

mGlu4. While these selectivity issues are mitigated with MTEP, it is a potent inhibitor of cytochrome P450 1A2 and is efficiently cleared following intravenous administration to rhesus monkeys.

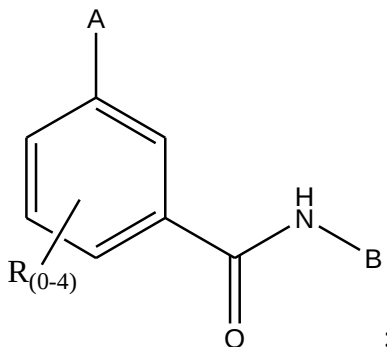
[0006] Potential adverse effects of known mGlu5 NAMs, however, could reduce their ultimate therapeutic utility. Further, conventional mGlu5 receptor modulators which target the orthosteric binding site can lack satisfactory aqueous solubility, exhibit poor oral bioavailability, and/or exhibit adverse effects. Therefore, there remains a need for methods and compositions that overcome these deficiencies and that effectively provide selective negative allosteric modulators for the mGlu5 receptor.

SUMMARY

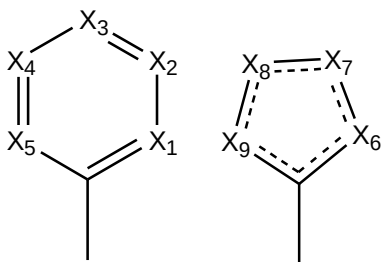
[0007] In accordance with the purpose(s) of the disclosure, as embodied and broadly described herein, the disclosure, in one example, relates to compounds useful as negative allosteric modulators of the metabotropic glutamate receptor subtype 5 (mGlu5), methods of making same, pharmaceutical compositions comprising same, and methods of treating disorders associated with glutamate dysfunction using same.

[0008] Disclosed are compounds, or pharmaceutically acceptable salts thereof, having a structure represented by a formula:

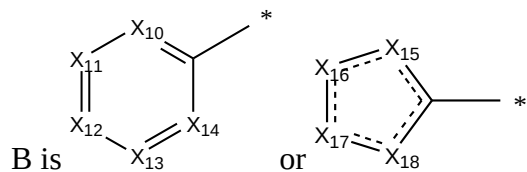
[0009] In an aspect, there is provided a compound having a structure represented by the following formula:



wherein each R, when present, is independent and chosen from H, D, OH, OR₅, CHF₂, CF₃, halogen, F, Cl, CH₃, alkyl, alkyl-halogen, CD₃, cycloalkyl, CN, methoxy, or alkoxy;



A is * or * ; wherein X₁ is CH, CR₁, or N; X₂ is CH, CR₁, or N; X₃ is CH, CR₁, or N; X₄ is CH, CR₁, or N; X₅ is CH, CR₁, or N; X₆ is CH, CR₁, S, O, NR₁, or N; X₇ is CH, CR₁, S, O, NR₁, or N; X₈ is CH, CR₁, S, O, NR₁, or N; X₉ is CH, CR₁, S, O, NR₁, or N;

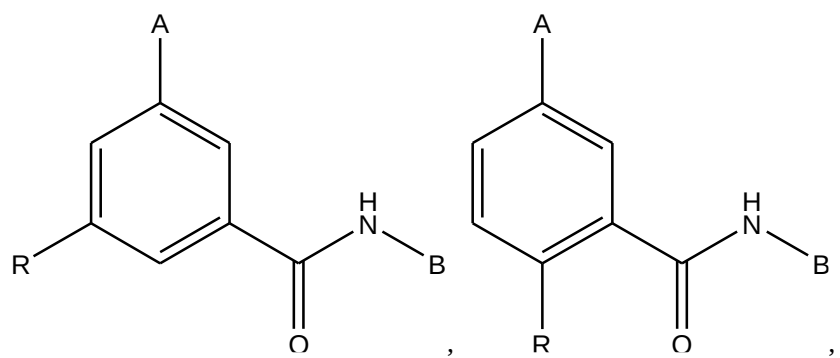
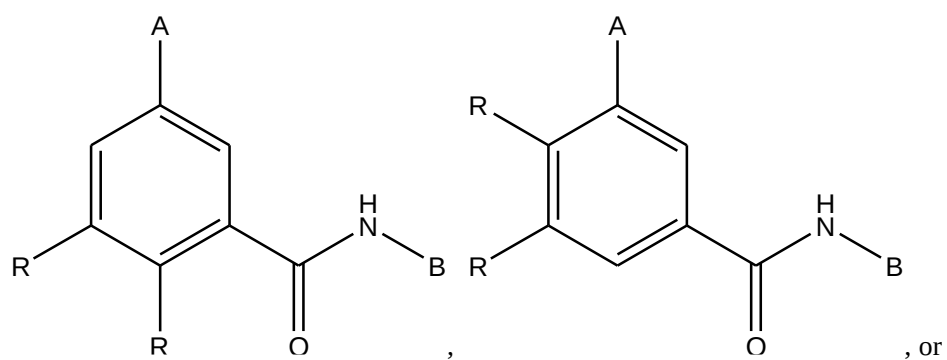
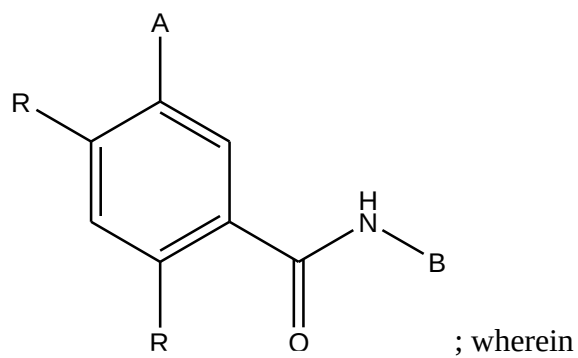


B is * or * ; wherein X₁₀ is CH, CR₁, or N; X₁₁ is CH, CR₁, or N; X₁₂ is CH, CR₁, or N; X₁₃ is CH, CR₁, or N; X₁₄ is CH, CR₁, or N; X₁₅ is CH, CR₁, S, O, NR₁, or N; X₁₆ is CH, CR₁, S, O, NR₁, or N; X₁₇ is CH, CR₁, S, O, NR₁, or N; X₁₈ is CH, CR₁, S, O, NR₁, or N;

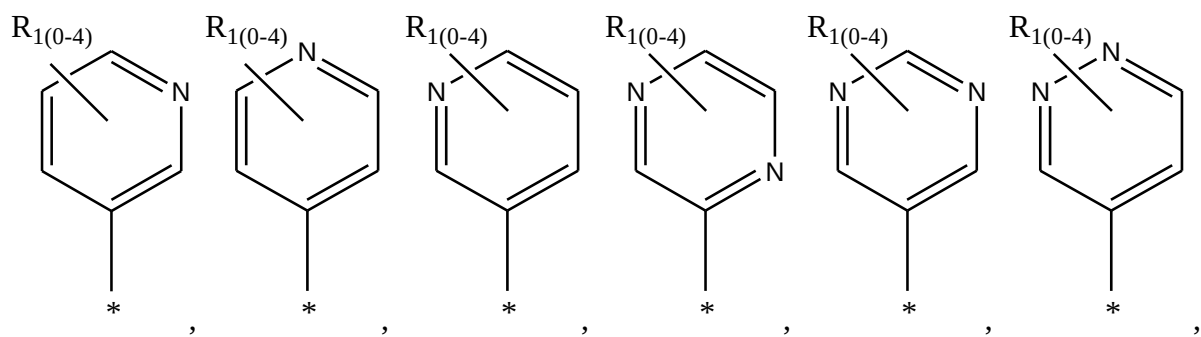
wherein at least one of X₁-X₅ is N, and wherein at least one of X₆-X₉ is O, S, NR₁ or N, and wherein at least one of X₁₀-X₁₄ is N and wherein at least one of X₁₅-X₁₈ is O, S, NR₁ or N;

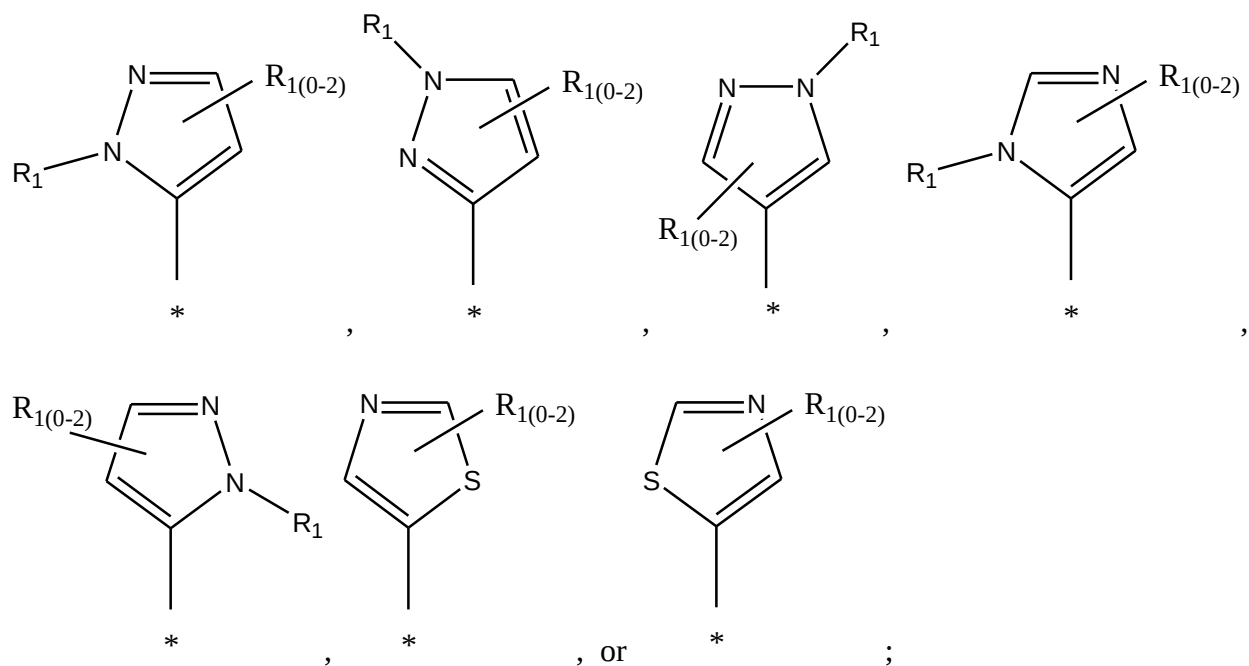
each R₁, when present, is independent and chosen from H, D, OH, NH₂, NR₃R₄, OR₅, CHF₂, CF₃, halogen, F, Cl, CH₃, alkyl, alkyl-halogen, CD₃, cycloalkyl, CN, methoxy, or alkoxy; R₃ is chosen from H, alkyl, or cycloalkyl; R₄ is chosen from H, alkyl, or cycloalkyl; R₅ is chosen from H, or alkyl; or a pharmaceutically acceptable salt thereof.

[0009a] In another aspect, there is provided a compound of the following formula:

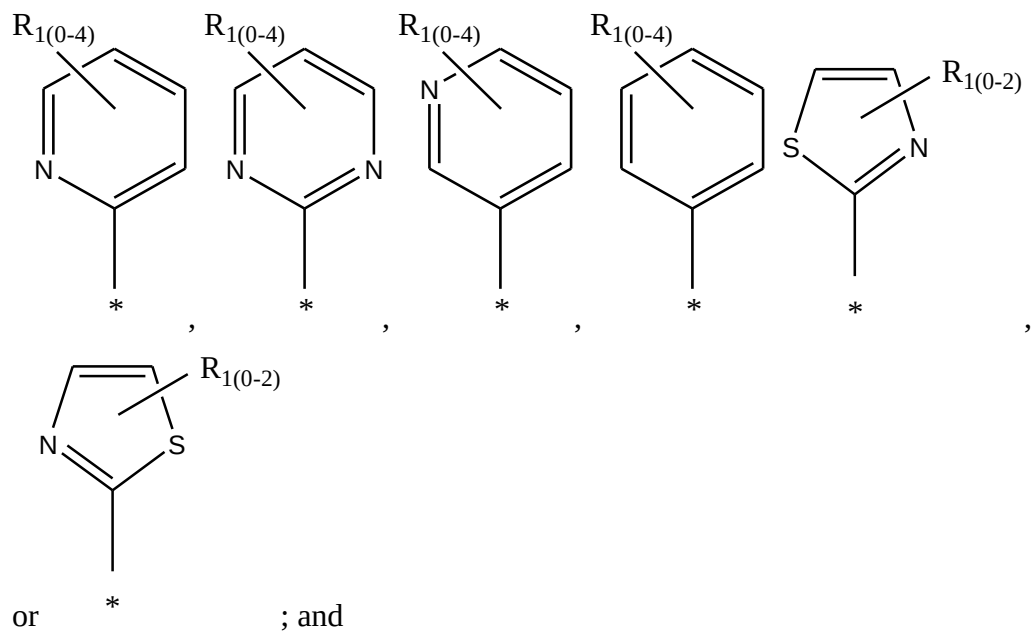


(i) A is chosen from:





(ii) B is chosen from:



(iii) each R_1 , when present, is independent and chosen from H, D, OH, CHF_2 , CF_3 , halogen, F, Cl, CH_3 , alkyl, CD_3 , cycloalkyl, CN, methoxy, or alkoxy;

or a pharmaceutically acceptable salt thereof.

[0009b] In another aspect, there is provided a compound described in TABLE 1.

[0010] Also disclosed are pharmaceutical compositions comprising an effective amount of at least one disclosed compound, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0010a] In another aspect, there is provided a pharmaceutical composition comprising a compound as defined above or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0018] Also disclosed are methods for modulating metabotropic glutamate receptor activity in at least one cell, comprising the step of contacting at least one cell with an effective amount of at least one disclosed compound, or a pharmaceutically acceptable salt thereof.

[0019] Also disclosed are methods for inhibiting metabotropic glutamate receptor activity in at least one cell, comprising the step of contacting at least one cell with at least one disclosed compound, or a pharmaceutically acceptable salt thereof.

[0020] Also disclosed are uses of at least one disclosed compound, or pharmaceutically acceptable salt, solvate, or polymorph thereof, in the manufacture of a medicament for the treatment of a disorder associated with glutamate dysfunction in a mammal.

[0020a] In another aspect, there is provided a use of at least one compound as defined above, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a disorder associated with metabotropic glutamate receptor activity in a subject.

[0020b] In another aspect, there is provided a compound as defined above for use in therapy.

[0021] Also disclosed are kits comprising at least one compound of any of the below listed claims, or a pharmaceutically acceptable salt thereof, and one or more of: (a) at least one agent known to increase mGlu5 activity; (b) at least one agent known to decrease mGlu5 activity; (c) at least one agent known to treat a neurological and/or psychiatric disorder; or (d) instructions for treating a disorder associated with glutamate dysfunction.

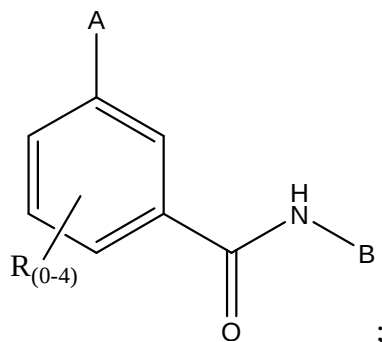
[0022] While examples of the present disclosure can be described and claimed in a particular statutory class, such as the system statutory class, this is for convenience only and one of skill in the art will understand that each example of the present disclosure can be described and claimed in any statutory class. Unless otherwise expressly stated, it is in no way intended that any method or example set forth herein be construed as requiring that its steps be performed in a specific order. Accordingly, where a method claim does not specifically state in the claims or descriptions that the steps are to be limited to a

specific order, it is no way intended that an order be inferred, in any respect. This holds for any possible non-express basis for interpretation, including matters of logic with respect to arrangement of steps or operational flow, plain meaning derived from grammatical organization or punctuation, or the number or type of examples described in the specification.

CLAIMS

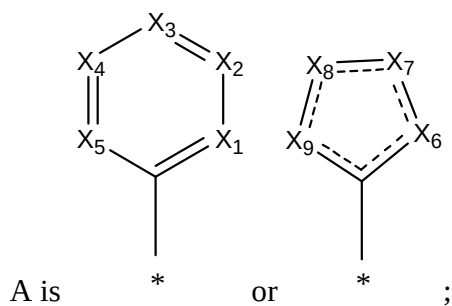
What is claimed is:

1. A compound having a structure represented by the following formula:



wherein:

each R, when present, is independent and chosen from H, D, OH, OR₅, CHF₂, CF₃, halogen, F, Cl, CH₃, alkyl, alkyl-halogen, CD₃, cycloalkyl, CN, methoxy, or alkoxy;



wherein:

X₁ is CH, CR₁, or N;

X₂ is CH, CR₁, or N;

X₃ is CH, CR₁, or N;

X₄ is CH, CR₁, or N;

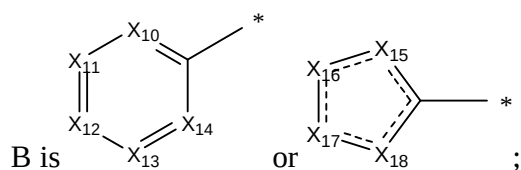
X₅ is CH, CR₁, or N;

X₆ is CH, CR₁, S, O, NR₁, or N;

X₇ is CH, CR₁, S, O, NR₁, or N;

X₈ is CH, CR₁, S, O, NR₁, or N;

X₉ is CH, CR₁, S, O, NR₁, or N;



wherein:

X₁₀ is CH, CR₁, or N;

X₁₁ is CH, CR₁, or N;

X₁₂ is CH, CR₁, or N;

X₁₃ is CH, CR₁, or N;

X₁₄ is CH, CR₁, or N;

X₁₅ is CH, CR₁, S, O, NR₁, or N;

X₁₆ is CH, CR₁, S, O, NR₁, or N;

X₁₇ is CH, CR₁, S, O, NR₁, or N;

X₁₈ is CH, CR₁, S, O, NR₁, or N;

wherein at least one of X₁-X₅ is N, and wherein at least one of X₆-X₉ is O, S, NR₁ or N, and

wherein at least one of X₁₀-X₁₄ is N and wherein at least one of X₁₅-X₁₈ is O, S, NR₁ or N;

each R₁, when present, is independent and chosen from H, D, OH, NH₂, NR₃R₄, OR₅, CHF₂, CF₃, halogen, F, Cl, CH₃, alkyl, alkyl-halogen, CD₃, cycloalkyl, CN, methoxy, or alkoxy;

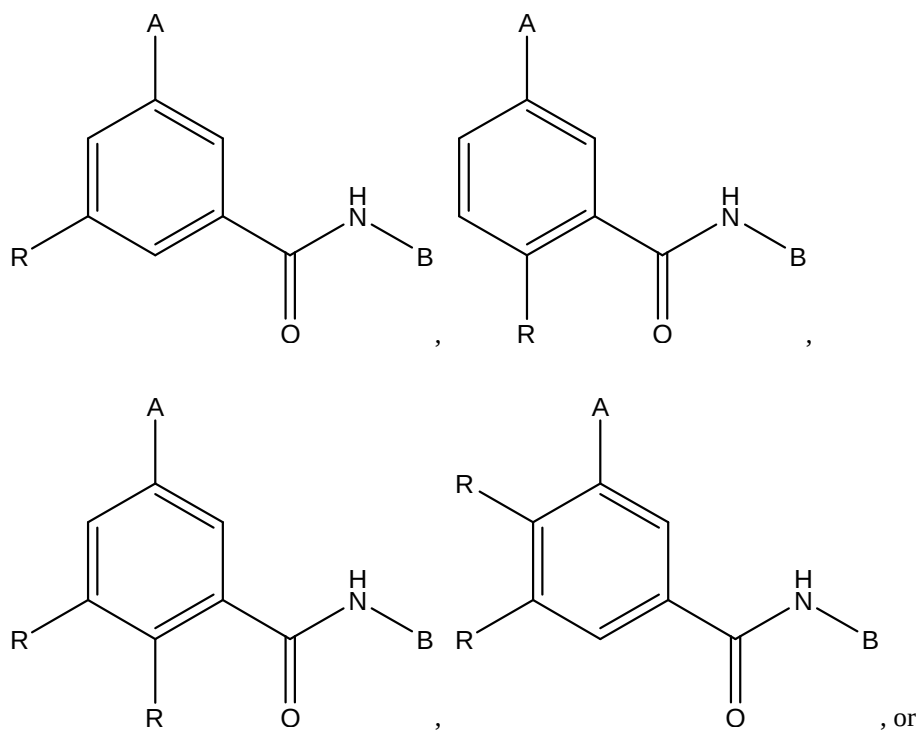
R₃ is chosen from H, alkyl, or cycloalkyl ;

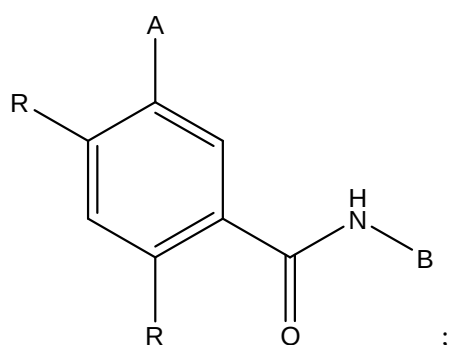
R₄ is chosen from H, alkyl, or cycloalkyl;

R₅ is chosen from H, or alkyl;

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1, of the following formula:

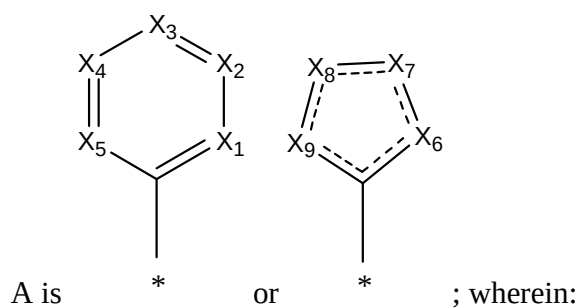




each R is independent and chosen from H, D, OH, OR₅, CHF₂, CF₃, halogen, F, Cl, CH₃, alkyl, alkyl-halogen, CD₃, cycloalkyl, CN, methoxy, or alkoxy;

or a pharmaceutically acceptable salt thereof.

3. A compound of claim 1, wherein:



X₁ is CH, or CR₁;

X₂ is CH, CR₁, or N;

X₃ is CH, CR₁, or N;

X₄ is CH, CR₁, or N;

X₅ is CH, or CR₁;

X₆ is CH, CR₁, S, NR₁, or N;

X₇ is CH, CR₁, S, NR₁, or N;

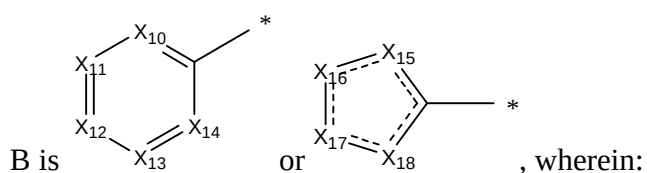
X₈ is CH, CR₁, S, NR₁, or N;

X₉ is CH, CR₁, S, NR₁, or N;

each R₁, when present, is independent and chosen from H, D, OH, CHF₂, CF₃, halogen, F, Cl, CH₃, alkyl, alkyl-halogen, CD₃, cycloalkyl, CN, methoxy, or alkoxy;

or a pharmaceutically acceptable salt thereof or;

wherein:



X₁₀ is CH, CR₁ or N;

X₁₁ is CH, CR₁ or N;

X₁₂ is CH, CR₁ or N;

X₁₃ is CH, CR₁ or N;

X₁₄ is CH, CR₁ or N;

X₁₅ is S, O, or N;

X₁₆ is CH, or CR₁;

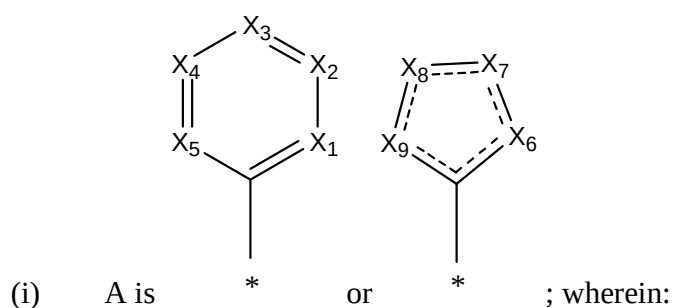
X₁₇ is CH, or CR₁;

X₁₈ is S, O, N;

each R₁, when present, is independent and chosen from H, D, OH, F, CHF₂, CF₃, halogen, F, Cl, CH₃, alkyl, CD₃, CN, cycloalkyl, methoxy, or alkoxy;

or a pharmaceutically acceptable salt thereof.

4. A compound of claim 1 or 2, wherein:



X₁ is CH, or CR₁;

X₂ is CH, CR₁, or N;

X₃ is CH, CR₁, or N;

X₄ is CH, CR₁, or N;

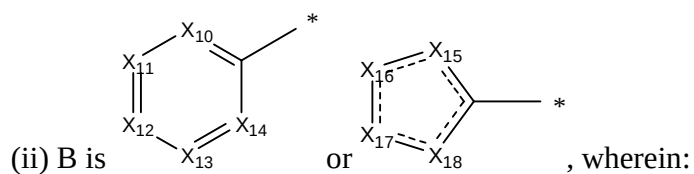
X₅ is CH, or CR₁;

X₆ is CH, CR₁, S, NR₁, or N;

X₇ is CH, CR₁, S, NR₁, or N;

X₈ is CH, CR₁, S, NR₁, or N;

X₉ is CH, CR₁, S, NR₁, or N;



X₁₀ is CH, CR₁ or N;

X₁₁ is CH, CR₁ or N;

X₁₂ is CH, CR₁ or N;

X₁₃ is CH, CR₁ or N;

X₁₄ is CH, CR₁ or N;

X₁₅ is S, O, or N;

X₁₆ is CH, or CR₁;

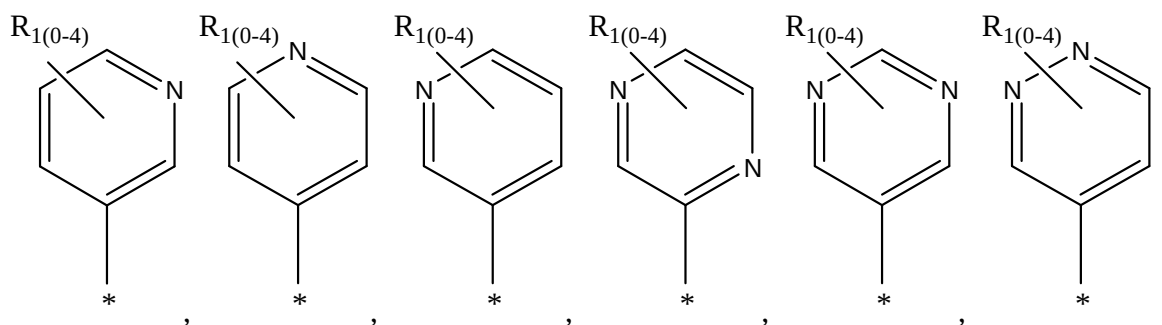
X₁₇ is CH, or CR₁;

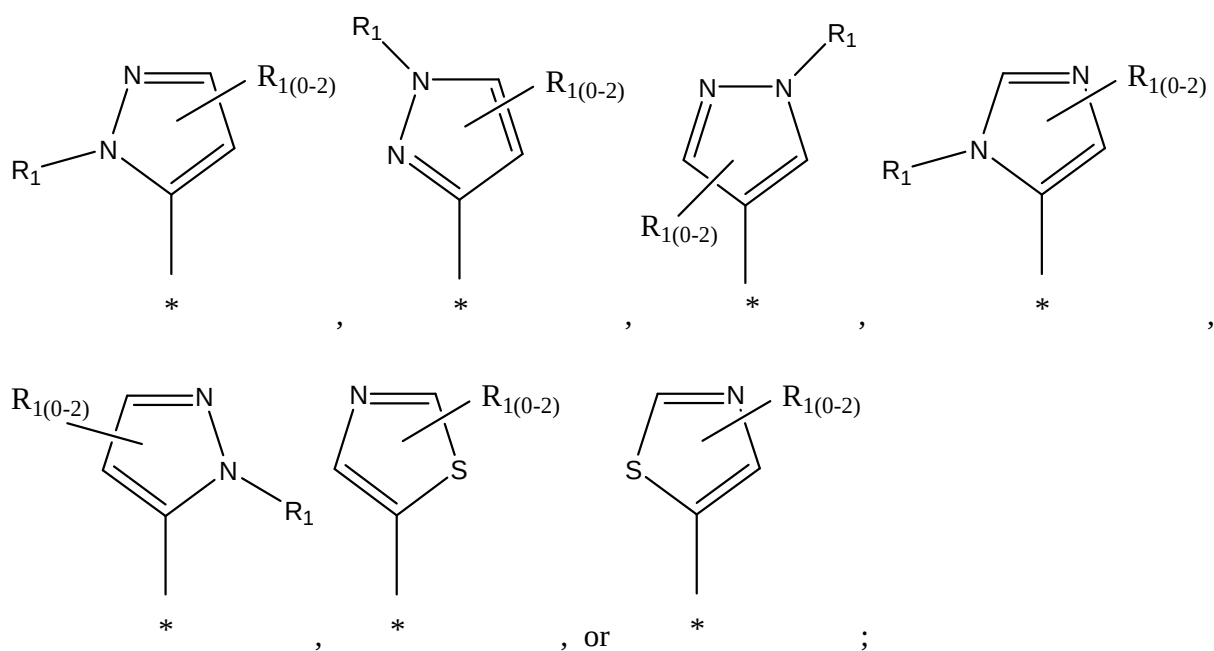
X₁₈ is S, O, N; and

(iii) each R₁, when present, is independent and chosen from H, D, OH, F, CHF₂, CF₃, halogen, F, Cl, CH₃, alkyl, CD₃, CN, cycloalkyl, methoxy, or alkoxy;

or a pharmaceutically acceptable salt thereof.

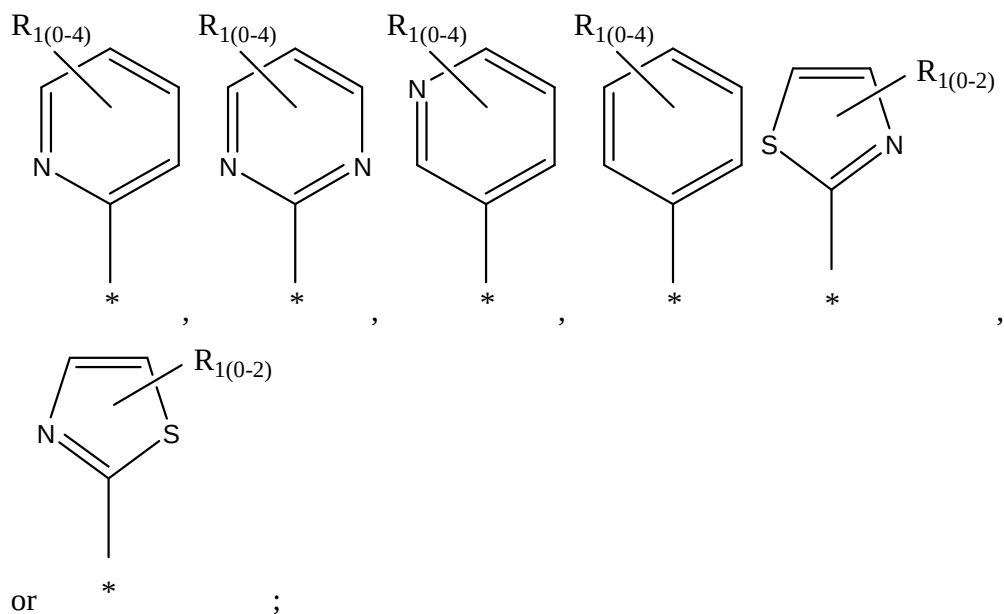
5. A compound of claim 1 or 2, wherein A is chosen from:





each R_1 , when present, is independent and chosen from H, D, OH, CHF_2 , CF_3 , halogen, F, Cl, CH_3 , alkyl, CD_3 , CN, cycloalkyl, methoxy, or alkoxy; or a pharmaceutically acceptable salt thereof.

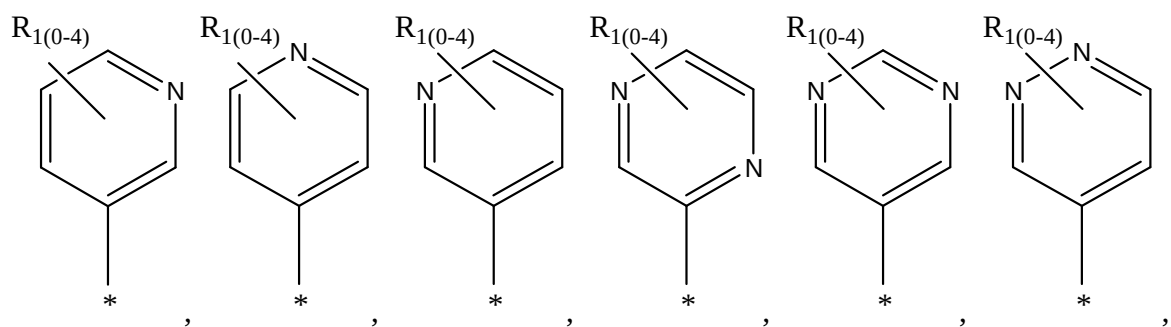
6. A compound of claim 1 or 2, wherein B is chosen from

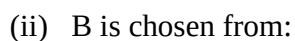
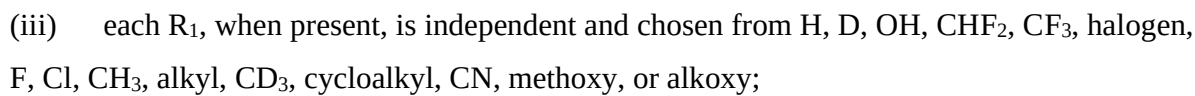


each R_1 , when present, is independent and chosen from H, D, OH, CHF_2 , CF_3 , halogen, F, Cl, CH_3 , alkyl, CD_3 , cycloalkyl, CN, methoxy, or alkoxy; or a pharmaceutically acceptable salt thereof.

7. A compound of claim 1 or 2, wherein:

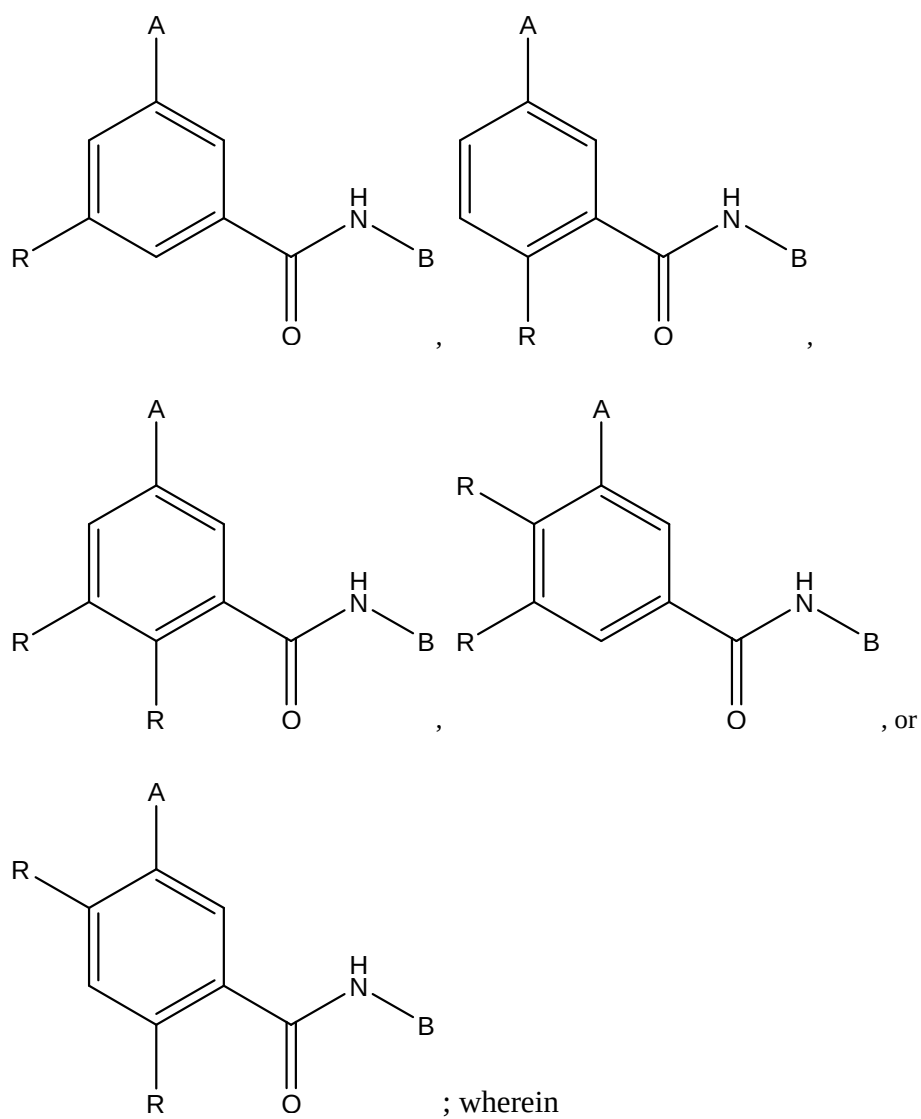
(i) A is chosen from:



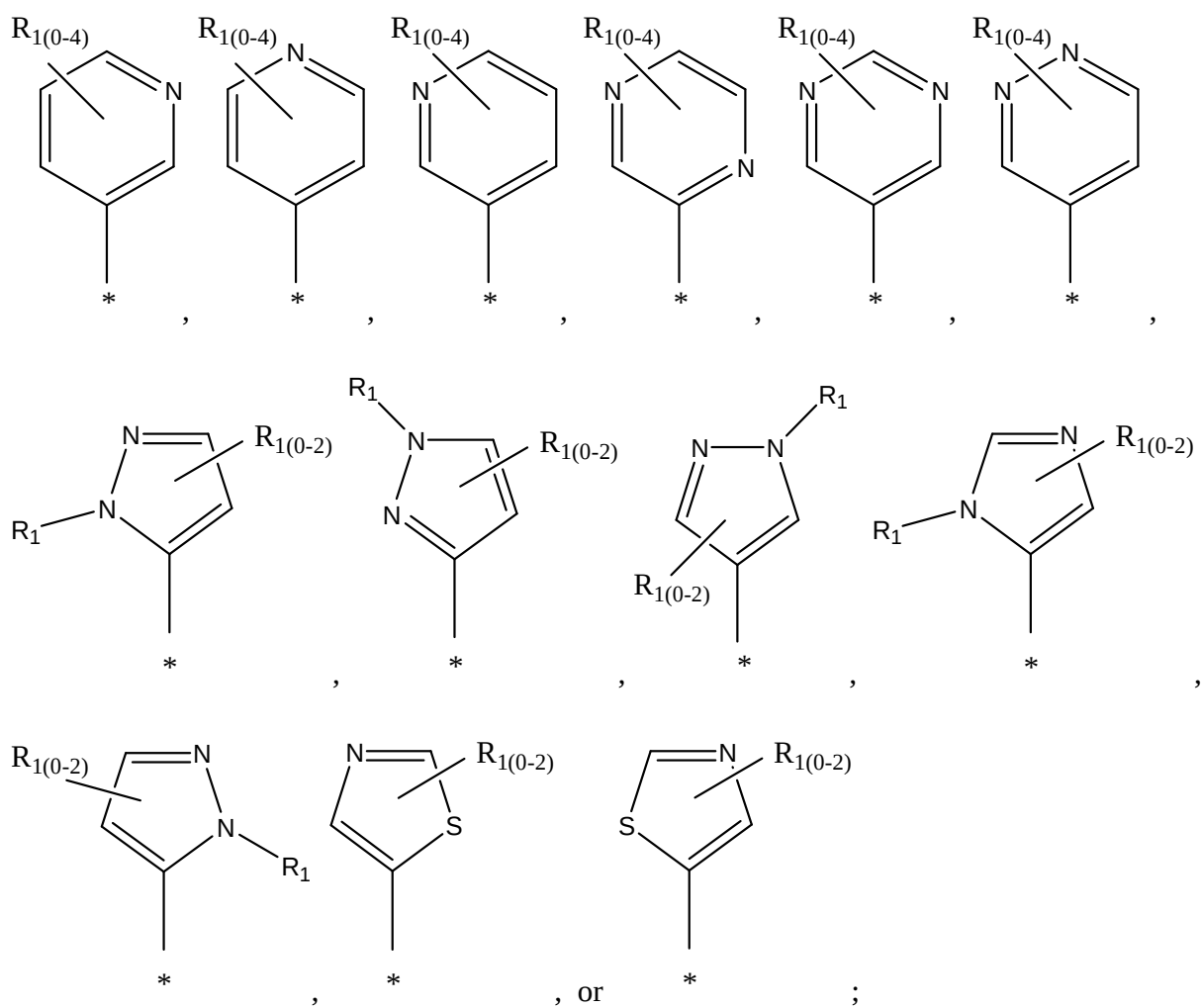


or a pharmaceutically acceptable salt thereof.

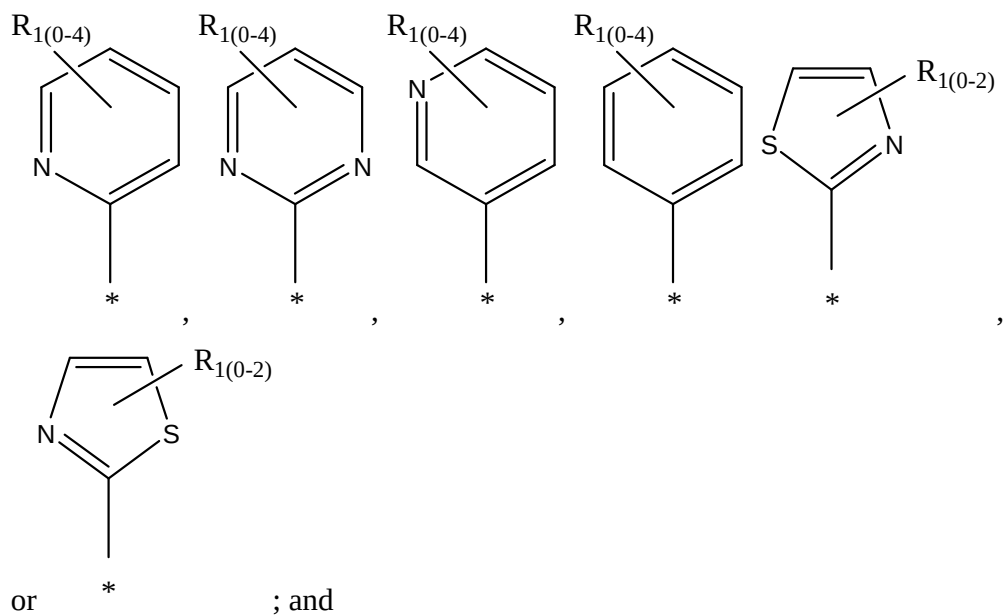
8. A compound of the following formula:



(i) A is chosen from:

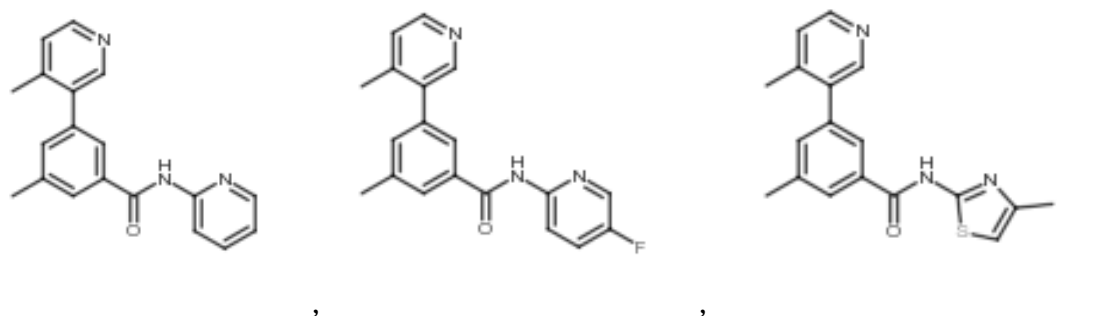


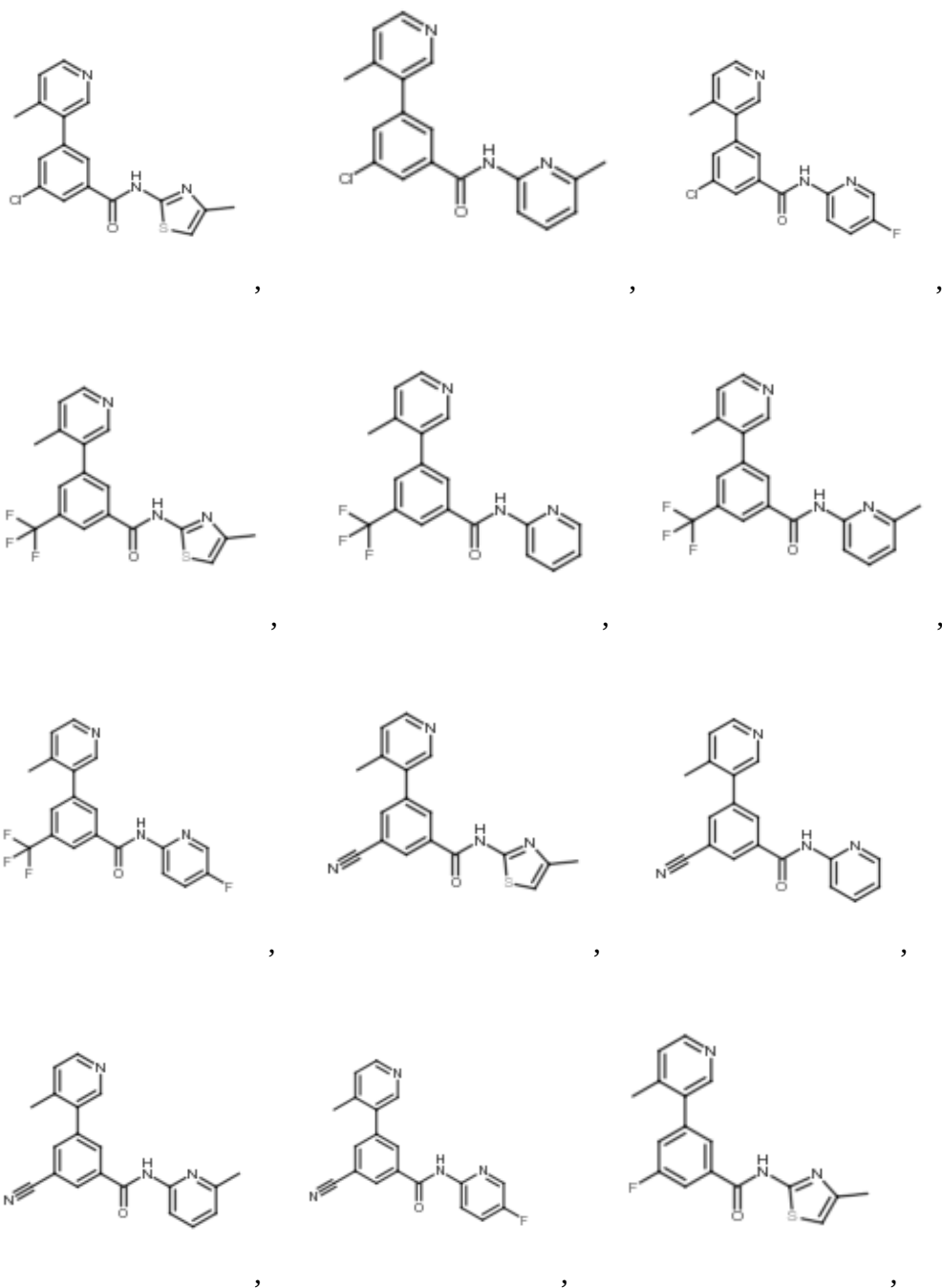
(ii) B is chosen from:

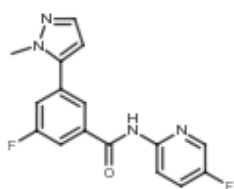


(iii) each R_1 , when present, is independent and chosen from H, D, OH, CHF_2 , CF_3 , halogen, F, Cl, CH_3 , alkyl, CD_3 , cycloalkyl, CN, methoxy, or alkoxy;
or a pharmaceutically acceptable salt thereof.

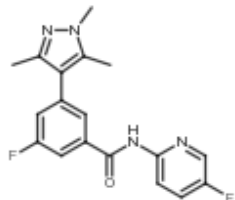
9. A compound of claim 1, of the following formula:



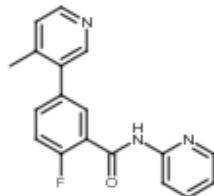




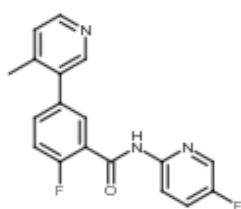
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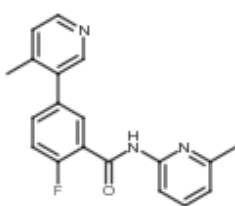
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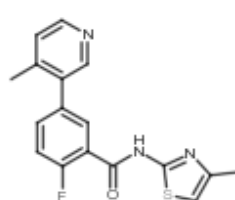
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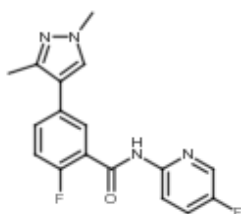
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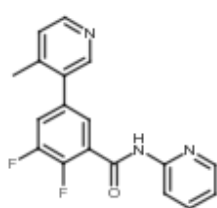
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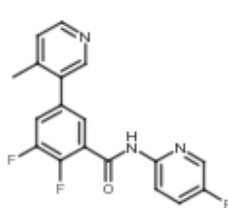
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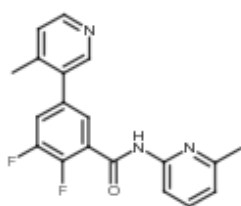
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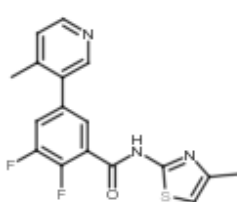
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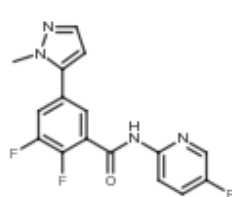
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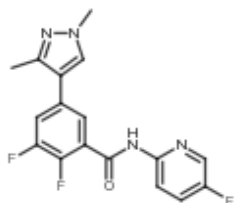
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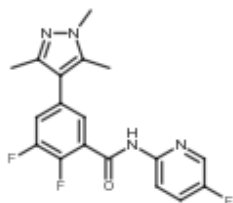
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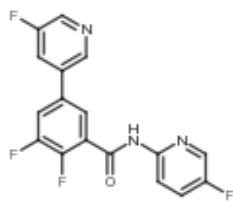
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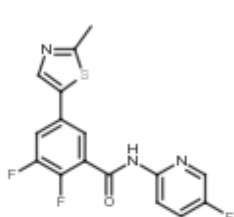
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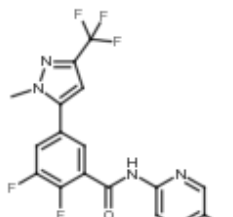
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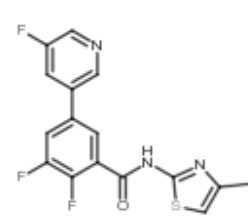
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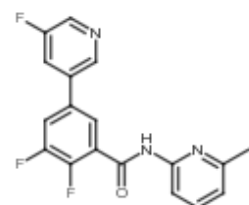
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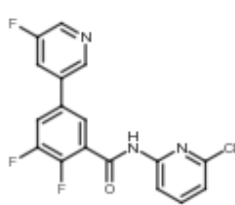
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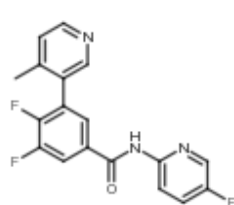
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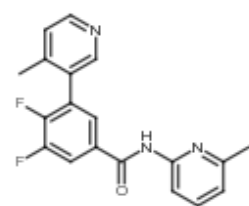
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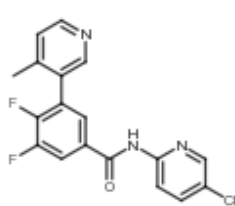
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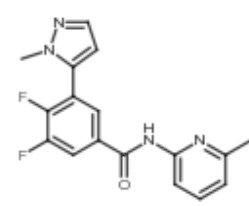
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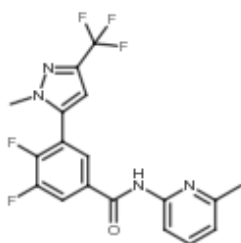
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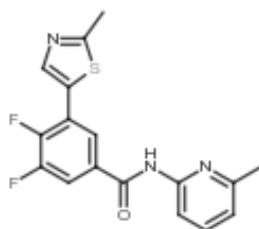
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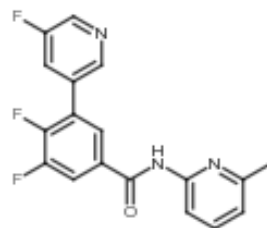
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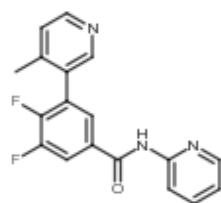
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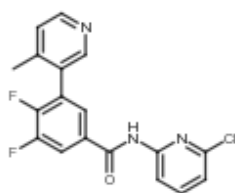
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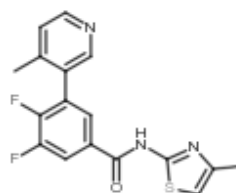
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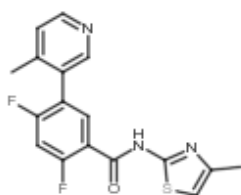
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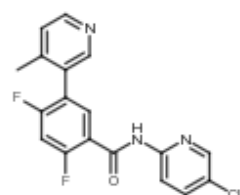
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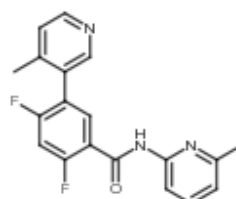
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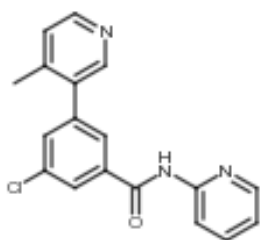
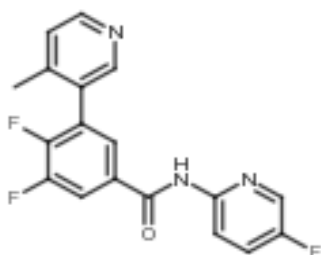
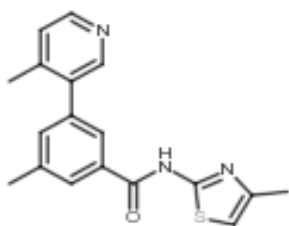
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, ;or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof.

10. A compound described in TABLE 1.

11. A pharmaceutical composition comprising a compound of one of claims 1-10, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

12. A pharmaceutical composition comprising a compound of claim 9, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

13. Use of at least one compound of one of claims 1-10, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a disorder associated with metabotropic glutamate receptor activity in a subject.

14. The use of claim 13, wherein the metabotropic glutamate receptor is mGlu5.
15. The use of claim 13, wherein the subject is a human.
16. The use of claim 13, wherein the subject has been diagnosed with a need for treatment of the disorder prior to the at least one compound of one of claims 1-10, or a pharmaceutically acceptable salt thereof to be administered.
17. The use of claim 13, further comprising a subject in need of treatment of the disorder to be identified.
18. The use of claim 13, wherein the disorder is a neurological and/or psychiatric disorder, preferably wherein the neurological and/or psychiatric disorder is selected from affective disorder, age-related cognitive decline, Alzheimer's disease, amnestic disorders, amyotrophic lateral sclerosis, anxiety disorders, Angelman syndrome, Asperger syndrome, attention deficit hyperactivity disorder, bipolar disorder, brain edema, chronic pain, delirium, dementia, depression, diabetes, Down Syndrome, dystonia, eating disorders, epilepsy, fibromyalgia, Huntington's-related chorea, levadopa-induced dyskinesia, manic-depressive illness, migraine, movement disorders, multiple sclerosis, narcolepsy, neurofibromatosis type 1, neuropathic pain, obesity, pain, paranoia, Parkinson's disease, post-herpetic neuropathic pain, psychotic disorders, PTEN hamartoma syndrome, senile dementia, sleep disorder, substance-related disorder, or unipolar depression, and more preferably wherein the neurological and/or psychiatric disorder is an autism spectrum disorder.

19. The use of claim 18, wherein the autism spectrum disorder is selected from autism, classical autism, Asperger syndrome, Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), sometimes called atypical autism, Fragile X syndrome, Rett syndrome, and Childhood Disintegrative Disorder.

20. A compound of one of claims 1-10 for use in therapy.