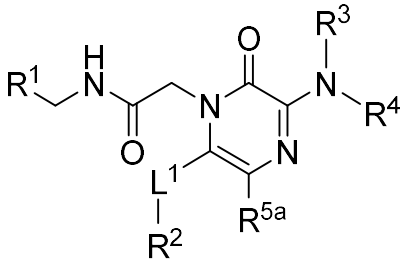
Mannan-binding lectin-associated serine protease-2 (MASP-2) has been shown to be required for the function of the lectin pathway, one of the principal complement activation pathways (Vorup-Jensen et al., J. Immunol 165:2093-2100, 2000; Ambrus et al., J Immunol. 170: 1374-1382, 2003; Schwaeble et al., PNAS 108:7523-7528, 2011). Importantly, inhibition of MASP-2 does not appear to interfere with the antibody-dependent classical complement activation pathway, which is a critical component of the acquired immune response to infection. As described in U.S. Patent No. 9,011,860 (assigned to Omeros Corporation), which is hereby incorporated by reference, discloses a fully human monoclonal antibody targeting human MASP-2 has been generated which binds to human MASP-2 with high affinity and blocks the lectin pathway complement activity and is therefore useful to treat various lectin complement pathway-associated diseases and disorders.

MASP-2-dependent complement activation has been implicated as contributing to the pathogenesis of numerous acute and chronic disease states. Therefore, a need exists for compounds that are suitable for administration/treatment of subject suffering from MASP-2 complement pathway-associated diseases and disorders, including diseases that are not suitably or efficiently treated with large molecule biologic inhibitors.

SUMMARY

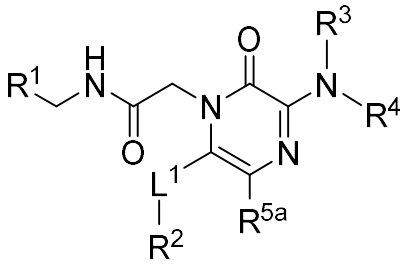
One example provides a compound having the following Structure (I):



(I)

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^{5a}, and L^1 are as defined below.

In one aspect, the present disclosure refers to a compound having the following Structure (I):



(I)

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

R^1 is a substituted or unsubstituted heteroaryl;

R^2 is a substituted or unsubstituted aryl or a substituted or unsubstituted heteroaryl;

R^3 is hydrogen or alkyl;

R^4 is alkyl, a substituted or unsubstituted arylalkyl, a heterocyclyl substituted with substituents selected from the group consisting of a substituted or unsubstituted phenyl or a substituted or unsubstituted pyridinyl, or R^3 and R^4, together with the nitrogen to which they are attached form an optionally substituted 4-10 membered heterocyclyl;

R^{5a} is hydrogen or halo;

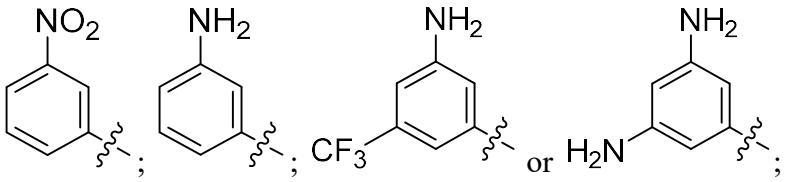
R^{5b} is hydrogen, alkyl, haloalkyl, (C=O)alkyl, (C=O)Oalkyl, (C=O)cycloalkyl, (C=O)Ocycloalkyl, (C=O)aryl, (C=O)Oaryl, (C=O)heteroaryl, (C=O)Oheteroaryl, (C=O)heterocyclyl, (C=O)Oheterocyclyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocyclyl, a substituted or unsubstituted arylalkyl, a substituted or unsubstituted heteroarylalkyl, a substituted or unsubstituted cycloalkylalkyl, or a substituted or unsubstituted heterocyclylalkyl;

L^1 is a direct bond, $-CH_2-$, $-S(O)_t-$, NR^{5b}, -O-, -C=C-, or -C≡C-; and

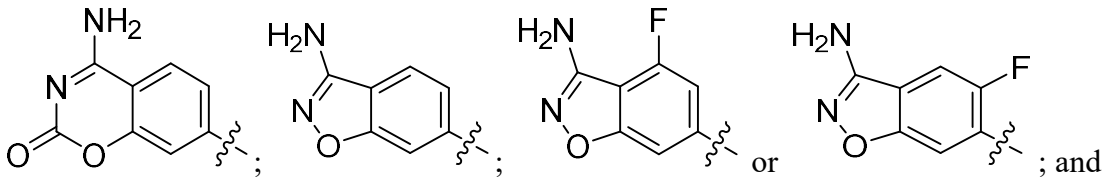
t is 0, 1, or 2,

provided that:

A) R^2 does not have one of the following structures:

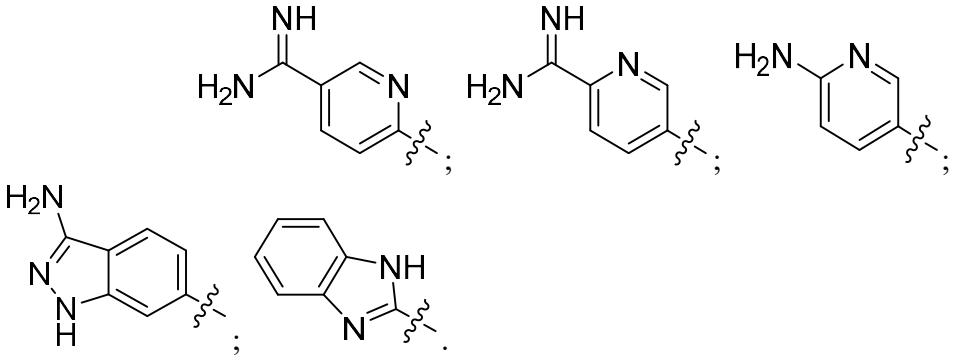


B) R^1 does not have one of the following structures:

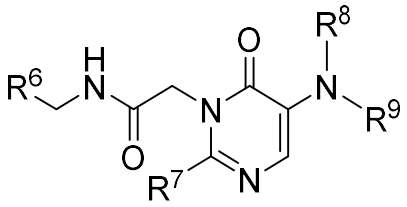


; and

C) when R^2 is unsubstituted phenyl, R^1 does not have one of the following structures:



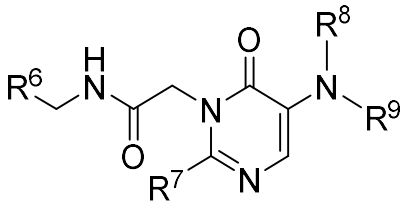
Another example provides a compound having the following Structure (II):



(II)

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^6, R^7, R^8, and R^9 are as defined below.

In one aspect, the present disclosure refers to a compound having the following Structure (II):



(II)

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

R^6 is a substituted or unsubstituted aryl or a substituted or unsubstituted heteroaryl;

R^7 is alkyl, $-NR^{10a}R^{10b}$, $-SR^{10c}$, a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

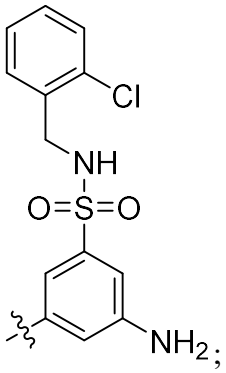
R^8 is hydrogen, alkyl, haloalkyl, cycloalkyl, or a substituted or unsubstituted arylalkyl;

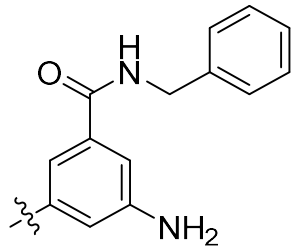
R^9 is alkyl, a substituted or unsubstituted $–S(O)_2$-arylalkyl, a substituted or unsubstituted arylalkyl, a substituted or unsubstituted heteroarylalkyl, or R^8 and R^9, together with the nitrogen to which they are attached, form an optionally substituted 4-10 membered heterocyclyl;

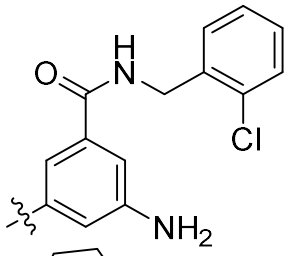
R^{10a}, R^{10b}, and R^{10c} are each independently hydrogen, alkyl, haloalkyl, or cycloalkyl;

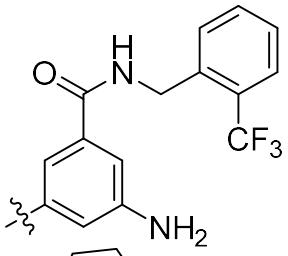
provided that:

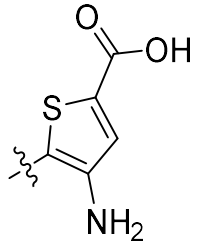
A) when R^7 is unsubstituted phenyl, 3-((methylsulfonyl)amino)phenyl, 2-methylphenyl, 3-(dimethylamino)phenyl, 3-(methylamino)phenyl, 3-methylphenyl, 3-aminomethylphenyl, 3-aminophenyl, unsubstituted pyridinyl, 3-(methylamino)-2-thienyl, 3,4-diamino-2-thienyl, 3-((methylsulfonyl)amino)-2-thienyl, 3-amino-2-thienyl, 3-amino-5-5(aminocarbonyl)phenyl, or has one of the following structures:

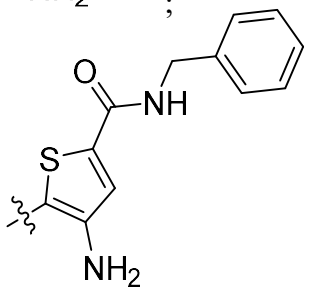


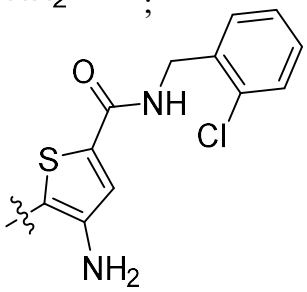
;


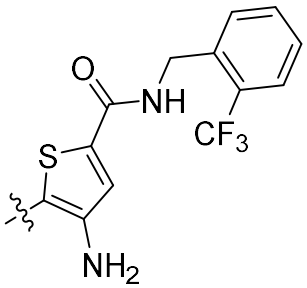
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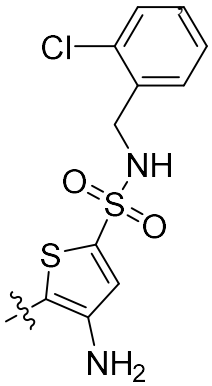
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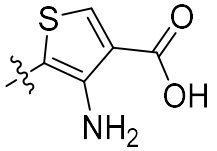
;


;


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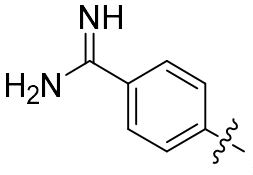
;


;


or


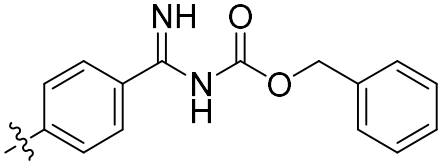
,

R^6 does not have the following structure:



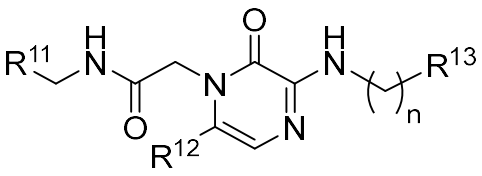
; and

B) when R^7 is unsubstituted phenyl, R^6 does not have the following structure:



.

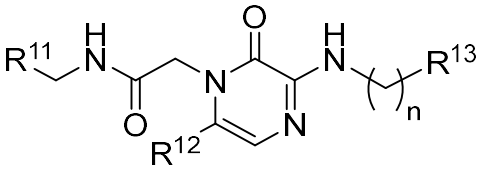
Another example provides a compound having the following Structure (III):



(III)

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^{11}, R^{12}, R^{13}, and n are as defined below.

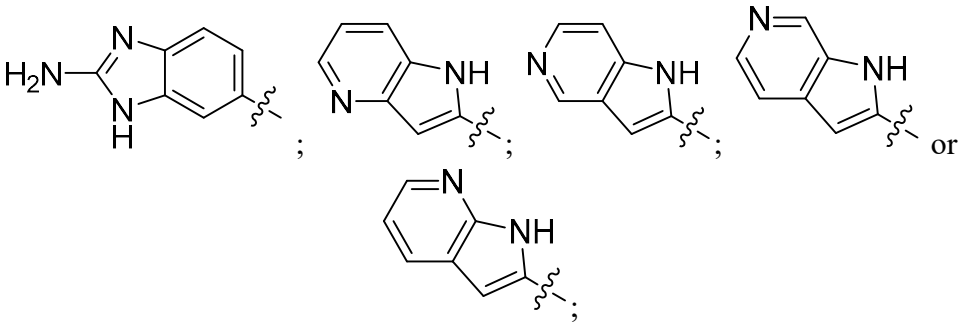
In one aspect, the present disclosure refers to a compound having the following Structure (III):



(III)

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

R^{11} has one of the following structures:



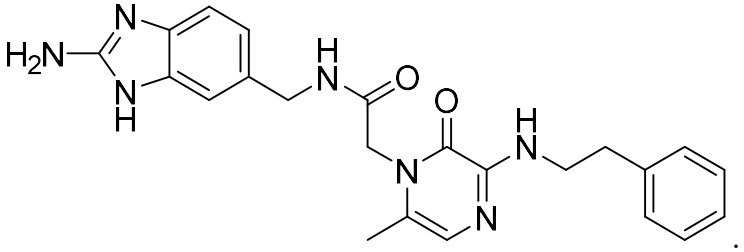
R^{12} is methyl, alkoxy, or halo;

R^{13} is a substituted or unsubstituted aryl; and

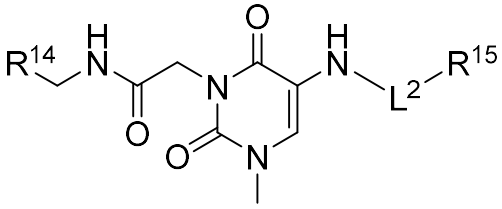
n is 1 or 2

provided that:

the compound of Structure (III) does not have the following structure:



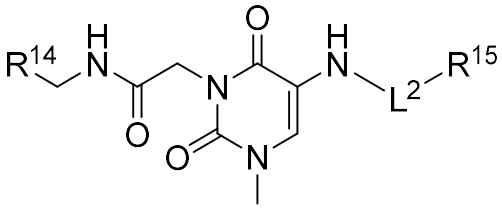
Another example provides a compound having the following Structure (IV):



(IV)

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^{14}, R^{15}, and L^2 are as defined below.

In one aspect, the present disclosure refers to a compound having the following Structure (IV):



(IV)

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

R^{14} is a substituted or unsubstituted aryl or a substituted or unsubstituted heteroaryl;

R^{15} is a substituted or unsubstituted arylalkyl, or a substituted or unsubstituted heteroarylalkyl;

L^2 is a direct bond, -C(=O), or -$S(=O)_t$-; and

t is 0, 1, or 2.

In one aspect, the present disclosure refers to a compound having a structure found in Table 1 or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

Additional examples of the present disclosure provide a pharmaceutical composition comprising a compound of Structure (I), (II), (III), or (IV),

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier or excipient.

In one aspect, the present disclosure refers to a pharmaceutical composition comprising a compound or pharmaceutically acceptable salt thereof disclosed herein and a pharmaceutically acceptable carrier or excipient.

The compounds of Structures (I), (II), (III), and (IV) are useful in the treatment of MASP-2-associated diseases and disorders, and in the manufacture of medicaments for treating MASP-2-associated diseases and disorders. Accordingly, other examples of the disclosure provide methods of treating a MASP-2-associated disease and disorder comprising administering to a patient a therapeutically effective amount of a compound of Structure (I), (II), (III), or (IV), or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

In one aspect, the present disclosure refers to use of a compound disclosed herein, in the manufacture of a medicament for treating a MASP-2-associated disease or disorder in a subject in need thereof.

These and other aspects, objects and examples will become more apparent when read with the detailed description and figures which follow.

DETAILED DESCRIPTION

I. Definitions

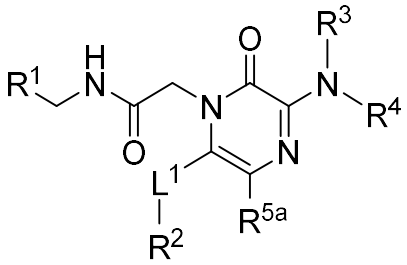
Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the subject matter of the present disclosure, suitable methods and materials are described below. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

In certain embodiments herein, reference is made to features and aspects of the disclosure, including method steps. All possible combinations of such features and aspects within the embodiments of the disclosure are included, at least to the extent that such combinations are non-contradictory. For example, if an embodiment presents aspects A, B, and C, it is understood that this also discloses embodiments including both aspects A and B, both aspects B and C, and both aspects A and C, as well as an embodiment with aspects A, B, and C.

The terms "a," "an," or "the" not only include aspects with one member, but also include aspects with more than one member. For instance, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise.

CLAIMS

1. A compound having the following Structure (I):



(I)

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

R^1 is a substituted or unsubstituted heteroaryl;

R^2 is a substituted or unsubstituted aryl or a substituted or unsubstituted heteroaryl;

R^3 is hydrogen or alkyl;

R^4 is alkyl, a substituted or unsubstituted arylalkyl, a heterocyclyl substituted with substituents selected from the group consisting of a substituted or unsubstituted phenyl or a substituted or unsubstituted pyridinyl, or R^3 and R^4, together with the nitrogen to which they are attached form an optionally substituted 4-10 membered heterocyclyl;

R^{5a} is hydrogen or halo;

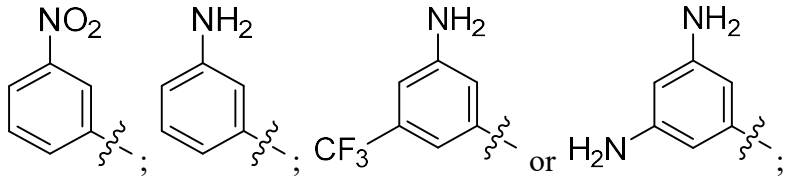
R^{5b} is hydrogen, alkyl, haloalkyl, (C=O)alkyl, (C=O)Oalkyl, (C=O)cycloalkyl, (C=O)Ocycloalkyl, (C=O)aryl, (C=O)Oaryl, (C=O)heteroaryl, (C=O)Oheteroaryl, (C=O)heterocyclyl, (C=O)Oheterocyclyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocyclyl, a substituted or unsubstituted arylalkyl, a substituted or unsubstituted heteroarylalkyl, a substituted or unsubstituted cycloalkylalkyl, or a substituted or unsubstituted heterocyclylalkyl;

L^1 is a direct bond, $-CH_2-$, $-S(O)_t-$, NR^{5b}, -O-, -C=C-, or -C≡C-; and

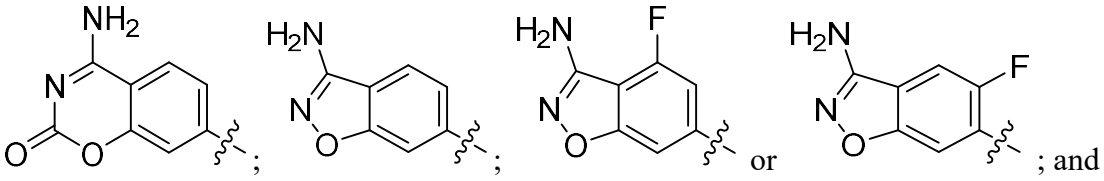
t is 0, 1, or 2,

provided that:

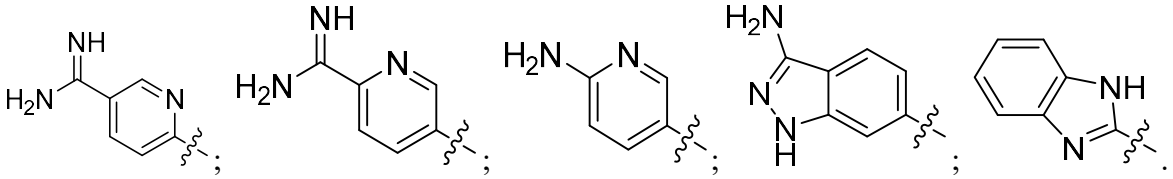
A) R^2 does not have one of the following structures:



B) R^1 does not have one of the following structures:



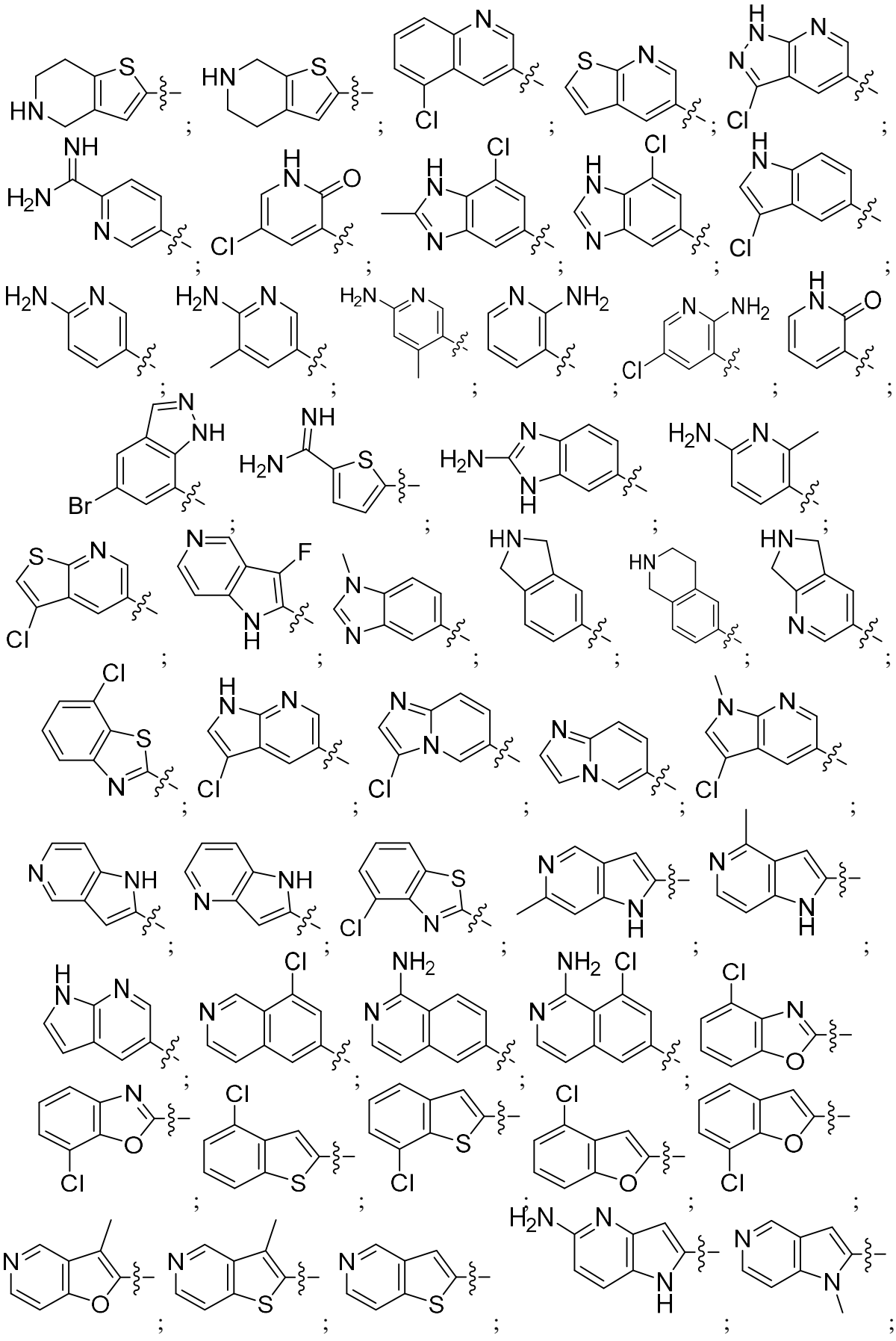
C) when R^2 is unsubstituted phenyl, R^1 does not have one of the following structures:

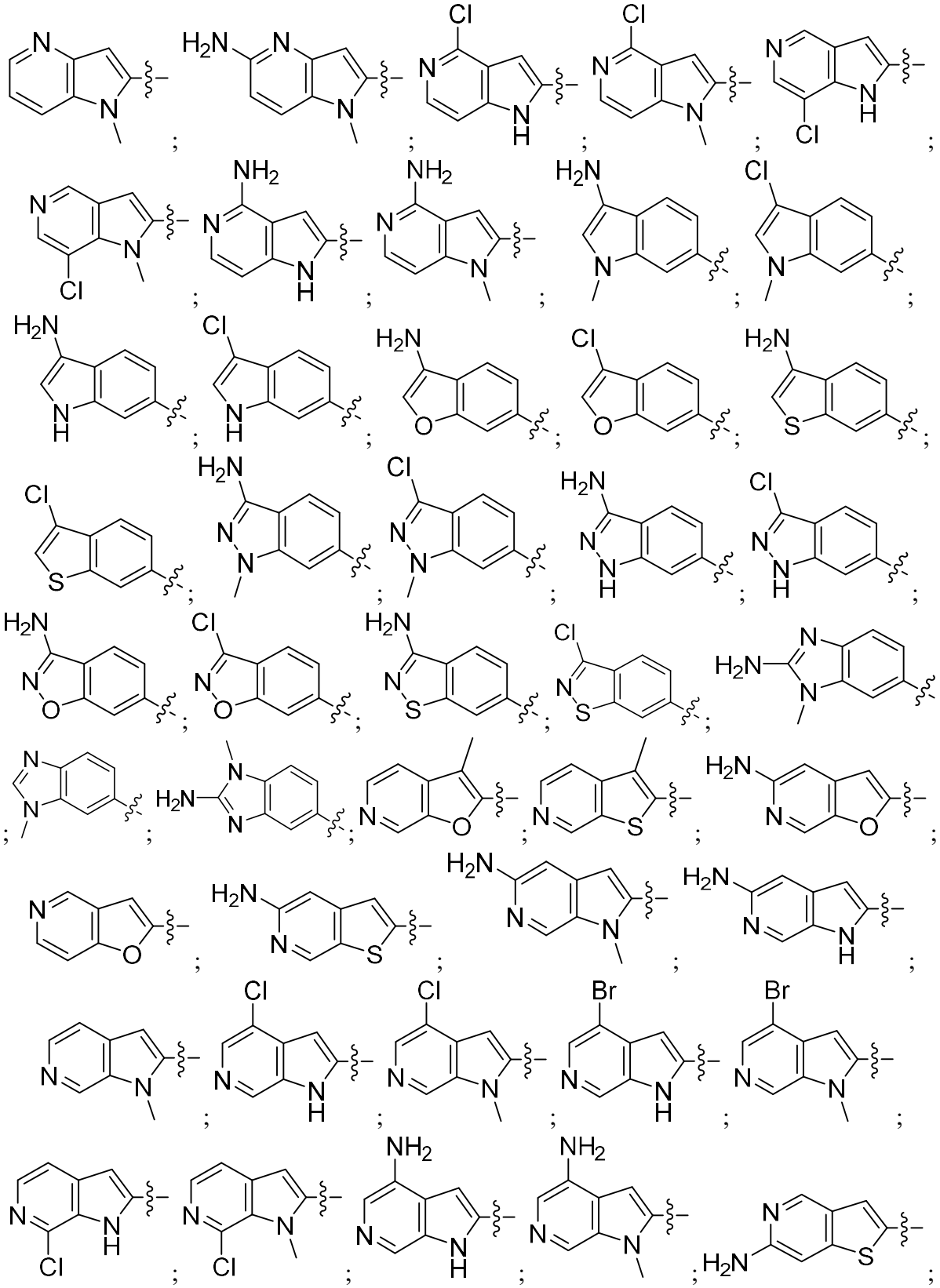


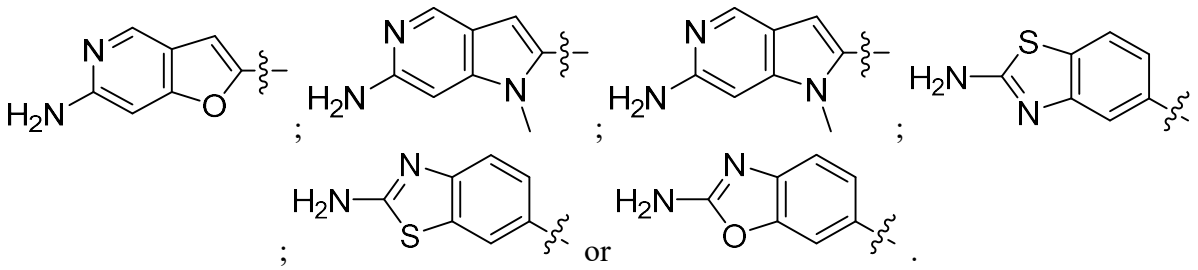
2. The compound of claim 1, wherein R^1 is substituted with one or more of R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} deuterated alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, C_{1-6} haloalkyl, aminylalkyl, hydroxyalkyl, cyano, nitro, OR^a, SR^a, $C(O)R^a$, $C(O)NR^aR^b$, $C(O)OR^a$, $OC(O)R^a$, $OC(O)OR^a$, $OC(O)NR^aR^b$, NR^aR^b, $N(R^a)C(O)R^b$, $N(R^a)C(O)NR^bR^c$, $N(R^a)C(O)OR^b$, $C(=NR^a)NR^bR^c$, $C(=NOR^a)NR^bR^c$, $C(=NOC(O)R^a)NR^bR^c$, $C(=NR^a)N(R^b)C(O)OR^c$, $N(R^a)C(=NR^b)NR^cR^d$, $S(O)R^a$, $S(O)NR^aR^b$, $S(O)_2R^a$, $N(R^a)S(O)_2R^b$, $S(O)_2NR^aR^b$, oxo, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted C_{6-10} arylalkyl, substituted or unsubstituted C_{6-10} aryloxy, substituted or unsubstituted C_{6-10} arylalkoxy, substituted or unsubstituted 5-10 membered heteroaryl, substituted or unsubstituted C_{3-10} cycloalkyl, and substituted or unsubstituted 4-10 membered heterocyclyl,

wherein R^a, R^b, R^c, and R^d, are, at each occurrence, independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hydroxyl, C_{1-6} alkoxy, aryl, arylalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, cycloalkyl, heterocyclyl, and heteroaryl.

3. The compound of claim 1, wherein R^1 has one of the following structures:

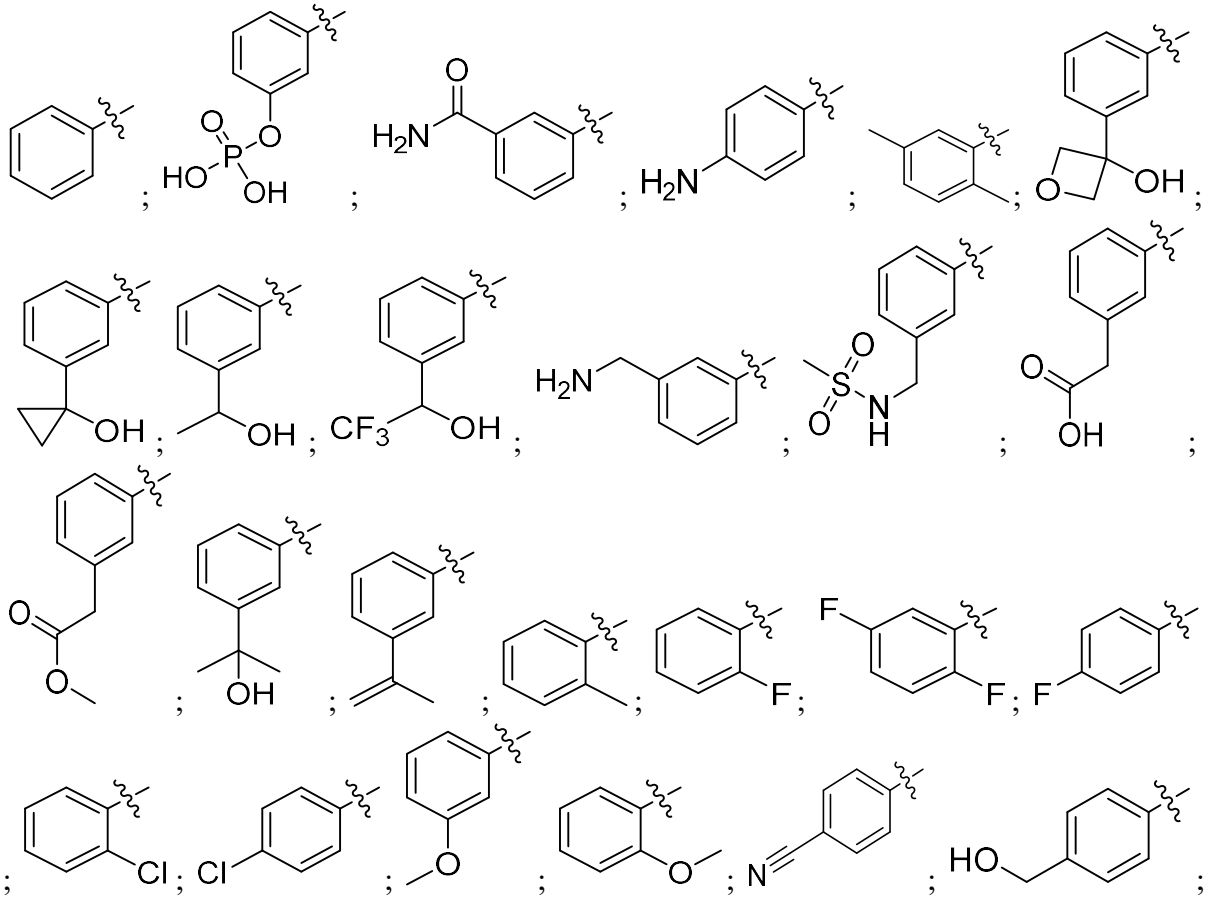


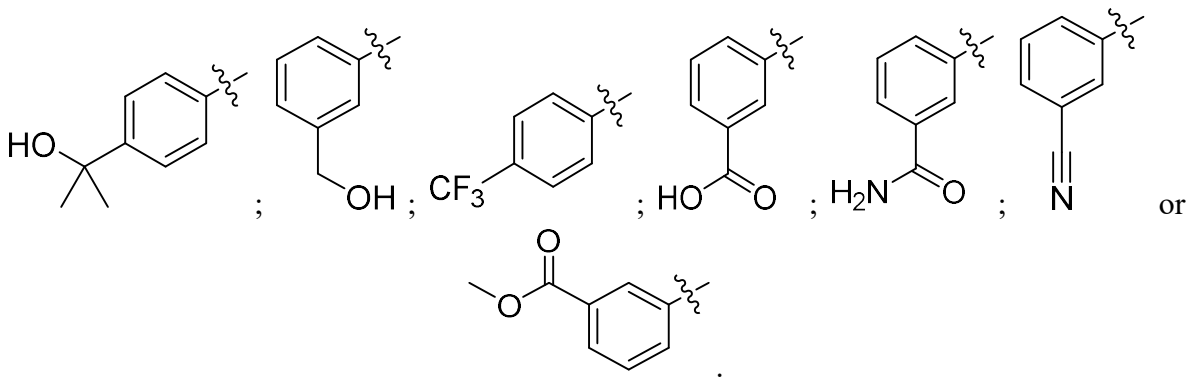




4. The compound of claim 1, wherein R^2 is a substituted or unsubstituted phenyl.

5. The compound of claim 1, wherein R^2 has one of the following structures:

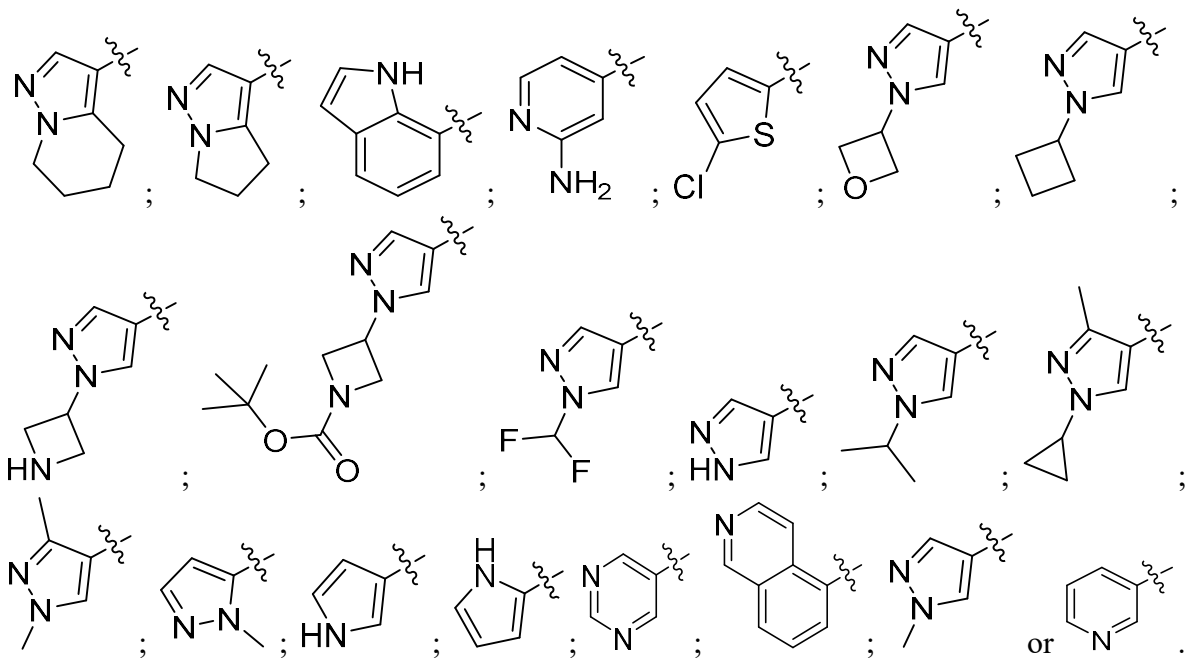




6. The compound of claim 1, wherein R^2 is a substituted or unsubstituted 5-10 membered heteroaryl.

7. The compound of claim 1, wherein R^2 is a substituted or unsubstituted pyridinyl, a substituted or unsubstituted pyrrolyl, a substituted or unsubstituted pyrimidinyl, a substituted or unsubstituted isoquinolinyl, a substituted or unsubstituted pyrazolyl, a substituted or unsubstituted pyrrolopyridinyl, or a substituted or unsubstituted benzoimidazolyl.

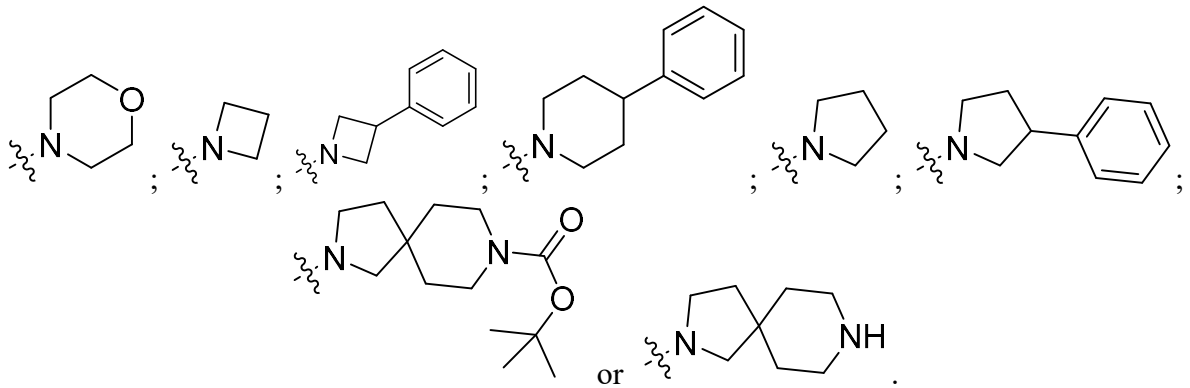
8. The compound of claim 1, wherein R^2 has one of the following structures:



9. The compound of claim 1, wherein R^3 is hydrogen or methyl.

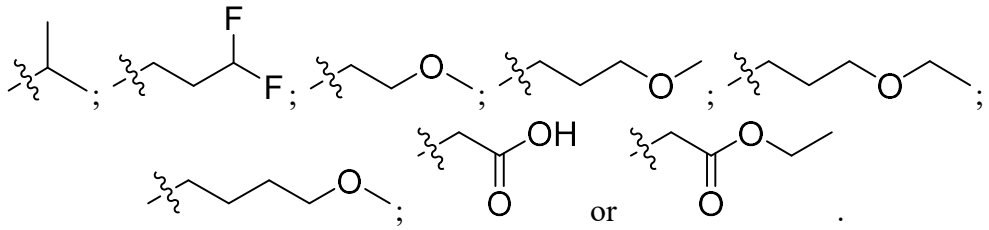
10. The compound of claim 1, wherein R^3 and R^4, together with the nitrogen to which they are attached form an optionally substituted 4-10 membered heterocyclyl.

11. The compound of claim 1, wherein R^3 and R^4, together with the nitrogen to which they are attached form one of the following structures:



or .

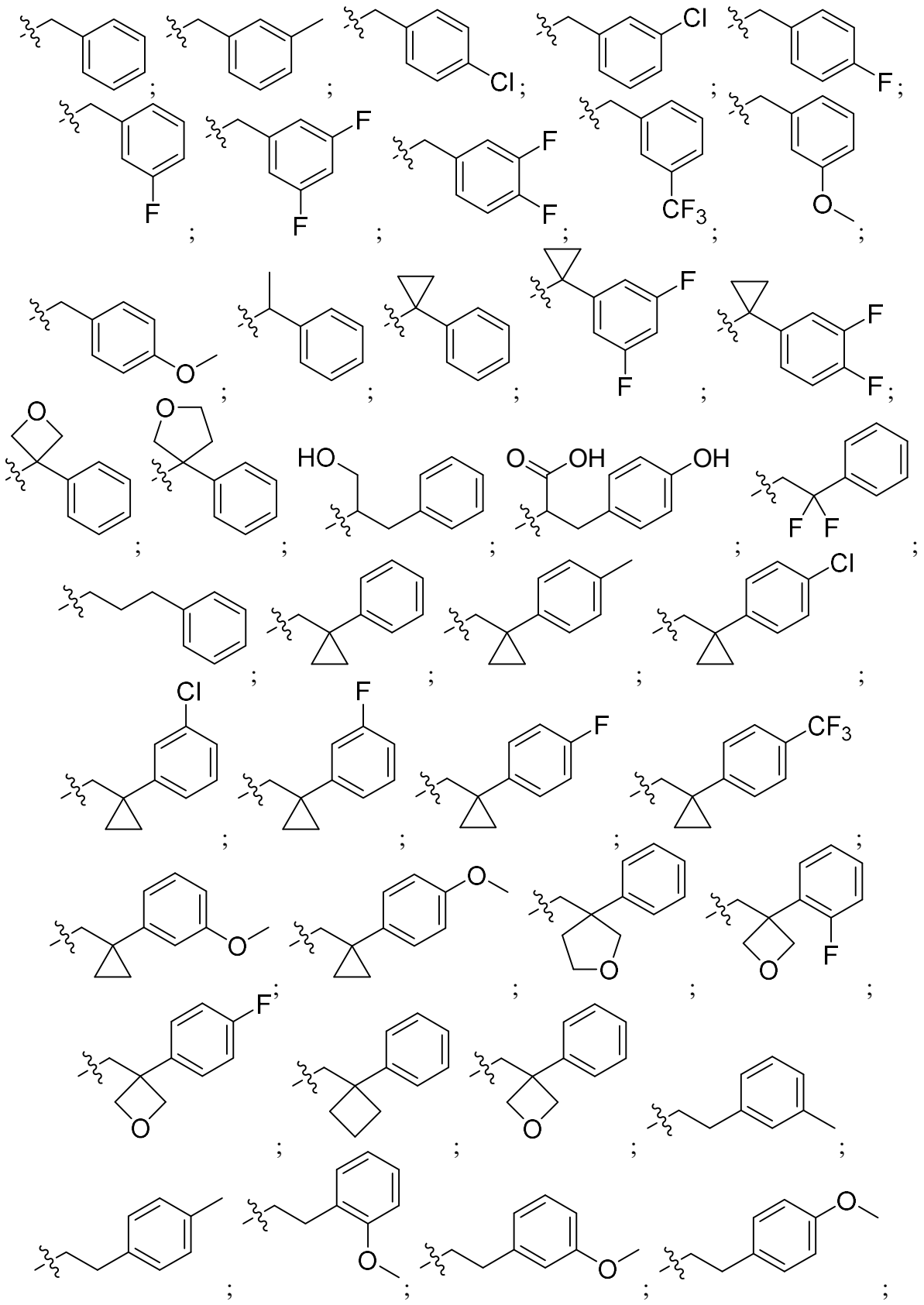
12. The compound of claim 1, wherein R^4 is methyl or has one of the following structures:

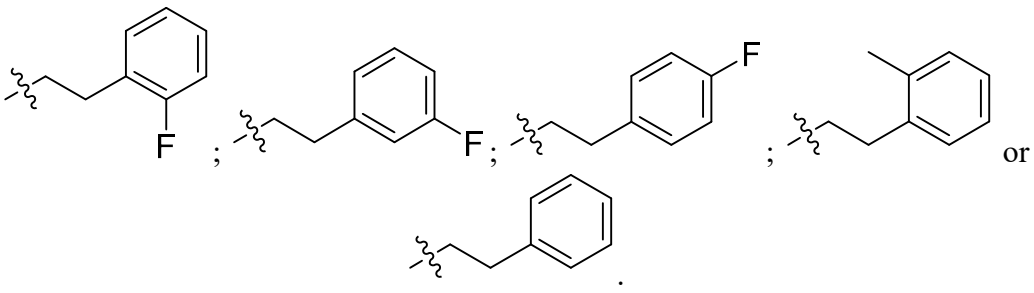


or .

13. The compound of claim 1, wherein R^4 is a substituted or unsubstituted arylalkyl.

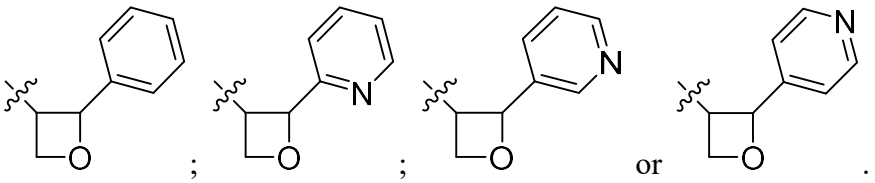
14. The compound of claim 1, wherein R^4 has the following structure:





15. The compound of claim 1, wherein R^4 is a heterocyclyl substituted with substituents selected from the group consisting of a substituted or unsubstituted phenyl or a substituted or unsubstituted pyridinyl.

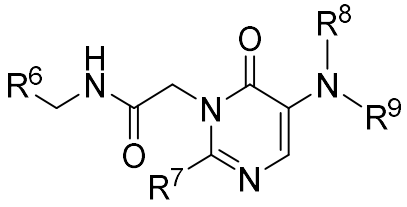
16. The compound of claim 1, wherein R^4 has one of the following structures:



17. The compound of claim 1, wherein L^1 is a direct bond, $-CH_2-$, or $-C\equiv C-$.

18. The compound of claim 1, wherein R^{5a} is hydrogen, F, Br, or Cl.

19. A compound having the following Structure (II):



(II)

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

R^6 is a substituted or unsubstituted aryl or a substituted or unsubstituted heteroaryl;

R^7 is alkyl, $-NR^{10a}R^{10b}$, $-SR^{10c}$, a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

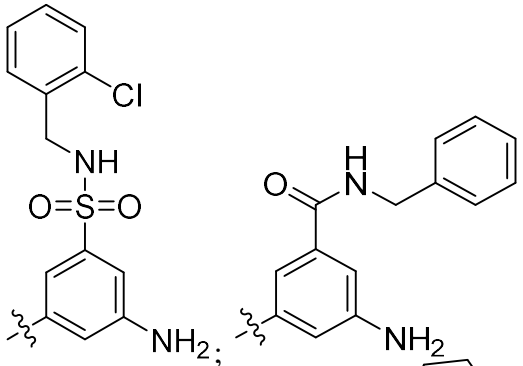
R^8 is hydrogen, alkyl, haloalkyl, cycloalkyl, or a substituted or unsubstituted arylalkyl;

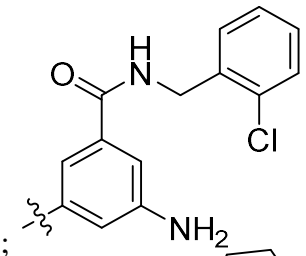
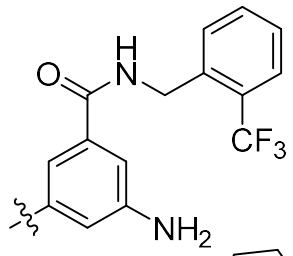
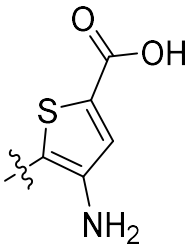
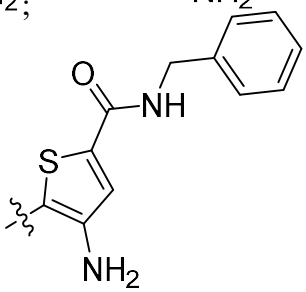
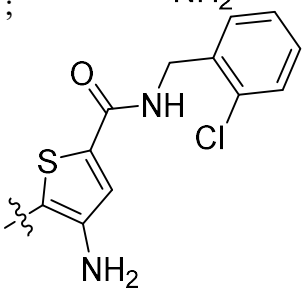
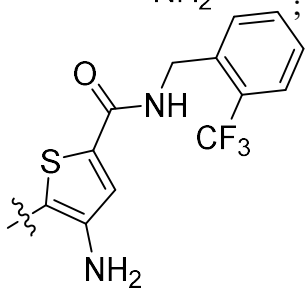
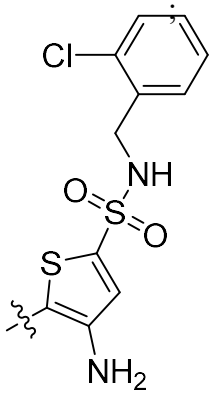
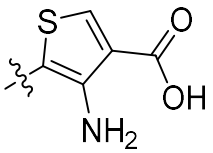
R^9 is alkyl, a substituted or unsubstituted $–S(O)_2$-arylalkyl, a substituted or unsubstituted arylalkyl, a substituted or unsubstituted heteroarylalkyl, or R^8 and R^9, together with the nitrogen to which they are attached, form an optionally substituted 4-10 membered heterocyclyl;

R^{10a}, R^{10b}, and R^{10c} are each independently hydrogen, alkyl, haloalkyl, or cycloalkyl;

provided that:

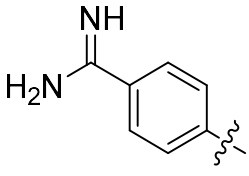
A) when R^7 is unsubstituted phenyl, 3-((methylsulfonyl)amino)phenyl, 2-methylphenyl, 3-(dimethylamino)phenyl, 3-(methylamino)phenyl, 3-methylphenyl, 3-aminomethylphenyl, 3-aminophenyl, unsubstituted pyridinyl, 3-(methylamino)-2-thienyl, 3,4-diamino-2-thienyl, 3-((methylsulfonyl)amino)-2-thienyl, 3-amino-2-thienyl, 3-amino-5-5(aminocarbonyl)phenyl, or has one of the following structures:



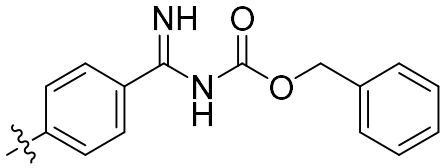
or ,

R^6 does not have the following structure:



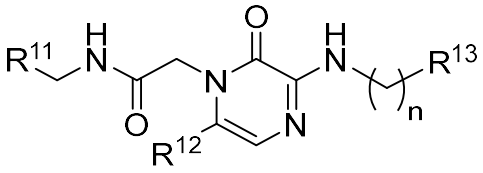
; and

B) when R^7 is unsubstituted phenyl, R^6 does not have the following structure:



.

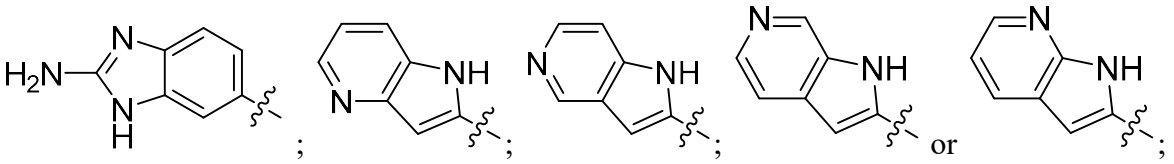
20. A compound having the following Structure (III):



(III)

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

R^{11} has one of the following structures:



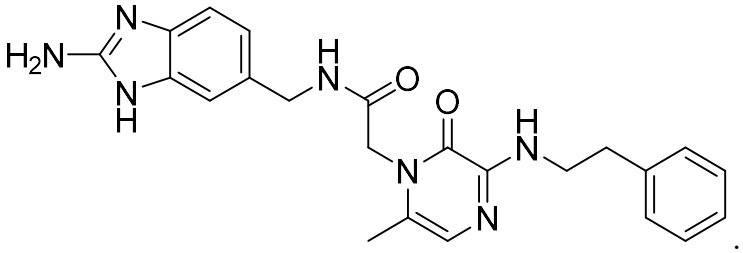
R^{12} is methyl, alkoxy, or halo;

R^{13} is a substituted or unsubstituted aryl; and

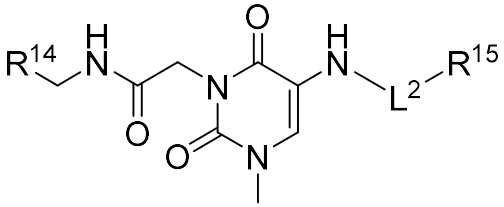
n is 1 or 2

provided that:

the compound of Structure (III) does not have the following structure:



21. A compound having the following Structure (IV):



(IV)

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

R^{14} is a substituted or unsubstituted aryl or a substituted or unsubstituted heteroaryl;

R^{15} is a substituted or unsubstituted arylalkyl, or a substituted or unsubstituted heteroarylalkyl;

L^2 is a direct bond, -C(=O), or -$S(=O)_t$-; and

t is 0, 1, or 2.

22. A compound having a structure found in Table 1 or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

23. A pharmaceutical composition comprising a compound or pharmaceutically acceptable salt thereof of claim 1 and a pharmaceutically acceptable carrier or excipient.

24. Use of a compound of claim 1, in the manufacture of a medicament for treating a MASP-2-associated disease or disorder in a subject in need thereof.