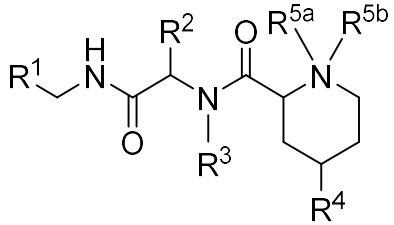
Mannan-binding lectin-associated serine protease-2 (MASP-2) has been shown to be required for the function of the lectin pathway, one of the principal complement activation pathways (Vorup-Jensen et al., J. Immunol 165:2093-2100, 2000; Ambrus et al., J Immunol. 170: 1374-1382, 2003; Schwaeble et al.,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

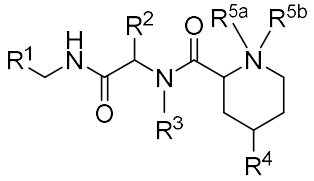
One example provides a compound having the following Structure (I):



(I)

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

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 aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or a substituted or unsubstituted heterocyclyl;

R^2 is hydrogen, alkyl, alkoxy, haloalkyl, 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 a substituted or unsubstituted heterocyclyl;

R^{5a} is hydrogen, alkyl, haloalkyl, cycloalkyl, phosphonalkyl, $(CH_2)_nC(=O)OR^6$, $C(=O)R^6$, $C(=O)OR^6$, or $C(=O)NR^6R^7$;

R^{5b} is an electron pair or alkyl;

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

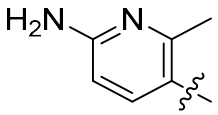
R^8 is alkyl, haloalkyl, aminylalkyl, substituted or unsubstituted arylalkyl; and

n is 1, 2, 3, 4, 5, 6, 7, or 8,

provided that

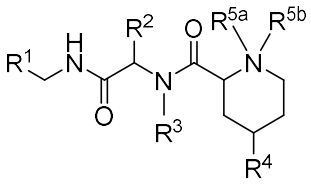
A) R^{5a} is alkyl, haloalkyl, cycloalkyl, phosphonalkyl, $(CH_2)_nC(=O)OR^6$, $C(=O)R^6$, $C(=O)OR^6$, or $C(=O)NR^6R^7$ or R^1 is substituted with one or more substituents selected from the group consisting of a substituted heteroaryl, $C(=NH)NHC(=O)OR^8$, $C(=NOC(=O)R^8)NH_2$, $C(=NOC(=O)OR^8)NH_2$, and $C(=NOH)NH_2$; and

B) when R^{5a} is alkyl or $(CH_2)_nC(=O)OR^6$, R^1 does not have the following structure:



unless 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.

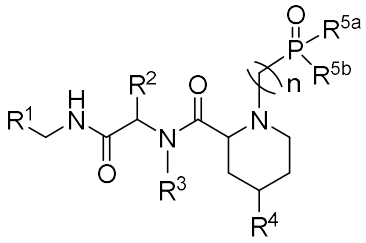
Another example provides a compound having the following Structure (II):



(II)

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

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



(III)

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

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.

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

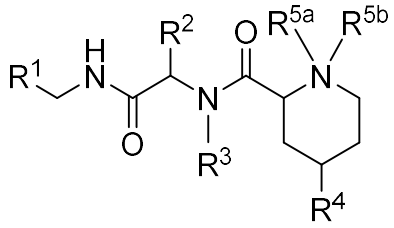
The compounds of Structures (I), (II), and (III) are useful in the treatment of MASP-2-associated diseases and disorders, and in the manufacture of medicaments for treating MASP-2-associated diseases and disorders. Accordingly, other examples of the disclosure provide methods of treating a MASP-2-associated disease and disorder comprising administering to a patient a therapeutically effective amount of a compound of Structure (I), Structure (II), or Structure (III), 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 examples, and objects will become more apparent when read with the detailed description and figures which follow.

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 aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or a substituted or unsubstituted heterocyclyl;

R^2 is hydrogen, alkyl, alkoxy, haloalkyl, 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 a substituted or unsubstituted heterocyclyl;

R^{5a} is hydrogen, alkyl, haloalkyl, cycloalkyl, phosphonalkyl, $(CH_2)_nC(=O)OR^6$, $C(=O)R^6$, $C(=O)OR^6$, or $C(=O)NR^6R^7$;

R^{5b} is an electron pair or alkyl;

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

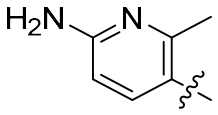
R^8 is alkyl, haloalkyl, aminylalkyl, substituted or unsubstituted arylalkyl; and

n is 1, 2, 3, 4, 5, 6, 7, or 8,

provided that

A) R^{5a} is alkyl, haloalkyl, cycloalkyl, phosphonalkyl, $(CH_2)_nC(=O)OR^6$, $C(=O)R^6$, $C(=O)OR^6$, or $C(=O)NR^6R^7$ or R^1 is substituted with one or more substituents selected from the group consisting of a substituted heteroaryl, $C(=NH)NHC(=O)OR^8$, $C(=NOC(=O)R^8)NH_2$, $C(=NOC(=O)OR^8)NH_2$, and $C(=NOH)NH_2$; and

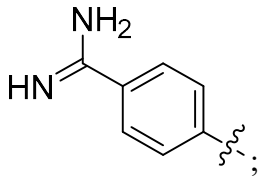
B) when R^{5a} is alkyl or $(CH_2)_nC(=O)OR^6$, R^1 does not have the following structure:



unless 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.

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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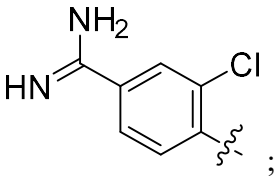
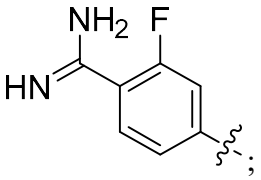
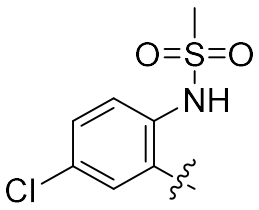
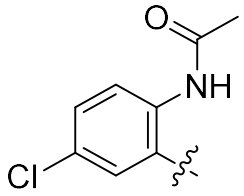

;

;

;

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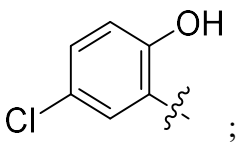
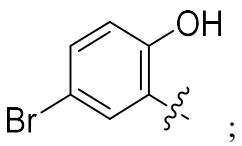
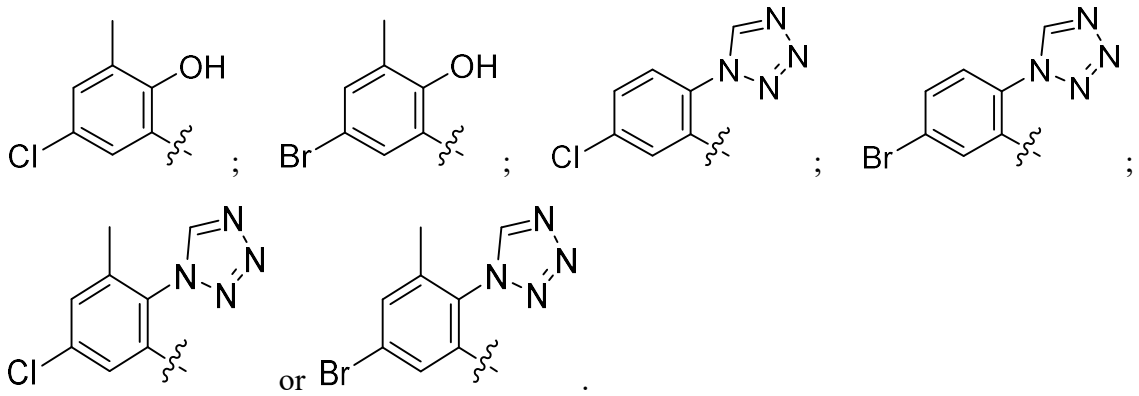
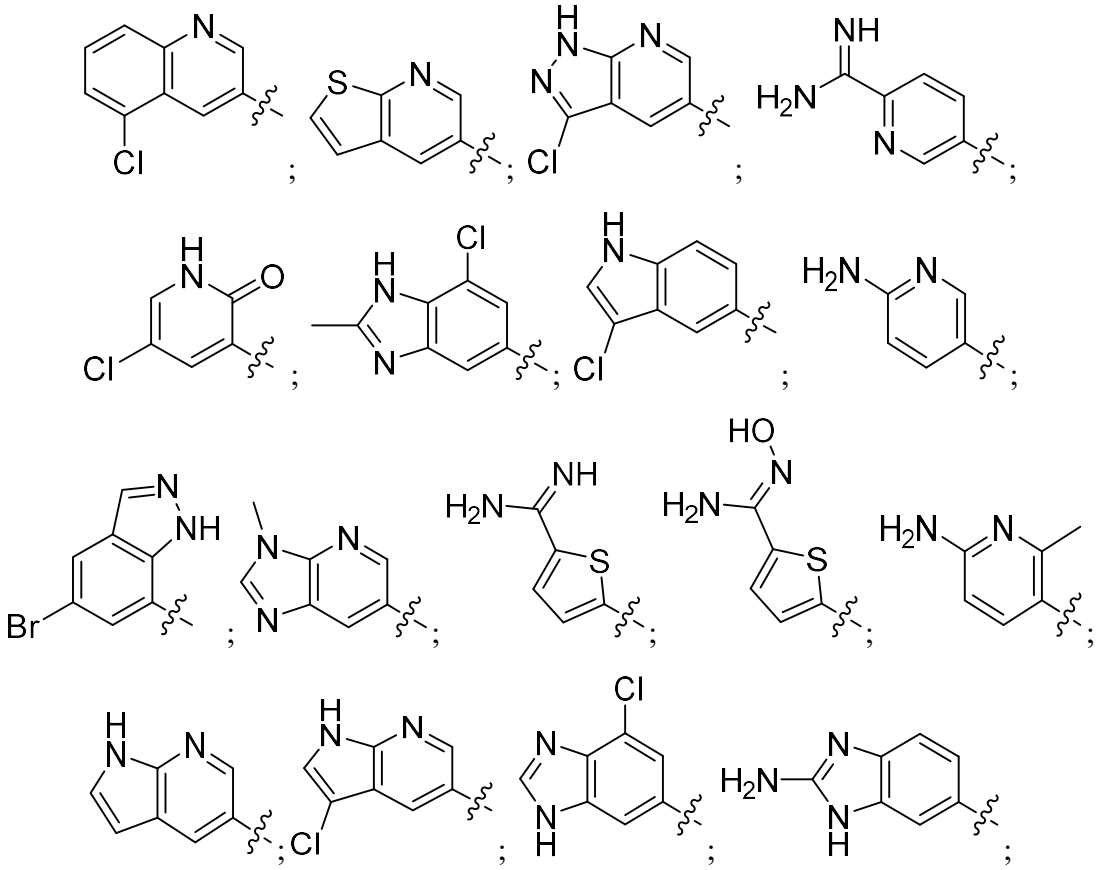
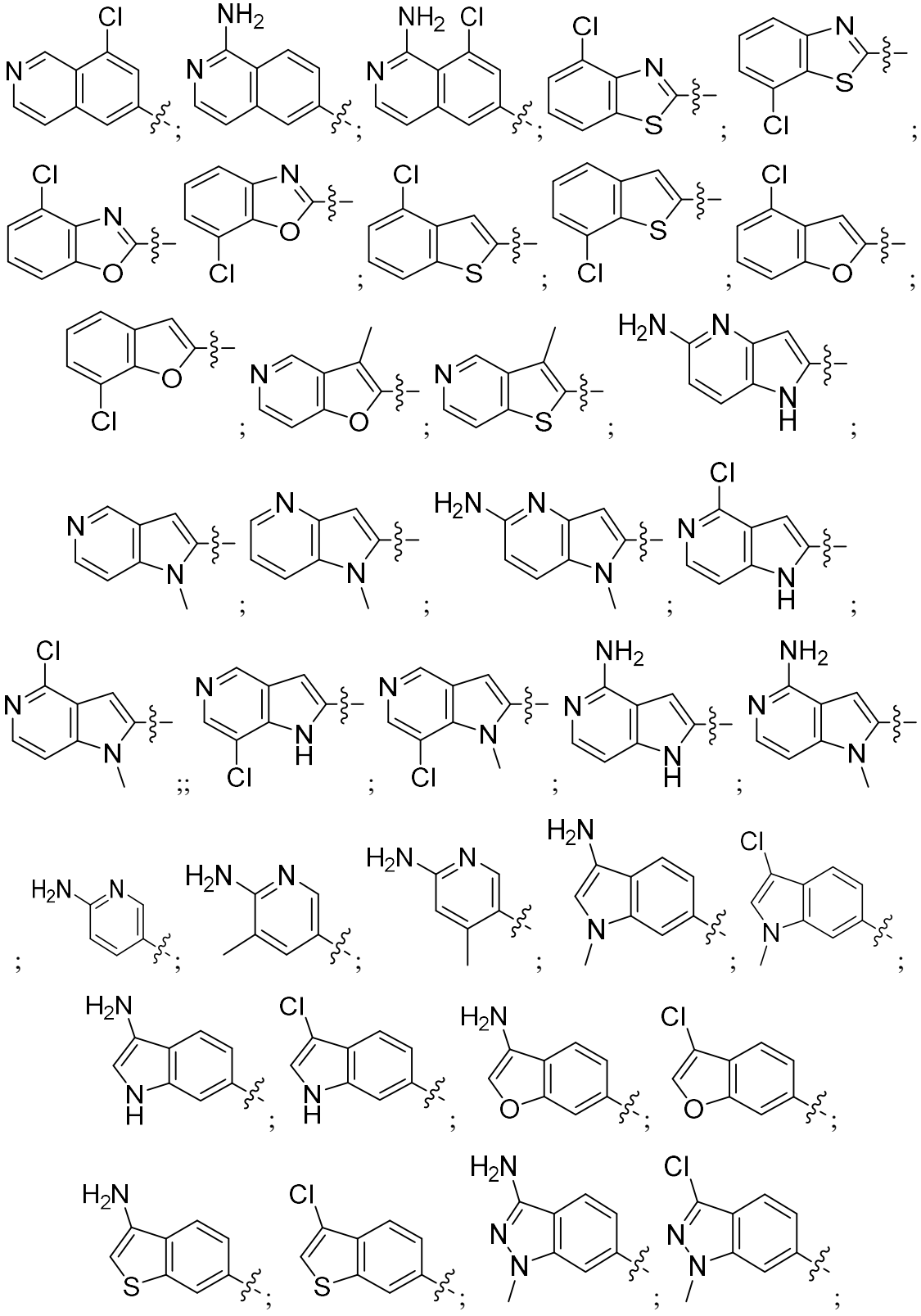

;

;

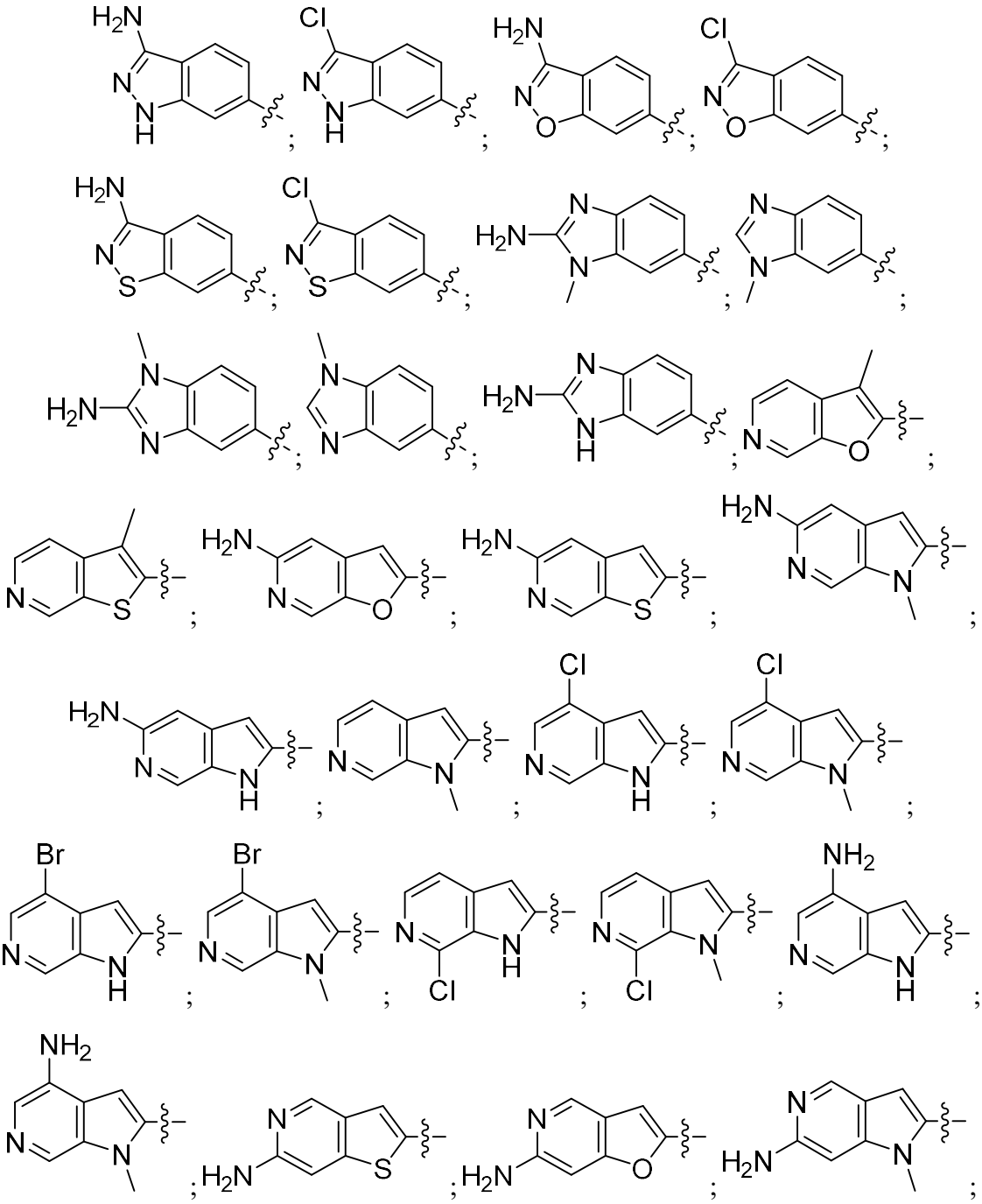


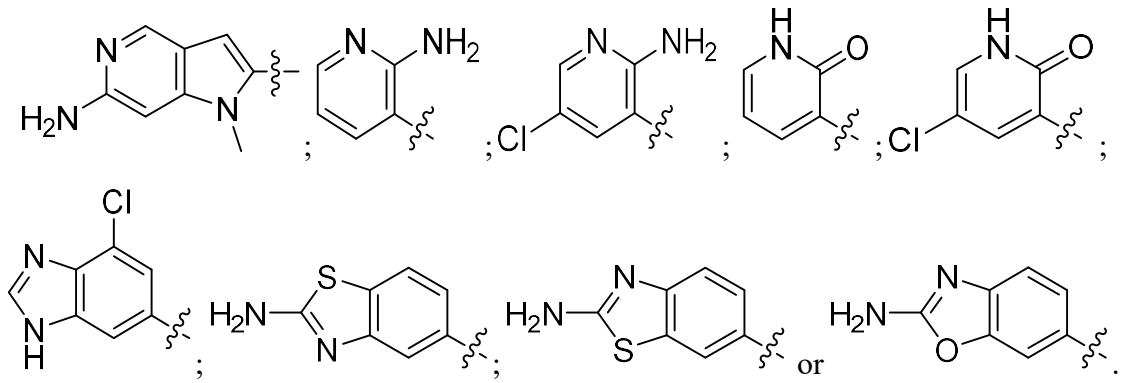
4. The compound of claim 1, wherein R^1 is a substituted or unsubstituted heteroaryl.

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

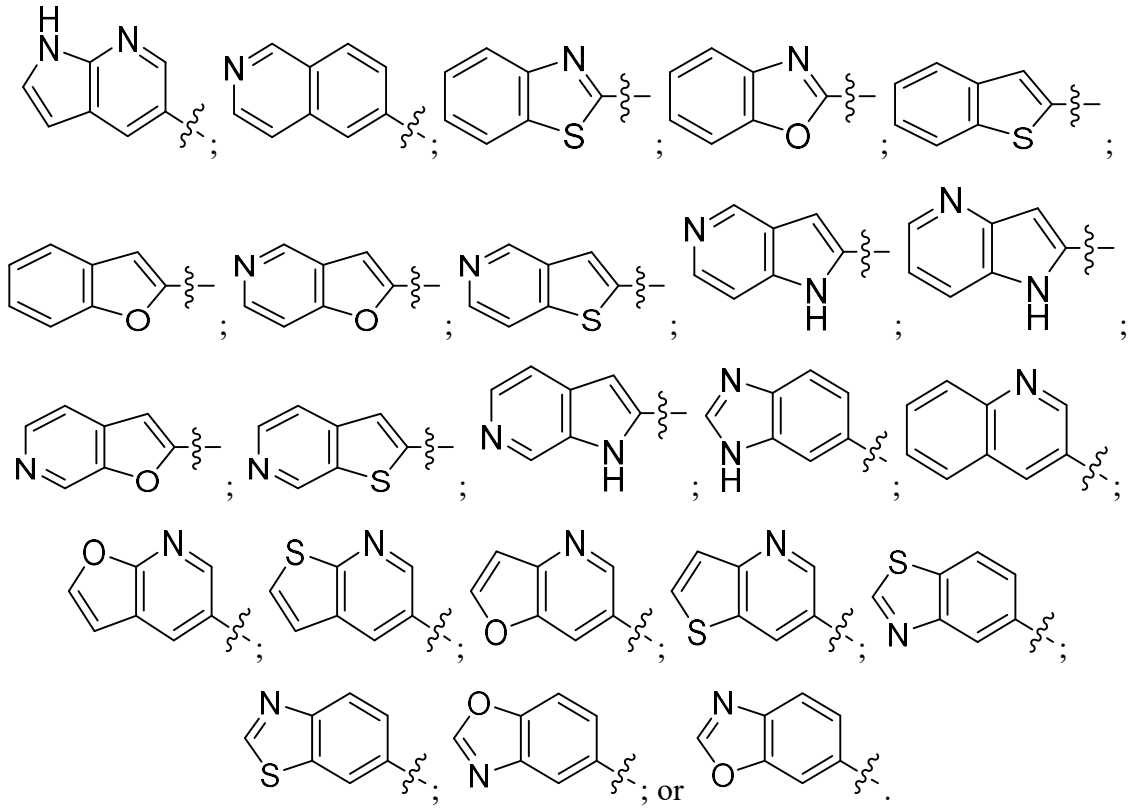








6. The compound of claim 1, wherein R^1 has one of the following structures:



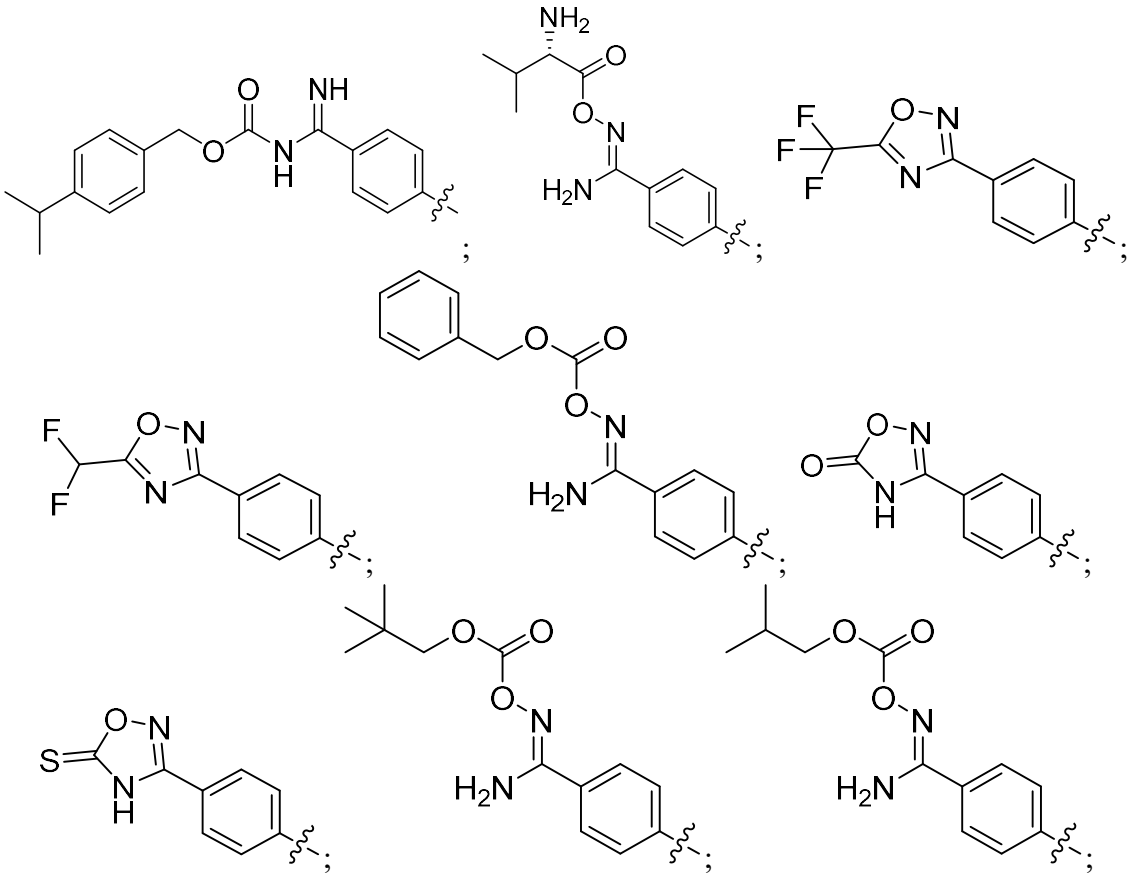
7. The compound of claim 1, wherein R^1 is substituted with one or more substituents selected from the group consisting of a substituted heteroaryl, $C(=NH)NHC(=O)OR^8$, $C(=NOC(=O)R^8)NH_2$, $C(=NOC(=O)OR^8)NH_2$, and $C(=NOH)NH_2$.

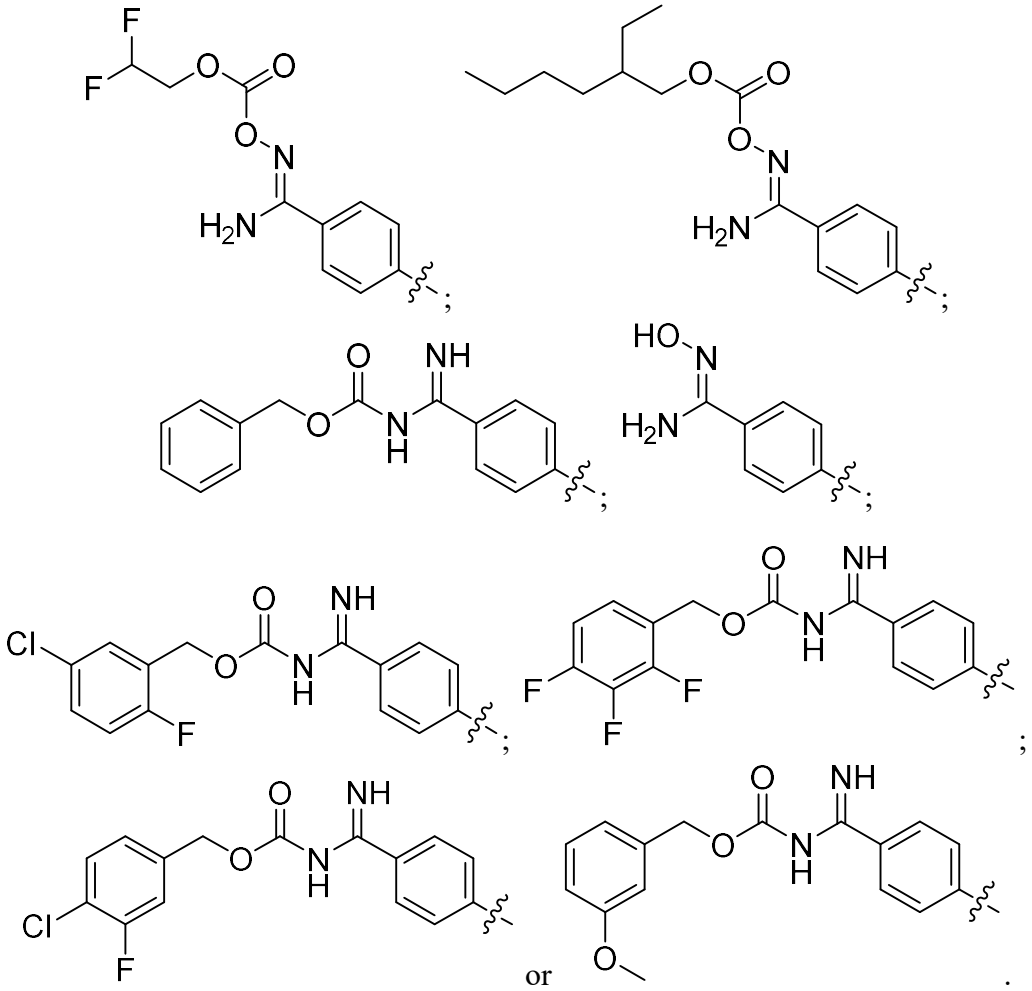
8. The compound of claim 7, wherein R^1 is substituted with $C(=NH)NHC(=O)OR^8$ and R^8 is a substituted or unsubstituted arylalkyl.

9. The compound of claim 7, wherein R^1 is substituted with $C(=NOC(=O)R^8)NH_2$ and R^8 is an aminylalkyl.

10. The compound of claim 7, wherein R^1 is substituted with $C(=NOC(=O)OR^8)NH_2$ and R^8 is an alkyl, a haloalkyl, or a substituted or unsubstituted arylalkyl.

11. The compound of claim 7, wherein R^1 has one of the following structures:





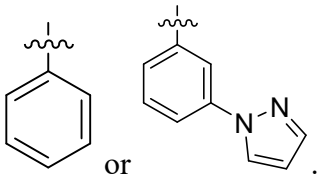
12. The compound of claim 1, wherein R^2 is hydrogen or C_1-C_6 alkyl.

13. The compound of claim 1, wherein R^2 is -CH_3.

14. The compound of claim 1, wherein R^2 and R^3, together with the carbon and nitrogen to which they are attached, respectively, form an optionally substituted 4, 5, or 6 membered heterocyclyl.

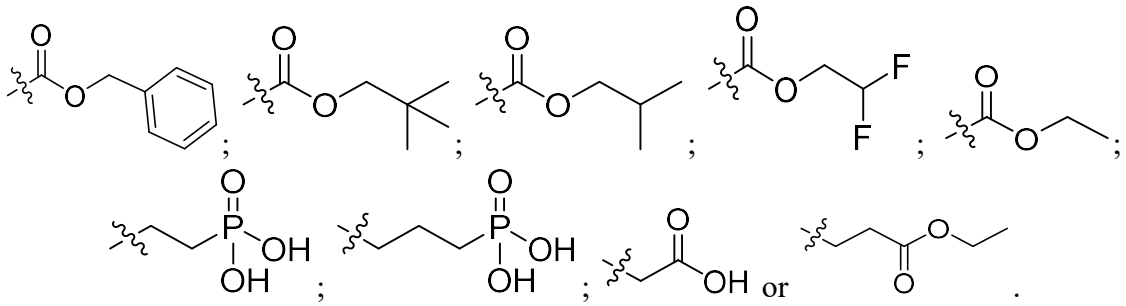
15. The compound of claim 1, wherein R^4 is a substituted or unsubstituted aryl.

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



17. The compound of claim 1, wherein R^{5a} is alkyl, $C(=O)OR^6$, phosphonalkyl, or $(CH_2)_nC(=O)OR^6$.

18. The compound of claim 17, wherein R^{5a} has one of the following structures:



19. The compound of claim 1, wherein R^{5b} is an electron pair or alkyl.

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

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

22. 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.