N-((1,2,3,5,6,7-HEXAHYDRO-S-INDACEN-4-YL)CARBAMOYL)-4,5,6,7-TETRAHYDROBENZOFURAN -2-SULFONAMIDE DERIVATIVES AND RELATED COMPOUNDS AS NLPR3 MODULATORS FOR THE TREATMENT OF MULTIPLE SCLEROSIS (MS)

CROSS-REFERENCE

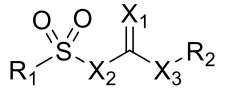
[0001] This application claims benefit of U.S. Provisional Application No. 62/875,402, filed on July 17, 2019, which is herein incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] The NOD-like receptor (NLR) family, pyrin domain-containing protein 3 (NLRP3) inflammasome is a critical component of the innate immune response and inflammatory process, and its aberrant activity is pathogenic in inherited disorders such as cryopyrin-associated periodic syndromes (CAPS) and complex diseases such as multiple sclerosis, type 2 diabetes, Alzheimer's disease and atherosclerosis. Current treatments for NLRP3-related diseases include biologic agents that target IL-1. Small molecule inhibitors of NLRP3 provide an attractive alternative to these biologics, given their potential for improved safety and patient comfort and compliance.

SUMMARY ~~OF THE INVENTION~~

[0002a] In an aspect of the present disclosure, there is provided a compound having the structure of Formula (I):



Formula (I);

wherein:

X_1 is O, S, $N(R_3)$, or $C(NO_2)(R_4)$;

X_2 is $-N(R_5)-$ or $-C(R_5)_2-$;

X_3 is $-N(R_5)-$ or $-C(R_5)_2-$;

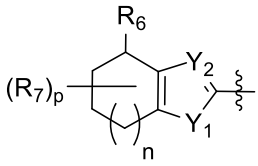
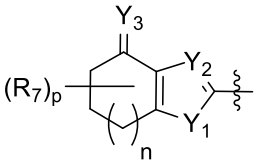
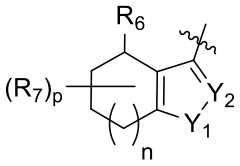
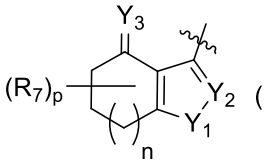
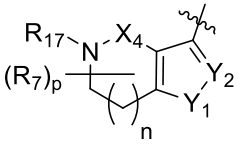
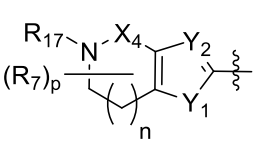
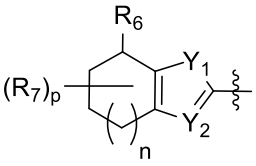
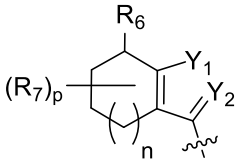
X_4 is $-C(O)-$ or $-CH_2-$;

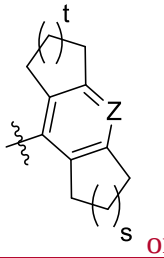
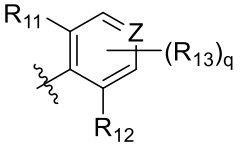
Y_1 is O, S, or $N(R_8)$;

Y_2 is N or $C(R_9)$;

Y_3 is O or $N(R_{10})$;

Z is N or $C(R_{19})$;

R_1 is  ,  ,  ,  ,  ,  ,  , or  ;

R_2 is  or  ;

R_3 is $-OR_{14}$, -CN, $-NO_2$, or $-S(=O)_2R_{15}$;

R_4 is hydrogen, C_1-C_6alkyl, or C_1-C_6heteroalkyl;

each R_5 is independently selected from hydrogen, C_1-C_6alkyl, and C_1-C_6heteroalkyl;

R_6 is -OH, -C_1-C_6alkyl-OH, or $-NH(R_{16})$;

each R_7 is independently selected from C_1-C_6alkyl, -C_1-C_6alkyl-CO_2R_{18}, C_1-C_6haloalkyl, and C_1-C_6heteroalkyl; or R_6 and R_7 are combined to form a 5-or 6-membered heteroaryl ring;

R_8 is hydrogen, C_1-C_6alkyl, or C_1-C_6heteroalkyl;

R_9 is hydrogen, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6heteroalkyl;

R_{10} is -OH or -O-C_1-C_6alkyl;

R_{11} is C_1-C_6alkyl;

R_{12} is C_1-C_6alkyl;

each R_{13} is independently selected from is halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, and C_1-C_6heteroalkyl;

R_{14} is hydrogen or C_1-C_6alkyl;

R_{15} is C_1-C_6alkyl;

R_{16} is hydrogen, C_1-C_6alkyl or -C(O)-C_1-C_6alkyl;

R_{17} is hydrogen or C_1-C_6alkyl;

R_{18} is hydrogen or C_1-C_6alkyl;

R_{19} is hydrogen, halogen, -CN, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6heteroalkyl;

n is 0, 1, 2, or 3;

p is 0, 1, 2, 3, or 4;

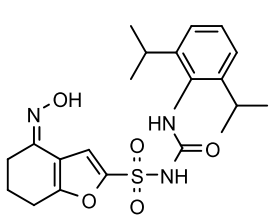
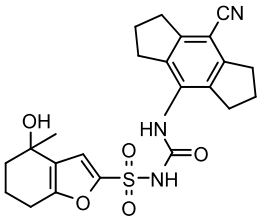
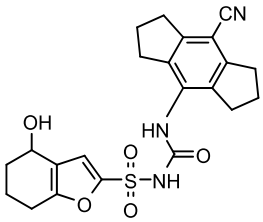
q is 0, 1, or 2;

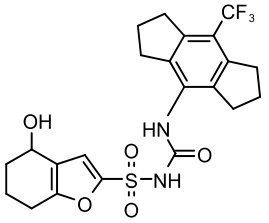
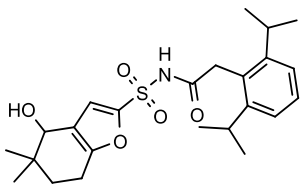
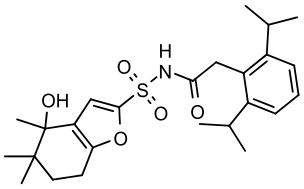
s is 1, 2, or 3; and

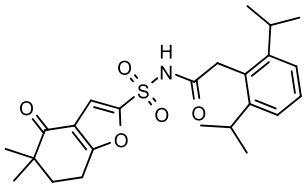
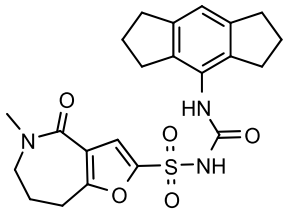
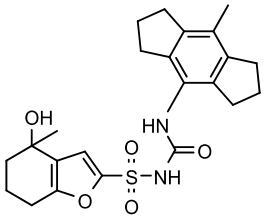
t is 1, 2, or 3;

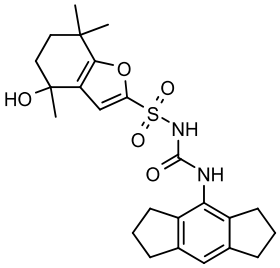
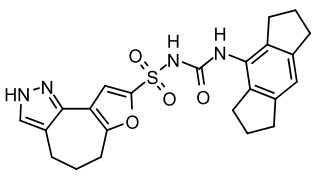
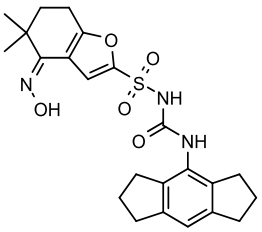
or a pharmaceutically acceptable salt or solvate thereof.

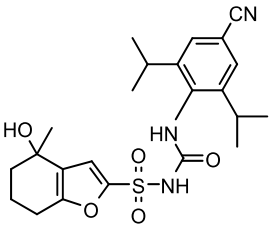
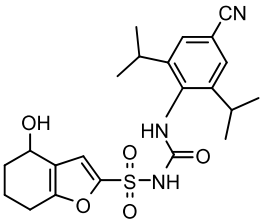
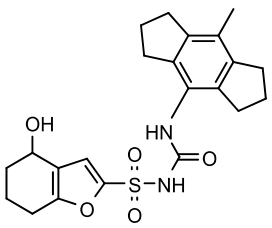
[0002b] In another aspect of the present disclosure, there is provided a compound selected from:

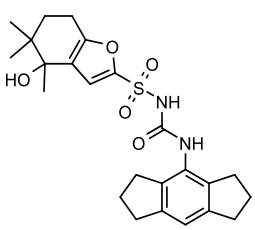
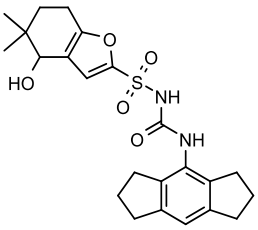
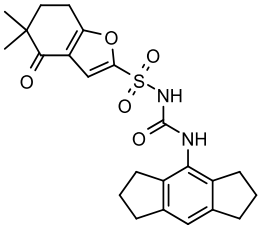
 ,  ,  ,

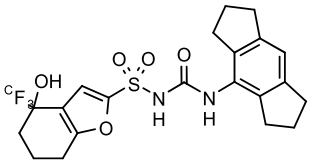
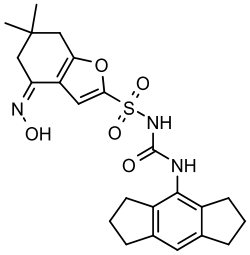
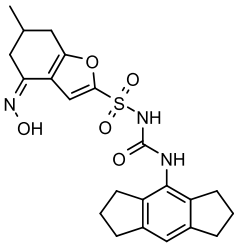
 ,  ,  ,

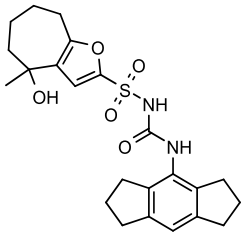
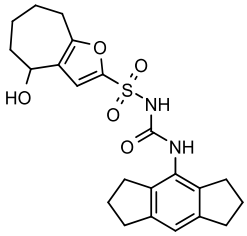
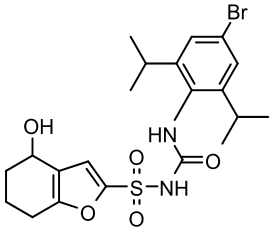
 ,  ,  ,

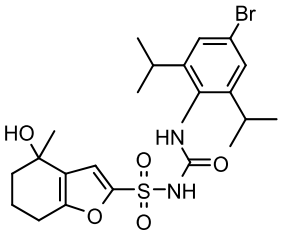
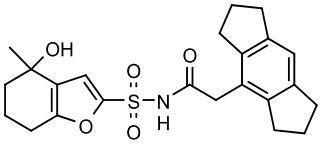
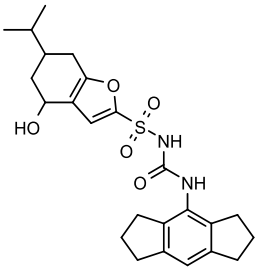
 ,  ,  ,

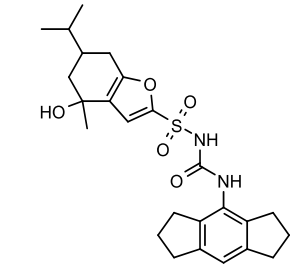
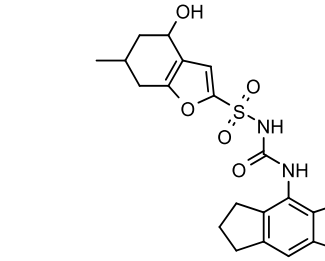
 ,  ,  ,

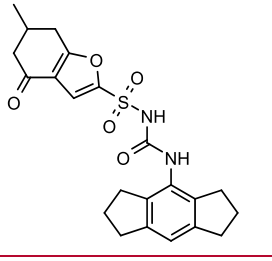
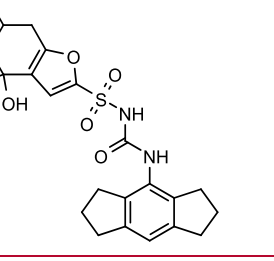
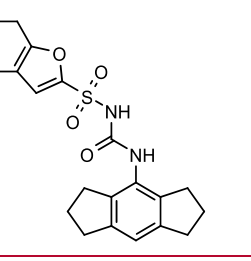




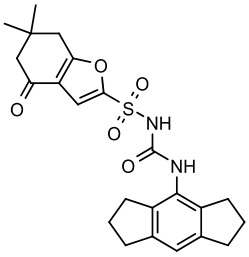
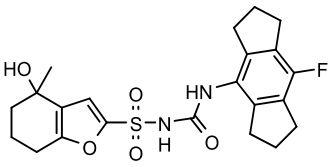
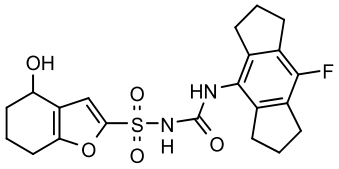




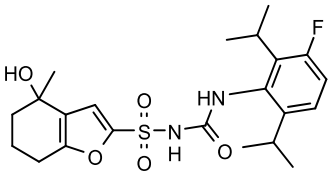
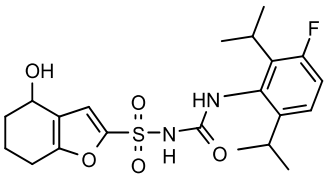
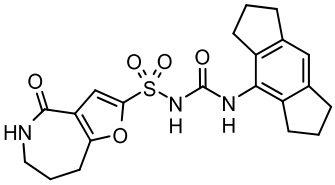




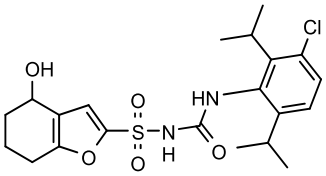
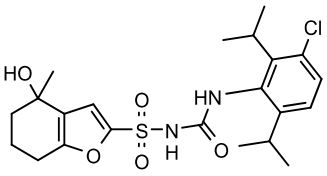
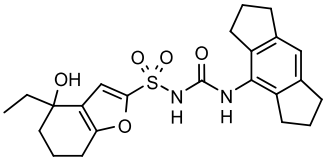




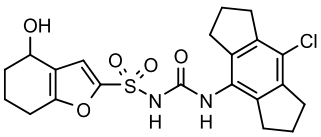
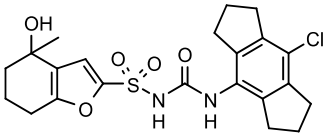
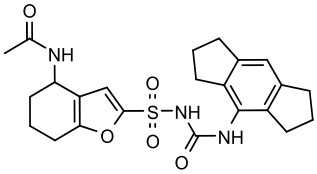



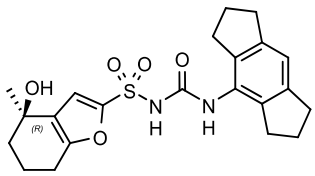
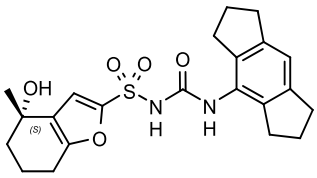
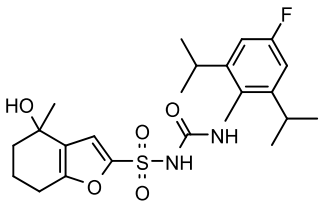




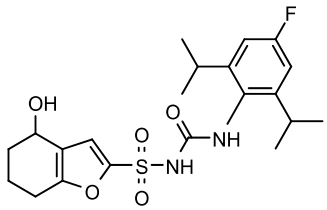
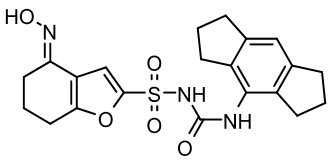
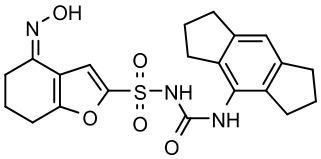




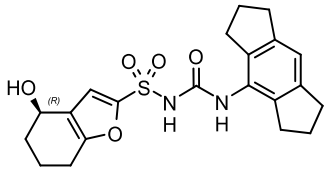
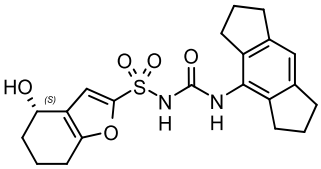
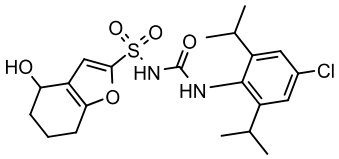




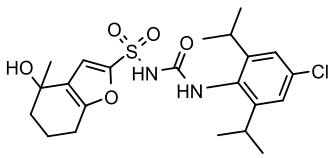
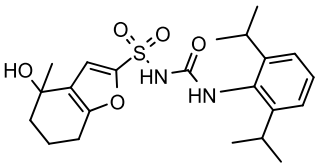
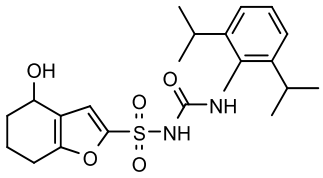




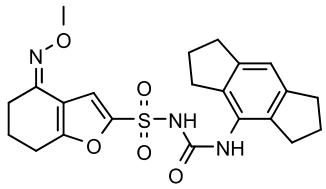
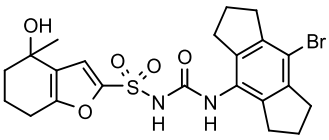
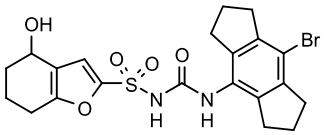




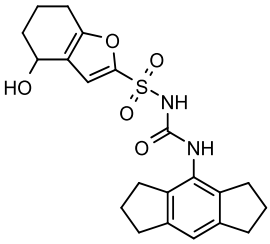
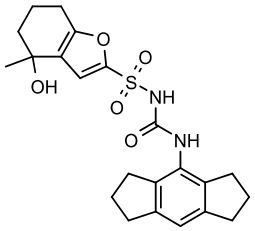
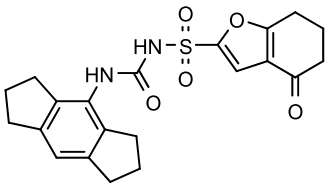




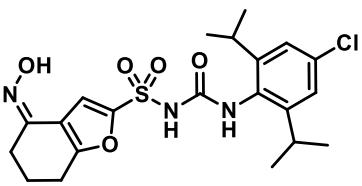
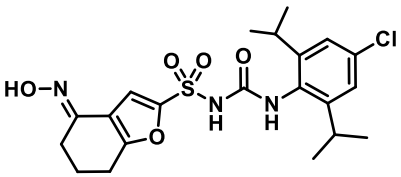
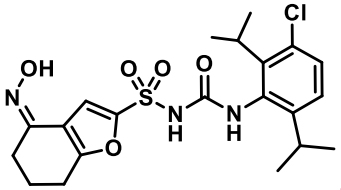




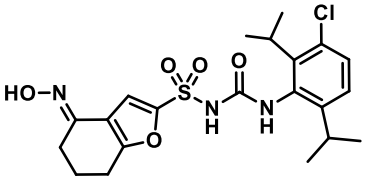
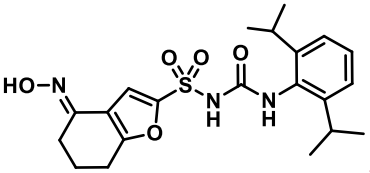
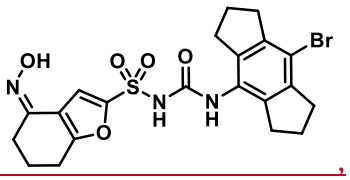




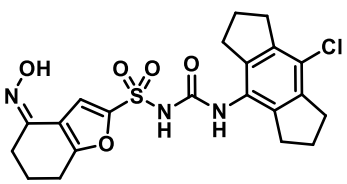
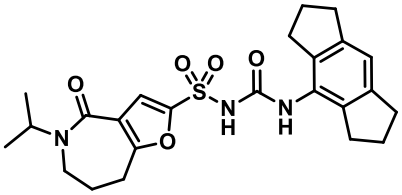
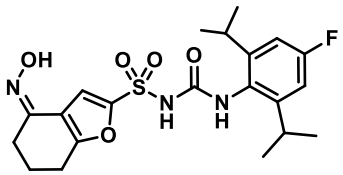




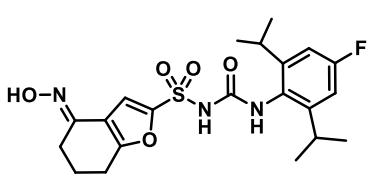
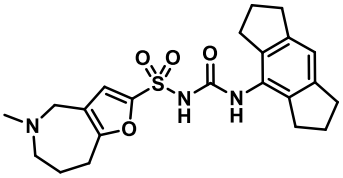
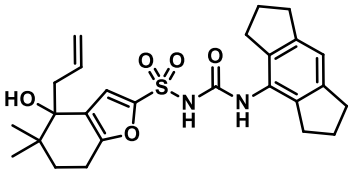
pharmaceutically acceptable salt or solvate thereof.

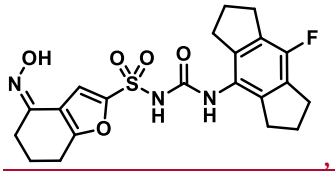
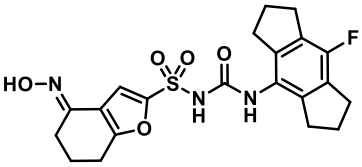
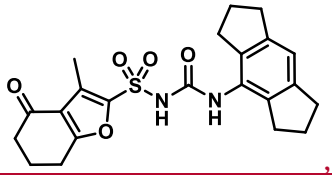
[0002c] In a further aspect of the present disclosure, there is provided a compound selected from:

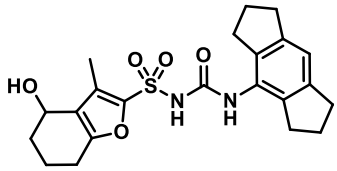
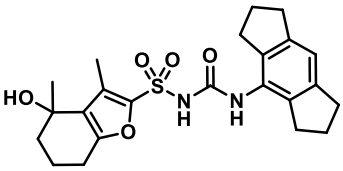
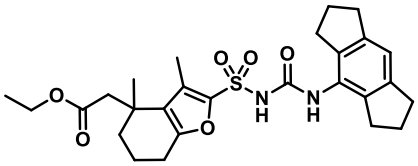




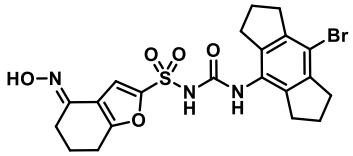
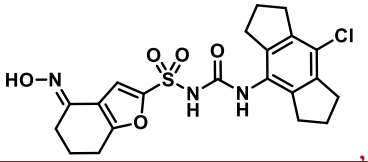




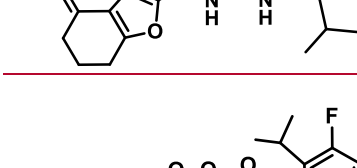
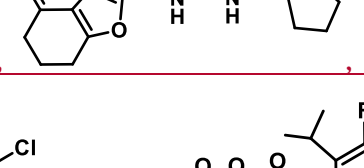
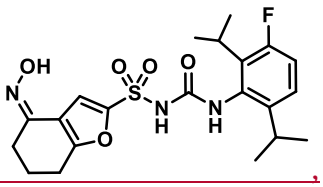




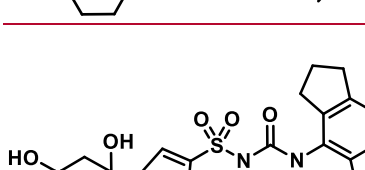
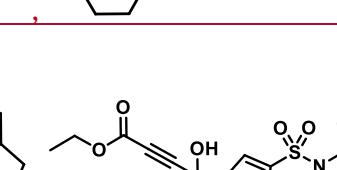
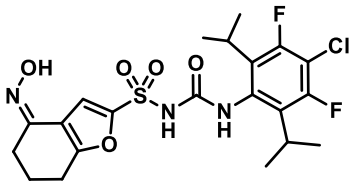




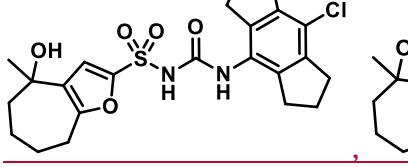
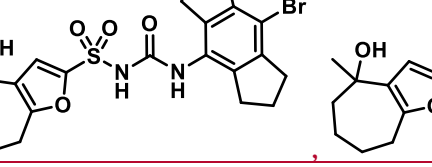
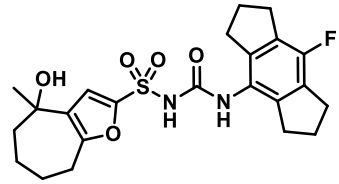




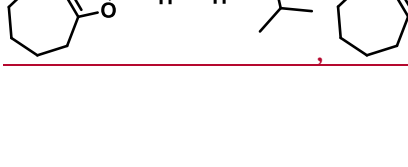
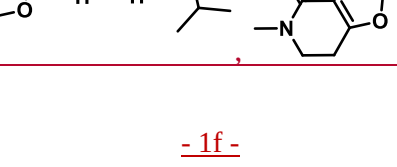
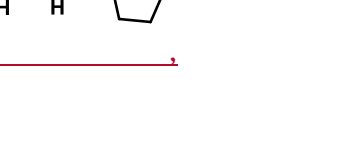




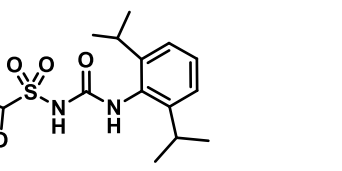



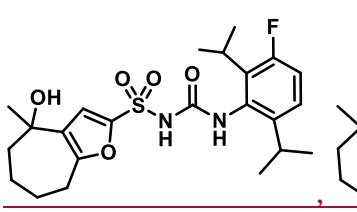
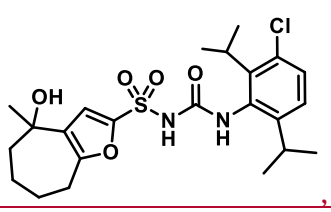
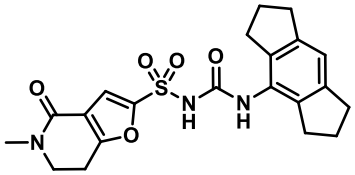




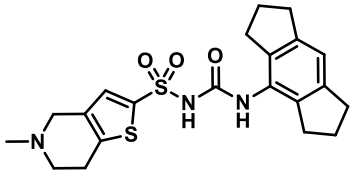
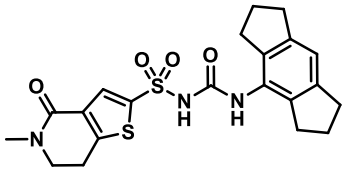
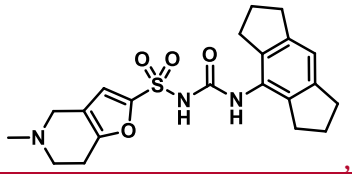






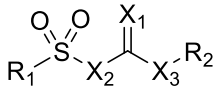
 ,  ,  ,

[0002i] In a further aspect of the present disclsosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating an inflammatory or autoimmune disease in a patient in need thereof.

[0002j] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating a cardiovascular disease in a patient in need thereof.

[0002k] In a further aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, for use in therapy.

[0003] In one ~~aspect~~example, provided herein are compounds of Formula (I):



Formula (I);

wherein:

X_1 is O, S, $N(R_3)$, or $C(NO_2)(R_4)$;

X_2 is $-N(R_5)-$ or $-C(R_5)_2-$;

X_3 is $-N(R_5)-$ or $-C(R_5)_2-$;

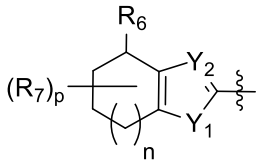
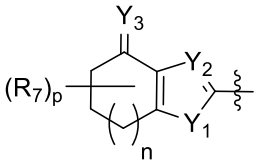
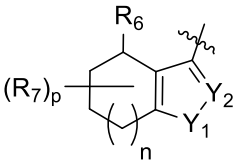
X_4 is $-C(O)-$ or $-CH_2-$;

Y_1 is O, S, or $N(R_8)$;

Y_2 is N or $C(R_9)$;

Y_3 is O or $N(R_{10})$;

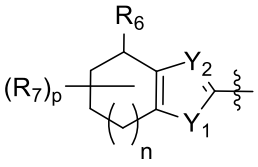
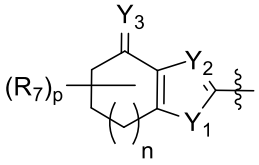
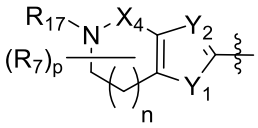
Z is N or $C(R_{19})$;

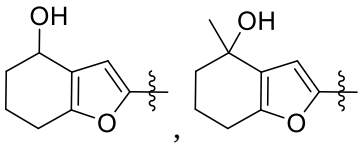
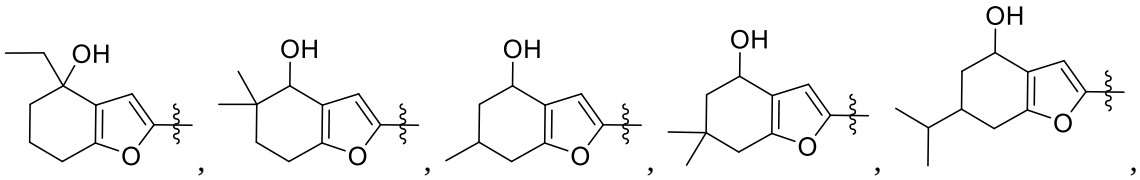
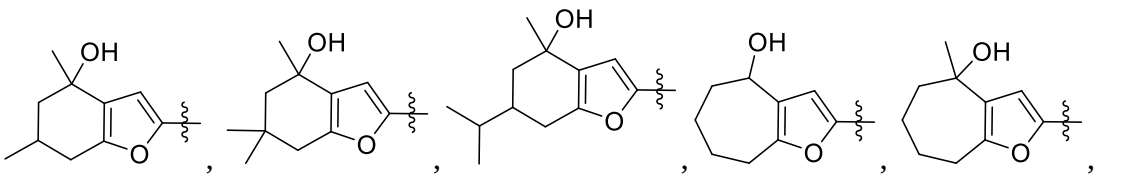
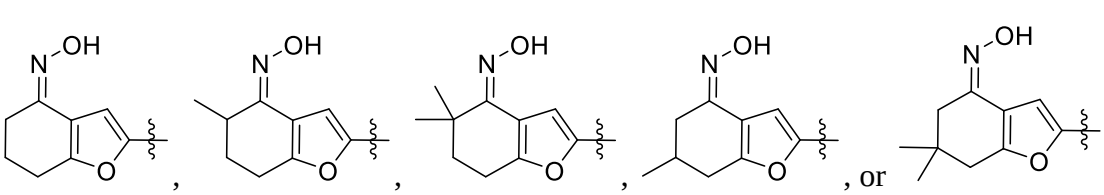
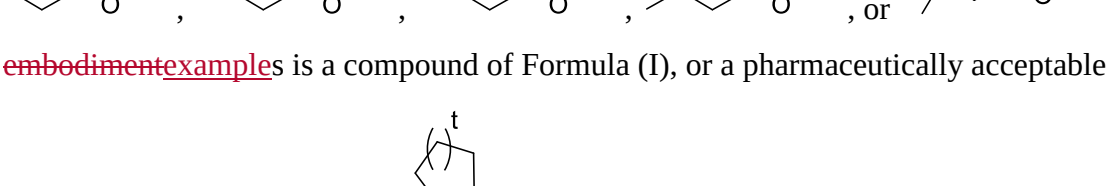
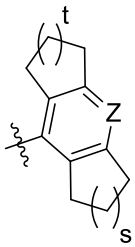
R_1 is  ,  ,  ,

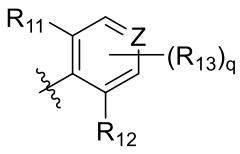
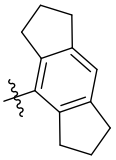
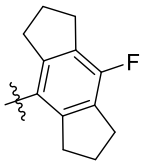
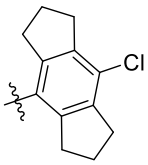
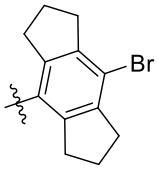
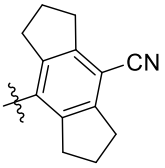
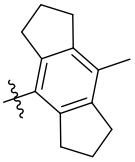
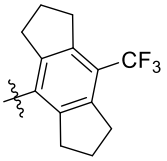
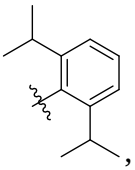
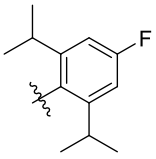
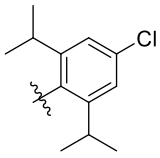
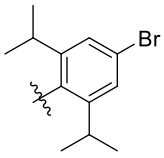
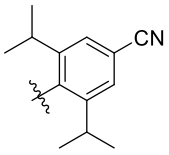
s is 1, 2, or 3; and

t is 1, 2, or 3;

or a pharmaceutically acceptable salt or solvate thereof.

[0004] In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is  . In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_6 is -OH. In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is  . In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein Y_3 is $N(R_{10})$. In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{10} is -OH. In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein Y_3 is O. In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is  . In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein X_4 is -C(O)-. In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein X_4 is $-CH_2-$. In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{17} is C_1-C_6alkyl. In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein Y_2 is $C(R_9)$. In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_9 is selected from hydrogen and C_1-C_6alkyl. In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_9 is hydrogen. In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein Y_1 is O. In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R_7 is independently selected from C_1-C_6alkyl. In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R_7 is $-CH_3$. In some ~~embodiment~~examples is a compound

of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein p is 1. In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein p is 2. In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein p is 3. In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein p is 0. In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 1. In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 2. In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is  ,  ,  ,  ,  , or . In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is  . In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein s is 1. In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein t is 1. In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate

thereof, wherein R_2 is  . In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R_{13} is independently selected from is halogen, C_1-C_6alkyl, and C_1-C_6haloalkyl. In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein q is 1. In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein q is 0. In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein Z is C(R_{19}). In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{19} is hydrogen, halogen, -CN, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{19} is hydrogen. In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{19} is halogen. In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  . In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein X_2 is -N(R_5)-. In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein X_3 is -N(R_5)-. In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is hydrogen. In some ~~embodiment~~examples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein X_1 is O.

[0005] In another ~~aspect~~example described herein is a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

[0006] In some ~~embodiment~~examples described herein is a method of treating a metabolic disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof. In some ~~embodiment~~examples described herein is a method of treating a metabolic disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein the metabolic disease is selected from type 2 diabetes, atherosclerosis, obesity, and gout.

[0007] In some ~~embodiment~~examples described herein is a method of treating a liver disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof. In some ~~embodiment~~examples described herein is a method of treating a liver disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein the liver disease is selected from non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH), viral hepatitis, and cirrhosis.

[0008] In some ~~embodiment~~examples described herein is a method of treating a lung disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof. In some ~~embodiment~~examples described herein is a method of treating a lung disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein the lung disease is selected from asthma, chronic obstructive pulmonary disease (COPD), and pulmonary idiopathic fibrosis.

[0009] In some ~~embodiment~~examples described herein is a method of treating a central nervous system disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof. In some ~~embodiment~~examples described herein is a method of treating a central nervous system disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein the central nervous system disease is selected from Alzheimer's disease, multiple sclerosis, Amyotrophic Lateral Sclerosis, and Parkinson's disease.

[0010] In some ~~embodiment~~examples described herein is a method of treating an inflammatory or autoimmune disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable

salt or solvate thereof. In some ~~embodiment~~examples described herein is a method of treating an inflammatory or autoimmune disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein the inflammatory or autoimmune disease is selected from rheumatoid arthritis, multiple sclerosis, psoriasis, lupus, inflammatory bowel disease, Crohn's disease, and ulcerative colitis.

[0011] In some ~~embodiment~~examples described herein is a method of treating a cardiovascular disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof. In some ~~embodiment~~examples described herein is a method of treating a cardiovascular disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein the cardiovascular disease is atherosclerosis or stroke.

INCORPORATION BY REFERENCE

[0012] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0013] In the context of this disclosure, a number of terms shall be utilized.

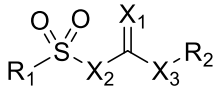
[0014] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood to which the claimed subject matter belongs. In the event that there are a plurality of definitions for terms herein, those in this section prevail. All patents, patent applications, publications and published nucleotide and amino acid sequences (*e.g.*, sequences available in GenBank or other databases) referred to herein are incorporated by reference. Where reference is made to a URL or other such identifier or address, it is understood that such identifiers can change and particular information on the internet can come and go, but equivalent information can be found by searching the internet. Reference thereto evidences the availability and public dissemination of such information.

[0015] It is to be understood that the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of any subject matter claimed. In this application, the use of the singular includes the plural unless specifically stated otherwise. It must be noted that, as used in the specification and the appended claims, the

CLAIMS

WHAT IS CLAIMED IS:

1. A compound having the structure of Formula (I):



Formula (I);

wherein:

X_1 is O, S, $N(R_3)$, or $C(NO_2)(R_4)$;

X_2 is $-N(R_5)-$ or $-C(R_5)_2-$;

X_3 is $-N(R_5)-$ or $-C(R_5)_2-$;

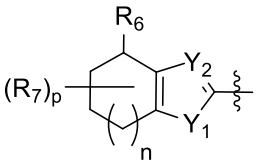
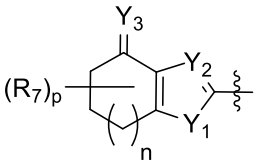
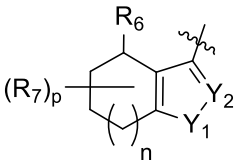
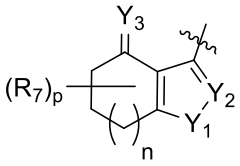
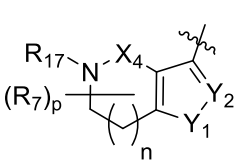
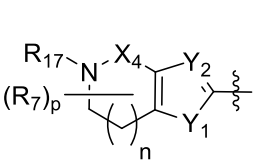
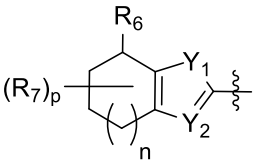
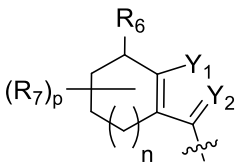
X_4 is $-C(O)-$ or $-CH_2-$;

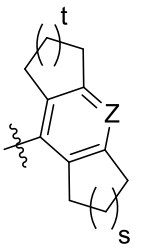
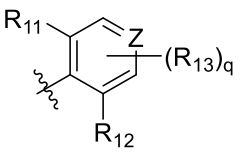
Y_1 is O, S, or $N(R_8)$;

Y_2 is N or $C(R_9)$;

Y_3 is O or $N(R_{10})$;

Z is N or $C(R_{19})$;

R_1 is  ,  ,  ,  ,  ,  ,  , or  ;

R_2 is  or  ;

R_3 is $-OR_{14}$, -CN, $-NO_2$, or $-S(=O)_2R_{15}$;

R_4 is hydrogen, C_1-C_6alkyl, or C_1-C_6heteroalkyl;

each R_5 is independently selected from hydrogen, C_1-C_6alkyl, and C_1-C_6heteroalkyl;

R_6 is -OH, -C_1-C_6alkyl-OH, or -NH(R_{16});

each R_7 is independently selected from C_1-C_6alkyl, -C_1-C_6alkyl-CO_2R_{18}, C_1-C_6haloalkyl, and C_1-C_6heteroalkyl; or R_6 and R_7 are combined to form a 5-or 6-membered heteroaryl ring;

R_8 is hydrogen, C_1-C_6alkyl, or C_1-C_6heteroalkyl;

R_9 is hydrogen, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6heteroalkyl;

R_{10} is -OH or -O-C_1-C_6alkyl;

R_{11} is C_1-C_6alkyl;

R_{12} is C_1-C_6alkyl;

each R_{13} is independently selected from is halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, and C_1-C_6heteroalkyl;

R_{14} is hydrogen or C_1-C_6alkyl;

R_{15} is C_1-C_6alkyl;

R_{16} is hydrogen, C_1-C_6alkyl or -C(O)-C_1-C_6alkyl;

R_{17} is hydrogen or C_1-C_6alkyl;

R_{18} is hydrogen or C_1-C_6alkyl;

R_{19} is hydrogen, halogen, -CN, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6heteroalkyl;

n is 0, 1, 2, or 3;

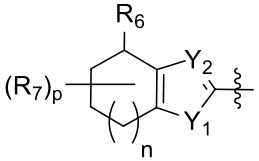
p is 0, 1, 2, 3, or 4;

q is 0, 1, or 2;

s is 1, 2, or 3; and

t is 1, 2, or 3;

or a pharmaceutically acceptable salt or solvate thereof.

2. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is 

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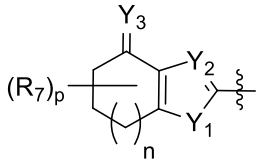
3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt or solvate thereof, wherein R_6 is -OH.

4. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is 

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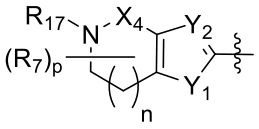
5. The compound of claim 4, or a pharmaceutically acceptable salt or solvate thereof, wherein Y_3 is $N(R_{10})$.
6. The compound of claim 5, or a pharmaceutically acceptable salt or solvate thereof, wherein R_{10} is -OH.
7. The compound of claim 4, or a pharmaceutically acceptable salt or solvate thereof, wherein Y_3 is O.
8. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof,

wherein R_1 is 

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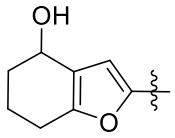
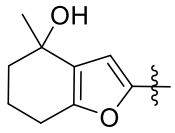
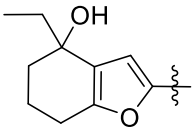
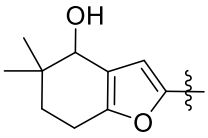
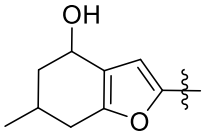
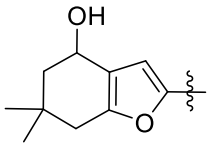
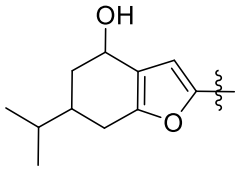
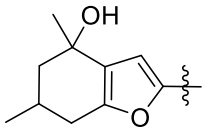
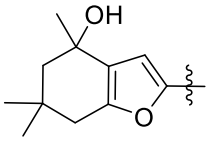
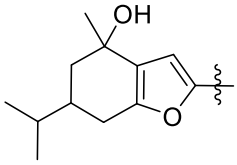
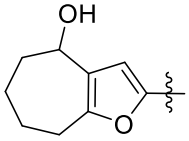
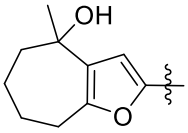
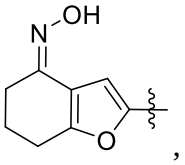
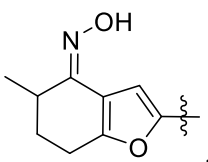
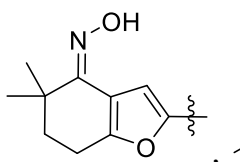
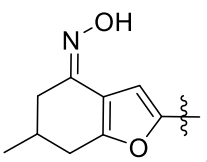
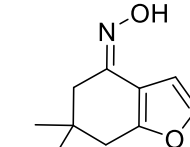
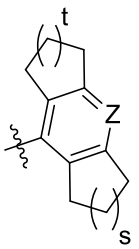
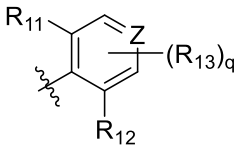
9. The compound of claim 8, or a pharmaceutically acceptable salt or solvate thereof, wherein X_4 is -C(O)-.
10. The compound of claim 8, or a pharmaceutically acceptable salt or solvate thereof, wherein X_4 is $-CH_2-$.
11. The compound of any one of claims 8-10, or a pharmaceutically acceptable salt or solvate thereof, wherein R_{17} is C_1-C_6alkyl.
12. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt or solvate thereof, wherein Y_2 is $C(R_9)$.
13. The compound of claim 12, or a pharmaceutically acceptable salt or solvate thereof, wherein R_9 is selected from hydrogen and C_1-C_6alkyl.
14. The compound of claim 13, or a pharmaceutically acceptable salt or solvate thereof, wherein R_9 is hydrogen.
15. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt or solvate thereof, wherein Y_1 is O.
16. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt or solvate thereof, wherein each R_7 is independently selected from C_1-C_6alkyl.
17. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt or solvate thereof, wherein each R_7 is $-CH_3$.
18. The compound of any one of claims 1-17, or a pharmaceutically acceptable salt or solvate thereof, wherein p is 1.
19. The compound of any one of claims 1-17, or a pharmaceutically acceptable salt or solvate thereof, wherein p is 2.
20. The compound of any one of claims 1-17, or a pharmaceutically acceptable salt or solvate thereof, wherein p is 3.

21. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt or solvate thereof, wherein p is 0.
22. The compound of any one of claims 1-21, or a pharmaceutically acceptable salt or solvate thereof, wherein n is 1.
23. The compound of any one of claims 1-21, or a pharmaceutically acceptable salt or solvate thereof, wherein n is 2.
24. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , , , or .
25. The compound of any one of claims 1-24, or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is  .
26. The compound of claim 25, or a pharmaceutically acceptable salt or solvate thereof, wherein s is 1.
27. The compound of claim 25 or claim 26, or a pharmaceutically acceptable salt or solvate thereof, wherein t is 1.

28. The compound of any one of claims 1-24, or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is 

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29. The compound of claim 28, or a pharmaceutically acceptable salt or solvate thereof, wherein each R_{13} is independently selected from is halogen, C_1-C_6alkyl, and C_1-C_6haloalkyl.

30. The compound of claim 28 or claim 29, or a pharmaceutically acceptable salt or solvate thereof, wherein q is 1.

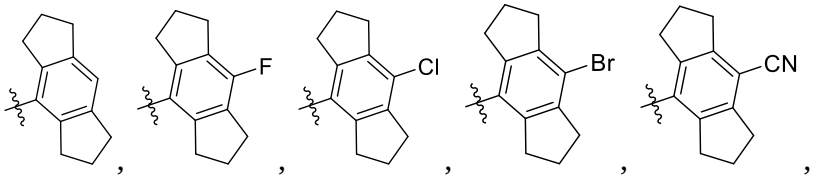
31. The compound of claim 28, or a pharmaceutically acceptable salt or solvate thereof, wherein q is 0.

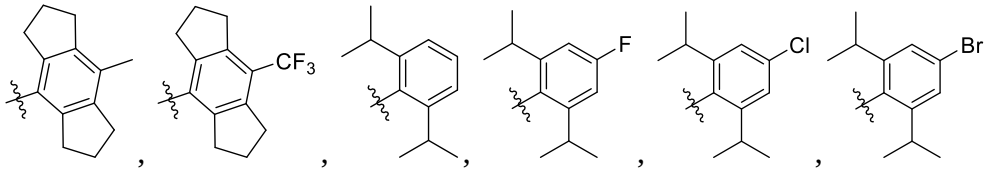
32. The compound of any one of claims 25-31, or a pharmaceutically acceptable salt or solvate thereof, wherein Z is $C(R_{19})$.

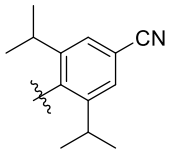
33. The compound of claim 32, or a pharmaceutically acceptable salt or solvate thereof, wherein R_{19} is hydrogen, halogen, -CN, C_1-C_6alkyl, or C_1-C_6haloalkyl.

34. The compound of claim 33, or a pharmaceutically acceptable salt or solvate thereof, wherein R_{19} is hydrogen.

35. The compound of claim 33, or a pharmaceutically acceptable salt or solvate thereof, wherein R_{19} is halogen.

36. The compound of any one of claims 1-24, or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is 

, 

, or 

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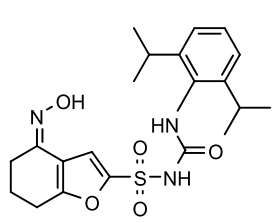
37. The compound of any one of claims 1-36, or a pharmaceutically acceptable salt or solvate thereof, wherein X_2 is -N(R_5)-.

38. The compound of any one of claims 1-36, or a pharmaceutically acceptable salt or solvate thereof, wherein X_3 is -N(R_5)-.

39. The compound of any one of claims 1-38, or a pharmaceutically acceptable salt or solvate thereof, wherein R_5 is hydrogen.

40. The compound of any one of claims 1-39, or a pharmaceutically acceptable salt or solvate thereof, wherein X_1 is O.

41. A compound selected from: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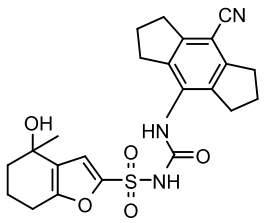
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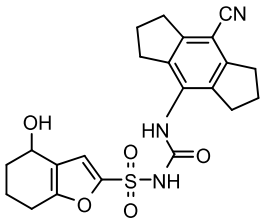
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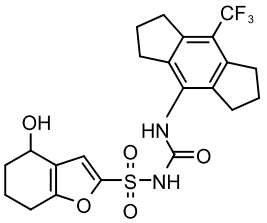
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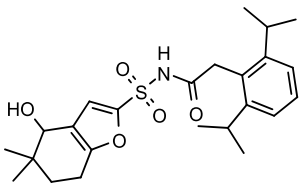
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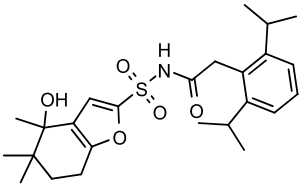
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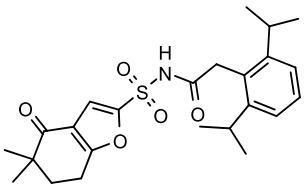
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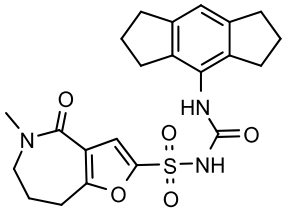
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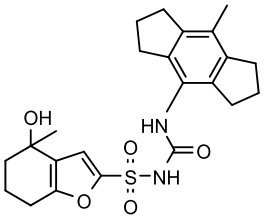
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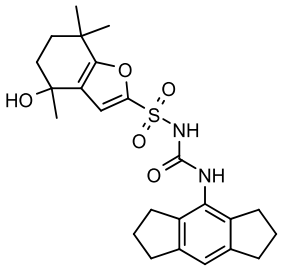
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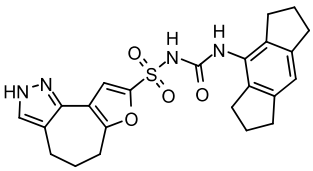
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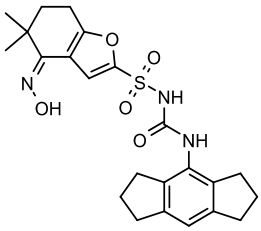
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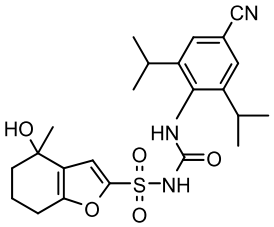
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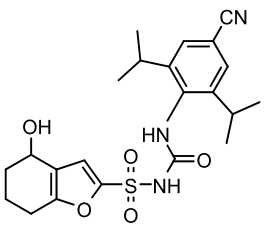
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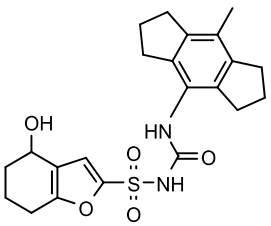
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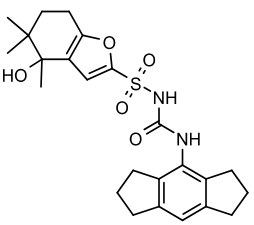
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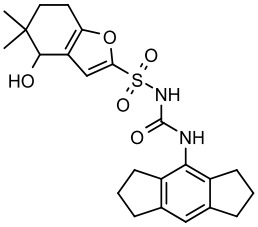
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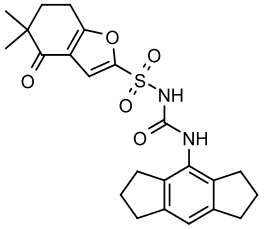
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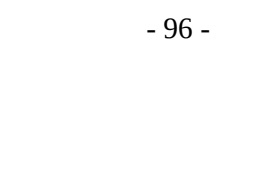
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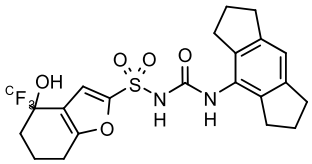
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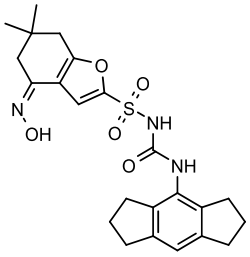
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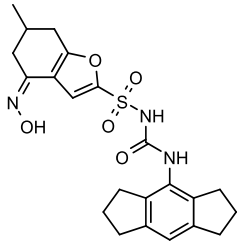
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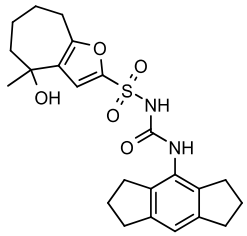
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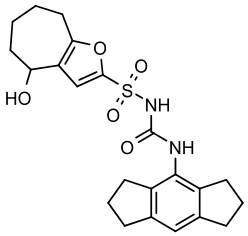
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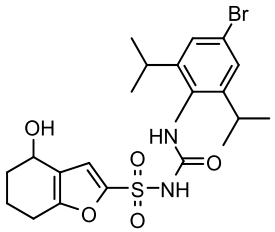
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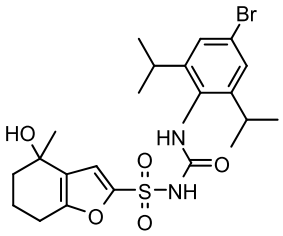
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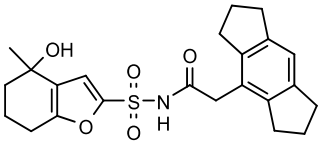
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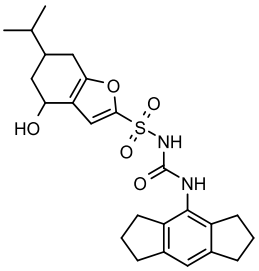
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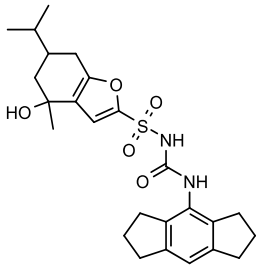
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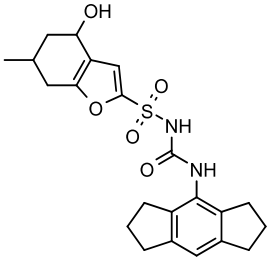
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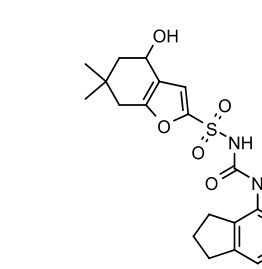
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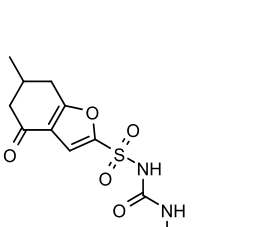
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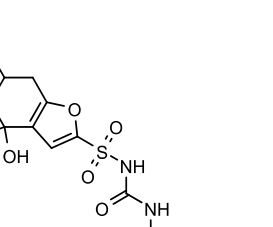
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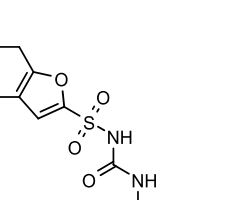
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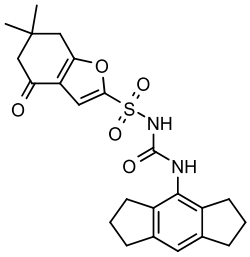
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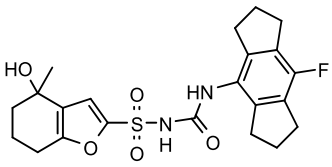
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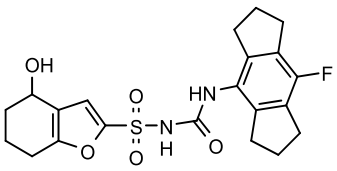
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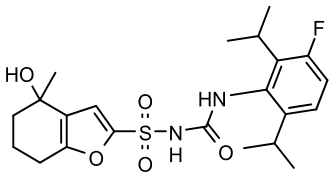
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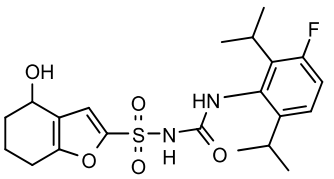
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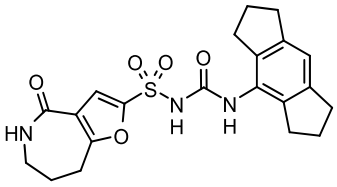
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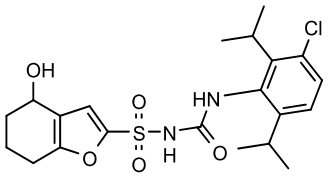
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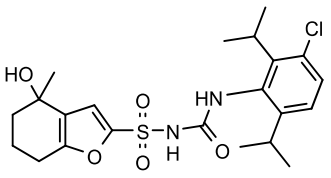
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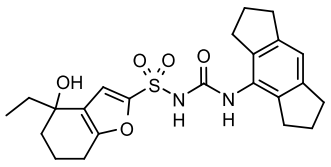
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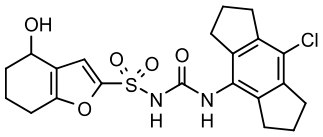
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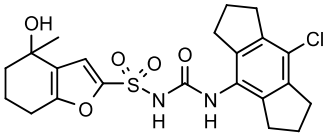
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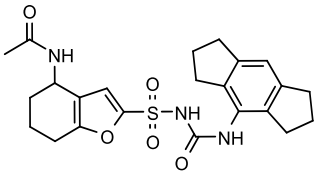
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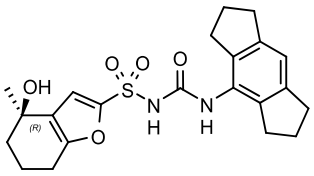
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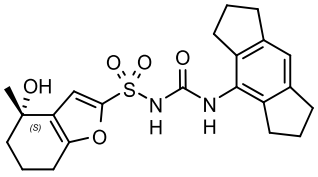
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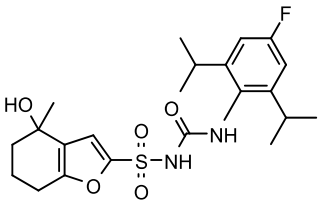
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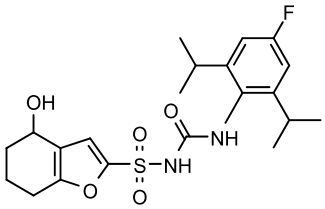
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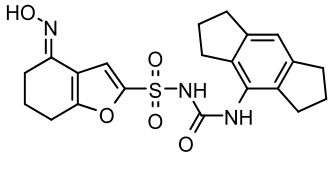
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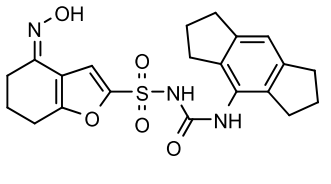
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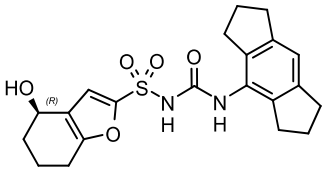
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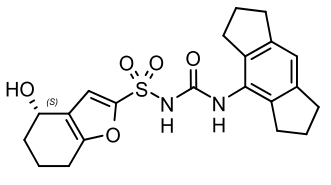
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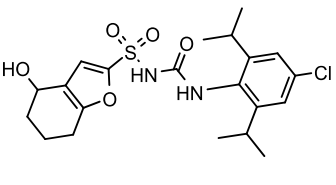
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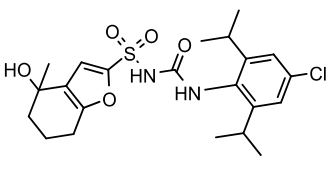
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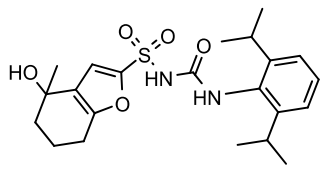
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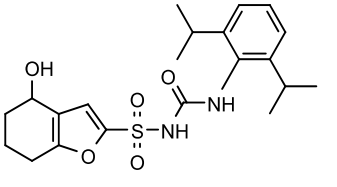
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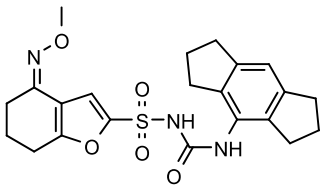
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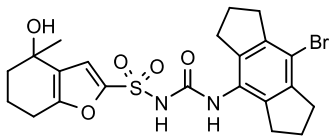
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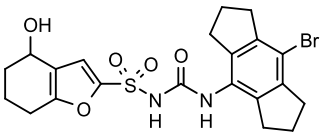
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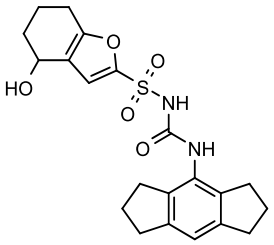
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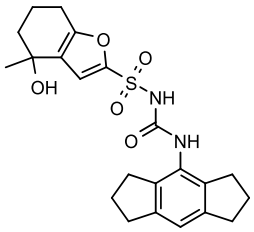
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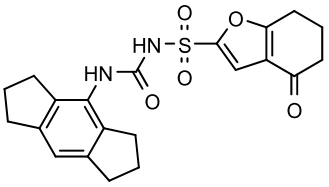
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a pharmaceutically acceptable salt or solvate thereof.

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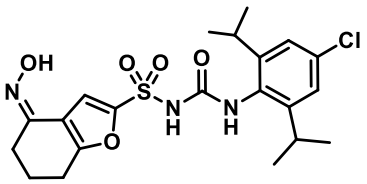
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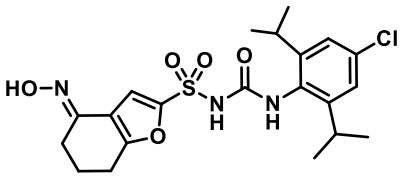
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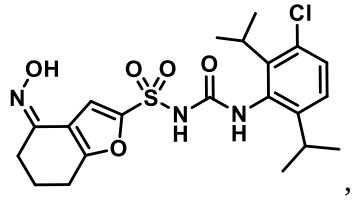
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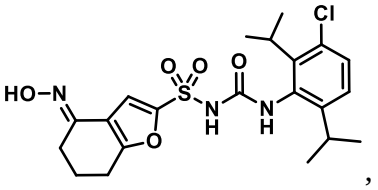
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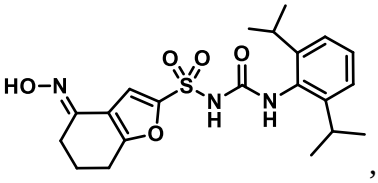
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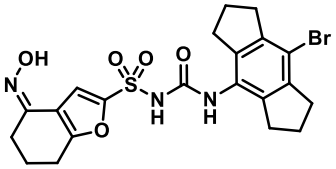
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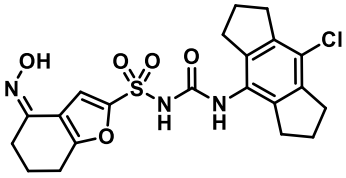
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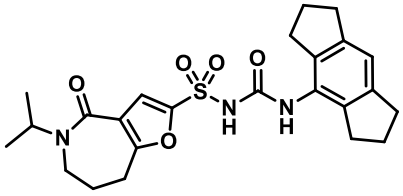
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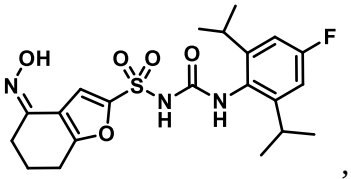
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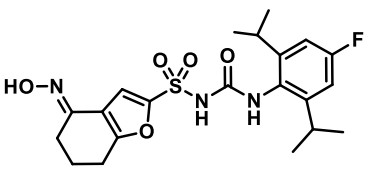
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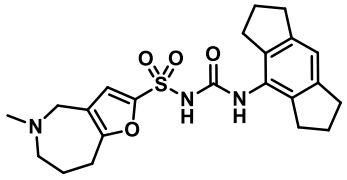
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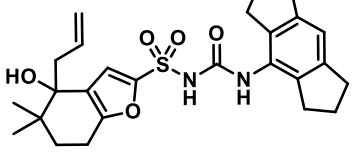
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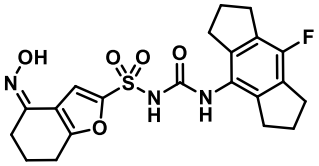
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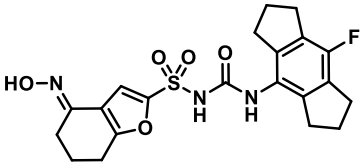
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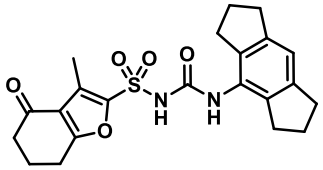
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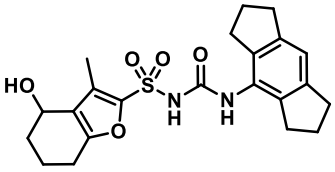
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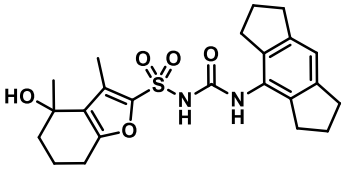
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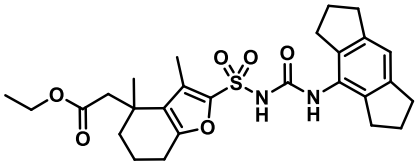
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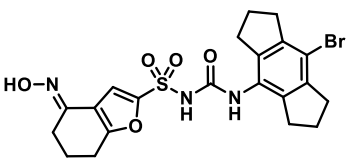
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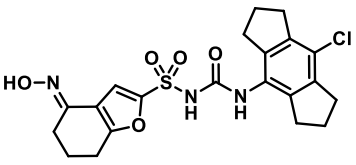
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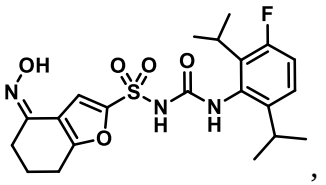
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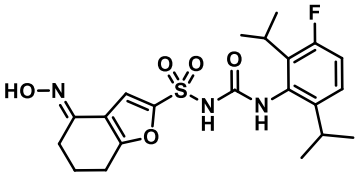
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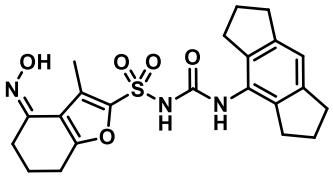
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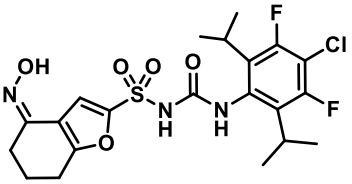
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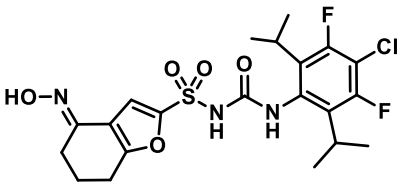
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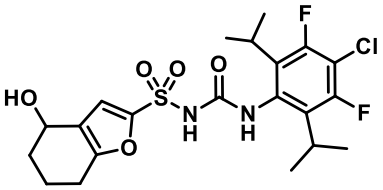
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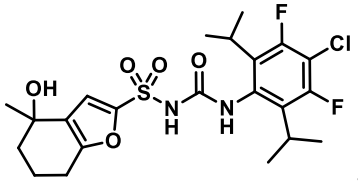
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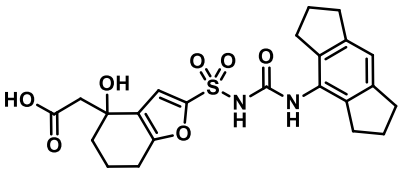
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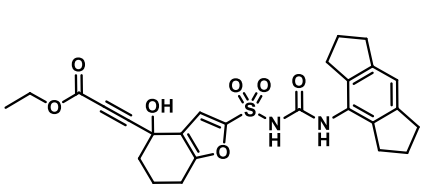
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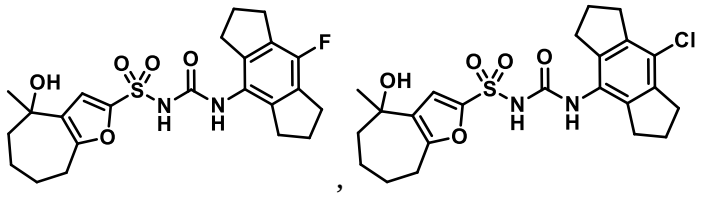
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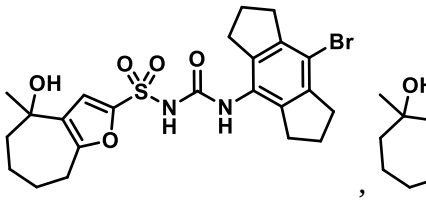
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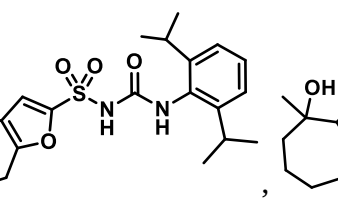
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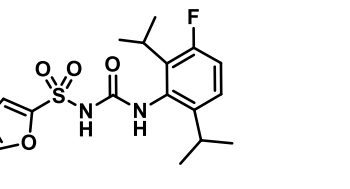
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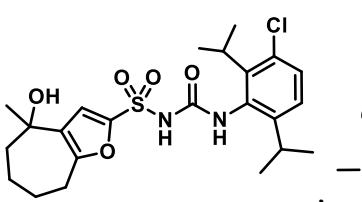
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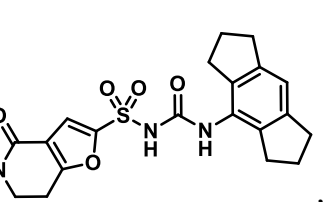
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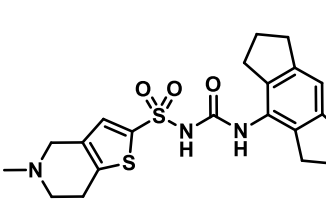
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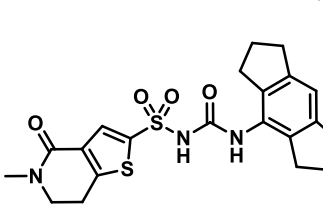
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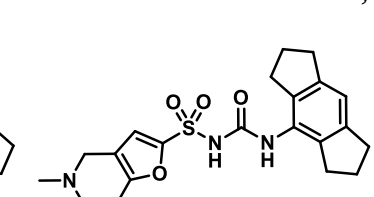
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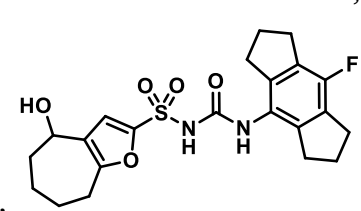
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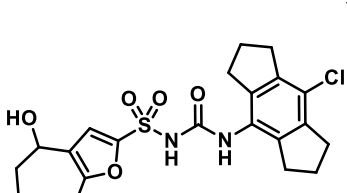
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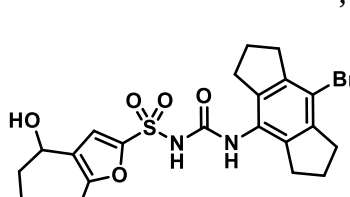
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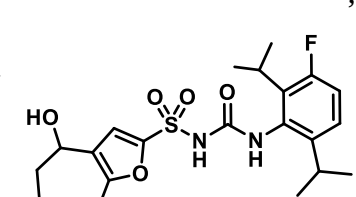
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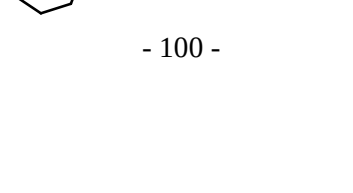
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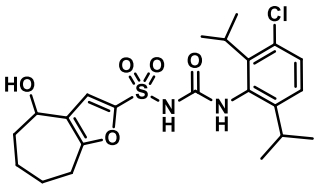
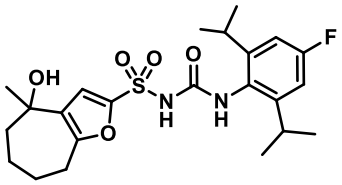
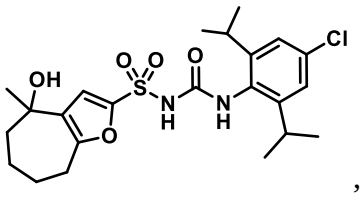
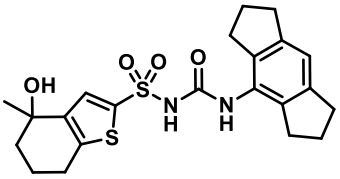
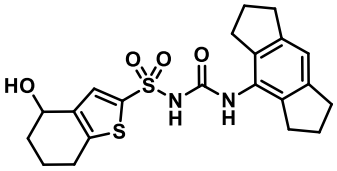
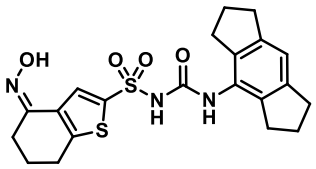
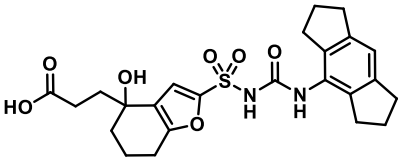
 ,  ,  ,

 ,  ,  , and

 ; or a pharmaceutically acceptable salt or solvate thereof.

43. A pharmaceutical composition comprising a compound of any one of claims 1-42, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

44. Use of a compound of any one of claims 1-42, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for ~~A method of~~ treating a metabolic disease in a patient in need thereof~~, comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1-42, or a pharmaceutically acceptable salt or solvate thereof~~.

45. The ~~method~~use of claim 44, wherein the metabolic disease is selected from type 2 diabetes, atherosclerosis, obesity and gout.

46. Use of a compound of any one of claims 1-42, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for ~~A method of~~ treating a liver disease in a patient in need thereof~~, comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1-42, or a pharmaceutically acceptable salt or solvate thereof~~.

47. The ~~method~~use of claim 46, wherein the liver disease is selected from non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH), viral hepatitis, and cirrhosis.

48. Use of a compound of any one of claims 1-42, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for ~~A method of~~ treating a lung disease in a patient in need thereof~~, comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1-42, or a pharmaceutically acceptable salt or solvate thereof~~.

49. The ~~method~~use of claim 48, wherein the lung disease is selected from asthma, chronic obstructive pulmonary disease (COPD), and pulmonary idiopathic fibrosis.
50. Use of a compound of any one of claims 1-42, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for ~~A method of~~ treating a central nervous system disease in a patient in need thereof~~, comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1-42, or a pharmaceutically acceptable salt or solvate thereof~~.
51. The ~~method~~use of claim 50, wherein the central nervous system disease is selected from Alzheimer's disease, multiple sclerosis, Amyotrophic Lateral Sclerosis, and Parkinson's disease.
52. Use of a compound of any one of claims 1-42, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for ~~A method of~~ treating an inflammatory or autoimmune disease in a patient in need thereof~~, comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1-42, or a pharmaceutically acceptable salt or solvate thereof~~.
53. The ~~method~~use of claim 52, wherein the inflammatory or autoimmune disease is selected from rheumatoid arthritis, multiple sclerosis, psoriasis, lupus, inflammatory bowel disease, Crohn’s disease, and ulcerative colitis.
54. Use of a compound of any one of claims 1-42, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for ~~A method of~~ treating a cardiovascular disease in a patient in need thereof~~, comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1-42, or a pharmaceutically acceptable salt or solvate thereof~~.
55. The ~~method~~use of claim 54, wherein the cardiovascular disease is atherosclerosis or stroke.
56. A compound of any one of claims 1-42, or a pharmaceutically acceptable salt or solvate thereof, for use in therapy.