

METHYL 2-(FLUOROMETHYL)-5-OXO-4-PHENYL-4,5,6,7-TETRAHYDRO-1H-CYCLOPENTA[B]PYRIDINE-3-CARBOXYLATES AND
METHYL 2-(FLUOROMETHYL)-5-OXO-4-PHENYL-1,4,5,7-TETRAHYDROFURO[3,4-B]PYRIDINE-3-CARBOXYLATES AS CAV1.2
ACTIVATORS

5 1. FIELD OF THE INVENTION

The present invention relates to methyl 2-(fluoromethyl)-5-oxo-4-phenyl-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate and methyl 2-(fluoromethyl)-5-oxo-4-phenyl-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate compounds, pharmaceutical compositions containing them, and the use of such compounds as Cav1.2 activators for the treatment of calcium signaling deficit and/or synaptic dysfunction in psychiatric disorders including schizophrenia, bipolar disorder, major depressive disorder, and substance use disorders; neurodevelopmental disorders, such as attention deficit hyperactivity disorder, Phelan-McDermid Syndrome, and autism spectrum disorders; neurodegenerative disorders, such as multiple sclerosis, frontotemporal dementia, and Alzheimer's disease; and cardiac conditions such as Brugada Syndrome, Short QT syndrome, and early repolarization syndrome.

2. BACKGROUND OF THE INVENTION

Advancements in human genomics have shed light on the genetic basis of psychiatric disorders. Genome wide association studies (GWAS) in schizophrenia have identified over one hundred disease-associated loci, including Cav1.2 and other genes involved in neuronal calcium signaling. A cross-disorder GWAS analysis has identified Cav1.2 and its channel-forming beta subunit (CACNB2) as strongly associated with schizophrenia, bipolar disorder, major depressive disorder, ADHD, and autism spectrum disorders. In addition to evidence from GWAS, exome sequencing in patients with schizophrenia showed enrichment of disruptive mutations in Cav1.2 and other gene members of the neuronal calcium-signaling pathway including the CACNA2D, CACNB, CAMK2 genes. Cav1.2 has been shown to be important for neuronal differentiation and migration, neurite outgrowth, synaptic signaling, gene expression and brain plasticity. It has been shown to play a role in emotion, learning and memory, executive function, and reward responses of the brain.

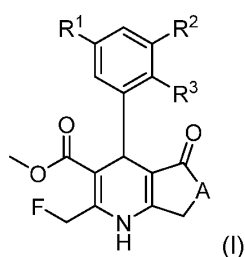
Cav1.2 is broadly expressed throughout the body and plays a major role in multiple organ systems including the cardiovascular system; however, the physiological function of Cav1.2 in the cardiovascular system is distinct from its function in the brain. Studies have shown that Cav1.2 is a key contributor to action potential generation in the heart while it is a key driver of intracellular signaling and gene expression in neurons with minimal role in action potential generation. In Timothy

Syndrome, $\text{Ca}_v1.2$ mutation p.G406R leads to distinct cellular phenotypes between cardiomyocytes and neurons. $\text{Ca}_v1.2$ mutations that cause cardiovascular specific disorders (Brugada Syndrome and Long QT syndrome type 8) are further evidence for the divergent functions of $\text{Ca}_v1.2$ in heart and brain.

5 Calcium channel activators have been previously reported, but further investigation into their use for neuropsychiatric disorders has been limited due to their effects on the cardiovascular system. In fact, many of these molecules were initially investigated and developed for their potential therapeutic use in heart failure. Most of the $\text{Ca}_v1.2$ SNPs associated from psychiatric GWAS studies reside in introns of the gene, and these risk SNPs have been shown to be associated with reduction
10 of mRNA expression that in many cases results in overall reduction of calcium current amplitude. Therefore, small molecules that can increase the overall current amplitude could be the most beneficial to patients.

3. SUMMARY OF THE INVENTION

15 The present disclosure provides a compound according to formula (I) or a pharmaceutically acceptable salt thereof



wherein:

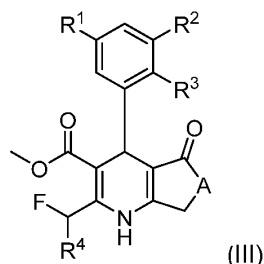
A is O or CH₂;

20 R¹ is H or F;

R² is H or F; and

R³ is OCHF₂, methyl, ethyl, or cyclopropyl each of which is optionally substituted with 1 to 3 F.

In a second aspect, the disclosure provides a compound according to formula (III) or a
25 pharmaceutically acceptable salt or solvate thereof,



wherein:

A is O or CH₂;

R¹ is H or F;

5 R² is H or F;

R³ is OCHF₂, methyl, ethyl, or cyclopropyl each of which is optionally substituted with 1 to 3 F; and

R⁴ is H or F.

10 In a third aspect, the disclosure provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In a fourth aspect, the disclosure provides for a compound of formula (I), or a pharmaceutically acceptable salt thereof for use in therapy, in particular in the treatment of psychiatric disorders including schizophrenia, bipolar disorder, major depressive disorder, and substance use disorders; neurodevelopmental disorders, such as attention deficit hyperactivity disorder, Phelan-McDermid
15 Syndrome, and autism spectrum disorders; neurodegenerative disorders, such as multiple sclerosis, frontotemporal dementia and Alzheimer's disease; and cardiac conditions such as Brugada Syndrome, Short QT syndrome, and early repolarization syndrome.

In a fifth aspect, the disclosure provides a method for the treatment of psychiatric disorders including schizophrenia, bipolar disorder, major depressive disorder, and substance use disorders; neurodevelopmental disorders, such as attention deficit hyperactivity disorder, Phelan-McDermid
20 Syndrome, and autism spectrum disorders; neurodegenerative disorders, such as multiple sclerosis, frontotemporal dementia and Alzheimer's disease; and cardiac conditions such as Brugada Syndrome, Short QT syndrome, and early repolarization syndrome. comprising administration of an effective amount of a compound according to formula (I), or a pharmaceutically acceptable salt
25 thereof, to a patient in need of treatment thereof.

In a sixth aspect, the disclosures provides for the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of

psychiatric disorders including schizophrenia, bipolar disorder, major depressive disorder, and substance use disorders; neurodevelopmental disorders, such as attention deficit hyperactivity disorder, Phelan-McDermid Syndrome, and autism spectrum disorders; neurodegenerative disorders, such as multiple sclerosis, frontotemporal dementia and Alzheimer's disease; and cardiac conditions such as Brugada Syndrome, Short QT syndrome, and early repolarization syndrome.

In a seventh aspect, the disclosure provides a method for the treatment of psychiatric disorders including schizophrenia, bipolar disorder, major depressive disorder, and substance use disorders; neurodevelopmental disorders, such as attention deficit hyperactivity disorder, Phelan-McDermid Syndrome, and autism spectrum disorders; neurodegenerative disorders, such as multiple sclerosis, frontotemporal dementia and Alzheimer's disease; and cardiac conditions such as Brugada Syndrome, Short QT syndrome, and early repolarization syndrome.comprising administration of a compound according to formula (I), or a pharmaceutically acceptable salt thereof, to a patient in need of treatment thereof.

In an eighth aspect, the disclosure provides a pharmaceutical composition comprising a compound of formula (III) or a pharmaceutically acceptable salt thereof.

In a ninth aspect, the disclosure provides for a compound of formula (III), or a pharmaceutically acceptable salt thereof for use in therapy, in particular in the treatment of psychiatric disorders including schizophrenia, bipolar disorder, major depressive disorder, and substance use disorders; neurodevelopmental disorders, such as attention deficit hyperactivity disorder, Phelan-McDermid Syndrome, and autism spectrum disorders; neurodegenerative disorders, such as multiple sclerosis, frontotemporal dementia and Alzheimer's disease; and cardiac conditions such as Brugada Syndrome, Short QT syndrome, and early repolarization syndrome.

In a tenth aspect, the disclosure provides a method for the treatment of psychiatric disorders including schizophrenia, bipolar disorder, major depressive disorder, and substance use disorders; neurodevelopmental disorders, such as attention deficit hyperactivity disorder, Phelan-McDermid Syndrome, and autism spectrum disorders; neurodegenerative disorders, such as multiple sclerosis, frontotemporal dementia and Alzheimer's disease; and cardiac conditions such as Brugada Syndrome, Short QT syndrome, and early repolarization syndrome.comprising administration of an effective amount of a compound according to formula (III), or a pharmaceutically acceptable salt thereof, to a patient in need of treatment thereof.

In a eleventh aspect, the disclosures provides for the use of a compound of formula (III) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of psychiatric disorders including schizophrenia, bipolar disorder, major depressive disorder, and substance use disorders; neurodevelopmental disorders, such as attention deficit

hyperactivity disorder, Phelan-McDermid Syndrome, and autism spectrum disorders; neurodegenerative disorders, such as multiple sclerosis, frontotemporal dementia and Alzheimer's disease; and cardiac conditions such as Brugada Syndrome, Short QT syndrome, and early repolarization syndrome.

5 In a twelfth aspect, the disclosure provides a method for the treatment of psychiatric disorders including schizophrenia, bipolar disorder, major depressive disorder, and substance use disorders; neurodevelopmental disorders, such as attention deficit hyperactivity disorder, Phelan-McDermid Syndrome, and autism spectrum disorders; neurodegenerative disorders, such as multiple sclerosis, frontotemporal dementia and Alzheimer's disease; and cardiac conditions such as Brugada
10 Syndrome, Short QT syndrome, and early repolarization syndrome.comprising administration of a compound according to formula (III), or a pharmaceutically acceptable salt thereof, to a patient in need of treatment thereof.

4. BRIEF DESCRIPTION OF THE DRAWINGS

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Figure 1: illustrates a representative XRPD of Form A of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate of the present disclosure. The x-axis shows the scattering angle in °2-Theta, the y-axis shows the intensity of the scattered X-ray beam in counts of detected photons.

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Figure 2: illustrates a representative XRPD of Form B of [methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate of the present disclosure. The x-axis shows the scattering angle in °2-Theta, the y-axis shows the intensity of the scattered X-ray beam in counts of detected photons.

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Figure 3: illustrates a representative XRPD of Form C of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate of the present disclosure of the present invention. The x-axis shows the scattering angle in °2-Theta, the y-axis shows the intensity of the scattered X-ray beam in counts of detected photons.

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Figure 4: illustrates a representative XRPD of Hydrate A of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate of the present disclosure. The x-axis shows the scattering angle in °2-Theta, the y-axis shows the intensity of the scattered X-ray beam in counts of detected photons.

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Figure 5: illustrates a representative XRPD of Hydrate B of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate of the present disclosure. The x-axis shows the scattering angle in °2-Theta, the y-axis shows the intensity of the scattered X-ray beam in counts of detected photons.

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Figure 6: illustrates simulated cardiac action potentials from an epicardial environment showing the impact of shifting the voltage of $Ca_v1.2$ activation to more negative membrane potentials. The x-axis is time (ms) and the y-axis is potential.

10 Figure 7: illustrates the single X-ray crystal of Example 6, methyl (R)-4-(2-((S)-1,2-difluoroethyl)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate, confirming that active enantiomer is the R-enantiomer.

15 Figure 8: illustrates the single X-ray crystal of Example 8, methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate, confirming that active enantiomer is the R-enantiomer.

20 Figure 9: illustrates the single X-ray crystal of Example 9, methyl (R)-4-(2-(difluoromethoxy)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate, confirming that active enantiomer is the R-enantiomer.

5. DETAILED DESCRIPTION OF THE INVENTION

5.1. Definitions

25 Generally, the nomenclature used herein and the laboratory procedures in organic chemistry, medicinal chemistry, and pharmacology described herein are those well-known and commonly employed in the art. Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

30 As used herein, “administration” and “administering” and “administer” refer to the manner in which a compound described herein is presented to a subject.

As used herein, “optionally substituted” means the group referred to can be substituted at one or more positions by any one or any combination of the radicals listed thereafter.

As used herein, "halo" or "halogen", as used herein, may be fluorine, chlorine, bromine or iodine.

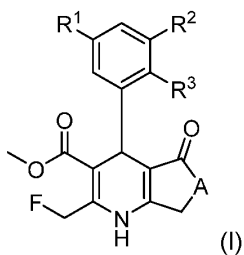
As used herein, "subject" refers to a living organism suffering from one or more of the diseases or disorders described here (e.g., psychiatric disorders including schizophrenia, bipolar disorder, major depressive disorder, and substance use disorders; neurodevelopmental disorders, such as attention deficit hyperactivity disorder, Phelan-McDermid Syndrome, and other autism spectrum disorders; neurodegenerative disorders, such as multiple sclerosis, frontotemporal dementia, and Alzheimer's disease; and cardiac conditions such as Brugada Syndrome, Short QT syndrome, and early repolarization syndrome) that can be treated by administration of a pharmaceutical composition described herein. Examples of subjects include mammals (e.g., humans and animals such as dogs, cows, horses, monkeys, pigs, sheep, goats, cats, mice, rabbits, rats, and transgenic non-human animals). In certain embodiments, the subject is a human, e.g., a human suffering from, at risk of suffering from, or potentially capable of suffering from a disease described herein (e.g., psychiatric disorders including schizophrenia, bipolar disorder, major depressive disorder, and substance use disorders; neurodevelopmental disorders, such as attention deficit hyperactivity disorder, Phelan-McDermid Syndrome, and other autism spectrum disorders; neurodegenerative disorders, such as multiple sclerosis, frontotemporal dementia, and Alzheimer's disease; and cardiac conditions such as Brugada Syndrome, Short QT syndrome, and early repolarization syndrome).

Throughout this specification and in the claims that follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", should be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

If there is a discrepancy between a depicted structure and a chemical name given to that structure, the depicted structure is to be accorded more weight. In addition, if the stereochemistry of a structure or a portion of a structure is not indicated with, for example, bold or dashed lines, the structure or portion of the structure is to be interpreted as encompassing all stereoisomers of the structure or portion of the structure.

5.2. Compounds

A compound according to formula (I) or a pharmaceutically acceptable salt or solvate thereof



wherein:

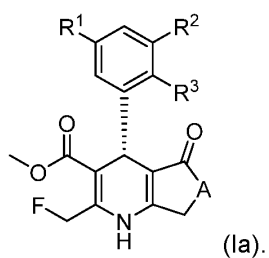
A is O or CH₂;

5 R¹ is H or F;

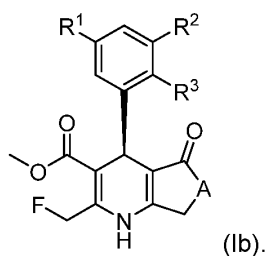
R² is H or F; and

R³ is OCHF₂, methyl, ethyl, or cyclopropyl each of which is optionally substituted with 1 to 3 F.

One embodiment is a compound of formula (Ia) or a pharmaceutically acceptable salt or solvate thereof,



Another embodiment is a compound of formula (Ib) or a pharmaceutically acceptable salt or solvate thereof,



In another embodiment, A is O.

In another embodiment, A is CH₂.

In another embodiment, R¹ is H.

In another embodiment, R¹ is F.

In another embodiment, R² is H.

5 In another embodiment, R² is F.

In another embodiment, R³ is OCHF₂.

In another embodiment, R³ is methyl, ethyl, or cyclopropyl each of which is optionally substituted with 1 to 3 F.

10 In another embodiment, R³ is methyl, ethyl, or cyclopropyl each of which is substituted with 1 to 3 F.

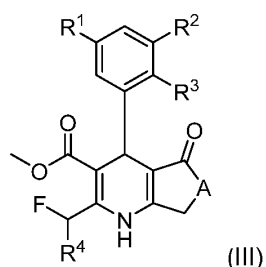
In another embodiment, R³ is CHF₂ or CF₃.

In another embodiment, R³ is ethyl substituted with 1 or 2 F.

In another embodiment, R³ is ethyl unsubstituted.

In another embodiment, R³ is cyclopropyl unsubstituted or substituted with 2 F.

15 A compound according to formula (III) or a pharmaceutically acceptable salt or solvate thereof,



wherein:

A is O or CH₂;

R¹ is H or F;

20 R² is H or F;

R³ is OCHF₂, methyl, ethyl, or cyclopropyl each of which is optionally substituted with 1 to 3 F; and

R^4 is H or F.

In another embodiment, A is O.

In another embodiment, A is CH_2 .

In another embodiment, R^1 is H.

5 In another embodiment, R^1 is F.

In another embodiment, R^2 is H.

In another embodiment, R^2 is F.

In another embodiment, R^3 is $OCHF_2$.

10 In another embodiment, R^3 is methyl, ethyl, or cyclopropyl each of which is optionally substituted with 1 to 3 F.

In another embodiment, R^3 is methyl, ethyl, or cyclopropyl each of which is substituted with 1 to 3 F.

In another embodiment, R^3 is CHF_2 or CF_3 .

In another embodiment, R^3 is ethyl substituted with 1 or 2 F.

15 In another embodiment, R^3 is ethyl unsubstituted.

In another embodiment, R^3 is cyclopropyl unsubstituted or substituted with 2 F.

In another embodiment, R^4 is F.

In another embodiment, R^4 is H.

20 Specific compounds include:

methyl (R)-4-(2-((R)-2,2-difluorocyclopropyl)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;

methyl (R)-4-(2-((S)-2,2-difluorocyclopropyl)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;

25 (R)-4-(2-cyclopropyl-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;

methyl (R)-4-(2-((R)-2,2-difluorocyclopropyl)-3,5-difluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;

- methyl (R)-4-(2-((S)-2,2-difluorocyclopropyl)-3,5-difluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- methyl (R)-4-(3,5-difluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- 5 methyl (R)-4-(3,5-difluoro-2-((S)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- methyl (R)-4-(2-((S)-1,2-difluoroethyl)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- methyl (R)-4-(2-((R)-1,2-difluoroethyl)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate;
- 10 methyl (R)-4-(2-((S)-1,2-difluoroethyl)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate;
- methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- 15 methyl (R)-4-(3-fluoro-2-((S)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- methyl (R)-4-(2-(difluoromethoxy)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- methyl (R)-4-(3,5-difluoro-2-(trifluoromethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- 20 methyl (R)-4-(2-(2,2-difluoroethyl)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- methyl (R)-4-(2-(2,2-difluoroethyl)-3,5-difluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- 25 methyl (R)-4-(2-cyclopropyl-3,5-difluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- methyl (R)-4-(2-cyclopropyl-3,5-difluorophenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate;
- methyl (R)-4-(2-(difluoromethyl)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- 30 methyl (R)-4-(2-((R)-1,2-difluoroethyl)-3,5-difluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- methyl (R)-4-(2-((S)-1,2-difluoroethyl)-3,5-difluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;

- methyl (R)-4-(3-fluoro-2-(trifluoromethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- methyl (R)-4-(2-(difluoromethyl)-3,5-difluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- 5 methyl (R)-4-(2-(difluoromethoxy)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- methyl 4-(2-(difluoromethoxy)-5-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- methyl (R)-4-(2-cyclopropyl-5-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- 10 methyl (R)-4-(2-cyclopropylphenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- methyl (R)-4-(5-fluoro-2-(trifluoromethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- 15 methyl (R)-2-(fluoromethyl)-5-oxo-4-(2-(trifluoromethyl)phenyl)-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- (R)-4-(3-fluoro-2-(2,2,2-trifluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate;
- methyl (R)-4-(2-(2,2-difluoroethyl)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-
- 20 1Hcyclopenta[b]pyridine-3-carboxylate;
- methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate;
- methyl (R)-4-(3-fluoro-2-((S)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate;
- 25 methyl (R)-4-(2-cyclopropyl-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate;
- methyl (S)-4-(3,5-difluoro-2-((S)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate; and
- methyl (S)-4-(3,5-difluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-
- 30 cyclopenta[b]pyridine-3-carboxylate.

Specific compounds further include:

methyl (R)-4-(2-ethylphenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate; and

methyl (R)-2-(difluoromethyl)-4-(3-fluoro-2-(1-fluoroethyl)phenyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.

Depending on the choice of the starting materials and procedures, the compounds can be present in the form of one of the possible stereoisomers or as mixtures thereof, for example as pure optical isomers, or as stereoisomer mixtures, such as racemates and diastereoisomer mixtures, depending on the number of asymmetric carbon atoms. The present disclosure is meant to include all such possible stereoisomers, including racemic mixtures, diastereomeric mixtures and optically pure forms. Optically active (*R*)- and (*S*)- stereoisomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. If the compound contains a double bond, the substituent may be E or Z configuration. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a cis- or trans-configuration. All tautomeric forms are also intended to be included.

As used herein, the terms "salt" or "salts" refers to an acid addition or base addition salt of a compound of the present disclosure. "Salts" include in particular "pharmaceutically acceptable salts". The term "pharmaceutically acceptable salts" refers to salts that retain the biological effectiveness and properties of the compounds of this disclosure and, which typically are not biologically or otherwise undesirable. In many cases, the compounds of the present disclosure are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids.

Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like.

Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, sulfosalicylic acid, and the like.

Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases.

Inorganic bases from which salts can be derived include, for example, ammonium salts and metals from columns I to XII of the periodic table. In certain embodiments, the salts are derived from sodium, potassium, ammonium, calcium, magnesium, iron, silver, zinc, and copper; particularly suitable salts include ammonium, potassium, sodium, calcium and magnesium salts.

Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like. Certain organic amines include isopropylamine, benzathine, choline, diethanolamine, diethylamine, lysine, meglumine, piperazine and tromethamine.

5 In another aspect, the present disclosure provides compounds of the present disclosure in acetate, ascorbate, adipate, aspartate, benzoate, besylate, bromide/hydrobromide, bicarbonate/carbonate, bisulfate/sulfate, camphorsulfonate, caprate, chloride/hydrochloride, chlorotheophyllonate, citrate, ethandisulfonate, fumarate, gluceptate, gluconate, glucuronate, glutamate, glutarate, glycolate, hippurate, hydroiodide/iodide, isethionate, lactate, lactobionate, 10 laurylsulfate, malate, maleate, malonate, mandelate, mesylate, methylsulphate, mucate, naphthoate, napsylate, nicotinate, nitrate, octadecanoate, oleate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, polygalacturonate, propionate, sebacate, stearate, succinate, sulfosalicylate, sulfate, tartrate, tosylate trifenate, trifluoroacetate or xinafoate salt form.

15 Compounds of the disclosure, i.e. compounds of formula (I) that contain groups capable of acting as donors and/or acceptors for hydrogen bonds may be capable of forming co-crystals with suitable co-crystal formers. These co-crystals may be prepared from compounds of formula (I) by known co-crystal forming procedures. Such procedures include grinding, heating, co-subliming, co-melting, or contacting in solution compounds of formula (I) with the co-crystal former under 20 crystallization conditions and isolating co-crystals thereby formed. Suitable co-crystal formers include those described in WO 2004/078163. Hence the disclosure further provides co-crystals comprising a compound of formula (I).

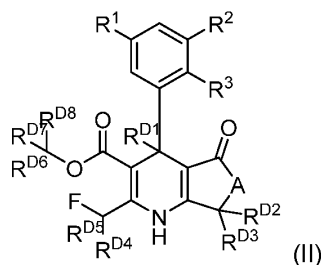
Furthermore, the compounds of the present disclosure, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization. The 25 compounds of the present disclosure may inherently or by design form solvates with pharmaceutically acceptable solvents (including water); therefore, it is intended that the disclosure embrace both solvated and unsolvated forms. The term "solvate" refers to a molecular complex of a compound of the present disclosure (including pharmaceutically acceptable salts thereof) with one or more solvent molecules. Such solvent molecules are those commonly used in the pharmaceutical art, which are 30 known to be innocuous to the recipient, e.g., water, ethanol, and the like. The term "hydrate" refers to the complex where the solvent molecule is water.

The disclosure includes unlabeled forms as well as isotopically labeled forms of compounds of formula (I). Isotopically labeled compounds have structures depicted by the formulae given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass

number. Isotopes that can be incorporated into compounds of the disclosure include, for example, isotopes of hydrogen.

Further, incorporation of certain isotopes, particularly deuterium (i.e., ^2H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index or tolerability. It is understood that deuterium in this context is regarded as a substituent of a compound of the present disclosure. The concentration of deuterium, may be defined by the isotopic enrichment factor. The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope. If a substituent in a compound of this disclosure is denoted as being deuterium, such compound has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation). It should be understood that the term "isotopic enrichment factor" can be applied to any isotope in the same manner as described for deuterium.

For example, formula (I) is deuterated as shown in formula (II):



or a pharmaceutically acceptable salt thereof, wherein R^1 , R^2 , R^3 , and A are as defined in formula (I); R^{D1} through R^{D8} are each independently H or D.

Other examples of isotopes that can be incorporated into compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}F , ^{31}P , ^{32}P , ^{35}S , ^{36}Cl , ^{123}I , ^{124}I , ^{125}I respectively. Accordingly, it should be understood that the disclosure includes compounds that incorporate one or more of any of the aforementioned isotopes, including for example, radioactive isotopes, such as ^3H and ^{14}C , or those into which non-radioactive isotopes, such as ^2H and ^{13}C are present. Such isotopically labelled compounds are useful in metabolic studies (with ^{14}C), reaction kinetic studies (with, for example ^2H or ^3H), detection

or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F or labeled compound may be particularly desirable for PET or SPECT studies. Isotopically-labeled compounds of the present disclosure can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

Any asymmetric atom (e.g., carbon or the like) of the compound(s) of the present disclosure can be present in racemic or enantiomerically enriched, for example the (*R*)-, (*S*)- or (*R,S*)- configuration. In certain embodiments, each asymmetric atom has at least 50 % enantiomeric excess, at least 60 % enantiomeric excess, at least 70 % enantiomeric excess, at least 80 % enantiomeric excess, at least 90 % enantiomeric excess, at least 95 % enantiomeric excess, or at least 99 % enantiomeric excess in the (*R*)- or (*S*)- configuration. Substituents at atoms with unsaturated double bonds may, if possible, be present in *cis*- (*Z*)- or *trans*- (*E*)- form.

Accordingly, as used herein a compound of the present disclosure can be in the form of one of the possible stereoisomers, rotamers, atropisomers, tautomers or mixtures thereof, for example, as substantially pure geometric (*cis* or *trans*) stereoisomers, diastereomers, optical isomers (antipodes), racemates or mixtures thereof.

Any resulting mixtures of stereoisomers can be separated on the basis of the physicochemical differences of the constituents, into the pure or substantially pure geometric or optical isomers, diastereomers, racemates, for example, by chromatography and/or fractional crystallization.

Any resulting racemates of compounds of the present disclosure or of intermediates can be resolved into the optical antipodes by known methods, e.g., by separation of the diastereomeric salts thereof, obtained with an optically active acid or base, and liberating the optically active acidic or basic compound. In particular, a basic moiety may thus be employed to resolve the compounds of the present disclosure into their optical antipodes, e.g., by fractional crystallization of a salt formed with an optically active acid, e.g., tartaric acid, dibenzoyl tartaric acid, diacetyl tartaric acid, di-*O*, *O'*-*p*-toluoyl tartaric acid, mandelic acid, malic acid or camphor-10-sulfonic acid. Racemic compounds of the present disclosure or racemic intermediates can also be resolved by chiral chromatography, e.g., high pressure liquid chromatography (HPLC) using a chiral adsorbent.

Methods of Use

The compounds of the present disclosure in free form or in pharmaceutically acceptable salt form, exhibit valuable pharmacological properties, e.g. $\text{Ca}_v1.2$ activation properties, e.g. as indicated

in vitro and in vivo tests as provided in the next sections, and are therefore indicated for therapy or for use as research chemicals, e.g. as tool compounds.

Compounds of the present disclosure may be useful in the treatment of an indication selected from the following list: psychiatric disorders including schizophrenia, bipolar disorder, major depressive disorder, and substance use disorders;

neurodevelopmental disorders, such as attention deficit hyperactivity disorder, Phelan-McDermid Syndrome, and autism spectrum disorders; and

neurodegeneration disorders, such as multiple sclerosis, frontotemporal dementia and Alzheimer's disease and

cardiac conditions, such as Brugada Syndrome, Short QT syndrome, and early repolarization syndrome. In one embodiment, the indication is a psychiatric disorder such as schizophrenia, bipolar disorder, major depressive disorder, and substance use disorders. In another embodiment, the indication is schizophrenia or bipolar disorder.

Thus, as a further aspect, the present disclosure provides the use of a compound of the present disclosure or a pharmaceutically acceptable salt thereof in therapy. In a further embodiment, the therapy is selected from a disease which may be treated by activation of $Ca_v1.2$. In another embodiment, the disease is selected from the afore-mentioned list of indications.

Thus, as a further aspect, the present disclosure provides a compound of the present disclosure or a pharmaceutically acceptable salt thereof for use in therapy. In a further embodiment, the therapy is selected from a disease which may be treated by activation of $Ca_v1.2$. In another embodiment, the disease is selected from the afore-mentioned list of indications.

In another aspect, the disclosure provides a method of treating a disease which is treated by activation of $Ca_v1.2$ comprising administration of a therapeutically effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof. In a further embodiment, the disease is selected from the afore-mentioned list of indications.

In another aspect, the disclosure provides a method of treating a disease which is treated by activation of $Ca_v1.2$ comprising administration of a compound of the present disclosure or a pharmaceutically acceptable salt thereof. In a further embodiment, the disease is selected from the afore-mentioned list of indications.

Thus, as a further aspect, the present disclosure provides the use of a compound of the present disclosure or a pharmaceutically acceptable salt thereof for the manufacture of a medicament. In a further embodiment, the medicament is for treatment of a disease which may be treated by activation of $Ca_v1.2$. In another embodiment, the disease is selected from the afore-mentioned list of indications.

In another aspect, the present disclosure provides a method for the treatment of schizophrenia, bipolar disorder, major depressive disorder, substance use disorder, ADHD, Phelan McDermid Syndrome, autism spectrum disorder, multiple sclerosis, frontotemporal dementia, Alzheimer's disease, Brugada Syndrome, Short QT syndrome, or early repolarization syndrome
5 which is treated by activation of $Ca_v1.2$ comprising administration of a therapeutically effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure provides a method for the treatment of schizophrenia, bipolar disorder, major depressive disorder, substance use disorder, ADHD, Phelan McDermid Syndrome, autism spectrum disorder, multiple sclerosis, frontotemporal dementia,
10 Alzheimer's disease, Brugada Syndrome, Short QT syndrome, or early repolarization syndrome which is treated by activation of $Ca_v1.2$ comprising administration of a compound of the present disclosure or a pharmaceutically acceptable salt thereof.

Thus, as a further aspect, the present disclosure provides the use of a compound of the present disclosure or a pharmaceutically acceptable salt thereof for treating a disease selected from
15 schizophrenia, bipolar disorder, major depressive disorder, substance use disorder, ADHD, Phelan McDermid Syndrome, autism spectrum disorder, multiple sclerosis, frontotemporal dementia, Alzheimer's disease, Brugada Syndrome, Short QT syndrome, or early repolarization syndrome.

Thus, as a further aspect, the present disclosure provides a compound of the present disclosure or a pharmaceutically acceptable salt thereof for use in treating a disease selected from
20 schizophrenia, bipolar disorder, major depressive disorder, substance use disorder, ADHD, Phelan McDermid Syndrome, autism spectrum disorder, multiple sclerosis, frontotemporal dementia, Alzheimer's disease, Brugada Syndrome, Short QT syndrome, or early repolarization syndrome.

In another aspect, the present disclosure provides a method for the treatment of schizophrenia, bipolar disorder, major depressive disorder, substance use disorder, ADHD, Phelan
25 McDermid Syndrome, autism spectrum disorder, multiple sclerosis, frontotemporal dementia, Alzheimer's disease, Brugada Syndrome, Short QT syndrome, or early repolarization syndrome comprising administration of a therapeutically effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure provides a method for the treatment of
30 schizophrenia, bipolar disorder, major depressive disorder, substance use disorder, ADHD, Phelan McDermid Syndrome, autism spectrum disorder, multiple sclerosis, frontotemporal dementia, Alzheimer's disease, Brugada Syndrome, Short QT syndrome, or early repolarization syndrome comprising administration of a compound of the present disclosure or a pharmaceutically acceptable salt thereof.

Thus, as a further aspect, the present disclosure provides the use of a compound of the present disclosure or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treatment of schizophrenia, bipolar disorder, major depressive disorder, substance use disorder, ADHD, Phelan McDermid Syndrome, autism spectrum disorder, multiple sclerosis, frontotemporal dementia, Alzheimer's disease, Brugada Syndrome, Short QT syndrome, or early repolarization syndrome.

Pharmaceutical Compositions

In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In a further embodiment, the composition comprises at least two pharmaceutically acceptable carriers, such as those described herein. The pharmaceutical composition can be formulated for particular routes of administration such as oral administration, parenteral administration (e.g. by injection, infusion, transdermal or topical administration), and rectal administration. Topical administration may also pertain to inhalation or intranasal application. The pharmaceutical compositions of the present disclosure can be made up in a solid form (including, without limitation, capsules, tablets, pills, granules, powders or suppositories), or in a liquid form (including, without limitation, solutions, suspensions or emulsions). Tablets may be either film coated or enteric coated according to methods known in the art. Typically, the pharmaceutical compositions are tablets or gelatin capsules comprising the active ingredient together with one or more of:

- a) diluents, e.g., lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine;
- b) lubricants, e.g., silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also
- c) binders, e.g., magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone; if desired
- d) disintegrants, e.g., starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and
- e) absorbents, colorants, flavors and sweeteners.

The pharmaceutical composition or combination of the present disclosure can be in unit dosage of about 1-1000 mg of active ingredient(s) for a subject of about 50-70 kg, or about 1-500 mg or about 1-250 mg or about 1-150 mg or about 0.5-100 mg, or about 1-50 mg of active ingredients. The therapeutically effective dosage of a compound, the pharmaceutical composition, or the combinations thereof, is dependent on the species of the subject, the body weight, age and individual

condition, the disorder or disease or the severity thereof being treated. A physician, clinician or veterinarian of ordinary skill can readily determine the effective amount of each of the active ingredients necessary to prevent, treat or inhibit the progress of the disorder or disease.

The above-cited dosage properties are demonstrable *in vitro* and *in vivo* tests using advantageously mammals, e.g., mice, rats, dogs, monkeys or isolated organs, tissues and preparations thereof. The compounds of the present disclosure can be applied *in vitro* in the form of solutions, e.g., aqueous solutions, and *in vivo* either enterally, parenterally, advantageously intravenously, e.g., as a suspension or in aqueous solution. The dosage *in vitro* may range between about 10^{-3} molar and 10^{-9} molar concentrations. A therapeutically effective amount *in vivo* may range depending on the route of administration, between about 0.1-500 mg/kg, or between about 1-100 mg/kg.

Crystalline Forms

The present disclosure relates to crystalline forms of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate and to a process for its preparation. Furthermore, the disclosure relates to a pharmaceutical composition comprising said crystalline form of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate, preferably in a predetermined and/or effective amount, and at least one pharmaceutically acceptable excipient. The pharmaceutical composition of the present disclosure can be used as a medicament, in particular for the treatment and/or prophylaxis of schizophrenia, bipolar disorder, major depressive disorder, substance use disorder, ADHD, Phelan-McDermid Syndrome, autism spectrum disorder, multiple sclerosis, frontotemporal dementia, Alzheimer's disease, Brugada Syndrome, Short QT syndrome, or early repolarization syndrome.

Different solid state forms of an active pharmaceutical ingredient often possess different properties. Differences in physicochemical properties of solid forms can play a crucial role for the improvement of pharmaceutical compositions, for example, pharmaceutical formulations with improved dissolution profile or with improved stability or shelf-life can become accessible due to an improved solid state form of an active pharmaceutical ingredient. Also processing or handling of the active pharmaceutical ingredient during the formulation process may be improved. New solid state forms of an active pharmaceutical ingredient can thus have desirable processing properties. They can be easier to handle, better suited for storage, and/or allow for better purification, compared to previously known solid forms.

Crystalline forms of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate may be characterized by analytical methods

well known in the field of the pharmaceutical industry for characterizing solids. Such methods comprise, but are not limited to, XRPD, SXRD, FTIR, Raman, DSC, TGA, and GMS (gravimetric measurement system). The forms may be characterized by one of the aforementioned analytical methods or by combining two or more of them.

5 Crystalline forms of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate may be referred to herein as being characterized by graphical data "as shown in" a figure. Such data include, for example, powder X-ray diffraction, FTIR and Raman spectroscopy. The person skilled in the art understands that factors such as variations in instrument type, response and variations in sample directionality, sample
10 concentration and sample purity may lead to small variations for such data when presented in graphical form, for example variations relating to the exact peak positions and intensities. However, a comparison of the graphical data in the figures herein with the graphical data generated for another or an unknown solid form and the confirmation that two sets of graphical data relate to the same crystal form is well within the knowledge of a person skilled in the art.

15 The term "reflection" with regard to powder X-ray diffraction as used herein, means peaks in an X-ray diffractogram, which are caused at certain diffraction angles (Bragg angles) by constructive interference from X-rays scattered by parallel planes of atoms in solid material, which are distributed in an ordered and repetitive pattern in a long-range positional order. Such a solid material is classified as crystalline material, whereas amorphous material is defined as solid material, which lacks long-
20 range order and only displays short-range order, thus resulting in broad scattering. According to literature, long-range order e.g. extends over approximately 100 to 1000 atoms, whereas short-range order is over a few atoms only (see *"Fundamentals of Powder Diffraction and Structural Characterization of Materials"* by Vitalij K. Pecharsky and Peter Y. Zavalij, Kluwer Academic Publishers, 2003, page 3).

25 The term "essentially the same" with reference to powder X-ray diffraction means that variabilities in reflection positions and relative intensities of the reflections are to be taken into account. For example, a typical precision of the 2-Theta values is in the range of $\pm 0.2^\circ$ 2-Theta, preferably in the range of $\pm 0.1^\circ$ 2-Theta.

30 Furthermore, one skilled in the art will appreciate that relative reflection intensities will show inter-apparatus variability as well as variability due to degree of crystallinity, preferred orientation, particle size, sample preparation and other factors known to those skilled in the art and should be taken as qualitative measure only.

 The terms "solid form" or "solid state form" as used herein interchangeably refer to any crystalline and/or amorphous phase of a compound.

As used herein, the term “amorphous” refers to a solid form of a compound that is not crystalline. An amorphous compound possesses no long-range order and does not display a definitive X-ray diffraction pattern with reflections.

As used herein the term “polymorph” refers to crystalline forms having the same chemical composition but different spatial arrangements of the molecules, atoms, and/or ions forming the crystal.

The term “co-crystal” as used herein refers to a crystalline material comprising two or more different molecular and/or ionic compounds in the same crystal lattice that are associated by nonionic and noncovalent bonds, wherein at least two of the individual molecular and/or ionic compounds are solids at room temperature.

The term “hydrate” as used herein, refers to a crystalline solid where either water is cooperated in or accommodated by the crystal structure e.g. is part of the crystal structure or entrapped into the crystal (water inclusions). Thereby, water can be present in a stoichiometric or non-stoichiometric amount. When water is present in stoichiometric amount, the hydrate may be referred to by adding greek numeral prefixes. For example, a hydrate may be referred to as a hemihydrate or as a monohydrate depending on the water/compound stoichiometry. The water content can be measured, for example, by Karl-Fischer-Coulometry.

The terms “dehydrating” or “dehydration” as used herein, describe the at least partial removal of water from the crystal structure of the host molecule.

The term “solvate” as used herein, refers to a crystalline solid where either one or more organic solvent(s) is/are cooperated in or accommodated by the crystal structure e.g. is/are part of the crystal structure or entrapped into the crystal (water inclusions). Thereby, the one or more organic solvent(s) can be present in a stoichiometric or non-stoichiometric amount. When the one or more organic solvent(s) is/are present in stoichiometric amount(s), the solvate may be referred to by adding greek numeral prefixes. For example, a solvate may be referred to as a hemisolvate or as a monosolvate depending on the solvent(s)/compound stoichiometry. The solvent content can be measured, for example, by GC, NMR, SXRD and/or TGA/MS.

The term “non-hygroscopic” as used herein refers to a compound showing a water uptake of at most 2 w-% in the sorption cycle when measured with GMS at a relative humidity in the range of from 0 to 95% RH and a temperature of $(25.0 \pm 0.1) ^\circ\text{C}$, based on the weight of the compound.

As used herein, the term “about” means within a statistically meaningful range of a value. Such a range can be within an order of magnitude, typically within 10%, more typically within 5%, even more typically within 1% and most typically within 0.1% of the indicated value or range. Sometimes, such a range can lie within the experimental error, typical of standard methods used for the measurement and/or determination of a given value or range.

As used herein, the term “substantially free of any other solid form” with reference to a composition comprising a particular solid form of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate means that the composition includes at most 20 w-%, preferably at most 10 w-%, more preferably at most 5 w-%, even more preferably at most 2 w-% and most preferably at most 1 w-% of any other solid form of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate, based on the weight of the composition.

As used herein, “substantially pure,” when used in reference to a form, means a compound having a purity greater than 90 w-%, including greater than 90, 91, 92, 93, 94, 95, 96, 97, 98, and 99 w-%, and also including equal to about 100 w-% of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate, based on the weight of the compound. The remaining material comprises other form(s) of the compound, and/or reaction impurities and/or processing impurities arising from its preparation. For example, a crystalline form of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate may be deemed substantially pure in that it has a purity greater than 90 w-%, as measured by means that are at this time known and generally accepted in the art, where the remaining less than 10 w-% of material comprises other form(s) of [Compound ABC] and/or reaction impurities and/or processing impurities.

Crystalline Form A

In a further aspect, the disclosure provides crystalline Form A of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate. The most prominent X-ray powder diffraction peaks for Form A of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate are shown in Table 1.

Table 1. The most prominent X-ray powder diffraction peaks for Form A

Peak	Angle [° 2theta]	d Value [Å]
1	6.7	13.218
2	7.2	12.255
3	8.5	10.387
4	10.4	8.481
5	10.8	8.220

6	13.5	6.543
7	14.4	6.160
8	15.6	5.685
9	18.5	4.795
10	21.6	4.116
11	22.4	3.963

One embodiment of the disclosure provides Form A of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate characterized by having a XRPD pattern comprising reflections at 2-Theta angles of:

- 5 (8.5 ± 0.2)°, (10.4 ± 0.2)° and (10.8 ± 0.2)°; or
 (8.5 ± 0.2)°, (10.4 ± 0.2)°, (10.8 ± 0.2)° and (22.4 ± 0.2)°; or
 (8.5 ± 0.2)°, (10.4 ± 0.2)°, (10.8 ± 0.2)°, (14.4 ± 0.2)° and (22.4 ± 0.2)°; or
 (8.5 ± 0.2)°, (10.4 ± 0.2)°, (10.8 ± 0.2)°, (14.4 ± 0.2)°, (21.6 ± 0.2)° and (22.4 ± 0.2)°; or
 (7.2 ± 0.2)°, (8.5 ± 0.2)°, (10.4 ± 0.2)°, (10.8 ± 0.2)°, (14.4 ± 0.2)°, (21.6 ± 0.2)° and (22.4 ± 0.2)°; or
 10 (7.2 ± 0.2)°, (8.5 ± 0.2)°, (10.4 ± 0.2)°, (10.8 ± 0.2)°, (14.4 ± 0.2)°, (18.5 ± 0.2)°, (21.6 ± 0.2)° and
 (22.4 ± 0.2)°; or
 (7.2 ± 0.2)°, (8.5 ± 0.2)°, (10.4 ± 0.2)°, (10.8 ± 0.2)°, (14.4 ± 0.2)°, (15.6 ± 0.2)°, (18.5 ± 0.2)°, (21.6
 ± 0.2)° and (22.4 ± 0.2)°; or
 (6.7 ± 0.2)°, (7.2 ± 0.2)°, (8.5 ± 0.2)°, (10.4 ± 0.2)°, (10.8 ± 0.2)°, (14.4 ± 0.2)°, (15.6 ± 0.2)°, (18.5
 15 ± 0.2)°, (21.6 ± 0.2)° and (22.4 ± 0.2)°; or
 (6.7 ± 0.2)°, (7.2 ± 0.2)°, (8.5 ± 0.2)°, (10.4 ± 0.2)°, (10.8 ± 0.2)°, (13.5 ± 0.2)°, (14.4 ± 0.2)°, (15.6 ±
 0.2)°, (18.5 ± 0.2)°, (21.6 ± 0.2)° and (22.4 ± 0.2)° when measured at a temperature in the range of
 from 20 to 30 °C with Cu-Kalpha_{1,2} radiation having a wavelength of 0.15419 nm.

In yet another embodiment, the present disclosure relates to a crystalline form of methyl (R)-
 20 4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-
 3-carboxylate, Form A characterized by having a XRPD pattern essentially the same as that shown
 in Figure 1 of the present disclosure, when measured at a temperature in the range of from 20 to
 30 °C with Cu-Kalpha_{1,2} radiation having a wavelength of 0.15418 nm.

In another embodiment, the present disclosure relates to a crystalline form of methyl (R)-
 25 (3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-
 carboxylate, Form A characterized by having a melting point onset temperature of 98 ± 5 °C, when
 measured with DSC at a heating rate of 10 K/min.

In another embodiment, the present disclosure relates to a crystalline form of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate Form A characterized by having a melting point peak maximum temperature of $104 \pm 5^\circ\text{C}$, when measured with DSC at a heating rate of 10 K/min.

5

Crystalline Form B

In a further aspect, the disclosure provides Form B of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate. The most prominent X-ray powder diffraction peaks for Form B of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate are shown in Table 2.

10

Table 2. The most prominent X-ray powder diffraction peaks for Form B

Peak	Angle [$^\circ$ 2theta]	d Value [Å]
1	9.1	9.658
2	12.0	7.344
3	13.7	6.458
4	14.5	6.122
5	15.7	5.637
6	18.3	4.838
7	21.4	4.151
8	23.0	3.861
9	23.8	3.736

15

In one embodiment, the disclosure provides Form B of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate characterized by having a XRPD pattern comprising reflections at 2-Theta angles of:

$(12.0 \pm 0.2)^\circ$, $(13.7 \pm 0.2)^\circ$ and $(21.4 \pm 0.2)^\circ$; or

20 $(12.0 \pm 0.2)^\circ$, $(13.7 \pm 0.2)^\circ$, $(18.3 \pm 0.2)^\circ$ and $(21.4 \pm 0.2)^\circ$; or

$(12.0 \pm 0.2)^\circ$, $(13.7 \pm 0.2)^\circ$, $(18.3 \pm 0.2)^\circ$, $(21.4 \pm 0.2)^\circ$ and $(23.8 \pm 0.2)^\circ$; or

$(12.0 \pm 0.2)^\circ$, $(13.7 \pm 0.2)^\circ$, $(18.3 \pm 0.2)^\circ$, $(21.4 \pm 0.2)^\circ$, $(23.0 \pm 0.2)^\circ$ and $(23.8 \pm 0.2)^\circ$; or

$(9.1 \pm 0.2)^\circ$, $(12.0 \pm 0.2)^\circ$, $(13.7 \pm 0.2)^\circ$, $(18.3 \pm 0.2)^\circ$, $(21.4 \pm 0.2)^\circ$, $(23.0 \pm 0.2)^\circ$ and $(23.8 \pm 0.2)^\circ$;

or

(9.1 ± 0.2)°, (12.0 ± 0.2)°, (13.7 ± 0.2)°, (14.5 ± 0.2)°, (18.3 ± 0.2)°, (21.4 ± 0.2)°, (23.0 ± 0.2)° and (23.8 ± 0.2)°; or

(9.1 ± 0.2)°, (12.0 ± 0.2)°, (13.7 ± 0.2)°, (14.5 ± 0.2)°, (15.7 ± 0.2)°, (18.3 ± 0.2)°, (21.4 ± 0.2)°, (23.0 ± 0.2)° and (23.8 ± 0.2)° when measured at a temperature in the range of from 20 to 30 °C

5 with Cu-K $\alpha_{1,2}$ radiation having a wavelength of 0.15419 nm.

In yet another embodiment, the present disclosure relates to a crystalline form of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate Form B characterized by having a XRPD pattern essentially the same as that shown in Figure 2 of the present invention, when measured at a temperature in the range of
10 from 20 to 30 °C with Cu-K $\alpha_{1,2}$ radiation having a wavelength of 0.15418 nm.

In another embodiment, the present disclosure relates to a crystalline form of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate Form B characterized by having a melting point onset temperature of 184 ± 5 °C, when measured with DSC at a heating rate of 10 K/min.

15 In another embodiment, the present disclosure relates to a crystalline form of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate Form B characterized by having a melting point peak maximum temperature of 185 ± 5 °C, when measured with DSC at a heating rate of 10 K/min.

20 Crystalline Form C

In a further embodiment, the disclosure provides Form C of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate. The most prominent X-ray powder diffraction peaks for Form C of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate are
25 shown in Table 3.

Table 3. The most prominent X-ray powder diffraction peaks for Form C

Peak	Angle [° 2theta]	d Value [Å]
1	7.0	12.613
2	10.3	8.554
3	11.3	7.844
4	12.3	7.162
5	12.8	6.914

6	14.0	6.331
7	15.5	5.701
8	16.6	5.338
9	17.3	5.109
10	18.2	4.874
11	20.6	4.310
12	22.0	4.036
13	22.7	3.908
14	23.2	3.831

In one embodiment, the disclosure provides Form C of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate characterized by having a XRPD pattern comprising reflections at 2-Theta angles of:

- 5 (10.3 ± 0.2)°, (15.5 ± 0.2)° and (20.6 ± 0.2)°; or
 (10.3 ± 0.2)°, (11.3 ± 0.2)°, (15.5 ± 0.2)° and (20.6 ± 0.2)°; or
 (10.3 ± 0.2)°, (11.3 ± 0.2)°, (15.5 ± 0.2)°, (20.6 ± 0.2)° and (22.7 ± 0.2)°; or
 (10.3 ± 0.2)°, (11.3 ± 0.2)°, (15.5 ± 0.2)°, (18.2 ± 0.2)°, (20.6 ± 0.2)° and (22.7 ± 0.2)°; or
 (10.3 ± 0.2)°, (11.3 ± 0.2)°, (15.5 ± 0.2)°, (18.2 ± 0.2)°, (20.6 ± 0.2)°, (22.7 ± 0.2)° and (22.0 ± 0.2)°;
 10 or
 (10.3 ± 0.2)°, (11.3 ± 0.2)°, (15.5 ± 0.2)°, (16.6 ± 0.2)°, (18.2 ± 0.2)°, (20.6 ± 0.2)°, (22.7 ± 0.2)° and
 (22.0 ± 0.2)°; or
 (10.3 ± 0.2)°, (11.3 ± 0.2)°, (12.8 ± 0.2)°, (15.5 ± 0.2)°, (16.6 ± 0.2)°, (18.2 ± 0.2)°, (20.6 ± 0.2)°,
 (22.7 ± 0.2)° and (22.0 ± 0.2)°; or
 15 (10.3 ± 0.2)°, (11.3 ± 0.2)°, (12.8 ± 0.2)°, (15.5 ± 0.2)°, (16.6 ± 0.2)°, (18.2 ± 0.2)°, (20.6 ± 0.2)°,
 (22.7 ± 0.2)°, (22.0 ± 0.2)° and (23.2 ± 0.2)°; or
 (10.3 ± 0.2)°, (11.3 ± 0.2)°, (12.3 ± 0.2)°, (12.8 ± 0.2)°, (15.5 ± 0.2)°, (16.6 ± 0.2)°, (18.2 ± 0.2)°,
 (20.6 ± 0.2)°, (22.7 ± 0.2)°, (22.0 ± 0.2)° and (23.2 ± 0.2)°; or
 (10.3 ± 0.2)°, (11.3 ± 0.2)°, (12.3 ± 0.2)°, (12.8 ± 0.2)°, (15.5 ± 0.2)°, (16.6 ± 0.2)°, (17.3 ± 0.2)°,
 20 (18.2 ± 0.2)°, (20.6 ± 0.2)°, (22.7 ± 0.2)°, (22.0 ± 0.2)° and (23.2 ± 0.2)°; or
 (10.3 ± 0.2)°, (11.3 ± 0.2)°, (12.3 ± 0.2)°, (12.8 ± 0.2)°, (14.0 ± 0.2)°, (15.5 ± 0.2)°, (16.6 ± 0.2)°,
 (17.3 ± 0.2)°, (18.2 ± 0.2)°, (20.6 ± 0.2)°, (22.7 ± 0.2)°, (22.0 ± 0.2)° and (23.2 ± 0.2)°; or
 (7.0 ± 0.2)°, (10.3 ± 0.2)°, (11.3 ± 0.2)°, (12.3 ± 0.2)°, (12.8 ± 0.2)°, (14.0 ± 0.2)°, (15.5 ± 0.2)°,
 (16.6 ± 0.2)°, (17.3 ± 0.2)°, (18.2 ± 0.2)°, (20.6 ± 0.2)°, (22.7 ± 0.2)°, (22.0 ± 0.2)° and (23.2 ± 0.2)°

when measured at a temperature in the range of from 20 to 30 °C with Cu-Kalpha_{1,2} radiation having a wavelength of 0.15419 nm.

In yet another embodiment, the present disclosure relates to a crystalline form of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate Form C characterized by having a XRPD pattern essentially the same as that shown in Figure 3 of the present invention, when measured at a temperature in the range of from 20 to 30 °C with Cu-Kalpha_{1,2} radiation having a wavelength of 0.15418 nm.

In another embodiment, the present disclosure relates to a crystalline form of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate Form C characterized by having a melting point onset temperature of 178 ± 5°C, when measured with DSC at a heating rate of 10 K/min.

In one embodiment, the present disclosure relates to a crystalline form of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate Form C characterized by having a melting point peak maximum temperature of 178 ± 5°C, when measured with DSC at a heating rate of 10 K/min.

Hydrate A

In a further aspect, the disclosure provides Hydrate A of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate. The most prominent X-ray powder diffraction peaks for crystalline form Hydrate A of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate are shown in Table 4.

Table 4. The most prominent X-ray powder diffraction peaks for Hydrate A

Peak	Angle [° 2theta]	d Value [Å]
1	10.0	8.857
2	10.6	8.323
3	11.5	7.709
4	12.8	6.937
5	14.4	6.154
6	17.5	5.051
7	18.1	4.893
8	20.0	4.436

9	20.8	4.273
10	22.9	3.878
11	23.5	3.787
12	25.0	3.553

In one embodiment, the disclosure provides Hydrate A methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate characterized by having a XRPD pattern comprising reflections at 2-Theta angles of:

(10.0 ± 0.2)°, (10.6 ± 0.2)° and (23.5 ± 0.2)°; or

(10.0 ± 0.2)°, (10.6 ± 0.2)°, (23.5 ± 0.2)° and (25.0 ± 0.2)°; or

(10.0 ± 0.2)°, (10.6 ± 0.2)°, (14.4 ± 0.2)°, (23.5 ± 0.2)° and (25.0 ± 0.2)°; or

(10.0 ± 0.2)°, (10.6 ± 0.2)°, (14.4 ± 0.2)°, (22.9 ± 0.2)°, (23.5 ± 0.2)° and (25.0 ± 0.2)°; or

(10.0 ± 0.2)°, (10.6 ± 0.2)°, (12.8 ± 0.2)°, (14.4 ± 0.2)°, (22.9 ± 0.2)°, (23.5 ± 0.2)° and (25.0 ± 0.2)°; or

(10.0 ± 0.2)°, (10.6 ± 0.2)°, (12.8 ± 0.2)°, (14.4 ± 0.2)°, (17.5 ± 0.2)°, (22.9 ± 0.2)°, (23.5 ± 0.2)° and (25.0 ± 0.2)°; or

(10.0 ± 0.2)°, (10.6 ± 0.2)°, (12.8 ± 0.2)°, (14.4 ± 0.2)°, (17.5 ± 0.2)°, (18.1 ± 0.2)°, (22.9 ± 0.2)°, (23.5 ± 0.2)° and (25.0 ± 0.2)°; or

(10.0 ± 0.2)°, (10.6 ± 0.2)°, (11.1 ± 0.2)°, (12.8 ± 0.2)°, (14.4 ± 0.2)°, (17.5 ± 0.2)°, (18.1 ± 0.2)°, (22.9 ± 0.2)°, (23.5 ± 0.2)° and (25.0 ± 0.2)°; or

(10.0 ± 0.2)°, (10.6 ± 0.2)°, (11.1 ± 0.2)°, (12.8 ± 0.2)°, (14.4 ± 0.2)°, (17.5 ± 0.2)°, (18.1 ± 0.2)°, (20.0 ± 0.2)°, (22.9 ± 0.2)°, (23.5 ± 0.2)° and (25.0 ± 0.2)°; when measured at a temperature in the range of from 20 to 30 °C with Cu-Kalpha_{1,2} radiation having a wavelength of 0.15419 nm.

In yet another embodiment, the present disclosure relates to a crystalline form of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate Hydrate A characterized by having a XRPD pattern essentially the same as that shown in Figure 4 of the present invention, when measured at a temperature in the range of from 20 to 30 °C with Cu-Kalpha_{1,2} radiation having a wavelength of 0.15418 nm.

In another embodiment, the present disclosure relates to a crystalline form of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate Hydrate A characterized by having a broad endothermic event with a peak maximum at temperature of 109 ± 10°C, when measured with DSC at a heating rate of 10 K/min.

30

Hydrate B

In a further aspect, the disclosure provides Hydrate B of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate. The most prominent X-ray powder diffraction peaks for crystalline Hydrate B of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate are shown in Table 5.

Table 5. The most prominent X-ray powder diffraction peaks for Hydrate B

Peak	Angle [° 2theta]	d Value [Å]
1	5.5	16.076
2	8.4	10.545
3	8.7	10.168
4	11.0	8.066
5	13.0	6.817
6	16.5	5.380
7	17.9	4.941
8	19.6	4.517
9	20.6	4.305
10	24.0	3.706

- In one embodiment, the disclosure provides Hydrate B of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate characterized by having a XRPD pattern comprising reflections at 2-Theta angles of:
- (5.5 ± 0.2)°, (8.4 ± 0.2)° and (13.0 ± 0.2)°; or
- (5.5 ± 0.2)°, (8.4 ± 0.2)°, (13.0 ± 0.2)° and (19.6 ± 0.2)°; or
- (5.5 ± 0.2)°, (8.4 ± 0.2)°, (8.7 ± 0.2)°, (13.0 ± 0.2)° and (19.6 ± 0.2)°; or
- (5.5 ± 0.2)°, (8.4 ± 0.2)°, (8.7 ± 0.2)°, (13.0 ± 0.2)°, (16.5 ± 0.2)° and (19.6 ± 0.2)°; or
- (5.5 ± 0.2)°, (8.4 ± 0.2)°, (8.7 ± 0.2)°, (13.0 ± 0.2)°, (16.5 ± 0.2)°, (19.6 ± 0.2)° and (20.6 ± 0.2)°; or
- (5.5 ± 0.2)°, (8.4 ± 0.2)°, (8.7 ± 0.2)°, (11.0 ± 0.2)°, (13.0 ± 0.2)°, (16.5 ± 0.2)°, (19.6 ± 0.2)° and (20.6 ± 0.2)°; or
- (5.5 ± 0.2)°, (8.4 ± 0.2)°, (8.7 ± 0.2)°, (11.0 ± 0.2)°, (13.0 ± 0.2)°, (16.5 ± 0.2)°, (17.9 ± 0.2)°, (19.6 ± 0.2)° and (20.6 ± 0.2)°; or

(5.5 ± 0.2)°, (8.4 ± 0.2)°, (8.7 ± 0.2)°, (11.0 ± 0.2)°, (13.0 ± 0.2)°, (16.5 ± 0.2)°, (17.9 ± 0.2)°, (19.6 ± 0.2)°, (20.6 ± 0.2)° and (24.0 ± 0.2)°; when measured at a temperature in the range of from 20 to 30 °C with Cu-K $\alpha_{1,2}$ radiation having a wavelength of 0.15419 nm.

In yet another embodiment, the present disclosure relates to a crystalline form of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate Hydrate B characterized by having a XRPD pattern essentially the same as that shown in Figure 5 of the present invention, when measured at a temperature in the range of from 20 to 30 °C with Cu-K $\alpha_{1,2}$ radiation having a wavelength of 0.15418 nm.

In another embodiment, the present disclosure relates to a crystalline form of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate Hydrate B characterized by having a broad endothermic event with a peak maximum at temperature of 93 ± 10 °C, when measured with DSC at a heating rate of 10 K/min.

In another aspect, the present invention relates to a composition comprising crystalline forms of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate as defined in any one of the embodiments described above, said composition being essentially free of any other solid form of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate. For example, a composition comprising the crystalline Hydrate A of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate of the present disclosure comprises at most 20 w-%, preferably at most 10 w-%, more preferably at most 5, 4, 3, 2 or 1 w-% of any other solid form of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate, based on the weight of the composition.

Ca_v1.2-HEK293(AUX) cell line

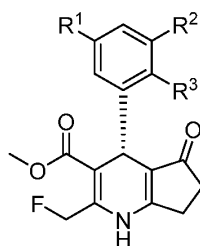
In one aspect, the present disclosure relates to a cell comprising a human Ca_v1.2 α 1C (α 1C) subunit (encoded by human *CACNA1C* transcript variant 14; GenBank ID: NM_001129840), an α 2 δ 2 (α 2 δ 2) auxiliary subunit (encoded by human *CACNA2D2* transcript variant 3; GenBank ID: NM_001174051), and a β 2 (β 2) auxiliary subunit (encoded by human *CACNB2* transcript variant 2; GenBank ID: NM_201596), wherein the α 1C subunit is constitutively expressed, and the α 2 δ 2 subunit and β 2 subunit are doxycycline-inducibly expressed. In another aspect, the present disclosure relates to the cell for use in a method for screening compounds for biological activity. In one aspect, the cell is comprised in a stable cell line, e.g., HEK293, constitutively expressing the α 1C subunit and doxycycline-inducibly expressing the α 2 δ 2 subunit and the β 2 subunit. In another aspect, the stable cell line is generated by DNA transfection or viral transduction,

e.g., via lentivirus or baculovirus. In one aspect, the cell is comprised in a cell line, e.g., HEK293, from transient DNA transfection constitutively expressing the $\alpha 1C$ subunit and doxycycline-inducibly expressing the $\alpha 2\Delta 2$ subunit and the $\beta 2$ subunit. In another aspect of the present disclosure, the compounds are $\text{Ca}_v1.2$ activators. In another aspect, the present disclosure relates to the cell for use in a method to identify an agent for treating, preventing, and/or diagnosing a disease or disorder, e.g., schizophrenia, bipolar disorder, major depressive disorder, substance use disorder, ADHD, Phelan-McDermid Syndrome, autism spectrum disorder, multiple sclerosis, frontotemporal dementia, Alzheimer's disease, Brugada Syndrome, Short QT syndrome, or early repolarization syndrome. In some aspects, the agent is a $\text{Ca}_v1.2$ activator.

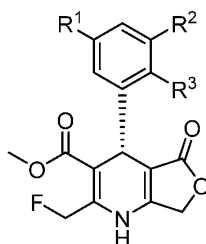
10 Intermediates and Examples

The following examples are intended to illustrate the disclosure and are not to be construed as being limitations thereon.

The examples were all separated into their single enantiomers and were tested in the Sophion Qpatch assay described in the Biological Data section below. However, the stereochemistry of each enantiomer was not determined. The stereochemistry of the active enantiomer for Example 6, methyl (R)-4-(2-((S)-1,2-difluoroethyl)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate, and Example 9, methyl (R)-4-(2-(difluoromethoxy)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate, were analyzed using single crystal x-ray crystallography and it was determined that the active enantiomer was the R-enantiomer. Therefore, it is assumed that the R-enantiomer of methyl 2-(fluoromethyl)-5-oxo-4-phenyl-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate and methyl 2-(fluoromethyl)-5-oxo-4-phenyl-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate compounds, depicted below, are the active enantiomers.



methyl (R)-2-(fluoromethyl)-5-oxo-4-phenyl-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate



methyl (R)-2-(fluoromethyl)-5-oxo-4-phenyl-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate

Example numbers (Example 1, 2, 3, etc.) are given for the active enantiomers which are all assumed to have the R-configuration. All other isomers isolated from the synthesis were given example numbers with letters (Example 1b, 2b, 3b etc.). Although there is strong evidence to suggest that the R-configuration is the desired stereochemistry, there is still the possibility that the S-enantiomer could be the active enantiomer.

Temperatures are given in degrees Celsius. If not mentioned otherwise, all evaporations are performed under reduced pressure, typically between about 15 mm Hg and 100 mm Hg (= 20-133 mbar). The structure of final products, intermediates and starting materials is confirmed by standard analytical methods, e.g., microanalysis and spectroscopic characteristics, e.g., MS, IR, NMR.

All starting materials, building blocks, reagents, acids, bases, dehydrating agents, solvents, and catalysts utilized to synthesis the compounds of the present disclosure are either commercially available or can be produced by organic synthesis methods known to one of ordinary skill in the art. Further, the compounds of the present disclosure can be produced by organic synthesis methods known to one of ordinary skill in the art as shown in the following examples. Abbreviations used are those conventional in the art or the following:

¹ H NMR	proton nuclear magnetic resonance
AUX	auxiliary subunit of Ca _v 1.2 channel
C	Celsius
CD ₃ OD	methanol-d ₄
CDCl ₃	chloroform-d
CHO	Chinese Hamster Ovary cells
Ct	threshold cycle in a quantitative polymerase chain reaction assay
d	doublet
DAST	diethylaminosulfur trifluoride
DCM	dichloromethane
dd	doublet of doublets

	DME	1,4-dimethoxyethane
	DMEM	Dulbecco's Modified Eagle Medium
	DMF	N,N-dimethylformamide
	DMSO	dimethylsulfoxide
5	DMSO-d6	dimethylsulfoxide-d6
	D-PBS	Dulbecco's Phosphate Buffered Saline
	EC50	Half maximal effective concentration
	EDTA	Ethylenediaminetetraacetic acid
	EGTA	Ethylene glycol-bis(β -aminoethyl ether)-N,N,N',N'-tetraacetic acid
10	Eq	equivalents
	EtOAc	ethyl acetate
	FAM	6-carboxyfluorescein
	FCS	Furin Cleavage Site
	FRT	Flippase recognition target site
15	g	gram
	h	hour(s)
	H ₂ O	water
	HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
	HOBT	1-hydroxy-7-azabenzotriazole
20	HPLC	high pressure liquid chromatography
	HRMS	high resolution mass spectrometry
	Hrs	hours
	Hz	hertz
	IACUC	Institutional Animal Care and Use Committee
25	IPA	isopropyl alcohol
	kg	kilogram
	L	liter
	LCMS	liquid chromatography mass spectrometry
	M	molar
30	m	multiplet
	m/z	mass to charge ratio
	mg	milligram
	MHz	mega hertz
	min	minutes
35	mL	milliliter

	ml	milliliter
	mL/min	milliliters per minute
	mm	millimeter
	mM	millimolar
5	mmol	millimoles
	mRNA	messenger ribonucleic acid
	MS	mass spectrometry
	mV	millivolt μ l
	N	normal
10	n-BuLi	n-butyllithium
	NMR	nuclear magnetic resonance
	NOESY	nuclear Overhauser effect spectroscopy
	pCMV	the cytomegalovirus promoter
	P2A	a peptide self-cleavage sequence derived from porcine teschovirus-1
15	PdCl ₂ (dppf)	Dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II)
	PD	Pharmacodynamics
	PK	Pharmacokinetics
	ppm	parts per million
	PyBOP	benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate
20	QT	the time interval between the Q wave and T wave of an electrocardiograph
	rac	racemic
	rpm	round per minute
	RNA	ribonucleic acid
	RT	room temperature
25	R _t	retention time
	RT-PCR	Reverse Transcription – Polymerase Chain Reaction
	s	singlet
	SFC	supercritical fluid chromatography
	SFM	Serum Free Medium
30	SNP	Single Nucleotide Polymorphism
	t	triplet
	TFA	trifluoroacetic acid
	THF	tetrahydrofuran
	uL	microliter
35	Um	micrometer

UPLC	ultra performance liquid chromatography
UV	ultraviolet
VIC	2'-chloro-7'-phenyl-1,4-dichloro-6-carboxy-fluorescein
v/v	volume/volume percent

5

Small molecule X-ray crystallography

Data collection

Intensity data were collected at 100 K on a Bruker AXS three-circle diffractometer with monochromated Cu(K α)-radiation, microfocus rotating anode generator, and a Smart 6000 CCD
10 detector using the SMART software (Bruker AXS (2003)). 16 ω -scans at different ϕ -Positions were performed to ensure appropriate data redundancy. Data processing and global cell refinement were performed with Saint (Bruker AXS (2012)). A semi-empirical absorption correction was applied, based on the intensities of symmetry-related reflections measured at different angular settings, using SADABS version 2016/2 (Krause L (2015)). The extinction
15 coefficient refined to 0.00048(11). Crystal data, data collection parameters, and convergence results are listed .

Structure solution and refinement

The structure was solved by dual space-recycling methods and subsequent DF syntheses and
20 refined based on full-matrix least-squares on F² using the SHELXTL program suite (Sheldrick GM (2001)) with SHELXL-2013/4.

References:

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25 and Neutron Diffraction. Part 1, Bond Lengths in Organic Compounds. J. Chem. Soc. Perkin Trans II; S1-S19.
- Bruker AXS (2005) SMART V5.632. Bruker AXS Inc., Madison, WI, USA.
- Bruker AXS (2012) SAINT V7.36A. Bruker AXS Inc., Madison, WI, USA.
- Krause L, Herbst-Irmer R, Sheldrick GM et al (2015) Comparison of silver and molybdenum
30 microfocus X-ray sources for single-crystal structure determination. J. Appl. Cryst.; 48: 3-10.
- Spek AL (2003) Single-crystal structure validation with the program PLATON. J. Appl. Cryst.; 36: 7-13.
- Sheldrick GM (2001) SHELXTL V6.12. Bruker AXS Inc.. Madison, WI, USA.

LCMS Method 1:

35

Instrument: Waters Acquity UPLC, photodiode array detector; Column: Acquity UPLC BEH C₁₈ 1.7µm, 21x30 mm; 2 min run time, 2% solvent B from 0 to 0.1 min, 2 → 98% solvent B:solvent A from 0.1 to 1.8 min, 98% solvent B for 0.2 min. Solvents: Solvent A = 0.1% formic acid in water (v/v), Solvent B = 0.1% formic acid in acetonitrile (v/v). Injection volume 2-5 µL; UV detection array 210-400, Mass detection 120-1250 (electrospray ionization); column at 50 °C; flow rate 1.0 mL/min.

LCMS Method 2:

Instrument: Waters Acquity UPLC, photodiode array detector; Column: Acquity UPLC BEH C₁₈ 1.7µm 21x50 mm; 2 min run time, 2% solvent B from 0 to 0.1 min, 2 → 98% solvent B:solvent A from 0.1 to 1.8 min, 98% solvent B for 0.2 min. Solvents: Solvent A = 5 mM ammonium hydroxide in water, solvent B = 5 mM ammonium hydroxide in acetonitrile. Injection volume 2-5 µL; UV detection array 210-400, Mass detection 120-1250 (electrospray ionization); column at 50 °C; flow rate 1.0 mL/min.

LCMS Method 3:

Instrument: Waters Acquity UPLC, photodiode array detector; Column Acquity UPLC BEH C₁₈ 1.7µm 21x30 mm; 5.2 min run time, 2 → 98% solvent B:solvent A from 0 to 5.15 min, 98% solvent B from 5.15 to 5.20 min. Solvents: Solvent A = 0.1% formic acid in water (v/v), solvent B = 0.1% formic acid in acetonitrile (v/v). Injection volume 2-5 µL; UV detection array 210-400, Mass detection 120-1600; column at 50 °C, flow rate 1.0 mL/min.

LCMS Method 4:

Instrument: Waters Acquity UPLC, photodiode array detector; Column Acquity UPLC BEH C₁₈ 1.7µm 21x30 mm; 5.2 min run time, 2 → 98% solvent B:solvent A from 0 to 5.15 min, 98% solvent B from 5.15 to 5.20 min. Solvents: Solvent A = 5 mM ammonium hydroxide in water, solvent B = 5 mM ammonium hydroxide in acetonitrile. Injection volume 2-5 µL; UV detection array 210-400, Mass detection 120-1600; column at 50 °C, flow rate 1.0 mL/min.

LCMS Method 5:

Instrument: Agilent 1200 LC/G1956A, diode array detector; Column: Chromolith Flash C₁₈, 1.6 micron 2x25 mm; 1.5 minute run time, 5 → 95% solvent B: solvent A from 0 → 1.2 minutes and then 95% solvent B from 1.21 → 1.5 minutes. Solvents: Solvent A= 0.0375% TFA in Water (v/v), Solvent B= 0.01875% TFA in Acetonitrile (v/v). Injection volume 2-5 µL; UV detection 220 and 254 nm, Mass detection 100-1000 (electrospray ionization); column at 50 °C; Flow rate 1.5 mL/min.

LCMS Method 6:

Instrument: SHIMADZU LCMS-2020, photo diode array detector; Column: Kinetex EVO C₁₈, 5µM, 1x30 mm; 1.55 minute run time, 5 → 95% solvent B:solvent A from 0 → 1.20 minutes and then 95% solvent B from 1.21 minutes to 1.55 minutes. Solvents: Solvent A= 0.025% NH₄OH in water (v/v), Solvent B= acetonitrile. Injection volume 2-5 µL; UV detection 220 and 254 nm, Mass detection 100-1000 (electrospray ionization); column at 40 °C; Flow rate 1.5 mL/min.

LCMS Method 7:

Instrument: API2000, column: Mercury MS Synergi 2 µm, 20X4.0mm, C12; gradient: A- 0.1% formic acid in water/B- acetonitrile: Time/%B: 0.0/30, 0.5/30, 1.5/95, 2.0/95, 2.5/30, 3.0/30, flow 2.0 mL / min; UV detection array 190-400, Mass detection 100-1000 (electrospray ionization); column temperature 30 °C.

LCMS Method 8:

Instrument: API3000, column: Synergi 2.5 µm MAX-RP, 20X4.0mm 100 A Mercury; gradient: 0.1% Formic acid in water B: acetonitrile: Time % B 0/10, 0.5/20, 1.5/95, 2.0/95, 2.5/10, 3/10, flow 2.0 mL / min; UV detection array 190-400 (Total Wavelength Chromatogram), Mass detection 100-1000 (electrospray ionization); column temperature 30 °C.

LCMS Method 9:

Instrument: API3000, column: Synergi 2.5 µm, 50x4.6mm ,MAX-RP 100 A ; gradient: 0.1% formic acid in water B: acetonitrile: Time 0.0/10, 0.2/50, 1.0/95, 1.5/100, 2.5/95, 2.9/50, 3.2/10, 4/10, flow 1.2 mL / min; UV detection array 190-400 (Total Wavelength Chromatogram), Mass detection 100-1000 (electrospray ionization); column temperature 30 °C.

LCMS Method 10:

Shimadzu, column: Mercury MS Synergi 2.5 µm, 20X4.0mm, C12; gradient: A- 0.1% formic acid in water/B- acetonitrile: Time/%B: 0.1/5, 0.5/5, 1.0/95, 1.5/95, 2.0/5, 3.0/5, flow 2.0 mL/min; UV detection array 200-400, Mass detection 100-1000 (electrospray ionization); column temperature 40 °C.

LCMS Method 11:

Shimadzu, column: Kinetex 5 µm EVO C18 100A, (100x2.1 mm); gradient: A- 0.1% formic acid in water/B- acetonitrile: Time/%B: 0/5, 1/30, 3/95, 4/95, 4.1/5, 6/5, flow 1.4 mL/min; UV detection array 200-400, Mass detection 100-1000 (electrospray ionization); column temperature 40 °C.

LCMS Method 12:

Shimadzu, column: Synergi 2.5µm MAX-RP 100 A, (20X4.0mm) Mercury; gradient: A- 0.1% formic acid in water/B- acetonitrile: Time/%B: 0.1/5, 0.5/5, 1.0/95, 1.5/95, 2.0/5, 3.0/5, flow 2.0 mL/min; UV detection array 200-400, Mass detection 100-1000 (electrospray ionization); column temperature 40 °C.

5

LCMS Method 13:

Acquity, Column: UPLC BEH C18 1.7 µm 2.1x50mm; Gradient: A- 0.1% formic acid in water/B- acetonitrile: 2.2min run time, 2 → 98% solvent B: solvent A from 0 → 1.76 minutes and then 95% solvent B from 1.76 minutes to 2.0 minutes; flow 1.0 mL/min; UV detection array 210-400 nm; Mass Range 100-2050 Da; HRMS_2min; Column Temperature 50 °C

10

Preparative HPLC methods for purification:

Method 1: HPLC Column: XBRIDGE -C18 (19.0 x 150 mm, 5 micron), Mobile phase-A: 0.1% TFA in H₂O, B: CH₃CN, gradient (Time / % B): 0/20, 2/20, 8/50) Flow rate: [19 mL / min].

15

Method 2: HPLC Column: ZORBAX ECLIPSE XDB C18 (21.2 X 150 mm, 5 micron), Mobile phase-A: 0.1% TFA in H₂O, B: CH₃CN, gradient (Time / % B): 0/10, 2/20, 10/40 and Flow rate: [20 mL / min].

Method 3: HPLC [Column: XBRIDGE C18 (21.2 x 150 mm, 5 micron), Mobile phase-A: 10 mM NH₄HCO₃ in water, B: CH₃CN, gradient (Time / % B): 0/10, 2/20, 8 /50 and Flow rate: [18 mL / min].

20

Method 4: HPLC Column: Gemini NX C18 (21.2 x 150.00 mm, 5 micron); Mobile Phase-(A): 0.1% TFA in water (B): Acetonitrile/Methanol; Flow: 15 mL/min; (Time/%B 0/20, 2/20, 8/20)

Method 5: HPLC Column: KINETEX EVO 5 µ C18 (21.2 X 150 mm), Mobile Phase: WATER (A) CH₃CN (B), gradient (Time / % B): 0/20, 2/30, 7/70 and Flow rate: [18 mL / min].

25

Method 6: HPLC column: KINETEX C18, (21.2 x 150mm), Mobile phases: A: WATER, B: CH₃CN:MeOH, gradient (Time / % B): 0/20, 2/30, 7/70, Flow rate: 18 mL/min].

Method 7: HPLC Column: KINETEX (21.2 x 150 mm, 5 micron), Mobile phases: A = 0.05% TFA in water, B = CH₃CN, gradient (Time / % B): 0/20, 2/30, 10/60, Flow rate: 20 mL/min].

Chiral preparative HPLC methods for separation of isomers:

30

Method 1: Column: CHIRALPAK IC (10 x 250 mm, 5 micron), Mobile Phase: Hexane (A) IPA: MeOH,1:1 (B); Flow rate : 8mL/min; Isocratic: 96:04(A: B).

Method 2: Column: REGIS WELKO (250 x 10mm, 5 micron), Mobile Phase: Hexane (A): EtOH, 1:1 (B); Flow rate : 9 mL/min; Isocratic: 85:15(A: B).

Method 3: Column: CHIRALPAC IG (250 x 10mm, 5 micron), Mobile Phase: IPA (A): MeOH, 1:1 (B); Flow rate : 6 mL/min; Isocratic: 98:2(A: B).

- 5 **Method 4:** Column: LUX CELLULOSE-4 (10 x 250 mm, 5 micron), Mobile Phase: Hexane (A) EtOH: IPA 1:1 (B); Flow rate: 8 mL/min; Isocratic: 90: 10(A: B).

Method 5: Column: LUX CELLULOSE-4 (10 x 250 mm, 5 micron), Mobile Phase: Hexane (A) EtOH: 1:1 (B); Flow rate: 8 mL/min; Isocratic: 90: 10(A: B).

- 10 **Method 6:** Column: LUX CELLULOSE-4 (10 x 250 mm, 5 micron), Mobile Phase: Hexane (A); EtOH: MeOH 1:1 (B); Flow rate: 18 mL/min; Isocratic: 90: 10(A: B).

Method 7: Column: LUX CELLULOSE-4 (21.2 x 250 mm, 5 micron), Mobile Phase: Hexane (A); EtOH: MeOH 1:1 (B); Flow rate: 19 mL/min; Isocratic: 80: 20(A: B).

Method 8: Column: REGIS (10 X 250 mm, 5 micron), MOBILE PHASE: CO₂ (A) MeOH: EtOH 1:1(B); FLOW: 13 mL/min, Isocratic: 80: 20(A: B).

- 15 **Method 9:** Column: LUX CELLULOSE-4 (10 x 250 mm, 5 micron), Mobile Phase: Hexane (A) 0.1 % DEA IN EtOH: MeOH(50:50) (B); Flow rate: 7 mL/min; Isocratic: 93: 07(A: B).

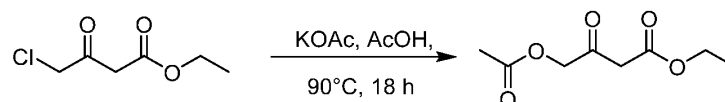
Chiral analytical HPLC methods for analysis of separated isomers:

Method 1: Column: Lux, Cellulose-4 (250 X 4.6 mm, 5 micron; Mobile Phase: A=n-HEXANE, B= 0.1% TFA IN ETHANOL; 1 mL/min; Isocratic: 70: 30 (A: B)

- 20 **Method 2:** Column: LUX CELLULOSE-4 (4.6 x 250 mm, 5 micron; Mobile Phase: Hexane (A) EtOH: 1:1 (B); Flow rate: 1 mL/min; Isocratic: 50: 50(A: B).

Method 3: Column: REGIS, (S, S) WHELK-01 (250 X 4.6 mm, 5 micron; Mobile Phase: A=n-HEXANE, B = ETHANOL; Flow rate: 1 mL/min; Isocratic: 70: 30 (A: B).

- 25 **Intermediate A:** Formation of ethyl 4-acetoxy-3-oxobutanoate



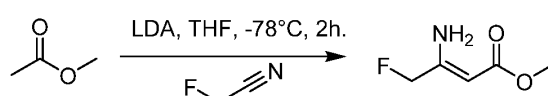
To a solution of ethyl 4-chloro-3-oxobutanoate (200 g, 1215.1 mmol) in acetic acid (1500 mL) was added potassium acetate (357 g, 3645.4 mmol). The resulting solution was stirred at 90 °C for 18

hrs. The solvent was dissolved in water (2 L) and extracted into ethyl acetate (1 L X 4 times). EtOAc phases were combined and washed with saturated NaHCO_3 solution (2 L), brine and dried over Na_2SO_4 . The solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography (0 $\rightarrow$ 15%) ethyl acetate in petroleum ether afforded the title compound as a light brown liquid ethyl 4-acetoxy-3-oxobutanoate. (152 g).

^1H NMR (400 MHz, CDCl_3) δ 4.78 (s, 2H), 4.20 (q, J = 14.1, 7.2 Hz, 2H), 3.49 (s, 2H), 2.16 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H).

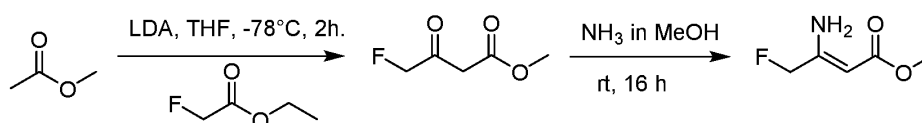
Intermediate B: Formation of methyl (Z)-3-amino-4-fluorobut-2-enoate

Method 1:



A solution of methyl acetate (36.5 g, 492.71 mmol) in tetrahydrofuran (200 mL) under nitrogen atmosphere was cooled to -78°C , lithium diisopropylamide in THF (246.44 mL, 2.0 M, 492.71 mmol) was added to reaction slowly over a period of 20 min, the resulting mixture was stirred for 1h at -78°C followed by addition of 2-fluoroacetonitrile (19.4 g, 328.9 mmol) in a solution of tetrahydrofuran (150 mL) dropwise. Reaction mixture and stirred at -78°C for another 1h before addition of saturated ammonium chloride solution (200 mL) was added and product extracted into ethyl acetate (5 L). EtOAc was washed with saturated brine solution (500 mL) and dried over Na_2SO_4 . The solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography (0 $\rightarrow$ 10%) ethyl acetate in petroleum ether afforded the title compound as a white crystalline solid methyl (Z)-3-amino-4-fluorobut-2-enoate (16 g).

Method 2:



Step 1: A solution of methyl acetate (83.78 g, 1131.0 mmol) in tetrahydrofuran (800 mL) under nitrogen atmosphere was cooled to -78°C , then lithium diisopropylamide in THF (565.5 mL, 2.0 M, 1131.0 mmol) was added to reaction slowly over a period of 20 min. Resulting mixture was stirred for 1h at -78°C and then ethyl 2-fluoroacetate (100 g, 942.5 mmol) was added in a solution of tetrahydrofuran (200 mL) drop wise and the reaction mixture and stirred at -78°C for another 1h. Saturated ammonium chloride solution (200 mL) was added to reaction mixture and product extracted into ethyl acetate (5 L). EtOAc was washed with saturated brine solution (500 mL) and dried over

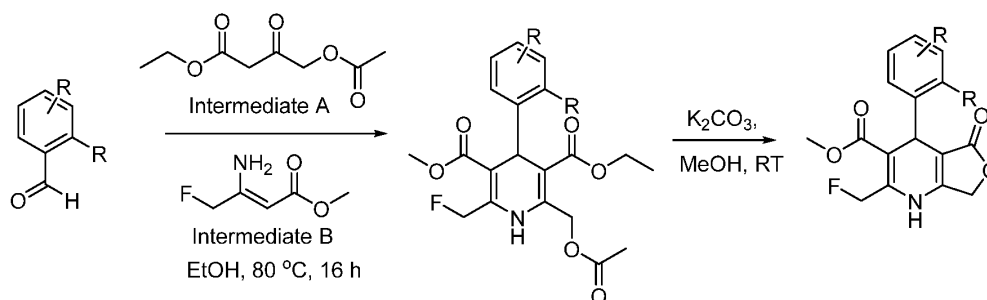
Na₂SO₄. The solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography (0 → 10%) ethyl acetate in petroleum ether to give yellow crystals of methyl 4-fluoro-3-oxobutanoate (60 g).

¹H NMR (400 MHz, CDCl₃) δ 4.97 (s, 1H), 4.85 (s, 1H), 3.76 (d, J = 2.3 Hz, 3H), 3.62 (d, J = 3.7 Hz, 2H).

Step 2: To methyl 4-fluoro-3-oxobutanoate (from step 1, 60 g) in a sealed tube was added saturated ammonia solution in methanol (300 mL) at room temperature. The resulting mixture was stirred at room temperature for 16 hrs. The solvent was removed under reduced pressure afforded the title compound as a white solid methyl (Z)-3-amino-4-fluorobut-2-enoate (51 g).

¹H NMR (300 MHz, DMSO-d₆) δ 4.98 (t, J = 0.7, 0.7 Hz, 1H), 4.82 (t, J = 0.7, 0.7 Hz, 1H), 4.53 (q, 1H), 3.53 (d, J = 1.2 Hz, 3H).

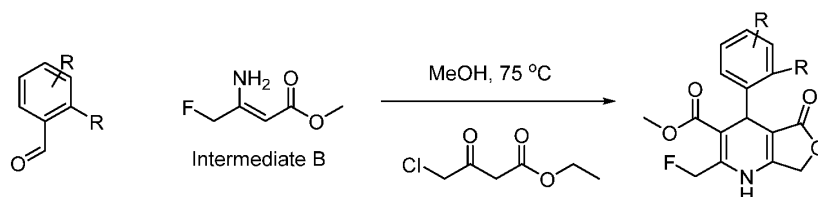
General Procedure I



Step 1: To a solution of aldehyde (1 mmol) in EtOH (10 mL) was added methyl (Z)-3-amino-4-fluorobut-2-enoate (intermediate B, 1 mmol or 1.2 mmol) and ethyl 4-acetoxy-3-oxobutanoate (intermediate A, 1 mmol or 1.2 mmol). The resulting solution was stirred at 80 °C for 16 hrs. The solvent was removed under reduced pressure afforded the title compound (crude).

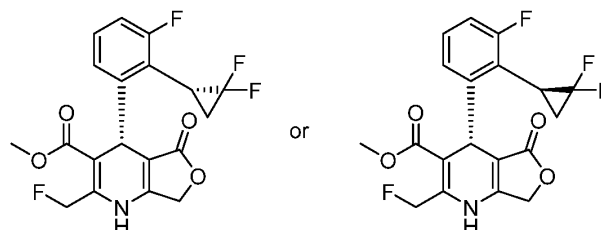
Step 2: To a crude intermediate from step 1 in methanol (10 mL) was added potassium carbonate (5 mmol). The resulting solution was stirred at room temperature for 2 hrs. The solvent was removed under reduced pressure and this added to water. Product extracted into ethyl acetate (100 mL), washed with brine and dried over Na₂SO₄. The solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography.

General Procedure II



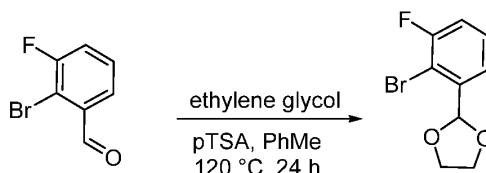
To a solution of aldehyde (1 mmol) in MeOH (10 mL) was added methyl (Z)-3-amino-4-fluorobut-2-enoate (intermediate B, 1 mmol or 1.2 mmol) and ethyl 4-acetoxy-3-oxobutanoate (intermediate A, 1 mmol or 1.2 mmol). The resulting solution was stirred at 75 °C for 16-48 hrs. The solvent was removed under reduced pressure and the product was purified using silica flash chromatography.

Example 1: methyl (R)-4-(2-((R or S)-2,2-difluorocyclopropyl)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate



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Step 1: 2-(2-bromo-3-fluorophenyl)-1,3-dioxolane

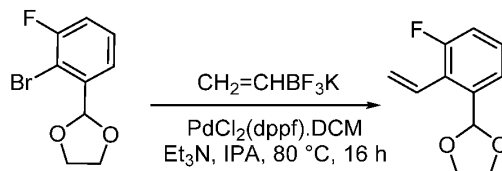


To a solution of 2-bromo-3-fluorobenzaldehyde (60 g, 295.56 mmol) and ethylene glycol (65.4 mL, 1182.2 mmol) in toluene (600 mL) was added p-toluenesulfonic acid monohydrate (28.11 g, 147.78 mmol). The resulting solution was stirred at 120 °C for 24 hrs using dean-stark apparatus. Reaction mixture was poured into water (2 L) and extracted into ethyl acetate (3 L). EtOAc was washed with saturated NaHCO₃ solution (1 L), brine and dried over Na₂SO₄. The solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography (0 → 10%) ethyl acetate in petroleum ether afforded the title compound 2-(2-bromo-3-fluorophenyl)-1,3-dioxolane (60 g) as a colorless liquid.

20

¹H NMR (400 MHz, CDCl₃) δ 7.42 - 7.37 (m, 1H), 7.34 - 7.29 (m, 1H), 7.16 - 7.10 (m, 1H), 6.10 (s, 1H), 4.19 - 4.09 (m, 4H).

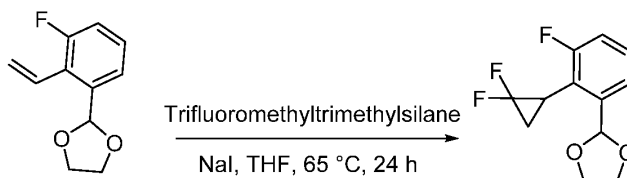
Step 2: 2-(3-fluoro-2-vinylphenyl)-1,3-dioxolane



To a solution of 2-(2-bromo-3-fluorophenyl)-1,3-dioxolane (from step 1, 15 g, 60.72 mmol) and
 5 potassium vinyltrifluoroborate (16.26 g, 121.45 mmol) in isopropyl alcohol (200 mL) was added
 triethylamine (25.5 mL, 182.16 mmol) and [1,1'-Bis(diphenylphosphino)ferrocene]
 dichloropalladium(II).DCM (4.95 g, 6.07 mmol). The resulting solution was degassed with Argon gas
 for 10 min and stirred at 80°C for 16 hrs. The reaction mixture was filtered and washed with ethyl
 acetate (100 mL). The filtrate was added to water (1 L) and product extracted into ethyl acetate (2 L).
 10 EtOAc phase was washed with brine and dried over Na₂SO₄. The solvent was removed under
 reduced pressure and purification of the crude product by silica flash chromatography (0 → 10%)
 ethyl acetate in petroleum ether afforded the title compound 2-(3-fluoro-2-vinylphenyl)-1,3-dioxolane
 (7.5 g) as a colorless liquid.

¹H NMR (400 MHz, CDCl₃) δ 7.45 - 7.41 (m, 1H), 7.27 - 7.20 (m, 1H), 7.10 - 7.03 (m, 1H), 6.82 (dd,
 15 J = 17.7, 11.7 Hz, 1H), 5.82 - 5.78 (m, 1H), 5.66 - 5.60 (m, 1H), 5.95 (s, 1H), 4.18 - 4.02 (m, 4H).

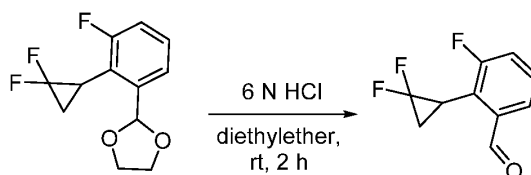
Step 3: 2-(2-(2,2-difluorocyclopropyl)-3-fluorophenyl)-1,3-dioxolane



To a solution of 2-(3-fluoro-2-vinylphenyl)-1,3-dioxolane (from step 2, 6.5 g, 33.47 mmol) and
 20 trifluoromethyltrimethylsilane (50 mL, 334.7 mmol) in tetrahydrofuran (120 mL) was added sodium
 iodide (2.5 g, 16.73 mmol). The resulting solution was stirred at 65°C for 24 hrs. The solvent was
 evaporated under reduced pressure and the residue was dissolved in dichloromethane (100 mL).
 This was washed with water (50 mL), brine and dried over Na₂SO₄. The solvent was removed under
 reduced pressure which afforded the title compound 2-(2-(2,2-difluorocyclopropyl)-3-fluorophenyl)-
 25 1,3-dioxolane (8 g) as a colorless liquid.

¹H NMR (400 MHz, CDCl₃) δ 7.42 (d, J = 7.5 Hz, 1H), 7.34-7.28 (m, 1H), 7.16 - 7.03 (m, 1H), 6.06
 (s, 1H), 4.20 - 4.01 (m, 4H), 2.77 - 2.66 (m, 1H), 2.02 - 1.72 (m, 2H).

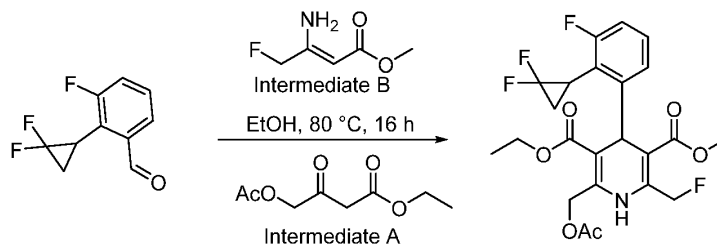
Step 4: 2-(2,2-difluorocyclopropyl)-3-fluorobenzaldehyde



To a solution of 2-(2,2-difluorocyclopropyl)-3-fluorophenyl-1,3-dioxolane (from step 3, 8 g, 32.76 mmol) and in diethyl ether (80 mL) was added 6N HCl (10 mL). The resulting solution was stirred at room temperature for 2 hrs. This was washed with water (50 mL), saturated NaHCO₃ solution (100 mL), brine and dried over Na₂SO₄. The solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography (0 → 5%) ethyl acetate in petroleum ether afforded the title compound 2-(2,2-difluorocyclopropyl)-3-fluorobenzaldehyde (3.8 g) as a colorless liquid.

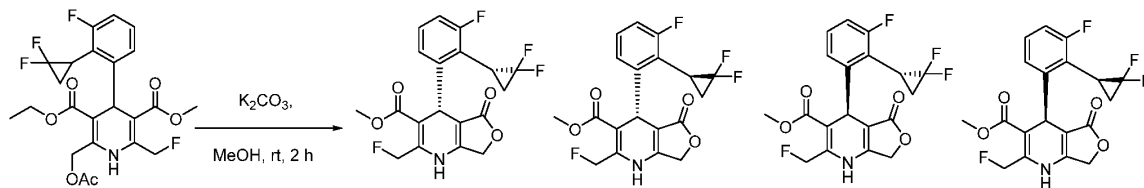
¹H NMR (400 MHz, CDCl₃) δ 10.28 (s, 1H), 7.70 (d, J = 6.9 Hz, 1H), 7.50 - 7.43 (m, 1H), 7.36 - 7.26 (m, 1H), 2.92 - 2.81 (m, 1H), 2.16 - 2.06 (m, 1H), 1.67 - 1.53 (m, 1H).

Step 5: 3-ethyl 5-methyl 2-(acetoxymethyl)-4-(2-(2,2-difluorocyclopropyl)-3-fluorophenyl)-6-(fluoromethyl)-1,4-dihydropyridine-3,5-dicarboxylate



Title compound was synthesized using step 1 of general procedure I (using the aldehyde from step 4, (1.0 g, 4.996 mmol), intermediate A, (945 mg, 4.996 mmol) and intermediate B, (665 mg, 4.996 mmol) to give 3-ethyl 5-methyl 2-(acetoxymethyl)-4-(2-(2,2-difluorocyclopropyl)-3-fluorophenyl)-6-(fluoromethyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.4 g, crude). The crude product was taken as such to next step without further purification and analysis.

Step 6: methyl 4-(2-(2,2-difluorocyclopropyl)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate



Title compound was synthesized using step 2 of general procedure I (using the intermediate from step 5, 1.4 g, 2.884 mmol). Crude product was purified by silica flash chromatography (0 → 50%) ethyl acetate in petroleum ether which afforded the title compound methyl 4-(2-(2,2-difluorocyclopropyl)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate (125 mg) as an off white solid. The sample was chirally separated into two products using chiral SFC: Column: Lux-cellulose-2 21x250mm 5μm; Flow rate: 80 g per minute; Cosolvent: 20% 1:1 MeOH:IPA; Detection: 344 nm; BPR Set Point: 125 bar.

Resulting peak 1 & 2 from previous separation were separated into 4 isomers using chiral SFC:

Column: WO1 SS 21 x 250mm; Flow Rate: 80 g per minute; Cosolvent: 15% IPA; Detection: 344 nm; BPR Set Point: 150 bar.

Example 1

20mg of the title compounds as the second eluting stereoisomer as a white solid (61%)

SFC Rt = 2.49; Mobile Phase: 5-55% (1:1) MeOH IPA w/ 10mM NH₄OH in CO₂ 5mL/min; Column: Lux Cellulose-2 4.6 x 100 mm 5μm

LCMS Rt = 2.12 min; MS m/z 398.3 [M+H]⁺; [Method 3]

¹H NMR (400 MHz, DMSO-d₆) δ 10.13 (d, J = 3.3 Hz, 1H), 7.31 (td, J = 8.0, 5.6 Hz, 1H), 7.20 – 6.83 (m, 2H), 5.78 – 5.41 (m, 2H), 5.22 (s, 1H), 5.03 – 4.73 (m, 2H), 3.51 (s, 3H), 2.86 (td, J = 12.4, 8.5 Hz, 1H), 2.64 – 2.53 (m, 1H), 2.18 (dt, J = 12.2, 5.5 Hz, 1H).

Example 1b

15mg of first eluting stereoisomer as a white solid (46%)

SFC Rt = 2.42; Mobile Phase: 5-55% (1:1) MeOH IPA w/ 10mM NH₄OH in CO₂ 5mL/min; Column: Lux Cellulose-2 4.6 x 100 mm 5μm

LCMS Rt = 2.15 min; MS m/z 398.2 [M+H]⁺; [Method 3]

¹H NMR (400 MHz, DMSO-d₆) δ 10.08 (d, J = 3.2 Hz, 1H), 7.33 (td, J = 8.1, 5.8 Hz, 1H), 7.25 – 6.92 (m, 2H), 5.94 – 5.54 (m, 2H), 5.27 (s, 1H), 4.79 (d, J = 1.4 Hz, 2H), 3.44 (s, 3H), 3.15 – 3.04 (m, 1H), 2.35 – 2.19 (m, 1H), 1.88 (dtd, J = 14.0, 8.2, 3.2 Hz, 1H).

Example 1c

24mg of third eluting stereoisomer as a white solid (73%)

SFC Rt = 2.73 min; Mobile Phase: 5-55% (1:1) MeOH IPA w/ 10mM NH₄OH in CO₂ 5mL/min;

Column: Lux Cellulose-2 4.6 x 100 mm 5μm

LCMS Rt = 2.16 mins; MS m/z 398.3 [M+H]⁺; [Method 3]

¹H NMR (400 MHz, DMSO-d₆) δ 10.13 (d, J = 3.3 Hz, 1H), 7.31 (td, J = 8.0, 5.6 Hz, 1H), 7.18 – 6.87 (m, 2H), 5.61 (dd, J = 47.8, 4.0 Hz, 2H), 5.22 (s, 1H), 4.98 – 4.78 (m, 2H), 3.51 (s, 3H), 2.86 (td, J = 12.5, 8.5 Hz, 1H), 2.64 – 2.55 (m, 1H), 2.18 (tt, J = 12.8, 6.8 Hz, 1H).

Example 1d

15mg of fourth eluting stereoisomer as a white solid (46%)

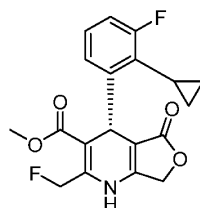
SFC Rt = 2.78 min; Mobile Phase: 5-55% (1:1) MeOH IPA w/ 10mM NH₄OH in CO₂ 5mL/min;

Column: Lux Cellulose-2 4.6 x 100 mm 5μm

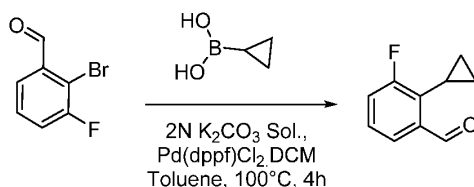
LCMS Rt = 2.11 mins; MS m/z 398.1 [M+H]⁺; [Method 3]

¹H NMR: (400 MHz, DMSO-d₆) δ 10.08 (d, J = 3.3 Hz, 1H), 7.33 (td, J = 8.0, 5.6 Hz, 1H), 7.14 – 6.94 (m, 2H), 5.72 (dd, J = 47.8, 4.8 Hz, 2H), 5.27 (s, 1H), 4.79 (d, J = 1.4 Hz, 2H), 3.44 (s, 3H), 3.15 (d, J = 14.7 Hz, 1H), 2.33 – 2.20 (m, 1H), 1.99 – 1.79 (m, 1H).

Example 2: Methyl (R)-4-(2-cyclopropyl-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate



Step 1: 2-cyclopropyl-3-fluorobenzaldehyde



To a solution of 2-bromo-3-fluorobenzaldehyde (15 g, 73.88 mmol) and cyclopropylboronic acid (7.61 g, 88.66 mmol) in toluene (160 mL) was added 2N K₂CO₃ (25.5 mL, 182.16 mmol) and [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II).DCM (6.03 g, 7.38 mmol). The resulting solution was degassed with Argon gas for 10 min and stirred at 100°C for 4 hrs. The reaction mixture was filtered and washed with ethyl acetate (200 mL). The filtrate was added to water (500 mL) and product extracted into ethyl acetate (2 L), EtOAc phase was washed with brine and dried over Na₂SO₄.

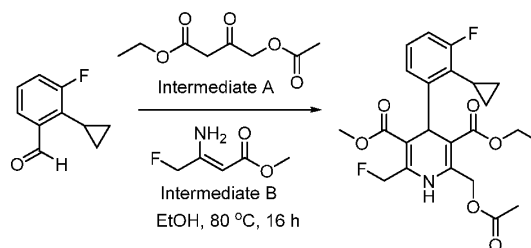
The solvent was removed under reduced pressure and purification of the crude product by silica flash

chromatography (0 → 1%) ethyl acetate in petroleum ether afforded the title compound 2-(3-fluoro-2-vinylphenyl)-1,3-dioxolane (11.2 g) as a colorless liquid.

¹H NMR (300 MHz, CDCl₃) δ 10.70 (s, 1H), 7.63 (dd, J = 1.2, 7.8 Hz, 1H), 7.35 – 7.15 (m, 2H), 2.14 – 2.02 (m, 1H), 1.19 – 1.09 (m, 2H), 0.85 – 0.75 (m, 2H).

5

Step 2: 3-ethyl 5-methyl 2-(acetoxymethyl)-4-(2-cyclopropyl-3-fluorophenyl)-6-(fluoromethyl)-1,4-dihydropyridine-3,5-dicarboxylate

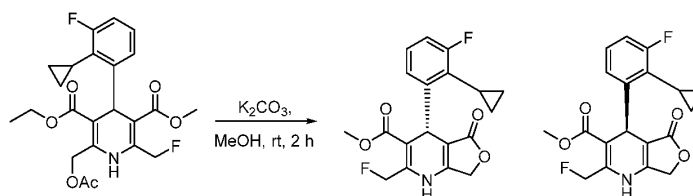


Title compound was synthesized using step 1 of general procedure I (using the aldehyde from step 1, 4.0 g, 24.36 mmol) to give 3-ethyl 5-methyl 2-(acetoxymethyl)-4-(2-cyclopropyl-3-fluorophenyl)-6-(fluoromethyl)-1,4-dihydropyridine-3,5-dicarboxylate (7.0 g, crude).

LCMS Rt = 1.806 min; MS m/z 450.3 [M+H]⁺; [Method 7]

Step 3: methyl 4-(2-cyclopropyl-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate

15



Title compound was synthesized using step 2 of general procedure I (using the intermediate from step 2, 7.0 g, 15.57 mmol). Crude product was purified by silica flash chromatography (0 → 50%) ethyl acetate in petroleum ether which afforded the title compound methyl 4-(2-cyclopropyl-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate (1.15 g) as an off white solid.

150 mg of racemic mixture was separated into its enantiomers using chiral prep-HPLC [method 6].

Example 2

50 mg of first eluting enantiomer obtained as a white solid.

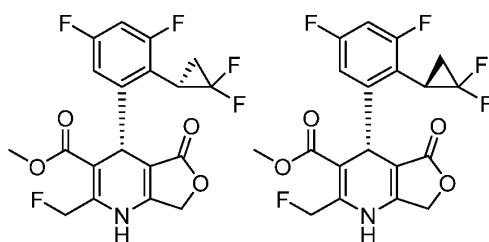
25 Chiral HPLC Rt = 6.129 min [chiral analytical method 1]

LCMS Rt = 1.538 min; MS m/z 360.0 [M-H]⁻; [Method 7]

¹H NMR (400 MHz, CDCl₃) δ 7.15 - 7.05 (m, 1H), 6.92 (ddd, J = 7.8, 1.2, 0.6 Hz, 1H), 6.82 (ddd, J = 10.8, 8.2, 1.3 Hz, 1H), 5.78 (d, J = 0.9 Hz, 1H), 5.71 – 5.59 (m, 2H), 4.80 – 4.69 (m, 2H), 3.55 (s, 3H), 2.19 – 2.15 (m, 1H), 1.34 – 1.20 (m, 1H), 1.06 – 0.96 (m, 2H), 0.82 – 0.71 (m, 1H). Exchangeable NH not seen in spectrum.

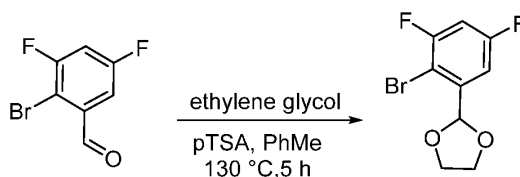
5

Example 3: Methyl (R)-4-(2-((R or S)-2,2-difluorocyclopropyl)-3,5-difluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate
and Example 4: Methyl (R)-4-(2-((R or S)-2,2-difluorocyclopropyl)-3,5-difluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate



10

Step 1: 2-(2-bromo-3,5-difluorophenyl)-1,3-dioxolane

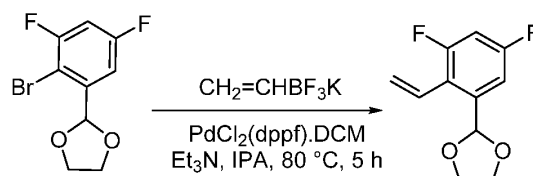


The title compound was synthesized following a procedure similar to step 1 of example 1 using 10 g of 2-bromo-3,5-difluorobenzaldehyde to obtain 11.5 g of desired product 2-(2-bromo-3,5-difluorophenyl)-1,3-dioxolane.

15

¹H NMR (300 MHz, CDCl₃) δ 7.20 - 7.15 (m, 1H), 6.49 - 6.87 (m, 1H), 6.08 (s, 1H), 4.17 - 4.04 (m, 4H).

Step 2: 2-(3,5-difluoro-2-vinylphenyl)-1,3-dioxolane

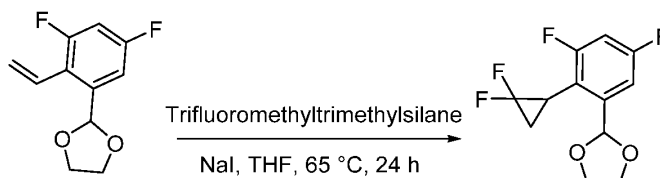


20

The title compound was synthesized following a procedure similar to step 2 of example 1 using 2-(2-bromo-3,5-difluorophenyl)-1,3-dioxolane producing 2-(3,5-difluoro-2-vinylphenyl)-1,3-dioxolane (3.45 g).

¹H NMR (300 MHz, CDCl₃) δ 7.20 - 7.16 (m, 1H), 6.94 - 6.83 (m, 1H), 6.82 (dd, J = 17.7, 11.7 Hz, 1H), 5.60 (dd, J = 1.2, 11.7 Hz, 1H), 5.66 - 5.60 (m, 1H), 5.95 (s, 1H), 4.18 - 4.02 (m, 4H).

Step 3: 2-(2-(2,2-difluorocyclopropyl)-3,5-difluorophenyl)-1,3-dioxolane

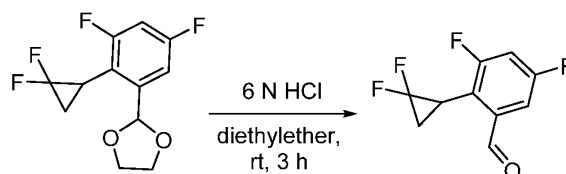


5

To a solution of 2-(3,5-difluoro-2-vinylphenyl)-1,3-dioxolane (from step 2, 2.4 g, 11.31 mmol) and trifluoromethyltrimethylsilane (16.1 g, 113.1 mmol) in tetrahydrofuran (15 mL) was added sodium iodide (850 mg, 5.65 mmol). The resulting solution was stirred at 65°C for 24 hrs. The reaction mixture was cooled to room temperature and trifluoromethyltrimethylsilane (16.1 g, 113.1 mmol) and sodium iodide (850 mg, 5.65 mmol) were added, the resulting solution was stirred at 65 °C for 24 hrs. The reaction mixture was then partitioned between ethyl acetate and water, the organic phase was washed with brine, and dried over Na₂SO₄. The solvent was removed under reduced pressure which afforded the title compound 2-(2-(2,2-difluorocyclopropyl)-3,5-difluorophenyl)-1,3-dioxolane (1.5 g) as a brown liquid.

15 ¹H NMR (400 MHz, CDCl₃) δ 7.26 - 7.14 (m, 1H), 6.90 - 6.77 (m, 1H), 6.04 (s, 1H), 4.17 - 4.03 (m, 4H), 2.77 - 2.66 (m, 1H), 1.98 - 1.70 (m, 2H).

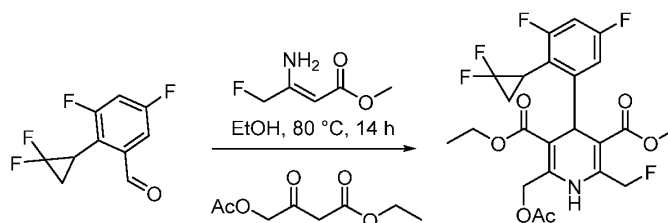
Step 4: 2-(2-(2,2-difluorocyclopropyl)-3,5-difluorobenzaldehyde



20 To a solution of 2-(2-(2,2-difluorocyclopropyl)-3,5-difluorophenyl)-1,3-dioxolane (from step 3, 1.5 g, 5.72 mmol) in diethyl ether (15 mL) was added 6N HCl (3 mL). The resulting solution was stirred at room temperature for 3 hrs. This was washed with water (50 mL), saturated NaHCO₃ solution (100 mL), and brine and dried over Na₂SO₄. The solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography (0 → 5%) ethyl acetate in hexane
25 afforded the title compound 2-(2-(2,2-difluorocyclopropyl)-3,5-difluorobenzaldehyde (1.25 g) as a colorless liquid.

¹H NMR (300 MHz, CDCl₃) δ 10.22 (s, 1H), 7.50 - 7.39 (m, 1H), 7.20 - 7.05 (m, 1H), 2.80 - 2.60 (m, 1H), 2.18 - 1.89 (m, 1H), 1.65 - 1.53 (m, 1H).

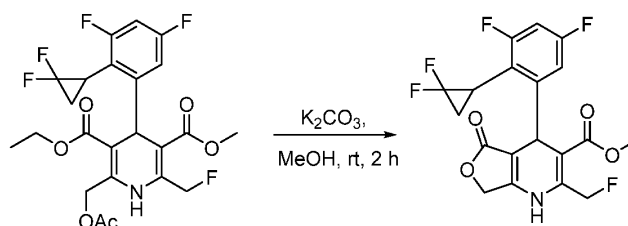
Step 5: 3-ethyl 5-methyl 2-(acetoxymethyl)-4-(2-(2,2-difluorocyclopropyl)-3,5-difluorophenyl)-6-(fluoromethyl)-1,4-dihydropyridine-3,5-dicarboxylate



Title compound was synthesized using general step 1 of method I (using the aldehyde from step 4, (1.0 g, 4.58 mmol), Intermediate A, (862 mg, 4.58 mmol) and intermediate B, (608 mg, 4.58 mmol)) to give 3-ethyl 5-methyl 2-(acetoxymethyl)-4-(2-(2,2-difluorocyclopropyl)-3,5-difluorophenyl)-6-(fluoromethyl)-1,4-dihydropyridine-3,5-dicarboxylate (2.5 g, crude).

LCMS Rt = 1.683 min; MS m/z 504 [M+H]⁺; [Method 7]

Step 6: methyl 4-(2-(2,2-difluorocyclopropyl)-3,5-difluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate



Title compound was synthesized using step 2 of general procedure I (using intermediate from step 5, 2.5 g, 4.97 mmol). Crude product was purified by silica flash chromatography (0 → 50%) ethyl acetate in petroleum ether which afforded the title compound methyl 4-(2-(2,2-difluorocyclopropyl)-3,5-difluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate (120 mg) as an off white solid. Racemic was separated into its enantiomers by chiral SFC (Mobile Phase: 20% IPA/CO₂ 80 g/min; Column: Whelk-O1 SS 21 x 250 mm; Instrument: Thar80_SN4740).

Example 3

20.9 mg of first eluting stereoisomer as a white solid (68.8%).

SFC Rt = 2.40 min ((SS) Whelk-O1 4.6 x 100 mm, 5 μm, 5 → 55% IPA in CO₂).

LCMS Rt = 2.27 min; MS m/z 416.2 [M+H]⁺; [Method 4]

¹H NMR (400 MHz, Methanol-d₄) δ 6.93 - 6.73 (m, 2H), 5.90 - 5.77 (m, 1H), 5.77 - 5.64 (m, 1H),

5.46 (s, 1H), 4.83 (s, 2H), 3.54 (s, 3H), 3.20 - 3.02 (m, 1H), 2.09 (tdd, J = 11.8, 7.5, 5.9 Hz, 1H),

1.95 (ddt, J = 16.5, 7.8, 3.4 Hz, 1H).

Example 4

20.6 mg of the second eluting stereoisomer as a white solid (67.8%).

SFC Rt = 2.43 min ((SS) Whelk-O1 4.6 x 100 mm, 5 μ m, 5 $\rightarrow$ 55% IPA in CO₂).

LCMS Rt = 2.21 min; MS m/z 416.4 [M+H]⁺; [Method 4]

- 5 ¹H NMR (400 MHz, Methanol-d₄) δ 6.93 - 6.72 (m, 2H), 5.74 (d, J=3.6 Hz, 1H), 5.62 (d, J=4.1 Hz, 1H), 5.42 (s, 1H), 5.00 - 4.90 (m, 2H), 3.60 (s, 3H), 2.97 - 2.80 (m, 1H), 2.68 - 2.49 (m, 1H), 2.02 (tdd, J = 11.9, 7.8, 5.9 Hz, 1H).

Remaining stereoisomers were isolated as Examples 3b and 4b

Example 3b

- 10 21.6 mg of the third eluting stereoisomer as a white solid (74.1%).

SFC Rt = 2.68 min ((SS) Whelk-O1 4.6 x 100 mm, 5 μ m, 5 $\rightarrow$ 55% IPA in CO₂).

LCMS Rt = 2.22 min; MS m/z 416.6 [M+H]⁺; [Method 4]

- ¹H NMR (400 MHz, Methanol-d₄) δ 6.78 - 6.63 (m, 2H), 5.76 - 5.64 (m, 1H), 5.64 - 5.52 (m, 1H), 5.33 (s, 1H), 4.70 (s, 2H), 3.41 (s, 3H), 3.07 - 2.91 (m, 1H), 1.96 (tdd, J = 11.8, 7.6, 5.9 Hz, 1H),
15 1.90 - 1.77 (m, 1H).

Example 4b

20.6 mg of the fourth eluting stereoisomer as a white solid (70.7%).

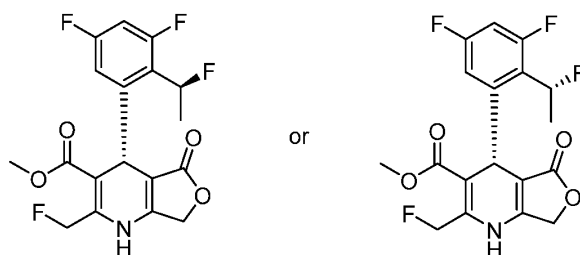
SFC Rt = 2.79 min ((SS) Whelk-O1 4.6 x 100 mm, 5 μ m, 5 $\rightarrow$ 55% IPA in CO₂).

LCMS Rt = 2.21 min; MS m/z 416.3 [M+H]⁺; [Method 4]

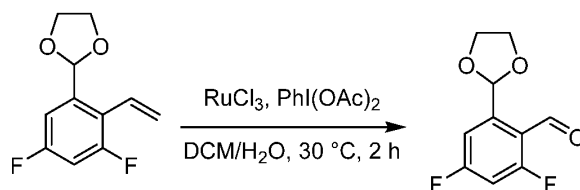
- 20 ¹H NMR (400 MHz, Methanol-d₄) δ 6.91 - 6.73 (m, 2H), 5.80 - 5.67 (m, 1H), 5.67 - 5.55 (m, 1H), 5.41 (d, J = 1.6 Hz, 1H), 4.98 - 4.88 (m, 2H), 3.59 (s, 3H), 2.98 - 2.81 (m, 1H), 2.68 - 2.48 (m, 1H), 2.00 (tdd, J = 11.8, 7.8, 5.9 Hz, 1H).

Example 5: methyl (R)-4-(3,5-difluoro-2-((R or S)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate

25



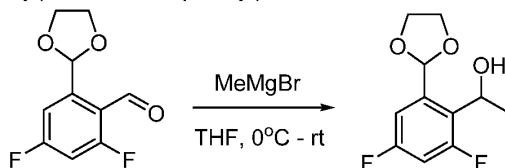
Step 1: 2-(1,3-dioxolan-2-yl)-4,6-difluorobenzaldehyde



To a solution of 2-(3,5-difluoro-2-vinylphenyl)-1,3-dioxolane (prepared in example 4 from step 2, 5 g, 23.58 mmol) and ruthenium chloride. XH_2O (490 mg, 2.35 mmol) in dichloromethane (50 mL) and water (10 mL) was added diacetoxyiodo benzene (11.4 g, 35.37 mmol). The resulting solution was stirred at 30°C for 2 hrs. The reaction mixture was filtered and washed with ethyl acetate (200 mL). The filtrate added to water (200 mL) and product extracted into ethyl acetate (500 mL). EtOAc phase was washed with brine and dried over Na_2SO_4 . The solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography (0 $\rightarrow$ 10%) ethyl acetate in petroleum ether afforded the title compound 2-(1,3-dioxolan-2-yl)-4,6-difluorobenzaldehyde (3 g) as a colorless liquid.

^1H NMR (300 MHz, CDCl_3) δ 10.41 (s, 1H), 7.35 (d, $J = 9.6$ Hz, 1H), 6.95 – 6.85 (m, 1H), 6.53 (s, 1H), 4.08 (s, 4H).

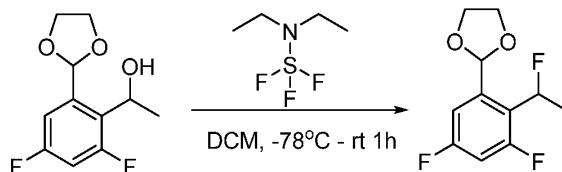
Step 2: 1-(2-(1,3-dioxolan-2-yl)-4,6-difluorophenyl)ethan-1-ol



To a solution of 2-(1,3-dioxolan-2-yl)-4,6-difluorobenzaldehyde (from step 1, 1.0 g, 4.67 mmol) in dry tetrahydrofuran (10 mL) at 0°C was added methyl magnesium bromide (2.33 mL, 3 M in ether, 4.67 mmol). The resulting solution was stirred at room temperature for 1 hr. The reaction mixture was quenched with saturated ammonium chloride (10 mL) at 0°C and diluted with ethyl acetate (100 mL). The organic phase was separated, washed with brine and dried over Na_2SO_4 . The solvent was removed under reduced pressure to afford the title compound 1-(2-(1,3-dioxolan-2-yl)-4,6-difluorophenyl)ethan-1-ol (950 mg) as a colorless liquid. The crude compound was carried forward to the next step without further purification.

^1H NMR (300 MHz, CDCl_3) δ 7.17 (dd, $J = 2.4, 6.3$ Hz, 1H), 6.89 – 6.72 (m, 1H), 6.17 (s, 1H), 5.31 (dd, $J = 6.9, 13.5$ Hz, 1H), 4.15 – 4.02 (m, 4H), 2.64 – 2.59 (m, 1H), 1.58 (d, $J = 9.0$ Hz, 3H).

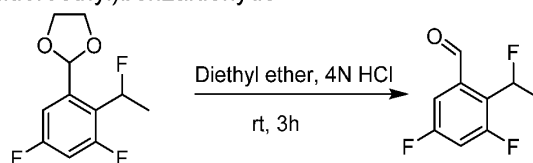
Step 3: 2-(3,5-difluoro-2-(1-fluoroethyl)phenyl)-1,3-dioxolane



To a solution of 1-(2-(1,3-dioxolan-2-yl)-4,6-difluorophenyl)ethan-1-ol (from step 2, 950 mg, 4.13 mmol) in dichloromethane (10 mL) at -78°C was added diethylaminosulfur trifluoride (1.0 g, 6.13 mmol). The resulting solution was stirred at room temperature for 1 hr. The reaction mixture was quenched with saturated ammonium chloride (10 mL) at 0°C and diluted with ethyl acetate (100 mL). The organic phase was separated, washed with brine and dried over Na₂SO₄. The solvent was removed under reduced pressure to afford the title compound 2-(3,5-difluoro-2-(1-fluoroethyl)phenyl)-1,3-dioxolane (600 mg) as a thick yellow liquid. The crude compound was carried forward to the next step without further purification.

¹H NMR (300 MHz, CDCl₃) δ 7.20 (dd, J = 2.4, 6.3 Hz, 1H), 6.87 – 6.75 (m, 1H), 6.15 – 5.98 (m, 1H), 6.11 (s, 1H), 4.15 – 4.02 (m, 4H), 1.70 (dd, J = 6.6, 22.8 Hz, 3H).

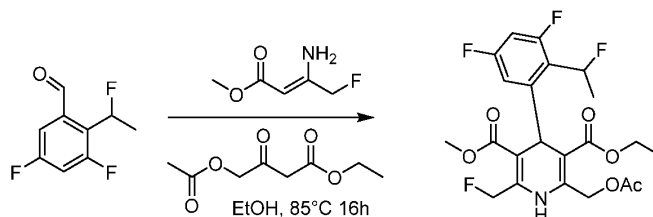
Step 4: 3,5-difluoro-2-(1-fluoroethyl)benzaldehyde



To a solution of 2-(3,5-difluoro-2-(1-fluoroethyl)phenyl)-1,3-dioxolane (from step 3, 600 mg, 2.58 mmol) in diethyl ether (10 mL) was added 4N HCl (2 mL) at room temperature. The resulting solution was stirred at room temperature for 3 hrs. This was washed with water (50 mL), saturated NaHCO₃ solution (100 mL), brine and dried over Na₂SO₄. The solvent was removed under reduced pressure which afforded the title compound 3,5-difluoro-2-(1-fluoroethyl)benzaldehyde (200 mg) as a colorless liquid. (Note: The obtained aldehyde is volatile in nature)

¹H NMR (300 MHz, CDCl₃) δ 10.44 (d, J = 3.0 Hz, 1H), 7.20 (d, J = 9.3 Hz, 1H), 7.10 – 6.98 (m, 1H), 6.43 – 6.19 (m, 1H), 1.78 (dd, J = 7.2, 23.1 Hz, 3H).

Step 5: 3-ethyl 5-methyl 2-(acetoxymethyl)-4-(3,5-difluoro-2-(1-fluoroethyl)phenyl)-6-(fluoromethyl)-1,4-dihydropyridine-3,5-dicarboxylate

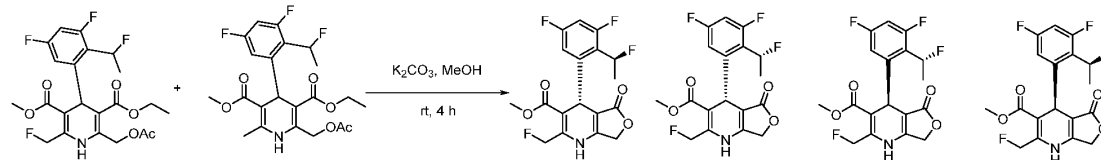


Title compound was synthesized using step 1 of general procedure I (using the aldehyde from step 4, (200 mg, 1.06 mmol)) to give 3-ethyl 5-methyl 2-(acetoxymethyl)-4-(3,5-difluoro-2-(1-fluoroethyl)phenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate as a mixture of diastereomers.

5 The crude product was carried forward to the next step without purification.

LCMS Rt = 2.272 min; MS m/z 472.3 [M-H]⁻; [Method 7]

Step 6: methyl 4-(3,5-difluoro-2-(1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate



10

Title compound was synthesized using step 2 of general procedure I (using the mixture of intermediates from step 5, 800 mg, 1.75 mmol) gave methyl 4-(3,5-difluoro-2-(1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate (2g crude) an off white solid.

15 The diastereomeric mixture was separated into its two isomers using combi-flash chromatography (0 → 80%) to give 100 mg of first diastereomer as a white solid and 80 mg of second diastereomer as a white solid.

Peak-1: 100 mg and Peak-2: 80 mg was further separated its enantiomers using preparative chiral HPLC [Method 7] to obtain four isomers.

20 Example 5

21 mg of first eluting enantiomer obtained as a white solid.

Chiral HPLC Rt = 4.418 min; [chiral analytical method 2]

LCMS Rt = 1.514 min; MS m/z 384.0 [M-H]⁻; [Method 7]

¹H NMR: (400 MHz, CD₃OD) δ 6.87 – 6.74 (m, 2H), 6.46 – 6.18 (m, 1H), 5.75 (t, J = 1.0 Hz, 1H), 5.63 (dd, J = 1.6, 0.7 Hz, 1H), 5.20 – 5.12 (m, 1H), 4.91 – 4.81 (m, 2H), 3.53 (s, 3H), 1.83 (ddd, J = 22.7, 6.6, 1.4 Hz, 3H).

25

Example 5b

22 mg of second eluting enantiomer obtained as a white solid.

Chiral HPLC Rt = 4.792 min; [chiral analytical method 2]

LCMS Rt = 1.513 min; MS m/z 384.0 [M-H]⁻; [Method 7]

¹H NMR (400 MHz, CD₃OD) δ 6.87 – 6.74 (m, 2H), 6.46 – 6.18 (m, 1H), 5.75 (t, J = 1.0 Hz, 1H), 5.63 (dd, J = 1.6, 0.7 Hz, 1H), 5.20 – 5.12 (m, 1H), 4.91 – 4.81 (m, 2H), 3.53 (s, 3H), 1.83 (ddd, J = 22.7, 6.6, 1.4 Hz, 3H).

Example 5c

18 mg of third eluting enantiomer obtained as a white solid.

Chiral HPLC Rt = 6.777 min; [chiral analytical method 2]

LCMS Rt = 1.476 min; MS m/z 384.1 [M-H]⁻; [Method 7]

¹H NMR: (400 MHz, CDCl₃) δ 6.77 – 6.63 (m, 2H), 6.48 (dd, J = 44.3, 6.6 Hz, 1H), 5.85 – 5.77 (m, 1H), 5.70 (d, J = 4.5 Hz, 1H), 5.10 (s, 1H), 4.83 – 4.77 (m, 2H), 3.56 (s, 3H), 1.79 (ddd, J = 22.5, 6.7, 1.1 Hz, 3H).

Example 5d

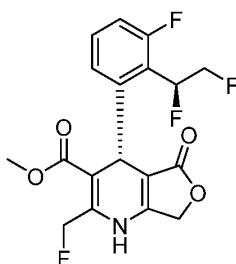
16 mg of fourth eluting enantiomer obtained as a white solid using chiral HPLC method 7.

Chiral HPLC Rt = 7.475 min; [chiral analytical method 2]

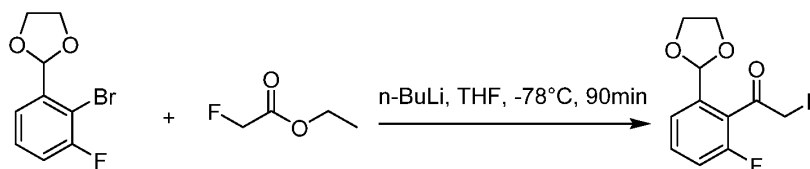
LCMS Rt = 2.00 min; MS m/z 384.2 [M-H]⁻; [Method 9]

¹H NMR (400 MHz, CDCl₃) δ 6.77 – 6.63 (m, 2H), 6.48 (dd, J = 44.3, 6.6 Hz, 1H), 5.85 – 5.77 (m, 1H), 5.70 (d, J = 4.5 Hz, 1H), 5.10 (s, 1H), 4.83 – 4.77 (m, 2H), 3.56 (s, 3H), 1.79 (ddd, J = 22.5, 6.7, 1.1 Hz, 3H).

Example 6: methyl (R)-4-(2-((S)-1,2-difluoroethyl)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate



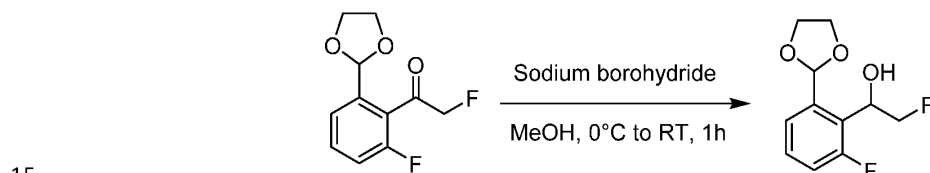
Step 1: 1-(2-(1,3-dioxolan-2-yl)-6-fluorophenyl)-2-fluoroethan-1-one



A solution of 2-(2-bromo-3-fluorophenyl)-1,3-dioxolane (from step 1, Example 1, 26 g, 105.23 mmol) in THF (250 mL) under nitrogen atmosphere was cooled to -78°C. Then n-butyllithium in n-hexane solution (44.19 mL, 2.5M, 110.49 mmol) was added, reaction stirred for 30 min at -78°C. Then ethyl 2-fluoroacetate (22.33 g, 210.47 mmol) was added to the reaction and the resulting mixture stirred for another 60 min. at -78°C. The reaction mixture was quenched with saturated ammonium chloride solution (100 mL) and extracted with ethyl acetate (2 x 250 mL). Combined organic phases were washed with water (250 mL), brine (250 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography (0 → 10%) ethyl acetate in petroleum ether afforded the title compound 1-(2-(1,3-dioxolan-2-yl)-6-fluorophenyl)-2-fluoroethan-1-one (16.2 g) as a colorless liquid.

¹H NMR (400 MHz, CDCl₃) δ 7.45 (m, 1H), 7.37 (d, J = 7.8, 1H), 7.13 (dd, J = 9.3, 8.2 Hz, 1H), 6.02 (s, 1H), 5.23 (d, J = 1.4 Hz, 1H), 5.11 (d, J = 1.3 Hz, 1H), 4.08 – 3.87 (m, 4H).

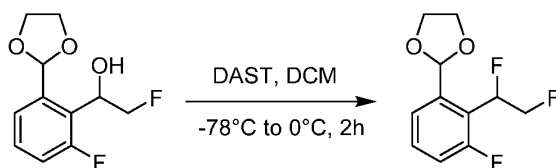
Step 2: 1-(2-(1,3-dioxolan-2-yl)-6-fluorophenyl)-2-fluoroethan-1-ol



To a stirred solution of 1-(2-(1,3-dioxolan-2-yl)-6-fluorophenyl)-2-fluoroethan-1-one (from step 1, 19.6 g, 85.89 mmol) in methanol (100 mL) was added sodium borohydride (3.9 g, 103.07 mmol) at 0°C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 1h. Reaction mixture was quenched with ice water and extracted with ethyl acetate (2 x 250 mL). Combined organic phases were washed with water (250 mL), followed by brine (250 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography (0 → 30%) ethyl acetate in petroleum ether afforded the title compound 1-(2-(1,3-dioxolan-2-yl)-6-fluorophenyl)-2-fluoroethan-1-ol (18 g) as a colorless liquid.

¹H NMR (400 MHz, CDCl₃) δ 7.44 (dd, J = 7.9, 1.2 Hz, 1H), 7.33 (dd, J = 8.0, 8.0 Hz, 1H), 7.10 (dd, J = 8.2, 1.3 Hz, 1H), 6.13 (s, 1H), 5.47 (m, 1H), 4.98 – 4.51 (m, 2H), 4.22 – 3.97 (m, 4H), 3.04 (m, 1H).

Step 3: 2-(2-(1,2-difluoroethyl)-3-fluorophenyl)-1,3-dioxolane

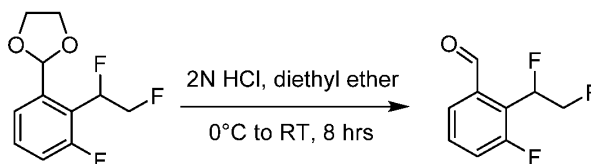


A solution of 1-(2-(1,3-dioxolan-2-yl)-6-fluorophenyl)-2-fluoroethan-1-ol (from step 2, 18 g, 78.18 mmol) in dichloromethane (150 mL) was cooled to -78°C then diethylaminosulfur trifluoride (DAST) (15.49 mL, 117.28 mmol) was added and the resulting reaction mixture was stirred at -78°C for 1h.

- 5 The reaction mixture was slowly brought to 0°C and stirred for another 1h. Water (150 mL) was added and product was extracted with dichloromethane (2 x 200 mL). The combined organic phases were combined, washed with saturated sodium bicarbonate solution (2 x 200 mL), water (200 mL), brine (200 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography (0 → 10%) ethyl acetate in petroleum ether
- 10 afforded the title compound 2-(2-(1,2-difluoroethyl)-3-fluorophenyl)-1,3-dioxolane (12.4 g) as a colorless liquid.

¹H NMR (400 MHz, CDCl₃) δ 7.45 (d, J = 7.8 Hz, 1H), 7.42 – 7.35 (m, 1H), 7.12 (dd, J = 10.6, 8.2 Hz, 1H), 6.21 (m, 1H), 6.04 (s, 1H), 5.22 – 4.85 (m, 1H), 4.75 – 4.42 (m, 1H), 4.20 – 3.97 (m, 4H).

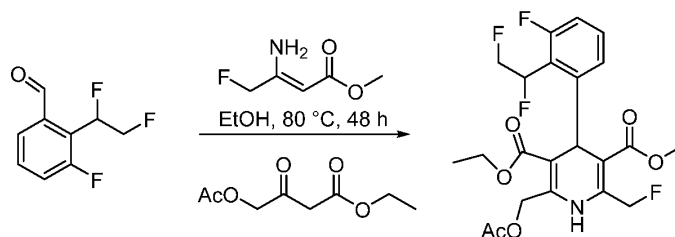
- 15 Step 4: 2-(1,2-difluoroethyl)-3-fluorobenzaldehyde



- To a solution of 2-(2-(1,2-difluoroethyl)-3-fluorophenyl)-1,3-dioxolane (from step 3, 12.4 g, 53.40 mmol) in diethyl ether (150 mL) was added 2N HCl (100 mL) at 0°C. The resulting reaction mixture was stirred at room temperature for 8 hrs. Reaction mixture was extracted with diethyl ether (200
- 20 mL), washed with water (2 x 100 mL), brine (100 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and purified by silica flash chromatography (0 → 10%) ethyl acetate in petroleum ether which afforded the title compound 2-(1,2-difluoroethyl)-3-fluorobenzaldehyde (10 g) as a colorless liquid.

- ¹H NMR (400 MHz, CDCl₃) δ 10.30 (s, 1H), 7.88 – 7.70 (m, 1H), 7.56 (m, 1H), 7.44 – 7.30 (m, 1H),
- 25 6.70 – 6.36 (m, 1H), 4.95 – 4.70 (m, 2H)

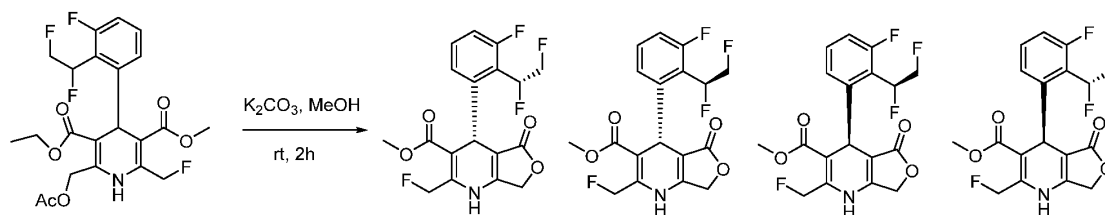
Step 5: 3-ethyl 5-methyl 2-(acetoxymethyl)-4-(2-(1,2-difluoroethyl)-3-fluorophenyl)-6-(fluoromethyl)-1,4-dihydropyridine-3,5-dicarboxylate



Title compound was synthesized using general step 1 of general procedure I (using the aldehyde from step 4, 9 g, 47.83 mmol) which afforded the title compound 3-ethyl 5-methyl 2-(acetoxymethyl)-4-(2-(1,2-difluoroethyl)-3-fluorophenyl)-6-(fluoromethyl)-1,4-dihydropyridine-3,5-dicarboxylate as a mixture of diastereomers (25.0 g, Crude) as an off white solid.

The crude product was used for the next step without further purification and analysis.

Step 6: methyl 4-(2-(1,2-difluoroethyl)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate



Title compound was synthesized using step 2 of general procedure I (using mixture of intermediates from step 5, 25 g, 52.8 mmol) afforded the title compound methyl 4-(2-(1,2-difluoroethyl)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate (1 g, crude) as an off white solid. Diastereomeric mixture was separated into its two isomers using silica flash chromatography (0 → 80%) giving 1.51 g of first diastereomer as a white solid and 820 mg of second diastereomer as a white solid.

Diastereomers from previous separation Peak-1: 200 mg and Peak-2: 200 mg were further separated into their enantiomers using preparative chiral HPLC [Method 7] to obtain four isomers.

Example 6

56 mg of first eluting enantiomer obtained as a white solid.

Chiral HPLC Rt = 7.623 min; [chiral analytical method 2]

LCMS Rt = 1.445 min; MS m/z 384.0 [M-H]⁻; [Method 7]

¹H NMR (400 MHz, CD₃OD) δ 7.41 – 7.35 (m, 1H), 7.17 (dt, J = 7.9, 1.3 Hz, 1H), 6.98 (dd, J = 11.4, 8.1 Hz, 1H), 6.66 – 6.33 (m, 1H), 5.75 (d, J = 3.7 Hz, 1H), 5.68 – 5.56 (m, 1H), 5.18 (s, 1H), 5.15 – 4.91 (m, 2H), 4.85 (s, 2H), 3.52 (s, 3H).

The stereochemistry of Example 6, methyl 2-methyl-5-oxo-4-phenyl-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate, was determined by single crystal x-ray crystallographic analysis and it confirmed that active enantiomer is the R-enantiomer (Figure 7).

5 Example 6b

54 mg of second eluting enantiomer obtained as a white solid.

Chiral HPLC Rt = 8.757 min; [chiral analytical method 2]

LCMS Rt = 1.443 min; MS m/z 386.3 [M+H]⁺; [Method 7]

¹H NMR: (400 MHz, CD₃OD) δ 7.41 – 7.35 (m, 1H), 7.17 (dt, J = 7.9, 1.3, 1.3 Hz, 1H), 7.10 – 6.88 (m, 1H), 6.67 – 6.26 (m, 1H), 5.82 – 5.70 (m, 1H), 5.69 – 5.57 (m, 1H), 5.18 (s, 1H), 5.15 – 4.91 (m, 2H), 4.85 (d, J = 0.7 Hz, 2H), 3.52 (s, 3H).

Example 6c

67 mg of third eluting enantiomer obtained as a white solid.

Chiral HPLC = Rt = 10.574 min; [chiral analytical method 2]

15 LCMS Rt = 1.379 min; MS m/z 384.0 [M-H]⁻; [Method 7]

¹H NMR (400 MHz, CD₃OD) δ 7.41 – 7.35 (m, 1H), 7.13 (dt, J = 7.9, 1.3, 1.3 Hz, 1H), 6.97 (dd, J = 11.3, 8.2 Hz, 1H), 6.60 (ddd, J = 47.2, 18.0, 8.4 Hz, 1H), 5.75 (s, 1H), 5.63 (s, 1H), 5.14 (s, 1H), 5.12 – 4.92 (m, 1H), 4.84 (s, 2H), 4.70 (ddd, J = 44.6, 32.7, 10.8 Hz, 1H), 3.53 (s, 3H).

Example 6d

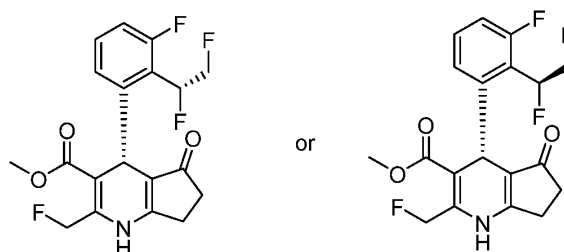
20 69 mg of fourth eluting enantiomer obtained as a white solid.

Chiral HPLC Rt = 13.93 min [chiral analytical method 2]

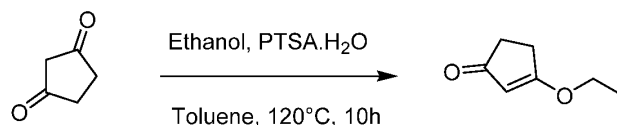
LCMS Rt = 1.379 min; MS m/z 384.0 [M-H]⁻; [Method 7]

¹H NMR (400 MHz, CD₃OD) δ 7.41 – 7.35 (m, 1H), 7.13 (dt, J = 7.8, 1.3 Hz, 1H), 6.97 (dd, J = 11.3, 8.2 Hz, 1H), 6.60 (ddd, J = 47.1, 17.9, 8.3 Hz, 1H), 5.75 (s, 1H), 5.63 (s, 1H), 5.17 – 5.11 (m, 1H), 5.11 – 4.92 (m, 1H), 4.84 (s, 2H), 4.70 (ddd, J = 45.1, 33.0, 11.1 Hz, 1H), 3.53 (s, 3H).

Example 7: methyl (R)-4-(2-((R or S)-1,2-difluoroethyl)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate



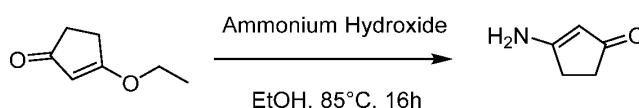
30 Step 1: 3-ethoxycyclopent-2-en-1-one



To a stirred solution of cyclopentane-1,3-dione (5.0 g, 50.96 mmol) in toluene (70 mL) was added pTSA (193 mg, 1.019 mmol) and EtOH (22.61 ml, 387.35 mmol) at room temperature. The resulting mixture was stirred at 120°C for 10 hrs using Dean-stark apparatus. The solvent was removed under reduced pressure giving the crude compound. Crude product was purified by silica flash chromatography (0 → 50%) ethyl acetate in petroleum ether to afford the title compound 3-ethoxycyclopent-2-en-1-one (4.3 g) as a brown solid.

¹H NMR (400 MHz, CDCl₃) δ 5.26 (s, 1H), 4.02 (q, J = 6.6 Hz, 2H), 2.60 – 2.55 (m, 2H), 2.44 – 2.40 (m, 2H), 1.39 (t, J = 7.2 Hz, 3H).

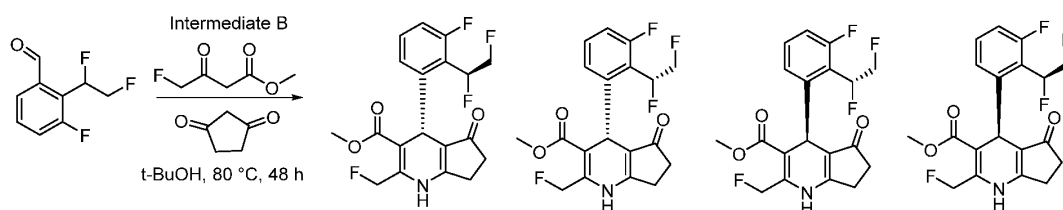
Step 2: 3-aminocyclopent-2-en-1-one



To a stirred solution of 3-ethoxycyclopent-2-en-1-one (from step 1, 4.3 g, 34.08 mmol) in ethanol (50 mL) was added ammonium hydroxide solution (25 mL, 387.35 mmol) at room temperature. The resulting mixture was stirred at 85°C for 16 hrs. Solvent removal under reduced pressure afforded the title compound 3-aminocyclopent-2-en-1-one (3.2 g) as a brown solid.

LCMS Rt = 0.114 min; MS m/z 98.2 [M+H]⁺; [Method 1]

Step 3: methyl 4-(2-(1,2-difluoroethyl)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate



To solution of aldehyde (from example 6, step 4, 3.0 g, 15.944 mmol) was added methyl (Z)-3-amino-4-fluorobut-2-enoate (intermediate B, 2.54 g, 19.133 mmol) and cyclopentane-1,3-dione (1.56 g, 15.944 mmol) in t-butanol (25 mL). The reaction mixture was stirred at 80°C for 48 hrs. The solvent was removed under reduced pressure resulting in crude compound. Crude product was purified by silica flash chromatography (0 → 70%) ethyl acetate in petroleum ether affording the title compound methyl 4-(2-(1,2-difluoroethyl)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-

cyclopenta[b]pyridine-3-carboxylate (500 mg, crude) as an off white solid and as a mixture of diastereomers. Diastereomeric mixture was separated into its two isomers using silica flash chromatography (0 → 80%) giving 12 mg of the first diastereomer as a white solid and 15 mg of the second diastereomer as a white solid.

- 5 Diastereomers from first separation Peak-1: 12 mg and Peak-2: 15 mg were further separated into their enantiomers using preparative chiral HPLC [Method 7] to obtain four isomers.

Example 7

2 mg of first eluting enantiomer obtained as a white solid.

Chiral HPLC Rt = 9.084 min; [chiral analytical method 4]

- 10 LCMS Rt = 1.477 min; MS m/z 384.05 [M+H]⁺; [method 2]

¹H NMR (400 MHz, Methanol-d₄) δ 7.36 – 7.24 (m, 1H), 7.06 (d, *J* = 7.8 Hz, 1H), 6.92 (dd, *J* = 11.4, 8.2 Hz, 1H), 6.87 – 6.60 (m, 1H), 5.72 (s, 1H), 5.60 (s, 1H), 5.05 (s, 1H), 4.69 (ddd, *J* = 44.8, 32.9, 10.8 Hz, 2H), 3.54 (s, 3H), 2.70 (t, *J* = 5.0 Hz, 2H), 2.43 – 2.29 (m, 2H).

Example 7b

- 15 4 mg of second eluting enantiomer obtained as a white solid.

Chiral HPLC Rt = 10.439 min; [chiral analytical method 4]

LCMS Rt = 1.477 min; MS m/z 384.2 [M+H]⁺; [method 2]

- 20 ¹H NMR (400 MHz, Methanol-d₄) δ 7.37 – 7.23 (m, 1H), 7.10 – 7.02 (m, 1H), 6.92 (dd, *J* = 11.4, 8.1 Hz, 1H), 6.86 – 6.60 (m, 1H), 5.72 (s, 1H), 5.60 (s, 1H), 5.05 (s, 1H), 4.69 (ddd, *J* = 44.9, 33.5, 11.1 Hz, 2H), 3.54 (s, 3H), 2.76 – 2.66 (m, 2H), 2.42 – 2.27 (m, 2H).

Example 7c

4 mg of third eluting enantiomer obtained as a white solid.

Chiral HPLC Rt = 12.453 min; [chiral analytical method 4]

LCMS Rt = 1.327 min; MS m/z 384.2 [M+H]⁺; [method 2]

- 25 ¹H NMR (400 MHz, Methanol-d₄) δ 7.32 (tdd, *J* = 8.1, 5.6, 1.5 Hz, 1H), 7.08 (dt, *J* = 7.8, 1.3 Hz, 1H), 6.93 (dd, *J* = 11.5, 8.1 Hz, 1H), 6.60 – 6.38 (m, 1H), 5.81 – 5.69 (m, 1H), 5.69 – 5.54 (m, 1H), 5.13 – 5.07 (m, 2H), 5.07 – 4.93 (m, 1H), 3.53 (s, 3H), 2.75 – 2.67 (m, 2H), 2.45 – 2.22 (m, 2H).

Example 7d

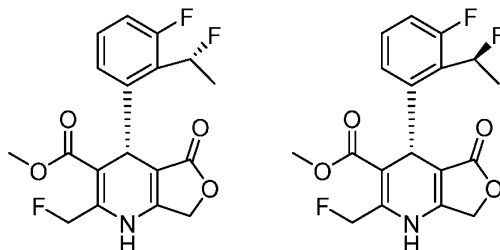
4 mg of fourth eluting enantiomer obtained as a white solid.

- 30 Chiral HPLC Rt = 13.173 min; [chiral analytical method 4]

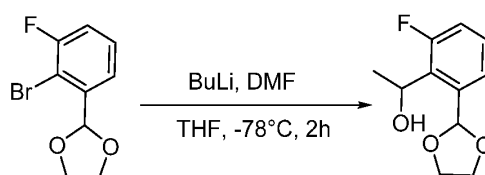
LCMS Rt = 1.33 min; MS m/z 384.2 [M+H]⁺; [method 2]

¹H NMR (400 MHz, Methanol-d₄) δ 7.40 – 7.25 (m, 1H), 7.14 – 7.05 (m, 1H), 6.93 (dd, *J* = 11.4, 8.2 Hz, 1H), 6.60 – 6.38 (m, 1H), 5.80 – 5.66 (m, 1H), 5.66 – 5.53 (m, 1H), 5.13 – 5.07 (m, 2H), 5.07 – 4.94 (m, 1H), 3.53 (s, 3H), 2.71 (t, *J* = 4.8 Hz, 2H), 2.44 – 2.21 (m, 2H).

Example 8: methyl (R)-4-(3-fluoro-2-((R or S)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate



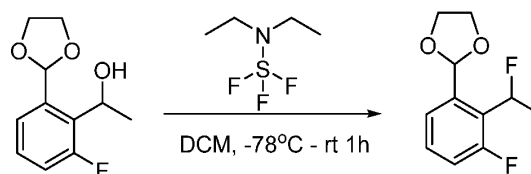
Step 1: 1-(2-(1,3-dioxolan-2-yl)-6-fluorophenyl)ethan-1-ol



5 A solution of 2-(2-bromo-3-fluorophenyl)-1,3-dioxolane (from step 1, Ex 1, 30 g, 121.42 mmol) in THF (300 mL) under nitrogen atmosphere was cooled to -78 °C. Then n-butyllithium in n-hexane solution (58.3 mL, 2.5M, 147.71 mmol) was added over 10 min, and the resulting mixture was stirred for 1 hr at -78°C. Acetaldehyde (6.42 g, 145.71 mmol) was added and the resulting mixture stirred for 1 hr at
 10 -78°C. The reaction mixture was quenched with saturated ammonium chloride solution (50 mL) and extracted with ethyl acetate (2 x 100 mL). Combined organic phases were washed with water (50 mL), brine (50 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography (0 → 10%) ethyl acetate in petroleum
 15 ether afforded the title compound 1-(2-(1,3-dioxolan-2-yl)-6-fluorophenyl)ethan-1-ol (15 g) as a colorless liquid.

¹H NMR (400 MHz, CDCl₃) δ 7.38 (d, J = 8.0 Hz, 1H), 7.30 – 7.18 (m, 1H), 7.10 – 7.01 (m, 1H), 6.15 (s, 1H), 5.30 – 5.25 (m, 1H), 4.15 – 3.95 (m, 4H), 2.75 – 2.69 (m, 1H), 1.58 (dd, J = 6.6, 22.8 Hz, 3H).

Step 2: 2-(3-fluoro-2-(1-fluoroethyl)phenyl)-1,3-dioxolane

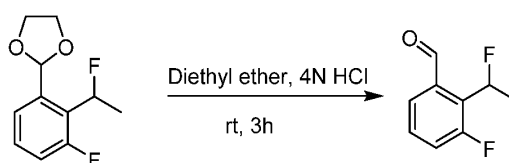


20 To a solution of 1-(2-(1,3-dioxolan-2-yl)-6-fluorophenyl)ethan-1-ol (from step 1, 15 g, 70.68 mmol) in dichloromethane (150 mL) at -78 °C was added diethylaminosulfur trifluoride (19.3 mL, 141.37 mmol). The resulting solution was stirred at room temperature for 1 hr. The reaction mixture was quenched

with saturated ammonium chloride (20 mL) at 0°C and diluted with ethyl acetate (100 mL). The organic phase was separated, washed with brine and dried over Na₂SO₄. The solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography (0 → 10%) ethyl acetate in petroleum ether afforded the title compound 2-(3-fluoro-2-(1-fluoroethyl)phenyl)-1,3-dioxolane (8.5 g) as a colorless liquid.

¹H NMR (300 MHz, CDCl₃) δ 7.38 (d, J = 7.5 Hz, 1H), 7.30 – 7.18 (m, 1H), 7.13 – 7.01 (m, 1H), 6.20 – 5.95 (m, 1H), 6.10 (s, 1H), 4.16 – 4.02 (m, 4H), 1.74 (dd, J = 7.2, 23.1 Hz, 3H).

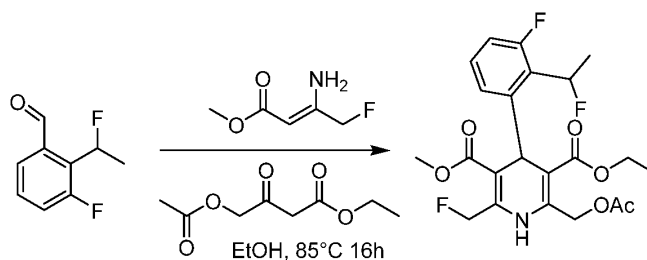
Step 3: 3-fluoro-2-(1-fluoroethyl)benzaldehyde



To a solution of 2-(3-difluoro-2-(1-fluoroethyl)phenyl)-1,3-dioxolane (from step 2, 8.5 g, 69.38 mmol) and in diethyl ether (150 mL) was added 4N HCl (85 mL) at room temperature. The resulting solution was stirred at room temperature for 3 hrs. This was washed with water (100 mL), saturated NaHCO₃ solution (200 mL), brine and dried over Na₂SO₄. The solvent was removed under reduced pressure affording the title compound 3-difluoro-2-(1-fluoroethyl) benzaldehyde (6.5 g) as a colorless liquid. (Note: The obtained aldehyde is volatile in nature).

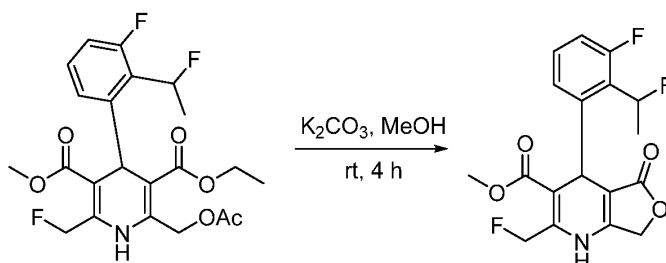
¹H NMR (300 MHz, CDCl₃) δ 10.44 (d, J = 1.0 Hz, 1H), 7.74 (d, J = 7.7 Hz, 1H), 7.45 – 7.42 (m, 1H), 7.35 – 7.30 (m, 1H), 6.45 – 6.38 (m, 1H), 1.92 – 1.72 (m, 3H).

Step 4: 3-ethyl 5-methyl 2-(acetoxymethyl)-4-(3-fluoro-2-(1-fluoroethyl)phenyl)-6-(fluoromethyl)-1,4-dihydropyridine-3,5-dicarboxylate



Title compound was synthesized using step 1 of general procedure I (using the aldehyde from step 3, 10 g, 58.76 mmol) to give 3-ethyl 5-methyl 2-(acetoxymethyl)-4-(3-fluoro-2-(1-fluoroethyl)phenyl)-6-(fluoromethyl)-1,4-dihydropyridine-3,5-dicarboxylate as a mixture of diastereomers (13 g, crude). LCMS Rt = 1.795 min; MS m/z 454.2 [M-H]⁻; [Method 9]

Step 5: methyl 4-(3-fluoro-2-(1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate



- 5 Title compound was synthesized using step 2 of general procedure I (using the mixture of intermediates from step 4 (13.0 g, 28.54 mmol)) affording the title compound methyl 4-(3-fluoro-2-(1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro [3,4-b]pyridine-3-carboxylate (5 g, crude) as an off white solid. Diastereomeric mixture was separated by silica flash chromatography (0 → 80%) ethyl acetate in hexane to give 1.04 g of first diastereomer and 1.45 g of second diastereomer.

Diastereomers were separated further using chiral SFC: Column 2.1 x 25.0 cm Chiralcel OX-H; CO₂ Co-solvent (Solvent B) Methanol Isocratic Method 25% Co-solvent at 80 g/min System Pressure 100 bar

Example 8

- 15 37mg of the title compound as the first eluting stereoisomer
LCMS Rt = 1.95 min; MS m/z 366.3 [M-H]⁻; [Method 4]
SFC Rt = 1.12 min; Mobile Phase: 20% MeOH (0.1% Isopropylamine) in CO₂ 4mL/min; Column: Chiralcel OX-H 4.6 x 100mm
¹H NMR (400 MHz, DMSO-d₆) δ 10.12 (d, J = 3.3 Hz, 1H), 7.34 (qd, J = 7.0, 2.9 Hz, 1H), 7.21 – 6.91 (m, 2H), 6.35 (dq, J = 45.6, 6.6 Hz, 1H), 5.87 – 5.45 (m, 2H), 5.03 (s, 1H), 4.86 (d, J = 2.8 Hz, 2H), 3.44 (s, 3H), 1.80 (dd, J = 22.9, 6.6 Hz, 3H).

Example 8b

- 38mg as the second eluting stereoisomer
LCMS Rt = 1.95 min; MS m/z 366.3 [M-H]⁻; [Method 4]
25 SFC Rt = 1.52 min; Mobile Phase: 20% MeOH (0.1% Isopropylamine) in CO₂ 4mL/min; Column: Chiralcel OX-H 4.6 x 100mm
¹H NMR: (400 MHz, DMSO-d₆) δ 10.12 (d, J = 3.3 Hz, 1H), 7.56 – 7.23 (m, 1H), 7.25 – 6.94 (m, 2H), 6.35 (dd, J = 45.5, 6.9 Hz, 1H), 5.66 (dd, J = 47.9, 2.7 Hz, 2H), 5.03 (s, 1H), 4.86 (d, J = 2.6 Hz, 2H), 3.44 (s, 3H), 1.80 (dd, J = 22.8, 6.5 Hz, 3H).

Example 8c

42mg as the third eluting stereoisomer

LCMS Rt = 1.88 min; MS m/z 366.3 [M-H]⁻; [Method 4]SFC Rt = 2.08 min; Mobile Phase: 20% MeOH (0.1% Isopropylamine) in CO₂ 4mL/min; Column:

5 Chiralcel OX-H 4.6 x 100mm

¹H NMR (400 MHz, DMSO-d₆) δ 10.13 (d, J = 3.3 Hz, 1H), 7.33 (td, J = 8.0, 5.4 Hz, 1H), 7.23 – 6.92 (m, 2H), 6.49 (dd, J = 44.7, 6.8 Hz, 1H), 5.68 (d, J = 47.8 Hz, 2H), 4.97 (s, 1H), 4.83 (s, 2H), 3.44 (s, 3H), 1.70 (dd, J = 22.7, 6.6 Hz, 3H).

Example 8d

10 40mg: as the fourth eluting stereoisomer

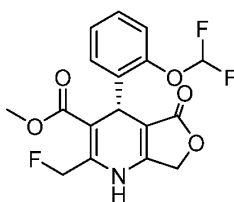
LCMS Rt = 1.88 min; MS m/z 366.3 [M-H]⁻; [Method 4]SFC Rt = 3.01 min; Mobile Phase: 20% MeOH (0.1% Isopropylamine) in CO₂ 4mL/min; Column:

Chiralcel OX-H 4.6 x 100mm

15 ¹H NMR: (400 MHz, DMSO-d₆) δ 10.13 (d, J = 3.4 Hz, 1H), 7.33 (td, J = 8.0, 5.4 Hz, 1H), 7.20 – 6.93 (m, 2H), 6.69 – 6.31 (m, 1H), 5.68 (d, J = 47.8 Hz, 2H), 4.97 (s, 1H), 4.83 (s, 2H), 3.44 (s, 3H), 1.70 (dd, J = 22.8, 6.5 Hz, 3H).

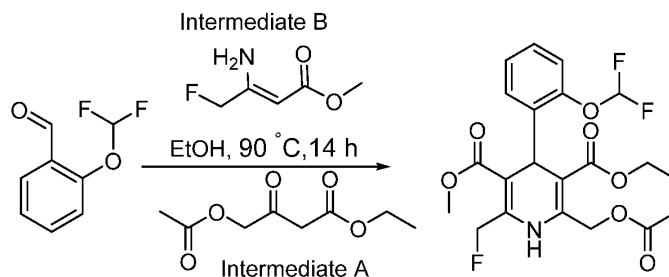
The stereochemistry of Example 8, methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate, was determined by single
20 crystal x-ray crystallographic analysis and it confirmed that active enantiomer is the R-enantiomer (Figure 8).

Example 9: methyl (R)-4-(2-(difluoromethoxy)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate



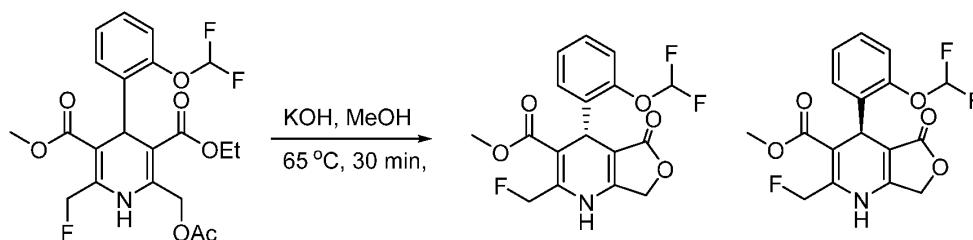
25

Step 1: 3-ethyl 5-methyl 2-(acetoxymethyl)-4-(2-(difluoromethoxy)phenyl)-6-(fluoromethyl)-1,4-dihydropyridine-3,5-dicarboxylate



Title compound was synthesized using step 1 of general procedure I (using 2-(difluoromethoxy)benzaldehyde, (350 mg, 2.033 mmol), Intermediate A, (382.3 mg, 2.033 mmol) and Intermediate B, (275.65 mg, 2.033 mmol)) to give 3-ethyl 5-methyl 2-(acetoxymethyl)-4-(2-(difluoromethoxy)phenyl)-6-(fluoromethyl)-1,4-dihydropyridine-3,5-dicarboxylate (600 mg, crude). Without analysis, it was carried forward to the next step.

Step 2: methyl 4-(2-(difluoromethoxy)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydro furo[3,4-b]pyridine-3-carboxylate



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To a crude intermediate (600 mg, 1.30 mmol) from step 1 in methanol (20 mL) was added potassium hydroxide (293.44 mg, 5.22 mmol). The resulting solution was stirred at 65 °C for 30 min. Water was added to reaction mixture and solid was precipitated out and filtered. The solid was washed with diethyl ether and the solid was collected and dried under reduced pressure which afforded the title compound methyl 4-(2-(difluoromethoxy)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydro furo[3,4-b]pyridine-3-carboxylate (100 mg).

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90 mg of racemic mixture was separated into its enantiomers using chiral HPLC [method 4].

Example 9

40 mg of first eluting enantiomer as a white solid, 44% yield.

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Chiral HPLC Rt = 6.481 min; [chiral analytical method 1]

LCMS Rt = 1.473 min; MS m/z 370 [M+H]⁺; [Method 7]

¹H NMR (400 MHz, CDCl₃) δ 7.30 (dd, J = 7.5, 1.9 Hz, 1H), 7.24 – 7.12 (m, 2H), 7.06 (d, J = 8.0 Hz, 1H), 6.81 – 6.43 (m, 1H), 5.82 – 5.69 (m, 1H), 5.68 – 5.56 (m, 1H), 5.19 (s, 1H), 4.77 (d, J = 1.6 Hz, 2H), 3.55 (d, J = 0.7 Hz, 3H). Exchangeable NH proton not seen.

The stereochemistry of Example 9, methyl (R)-4-(2-(difluoromethoxy)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate, was determined by single crystal x-ray crystallographic analysis and it confirmed that active enantiomer is the R-enantiomer (Figure 9).

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Example 9b

38 mg of second eluting enantiomer as a white solid, 42% yield.

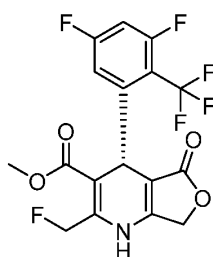
Chiral HPLC Rt = 10.303 min; [chiral analytical method 1]

LCMS Rt = 1.475 min; MS m/z 370.1 [M+H]⁺; [Method 7]

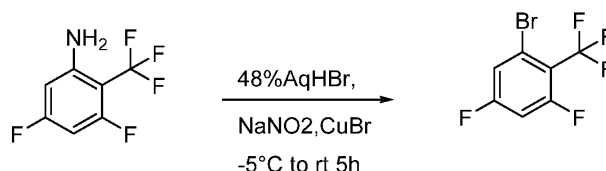
10 ¹H NMR: (400 MHz, CDCl₃) δ 7.30 (dd, J = 7.5, 1.9 Hz, 1H), 7.24 – 7.12 (m, 2H), 7.06 (d, J = 8.0 Hz, 1H), 6.81 – 6.43 (m, 1H), 5.82 – 5.69 (m, 1H), 5.68 – 5.56 (m, 1H), 5.19 (s, 1H), 4.77 (d, J = 1.6 Hz, 2H), 3.55 (d, J = 0.7 Hz, 3H).

Example 10: methyl (R)-4-(3,5-difluoro-2-(trifluoromethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate

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Step 1: 1-bromo-3,5-difluoro-2-(trifluoromethyl)benzene



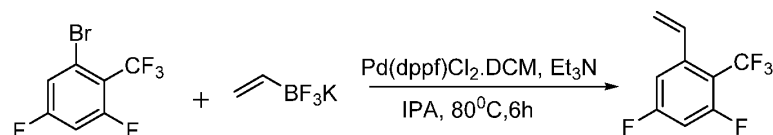
A solution of 3,5-difluoro-2-(trifluoromethyl)aniline (10 g, 50.735 mmol) in 48% aqueous HBr/H₂O (80 mL/80 mL) was cooled to -5 °C, then NaNO₂ (8.74 g in 100 mL H₂O, 126.83 mmol) was added slowly over a period of 5 min, then the resulting mixture was stirred for 1h at -5 °C. The reaction mixture was treated with CuBr (10.92 g, 76.103 mmol) portion wise at -5°C. The reaction mixture was slowly raised to room temperature and stirred for 4 hrs. The reaction mixture was extracted with hexane (3 X 200 mL). The organic phases were combined, washed with saturated brine solution (100 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and purification of the crude

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product by silica flash chromatography in petroleum ether afforded the title compound 1-bromo-3,5-difluoro-2-(trifluoromethyl)benzene (8 g) as a colorless liquid.

^1H NMR (400 MHz, CDCl_3) δ 7.31 (dt, $J = 7.6, 2.2$ Hz, 1H), 6.95 – 6.88 (m, 1H).

Step 2: 1,5-difluoro-2-(trifluoromethyl)-3-vinylbenzene



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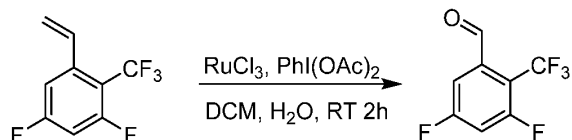
To a solution of 1-bromo-3,5-difluoro-2-(trifluoromethyl)benzene (from step 1, 12.0 g, 45.99 mmol) and trifluoro(vinyl)-I4-borane in Isopropyl alcohol (120 mL) was added potassium salt (12.3 g, 91.98 mmol) and triethylamine (19.16 mL, 137.98 mmol). The resulting solution was purged by argon for 10 min, after that [1,1'-Bis (diphenylphosphino)ferrocene]dichloropalladium(II).DCM (3.75 g, 4.599 mmol) was added. The reaction mixture was stirred at 80°C for 6 hrs. The reaction mixture was filtered through a celite pad and washed with ethyl acetate (100 mL) and dried over Na_2SO_4 . The solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography in petroleum ether afforded the title compound 1,5-difluoro-2-(trifluoromethyl)-3-vinylbenzene (6.5 g) as a colorless liquid.

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^1H NMR (300 MHz, CDCl_3) δ 7.16 – 6.97 (m, 2H), 6.85 – 6.80 (m, 1H), 5.67 (d, $J = 17.2$ Hz, 1H), 5.49 (d, $J = 10.9$ Hz, 1H).

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Step 3: 3,5-difluoro-2-(trifluoromethyl)benzaldehyde

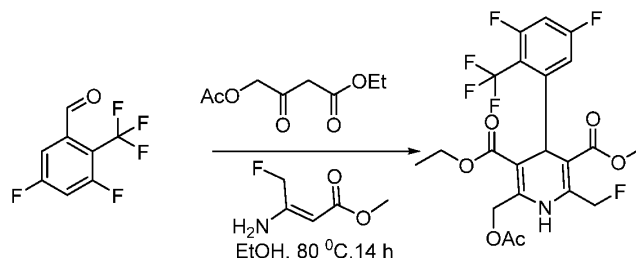


1,5-difluoro-2-(trifluoromethyl)-3-vinylbenzene (from step 2, 6.5 g, 31.23 mmol) and $\text{RuCl}_3 \cdot \text{XH}_2\text{O}$ (647 mg, 3.123 mmol) was added to a solution of diacetoxiodo benzene (20 g, 62.46 mmol) in dichloromethane: H_2O (130 mL : 30 mL). The resulting solution was stirred at room temperature for 2h. The reaction mixture was filtered through a celite pad and washed with dichloromethane (200 mL) and dried over Na_2SO_4 . The solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography (0 → 5%) ethyl acetate in petroleum ether afforded the title compound 3,5-difluoro-2-(trifluoromethyl)benzaldehyde (3.0 g) as a colorless liquid. ^1H NMR (300 MHz, CDCl_3) δ 10.34 (m, 1H), 7.82 – 7.52 (m, 1H), 7.22 – 7.07 (m, 1H).

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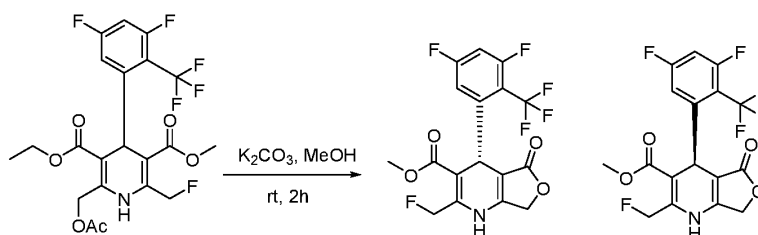
25

Step 4: 3-ethyl 5-methyl 2-(acetoxymethyl)-4-(3,5-difluoro-2-(trifluoromethyl)phenyl)-6-(fluoromethyl)-1,4-dihydropyridine-3,5-dicarboxylate



Title compound was synthesized using step 1 of general procedure I (using the aldehyde from step 3 (400 mg, 1.903 mmol)) to give 3-ethyl 5-methyl 2-(acetoxymethyl)-4-(3,5-difluoro-2-(trifluoromethyl)phenyl)-6-(fluoromethyl)-1,4-dihydropyridine-3,5-dicarboxylate (900 mg, crude).
LCMS Rt = 1.76 min; MS m/z 496.0 [M+H]⁺; [Method 7]

Step 5: methyl 4-(3,5-difluoro-2-(trifluoromethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate



Title compound was synthesized using step 2 of general procedure I (using intermediate from step 4 (900 mg, 1.8 mmol)). Crude product by silica flash chromatography (0 → 50%) ethyl acetate in petroleum ether afforded the title compound methyl 4-(3,5-difluoro-2-(trifluoromethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate (90 mg) as an off white solid.
Racemic mixture was separated into its enantiomers using chiral HPLC [method 7].

Example 10

30 mg of first eluting enantiomer obtained as a white solid.

Chiral HPLC Rt = 5.502 min; [chiral analytical method 2]

LCMS Rt = 1.542 min; MS m/z 406 [M-H]⁻; [Method 7]

¹H NMR: (400 MHz, CDCl₃) δ 7.30 (d, J = 7.2 Hz, 1H), 6.87 (d, J = 9.5 Hz, 1H), 6.85-6.75 (m, 1H), 5.79 (t, J = 1.2, 1.2 Hz, 1H), 5.67 (t, J = 1.1 Hz, 1H), 5.62 (s, 1H), 4.80 (d, J = 1.2 Hz, 2H), 3.54 (s, 3H).

Example 10b

30 mg of second eluting enantiomer obtained as a white solid.

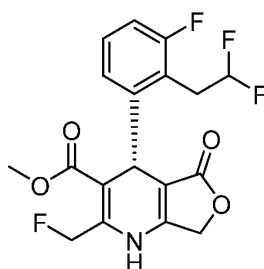
Chiral HPLC Rt = 6.935 min; [chiral analytical method 1]

LCMS Rt = 1.542 min; MS m/z 406 [M-H]⁻; [Method 7]

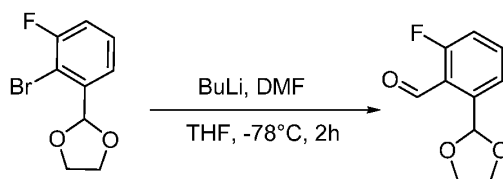
¹H NMR: (400 MHz, CDCl₃) δ 7.30 (d, J = 7.2 Hz, 1H), 6.87 (d, J = 9.5 Hz, 1H), 6.85–6.75 (m, 1H), 5.79 (t, J = 1.2, 1.2 Hz, 1H), 5.67 (t, J = 1.1 Hz, 1H), 5.62 (s, 1H), 4.80 (d, J = 1.2 Hz, 2H), 3.54 (s, 3H).

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Example 11: methyl (R)-4-(2-(2,2-difluoroethyl)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate



Step 1: 2-(1,3-dioxolan-2-yl)-6-fluorobenzaldehyde



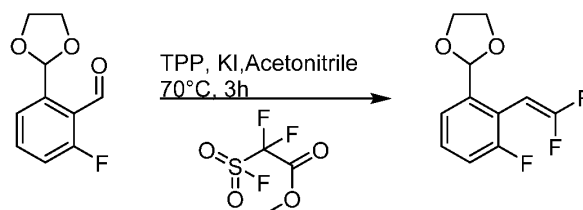
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A solution of 2-(2-bromo-3-fluorophenyl)-1,3-dioxolane (from step 1, example 1, 7 g, 28.45 mmol) in THF (70 mL) under nitrogen atmosphere was cooled to -78°C. Then n-butyllithium in n-Hexane solution (13.66 mL, 2.5M, 58.5 mmol) was added over 10 min, the resulting mixture was stirred for 45 min at -78°C. DMF (2.5 g, 34.15 mmol) was added to and resulting mixture stirred for 1.15 h at -78°C. The reaction mixture was quenched with saturated ammonium chloride solution (50 mL) and extracted with ethyl acetate (2 x 100 mL). Combined organic phases were washed with water (50 mL), followed by brine (50 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography (0 → 50%) ethyl acetate in petroleum ether afforded the title compound 2-(1,3-dioxolan-2-yl)-6-fluorobenzaldehyde (5 g) as a colorless liquid.

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¹H NMR (300 MHz, CDCl₃) δ 10.52 (s, 1H), 7.67 – 7.53 (m, 2H), 7.22 – 7.12 (m, 1H), 6.50 (s, 1H), 4.27 – 3.99 (m, 4H).

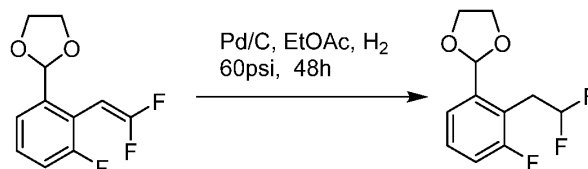
Step 2: 2-(2-(2,2-difluorovinyl)-3-fluorophenyl)-1,3-dioxolane



A solution of acetonitrile (65 mL), triphenylphosphine (28.1 g, 107.1 mmol), potassium iodide (11.85 g, 71.4 mmol) and 2-(1,3-dioxolan-2-yl)-6-fluorobenzaldehyde (from step 1, 7 g, 35.7 mmol) was heated to 70°C under nitrogen atmosphere and stirred for 30 min. Methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (12 g, 62.4 mmol) was added slowly over a period of 10 min (mass color was turned to yellow during addition). The resulting mixture was stirred for another 3 hrs at 70°C, then cooled to room temperature and diluted with diethyl ether. Precipitated solids were filtered and washed with diethyl ether (100 mL). The solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography (0 → 5%) ethyl acetate in petroleum ether afforded the title compound 2-(2-(2,2-difluorovinyl)-3-fluorophenyl)-1,3-dioxolane (6.9 g) as a light yellow liquid.

¹H NMR: (300 MHz, CDCl₃) δ 7.39 (dd, J = 7.8, 1.4 Hz, 1H), 7.31 (m, 1H), 7.11 (m, 1H), 5.87 (s, 1H), 5.39 (m, 1H), 4.21 – 3.95 (m, 4H).

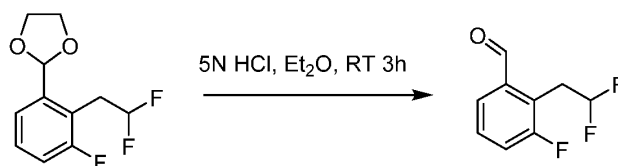
Step 3: 2-(2-(2,2-difluoroethyl)-3-fluorophenyl)-1,3-dioxolane



To a solution of 2-(2-(2,2-difluorovinyl)-3-fluorophenyl)-1,3-dioxolane (from step 2, 3 g, 13.04 mmol) in ethyl acetate (60 mL) was added 10% Pd-C (1 g). The resulting reaction mixture was kept in Parr-Shaker for 48 hrs at 60 psi of pressure under hydrogen atmosphere at room temperature. The reaction mixture was filtered on a celite pad, and washed with ethyl acetate (30 mL). The filtrate was concentrated under reduced pressure and purification of the crude product by silica flash chromatography (0 → 30%) ethyl acetate in petroleum ether afforded the title compound 2-(2-(2,2-difluoroethyl)-3-fluorophenyl)-1,3-dioxolane (3 g) as a colorless liquid.

¹H NMR (300 MHz, CDCl₃) δ 7.42 – 7.35 (m, 1H), 7.34 – 7.27 (m, 1H), 7.15 – 7.08 (m, 1H), 6.31 – 5.78 (m, 2H), 4.19 – 4.02 (m, 4H), 3.38 (m, 2H).

Step 4: 2-(2-(2,2-difluoroethyl)-3-fluorobenzaldehyde

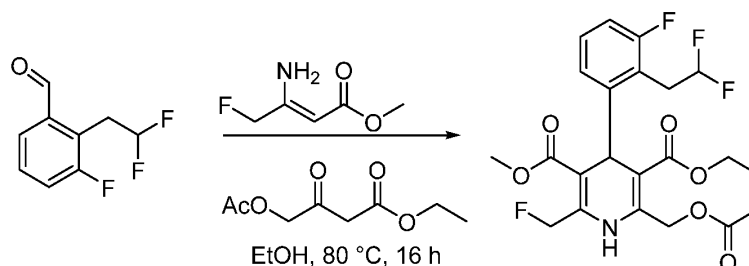


To a solution of 2-(2-(2,2-difluoroethyl)-3-fluorophenyl)-1,3-dioxolane (from step 3, 3 g, 12.93 mmol) in diethyl ether (40 mL) was added 6N HCl (5 mL). The resulting solution was stirred at room temperature for 3 hrs. This was washed with water (50 mL), saturated NaHCO₃ solution (100 mL),
 5 brine and dried over Na₂SO₄. The solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography (0 → 5%) ethyl acetate in petroleum ether afforded the title compound 2-(2-(2,2-difluoroethyl)-3-fluorobenzaldehyde (1.9 g) as a colorless liquid.

¹H NMR (400 MHz, CDCl₃) δ 10.14 (d, J = 1.6 Hz, 1H), 7.70 – 7.63 (m, 1H), 7.52 (td, J = 8.0, 7.9, 5.2 Hz, 1H), 7.35 – 7.30 (m 1H), 6.03 (m, 1H), 3.83 – 3.58 (m, 2H).

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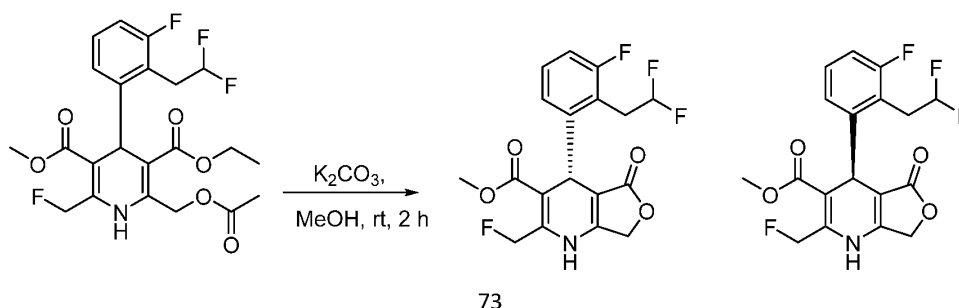
Step 5: 3-ethyl 5-methyl 2-(acetoxymethyl)-4-(2-(2,2-difluoroethyl)-3-fluorophenyl)-6-(fluoromethyl)-1,4-dihydropyridine-3,5-dicarboxylate



Title compound was synthesized using step 1 of general procedure I (using aldehyde from step 4, 400 mg, 2.12 mmol) to give title compound 3-ethyl 5-methyl 2-(acetoxymethyl)-4-(2-(2,2-difluoroethyl)-3-fluorophenyl)-6-(fluoromethyl)-1,4-dihydropyridine-3,5-dicarboxylate (1 g, crude).
 LCMS Rt = 1.764 min; MS m/z 473.4 [M+H]⁺; [Method 7]

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Step 6: methyl 4-(2-(2,2-difluoroethyl)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate



Title compound was synthesized using step 2 of general procedure I (using intermediate from step 5, 1 g, 2.11 mmol). Crude product was purified by silica flash chromatography (0 → 50%) ethyl acetate in petroleum ether affording the title compound methyl 4-(2-(2,2-difluoroethyl)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate (85 mg) as an off white solid. Racemic mixture was separated into its enantiomers using chiral preparative HPLC [method 6].

Example 11

30 mg of first eluting enantiomer obtained as a white solid.

Chiral HPLC Rt = 6.325 min; [chiral analytical method 2]

LCMS Rt = 1.508 min; MS m/z 386.0 [M+H]⁺; [Method 7]

¹H NMR (400 MHz, CDCl₃) δ 7.34 – 7.27 (m, 1H), 7.21 (m, 1H), 7.01 – 6.89 (m, 2H), 6.55 – 6.17 (m, 1H), 5.81 (dd, J = 1.7, 0.8 Hz, 1H), 5.69 (t, J = 1.1 Hz, 1H), 5.08 (s, 1H), 4.78 (d, J = 0.9 Hz, 2H), 3.94 – 3.73 (m, 1H), 3.60 – 3.55 (m, 1H), 3.54 (s, 3H).

Example 11b

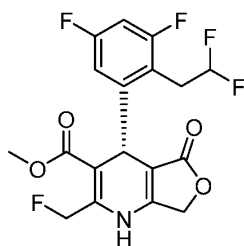
30 mg of first eluting enantiomer obtained as a white solid.

Chiral HPLC Rt = 8.402 min; [chiral analytical method 2]

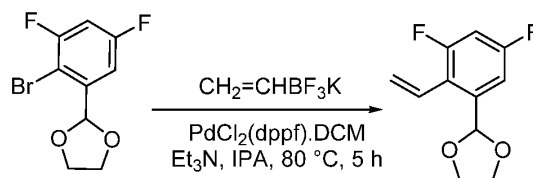
LCMS Rt = 1.508 min; MS m/z 386.4 [M+H]⁺; [Method 7]

¹H NMR (400 MHz, CDCl₃) δ 7.34 – 7.27 (m, 1H), 7.21 (td, J = 8.0, 8.0, 5.6 Hz, 1H), 7.01 – 6.89 (m, 2H), 6.55 – 6.17 (m, 1H), 5.81 (dd, J = 1.7, 0.8 Hz, 1H), 5.69 (t, J = 1.1, 1.1 Hz, 1H), 5.08 (s, 1H), 4.78 (d, J = 0.9 Hz, 2H), 3.94 – 3.73 (m, 1H), 3.60 – 3.55 (m, 1H), 3.54 (s, 3H).

Example 12: methyl (R)-4-(2-(2,2-difluoroethyl)-3,5-difluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate



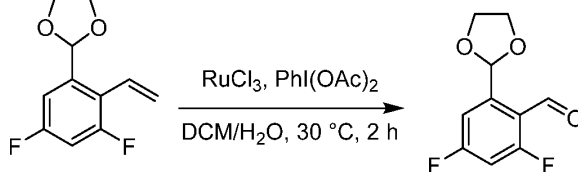
Step 2: 2-(3, 5-difluoro-2-vinylphenyl)-1,3-dioxolane



A solution of 2-(2-bromo-3,5-difluorophenyl)-1,3-dioxolane (from step 1, example 3, 5 g, 18.94 mmol) and potassium vinyltrifluoroborate (5.8 g, 37.89 mmol), triethylamine (7.91 mL, 56.82 mmol) in isopropyl alcohol (50 mL) was degassed for 10 min using Argon gas and was added [1,1'-Bis (diphenylphosphino)ferrocene]dichloropalladium(II).DCM (1.55 g, 1.89 mmol). The resulting solution
 5 was degassed again with Argon gas for 10 min and stirred at 80°C for 5 hrs. The reaction mixture was filtered and washed with ethyl acetate (100 mL). The filtrate was dissolved in water (1 L) and extracted into ethyl acetate (2 L). EtOAc was washed with brine and dried over Na₂SO₄. The solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography (0 → 10%) ethyl acetate in petroleum ether afforded the title compound 2-(3,5-
 10 difluoro-2-vinylphenyl)-1,3-dioxolane (3.45 g) as a colorless liquid. Note: Compound is volatile in nature, hexane present in the compound.

¹H NMR (300 MHz, CDCl₃) δ 7.20 - 7.16 (m, 1H), 6.94 - 6.83 (m, 1H), 6.82 (dd, J = 17.7, 11.7 Hz, 1H), 5.60 (dd, J = 1.2, 11.7 Hz, 1H), 5.66 - 5.60 (m, 1H), 5.95 (s, 1H), 4.18 - 4.02 (m, 4H).

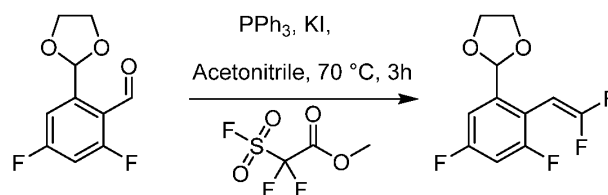
15 Step 3: 2-(1,3-dioxolan-2-yl)-4,6-difluorobenzaldehyde



To a solution of 2-(3,5-difluoro-2-vinylphenyl)-1,3-dioxolane (from step 2, 5 g, 23.58 mmol) and ruthenium chloride.XH₂O (490 mg, 2.35 mmol) in dichloromethane (50 mL) and water (10 mL) was added (diacetoxyiodo)benzene (11.4 g, 35.37 mmol). The resulting solution was stirred at 30°C for 2
 20 hrs. The reaction mixture was filtered and washed with ethyl acetate (200 mL). The filtrate was dissolved in water (200 mL) and product extracted into ethyl acetate (500 mL). Organics were washed with brine and dried over Na₂SO₄. The solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography (0 → 10%) ethyl acetate in petroleum ether afforded the title compound 2-(1,3-dioxolan-2-yl)-4,6-difluorobenzaldehyde (3 g) as a colorless liquid.
 25 Note: Compound is volatile in nature, hexane present in the compound.

¹H NMR (300 MHz, CDCl₃) δ 10.41 (s, 1H), 7.35 (d, J = 9.6 Hz, 1H), 6.95 – 6.85 (m, 1H), 6.53 (s, 1H), 4.08 (s, 4H).

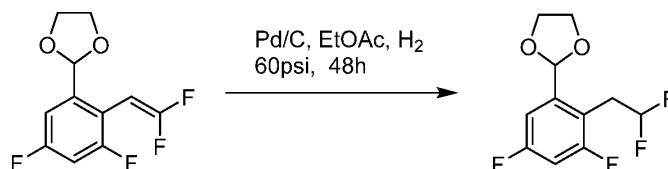
Step 4: 2-(2-(2,2-difluorovinyl)-3,5-difluorophenyl)-1,3-dioxolane



To acetonitrile (4.5 mL) under nitrogen atmosphere was added triphenylphosphine (1.83 g, 7.0 mmol), potassium iodide (775 mg, 4.66 mmol) and 2-(1,3-dioxolan-2-yl)-6-fluorobenzaldehyde (from step 3, 500 mg, 2.33 mmol). Reaction stirred for 30 min at 70°C . Then 2-(1,3-dioxolan-2-yl)-4,6-difluorobenzaldehyde (783 mg, 4.07 mmol) was added slowly over a period of 10 min (mass color turned to yellow during addition) and the resulting mixture was stirred at 70°C for another 3 hrs. Then the reaction mixture was cooled to room temperature and diluted with diethyl ether, precipitated solids were filtered, and washed with diethyl ether (100 mL). The solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography (0 $\rightarrow$ 5%) ethyl acetate in petroleum ether afforded the title compound 2-(2-(2,2-difluorovinyl)-3,5-difluorophenyl)-1,3-dioxolane (400 mg) as a light yellow liquid.

^1H NMR (300 MHz, CDCl_3) δ 7.19 – 7.12 (m, 1H), 6.89 – 6.80 (m, 1H), 5.85 (d, J = 0.9 Hz, 1H), 5.31 (dt, J = 26.1, 1.5 Hz, 1H), 4.16 – 3.98 (m, 4H).

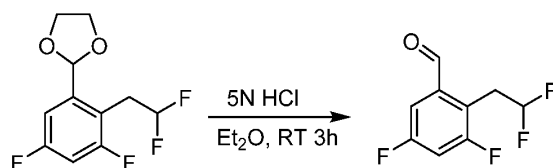
15 Step 5: 2-(2-(2,2-difluoroethyl)-3,5-difluorophenyl)-1,3-dioxolane



To a solution of 2-(2-(2,2-difluorovinyl)-3,5-difluorophenyl)-1,3-dioxolane (from step 4, 400 mg, 1.61 mmol) in ethyl acetate (10 mL) was added 10% Pd-C (180 mg). The resulting reaction mixture was kept in Parr-Shaker for 48 hrs at 60psi pressure at room temperature under hydrogen atmosphere. The reaction mixture was filtered through a celite pad and washed with ethyl acetate (30 mL). The filtrate was concentrated under reduced pressure and purification of the crude product by silica flash chromatography (0 $\rightarrow$ 30%) ethyl acetate in petroleum ether afforded the title compound 2-(2-(2,2-difluoroethyl)-3,5-difluorophenyl)-1,3-dioxolane (400 mg) as a colorless liquid.

^1H NMR (300 MHz, CDCl_3) δ 7.22 – 7.12 (m, 1H), 6.81 – 6.75 (m, 1H), 6.26 – 5.75 (m, 2H), 4.20 – 3.99 (m, 4H), 3.36 – 3.33 (m, 2H).

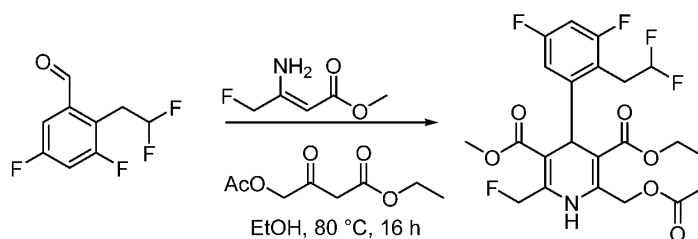
Step 6: 2-(2,2-difluoroethyl)-3,5-difluorobenzaldehyde



To a solution of 2-(2-(2,2-difluoroethyl)-3,5-difluorophenyl)-1,3-dioxolane (from step 5, 400 mg, 1.6 mmol) in diethyl ether (10 mL) was added 5N HCl (1 mL). The resulting solution was stirred at room temperature for 3 hrs. This was washed with water (50 mL), saturated NaHCO₃ solution (100 mL), and brine and dried over Na₂SO₄. The solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography (0 → 5%) ethyl acetate in petroleum ether afforded the title compound 2-(2-(2,2-difluoroethyl)-3,5-difluorobenzaldehyde (250 mg) as a colorless liquid.

¹H NMR (300 MHz, CDCl₃) δ 10.11 (d, J = 1.3 Hz, 1H), 7.51 – 7.34 (m, 1H), 7.20 – 7.07 (m, 1H), 6.31 – 5.73 (m, 1H), 3.79 – 3.56 (m, 2H).

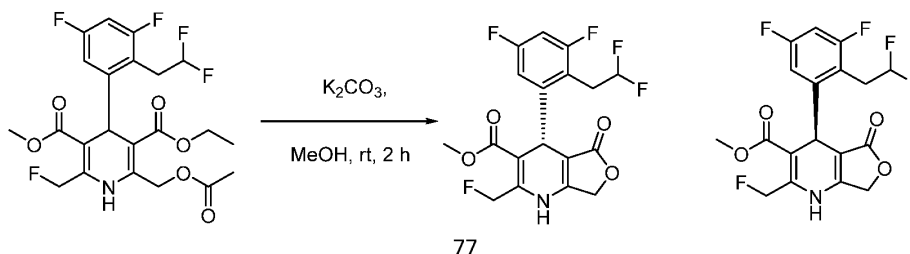
Step 7: 3-ethyl 5-methyl 2-(acetoxymethyl)-4-(2-(2,2-difluoroethyl)-3,5-difluorophenyl)-6-(fluoromethyl)-1,4-dihydropyridine-3,5-dicarboxylate



Title compound was synthesized using step 1 of general procedure I (using the aldehyde from step 6 (250 mg, 1.21 mmol)) to give title compound 3-ethyl 5-methyl 2-(acetoxymethyl)-4-(2-(2,2-difluoroethyl)-3,5-difluorophenyl)-6-(fluoromethyl)-1,4-dihydropyridine-3,5-dicarboxylate (800 mg, crude).

LCMS Rt = 1.77 min; MS m/z 491.0 [M]⁺; [Method 7]

Step 8: methyl 4-(2-(2,2-difluoroethyl)-3,5-difluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate



Title compound was synthesized using step 2 of general procedure I (using intermediate from step 7, 800 mg, 1.62 mmol). Crude product was purified by silica flash chromatography (0 → 50%) ethyl acetate in petroleum ether to afford the title compound methyl 4-(2-(2,2-difluoroethyl)-3,5-difluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate (44 mg) as an off white solid. Racemic mixture was separated into its enantiomers using chiral preparative HPLC [method 6].

Example 12

11 mg of first eluting enantiomer obtained as a white solid.

Chiral HPLC Rt = 5.674 min; [chiral analytical method 2]

10 LCMS Rt = 1.561 min; MS m/z 403.9 [M]⁺; [Method 7]

¹H NMR (400 MHz, CD₃OD) δ 6.87 – 6.76 (m, 2H), 6.64 – 6.26 (m, 1H), 5.76 (s, 1H), 5.64 (s, 1H), 5.13 (d, J = 1.4 Hz, 1H), 4.87 – 4.83 (m, 2H), 3.50 – 3.36 (m, 1H), 3.70 (s, 2H), 3.53 (s, 3H).

Example 12b

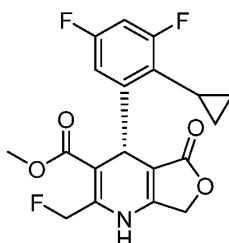
10 mg of second eluting enantiomer obtained as a white solid.

15 Chiral HPLC Rt = 7.215 min; [chiral analytical method 2]

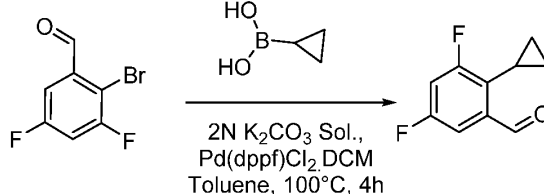
LCMS Rt = 1.557 min; MS m/z 403.9 [M]⁺; [Method 7]

¹H NMR (400 MHz, CD₃OD) δ 6.87 – 6.76 (m, 2H), 6.64 – 6.26 (m, 1H), 5.76 (s, 1H), 5.64 (s, 1H), 5.13 (d, J = 1.4 Hz, 1H), 4.87 – 4.83 (m, 2H), 3.50 – 3.36 (m, 1H), 3.70 (s, 2H), 3.53 (s, 3H).

20 Example 13: methyl (R)-4-(2-cyclopropyl-3,5-difluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate



Step 1: 2-cyclopropyl-3,5-difluorobenzaldehyde

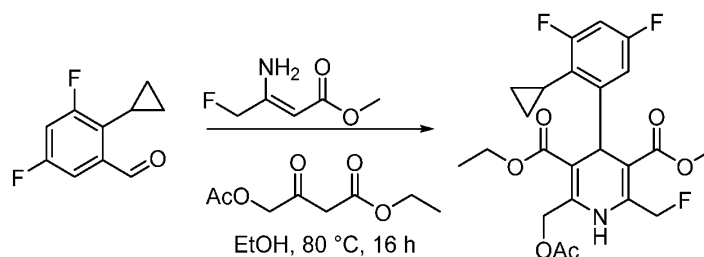


25 To a solution of 2-bromo-3,5-difluorobenzaldehyde (10 g, 45.20 mmol) and cyclopropylboronic acid (4.67 g, 54.2 mmol) in toluene (100 mL) was added 2N K₂CO₃ (102 mL, 204 mmol) and [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II).DCM (3.17 g, 3.88 mmol). The resulting

solution was degassed with Argon gas for 10 min and stirred at 100 °C for 4 hrs. The reaction mixture was filtered and washed with ethyl acetate (200 mL). The filtrate was added to water (500 mL) and product extracted into ethyl acetate (2 L). EtOAc phase was washed with brine and dried over Na₂SO₄. The solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography (0 → 1%) ethyl acetate in petroleum ether afforded the title compound 2-cyclopropyl-3,5-difluorobenzaldehyde (8 g) as a colorless liquid.

¹H NMR (300 MHz, CDCl₃) δ 10.71 (d, J = 3 Hz, 1H), 7.40 - 7.30 (m, 1H), 7.05 - 6.90 (m, 1H), 2.05 - 1.95 (m, 1H), 1.19 - 1.09 (m, 2H), 0.85 - 0.75 (m, 2H).

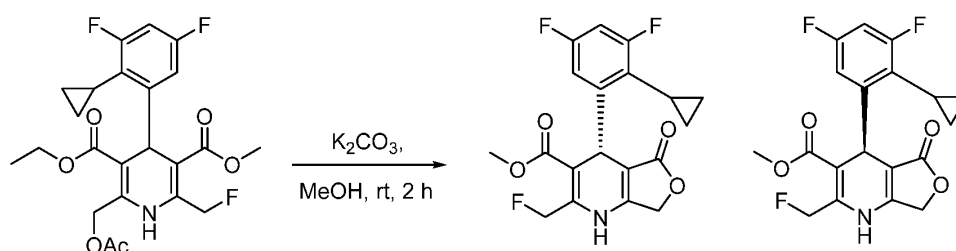
- 10 Step 2: 3-ethyl 5-methyl 2-(acetoxymethyl)-4-(2-cyclopropyl-3,5-difluorophenyl)-6-(fluoromethyl)-1,4-dihydropyridine-3,5-dicarboxylate



Title compound was synthesized using general step 1 of general procedure I (using the aldehyde from step 1 (1.8 g, 9.88 mmol)) to give 3-ethyl 5-methyl 2-(acetoxymethyl)-4-(2-cyclopropyl-3,5-difluorophenyl)-6-(fluoromethyl)-1,4-dihydropyridine-3,5-dicarboxylate (4.61 g, crude).

LCMS Rt = 1.586 min; MS m/z 477.0 [M+H]⁺; [Method 10]

- Step 3: methyl 4-(2-cyclopropyl-3,5-difluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate



Title compound was synthesized using step 2 of general procedure I (using intermediate from step 2, 4.61 g, 9.871 mmol). Crude product was purified by silica flash chromatography (0 → 50%) ethyl acetate in petroleum ether which afforded the title compound methyl 4-(2-cyclopropyl-3,5-difluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate (350 mg) as an off white solid.

Racemic mixture was separated into its enantiomers using chiral preparative HPLC [method 9].

Example 13

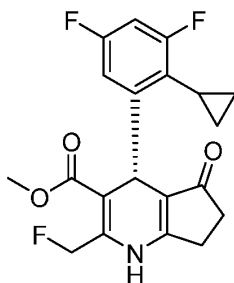
135 mg of first eluting enantiomer obtained as a white solid.

Chiral HPLC Rt = 5.33 min; [chiral analytical method 2]

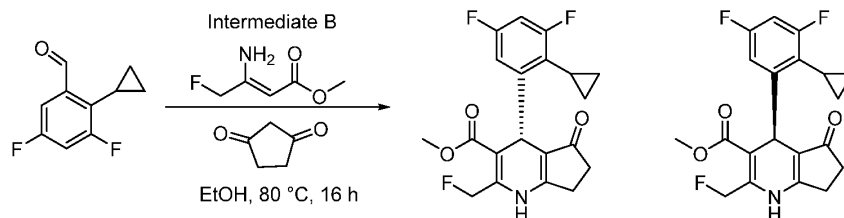
5 LCMS Rt = 1.591 min; MS m/z 380.2 [M+H]⁺; [Method 7]

¹H NMR (300 MHz, CD₃OD) δ 6.78 – 6.70 (m, 1H), 6.66 (m, 1H), 5.75 (s, 1H), 5.61 (d, J = 14.1 Hz, 2H), 4.84 (q, J = 1.7, 1.7, 0.9 Hz, 2H), 3.53 (s, 3H), 2.08 (m, 1H), 1.18 (m, 1H), 1.07 – 0.87 (m, 2H), 0.75 (m, 1H).

10 **Example 14: methyl (R)-4-(2-cyclopropyl-3,5-difluorophenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate**



Step 2: methyl 4-(2-cyclopropyl-3,5-difluorophenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate



15

To solution of aldehyde (from step 1, example 13, 300 mg, 1.64 mmol) was added methyl (Z)-3-amino-4-fluorobut-2-enoate (intermediate B, 220 mg, 1.64 mmol) and cyclopentane-1,3-dione (161 mg, 1.64 mmol) in ethanol (5 mL). The reaction mixture was stirred at 80°C for 16 hrs. The solvent was removed under reduced pressure giving crude compound. Crude product was purified by silica flash chromatography (0 → 70%) ethyl acetate in petroleum ether affording the title compound methyl 4-(2-cyclopropyl-3,5-difluorophenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (55 mg) as an off white solids. Racemic mixture was separated into its enantiomers using chiral preparative HPLC [method 3].

20

Example 14

25 17 mg of first eluting enantiomer obtained as a white solid.

Chiral HPLC Rt = 8.588 min; [chiral analytical method 3]

LCMS Rt = 1.548 min; MS m/z 378.0 [M+H]⁺; [Method 7]

¹H NMR (400 MHz, CDCl₃) δ 7.21 (d, J = 7.2 Hz, 1H), 6.65 – 6.48 (m, 2H), 5.78 (d, J = 0.9 Hz, 1H), 5.65 (d, J = 0.8 Hz, 1H), 5.60 – 5.52 (m, 1H), 3.56 (s, 3H), 2.75 – 2.56 (m, 2H), 2.52 – 2.32 (m, 2H),
 5 2.20 – 2.13 (m, 1H), 1.34 – 1.13 (m, 1H), 1.05 – 0.98 (m, 2H), 0.83 – 0.69 (m, 1H).

Example 14b

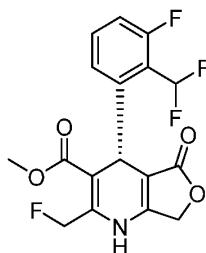
17 mg of second eluting enantiomer obtained as a white solid.

Chiral HPLC Rt = 11.651 min; [chiral analytical method 3]

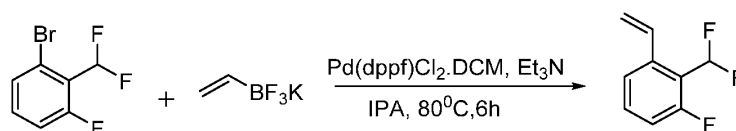
LCMS Rt = 1.548 min; MS m/z 378.0 [M+H]⁺; [Method 7]

10 ¹H NMR (400 MHz, CDCl₃) δ 7.21 (d, J = 7.2 Hz, 1H), 6.65 – 6.48 (m, 2H), 5.78 (d, J = 0.9 Hz, 1H), 5.65 (d, J = 0.8 Hz, 1H), 5.60 – 5.52 (m, 1H), 3.56 (s, 3H), 2.75 – 2.56 (m, 2H), 2.52 – 2.32 (m, 2H), 2.20 – 2.13 (m, 1H), 1.34 – 1.13 (m, 1H), 1.05 – 0.98 (m, 2H), 0.83 – 0.69 (m, 1H).

15 **Example 15: methyl (R)-4-(2-(difluoromethyl)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate**



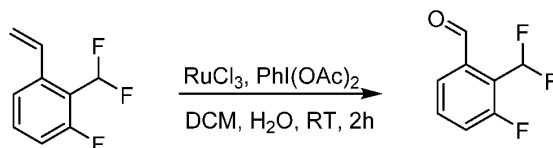
Step 1: 2-(difluoromethyl)-1-fluoro-3-vinylbenzene



To a solution of 1-bromo-2-(difluoromethyl)-3-fluorobenzene (2.0 g, 8.889 mmol) was added
 20 potassium vinyltrifluoroborate (2.38 g, 17.78 mmol) and triethylamine (3.7 mL, 26.66 mmol) in isopropyl alcohol (20 mL). The resulting solution was purged by argon for 10 min and [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II).DCM (725 mg, 0.889 mmol) was added. The reaction mixture was stirred at 80 °C for 6 hrs. The reaction mixture was filtered through a celite pad and washed with ethyl acetate (100 mL) and dried over Na₂SO₄. The solvent was removed under
 25 reduced pressure and purification of the crude product by silica flash chromatography in petroleum ether afforded the title compound 2-(difluoromethyl)-1-fluoro-3-vinylbenzene (1.2 g) as a colorless liquid.

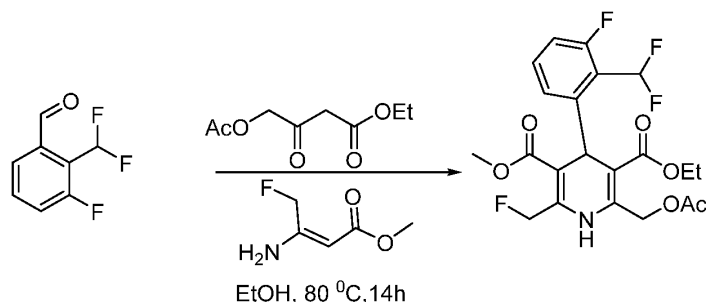
^1H NMR (400 MHz, CDCl_3) δ 7.48 – 7.40 (m, 1H), 7.30 – 7.15 (m, 1H), 7.04 (t, J = 53.4 Hz, 1H), 7.04 – 6.90 (m, 2H), 5.44 (d, J = 11.2 Hz, 1H), 5.70 (d, J = 11.2 Hz, 1H).

Step 2: 2-(difluoromethyl)-3-fluorobenzaldehyde



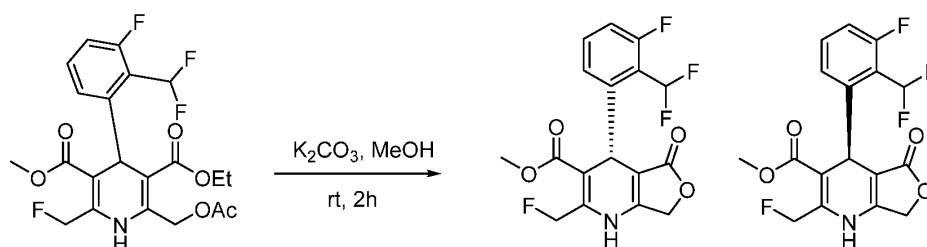
- 5 To a solution of 2-(difluoromethyl)-1-fluoro-3-vinylbenzene (from step 1, 1.2 g, 6.970 mmol), was added $\text{RuCl}_3 \cdot \text{XH}_2\text{O}$ (145 mg, 0.697 mmol) and diacetoxiodo benzene (6.73 g, 20.91 mmol) in dichloromethane: H_2O (20 mL: 6 mL). The resulting solution was stirred at room temperature for 2 hrs. The reaction mixture was filtered through a celite pad and washed with dichloromethane (200 mL) and dried over Na_2SO_4 . The solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography (0 $\rightarrow$ 5%) ethyl acetate in petroleum ether afforded the title compound 2-(difluoromethyl)-3-fluorobenzaldehyde (500 mg) as a colorless liquid.
- 10 ^1H NMR (400 MHz, CDCl_3) δ 10.42 (t, J = 2.0 Hz, 1H), 8.44 (d, J = 8.0 Hz, 1H), 7.70 – 7.59 (m, 1H), 7.45 – 7.35 (m, 1H), 7.30 (t, J = 53.2 Hz, 1H).

- 15 Step 3: 3-ethyl 5-methyl 2-(acetoxymethyl)-4-(2-(difluoromethyl)-3-fluorophenyl)-6-(fluoromethyl)-1,4-dihydropyridine-3,5-dicarboxylate



- Title compound was synthesized using step 1 of general procedure I (using the aldehyde from step 2, 500 mg, 2.871 mmol) to give 3-ethyl 5-methyl 2-(acetoxymethyl)-4-(2-(difluoromethyl)-3-fluorophenyl)-6-(fluoromethyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.5 g, crude).
- 20 LCMS R_t = 1.716 min; MS m/z 460.1 $[\text{M}+\text{H}]^+$; [Method 7]

Step 4: methyl 4-(2-(difluoromethyl)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate



Title compound was synthesized using step 2 of general procedure I (using intermediate from step 3, 1.0 g, 2.177 mmol). Crude product purification by silica flash chromatography (0 → 50%) ethyl acetate in petroleum ether afforded the title compound methyl 4-(2-(difluoromethyl)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate (280 mg) as an off white solid. Racemic mixture was separated into its enantiomers using chiral preparative HPLC [method 5].

Example 15

90 mg of first eluting enantiomer obtained as a white solid.

Chiral HPLC Rt = 10.05 min; [Chiral analytical method 2]

LCMS Rt = 1.947 min; MS m/z 372.2 [M+H]⁺; [Method 9]

¹H NMR (400 MHz, CDCl₃) δ 7.44 – 7.28 (m, 2H), 7.09 – 6.96 (m, 2H), 5.80 (d, J = 0.8 Hz, 1H), 5.68 (d, J = 0.9 Hz, 1H), 5.20 (s, 1H), 4.80 (d, J = 1.1 Hz, 2H), 3.54 (s, 3H). Exchangeable NH proton not seen in spectra.

15

Example 15b

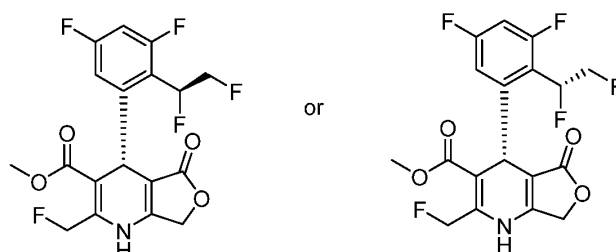
90 mg of second eluting enantiomer obtained as a white solid.

Chiral HPLC Rt = 12.05 min; [Chiral analytical method 2]

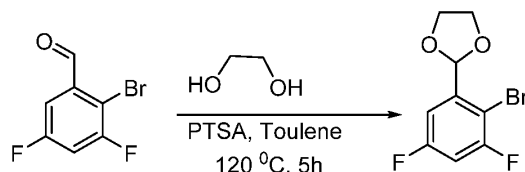
LCMS Rt = 2.09 min; MS m/z 372.2 [M+H]⁺; [Method 9]

¹H NMR (400 MHz, CDCl₃) δ 7.43 – 7.33 (m, 2H), 7.10 – 6.93 (m, 2H), 5.80 (d, J = 0.8 Hz, 1H), 5.68 (d, J = 0.9 Hz, 1H), 5.20 (s, 1H), 4.80 (d, J = 0.9 Hz, 2H), 3.54 (s, 3H).

Example 16: methyl (R)-4-(2-((R or S)-1,2-difluoroethyl)-3,5-difluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate



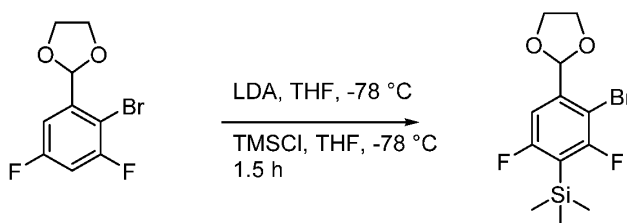
Step 1: 2-(2-bromo-3,5-difluorophenyl)-1,3-dioxolane



The title compound was synthesized following a procedure similar to step 1 of example 1 using 15 g of 2-bromo-3,5-difluorobenzaldehyde to obtain 15 g of desired product 2-(2-bromo-3,5-difluorophenyl)-1,3-dioxolane.

¹H NMR (300 MHz, CDCl₃) δ 7.23 – 7.18 (m, 1H), 6.95 – 6.90 (m, 1H), 6.08 (t, J = 1.1 Hz, 1H), 4.24 – 3.99 (m, 4H).

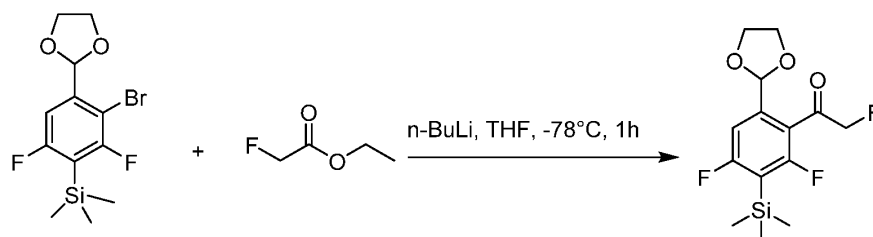
Step 2: (3-bromo-4-(1,3-dioxolan-2-yl)-2,6-difluorophenyl)trimethylsilane



To a solution of 2-(2-bromo-3,5-difluorophenyl)-1,3-dioxolane (from step 1, 15.0 g, 56.59 mmol) in freshly distilled THF (150 mL) under inert atmosphere was added lithium diisopropylamide (31.1 mL, 2.0 M in hexane, 62.25 mmol) at -78°C and stirred for 30 min. Trimethylsilyl chloride (7.37 g, 67.91 mmol) was added to the reaction mixture and stirred for 1h at -78 °C. The reaction mixture was quenched with saturated NH₄Cl solution (250 mL) and product extracted into ethyl acetate (2 X 500 mL). The combined EtOAc phases were washed with brine solution (250 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography in petroleum ether (100 %) afforded the title compound (3-bromo-4-(1,3-dioxolan-2-yl)-2,6-difluorophenyl)trimethylsilane (9.0 g) as a colorless liquid.

¹H NMR (300 MHz, CDCl₃) δ 7.08 (dd, J = 8.9, 1.6 Hz, 1H), 6.07 (d, J = 1.3 Hz, 1H), 4.33 – 3.89 (m, 4H), 0.37 (t, J = 1.6 Hz, 9H).

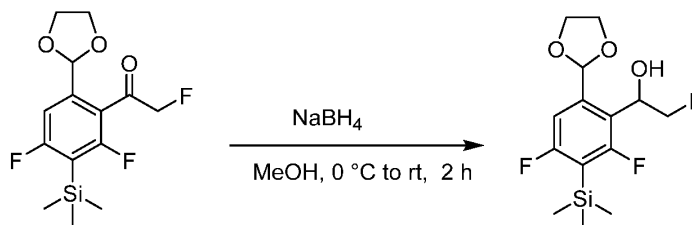
Step 3: 1-(6-(1,3-dioxolan-2-yl)-2,4-difluoro-3-(trimethylsilyl)phenyl)-2-fluoroethan-1-one



To a solution of (3-bromo-4-(1,3-dioxolan-2-yl)-2,6-difluorophenyl)trimethylsilane (from step 2, 5.0 g, 14.961 mmol) in freshly distilled THF (50 mL) under inert atmosphere was added n-butyl lithium (6.0 mL, 2.5M in hexane, 14.961 mmol) slowly at -78 °C. Then ethyl 2,2-difluoroacetate (3.1 g, 29.9 mmol) was added to reaction mixture and stirred for 1h at -78 °C. The reaction was quenched with saturated NH₄Cl solution (250 mL) and extracted into ethyl acetate (2 X 200 mL). The combined EtOAc phases were washed with brine solution (50 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography (0 → 10%) ethyl acetate in petroleum ether afforded the title compound 1-(6-(1,3-dioxolan-2-yl)-2,4-difluoro-3-(trimethylsilyl)phenyl)-2-fluoroethan-1-one (2.5 g) as a colorless liquid.

¹H NMR (300 MHz, CDCl₃) δ 7.04 (dt, J = 8.9, 0.8 Hz, 1H), 6.02 (s, 1H), 5.22 (d, J = 1.6 Hz, 1H), 5.07 (d, J = 1.6 Hz, 1H), 4.03 – 3.79 (m, 4H), 0.37 (s, 9H).

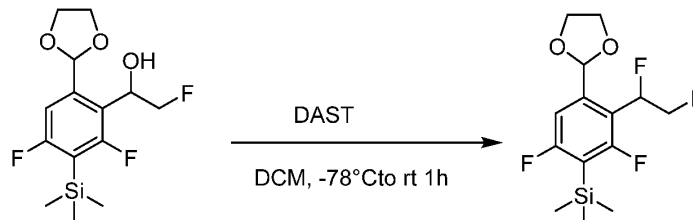
Step 4: 1-(6-(1,3-dioxolan-2-yl)-2,4-difluoro-3-(trimethylsilyl)phenyl)-2-fluoroethan-1-ol



To a solution of 1-(6-(1,3-dioxolan-2-yl)-2,4-difluoro-3-(trimethylsilyl)phenyl)-2-fluoroethan-1-one (from step 3, 2.5 g, 7.854 mmol) in methanol (20 mL) was added sodium borohydride (594.2 mg, 15.70 mmol) portion wise at 0°C. Temperature was allowed to rise to room temperature slowly over 1 hour and stirred at room temperature for another for 2 hrs. The reaction mixture was quenched with saturated ammonium chloride solution (50 mL) and extracted into ethyl acetate (200 mL). EtOAc was washed with brine solution (50 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography (0 → 30%) ethyl acetate in petroleum ether afforded the title compound 1-(6-(1,3-dioxolan-2-yl)-2,4-difluoro-3-(trimethylsilyl)phenyl)-2-fluoroethan-1-ol (2.5 g) as a colorless liquid.

¹H NMR (400 MHz, CDCl₃) δ 7.12 (dd, J = 9.4, 1.2 Hz, 1H), 6.15 (s, 1H), 5.42 – 5.35 (m, 1H), 4.93 – 4.47 (m, 2H), 4.19 – 3.88 (m, 4H), 2.96 (dd, J = 6.1, 2.8 Hz, 1H), 0.36 (s, 9H).

Step 5: (3-(1,2-difluoroethyl)-4-(1,3-dioxolan-2-yl)-2,6-difluorophenyl)trimethylsilane

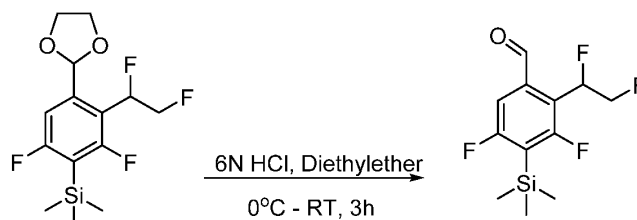


To a solution of 1-(6-(1,3-dioxolan-2-yl)-2,4-difluoro-3-(trimethylsilyl)phenyl)-2-fluoroethan-1-ol (from
 5 step 4, 2.0 g, 6.24 mmol) in dichloromethane (20 mL) was added diethylaminosulfur trifluoride (DAST)
 (1.24 mL, 9.36 mmol) at 0 °C. Reaction was allowed to warm to room temperature and stirred for 1
 h. To the reaction mixture was added water (50 mL) and product extracted into dichloromethane (3
 X 50 mL). DCM phases were combined and washed with saturated NaHCO₃ solution (50 mL), brine
 and dried over Na₂SO₄. The solvent was removed under reduced pressure and purification of the
 10 crude product by silica flash chromatography (0 → 2%) ethyl acetate in petroleum ether afforded the
 title compound (3-(1,2-difluoroethyl)-4-(1,3-dioxolan-2-yl)-2,6-difluorophenyl)trimethylsilane (1.1 g)
 as a colorless liquid.

¹H NMR (400 MHz, CDCl₃) δ 7.23 – 7.04 (m, 1H), 6.24 – 6.05 (m, 1H), 6.04 (s, 1H), 5.15 – 4.89 (m,
 1H), 4.70 – 4.39 (m, 1H), 4.14 – 3.99 (m, 4H), 0.36 (s, 9H).

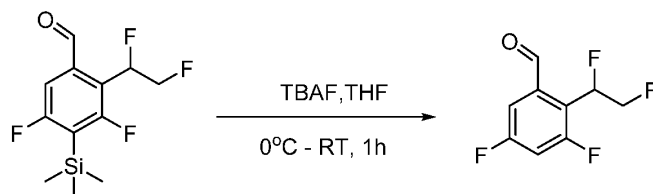
15

Step 6: 2-(1,2-difluoroethyl)-3,5-difluoro-4-(trimethylsilyl)benzaldehyde



To a solution of (3-(1,2-difluoroethyl)-4-(1,3-dioxolan-2-yl)-2,6-difluorophenyl)trimethylsilane (from
 step 5, 1.1 g, 3.41 mmol) in diethyl ether (10 mL) was added 6N HCl (11 mL). The resulting solution
 20 was stirred at room temperature for 3 hrs. This was washed with water (50 mL), saturated NaHCO₃
 solution (100 mL), and brine and dried over Na₂SO₄. The solvent was removed under reduced
 pressure affording the title compound 2-(1,2-difluoroethyl)-3,5-difluoro-4-(trimethylsilyl)benzaldehyde
 (900 mg) as a colorless liquid. Without further purification and analysis, product was used for the next
 step.

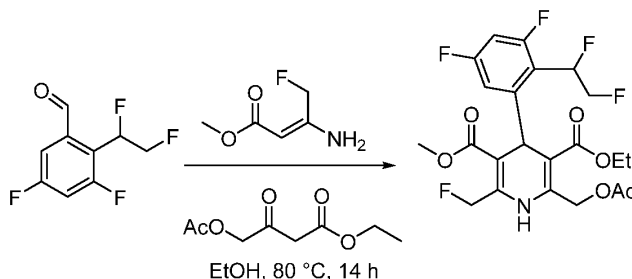
25 Step 7: 2-(1,2-difluoroethyl)-3,5-difluorobenzaldehyde



To a solution of (2-(1,2-difluoroethyl)-3,5-difluoro-4-(trimethylsilyl)benzaldehyde (from step 6, 900 mg, 3.23 mmol) in THF (20 mL), was added TBAF (8.0 mL, 1.0M in THF, 8.08 mmol). The resulting solution was stirred at room temperature for 1h. Reaction mixture was diluted with EtOAc (50 mL) and this was washed with water (50 mL), saturated NaHCO₃ solution (100 mL), and brine and dried over Na₂SO₄. The solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography (5 → 10%) ethyl acetate in petroleum ether afforded the title compound 2-(1,2-difluoroethyl)-3,5-difluorobenzaldehyde (400 mg) as a colorless liquid.

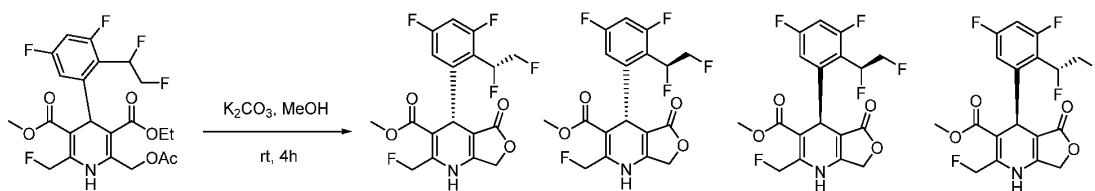
¹H NMR (600 MHz, CDCl₃) δ 10.41 – 10.14 (m, 1H), 7.54 (d, J = 8.3 Hz, 1H), 7.15 – 7.06 (m, 1H), 6.34 – 6.30 (m, 1H), 4.95 – 4.67 (m, 2H).

Step 8: 3-ethyl 5-methyl 2-(acetoxymethyl)-4-(2-(1,2-difluoroethyl)-3,5-difluorophenyl)-6-(fluoromethyl)-1,4-dihydropyridine-3,5-dicarboxylate



Title compound was synthesized using step 1 of general procedure I (using the aldehyde from step 7, 490 mg, 2.377 mmol) to give 3-ethyl 5-methyl 2-(acetoxymethyl)-4-(2-(1,2-difluoroethyl)-3,5-difluorophenyl)-6-(fluoromethyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.0 g, crude). Without further purification and analysis product was used for the next step.

Step 9: methyl 4-(2-(1,2-difluoroethyl)-3,5-difluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate



Title compound was synthesized using step 2 of general procedure I (using intermediate from step 8, 1.0 g, 2.03 mmol). Crude product by silica flash chromatography (0 → 50%) ethyl acetate in petroleum ether afforded the title compound methyl 4-(2-(1,2-difluoroethyl)-3,5-difluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate (1.0 g, crude) as an off white solid. Diastereomeric mixture was separated into its two isomers using silica flash chromatography (0 → 80%) to give 70 mg of first diastereomer as a white solid and 50 mg of second diastereomer as a white solid. Diastereomers from first separation Peak-1: 70 mg and Peak-2: 50 mg were further separated into their enantiomers using preparative chiral SFC [Method 8] to obtain four isomers.

10 Example 16

25 mg of second eluting enantiomer obtained as a white solid

Chiral HPLC Rt = 12.95 min; [chiral analytical method 3]

LCMS Rt= 1.52 min; MS m/z 402.2 [M-H]⁻; [Method 7]

¹H NMR (600 MHz, CDCl₃) δ 7.29 (d, J = 6.8 Hz, 1H), 6.80 – 6.69 (m, 2H), 6.41 (dd, J = 48.5, 17.2 Hz, 1H), 5.80 (s, 1H), 5.72 (s, 1H), 5.36 – 4.69 (m, 5H), 3.59 (s, 3H).

Example 16b

25 mg of first eluting enantiomer obtained as a white solid

Chiral HPLC RT 10.54 min; [chiral analytical method 3]

LCMS Rt= 1.52 min; MS m/z 402.0 [M-H]⁻; [Method 7]

¹H NMR (600 MHz, CDCl₃) δ 7.29 (d, J = 6.8 Hz, 1H), 6.80 – 6.69 (m, 2H), 6.41 (dd, J = 48.5, 17.2 Hz, 1H), 5.80 (s, 1H), 5.72 (s, 1H), 5.36 – 4.69 (m, 5H), 3.59 (s, 3H).

Example 16c

15 mg of third eluting enantiomer as a white solid

Chiral HPLC Rt = 14.54 min; [chiral analytical method 3]

25 LCMS Rt = 1.472 min; MS m/z 402.0 [M-H]⁻; [Method 7]

¹H NMR (400 MHz, CD₃OD) δ 6.92 – 6.80 (m, 2H), 6.70 – 6.48 (m, 1H), 5.76 (s, 1H), 5.64 (s, 1H), 5.48 (s, 1H), 5.16 (s, 1H), 5.15 – 4.51 (m, 4H), 3.55 (s, 3H).

Example 16d

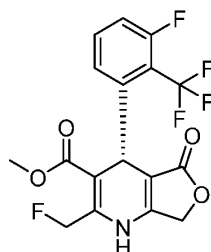
15 mg of fourth eluting enantiomer as a white solid

30 Chiral HPLC Rt = 18.97 min; [chiral analytical method 3]

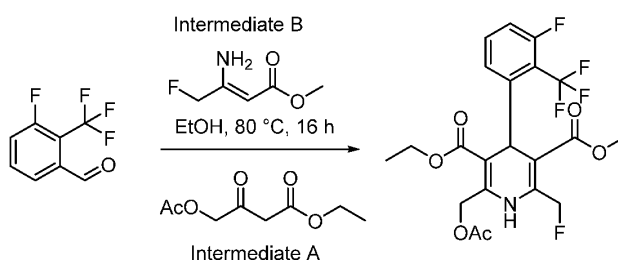
LCMS Rt = 1.466 min; MS m/z 402.2 [M-H]⁻; [Method 7]

¹H NMR (400 MHz, CD₃OD) δ 6.92 – 6.80 (m, 2H), 6.70 – 6.48 (m, 1H), 5.76 (s, 1H), 5.64 (s, 1H), 5.48 (s, 1H), 5.16 (s, 1H), 5.15 – 4.51 (m, 4H), 3.55 (s, 3H).

Example 17: methyl (R)-4-(3-fluoro-2-(trifluoromethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate

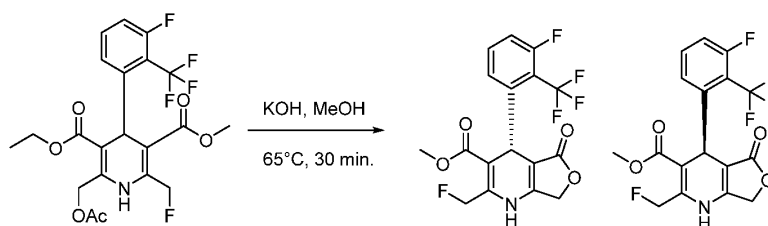


Step 1: 3-ethyl 5-methyl 2-(acetoxymethyl)-4-(3-fluoro-2-(trifluoromethyl)phenyl)-6-(fluoromethyl)-1,4-dihydropyridine-3,5-dicarboxylate



- 10 Title compound was synthesized using general procedure I (using commercially available 3-fluoro-2-(trifluoromethyl)benzaldehyde, 1.4 g, 7.28 mmol) to give 3-ethyl 5-methyl 2-(acetoxymethyl)-4-(3-fluoro-2-(trifluoromethyl)phenyl)-6-(fluoromethyl)-1,4-dihydropyridine -3,5-dicarboxylate (2 g, crude). Without further purification and analysis, the product was used for the next step.

- 15 Step 2: methyl 4-(3-fluoro-2-(trifluoromethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate



- Title compound was synthesized using step 2 of general procedure I (from step 2, 2 g, 4.18 mmol). Crude product purification by silica flash chromatography (0 → 70%) ethyl acetate in petroleum ether afforded the title compound methyl 4-(3-fluoro-2-(trifluoromethyl)phenyl)-2-(fluoromethyl)-5-

oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate (240 mg) as an off white solid. Racemic mixture was separated into its enantiomers using preparative chiral HPLC [method 5].

Example 17

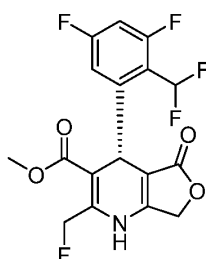
80 mg of first eluting enantiomer as a white solid, 33% yield.

5 Chiral HPLC Rt = 7.549 min; [chiral analytical method 1]

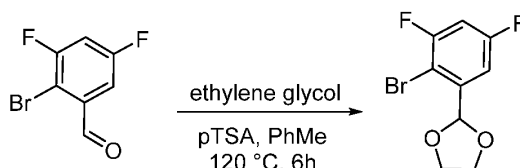
LCMS Rt = 1.485 min; MS m/z 390.1 [M+H]⁺; [Method 7]

¹H NMR (600 MHz, CD₃OD) δ 7.62 – 7.46 (m, 1H), 7.35 – 7.30 (m, 1H), 7.20 – 7.02 (m, 1H), 5.75 – 5.69 (m, 1H), 5.68 – 5.60 (m, 1H), 5.58 – 5.50 (m, 1H), 4.84 (d, J = 5.1 Hz, 2H), 3.47 (s, 3H).

10 **Example 18: methyl (R)-4-(2-(difluoromethyl)-3,5-difluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate**



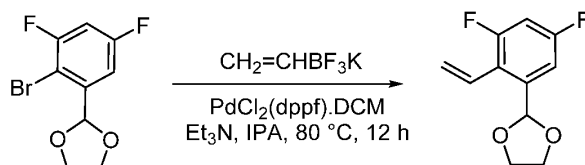
Step 1: 2-(2-bromo-3,5-difluorophenyl)-1,3-dioxolane



15 The title compound was synthesized following a procedure similar to step 1 of example 1 using 15 g of 2-bromo-3,5-difluorobenzaldehyde obtained 15.4 g of 2-(2-bromo-3,5-difluorophenyl)-1,3-dioxolane.

¹H NMR (300 MHz, CDCl₃) δ 7.20 - 7.15 (m, 1H), 6.49 - 6.87 (m, 1H), 6.08 (s, 1H), 4.17 - 4.04 (m, 4H).

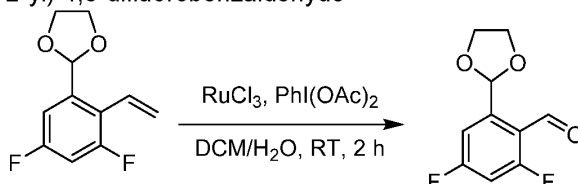
20 Step 2: 2-(3,5-difluoro-2-vinylphenyl)-1,3-dioxolane



The title compound was synthesized following a procedure similar to step 2 of example 1 using 2-(2-bromo-3,5-difluorophenyl)-1,3-dioxolane giving 2-(3,5-difluoro-2-vinylphenyl)-1,3-dioxolane (3.0 g).
¹H NMR (300 MHz, CDCl₃) δ 7.20 - 7.16 (m, 1H), 6.94 - 6.83 (m, 1H), 6.82 (dd, J = 17.7, 11.7 Hz, 1H), 5.60 (dd, J = 1.2, 11.7 Hz, 1H), 5.66 - 5.60 (m, 1H), 5.95 (s, 1H), 4.18 - 4.02 (m, 4H).

5

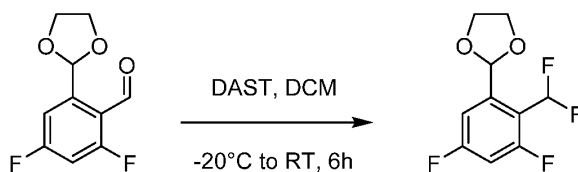
Step 3: 2-(1,3-dioxolan-2-yl)-4,6-difluorobenzaldehyde



The title compound was synthesized following a procedure similar to step 1 of example 5 giving 2-(1,3-dioxolan-2-yl)-4,6-difluorobenzaldehyde (1.0 g).

10 ¹H NMR (300 MHz, CDCl₃) δ 10.41 (s, 1H), 7.35 (d, J = 9.6 Hz, 1H), 6.95 - 6.85 (m, 1H), 6.53 (s, 1H), 4.08 (s, 4H).

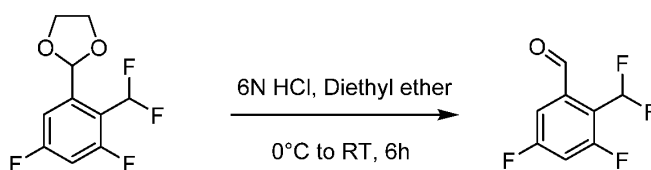
Step 4: 2-(2-(difluoromethyl)-3,5-difluorophenyl)-1,3-dioxolane



15 The title compound was synthesized following a procedure similar to step 3 of example 5 giving 2-(2-(difluoromethyl)-3,5-difluorophenyl)-1,3-dioxolane (570 mg)

¹H NMR (300 MHz, CDCl₃) δ 7.29 - 7.25 (m, 1H), 7.06 (t, J = 1.1 Hz, 1H), 6.95 - 6.84 (m, 1H), 6.13 (t, J = 1.2 Hz, 1H), 4.30 - 3.86 (m, 4H).

20 Step 5: 2-(difluoromethyl)-3,5-difluorobenzaldehyde



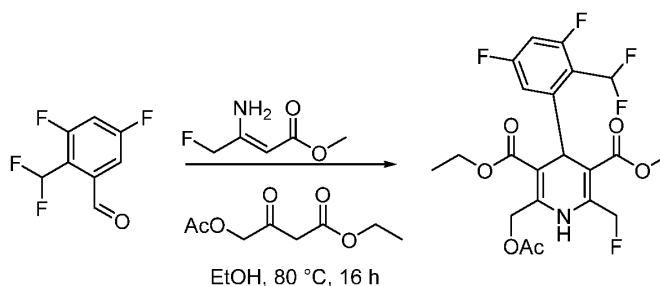
To a solution of 2-(2-(difluoromethyl)-3,5-difluorophenyl)-1,3-dioxolane (from step 4, 570 mg, 2.41 mmol) in diethyl ether (10 mL) was added 6N HCl (10 mL) at 0 °C. The resulting reaction mixture was stirred at room temperature for 6 hrs. Reaction mixture was extracted into diethyl ether (50 mL)
 25 and washed with water (30 mL). Organic phase was washed with saturated NaHCO₃ solution (30 mL), brine (30 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure

resulting in crude compound 2-(difluoromethyl)-3,5-difluorobenzaldehyde (360 mg) as a colorless liquid.

^1H NMR (300 MHz, CDCl_3) δ 10.42 (s, 1H), 7.74 – 7.54 (m, 1H), 7.25 (dd, J = 46.8, 10.4 Hz, 1H), 7.15 – 7.10 (m, 1H).

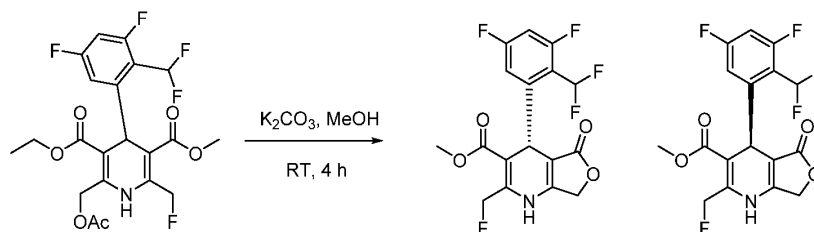
5

Step 6: 3-ethyl 5-methyl 2-(acetoxymethyl)-4-(2-(difluoromethyl)-3,5-difluorophenyl)-6-(fluoromethyl)-1,4-dihydropyridine-3,5-dicarboxylate



Title compound was synthesized using step 1 of general procedure I (using the aldehyde from step 5, 360 mg, 1.87 mmol) to give 3-ethyl 5-methyl 2-(acetoxymethyl)-4-(2-(difluoromethyl)-3,5-difluorophenyl)-6-(fluoromethyl)-1,4-dihydropyridine-3,5-dicarboxylate (720 mg, crude). LCMS R_t = 1.698 min; MS m/z 476.1 $[\text{M}-\text{H}]^-$; [Method 7]

Step 7: methyl 4-(2-(difluoromethyl)-3,5-difluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate



Title compound was synthesized using step 2 of general procedure I (using intermediate from step 6, 720 mg, 1.50 mmol). Crude product purification by silica flash chromatography (0 → 70%) ethyl acetate in petroleum ether afforded the title compound methyl 4-(2-(difluoromethyl)-3,5-difluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate (120 mg) as an off white solid. Racemic mixture was separated into its enantiomers using chiral preparative HPLC [method 7].

Example 18

30 mg of first eluting enantiomer obtained as a white solid, 25% yield.

Chiral HPLC R_t = 17.629 min; [chiral analytical method 1]

LCMS Rt = 1.454 min; MS m/z 388.2 [M-H]⁻; [Method 7]

¹H NMR (400 MHz, CD₃OD) δ 7.40 - 7.38 (m, 1H), 6.93 (dd, J = 10.3, 7.6 Hz, 2H), 5.77 (d, J = 0.8 Hz, 1H), 5.65 (d, J = 0.7 Hz, 1H), 5.27 (d, J = 1.6 Hz, 1H), 4.89 – 4.86 (m, 2H), 3.51 (s, 3H).

Example 18b

36 mg of second eluting enantiomer obtained as a white solid, 30% yield.

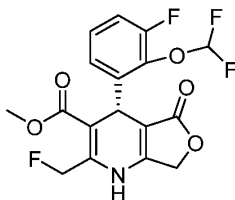
Chiral HPLC Rt = 19.634 min; [chiral analytical method 1]

LCMS Rt = 1.454 min; MS m/z 388.0 [M-H]⁻; [Method 7]

¹H NMR (400 MHz, CD₃OD) δ 7.40 - 7.38 (m, 1H), 6.93 (dd, J = 10.3, 7.6 Hz, 2H), 5.77 (d, J = 0.8 Hz, 1H), 5.65 (d, J = 0.7 Hz, 1H), 5.27 (d, J = 1.6 Hz, 1H), 4.89 – 4.86 (m, 2H), 3.51 (s, 3H).

10

Example 19: methyl (R)-4-(2-(difluoromethoxy)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate



Title compound was prepared using general procedure II using commercially available 2-

(difluoromethoxy)-3-fluorobenzaldehyde (249 mg, 1.311 mmol). Crude was purified by automated flash column chromatography eluting with 0-100% gradient of EtOAc in heptane on a 24g Si-column and further purified by mass directed reverse phase prep chromatography; Conditions: Xbridge C18 OBD 30x50mm 5um column ACN/H₂O w/ NH₃OH 5 mL/min 1.5 mL injection. The racemate was separated into its individual enantiomers using chiral SFC (Mobile Phase: 5-25% MeOH in C02 80g/min; Column: (RR) Whelk-O1 21 x 250 mm).

20

Example 19

8.6mg of second eluting enantiomer (4%)

Chiral SFC Rt = 2.61 min (Mobile Phase: 5-55% MeOH in Column: (RR) Whelk-O1 4.6 x 100mm 5um column; 6mins run)

25 LCMS Rt = 1.94 min; MS m/z 388.2 [M+H]⁺; [Method 4]

¹H NMR (400 MHz, Methylene Chloride-d₂) δ 7.46 (d, J = 6.8 Hz, 1H), 7.29 – 7.05 (m, 3H), 6.93 (t, J = 74.16 Hz, 1H), 5.88 – 5.56 (m, 2H), 5.23 (s, 1H), 4.81 (s, 2H), 3.57 (s, 3H).

Example 19b

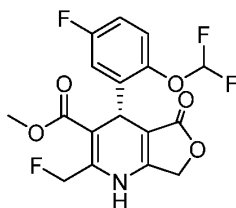
9.5mg of first eluting enantiomer (4%)

30 Chiral SFC Rt = 2.41 min (Mobile Phase: 5-55% MeOH in Column: (RR) Whelk-O1 4.6 x 100mm 5um column; 6mins run)

LCMS Rt = 1.90 min; MS m/z 388.2 [M+H]⁺; [Method 4]

¹H NMR (400 MHz, Methylene Chloride-d₂) δ 7.46 (d, J = 6.8 Hz, 1H), 7.29 – 7.05 (m, 3H), 6.93 (t, J = 74.16 Hz, 1H), 5.88 – 5.56 (m, 2H), 5.23 (s, 1H), 4.81 (s, 2H), 3.57 (s, 3H).

5 **Example 20: methyl (R)-4-(2-(difluoromethoxy)-5-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate**



Title compound was prepared using general procedure II using commercially available 2-(difluoromethoxy)-5-fluorobenzaldehyde (229 mg, 1.206 mmol). Crude was purified by automated
10 flash column chromatography eluting with 0-100% gradient of EtOAc in heptane on a 24g Si-column and further purified by mass directed reverse phase prep chromatography; Conditions: Xbridge C18 OBD 30x50mm 5um column ACN/H₂O w/ NH₃OH 5 mL/min 1.5mL injection. The racemate was separated into its individual enantiomers using chiral SFC (Mobile Phase: 5-25% MeOH in CO₂ 80g/min; Column: (RR) Whelk-O1 21 x 250 mm).

15 **Example 20**

10mg of second eluting enantiomer

Chiral SFC Rt = 2.51 min (Mobile Phase: 5-55% MeOH in Column: (RR) Whelk-O1 4.6 x 100mm 5um column; 6mins run)

LCMS Rt = 1.91 mins; MS m/z 388.1 [M+H]⁺; [Method 4]

20 ¹H NMR (400 MHz, DMSO-d₆) δ 10.11 (d, J = 3.3 Hz, 1H), 7.32 – 6.85 (m, 4H), 5.79 – 5.65 (m, 1H), 5.65 – 5.48 (m, 1H), 5.05 (s, 1H), 4.83 (s, 2H), 3.45 (s, 3H).

Example 20b

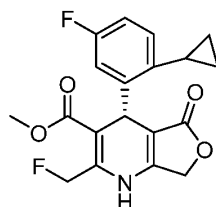
12mg of first eluting enantiomer

Chiral SFC Rt = 2.31 min (Mobile Phase: 5-55% MeOH in Column: (RR) Whelk-O1 4.6 x 100mm 5um column; 6mins run)

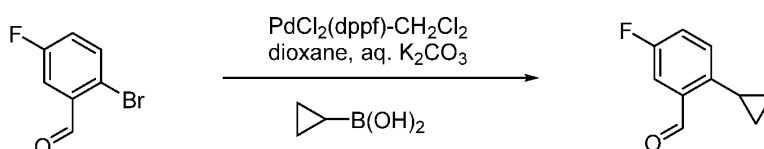
25 LCMS Rt = 1.91 mins; MS m/z 388.0 [M+H]⁺; [Method 4]

¹H NMR (400 MHz, DMSO-d₆) δ 10.11 (d, J = 2.0 Hz, 1H), 7.33 – 6.80 (m, 4H), 5.77 – 5.65 (m, 1H), 5.64 – 5.51 (m, 1H), 5.05 (s, 1H), 4.83 (s, 2H), 3.45 (s, 3H).

Example 21: methyl (R)-4-(2-cyclopropyl-5-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate

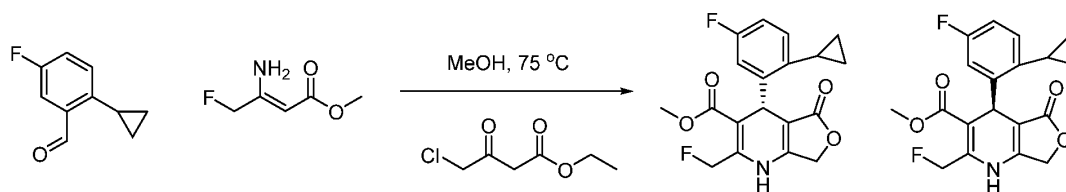


5 Step 1: 2-cyclopropyl-5-fluorobenzaldehyde



A degassed solution of 2-bromo-5-fluorobenzaldehyde (2.03 g, 10.00 mmol), cyclopropane boronic acid (1.031 g, 12.00 mmol), and PdCl₂(dppf)-CH₂Cl₂ adduct (0.817 g, 1.000 mmol) in dioxane (20 mL) and 2.0 M aq. K₂CO₃ (10.00 mL, 20.00 mmol) was stirred and heated to 80 °C. At completion, the reaction mixture was cooled to room temperature then partitioned between water and ethyl acetate. The organics phase was washed with water and brine, then dried over MgSO₄ and concentrated. The crude was purified by silica flash chromatography [0-20% Ethyl acetate in heptane] to provide 800 mg of title compound, 49% yield. Crude product was taken on without further purification.

15 Step 2: methyl 4-(2-cyclopropyl-5-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate



The title compound was prepared according to general procedure II from ethyl 4-chloro-3-oxobutanoate (346 mg, 2.10 mmol), 2-cyclopropyl-5-fluorobenzaldehyde (345 mg, 2.10 mmol) prepared in step 1, and methyl (Z)-3-amino-4-fluorobut-2-enoate (Intermediate B, 280 mg, 2.10 mmol). Racemic methyl 4-(2-cyclopropyl-5-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate was separated into its enantiomers using chiral SFC (Mobile Phase: 25% Methanol with 0.2% NH₄OH/CO₂ at 80 g/min; Column: (SS) Whelk-O1 4.6 x 100 mm).

Example 21

21.4 mg First eluting enantiomer as a white solid (5.6%).

Chiral SFC Rt = 2.41 min (Mobile Phase: 5-55% MeOH w/ 10mM NH₄OH/CO₂ 5mL/min 120bar;
Column: (SS) Whelk-O1 4.6 x 100 mm 5μm).

5 LCMS Rt = 0.95 min; MS m/z 362.5 [M+H]⁺; [Method 4].

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.08 (s, 1 H), 7.08 - 6.95 (m, 1 H), 6.93 - 6.82 (m, 2 H), 5.78 - 5.58 (m, 2 H), 5.37 (s, 1 H), 4.90 - 4.77 (m, 2 H), 3.45 (s, 3 H), 1.00 - 0.80 (m, 3 H), 0.54 - 0.46 (m, 1 H). Benzylic CH on cyclopropyl is hidden under DMSO peak.

Example 21b

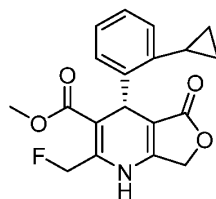
10 10.3 mg Second eluting enantiomer as a white solid (2.7%).

Chiral SFC Rt = 2.69 min (Mobile Phase: 5-55% MeOH w/ 10mM NH₄OH/CO₂ 5mL/min 120bar;
Column: (SS) Whelk-O1 4.6 x 100 mm 5μm).

LCMS Rt = 0.95 min; MS m/z 362.5 [M+H]⁺; [Method 4].

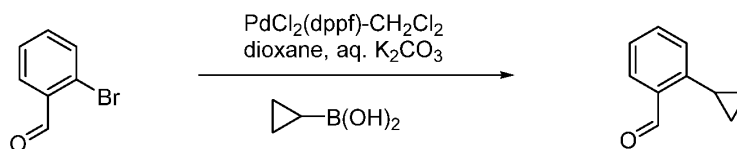
15 ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.08 (s, 1 H), 7.08 - 6.95 (m, 1 H), 6.93 - 6.82 (m, 2 H), 5.78 - 5.58 (m, 2 H), 5.37 (s, 1 H), 4.90 - 4.77 (m, 2 H), 3.45 (s, 3 H), 1.00 - 0.80 (m, 3 H), 0.54 - 0.46 (m, 1 H).

Example 22: methyl (R)-4-(2-cyclopropylphenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate



20

Step1: 2-cyclopropylbenzaldehyde

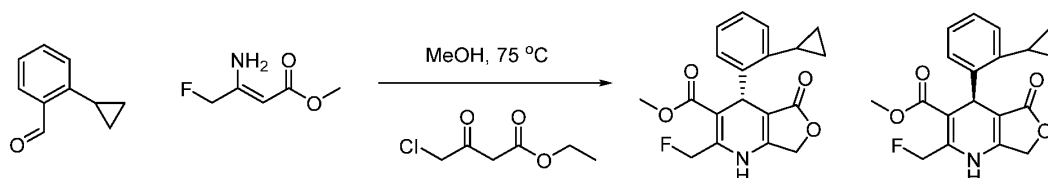


25

A degassed solution of the 2-bromobenzaldehyde (1g, 5.40 mmol), cyclopropane boronic acid (0.557 g, 6.49 mmol), PdCl₂(dppf).CH₂Cl₂ adduct (0.441 g, 0.540 mmol) in Dioxane (15 mL) and 2.0 M aq K₂CO₃ (5.40 mL, 10.81 mmol) was stirred and heated to 80 °C. At completion, the reaction mixture was cooled to room temperature then partitioned between water and ethyl acetate. The organics phase was washed with water and brine, then dried over MgSO₄ and concentrated. The crude was

purified by silica flash chromatography [0-20% Ethyl acetate in heptane] to provide 420mg mg of the title compound, 53% yield. Crude product was taken on without further purification.

Step 2: methyl 4-(2-cyclopropylphenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate



The title compound was prepared according to general procedure II from ethyl 4-chloro-3-oxobutanoate (0.204 mL, 1.500 mmol) 2-cyclopropylbenzaldehyde (219 mg, 1.5 mmol) prepared in step 1 and methyl (Z)-3-amino-4-fluorobut-2-enoate (Intermediate B, 200 mg, 1.50mmol). Racemic methyl-4-(2-cyclopropylphenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate was separated into its enantiomers using chiral SFC (Mobile Phase: 5-55% Methanol with 10 mM NH₄OH/CO₂ at 3 mL/min; Column: (SS) WHO;1 4.6 x 100 mm).

Example 22

7.9 mg First eluting enantiomer as a white solid (3.0 %).

Chiral SFC Rt = 2.77 min

LCMS Rt = 0.93 min; MS m/z 344.5 [M+H]⁺; [Method 4].

¹H NMR (400 MHz, METHANOL-d₄) δ ppm 6.91 - 7.23 (m, 4 H), 5.73 (d, J=1.96 Hz, 1 H), 5.61 (d, J=2.93 Hz, 1 H), 5.48 (s, 1 H), 4.82 (s, 2 H), 3.50 (s, 3 H), 2.53 - 2.65 (m, 1 H), 0.86 - 0.99 (m, 3 H), 0.58 (d, J=5.87 Hz, 1 H).

Example 22b

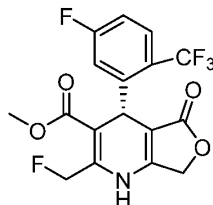
7.5 mg Second eluting enantiomer as a white solid (2.9%).

Chiral SFC Rt = 3.19 min

LCMS Rt = 0.93 min; MS m/z 344.5 [M+H]⁺; [Method 4].

¹H NMR (400 MHz, METHANOL-d₄) δ ppm 6.91 - 7.23 (m, 4 H), 5.73 (d, J=1.96 Hz, 1 H), 5.61 (d, J=2.93 Hz, 1 H), 5.48 (s, 1 H), 4.82 (s, 2 H), 3.50 (s, 3 H), 2.53 - 2.65 (m, 1 H), 0.86 - 0.99 (m, 3 H), 0.58 (d, J=5.87 Hz, 1 H).

Example 23: Methyl (R)-4-(5-fluoro-2-(trifluoromethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate



The title compound was prepared according to general procedure II from ethyl 4-chloro-3-oxobutanoate (0.318 mL, 2.342 mmol), commercially available 5-fluoro-2-(trifluoromethyl)benzaldehyde (450 mg, 2.342 mmol) and methyl (Z)-3-amino-4-fluorobut-2-enoate (Intermediate B, 312 mg, 2.342 mmol). Racemic methyl 4-(5-fluoro-2-(trifluoromethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate was separated into its enantiomers using chiral SFC (Mobile Phase: 15% Methanol with 0.2% Ammonium Hydroxide/CO₂ at 80 g/min; Column: 2.0 x 25.0 cm ChromegaChiral CC4).

Example 23

12.2 mg First eluting enantiomer as a white solid (2.7 %).

Chiral SFC Rt = 1.29 min (Column: 4.6 x 100 mm Chiralcel OZ-H ; isocratic 15% Methanol with 0.1% Isopropylamine; 125 bar

15 LCMS Rt = 0.92 min; MS m/z 390.0 [M+H]⁺; [Method 4].

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.16 (br s, 1 H), 7.70 (dd, J=8.80, 5.38 Hz, 1 H), 7.20 - 7.30 (m, 2 H), 5.72 (s, 1 H), 5.60 (s, 1 H), 5.20 (s, 1 H), 4.74 - 4.91 (m, 2 H), 3.38 (s, 3 H).

Example 23b

14.0 mg Second eluting enantiomer as a white solid (3.0%).

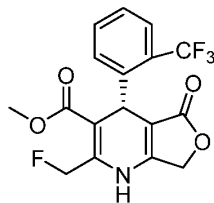
20 Chiral SFC Rt = 1.74 min (Column: 4.6 x 100 mm Chiralcel OZ-H; isocratic 15% Methanol with 0.1% Isopropylamine; 125 bar)

LCMS Rt = 0.92 min; MS m/z 390.0 [M+H]⁺; [Method 4].

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.16 (br s, 1 H), 7.70 (dd, J=8.80, 5.38 Hz, 1 H), 7.20 - 7.30 (m, 2 H), 5.72 (s, 1 H), 5.60 (s, 1 H), 5.20 (s, 1 H), 4.74 - 4.91 (m, 2 H), 3.38 (s, 3 H).

25

Example 24: Methyl (R)-2-(fluoromethyl)-5-oxo-4-(2-(trifluoromethyl)phenyl)-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate



The title compound was prepared according to general procedure II from ethyl 4-chloro-3-oxobutanoate (0.286 mL, 2.10 mmol), commercially available 2-trifluoromethylbenzaldehyde (366 mg, 2.10 mmol) and methyl (Z)-3-amino-4-fluorobut-2-enoate (Intermediate B, 280 mg, 2.10 mmol). Racemic methyl 2-(fluoromethyl)-5-oxo-4-(2-(trifluoromethyl)phenyl)-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate was separated into its enantiomers using chiral SFC (Mobile Phase: 20% Methanol with 0.2% Ammonium Hydroxide at 80g/min; Column: 2.0 x 25.0 cm ChromegaChiral CC4).

Example 24

7.9 mg First eluting enantiomer as a white solid (2.0 %).

Chiral SFC Rt = 1.19 min (Mobile Phase: 20% Methanol with 0.1% Isopropylamine/CO₂ at 4 mL/min; Column: Chiralcel OZ-H; 1 4.6 x 100 mm).

LCMS Rt = 0.91 min; MS m/z 370.0 [M+H]⁺; [Method 4].

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.12 (br s, 1 H), 7.60 (d, J=7.82 Hz, 2 H), 7.49 (d, J=7.83 Hz, 1 H), 7.31 - 7.42 (m, 1 H), 5.70 (s, 1 H), 5.58 (s, 1 H), 5.19 (s, 1 H), 4.81 (s, 2 H), 3.37 (s, 3 H).

Example 24b

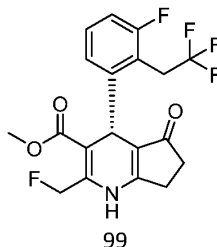
9.3 mg Second eluting enantiomer as a white solid (2.4%).

Chiral SFC Rt = 1.72 min (Mobile Phase: 20% Methanol with 0.1% Isopropylamine/CO₂ at 4 mL/min; Column: Chiralcel OZ-H; 1 4.6 x 100 mm).

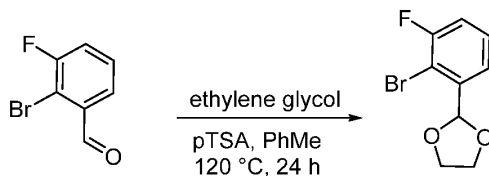
LCMS Rt = 0.91 min; MS m/z 370.0 [M+H]⁺; [Method 4].

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.12 (br s, 1 H), 7.60 (d, J=7.82 Hz, 2 H), 7.49 (d, J=7.83 Hz, 1 H), 7.31 - 7.42 (m, 1 H), 5.70 (s, 1 H), 5.58 (s, 1 H), 5.19 (s, 1 H), 4.81 (s, 2 H), 3.37 (s, 3 H).

Example 25: Methyl (R)-4-(3-fluoro-2-(2,2,2-trifluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate



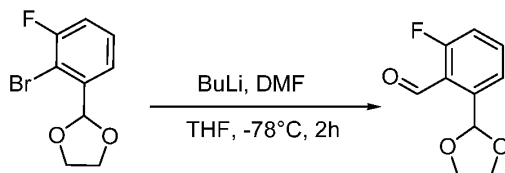
Step 1: 2-(2-bromo-3-fluorophenyl)-1,3-dioxolane



To a solution of 2-bromo-3-fluorobenzaldehyde (60 g, 295.56 mmol) and ethylene glycol (65.4 mL, 1182.2 mmol) in toluene (600 mL) was added p-toluenesulfonic acid monohydrate (28.11 g, 147.78 mmol). The resulting solution was stirred at 120 °C for 24 hrs using dean-stark apparatus. The solvent was added to water (2 L) and extracted into EtOAc (3 L). EtOAc was washed with saturated NaHCO₃ solution (1 L), brine and dried over Na₂SO₄. The solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography (0 → 10%) ethyl acetate in petroleum ether afforded the title compound 2-(2-bromo-3-fluorophenyl)-1,3-dioxolane (60 g) as a colorless liquid.

¹H NMR (400 MHz, CDCl₃) δ 7.42- 7.37 (m, 1H), 7.34- 7.29 (m, 1H), 7.16- 7.10 (m, 1H), 6.10 (s, 1H), 4.19-4.09 (m, 4H).

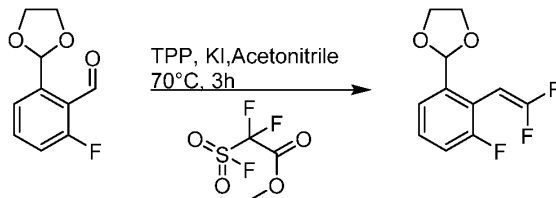
Step 2: 2-(1,3-dioxolan-2-yl)-6-fluorobenzaldehyde



To a solution of 2-(2-bromo-3-fluorophenyl)-1,3-dioxolane (from step 1, 7 g, 28.45 mmol) in THF (70 mL) under nitrogen atmosphere was cooled to -78 °C. Then n-butyllithium in n-Hexane solution (13.66 mL, 2.5M, 58.5 mmol) was added over 10 min. The resulting mixture was stirred for 45 min at -78 °C, then DMF (2.5 g, 34.15 mmol) was added and resulting mixture stirred for 1.15 h at -78 °C. The reaction mixture was quenched with saturated ammonium chloride solution (50 mL) and extracted with ethyl acetate (2 x 100 mL). Combined organic phases were washed with water (50 mL), followed by brine (50 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography (0 → 50%) ethyl acetate in petroleum ether afforded the title compound 2-(1,3-dioxolan-2-yl)-6-fluorobenzaldehyde (5 g) as a colorless liquid.

¹H NMR (300 MHz, Chloroform-d) δ 10.52 (s, 1H), 7.67 – 7.53 (m, 2H), 7.22 – 7.12 (m, 1H), 6.50 (s, 1H), 4.27 – 3.99 (m, 4H).

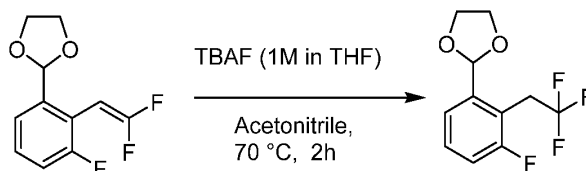
Step 3: 2-(2-(2,2-difluorovinyl)-3-fluorophenyl)-1,3-dioxolane



To solution of acetonitrile (65 mL) under nitrogen atmosphere was added triphenylphosphine (28.1 g, 107.1 mmol), potassium iodide (11.85 g, 71.4 mmol) and 2-(1,3-dioxolan-2-yl)-6-fluorobenzaldehyde (from step 2, 7 g, 35.7 mmol). Reaction stirred for 30 min at 70 °C, then methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (12 g, 62.4 mmol) was added slowly over a period of 10 min (mass color was turned to yellow while addition). Resulting mixture was stirred for another 3 hrs at 70°C, then cooled to room temperature, diluted with diethyl ether, precipitated solids were removed by filtration and washed with diethyl ether (100 mL). The resulting solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography (0 → 5%) ethyl acetate in petroleum ether afforded the title compound 2-(2-(2,2-difluorovinyl)-3-fluorophenyl)-1,3-dioxolane (6.9 g) as a light yellow liquid.

¹H NMR (300 MHz, Chloroform-d) δ 7.39 (dd, J = 7.8, 1.4 Hz, 1H), 7.31 (m, 1H), 7.11 (m, 1H), 5.87(s, 1H), 5.39 (m, 1H), 4.21 – 3.95 (m, 4H).

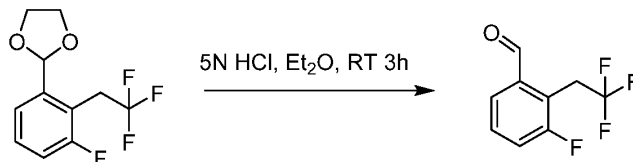
Step 4: 2-(3-fluoro-2-(2,2,2-trifluoroethyl)phenyl)-1,3-dioxolane



A solution of 2-(2-(2,2-difluorovinyl)-3-fluorophenyl)-1,3-dioxolane (from step 3, 2.7 g, 11.73 mmol) and tetrabutylammonium fluoride in THF (13.7 g, 1M, 13.7 mmol) was heated to 70 °C in closed system for 2 hrs. Reaction was allowed to cool, diluted with diethyl ether and this washed with water (50 mL), saturated NaHCO₃ solution (100 mL), and brine and dried over Na₂SO₄. The solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography (0 → 10%) ethyl acetate in petroleum ether afforded the title compound 2-(3-fluoro-2-(2,2,2-trifluoroethyl)phenyl)-1,3-dioxolane (1.2 g) as a colorless liquid.

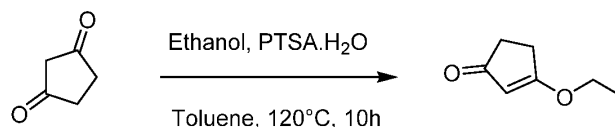
¹H NMR (300 MHz, Chloroform-d) δ 7.49 – 7.42 (m, 1H), 7.35 (m, 1H), 7.17 – 7.05 (m, 1H), 6.03 (s, 1H), 4.25 – 3.90 (m, 4H), 3.75 (m, 2H).

Step 5: 3-fluoro-2-(2,2,2-trifluoroethyl)benzaldehyde



To a solution of 2-(3-fluoro-2-(2,2,2-trifluoroethyl)phenyl)-1,3-dioxolane (from step 4, 2 g, 8.0 mmol) in diethyl ether (40 mL) was added 6N HCl (5 mL). The resulting solution was stirred at room temperature for 3 hrs. This was washed with water (50 mL), saturated NaHCO₃ solution (100 mL), brine and dried over Na₂SO₄. The solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography (0 → 5%) ethyl acetate in petroleum ether afforded the title compound 3-fluoro-2-(2,2,2-trifluoroethyl)benzaldehyde (1.2 g) as a colorless liquid. The crude product was taken as such to next step without further purification.

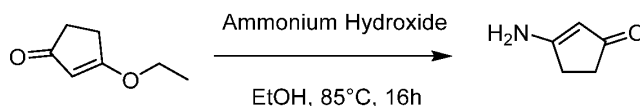
Step 6: 3-ethoxycyclopent-2-en-1-one



To a stirred solution of cyclopentane-1,3-dione (5.0 g, 50.96 mmol) in toluene (70 mL) was added pTSA (193 mg, 1.019 mmol) and EtOH (22.61 mL, 387.35 mmol) at room temperature. The resulting mixture was stirred at 120 °C for 10 hrs using Dean-stark apparatus. The solvent was removed under reduced pressure. Crude product was purified by silica flash chromatography (0 → 50%) ethyl acetate in petroleum ether to afford the title compound 3-ethoxycyclopent-2-en-1-one (4.3 g) as a brown solid.

¹H NMR (400 MHz, CDCl₃) δ 5.26 (s, 1H), 4.02 (q, J = 6.6 Hz, 2H), 2.60 – 2.55 (m, 2H), 2.44 – 2.40 (m, 2H), 1.39 (t, J = 7.2 Hz, 3H).

Step 7: 3-aminocyclopent-2-en-1-one



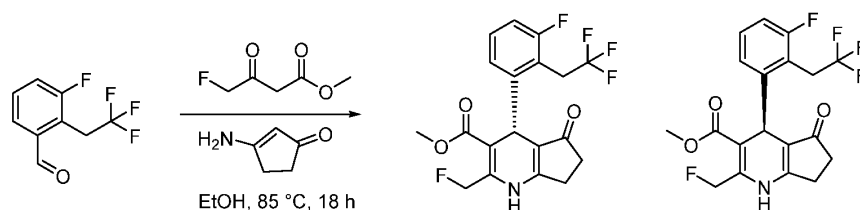
To a stirred solution of 3-ethoxycyclopent-2-en-1-one (from step 6, 4.3 g, 34.08 mmol) in ethanol (50 mL) was added ammonium hydroxide solution (25 mL, 387.35 mmol) at room temperature. The

resulting mixture was stirred at 85 °C for 16 hrs. Solvent removal under reduced pressure afforded the title compound 3-aminocyclopent-2-en-1-one (3.2 g) as a brown solid.

LCMS Rt = 0.114 min; MS m/z 98.2 [M+H]⁺; [Method 7]

5

Step 8: methyl 4-(3-fluoro-2-(2,2,2-trifluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate



To solution of the aldehyde (from step 5, 200 mg, 0.9708 mmol), methyl 4-fluoro-3-oxobutanoate (method 2, step 1 of intermediate B, 130 mg, 0.9708 mmol) in EtOH (2 mL) was added 3-aminocyclopent-2-en-1-one (from step 7, 94 mg, 0.9708 mmol). The reaction mixture was stirred at 80 °C for 18 hrs. The solvent was removed under reduced pressure. Crude product was purified by silica flash chromatography (0 → 70%) ethyl acetate in petroleum ether afforded the title compound as an off white solid. Racemic mixture was separated into its enantiomers using chiral preparative HPLC [method 6].

Example 25

Second eluting enantiomer obtained as a white solid (25mg).

Chiral HPLC Rt = 7.610 min; [chiral analytical method 4]

LCMS Rt = 1.533 min; MS m/z 401.75 [M+]⁺; [Method 12]

¹H NMR (400 MHz, CD₃OD) δ 7.31 – 7.25 (m, 1H), 7.04 (d, J = 8 Hz, 1H), 6.97 – 6.90 (m, 1H), 5.76 (d, J = 3.2 Hz, 1H), 5.64 (d, J = 2.8 Hz, 2H), 5.08 (s, 1H), 4.79 – 4.60 (m, 2H), 3.70 – 3.55 (m, 2H), 3.44 (s, 3H), 2.66 – 2.61 (m, 2H).

Example 25b

First eluting enantiomer as a white solid (24mg).

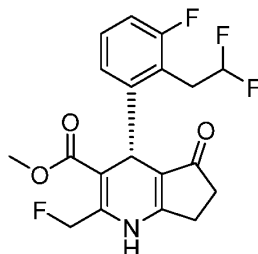
Chiral HPLC Rt 7.103 min; [chiral analytical method 4]

LCMS Rt = 1.533 min; MS m/z 401.75 [M+]⁺; [Method 12]

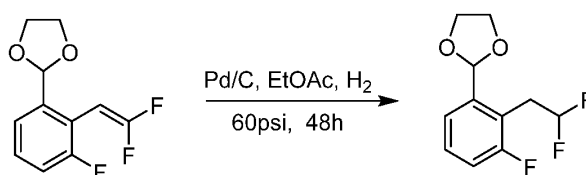
¹H NMR (400 MHz, CD₃OD) δ 7.31 – 7.25 (m, 1H), 7.04 (d, J = 8 Hz, 1H), 6.97 – 6.90 (m, 1H), 5.76 (d, J = 3.2 Hz, 1H), 5.64 (d, J = 2.8 Hz, 2H), 5.08 (s, 1H), 4.79 – 4.60 (m, 2H), 3.70 – 3.55 (m, 2H), 3.44 (s, 3H), 2.66 – 2.61 (m, 2H).

30

Example 26: methyl (R)-4-(2-(2,2-difluoroethyl)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate



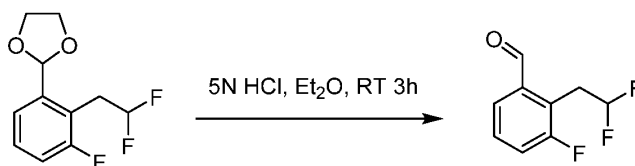
Step 1: 2-(2-(2,2-difluoroethyl)-3-fluorophenyl)-1,3-dioxolane



To a solution of 2-(2-(2,2-difluorovinyl)-3-fluorophenyl)-1,3-dioxolane (from example 25, step 3, 3 g, 13.04 mmol) in ethyl acetate (60 mL) was added 10% Pd-C (1 g). The resulting reaction mixture was kept in Parr-Shaker for 48 hrs at 60 psi of pressure under hydrogen atmosphere at room temperature. The reaction mixture was filtered through a celite pad, washed with ethyl acetate (30 mL). The filtrate was concentrated under reduced pressure and purification of the crude product by silica flash chromatography (0 → 30%) ethyl acetate in petroleum ether afforded the title compound 2-(2-(2,2-difluoroethyl)-3-fluorophenyl)-1,3-dioxolane (3 g) as a colorless liquid.

¹H NMR (300 MHz, CDCl₃) δ 7.42 – 7.35 (m, 1H), 7.34 – 7.27 (m, 1H), 7.15 – 7.08 (m, 1H), 6.31 – 5.78 (m, 2H), 4.19 – 4.02 (m, 4H), 3.38 (m, 2H).

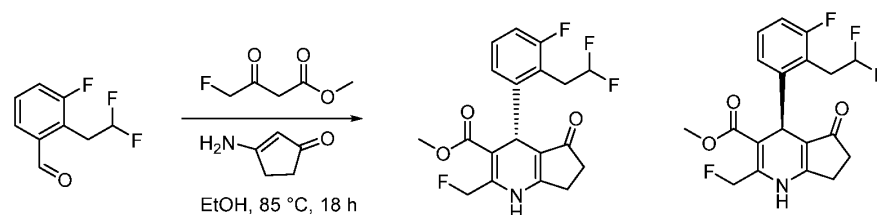
Step 2: 2-(2,2-difluoroethyl)-3-fluorobenzaldehyde



To a solution of 2-(2-(2,2-difluoroethyl)-3-fluorophenyl)-1,3-dioxolane (from step 1, 3 g, 12.93 mmol) in diethyl ether (40 mL) was added 6N HCl (5 mL). The resulting solution was stirred at room temperature for 3 hrs. This was washed with water (50 mL), saturated NaHCO₃ solution (100 mL), and brine and dried over Na₂SO₄. The solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography (0 → 5%) ethyl acetate in petroleum ether afforded the title compound 2-(2,2-difluoroethyl)-3-fluorobenzaldehyde (1.9 g) as a colorless liquid.

¹H NMR (400 MHz, CDCl₃) δ 10.14 (d, J = 1.6 Hz, 1H), 7.70 – 7.63 (m, 1H), 7.52 (td, J = 8.0, 7.9, 5.2 Hz, 1H), 7.35 – 7.30 (m 1H), 6.03 (m, 1H), 3.83 – 3.58 (m, 2H).

Step 3: methyl (R)-4-(2-(2,2-difluoroethyl)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-
5 1H-cyclopenta[b]pyridine-3-carboxylate and methyl (S)-4-(2-(2,2-difluoroethyl)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate



To solution of the aldehyde (from step 2, 200 mg, 1.063 mmol), methyl 4-fluoro-3-oxobutanoate (Method 2, step 1 of intermediate B, 142 mg, 1.063 mmol) in EtOH (2 mL) was added 3-aminocyclopent-2-en-1-one (example 25, step 7, 103 mg, 1.063 mmol). The reaction mixture was stirred at 80 °C for 18 hrs. The solvent was removed under reduced pressure gave crude compound. Crude product was purified by silica flash chromatography (0 → 70%) ethyl acetate in petroleum ether afforded the title compound as an off white solid (100 mg). Racemic mixture was separated into its enantiomers using chiral preparative HPLC [method 6].

15 Example 26

First eluting enantiomer obtained as a white solid (25mg).

Chiral HPLC Rt 7.341 min; [chiral analytical method 4]

LCMS Rt = 1.505 min; MS m/z 384.2 [M+1]⁺; [Method 12]

¹H NMR (400 MHz, CD₃OD) δ 7.25 – 7.17 (m, 1H), 7.01 (d, J = 8 Hz, 1H), 6.92 – 6.85 (m, 1H), 6.80 – 6.40 (m, 1H), 5.76 (d, J = 3.2 Hz, 1H), 5.64 (d, J = 2.8 Hz, 1H), 5.08 (s, 1H), 4.79 – 4.60 (m, 2H), 3.70 – 3.55 (m, 2H), 3.60 – 3.40 (m, 1H), 3.52 (s, 3H), 2.75 – 2.65 (m, 2H).

Example 26b

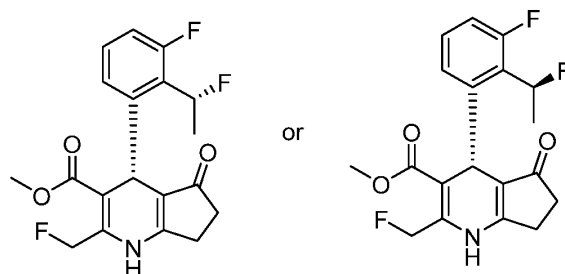
Second eluting enantiomer obtained as a white solid (26mg).

Chiral HPLC Rt 9.044 min; [chiral analytical method 4]

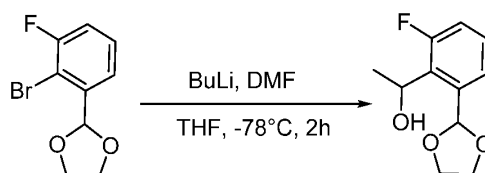
25 LCMS Rt = 1.505 min; MS m/z 384.2 [M+1]⁺; [Method 12]

¹H NMR (400 MHz, CD₃OD) δ 7.25 – 7.17 (m, 1H), 7.01 (d, J = 8 Hz, 1H), 6.92 – 6.85 (m, 1H), 6.80 – 6.40 (m, 1H), 5.76 (d, J = 3.2 Hz, 1H), 5.64 (d, J = 2.8 Hz, 1H), 5.08 (s, 1H), 4.79 – 4.60 (m, 2H), 3.70 – 3.55 (m, 2H), 3.60 – 3.40 (m, 1H), 3.52 (s, 3H), 2.75 – 2.65 (m, 2H).

Example 27: methyl (R)-4-(3-fluoro-2-((R or S)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate



Step 1: 1-(2-(1,3-dioxolan-2-yl)-6-fluorophenyl)ethan-1-ol



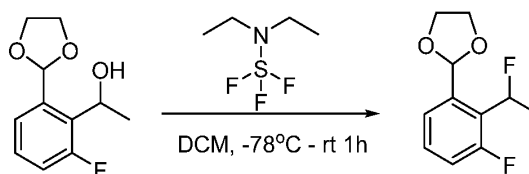
5

To a solution of 2-(2-bromo-3-fluorophenyl)-1,3-dioxolane (from example 25, step 1, 30 g, 121.42 mmol) in THF (300 mL) under nitrogen atmosphere at -78 °C was added n-BuLi in n-Hexane solution (58.3 mL, 2.5M, 147.71 mmol) dropwise over 10 min. The resulting mixture was stirred for 1 h at -78 °C then acetaldehyde (6.42 g, 145.71 mmol) was added and reaction stirred for 1 h at -78 °C. The reaction mixture was quenched with saturated ammonium chloride solution (50 mL) and extracted with ethyl acetate (2 x 100 mL). Combined organic phases were washed with water (50 mL), washed with brine (50 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography (0 → 10%) ethyl acetate in petroleum ether afforded the title compound 1-(2-(1,3-dioxolan-2-yl)-6-fluorophenyl)ethan-1-ol (15 g) as a colorless liquid.

15

¹H NMR (400 MHz, CDCl₃) δ 7.38 (d, J = 8.0 Hz, 1H), 7.30 – 7.18 (m, 1H), 7.10 – 7.01 (m, 1H), 6.15 (s, 1H), 5.30 – 5.25 (m, 1H), 4.15 – 3.95 (m, 4H), 2.75 – 2.69 (m, 1H), 1.58 (dd, J = 6.6, 22.8 Hz, 3H).

Step-2: 2-(3-fluoro-2-(1-fluoroethyl)phenyl)-1,3-dioxolane



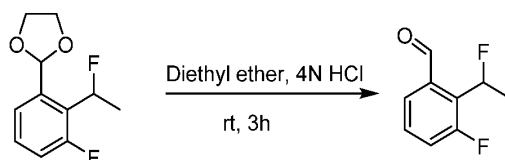
20

To a solution of 1-(2-(1,3-dioxolan-2-yl)-6-fluorophenyl)ethan-1-ol (from step 1, 15 g, 70.68 mmol) in dichloromethane (150 mL) at -78 °C was added diethylaminosulfur trifluoride (19.3 mL, 141.37 mmol).

The resulting solution was allowed to warm to RT and stirred for 1 hr. The reaction mixture was quenched with saturated ammonium chloride (20 mL) at 0 °C and diluted with ethyl acetate (100 mL). The organic layer was separated, washed with brine and dried over Na₂SO₄. The solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography (0 → 10%) ethyl acetate in petroleum ether afforded the title compound 2-(3-fluoro-2-(1-fluoroethyl)phenyl)-1,3-dioxolane (8.5 g) as a colorless liquid.

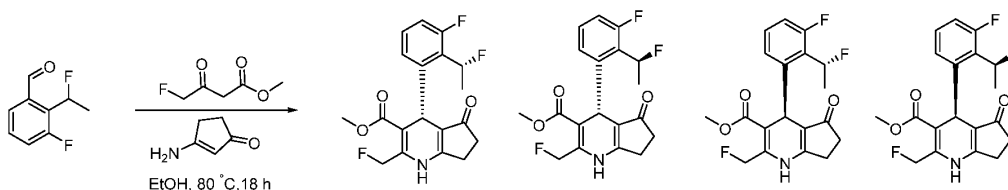
¹H NMR (300 MHz, CDCl₃) δ 7.38 (d, J = 7.5 Hz, 1H), 7.30 – 7.18 (m, 1H), 7.13 – 7.01 (m, 1H), 6.20 – 5.95 (m, 1H), 6.10 (s, 1H), 4.16 – 4.02 (m, 4H), 1.74 (dd, J = 7.2, 23.1 Hz, 3H).

10 Step-3: 3-fluoro-2-(1-fluoroethyl)benzaldehyde



To a solution of 2-(3-fluoro-2-(1-fluoroethyl)phenyl)-1,3-dioxolane (from step 2, 8.5 g, 69.38 mmol) in diethyl ether (150 mL) was added 4N HCl (85 mL) at room temperature. The resulting solution was stirred at room temperature for 3 hrs. This was washed with water (100 mL), saturated NaHCO₃ solution (200 mL), and brine and dried over Na₂SO₄. The solvent was removed under reduced pressure to afford the title compound 3-fluoro-2-(1-fluoroethyl)benzaldehyde (6.5 g) as a colorless liquid. (Note: The obtained aldehyde is volatile in nature).

20 Step-4: methyl 4-(3-fluoro-2-((R or S)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate



To solution of the aldehyde (from step 3, 1 g, 5.876 mmol), methyl 4-fluoro-3-oxobutanoate (Method 2, step 1 of intermediate B, 780 mg, 5.876 mmol) in EtOH (10 mL) was added 3-aminocyclopent-2-en-1-one (example 25, step 7, 570 mg, 5.876 mmol). The reaction mixture was stirred at 80 °C for 18 hrs. The solvent was removed under reduced pressure and crude product was purified by silica flash chromatography (0 → 70%) ethyl acetate in petroleum ether afforded the title compound as an off white solids as a diastereomeric mixture of methyl 4-(3-fluoro-2-(1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (220 mg).

Diastereomeric mixture was separated into its two isomers using chiral prep-purification [method 2]. First peak from diastereomer separation was separated into its enantiomers Peak 1 and Peak 2 using chiral prep-purification [method 5].

Example 27

5 Second eluting enantiomer obtained as a white solid (55mg)

Chiral HPLC Rt = 5.729 min; [chiral analytical method 2]

LCMS Rt = 2.25 min; MS m/z 364.1 [M-H]⁻; [Method 7]

¹H NMR (400 MHz, CDCl₃) δ 7.25 – 7.15 (m, 2H), 6.96 – 6.75 (m, 2H), 6.52 – 6.30 (m, 1H),
5.79 (s, 1H), 5.67 (s, 1H), 5.05 (s, 1H), 3.59 (s, 3H), 2.80 – 2.60 (m, 2H), 2.50 – 2.35 (m,
10 2H), 2.01 (dd, J = 6.4, 23.2 HZ, 3H).

Example 27b

First eluting enantiomer obtained as a white solid (55mg).

Chiral HPLC Rt = 5.678 min; [chiral analytical method 2]

LCMS Rt = 2.25 min; MS m/z 364.1 [M-H]⁻; [Method 7]

15 ¹H NMR (400 MHz, CDCl₃) δ 7.25 – 7.15 (m, 2H), 6.96 – 6.75 (m, 2H), 6.52 – 6.30 (m, 1H),
5.79 (s, 1H), 5.67 (s, 1H), 5.05 (s, 1H), 3.59 (s, 3H), 2.80 – 2.60 (m, 2H), 2.50 – 2.35 (m,
2H), 2.01 (dd, J = 6.4, 23.2 HZ, 3H).

Second peak from diastereomer separation was separated into its enantiomers peak 3 and peak 4 using chiral prep-purification [method 10].

20 Example 27c

Third eluting enantiomer as a white solid (10mg).

Chiral HPLC Rt = 8.702 min; [chiral analytical method 2]

LCMS Rt = 2.22 min; MS m/z 364.1 [M-H]⁻; [Method 7]

¹H NMR (400 MHz, CDCl₃) δ 7.25 – 7.15 (m, 2H), 6.96 – 6.75 (m, 2H), 6.80 – 6.60 (m, 1H),
25 5.79 (s, 1H), 5.69 (s, 1H), 5.03 (s, 1H), 3.54 (s, 3H), 2.75– 2.58 (m, 2H), 2.50 – 2.45 (m,
2H), 1.83 (dd, J = 6.4, 22.4 HZ, 3H).

Example 27d

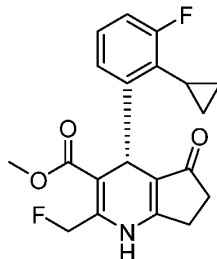
Fourth eluting enantiomer as a white solid (10mg).

Chiral HPLC Rt = 9.851 min; [chiral analytical method 2]

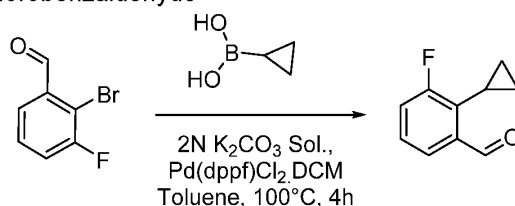
30 LCMS Rt = 2.22 min; MS m/z 364.1 [M-H]⁻; [Method 7]

¹H NMR (400 MHz, CDCl₃) δ 7.25 – 7.15 (m, 2H), 6.96 – 6.75 (m, 2H), 6.80 – 6.60 (m, 1H),
5.79 (s, 1H), 5.69 (s, 1H), 5.03 (s, 1H), 3.54 (s, 3H), 2.75– 2.58 (m, 2H), 2.50 – 2.45 (m,
2H), 1.83 (dd, J = 6.4, 22.4 HZ, 3H).

Example 28: methyl (R)-4-(2-cyclopropyl-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate

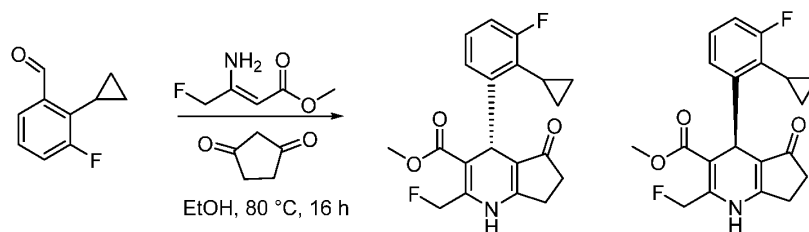


Step 1: 2-cyclopropyl-3-fluorobenzaldehyde



- 5 To a solution of 2-bromo-3-fluorobenzaldehyde (15 g, 73.88 mmol) and cyclopropylboronic acid (7.61 g, 88.66 mmol) in toluene (160 mL) was added 2N K₂CO₃ (25.5 mL, 182.16 mmol) and [1,1' - Bis(diphenylphosphino)ferrocene]dichloropalladium(II).DCM (6.03 g, 7.38 mmol). The resulting solution was degassed with Argon gas for 10 min and stirred at 100 °C for 4 hrs. The reaction mixture
- 10 was filtered and washed with ethyl acetate (200 mL). The filtrate was added to water (500 mL) and product extracted into ethyl acetate (2 L). EtOAc phase was washed with brine and dried over Na₂SO₄. The solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography (0 → 1%) ethyl acetate in petroleum ether afforded the title compound 2-cyclopropyl-3-fluorobenzaldehyde (11.2 g) as a colorless liquid.
- 15 ¹H NMR (300 MHz, CDCl₃) δ 10.70 (s, 1H), 7.63 (dd, J = 1.2, 7.8 Hz, 1H), 7.35 – 7.15 (m, 2H), 2.14 – 2.02 (m, 1H), 1.19 – 1.09 (m, 2H), 0.85 – 0.75 (m, 2H).

Step 2: methyl 4-(2-cyclopropyl-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate



To a solution of the aldehyde (from step 1, 900 mg, 5.481 mmol), methyl (Z)-3-amino-4-fluorobut-2-enoate (intermediate B, 537.76 mg, 5.481 mmol) in ethanol (5 mL) was added cyclopentane-1,3-dione (875.68161 mg, 5.481 mmol). The reaction mixture was stirred at 80 °C for 16 hrs. The solvent was removed under reduced pressure and crude product was purified by silica flash chromatography (0 → 70%) ethyl acetate in petroleum ether afforded the title compound methyl-4-(2-cyclopropyl-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (130 mg) as an off white solids. Racemic mixture was separated into its enantiomers using chiral preparative HPLC [method 11].

Example 28

First eluting enantiomer obtained as a white solid (46mg).

Chiral HPLC Rt = 10.37 min; [chiral analytical method 3]

LCMS Rt = 1.47 min; MS m/z 360.2 [M+H]⁺; [Method 7]

¹H NMR (400 MHz, CDCl₃) δ 7.10 – 7.01(m, 1H), 6.95 – 6.90 (m, 1H), 6.78 – 6.71 (m, 1H), 5.68 (d, J = 0.9 Hz, 1H), 5.58 - 5.52 (m, 2H), 3.53 (s, 3H), 2.70 – 2.65 (m, 2H), 2.45 – 2.12 (m, 4H), 1.34 – 1.25 (m, 1H), 1.05 – 0.89 (m, 2H), 0.80 – 0.69 (m, 1H).

Example 28b

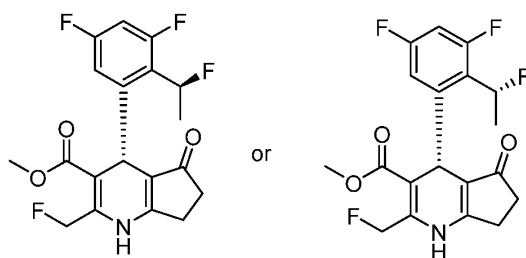
Second eluting enantiomer obtained as a white solid (48mg).

Chiral HPLC Rt = 15.216 min; [chiral analytical method 3]

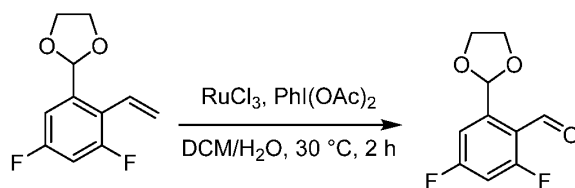
LCMS Rt = 1.47 min; MS m/z 360.2 [M+H]⁺; [Method 7]

¹H NMR (400 MHz, CDCl₃) δ 7.10 – 7.01(m, 1H), 6.95 – 6.90 (m, 1H), 6.78 – 6.71 (m, 1H), 5.68 (d, J = 0.9 Hz, 1H), 5.58 - 5.52 (m, 2H), 3.53 (s, 3H), 2.70 – 2.65 (m, 2H), 2.45 – 2.12 (m, 4H), 1.34 – 1.25 (m, 1H), 1.05 – 0.89 (m, 2H), 0.80 – 0.69 (m, 1H).

Example 29: methyl (R)-4-(3,5-difluoro-2-((S or R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate



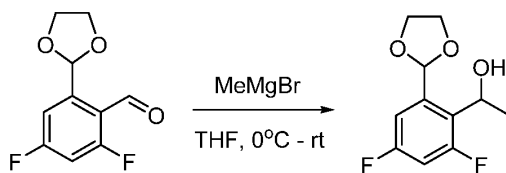
Step 1: 2-(1,3-dioxolan-2-yl)-4,6-difluorobenzaldehyde



To a solution of 2-(3,5-difluoro-2-vinylphenyl)-1,3-dioxolane (step 2 from example 3, 5 g, 23.58 mmol) and ruthenium chloride. XH_2O (490 mg, 2.35 mmol) in dichloromethane (50 mL) and water (10 mL) was added diacetoxyiodo benzene (11.4 g, 35.37 mmol). The resulting solution was stirred at $30\text{ }^\circ\text{C}$ for 2 hrs. The reaction mixture was filtered and washed with ethyl acetate (200 mL). The filtrate was dissolved in water (200 mL) and extracted into ethyl acetate (500 mL) and dried over Na_2SO_4 . The solvent was removed under reduced pressure and purification of the crude product by silica flash chromatography (0 $\rightarrow$ 10%) ethyl acetate in petroleum ether afforded the title compound 2-(1,3-dioxolan-2-yl)-4,6-difluorobenzaldehyde (3 g) as a colorless liquid.

^1H NMR (300 MHz, CDCl_3) δ 10.41 (s, 1H), 7.35 (d, $J = 9.6\text{ Hz}$, 1H), 6.95 – 6.85 (m, 1H), 6.53 (s, 1H), 4.08 (s, 4H).

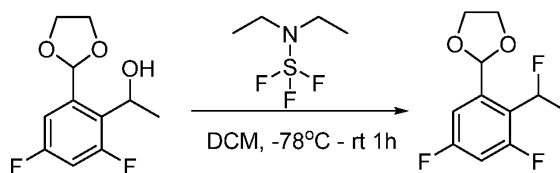
Step 2: 1-(2-(1,3-dioxolan-2-yl)-4,6-difluorophenyl)ethan-1-ol



To a solution of 2-(1,3-dioxolan-2-yl)-4,6-difluorobenzaldehyde (from step 1, 1.0 g, 4.67 mmol) in dry tetrahydrofuran (10 mL) at $0\text{ }^\circ\text{C}$ was added methyl magnesium bromide (2.33 mL, 3 M in ether, 4.67 mmol). The resulting solution was stirred at room temperature for 1 hrs. The reaction mixture was quenched with saturated ammonium chloride (10 mL) at $0\text{ }^\circ\text{C}$ and diluted with ethyl acetate (100 mL). The organic layer was separated and dried over Na_2SO_4 . The solvent was removed under reduced pressure afforded the title compound 1-(2-(1,3-dioxolan-2-yl)-4,6-difluorophenyl)ethan-1-ol (950 mg) as a colorless liquid. The crude compound was carry forwarded to next step without further purification.

^1H NMR (300 MHz, CDCl_3) δ 7.17 (dd, $J = 2.4, 6.3\text{ Hz}$, 1H), 6.89 – 6.72 (m, 1H), 6.17 (s, 1H), 5.31 (dd, $J = 6.9, 13.5\text{ Hz}$, 1H), 4.15 – 4.02 (m, 4H), 2.64 – 2.59 (m, 1H), 1.58 (d, $J = 9.0\text{ Hz}$, 3H).

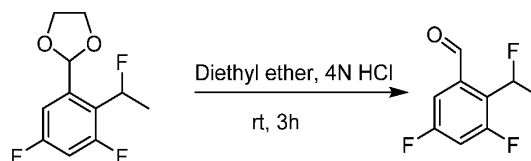
Step 3: 2-(3,5-difluoro-2-(1-fluoroethyl)phenyl)-1,3-dioxolane



To a solution of 1-(2-(1,3-dioxolan-2-yl)-4,6-difluorophenyl)ethan-1-ol (from step 2, 950 mg, 4.13 mmol) in dichloromethane (10 mL) at -78 °C was added diethylaminosulfur trifluoride (1.0 g, 6.13 mmol). The resulting solution was stirred at room temperature for 1 hr. The reaction mixture was quenched with saturated ammonium chloride (100 mL) at 0 °C and diluted with ethyl acetate (100 mL). The organic layer was separated and dried over Na₂SO₄. The solvent was removed under reduced pressure afforded the title compound 2-(3,5-difluoro-2-(1-fluoroethyl)phenyl)-1,3-dioxolane (600 mg) as a thick yellow liquid. The crude compound was carry forwarded to next step without further purification.

¹H NMR (300 MHz, CDCl₃) δ 7.20 (dd, J = 2.4, 6.3 Hz, 1H), 6.87 – 6.75 (m, 1H), 6.15 – 5.98 (m, 1H), 6.11 (s, 1H), 4.15 – 4.02 (m, 4H), 1.70 (dd, J = 6.6, 22.8 Hz, 3H).

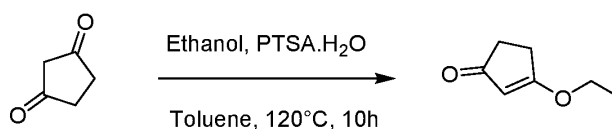
Step 4: 3,5-difluoro-2-(1-fluoroethyl) benzaldehyde



To a solution of 2-(3,5-difluoro-2-(1-fluoroethyl)phenyl)-1,3-dioxolane (from step 3, 600 mg, 2.58 mmol) in diethyl ether (10 mL) was added 4N HCl (2 mL) at room temperature. The resulting solution was stirred at room temperature for 3 hrs. This was washed with water (50 mL) and saturated NaHCO₃ solution (100 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure afforded the title compound 3,5-difluoro-2-(1-fluoroethyl)benzaldehyde (200 mg) as a colorless liquid. (Note: The obtained aldehyde is volatile nature)

¹H NMR (300 MHz, CDCl₃) δ 10.44 (d, J = 3.0 Hz, 1H), 7.20 (d, J = 9.3 Hz, 1H), 7.10 – 6.98 (m, 1H), 6.43 – 6.19 (m, 1H), 1.78 (dd, J = 7.2, 23.1 Hz, 3H).

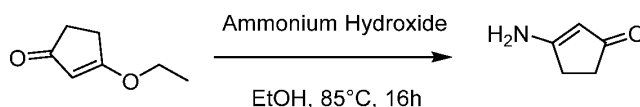
Step 5: 3-ethoxycyclopent-2-en-1-one



To a stirred solution of cyclopentane-1,3-dione (5.0 g, 50.96 mmol) in toluene (70 mL) was added pTSA (193 mg, 1.019 mmol) and EtOH (22.61 mL, 387.35 mmol) at room temperature. The resulting mixture was stirred at 120 °C for 10 hrs using Dean-stark apparatus. The solvent was removed under reduced pressure gave crude compound. Crude product was purified by silica flash chromatography (0 → 50%) ethyl acetate in petroleum ether to afford the title compound 3-ethoxycyclopent-2-en-1-one (4.3 g) as a brown solid.

¹H NMR (400 MHz, CDCl₃) δ 5.26 (s, 1H), 4.02 (q, J = 6.6 Hz, 2H), 2.60 – 2.55 (m, 2H), 2.44 – 2.40 (m, 2H), 1.39 (t, J = 7.2 Hz, 3H).

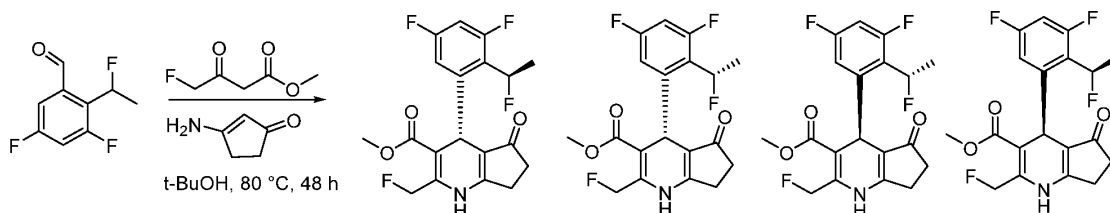
Step 6: 3-aminocyclopent-2-en-1-one



To a stirred solution of 3-ethoxycyclopent-2-en-1-one (from step 5, 4.3 g, 34.08 mmol) in ethanol (50 mL) was added ammonium hydroxide solution (25 mL, 387.35 mmol) at room temperature. The resulting mixture was stirred at 85 °C for 16 hrs. Solvent removal under reduced pressure afforded the title compound 3-aminocyclopent-2-en-1-one (3.2 g) as a brown solid.

LCMS RT = 0.114 min; MS m/z 98.2 [M+H]⁺; [Method 7]

Step 7: methyl 4-(3,5-difluoro-2-(1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate



To a solution of the aldehyde (from step 4, 700 mg, 3.7204 mmol), methyl 4-fluoro-3-oxobutanoate (step 1; method 2 of intermediate B, 598.73mg, 4.4645mmol) and 3-aminocyclopent-2-en-1-one (step 6, 361.32mg, 3.7204mmol) in t-butanol (15 mL). The reaction mixture was stirred at 80 °C for 48 hrs. The solvent was removed under reduced pressure gave crude compound. Crude product was purified by silica flash chromatography (0 → 50%) ethyl acetate in petroleum ether afforded the title compound methyl 4-(3,5-difluoro-2-(1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (580 mg) as an off white solids and as mixture of diastereomers and off white solid first diastereomer (320 mg, Peak-1). The mixture (580 mg) was

further purified by prep-HPLC purification (Method 8) gave off white solid second diastereomer (80 mg, Peak-2).

Peak-1: 160 mg and Peak-2: 80 mg was further separated into its enantiomers using preparative chiral HPLC [Method 11] to obtain four isomers of example 29

5 Example 29

50 mg of first eluting enantiomer obtained as a white solid using chiral HPLC [method 11].

LCMS RT = 1.445 min; MS m/z 382.1 [M-H]⁻; [Method 7]

This was further purified by preparative HPLC purification [Method 9] gave off white solid (25 mg).

Chiral HPLC: RT: 8.905 min; [chiral analytical method 3]

10 LCMS RT = 1.445 min; MS m/z 382.1 [M-H]⁻; [Method 13]

¹H NMR (400 MHz, DMSO-d₆) δ 10.10 (s, 1H), 7.06 (ddd, *J* = 11.6, 8.8, 2.6 Hz, 1H), 6.82 – 6.68 (m, 1H), 6.36 (dq, *J* = 45.3, 6.5 Hz, 1H), 5.75 – 5.64 (m, 1H), 5.63 – 5.50 (m, 1H), 4.97 (s, 1H), 3.45 (s, 3H), 2.70 – 2.59 (m, 2H), 2.25 – 2.09 (m, 2H), 1.84 (dd, *J* = 23.0, 6.5 Hz, 3H).

Example 29b

15 55 mg of second eluting enantiomer obtained as a white solid using chiral HPLC [method 11].

Chiral HPLC: RT: 10.197 min; [chiral analytical method 3]

LCMS RT = 1.510 min; MS m/z 382.1 [M-H]⁻; [Method 13]

¹H NMR (400 MHz, DMSO-d₆) δ 10.10 (s, 1H), 7.06 (ddd, *J* = 11.6, 8.8, 2.6 Hz, 1H), 6.82 – 6.67 (m, 1H), 6.36 (dq, *J* = 45.4, 6.6 Hz, 1H), 5.75 – 5.64 (m, 1H), 5.63 – 5.48 (m, 1H), 4.97 (s, 1H), 3.45 (s, 3H), 2.71 – 2.59 (m, 2H), 2.27 – 2.16 (m, 2H), 1.84 (dd, *J* = 23.0, 6.5 Hz, 3H).

20 Example 29c

24.2 mg of third eluting enantiomer obtained as a white solid using chiral HPLC [method 11].

Chiral HPLC: RT: 14.455 min; [chiral analytical method 3]

LCMS RT = 1.504 min; MS m/z 382.0 [M-H]⁻; [Method 10]

25 ¹H NMR (400 MHz, DMSO-d₆) δ 10.13 (s, 1H), 7.14 – 6.96 (m, 1H), 6.75 (d, *J* = 9.8 Hz, 1H), 6.63 (dq, *J* = 44.2, 6.8 Hz, 1H), 5.71 (s, 1H), 5.59 (s, 1H), 4.88 (s, 1H), 3.47 (s, 3H), 2.62 (q, *J* = 4.5 Hz, 2H), 2.25 (t, *J* = 4.9 Hz, 2H), 1.68 (dd, *J* = 22.8, 6.5 Hz, 3H).

Example 29d

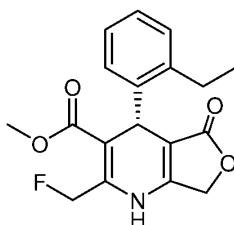
32.4 mg of fourth eluting enantiomer obtained as a white solid using chiral HPLC [method 11].

30 Chiral HPLC: RT: 18.561 min [chiral analytical method 3]

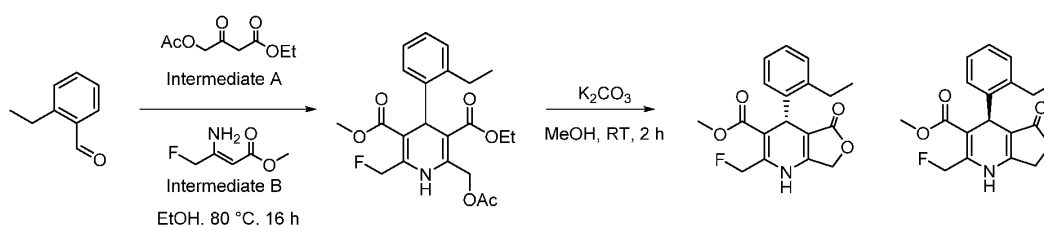
LCMS RT = 1.514 min; MS m/z 382.0 [M-H]⁻; [Method 10]

¹H NMR (400 MHz, DMSO-d₆) δ 10.13 (s, 1H), 7.05 – 7.00 (m, 1H), 6.75 (d, *J* = 9.7 Hz, 1H), 6.62 (dt, *J* = 44.2, 6.6 Hz, 1H), 5.71 (s, 1H), 5.59 (s, 1H), 4.88 (s, 1H), 3.47 (s, 3H), 2.62 (q, *J* = 4.6 Hz, 2H), 2.25 (t, *J* = 4.9 Hz, 2H), 1.68 (dd, *J* = 22.8, 6.4 Hz, 3H).

Example 30: methyl (R)-4-(2-ethylphenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate



Step 1: methyl 4-(2-ethylphenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate



The title compound was synthesized using general method I (using 2-ethylbenzaldehyde, 0.2 g, 1.44 mmol). Crude product was purified by silica column chromatography (2 → 3% methanol in DCM) which afforded the title compound as a cream color solid. Methyl methyl 4-(2-ethylphenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate (0.165 g, 43%). LCMS Rt = 1.506 min; MS m/z 331.85 [M+H]⁺; [Method 10]

The racemic sample was separated into its enantiomers by chiral HPLC (Column: LUX CELLULOSE-4, (250 MM X 21.2 MM X 5 MICRON); Mobile Phase: N-HEXANE (A) EtOH: MeOH, 1:1 (B), FLOW: 15 mL).

Example 30

The first eluting enantiomer, 30mg as a pale yellow solid.

Chiral HPLC Rt = 5.952 min (Column: LUX CELLULOSE-4 (150X4.6mmX5μ); Mobile Phase: A= n-HEXANE, B: ETHANOL: METHANOL (50:50); Flow: 1.0 mL/min).

LCMS Rt = 1.53 min; MS m/z 332.0 [M+H]⁺; [Method 7]

¹H NMR (400 MHz, DMSO-d₆) δ 10.03 (s, 1H), 7.13 - 7.10 (m, 4H), 5.71 (s, 1H), 5.59 (s, 1H), 4.98 (s, 1H), 4.82 (s, 2H), 3.44 (s, 3H), 2.98 - 2.92 (m, 2H), 1.25 (t, J = 7.8 Hz, 3H).

Example 30b

The second eluting enantiomer, 29mg as a pale yellow solid.

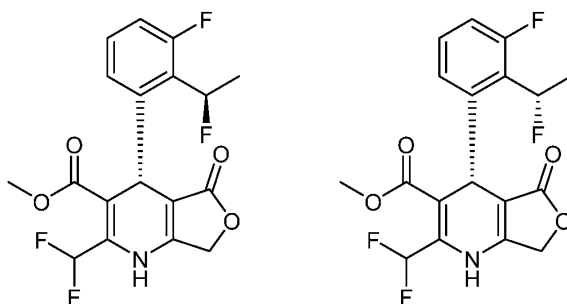
Chiral HPLC Rt = 7.581 min (Column: LUX CELLULOSE-4 (150X4.6mmX5μ); Mobile Phase: A= n-HEXANE, B: ETHANOL: METHANOL (50:50); Flow: 1.0 ml/min).

5 LCMS Rt = 1.528 min; MS m/z 332.0 [M+H]⁺; [Method 7]

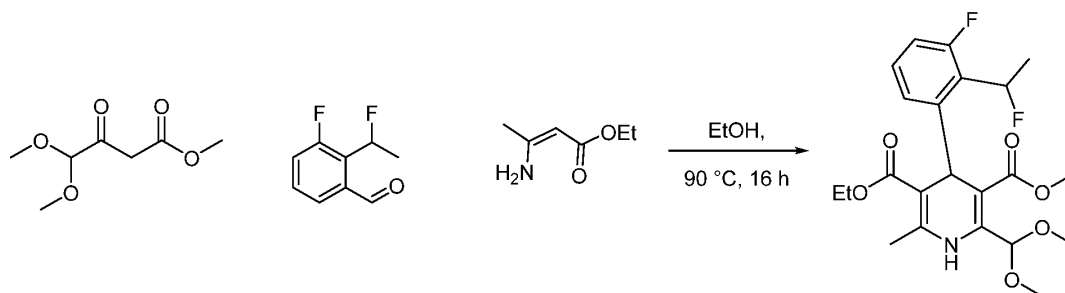
¹H NMR (400 MHz, DMSO-d₆) δ 10.03 (s, 1H), 7.13 - 7.10 (m, 4H), 5.71 (s, 1H), 5.59 (s, 1H), 4.98 (s, 1H), 4.82 (s, 2H), 3.44 (s, 3H), 2.98 - 2.92 (m, 2H), 1.25 (t, J = 7.8 Hz, 3H).

Example 31: methyl (R)-2-(difluoromethyl)-4-(3-fluoro-2-((R or S)-1-fluoroethyl)phenyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate

10



Step 1: 5-ethyl 3-methyl 2-(dimethoxymethyl)-4-(3-fluoro-2-(1-fluoroethyl)phenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate



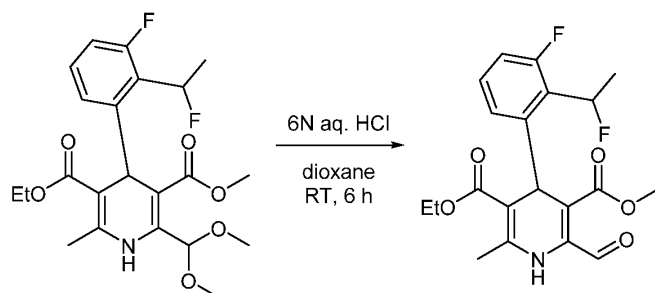
15 A stirred solution of methyl 4,4-dimethoxy-3-oxobutanoate (2.0 g, 11.35 mmol), 3-fluoro-2-(1-fluoroethyl)benzaldehyde (from example 27 step 3, 1.93 g, 11.35 mmol) and ethyl (Z)-3-aminobut-2-enoate (1.46 g, 11.35 mmol) in ethanol (20 mL) was heated to 90 °C for 16 h. Reaction mixture was concentrated under reduced pressure to afford crude compound as a brown colored liquid. Crude compound was purified by silica flash chromatography (9 → 10% ethyl acetate in hexane to

afford title compound as yellow sticky liquid. 5-ethyl 3-methyl 2-(dimethoxymethyl)-4-(3-fluoro-2-(1-fluoroethyl)phenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate (1.7 g, 34%).

Compound taken directly on as crude without further analysis

Step 2: 3-ethyl 5-methyl 4-(3-fluoro-2-(1-fluoroethyl)phenyl)-6-formyl-2-methyl-1,4-dihydropyridine-3,5-dicarboxylate

5



A stirred solution of 5-ethyl 3-methyl 2-(dimethoxymethyl)-4-(3-fluoro-2-(1-fluoroethyl)phenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate (from step 1, 1.7 g, 3.86 mmol) in 1,4-Dioxane (10.0 mL) was cooled to 0 ° C. 6 N aqueous hydrochloric acid solution (15.0 mL) was added at 0 ° C and reaction mixture was stirred at room temperature for 16 h. Reaction mixture was diluted with water and product extracted into ethyl acetate. Combined organic layers were washed with saturated solution of sodium bicarbonate, dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure. Crude compound was purified by silica flash chromatography (12 → 15% ethyl acetate in hexane) to afford the diastereomer 1 (400 mg, 26%) and diastereomer 2 (300 mg, 20%) of title compound as yellow sticky liquid.

10

15

Diastereomer 1

LCMS Rt = 1.606 min; MS m/z 392.0 [M-H]⁻; [Method 10]

¹H NMR (300 MHz, DMSO-*d*₆) δ 10.13 (s, 1H), 9.05 (s, 1H), 7.33 (dd, J = 13.8, 7.2 Hz, 1H), 7.10 - 7.02 (m, 2H), 6.45 - 6.23 (m, 1H), 5.19 (s, 1H), 4.06 - 3.98 (m, 2H), 3.63 (s, 3H), 2.35 (s, 3H), 1.76 (dd, J = 22.8, 6.6 Hz, 3H), 1.13 (t, J = 6.9 Hz, 3H)

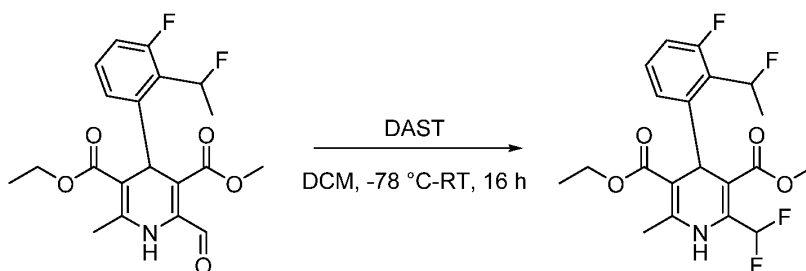
20

Diastereomer 2

LCMS Rt = 1.461 min; MS m/z 392.0 [M-H]⁻; [Method 14]

^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 10.12 (s, 1H), 9.07 (s, 1H), 7.33 (dd, $J = 13.8, 7.2$ Hz, 1H), 7.10 - 7.03 (m, 2H), 6.44 - 6.22 (m, 1H), 5.18 (s, 1H), 4.13 - 3.87 (m, 2H), 3.67 (s, 3H), 2.35 (s, 3H), 1.74 (dd, $J = 22.8, 6.6$ Hz, 3H), 1.11 (t, $J = 6.9$ Hz, 3H).

Step 3: 5-ethyl 3-methyl 2-(difluoromethyl)-4-(3-fluoro-2-(1-fluoroethyl)phenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate

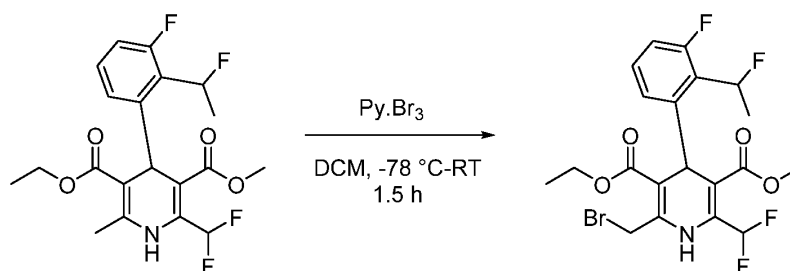


A stirred solution of 3-ethyl 5-methyl 4-(3-fluoro-2-(1-fluoroethyl)phenyl)-6-formyl-2-methyl-1,4-dihydropyridine-3,5-dicarboxylate (from diastereoisomer 1 of step 2, 0.40 g, 1.01 mmol) in dichloromethane (5.0 mL) was cooled to -78 °C. Diethylaminosulfur trifluoride (0.16 mL, 1.22 mmol) was added portion wise at -78 °C and the reaction mixture was stirred at room temperature for 16 h. Reaction mixture was quenched by ice cold water and product extracted into dichloromethane. The combined organic layers were washed with saturated sodium bicarbonate solution, dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure to afford the title compound as brown sticky liquid. 5-ethyl 3-methyl 2-(difluoromethyl)-4-(3-fluoro-2-(1-fluoroethyl)phenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate (0.3 g).

LCMS $R_t = 1.632$ min; MS m/z 414.0 $[\text{M}-\text{H}]^-$; [Method 10]

^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 9.38 (s, 1H), 7.58 - 7.23 (m, 2H), 7.09 - 7.01 (m, 2H), 6.43 - 6.22 (m, 1H), 5.12 (s, 1H), 4.08 - 3.97 (m, 2H), 3.58 (s, 3H), 2.34 (s, 3H), 1.75 (dd, $J = 23.1, 6.0$ Hz, 3H), 1.13 (t, $J = 6.9$ Hz, 3H)

Step 4: 3-ethyl 5-methyl 2-(bromomethyl)-6-(difluoromethyl)-4-(3-fluoro-2-(1-fluoroethyl)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate

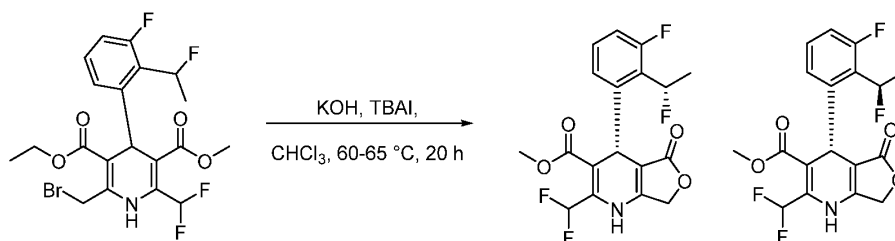


A solution of 5-ethyl 3-methyl 2-(difluoromethyl)-4-(3-fluoro-2-(1-fluoroethyl)phenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate (from step 3, 0.3 g, 0.722 mmol) in dichloromethane (5.0 mL) was cooled to -78 °C. Pyridinium tribromide (0.254 g, 0.794 mmol) was added at -78 °C and stirred for 1 h, at same temperature. Then the reaction mixture was stirred at room temperature for 30 minutes. Reaction mixture was diluted with ice cold water and product extracted into dichloromethane. Combined organic layers were dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure. Crude compound was purified by silica flash chromatography (10 → 12% ethyl acetate in Hexane) to afford the title compound as yellow sticky liquid. 3-ethyl 5-methyl 2-(bromomethyl)-6-(difluoromethyl)-4-(3-fluoro-2-(1-fluoroethyl)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate (0.2 g, 56%)

LCMS Rt = 1.653 min; MS m/z 491.95 [M-H]⁻; [Method 10]

¹H NMR (400 MHz, DMSO-*d*₆) δ 9.73 (s, 1H), 7.40 - 7.34 (m, 2H), 7.11 - 7.02 (m, 2H), 6.40 - 6.24 (m, 1H), 5.16 (s, 1H), 4.73 (dd, J = 34, 9.2 Hz, 2H), 4.14 - 4.05 (m, 2H), 3.58 (s, 3H), 1.75 (dd, J = 22.4, 6.4 Hz, 3H), 1.18 (t, J = 7.4 Hz, 3H)

Step 5: methyl 2-(difluoromethyl)-4-(3-fluoro-2-(1-fluoroethyl)phenyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate



To a solution of 3-ethyl 5-methyl 2-(bromomethyl)-6-(difluoromethyl)-4-(3-fluoro-2-(1-fluoroethyl)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate (from step 4, 0.1 g, 0.202 mmol) in chloroform (5.0 mL), was added potassium hydroxide (0.005 g, 0.101 mmol) at room temperature.

The reaction mixture was heated to 60°C and stirred for 8 h. Tetra-n-butylammonium iodide (0.007 g, 0.020 mmol) was added at room temperature and the reaction mixture was heated to 65 °C for 12 h. Reaction mixture was diluted with water and product extracted into dichloromethane.

- 5 Combined organic layers were washed with brine, dried over anhydrous sodium sulfate filtered and the solvent removed under reduced pressure. Crude product was purified by Prep HPLC (Column: ZORBAX XDB (250mmx21.2mm), 5.0μ; Mobile phase: A= WATER B = ACN; Flow: 18 ml/min) to afford the title compound as a cream color solid. methyl 2-(difluoromethyl)-4-(3-fluoro-2-(1-fluoroethyl)phenyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate (20 mg, 26%).

LCMS Rt = 1.503 min; MS m/z 384.05 [M-H]⁻; [Method 10]

- 10 The racemic sample was separated into its enantiomers by chiral HPLC (Column: CHIRALPAK IJ, 250 MM X 4.3 MM X 5 MICRON; Mobile Phase: A= HEXANE, B = 0.1% HCOOH IN MeOH: EtOH,1:1, FLOW: 5 mL).

Example 31:

First eluting peak of chiral HPLC, 3.4 mg as a cream color solid.

- 15 Chiral HPLC Rt = 6.393 min (Column: CHIRAL PAK IJ (250 X 4.6mm X 5μ); Mobile Phase: A: n-HEXANE B: Ethanol; FLOW: 1.0 mL/min.

LCMS Rt = 1.502 min; MS m/z 384.05 [M-H]⁻; [Method 10]

¹H NMR (300 MHz, DMSO-*d*₆) δ 10.43 (s, 1H), 7.64 - 7.28 (m, 2H), 7.10 - 7.02 (m, 2H), 6.44 - 6.22 (m, 1H), 5.13 (s, 1H), 4.88 (s, 2H), 3.49 (s, 3H), 1.80 (dd, J = 22.8, 6.0 Hz, 3H)

- 20 Example 31b

Second eluting peak of chiral HPLC, 3mg as a cream color solid.

Chiral HPLC Rt = 7.605 min (Column: CHIRAL PAK IJ (250 X 4.6mm X 5μ); Mobile Phase: A: n-HEXANE B: Ethanol; FLOW: 1.0 mL/min.

LCMS Rt = 1.500 min; MS m/z 384.05 [M-H]⁻; [Method 10]

- 25 ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.42 (s, 1H), 7.59 - 7.32 (m, 2H), 7.10 - 7.02 (m, 2H), 6.42 - 6.25 (m, 1H), 5.13 (s, 1H), 4.88 (dd, J = 19.2, 16.4 Hz, 2H), 3.49 (s, 3H), 1.80 (dd, J = 23.2, 6.4 Hz, 3H).

Crystalline Forms

X-ray Powder Diffraction Measurements (XRPD)

XRPD was performed with a Bruker D8 Advance diffractometer equipped with a nickel filter monochromator and a LYNXEYE (1D mode) detector with an open angle: 2.948° using Cu-K $\alpha_{1,2}$ radiation (wavelength 0.15419 nm). The diffractogram was recorded at a tube voltage of 40 kV and
5 a tube current of 40 mA, applying a step size of 0.0164° (2-theta value) with 0.3 seconds per step in the angular range of 2° to 40° 2-Theta at ambient conditions. The scan time was 768 seconds. A typical precision of the 2-theta values is in the range of $\pm 0.2^\circ$ 2-Theta, preferably of $\pm 0.1^\circ$ 2-Theta. Thus, for example, the diffraction peak of crystalline Form A of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate that
10 appears for example at 10.4° 2-Theta can appear in the range of from $(10.4-0.2)^\circ$ to $(10.4+0.2)^\circ$ 2-Theta, preferably from $(10.4-0.1)^\circ$ to $(10.4+0.1)^\circ$ 2-Theta on most X-ray diffractometers under standard conditions.

Crystalline Form A

Crude methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate (130 g, 0.35 mol) was slurried in ethyl ether (520 ml) for
15 3 hours at room temperature to obtain a suspension which was filtered. The wetcake was then dried under vacuum at 60°C for 72 hours to provide methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate Form A (100 g, 0.27 mol) with the yield of 77%.

20 Crystalline Form B

Crystalline Form B was prepared by dissolving 100mg of Form A in sufficient isopropyl acetate to obtain a solution. Then sufficient heptane was added at 55°C until a cloudy suspension was obtained. The suspension was kept at a certain time at 55°C and then cooled 25°C and
25 equilibrated for 2 to 4 hours at 25°C . The solid part was isolated and analysed by XRPD, which confirmed the presence of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate Form B.

Alternative synthesis: 400mL heptane was added into a 500mL reactor and heated to 55°C . 20g Form A was added into 60mL isopropyl acetate at room temperature. About 2g of Form B was added as seed into the reactor at 55°C and the resulting mixture was equilibration for 30min at
30 55°C . Then the isopropyl acetate solution of Form A free form was added dropwise into the reactor within 2 hours using a syringe pump. The resulting mixture was equilibrated at 55°C for 2 hours. The mixture was then cooled to 25°C within 6 hours and then equilibrated at 25°C for

further 10 hours. The suspension was then filtrated and the wet cake was dried at 50 °C under vacuum for 4 hours. About 21g of final product was obtained, which was confirmed by XRPD to correspond to Form B. The water content by KF was 0.3%.

Crystalline Form C

- 5 About 100mg of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate and various stoichiometric amounts of citric acid (base : acid ratios of 4:1, 3:1, 2:1 or 1:1) were crystallized in tert-butyl methyl ether. The solid forms obtained corresponded to methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate Form C.
- 10 Alternative synthesis: 40 mL of heptane was added into a 100 mL EasyMax reactor at 25 °C. 2 g of Form A was dissolved in 5mL isopropyl acetate at room temperature. Then 20 mg of seeds of Form C were added to the reactor at 25 °C. The resulting mixture was equilibrated for 30 min at 25 °C. The isopropyl acetate solution of Form A free form was added dropwise to the reactor within 2 hours period using a syringe pump. The resulting mixture was equilibrated at 25 °C for 2 hours. The in
- 15 process control showed a mixture of Form C and Hydrate A. The solid material was then slurried in 10 mL isopropyl acetate/heptane (1/7) for 2 days. The suspension was then filtrated and dried at 40 °C for 18 hours. The XRPD of the final product corresponded to Form C. The water content by KF was 0.3%.

20 Crystalline Form Hydrate A

- 1.97 g of Form A was weighted into a 100 mL EasyMax glass vial and dispersed in 35 mL of water, the suspension was stirred at 300 rpm by overhead stirring under 50 °C for 3 hours, then cool to 25 °C in 6 hours at about 0.07 °C/min, after that, kept stirring at 25 °C for 24 hours. The solid material was isolated by filtration. The XRPD of the solid form corresponded to Hydrate A.
- 25 Alternative synthesis: Hydrate A was obtained e.g. by evaporation crystallization of a clear saturated solution of Crystalline Form B in acetone, acetonitrile/water (99.5:0.5), ethyl acetate or water. Hydrate A shows a loss of mass by TGA of about 4.1%, which is close to a monohydrate (calculated water content of 4.7%). Hydrate A is slightly hygroscopic. The water uptake between 10% to 95% RH is about 0.2% at 25 °C.

30

Crystalline Form Hydrate B

2 g of Form A was weighted into a 100 mL EasyMax glass vial and dispersed in 30 mL of methanol, the suspension was stirred at 300 rpm by overhead stirring under 25 °C for 20 hours. The solid material was isolated by filtration and the solids were exposed to 92% RH for 1 days. The solid material corresponded to Hydrate B as confirmed by XRPD.

- 5 Alternative synthesis: Hydrate B was obtained by air drying of Crystalline Form B in methanol solvate. Hydrate B shows a loss of mass by TGA of about 4.4%, which is also close to a monohydrate (calculated water content of 4.7%). Hydrate B starts to dehydrate below 20% RH and loses about 4.4% of water until 0% RH. Upon subsequent increase of the relative humidity it only takes up about 3% of water at 25 °C.

10

Differential Scanning Calorimetry

Differential scanning calorimetry was performed using a TA Discovery DSC with a temperature range of 30 to 300 C at a scan rate of 10C/min under nitrogen with a flow rate of 25 mL/min. The sample mass used was about 2mg.

15 Biological Data

- Many known calcium channel activators have shown complex mechanisms of activating $Ca_v1.2$. These molecules not only increase peak currents, but also have additional mechanisms that increase intracellular calcium concentration, for example, by shifting the voltage sensitivity of the channel to more negative membrane potentials. Figure 6 illustrates these additional mechanisms by depicting simulated cardiac action potentials from an epicardial environment and showing the impact of shifting the voltage of $Ca_v1.2$ activation to more negative membrane potentials at a Potential (mV) versus Time (ms). These additional mechanisms could drive or facilitate cardiovascular effects such as increase in blood pressure, change in heart rate or contractility, and/or arrhythmia due to QT prolongation. For example, the O'Hara-Rudy model was used to investigate the effect of $Ca_v1.2$ modulation on action potential duration and arrhythmic liability. It was identified that a > 12 mV hyperpolarizing shift in the activation curve could potentially lead to > 15% QT prolongation and an increased risk of arrhythmia. Therefore, minimizing any shifts in voltage sensitivity may lead to compounds with a reduced risk of QT prolongation and cardiac arrhythmia.

- The compounds of formula (I) are highly potent $Ca_v1.2$ activators having a biophysical profile which minimizes the cardiovascular risks outlined above. First, the compounds of formula (I) limit their effects on the voltage sensitivity by minimizing hyperpolarizing shifts to < 9mV to mitigate for an arrhythmia potential. Second, the compounds of formula (I) increase $Ca_v1.2$ peak currents by no more than 2.5 fold, thereby limiting over-activation of the channel. Third, the compounds of formula (I) do not delay $Ca_v1.2$ channel inactivation, a pathophysiological mechanism underlying cardiac

symptoms of Timothy Syndrome. Moreover, compounds of formula (I) are designed to maximize brain exposure by showing no significant efflux in the brain.

Generation and Maintenance of the Ca_v1.2-HEK293(AUX) cell line

5 The monoclonal Ca_v1.2-HEK293(AUX) cell line constitutively expresses human Ca_v1.2 alpha1C (α 1C) subunit (*CACNA1C*) and has doxycycline-inducible expression of the alpha2delta (α 2 Δ 2) auxiliary subunit (*CACNA2D2*) and beta2 (β 2) auxiliary subunit (*CACNB2*). To generate the cell line, expression vectors *pcDNA5.0/FRT-TO-CACNA2D2-FCS-P2A-CACNB2* and *pCMV6-entry-CACNA1C* were established via gene synthesis and cloning. Here, *pcDNA5.0/FRT-TO* plasmid is
10 from Invitrogen, *pCMV6-entry* is from Origene, FCS stands for Furin Cleavage Site, P2A is a peptide self-cleavage sequence derived from porcine teschovirus-1, and FRT is the Flippase recognition target site. Next, parental line Flp-In™ 293 T-Rex (Invitrogen) was transfected with *pcDNA5.0/FRT-TO-CACNA2D2-FCS-P2A-CACNB2* and Flippase vector pOG44 (Invitrogen) to establish targeted integration of the *CACNA2D2-FCS-P2A-CACNB2* expression cassette into the pre-engineered FRT
15 site in Flp-In™ 293 T-Rex. This intermediate cell line was then transfected with *pCMV6-entry-CACNA1C* to establish stable *CACNA1C* expression. Clonal isolation was achieved under Neomycin selection. A cell clone (2-19B) with good voltage-dependent Barium current (see electrophysiology methods below) was selected for characterization of Ca_v1.2 activators.

To maintain the cell line, cells were passaged twice per week. At each passage, growth media
20 (Table 6) were completely removed and cells were rinsed sequentially with 10 ml of D-PBS and 5 ml of warm TrypLE™ Express Enzyme (Gibco). Both D-PBS and TrypLE™ Express Enzyme were immediately removed after rinsing. Plates were then placed at room temperature for 3-5 minutes. Next, 10 mL of warm 37°C complete media was added to flush the cell-growing surface and collect dissociated cells. Cells were counted and seeded into new flasks, targeting a density of 2-3×10⁶ cells
25 per T175 cm² flask.

Table 6. Growth medium for HEK293-Ca_v1.2(AUX) cells

Reagent	Concentration
DMEM	
Heat inactivated fetal bovine serum	10%
Hygromycin B	100ug/ml 30
Blasticidin	10ug/ml
Geneticin (G418)	200 ug/mL

Electrophysiological characterization of Ca_v1.2 activators using Ca_v1.2-HEK293(AUX) cell line and QPatch

24 hours prior an electrophysiology experiment, doxycycline (1 µg/ml) was added to the growth medium (Table 6), and 25 µM of verapamil was co-applied to prevent calcium influx triggered cell death. Cell confluency should reach 70%-80% right before the experiment.

To harvest cells (from a T175 cm² flask as an example), growth media were removed completely, and the cells were rinsed with 10 mL of D-PBS. D-PBS was aspirated, and 10 mL of Detachin (Genlantis) was added and the plate was placed in a 37°C incubator for 10 minutes. Detached cells were placed into a 15 mL conical tube and spun at 1000 rpm for 2 minutes. Supernatant was removed, and cells were re-suspended in QPatch complete media (Table 7) to desired cell density of 1.5-3 million cells per QPatch run. Each experimental run uses 1.5 mL of cells.

The cells suspension was taken to the Sophion QPatch platform that uses whole-cell voltage clamp to measure barium currents conducted through Cav1.2 on single-hole QPlates. Extracellular and intracellular patch clamp solutions are described in Tables 7 and 8, respectively. A dose-response assay protocol was used to determine the maximal fold change of peak inward current (E_{max}) and potency (EC₅₀) of each compound. The protocol had eight liquid periods. The first liquid period was to stabilize current amplitude, which was monitored using repetitive 200-ms voltage pulses stepping from -80 mV to 0 mV. The second liquid period was to determine baseline current amplitude in the presence of vehicle control, using a single 20-ms voltage pulse stepping from -80 mV to 0 mV. The third through eighth liquid periods were used to ascertain a 6-dose response to compound treatments, also using single 20-ms voltage pulses stepping from -80 mV to 0 mV. The EC₅₀ was generated using the following equation $I_{\text{concentration}} = I_{\text{base}} + (I_{\text{full}} - I_{\text{base}}) \cdot c^n / (XC_{50}^n + c^n)$, where c is the concentration and n is the Hill coefficient constant. I_{full} is the maximal current achievable, and I_{base} is 0. A channel biophysics assay protocol was used to determine channel gating properties including current – voltage relationship (IV curves), half-way channel activation voltage ($V_{1/2}$), rate of channel inactivation (τ), and amplitude of tail current. Among these, $V_{1/2}$ was derived from fitting equation $G(V) = G_{V_{\text{min}}} + (G_{V_{\text{max}}} - G_{V_{\text{min}}}) / (1 + \exp(-(V - V_{1/2})/V_{\text{slope}}))$, where G stands for conductance, $G_{V_{\text{min}}}$ equals 0, $G_{V_{\text{max}}}$ is the maximal conductance, and V_{slope} is a slope factor. $G(V)$ was pre-calculated from equation $G(V) = I(V)/(V - 0.06)$, for each experimentally applied depolarization potential (V) and the corresponding current amplitude ($I(V)$), and 0.06 in the equation was the experimentally determined reversal potential in volts. The protocol had four liquid periods. The first liquid period was to stabilize current amplitude, which was monitored using repetitive 200-ms voltage pulses stepping from -80 mV to 0 mV. Upon stabilization of current amplitude, a baseline value for the τ of inactivation was determined, via a single-exponential fit of the inactivation phase of the current trace. The second liquid period was to measure the baseline values constituting the current-voltage relationship in the presence of vehicle control, and the third liquid period was to measure the compound effect on the current-voltage relationship. During each of these two liquid periods, cells

were given ten 20-ms voltage pulses, each stepping from -80 mV to an incremental value that ranges from -55 mV to +35 mV (increment size 10 mV). During the fourth liquid period a 200-ms voltage pulse from -80mV to 0 mV was delivered again to measure the compound effect on tau of inactivation.

Table 6. QPatch complete media:

Reagent	Concentration
CHO-Serum free Media (SFM)	
1M HEPES	25 mM

5

Table 7. Extracellular solution for QPatch experiments

Chemical	Concentration (mM)
Sodium Chloride	145
Barium Chloride	10
Potassium Chloride	4
HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid))	10
HEPES	10
pH to 7.4 with NaOH for a final osmolarity of ~315 mOsm, filter solution through 0.2 μ M filter.	

Table 8. Intracellular solution for QPatch experiments. The solution is a mix of 80% part two (stored at -80°C) and 20% part one:

10 Part One:

Chemical	Concentration (mM)
Cesium Fluoride	135
HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid))	10
Sodium Chloride	10
EGTA (Ethylene glycol-bis(2-aminoethylether)-N,N,N',N'-tetraacetic acid)	1

pH to 7.2 with CsOH for a final osmolarity of ~295 mOsm, filter solution through 0.2 μ M filter.

Part Two:

Chemical	Concentration (mM)
Cesium Chloride	140
EGTA (Ethylene glycol-bis(2-aminoethylether)-N,N,N',N'-tetraacetic acid)	10
HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid))	10
Adenosine 5'-triphosphate magnesium salt	5
pH to 7.2 with KOH for a final osmolarity of ~295 mOsm, filter solution through 0.2 μ M filter.	

Assessment of compound exposure – cFos induction (PK-PD) relationship in wild-type mice

Animal maintenance and ethics. All animals were housed with regulated temperature and light cycle (22°C, 12-hour light/12-hour dark cycle) with unrestricted access to food and water. All animal experiments were performed in accordance with institutional guidelines for the care and use of laboratory animals as approved by the Institutional Animal Care and Use Committee (IACUC) of the Novartis Institutes for BioMedical Research, Inc. (Cambridge, MA, USA).

Compound administration and brain tissue collection. Wild-type C57BL/6J male mice were obtained from Jackson laboratories (Bar Harbor, ME). The acute, single-dose effects of Ca_v1.2 activators of the present disclosure were evaluated in male eight-week old mice (n = 6 mice per compound). Each compound was dissolved in 10% PEG300, 10% Solutol, 10% Cremophore EL, and 70% Phosphate Buffered Saline and administered intraperitoneal (i.p.) at a concentration of 1 mg/kg up to 30 mg/kg depending on the compound. Animals were euthanized one hour after compound administration via exsanguination under deep anesthesia. Blood was collected in EDTA tubes for downstream analysis of drug levels. Brains were rapidly removed from the skull, and the cerebral cortex and cerebellum were regionally dissected. Cerebellar samples were snap frozen in liquid nitrogen to assess compound exposure. Cortical samples for cFos assessment were placed in 500 μ l of RNeasy lysis solution (Qiagen) to preserve the integrity of RNA in the sample. Samples remained in RNeasy lysis solution for at least 24 hours at 4 °C before moving to -80°C for storage before processing.

Quantification of cFos mRNA induction. Tissue homogenization was performed using TissueLyser system for 96 well plates (Qiagen). First, frozen cortical samples were thawed, removed from RNAlater, and placed into TissueLyser tubes along with Buffer RLT containing 0.5% Reagent DX and one 5mm TissueLyser metal bead. The TissueLyser tubes were loaded into a TissueLyser II
5 tissue homogenizer for 3 rounds of homogenization, with each round lasting 5 minutes at 30Hz bead-beating frequency. Total RNA was purified from the homogenate using RNeasy 96 Plus kit (Qiagen), RNA concentration and A260/A280 ratio were quantified via the Nanodrop (ThermoFisher), and all samples were normalized to 100ng/ μ L concentration. RNA was reverse transcribed into cDNA using the Superscript III First-strand synthesis SuperMix Kit (ThermoFisher). For each sample, 6 μ L of RNA
10 (600ng total) was mixed with 1 μ L of Oligo dT and 1 μ L of annealing buffer and heated to 65 °C for 5 minutes. Next, 10 μ L of 2X First-Strand Reaction Mix and 2 μ L of the Enzyme mix were added to achieve a total reaction volume of 20 μ L. The samples were heated to 50 °C for 50 minutes then 85 °C for 5 minutes to complete cDNA synthesis.

Quantitative PCR was performed on the cDNA samples using Quantitect Multiplex RT-PCR kit
15 (Qiagen) in a 384-well assay format. Each PCR well contained 2 μ L of cDNA (60ng total), 10 μ L of RT-PCR mastermix, 1 μ L of cFos FAM Taqman probe (Mm00487425_m1 (FAM) #4351368), 1 μ L of GAPDH VIC Taqman probe (Mm99999915-g1 (VIC) #4448486), 0.2 μ L of Multiplex RT mix and 5.8 μ L of RNase-free water. On the ViiA7 Real-Time PCR system (ThermoFisher), the samples were heated to 95 °C for 15 minutes then cycled between 94°C for 45 seconds and 60 °C for 45 seconds
20 for 45 cycles. cFos Ct values were exported, normalized to GAPDH Ct values, and converted to relative fold change in expression using the delta-delta Ct relative quantification method. cFos fold changes between compound treatments and vehicle were analyzed by one-way ANOVA, followed by Tukey's post-hoc comparisons.

Quantification of compound exposure. Cerebellar tissue samples were homogenized in 4 ml of
25 20% acetonitrile and 80% Phosphate buffered saline for every 1 g of tissue (5x dilution). Tissue was homogenized using either of the following three methods: hand held probe system, TissueLyser system with 5mm steel bead at a frequency of 30 s⁻¹ for 4 min, or OMNI Bead Ruptor Elite homogenizer for 30 seconds to 1 minute depending on tissue type. Tissue samples were added to a 96-well plate (12.5 μ L sample) and processed for quantification by mass spectrometry.

Results

Table 9: Compound data

Example	Qpatch EC50 (μ M)	Qpatch Emax	Biophysics voltage shift (mV)	Brain: blood ratio	% $\uparrow$ cFOS mRNA cortex (3mg/kg ip)	% $\uparrow$ cFOS mRNA cortex (10mg/kg ip)
1	0.024	1.9	-5.9	2.9	254%	nd
2	0.012	2.3	-4.5	1.5	378%	nd
3	0.05	1.6	0.1	2.8	204%	nd
4	0.02	1.9	-4.4	1.4	161%	nd
5	0.02	1.9	-4.6	3.3	400%	nd
6	0.017*	1.4*	-6.3	1.5	199%	nd
7	0.03	1.8	-6.3	nd	262%	nd
8	0.02	2.0	-5.4	3.5	496%	nd
9	0.10	1.5	-4.5	1.5	290%	525%
10	0.04	1.8	-2.3	0.9	225%	nd
11	0.07	2.0	-5.0	1.1	160%	nd
12	0.08	2.3	-3.4	nd	nd	nd
13	0.02*	1.6*	-0.7	3.5	225%	444%
14	0.09	1.9	-5.5	nd	nd	nd
15	0.29	1.3	-5.7	1.7	176%	294%
16	0.01	1.5	-5.8	3.2	234%	nd
17	0.12	1.2	-6.8	2.1	201%	nd
18	0.21	1.8	-5.2	1.0	173%	280%
19	0.06	1.8	-6.7	nd	nd	nd
20	0.22	3.0	-8.5	nd	nd	nd
21	0.03	2.8	-8.1	nd	nd	nd
22	0.05	2.8	-8.6	nd	nd	nd
23	0.12	3.5	-6.2	1.2	365	nd
24	0.16	2.4	-7.5	nd	nd	nd
25	0.04	1.7	-4.2	nd	nd	nd
26	0.30	2.0	-4.3	nd	nd	nd
27	0.03	1.5	-8.7	nd	nd	nd
28	0.06	1.9	-7.2	1.1	293%	nd
29	0.05	1.4	TBD	nd	nd	nd

Example	Qpatch EC50 (μ M)	Qpatch Emax	Biophysics voltage shift (mV)	Brain: blood ratio	% $\uparrow$ cFOS mRNA cortex (3mg/kg ip)	% $\uparrow$ cFOS mRNA cortex (10mg/kg ip)
30	0.09	1.8	nd	nd	nd	nd
31	0.29	1.6	nd	nd	nd	nd

Qpatch was conducted as a 6-point dose response with 10 individual determinations at each concentration. Unless stated only one experimental replicate (n=1)

* n=2

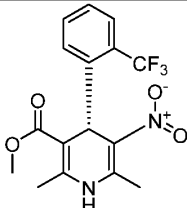
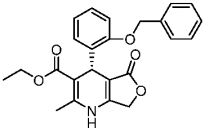
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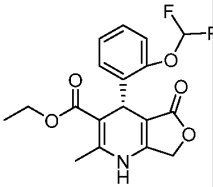
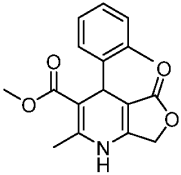
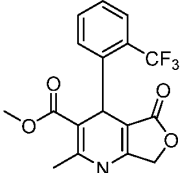
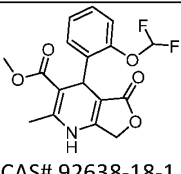
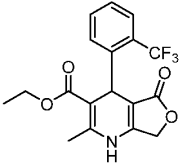
5 nd = not determined

Comparative Examples

Other Ca_v1.2 activators are known, however these compounds are not as potent and/or do not have the desired biophysical properties needed to activate the channel and have sufficient brain exposure, while at the same time minimizing cardiovascular risks, such as increase in blood pressure, altered heart rate or contractility, and/or arrhythmia due to QT prolongation.

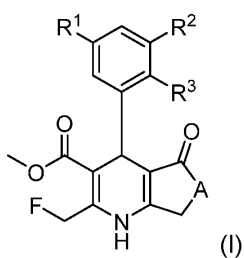
Table 10. Comparative examples to other known Ca_v1.2 activators

Structure Name	Qpatch EC50 (μ M)	Qpatch Emax	Biophysics voltage shift (mV)	Brain: blood ratio
Reported calcium channel activators (single enantiomers of reported racemates) showing various Qpatch profiles (Emax & V-shift)				
 (BayK8644)	0.021	3.9	-10.11	Not determined
 (RS30124)	0.045	4.3	-15.4	Not determined

Structure Name	Qpatch EC50 (μ M)	Qpatch Emax	Biophysics voltage shift (mV)	Brain: blood ratio
 (CGP028392)	0.28	2.2	-6.7	0.23
 CAS# 85825-32-7	2.24	Not determined	Not determined	Not determined
 CAS# 85825-31-6	0.36	1.4	-4.3	Not determined
 CAS# 92638-18-1	0.51	1.7	-7.1	Not determined
 CAS# 92638-18-1	0.93	1.9	Not determined	Not determined

What is claimed is:

1. A compound according to formula (I) or a pharmaceutically acceptable salt or solvate thereof



wherein:

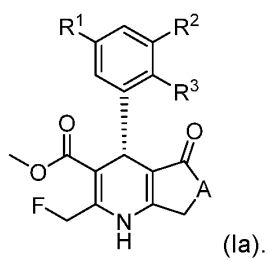
A is O or CH₂;

R¹ is H or F;

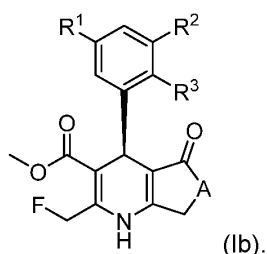
10 R² is H or F; and

R³ is OCHF₂, methyl, ethyl, or cyclopropyl each of which is optionally substituted with 1 to 3 F.

2. The compound according to claim 1 which is compound of formula (Ia) or a pharmaceutically acceptable salt or solvate thereof
- 15



3. The compound according to claim 1 which is a compound of formula (Ib) or a pharmaceutically acceptable salt or solvate thereof



5

4. The compound according to any one of claims 1-3 wherein A is O.

5. The compound according to claim 4 wherein R² is F.

10

6. The compound according to claim 4 wherein R² is H.

7. The compound according to claim 4 wherein R³ is OCHF₂.

15

8. The compound according to claim 4 wherein R³ is methyl, ethyl, or cyclopropyl each of which is substituted with 1 to 3 F.

9. The compound according to claim 4 wherein R³ is CHF₂ or CF₃.

20

10. The compound according to claim 4 wherein R³ is ethyl substituted with 1 or 2 F or cyclopropyl either unsubstituted or substituted with 2 F.

11. The compound according to any one of claims 1-3 where in A is CH₂.

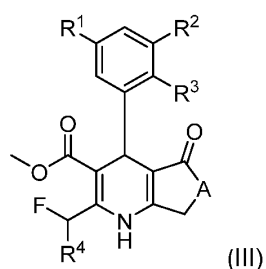
25

12. The compound according to claim 11 wherein R² is F.

13. The compound according to claim 11 or claim 12 wherein R³ is ethyl substituted with 1 to 3 F.

14. A compound according to formula (III) or a pharmaceutically acceptable salt or solvate thereof

5



wherein:

A is O or CH₂;

10 R¹ is H or F;

R² is H or F;

R³ is OCHF₂, methyl, ethyl, or cyclopropyl each of which is optionally substituted with 1 to 3 F; and

R⁴ is H or F.

15

15. The compound according to claim 14 wherein A is O.

16. The compound according to claim 15 wherein R² is F.

20 17. The compound according to claim 15 wherein R² is H.

18. The compound according to claim 15 wherein R³ is OCHF₂.

25 19. The compound according to claim 15 wherein R³ is methyl, ethyl, or cyclopropyl each of which is optionally substituted with 1 to 3 F.

20. The compound according to claim 15 wherein R³ is CHF₂ or CF₃.
21. The compound according to claim 15 wherein R³ is ethyl optionally substituted with 1 or 2 F
5 or cyclopropyl either unsubstituted or substituted with 2 F.
22. The compound according to claim 15 wherein R³ is ethyl.
23. The compound according to claim 15 wherein R⁴ is F.
10
24. The compound according to claim 15 wherein R⁴ is H.
25. The compound according to claim 14 where in A is CH₂.
- 15 26. The compound according to claim 23 wherein R² is F.
27. The compound according to claim 23 wherein R³ is ethyl substituted with 1 to 3 F.
28. The compound according to claim 23 wherein R⁴ is F.
20
29. The compound according to claim 23 wherein R⁴ is H.
30. The compound according to claim 1 selected from the group consisting of:
methyl (R)-4-(2-((R)-2,2-difluorocyclopropyl)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-
25 tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
methyl (R)-4-(2-((S)-2,2-difluorocyclopropyl)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-
tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
(R)-4-(2-cyclopropyl-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-
b]pyridine-3-carboxylate;
30 Methyl (R)-4-(2-((R)-2,2-difluorocyclopropyl)-3,5-difluorophenyl)-2-(fluoromethyl)-5-oxo-
1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
Methyl (R)-4-(2-((S)-2,2-difluorocyclopropyl)-3,5-difluorophenyl)-2-(fluoromethyl)-5-oxo-
1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;

- methyl (R)-4-(3,5-difluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- methyl (R)-4-(3,5-difluoro-2-((S)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- 5 methyl (R)-4-(2-((S)-1,2-difluoroethyl)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- 10 methyl (R)-4-(3-fluoro-2-((S)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- methyl (R)-4-(2-(difluoromethoxy)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- methyl (R)-4-(3,5-difluoro-2-(trifluoromethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- 15 methyl (R)-4-(2-(2,2-difluoroethyl)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- methyl (R)-4-(2-(2,2-difluoroethyl)-3,5-difluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro [3,4-b]pyridine-3-carboxylate;
- methyl (R)-4-(2-cyclopropyl-3,5-difluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- 20 methyl (R)-4-(2-(difluoromethyl)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- methyl (R)-4-(2-((R)-1,2-difluoroethyl)-3,5-difluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- 25 methyl (R)-4-(2-((S)-1,2-difluoroethyl)-3,5-difluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- methyl (R)-4-(3-fluoro-2-(trifluoromethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine -3-carboxylate;
- methyl (R)-4-(2-(difluoromethyl)-3,5-difluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- 30 methyl (R)-4-(2-(difluoromethoxy)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- methyl 4-(2-(difluoromethoxy)-5-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;

- methyl (R)-4-(2-cyclopropyl-5-fluorophenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- methyl (R)-4-(2-cyclopropylphenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- 5 methyl (R)-4-(5-fluoro-2-(trifluoromethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate;
- methyl 4-(2-ethylphenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate; and
- 10 methyl (R)-2-(fluoromethyl)-5-oxo-4-(2-(trifluoromethyl)phenyl)-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate; or a pharmaceutically acceptable salt or solvate thereof.
31. The compound according to claim 1 selected from the group consisting of
- ethyl (R)-4-(2-((R)-1,2-difluoroethyl)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate;
- 15 methyl (R)-4-(2-((S)-1,2-difluoroethyl)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate;
- (R)-4-(3-fluoro-2-(2,2,2-trifluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate;
- methyl (R)-4-(2-cyclopropyl-3,5-difluorophenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate;
- 20 methyl (R)-4-(2-(2,2-difluoroethyl)-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate;
- methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate;
- 25 methyl (R)-4-(3-fluoro-2-((S)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate;
- methyl (R)-4-(2-cyclopropyl-3-fluorophenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate;
- methyl (S)-4-(3,5-difluoro-2-((S)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate; and
- 30 methyl (S)-4-(3,5-difluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate; or a pharmaceutically acceptable salt or solvate thereof.

32. The compound according to claim 14, wherein the compound is methyl 2-(difluoromethyl)-4-(3-fluoro-2-(1-fluoroethyl)phenyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate or a pharmaceutically acceptable salt or solvate thereof.
- 5 33. A crystalline form of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
34. The crystalline form according to claim 33, wherein the form is Form A.
- 10 35. The crystalline form according to claim 33, wherein the form is Form B.
36. The crystalline form according to claim 33, wherein the form is Form C.
- 15 37. A crystalline hydrated form of methyl (R)-4-(3-fluoro-2-((R)-1-fluoroethyl)phenyl)-2-(fluoromethyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine-3-carboxylate.
38. The crystalline hydrated form according to claim 37, wherein the hydrated form is Hydrate A.
- 20 39. The crystalline hydrated form according to claim 37, wherein the hydrated form is Hydrate B.
40. A pharmaceutical composition comprising a compound according to any one of claims 1-32 and a pharmaceutically acceptable excipient.
- 25 41. A method for the treatment of schizophrenia, bipolar disorder, major depressive disorder, substance use disorder, ADHD, Phelan-McDermid Syndrome, autism spectrum disorder, multiple sclerosis, frontotemporal dementia, Alzheimer's disease, Brugada Syndrome, Short QT syndrome, or early repolarization syndrome comprising administration of an effective amount of a compound according to any one of claims 1-32, or a pharmaceutically acceptable salt thereof to a patient in need of treatment thereof.
- 30 42. A method for the treatment of schizophrenia, bipolar disorder, major depressive disorder, substance use disorder, ADHD, Phelan-McDermid Syndrome, autism spectrum disorder, multiple sclerosis, frontotemporal dementia, Alzheimer's disease, Brugada Syndrome, Short QT syndrome, or early repolarization syndrome comprising administration of a compound
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according to any one of claims 1-32, or a pharmaceutically acceptable salt thereof to a patient in need of treatment thereof.