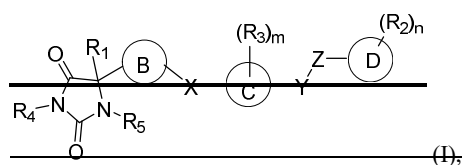


## Claims CLAIMS

We claim:

1. — A compound of formula (I):



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

wherein:

— ring B is an optionally substituted aryl or optionally substituted heteroaryl;

— ring C is aryl or heteroaryl;

ring D is aryl or heteroaryl;

— each of X, Y, and Z is independently selected from the group consisting of O, CH<sub>2</sub>, NR<sub>x</sub>, and S(O)<sub>q</sub>, wherein R<sub>x</sub> is hydrogen or alkyl;

— R<sub>1</sub> is hydrogen or alkyl;

each R<sub>2</sub> is independently selected from the group consisting of hydrogen, alkyl, halo, hydroxyl, haloalkyl, alkoxy, alkylthio, amino, amide, alkylamine, aminoalkyl, cyano, hydroxyalkyl, (CH<sub>2</sub>)<sub>p</sub>C(O)OR<sub>6</sub>, and (CH<sub>2</sub>)<sub>p</sub>OC(O)R<sub>6</sub>;

each R<sub>3</sub> is independently selected from the group consisting of hydrogen, alkyl and halo;

R<sub>4</sub> is hydrogen or alkyl;

— R<sub>5</sub> is hydrogen;

— each R<sub>6</sub> 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

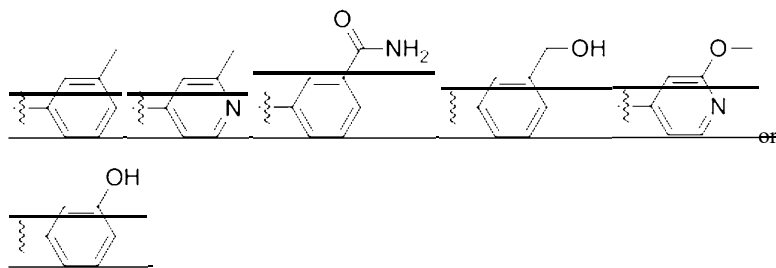
q is 0, 1, or 2;

provided that ring B is not furanyl.

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

3. The compound of claim 1, wherein ring D is pyridinyl or phenyl.

4. The compound of claim 1, wherein ring D is:



5. The compound of claim 1, wherein each of  $R_1$ ,  $R_4$  and  $R_5$  is hydrogen.

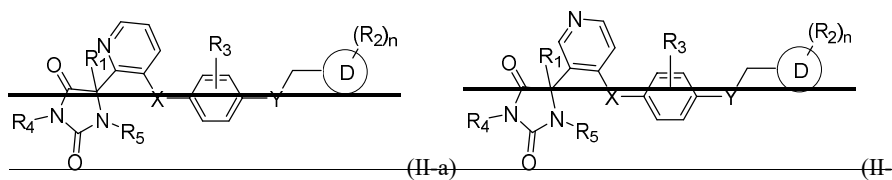
6. The compound of claim 1, wherein X is S; Y is O; and Z is  $CH_2$ .

7. The compound of claim 1, wherein ring B is a five or six membered monocyclic heteroaryl having 1-2 heteroatoms independently selected from N, S, and O, wherein the five or six membered monocyclic heteroaryl is optionally substituted with  $CH_3$ .

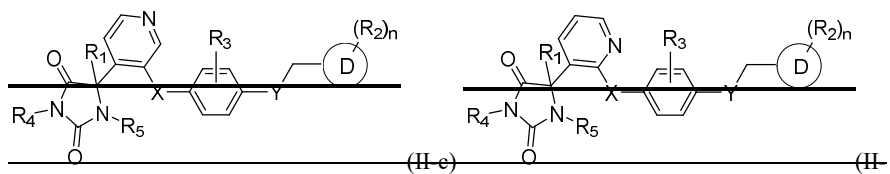
8. The compound of claim 7, wherein ring B is pyridinyl, thiophenyl, imidazolyl, pyrazolyl, or oxazolyl, wherein each of pyridinyl, thiophenyl, imidazolyl, pyrazolyl, and oxazolyl is optionally substituted with  $CH_3$ .

9. The compound of claim 7, wherein ring B is pyridinyl.

10. The compound of claim 9, wherein the compound is selected from the group consisting of a compound of formula (II-a), a compound of formula (II-b), a compound of formula (II-c), and a compound of formula (II-d):



b)



d)

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

wherein:

—  $R_1$  is hydrogen,  $CH_3$ , or  $CH_2CH_3$ ;

—  $R_4$  is hydrogen or  $CH_3$ ;

—  $R_5$  is hydrogen or  $CH_3$ ;

—  $R_3$  is hydrogen, F, Cl, or  $CH_3$ ;

— X is S, SO, or  $SO_2$ ;

— Y is O, NH,  $CH_2$ , or  $NHCH_3$ ;

— ring D is pyridinyl or phenyl;

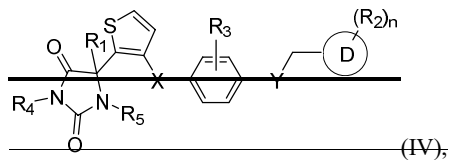
$R_2$  is  $CH_3$ ,  $CH_2OH$ , OH,  $CH_2OC(O)CH(NH_2)CH(CH_3)_2$ , COOH,  $C(O)NH_2$ ,

$C(O)NHCH_3$ ,  $OCH_3$ ,  $OCH_2CH_3$ ,  $OCH(CH_3)_2$ , or  $CH_2CH(CH_3)_2$ ; and

— n is 0 or 1.

11. The compound of claim 7, wherein ring B is thiophenyl.

12. The compound of claim 11, wherein the compound is a compound of formula (IV):



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

wherein:

each of  $R_1$ ,  $R_4$  and  $R_5$  is hydrogen;

$X$  is S;

$Y$  is O;

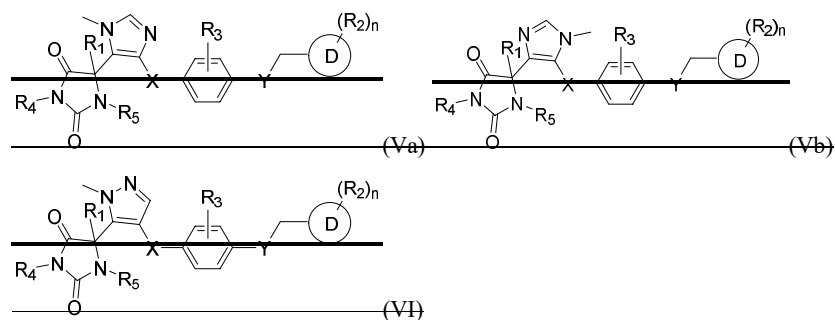
$R_3$  is hydrogen;

ring D is phenyl or pyridinyl;

$R_2$  is  $\text{CH}_3$ ,  $\text{C}(\text{O})\text{NH}_2$ ,  $\text{CH}_2\text{OH}$ ,  $\text{OCH}_3$ , or  $\text{OH}$ ; and

$n$  is 0 or 1.

13. The compound of claim 7, wherein the compound is selected from the group consisting of a compound of formula (Va), a compound of formula (Vb) and a compound of formula (VI):



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

each of  $R_1$ ,  $R_3$ ,  $R_4$ , and  $R_5$  is hydrogen;

$X$  is S;

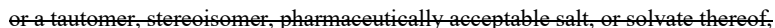
$Y$  is O;

ring D is phenyl or pyridinyl;

$R_2$  is  $\text{CH}_3$ ,  $\text{C}(\text{O})\text{NH}_2$ ,  $\text{CH}_2\text{OH}$ ,  $\text{OCH}_3$ , or  $\text{OH}$ ; and

$n$  is 0 or 1.

14. The compound of claim 7, wherein the compound is selected from the group consisting of a compound of formula (VII-a) and a compound of formula (VII-b):



~~each of R<sub>1</sub>, R<sub>3</sub>, R<sub>4</sub>, and R<sub>5</sub> is hydrogen;~~

---

X is S;

---

Y is 0:

~~ring D is phenyl or pyridinyl;~~

~~R<sub>2</sub> is CH<sub>3</sub>, C(O)NH<sub>2</sub>, CH<sub>2</sub>OH, OCH<sub>3</sub>, or OH; and~~

---

~~n is 0 or 1.~~

~~15. The compound of claim 1 being a compound of formula (I-a):~~



~~ring B is pyridinyl;~~

~~Q is CH or N;~~~~R<sub>1</sub> is hydrogen, CH<sub>3</sub>, or CH<sub>2</sub>CH<sub>3</sub>;~~~~R<sub>4</sub> is hydrogen or CH<sub>3</sub>;~~~~R<sub>5</sub> is hydrogen or CH<sub>3</sub>;~~

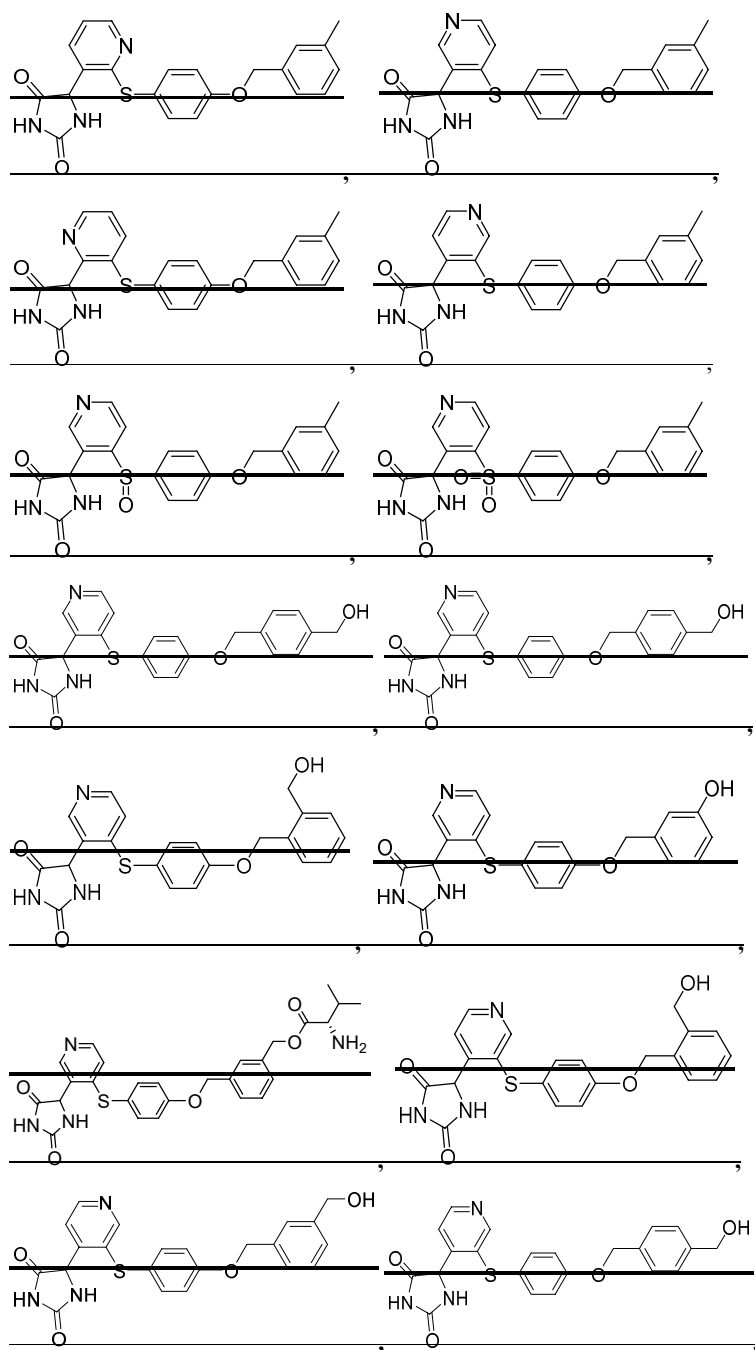
~~R<sub>2</sub> is selected from the group consisting of CH<sub>3</sub>, C(O)NH<sub>2</sub>, CH<sub>2</sub>OH, OCH<sub>3</sub>, or OH;~~

~~X is S; and~~

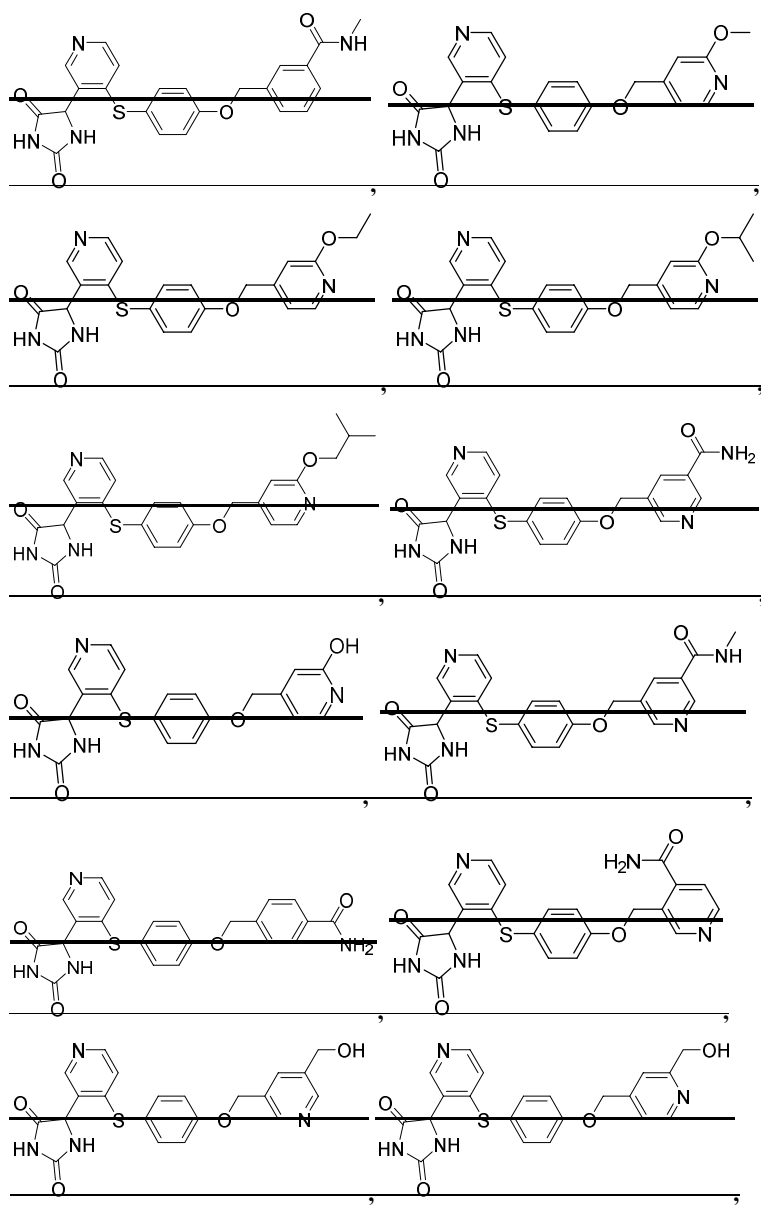
~~Y is 0.~~

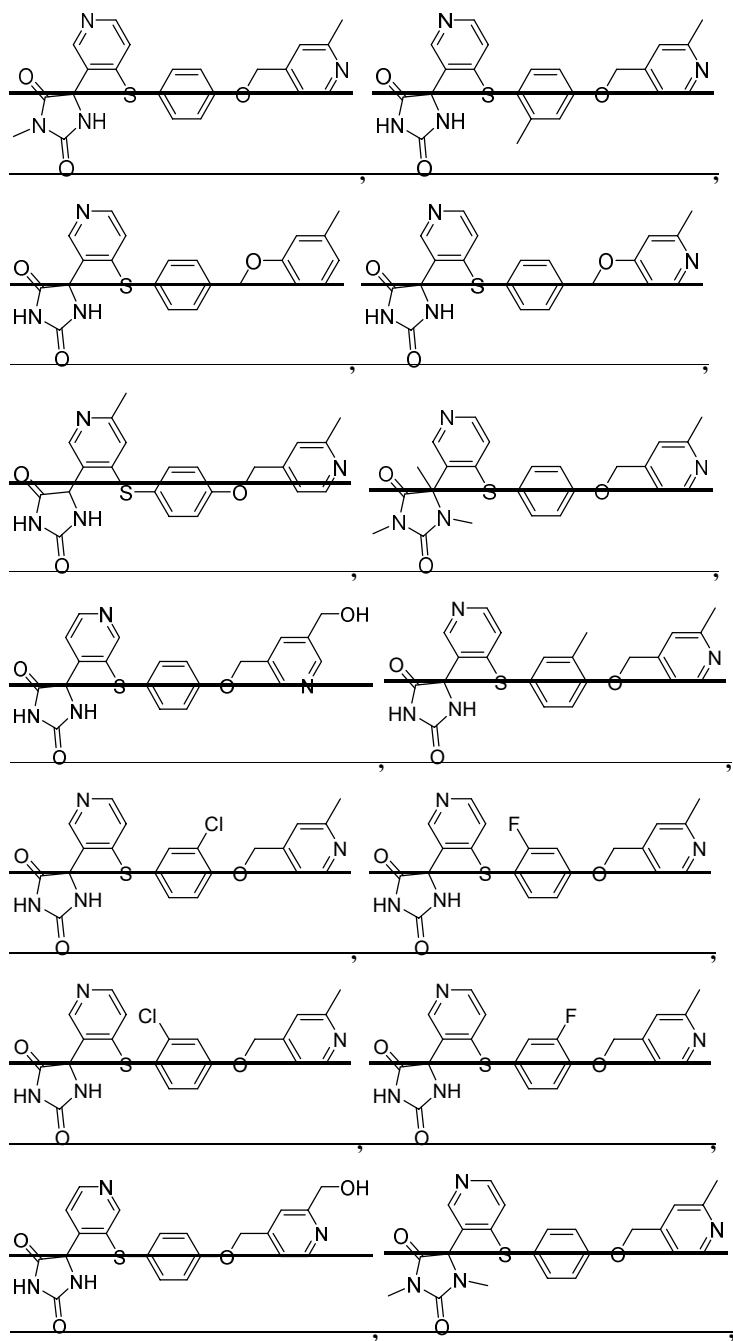
~~16. The compound of claim 15, wherein each of R<sub>1</sub>, R<sub>4</sub>, and R<sub>5</sub> is hydrogen.~~

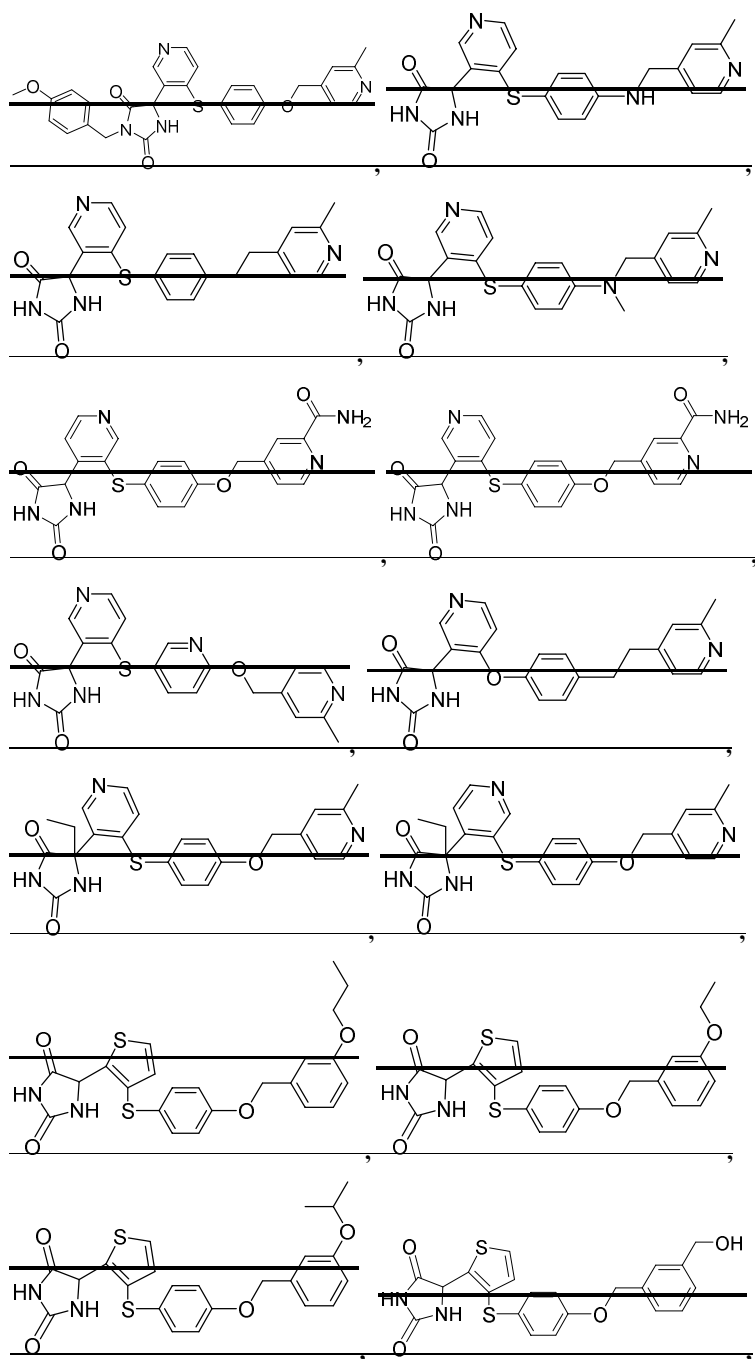
~~17. A compound selected from the group consisting of:~~

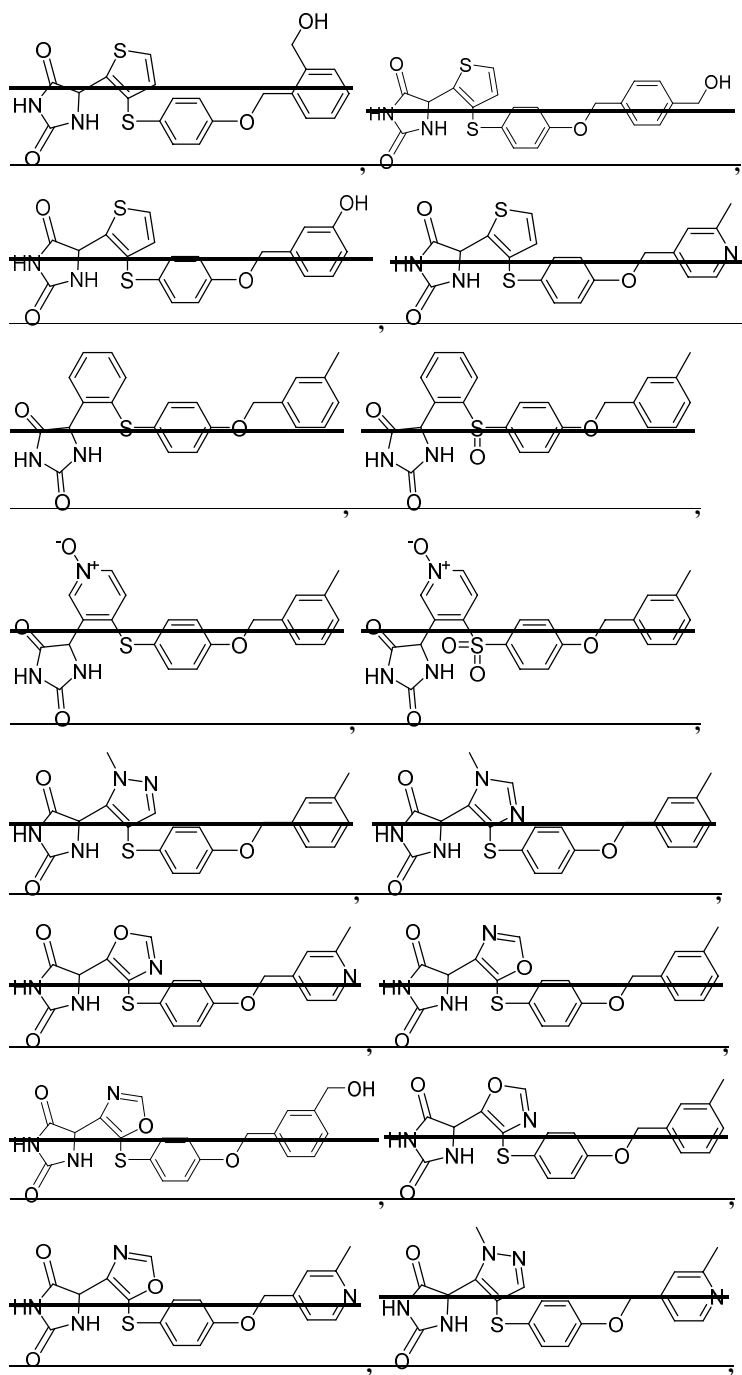


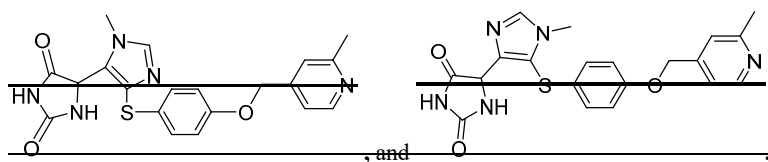












or a tautomer, stereoisomer, pharmaceutically acceptable salt, or solvate thereof.

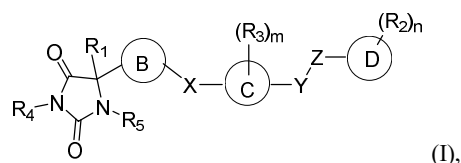
18. The compound of claim 17, or a pharmaceutically acceptable salt thereof.

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

20. A method of inhibiting macrophage elastase (MMP-12) in a subject in need thereof, the method comprising administering to the subject the pharmaceutical composition of claim 19.

21. 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), a 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.

1. A compound of formula (I):



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

\_\_\_\_\_ ring B is pyridinyl, thiophenyl, imidazolyl, pyrazolyl, or oxazolyl, wherein each of pyridinyl, thiophenyl, imidazolyl, pyrazolyl, and oxazolyl is optionally substituted with -CH<sub>3</sub>;

\_\_\_\_\_ ring C is phenyl;

\_\_\_\_\_ ring D is phenyl or pyridinyl;

\_\_\_\_\_ X is O or S;

\_\_\_\_\_ each of Y, and Z is independently selected from the group consisting of O, CH<sub>2</sub>, NR<sub>x</sub>, and S(O)<sub>q</sub>, wherein R<sub>x</sub> is hydrogen or alkyl;

\_\_\_\_\_ R<sub>1</sub> is hydrogen or alkyl;

\_\_\_\_\_ each R<sub>2</sub> is independently selected from the group consisting of hydrogen, alkyl, halo, hydroxyl, haloalkyl, alkoxy, alkylthio, amino, amide, alkylamine, aminoalkyl, cyano, hydroxyalkyl, -(CH<sub>2</sub>)<sub>p</sub>C(O)OR<sub>6</sub>, and -(CH<sub>2</sub>)<sub>p</sub>OC(O)R<sub>6</sub>;

\_\_\_\_\_ each R<sub>3</sub> is independently selected from the group consisting of hydrogen, alkyl and halo;

\_\_\_\_\_ R<sub>4</sub> is hydrogen or alkyl;

\_\_\_\_\_ R<sub>5</sub> is hydrogen;

\_\_\_\_\_ each R<sub>6</sub> 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;

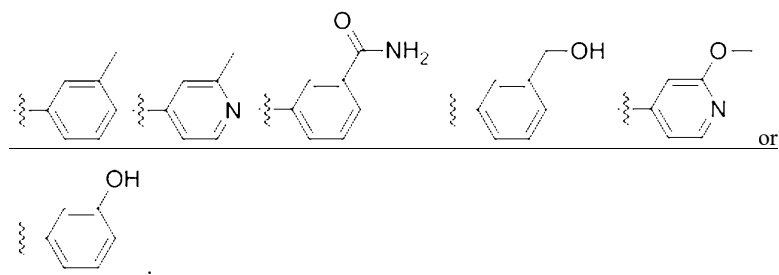
\_\_\_\_\_ m is 1, 2, 3, or 4;

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

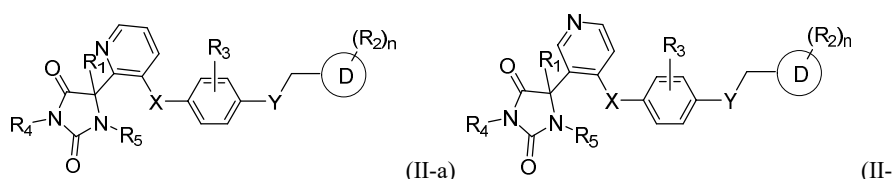
\_\_\_\_\_ p is 0, 1, 2, 3, 4, or 5; and

\_\_\_\_\_ q is 0, 1, or 2.

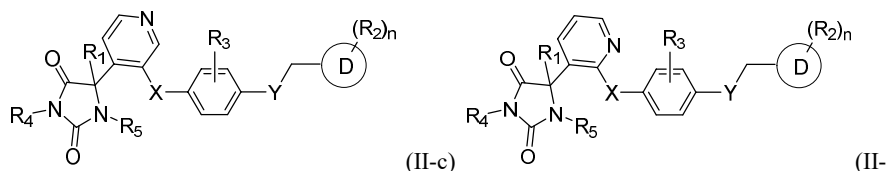
2. The compound of claim 1, wherein ring D is:



3. The compound of claim 1, wherein the compound is selected from the group consisting of a compound of formula (II-a), a compound of formula (II-b), a compound of formula (II-c), and a compound of formula (II-d):



b)



d)

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

wherein:

R<sub>1</sub> is hydrogen, -CH<sub>3</sub>, or -CH<sub>2</sub>CH<sub>3</sub>;

R<sub>4</sub> is hydrogen or -CH<sub>3</sub>;

R<sub>5</sub> is hydrogen or -CH<sub>3</sub>;

R<sub>3</sub> is hydrogen, -F, -Cl, or CH<sub>3</sub>;

X is S, SO, or SO<sub>2</sub>;

Y is O, NH, CH<sub>2</sub>, or NHCH<sub>3</sub>;

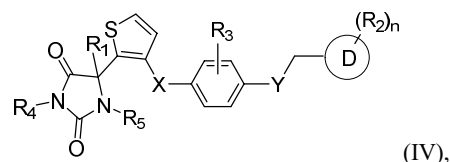
ring D is pyridinyl or phenyl;

R<sub>2</sub> is -CH<sub>3</sub>, -CH<sub>2</sub>OH, -OH, CH<sub>2</sub>OC(O)CH(NH<sub>2</sub>)CH(CH<sub>3</sub>)<sub>2</sub>, -COOH, -

C(O)NH<sub>2</sub>, -C(O)NHCH<sub>3</sub>, -OCH<sub>3</sub>, -OCH<sub>2</sub>CH<sub>3</sub>, -OCH(CH<sub>3</sub>)<sub>2</sub>, or -CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>; and

n is 0 or 1.

4. The compound of claim 1, wherein the compound is a compound of formula (IV):



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

wherein:

each of R<sub>1</sub>, R<sub>4</sub> and R<sub>5</sub> is hydrogen;

X is S;

Y is O;

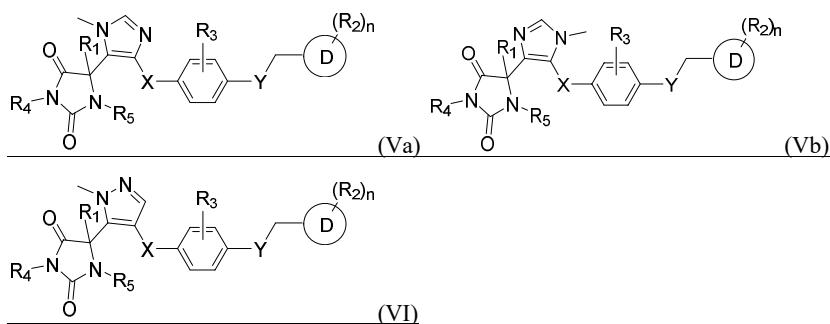
R<sub>3</sub> is hydrogen;

ring D is phenyl or pyridinyl;

R<sub>2</sub> is -CH<sub>3</sub>, -C(O)NH<sub>2</sub>, -CH<sub>2</sub>OH, -OCH<sub>3</sub>, or -OH; and

n is 0 or 1.

5. The compound of claim 1, wherein the compound is selected from the group consisting of a compound of formula (Va), a compound of formula (Vb) and a compound of formula (VI):



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

wherein:

each of R<sub>1</sub>, R<sub>3</sub>, R<sub>4</sub>, and R<sub>5</sub> is hydrogen;

X is S;

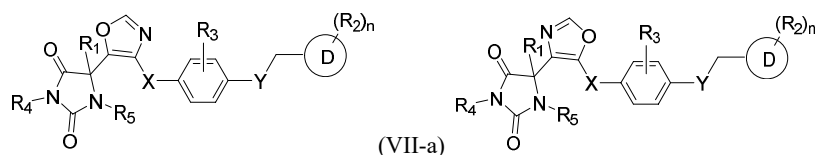
Y is O;

ring D is phenyl or pyridinyl;

R<sub>2</sub> is -CH<sub>3</sub>, -C(O)NH<sub>2</sub>, -CH<sub>2</sub>OH, -OCH<sub>3</sub>, or -OH; and

n is 0 or 1.

6. The compound of claim 1, wherein the compound is selected from the group consisting of a compound of formula (VII-a) and a compound of formula (VII-b):



(VII-b)

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

wherein:

each of R<sub>1</sub>, R<sub>3</sub>, R<sub>4</sub>, and R<sub>5</sub> is hydrogen;

X is S;

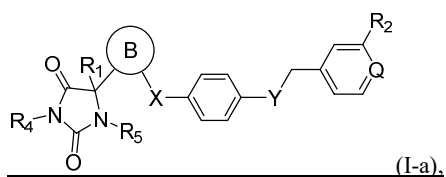
Y is O;

ring D is phenyl or pyridinyl;

R<sub>2</sub> is -CH<sub>3</sub>, -C(O)NH<sub>2</sub>, -CH<sub>2</sub>OH, -OCH<sub>3</sub>, or -OH; and

n is 0 or 1.

7. The compound of claim 1 being a compound of formula (I-a):



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

wherein:

ring B is pyridinyl;

Q is CH or N;

R<sub>1</sub> is hydrogen, -CH<sub>3</sub>, or -CH<sub>2</sub>CH<sub>3</sub>;

R<sub>4</sub> is hydrogen or -CH<sub>3</sub>;

R<sub>5</sub> is hydrogen or -CH<sub>3</sub>;

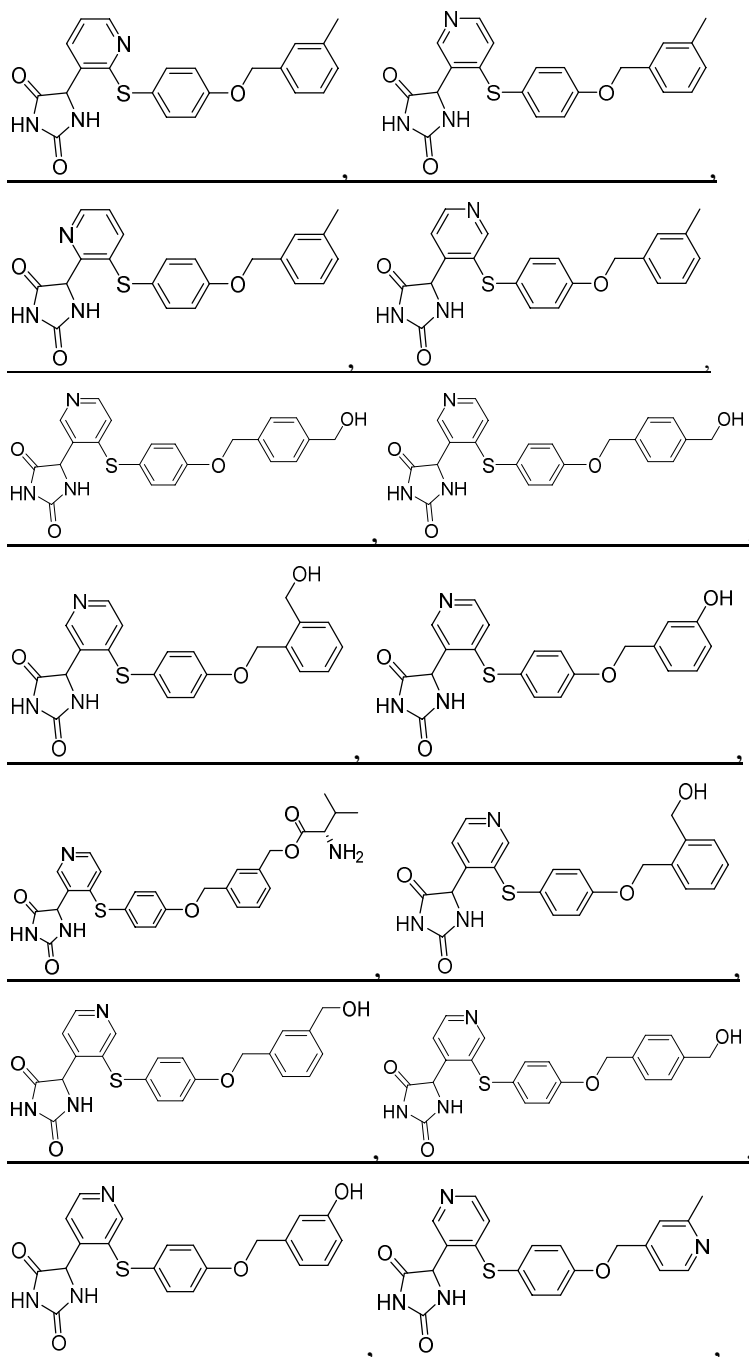
R<sub>2</sub> is selected from the group consisting of -CH<sub>3</sub>, -C(O)NH<sub>2</sub>, -CH<sub>2</sub>OH, -OCH<sub>3</sub>, or -

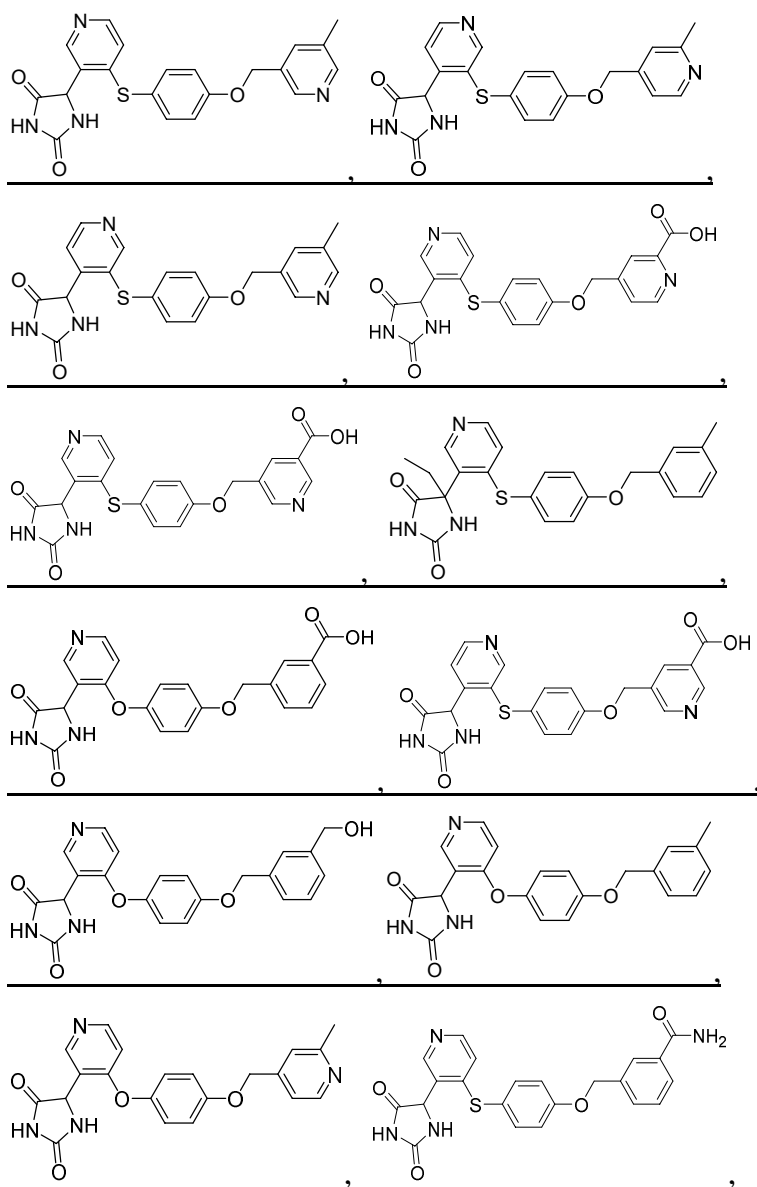
OH;

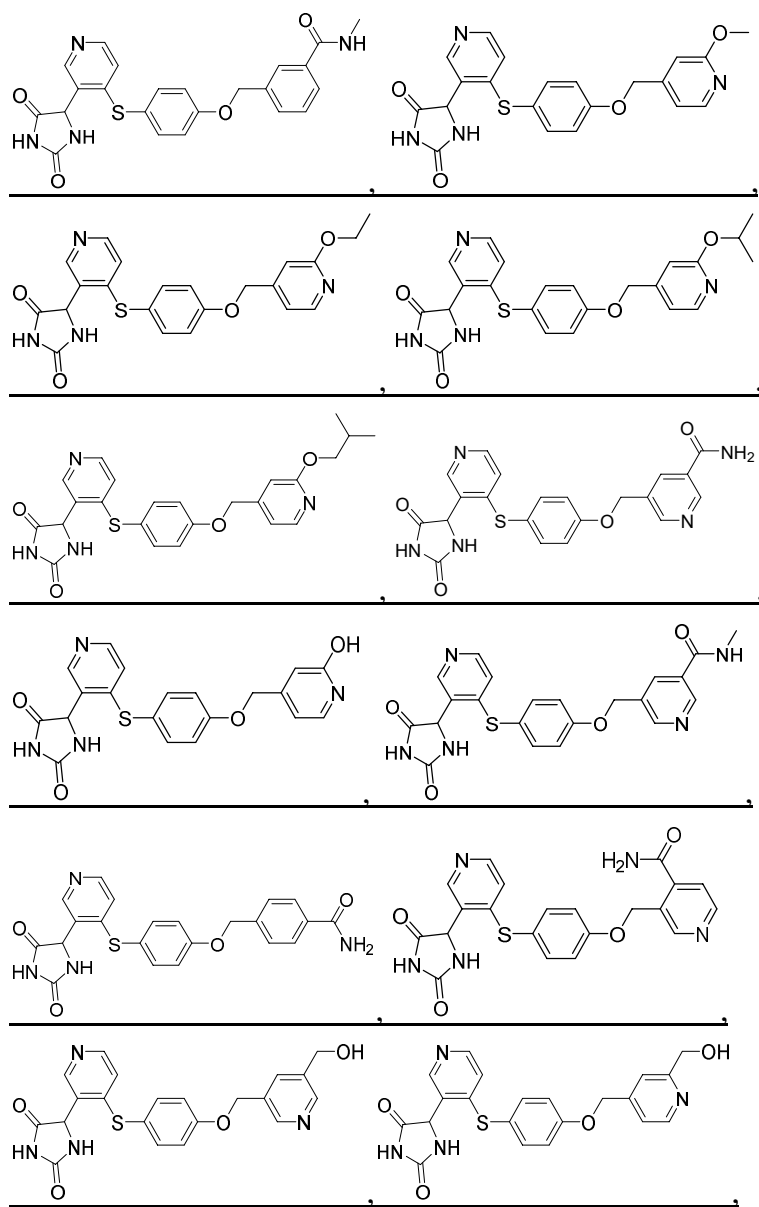
X is S; and

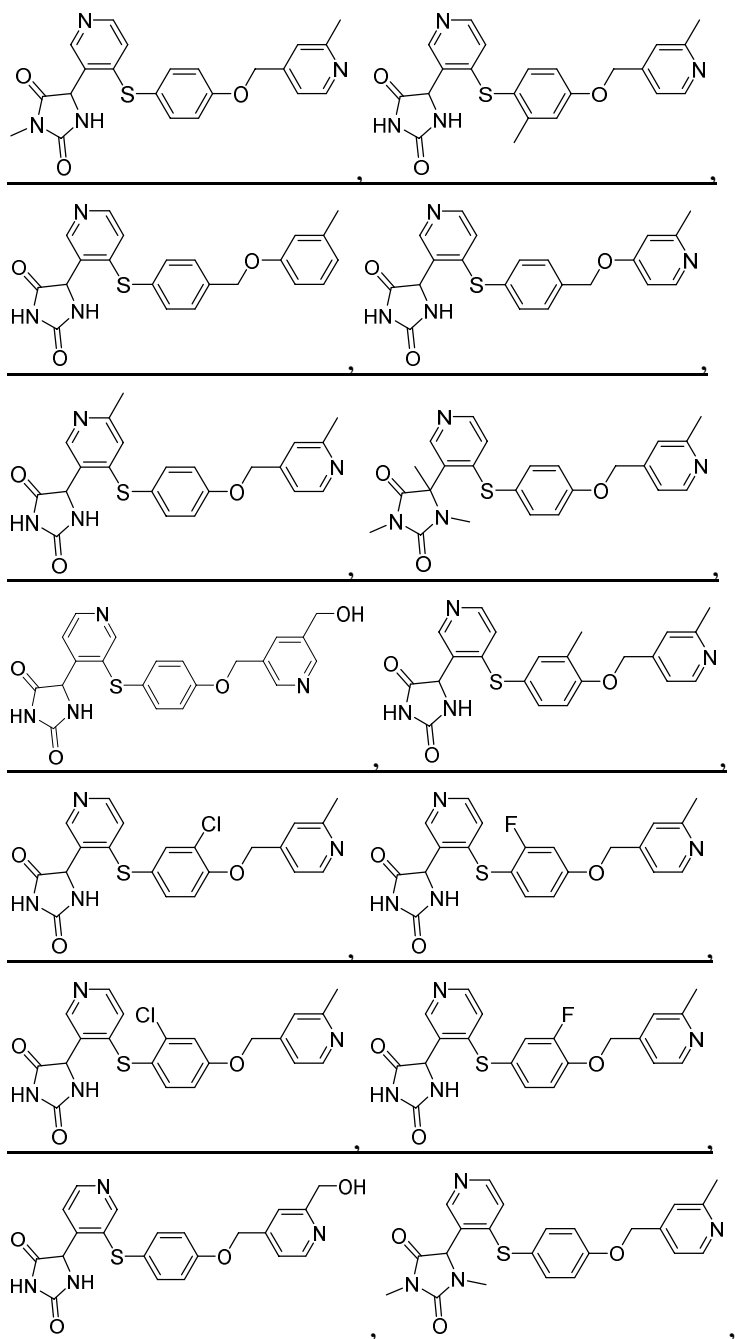
Y is O.

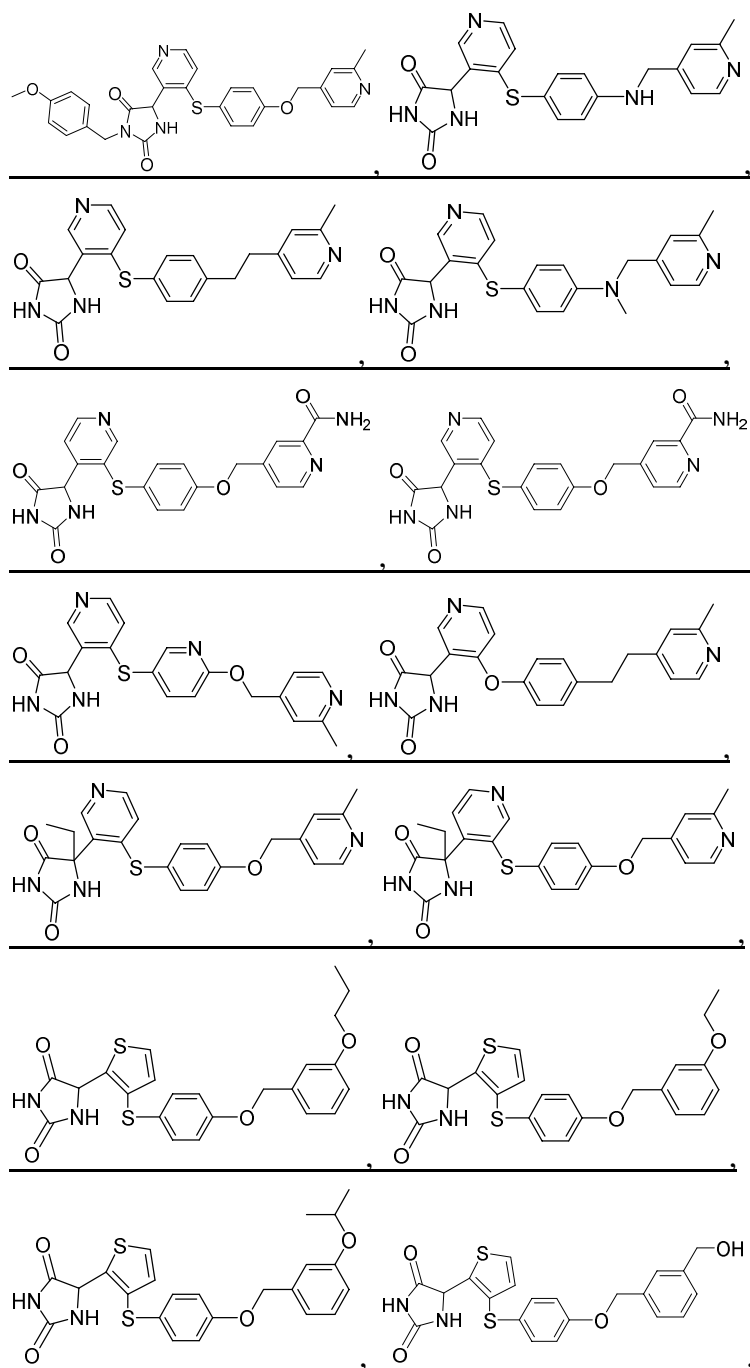
8. The compound according to any one of claims 1 to 2, being a compound selected from the group consisting of:

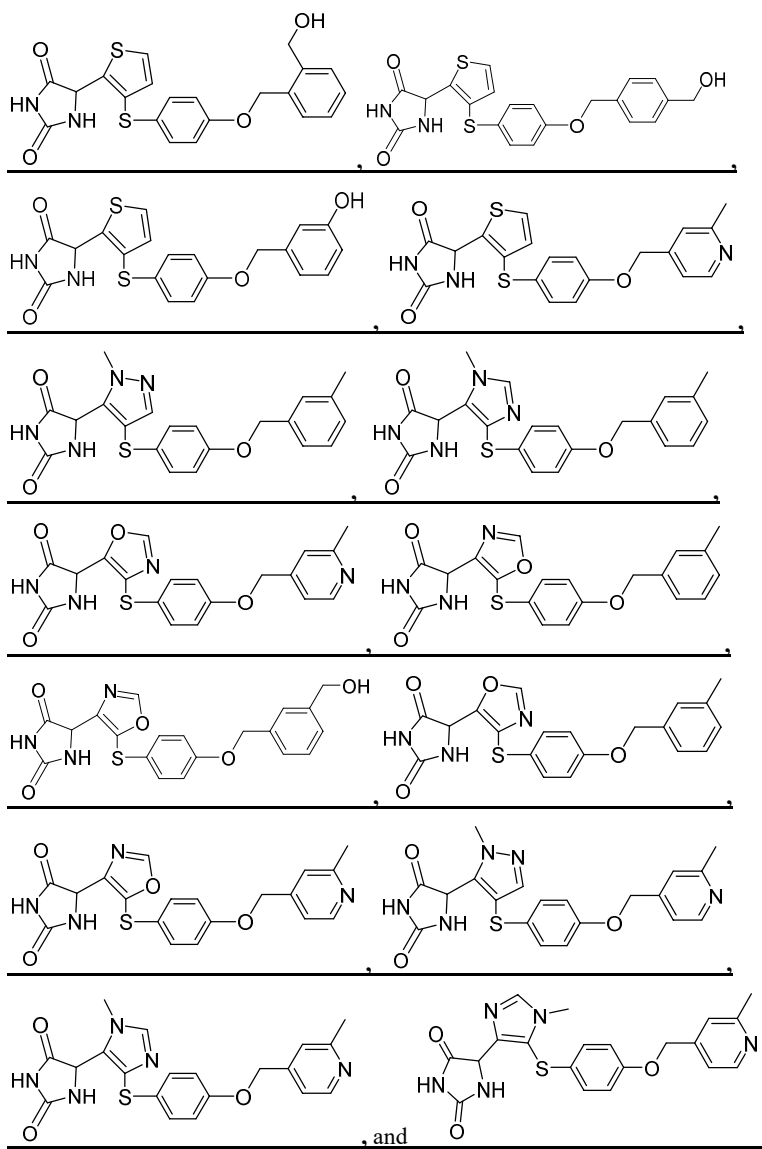












or a tautomer, stereoisomer, pharmaceutically acceptable salt, or solvate thereof.

9. A pharmaceutical composition comprising the compound of any one of claims 1-8,  
and at least one pharmaceutically acceptable carrier.

10. The pharmaceutical composition of claim 9 for use in a method of inhibiting macrophage elastase (MMP-12) in a subject in need thereof.

11. Use of the pharmaceutical composition of claim 9 in the manufacture of a medicament for the treatment of a disease mediated by macrophage elastase (MMP-12) in a subject in need thereof.

12. The use of claim 11, wherein the disease is selected from the group consisting of asthma, chronic obstructive pulmonary disease (COPD), a 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.