NLRP3 MODULATORS

CROSS-REFERENCE

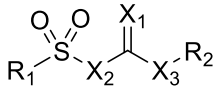
[0001] This application claims benefit of U.S. Provisional Application No. 62/990,363, filed on March 16, 2020, which is herein incorporated by reference in its entirety.

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

[0002a] In an aspect of the present disclosure, there is provided a compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I');

wherein:

X_1 is O, S, or N(R_3);

X_2 is -N(R_4)- or -C(R_4)$_2$-;

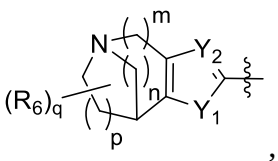
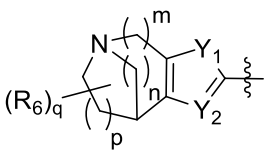
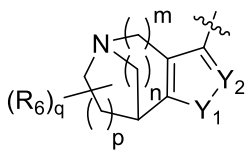
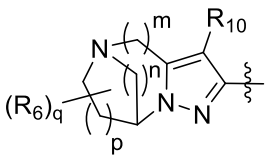
X_3 is -N(R_5)- or -C(R_5)$_2$-;

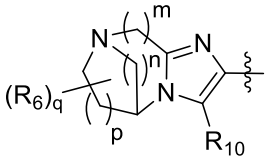
Y_1 is O, S, or N(R_8);

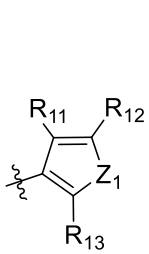
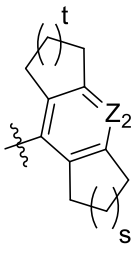
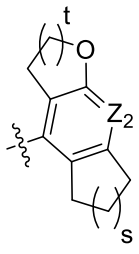
Y_2 is N or C(R_9);

Z_1 is O, S, N(R_3), or -C(R_{17})=C(R_{17})-;

Z_2 is N or C(R_{19});

R_1 is , , , ,

or ;

R_2 is , , or ;

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

each R_4 is independently selected from hydrogen, C_1-C_6alkyl, -C_1-C_6alkyl-OR_7, and -C_1-C_6alkyl-$N(R_7)_2$;

each R_5 is independently selected from hydrogen, C_1-C_6alkyl, -C_1-C_6alkyl-OR_7, and -C_1-C_6alkyl-$N(R_7)_2$;

each R_6 is independently selected from C_1-C_6alkyl, -C_1-C_6alkyl-CO_2R_{18}, C_1-C_6haloalkyl, -C_1-C_6alkyl-OR_7, and -C_1-C_6alkyl-$N(R_7)_2$;

each R_7 is independently selected from hydrogen and C_1-C_6alkyl;

R_8 is hydrogen, C_1-C_6alkyl, -C_1-C_6alkyl-OR_7, -C_1-C_6alkyl-$N(R_7)_2$, or C_3-C_6cycloalkyl;

R_9 is hydrogen, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_3-C_6cycloalkyl;

R_{10} is hydrogen, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkyl-OR_7, or -C_1-C_6alkyl-$N(R_7)_2$;

R_{11} and R_{12} are independently selected from hydrogen, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkyl-OR_7, and -C_1-C_6alkyl-$N(R_7)_2$; or R_{11} and R_{12} are combined to form a 5- or 6-membered cycloalkyl ring;

R_{13} is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_5cycloalkyl, C_2-C_9heterocycloalkyl, phenyl, or C_2-C_9heteroaryl, wherein C_3-C_5cycloalkyl, C_2-C_9heterocycloalkyl, phenyl, and C_2-C_9heteroaryl are optionally substituted by 1, 2, 3, or 4 R_{16};

R_{14} is hydrogen or C_1-C_6alkyl;

R_{15} is C_1-C_6alkyl;

each R_{16} is independently selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_6cycloalkyl, C_2-C_9heterocycloalkyl, C_6-C_{10}aryl, C_2-C_9heteroaryl,

wherein C_3-C_6cycloalkyl, C_2-C_9heterocycloalkyl, C_6-C_{10}aryl, C_2-C_9heteroaryl are optionally substituted with 1, 2, or 3 groups selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, and C_1-C_6haloalkoxy;

each R_{17} is independently selected from hydrogen, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkyl-OR_7, and -C_1-C_6alkyl-$N(R_7)_2$;

R_{18} is hydrogen or C_1-C_6alkyl;

R_{19} is hydrogen, halogen, -CN, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkyl-OR_7, or -C_1-C_6alkyl-$N(R_7)_2$;

m is 0, 1, or 2;

n is 1, 2, or 3;

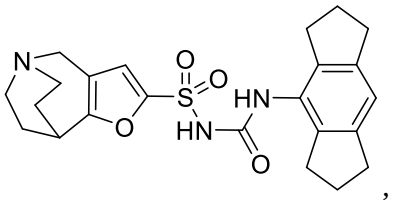
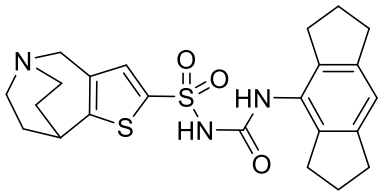
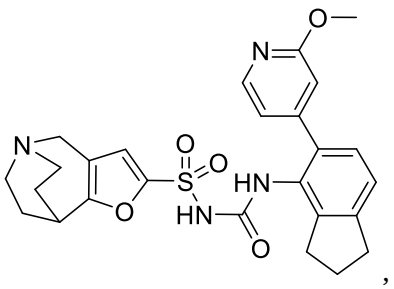
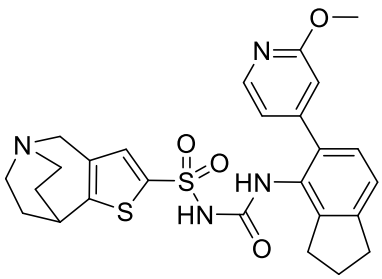
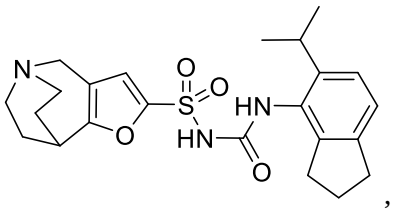
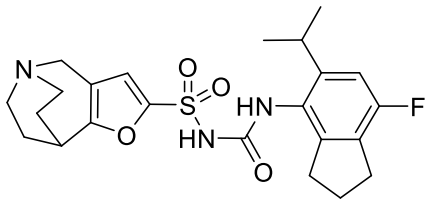
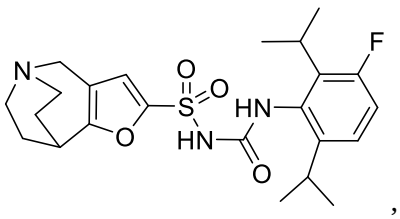
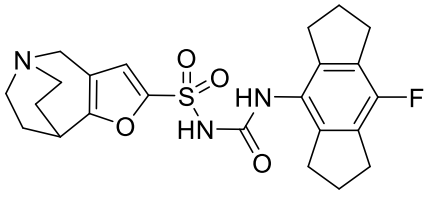
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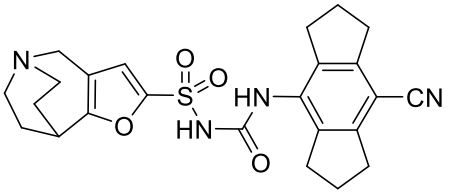
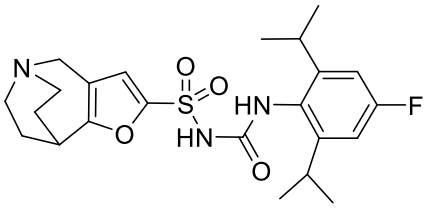
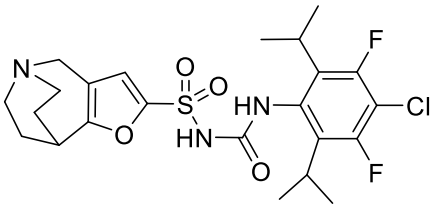
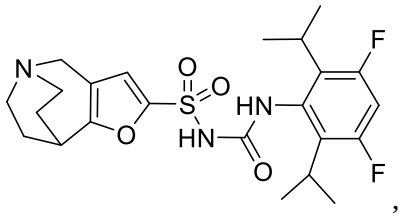
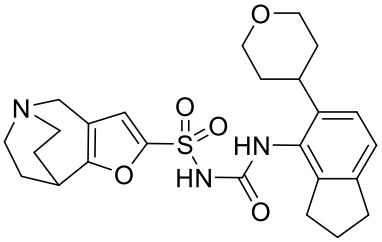
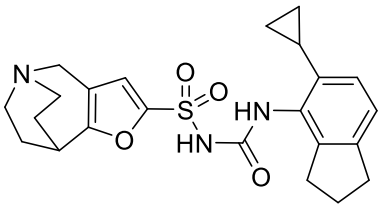
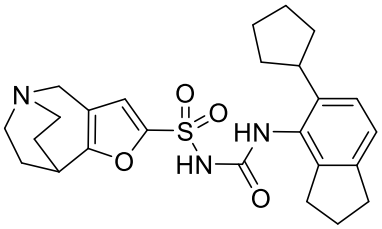
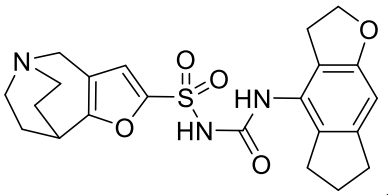
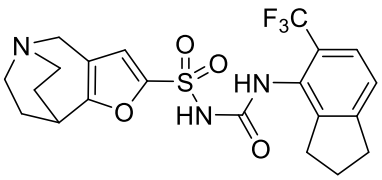
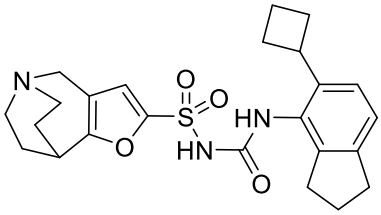
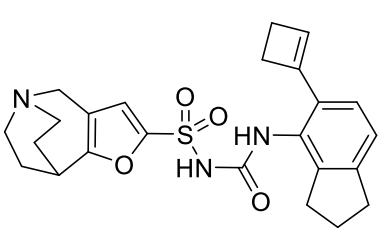
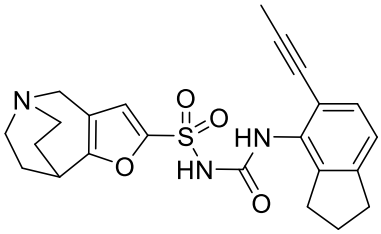
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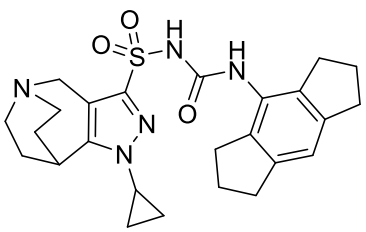
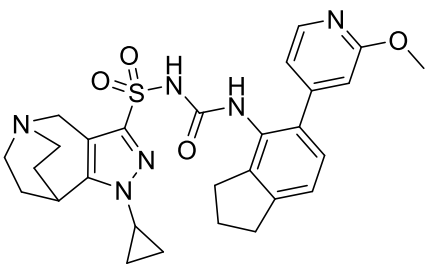
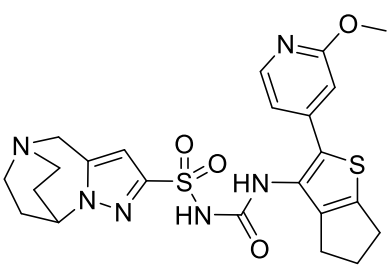
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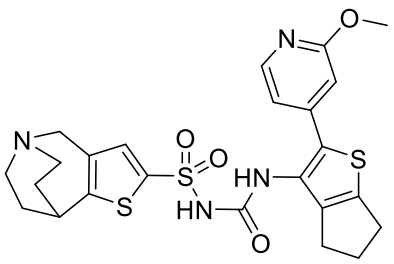
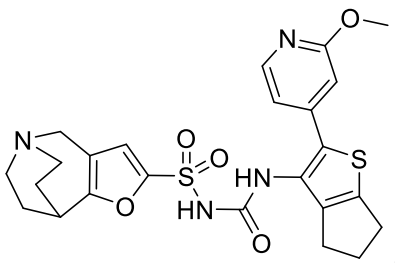
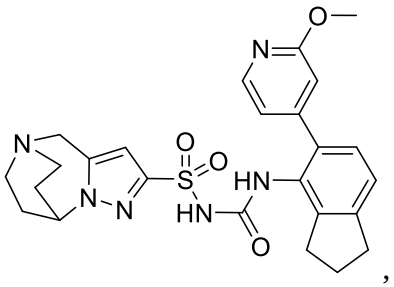
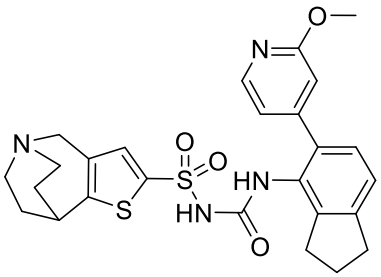
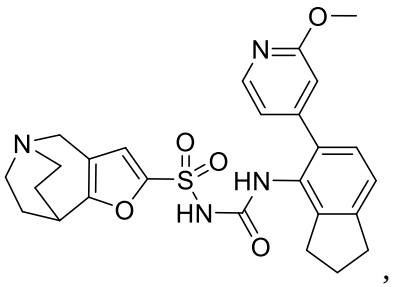
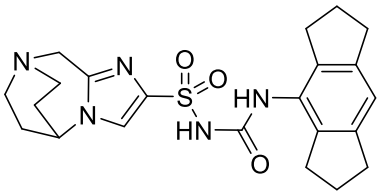
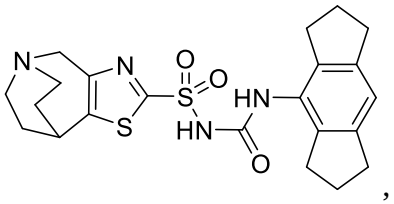
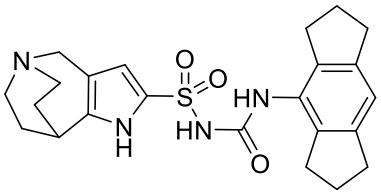
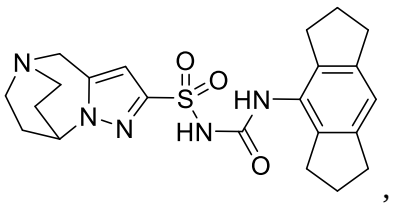
[0002b] In another aspect of the present disclosure, there is provided a compound selected from:


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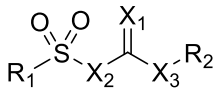

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[0002c] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

[0002d] 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 cryopyrin-associated periodic syndromes (CAPS) in a patient in need thereof.

[0002e] 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 example, provided herein are compounds of Formula (I') , or a pharmaceutically acceptable salt or solvate thereof:



Formula (I');

wherein:

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

X_2 is $-N(R_4)-$ or $-C(R_4)_2-$;

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

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

Y_2 is N or $C(R_9)$;

Z_1 is O, S, $N(R_3)$, or $-C(R_{17})=C(R_{17})-$;

Z_2 is N or $C(R_{19})$;

wherein C_3-C_6cycloalkyl, C_2-C_9heterocycloalkyl, C_6-C_{10}aryl, C_2-C_9heteroaryl are optionally substituted with 1, 2, or 3 groups selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, and C_1-C_6haloalkoxy;

each R_{17} is independently selected from hydrogen, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkyl-OR_7, and -C_1-C_6alkyl-$N(R_7)_2$;

R_{18} is hydrogen or C_1-C_6alkyl;

R_{19} is hydrogen, halogen, -CN, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkyl-OR_7, or -C_1-C_6alkyl-$N(R_7)_2$;

m is 0, 1, or 2;

n is 1, 2, or 3;

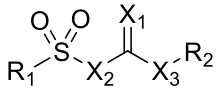
p is 0, 1, or 2;

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

s is 1, 2, or 3; and

t is 1, 2, or 3.

[0004] In another example, provided herein are compounds of Formula (I) , or a pharmaceutically acceptable salt or solvate thereof:



Formula (I);

wherein:

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

X_2 is -$N(R_4)$- or -$C(R_4)_2$-;

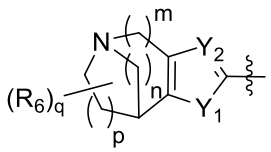
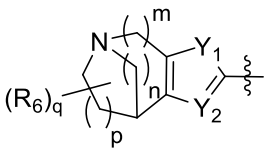
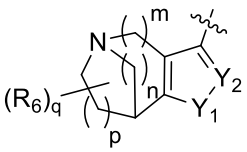
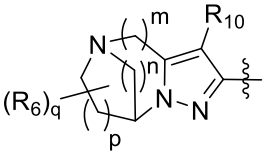
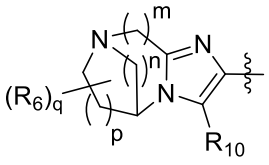
X_3 is -$N(R_5)$- or -$C(R_5)_2$-;

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

Y_2 is N or $C(R_9)$;

Z_1 is O, S, $N(R_3)$, or -$C(R_{17})$=$C(R_{17})$-;

Z_2 is N or $C(R_{19})$;

R_1 is , , , ,  or ;

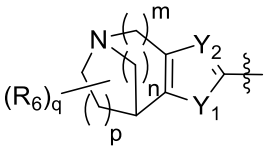
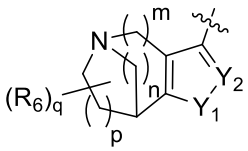
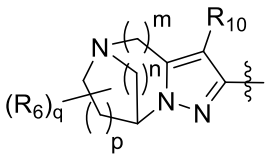
n is 1, 2, or 3;

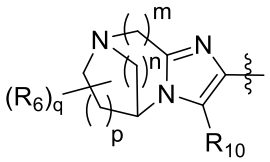
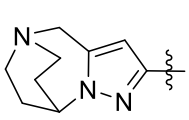
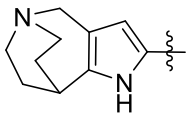
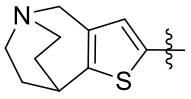
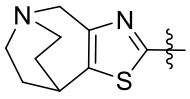
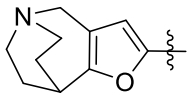
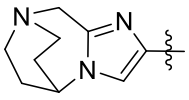
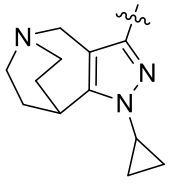
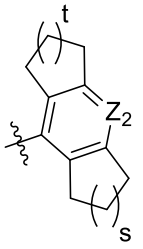
p is 0, 1, or 2;

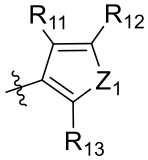
q is 0, 1, 2, 3, or 4;

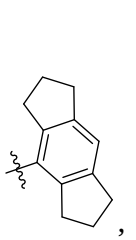
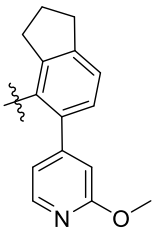
s is 1, 2, or 3; and

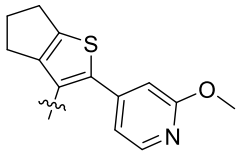
t is 1, 2, or 3.

[0005] In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is . In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is . In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein Y_2 is $C(R_9)$. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_9 is hydrogen or C_1-C_6alkyl. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_9 is hydrogen. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein Y_2 is N. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein Y_1 is O. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein Y_1 is S. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein Y_1 is $N(R_8)$. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_8 is hydrogen, C_1-C_6alkyl, or C_3-C_6cycloalkyl. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_8 is hydrogen. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_8 is C_1-C_6alkyl. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_8 is C_3-C_6cycloalkyl. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is . In some examples is a compound of Formula (I') or (I), or a

pharmaceutically acceptable salt or solvate thereof, wherein R_1 is . In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{10} is hydrogen. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R_6 is independently selected from C_1-C_6alkyl. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R_6 is -CH_3. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein q is 1. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein q is 2. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein q is 3. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein q is 0. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 2. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 1. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein m is 1. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein p is 1. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is , , , , , , or . In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is . In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein s is 1. In some examples is a compound of Formula (I') or (I), or a

pharmaceutically acceptable salt or solvate thereof, wherein t is 1. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein Z_2 is $C(R_{19})$. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{19} is hydrogen. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein Z_2 is N. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is 

. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein Z_1 is S. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein Z_1 is O. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein Z_1 is $-C(R_{17})=C(R_{17})-$. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R_{17} is hydrogen. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{11} and R_{12} are combined to form a 5- or 6-membered cycloalkyl ring. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{13} is phenyl optionally substituted by 1, 2, 3, or 4 R_{16}. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{13} is C_2-C_9heteroaryl optionally substituted by 1, 2, 3, or 4 R_{16}. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_{13} is pyridyl optionally substituted by 1, 2, 3, or 4 R_{16}. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R_{16} is independently selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, and C_1-C_6alkoxy. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R_{16} is C_1-C_6alkoxy. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is 
, 

, or 

. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein X_2 is $-N(R_4)-$. In some examples is a compound of Formula (I') or

(I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R_4 is hydrogen. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein X_3 is -N(R_5)-. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein X_3 is -C(R_5)$_2$-. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R_5 is hydrogen. In some examples is a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, wherein X_1 is O.

[0006] In another example described herein is a pharmaceutical composition comprising a compound of Formula (I') or (I), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

[0007] In some 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 (I), or a pharmaceutically acceptable salt or solvate thereof. In some 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 (I), or a pharmaceutically acceptable salt or solvate thereof, wherein the metabolic disease is selected from type 2 diabetes, atherosclerosis, obesity, and gout.

[0008] In some 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 (I), or a pharmaceutically acceptable salt or solvate thereof. In some 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 (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.

[0009] In some 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 (I), or a pharmaceutically acceptable salt or solvate thereof. In some 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 (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.

[0010] In some 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 (I), or a pharmaceutically acceptable salt or solvate thereof. In some 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 (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.

[0011] In some 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 (I), or a pharmaceutically acceptable salt or solvate thereof. In some 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 (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.

[0012] In some 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 (I), or a pharmaceutically acceptable salt or solvate thereof. In some 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 (I), or a pharmaceutically acceptable salt or solvate thereof, wherein the cardiovascular disease is atherosclerosis or stroke.

INCORPORATION BY REFERENCE

[0013] 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

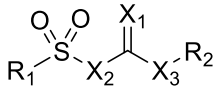
[0014] In the context of this disclosure, a number of terms shall be utilized.

[0015] 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

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I');

wherein:

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

X_2 is $-N(R_4)-$ or $-C(R_4)_2-$;

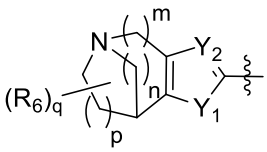
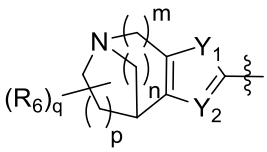
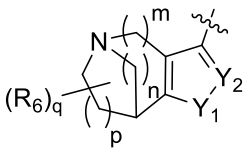
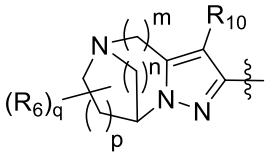
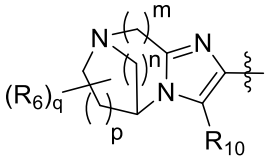
X_3 is $-N(R_5)-$ or $-C(R_5)_2-$;

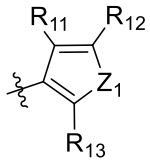
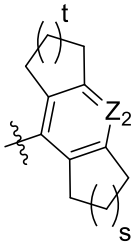
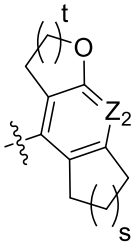
Y_1 is O, S, or $N(R_8)$;

Y_2 is N or $C(R_9)$;

Z_1 is O, S, $N(R_3)$, or $-C(R_{17})=C(R_{17})-$;

Z_2 is N or $C(R_{19})$;

R_1 is , , , , or ;

R_2 is , , or ;

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

each R_4 is independently selected from hydrogen, C_1-C_6alkyl, -C_1-C_6alkyl-OR_7, and -C_1-C_6alkyl-$N(R_7)_2$;

each R_5 is independently selected from hydrogen, C_1-C_6alkyl, -C_1-C_6alkyl-OR_7, and -C_1-C_6alkyl-$N(R_7)_2$;

each R_6 is independently selected from C_1-C_6alkyl, -C_1-C_6alkyl-CO_2R_{18}, C_1-C_6haloalkyl, -C_1-C_6alkyl-OR_7, and -C_1-C_6alkyl-$N(R_7)_2$;

each R_7 is independently selected from hydrogen and C_1-C_6alkyl;

R_8 is hydrogen, C_1-C_6alkyl, -C_1-C_6alkyl-OR_7, -C_1-C_6alkyl-$N(R_7)_2$, or C_3-C_6cycloalkyl;

R_9 is hydrogen, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_3-C_6cycloalkyl;

R_{10} is hydrogen, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkyl-OR_7, or -C_1-C_6alkyl-$N(R_7)_2$;

R_{11} and R_{12} are independently selected from hydrogen, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkyl-OR_7, and -C_1-C_6alkyl-$N(R_7)_2$; or R_{11} and R_{12} are combined to form a 5- or 6-membered cycloalkyl ring;

R_{13} is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_5cycloalkyl, C_2-C_9heterocycloalkyl, phenyl, or C_2-C_9heteroaryl, wherein C_3-C_5cycloalkyl, C_2-C_9heterocycloalkyl, phenyl, and C_2-C_9heteroaryl are optionally substituted by 1, 2, 3, or 4 R_{16};

R_{14} is hydrogen or C_1-C_6alkyl;

R_{15} is C_1-C_6alkyl;

each R_{16} is independently selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_6cycloalkyl, C_2-C_9heterocycloalkyl, C_6-C_{10}aryl, C_2-C_9heteroaryl, wherein C_3-C_6cycloalkyl, C_2-C_9heterocycloalkyl, C_6-C_{10}aryl, C_2-C_9heteroaryl are optionally substituted with 1, 2, or 3 groups selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, and C_1-C_6haloalkoxy;

each R_{17} is independently selected from hydrogen, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkyl-OR_7, and -C_1-C_6alkyl-$N(R_7)_2$;

R_{18} is hydrogen or C_1-C_6alkyl;

R_{19} is hydrogen, halogen, -CN, C_1-C_6alkyl, C_1-C_6haloalkyl, -C_1-C_6alkyl-OR_7, or -C_1-C_6alkyl-$N(R_7)_2$;

m is 0, 1, or 2;

n is 1, 2, or 3;

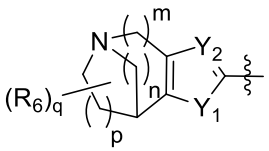
p is 0, 1, or 2;

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

s is 1, 2, or 3; and

t is 1, 2, or 3.

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

wherein R_1 is 

.

3. The compound of claim 2, or a pharmaceutically acceptable salt or solvate thereof, wherein:

Y_2 is $C(R_9)$;

R_9 is hydrogen; and

Y_1 is O.

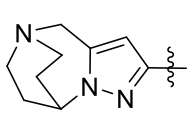
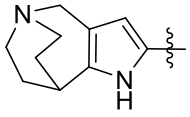
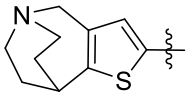
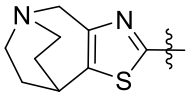
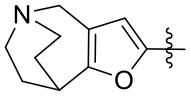
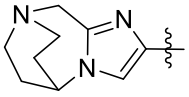
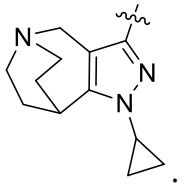
4. The compound of claim 3, or a pharmaceutically acceptable salt or solvate thereof, wherein:

   q is 0;

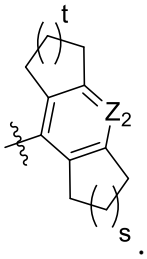
   n is 2;

   m is 1; and

   p is 1.

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

6. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein:



R_2 is .

7. The compound of claim 6, or a pharmaceutically acceptable salt or solvate thereof, wherein:

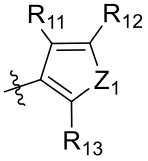
   s is 1;

   t is 1;

   Z_2 is $C(R_{19})$; and

   R_{19} is hydrogen or halogen.

8. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof,



wherein R_2 is .

9. The compound of claim 8, or a pharmaceutically acceptable salt or solvate thereof, wherein:

Z_1 is S or -C(R_{17})=C(R_{17})-; and

each R_{17} is independently selected from hydrogen and halogen.

10. The compound of claim 9, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R_{11} and R_{12} are combined to form a 5-membered cycloalkyl ring; or

R_{11} and R_{12} are independently selected from hydrogen, halogen, and C_1-C_6alkyl.

11. The compound of claim 9, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R_{13} is C_2-C_9heteroaryl optionally substituted by 1, 2, 3, or 4 R_{16}.

12. The compound of claim 11, or a pharmaceutically acceptable salt or solvate thereof, wherein:

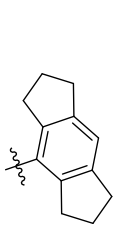
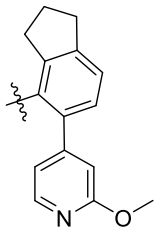
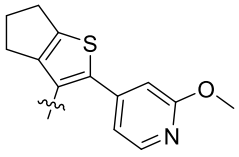
R_{13} is pyridyl optionally substituted by 1, 2, 3, or 4 R_{16}.

13. The compound of claim 12, or a pharmaceutically acceptable salt or solvate thereof, wherein:

each R_{16} is independently selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, and C_1-C_6alkoxy.

14. The compound of claim 9, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R_{13} is C_1-C_6alkyl or C_3-C_5cycloalkyl.

15. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein R_2 is , , or .

16. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein:

X_2 is -N(R_4)-;

X_3 is -N(R_5)-; and

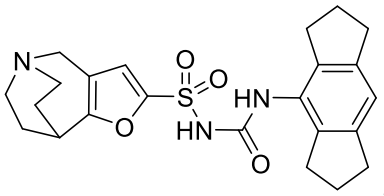
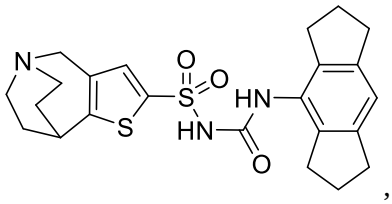
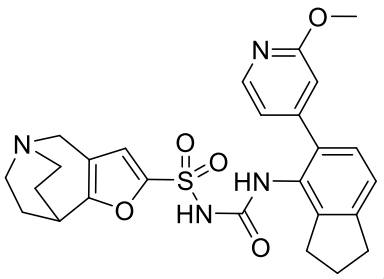
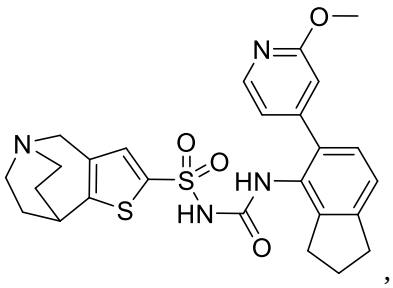
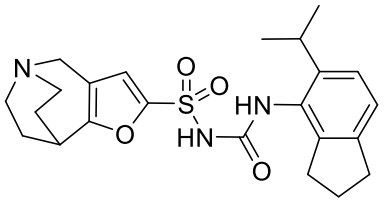
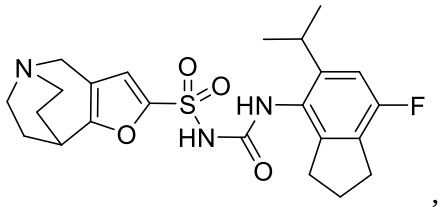
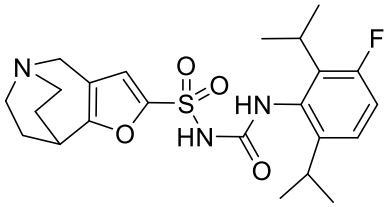
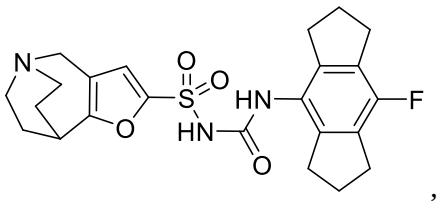
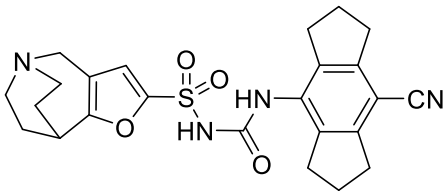
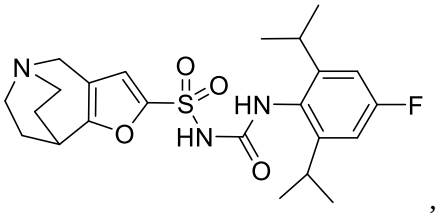
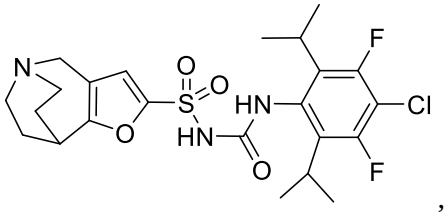
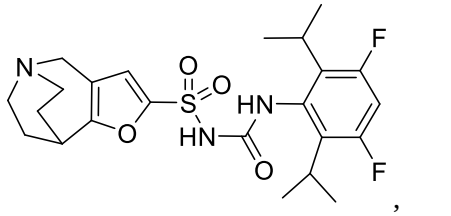
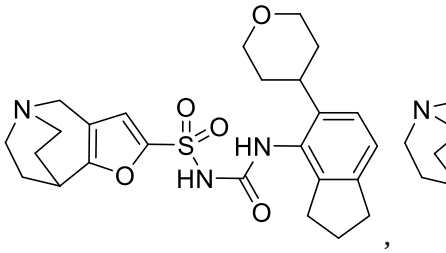
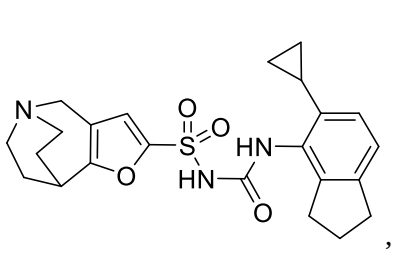
X_1 is O.

17. The compound of claim 16, or a pharmaceutically acceptable salt or solvate thereof, wherein:

each R_4 is hydrogen; and

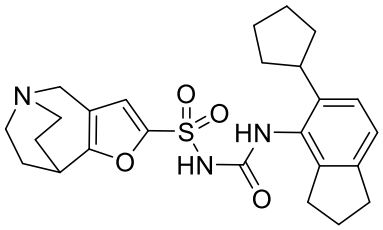
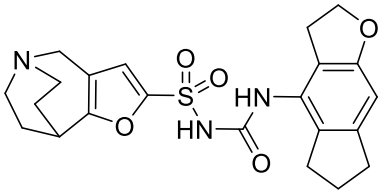
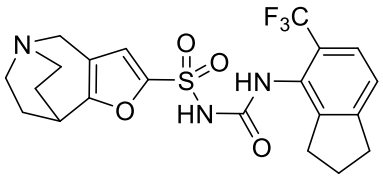
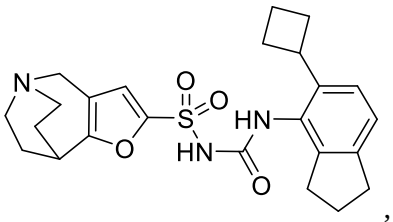
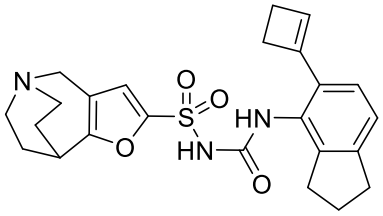
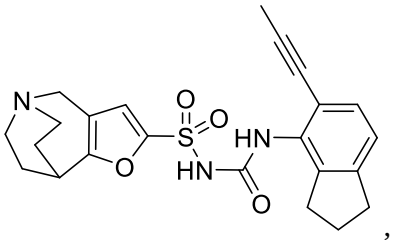
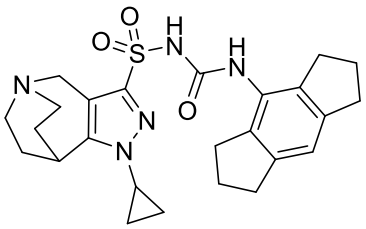
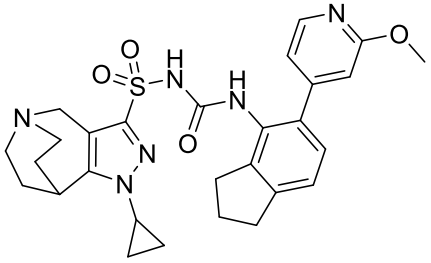
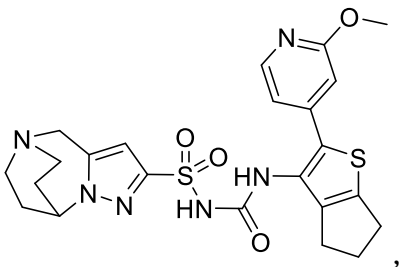
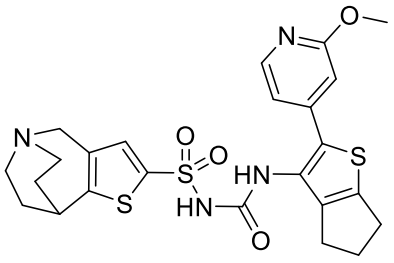
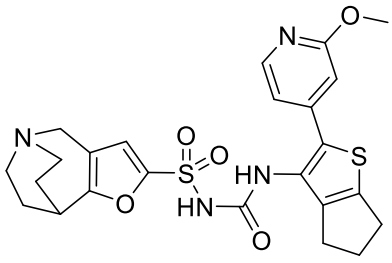
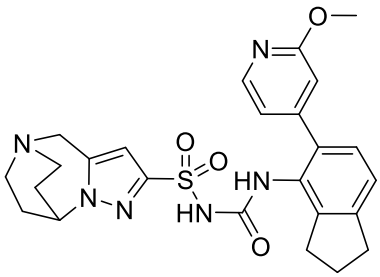
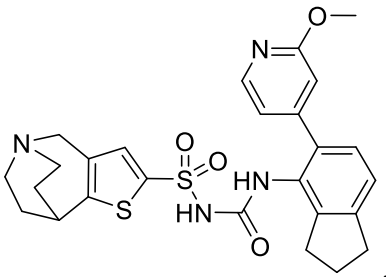
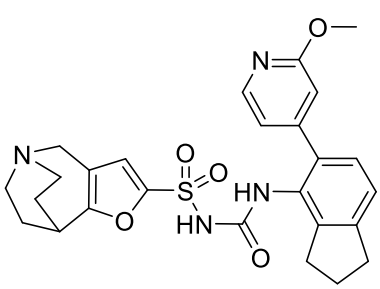
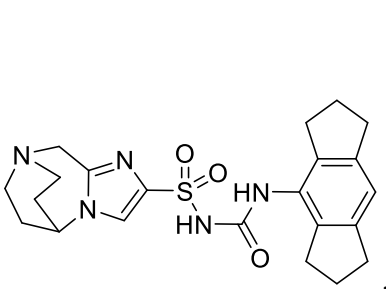
each R_5 is hydrogen.

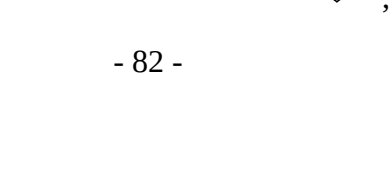
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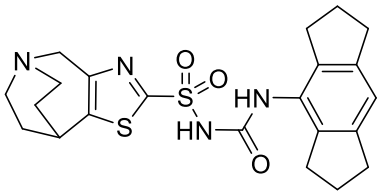

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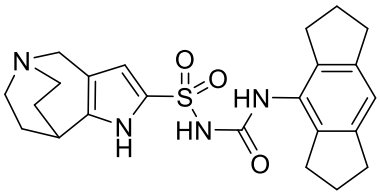
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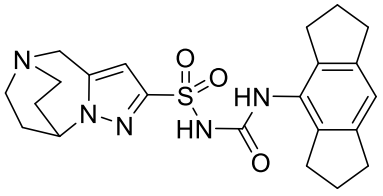
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or a pharmaceutically acceptable salt or solvate thereof.

19. A pharmaceutical composition comprising a compound of any one of claims 1-18, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.
20. Use of a compound of any one of claims 1-18, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating cryopyrin-associated periodic syndromes (CAPS) in a patient in need thereof.
21. A compound of any one of claims 1-18, or a pharmaceutically acceptable salt or solvate thereof, for use in therapy.