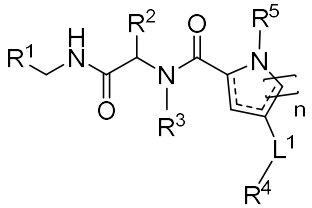
Mannan-binding lectin-associated serine protease-2 (MASP-2) has been shown to be required for the function of the lectin pathway, one of the principal complement activation pathways (Vorup-Jensen et al., J. Immunol 165:2093-2100, 2000; Ambrus et al., J Immunol. 170: 1374-1382, 2003; Schwaeble et al., 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):



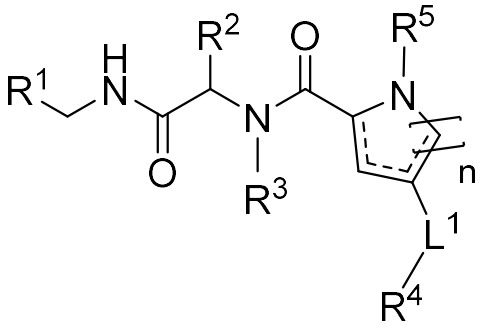
(I)

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein ----, R^1, R^2, R^3, R^4, R^5, L^1, and n are as defined herein.

Additional examples of the present disclosure provide a pharmaceutical composition comprising a compound of Structure (I), 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 compound having the following Structure (I):



(I)

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

---- at each occurrence, independently represents a double or single bond;

R^1 is a substituted or unsubstituted aryl or a substituted or unsubstituted heteroaryl;

R^2 is hydrogen, alkyl, alkoxy, haloalkyl, hydroxyalkyl, haloalkoxy, or cycloalkyl;

R^3 is hydrogen, alkyl, haloalkyl, or cycloalkyl, or R^2 and R^3, together with the carbon and nitrogen to which they are attached, respectively, form an optionally substituted 4-7 membered heterocyclyl;

R^4 is a substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclyl;

R^5 is hydrogen, alkyl, haloalkyl, cycloalkyl, phosphonalkyl, $(CH_2)_mC(=O)OR^6$, $C(=O)R^6$, $C(=O)OR^6$, $(CH_2)_mNR^6S(O)_2R^7$, or $C(=O)NR^6R^7$;

R^6 and R^7 are, at each occurrence, independently hydrogen, alkyl, haloalkyl, cycloalkyl, or arylalkyl;

L^1 is a direct bond, $-CR^{8a}R^{8b}-$, $-S(O)_t-$, NR^{8c}, or -O-;

R^{8a} and R^{8b} are each independently hydrogen, alkyl, or R^{8a} and R^{8b}, together with the carbon to which they are attached form an optionally substituted 3-6 membered cycloalkyl;

R^{8c} 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)O heterocyclyl, 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;

n is 1 or 2;

m is 1, 2, 3, 4, 5, or 6; and

t is 0, 1, or 2,

provided that the compound of Structure (I) does not have a structure in Table A.

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

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

In one aspect, the present disclosure refers to use of a compound disclosed herein or a pharmaceutical composition 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 examples, and objects will become more apparent when read with the detailed description and figures which follow.

DETAILED DESCRIPTION

I. Definitions

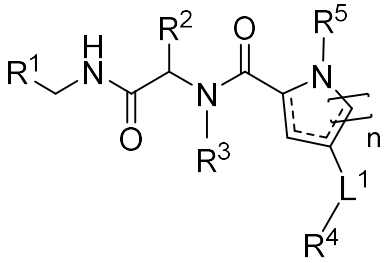
Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing 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:

---- at each occurrence, independently represents a double or single bond;

R^1 is a substituted or unsubstituted aryl or a substituted or unsubstituted heteroaryl;

R^2 is hydrogen, alkyl, alkoxy, haloalkyl, hydroxyalkyl, haloalkoxy, or cycloalkyl;

R^3 is hydrogen, alkyl, haloalkyl, or cycloalkyl, or R^2 and R^3, together with the carbon and nitrogen to which they are attached, respectively, form an optionally substituted 4-7 membered heterocyclyl;

R^4 is a substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclyl;

R^5 is hydrogen, alkyl, haloalkyl, cycloalkyl, phosphonalkyl, $(CH_2)_mC(=O)OR^6$, $C(=O)R^6$, $C(=O)OR^6$, $(CH_2)_mNR^6S(O)_2R^7$, or $C(=O)NR^6R^7$;

R^6 and R^7 are, at each occurrence, independently hydrogen, alkyl, haloalkyl, cycloalkyl, or arylalkyl;

L^1 is a direct bond, $-CR^{8a}R^{8b}-$, $-S(O)_t-$, NR^{8c}, or -O-;

R^{8a} and R^{8b} are each independently hydrogen, alkyl, or R^{8a} and R^{8b}, together with the carbon to which they are attached form an optionally substituted 3-6 membered cycloalkyl;

R^{8c} 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)O heterocyclyl, 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;

n is 1 or 2;

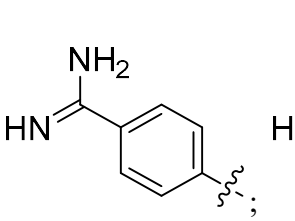
m is 1, 2, 3, 4, 5, or 6; and

t is 0, 1, or 2,

provided that the compound of Structure (I) does not have a structure in Table A.

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

3. The compound of claim 1, wherein R^1 has one of the following structures: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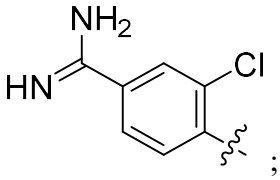
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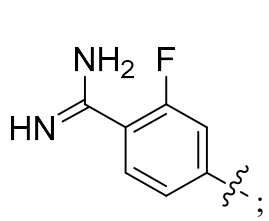
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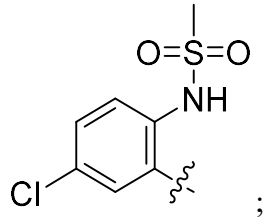
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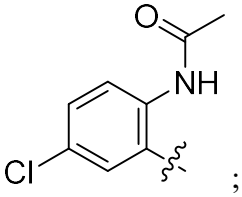
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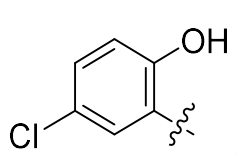
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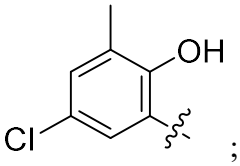
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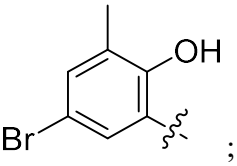
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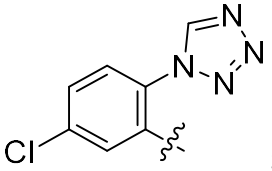
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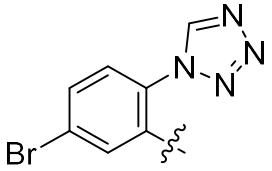
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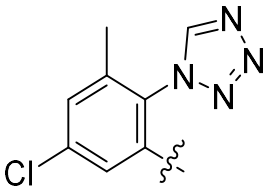
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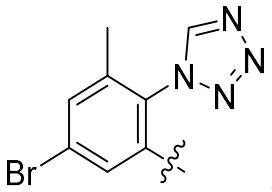
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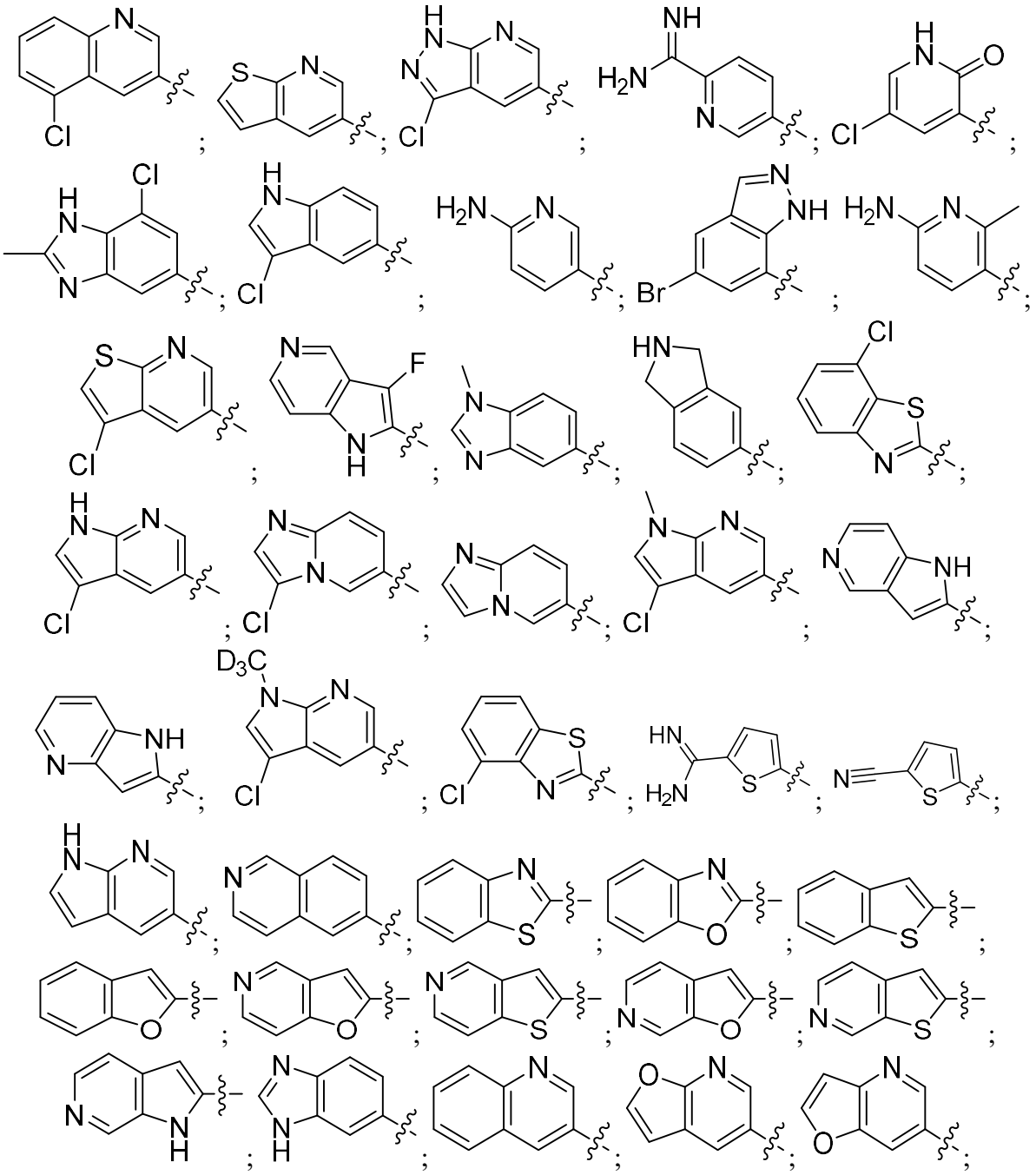
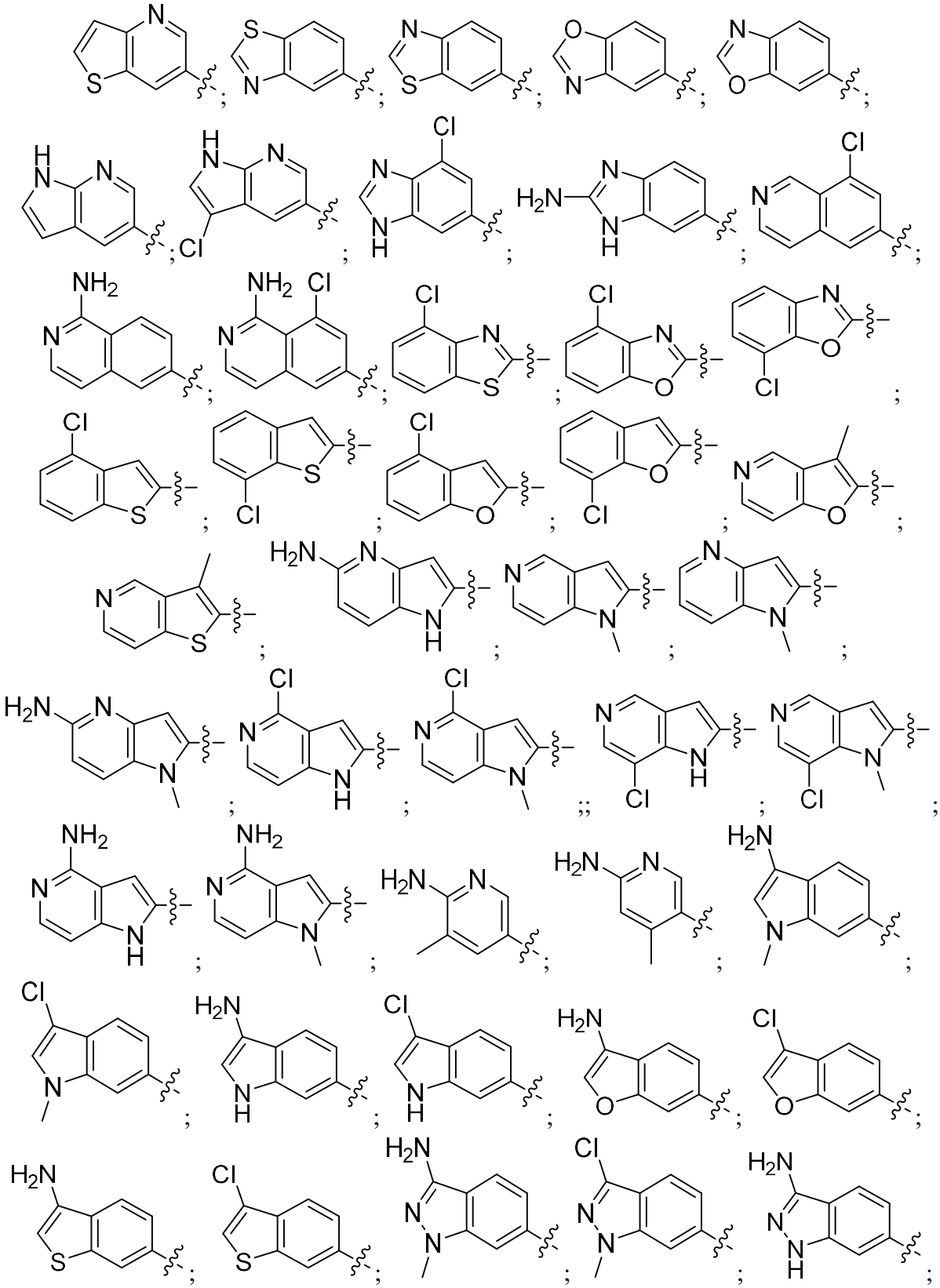
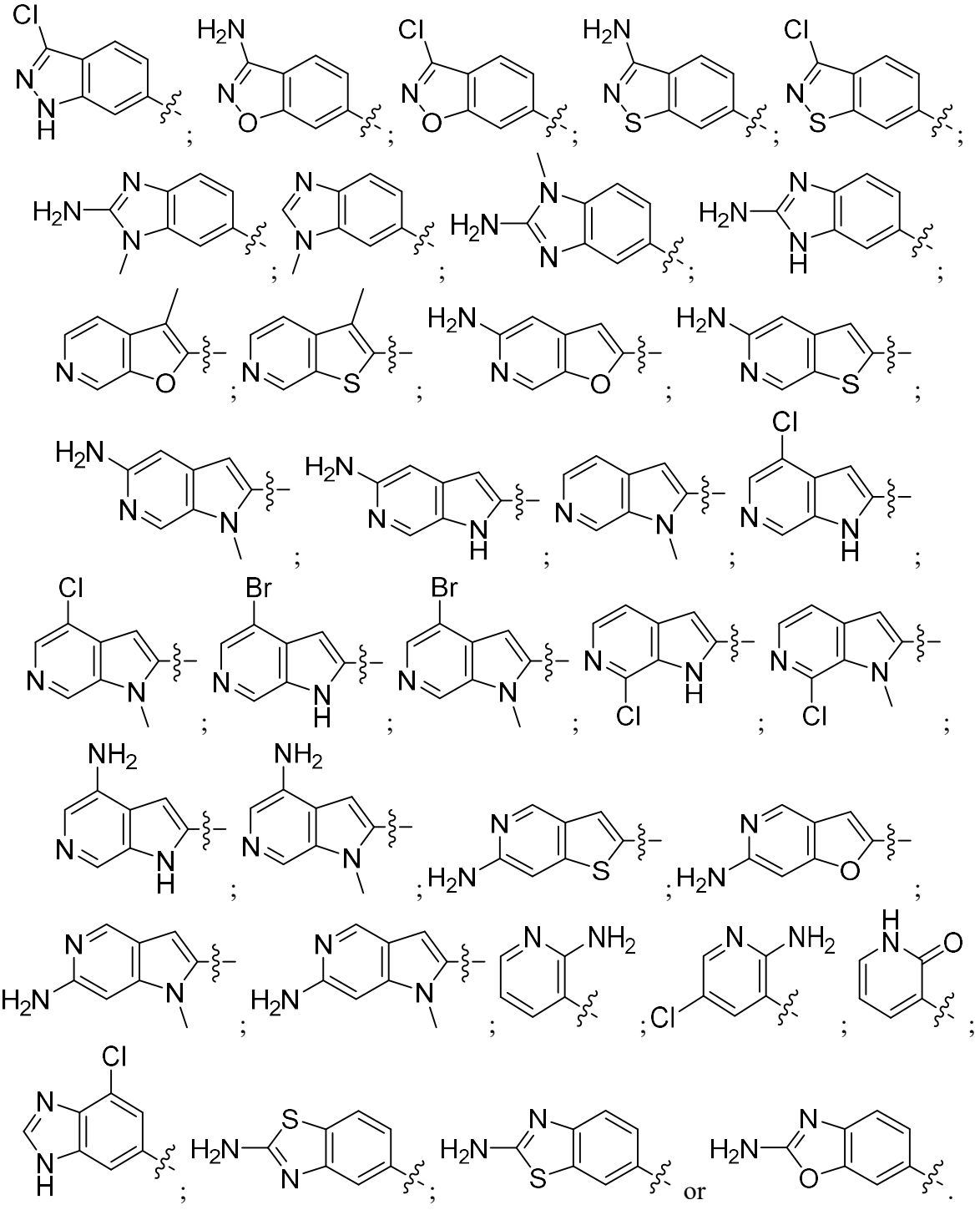
4. The compound of claim 1, wherein R^1 is a substituted or unsubstituted heteroaryl.

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







6. The compound of claim 1, wherein R^1 is a substituted or unsubstituted cycloalkyl.

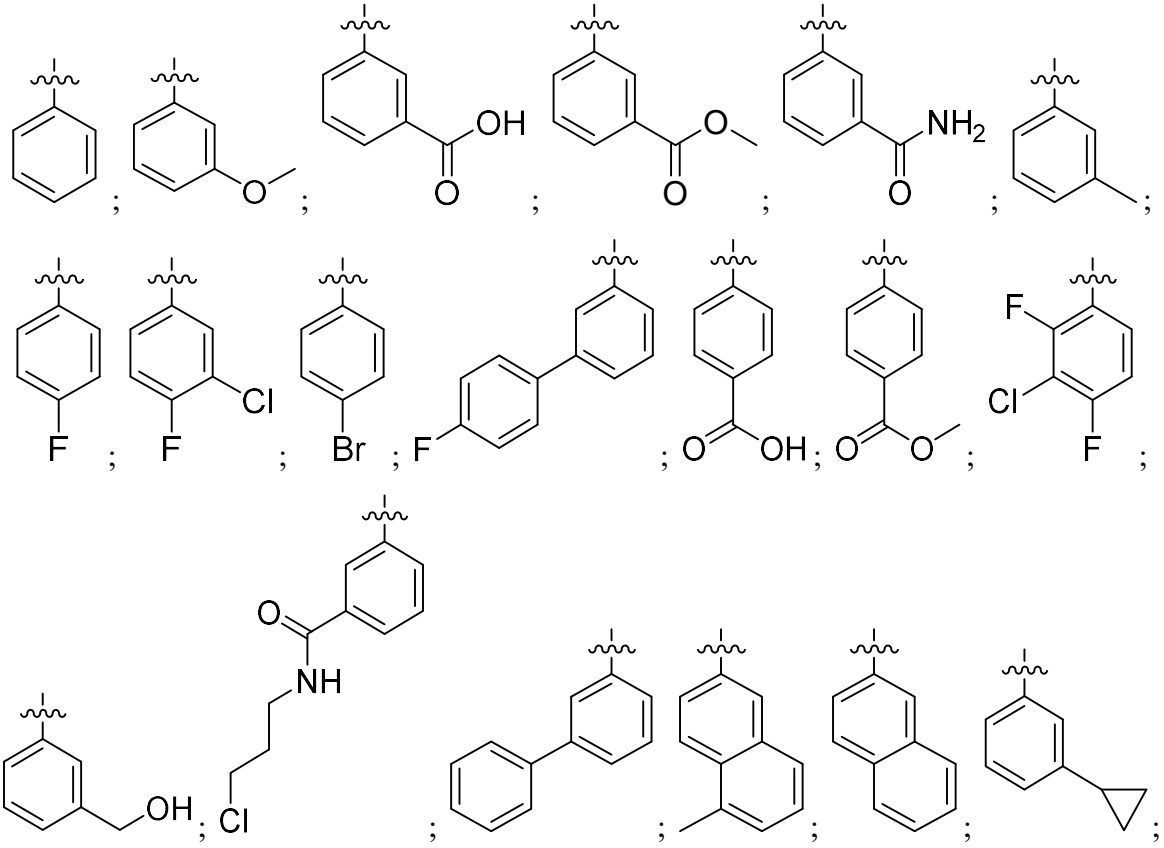
7. The compound of claim 1, wherein R^1 is a substituted or unsubstituted heterocyclyl.

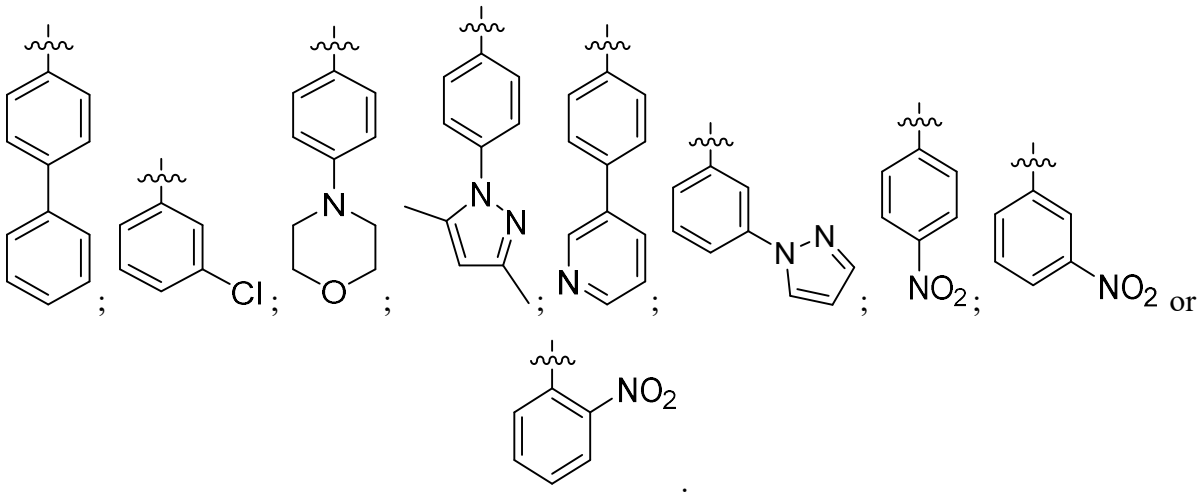
8. The compound of claim 1, wherein R^2 is hydrogen, C_1-C_6 alkyl, or R^2 and R^3, together with the carbon and nitrogen to which they are attached, respectively, form an optionally substituted 4-7 membered heterocyclyl.

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

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

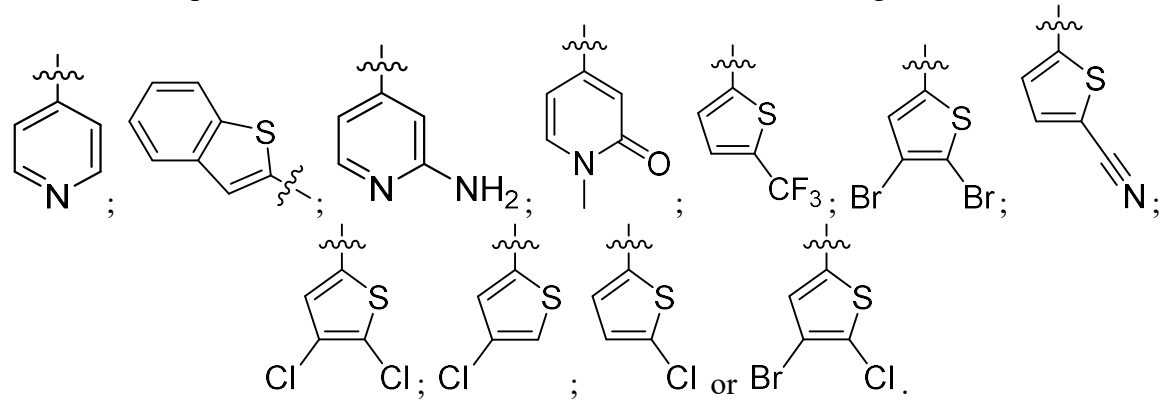
11. The compound of claim 1, wherein R^4 has one of the following structures:





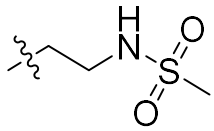
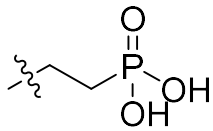
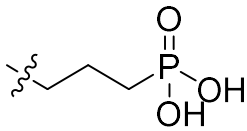
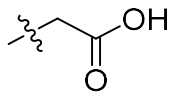
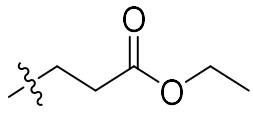
12. The compound of claim 1, wherein R^4 is a substituted or unsubstituted heteroaryl.

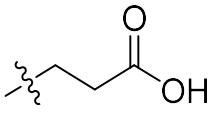
13. The compound of claim 1, wherein R^4 has one of the following structures:



14. The compound of claim 1, wherein R^5 is hydrogen, alkyl, phosphonalkyl, $(CH_2)_mNR^6S(O)_2R^7$, or $(CH_2)_mC(=O)OR^6$.

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

 ;  ;  ;  ; 

or  .

16. The compound of claim 1, wherein L^1 is a direct bond, -O-, or $-CH_2-$.

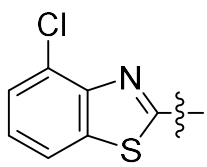
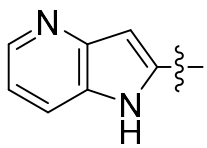
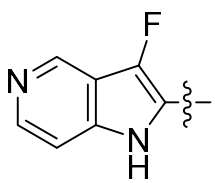
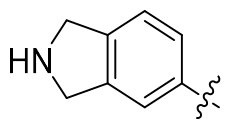
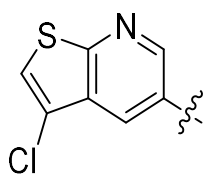
17. The compound of claim 1, wherein L^1 is $-CR^{8a}R^{8b}-$ and R^{8a} and R^{8b} together with the carbon to which they are attached form an optionally substituted 3, 4, or 5 membered cycloalkyl.

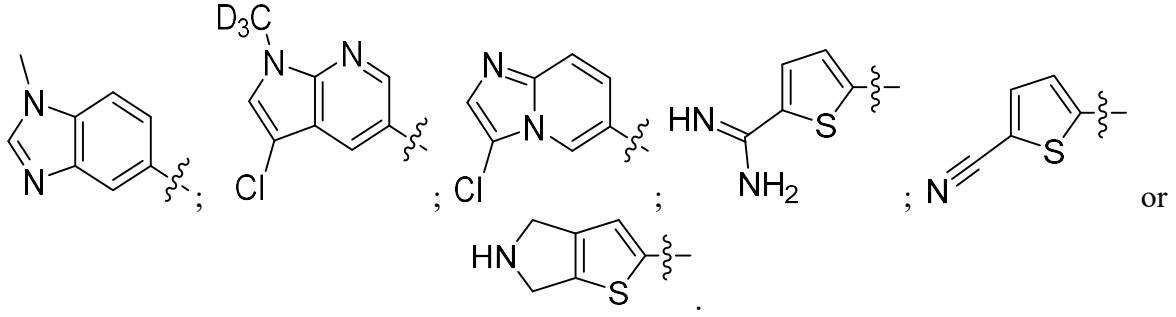
18. A compound having one of the structures in Table 1 or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof.

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

20. Use of a compound of claim 1 or a pharmaceutical composition according to claim 19, in the manufacture of a medicament for treating a MASP-2-associated disease or disorder in a subject in need thereof.

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

 ;  ;  ;  ;  ;



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