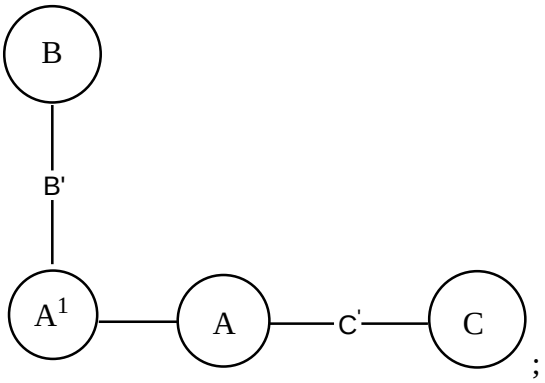
[0006] Potential adverse effects of known mGlu5 NAMs, however, could reduce their ultimate therapeutic utility. Further, conventional mGlu5 receptor modulators which target the orthosteric binding site can lack satisfactory aqueous solubility, exhibit poor oral bioavailability, and/or exhibit adverse 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.

[0007a] In one aspect, the present disclosure refers to a compound of the following formula:



;

wherein:

A is chosen from oxadiazole, imidazole, or triazole;

A^1 is substituted or unsubstituted pyridine;

B is chosen from substituted or unsubstituted pyridine, substituted or unsubstituted pyrazole, substituted or unsubstituted phenyl, tetrahydropyran, tetrahydrofuran, oxytetrahydrofuran;

B' is a bond, -O-, or substituted or unsubstituted C_1-C_6 alkyl;

C is chosen from substituted or unsubstituted pyridine, substituted or unsubstituted thiazole,

substituted or unsubstituted phenyl, cyclohexyl, tetrahydropyran, substituted or unsubstituted pyrazole, pyridazine, pyrazine,

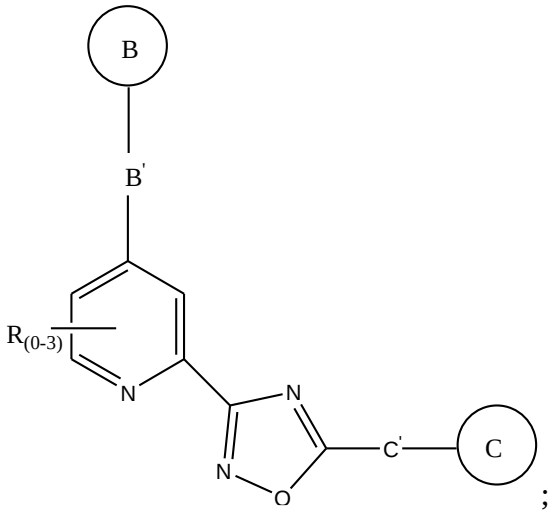
C' is a bond, or substituted or unsubstituted C_1-C_6 alkyl;
or a pharmaceutically acceptable salt thereof.

[0007b] In another aspect, the present disclosure refers to a pharmaceutical composition comprising a compound as defined above, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0007c] In another aspect, there is provided the use of compound as defined above, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disorder associated with metabotropic glutamate receptor activity in a subject.

[0007d] In another aspect, the present disclosure refers to a compound as defined above for use in the treatment of a disorder associated with metabotropic glutamate receptor, such as mGlu5, activity in a subject.

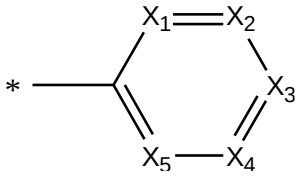
[0007e] In another aspect, the present disclosure refers to a compound of the following formula:



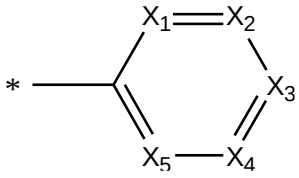
;

wherein B' is a bond, -O-, or substituted or unsubstituted C_1-C_6 alkyl; C' is a bond, or substituted or unsubstituted C_1-C_6 alkyl;

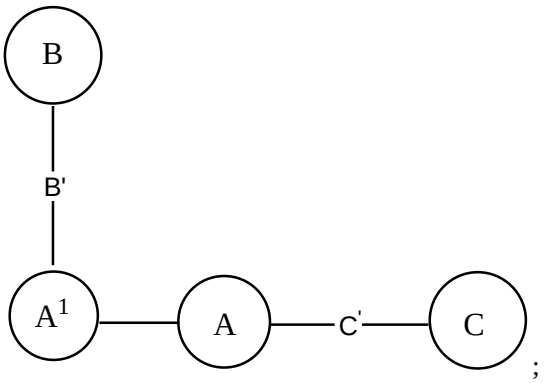
wherein each R, when present, is independent and chosen from H, D, OH, OR_A, F, CHF_2, CF_3, halogen, F, Cl, CH_3, alkyl, alkyl-halogen,-O-CD_3, CD_3, cycloalkyl, CN, methoxy, or alkoxy; R_A is CH_3, C_1-C_6 alkyl, -CH_2-CH_2-O-CH_3;

B is  ; wherein X_1 is CH, C-R_1, or N; X_2 is CH, C-R_1, or N; X_3 is CH, C-R_1, or N; X_4 is CH, C-R_1, or N; X_5 is CH, C-R_1, or N;

each R_1, when present, is independent and chosen from H, D, OH, NH_2, N(alkyl)(alkyl), CHF_2, CF_3, halogen, F, Cl, CH_3, alkyl, cycloalkyl, alkyl-halogen, CD_3, aryl, heterocycle, CN, methoxy, or alkoxy;

C is  ; wherein X_1 is CH, C-R_2, or N; X_2 is CH, C-R_2, or N; X_3 is CH, C-R_2, or N; X_4 is CH, C-R_2, or N; X_5 is CH, C-R_2, or N; each R_2, when present, is independent and chosen from H, D, OH, NH_2, N(alkyl)(alkyl), CHF_2, CF_3, halogen, F, Cl, CH_3, alkyl, cycloalkyl, alkyl-halogen, CD_3, aryl, heterocycle, CN, methoxy, or alkoxy; or a pharmaceutically acceptable salt thereof.

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



;

wherein A is chosen from oxadiazole, imidazole, or triazole; A^1 is substituted or unsubstituted pyridine; B is chosen from substituted or unsubstituted pyridine, substituted or unsubstituted pyrazole, substituted or unsubstituted phenyl, tetrahydropyran, tetrahydrofuran, oxytetrahydrofuran; B' is a bond, -O-, or substituted or unsubstituted C_1-C_6 alkyl;
C is chosen from substituted or unsubstituted pyridine, substituted or unsubstituted thiazole, substituted or unsubstituted phenyl, cyclohexyl, tetrahydropyran, substituted or unsubstituted

[0017] Also disclosed are methods for modulating metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal a therapeutically effective amount of at least one disclosed compound, or a pharmaceutically acceptable salt thereof.

[0018] Also disclosed are methods for modulating metabotropic glutamate receptor activity in at least one cell, comprising the step of contacting said 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 said 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.

[0021] Also disclosed are kits comprising at least one compound of any of the below listed exemplary claims, or 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.

BRIEF DESCRIPTION OF THE FIGURES

[0023] The accompanying figures, which are incorporated in and constitute a part of this specification, illustrate several aspects and together with the description serve to explain the principles of the invention.

[0024] **FIG. 1** shows a schematic representation of an mGlu.

[0025] **FIG. 2** shows a representative illustration of allosteric modulation of mGlu5.

[0026] Additional advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or can be learned by practice of the invention. The advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

DESCRIPTION

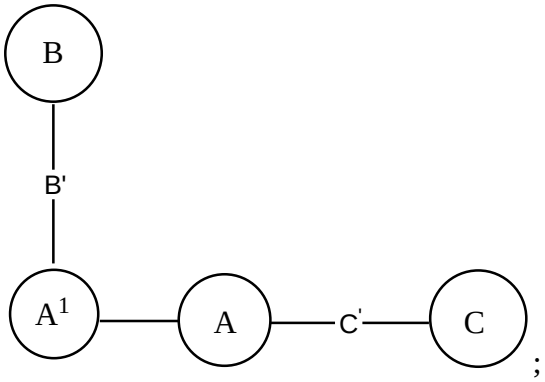
[0027] The present invention can be understood more readily by reference to the following detailed description of the invention and the Examples and Figures included herein.

[0028] Before the present compounds, compositions, articles, systems, devices, and/or methods are disclosed and described, it is to be understood that they are not limited to specific synthetic methods unless otherwise specified, or to particular reagents unless otherwise specified, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular aspects only and is not intended to be limiting. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, example methods and materials are now described.

CLAIMS

What is claimed is:

1. A compound of the following formula:



;

wherein:

A is chosen from oxadiazole, imidazole, or triazole;

A^1 is substituted or unsubstituted pyridine;

B is chosen from substituted or unsubstituted pyridine, substituted or unsubstituted pyrazole, substituted or unsubstituted phenyl, tetrahydropyran, tetrahydrofuran, oxytetrahydrofuran;

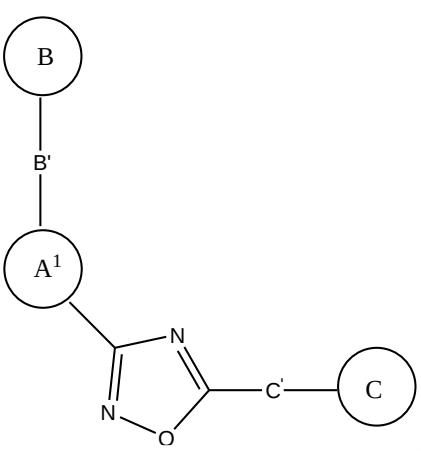
B' is a bond, -O-, or substituted or unsubstituted C_1-C_6 alkyl;

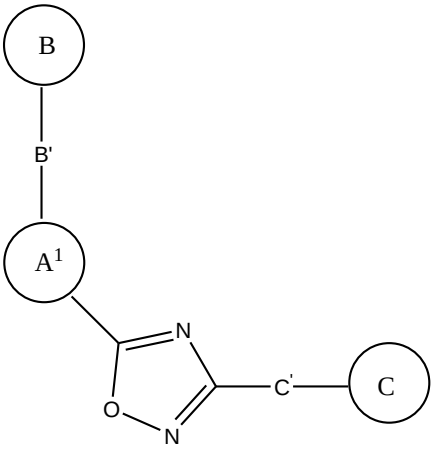
C is chosen from substituted or unsubstituted pyridine, substituted or unsubstituted thiazole, substituted or unsubstituted phenyl, cyclohexyl, tetrahydropyran, substituted or unsubstituted pyrazole, pyridazine, pyrazine,

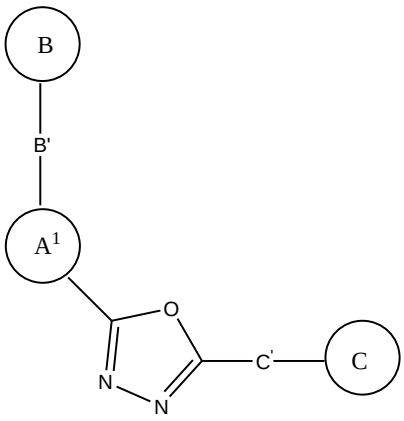
C' is a bond, or substituted or unsubstituted C_1-C_6 alkyl;

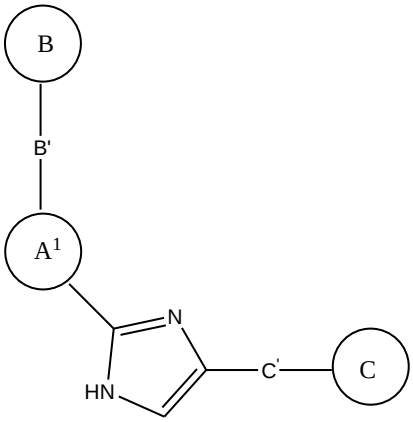
or a pharmaceutically acceptable salt thereof.

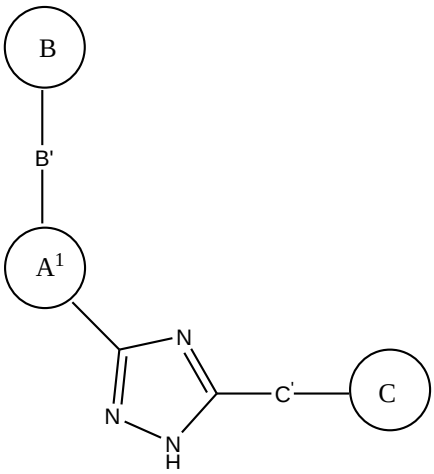
2. A compound of claim 1, of the following formula:



;


;


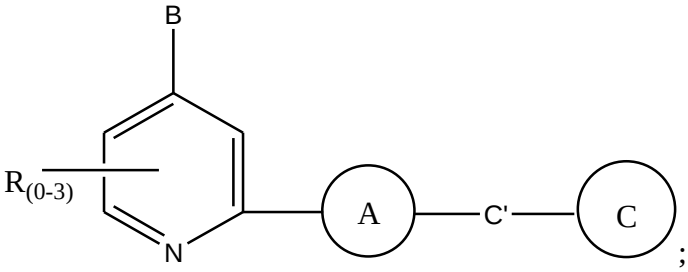
;


; or


;

or a pharmaceutically acceptable salt thereof.

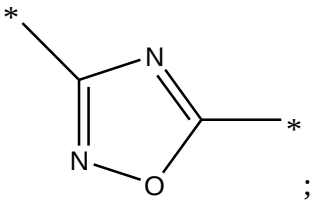
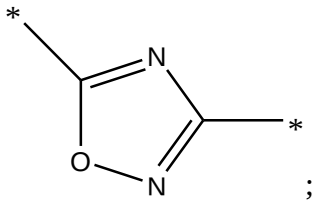
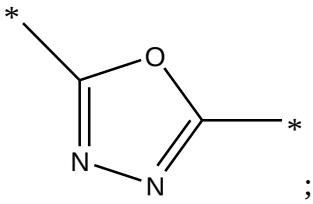
3. The compound of claim 1, of the following formula:

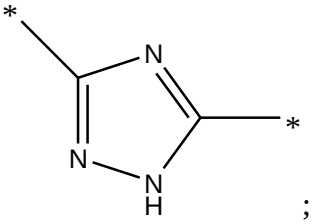
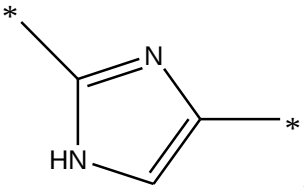


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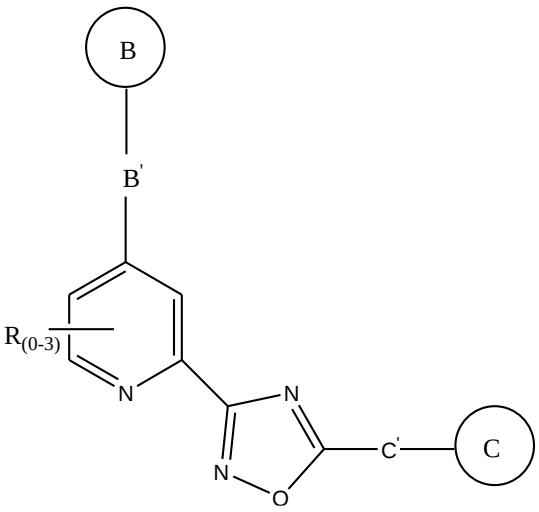
wherein each R, when present, is independent and chosen from H, D, OH, OR_A, F, CHF_2, CF_3, halogen, F, Cl, CH_3, alkyl, alkyl-halogen,-O-CD_3, CD_3, cycloalkyl, CN, methoxy, or alkoxy;

R_A is CH_3, C_1-C_6 alkyl, -CH_2-CH_2-O-CH_3, or wherein A is chosen from 1,2,4-oxadiazole or 1,3,4-oxadiazole, or wherein A is chosen from:

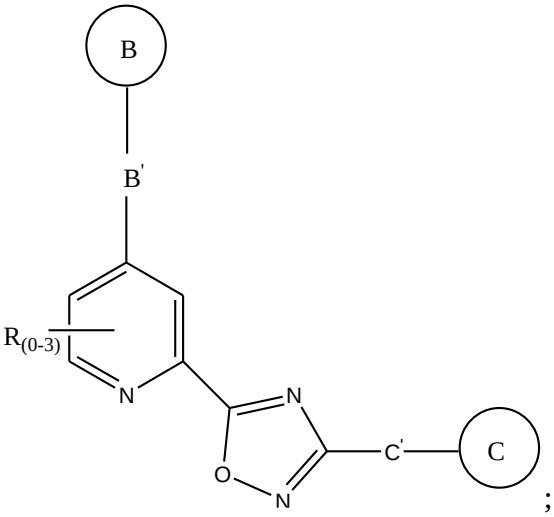
(i)  ; (ii)  ; (iii)  ;

(iv)  ; or (v)  .

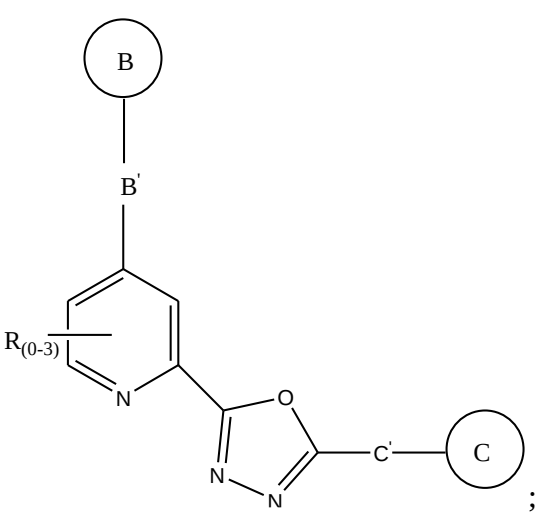
4. The compound of claim 1, of the following formula:



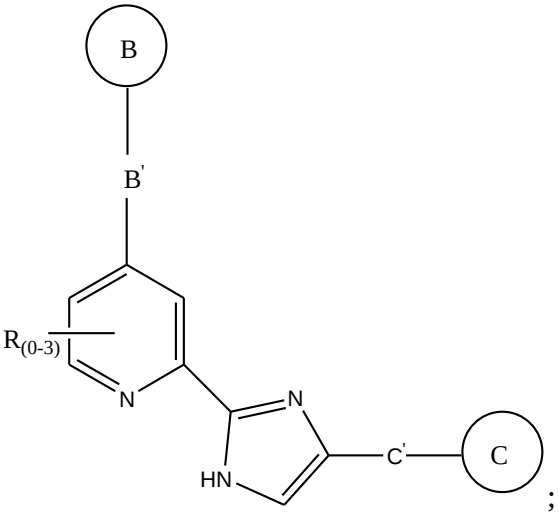
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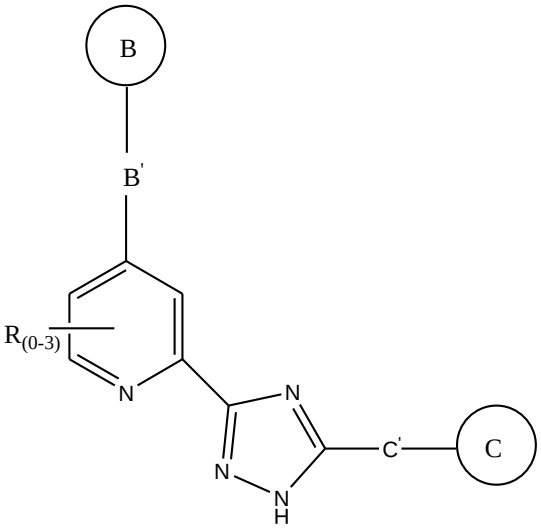
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;



;

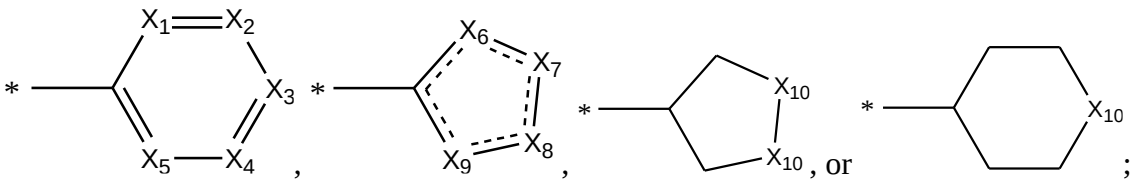


;

wherein each R, when present, is independent and chosen from H, D, OH, OR_A, F, CHF_2, CF_3, halogen, F, Cl, CH_3, alkyl, alkyl-halogen,-O-CD_3, CD_3, cycloalkyl, CN, methoxy, or alkoxy;

R_A is CH_3, C_1-C_6 alkyl, -CH_2-CH_2-O-CH_3; or

wherein:

B is 

, , , or ;

X_1 is CH, C-R_1, or N;

X_2 is CH, C-R_1, or N;

X_3 is CH, C-R_1, or N;

X_4 is CH, C-R_1, or N;

X_5 is CH, C-R_1, or N;

X_6 is CH, CR_1, S, NR_1, or N;

X_7 is CH, CR_1, S, NR_1, or N;

X_8 is CH, CR_1, S, NR_1, or N;

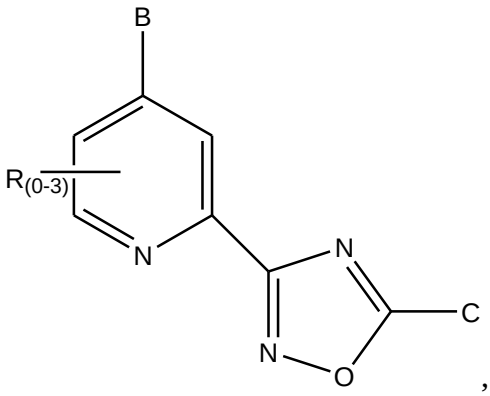
X_9 is CH, CR_1, S, NR_1, or N;

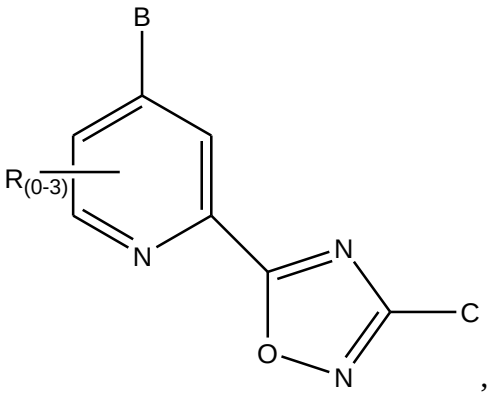
X_{10} is CH_2 or O;

each R_1, when present, is independent and chosen from H, D, OH, NH_2, N(alkyl)(alkyl), CHF_2, CF_3, halogen, F, Cl, CH_3, alkyl, cycloalkyl, alkyl-halogen, CD_3, aryl, heterocycle, CN, methoxy, or alkoxy;

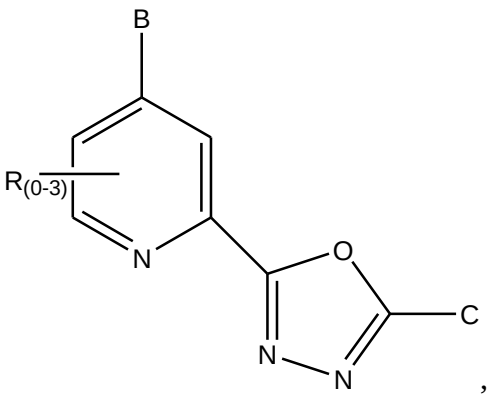
or a pharmaceutically acceptable salt thereof.

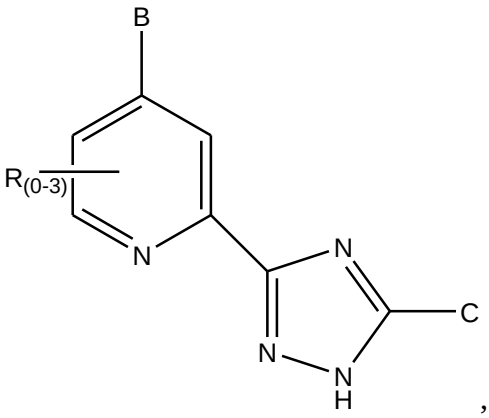
5. The compound of claim 1, of the following formula:

(i) 

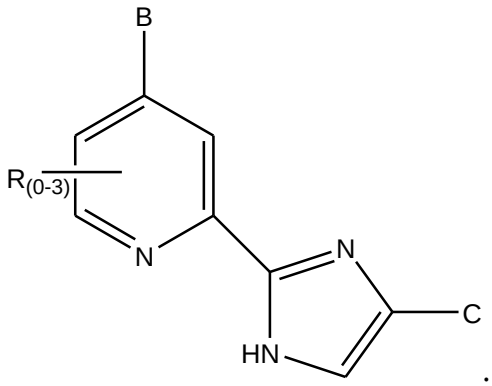
, (ii) 

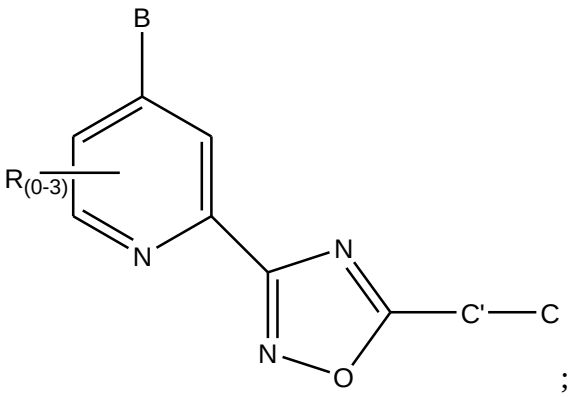
,

(iii) 

, (iv) 

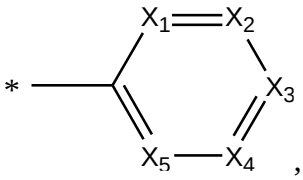
, or

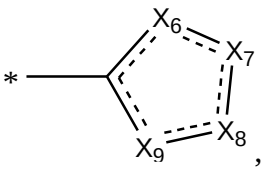
(v) 

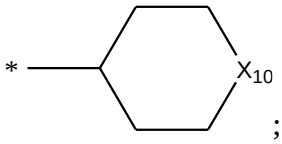
. (vi) 

; or

wherein:

C is 

, 

, or 

;

X_1 is CH, C-R_2, or N;

X_2 is CH, C-R_2, or N;

X_3 is CH, C-R_2, or N;

X_4 is CH, C-R_2, or N;

X_5 is CH, C-R_2, or N;

X_6 is CH, CR_2, S, NR_2, or N;

X_7 is CH, CR_2, S, NR_2, or N;

X_8 is CH, CR_2, S, NR_2, or N;

X_9 is CH, CR_2, S, NR_2, or N;

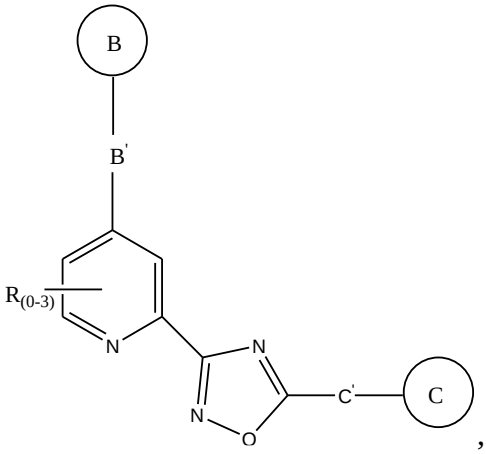
X_{10} is CH_2 or O;

each R_2, when present, is independent and chosen from H, D, OH, NH_2, N(alkyl)(alkyl), CHF_2, CF_3, halogen, F, Cl, CH_3, alkyl, cycloalkyl, alkyl-halogen, CD_3, aryl, heterocycle, CN, methoxy, or alkoxy;

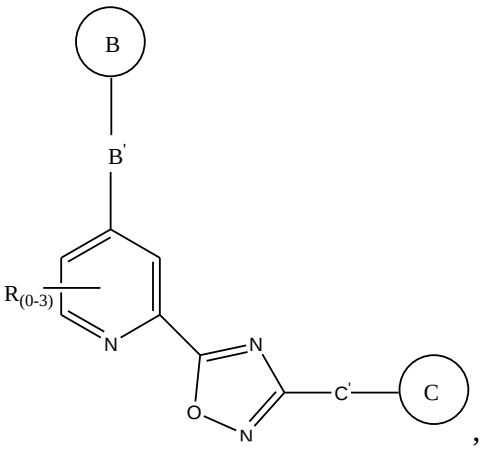
or a pharmaceutically acceptable salt thereof.

6. A compound of claim 1, wherein:

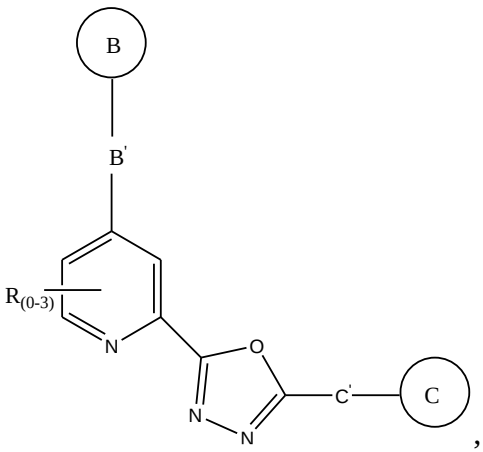
(i) A^1 and A together form:



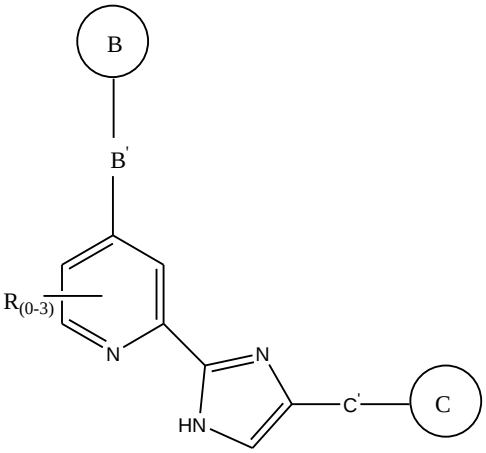
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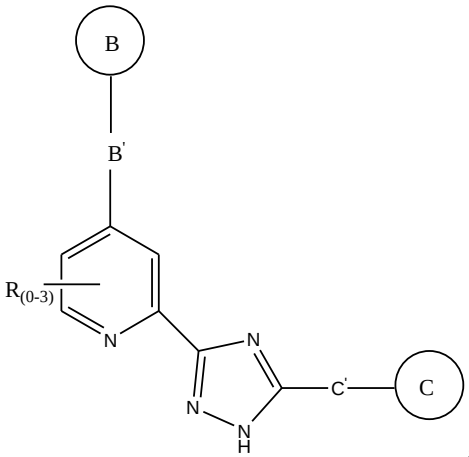
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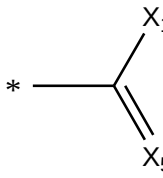
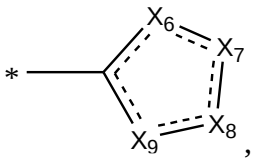
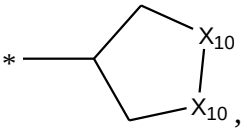
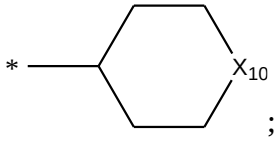
,or



;

wherein each R, when present, is independent and chosen from H, D, OH, OR_A, F, CHF_2, CF_3, halogen, F, Cl, CH_3, alkyl, alkyl-halogen,-O-CD_3, CD_3, cycloalkyl, CN, methoxy, or alkoxy;

R_A is CH_3, C_1-C_6 alkyl, -CH_2-CH_2-O-CH_3;

(ii) B is  ,  ,  , or  ;

X_1 is CH, C-R_1, or N;

X_2 is CH, C-R_1, or N;

X_3 is CH, C-R_1, or N;

X_4 is CH, C-R_1, or N;

X_5 is CH, C-R_1, or N;

X_6 is CH, CR_1, S, NR_1, or N;

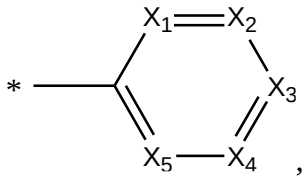
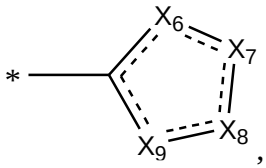
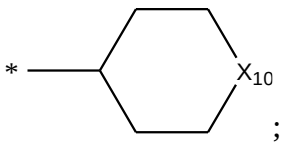
X_7 is CH, CR_1, S, NR_1, or N;

X_8 is CH, CR_1, S, NR_1, or N;

X_9 is CH, CR_1, S, NR_1, or N;

X_{10} is CH_2 or O;

each R_1, when present, is independent and chosen from H, D, OH, NH_2, N(alkyl)(alkyl), CHF_2, CF_3, halogen, F, Cl, CH_3, alkyl, cycloalkyl, alkyl-halogen, CD_3, aryl, heterocycle, CN, methoxy, or alkoxy; and

(iii) C is  ,  , or  ;

X_1 is CH, C-R_2, or N;

X_2 is CH, C-R_2, or N;

X_3 is CH, C-R_2, or N;

X_4 is CH, C-R_2, or N;

X_5 is CH, C-R_2, or N;

X_6 is CH, CR_2, S, NR_2, or N;

X_7 is CH, CR_2, S, NR_2, or N;

X_8 is CH, CR_2, S, NR_2, or N;

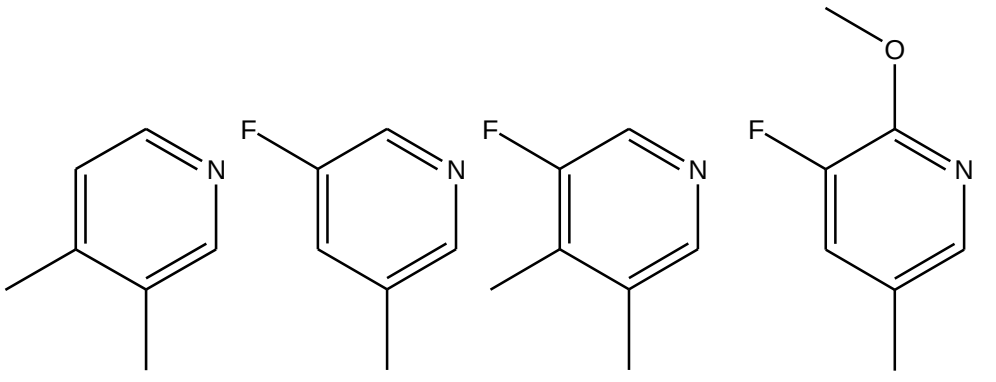
X_9 is CH, CR_2, S, NR_2, or N;

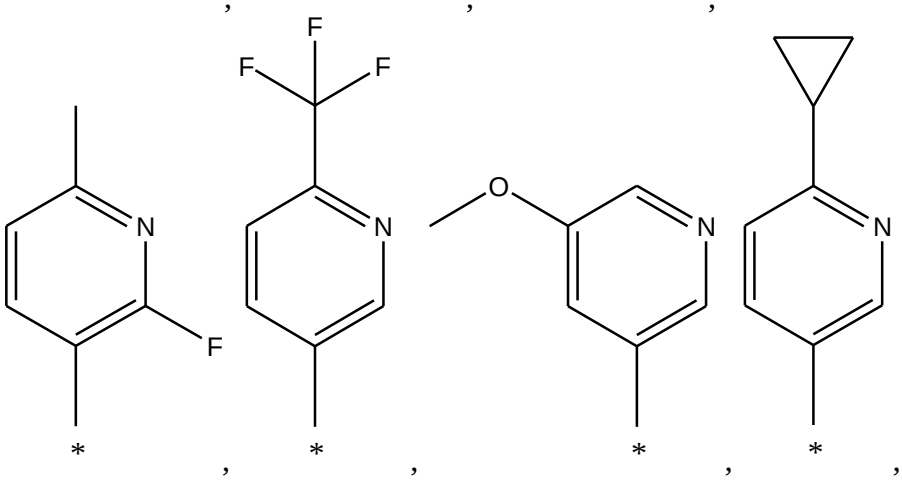
X_{10} is CH_2 or O;

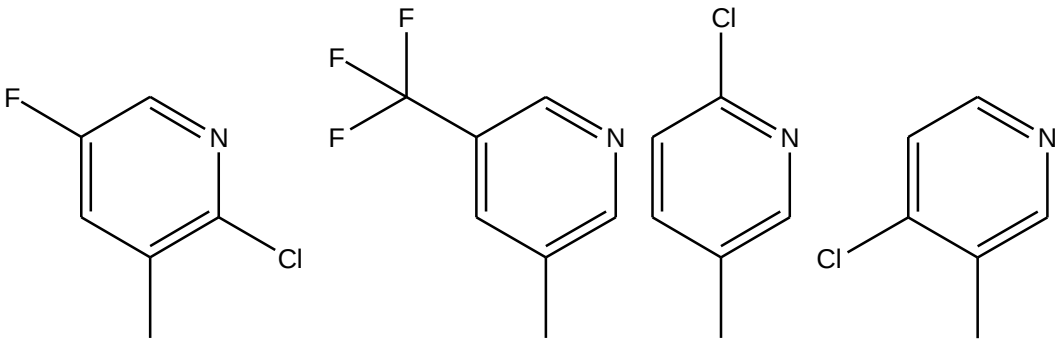
each R_2, when present, is independent and chosen from H, D, OH, NH_2, N(alkyl)(alkyl), CHF_2, CF_3, halogen, F, Cl, CH_3, alkyl, cycloalkyl, alkyl-halogen, CD_3, aryl, heterocycle, CN, methoxy, or alkoxy;

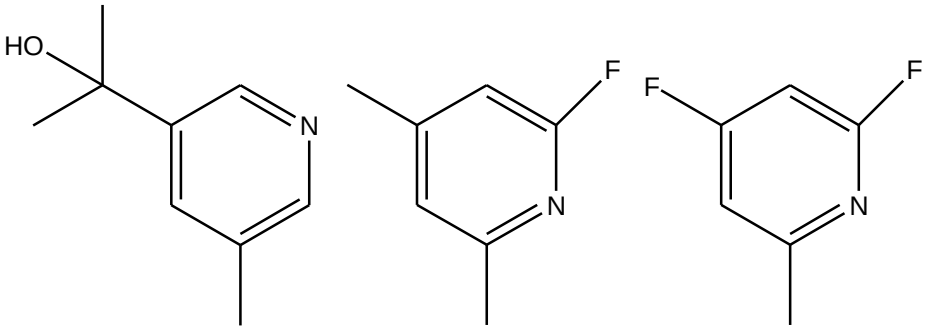
or a pharmaceutically acceptable salt thereof.

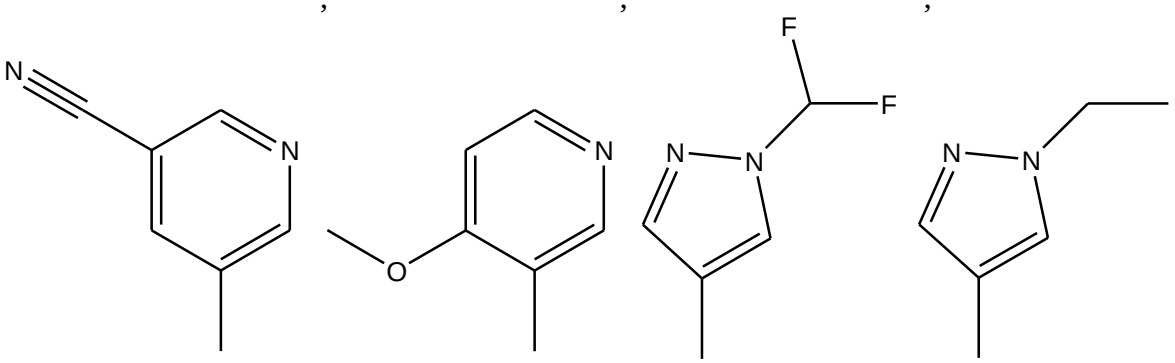
7. The compound of claim 1 or claim 6, wherein B chosen from:

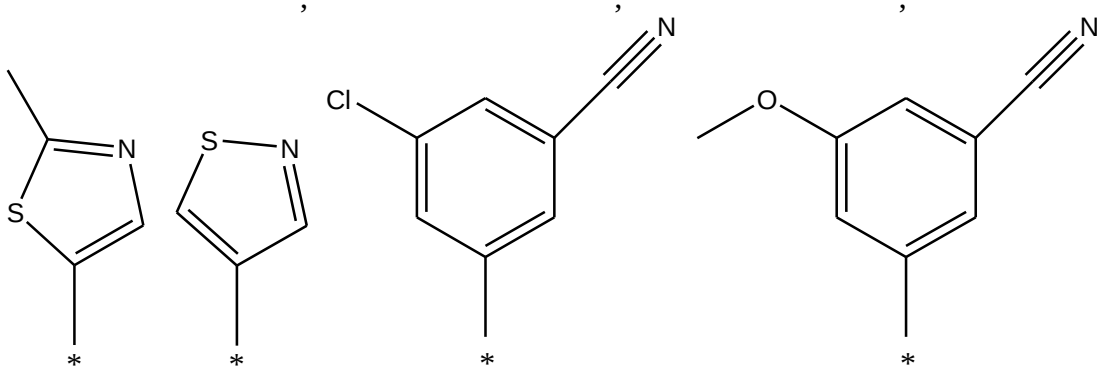


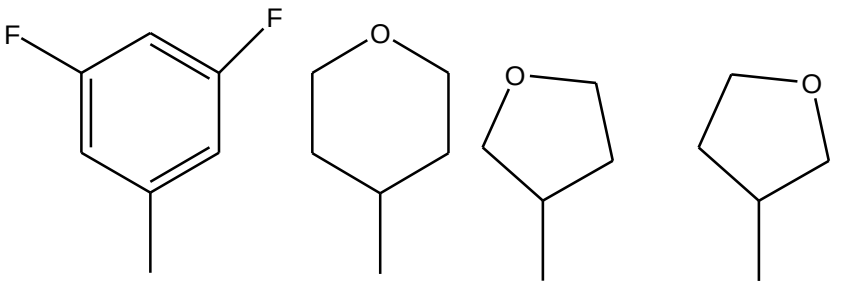






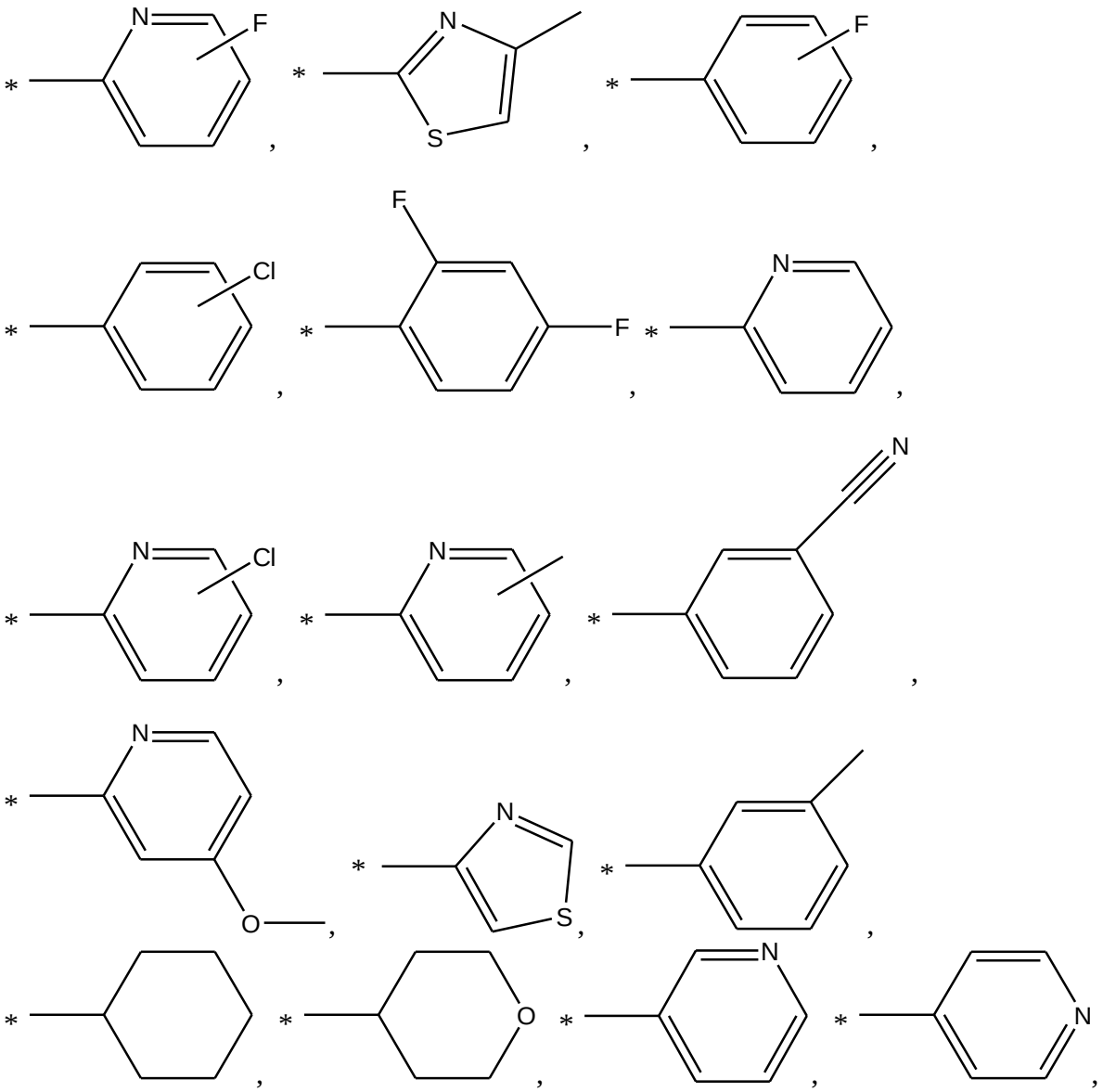


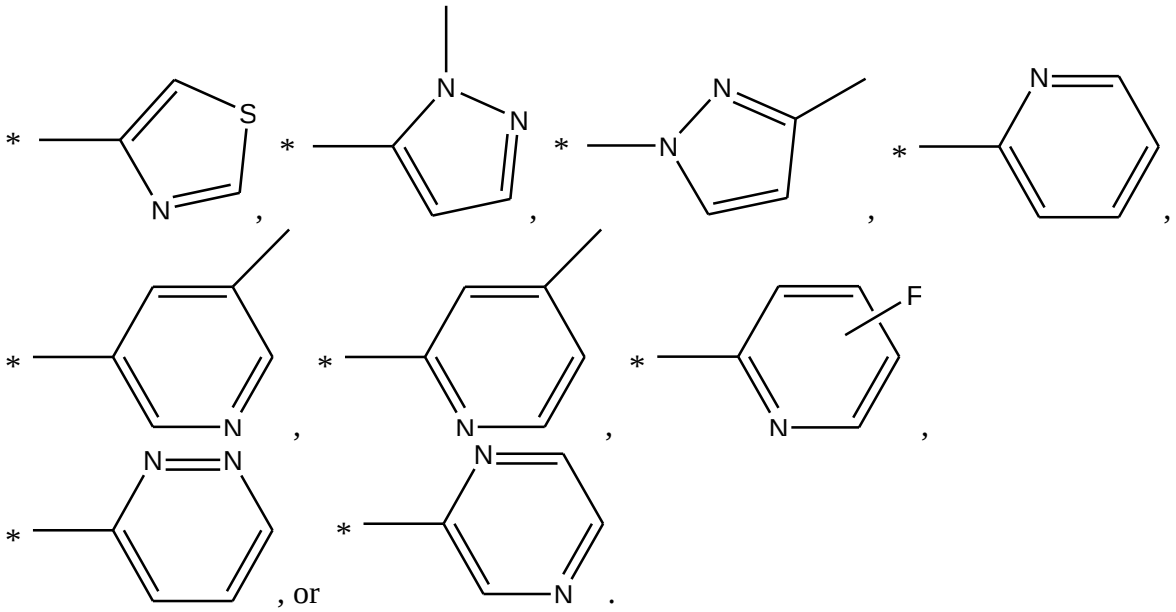




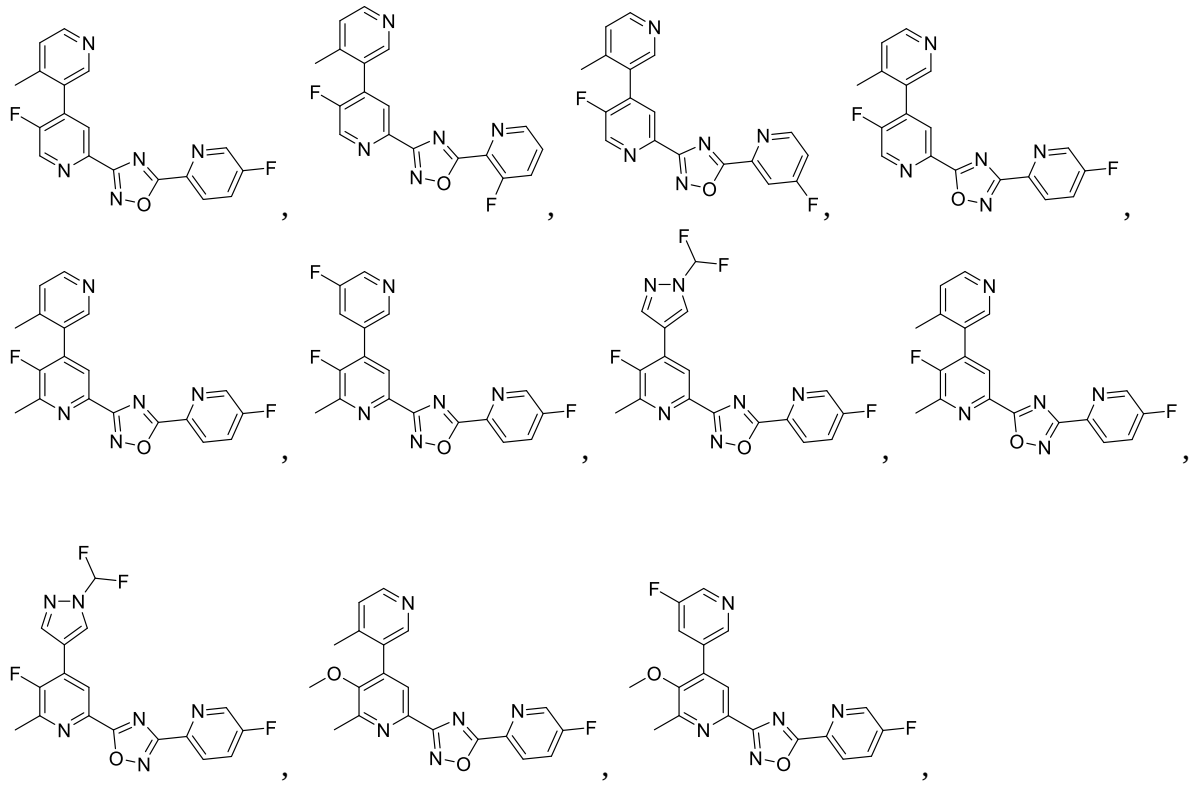
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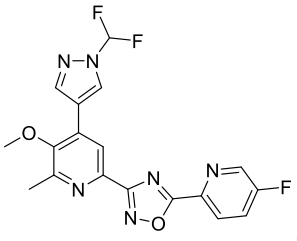
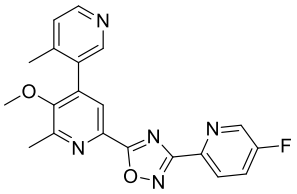
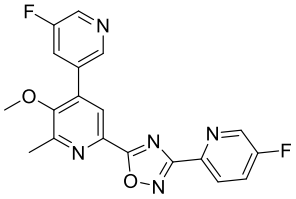
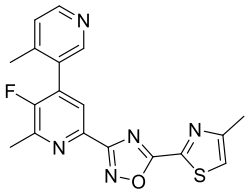
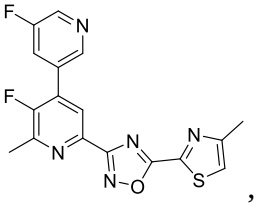
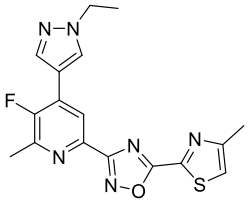
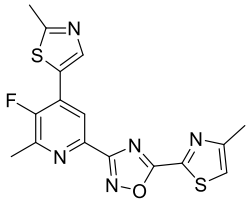
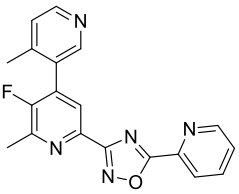
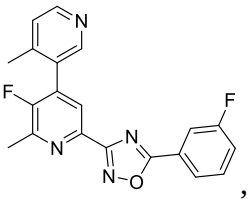
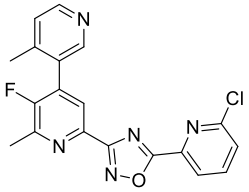
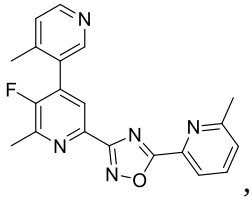
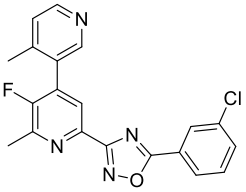
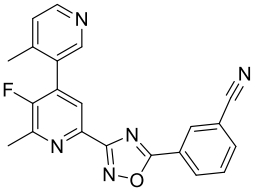
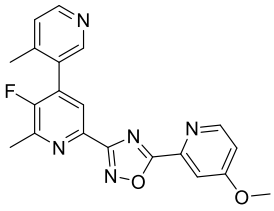
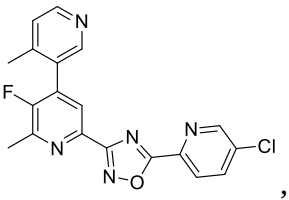
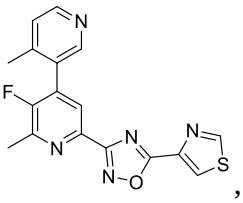
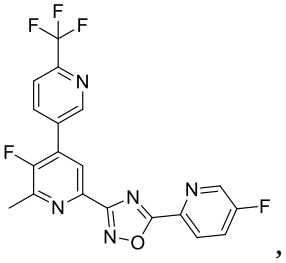
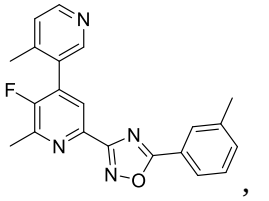
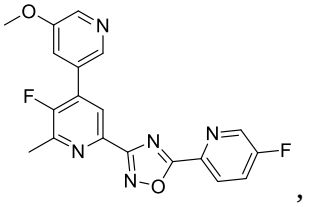
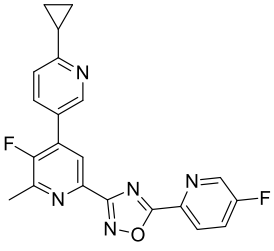
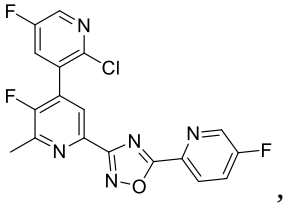
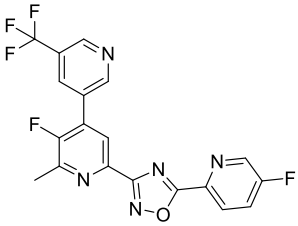
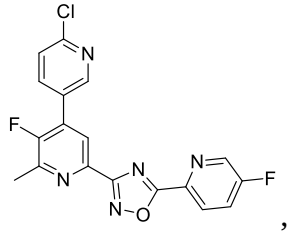
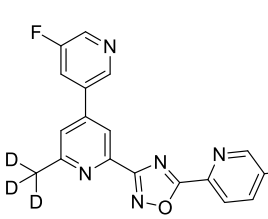
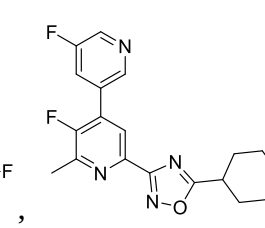
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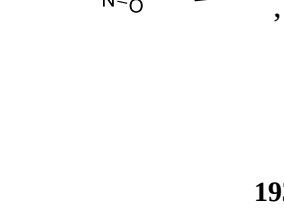


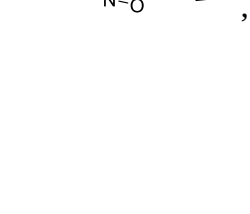


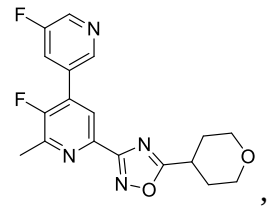
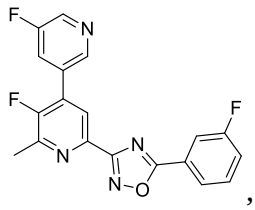
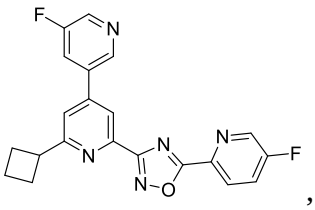
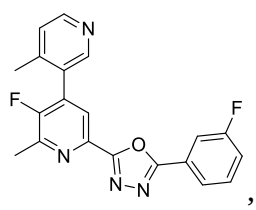
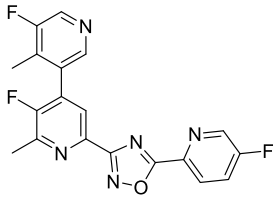
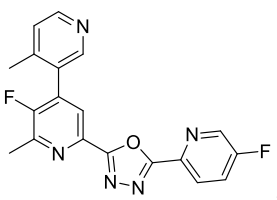
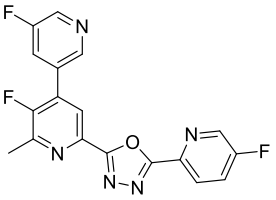
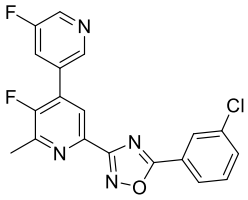
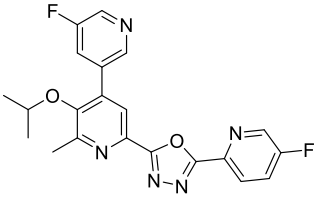
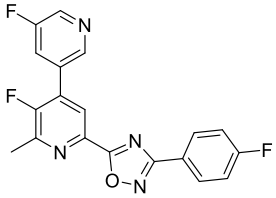
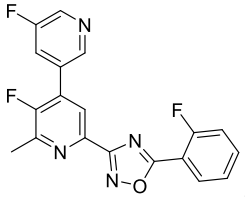
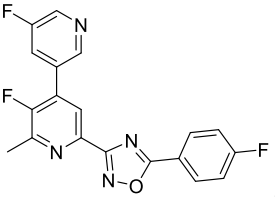
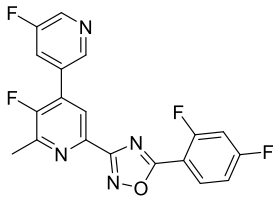
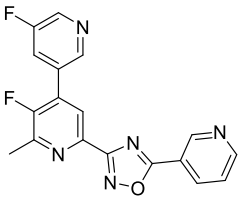
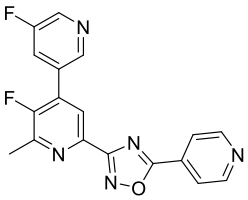
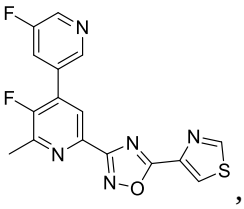
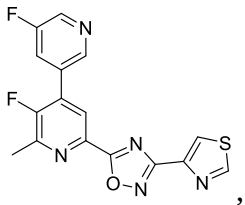
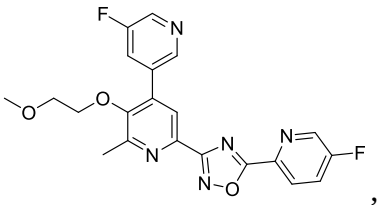
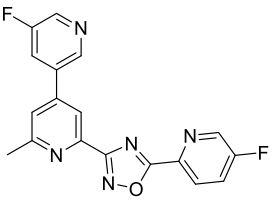
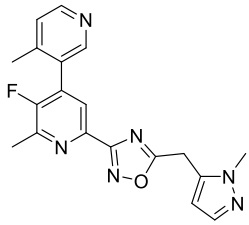
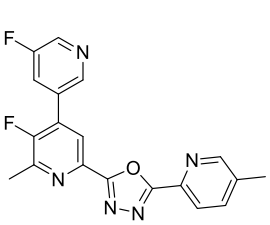
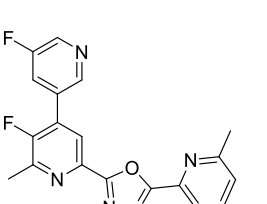
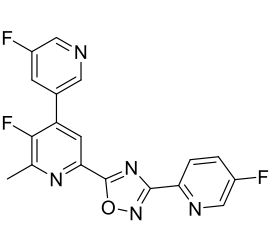
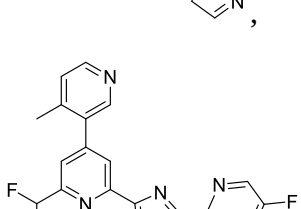
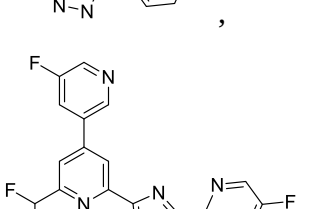
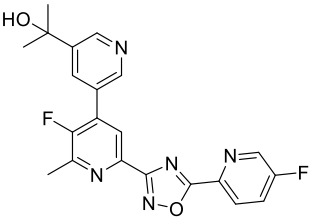
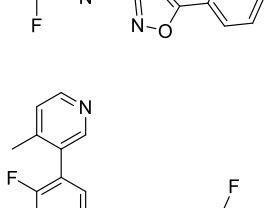
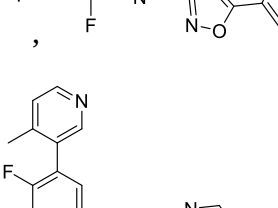
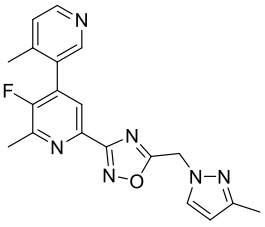
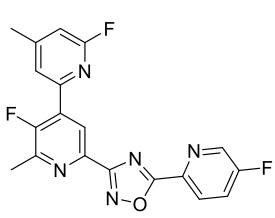
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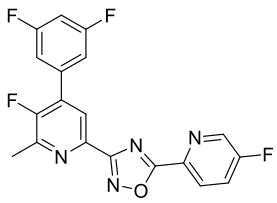
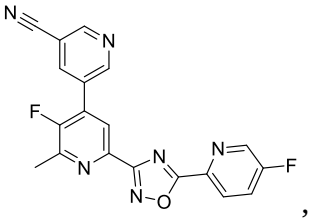
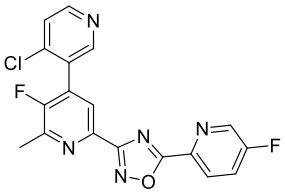
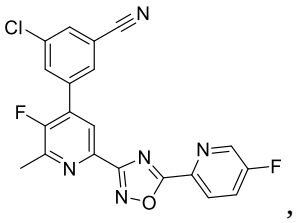
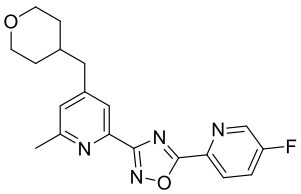
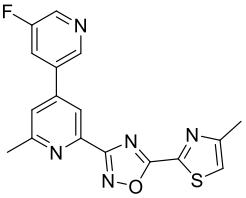
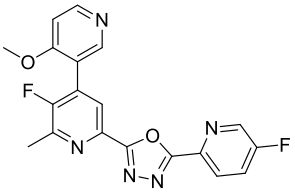
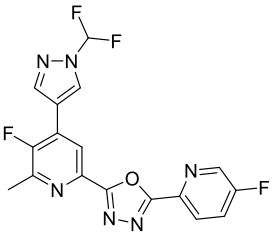
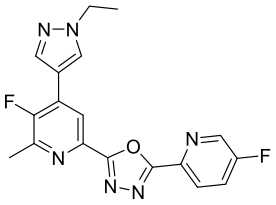
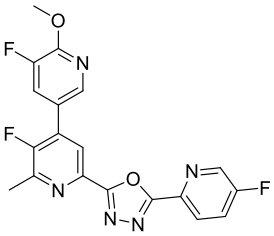
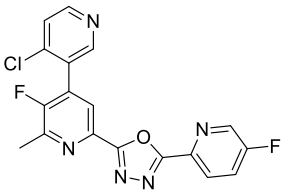
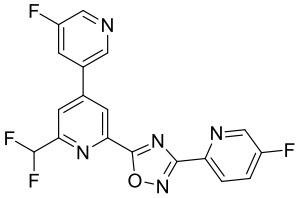
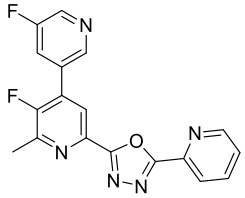
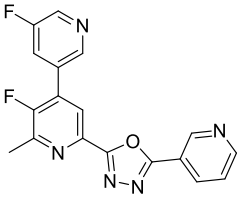
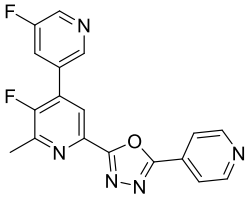
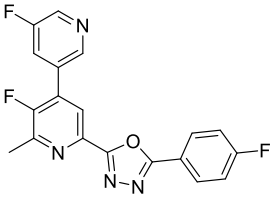
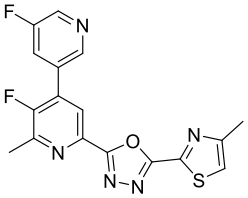
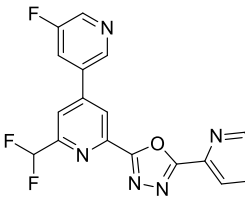
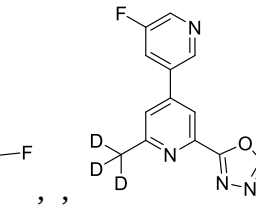
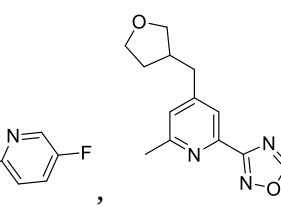
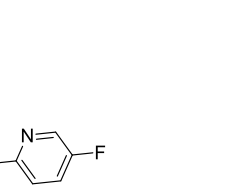
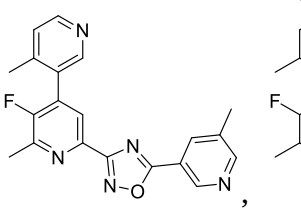
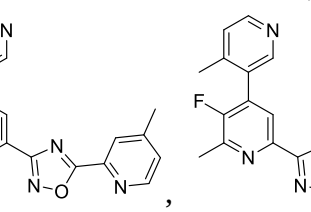
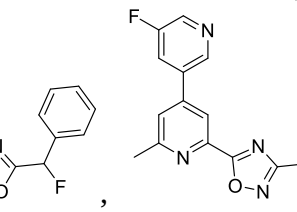
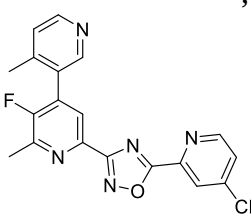
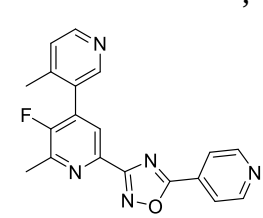
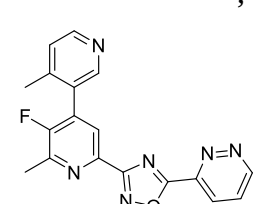
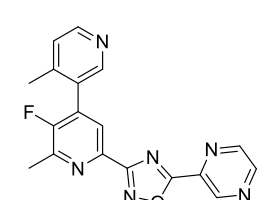



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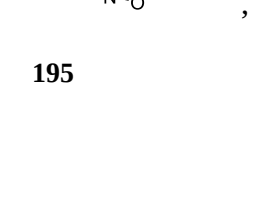
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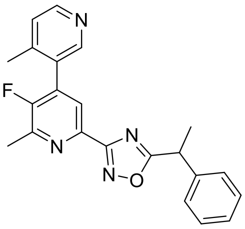

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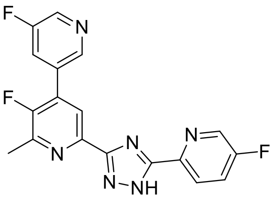

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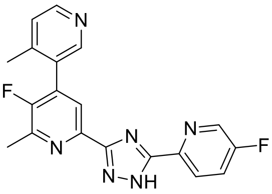
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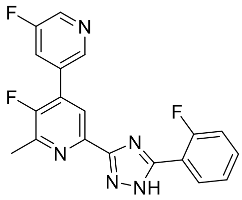
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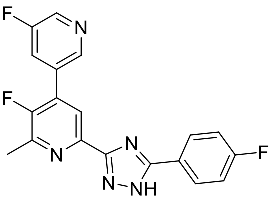


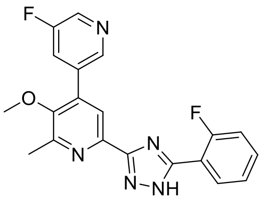
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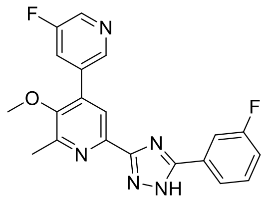
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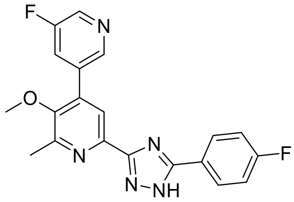
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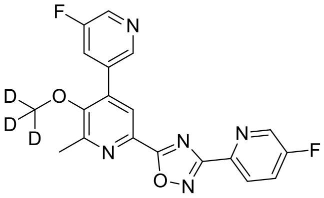


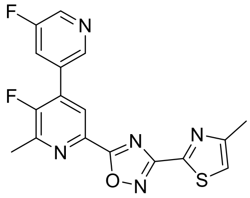
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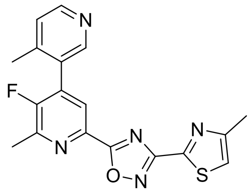
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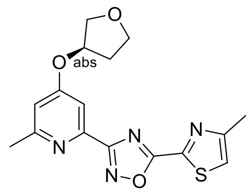
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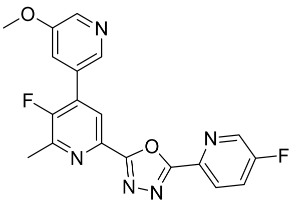


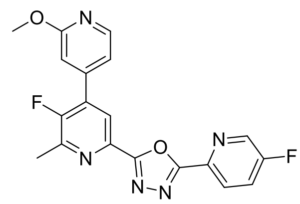
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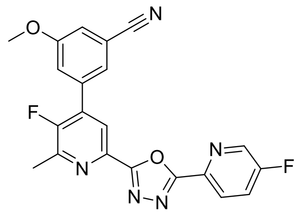
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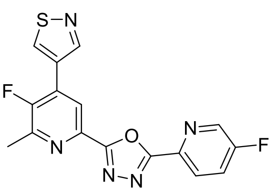
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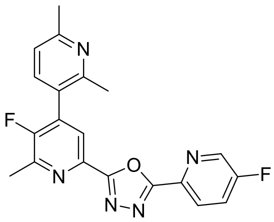


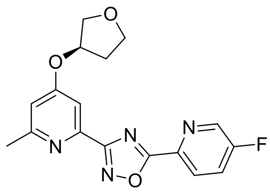
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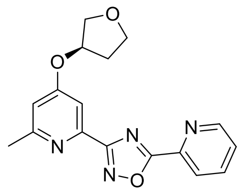
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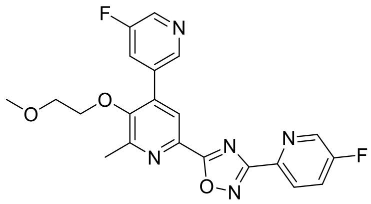


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, and



, or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition comprising a compound of one of claims 1, 6 or 8, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

10. Use of compound according to claims 1-8, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disorder associated with metabotropic glutamate receptor activity in a subject.

11. The use of claim 10, wherein the metabotropic glutamate receptor is mGlu5.

12. The use of claim 10, wherein the subject is a human, or wherein the subject has been diagnosed with a need for treatment of the disorder prior to administering.

13. The use of claim 10, further comprising a subject in need of treatment of the disorder to be identified.

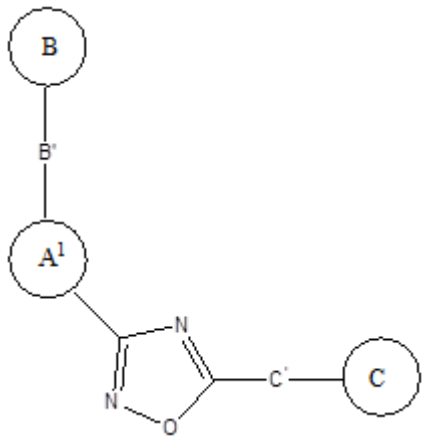
14. The use of claim 10, wherein the disorder is a neurological and/or psychiatric disorder.

15. The use of claim 14, 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 harmartoma syndrome, senile dementia, sleep disorder, substance-related disorder, post-traumatic stress disorder (PTSD) or unipolar depression, or wherein the neurological and/or psychiatric disorder is an autism spectrum disorder.

16. The use of claim 15, 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.

17. A compound of one of claims 1-7 for use in the treatment of a disorder associated with metabotropic glutamate receptor, such as mGlu5, activity in a subject.

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



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wherein:

A^1 is substituted or unsubstituted pyridine;

B is chosen from substituted or unsubstituted pyridine, substituted or unsubstituted pyrazole, substituted or unsubstituted phenyl, tetrahydropyran, tetrahydrofuran, oxytetrahydrofuran;

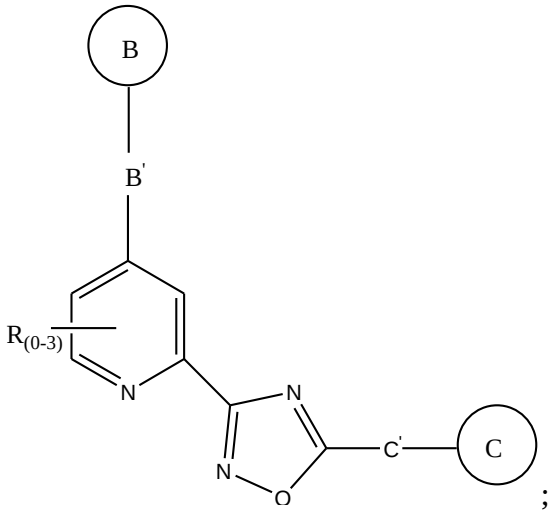
B' is a bond, -O-, or substituted or unsubstituted C_1-C_6 alkyl;

C is chosen from substituted or unsubstituted pyridine, substituted or unsubstituted thiazole, substituted or unsubstituted phenyl, cyclohexyl, tetrahydropyran, substituted or unsubstituted pyrazole, pyridazine, pyrazine,

C' is a bond, or substituted or unsubstituted C_1-C_6 alkyl;

or a pharmaceutically acceptable salt thereof.

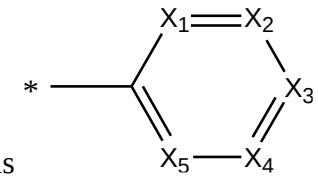
19. A compound of the following formula:



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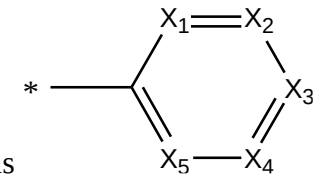
wherein B' is a bond, -O-, or substituted or unsubstituted C_1-C_6 alkyl; C' is a bond, or substituted or unsubstituted C_1-C_6 alkyl;

wherein each R, when present, is independent and chosen from H, D, OH, OR_A, F, CHF_2, CF_3, halogen, F, Cl, CH_3, alkyl, alkyl-halogen,-O-CD_3, CD_3, cycloalkyl, CN, methoxy, or alkoxy; R_A is CH_3, C_1-C_6 alkyl, -CH_2-CH_2-O-CH_3;

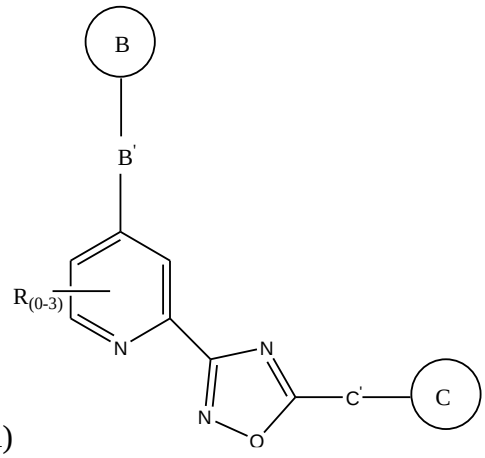
B is 

; wherein X_1 is CH, C-R_1, or N; X_2 is CH, C-R_1, or N; X_3 is CH, C-R_1, or N; X_4 is CH, C-R_1, or N; X_5 is CH, C-R_1, or N;

each R_1, when present, is independent and chosen from H, D, OH, NH_2, N(alkyl)(alkyl), CHF_2, CF_3, halogen, F, Cl, CH_3, alkyl, cycloalkyl, alkyl-halogen, CD_3, aryl, heterocycle, CN, methoxy, or alkoxy;

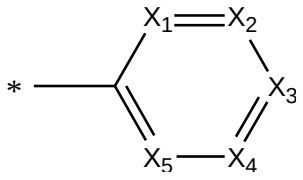
C is  ; wherein X_1 is CH, C-R_2, or N; X_2 is CH, C-R_2, or N; X_3 is CH, C-R_2, or N; X_4 is CH, C-R_2, or N; X_5 is CH, C-R_2, or N; each R_2, when present, is independent and chosen from H, D, OH, NH_2, N(alkyl)(alkyl), CHF_2, CF_3, halogen, F, Cl, CH_3, alkyl, cycloalkyl, alkyl-halogen, CD_3, aryl, heterocycle, CN, methoxy, or alkoxy; or a pharmaceutically acceptable salt thereof.

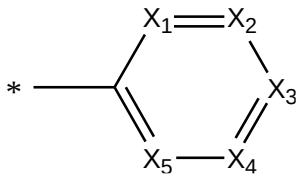
20. The compound of claim 19, of the following formula:

(i) 

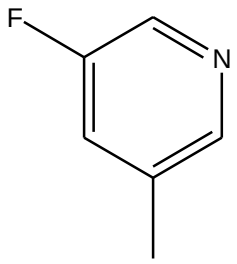
B' is a bond, -O-, or substituted or unsubstituted C_1-C_6 alkyl;

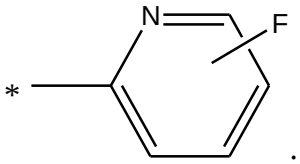
C' is a bond, or substituted or unsubstituted C_1-C_6 alkyl;

(ii) B is  ; X_1 is N; X_2 is CH, C-R_1, or N; X_3 is CH, C-R_1, or N; X_4 is CH, C-R_1, or N; X_5 is CH, C-R_1, or N; each R_1, when present, is independent and chosen from H, D, OH, NH_2, N(alkyl)(alkyl), CHF_2, CF_3, halogen, F, Cl, CH_3, alkyl, cycloalkyl, alkyl-halogen, CD_3, aryl, heterocycle, CN, methoxy, or alkoxy; and

(iii) C is 

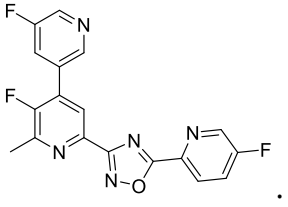
; X_1 is N; X_2 is CH, C-R_2, or N; X_3 is CH, C-R_2, or N; X_4 is CH, C-R_2, or N; X_5 is CH, C-R_2, or N; each R_2, when present, is independent and chosen from H, D, OH, NH_2, N(alkyl)(alkyl), CHF_2, CF_3, halogen, F, Cl, CH_3, alkyl, cycloalkyl, alkyl-halogen, CD_3, aryl, heterocycle, CN, methoxy, or alkoxy; or a pharmaceutically acceptable salt thereof.

21. The compound of claim 19, wherein B is 

or wherein C is 

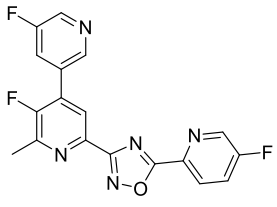
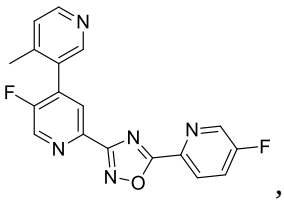
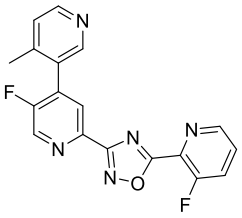
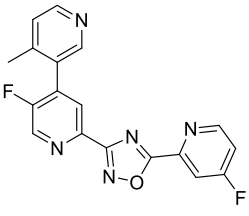
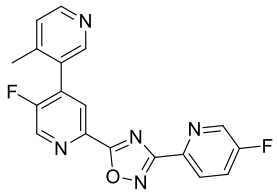
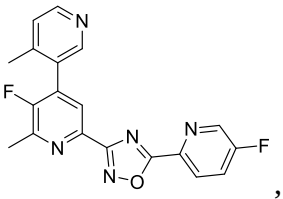
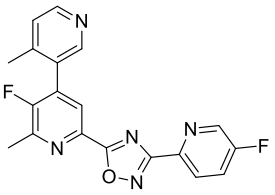
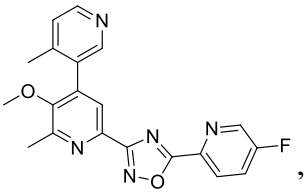
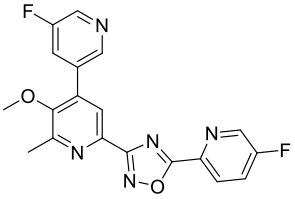
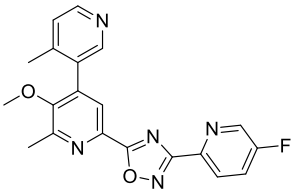
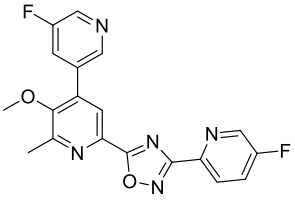
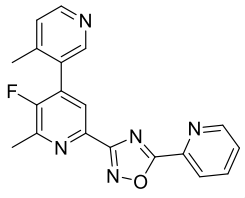
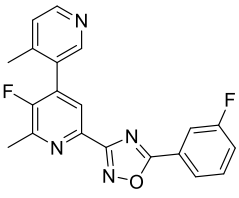
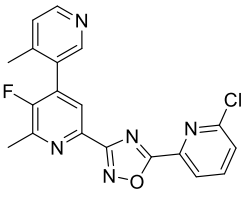
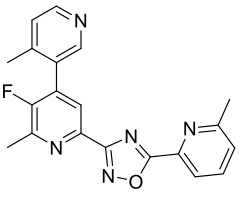
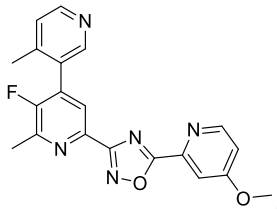
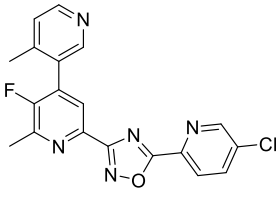
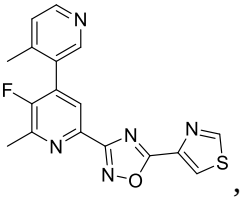
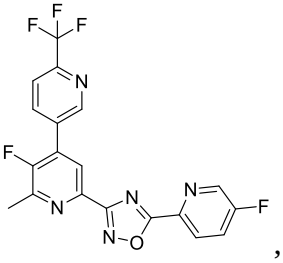
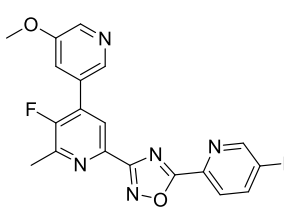
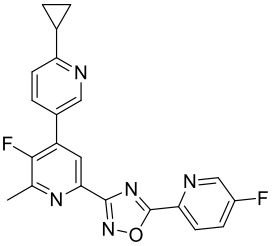
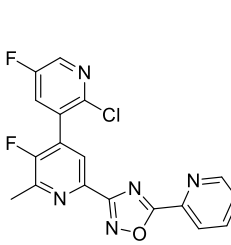
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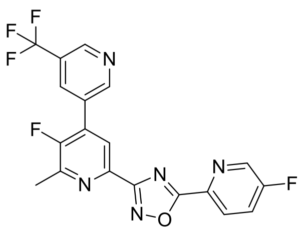
22. The compound of claim 19, wherein the compound is:

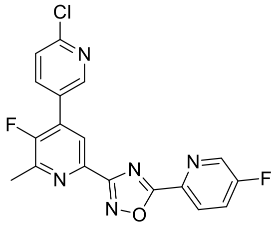
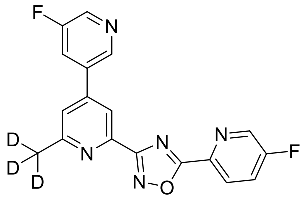
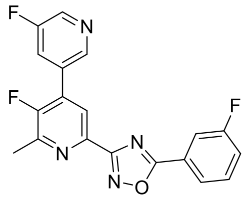
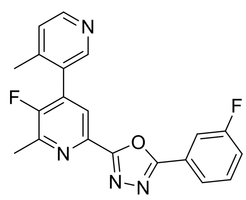


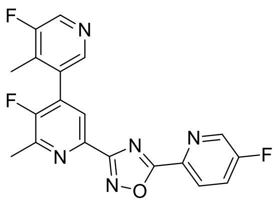
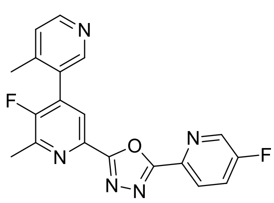
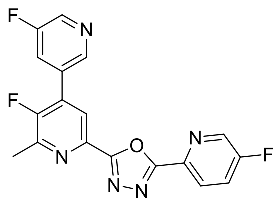
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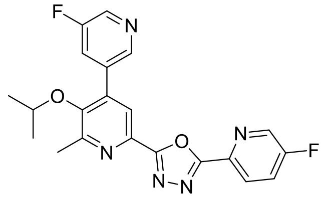
or wherein the compound is chosen from:

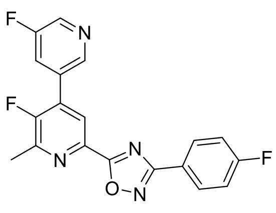
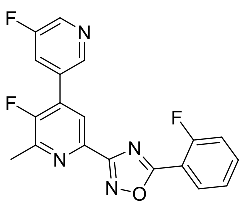
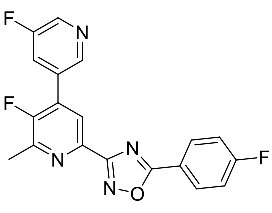
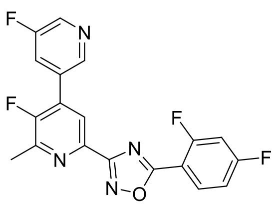
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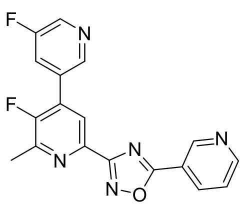
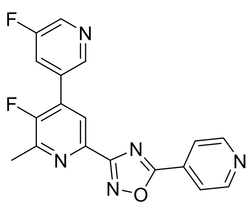
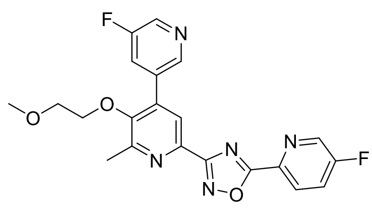
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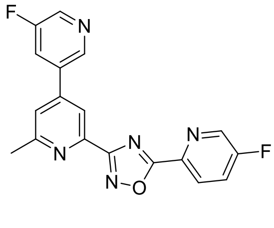
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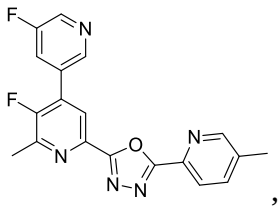
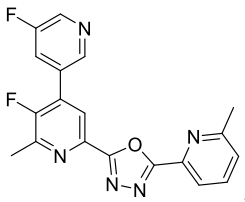
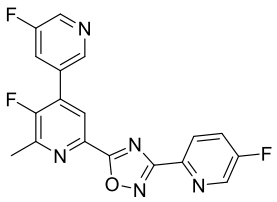
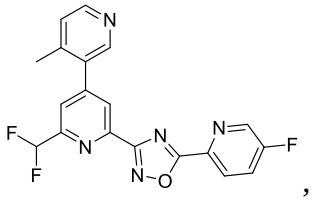
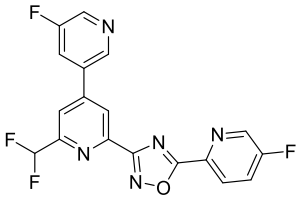
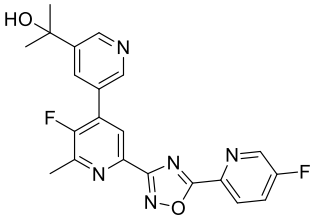
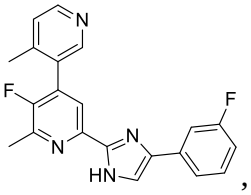
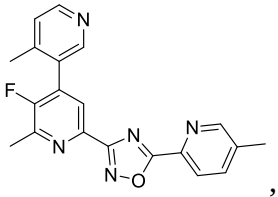
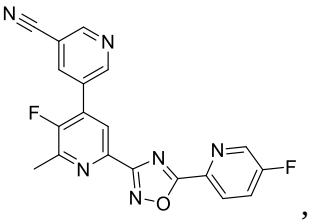
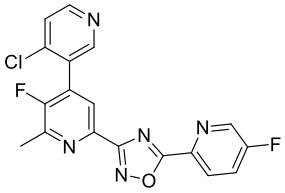
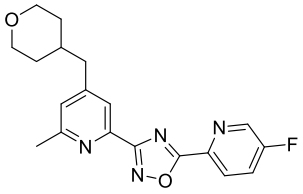
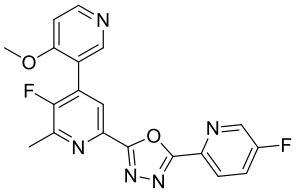
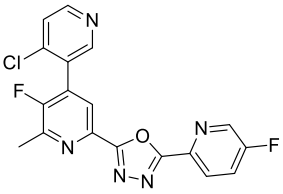
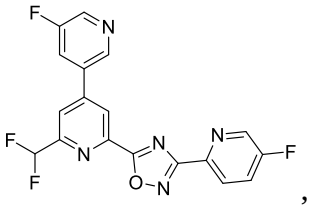
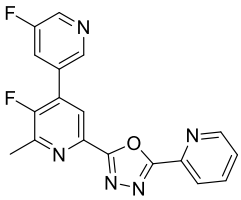
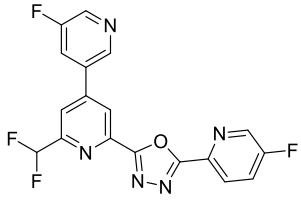
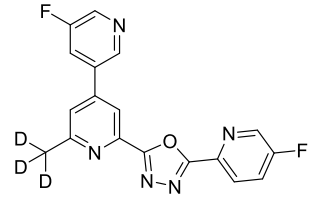
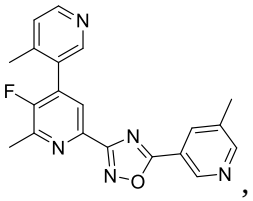
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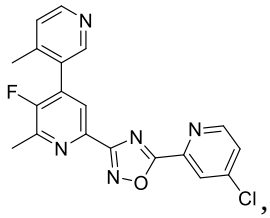
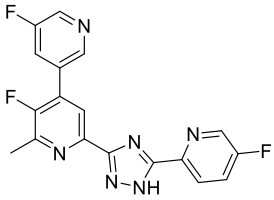
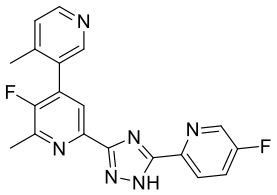
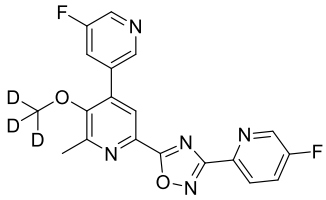
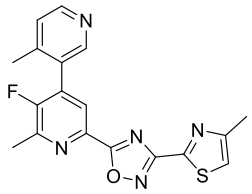
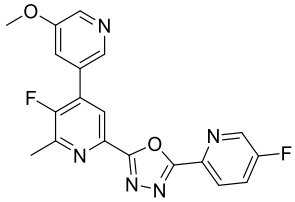
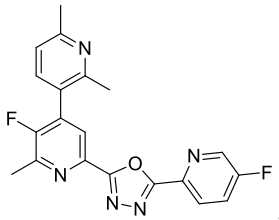
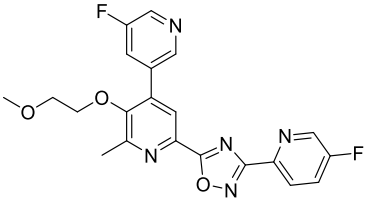
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