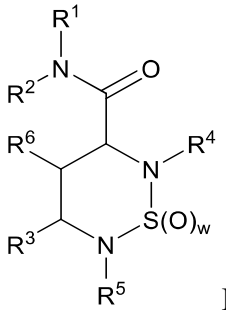
of interferon α can result in poor tolerability, and many patients are unable to complete therapy. Moreover, only a small percentage of patients are considered appropriate for interferon therapy, as only a small subset of patients are likely to have a sustained clinical response to a course of interferon therapy. As a result, interferon-based therapies are used in only a small percentage of all diagnosed patients who elect treatment.

Thus, current HBV treatments can range from palliative to watchful waiting. Nucleotide analogs suppress virus production, treating the symptom, but leave the infection intact. Interferon α has severe side effects and less tolerability among patients and is successful as a finite treatment strategy in only a small minority of patients. There is a clear on-going need for more effective treatments for HBV infections.

SUMMARY

The present disclosure provides, in part, cyclic sulfamide compounds and pharmaceutical compositions thereof, useful for modulation of HBV core protein, and methods of treating HBV infections.

In one aspect, the present disclosure provides a compound of Formula I:



Formula I

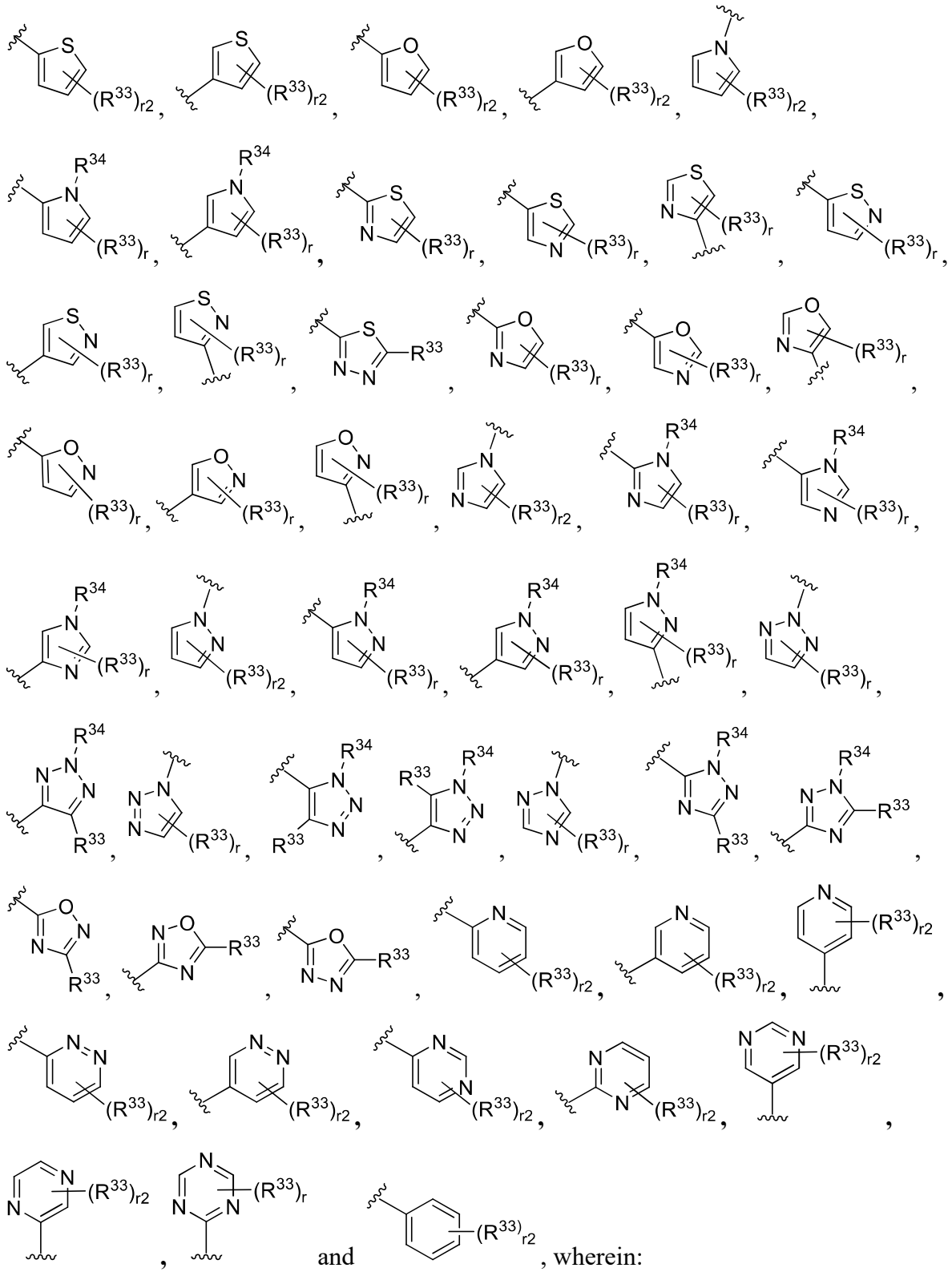
or a pharmaceutically acceptable salt thereof, wherein:

w is 2;

R^1 is of phenyl or pyridyl, each or which is optionally substituted with one, two, or three substituents independently selected from the group consisting of halo, -OH, -CN, -NO_2, oxo, hydrazino, formyl, azido, silyl, siloxy, -$S(O)_q$-C_{1-6}alkyl, -NR^aR^b, -NR^c-$S(O)_t$-C_{1-6}alkyl, -$S(O)_t$-NR^aR^b, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, R^aR^bN-C_{1-6}alkyl-, C_{1-6}alkoxy, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkoxy-, R^aR^bN-C_{1-6}alkoxy-, C_{1-6}alkoxyC_{1-6}alkyl, -C(O)NR^aR^b, -C(O)-C_{1-6}alkyl, -C(O)OH, and -C(O)O-C_{1-6}alkyl;

R^2 is hydrogen;

R^3 is selected from the group consisting of:



, wherein:

R^4 is hydrogen or C_{1-6}alkyl optionally substituted with one, two, or three substituents independently selected from the group consisting of: halogen, -OH, -CN, -$S(O)_q$-C_{1-6}alkyl, -NR^aR^b, -NR^c-$S(O)_t$-C_{1-6}alkyl, -$S(O)_t$-NR^aR^b, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, -C(O)NR^aR^b, -C(O)-C_{1-6}alkyl, formyl, -C(O)OH, -C(O)O-

C_{1-6}alkyl, benzyloxy, C_{1-4}alkoxyphenyl, pyrrolidinyl, morpholinyl, tetrahydrofuranyl and triazolyl;

R^5 is hydrogen or C_{1-6}alkyl optionally substituted with a substituent selected from the group consisting of halogen, -OH, C_{1-6}alkoxy, $-NR^aR^b$, and R^aR^bN-C_{1-4}alkyl;

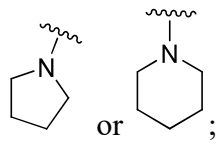
R^6 is hydrogen or C_{1-6}alkyl;

R^{33} is independently selected for each occurrence from the group consisting of: halo, -OH, -CN, $-NO_2$, oxo, hydrazino, formyl, azido, silyl, siloxy, $-S(O)_q$-C_{1-6}alkyl, $-NR^aR^b$, $-NR^c$-$S(O)_t$-C_{1-6}alkyl, $-S(O)_t$-NR^aR^b, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, R^aR^bN-C_{1-6}alkyl-, C_{1-6}alkoxy, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkoxy-, R^aR^bN-C_{1-6}alkoxy-, C_{1-6}alkoxyC_{1-6}alkyl, $-C(O)NR^aR^b$, -C(O)-C_{1-6}alkyl, -C(O)OH, and -C(O)O-C_{1-6}alkyl phenyl, and a 5-6 membered monocyclic heteroaryl having one, two, or three heteroatoms selected from the group consisting of O, N, and S, wherein the phenyl and 5-6 membered monocyclic heteroaryl is optionally substituted with one, two or three substituents independently selected from the group consisting of: halo, -OH, -CN, $-NO_2$, oxo, hydrazino, formyl, azido, silyl, siloxy, $-S(O)_q$-C_{1-6}alkyl, $-NR^aR^b$, $-NR^c$-$S(O)_t$-C_{1-6}alkyl, $-S(O)_t$-NR^aR^b, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, R^aR^bN-C_{1-6}alkyl-, C_{1-6}alkoxy, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkoxy-, R^aR^bN-C_{1-6}alkoxy-, C_{1-6}alkoxyC_{1-6}alkyl, $-C(O)NR^aR^b$, -C(O)-C_{1-6}alkyl, -C(O)OH, and -C(O)O-C_{1-6}alkyl;

R^{34} is selected from the group consisting of hydrogen, C_{1-4}alkyl and hydroxyC_{1-4}alkyl;

R^a and R^b are independently hydrogen or C_{1-6}alkyl; or

R^a and R^b may be taken together with the nitrogen to which R^a and R^b are attached to form:



or ;

R^c is hydrogen or C_{1-6}alkyl;

for each occurrence, q is 0, 1, or 2,

for each occurrence, t is 1 or 2;

r is 0, 1 or 2;

r2 is 0, 1, 2 or 3;

with the provisos that:

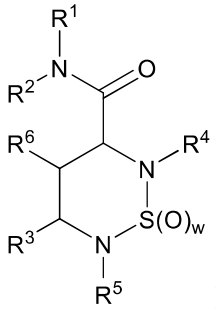
when R^3 is thiophen-2-yl or furan-2-yl, r2 is 1, 2 or 3;

when R^3 is pyrazol-4-yl, in at least one instance, R^{33} is other than C_{1-6}alkyl; and

when R^3 is phenyl, at least one of R^{35}, R^{36} and R^{37} is other than halo and C_{1-6}alkoxy.

In another aspect, the present disclosure provides the compound as described herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition as described herein, for use in therapy. In yet another aspect, the present disclosure provides use of the compound as described herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition as described herein, in the manufacture of a medicament for treating Hepatitis B (HBV) infection in a patient.

In one example, the disclosure provides compounds of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, where the variables are described in the detailed description.

In another example, the disclosure provides pharmaceutical compositions comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In another example, the disclosure provides a method of treating HBV infection in a subject in need thereof comprising: administering to the subject an effective amount of compound of Formula I, or a pharmaceutically acceptable salt thereof.

In another example, the disclosure provides a method of treating HBV infection in a subject in need thereof comprising: administering to the subject a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

BRIEF DESCRIPTION OF DRAWINGS

FIGURE 1 is the crystal structure of HBV-CSU-016-ISO-I as described herein.

DETAILED DESCRIPTION

The features and other details of the disclosure will now be more particularly described. Before further description of the present disclosure, certain terms employed in the specification, examples and appended claims are collected here. These definitions should be read in light of the remainder of the disclosure and as understood by a person of skill in the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art.

Definitions

"Treating" includes any effect, e.g., lessening, reducing, modulating, or eliminating, that results in the improvement of the condition, disease, disorder and the like.

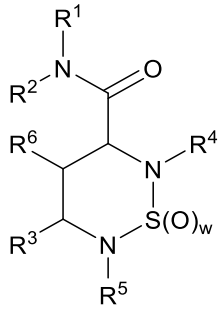
The term "alkenyl" as used herein refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon double bond. Exemplary alkenyl groups include, but are not limited to, a straight or branched group of 2-6 or 3-4 carbon atoms, referred to herein as C_{2-6}alkenyl, and C_{3-4}alkenyl, respectively. Exemplary alkenyl groups include, but are not limited to, vinyl, allyl, butenyl, pentenyl, etc.

The term "alkoxy" as used herein refers to a straight or branched alkyl group attached to oxygen (alkyl-O-). Exemplary alkoxy groups include, but are not limited to, alkoxy groups of 1-6 or 2-6 carbon atoms, referred to herein as C_{1-6}alkoxy, and C_{2-6}alkoxy, respectively. Exemplary alkoxy groups include, but are not limited to methoxy, ethoxy, isopropoxy, etc.

The term "alkoxyalkyl" as used herein refers to an alkyl group substituted with an alkoxy group. Examples include but are not limited to $CH_3CH_2OCH_2$-, $CH_3OCH_2CH_2$- and CH_3OCH_2-.

Claims

1. A compound of Formula I:



Formula I

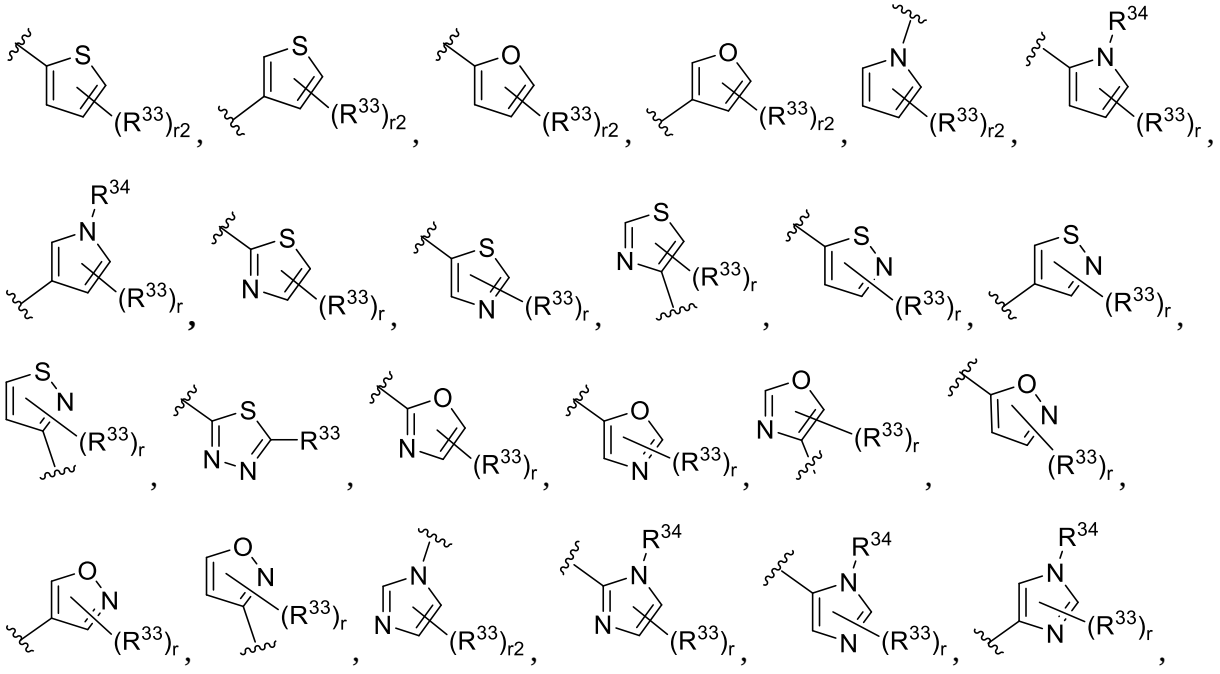
or a pharmaceutically acceptable salt thereof, wherein:

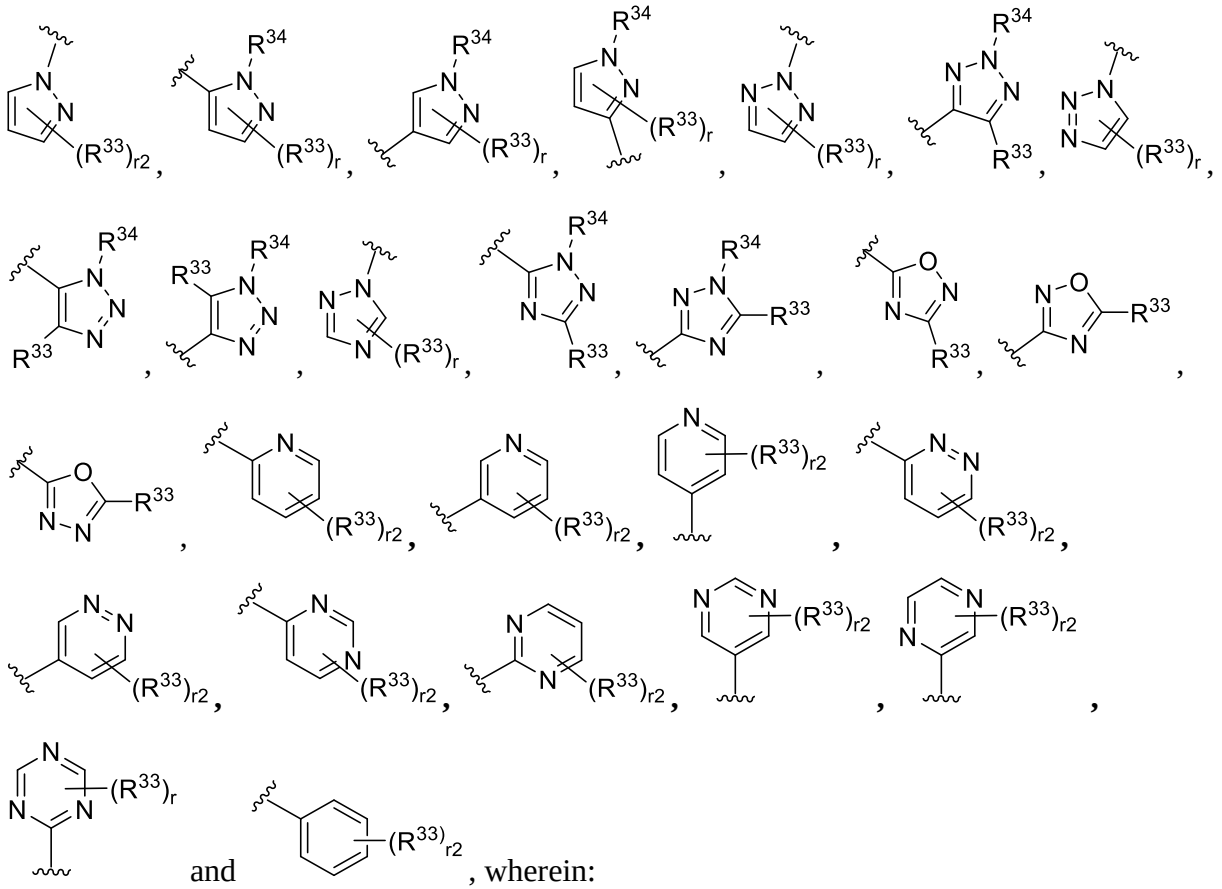
w is 2;

R^1 is of phenyl or pyridyl, each or which is optionally substituted with one, two, or three substituents independently selected from the group consisting of halo, -OH, -CN, -NO_2, oxo, hydrazino, formyl, azido, silyl, siloxy, -$S(O)_q$-C_{1-6}alkyl, -NR^aR^b, -NR^c-$S(O)_t$-C_{1-6}alkyl, -$S(O)_t$-NR^aR^b, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, R^aR^bN-C_{1-6}alkyl-, C_{1-6}alkoxy, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkoxy-, R^aR^bN-C_{1-6}alkoxy-, C_{1-6}alkoxyC_{1-6}alkyl, -C(O)NR^aR^b, -C(O)-C_{1-6}alkyl, -C(O)OH, and -C(O)O-C_{1-6}alkyl;

R^2 is hydrogen;

R^3 is selected from the group consisting of:





and , wherein:

R^4 is hydrogen or C_{1-6}alkyl optionally substituted with one, two, or three substituents independently selected from the group consisting of: halogen, -OH, -CN, -$S(O)_q$-C_{1-6}alkyl, -NR^aR^b, -NR^c-$S(O)_t$-C_{1-6}alkyl, -$S(O)_t$-NR^aR^b, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, -$C(O)NR^aR^b$, -C(O)-C_{1-6}alkyl, formyl, -C(O)OH, -C(O)O-C_{1-6}alkyl, benzyloxy, C_{1-4}alkoxyphenyl, pyrrolidinyl, morpholinyl, tetrahydrofuranyl and triazolyl;

R^5 is hydrogen or C_{1-6}alkyl optionally substituted with a substituent selected from the group consisting of halogen, -OH, C_{1-6}alkoxy, -NR^aR^b, and R^aR^bN-C_{1-4}alkyl;

R^6 is hydrogen or C_{1-6}alkyl;

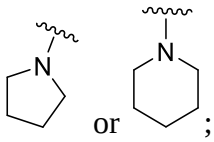
R^{33} is independently selected for each occurrence from the group consisting of: halo, -OH, -CN, -NO_2, oxo, hydrazino, formyl, azido, silyl, siloxy, -$S(O)_q$-C_{1-6}alkyl, -NR^aR^b, -NR^c-$S(O)_t$-C_{1-6}alkyl, -$S(O)_t$-NR^aR^b, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, R^aR^bN-C_{1-6}alkyl-, C_{1-6}alkoxy, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkoxy-, R^aR^bN-C_{1-6}alkoxy-, C_{1-6}alkoxyC_{1-6}alkyl, -$C(O)NR^aR^b$, -C(O)-C_{1-6}alkyl, -C(O)OH, and -C(O)O-C_{1-6}alkyl phenyl, and a 5-6 membered monocyclic heteroaryl having one, two, or three heteroatoms selected from the group consisting of O, N, and S, wherein the phenyl and 5-6 membered

monocyclic heteroaryl is optionally substituted with one, two or three substituents independently selected from the group consisting of: halo, -OH, -CN, -NO_2, oxo, hydrazino, formyl, azido, silyl, siloxy, -$S(O)_q$-C_{1-6}alkyl, -NR^aR^b, -NR^c-$S(O)_t$-C_{1-6}alkyl, -$S(O)_t$-NR^aR^b, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, R^aR^bN-C_{1-6}alkyl-, C_{1-6}alkoxy, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkoxy-, R^aR^bN-C_{1-6}alkoxy-, C_{1-6}alkoxyC_{1-6}alkyl, -C(O)NR^aR^b, -C(O)-C_{1-6}alkyl, -C(O)OH, and -C(O)O-C_{1-6}alkyl;

R^{34} is selected from the group consisting of hydrogen, C_{1-4}alkyl and hydroxyC_{1-4}alkyl;

R^a and R^b are independently hydrogen or C_{1-6}alkyl; or

R^a and R^b may be taken together with the nitrogen to which R^a and R^b are attached to form:



or ;

R^c is hydrogen or C_{1-6}alkyl;

for each occurrence, q is 0, 1, or 2,

for each occurrence, t is 1 or 2;

r is 0, 1 or 2;

r2 is 0, 1, 2 or 3;

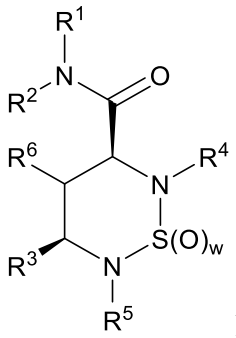
with the provisos that:

when R^3 is thiophen-2-yl or furan-2-yl, r2 is 1, 2 or 3;

when R^3 is pyrazol-4-yl, in at least one instance, R^{33} is other than C_{1-6}alkyl; and

when R^3 is phenyl, at least one of R^{35}, R^{36} and R^{37} is other than halo and C_{1-6}alkoxy.

2. The compound of claim 1, wherein the compound of Formula I is of Formula II:



Formula II

or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the 5-6 membered monocyclic heteroaryl having one, two, or three heteroatoms each selected from O, N, and S, is selected from the group consisting of: furanyl, thienyl, pyrrolyl, thiazolyl, oxazolyl, isothiazolyl, isoxazolyl, imidazolyl, pyrazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, 1,2,4-triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl and 1,2,5-thiadiazolyl.

4. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein r and r2 are 1.

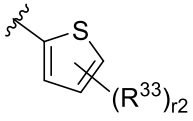
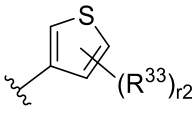
5. The compound according claim 1, or a pharmaceutically acceptable salt thereof, wherein R^6 is hydrogen.

6. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen.

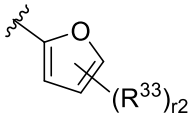
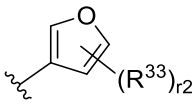
7. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R^4 is methyl or methoxyethyl.

8. The compound of claim 7, or a pharmaceutically acceptable salt thereof, wherein R^4 is methyl.

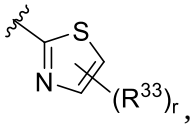
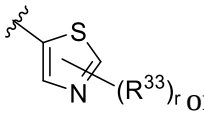
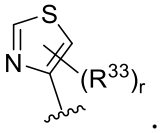
9. The compound according to claim 1, or a pharmaceutically acceptable salt thereof,

wherein R^3 is  or  .

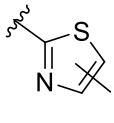
10. The compound according to claim 1, or a pharmaceutically acceptable salt thereof,

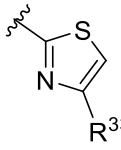
wherein R^3 is  or  .

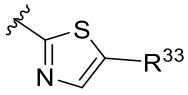
11. The compound according to claim 1, or a pharmaceutically acceptable salt thereof,

wherein R^3 is  ,  or  .

12. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein r is 1.

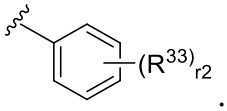
13. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein R^3 is  .

14. The compound of claim 13, or a pharmaceutically acceptable salt thereof, wherein R^3 is  .

15. The compound of claim 13, or a pharmaceutically acceptable salt thereof, wherein R^3 is  .

16. The compound according to claim 9, wherein R^{33} is independently selected for each occurrence from the group consisting of: halo, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxy, hydroxyC_{1-4}alkoxy, R^aR^bN-C_{1-4}alkoxy, benzyl, thienyl, thiazolyl, pyrazolyl, imidazolyl, phenyl, pyridyl, and pyrimidinyl, wherein the benzyl, thienyl, thiazolyl, pyrazolyl, imidazolyl, phenyl, pyridyl, and pyrimidinyl are optionally substituted with one or two substituents independently selected from the group consisting of halo, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxy, and C_{1-4}alkylsulfonylamino.

17. The compound of claim 16, R^{33} is independently selected for each occurrence from the group consisting of: halo, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxy, R^aR^bN-C_{1-4}alkoxy, benzyl, thienyl, thiazolyl, pyrazolyl optionally substituted with C_{1-4}alkyl, imidazolyl optionally substituted with C_{1-4}alkyl, phenyl, pyridyl, and pyrimidinyl, wherein the phenyl, pyridyl and pyrimidinyl are optionally substituted with one or two substituents independently selected from the group consisting of halo, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxy, and C_{1-4}alkylsulfonylaminoimidazoly.

18. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R^3 is  .

19. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is phenyl optionally substituted with one, two or three substituents independently selected from halo, cyano, methyl and trifluoromethyl.

20. The according of claim 19, or a pharmaceutically acceptable salt thereof, wherein R^1 is phenyl optionally substituted with one, two or three substituents independently selected from F, Cl, Br and CF_3.

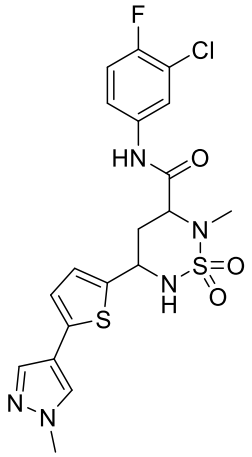
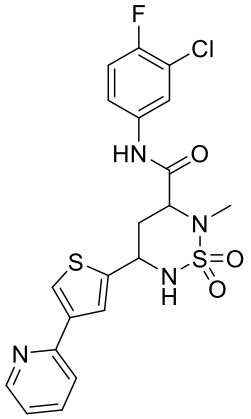
21. The compound of claim 20, or a pharmaceutically acceptable salt thereof, wherein R^1 is 3-chloro-4-fluorophenyl.

22. A pharmaceutical composition comprising the compound according to claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

23. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 22, for use in therapy.

24. Use of the compound according to claim 1, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 22, in the manufacture of a medicament for treating Hepatitis B (HBV) infection in a patient.

25. The compound of claim 1 selected from the group consisting of:


,

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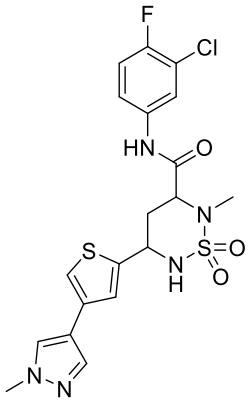
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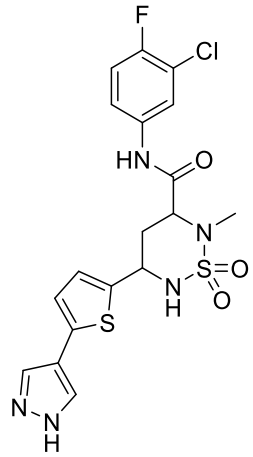
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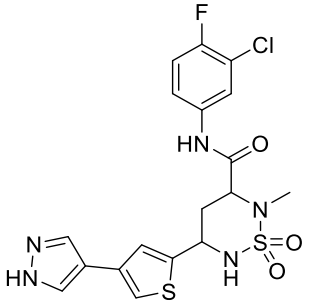
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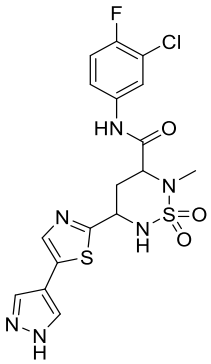
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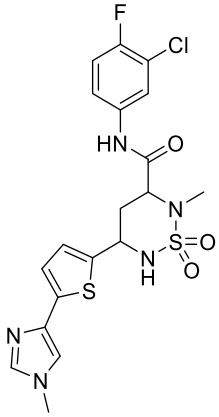
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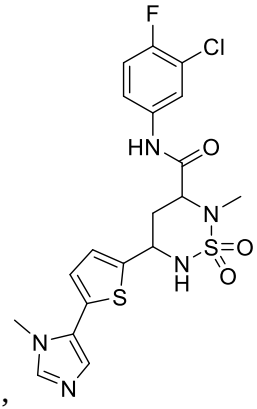
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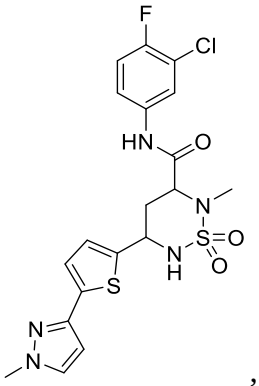
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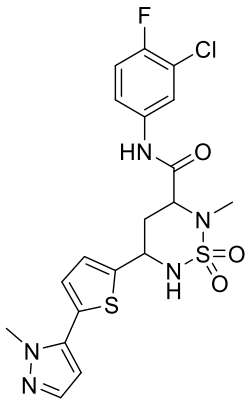
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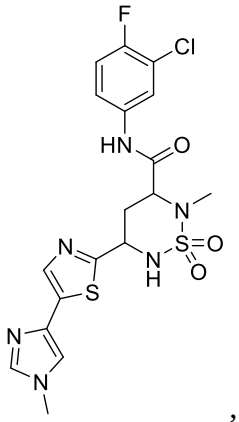
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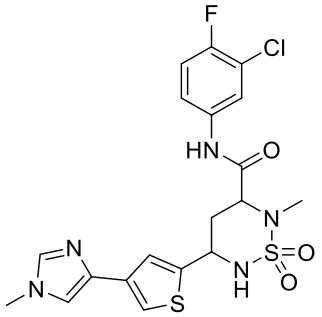
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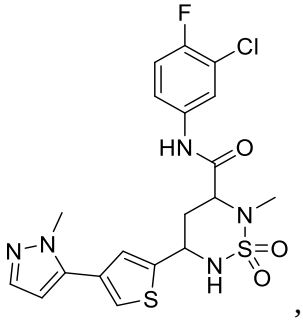
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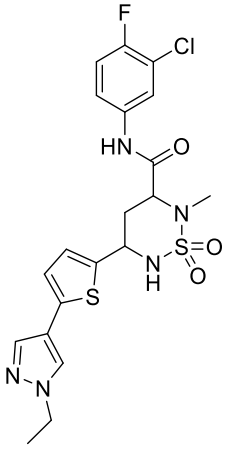
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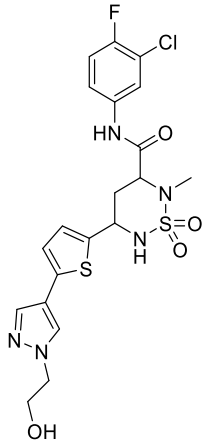
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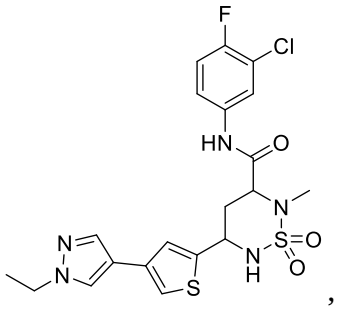
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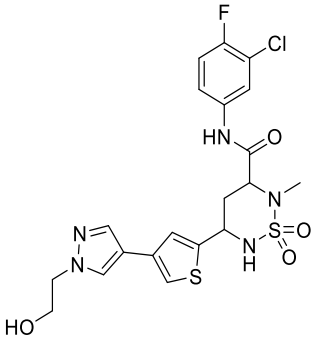
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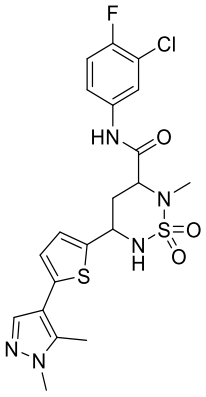
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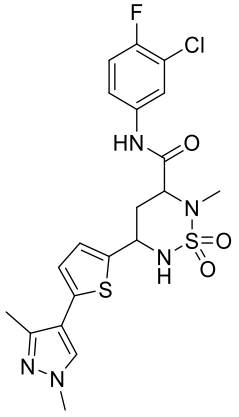
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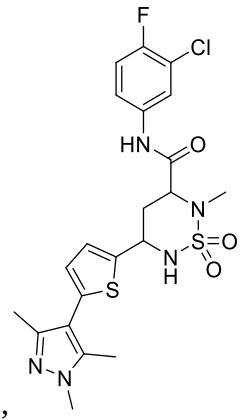
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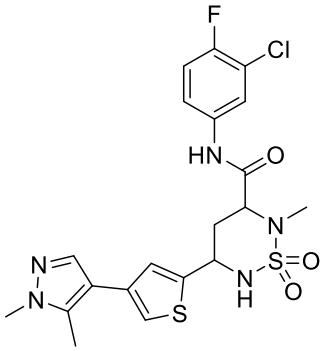
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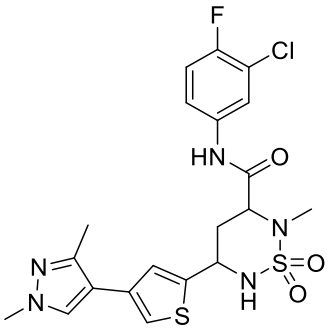
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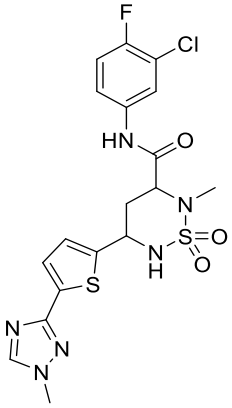
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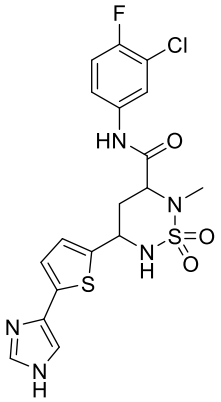
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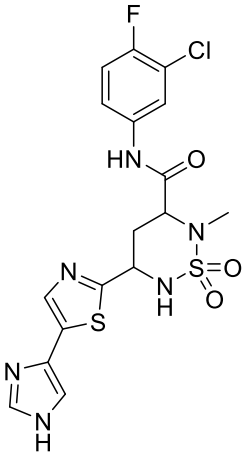
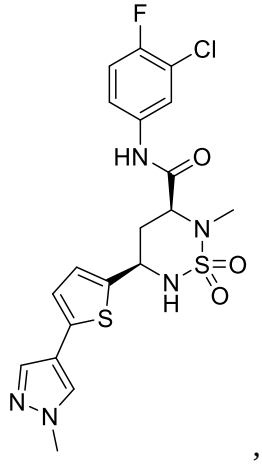

and , or a pharmaceutically acceptable salt thereof.

26. The compound of claim 25 selected from the group consisting of: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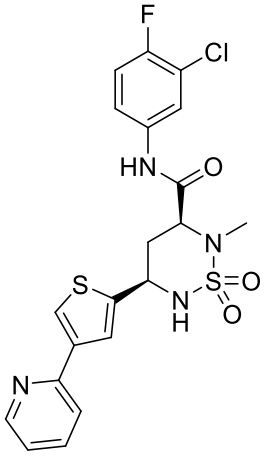
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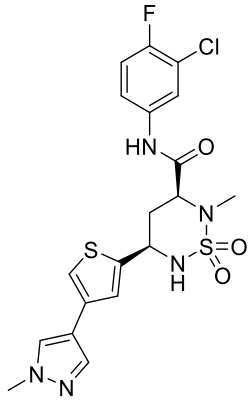
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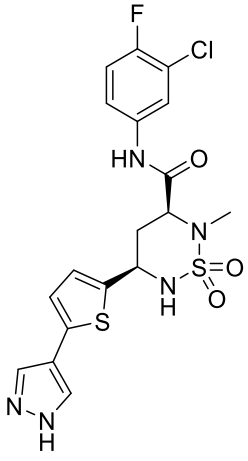
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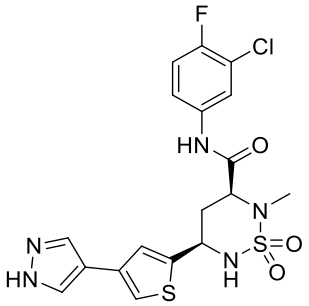
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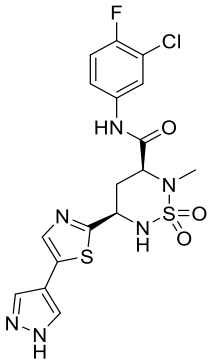
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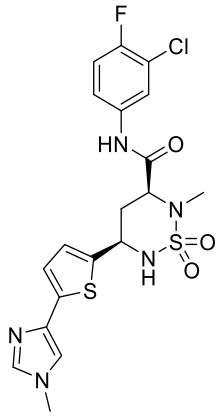
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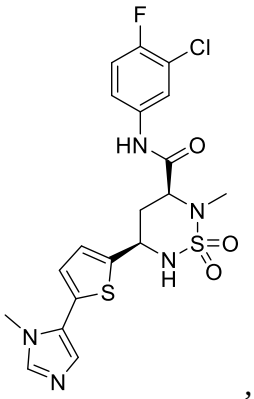
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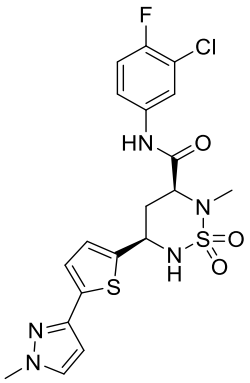
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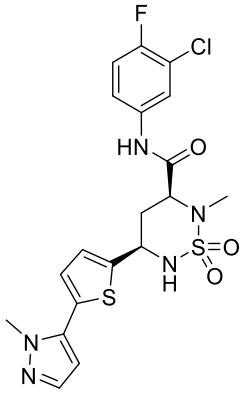
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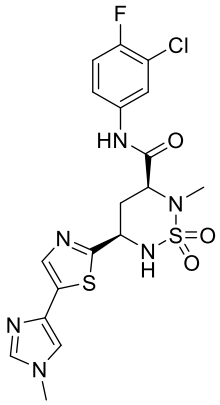
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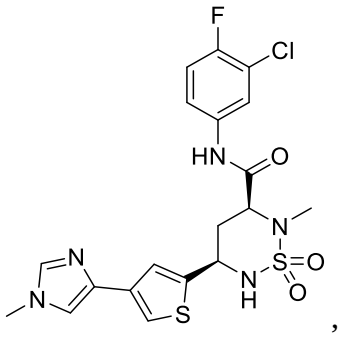
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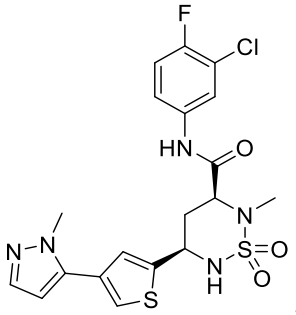
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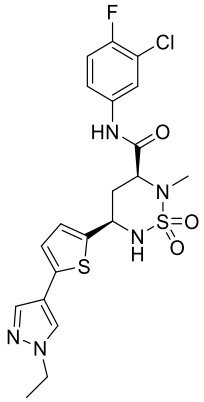
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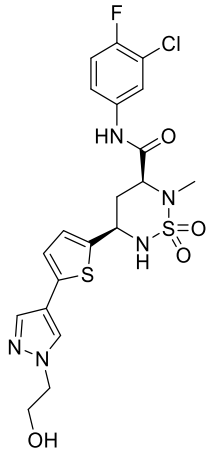
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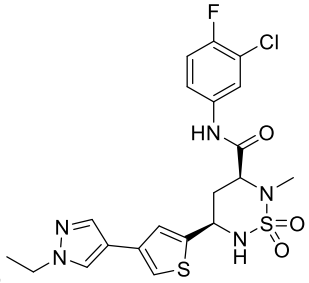
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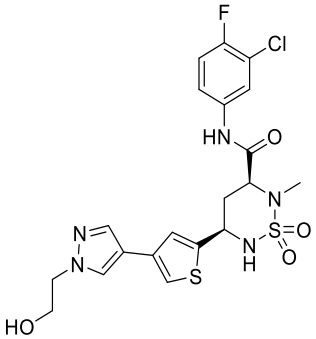
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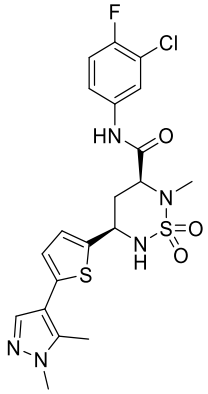
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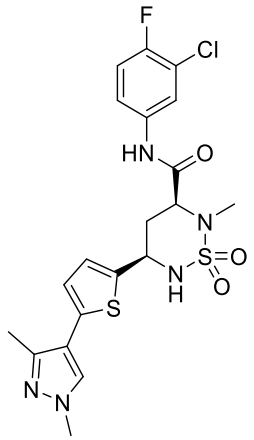
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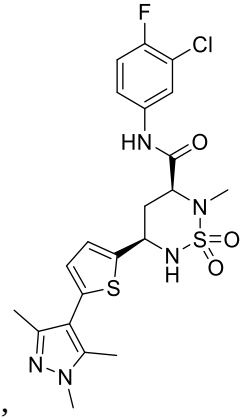
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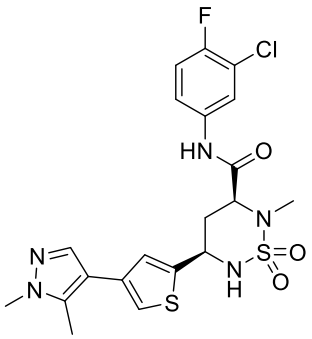
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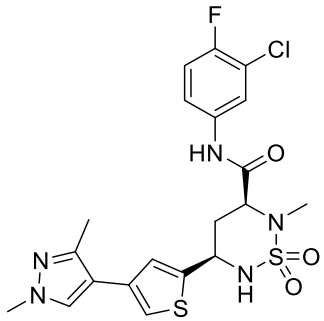
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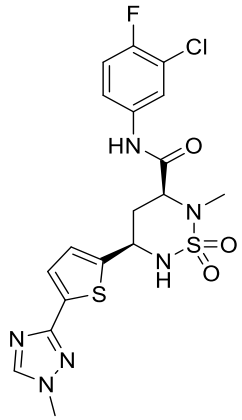
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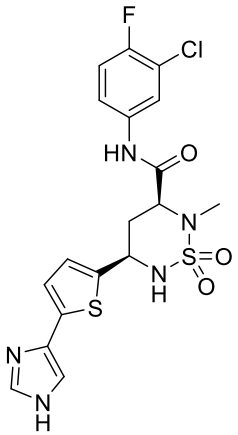
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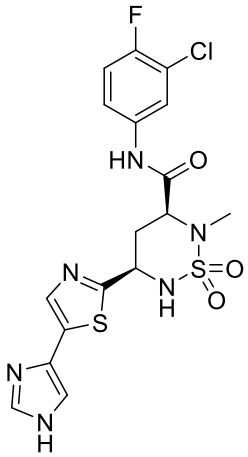
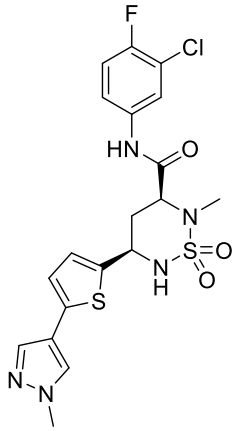
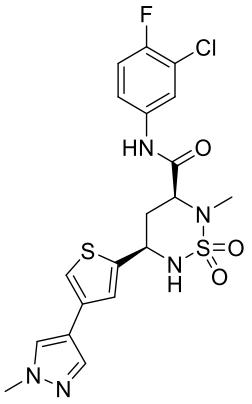

and , or a pharmaceutically acceptable salt thereof.

27. The compound of claim 26 of the following formula:



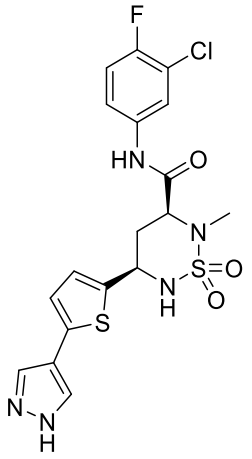
, or a pharmaceutically acceptable salt thereof.

28. The compound of claim 26 of the following formula:



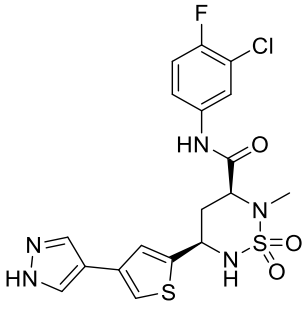
, or a pharmaceutically acceptable salt thereof.

29. The compound of claim 26 of the following formula:



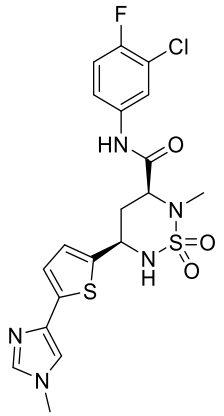
, or a pharmaceutically acceptable salt thereof.

30. The compound of claim 26 of the following formula:



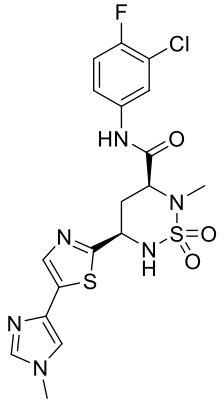
, or a pharmaceutically acceptable salt thereof.

31. The compound of claim 26 of the following formula:



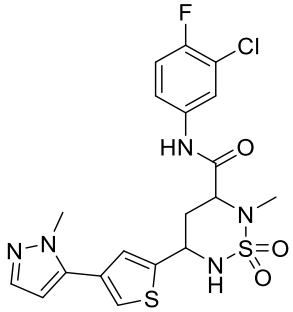
, or a pharmaceutically acceptable salt thereof.

32. The compound of claim 26 of the following formula:



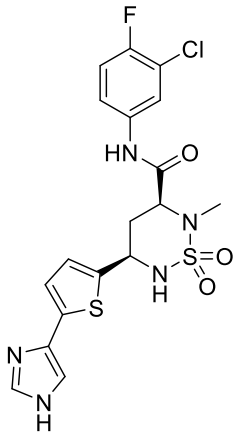
, or a pharmaceutically acceptable salt thereof.

33. The compound of claim 26 of the following formula:



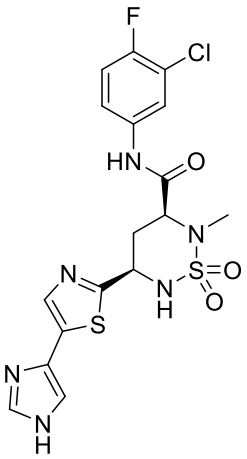
, or a pharmaceutically acceptable salt thereof.

34. The compound of claim 26 of the following formula:



, or a pharmaceutically acceptable salt thereof.

35. The compound of claim 26 of the following formula:



, or a pharmaceutically acceptable salt thereof.