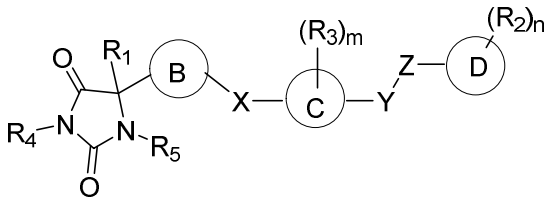
CLAIMS

~~We claim:~~

1. A compound of formula (II):



(II),

or a tautomer, stereoisomer, pharmaceutically acceptable salt, or solvate thereof,

wherein:

ring B is optionally substituted furanyl;

ring C is aryl or heteroaryl;

ring D is ~~aryl or heteroaryl;~~phenyl, pyridinyl, or pyridinyl N-oxide;

each of X, Y, and Z is independently selected from the group consisting of O, CH_2, NR_x and $S(O)_q$, wherein R_x is hydrogen or alkyl;

R_1 is hydrogen or alkyl;

each R_2 is independently selected from the group consisting of hydrogen, alkyl, halo, hydroxyl, haloalkyl, alkoxy, alkylthio, amino, amide, alkylamine, aminoalkyl, cyano, hydroxyalkyl, $-(CH_2)_pC(O)OR_6$, and $-(CH_2)_pOC(O)R_6$;

each R_3 is independently selected from the group consisting of hydrogen, alkyl and halo;

R_4 is hydrogen or alkyl;

R_5 is hydrogen;

each R_6 is independently selected from the group consisting of hydrogen and alkyl, wherein the alkyl is unsubstituted or substituted with one or more groups independently selected from the group consisting of amino, hydroxyl, halo, and alkoxy;

m is 1, 2, 3, or 4;

n is 1, 2, 3, 4, or 5;

p is 0, 1, 2, 3, 4, or 5; and

q is 0, 1, or 2;

provided that when ring D is phenyl, at least one of the following is true:

(i) R_1 is alkyl;

(ii) R_2 is not methoxy, chloro, or trifluoromethyl; and

(iii) ring C is not unsubstituted phenyl.

2. The compound of claim 1, wherein ring C is phenyl.

3. The compound of claim 1, wherein ring D is pyridinyl or pyridinyl N-oxide.

4. The compound of claim 1, wherein R_4 is hydrogen.

5. The compound of claim 1, wherein R_1 is alkyl.

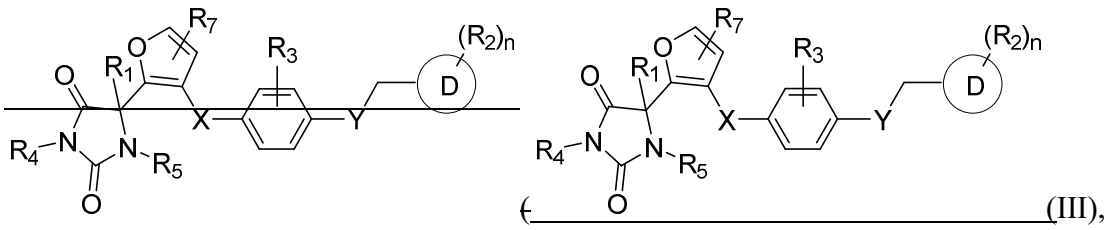
6. The compound of claim 1, wherein X is S and Z is CH_2.

7. The compound of claim 1, wherein X is S, -Y is O, and Z is CH_2.

8. The compound of claim 1, wherein n is 1; and R_2 is alkyl, alkoxy, hydroxy, hydroxyalkyl or amide.

9. The compound of claim 1, wherein n is 1; and R_2 is $-CH_3$, C_{1-4} alkoxy, -OH, $-CH_2OH$, or $-C(O)NH_2$.

10. The compound of claim 1, being a compound of formula (III):



(III),

or a tautomer, stereoisomer, pharmaceutically acceptable salt, or solvate thereof, wherein:

R_1 is hydrogen or C_{1-4} alkyl;

X is S;

Y is O, CH_2, NH, or $N(CH_3)$;

each R_2 is independently selected from the group consisting of hydrogen, alkyl, hydroxyl, alkoxy, amide, and hydroxyalkyl;

each R_3 is hydrogen, alkyl or halo;

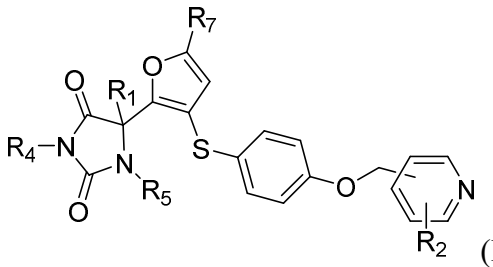
ring D is phenyl, pyridinyl, or pyridinyl N-oxide;

each of R_4 and R_5 is hydrogen;

R_7 is hydrogen or methyl; and

n is 1 or 2.

11. A compound of formula (IV):



(IV),

or a tautomer, stereoisomer, pharmaceutically acceptable salt, or solvate thereof, wherein:

R_1 is hydrogen or alkyl;

R_2 is selected from the group consisting of alkyl, amide, hydroxyl, alkoxy, and hydroxylalkyl;

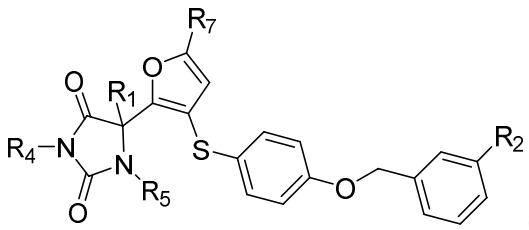
each of R_4 and R_5 is hydrogen; and

R_7 is methyl or hydrogen.

12. The compound of claim 11, wherein R_2 is $-CH_3$, C_{1-4} alkoxy, -OH, $-CH_2OH$, or $-C(O)NH_2$.

13. The compound of claim 11, wherein R_1 is C_{1-4} alkyl.

14. A compound of formula (V):



(V),

or a tautomer, stereoisomer, pharmaceutically acceptable salt, or solvate thereof,

wherein:

R_1 is alkyl;

R_2 is selected from the group consisting of alkyl, amide, alkoxy, hydroxyl, and hydroxyalkyl;

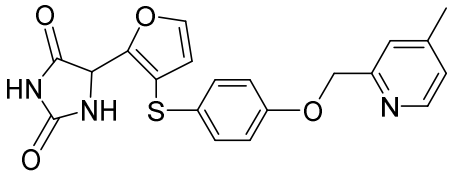
each of R_4 and R_5 is hydrogen; and

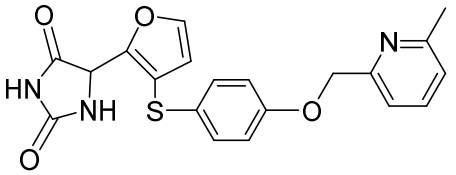
R_7 is methyl or hydrogen.

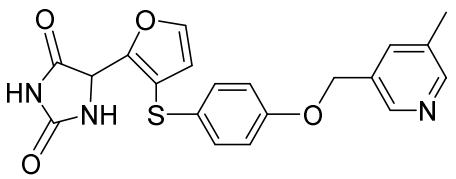
15. The compound of claim 14, wherein R_2 is $-CH_3$, C_{1-4} alkoxy, -OH, $-CH_2OH$, or $-C(O)NH_2$.

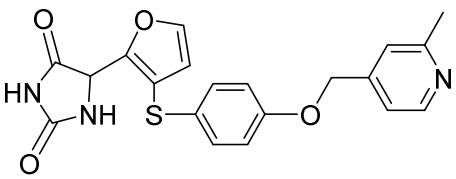
16. The compound of claim 14, wherein R_1 is C_{1-4} alkyl.

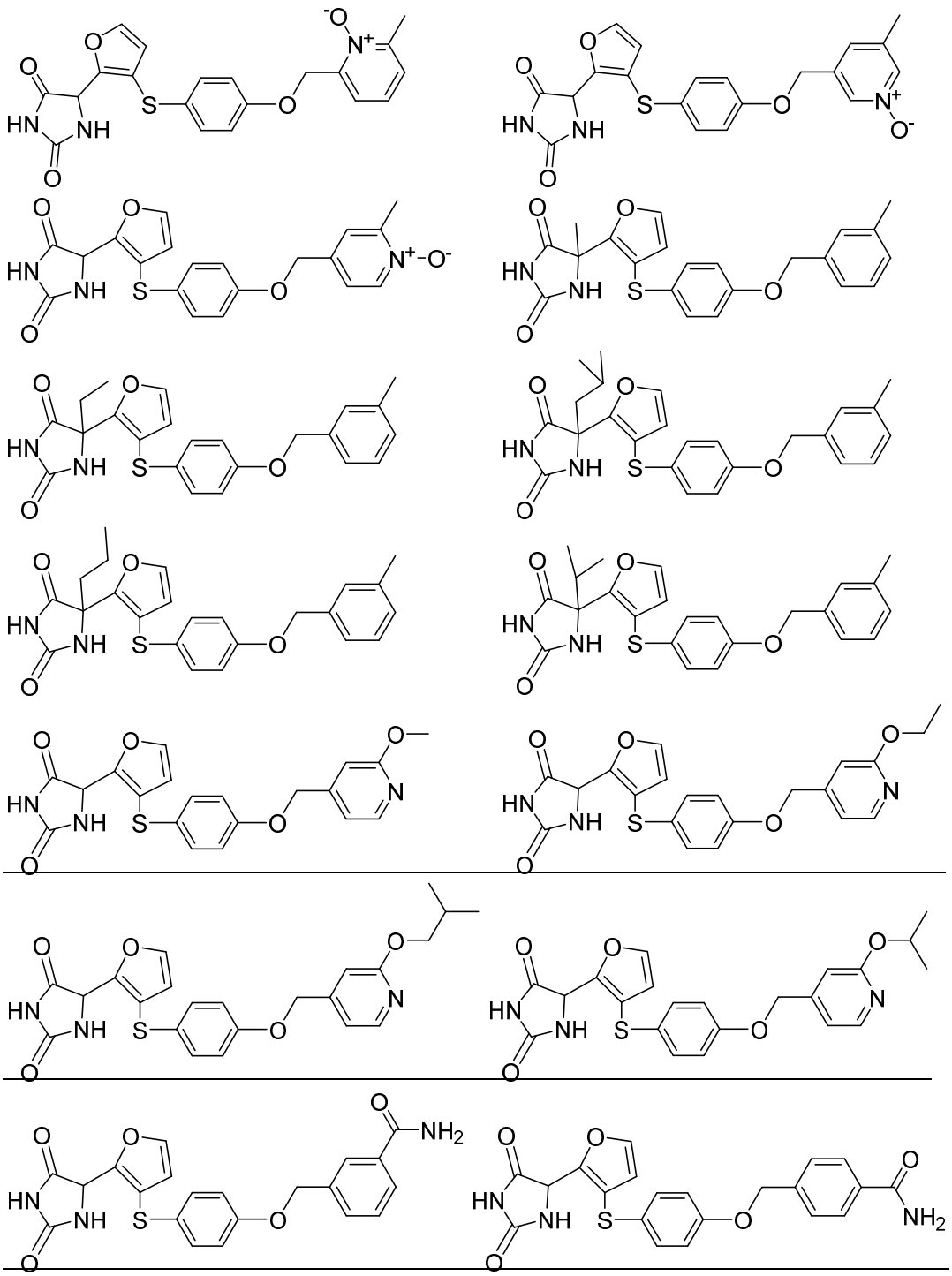
17. The compound of claim 1, being a compound selected from the group consisting of:

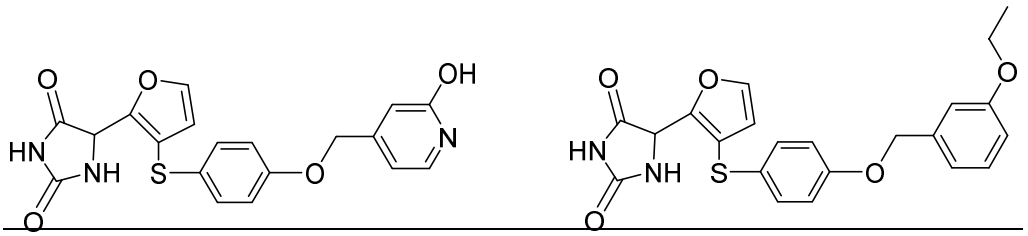
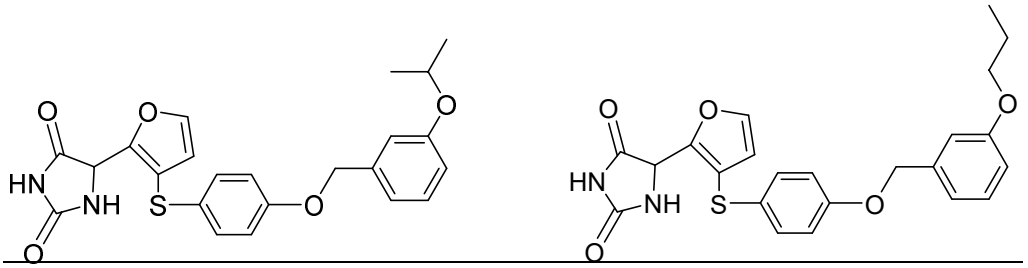
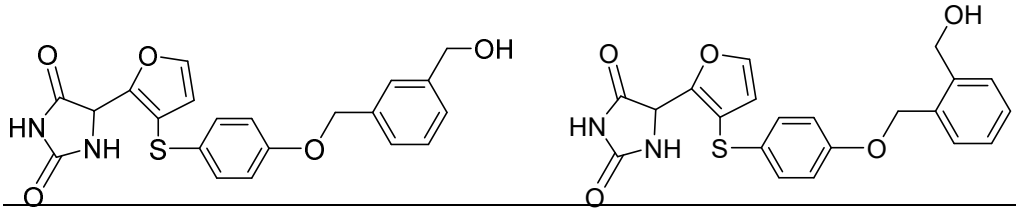
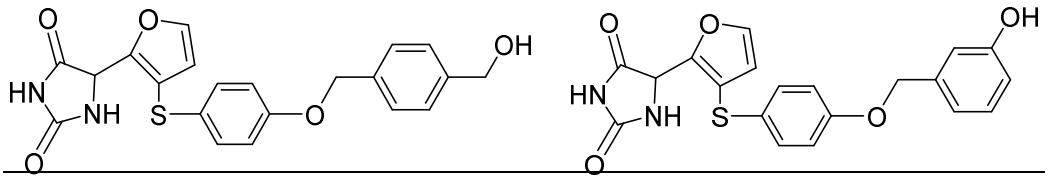
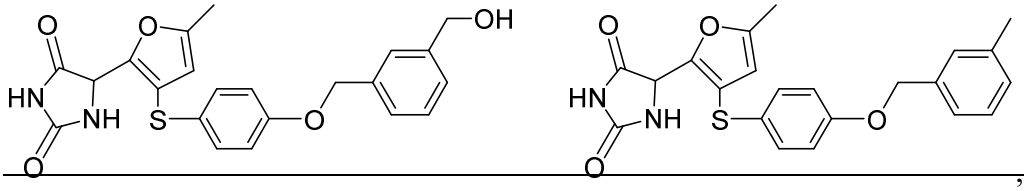
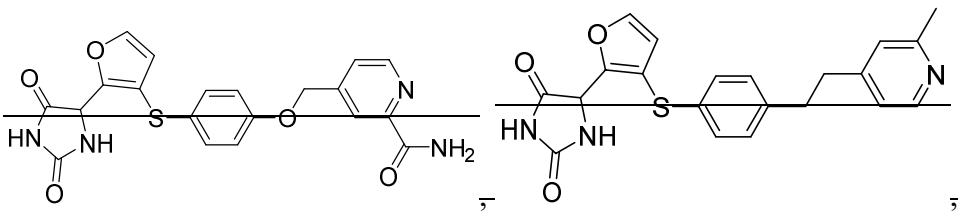
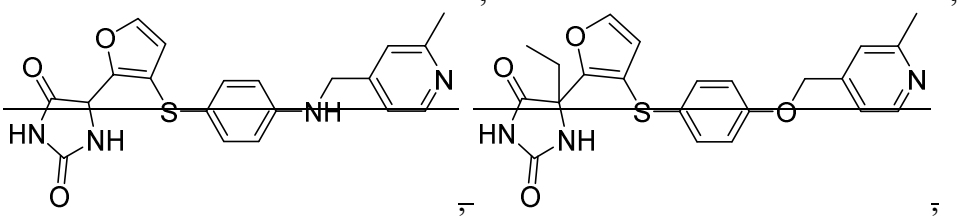




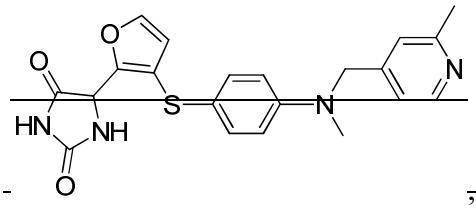
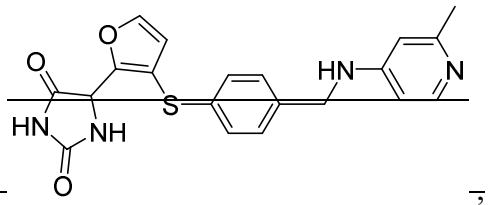
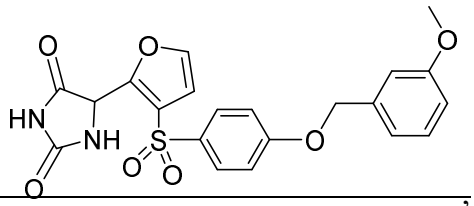
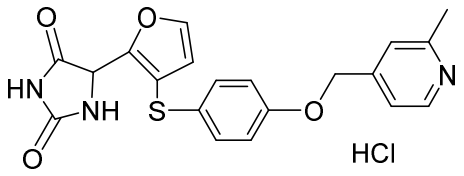
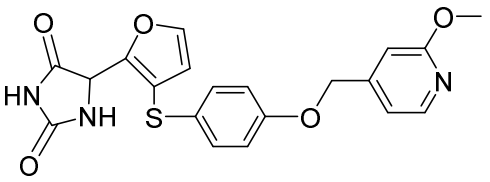
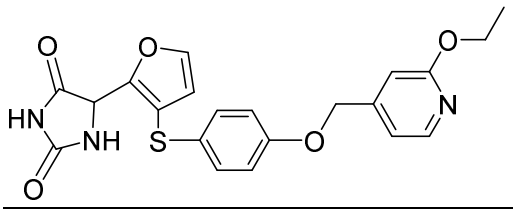
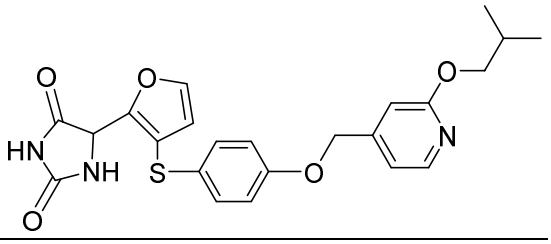
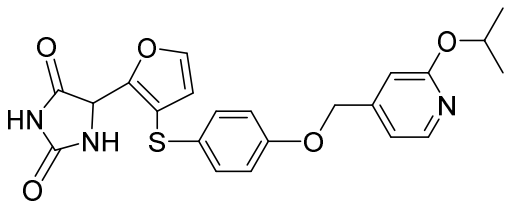
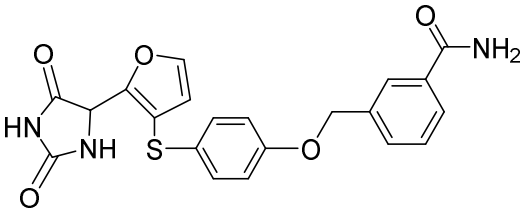
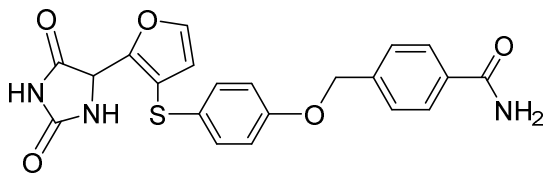
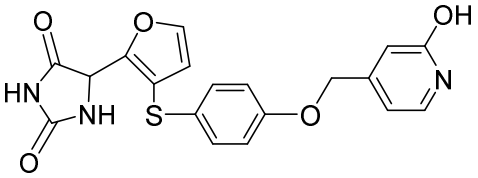
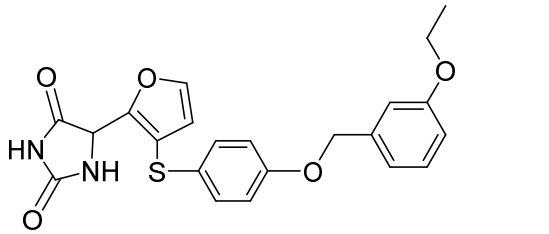
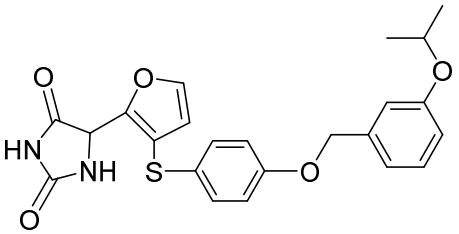


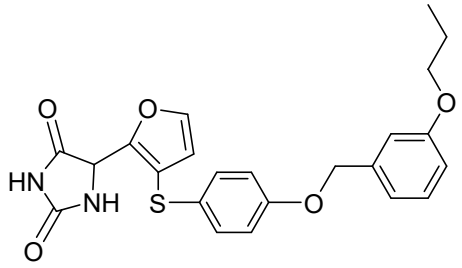
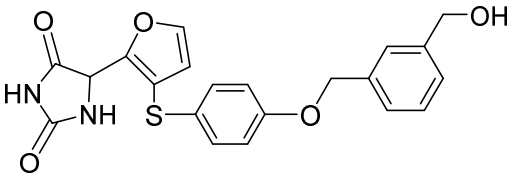


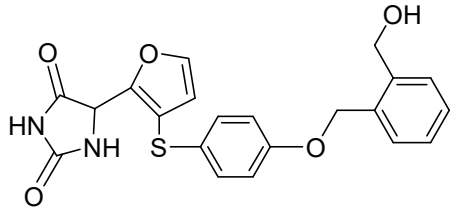
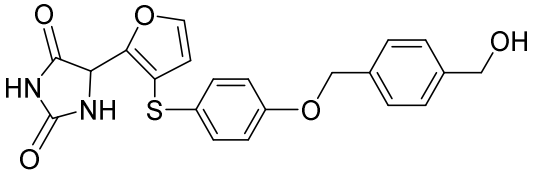


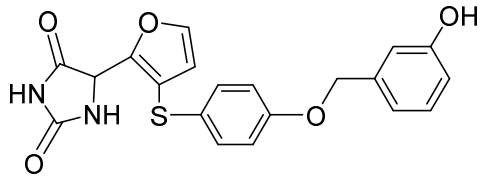
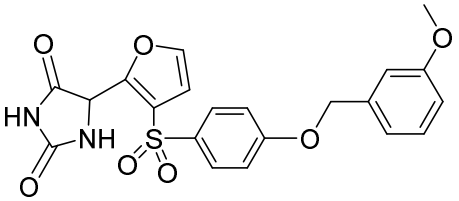








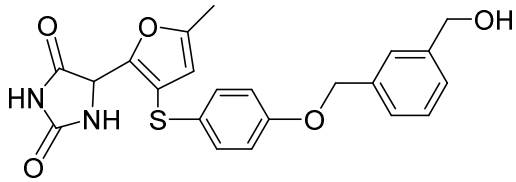
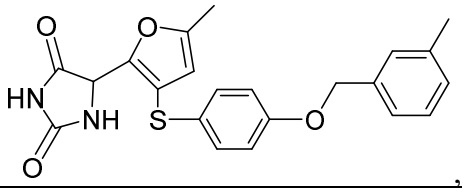
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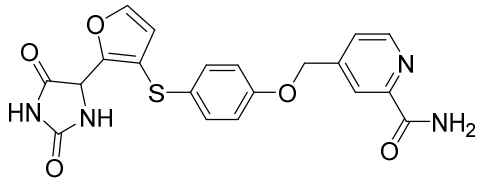
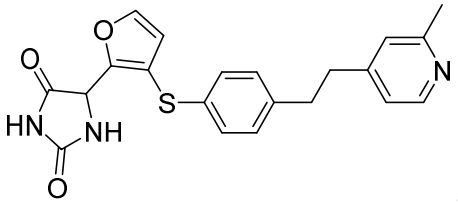




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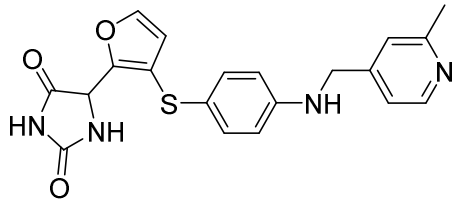
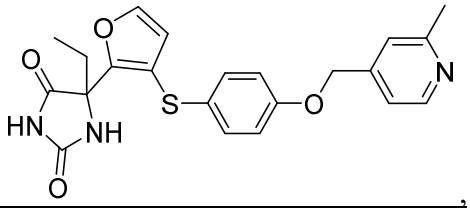



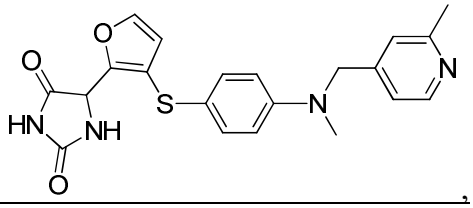





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and .

or a tautomer, stereoisomer, pharmaceutically acceptable salt, or solvate thereof.

18. The compound of claim 17, or a pharmaceutically acceptable salt thereof.

19. A pharmaceutical composition comprising the compound of ~~any one of claims~~ claim 1 ~~to 18~~, and at least one pharmaceutically acceptable carrier.

20. ~~A method of~~ The pharmaceutical composition of claim 19 for use in inhibiting macrophage elastase (MMP-12) in a subject in need thereof, ~~the method comprising administering~~wherein the pharmaceutical composition is to be administered to the subject ~~the pharmaceutical composition of claim 19~~.

21. ~~A~~The pharmaceutical composition of claim 19 for use in a method of treating a disease mediated by macrophage elastase MMP-12 in a subject in need thereof~~, the method comprising administering to the subject the pharmaceutical composition of claim 19~~, wherein the disease is selected from the group consisting of asthma, chronic obstructive pulmonary disease (COPD), emphysema, acute lung injury, idiopathic pulmonary fibrosis (IPF), sarcoidosis, systemic sclerosis, liver fibrosis, nonalcoholic steatohepatitis (NASH), arthritis, cancer, heart disease, inflammatory bowel disease (IBD), acute kidney injury (AKI), chronic kidney disease (CKD), Alport syndrome, and nephritis, and wherein the pharmaceutical composition is to be administered to the subject.

22. Use of the pharmaceutical composition of claim 19 in the manufacture of a medicament for the treatment of a disease mediated by macrophage elastase MMP-12 in a subject in need thereof, wherein the disease is selected from the group consisting of asthma, chronic obstructive pulmonary disease (COPD), emphysema, acute lung injury, idiopathic pulmonary fibrosis (IPF), sarcoidosis, systemic sclerosis, liver fibrosis, nonalcoholic steatohepatitis (NASH), arthritis, cancer, heart disease, inflammatory bowel disease (IBD), acute kidney injury (AKI), chronic kidney disease (CKD), Alport syndrome, and

nephritis, and wherein the pharmaceutical composition is to be administered to the subject.