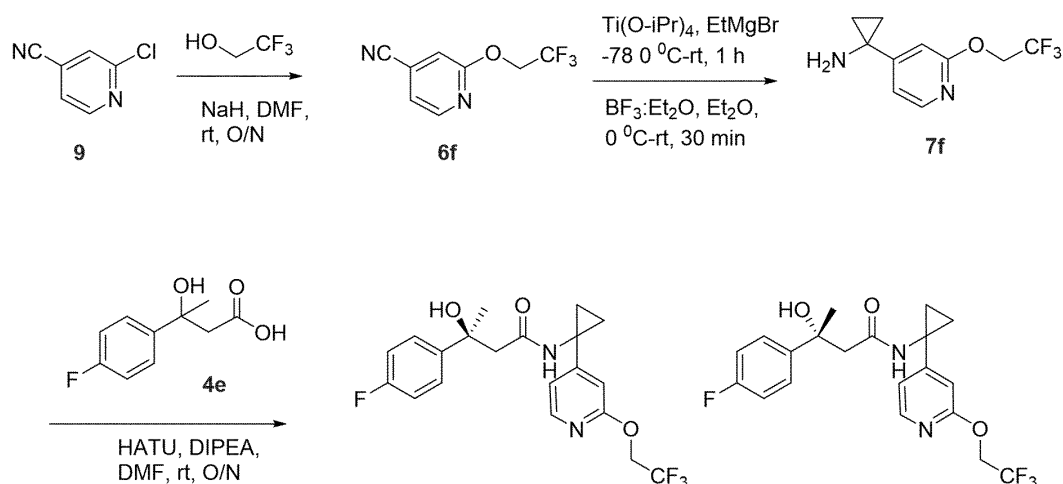
25 diluent EtOH : DCM (1:1, 3.5 mL), Injection volume-0.5 mL, run time 13 min, to get Peak-1 (41.2 mg) Peak-2: (29.8 mg) as off white solids; H-NMR (DMSO- d_6 , 400 MHz): δ 0.86-0.99 (m, 2 H), 1.17-1.24 (m, 2 H), 1.45 (s, 3 H), 2.53-2.71 (m, 2 H), 5.67 (s, 1 H), 6.78 (d, j = 8 Hz, 1 H), 6.85 (s, 1 H), 7.07-7.13 (m, 3 H), 7.24 (d, J = 8 Hz, 1 H), 7.45-7.48 (m, 2 H), 8.57 (s, 1H), HRMS calculated for: $[C_{20}H_{19}F_4NO_3+H-H_2O]^+$

30 380.1268; found: 380.1281 (**Example 7 peak-1**), 380.1279 (**Example 7 peak-2**). Analytical Chiral HPLC

: CHIRALPAK-IH (150X4.6mmX5μm) Mobile Phase: (A) n-HEXANE (B)IPA :
MeOH(50:50) Isocratic: 93:07 (A:B) Flow : 1.0ml/min Diluent: EtOH Column Temp:
25°C, Inj. volume: 10.000, Acq. method: IH_9307_7_C_30MIN.amx. Peak-1 (Rt: 7.293,
100% ee) Peak-2: (Rt: 7.286, 100% ee)

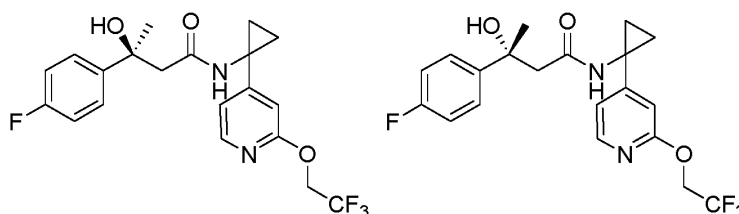
5

Example 8: Synthesis of 3-(4-fluorophenyl)-3-hydroxy-N-(1-(2-(2,2,2-trifluoroethoxy)pyridin-4-yl)cyclopropyl)butanamide



- 10 **Synthesis of 2-(2,2,2-trifluoroethoxy)isonicotinonitrile (6f):** To a stirred suspension of sodium hydride (2.89 g, 72.173 mmol) in anhydrous DMF (10 mL) at 0 °C added a solution of 2,2,2-trifluoroethan-1-ol (5.45 mL, 72.173 mmol) in anhydrous DMF (10 mL). After stirring at 0 °C for 10 min added a solution of 2-chloroisonicotinonitrile (5 g, 36.086 mmol) in anhydrous DMF (30 mL). Resulting reaction mixture stirred at rt
- 15 overnight. Reaction was quenched using sat. solution of ammonium chloride and extracted using EtOAc (3 x 100 mL). Combined organic layer given brine wash and dried over anhydrous Na₂SO₄. Organic layer removed under *vacuo* to get crude product which was purified by flash chromatography (EtOAc:Hexane 5:95) as eluent to get compound-6f (2.5 g, 34%) as colourless gum; m/z (LC-MS): 203.1 [M+H]⁺.
- 20 **Synthesis of 1-(2-(2,2,2-trifluoroethoxy)pyridin-4-yl)cyclopropan-1-amine (7f):** Compound-6f (0.1 g, 0.495 mmol) converted to compound-7f (80 mg, 71%) using general procedure for compound-7. After basification using NaHCO₃, compound extracted as free base, m/z (LC-MS): 232.95 [M+H]⁺.

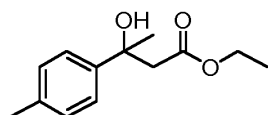
Example 8: Synthesis of 3-(4-fluorophenyl)-3-hydroxy-N-(1-(2-(2,2,2-trifluoroethoxy)pyridin-4-yl)cyclopropyl)butanamide (Example 8 peak-1 & Example 8 peak-2):



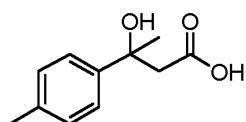
- 5 Following general procedure for compound-8, compound-4e (0.1 g, 0.303 mmol) converted to **Example 8** (45 mg, 22%) using compound-7f. The enantiomers were separated using Chiral prep HPLC, Column: (Chiralpak IH, 250mmX21 mm, 5 μ m), Eluent: n-Hexane(A) and IPA : MeOH 1:1 (B), Flow: 15 mL/min, Isocratic: 85(A):15(B), diluent EtOH: : DCM, 3:1, 4 mL, Injection vol, 0.9 mL, run time 13 min, to get Peak-1
- 10 (16.7 mg) Peak-2: (15.9 mg). H-NMR (DMSO-d₆, 400 MHz): δ 0.99-1.03 (m, 2 H), 1.05-1.27 (m, 2 H), 1.47 (s, 3H), 2.60 (dd, J = 14.1 Hz, 2 H), 4.92 (q, J = 8.6 Hz, 2 H), 5.64 (s, 1 H), 6.43 (dd, J = 1.2 Hz, 9.4 Hz. 2 H), 7.11-7.15 (m, 2 H), 7.48 (dd, J = 5.6 Hz, 10.8Hz, 2 H), 7.88 (d, J = 5.6 Hz, 1 H), 8.537 (s, 1 H), HRMS calculated for: [C₂₀H₂₀F₄N₂O₃+H]⁺ 413.1483; found: 413.1492 (**Example 8 peak-1**), 413.1494 (**Example 8 peak-2**). Analytical Chiral HPLC: CHIRALPAK-IH (150X4.6mmX5 μ m) Mobile Phase: (A) n-HEXANE (B) IPA : MeOH (50:50) Isocratic: 80:20(A:B) Flow: 1.0ml/min Diluent: EtOH, Column Temp: 25°C. Peak-1 (Rt: 2.59, 100% ee) Peak-2: (Rt: 3.50, 100% ee)

20 Example 9: Synthesis of 3-hydroxy-3-(p-tolyl)-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)butanamide

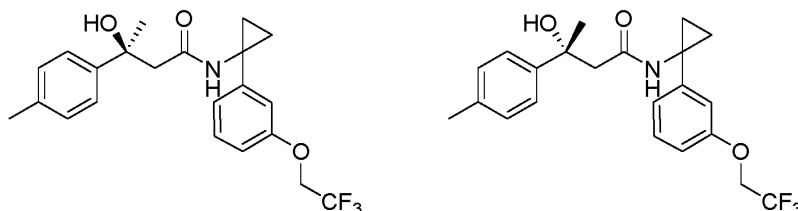
- Synthesis of ethyl 3-hydroxy-3-(p-tolyl)butanoate (3f):** 1-(p-Tolyl)ethan-1-one (1 g, 7.453 mmol) converted to compound-3f (380 mg, 24%) using general procedure A for compound-3, H-NMR (DMSO-d₆, 400 MHz): δ 1.04 (t, J = 7.2 Hz, 3 H), 1.51 (s, 3 H), 2.26 (s, 3 H), 2.68 (s, 2 H), 3.92 (q, J = 7.2 Hz, 2 H), 5.14 (s, 1 H), 7.08 (d, J = 8 Hz, 2 H), 7.31 (d, J = 8 Hz, 2 H).



Synthesis of 3-hydroxy-3-(p-tolyl)butanoic acid (4f): Compound-3f (380 mg, 1.709 mmol) converted to compound-4f (300 mg, 90%) as reddish oil using general procedure for compound-4, H-NMR (DMSO-d₆, 400 MHz): δ 1.49 (s, 3 H), 2.26 (s, 3 H), 2.65 (s, 2 H), 5.14 (bs, 1 H), 7.08 (d, J = 8 Hz, 2 H), 7.32 (d, J = 8 Hz, 2 H), 11.99 (bs, 1 H).



Example 9: Synthesis of 3-hydroxy-3-(p-tolyl)-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)butanamide (Example 9 peak-1 & Example 9 peak-2):

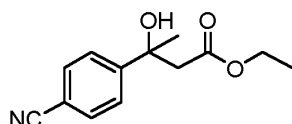


Following general procedure for compound-8, compound-4f (0.15 g, 0.772 mmol) converted to **Example 9** (120 mg, 38%) using compound-7a. The enantiomers were separated using Chiral prep HPLC, Column: (Chiralpak IH, 250mmX21 mm, 5 μ m), Eluent: n-Hexane(A) and IPA (B), Flow: 15 mL/min, Isocratic: 80(A):20(B), diluent EtOH : DCM, 3:1, 5 mL, Injection vol, 0.5 mL, run time 22 min, to get Peak-1 (50 mg) Peak-2: (43 mg). H-NMR (DMSO-d₆, 400 MHz): δ 0.70-1.00 (m, 2 H), 1.05-1.20 (m, 2 H), 1.42 (s, 3H), 2.67 (dd, J = 14.1 Hz, 2 H), 4.67 (q, J = 8.8 Hz, 2 H), 5.61 (s, 1 H), 6.43 (d, J = 7.6 Hz, 1 H), 6.58-6.59 (m, 1 H), 6.78 (dd, J = 2.4 Hz, 8.4 Hz, 1 H), 7.00-7.04 (m, 1 H), 7.12 (d, J = 8 Hz, 2 H), , 7.32 (d, J = 8 Hz, 2 H), 8.50 (s, 1 H), HRMS calculated for: [C₂₂H₂₄F₃NO₃+H-H₂O]⁺ 390.1675; found: 390.1682 (**Example 9 peak-1**), 390.1682 (**Example 9 peak-2**). Analytical Chiral HPLC: CHIRALPAK-IH (150X4.6mmX5 μ m) Mobile Phase: (A) n-HEXANE (B) IPA Isocratic: 95:05(A:B) Flow : 1.0ml/min Diluent: EtOH Column Temp: 25°C, Inj. volume: 3.000, Acq. method: IH_9505_7_C_30MIN.amx. Peak-1 (Rt: 8.65, 100% ee) Peak-2: (Rt: 12.54, 100% ee).

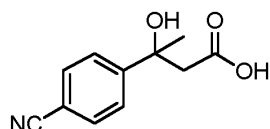
Example 10: Synthesis of 3-(4-cyanophenyl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)butanamide

Synthesis of ethyl 3-(4-cyanophenyl)-3-hydroxybutanoate (3g): 4-

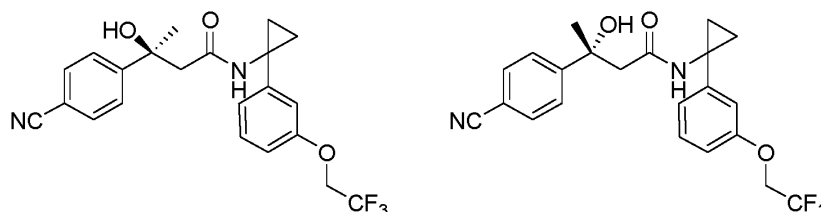
Acetylbenzonitrile (1 g, 6.889 mmol) converted to compound-**3g** (400 mg, 25%) using
 5 general procedure **A** for compound-**3**, H-NMR (DMSO- d_6 , 400 MHz): δ 1.01 (t, J = 7.2 Hz, 3 H), 1.52 (s, 3 H), 2.78 (dd, J = 14 Hz, 2 H), 3.90 (q, J = 7.2 Hz, 2 H), 5.53 (s, 1 H), 7.65 (d, J = 8.4 Hz, 2 H), 7.76 (d, J = 8.4 Hz, 2 H).



Synthesis of 3-(4-cyanophenyl)-3-hydroxybutanoic acid (4g): Compound-**3g** (400
 10 mg, 1.715 mmol) converted to compound-**4g** (320 mg, 91%) as colourless oil using
 general procedure for compound-**4**, H-NMR (DMSO- d_6 , 400 MHz): δ 1.51 (s, 3 H), 2.74 (dd, J = 14.4 Hz, 2 H), 5.46 (bs, 1 H), 7.65 (d, J = 6.8 Hz, 2 H), 7.77 (d, J = 6.8 Hz, 2 H), 12.03 (bs, 1 H)



Example 10: Synthesis of 3-(4-cyanophenyl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)butanamide (Example 10 peak-1 & Example 10 peak-2):

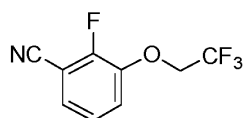


Following general procedure for compound-**8**, compound-**4g** (0.15 g, 0.731 mmol)
 20 converted to **Example 10** (90 mg, 33%) using compound-**7a**. The enantiomers were
 separated using Chiral prep HPLC, Column: (Chiralpak IH, 250mmX21 mm, 5 μ m),
 Eluent: n-Hexane(A) and IPA: : MeOH, 1:1 (B), Flow: 15 mL/min, Isocratic: 80(A):20(B),
 diluent EtOH : DCM, 3:1, 6 mL, Injection vol, 0.9 mL, run time 18 min, to get Peak-1 (37
 mg) Peak-2: (30 mg). H-NMR (DMSO- d_6 , 400 MHz): δ 0.85-0.95 (m, 2 H), 1.02-1.15
 25 (m, 2 H), 1.47 (s, 3 H), 2.65 (dd, J = 14 Hz, 2 H), 4.68 (q, J = 8.8 Hz, 2 H), 5.86 (s, 1 H), 6.44 (d, J = 8.4 Hz, 1 H), 6.58-6.59 (m, 1 H), 6.80 (dd, J = 2.4 Hz, 8.4 Hz, 1 H),

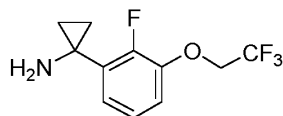
- 7.00-7.04 (m, 1 H), 7.63 (d, J = 8.4 Hz, 2 H), , 7.78 (d, J = 8.4 Hz, 2 H), 8.55 (s, 1 H), HRMS calculated for: $[C_{22}H_{21}F_3N_2O_3+H]^+$ 419.1577; found: 419.1586 (**Example 10 peak-1**), 419.1585 (**Example 10 peak-2**). Analytical Chiral HPLC: CHIRALPAK-IH (150X4.6mmX5 μ m) Mobile Phase: (A) n-HEXANE (B) IPA : MeOH (50:50) Isocratic: 90:10(A:B) Flow : 1.0ml/min Diluent: EtOH Column Temp: 25°C. Peak-1 (Rt: 7.02, 100% ee) Peak-2: (Rt: 12.84, 100% ee).

Example 11: Synthesis of 3-(2,4-difluorophenyl)-N-(1-(2-fluoro-3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide

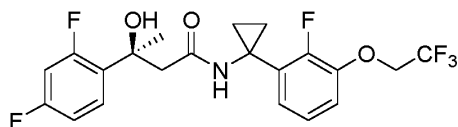
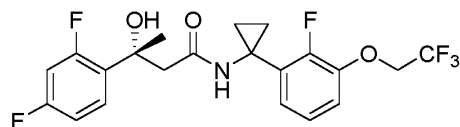
- Synthesis of 2-fluoro-3-(2,2,2-trifluoroethoxy)benzonitrile (6g):** 2-Fluoro-3-hydroxybenzonitrile (2 g, 14.587 mmol) converted to **6g** (2.3 g, 72%) using general procedure for compound-6, H-NMR (DMSO- d_6 , 300 MHz): δ 4.94 (q, J = 8.4 Hz, 2 H), 7.34-7.40 (m, 1 H), 7.52-7.57 (m, 1 H), 7.65-7.71 (m, 1H).



- Synthesis of 1-(2-fluoro-3-(2,2,2-trifluoroethoxy)phenyl)cyclopropan-1-amine (7g):** Compound-**6g** (0.5 g, 2.282 mmol) converted to compound-**7g** (0.2 g, 35%) as yellowish oil using general procedure for compound-7, m/z (LC-MS): 249.95 $[M+H]^+$.



- Example 11: Synthesis of 3-(2,4-difluorophenyl)-N-(1-(2-fluoro-3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide (Example 11 peak-1 & Example 11 peak-2):**

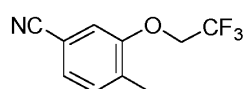


- Following general procedure for compound-8, compound-**4d** (0.087 g, 0.401 mmol) converted to **Example 11** (100 mg, 56%) using compound-**7g**. The enantiomers were separated using Chiral prep HPLC, Column: (Chiralpak IH, 250mmX21 mm, 5 μ m), Eluent: n-Hexane(A) and EtOH (B), Flow: 15 mL/min, Isocratic: 90(A):10(B), diluent EtOH : DCM, 1:1, 5 mL, Injection vol, 0.3 mL, run time 13 min, to get Peak-1 (43.3 mg) Peak-2: (46.4 mg). H-NMR (DMSO- d_6 , 400 MHz): δ 0.76-0.80 (m, 2 H), 0.86-1.05 (m, 2

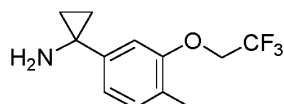
H), 1.40 (s, 3 H), 2.55 (dd, J = 14 Hz, 2 H), 4.75 (q, J = 8.8 Hz, 2 H), 5.96 (s, 1 H), 6.91-6.96 (m, 3 H), 7.03-7.12 (m, 2 H), 7.44-7.51 (m, 1 H), 8.64 (s, 1 H), HRMS calculated for: $[C_{21}H_{19}F_6NO_3+H]^+$ 448.1342; found: 448.1347 (**Example 11 peak-1**), 448.1347 (**Example 11 peak-2**). Analytical Chiral HPLC: CHIRALPAK-IH (150X4.6mmX5 μ m), Mobile Phase: (A) n-HEXANE (B) IPA: MeOH (50:50), Isocratic: 85:15 (A:B), Flow: 1.0ml/min, Diluent: EtOH, Column Temp: 25 °C, Inj. volume: 5.000, Acq. method: IH_8515_7_C-15min.amx. Peak-1 (Rt: 2.71, 100% ee) Peak-2: (Rt: 3.38, 100% ee).

10 Example 12: Synthesis of 3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(4-methyl-3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)butanamide

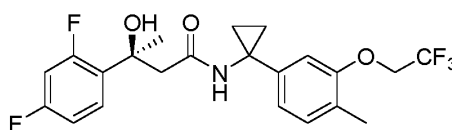
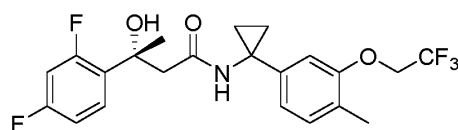
Synthesis of 4-methyl-3-(2,2,2-trifluoroethoxy)benzonitrile (6h): 3-Hydroxy-4-methylbenzonitrile (2 g, 15.021 mmol) converted to **6h** (2.9 g, 91%) using general procedure for compound-6, H-NMR (CDCl₃, 300 MHz): δ 2.32 (s, 3 H), 4.38 (q, J = 8.4 Hz, 2 H), 7.01 (s, 1 H), 7.25-7.28 (m, 2 H).



Synthesis of 1-(4-methyl-3-(2,2,2-trifluoroethoxy)phenyl)cyclopropan-1-amine (7h): Compound-6h (1.5 g, 6.971 mmol) converted to compound-7h (550 mg, 31%) as yellowish oil using general procedure for compound-7, m/z (LC-MS): 246.00 [M+H]⁺.



20 **Example 12: Synthesis of 3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(4-methyl-3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)butanamide (Example 12 peak-1 & Example 12 peak-2):**

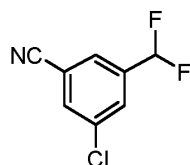


25 Following general procedure for compound-8, compound-4d (0.132 g, 0.612 mmol) converted to **Example 12** (150 mg, 55%) using compound-7h. The enantiomers were separated using Chiral prep HPLC, Column: (Chiralpak IH, 250mmX21 mm, 5 μ m), Eluent: n-Hexane(A) and IPA: : MeOH (1:1) (B), Flow: 15 mL/min, Isocratic: 90(A):10(B), diluent EtOH:DCM, 1:1, 5 mL, Injection vol, 0.25 mL, run time 11 min, to

get Peak-1 (75.9 mg) Peak-2: (69.9 mg). H-NMR (DMSO- d_6 , 400 MHz): δ 0.76-0.95 (m, 2 H), 1.09-1.15 (m, 2 H), 1.48 (s, 3 H), 2.08 (s, 3 H), 2.70 (dd, J = 14 Hz, 2 H), 4.65 (q, J = 8.8 Hz, 2 H), 6.06 (s, 1 H), 6.37-6.39 (m, 1 H), 6.56 (s, 1 H), 6.88 (d, J = 8 Hz, 1 H), 7.01-7.06 (m, 1 H), 7.13-7.22 (m, 1 H), 7.55-7.62 (m, 1 H), 8.60 (s, 1 H), HRMS calculated for: $[C_{22}H_{22}F_5NO_3+H]^+$ 444.1593; found: 444.1598 (**Example 12 peak-1**), 444.1600 (**Example 12 peak-2**). Analytical Chiral HPLC: CHIRALPAK-IH (150X4.6mmX5 μ m) Mobile Phase: (A) n-HEXANE (B) IPA : MeOH (50:50) Isocratic: 93:07(A:B) Flow: 1.0ml/min Diluent: EtOH, Column Temp: 25°C, Inj. volume: 5.000, Acq. method: IH_9307_7_C_30MIN.amx. Peak-1 (Rt: 2.98, 100% ee) Peak-2: (Rt: 3.44, 100% ee).

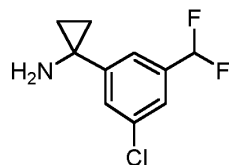
Example 13: Synthesis of N-(1-(3-chloro-5-(difluoromethyl)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide

Synthesis of 3-chloro-5-(difluoromethyl)benzonitrile (6i): To a solution of 3-chloro-5-formylbenzonitrile (1 g, 6.04 mmol) in anhydrous dichloromethane (10 mL) at 0 °C dropwise added diethylaminosulfur trifluoride (1.4 mL, 12.08 mmol). Resulting reaction mixture stirred at rt for 4 h. Reaction was quenched using sat. solution of ammonium chloride and extracted using EtOAc (2 x 20 mL). Combined organic layer given brine wash and dried over anhydrous Na_2SO_4 . Organic layer concentrated under *vacuo* to get compound-6i (1 g, 89%) as yellow oil, H-NMR (DMSO- d_6 , 400 MHz): δ 7.09 (t, J = 55.2 Hz, 1 H), 8.04 (d, J = 1.2 Hz, 1 H), 8.10 (dd, J = 1.2 Hz, 1.2 Hz, 1 H), 8.27 (d, J = 1.2 Hz, 1 H).

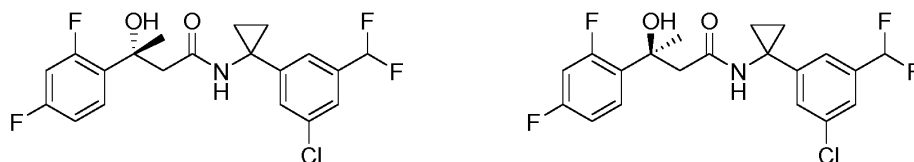


Synthesis of 1-(3-chloro-5-(difluoromethyl)phenyl)cyclopropan-1-amine (7i):

Compound-6i (1 g, 5.331 mmol) converted to compound-7i (550 mg, 47%) as yellowish oil using general procedure for compound-7, m/z (LC-MS): 217.90 $[M+H]^+$.



Example 13: Synthesis of N-(1-(3-chloro-5-(difluoromethyl)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide (Example 13 peak-1 & Example 13 peak-2):

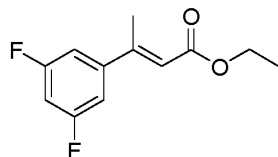


Following general procedure for compound-8, compound-4d (0.15 g, 0.694 mmol) converted to **Example 13** (160 mg, 56%) as off white solid using compound-7i. The enantiomers were separated using Chiral prep HPLC, Column: (Chiralpak IH, 250mmX21 mm, 5 μ m), Eluent: n-Hexane(A) and IPA : MeOH (1:1) (B), Flow: 15 mL/min, Isocratic: 90(A):10(B), diluent EtOH : DCM, 1:1, 4.5 mL, Injection vol, 0.2 mL, run time 18 min, to get Peak-1 (47.2 mg) Peak-2: (69.9 mg). H-NMR (DMSO-d₆, 400 MHz): δ 0.96-1.04 (m, 2 H), 1.18-1.23 (m, 2 H), 1.49 (s, 3 H), 2.65 (dd, J = 14 Hz, 2 H), 5.94 (s, 1 H), 6.93 (t, J = 55.6 Hz, 1 H), 6.98-7.02 (m, 1 H), 7.10-7.17 (m, 2 H), 7.16-7.23 (m, 1 H), 7.38 (s, 1 H), 7.58-7.62 (m, 1 H), 8.67 (s, 1 H), HRMS calculated for: [C₂₀H₁₈ClF₄NO₂+H-H₂O]⁺ 398.0929; found: 398.0930 (**Example 13 peak-1**), 398.0934 (**Example 13 peak-2**). Analytical Chiral HPLC: CHIRALPAK-IH (150X4.6mmX5 μ m), Mobile Phase: (A) n-HEXANE (B) IPA : MeOH (50:50) Isocratic: 85:15(A:B), Flow: 1.0ml/min Diluent: EtOH, Column Temp: 25°C, Inj. volume: 5.000, Acq. method: IH_8515_7_C-20min.amx. Peak-1 (Rt: 2.97, 100% ee) Peak-2: (Rt: 4.27, 100% ee).

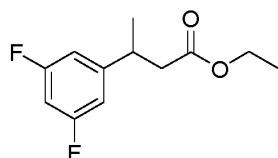
Example 14: Synthesis of 3-(3,5-difluorophenyl)-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)butanamide

- Synthesis of ethyl (E)-3-(3,5-difluorophenyl)but-2-enoate (10):** To a stirred suspension of sodium hydride (0.192 g, 4.803 mmol) in anhydrous THF (10 mL) at 0 °C added triethyl phosphonoacetate (1 g, 4.803 mmol). To a resulting reaction mixture added a dropwise solution of 1-(3,5-difluorophenyl)ethan-1-one (500 mg, 3.202 mmol) in anhydrous THF (2 mL) and stirred at rt for 30 min. Reaction was quenched using saturated solution of ammonium chloride and extracted using EtOAc (2 x 15 mL).
- Combined organic layer given brine wash, dried over anhydrous Na₂SO₄ and concentrated under *vacuo* to get compound-10 (320 mg, 44%) as colourless liquid. m/z (LC-MS): 227.1 [M+H]⁺; H-NMR (DMSO-d₆, 300 MHz): δ 1.23 (t, J = 6.9 Hz, 3 H), 2.47

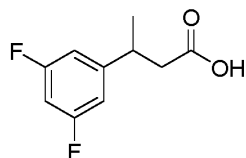
(s, 3 H), 4.16 (q, $J = 7.2$ Hz & 14.4 Hz, 2 H), 6.26 (s, 1 H), 7.29-7.32 (m, 1 H), 7.32-7.36 (m, 2 H).



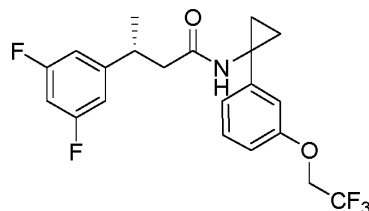
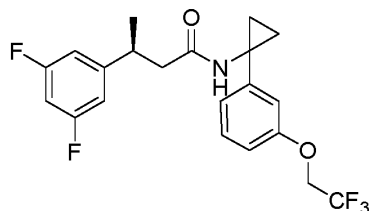
Synthesis of Ethyl 3-(3,5-difluorophenyl)-3-hydroxypropanoate (3h): To a stirred solution of compound-10 in ethanol was added palladium on carbon (10%) at rt under argon atmosphere. The resulting mixture was allowed to stir under hydrogen balloon pressure until completion. The progress of the reaction monitored by TLC. After completion of the reaction, filtered through celite bed and washed with EtOH (2 x 10 mL). The resulting filtrate was concentrated under reduced pressure to afford the crude compound-3h which was used in next step without purification; H-NMR (DMSO- d_6 , 400 MHz): δ 1.09 (t, $J = 7.2$ Hz, 3 H), 1.20 (d, $J = 6.8$ Hz, 3 H), 2.61 (d, $J = 7.6$ Hz, 2 H), 3.15-3.11 (m, 1 H), 4.02 (q, $J = 5.2$ Hz, 2 H), 6.99-7.06 (m, 3 H).



Synthesis of 3-(3,5-difluorophenyl)butanoic acid (4h): Compound-3h (0.31 g, 1.35 mmol) converted to compound-4h (0.22 g, 1.1%) as off white solid using general procedure for compound-4, H-NMR (DMSO- d_6 , 300 MHz): δ 1.17-1.20 (m, 3 H), 2.49-2.57 (m, 2 H), 3.16-3.1 (m, 1 H), 6.99-7.04 (m, 3 H); LCMS (ESI+, m/z): 198.95 (M+H) $^+$.



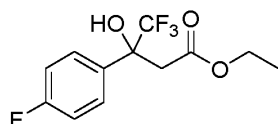
Example 14: Synthesis of 3-(3,5-difluorophenyl)-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)butanamide (Example 14 peak-1 & Example 14 peak-2):



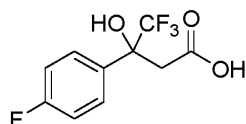
Following general procedure for compound-8, compound-4h (0.22 g, 0.462 mmol) converted to **Example 14** (0.22 g, 43%) as off white solid using compound-7a. The enantiomers were separated using Chiral prep HPLC, Column: (Chiralpak IH, 250x21mm, 5µm), Eluent: n-Hexane(A) and EtOH : IPA 1:1 (B), Flow: 15 mL/min, Isocratic: 80(A):20(B), diluent EtOH : DCM (3:1, 5 mL), Injection volume-0.2 mL, run time 15 min, to get Peak-1 (93.1 mg) Peak-2: (97.3 mg) as colourless gummy oil; H-NMR (DMSO-d₆, 400 MHz): δ 0.91-0.97 (m, 2 H), 1.04-1.33 (m, 5 H), 2.37-2.49 (m, 2 H), 3.17-3.22 (m, 1 H), 4.68 (q, J = 8.8 Hz, 2 H), 6.55-6.57 (m, 2 H), 6.78-6.81 (m, 1 H), 6.94-6.97 (m, 2 H), 7.01-7.11 (m, 2 H), 8.49 (s, 1 H), HRMS calculated for: [C₂₁H₂₀F₅NO₂+H]⁺ 414.1487; found: 414.1495 (**Example 14 peak-1**), 414.1491 (**Example 14 peak-2**). Analytical Chiral HPLC: REGIS (S,S) WHELK-01(150X4.6mmX5µm) Mobile Phase: (A) n-HEXANE (B) IPA : MeOHL (50:50) Isocratic : 90:10(A:B) Flow: 1.0 ml/min, Diluent: EtOH, Column Temp: 25°C, Inj. volume: 5.000, Acq. method: REG_9010_8_C_30MIN.amx. Peak-1 (Rt: 11.93, 100% ee) Peak-2: (Rt: 13.62, 100% ee).

Example 15: Synthesis of 4,4,4-trifluoro-3-(4-fluorophenyl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)butanamide

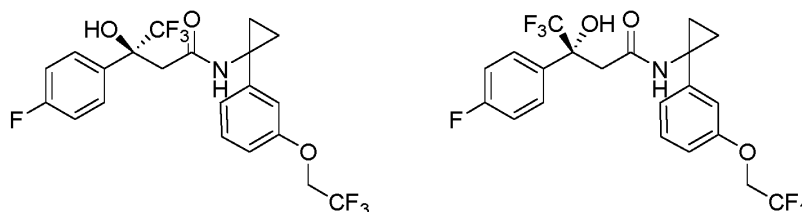
Synthesis of ethyl 4,4,4-trifluoro-3-(4-fluorophenyl)-3-hydroxybutanoate: 2,2,2-Trifluoro-1-(4-fluorophenyl)ethan-1-one (1 g, 6.405 mmol) converted to compound-3i (0.45 g, 62%) using general procedure A for compound-3; H-NMR (DMSO-d₆, 400 MHz): δ 0.96 (t, J = 8 Hz, 2 H), 3.01 (d, J = 15.2 Hz, 1 H), 3.42 (dd, J = 15.2 Hz, 2 H), 4.14 (q, J = 7.2 Hz, 2 H), 6.93 (s, 1 H), 7.18-7.22 (m, 2 H), 7.60-7.63 (m, 2 H).



Synthesis of 4,4,4-trifluoro-3-(4-fluorophenyl)-3-hydroxybutanoic acid (4i): Compound-3i (450 mg, 1.46 mmol) converted to compound-4i (250 mg, 61.80%) as off-white solid using general procedure for compound-4; m/z (LC-MS): 252.01 [M+H]⁻.



Example 15: Synthesis of 4,4,4-trifluoro-3-(4-fluorophenyl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)butanamide (Example 15 peak-1 & Example 15 peak-2):

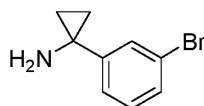


- 5 Following general procedure for compound-8, compound-4i (250 mg, 0.99 mmol) converted to **Example 15** (250 mg, 54%) as off white solid using compound-7a. The enantiomers were separated using Chiral prep HPLC, Column: (Chiralpak IH, 250x21mm, 5µm), Eluent: n-Hexane(A) and EtOH : IPA 1:1 (B), Flow: 15 mL/min, Isocratic: 80(A):20(B), diluent EtOH : DCM (3:1, 5 mL), Injection volume-0.2 mL, run
- 10 time 15 min, to get Peak-1 (110 mg) Peak-2: (108 mg) as colourless gummy oil; H-NMR (DMSO-d₆, 400 MHz): δ 0.88-0.99 (m, 2 H), 1.15-1.20 (m, 2 H), 1.35 (d, J = 3.6 Hz, 3H), 3.16-3.22 (m, 1 H), 4.68 (d, J = 8.8 Hz, 2 H), 6.55-6.57 (m, 2 H), 6.78-6.81 (m, 1 H), 6.95-6.97 (m, 1 H), 7.01-7.11 (m, 2 H), 8.49 (s, 1 H), HRMS calculated for: [C₂₁H₁₈F₇NO₃+H]⁺ 466.1248; found: 466.1258 (**Example 15 peak-1**), 466.1260 (**Example 15 peak-2**). Analytical Chiral HPLC: CHIRALPAK-IH (150X4.6mmX5µm) Mobile Phase: (A) n-HEXANE (B) 0.1% HCOOH IN EtOH:MeOH (80:20) Isocratic: 90:10 (A:B), Flow: 1.0 ml/min, Diluent: EtOH, Column Temp: 25°C, Inj. volume: 5.000, Acq. method: IH_9010_7_B_10MIN.amx. Peak-1 (Rt: 3.19, 100% ee), Peak-2: (Rt: 4.09, 100% ee).

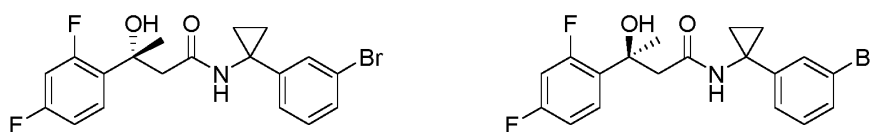
20

Example 16: Synthesis of N-(1-(3-bromophenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide

- Synthesis of 1-(3-bromophenyl)cyclopropan-1-amine hydrochloride (7j):** 3-Bromobenzonitrile (1 g, 5.43 mmol) converted to compound-7j (600 mg, crude) using
- 25 general procedure for compound-7. After acidification during work up compound-7j extracted as HCl salt in diethyl ether, m/z (LC-MS): 213.75 [M+H]⁺.



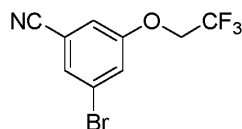
Example 16: Synthesis of N-(1-(3-bromophenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide (Example 16 peak-1 & Example 16 peak-2):



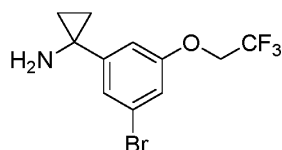
Following general procedure for compound-8, compound-4d (200 mg, 0.92 mmol) converted to **Example 16** (80 mg, 21%) as off white solid using compound-7j. The enantiomers were separated using Chiral prep HPLC, Column: (Chiralpak IH, 250x21mm, 5 μ m), Eluent: n-Hexane(A) and EtOH:IPA 1:1 (B), Flow: 20 mL/min, Isocratic: 85(A):15(B), diluent EtOH : DCM (1:1, 3 mL), Injection volume-0.5 mL, run time 11 min, to get Peak-1 (6.2 mg) Peak-2: (6.3 mg) as colourless gummy oil; H-NMR (DMSO-d₆, 400 MHz): δ 0.85-0.97 (m, 2 H), 1.11-1.23 (m, 2 H), 1.48 (s, 3H), 2.49-2.78 (m, 2 H), 5.99 (s, 1 H), 4.73 (q, J = 8.8 Hz & 17.6 Hz, 2 H), 5.99 (s, 1 H), 6.79 (d, J = 8.4 Hz, 1 H), 7.01-7.14 m, 1 H), 7.15-7.19 (m, 1 H), 7.29 (d, J= 7.6 Hz, 1 H), 7.58-7.64 (m, 1 H), 7.59-7.60 (m, 1 H), 8.64 (s, 1 H), HRMS calculated for: [C₁₉H₁₈BrF₂NO₂+H-H₂O]⁺ 392.0456; found: 392.0462 (**Example 16 peak-1**), 392.0471 (**Example 16 peak-2**). Analytical Chiral HPLC: CHIRALPAK-IH (150X4.6mmX5 μ m) Mobile Phase: (A) n-HEXANE (B) IPA : MeOH (50:50), Isocratic: 85:15 (A:B), Flow: 1.0 ml/min, Diluent: EtOH, Column Temp: 25°C, Inj. volume: 10.000, Acq. method: IH_8515_7_C-15min.amx. Peak-1 (Rt: 2.74, 100% ee) Peak-2: (Rt: 3.54, 100% ee).

Example 17: Synthesis of N-(1-(3-cyano-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(4-fluorophenyl)-3-hydroxybutanamide

Synthesis of 3-bromo-5-(2,2,2-trifluoroethoxy)benzonitrile (6k): 3-Bromo-5-hydroxybenzonitrile (10 g, 50.50 mmol) converted to **6k** (15 g, 98%) using general procedure for compound-6, H-NMR (DMSO-d₆, 400 MHz): δ 4.92 (q, J = 9 Hz, 2 H), 7.67 (s, 1 H), 7.73 (s, 1 H), 7.83 (s, 1H).

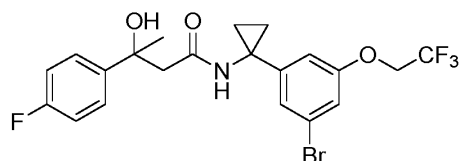


Synthesis of 1-(3-bromo-5-(2,2,2-trifluoroethoxy)phenyl)2-cyclopropane-1-amine hydrochloride (7k): Compound-6k (100 mg, 0.32 mmol) converted to compound-7k (30 mg, 30%) as off white solid using general procedure for compound-7. After acidification solids obtained washed with hexane to get desired compound as HCl salt, m/z (LC-MS): 265.90 [M+H]⁺.

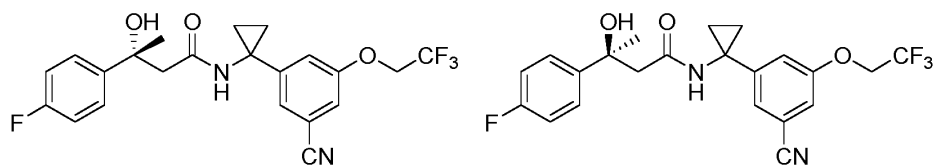


Synthesis of N-(1-(3-bromo-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(4-fluorophenyl)-3-hydroxybutanamide (8k):

Following general procedure for compound-8, compound-4e (100 mg, 0.50 mmol) converted to compound-8k (60 mg, 24%) as colorless gummy using compound-7k, m/z (LC-MS): 489.95 [M+H]²⁺.



Example 17: Synthesis of N-(1-(3-cyano-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(4-fluorophenyl)-3-hydroxybutanamide (Example 17 peak-1 & Example 17 peak-2):

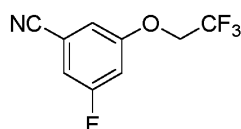


In a seal tube charged compound-8k (60 mg, 0.12 mmol) in N,N-dimethylformamide at rt. Added zinc cyanide (14.5 mg, 0.12 mmol) at rt under argon atmosphere. The resulting mixture was degassed with argon for 15 min and then added tetrakis(triphenylphosphine)palladium(0) (565 mg, 0.48 mmol). Resulting reaction mixture was stirred at 150 °C in MW for 2 h. The reaction mixture was diluted with cold water and extracted with EtOAc (3 x 15 mL). The combined organic layer given brine wash and dried over anhydrous Na₂SO₄. Organic layer concentrated under *vacuo* to afford crude **Example 17** which was purified by prep TLC using 30% of EtOAc in hexane as mobile phase to isolate pure **Example 17a/b** (15 mg, 27%) as off white solid which was separated using Chiral prep HPLC, Column: (Regis (S,S) Whelk-01,, 250mmX21.1mm, 5μm), Eluent: n-Hexane(A) and IPA : MeOH(1:1) (B), Flow: 15 ml/min, Isocratic: 90(A):10(B), diluent EtOH : DCM (1:1, 3.5 mL), Injection volume-0.25 mL, run time 33 min, to get Peak-1 (7.8 mg) Peak-2: (6.2 mg) as colourless gummy oil; H-NMR (DMSO-d₆, 400 MHz): δ 0.97-0.99 (m, 2 H), 1.11-1.15 (m, 2 H), 1.46 (s, 3H), 2.60-2.69 (m, 2 H), 4.80 (q, J= 8.8 Hz & 17.6 Hz, 2 H), 5.61 (s, 1 H), 6.92 (s, 1 H), 7.07-7.11 (m, 3 H), 7.35 (s, 1 H), 7.44-7.48 (m, 2 H), 8.49 (s, 1 H), HRMS calculated

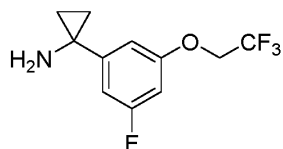
for: $[C_{22}H_{20}F_4N_2O_3 + H-H_2O]^+$ 419.1377; found: 419.1387 (**Example 17 peak-1**), 419.1386 (**Example 17 peak-2**). Analytical Chiral HPLC: REGIS(S,S) WHELK-01 (250X4.6mmX5 μ m) Mobile Phase: (A) n-HEXANE (B) IPA : MeOH (50:50), Isocratic: 80:20(A:B), Flow: 1.0 ml/min, Diluent: EtOH, Column Temp: 25°C, Inj. volume: 10.000, Acq. method: REG_8020_8_C_20MIN.amx. Peak-1 (Rt: 9.40, 100% ee) Peak-2: (Rt: 10.04, 100% ee).

Example 18 Synthesis of 3-(2,4-difluorophenyl)-N-(1-(3-fluoro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide

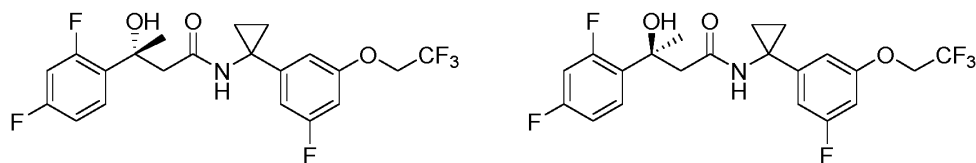
Synthesis of 3-fluoro-5-(2,2,2-trifluoroethoxy)benzonitrile (6I): 3-Fluoro-5-hydroxybenzonitrile (4 g, 36.48 mmol) converted to compound-6I (5 g, 63%) using general procedure for compound-6, H-NMR (DMSO- d_6 , 400 MHz): δ 4.92 (q, J = 8.8 Hz, 2 H), 7.43-7.47 (m, 1 H), 7.52-7.56 (m, 2 H).



Synthesis of 1-(3-fluoro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropan-1-amine (7I): Compound-6I (3 g, 13.69 mmol) converted to compound-7I (1.5 g, 44%) using general procedure for compound-7. After basification using $NaHCO_3$, compound extracted as free base; H-NMR (DMSO- d_6 , 400 MHz): δ 0.93-0.99 (m, 4H), 2.35 (bs, 2 H), 4.73 (q, J = 8.8 Hz, 2 H), 6.72-6.73 (m, 1 H), 6.78-6.80 (m, 2 H).



Example 18: Synthesis of 3-(2,4-difluorophenyl)-N-(1-(3-fluoro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide (Example 18 peak-1 & Example 18 peak-2):

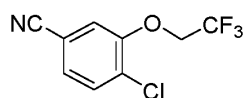


Following general procedure for compound-8, compound-4d (150 mg, 0.60 mmol) converted to **Example 18** (220 mg, 82%) as off-white solid using compound-7I. The enantiomers were separated using Chiral prep HPLC, Column: (Chiralpak IH,

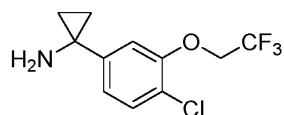
250x21mm, 5 μ m), Eluent: n-Hexane(A) and EtOH : IPA 1:1 (B), Flow: 15 mL/min, Isocratic: 90(A):10(B), diluent EtOH : DCM (3:1, 6 mL), Injection volume-0.5 mL, run time 17 min, to get Peak-1 (97.1 mg) Peak-2: (93.5 mg) as colourless gummy oil; H-NMR (DMSO-d₆, 400 MHz): δ 0.97-0.98 (m, 2 H), 1.14-1.23 (m, 2 H), 1.49 (s, 3H), 2.60-2.79 (m, 2 H), 4.73 (q, J = 8.8 Hz & 17.6 Hz, 2 H), 5.99 (s, 1 H), 6.34 (d, J = 10.4 Hz, 1 H), 6.41 (s, 1 H), 6.74 (d, J = 10.4 Hz, 1 H), 6.98-7.02 (m, 1 H), 7.11-7.17 (m, 1 H), 7.59-7.60 (m, 1 H), 8.60 (s, 1 H), HRMS calculated for: [C₂₁H₁₉F₆NO₃+H]⁺ 448.1342; found: 448.1350 (**Example 18 peak-1**), 448.1350 (**Example 18 peak-2**). Analytical Chiral HPLC: CHIRALPAK-IH (150X4.6mmX5 μ m) Mobile Phase: (A) n-HEXANE (B) IPA : MeOH (50:50), Isocratic: 80:20 (A:B), Flow: 1.0 ml/min Diluent: EtOH, Column Temp: 25°C, Inj. volume: 5.000, Acq. method: IH_8020_7_C_20MIN.amx. Peak-1 (Rt: 2.40, 100% ee) Peak-2: (Rt: 3.00, 100% ee).

Example 19 Synthesis of N-(1-(4-chloro-3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide

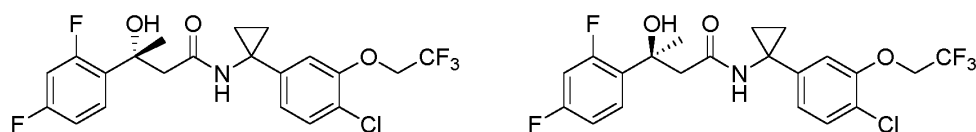
Synthesis of 4-chloro-3-(2,2,2-trifluoroethoxy)benzonitrile (6m): 4-Chloro-3-hydroxybenzonitrile (3 g, 19.53 mmol) converted to **6m** (4 g, 87%) as white solid using general procedure for compound-6, H-NMR (DMSO-d₆, 300 MHz): δ 4.98 (q, J = 8.8 Hz, 2 H), 7.55-7.58 (dd, J = 1.6 Hz & 8.4 Hz, 1 H), 7.74 (d, J = 8.4 Hz, 1 H) 7.84 (d, J = 1.6 Hz, 1 H),



Synthesis of 1-(4-chloro-3-(2,2,2-trifluoroethoxy)phenyl)cyclopropane-1-amine (7m): Compound-**6m** (1 g, 4.24 mmol) converted to compound-**7m** (350 mg, crude) using general procedure for compound-7. After basification using NaHCO₃, compound extracted as free base, m/z (LC-MS): 266.1 [M+H]⁺; H-NMR (DMSO-d₆, 400 MHz): δ 0.97-0.98 (m, 4H), 2.77 (bs, 2 H), 4.86 (q, J = 8.4 Hz, 2 H), 6.96-6.98 (dd, J = 2.4 Hz & 8.4 Hz, 1 H), 7.14 (d, J = 2.4 Hz, 1 H), 7.34 (d, J = 8.4 Hz, 1 H).



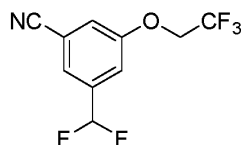
Example 19: Synthesis of N-(1-(4-chloro-3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide (Example 19 peak-1 & Example 19 peak-2):



Following general procedure for compound-8, compound-4d (100 mg, 0.37 mmol) converted to **Example 19** (100 mg, 57%) as off-white solid using compound-7m. The enantiomers were separated using Chiral prep HPLC, Column: (Chiralpak IH, 5 250x21mm, 5 μ m), Eluent: n-Hexane(A) and MeOH : IPA 1:1 (B), Flow: 15 mL/min, Isocratic: 88(A):12(B), diluent EtOH : DCM (1:1, 5 mL), Injection volume-0.4 mL, run time 15 min, to get Peak-1 (30 mg) Peak-2: (31 mg) as colourless gummy oil; H-NMR (DMSO-d₆, 400 MHz): δ 0.93-0.97 (m, 2 H), 1.13-1.24 (m, 2 H), 1.49 (s, 3H), 2.59-2.77 (m, 2 H), 4.76 (q, J = 8.8 Hz & 17.6 Hz, 2 H), 5.99 (s, 1 H), 6.47-6.50 (dd, J = 4 Hz, 1 H), 10 6.74-6.75 (m, 1 H), 7.03-7.07 (m, 1 H), 7.13-7.21 (m, 2 H), 7.55-7.62 (m, 1 H), 8.63 (s, 1 H), HRMS calculated for: [C₂₁H₁₉ClF₅NO₃+H-H₂O]⁺ 446.0941; found: 446.0949 (**Example 19 peak-1**), 446.0947 (**Example 19 peak-2**). Analytical Chiral HPLC: CHIRALPAK-IH (150X4.6mmX5 μ m) Mobile Phase: (A) n-HEXANE (B) IPA : MeOH (50:50) Isocratic: 90:10 (A:B), Flow: 1.0ml/min, Diluent: EtOH, Column Temp: 25°C, Inj. 15 volume: 5.000, Acq. method: IH_9010_7_C_30MIN.amx. Peak-1 (Rt: 3.321, 100% ee) Peak-2: (Rt: 5.602, 100% ee).

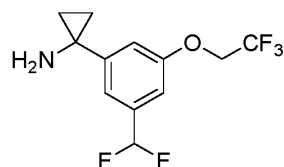
Example 20: Synthesis of N-(1-(3-(difluoromethyl)-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide

20 **Synthesis of 3-(difluoromethyl)-5-(2,2,2-trifluoroethoxy)benzonitrile (6n)**: 3-(Difluoromethyl)-5-hydroxybenzonitrile (1 g, 2.95 mmol) converted to **6n** (550 mg, 74%) using general procedure for compound-6, H-NMR (DMSO-d₆, 400 MHz): δ 4.95 (q, J = 8.7 Hz, 2 H), 7.05 (t, J = 55.2 Hz, 1 H), 7.62 (s, 1 H), 7.75 (s, 1 H), 7.81 (s, 1 H).



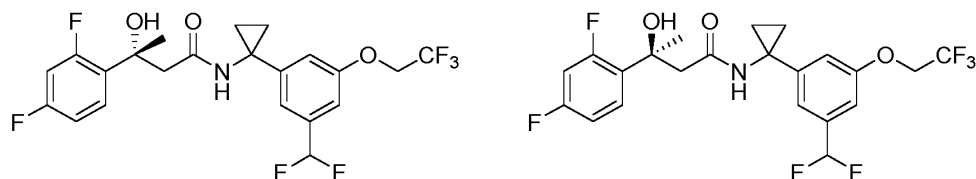
25 **Synthesis of 1-(3-(difluoromethyl)-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropane-1-amine (7n)**: Compound-6n (700 mg, 2.78 mmol) converted to compound-7n (170 mg, 22%) using general procedure for compound-7. After basification using NaHCO₃, compound extracted as free base, m/z (LC-MS): 282.1 [M+H]⁺; H-NMR (DMSO-d₆, 400 MHz): δ 0.98-1.17 (m, 4H), 2.93 (bs, 2

H), 4.82 (q, $J = 8.8$ Hz, 2 H), 6.94 (t, $J = 50.4$ Hz, 1 H), 6.93 (s, 1 H), 7.13 (s, 1 H), 7.17 (s, 1 H).



Example 20: Synthesis of N-(1-(3-(difluoromethyl)-5-(2,2,2-

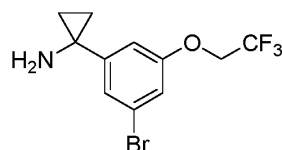
trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide
(Example 20 peak-1 & Example 20 peak-2):



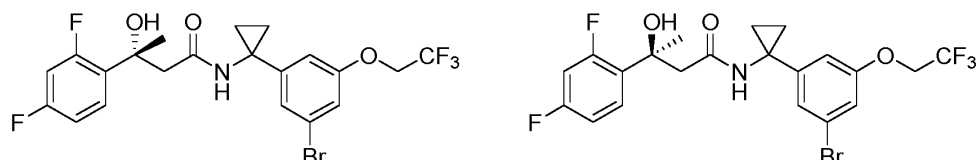
Following general procedure for compound-8, compound-4d (80 mg, 0.28 mmol) converted to **Example 20** (50 mg, 37%) as off white solid using compound-7n. The enantiomers were separated using Chiral prep HPLC, Column: (Chiralpak IH, 250x21mm, 5 μ m), Eluent: n-Hexane(A) and IPA : MeOH 1:1(B), Flow: 15 mL/min, Isocratic: 85(A):15(B), diluent EtOH : DCM (1:1, 4 mL), Injection volume-0.4 mL, run time 11 min, to get Peak-1 (15 mg) Peak-2: (14 mg) as colourless gummy oil; H-NMR (DMSO- d_6 , 400 MHz): δ 0.99-1.06 (m, 2 H), 1.14 (s, 2 H), 1.49 (s, 3H), 2.66-2.74 (m, 2 H), 4.76 (q, $J = 8.8$ Hz & 17.6 Hz, 2 H), 5.94 (s, 1 H), 6.73-7.01 (m, 5 H), 7.09-7.15 (m, 1 H), 7.57-7.63 (m, 1 H), 8.63 (s, 1 H), HRMS calculated for: $[C_{22}H_{20}F_7NO_3 + H - H_2O]^+$ 462.1299; found: 462.1306 (**Example 20 peak-1**), 462.1306 (**Example 20 peak-2**). Analytical chiral HPLC: CHIRALPAK-IH (150X4.6mmX5 μ m) Mobile Phase: (A) n-HEXANE (B) IPA : MeOH (50:50), Isocratic: 90:10 (A:B), Flow: 1.0ml/min, Diluent : EtOH, Column Temp: 25°C, Inj. volume: 5.000, Acq. method: IH_9010_7_C_30MIN.amx. Peak-1 (Rt: 3.72, 100% ee) Peak-2: (Rt: 6.011, 100% ee).

Example 21: Synthesis of N-(1-(3-bromo-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide

Synthesis of 1-(3-bromo-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropane-1-amine (7k'): Compound-6k (1 g, 3.57 mmol) converted to compound-7k' (300 mg, 35%) using general procedure for compound-7. After basification using $NaHCO_3$, compound extracted as free base, m/z (LC-MS): 311.1 $[M+H]^+$.



Example 21: Synthesis of N-(1-(3-bromo-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide (Example 21 peak-1 & Example 21 peak-2):

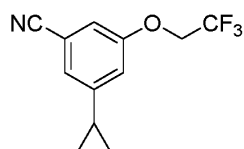


5
Following general procedure for compound-8, compound-4d (100 mg, 0.462 mmol) converted to **Example 21** (25 mg, 18%) as off white solid using compound-7k'. The enantiomers were separated using Chiral prep HPLC, Column: (Chiralpak IH, 250x21mm, 5µm), Eluent: n-Hexane(A) and MeOH : IPA 1:1 (B), Flow: 15 mL/min, Isocratic: 90(A):10(B), diluent EtOH : DCM (1:1, 2 mL), Injection volume-0.5 mL, run
10 time 14 min, to get Peak-1 (7.7 mg) Peak-2: (7.8 mg) as colourless gummy oil; H-NMR (DMSO-d₆, 400 MHz): δ 0.90-0.94 (m, 2 H), 1.15-1.23 (m, 2 H), 1.49 (s, 3 H), 2.61-2.72 (m, 2 H), 4.76 (q, J = 8.8 Hz, 2 H), 5.94 (s, 1 H), 6.60 (s, 1 H), 6.88 (s, 1 H), 6.99-7.02 (m, 1 H), 7.07-7.12 (m, 2 H), 7.61-7.62 (m, 1 H), 8.58 (s, 1 H), HRMS calculated for: [C₂₁H₁₉BrF₅NO₃+H-H₂O]⁺ 490.0436; found: 490.0443 (**Example 21 peak-1**), 490.0443 (**Example 21 peak-2**). Analytical Chiral HPLC: CHIRALPAK-IH (150X4.6mmX5µm) Mobile Phase: (A) n-HEXANE (B) IPA : MeOH (50:50) Isocratic: 85:15 (A:B), Flow: 1.0ml/min, Diluent: EtOH, Column Temp: 25°C, Inj. volume: 5.000, Acq. method: IH_8515_7_C-30min.amx. Peak-1 (Rt: 2.74, 100% ee) Peak-2: (Rt: 3.54, 100% ee).
20

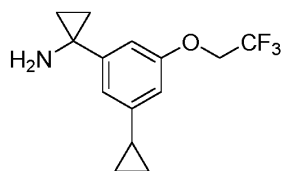
Example 22: Synthesis of N-(1-(3-cyclopropyl-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide

Synthesis of 3-cyclopropyl-5-(2,2,2-trifluoroethoxy)benzonitrile (6o): In a sealed tube charged 3-bromo-5-(2,2,2-trifluoroethoxy)benzonitrile (500 mg, 1.78 mmol) in
25 toluene : water (5:1), was added cyclopropylboronic acid (766 mg, 8.92 mmol), K₃PO₄ (1.13 g, 3.35 mmol), tricyclohexylphosphine (25.8 mg, 0.08 mmol) and palladium(II)acetate (20.3 mg, 0.08 mmol) at rt under argon atmosphere. The resulting mixture was purged under argon atmosphere for 10 min and stirred at 100 °C for 12 h. After completion of the reaction, added water and extracted with EtOAc (3 x 10 mL).

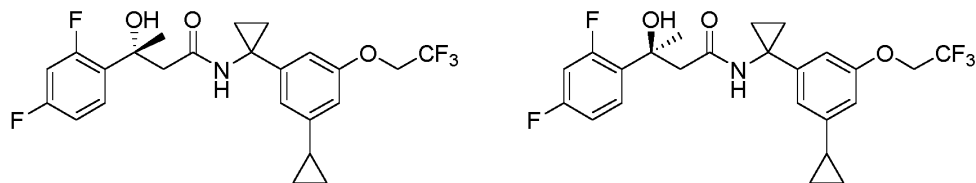
Combined all organic layers washed with brine and concentrated under reduced pressure to afford crude compound-**6o**. The crude material was purified by combiflash (12 g column, 0-10% EtOAc in Hexane as eluent) to afford pure compound-**6o** as off white solid (300 mg, 80%); H-NMR (DMSO- d_6 , 400 MHz): δ 0.78-0.79 (m, 2 H), 0.97-0.99 (m, 2 H), 1.96 (bs, 1 H), 4.84 (q, J = 8.8 Hz, 2 H), 7.09 (s, 1 H), 7.24 (s, 1 H), 7.32 (s, 1 H).



Synthesis of 1-(3-cyclopropyl-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropane-1-amine (7o): Compound-**6o** (300 mg, 1.24 mmol) converted to compound-**7o** (150 mg, 38%) using general procedure for compound-**7**. After basification using NaHCO_3 , compound extracted as free base, m/z (LC-MS): 272.0 $[\text{M}+\text{H}]^+$.



Example 22: Synthesis of N-(1-(3-cyclopropyl-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide (Example 22 peak-1 & Example 22 peak-2):

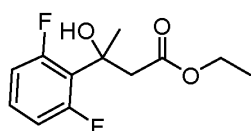


Following general procedure for compound-**8**, compound-**4d** (100 mg, 0.368 mmol) converted to **Example 22** (40 mg, 35%) as off white solid using compound-**7o**. The enantiomers were separated using Chiral prep HPLC, Column: (Chiralpak IH, 250x21mm, 5 μ m), Eluent: n-Hexane(A) and EtOH : IPA 1:1 (B), Flow: 15 mL/min, Isocratic: 80(A):20(B), diluent EtOH : DCM (3:1, 5 mL), Injection volume-0.2 mL, run time 15 min, to get Peak-1 (13.2 mg) Peak-2: (10 mg) as colourless gummy oil; H-NMR (DMSO- d_6 , 400 MHz): δ 0.28-0.37 (m, 2 H), 0.88-0.92 (m, 4 H), 1.09 (s, 1 H), 1.48 (s, 3 H), 1.73-1.79 (m, 1 H), 2.51-2.76 (m, 3 H), 4.68 (d, J= 8.8 Hz, 2 H), 6.02 (s, 1 H), 6.38-6.45 (m, 3 H), 6.98-7.03 (m, 1 H), 7.10-7.16 (m, 1 H), 7.57-7.69 (m, 1 H), 8.56 (s, 1 H), HRMS calculated for: $[\text{C}_{24}\text{H}_{24}\text{F}_5\text{NO}_3+\text{H}]^+$ 470.1749; found: 470.1757 (**Example 22**)

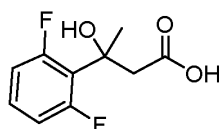
peak-1), 470.1755 (**Example 22 peak-2**). Analytical chiral HPLC: CHIRALPAK-IH (150X4.6mmX5μm) Mobile Phase: (A) n-HEXANE (B) IPA: MeOH (50:50) Isocratic: 85:15(A:B) Flow: 1.0ml/min Diluent: EtOH, Column Temp: 25°C, Inj. volume: 5.000, Acq. method: IH_8515_7_C-15min.amx. Peak-1 (Rt: 2.612, 100% ee) Peak-2: (Rt: 3.426, 100% ee).

Example 23: Synthesis of N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,6-difluorophenyl)-3-hydroxybutanamide

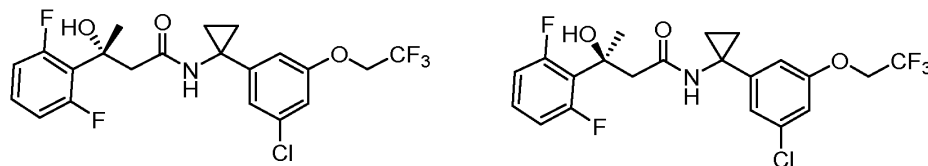
Synthesis of ethyl 3-(2,6-difluorophenyl)-3-hydroxybutanoate (3j): 1-(2,6-difluorophenyl)ethan-1-one (1 g, 6.40 mmol) converted to compound-3j (**1.7 g, Crude**) using general procedure A for compound-3, used for the next step without purification. H-NMR (DMSO-d₆, 400 MHz): δ 1.16 (t, J = 7.2, 3 H), 1.69 (s, 3 H), 2.77 (d, J = 15 Hz, 1 H), 3.25 (d, J = 15 Hz, 1 H), 4.06-4.11 (q, J = 7.2 Hz, 2 H), 4.56 (bs, 1 H), 6.88-6.81 (m, 2 H), 6.97-6.95 (m, 1 H).



Synthesis of 3-(2,6-difluorophenyl)-3-hydroxybutanoic acid (4j): Compound-3j (1.5 g, 6.14 mmol) converted to compound-4j (1 g, 76.92%) as yellow gummy using general procedure for compound-4, H-NMR (CDCl₃, 400 MHz): δ 1.70 (s, 3 H), 2.85 (d, J = 16.8 Hz, 1 H), 3.30 (d, J = 16.8 Hz, 1 H), 6.88-6.83 (m, 2 H), 7.26-7.18 (m, 1 H).



Example 23: Synthesis of N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,6-difluorophenyl)-3-hydroxybutanamide (Example 23 peak-1 & Example 23 peak-2):



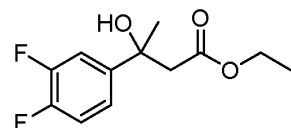
Following general procedure for compound-8, compound-4j (0.2 g, 0.927 mmol) converted to **Example 23** (180 mg, 42%) using compound-7b. The enantiomers were separated using Chiral prep HPLC, Column: (Chiralpak IH, 250mmX21 mm, 5μm), Eluent: n-Hexane(A) and IPA : EtOH 1:1 (B), Flow: 15 mL/min, Isocratic: 90(A):10(B),

diluent EtOH : DCM, 1:1, 3.5 mL, Injection vol, 0.4 mL, run time 20 min, to get Peak-1 (58.18 mg), Peak-2: (62.05 mg); ^1H NMR (400 MHz, CDCl_3) δ ppm 0.87-1.01 (m, 1 H), 1.10-1.22 (m, 3 H), 1.67 (s, 3 H), 2.71 (d, $J = 15.11$ Hz, 1 H), 3.06 (d, $J = 15.11$ Hz, 1 H), 4.27 (q, $J = 8.07$ Hz, 2 H), 4.94 (bs, 1 H), 6.45 (bs, 1 H), 6.63-6.64 (m, 1 H), 6.70-6.73 (m, 2 H), 6.80-6.86 (m, 2 H), 7.13-7.20 (m, 1 H), HRMS calculated for: $[\text{C}_{21}\text{H}_{19}\text{ClF}_5\text{NO}_3 + \text{H}]^+$ 464.1052; found: 464.1055 (**Example 23 peak-1**), 464.1067 (**Example 23 peak-2**). Analytical Chiral HPLC: CHIRALPAK-IH (150X4.6mmX5 μm) Mobile Phase: (A) n-HEXANE (B) IPA : EtOH (50:50) Isocratic : 85:15 (A:B) Flow : 1.0ml/min Diluent : EtOH, Column Temp : 25°C, Inj. volume: 5.000, Acq. method: IH_8515_7_C-30min.amx. Peak-1 (Rt: 4.961, 100% ee) Peak-2: (Rt: 11.357, 100% ee).

Example 24: Synthesis of N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(3,4-difluorophenyl)-3-hydroxybutanamide

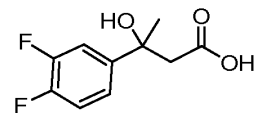
Synthesis of Ethyl 3-(3,4-difluorophenyl)-3-hydroxybutanoate (3k):

1-(3,4-difluorophenyl)ethan-1-one (1 g, 6.40 mmol) converted to compound-**3k** (0.5 g, 33.33%) as colourless gummy using general procedure A for compound-**3**, ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 1.04 (q, $J = 7.2$ Hz, 3 H), 1.51 (s, 3 H), 2.77 (dd, $J = 14$ Hz, 2 H), 3.92 (q, $J = 7.2$ Hz, 2 H), 5.44 (bs, 1 H), 7.36-7.24 (m, 2 H), 7.48-7.42 (m, 1 H).

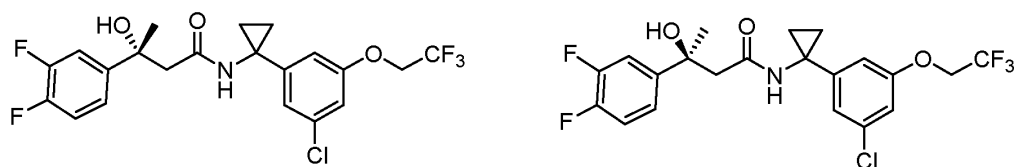


Synthesis of 3-(3,4-difluorophenyl)-3-hydroxybutanoic acid (4k):

Compound-**3k** (0.5 g, 2.047 mmol) converted to compound-**4k** (0.4 g, 90.47%) as pale reddish gummy using general procedure for compound-**4**, ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 1.47 (s, 3 H), 2.67 (dd, $J = 14$ Hz, 2 H), 7.30-7.25 (m, 2 H), 7.47-7.40 (m, 1 H).



Example 24: Synthesis of N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(3,4-difluorophenyl)-3-hydroxybutanamide (Example 24 peak-1 & Example 24 peak-2):

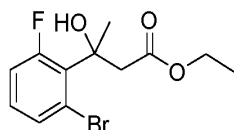


Following general procedure for compound-8, compound-4k (0.15 g, 0.693 mmol) converted to **Example 24** (190 mg, 59.37%) using compound-7b. The enantiomers were separated using Chiral prep HPLC, Column: (Chiralpak IH, 150mmX4.6 mm, 5 μ m), Eluent: n-Hexane(A) and IPA : MeOH 1:1 (B), Flow: 1 mL/min, Isocratic: 90(A):10(B), diluent EtOH, Injection vol, 5 mL, run time 15 min, to get Peak-1 (75.8 mg), Peak-2: (80.5 mg); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.94-0.97 (m, 2 H), 1.17-1.20 (m, 2 H), 1.45 (s, 3 H), 2.56 (d, J = 14 Hz, 1 H), 2.70 (d, J = 14 Hz, 1 H), 4.75 (q, J = 8.8 Hz, 2 H), 5.75 (s, 1 H), 6.53-6.54 (m, 1 H), 6.64-6.65 (m, 1 H), 6.94-6.95 (m, 1 H), 7.23-7.34 (m, 2 H), 7.40-7.46 (m, 1 H), 8.52 (bs, 1 H), HRMS calculated for: [C₂₁H₁₉ClF₅NO₃+H-H₂O]⁺ 446.0941; found: 446.0955 (**Example 24 peak-1**), 446.0957 (**Example 24 peak-2**). Analytical Chiral HPLC: CHIRALPAK-IH (150X4.6mmX5 μ m) Mobile Phase: (A) n-HEXANE (B) IPA: MeOH (50:50) Isocratic: 90:10 (A:B) Flow : 1.0ml/min Diluent : EtOH, Column Temp : 25 °C, Inj. volume: 5.000, Peak-1 (Rt: 3.613, 100% ee) Peak-2: (Rt: 5.134, 100% ee).

Example 25: Synthesis of 3-(2-bromo-6-fluorophenyl)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl) cyclopropyl)-3-hydroxybutanamide

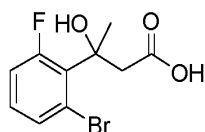
Synthesis of Ethyl 3-(2-bromo-6-fluorophenyl)-3-hydroxybutanoate (3I)

1-(2-bromo-6-fluorophenyl)ethan-1-one (0.5 g, 2.30 mmol) converted to compound-3I (0.36 g, 51.30%) using general procedure A used for compound-3, m/z (LC-MS): 288.90 [M-17+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.16 (t, J = 7.2 Hz, 3 H), 1.57 (s, 3 H), 2.79 (dd, J = 4.4 Hz & 16.4 Hz, 1 H), 2.83 (dd, J = 4.4 Hz & 16.4 Hz, 1 H), 4.09 (q, J = 7.2 Hz, 2 H), 4.50 (bs, 1 H), 6.94-7.07 (m, 2 H), 7.43-7.45 (m, 1 H).

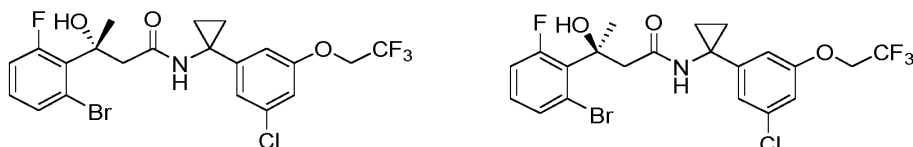


Synthesis of 3-(2-bromo-6-fluorophenyl)-3-hydroxybutanoic acid (4I):

Compound-3I (0.54 g, 1.769 mmol) hydrolysed to get 4I (0.450 g, 91.83%) using general procedure used for compound-4, m/z (LC-MS): 274.95 [M-H]⁺.



Example 25: Synthesis of 3-(2-bromo-6-fluorophenyl)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl) cyclopropyl)-3-hydroxybutanamide (Example 25 peak-1 & Example 25 peak-2):



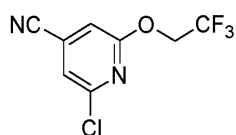
5
Following general procedure used for compound-8, compound-4I (0.45 g, 1.62 mmol) converted to **Example 25** (0.68 g, 59.37%) using compound-7b. The enantiomers were separated on 30 mg scale using Chiral SFC, Column: (CHIRALPAK-IG, 4.6 MM x150MM x 5µm), Co-Solvent Name : IPA : EtOH : MeOH (1:1:1); Flow: 3 mL/min, Injection vol, 15 µl, Outlet Pressure: 100 bar; Temperature : 40 °C to get Peak-1 (8.8 mg), Peak-2: (8.2 mg); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.15-1.18 (m, 2 H), 1.21-1.33 (m, 2 H), 1.60 (s, 3 H), 2.70-2.74 (dd, J = 2.8 Hz & 14.8 Hz, 1 H), 3.07-3.02 (dd, J = 2.8 Hz & 14.8 Hz, 1 H), 4.75 (q, J = 8.8 Hz, 2 H), 5.70 (s, 1 H), 6.58 (bs, 1 H), 6.74 (s, 1 H), 7.10-7.19 (m, 2 H), 7.43-7.45 (m, 2 H), 8.52 (s, 1 H), HRMS calculated for: 10
[C₂₁H₁₉BrClF₄NO₃+H]⁺ 524.0251; found: 524.0243 (**Example 25 peak-1**), 524.0260 (**Example 25 peak-2**). Analytical Chiral HPLC: (CHIRALPAK-IG, 4.6 MM x150MM x 5µm), Co-Solvent Name : IPA : EtOH : MeOH (1 : 1 : 1); Flow: 3 mL/min, Injection vol, 15 µl, Outlet Pressure: 100 bar; Temperature : 40 °C Acq. method: C:\Pic
Solution\Methode\Analytical\3-20-30Min.met. Peak-1 (Rt: 1.86, 100% ee) Peak-2: (Rt: 15
2.51, 100% ee). 20

Example 26: Synthesis of N-(1-(2-chloro-6-(2,2,2-trifluoroethoxy)pyridin-4-yl)cyclopropyl)-3-(2,6-difluorophenyl) -3-hydroxybutanamide

Synthesis of 2-chloro-6-(2,2,2-trifluoroethoxy)isonicotinonitrile (6p):

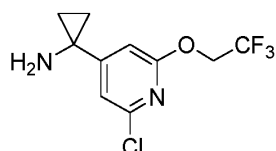
25 To a stirred solution 2,6-dichloroisonicotinonitrile (1 g, 5.7803 mmol) in acetonitrile (10 vol) added K₂CO₃ (0.798 g, 5.7803 mmol) and 2,2,2-trifluoroethanol (0.34 mL, 4.6242 mmol). Resulting reaction mixture stirred at room temperature for overnight and quenched with water. Reaction mixture was extracted with EtOAc (3 X 10 vol). Organic layer dried over anhydrous Na₂SO₄ and concentrated under high *vacuo* to get crude compound which was purified using combi flash chromatography (5 to 10% EtOAc in 30

Hexane) to get pure enough compound-**6p** (600 mg, 44.11%) as off white solid, ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 5.05 (q, J = 8.8 Hz, 2 H), 7.6 (s, 1 H), 7.9 (s, 1 H).

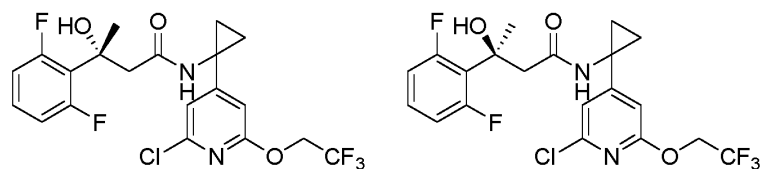


Synthesis of 1-(2-chloro-6-(2,2,2-trifluoroethoxy)pyridin-4-yl)cyclopropan-1-amine (7p):

Compound-**6p** (0.4 g, 1.60 mmol) converted to compound-**7p** (60 mg, 26.66%) using general procedure used for compound-**7**. After basification using NaHCO₃, compound extracted as free base. m/z (LC-MS): 266.9 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.07-1.09 (m, 4 H), 4.94 (q, J = 9.2 Hz, 2 H), 6.87 (d, J = 1.2 Hz, 1 H), 7.07 (d, J = 1.2 Hz, 1 H).



Example 26: Synthesis of N-(1-(2-chloro-6-(2,2,2-trifluoroethoxy)pyridin-4-yl)cyclopropyl)-3-(2,6-difluorophenyl)-3-hydroxybutanamide (Example 26 peak-1 & Example 26 peak-2):



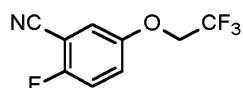
Following general procedure for compound-**8**, compound-**4k** (0.48 g, 0.22 mmol) converted to Example 26 (70 mg, 47.61%) using compound-**7p**. The enantiomers were separated using Chiral prep HPLC, Column Column: CHIRALPAK IH, 250mmX20mm, 5μm, Eluent: n-Hexane(A) and IPA:MeOH 1:1 (B), Flow: 15 ml/min, Isocratic: 90(A):10(B), diluent EtOH:DCM, 1:1, 3 mL, Injection vol, 0.5 mL, run time 20 min, to get Peak-1 (14.6 mg, Rt: 4.315) and Peak-2 (13.1 mg, Rt: 5.080). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.02-1.06 (m, 2 H), 1.23-1.34 (m, 2 H), 1.63 (s, 3 H), 2.74 (d, J = 14.4 Hz, 1 H), 2.86 (d, J = 14.4 Hz, 1 H), 4.92 (q, J = 8.95 Hz, 2 H), 5.72 (bs, 1 H), 6.45 (d, J = 1 Hz, 1 H), 6.76 (d, J = 1 Hz, 1 H), 6.96-6.99 (m, 2 H), 7.26-7.32 (m, 1 H), 8.72 (s, 1 H), HRMS calculated for: [C₂₀H₁₈ClF₅N₂O₃+H]⁺ 465.1004; found: 465.1011 (Example 26 peak-1), found: 465.1014 (Example 26 peak-2). Analytical Chiral HPLC: CHIRALPAK-IH (150X4.6mmX5μm) Mobile Phase: (A) n-HEXANE (B) IPA :

METHANOL (50:50), Isocratic : 90:10 (A:B) Flow : 1.0ml/min Diluent : EtOH, Column Temp : 25°C, Inj. volume: 5.000, Peak-1 (Rt: 4.315, 100% ee) Peak-2: (Rt: 5.080, 100% ee).

5 Example 27: Synthesis of 3-(2,4-difluorophenyl)-N-(1-(2-fluoro-5-(2,2,2-trifluoroethoxy)phenyl) cyclopropyl)-3-hydroxybutanamide

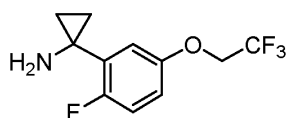
Synthesis of 2-fluoro-5-(2,2,2-trifluoroethoxy)benzonitrile (6q):

2-fluoro-5-hydroxybenzonitrile (300 mg g, 0.365 mmol mmol) converted to compound-**6q** (380 mg, 79.33%) as white crystalline solid using general procedure used for compound-**6**. m/z (LC-MS): 250.05 [M+H]⁺. H NMR (300 MHz, DMSO-d₆) δ ppm 4.85 (q, J = 8.7 Hz, 2 H), 7.48-7.53 (m, 2 H), 7.68-7.71 (m, 1 H).

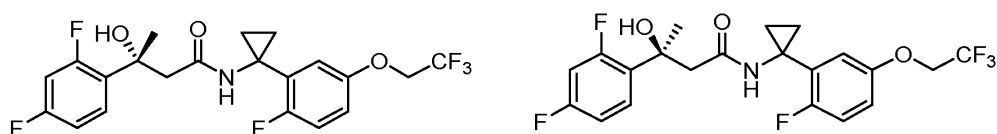


Synthesis of 1-(2-fluoro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropan-1-amine (7q):

15 Compound-**6q** (0.08 g, 0.365 mmol mmol) converted to compound-**7q** (45 mg, 7.9%) using general procedure used for compound-**7**. After basification using NaHCO₃, compound extracted as free base. m/z (LC-MS): 250.05 [M+H]⁺.



20 **Example 27: Synthesis of 3-(2,4-difluorophenyl)-N-(1-(2-fluoro-5-(2,2,2-trifluoroethoxy)phenyl) cyclopropyl)-3-hydroxybutanamide (Example 27 peak-1 & Example 27 peak-2):**



25 Following general procedure for compound-**8**, compound-**4d** (0.043 g, 0.198 mmol) converted to **Example 27** (20 mg, 22%) using compound-**7q**. The enantiomers were separated using Chiral prep HPLC, Column: CHIRALPAK-IG(250X4.6mmX5μm), Mobile Phase: (A) n-HEXANE (B)IPA : METHANOL(50:50), Flow: 15 mL/min, Isocratic: 93 (A):07 (B), diluent: EtOH : DCM, 1:1, 2 mL, Injection vol: 0.35 mL, run time 14 min, to get Peak-1 (1.5 mg), Peak-2: (2.1 mg); H NMR (400 MHz, CDCl₃) δ ppm

0.83-0.96 (m, 2 H), 0.92-1.02 (m, 2 H), 1.47 (s, 3 H), 2.55 (d, J = 14.4, 1 H), 2.80 (d, J = 14.4, 1 H), 4.28 (q, J = 6.8 Hz, 2 H), 5.39 (s, 1 H), 6.28 (bs, 1 H), 6.59-6.67 (m, 2 H), 6.72-6.76 (m, 1 H), 6.82-6.92 (m, 2 H), 7.46-7.53 (m, 1 H). HRMS calculated for:

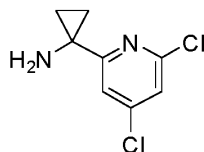
$[C_{21}H_{19}F_6NO_3 + H - H_2O]^+$ 430.1242; found: 430.1246 (**Example 27 peak-1**), 430.1245

- 5 (**Example 27 peak-2**). Analytical Chiral HPLC: CHIRALPAK-IG (150X4.6mmX5 μ m), Mobile Phase: (A) n-HEXANE (B) IPA : METHANOL(50:50), Isocratic : 95:05 (A:B) Flow : 1.0ml/min Diluent : EtOH, Column Temp : 25°C, Inj. volume: 5.000, Peak-1 (Rt: 5.00, 100% ee) Peak-2: (Rt: 7.60, 100% ee).

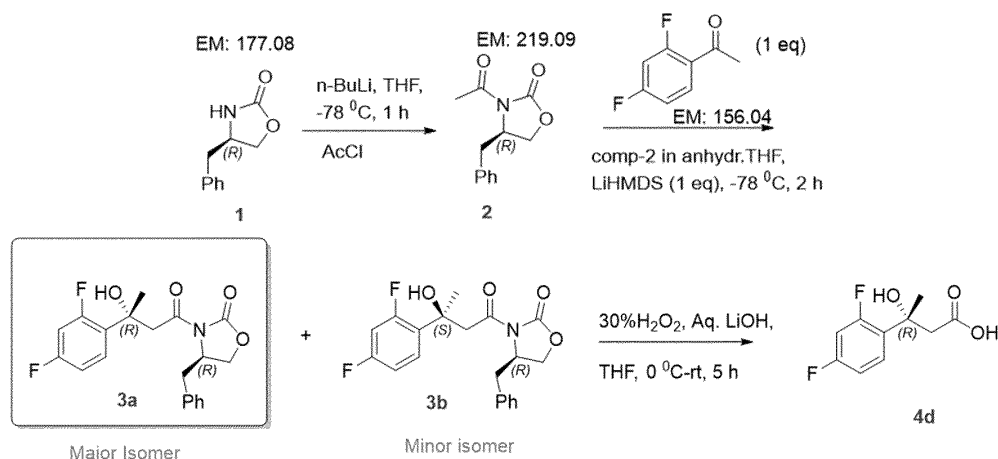
- 10 Example 28: Synthesis of (R)-N-(1-(4,6-dichloropyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide

Synthesis of 1-(4,6-dichloropyridin-2-yl)cyclopropan-1-amine (7r):

4,6-dichloropicolinonitrile (0.5 g, 2.890 mmol mmol) converted to compound-7r (45 mg, 7.9%) using general procedure used for compound-7. After basification using NaHCO₃, compound extracted as free base. m/z (LC-MS): 202.95 [M+H]⁺.



Synthesis of (R)-3-(2,4-difluorophenyl)-3-hydroxybutanoic acid (R-4d)



- 20

Synthesis of (R)-3-acetyl-4-benzylloxazolidin-2-one (2):

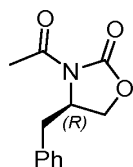
To a stirred solution of (R)-4-benzylloxazolidin-2-one (50 g, 1.0 eq, 282.16 mmol) in anhydrous tetrahydrofuran (10 vol) was stirred for 10 minutes. The reaction mixture was cooled to -78°C and was added n-Butyllithium (2.5 M in Hexane) (113.99 mL, 1.01

- 25

eq, 284.98 mmol) dropwise (30 min) and the reaction mixture was stirred for about 30 minutes. A solution of Acetyl chloride (22.29 mL, 1.1 eq, 310.38 mmol) was added dropwise (15 min) at the same temperature. Then the reaction mixture was warmed to room temperature and stirred for further 1 h. The resulting mixture was monitored by

5 TLC and LCMS. After completion of the reaction quenched with sat. NH_4Cl solution (2 vol) was extracted with EtOAc (3 X 10 vol). The organic layer was washed with water (3 x 100 mL) and brine solution (1 X 10 vol). Resulting organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give off white product (55.6 g, 253.18 mmol, 89.88%). m/z (LC-MS): 220.15 $[\text{M}+\text{H}]^+$; ^1H NMR (300 MHz,

10 CDCl_3) δ ppm 2.55 (s, 3 H), 2.73-2.81 (m, 1 H), 3.27-3.32 (m, 1 H), 4.17-4.23 (m, 2 H), 4.64-4.69 (m, 1 H), 7.19-7.21 (m, 2 H), 7.25-7.36 (m, 3 H).



Synthesis of (R)-4-benzyl-3-((R)-3-(2,4-difluorophenyl)-3-hydroxybutanoyl)oxazolidin-2-one (3a):

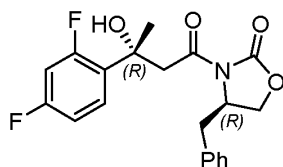
15 To a stirred solution of Lithium bis(trimethylsilyl)amide (228.06 mL, 228.06 mmol, 1eq) under argon atmosphere at -78°C was added compound-2 (50 g, 228.06 mmol, 1 eq) in anhydrous THF (10 vol) dropwise for 45 min. Then reaction mixture was stirred for 2 h at -78°C followed by addition of 2, 4-Difluoro acetophenone (32.37 mL, 228.06 mmol, 1 eq) in anhydrous THF (6 vol) at -78°C for 30 min. Then reaction mixture was stirred

20 for 1 h at -78°C . The resulting mixture was monitored by TLC and LCMS. After completion of the reaction was quenched with 0.5M HCl (2 vol) at -78°C , temperature was slowly raised to rt (30 min) and extracted with ethyl acetate (3 x 10 vol), Combined all organic layers washed with water (2 x 10 vol) and brine solution (2 x vol) and concentrated under vacuo to afford crude material. To obtain a clear solution, the crude

25 material was recrystallized in a 1: 1 ratio of IPA and t-Butanol (10 vol) and heated at 50°C h for 10 minutes. The resulting solution was left for 24 hours to form crystals. It was filtered through a Buchner funnel and washed with 1 vol of 1: 1 IPA and t-Butanol to obtain pure (R)-4-benzyl-3-((R)-3-(2,4-difluorophenyl)-3-hydroxybutanoyl)oxazolidin-2-one **3a** (19.1 g, 22.31%). Filtrate contains a mixture of diastereomers (44 g crude,

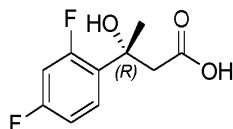
30 ~1:1 ratio), m/z (LC-MS): 358.1 $[\text{M}-17]^+$; Chiral HPLC: 99.41%, R_t = 11.70 min, ^1H NMR (300 MHz, CDCl_3) δ ppm 1.63 (s, 3 H), 2.56-2.63 (m, 1 H), 2.96 (d, J = 13.2 Hz, 1 H),

3.28 (d, $J = 17.1$ Hz, 1 H), 4.08-4.23 (m, 3 H), 4.60-4.63 (m, 2 H), 6.79 (t, $J = 9$ Hz, 1 H), 6.89 (t, $J = 7.8$ Hz, 1 H), 7.04-7.05 (m, 2 H), 7.27-7.29 (m, 3 H), 7.67-7.75 (m, 1 H).

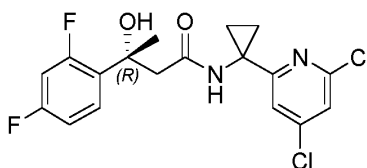


Synthesis of (R)-3-(2,4-difluorophenyl)-3-hydroxybutanoic acid (R-4d):

- 5 To a solution of **3a** (9 g, 23.97 mmol, 1 eq) in Tetrahydrofuran and Water (4 : 1, 15 vol) was added Hydrogen peroxide (9.8 mL, 95.90 mmol, 4 eq) , The reaction mixture was cooled to 0°C and added Lithium Hydroxide Monohydrate (4.02 g, 95.90 mmol, 4 eq). The resulting mixture was stirred at RT for 2h. Progress reaction mass was monitored by TLC and LCMS. After completion of reaction was diluted with water (3 x 10 vol) and
- 10 extracted with Dichloromethane (5 x 3 vol) to remove biproduct impurities. Aqueous was acidified by 1N HCl and extracted with Dichloromethane (4 x 20 vol). Combined all organic layer washed with water (3 x 2 vol), and brine (1 x 5 vol) and concentrated by reduce pressure to afford crude title compound as pale-yellow gummy (5 g, 96.52%) was used to next step without any purification. m/z (LC-MS): 215.1 $[M-1]^+$; Chiral HPLC: 11.70 min, 93.12%; 1H NMR (300 MHz, DMSO- d_6) δ ppm 1.52 (s, 3 H), 2.68-2.78 (m, 2 H), 5.56 (bs, 1 H), 7.01-7.16 (m, 2 H), 7.57-7.66 (m, 1 H), 12.10 (bs, 1 H).
- 15



Example 28: Synthesis of (R)-N-(1-(4,6-dichloropyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide:



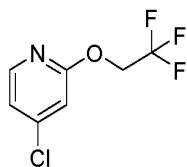
- 20 Following general procedure for compound-**8**, enantiopure compound-**4d** (0.047 g, 0.221 mmol) converted to **Example 28** (3 mg, 5.05%) using compound-**7r**. It was purified using prep HPLC Column: X SELECT (250mmx20.0mm), 5.0 μ , Eluent: 0.1% $HCOOH$ in water (A) and ACN (B), Flow: 15 ml/min, Gradient Programmer: Time
- 25 (%B): 0/30, 2/40, 6/75, 1H NMR (400 MHz, DMSO- d_6) δ ppm 1.02-1.09 (m, 2 H), 1.32-1.36 (m, 2 H), 1.52 (s, 3 H), 2.65 (d, $J = 14.4$ Hz, 1 H), 2.70 (d, $J = 14.4$ Hz, 1 H), 5.97 (s, 1 H), 7.01-7.06 (m, 1 H), 7.14-7.20 (m, 2 H), 7.49 (d, $J = 1.6$ Hz, 1 H), 7.62-7.69 (m,

1 H), 8.69 (bs, 1 H), HRMS calculated for: $[C_{18}H_{16}Cl_2F_2N_2O_2+H]^+$ 401.0635; found: 401.0644, Analytical Chiral HPLC: Column: REGIS(S,S) WHELK-01 (250X4.6mmX5 μ m), Mobile Phase: (A) n-HEXANE (B) 0.1% HCOOH IN ETHANOL : METHANOL (80:20), Isocratic : 70:30 (A:B), Flow : 1.0ml/min, Diluent : EtOH, Column Temp : 25°C, Inj. volume: 10, (Rt: 4.40, 97.11%)

Example 29: Synthesis of (R)-N-(1-(4-chloro-6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide

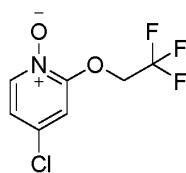
Synthesis of 4-chloro-2-(2,2,2-trifluoroethoxy)pyridine:

10 To a stirred suspension of sodium hydride (3.04 g, 76.0244 mmol) in anhydrous DMF (80 mL) at 0 °C added a solution of 2,2,2-trifluoroethan-1-ol (7.6055 g, 76.0244 mmol) in anhydrous DMF (10 mL). After stirring at 0 °C for 15 min added a solution of 4-chloro-2-fluoropyridine (10 g, 76.0244 mmol) in anhydrous DMF (20 mL). Resulting reaction mixture stirred at room temperature overnight. Reaction was quenched using
15 sat. solution of ammonium chloride and extracted using EtOAc (3 x 200 mL). Combined Organic layer given brine wash and dried over anhydrous Na_2SO_4 . Organic layer removed under *vacuo* to get crude product which was purified by flash chromatography (EtOAc : Hexane 5 : 95) as eluent to get 4-chloro-2-(2,2,2-trifluoroethoxy)pyridine (10.2 g, 63.43%) as colourless liquid; m/z (LC-MS): 211.95 $[M+H]^+$.



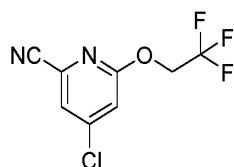
Synthesis of 4-chloro-2-(2,2,2-trifluoroethoxy) pyridine 1-oxide:

To a stirred solution of 4-chloro-2-(2,2,2-trifluoroethoxy) pyridine (10.2 g, 48.211 mmol) in TFA (42 mL) at 0 °C was added Hydrogen peroxide (22 mL). Reaction mixture was stirred for overnight at 80 °C. The reaction mixture was concentrated under *vacuo*
25 and diluted with water and cooled to 0 °C, then slowly basified with ammonium hydroxide solution till pH = 7-8. The resulting solution was extracted with DCM. The combined organic layers were washed with brine solution, dried over Na_2SO_4 and concentrated under *vacuo* to afford crude 4-chloro-2-(2,2,2-trifluoroethoxy) pyridine 1-oxide (7.6 g, 69.27%) as off white solid; m/z (LC-MS): 227.90 $[M+H]^+$.



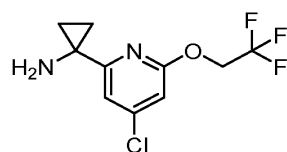
Synthesis of 4-chloro-6-(2,2,2-trifluoroethoxy) picolinonitrile:

In 250 ml seal tube a stirred solution of 4-chloro-2-(2,2,2-trifluoroethoxy) pyridine 1-oxide (7.5 g, 32.957 mmol) in Acetonitrile (70 mL) were added Trimethylsilyl cyanide (22.65 mL, 164.78 mmol), Triethylamine (22.96 mL, 164.78 mmol) at room temperature. The reaction mixture was stirred for overnight at 80 °C. the reaction mixture was concentrated under vacuo and filtered through celite bed. The filtrate was diluted with water and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine solution and concentrated under vacuo to obtain crude product which was purified by flash chromatography (EtOAc:Hexane 20:80) as eluent to get 4-chloro-6-(2,2,2-trifluoroethoxy) picolinonitrile (2.5 g, 32.09%) as yellow liquid; H-NMR (CDCl₃, 400 MHz) δ ppm 4.79 (s, 2 H), 7.15 (d, J = 1.47 Hz, 1 H), 7.41 (d, J = 1.47 Hz, 1 H).

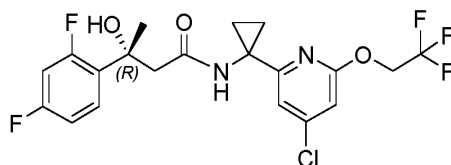


15 Synthesis of 1-(4-chloro-6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropan-1-amine (7s):

4-Chloro-6-(2,2,2-trifluoroethoxy) picolinonitrile (1.2 g, 5.072 mmol) converted to compound-7s (700 mg, 51.85%) using general procedure used for compound-7. After acidification using 4M HCl in Dioxane, compound extracted as HCl salt, m/z (LC-MS): 166.85 [M+H]⁺.



Example 29: Synthesis of (R)-N-(1-(4-chloro-6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide:

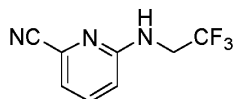


Following general procedure for compound- **8**, enantiopure compound-**4d** (0.040 g, 0.187 mmol) converted to **Example 29** (13.3 mg, 44.33%) using compound-**7s**, using prep HPLC, Column: (X SELECT (250mmx20.0mm), 5.0μ), Eluent: A= 0.1%HCOOH IN WATER, B= ACN, Flow: 15 ml/min, to get **Example 29**. H-NMR (DMSO-d6, 400 MHz): δ ppm 0.96-1.01 (m, 2 H), 1.44-1.47 (m, 2 H), 1.52 (s, 3 H), 2.68 (d, J = 14 Hz, 1 H), 2.81 (d, J = 14 Hz, 1 H), 4.9 (q, J = 9.10 Hz, 2 H), 6.01 (s, 1 H), 6.78 (d, J = 1.61 Hz, 1 H), 6.89 (d, J = 1.61 Hz, 1 H), 7.01-7.06 (m, 1 H), 7.14-7.20 (m, 1 H), 7.62-7.69 (m, 1 H), 8.65 (s, 1 H). HRMS calculated for: [C20H18ClF5N2O3+H]^+ 465.1004; found: 465.1010, Analytical Chiral HPLC: Column: REGIS(S,S) WHELK-01 (250X4.6mmX5μm), Mobile Phase: (A) n-HEXANE (B) 0.1%DEA IN EtOH : MeOH (70:30), Isocratic : 70:30 (A:B), Flow : 1.0ml/min, Diluent : EtOH, Column Temp : 25°C, Inj. volume: 5.000, (Rt: 4.08, 98.90%).

Example 30: Synthesis of 3-(2,6-difluorophenyl)-3-hydroxy-N-(1-(6-((2,2,2-trifluoroethyl)amino)pyridin-2-yl)cyclopropyl)butanamide

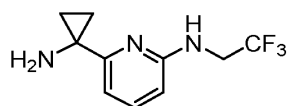
Synthesis of 6-((2,2,2-trifluoroethyl)amino)picolinonitrile:

To a stirred solution 6-fluoropicolinonitrile (1 g, 8.18 mmol, 1 eq) in DMSO (10 vol) added 2,2,2-trifluoroethylamine (0.97 mL, 9.82 mmol). Resulting reaction mixture was heated on preheated oil bath at 150 °C for 16 h. Reaction mixture was quenched using water and extracted with EtOAc (3 x 20 vol) to get crude compound. It was purified using combiflash chromatography (EtOAc : Hexane 1:3 as eluent) to get 6-((2,2,2-trifluoroethyl)amino)picolinonitrile (0.8 g, 50 %) as an off white solid ; m/z (LC-MS): 201.95 $[M+H]^+$.

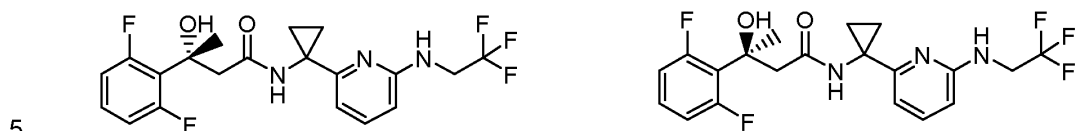


Synthesis of 6-(1-aminocyclopropyl)-N-(2,2,2-trifluoroethyl)pyridin-2-amine :

6-((2,2,2-trifluoroethyl)amino)picolinonitrile (0.4 g, 1.98 mmol) converted to get **7t** (0.2 g, 44 %) as a yellow solid, using general procedure used for compd-**7**. m/z (LC-MS): 232.15 $[M+H]^+$.



Example 30: Synthesis of 3-(2,6-difluorophenyl)-3-hydroxy-N-(1-(6-((2,2,2-trifluoroethyl) amino) pyridin-2-yl)cyclopropyl)butanamide (Example 30 peak-1 & Example 30 peak-2):

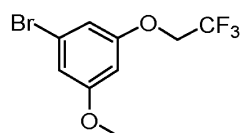


Following general procedure 8, Compound-4j (0.103 g, 0.472 mmol) converted to **Example 30** (33 mg, 17.83%) using compound-7t. The enantiomers were separated using chiral prep HPLC, Column: (Chiralpak IH, 150mmX4.6 mm, 5µm), Eluent: n-Hexane(A) and IPA : MeOH 1:1 (B), Flow: 1 mL/min, Isocratic: 90(A):10(B), diluent: EtOH, Injection vol, 5 mL, run time 20 min, to get Peak-1 (8.9 mg), Peak-2: (6.4 mg) as off white solid, ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 0.81-0.86 (m, 2 H), 1.23-1.35 (m, 2 H), 1.63 (s, 3 H), 2.69 (d, J = 14 Hz, 1 H), 2.9 (d, J = 14 Hz, 1 H), 3.98-4.05 (m, 2 H), 5.75 (s, 1 H), 5.98 (d, J = 7.6 Hz, 1 H), 6.27 (d, J = 7.6 Hz, 1 H), 6.95-7.03 (m, 3 H), 7.07-7.12 (m, 1 H), 7.33-7.38 (m, 1 H), 8.66 (s, 1 H). HRMS : m/z (LC-MS): 430.05 [M+H]⁺. HRMS calculated for: [C₂₀H₂₀F₅N₃O₂+H]⁺ 430.1554; found: 430.1554 (**Example 30 peak-1**), 430.1558 (**Example 30 peak-2**). Analytical Chiral HPLC: CHIRALPAK-IH (150X4.6mmX5µm) Mobile Phase: (A) n-HEXANE (B) IPA : MeOH (50:50) Isocratic : 85:15 (A:B) Flow : 1.0ml/min Diluent : EtOH, Column Temp : 25°C, Inj. volume: 12.000, . Peak-1 (Rt: 9.549, 100% ee) Peak-2: (Rt: 12.546, 100% ee).

Example 31: Synthesis of 3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(3-methoxy-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)butanamide

Synthesis of 1-bromo-3-methoxy-5-(2,2,2-trifluoroethoxy)benzene:

3-bromo-5-methoxyphenol (1 g, 4.92 mmol) converted to 1-bromo-3-methoxy-5-(2,2,2-trifluoroethoxy)benzene (1.6 g, Crude) using general procedure for compound-6. H-NMR (CDCl₃, 300 MHz): δ 3.77 (s, 3 H), 4.30 (q, J = 8.7 Hz, 2 H), 6.42 (s, 1 H), 6.67 (s, 1 H), Hz, 2 H), 6.74 (s, 1 H).

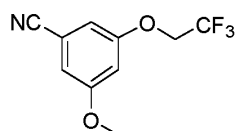


Synthesis of 3-methoxy-5-(2,2,2-trifluoroethoxy)benzonitrile (6u):

To a stirred solution of 1-bromo-3-methoxy-5-(2,2,2-trifluoroethoxy)benzene (0.7 g, 2.45 mmol, 1 eq) in DMF (10 vol) added ZnCN_2 (1.16 g, 9.82 mmol, 4 eq), Resulting reaction mixture was degassed with argon and added

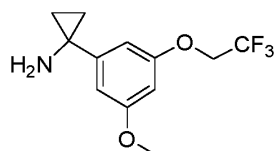
5 Tetrakis(triphenylphosphine)palladium(0) (0.28 g, 0.240.1 eq). Reaction mixture was heated at 120 °C in MW for 1h. The reaction mixture was diluted with cold water and extracted with EtOAc (3 X 5 vol) then combined layers are separated. The combined organic phases are dried over anhydrous Na_2SO_4 , concentrated under vacuum.

10 Residue purified by column chromatography using silica gel as ethyl acetate and hexane solvent system to afford title compound **6u** as off white solid. H-NMR (DMSO-d_6 , 300 MHz): δ 3.82 (s, 3 H), 4.36 (q, $J = 8$ Hz, 2 H), 6.72-6.71 (m, 1 H), 6.79-6.78 (m, 1 H), 6.87-6.86 (m, 1 H).

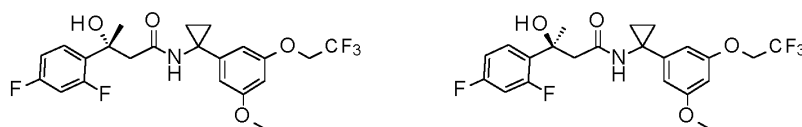


Synthesis of 1-(3-methoxy-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropan-1-amine (7u):

15 3-methoxy-5-(2,2,2-trifluoroethoxy)benzonitrile **6u** (0.75 g, 3.24 mmol) converted to compound-**7u** (0.3 g, 35.41%) using general procedure A for compound-**7**, m/z (LC-MS): 262.0 $[\text{M}+\text{H}]^+$.



20 **Example 31: Synthesis of 3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(3-methoxy-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)butanamide (Example 31 peak-1 & Example 31 peak-2):**



Following general procedure for compound-**8**, compound-**4d** (0.13 g, 0.49 mmol) converted to **Example 31** (45 mg, 20.20%) using compound-**7u**. The enantiomers were

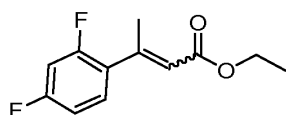
25 separated using Chiral prep HPLC, Column: (Chiralpak IH, 150mmX4.6 mm, 5 μ m), Eluent: n-Hexane(A) and IPA : MeOH 1:1 (B), Flow: 1 mL/min, Isocratic: 90(A):10(B), diluent: EtOH, Injection vol, 10 mL, run time 15 min, to get Peak-1 (10.9 mg), Peak-2: (11 mg); H NMR (400 MHz, DMSO-d_6) δ ppm 0.77-0.88 (m, 2 H), 1.01-1.15 (m, 2 H),

1.56 (s, 3 H), 2.63 (d, J = 14 Hz, 1 H), 2.92 (d, J = 14 Hz, 1 H), 3.72 (s, 3 H), 4.24 (q, J = 8.4 Hz, 2 H), 5.55 (bs, 1 H), 6.14 (bs, 1H), 6.22-6.28 (m, 3 H), 6.66-6.69 (m, 1 H), 6.79-6.84 (m, 1 H), 7.61-7.65 (m, 1 H), HRMS calculated for: $[C_{22}H_{22}F_5NO_4+H]^+$ 460.1547; found: 460.1558 (**Example 31 peak-1**), 460.1555 (**Example 31 peak-2**).

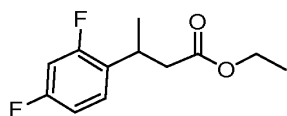
5 Analytical Chiral HPLC: CHIRALPAK-IH (150X4.6mmX5 μ m) Mobile Phase: (A) n-HEXANE (B) IPA : MeOH (50:50) Isocratic : 90:10 (A:B) Flow : 1.0ml/min Diluent : EtOH, Column Temp : 25°C, Inj. volume: 5.000, Peak-1 (Rt: 4.0, 100% ee) Peak-2: (Rt: 5.888, 100% ee).

10 Example 32: Synthesis of N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,6-difluorophenyl)-3-hydroxybutanamide

Synthesis of ethyl 3-(2,4-difluorophenyl)but-2-enoate: To a stirred suspension of sodium hydride (0.768 g, 19.214mmol) in anhydrous THF (20 mL) at 0 °C added triethyl phosphonoacetate (4.02 g, 17.93 mmol). To a resulting reaction mixture added a dropwise solution of 1-(2,4-difluorophenyl)ethan-1-one (2 g, 12.81 mmol) in anhydrous THF (20 mL) and stirred at room temperature for 30 min. Reaction was quenched using saturated solution of ammonium chloride and extracted using EtOAc (2 x 50 mL). Combined organic layer given brine wash, dried over anhydrous Na₂SO₄ and concentrated under *vacuo* to get ethyl 3-(2,4-difluorophenyl)but-2-enoate (2.4 g, 82.84%) as colourless liquid. m/z (LC-MS): 226.95 [M+H]⁺. H-NMR (CDCl₃, 300 MHz): δ 1.31 (t, J = 6.9 Hz, 3 H), 2.50 (s, 3 H), 4.21 (q, J = 6.9 Hz, 2 H), 5.96 (s, 3 H), 6.79-6.95 (m, 2 H), 7.21-7.29 (m, 1 H).

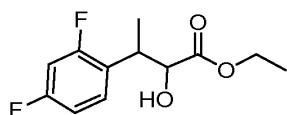


Synthesis of ethyl 3-(2,4-difluorophenyl)butanoate: To a stirred solution of ethyl 3-(2,4-difluorophenyl)but-2-enoate (500 mg, 2.210 mmol) in anhydrous EtOAc (10 mL) under nitrogen added Pd-C (10%, 0.047 g, 0.442 mmol). Resulting reaction mixture flushed with hydrogen and hydrogenated under balloon pressure of hydrogen for 16 h. After completion of the reaction, filtered through celite bed and washed with EtOAc (2 x 10 mL). The resulting filtrate was concentrated under reduced pressure to get ethyl 3-(2,4-difluorophenyl)butanoate (410 mg, 81.34%) as crude oil, m/z (LC-MS): 229.0 [M+H]⁺. H-NMR (CDCl₃, 300 MHz): δ 1.1.7 (t, J = 7.2 Hz, 3 H), 1.30 (d, J = 6.8 Hz, 3 H), 2.53-2.67 (m, 2 H), 3.51 (q, J = 7.52 Hz, 2 H), 4.08 (q, J = 7.2 Hz, 2 H), 6.73-6.83 (m, 2 H), 7.14-7.19 (m, 1 H).



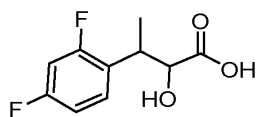
Synthesis of ethyl 3-(2,4-difluorophenyl)-2-hydroxybutanoate:

To a stirred solution of ethyl 3-(2,4-difluorophenyl)butanoate (400 mg, 1.75 mmol) in anhydrous THF (5 mL) under argon atmosphere cooled to -78 °C followed by added
 5 KHMDS (704 mg, 3.50 mmol) was added dropwise. Then reaction mixture was stirred for 30 min at -78°C followed by addition of 3-phenyl-2-(phenylsulfonyl)-1,2-oxaziridine (544 mg, 2.104 mmol) in THF at -78° C. Then reaction mixture was stirred for 2 h at -78°C. Progress of the reaction was monitored by TLC. After Completion of the reaction, it was quenched with NH₄Cl then diluted with water and extracted with EtOAc (4 X 10
 10 ml). Combined all organic layers washed with brine and concentrated under reduced pressure to afford crude material which was purified using combiflash chromatography (10% EtOAc in hexane) to get racemic trans ethyl 3-(2,4-difluorophenyl)-2-hydroxybutanoate (240 mg, 56.07%)

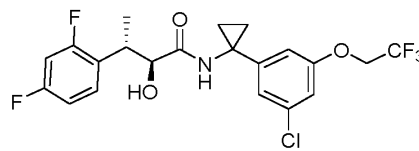
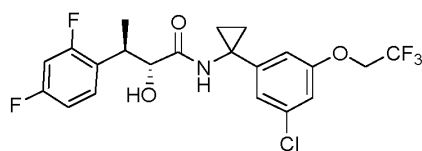


Synthesis of 3-(2,4-difluorophenyl)-2-hydroxybutanoic acid (4I):

To a stirred solution of ethyl 3-(2,4-difluorophenyl)butanoate (240 mg, 0.983 mmol) in THF : water (10 vol, 1:1) added LiOH (164.9 mg, 3.930 mmol) at 0 °C. Reaction mixture stirred at 0 °C- ethyl 3-(2,4-difluorophenyl)-2-hydroxybutanoate rt for 4 h. It was quenched with water (3 mL), extracted with EtOAc (2 x 20 mL). Organic layer dried
 20 over anhydrous Na₂SO₄ and concentrated under *vacuo* to get crude compound-4I (165 mg, 77.67%); m/z (LC-MS): 215.0 [M-H]⁺.



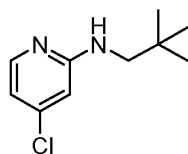
Example 32: Synthesis of N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,6-difluorophenyl)-3-hydroxybutanamide (Example 32 peak-1 & Example 32 peak-2):



Following general procedure for compound-8, compound-4I (160 mg, 0.740 mmol) converted to **Example 32** (60 mg, 17.49%) using compound-7b. The enantiomers were separated using Chiral SFC, Column: (2 X Regis (S,S) Whelk-01, 250mmX21.1mm, 5µm), Mobile Phase: CO₂(A) and IPA: EtOH:MeOH,1:1:1(B), Flow: 50 mL, Isocratic: 90(A):10(B), diluent EtOH : DCM, 1:1, 3 mL, Injection vol, 0.2 mL, run time 22 min, to get Peak-1 (22.2 mg), Peak-2: (23.8 mg); H-NMR (DMSO-d₆, 400 MHz): δ 0.89-1.05 (m, 2 H), 1.13 (d, J = 7.2 Hz, 2 H), 1.20-1.23 (m, 2 H), 3.31-3.42 (m, 1 H), 3.94-3.96 (m, 1 H), 4.77 (q, J = 8.8 Hz, 2 H), 5.72 (bs, 1 H), 6.67-6.68 (m, 1 H), 6.85-6.86 (m, 1 H), 6.98-7.03 (m, 2 H), 7.09-7.15 (m, 1 H), 7.34-7.41 (m, 1 H), 8.57 (s, 1 H), HRMS calculated for: [C₂₁H₁₉ClF₅NO₃+H]⁺ 464.1052; found: 464.1056 (**Example 32 peak-1**), 464.1050 (**Example 32 peak-2**). Analytical Chiral SFC: REGIS(S,S) WHELK-01, 4.6 MM x150MM x 5µm, Flow Rate : 3 ml/min, Co-Solvent : 10%, Co-Solvent Name : IPA: EtOH: MeOH (1:1:1), Temperature : 40 °C. Peak-1 (Rt: 5.41, 100% ee), Peak-2: (Rt: 5.8, 100% ee).

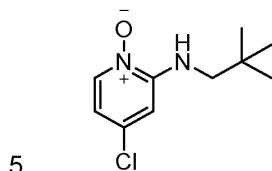
Example 33: Synthesis of (R)-N-(1-(4-chloro-6-(neopentylamino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide)

Synthesis of 4-chloro-N-neopentylpyridin-2-amine: To a sealed tube containing stirred solution of 4-chloro-2-fluoropyridine (1 g, 7.602 mmol) in DMSO (5 mL) added neopentylamine (1.325 g, 15.205 mmol). Resulting reaction mixture heated at 150 °C for overnight. After completion of the reaction it was diluted with water (10 mL) and extracted with EtOAc (3 x 20 mL), Combined all organic layers washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford crude material. It was purified further using combi flash (30% EtOAc in Hexane as eluent, 24 g column) to get pure enough 4-chloro-N-neopentylpyridin-2-amine (1.25 g, 82.78%) as yellow solid. m/z (LC-MS): 199.00 [M-H]⁺.

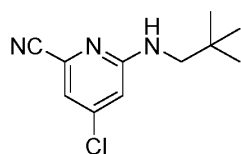


Synthesis of 4-chloro-2-(neopentylamino)pyridine 1-oxide : To a stirred solution of 4-chloro-N-neopentylpyridin-2-amine (1.2 g, 6.038 mmol) in anhydrous DCM (12 mL) at 0 °C under argon atmosphere added m-CPBA (2.083 g, 12.077 mmol). Resulting reaction mixture stirred at room temperature for 4 h. Reaction mixture was quenched

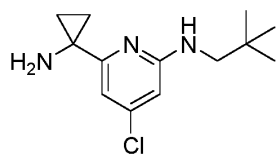
with aq. NaHCO_3 solution (PH = 8). Reaction mixture was extracted with MeOH : DCM (1:10, 2 x 15 mL). Organic layer given brine wash dried over anhydrous Na_2SO_4 and concentrated under vacuo to get crude 4-chloro-2-(neopentylamino)pyridine 1-oxide (1.9 g); m/z (LC-MS): 215.00 $[\text{M}-\text{H}]^+$.



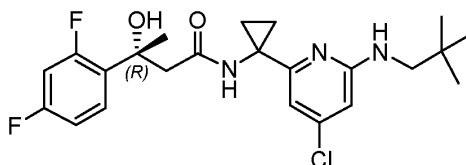
Synthesis of 4-chloro-6-(neopentylamino)picolinonitrile: To a stirred solution of 4-chloro-2-(neopentylamino)pyridine 1-oxide (1.9 g, 8.874 mmol) in acetonitrile (20 mL) added triethylamine (14.367 g, 141.984 mmol) followed by trimethylsilylcyanide (14.521 g, 141.984 mmol) at room temperature. Resulting reaction mixture stirred at 80 °C for 16 h. After completion of the reaction, solvent was removed under *vacuo*, quenched using aq. NaHCO_3 and extracted with EtOAc (3 x 20 mL). Combined organic layer given brine wash, dried over anhydrous Na_2SO_4 . Combined organic layer concentrated under *vacuo* to get crude compound which was purified using combiflash chromatography (10-20% EtOAc : Hexane as eluent) to get pure enough 4-chloro-6-(neopentylamino)picolinonitrile (152 mg, 7.67%) (m/z (LC-MS): 224.20 $[\text{M}-\text{H}]^+$).



Synthesis of 6-(1-aminocyclopropyl)-4-chloro-N-neopentylpyridin-2-amine (7v): Using general procedure for compound-7, 4-chloro-6-(neopentylamino)picolinonitrile (100 mg, 0.447 mmol) converted to crude compound-7v (60 mg, 46.15%) as brown solid. (m/z (LC-MS): 224.20 $[\text{M}-\text{H}]^+$).



Example 33: Synthesis of (R)-N-(1-(4-chloro-6-(neopentylamino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide:

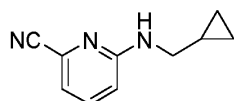


Following general procedure for compound-8, enantiopure compound-4d (40 mg, 0.185 mmol) converted to crude **Example 33** using compound-7v (47 mg, 0.185 mmol).

Crude compound purified using combiflash chromatography followed by prep HPLC, Column (X SELECT (250 mm x 20mm), 5.0 μ , Mobile Phase: A = 0.1% HCOOH in water and B = Acetonitrile, Flow: 15 mL/ min to get pure compound (4.4 mg, 5.3%); ¹H-NMR (DMSO-d₆, 400 MHz): δ 0.85 (s, 9 H), 0.86-0.90 (m, 2 H), 1.23-1.27 (m, 2 H), 1.49 (s, 3 H), 2.70 (dd, J = 13.8 Hz, 2 H), 3.02 (d, J = 6.4 Hz, 2 H), 6.06 (d, J = 1.6 Hz, 2 H), 6.30 (s, 1 H), 6.61-6.63 (m, 1 H), 6.99-7.05 (m 1 H), 7.13-7.19 (m, 1 H), 7.60-7.66 (m, 1 H), 8.56 (s, 1 H), HRMS calculated for: [C₂₃H₂₈ClF₂N₃O₂+H]⁺ 452.1916; found: 452.1926, Analytical Chiral HPLC: Column: REGIS(S,S) WHELK-01 (250X4.6mmX5 μ m), Mobile Phase: (A) n-HEXANE (B) 0.1% HCOOH IN EtOH : MeOH (80:20), Isocratic : 70:30 (A:B), Flow : 1.0ml/min, Diluent : EtOH, Column Temp : 25°C, Inj. volume: 5.000, (Rt: 4.79, 98.88%).

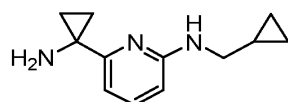
Example 34: Synthesis of (R)-N-(1-(6-((cyclopropylmethyl)amino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide

Synthesis of 6-((cyclopropylmethyl)amino)picolinonitrile: To a sealed tube containing stirred solution of 6-chloropicolinonitrile (0.5 g, 3.608 mmol) in acetonitrile (5 mL) under argon added DIPEA (0.95 mL, 5.413 mmol) and cyclopropyl methylamine (0.33 g, 4.69 mmol). Resulting reaction mixture heated at 160 °C in MW for 3 h. Reaction mixture was concentrated under *vacuo*, diluted with water and extracted with EtOAc (3 X 15 mL), Combined all organic layers dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford as crude product. Crude product was purified using combiflash (40 g column, 15% EtOAc:Hexane as eluent) to get 6-((cyclopropylmethyl)amino)picolinonitrile (270 mg, 43.2%), as off white gum. (m/z (LC-MS): 174.10 [M-H]⁺.

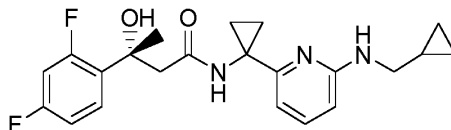


Synthesis of 6-(1-aminocyclopropyl)-N-(cyclopropylmethyl)pyridin-2-amine (7w):

Using general procedure used for compound-7, 6-((cyclopropylmethyl)amino)picolinonitrile (200 mg, 1.155 mmol) converted to compound-7w (47 mg, 20.08%) as yellow gum. (m/z (LC-MS): 204.25 [M-H]⁺.



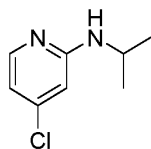
Example 34: Synthesis of (R)-N-(1-(6-((cyclopropylmethyl)amino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide:



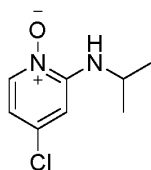
Following general procedure for compound-8, enantiopure compound-4d (50 mg, 0.2313 mmol) converted to crude **Example 34** using compound-7w (47 mg, 0.2313 mmol). Crude compound purified using combiflash chromatography followed by prep HPLC, Column (X SELECT (250 mm x 20mm), 5.0 μ , Mobile Phase: A = 0.1% HCOOH in water and B = Acetonitrile, Flow: 15 mL/min to get pure compound (3.5 mg, 5.3%); H-NMR (DMSO- d_6 , 400 MHz): δ 0.11-0.15 (m, 2 H), 0.35-0.39 (m, 2 H), 0.76-0.82 (m, 2 H), 0.95-0.98 (m, 1 H), 1.23-1.26 (m, 1 H), 1.33-1.36 (m, 1 H), 1.49 (s, 3 H), 2.58 (d, J = 14.4 Hz, 1 H), 2.83 (d, J = 14.4 Hz, 1 H), 2.98-3.00 (m, 2 H), 5.78 (d, J = 7.2 Hz, 1 H), 6.14-6.16 (m, 2 H), 6.34-6.37 (m, 1 H), 6.94-6.98 (m, 1 H), 7.03-7.07 (m, 1 H), 7.18-7.24 (m, 1 H), 7.57-7.64 (m, 1 H), 8.63 (bs, 1 H), HRMS calculated for: $[C_{22}H_{25}F_2N_3O_2+H]^+$ 402.1993; found: 402.1994.1051, Analytical Chiral HPLC: Column: CHIRALPAK-1K 250X4.6mm, 5.0 μ m, Mobile Phase: (A) D)0.1% DEA IN n-Hexane: ETHNAOL: DCM (60:20:20), Isocratic : (C) 100%;Flow : 1.0ml/min, Column Temp : 25°C, Inj. volume: 5.000, (Rt: 4.55, 99.13%).

Example 35: Synthesis of (R)-N-(1-(4-chloro-6-(isopropylamino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide

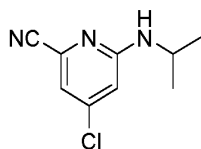
Synthesis of 4-chloro-N-neopentylpyridin-2-amine: To a sealed tube containing stirred solution of 4-chloro-2-fluoropyridine (1 g, 7.602 mmol) in DMSO (5 mL) added isopropylamine (0.654 mL, 7.602 mmol). Resulting reaction mixture heated at 150 °C for 8 h. After completion of the reaction, added water and extracted with EtOAc (3 x 20 mL), Combined all organic layers washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford crude material. It was purified further using combi flash (10% Ethyl acetate in Hexane as eluen, 24 g column) to get pure enough 4-chloro-N-neopentylpyridin-2-amine (1.1 g, 85.26%) as colourless liquid. m/z (LC-MS): 171.15 $[M-H]^+$.



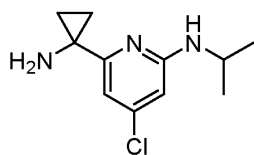
Synthesis of 4-chloro-2-(isopropylamino)pyridine 1-oxide: To a stirred solution of 4-chloro-N-neopentylpyridin-2-amine (1.1 g, 6.446 mmol) in anhydrous DCM (12 mL) at 0 °C under argon atmosphere added m-CPBA (2.225 g, 12.892 mmol). Resulting reaction mixture stirred at room temperature for 3 h. Reaction mixture was quenched with aq. NaHCO₃ solution (PH = 8). Reaction mixture was extracted with MeOH: DCM (1:10, 2 x 15 mL). Organic layer given brine wash dried over anhydrous Na₂SO₄ and concentrated under *vacuo* to get crude 4-chloro-2-(isopropylamino)pyridine 1-oxide (1.4 g); m/z (LC-MS): 187.15 [M-H]⁺.



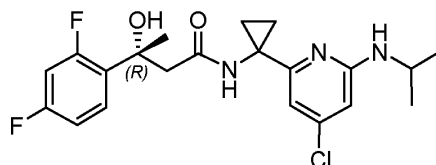
Synthesis of 4-chloro-6-(isopropylamino)picolinonitrile: To a stirred solution of 4-chloro-2-(isopropylamino)pyridine 1-oxide (0.5 g, 2.679 mmol) in acetonitrile (5 mL) added triethylamine (1.87 mL, 40.184 mmol) followed by trimethylsilylcyanide (5.35 mL, 40.184 mmol) at room temperature. Resulting reaction mixture stirred at 80 °C for 16 h. After completion of the reaction, solvent was removed under *vacuo*, quenched using aq. NaHCO₃ and extracted using EtOAc (3 x 10 mL). Combined organic layer given brine wash. Organic layer dried over anhydrous Na₂SO₄ and concentrated under *vacuo* to get crude compound which was purified using combiflash chromatography (24 g column, 0-15% EtOAc: Hexane as eluent) to get pure enough 4-chloro-6-(isopropylamino)picolinonitrile (209 mg, 39.88%) (m/z (LC-MS): 195.95 [M-H]⁺.



Synthesis of 6-(1-aminocyclopropyl)-4-chloro-N-isopropylpyridin-2-amine (7x): To a solution of 4-chloro-6-(isopropylamino)picolinonitrile (100 mg, 0.511 mmol) in anhydrous diethylether (2 mL) added Ti(OiPr)₄ (0.470 mmol, 1.533 mmol), at -78 °C followed by dropwise addition of EtMgBr (3 M in Et₂O, 0.852 mL, 2.555 mmol). Resulting reaction mixture stirred for 2 h and quenched using BF₃·Et₂O (2 eq). After overnight stirring added 1 N HCl and extracted reaction mixture with Et₂O. Aq. layer basified and extracted with Et₂O. Organic layer obtained after basification given brine wash, dried over anhydrous Na₂SO₄ and concentrated under *vacuo* to get crude compound-**7x** (100 mg, 86.95%) as orange gum. (m/z (LC-MS): 226.05 [M-H]⁺.



Example 35: Synthesis of (R)-N-(1-(4-chloro-6-(isopropylamino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide:



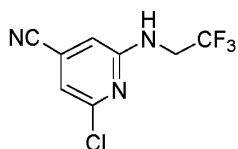
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Following general procedure for compound-8, enantiopure compound-4d (96 mg, 0.443 mmol) converted to crude **Example 35** using compound-7x (100 mg, 0.443 mmol).

Crude compound purified using combiflash chromatography followed by prep HPLC, Column (X SELECT (250 mm x 20mm), 5.0 μ , Mobile Phase: A = 0.02% NH_4OH in water and B = Acetonitrile, Flow: 15 mL/min to get pure compound (15 mg, 8%); H-NMR (DMSO-d_6 , 400 MHz): δ 0.82-0.88 (m, 2 H), 1.08 (d, J = 6.50 Hz, 6 H), 1.31-1.35 (m, 2 H), 1.51 (s, 3 H), 2.64 (d, J = 14.38 Hz, 1 H), 2.83 (d, J = 14.38 Hz, 1 H), 3.78-3.83 (m, 1 H), 6.07-6.10 (m, 2 H), 6.19 (d, J = 1.63 Hz, 1 H), 6.49 (d, J = 7.13 Hz, 1 H), 7.01-7.06 (m, 1 H), 7.14-7.17 (m, 1 H), 7.61-7.67 (m, 1 H), 8.58 (s, 1 H), HRMS calculated for: $[\text{C}_{21}\text{H}_{24}\text{ClF}_2\text{N}_3\text{O}_2+\text{H}]^+$ 424.1603; found: 424.1607, Analytical Chiral HPLC: Column: REGIS(S,S) WHELK-01 (250X4.6mmX5 μ m, Mobile Phase : (A) n-HEXANE (B) 0.1% HCOOH IN EtOH : MeOH (80:20), Isocratic : 70:30(A:B), Flow : 1.0ml/min, Diluent : EtOH, Column Temp : 25°C, Inj. volume: 5.000, (Rt: 5.03, 97.81%).

20 Example 36: (R)-N-(1-(2-chloro-6-((2,2,2-trifluoroethyl)amino)pyridin-4-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide

Synthesis of 2-chloro-6-((2,2,2-trifluoroethyl)amino)isonicotinonitrile (6y):

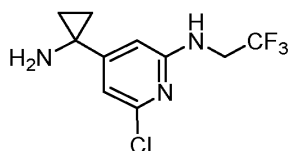


To a stirred solution of 2,6-dichloroisonicotinonitrile (1.0 g, 5.7803 mmol) in anhydrous DMSO (10 mL) was added N,N-Diisopropyl ethylamine (2.51 mL, 14.4507 mmol) and 2,2,2-Trifluoroethylamine (0.57 g, 5.7803 mmol) at room temperature. Resulting

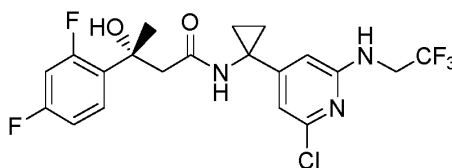
25

reaction mixture stirred at 100 °C for 16 h. Reaction was quenched using ice cold water and extracted using EtOAc (3 x 20 mL). Combined Organic layer given brine wash and dried over anhydrous Na₂SO₄. Organic layer removed under *vacuo* to get crude product which was purified by flash chromatography (EtOAc:Hexane 20:80) as eluent to get 2-chloro-6-((2,2,2-trifluoroethyl)amino)isonicotinonitrile **6y** (0.75 g, 54.17%) as brownish solid; m/z (LC-MS): 235.90 [M+H]⁺.

4-(1-aminocyclopropyl)-6-chloro-N-(2,2,2-trifluoroethyl)pyridin-2-amine (7y):
2-chloro-6-((2,2,2-trifluoroethyl)amino)isonicotinonitrile **6y** (0.1 g, 0.4245 mmol) converted to compound-**7y** (60 mg, Crude) using general procedure used for compound-**7**, m/z (LC-MS): 264.9 [M+H]⁺.



Example 36: (R)-N-(1-(2-chloro-6-((2,2,2-trifluoroethyl)amino)pyridin-4-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide:

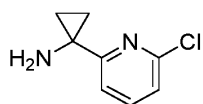


Following general procedure **8**, enantiopure compound-**4d** (0.03 g, 0.1129 mmol) converted to **Example 36** using compound-**7y** which was subsequently purified by prep HPLC. Mobile Phase:A= 0.2%HCOOH IN WATER, B= Acetonitrile, Column: X SELECT (250mmx20.0mm), 5.0μ, Flow: 15ml/min; Gradient Programmer: Time %B, 0 30, 1 30, 8 70 as Off white solid; ¹H NMR (400 MHz, CDCl₃) δ ppm 0.85-0.98 (m, 1 H), 1.10-1.30 (m, 6 H), 2.71 (d, J = 14.5 Hz, 1 H), 3.01 (d, J = 14.5 Hz, 1 H), 3.99-4.07 (m, 2 H), 4.37 (t, J = 6.31 Hz, 1 H), 5.4 (s, 1 H), 5.7 (d, J = 1.17 Hz, 1 H), 6.08 (s, 1 H), 6.14 (s, 1 H), 6.78-6.83 (m, 1 H), 6.89-6.95 (m, 1 H), 7.69-7.7573 (m, 1 H), HRMS calculated for: [C₂₀H₁₉ClF₂N₃O₂+H]⁺ 464.1164; found: 464.1177; Analytical Chiral HPLC: Column: REGIS(S,S) WHELK-01 (250X4.6mmX5μm, Mobile Phase : (A) n-HEXANE (B) IPA : MeOH (50:50), Isocratic : 90 : 10 (A:B), Flow : 1.0ml/min, Diluent : EtOH, Column Temp : 25°C, Inj. volume: 5.000, (Rt: 16.54, 95.34%).

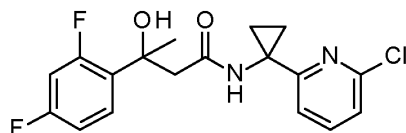
Example 37: Synthesis of N-(1-(6-chloropyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide

Synthesis of 1-(6-chloropyridin-2-yl)cyclopropan-1-amine (7t)

To a solution of 6-chloropicolinonitrile (5 g, 36.086 mmol) in anhydrous diethyl ether (50 mL) added $\text{Ti}(\text{OiPr})_4$ (12.18 mL, 39.70 mmol), at -78°C followed by dropwise addition of EtMgBr (3 M in Et_2O , 30.07 mL, 90.2126 mmol). Resulting reaction mixture stirred for 2 h and quenched using $\text{BF}_3:\text{Et}_2\text{O}$ (4.233 mL, 36.086 mmol). After overnight stirring added 1 N HCl and extracted reaction mixture with Et_2O . Aq. layer basified and extracted with Et_2O . Organic layer obtained after basification using 2 N NaOH, given brine wash, dried over anhydrous Na_2SO_4 and concentrated under *vacuo* to get crude compound-7t which was purified using combiflash chromatography (24 g column, 30% EtOAc : Hexane) to get pure enough compound-7t (470 mg, 7.8%) as yellow solid. $^1\text{H-NMR}$ (DMSO-d_6 , 300 MHz): δ 0.99 1.00 (m, 2 H), 1.16-1.17 (m, 2 H), 7.17-7.21 (m, 1 H), 7.72-7.80 (m, 2 H),

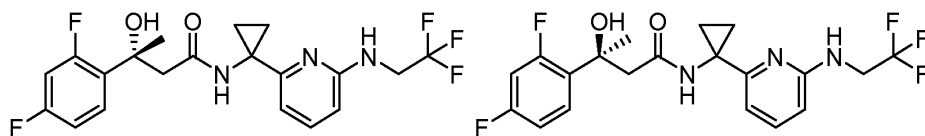


Synthesis of N-(1-(6-chloropyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide:



Following general procedure for compound-8, compound-4d (150 mg, 0.694 mmol) converted to crude N-(1-(6-chloropyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide using compound-7t (117 mg, 0.694 mmol). Crude compound purified using combiflash chromatography (30% EtOAc: Hexane as eluent) to get pure enough N-(1-(6-chloropyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide (130 mg, 51.08%) as brownish gummy.

Example 37: Synthesis of 3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(6-((2,2,2-trifluoroethyl)amino)pyridin-2-yl)cyclopropyl)butanamide

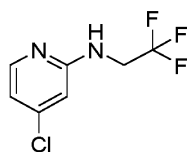


To sealed tube containing a stirred solution of N-(1-(6-chloropyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide (100 mg, 0.273 mmol) in dioxane : DME (1 mL, 1:1) added Cs₂CO₃ (222 mg, 0.682 mmol) followed by 2,2,2-Trifluoroethylamine hydrochloride (55.4 mg, 0.409 mmol). Resulting reaction mixture purged with argon for 5 min. then added XPhos-Pd-G₂ (21.5 mg, 0.0273 mmol) and again purged with argon for 5 min. Reaction mixture heated at 110 °C for 16 h. After completion of the reaction added water and extracted with EtOAc (3 x 5 mL). All organic layers dried given brine wash and over anhydrous Na₂SO₄ and concentrated under *vacuo* to get crude compound which was purified using prep HPLC (X-SELECT (C18 , 21.2mm X 150mm), Eluent: 0.1% HCOOH IN WATER (A) and Acetonitrile (B), Flow: 18 mL/ min to get pure enough racemic compound (25 mg, 21.34%) which was further purified using chiral HPLC, (CHIRALPAK IH, 250mmX21mm, 5µm), Eluent: n-Hexane(A) and IPA : MeOH 1:1 (B), Isocratic; 85 (A): 15 (B), Flow: 15 mL/min, Injection vol, 0.6 mL, run time 20 min, to get Peak-1 (14 mg), Peak-2: (13 mg); H-NMR (DMSO-d₆, 400 MHz): δ 0.80-0.85 (m, 2 H), 1.23-1.38 (m, 2 H), 1.49 (s, 3 H), 2.60 (dd, J = 13.8 Hz, 2 H), 3.95-4.05 (m, 2 H), 5.92 (d, J = 7.2 Hz, 1 H), 6.12 (bs, 1 H), 6.30 (d, J = 8 Hz, 1 H), 6.96-7.00 (m, 1 H), 7.05-7.09 (m, 2 H), 7.19-7.25 (m, 1 H), 7.58-7.64 (m, 1 H), 8.65 (bs, 1 H), HRMS calculated for: [C₂₀H₂₀F₅N₃O₂+H]⁺ 430.1554; found: 430.1564 (**Example 37 peak-1**), 430.1559 (**Example 37 peak-2**). Analytical Chiral HPLC: CHIRALPAK-IH (150X4.6mmX5µm), Mobile Phase: (A) n-HEXANE (B) 0.1% HCOOH IN EtOH : MeOH (80:20) Isocratic : 90:10 (A:B) Flow : 1.0ml/min, Diluent : EtOH, Column Temp : 25°C, Inj. volume: 10.000, Peak-1 (Rt: 5.87, 100% ee), Peak-2: (Rt: 9.60, 100% ee).

Example 38: Synthesis of (R)-N-(1-(4-chloro-6-((2,2,2-trifluoroethyl)amino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide

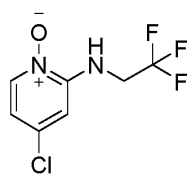
Synthesis of 4-chloro-N-(2,2,2-trifluoroethyl)pyridin-2-amine

To a sealed tube containing stirred solution of 4-chloro-2-fluoropyridine (1 g, 7.602 mmol) in DMSO (5 mL) added 2,2,2-trifluoroethan-1-amine (0.72 mL, 9.123 mmol). Resulting reaction mixture heated at 150 °C for 4 h. After completion of the reaction, added water and extracted with EtOAc (3 x 20 mL), Combined all organic layers washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford crude material. It was purified further using combiflash (10% EtOAc in Hexane as eluent, 24 g column) to get pure enough 4-chloro-N-(2,2,2-trifluoroethyl)pyridin-2-amine (150 mg, 9.36%) as white solid. m/z (LC-MS): 211.05 [M-H]⁺.



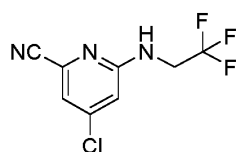
Synthesis of 4-chloro-2-((2,2,2-trifluoroethyl)amino)pyridine 1-oxide

To a stirred solution of 4-chloro-N-((2,2,2-trifluoroethyl)amino)pyridin-2-amine (150 mg, 0.712 mmol) in anhydrous DCM (2 mL) at 0 °C under argon atmosphere added m-CPBA (0.246 g, 1.425 mmol). Resulting reaction mixture stirred at room temperature for 3 h. Reaction mixture was quenched with aq. NaHCO₃ solution (PH = 8). Reaction mixture was extracted with MeOH : DCM (1:10, 2 x 5 mL). Organic layer given brine wash dried over anhydrous Na₂SO₄ and concentrated under *vacuo* to get crude 4-chloro-2-((2,2,2-trifluoroethyl)amino)pyridine 1-oxide (145 mg); m/z (LC-MS): 227.10 [M-H]⁺.



Synthesis of 4-chloro-6-(isopropylamino)picolinonitrile

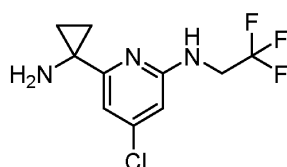
To a stirred solution of 4-chloro-2-((2,2,2-trifluoroethyl)amino)pyridine 1-oxide (145 mg, 0.64 mmol) in acetonitrile (5 mL) added triethylamine (1.43 mL, 10.24 mmol) followed by trimethylsilylcyanide (1.41 mL, 10.24 mmol) at room temperature. Resulting reaction mixture stirred at 80 °C for 16 h. After completion of the reaction, solvent was removed under *vacuo*, quenched using aq. NaHCO₃ and extracted using EtOAc (3 x 5 mL). Combined organic layer given brine wash, dried over anhydrous Na₂SO₄. Combined organic layer concentrated under *vacuo* to get crude compound which was purified using combiflash chromatography (4 g column, 0-15% EtOAc : Hexane as eluent) to get pure enough 4-chloro-6-(isopropylamino)picolinonitrile (69 mg, 39.78%) (m/z (LC-MS): 234.00 [M-H]⁺.



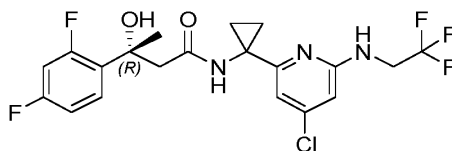
Synthesis of 6-(1-aminocyclopropyl)-4-chloro-N-(2,2,2-trifluoroethyl)pyridin-2-amine (7z)

To a solution of 4-chloro-6-(isopropylamino)picolinonitrile (50 mg, 0.212 mmol) in anhydrous diethyl ether (2 mL) added Ti(OiPr)₄ (0.098 mmol, 0.318 mmol), at -78 °C followed by dropwise addition of EtMgBr (3 M in Et₂O, 0.14 mL, 0.414 mmol). Resulting reaction mixture stirred for 2 h at room temperature and quenched using

BF₃:Et₂O (0.033 mL, 0.424 mmol). After overnight stirring added 1 N HCl and extracted reaction mixture with Et₂O. Aq. layer basified and extracted with Et₂O. Organic layer obtained after basification given brine wash, dried over anhydrous Na₂SO₄ and concentrated under *vacuo* to get crude compound-**7z** (30 mg, 53.56%) as brownish solid, (m/z (LC-MS): 266.05 [M+H]⁺.



Example 38: Synthesis of (R)-N-(1-(4-chloro-6-((2,2,2-trifluoroethyl)amino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide



- Following general procedure for compound-**8**, enantiopure compound-**4d** (24 mg, 0.113 mmol) converted to crude **Example 38** using compound-**7z** (30 mg, 0.113 mmol). Crude compound purified by prep HPLC, Column (X-BRIDGE (C18, 20mm X 150mm), Mobile Phase: A = 0.1% HCOOH in water and B = Acetonitrile, Flow: 16 mL/min to get pure compound (2.1 mg, 4.03%) as off white solid; H-NMR (DMSO-d₆, 400 MHz): δ 0.89-0.93 (m, 2 H), 1.32-1.36 (m, 2 H), 1.50 (s, 3 H), 2.66 (d, J = 14 Hz, 1 H), 2.80 (d, J = 14 Hz, 1 H), 3.98-4.07 (m, 2 H), 6.03 (s, 1 H), 6.26 (d, J = 1.2 Hz, 1 H), 6.39 (d, J = 1.2 Hz, 1 H), 7.01-7.05 (m, 1 H), 7.13-7.20 (m, 1 H), 7.26-7.30 (m, 1 H), 7.61-7.67 (m, 1 H), 8.59 (s, 1 H), HRMS calculated for: [C₂₀H₁₉ClF₅N₃O₂+H]⁺ 464.1164; found: 464.1177; Analytical Chiral HPLC: Column: REGIS(S,S) WHELK-01 (250X4.6mmX5 μ m, Mobile Phase : (A) n-HEXANE (B) 0.1%HCOOH IN ETHANOL : METHANOL(80:20) Isocratic : 70 : 30 (A:B), Flow : 1.0ml/min, Diluent : EtOH, Column Temp : 25°C, Inj. volume: 5.000, (Rt: 4.88, 98.15%).

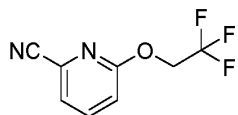
Example 39: Synthesis of 3-(2,6-difluorophenyl)-3-hydroxy-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)butanamide

Synthesis of 2-(2,2,2-trifluoroethoxy)isonicotinonitrile:

To a stirred solution of 6-chloropicolinonitrile (10 g, 72.1726 mmol) in anhydrous DMF (80 mL) was added K₂CO₃ (39.89 g, 288.6905 mmol) and 2,2,2-trifluoroethan-1-ol (3.61g, 267.0387 mmol) at RT. Resulting reaction mixture stirred at 60 °C for 24 h.

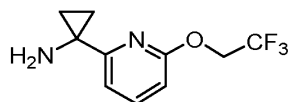
Reaction was quenched using ice cold water and extracted using EtOAc (3 x 500 mL). Combined Organic layer given brine wash and dried over anhydrous Na₂SO₄. Organic layer removed under vacuo to get crude product which was purified by flash chromatography (EtOAc:Hexane 5:95) as eluent to get 2-(2,2,2-

- 5 trifluoroethoxy)isonicotinonitrile (11.5 g, 79.3%) as off white crystalline solid; m/z (LC-MS): 202.90 [M+H]⁺.



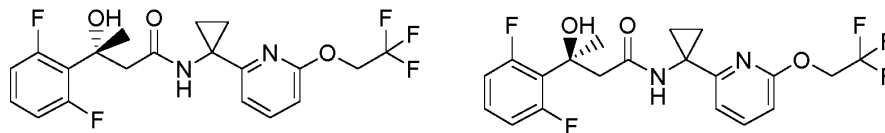
1-(6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropan-1-amine (7aa):

- 2-(2,2,2-trifluoroethoxy)isonicotinonitrile (6 g, 29.6833 mmol) converted to compound-
 10 **7aa** (5.1 g, 64.55%) using general procedure used for compound-7. After basification using NaHCO₃, compound extracted as free base, m/z (LC-MS): 233.00 [M+H]⁺.



Example 39: Synthesis of 3-(2,6-difluorophenyl)-3-hydroxy-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)butanamide (Example 39 peak-1 & Example 39 peak-2):

15

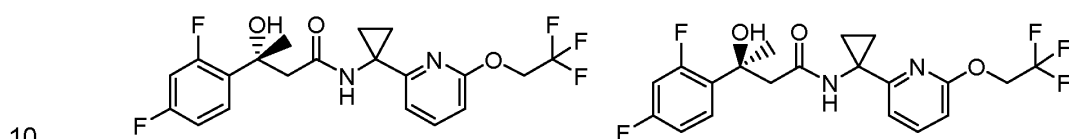


- Following general procedure 8, compound-4j (0.11 g, 0.5088 mmol) converted to **Example 39** (175 mg, 80.19%) using compound **7aa** (0.141 g, 0.610 mmol). The products were separated using Chiral prep HPLC, Column: CHIRALPAK IH, 20 250mmX20mm,5μm; Mobile Phase :n-Hexane(A) and 10mM ;Ammonia in IPA:EtOH(1:1)(B); Flow :15 ml, Isocratic : 90(A) : 10(B), Diluents: EtOH : DCM, 1:1, 3ml, Injection: Volume-0.4 ml; Run Time-21 min; to get Peak-1 (63.8 mg, Rt: 5.41) Peak-2: (55.3 mg, Rt: 7.47). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 0.94-0.98 (m, 2 H), 1.35-1.48 (m, 2 H), 1.66 (s, 3 H), 2.72 (d, J = 14.53 Hz, 1 H), 2.92 (d, J = 14.53 Hz, 1 H), 4.86 (q, J = 9.15 Hz, 2 H), 5.84 (s, 1 H), 6.45 (d, J = 7.48 Hz, 1 H), 6.65 (d, J = 8.22 Hz, 1 H), 6.99-7.04 (m, 2 H), 7.35-7.39 (m, 1 H), 7.42-7.46 (m, 1 H), 8.75 (bs, 1 H); HRMS calculated for: [C₂₀H₁₉F₅N₂O₃+H]⁺ 431.1394; found: 431.1402 (**Example 39 peak-1**), 431.1395 (**Example 39 peak-2**). Analytical Chiral HPLC: REGIS(S,S) WHELK-01 (250X4.6mmX5μm), Mobile Phase: (A) n-HEXANE (B) 0.1% HCOOH IN

EtOH : MeOH (80 : 20), Isocratic : 70:30 (A:B) Flow : 1.0ml/min, Diluent : EtOH, Column Temp : 25°C, Inj. volume: 10.000, Peak-1 (Rt: 4.55, 100% ee), Peak-2: (Rt: 4.40, 100% ee).

5 Example 40: Synthesis of 3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)butanamide

Example 40: Synthesis of 3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)butanamide (Example 40 peak-1 & Example 40 peak-2):

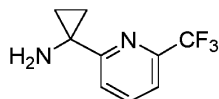


Following general procedure **8**, Compound-**4d** (0.25 g, 1.1564 mmol) converted to **Example 40** (220 mg, 44.89%) using compound **7aa** (0.295 g, 1.272 mmol). The products were separated using Chiral prep HPLC, Column: Chiralpak IH, 250mmX20mm, 5µm, Mobile Phase : n-Hexane(A) and 0.1% HCOOH in IPA:MeOH (1:1)(B), Flow : 15ml, Isocratic : 80(A):20(B), Diluents: EtOH:DCM, 1:1, 3.5 ml, Injection: Volume-0.2ml, Run Time-10min, Instrument Make and Model: Agilent-1200 Series, to get Peak-1 (101 mg, Rt: 2.13) Peak-2: (90 mg, Rt: 2.63). ¹H NMR (400 MHz, DMSO-d₆) δ 0.87-1.02 (m, 2 H), 1.34-1.48 (m, 2 H), 1.51 (s, 3 H), 2.66 (d, J = 14.4 Hz, 1 H), 2.85 (d, J = 14.4 Hz, 1 H), 4.88 (q, J = 9.1 Hz, 2H), 6.06 (s, 1 H), 6.39 (d, J = 7.6 Hz, 1 H), 6.66 (d, J = 8.0 Hz, 1 H), 7.06-7.11 (m, 1 H), 7.20-7.27 (m, 1 H), 7.40-7.44 (m, 1 H), 7.61-7.66 (m, 1 H), 8.73 (s, 1 H); HRMS calculated for: [C₂₀H₁₉F₅N₂O₃+H]⁺ 431.1394; found: 431.1404 (**Example 40 peak-1**), 431.1406 (**Example 40 peak-2**). Analytical Chiral HPLC: REGIS(S,S) WHELK-01 (250X4.6mmX5µm), Mobile Phase: (A) n-HEXANE (B) 0.1% HCOOH IN ETHANOL : METHNAOL(80:20), Isocratic : 70:30 (A:B) Flow : 1.0ml/min, Diluent : EtOH, Column Temp : 25°C, Inj. volume: 10.000, Acq. method: REG_7030_8_B_15MIN.amx, Peak-1 (Rt: 4.40, 100% ee), Peak-2: (Rt: 4.44, 100% ee).

30 Example 41: Synthesis of 3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(6-(trifluoromethyl)pyridin-2-yl)cyclopropyl)butanamide

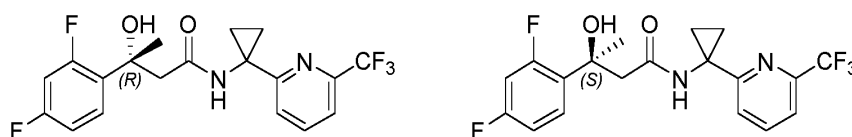
1-(6-(trifluoromethyl)pyridin-2-yl)cyclopropan-1-amine (7ab):

2-Cyano-6-trifluoromethylpyridine (0.8 g, 4.648 mmol) converted to compound-**7ab** (300 mg, 32.25 %) using general procedure used for compound-**7**, m/z (LC-MS): 202.18 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ = 1.03-1.06 (m, 2 H), 1.22-1.24 (m, 2 H), 2.78 (bs, 2 H), 7.59-7.61 (dd, J = 1.2 Hz & 7.6 Hz, 1H), 8.00-8.06 (m, 2H).



5

Example 41: Synthesis of 3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(6-(trifluoromethyl)pyridin-2-yl)cyclopropyl)butanamide (Example 41 peak-1 & Example 41 peak-2):



10 Following general procedure **8**, Compound-**4d** (100 mg, 0.462 mmol) converted to Example 41 (105 mg, 56.75% yield) using compound **7ab** (0.093 mg, 0.462 mmol). The products were separated using chiral prep HPLC; Column: Chiralpak IH, 250mmX21mm, 5 μ m, Eluent: A: n-Hexane, B: 10mM Ammonia in IPA : MeOH (1:1), Flow: 15 ml/min, Isocratic: 90(A):10(B) to get Peak-1 (36 mg, Rt: 3.44), Peak-2: (40

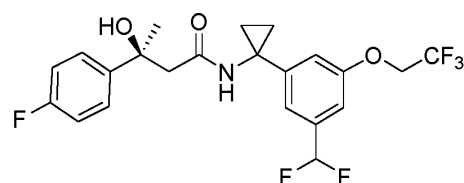
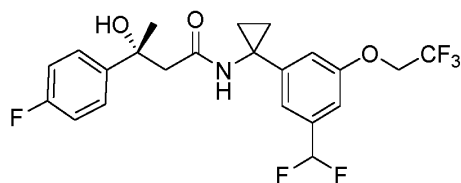
15 mg, Rt: 5.75). 1H NMR (400 MHz, DMSO- d_6) δ 0.981.07 (m, 2 H), 1.32-1.44 (m, 2 H), 1.52 (s, 3 H), 2.69 (d, J = 14.4 Hz, 1 H), 2.85 (d, J = 14.4 Hz, 1 H), 5.98 (s, 1 H), 7.06-7.12 (m, 2 H), 7.19-7.26 (m, 1 H), 7.59- 7.67 (m, 2 H), 7.73-7.77 (m, 1 H), 8.82 (bs, 1 H), HRMS: 401.00 $[M+H]^+$, HRMS calculated for: $[C_{19}H_{17}F_5N_2O_2+H]^+$ 401.1288; found: 401.1296 (**Example 41 peak-1**), 401.1295 (**Example 41 peak-2**). Analytical Chiral

20 HPLC: CHIRALPAK-IH (250X4.6mmX5 μ m) Mobile Phase: (A) n-HEXANE (B) 0.1% NH_4OH IN IPA : EtOH : MeOH (1:1:1), Flow : 1.0 ml/min, Diluent : EtOH, Column Temp : 25°C, Inj. volume: 5.000, Peak-1 (Rt: 3.40, 100% ee) Peak-2: (Rt: 5.66, 100% ee).

Example 42: Synthesis of N-(1-(3-(difluoromethyl)-5-(2,2,2-

25 trifluoroethoxy)phenyl)cyclopropyl)-3-(4-fluorophenyl)-3-hydroxybutanamide

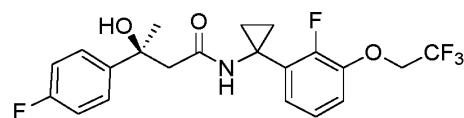
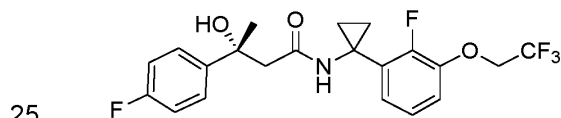
Example 42: Synthesis of N-(1-(3-(difluoromethyl)-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(4-fluorophenyl)-3-hydroxybutanamide (Example 42 peak-1 & Example 42 peak-2):



Following general procedure for compound-8, compound-4e (59.2 mg, 0.298 mmol) converted to crude Example 42 using compound 7n (70 mg, 0.249 mmol). The products were purified using prep HPLC Column: X SELECT (250mmx20.0mm), 5.0 μ Mobile Phase: A = 0.1% HCOOH in water and B = Acetonitrile, Flow: 15 mL/min to get pure compound (11 mg, 9.64%) as brownish solid, which was separated using Chiral prep HPLC, Column: (Chiralpak IH, 250x21mm, 5 μ m), Eluent: n-Hexane (A) and IPA : EtOH : MeOH, 1:1:1 (B), Flow: 15 ml/min, Isocratic: 85(A):15(B), diluent EtOH : DCM (1:1, 2 ML), Injection volume-0.3 mL, run time 11 min, to get Peak-1 (2.5 mg, Rt: 3.03, 100% ee) Peak-2: (1.1 mg, Rt: 3.99, 100% ee) as off white solid; H-NMR (CDCl₃, 400 MHz): δ 0.99-1.33 (m, 4 H), 1.49 (s, 3 H), 2.66 (s, 2 H), 4.28-4.35 (m, 2 H), 4.85 (s, 1 H), 6.24 (bs, 1 H), 6.50 (t, J = 56.4 Hz, 1 H), 6.80 (s, 1 H), 6.83-6.85 (m, 2 H), 6.94-6.99 (m, 2 H), 7.35-7.38 (m, 2 H), HRMS calculated for: [C₂₂H₂₁F₆NO₃+H-H₂O]⁺ 444.1398; found: 444.1399 (**Example 42 peak-1**), 444.1406 (**Example 42 peak-2**). Analytical chiral HPLC; Column : CHIRALPAK-IH(150X4.6mmX5 μ m) Mobile Phase : (A) n-HEXANE (B)IPA : MeOH (50:50), Isocratic : 85:15 (A:B), Flow : 1.0ml/min, Diluent : EtOH, Column Temp : 25°C, Inj. volume: 10.000. Peak-1 (Rt: 3.03, 100% ee) Peak-2: (Rt: 3.99, 100% ee)

Example 43: Synthesis of 3-(4-fluorophenyl)-N-(1-(2-fluoro-3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide

Example 43: Synthesis of 3-(4-fluorophenyl)-N-(1-(2-fluoro-3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide (Example 43 peak-1 & Example 43 peak-2):

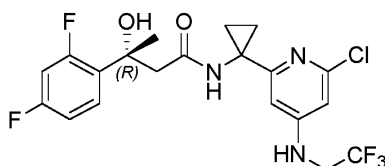


Following general procedure for compound-8, compound-4e (119 mg, 0.602 mmol) converted to Example 43 using compound 7g (150 mg, 0.602 mmol). The products were purified using combiflash (20% EtOAc : Hexane, 4 g column) to get pure compound (120 mg, 46.51%) as yellowish solid, which was separated using Chiral prep

HPLC, Column: (Chiralpak IH, 250mmX21 mm, 5 μ m), Eluent: n-Hexane(A) and IPA: MEOH (1:1) (B), Flow: 15 ml/min, Isocratic: 93(A):07(B), diluent EtOH:DCM, 1:1, 3.5 mL, Injection vol, 0.35 mL, run time 18 min, to get Peak-1 (33.6 mg, Rt: 3.18, 100% ee) Peak-2: (46.5 mg, Rt: 3.21, 100% ee), H-NMR (DMSO-d₆, 400 MHz): δ 0.74-0.81 (m, 2 H), 1.01-1.04 (m, 2 H), 1.36 (s, 3 H), 2.55 (dd, J = 14 Hz, 2 H), 4.75 (q, J = 8.8 Hz, 2 H), 5.59 (s, 1 H), 6.97-7.04 (m, 4 H), 7.08-7.11 (m, 1 H), 7.32-7.37 (m, 2 H), 8.54 (s, 1 H), HRMS calculated for: [C₂₁H₂₀F₅NO₃+H-H₂O]⁺ 412.1330; found: 412.1338 (Example 43 peak-1), 412.1344 (Example 43 peak-2). Chiral HPLC Column : CHIRALPAK-IH (150X4.6mmX5 μ m), Mobile Phase : (A) n-HEXANE (B)IPA: MeOH (50:50), Isocratic : 85:15(A:B), Flow : 1.0ml/min, Diluent : EtOH, Column Temp : 25 °C, Inj. volume: 5.000. Peak-1 (Rt: 3.18, 100% ee) Peak-2: (Rt: 3.21, 100% ee)

Example 44: Synthesis of (R)-N-(1-(6-chloro-4-((2,2,2-trifluoroethyl)amino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide:

Synthesis of ((R)-N-(1-(6-chloro-4-((2,2,2-trifluoroethyl)amino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide:



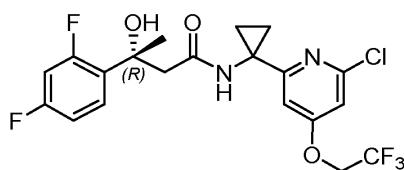
To a solution of Example-28 (40 mg, 0.0997 mmol) in dioxane : DME (1:1, 1 mL) added Cs₂CO₃ (81.2 mg, 0.249 mmol), at rt followed by 2,2,2-Trifluoroethylamine.HCl Salt (20.3 mg, 1.495 mmol). Resulting reaction mixture purged with argon for 15 min then added XPhosPdG2 (7.9 mg, 0.01 mmol). Resulting reaction mixture again purged with argon for 5 min and heated at 110 °C for 16 h. After completion of the reaction added water and extracted with EtOAc, Combined all organic layers washed with brine and dried over anhydrous Na₂SO₄. Organic layer concentrated under reduced pressure to get crude compound which was purified using prep HPLC, Gemini NX (250mmx21.2mm), 5.0 μ , (A) 10 Mm (NH₄)HCO₃ in water (B) Acetonitrile, Flow: 18 mL/min to get pure ((R)-N-(1-(6-chloro-4-((2,2,2-trifluoroethyl)amino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide (3.3 mg, 7.14%) as off white solid; H-NMR (DMSO-d₆, 400 MHz): δ 0.79-0.82 (m, 2 H), 1.24-1.25 (m, 2 H), 1.52 (s, 3 H), 2.68 (s, 2 H), 4.00-4.06 (m, 2 H), 5.91 (bs, 1 H), 6.56 (bs, 1 H), 6.64-6.66 (m, 1 H), 7.02-7.06 (m, 1 H), 7.15-7.19 (m, 1 H), 7.22-7.26 (m, 1 H), 7.58-7.64 (m, 1 H), 8.58 (bs, 1 H), HRMS calculated for: [C₂₀H₁₉ClF₅N₃O₂+H]⁺ 464.1164; found:

464.1174; Analytical Chiral HPLC: Column: REGIS(S,S) WHELK-01 (250X4.6mmX5µm, Mobile Phase : (A) n-HEXANE (B) 0.1%HCOOH IN EtOH : MeOH (80:20), Isocratic : 70 : 30 (A:B), Flow : 1.0ml/min, Diluent : EtOH, Column Temp : 25°C, Inj. volume: 5.000, (Rt: 4.47, 98.91%).

5

Example 45: Synthesis of (R)-N-(1-(6-chloro-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide:

Example 45: Synthesis of (R)-N-(1-(6-chloro-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide:



10

To a solution of Example 28 (40 mg, 0.0997 mmol) in anhydrous DMF (1 mL) added K_2CO_3 (13.8 mg, 0.249 mmol), at rt followed by 2,2,2-Trifluoroethanol (25 mg, 1.495 mmol). Resulting reaction mixture heated at 80 °C for 16 h. After completion of the reaction added water and extracted with EtOAc, Combined all organic layers washed with brine and dried over anhydrous Na_2SO_4 . Organic layer concentrated under reduced pressure to get crude compound which was purified using prep HPLC, Gemini NX (250mmx21.2mm), 5.0µ, (A) 10 Mm $(NH_4)HCO_3$ in water (B) Acetonitrile : MeOH, Flow: 18 mL/ min to get pure compound (7.7 mg, 16.%) as off white solid; H-NMR (DMSO- d_6 , 400 MHz): δ 0.93-1.01 (m, 2 H), 1.29-1.35 (m, 2 H), 1.52 (s, 3 H), 2.70 (dd, J = 14 Hz, 2 H), 4.87-4.94 (m, 2 H), 5.94 (bs, 1 H), 6.77 (d, J = 2 Hz, 1 H), 6.96-7.00 (m, 1 H), 7.09 (d, J = 2 Hz, 1 H), 7.10-7.15 (m, 1 H), 7.59-7.65 (m, 1 H), 8.61 (bs, 1 H), HRMS calculated for: $[C_{20}H_{18}ClF_5N_2O_3+H]^+$ 465.1004; found: 465.1015; Analytical Chiral HPLC: Column: REGIS(S,S) WHELK-01 (250X4.6mmX5µm, Mobile Phase : (A) n-HEXANE (B) 0.1%HCOOH IN EtOH : MeOH (80:20), Isocratic : 70 : 30 (A:B), Flow : 1.0ml/min, Diluent : EtOH, Column Temp : 25°C, Inj. volume: 5.000, (Rt: 4.62, 99.38%).

15

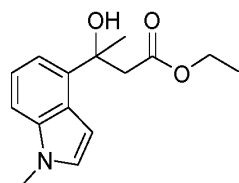
20

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Example 46: Synthesis of N-(1-(4-chloro-6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-hydroxy-3-(1-methyl-1H-indol-4-yl)butanamide:

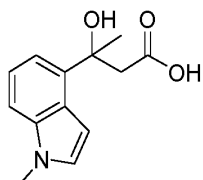
Synthesis of ethyl 3-hydroxy-3-(1-methyl-1H-indol-4-yl)butanoate:

1-(1-methyl-1H-indol-4-yl)ethan-1-one (0.1 g, 2.30 mmol) converted to compound-3m (0.08 g, 51.30%) using general procedure A used for compound-3, m/z (LC-MS): 244.1 [M-17+H]⁺.

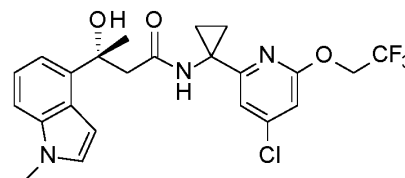
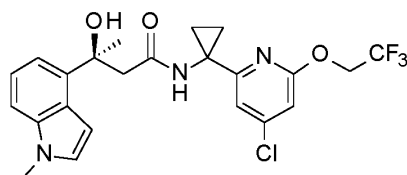


5 **Synthesis of 3-hydroxy-3-(1-methyl-1H-indol-4-yl)butanoic acid (4m):**

Ethyl 3-hydroxy-3-(1-methyl-1H-indol-4-yl)butanoate (0.15 g, 0.57 mmol) hydrolysed to get 4m (0.12 g, 80%) using general procedure used for compound-4, m/z (LC-MS): 232.15 [M-H]⁺.



10 **Example 46: Synthesis of N-(1-(4-chloro-6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-hydroxy-3-(1-methyl-1H-indol-4-yl)butanamide (Example 46 peak-1 & Example 46 peak-2):**

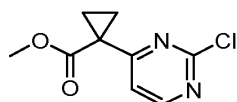


By following general procedure for compound-8, compound-4m (120 mg, 0.514 mmol) converted to **Example 46** using compound 7s (100 mg, 0.249 mmol). The products were purified using prep HPLC Column: REGIS(S,S) WHELK-01 (250X4.6mmX5μm), Eluent: n-Hexane(A) and IPA : MeOH 1:1 (B), Flow: 1 mL/min, Isocratic: 70(A):30(B), diluent: EtOH, Injection vol, 5 mL, run time 15 min, to get Peak-1 (25.5 mg), Peak-2: (23.3 mg); ¹H NMR (400 MHz, DMSO-d₆) δ ppm 0.80-94 (m, 2 H), 1.13-1.24 (m, 2 H), 1.58 (s, 3 H), 2.83 (q, J = 14 Hz, 2 H), 3.76 (s, 3 H), 4.75 (q, J = 8.8 Hz, 2 H), 5.70 (bs, 1 H), 6.63 (s, 1 H), 6.68 (d, J = 2.8 Hz, 1H), 6.77 (bs, 1 H), 6.94 (s, 1 H), 7.06-7.12 (m, 2 H), 7.28-7.31 (m, 2 H), 8.53 (bs, 1 H); HRMS : m/z (LC-MS): 430.05 [M+H]⁺. HRMS calculated for: [C₂₄H₂₄ClF₃N₂O₃+H-H₂O]⁺ 463.1400; found: 463.1403 (**Example 46 peak-1**), 463.1405 (**Example 46 peak-2**). Analytical Chiral HPLC: CHIRALPAK-IH

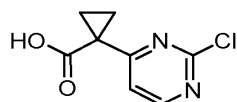
(250X4.6mmX5µm) Mobile Phase: (A) n-HEXANE (B) IPA : MeOH (70:30), Flow : 1.0ml/min Diluent : EtOH, Column Temp : 25°C, Inj. volume: 5.000, Peak-1 (Rt: 8.406, 100% ee) Peak-2: (Rt: 7.529, 100% ee).

5 Example 47: (R)-3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(2-((2,2,2-trifluoroethyl)amino)pyrimidin-4-yl)cyclopropyl)butanamide

Synthesis of Methyl 1-(2-chloropyrimidin-4-yl)cyclopropane-1-carboxylate: To a stirred solution of methyl 2-(2-chloropyrimidin-4-yl)acetate (1 g, 5.399 mmol) in anhydrous N,N-Dimethylformamide (10 mL) was added Sodium hydroxide (5.399 mmol), at room temperature under argon atmosphere. Stirred the reaction mixture for 20 min then added 1,2-dibromoethane (0.924 mL, 10.72 mmol) at room temperature. Resulting reaction mixture stirred at room temperature for 4 h. The reaction mixture was quenched with sat. aq. NH₄Cl and extracted with EtOAc (3 x 20 mL), to get crude compound which was purified using combi flash chromatography (EtOAc : Hexane, 3:7 as eluent) to get Methyl 1-(2-chloropyrimidin-4-yl)cyclopropane-1-carboxylate (580 mg, 51.32%) as colourless liquid, m/z (LC-MS): 212.90 [M+H]⁺.

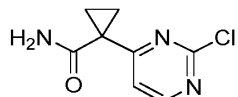


Synthesis of 1-(2-chloropyrimidin-4-yl)cyclopropane-1-carboxylic acid: To stirred solution of Methyl 1-(2-chloropyrimidin-4-yl)cyclopropane-1-carboxylate (0.580 g, 2.7276 mmol) in Tetrahydrofuran at 0 °C was added aqueous Lithium Hydroxide Monohydrate dropwise (1 ml), and reaction mixture was maintain same temperature 10 mins. Reaction mixture then allowed to stir at room temperature for 4. The reaction mixture was diluted with water and extracted with EtOAc (3 x 5 mL) to remove impurities. Aqueous was acidified by 1N HCl and extracted with EtOAc, then the organic layer was washed with water (3 x 5ml), to get crude 1-(2-chloropyrimidin-4-yl)cyclopropane-1-carboxylic acid (0.390 g, 72.08%), m/z (LC-MS): 199.15 [M+H]⁺.



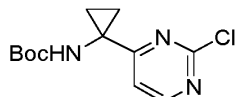
Synthesis of 1-(2-chloropyrimidin-4-yl)cyclopropane-1-carboxamide: To a stirred solution of 1-(2-chloropyrimidin-4-yl)cyclopropane-1-carboxylic acid (0.390 g, 1.9637 mmol) in N,N-dimethylformamide at 0 °C, was added DIPEA (1.03 mL, 5.90 mmol) and HATU (1.12 g, 2.945 mmol). Resulting reaction mixture was stirred for 30

mins under argon atmosphere then added Ammonium chloride (1.072 g, 19.64 mmol). Resulting homogeneous brown solution was stirred at room temperature for 4 h under argon atmosphere. The reaction mixture was quenched with ice cold water and extracted with EtOAc (3 x 10 mL). Combined all organic layers washed with brine to get crude compound which was purified using combi flash chromatography (EtOAc : Hexane as eluent) to get 1-(2-chloropyrimidin-4-yl)cyclopropane-1-carboxamide (0.210 g, 54.10%); m/z (LC-MS): 197.95 [M+H]⁺.



Synthesis of tert-butyl (1-(2-chloropyrimidin-4-yl)cyclopropyl)carbamate:

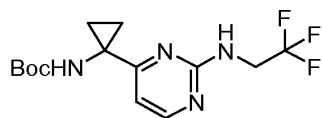
To stirred solution of 1-(2-chloropyrimidin-4-yl)cyclopropane-1-carboxamide (100 mg, 0.506 mmol) in t-Butanol (10 vol) added Lead Tetraacetate (0.673 g, 1.518 mmol) was added under argon atmosphere. Resulting reaction mixture was heated at 70 °C for 6 h, The reaction mass was monitored by TLC. The reaction mixture was quenched with ice cold water and extracted with ethyl acetate (3 x 5 mL). Organic layer collected given brine wash and dried over anhydrous Na₂SO₄. Organic layer concentrated and crude compound purified using combi flash chromatography (EtOAc:Hexane as eluent, 20% EtOAc in Hexane) to get tert-butyl (1-(2-chloropyrimidin-4-yl)cyclopropyl)carbamate (70 mg, 51.475), m/z (LC-MS): 269.95 [M+H]⁺.



Synthesis of tert-butyl (1-(2-((2,2,2-trifluoroethyl)amino)pyrimidin-4-yl)cyclopropyl)carbamate:

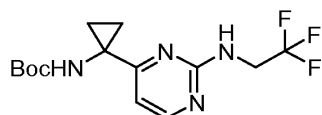
To a sealed tube containing stirred solution of tert-butyl (1-(2-chloropyrimidin-4-yl)cyclopropyl)carbamate (50 mg, 0.1854 mmol) in Toluene : Dioxane (1:1, 1 mL) added Cs₂CO₃ (121 mg, 0.371 mmol), XANTPHOS (10.7 mg, 0.0185 mmol). Resulting reaction mixture purged with argon for 10 mins, then added 2,2,2-Trifluoroethylamine (0.022 g, 0.222 mmol) and Pd(OAc)₂ (4.2 mg, 0.0185 mmol). Reaction mixture was purged with argon again for 5 min and heated 80 °C at 5 h. The reaction mass was monitored by TLC. The reaction mixture was quenched with water and extracted with EtOAc (3 x 5 mL). Combined organic layer given brine wash and dried over anhydrous Na₂SO₄. Organic layer concentrated under *vacuo* to get crude compound which was purified using combi flash chromatography (EtOAc : Hexane as eluent, 3:7 as eluent) to

get tert-butyl (1-(2-((2,2,2-trifluoroethyl)amino)pyrimidin-4-yl)cyclopropyl)carbamate (42 mg, 68.18%); m/z (LC-MS): 333.1 [M+H]⁺.



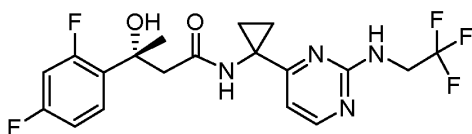
Synthesis of 4-(1-aminocyclopropyl)-N-(2,2,2-trifluoroethyl)pyrimidin-2-amine

- 5 **(7ae)**: To stirred solution of tert-butyl (1-(2-((2,2,2-trifluoroethyl)amino)pyrimidin-4-yl)cyclopropyl)carbamate (0.042 g, 0.1264 mmol) in Dichloromethane (1 mL) at 0 °C was added Trifluoroacetic acid dropwise (0.1 mL). Reaction mixture was allowed stirr at rt for 4 h and concentrated under vacuo to get crude compound which was washed with hexane to get pure enough 4-(1-aminocyclopropyl)-N-(2,2,2-
- 10 trifluoroethyl)pyrimidin-2-amine **7ae** (40 mg, Crude%); m/z (LC-MS): 233.00 [M+H]⁺.



Example 47: (R)-3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(2-((2,2,2-trifluoroethyl)amino)pyrimidin-4-yl)cyclopropyl)butanamide:

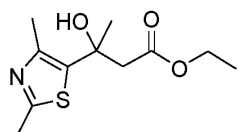
15



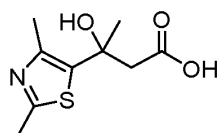
- Following general procedure for compound-8, compound-**4d** (30 mg, 0.139 mmol) converted to crude **Example 47** using compound-**7ae** (38.7 mg, 0.166 mmol). Crude compound purified by prep HPLC, Column: Gemini NX (250mmx21.2mm), 5.0μ, Mobile
- 20 Phase: A = 0.1% HCOOH in water and B = Acetonitrile, Flow: 18 mL/ min to get pure compound-48 (27 mg, 45.22%) as off white solid; H-NMR (DMSO-d₆, 400 MHz): δ 0.93-0.97 (m, 2 H), 1.33-1.36 (m, 1 H), 1.42-1.45 (m, 1 H), 1.53 (s, 3 H), 2.63 (d, J = 14.0 Hz, 1 H), 2.81 (d, J = 14.4 Hz, 1 H), 3.99-4.03 (m, 2 H), 5.99 (s, 1 H), 6.12 (d, J = 5.2 Hz, 1 H), 7.06-7.11 (m, 1H), 7.18-7.24 (m, 1 H), 7.53 (bs, 1 H), 7.58-7.65 (m, 1 H),
- 25 7.98 (d, J = 5.2 Hz, 1 H), 8.68 (bs, 1 H); HRMS calculated for: [C₁₉H₁₉F₅N₄O₂+H]⁺ 430.14; found:; Analytical Chiral HPLC: Column: CHIRALPAK-IG 250X4.6mm,5μm, Mobile Phase : (A) n-HEXANE (B) 0.1% NH₄OH IN (ETHANOL: :DCM)(50:50), Isocratic : (A:B) (50:50), Flow : 1.0ml/min, Diluent : EtOH, Column Temp : 25 °C, Inj. volume: 10.000, (Rt: 5.38, 98%).

Example 48: Synthesis of N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-dimethylthiazol-5-yl)-3-hydroxybutanamide

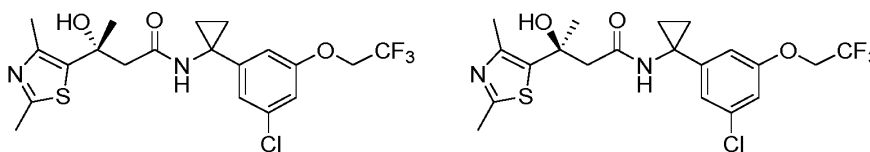
Synthesis of Ethyl 3-(2,4-dimethylthiazol-5-yl)-3-hydroxybutanoate (3n): 1-(2,4-dimethylthiazol-5-yl)ethan-1-one (2 g, 12.885 mmol) converted to compound-**3n** (2.4 g 76.92%) using general procedure **A** used for compound-**3**, m/z (LC-MS): 243.95 [M+H]⁺.



Synthesis of 3-(2,4-dimethylthiazol-5-yl)-3-hydroxybutanoic acid (4n): Compound-**3n** (2.4 g, 9.863 mmol) hydrolysed to get **4n** (0.5 g, 23.80%) as reddish gum using general procedure used for compound-**4**, m/z (LC-MS): 216 [M+H]⁺.



Example 48: Synthesis of N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-dimethylthiazol-5-yl)-3-hydroxybutanamide (Example 48 peak-1 & Example 48 peak-2):



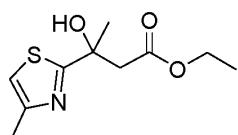
Following general procedure for compd-**8**, compound-**4n** (100 mg, 0.465 mmol) converted to **Example 48** (60 mg, 27.90%) using compound **7b**. The products were separated using Chiral prep HPLC, Column: CHIRALPAK IH, 250mmX20mm, 5μm, Mobile Phase : n-Hexane (A) and 0.2% HCOOH in EtOH(B), Flow: 15ml, Isocratic :90(A):10(B), Diluents: EtOH:DCM, 1:1, 4 ml, Injection: Volume-0.05 ml, Run Time: 17 min, to get Peak-1 (11 mg) and Peak-2 (13.5 mg), ¹H NMR (400 MHz, DMSO-d₆) δ 0.99-1.06 (m, 2 H), 1.17-1.26 (m, 2 H), 1.52 (s, 3 H), 2.33 (s, 3 H), 2.47 (s, 3 H), 2.66 (dd, J = 14 Hz, 2 H), 4.76 (q, J = 8.9 Hz, 2 H), 6.10 (bs, 1 H), 6.64 (m, 1 H), 6.81 (m, 1 H), 6.96 (m, 1 H), 8.64 (bs, 1 H); HRMS calculated for: [C₂₀H₂₂ClF₃N₂O₃S+H]⁺ 463.1070; found: 463.1072 (**Example 48 peak-1**), 463.1089 (**Example 48 peak-2**). Analytical Chiral HPLC: CHIRALPAK-IH(150X4.6mmX5μm), Mobile Phase : (A) n-

Hexane (B) EtOH (B), Flow : 1.0ml/min, Isocratic : 90:10(A:B), Column Temp : 25 °C, Diluent : EtOH, Inj. volume: 5 µl; Peak-1 (Rt: 3.08, 100% ee) Peak-2: (Rt: 3.52, 100% ee).

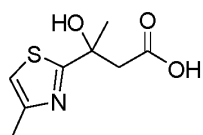
5 Example 49: Synthesis of N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxy-3-(4-methylthiazol-2-yl)butanamide

Synthesis of Ethyl 3-hydroxy-3-(4-methylthiazol-2-yl)butanoate (3o):

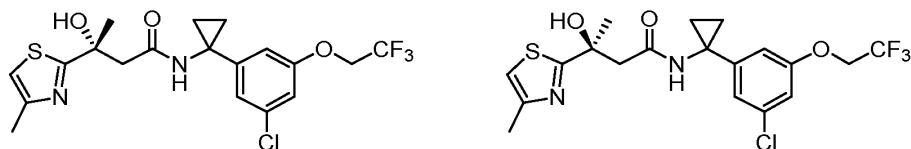
1-(4-methylthiazol-2-yl)ethan-1-one (0.5 g, 3.5413 mmol) converted to compound-3o (0.1 g 12.31%) using general procedure A used for compound-3, m/z (LC-MS): 230.00 [M+H]⁺.



Synthesis of 3-hydroxy-3-(4-methylthiazol-2-yl)butanoic acid (4o): Compound-3o (0.1 g, 0.4361 mmol) hydrolysed to get 4o (0.048 g, 55.17%) using general procedure used for compound-4, m/z (LC-MS): 201.95 [M+H]⁺.



15 **Example 49: Synthesis of N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxy-3-(4-methylthiazol-2-yl)butanamide (Example 49 peak-1 & Example 49 peak-2):**



20 Following general procedure for compound-8, compound-4o (0.048 g, 0.2385 mmol) converted **Example 49** (0.037 g, 33.33%) using compound 7b. The products were separated using Chiral SFC, Column: Chiralpak IG, 250mmX21mm, 5µm, Mobile Phase : CO₂(A) and IPA : MeOH (1:1) (B), Flow:50ml, Isocratic :85(A):15(B), Diluents: EtOH:DCM, 1:1, 3.5ml, Injection: Volume-0.75ml, Run Time: 8 min, to get Peak-1 (10.5 mg) and Peak-2 (9.8 mg), ¹H NMR (400 MHz, DMSO-d₆) δ 0.97-1.10 (m, 2 H), 1.15-1.23 (m, 2 H), 1.49 (s, 3 H), 2.32 (s, 3 H), 2.63 (d, J = 14 Hz, 1H), 2.81 (d, J = 14 Hz, 1 H), 4.76 (q, J = 8.9 Hz, 2 H), 6.38 (bs, 1 H), 6.59 (s, 1H), 6.75 (s, 1 H), 6.94-6.96 (m, 1

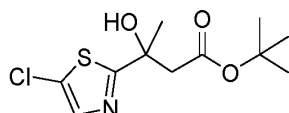
25

- H), 7.20 (s, 1 H), 8.67 (s, 1 H); HRMS calculated for: $[C_{19}H_{20}ClF_3N_2O_3S+H]^+$ 449.0914; found: 449.0919 (**Example 49 peak-1**), 449.0920 (**Example 49 peak-2**). Analytical Chiral SFC: CHIRALPAK-IG (150X4.6mmX5 μ m), Mobile Phase : CO₂(A) and IPA : EtOH: MeOH (1:1:1) (B), Flow : 3.0ml/min, Column Temp : 40°C, Inj. volume: 15 μ l; Peak-1 (Rt: 1.45, 100% ee), Peak-2: (Rt: 2.21, 100% ee).

Example 50: Synthesis of N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(5-chlorothiazol-2-yl)-3-hydroxybutanamide

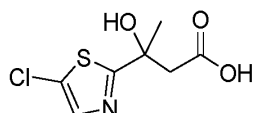
Synthesis of tert-butyl 3-(5-chlorothiazol-2-yl)-3-hydroxybutanoate (3p):

- Using general procedure **B** used for compound-**3** (using Ether as solvent instead of THF and tertbutyl bromoacetate instead of ethyl bromoacetate) 1-(5-chlorothiazol-2-yl)ethan-1-one (0.250 g, 1.5469 mmol) converted to compound-**3p** (0.4 g Crude). m/z (LC-MS): 277.85 $[M+H]^+$.

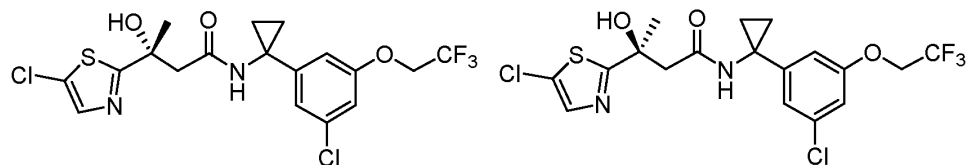


- Synthesis of 3-(5-chlorothiazol-2-yl)-3-hydroxybutanoic acid (4p):**

To a stirred solution of Compound-**3p** (0.2 g, 0.72 mmol) in Dichloromethane at 0 °C, was added HCl in dioxane dropwise. Reaction mixture was stirred at room temperature for 2 h. Excess of HCl in dioxane removed under vacuo and triturated with ether to get crude product (0.150 g, Crude). m/z (LC-MS): 221.90 $[M+H]^+$.



Example 50: Synthesis of N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(5-chlorothiazol-2-yl)-3-hydroxybutanamide (Example 50 peak-1 & Example 50 peak-2):

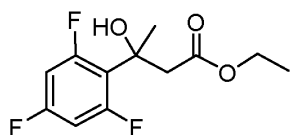


- Following general procedure for compd-**8**, compound-**4p** (0.150 g, 0.6767 mmol) converted to Example 50 (0.110 g, 34.70%) using compound **7b**. The products were separated using Chiral SFC, Column : 2 X LUX AMYLOSE 2-, 250mmX19mm, 5 μ m,

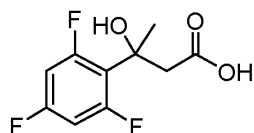
Mobile Phase : CO₂(A) and IPA (B) Flow: 50ml, ISO-90:10, Diluents: EtOH:DCM, 1:1
 5ml, Injection: Volume-0.3ml, Run Time: 16 min,
 to get Peak-1 (44 mg) and peak-2 (41 mg), ¹H NMR (400 MHz, DMSO-d₆) δ 1.08-1.17
 (m, 2 H), 1.19-1.26 (m, 2 H), 1.50 (s, 3 H), 2.64 (d, J = 14 Hz, 1H), 2.80 (d, J = 14 Hz, 1
 5 H), 4.75 (q, J = 8.9 Hz, 2 H), 6.61-6.64 (m, 2 H), 6.77-6.78 (m, 1 H), 6.96-6.97 (m, 1 H),
 7.67 (s, 1H), 8.70 (s, 1H), HRMS calculated for: [C₁₈H₁₇Cl₂F₃N₂O₃S+H]⁺ 469.0367;
 found: 469.0381 (**Example 50 peak-1**), 469.0372 (**Example 50 peak-2**). Analytical
 Chiral SFC: LUX AMYLOSE 2-, 250mmX19mm, 5μm, Mobile Phase : CO₂(A) and
 10mM Ammonia in IPA:EtOH:MeOH(1:1:1) (B), Flow : 3.0ml/min, Column Temp :
 10 40°C, Inj. volume: 15 μl; Peak-1 (Rt: 2.18, 100% ee), Peak-2: (Rt: 2.58, 100% ee).

Example 51: Synthesis of 3-hydroxy-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-2-
 yl)cyclopropyl)-3-(2,4,6-trifluorophenyl)butanamide

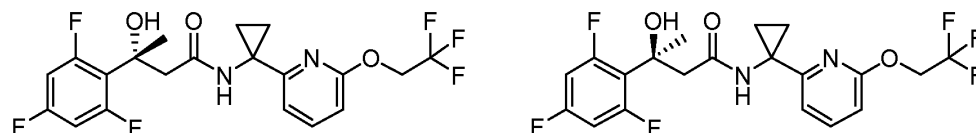
Synthesis of ethyl 3-hydroxy-3-(2,4,6-trifluorophenyl)butanoate (3q): Using general
 15 procedure **A** used for compound-**3**, 1-(2,4,6-trifluorophenyl)ethan-1-one (500 mg, 2.872
 mmol) converted to compound-**3q** (0.9 g Crude). m/z (LC-MS): 244.95 [M-18]⁺.



Synthesis of 3-hydroxy-3-(2,4,6-trifluorophenyl)butanoic acid (4q): Compound-**3q**
 20 (750 mg, 2.860 mmol) hydrolysed to get **4q** (600 mg, 90.9%) using general procedure
 used for compound-**4**, m/z (LC-MS): 232.85 [M-H]⁺.



**Example 51: Synthesis of 3-hydroxy-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-2-
 yl)cyclopropyl)-3-(2,4,6-trifluorophenyl)butanamide (Example 51 peak-1 &
 25 Example 51 peak-2):**



Following general procedure for compd-**8**, compound-**4q** (0.1 g, 0.427 mmol) converted
 to Example 51 (0.125 g, 65.78%) using **7aa**, which was separated using chiral HPLC,

Column Chiralpak IH, 250mmX21mm, 5µm, Mobile Phase : n-Hexane(A) and 10mM Ammonia in IPA:EtOH(1:1)(B), Flow: 15 ml, Isocratic: 90 (A) :10 (B), Diluents: EtOH:DCM,1:1 3 ml, Injection: Volume-0.2ml, Run Time:19 min, to get Peak-1 (45 mg) and peak-2 (48.4 mg) as off white gum, ¹H NMR (400 MHz, DMSO-d₆) δ 0.99-1.01 (m, 2 H), 1.19-1.26 (m, 2 H), 1.38-1.48 (m, 2 H), 1.64 (s, 3 H), 2.73 (d, J = 14.4 Hz, 1H), 2.83 (d, J = 14.4 Hz, 1 H), 4.86 (q, J = 8.8 Hz, 2 H), 5.82 (s, 1 H), 6.58 (d, J = 7.2 Hz, 1 H), 6.67 (d, J = 7.2 Hz, 1 H), 7.08-7.13 (m, 2 H), 7.46-7.50 (m, 1 H), 8.77 (bs, 1 H), HRMS calculated for: [C₂₀H₁₈F₆N₂O₃+H]⁺ 448.12; found: 448. (**Example 51 peak-1**), 448. (**Example 51 peak-2**). Analytical Chiral HPLC: Column: CHIRALPAK-IH (150X4.6mmX5µm), Mobile Phase : (A) n-HEXANE (B) 0.1% NH₄OH IN IPA : EtOH: MeOH (1:1:1), Isocratic: 95 (A) :05 (B), Flow : 1.0 ml/min, Diluent: EtOH, Column Temp : 25 °C, Inj. volume: 5 µl; Peak-1 (Rt: 3.47, 100% ee), Peak-2: (Rt: 4.37, 95.28% ee).

Example 52: Kv7 modulating activity

15

Aim

To demonstrate the ability of the compounds according to the present disclosure to modulate the activity of Kv7 potassium channels.

20

Materials and Methods

Cell seeding. HEK293 cells stably expressing concatenated hK_v7.3-hK_v7.2 were seeded on poly-D-lysine (10 µg/ml) coated 384-well, clear bottomed, black-walled Corning Optiplates. The cells were seeded at a density of approximately 3x10⁶ cells/ml in 20 µl DMEM containing 10% FCS per well and left overnight at 37 °C in a 5% CO₂ incubator.

25

Fluorescence-based TI⁺ influx assay (FLIPR). Prior to an experiment, the cells were loaded with the fluorescent dye benzothiazolecoumarin-acetoxymethyl ester (BTC-AM). In brief, the cells were washed thrice in Cl⁻-free assay buffer (in mM: 140 Na⁺-gluconate, 2.5 K⁺-gluconate, 6 Ca²⁺-gluconate, 1 Mg²⁺-gluconate, 5 glucose, 10 HEPES, pH 7.3). Hereafter, the buffer was aspirated, and 25 µl Cl⁻-free loading buffer (assay buffer containing an additional 2 µM BTC-AM, 2 mM amaranth and 1 mM tartrazine) was added to each well. The cells were incubated at 37 °C for 1 h and, subsequently, transferred to a fluorometric imaging plate reader (FLIPR). Assay plates were tested using a two-addition protocol (1st add.: test compound, 2nd add.: stimulus

35

buffer). 10 mM DMSO stock solution of the compounds were diluted in Cl⁻-free assay buffer and ½ log serial dilutions (31.6 μM-0.316 nM) were prepared in 384-well plates. In the hK_v7.3–hK_v7.2 assay the stimulus buffer consisted of Cl⁻-free assay buffer supplemented with 2 mM Tl₂SO₄ (Thallium sulphate) and 5 mM K₂SO₄ (final concentrations) as well as the quenchers amaranth (2 mM) and tartrazine (1 mM). The stimulus buffer in the hK_v7.5 assay was similar to the stimulus buffer used in the hK_v7.3–hK_v7.2 assay, but with a final K₂SO₄ concentration of 10 mM. The cells were stimulated in quadruplicate, i.e., four individual wells were stimulated per compound test concentration. In addition, 16 wells/plate served as negative controls (buffer addition) and another 16 wells/plate as positive controls (30 μM retigabine).

Data analysis. The data from the individual wells were expressed as fold increase (maximal signal (after addition of stimulus buffer) divided by the average baseline value (immediately prior to the addition)). Next, the data were background corrected by subtraction of the averaged value of the fold increase for the negative control wells. The data were subsequently analyzed by normalizing the corrected fold increase values to the maximal positive control response and fitting the data to the Hill equation. EC₅₀ and efficacy (% of positive control) values are reported, where positive control is defined as response to 30 μM retigabine.

Results

Table 1 below displays the results obtained when assessing the compounds according to the present disclosure to modulate the activity of K_v7 potassium channels, respectively Kv7.2/7.3 and Kv7.5.

Table 1:

Test example	FLIPR: Kv7.2/Kv7.3		FLIPR: Kv7.5	
	EC50 (μM)	Efficacy (%)	EC50 (μM)	Efficacy (%)
Example 1 peak-1	0.71	63	>30	0
Example 1 peak-2	5.6	88	>30	0
Example 2 peak-1	3.9	86	>30	0
Example 2 peak-2	8.3	95	>30	0
Example 3 peak-1	1.7	67	>30	0
Example 3 peak-2	10	91	>30	0
Example 4 peak-1	0.13	101	>30	0

Example 4 peak-2	0.049	100	0.37	100
Example 5 peak-1	1.0	97	>30	0
Example 5 peak-2	0.40	110	>30	0
Example 6 peak-1	1.1	79	1.6	39
Example 6 peak-2	5.5	95	8.6	44
Example 7 peak-1	1.2	96	>30	0
Example 7 peak-2	2.6	103	6.8	59
Example 8 peak-1	1.2	58	>30	0
Example 8 peak-2	3.5	92	>30	0
Example 9 peak-1	0.051	86	>30	0
Example 9 peak-2	0.089	110	>30	0
Example 10 peak-1	1.0	55	>30	0
Example 10 peak-2	3.1	74	>30	0
Example 11 peak-1	0.22	79	>30	0
Example 11 peak-2	0.13	99	>30	0
Example 12 peak-1	0.23	89	>30	0
Example 12 peak-2	0.30	101	>30	0
Example 13 peak-1	2.5	102	5.6	60
Example 13 peak-2	1.5	104	2.7	113
Example 14 peak-1	0.00082	77	>30	0
Example 14 peak-2	0.12	97	>30	0
Example 15 peak-1	0.069	39	>30	0
Example 15 peak-2	0.13	74	>30	0
Example 16 peak-1	3.6	100	>30	0
Example 16 peak-2	3.4	108	0.8	34
Example 17 peak-1	15	99	17	59
Example 17 peak-2	20	103	>30	0
Example 18 peak-1	0.059	92	>30	0
Example 18 peak-2	0.023	102	0.5	33
Example 19 peak-1	0.81	105	>30	0
Example 19 peak-2	0.96	110	>30	0
Example 20 peak-1	0.33	110	>30	0
Example 20 peak-2	0.34	111	1	132
Example 21 peak-1	0.27	103	>30	0

Example 21 peak-2	0.085	102	0.8	162
Example 22 peak-1	0.42	108	>30	0
Example 22 peak-2	1.2	106	1.9	69
Example 23 peak-1	0.19	96	>30	0
Example 23 peak-2	0.16	99	>30	0
Example 24 peak-1	0.35	75	>30	0
Example 24 peak-2	0.81	110	9.4	66
Example 25 peak-1	0.5	94	>30	0
Example 25 peak-2	0.24	104	>30	0
Example 26 peak-1	0.62	90	>30	0
Example 26 peak-2	0.52	106	>30	0
Example 27 peak-1	5.5	52	>30	0
Example 27 peak-2	6.3	78	>30	0
Example 28 peak-1	2.3	105	>30	0
Example 29 peak-1	0.3	97	>30	0
Example 30 peak-1	0.34	106	>30	0
Example 30 peak-2	0.64	110	0.97	46
Example 31 peak-1	0.35	96	>30	0
Example 31 peak-2	0.16	93	0.87	62
Example 32 peak-1	3.3	80	>30	0
Example 32 peak-2	0.33	38	>30	0
Example 33 peak-1	2.0	90	>30	0
Example 34 peak-1	0.36	99	>30	0
Example 35 peak-1	1.5	99	>30	0
Example 36 peak-1	8.6	77	>30	0
Example 37 peak-1	0.027	98	>3	0
Example 37 peak-2	0.038	97	0.03	61
Example 38 peak-1	0.07	103	>30	0
Example 39 peak-1	0.13	100	0.18	71
Example 39 peak-2	0.88	100	0.79	53
Example 40 peak-1	0.099	101	>30	0
Example 40 peak-2	0.07	101	0.011	52
Example 41 peak-1	0.94	78	>30	0
Example 41 peak-2	1.2	84	30	88

Example 42 peak-1	0.44	99	>30	0
Example 42 peak-2	1.3	102	16	40
Example 43 peak-1	0.35	75	0.48	19
Example 43 peak-2	1.1	83	>30	0
Example 44 peak-1	8.0	98	27	42
Example 45 peak-1	3.1	96	>30	0
Example 46 peak-1	3.1	93	>30	0
Example 46 peak-2	1.5	93	>30	0
Example 47 peak-1	1.2	113	>30	0
Example 48 peak-1	3.2	90	>30	0
Example 48 peak-2	0.66	81	14	87
Example 49 peak-1	3.4	104	>30	0
Example 49 peak-2	0.84	97	>30	0
Example 50 peak-1	0.25	103	>30	0
Example 50 peak-2	0.18	105	1.5	100
Example 51 peak-1	0.13	101	>30	0
Example 51 peak-2	0.12	100	>30	0

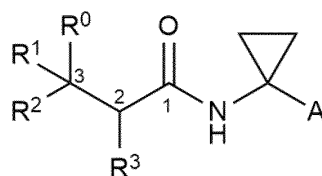
Conclusion

5 The compounds according to the present disclosure are able to modulate the activity of K_v7 channels.

As demonstrated in the example, the compounds of the present invention provides for smaller EC₅₀ values for Kv7.2/Kv7.3 channels compared to Kv7.5 channels. As also demonstrated in the example, the compounds of the present invention provides larger efficacy values for Kv7.2/Kv7.3 channels compared to Kv7.5 channels. Thus it can be
10 concluded that the compounds of the current invention are subtype-selective Kv7 modulators, selective for Kv7.2/Kv7.3 over Kv7.5.

Claims

1. A compound according to formula (I):



formula (I)

5 or a tautomer, a mesomer, a racemate, an enantiomer or a diastereoisomer thereof,
or a mixture thereof; or a pharmaceutically acceptable salt thereof;
wherein,

R^0 is selected from the group consisting of $-OH$, and $-CH_3$;

R^1 is aryl optionally substituted with one or more, identical or different, substituents

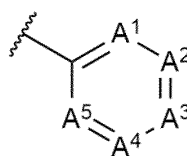
10 R^4 , or heteroaryl optionally substituted with one or more, identical or different,
substituents R^4 ;

R^4 is selected from the group consisting of C_{1-5} alkyl optionally substituted with one
or more F, C_{1-5} alkoxy, halogen and CN;

R^2 is selected from the group consisting of $-H$, $-CH_3$, and $-CF_3$;

15 R^3 is selected from the group consisting of $-H$ and $-OH$;

A is of formula (II):



formula (II)

wherein

20 A^1 is $C-R^5$ or N;

R^5 is $-H$ or halogen;

A^2 is $C-R^6$;

R^6 is selected from the group consisting of C_{1-5} alkoxy optionally substituted with
one or more F; C_{1-5} alkyl optionally substituted with one or more F; halogen; and

25 $N(R^{10})(R^{11})$;

R^{10} is C_{1-5} alkyl optionally substituted with one or more, identical or different,
substituents R^{12} ;

R^{11} is $-H$;

R^{12} is selected from the group consisting of halogen, C_{3-5} cycloalkyl and C_{1-3} alkyl;

A^3 is $C-R^7$ or N;

R^7 is selected from the group consisting of -H, halogen and C_{1-5} alkyl;

A^4 is $C-R^8$ or N;

- 5 R^8 is selected from the group consisting of -H, halogen, C_{3-5} cycloalkyl, C_{1-5} alkyl optionally substituted with one or more F, C_{1-5} alkoxy, and -CN;

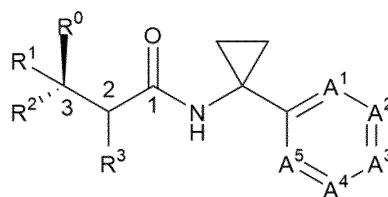
A^5 is $C-R^9$ or N;

R^9 is -H or halogen;

with the proviso that the compound is not

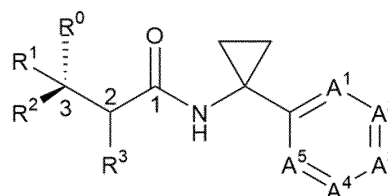
- 10 N -[1-(3,5-Difluorophenyl)cyclopropyl]- β -methyl-1*H*-imidazole-1-propanamide;
 N -[1-(3-Chlorophenyl)cyclopropyl]- β -hydroxybenzenepropanamide;
 N -[1-(3-Fluorophenyl)cyclopropyl]- β -hydroxybenzenepropanamide; or
 3-Fluoro- N -[1-(3-fluorophenyl)cyclopropyl]- β -hydroxybenzenepropanamide.

- 15 2. The compound according to claim 1, wherein the compound is of formula (IIIa):



formula (IIIa)

3. The compound according to claim 1, wherein the compound is of formula (IIIb):



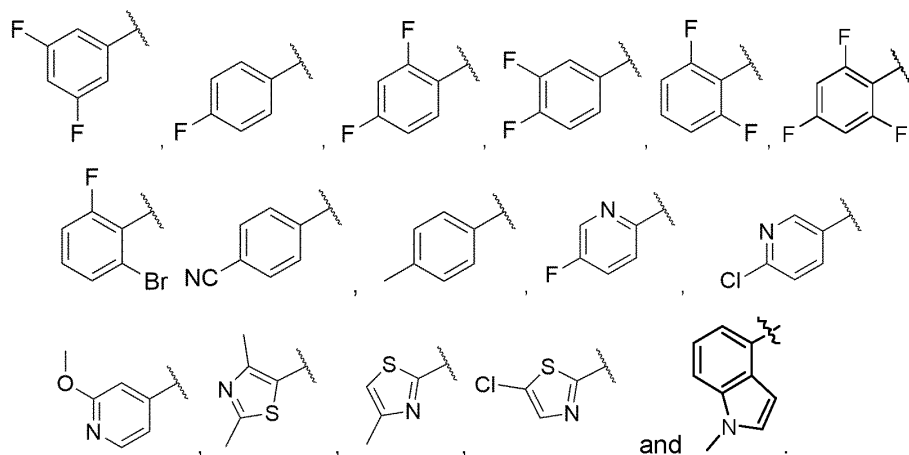
formula (IIIb)

4. The compound according to any one of the preceding claims, wherein R^1 is phenyl, pyridin-4-yl, pyridin-3-yl, pyridin-2-yl, thiazol-2-yl or thiazol-5-yl
 25 optionally substituted with one or more, identical or different substituents R^4

selected from the group consisting of -F, -Cl, -Br, C₁₋₅ alkoxy, C₁₋₅ alkyl, and -CN.

- 5 5. The compound according to any one of claims 1 to 3, wherein R¹ is phenyl substituted with one or more, identical or different, substituents R⁴ selected from the group consisting of -F, -Cl, -Br, C₁₋₅ alkoxy, C₁₋₅ alkyl, and -CN.
- 10 6. The compound according to any one of claims 1 to 3, wherein R¹ is phenyl substituted with one or more, identical or different, substituents R⁴ selected from the group consisting of -F, -Br, C₁₋₅ alkyl, and -CN.
- 15 7. The compound according to any one of claims 1 to 3, wherein R¹ is phenyl substituted with one or more -F.
- 15 8. The compound according to any one of claims 1 to 3, wherein R¹ is pyridinyl substituted with one or more, identical or different, substituents R⁴ selected from the group consisting of -F, -Cl, -Br, C₁₋₅ alkoxy, C₁₋₅ alkyl, and -CN.
- 20 9. The compound according to any one of claims 1 to 3, wherein R¹ is pyridinyl substituted with one or more, identical or different, substituents R⁴ selected from the group consisting of -F, -Cl, -Br, and C₁₋₅ alkoxy.
- 25 10. The compound according to any one of claims 1 to 3, wherein R¹ is thiazolyl substituted with one or more, identical or different substituents R⁴ selected from the group consisting of -F, -Cl, -Br, and C₁₋₅ alkyl.
- 30 11. The compound according to any one of claims 1 to 3, wherein R¹ is thiazolyl substituted with one or more, identical or different substituents R⁴ selected from the group consisting of -F, -Cl, -Br, and C₁₋₅ alkyl,
12. The compound according to any one of claims 1 to 3, wherein R¹ is indolyl substituted with one or more, identical or different substituents R⁴ selected from the group consisting of -F, -Cl, -Br, and C₁₋₅ alkyl.

13. The compound according to any one of claims 1 to 3, wherein R¹ is selected from:



14. The compound according to any one of the preceding claims, wherein R² is -CH₃ and R⁰ is -OH.

10 15. The compound according to any one of the preceding claims, wherein R⁰ is -OH, R² is -CH₃, and R³ is -H.

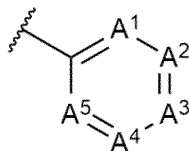
16. The compound according to any one of claims 1 to 12, wherein R² is -CF₃ and R⁰ is -OH.

15

17. The compound according to any one of the preceding claims, wherein R³ is -H.

18. The compound according to any one of the preceding claims, wherein A is of formula (II),

20



formula (II)

wherein:

- a) A¹ is C-R⁵; A² is C-R⁶; A³ is C-R⁷; A⁴ is C-R⁸; and A⁵ is C-R⁹, or
- b) A¹ is N; A² is C-R⁶; A³ is C-R⁷; A⁴ is C-R⁸; and A⁵ is C-R⁹, or

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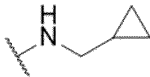
- c) A¹ is C-R⁵; A² is C-R⁶; A³ is N; A⁴ is C-R⁸; and A⁵ is C-R⁹, or
 d) A¹ is C-R⁵; A² is C-R⁶; A³ is C-R⁷; A⁴ is N; and A⁵ is C-R⁹, or
 e) A¹ is N; A² is C-R⁶; A³ is N; A⁴ is C-R⁸; and A⁵ is C-R⁹, or
 f) A¹ is C-R⁵; A² is C-R⁶; A³ is C-R⁷; A⁴ is C-R⁸; and A⁵ is N.

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19. The compound according to any one of the preceding claims, wherein

- R⁵ is -H or -F,
- R⁶ is -CF₃, -Cl, -Br, -CH₃, -OCH₂CF₃, -OCF₃, -OCH₃, -OCH₂CF₂H, -

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OCF₂H, -N(H)(CH₂CF₃), , -N(H)CH₂C(CH₃)₃, or -N(H)C(H)(CH₃)₂,

- R⁷ is -H, -Cl, -F or -CH₃,
- R⁸ is -H, -F, -Cl, -Br, -CN, -CF₂H, cyclopropyl, or -OCH₃.
- R⁹ is -H or -F.

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20. The compound according to any one of the preceding claims, wherein A¹ is C(H), A² is C(OCH₂CF₃) and A⁵ is C(H).

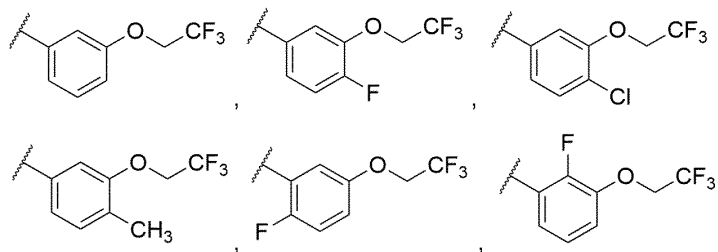
21. The compound according to any one of claims 1 to 17, wherein A¹ is N, A³ is C(H) and A⁵ is C(H).

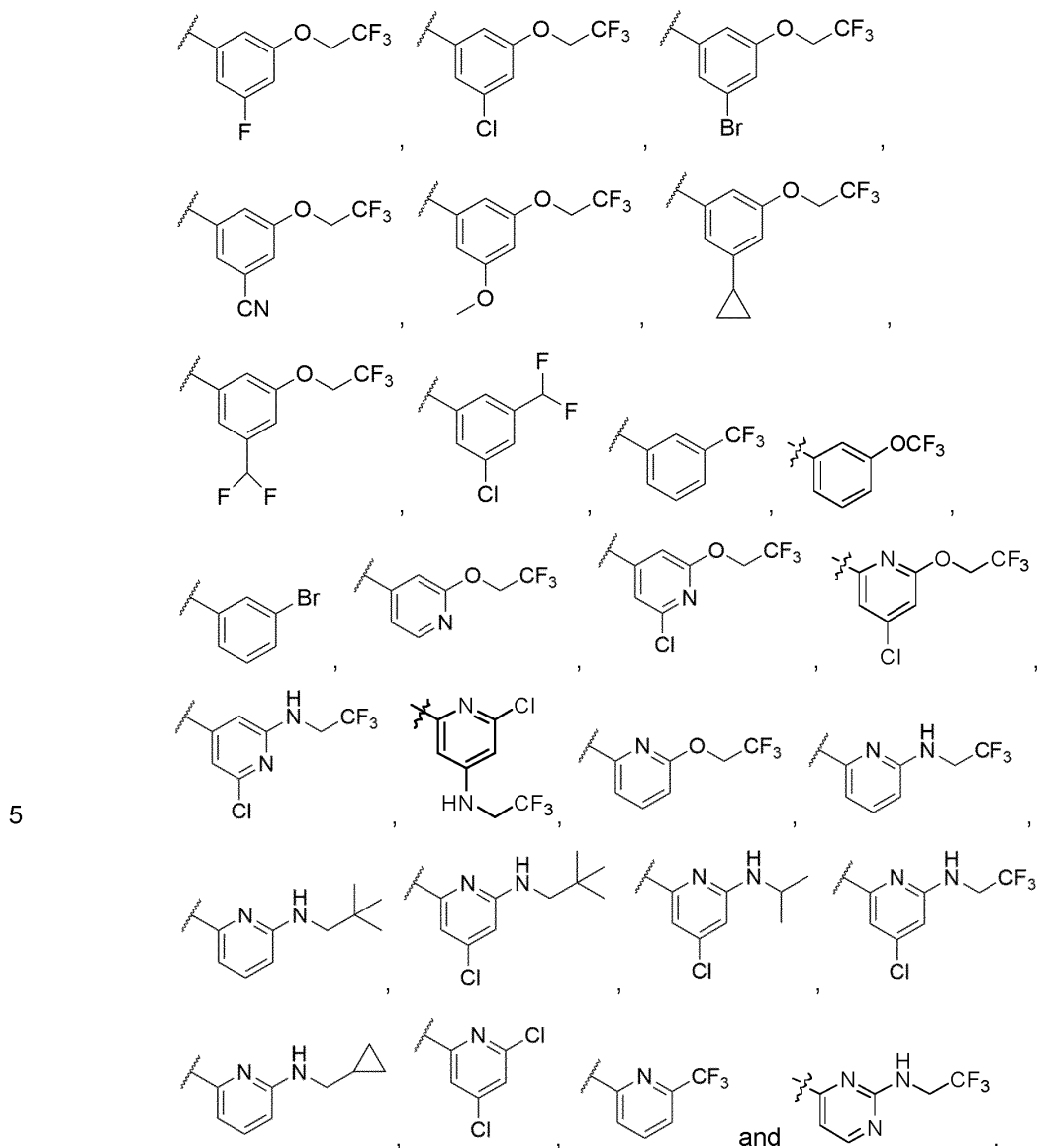
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22. The compound according to any one of the preceding claims, wherein at least one of A¹, A³ and A⁴ is not -C(H).

23. The compound according to any one of claims 1 to 17, wherein A is selected from:

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24. The compound according to claim 1, wherein the compound is (R)-3-(6-chloropyridin-3-yl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)-cyclopropyl)butanamide,
(R)-3-(5-fluoropyridin-2-yl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)-cyclopropyl)-butanamide,
(R)-3-hydroxy-3-(2-methoxypyridin-4-yl)-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)-cyclopropyl)butanamide,

- (R)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (R)-3-(2,4-difluorophenyl)-N-(1-(4-fluoro-3-(2,2,2-trifluoroethoxy)phenyl)-cyclopropyl)-3-hydroxybutanamide,
- 5 (R)-3-(4-fluorophenyl)-3-hydroxy-N-(1-(3-(trifluoromethyl)phenyl)cyclopropyl)-butanamide,
- (R)-3-(4-fluorophenyl)-3-hydroxy-N-(1-(3-(trifluoromethoxy)phenyl)cyclopropyl)-butanamide,
- (R)-3-(4-fluorophenyl)-3-hydroxy-N-(1-(2-(2,2,2-trifluoroethoxy)pyridin-4-yl)cyclopropyl)butanamide,
- 10 (R)-3-hydroxy-3-(p-tolyl)-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)-cyclopropyl)butanamide,
- (R)-3-(4-cyanophenyl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)-cyclopropyl)-butanamide,
- 15 (R)-3-(2,4-difluorophenyl)-N-(1-(2-fluoro-3-(2,2,2-trifluoroethoxy)phenyl)-cyclopropyl)-3-hydroxybutanamide,
- (R)-3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(4-methyl-3-(2,2,2-trifluoroethoxy)-phenyl)cyclopropyl)butanamide,
- (R)-N-(1-(3-chloro-5-(difluoromethyl)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- 20 (R)-3-(3,5-difluorophenyl)-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-butanamide,
- (R)-4,4,4-trifluoro-3-(4-fluorophenyl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)-phenyl)cyclopropyl)butanamide,
- 25 (R)-N-(1-(3-bromophenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (R)-N-(1-(3-cyano-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(4-fluorophenyl)-3-hydroxybutanamide,
- (R)-3-(2,4-difluorophenyl)-N-(1-(3-fluoro-5-(2,2,2-trifluoroethoxy)-phenyl)cyclopropyl)-3-hydroxybutanamide,
- 30 (R)-N-(1-(4-chloro-3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (R)-N-(1-(3-(difluoromethyl)-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,

- (R)-N-(1-(3-bromo-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (R)-N-(1-(3-cyclopropyl-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- 5 (R)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,6-difluorophenyl)-3-hydroxybutanamide,
- (R)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(3,4-difluorophenyl)-3-hydroxybutanamide,
- (R)-3-(2-bromo-6-fluorophenyl)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide,
- 10 (R)-N-(1-(2-chloro-6-(2,2,2-trifluoroethoxy)pyridin-4-yl)cyclopropyl)-3-(2,6-difluorophenyl)-3-hydroxybutanamide,
- (R)-3-(2,4-difluorophenyl)-N-(1-(2-fluoro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide,
- 15 (R)-N-(1-(4,6-dichloropyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (R)-N-(1-(4-chloro-6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (R)-3-(2,6-difluorophenyl)-3-hydroxy-N-(1-(6-((2,2,2-trifluoroethyl) amino)pyridin-2-yl)cyclopropyl)butanamide,
- 20 (R)-3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(3-methoxy-5-(2,2,2-trifluoroethoxy)phenyl)-cyclopropyl)butanamide,
- (R)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,6-difluorophenyl)-3-hydroxybutanamide,
- 25 (R)-N-(1-(4-chloro-6-(neopentylamino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (R)-N-(1-(6-((cyclopropylmethyl)amino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (R)-N-(1-(4-chloro-6-(isopropylamino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- 30 (R)-N-(1-(2-chloro-6-((2,2,2-trifluoroethyl)amino)pyridin-4-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (R)-N-(1-(6-chloropyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,

- (R)-N-(1-(4-chloro-6-((2,2,2-trifluoroethyl)amino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (R)-3-(2,6-difluorophenyl)-3-hydroxy-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)butanamide,
- 5 (R)-3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)butanamide,
- (R)-3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(6-(trifluoromethyl)pyridin-2-yl)cyclopropyl)butanamide,
- (R)-N-(1-(3-(difluoromethyl)-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(4-fluorophenyl)-3-hydroxybutanamide,
- 10 (R)-3-(4-fluorophenyl)-N-(1-(2-fluoro-3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide,
- (R)-N-(1-(6-chloro-4-((2,2,2-trifluoroethyl)amino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- 15 (R)-N-(1-(6-chloro-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (R)-N-(1-(4-chloro-6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-hydroxy-3-(1-methyl-1H-indol-4-yl)butanamide,
- (R)-3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(2-((2,2,2-trifluoroethyl)amino)pyrimidin-4-yl)cyclopropyl)butanamide,
- 20 (R)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-dimethylthiazol-5-yl)-3-hydroxybutanamide,
- (R)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxy-3-(4-methylthiazol-2-yl)butanamide,
- 25 (R)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(5-chlorothiazol-2-yl)-3-hydroxybutanamide,
- (R)-3-hydroxy-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-(2,4,6-trifluorophenyl)butanamide,
- (S)-3-(6-chloropyridin-3-yl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)butanamide,
- 30 (S)-3-(5-fluoropyridin-2-yl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-butanamide,
- (S)-3-hydroxy-3-(2-methoxypyridin-4-yl)-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)butanamide,

- (S)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (S)-3-(2,4-difluorophenyl)-N-(1-(4-fluoro-3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide,
- 5 (S)-3-(4-fluorophenyl)-3-hydroxy-N-(1-(3-(trifluoromethyl)phenyl)cyclopropyl)-butanamide,
- (S)-3-(4-fluorophenyl)-3-hydroxy-N-(1-(3-(trifluoromethoxy)phenyl)cyclopropyl)butanamide,
- (S)-3-(4-fluorophenyl)-3-hydroxy-N-(1-(2-(2,2,2-trifluoroethoxy)pyridin-4-yl)cyclopropyl)butanamide,
- 10 (S)-3-hydroxy-3-(p-tolyl)-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)butanamide,
- (S)-3-(4-cyanophenyl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-butanamide,
- 15 (S)-3-(2,4-difluorophenyl)-N-(1-(2-fluoro-3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide,
- (S)-3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(4-methyl-3-(2,2,2-trifluoroethoxy)phenyl)-cyclopropyl)butanamide,
- (S)-N-(1-(3-chloro-5-(difluoromethyl)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- 20 (S)-3-(3,5-difluorophenyl)-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-butanamide,
- (S)-4,4,4-trifluoro-3-(4-fluorophenyl)-3-hydroxy-N-(1-(3-(2,2,2-trifluoroethoxy)phenyl)-cyclopropyl)butanamide,
- 25 (S)-N-(1-(3-bromophenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (S)-N-(1-(3-cyano-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(4-fluorophenyl)-3-hydroxybutanamide,
- (S)-3-(2,4-difluorophenyl)-N-(1-(3-fluoro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide,
- 30 (S)-N-(1-(4-chloro-3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (S)-N-(1-(3-(difluoromethyl)-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,

- (S)-N-(1-(3-bromo-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (S)-N-(1-(3-cyclopropyl-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- 5 (S)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,6-difluorophenyl)-3-hydroxybutanamide,
- (S)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(3,4-difluorophenyl)-3-hydroxybutanamide,
- (S)-3-(2-bromo-6-fluorophenyl)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide,
- 10 (S)-N-(1-(2-chloro-6-(2,2,2-trifluoroethoxy)pyridin-4-yl)cyclopropyl)-3-(2,6-difluorophenyl)-3-hydroxybutanamide,
- (S)-3-(2,4-difluorophenyl)-N-(1-(2-fluoro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide,
- 15 (S)-N-(1-(4,6-dichloropyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (S)-N-(1-(4-chloro-6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (S)-3-(2,6-difluorophenyl)-3-hydroxy-N-(1-(6-((2,2,2-trifluoroethyl) amino)pyridin-2-yl)cyclopropyl)butanamide,
- 20 (S)-3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(3-methoxy-5-(2,2,2-trifluoroethoxy)phenyl)-cyclopropyl)butanamide,
- (S)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,6-difluorophenyl)-3-hydroxybutanamide,
- 25 (S)-N-(1-(4-chloro-6-(neopentylamino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (S)-N-(1-(6-((cyclopropylmethyl)amino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (S)-N-(1-(4-chloro-6-(isopropylamino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- 30 (S)-N-(1-(2-chloro-6-((2,2,2-trifluoroethyl)amino)pyridin-4-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,
- (S)-N-(1-(6-chloropyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,

(S)-N-(1-(4-chloro-6-((2,2,2-trifluoroethyl)amino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,

(S)-3-(2,6-difluorophenyl)-3-hydroxy-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)butanamide,

5 (S)-3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)butanamide,

(S)-3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(6-(trifluoromethyl)pyridin-2-yl)cyclopropyl)butanamide,

10 (S)-N-(1-(3-(difluoromethyl)-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(4-fluorophenyl)-3-hydroxybutanamide,

(S)-3-(4-fluorophenyl)-N-(1-(2-fluoro-3-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxybutanamide,

(S)-N-(1-(6-chloro-4-((2,2,2-trifluoroethyl)amino)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,

15 (S)-N-(1-(6-chloro-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-(2,4-difluorophenyl)-3-hydroxybutanamide,

(S)-N-(1-(4-chloro-6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-hydroxy-3-(1-methyl-1H-indol-4-yl)butanamide,

20 (S)-3-(2,4-difluorophenyl)-3-hydroxy-N-(1-(2-((2,2,2-trifluoroethyl)amino)pyrimidin-4-yl)cyclopropyl)butanamide,

(S)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(2,4-dimethylthiazol-5-yl)-3-hydroxybutanamide,

(S)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-hydroxy-3-(4-methylthiazol-2-yl)butanamide,

25 (S)-N-(1-(3-chloro-5-(2,2,2-trifluoroethoxy)phenyl)cyclopropyl)-3-(5-chlorothiazol-2-yl)-3-hydroxybutanamide or

(S)-3-hydroxy-N-(1-(6-(2,2,2-trifluoroethoxy)pyridin-2-yl)cyclopropyl)-3-(2,4,6-trifluorophenyl)butanamide

or a pharmaceutically acceptable salt thereof.

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25. The compound according to any one of the preceding claims, wherein the compound is able to produce an increase in the activity of the $K_v7.2/K_v7.3$ heteromeric channel with an EC_{50} of less than 20 μM , as measured by a thallium ion (Tl^+) influx assay.

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26. A compound according to any one of claims 1 to 25 for use in a method of increasing the activity of a $K_v7.2/K_v7.3$ heteromeric channel in a subject, the method comprising administering an effective amount of the compound to the subject.

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27. A compound according to any one of claims 1 to 25 for use in an method of treatment, prevention or alleviation of epilepsy or pain in a subject, the method comprising administering an effective amount of the compound to the subject.

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