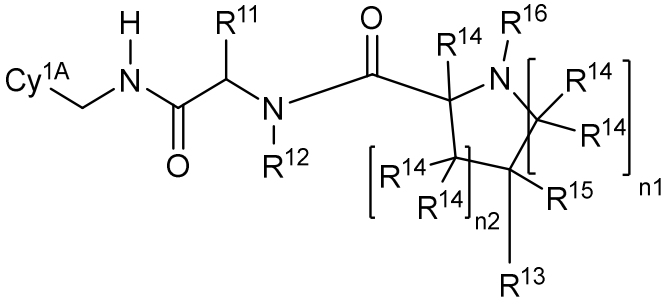


(**I-1**)



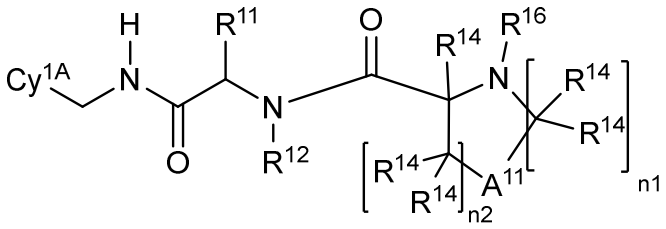
(**I-2**)

or a salt thereof; wherein the variables are as defined below.

The present disclosure also provides a pharmaceutical composition comprising a compound of Formula (**I-1**) or (**I-2**), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier or excipient.

The compounds of Formula (**I-1**) or (**I-2**) 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. The present disclosure also provides methods of treating a MASP-2-associated disease and disorder comprising administering to a patient a therapeutically effective amount of a compound of Formula (**I-1**) or (**I-2**), or a salt thereof.

In one aspect, the present disclosure refers to a compound of Formula (**I-1**):



(**I-1**)

or a salt thereof, wherein:

Cy^{1A} is unsubstituted or substituted C_{6-10} aryl or unsubstituted or substituted 5-10 membered heteroaryl; wherein the ring atoms of the 5-10 membered heteroaryl forming Cy^{1A} consist of carbon atoms and 1, 2, or 3 heteroatoms selected from O, N and S; wherein the substituted C_{6-10} aryl or substituted 5-10 membered heteroaryl forming Cy^{1A} are substituted with 1, 2, 3, 4 or 5 substituents each independently selected from R^{Cy1A}, halogen, C_{1-6} haloalkyl, CN, OR^{a11}, S^{Ra11}, $C(O)R^{b11}$,

$C(O)NR^{c11}R^{d11}$, $C(O)OR^{a11}$, $OC(O)R^{b11}$, $OC(O)NR^{c11}R^{d11}$, $NR^{c11}R^{d11}$, $NR^{c11}C(O)R^{b11}$, $NR^{c11}C(O)NR^{c11}R^{d11}$, $NR^{c11}C(O)OR^{a11}$, $C(=NR^{e11})NR^{c11}R^{d11}$, $C(=NOR^{a11})NR^{c11}R^{d11}$, $C(=NOC(O)R^{b11})NR^{c11}R^{d11}$, $C(=NR^{e11})NR^{c11}C(O)OR^{a11}$, $NR^{c11}C(=NR^{e11})NR^{c11}R^{d11}$, $S(O)R^{b11}$, $S(O)NR^{c11}R^{d11}$, $S(O)_2R^{b11}$, $NR^{c11}S(O)_2R^{b11}$, $S(O)_2NR^{c11}R^{d11}$ and oxo;

each R^{Cy1A} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, wherein the ring atoms of the 5-10 membered heteroaryl or 4-10-membered heterocycloalkyl forming R^{Cy1A} consist of carbon atoms and 1, 2, 3 or 4 heteroatoms selected from O, N and S, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl forming R^{Cy1A} is independently unsubstituted or substituted with 1, 2 or 3 substituents independently selected from halogen, CN, OR^{a11}, SR^{a11}, $C(O)R^{b11}$, $C(O)NR^{c11}R^{d11}$, $C(O)OR^{a11}$, $OC(O)R^{b11}$, $OC(O)NR^{c11}R^{d11}$, $NR^{c11}R^{d11}$, $NR^{c11}C(O)R^{b11}$, $NR^{c11}C(O)NR^{c11}R^{d11}$, $NR^{c11}C(O)OR^{a11}$, $C(=NR^{e11})NR^{c11}R^{d11}$, $NR^{c11}C(=NR^{e11})NR^{c11}R^{d11}$, $S(O)R^{b11}$, $S(O)NR^{c11}R^{d11}$, $S(O)_2R^{b11}$, $NR^{c11}S(O)_2R^{b11}$, $S(O)_2NR^{c11}R^{d11}$ and oxo, and wherein each C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl forming R^{Cy1A} is independently unsubstituted or substituted with 1, 2 or 3 substituents independently selected from halogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, OR^{a11}, SR^{a11}, $C(O)R^{b11}$, $C(O)NR^{c11}R^{d11}$, $C(O)OR^{a11}$, $OC(O)R^{b11}$, $OC(O)NR^{c11}R^{d11}$, $NR^{c11}R^{d11}$, $NR^{c11}C(O)R^{b11}$, $NR^{c11}C(O)NR^{c11}R^{d11}$, $NR^{c11}C(O)OR^{a11}$, $C(=NR^{e11})NR^{c11}R^{d11}$, $NR^{c11}C(=NR^{e11})NR^{c11}R^{d11}$, $S(O)R^{b11}$, $S(O)NR^{c11}R^{d11}$, $S(O)_2R^{b11}$, $NR^{c11}S(O)_2R^{b11}$, $S(O)_2NR^{c11}R^{d11}$ and oxo;

R^{11} is H or C_{1-6} alkyl, C_{6-10} aryl-C_{1-6} alkyl or 5-10 membered heteroaryl-C_{1-6} alkyl, wherein the C_{1-6} alkyl forming R^{11} is unsubstituted or substituted by 1, 2 or 3 substituents independently selected from halogen, CN, OR^{a11}, SR^{a11}, $C(O)R^{b11}$, $C(O)NR^{c11}R^{d11}$, $C(O)OR^{a11}$, $OC(O)R^{b11}$, $OC(O)NR^{c11}R^{d11}$, $NR^{c11}R^{d11}$, $NR^{c11}C(O)R^{b11}$, $NR^{c11}C(O)NR^{c11}R^{d11}$, $NR^{c11}C(O)OR^{a11}$, $C(=NR^{e11})NR^{c11}R^{d11}$, $NR^{c11}C(=NR^{e11})NR^{c11}R^{d11}$, $S(O)R^{b11}$, $S(O)NR^{c11}R^{d11}$, $S(O)_2R^{b11}$, $NR^{c11}S(O)_2R^{b11}$, $S(O)_2NR^{c11}R^{d11}$ and oxo, and wherein the C_{6-10} aryl-C_{1-6} alkyl or 5-10 membered heteroaryl-C_{1-6} alkyl forming R^{11} is unsubstituted or substituted by 1, 2 or 3 substituents independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, OR^{a11}, SR^{a11}, $C(O)R^{b11}$, $C(O)NR^{c11}R^{d11}$, $C(O)OR^{a11}$, $OC(O)R^{b11}$, $OC(O)NR^{c11}R^{d11}$, $NR^{c11}R^{d11}$, $NR^{c11}C(O)R^{b11}$, $NR^{c11}C(O)NR^{c11}R^{d11}$, $NR^{c11}C(O)OR^{a11}$,

$C(=NR^{e11})NR^{c11}R^{d11}$, $NR^{c11}C(=NR^{e11})NR^{c11}R^{d11}$, $S(O)R^{b11}$, $S(O)NR^{c11}R^{d11}$, $S(O)_2R^{b11}$, $NR^{c11}S(O)_2R^{b11}$, $S(O)_2NR^{c11}R^{d11}$ and oxo;

R^{12} is H or C_{1-6} alkyl; or

R^{11} and R^{12}, together with the groups to which they are attached, form a 4-6 membered heterocycloalkyl ring;

A^{11} is $CR^{13}R^{15}$ or N;

each R^{13} is independently Cy^{1B}, $(CR^{13A}R^{13B})_{n3}Cy^{1B}$, ($C_{1-6}$ alkylene)Cy^{1B}, (C_{2-6} alkenylene)Cy^{1B}, (C_{2-6} alkynylene)Cy^{1B} or OCy^{1B}, wherein the C_{1-6} alkylene, C_{2-6} alkenylene, or C_{2-6} alkynylene component of R^{13} is unsubstituted or substituted by 1, 2, 3, 4 or 5 substituents each independently selected from the group consisting of halogen, CN, OR^{a11}, SR^{a11}, $C(O)R^{b11}$, $C(O)NR^{c11}R^{d11}$, $C(O)OR^{a11}$, $OC(O)R^{b11}$, $OC(O)NR^{c11}R^{d11}$, $NR^{c11}R^{d11}$, $NR^{c11}C(O)R^{b11}$, $NR^{c11}C(O)NR^{c11}R^{d11}$, $NR^{c11}C(O)OR^{a11}$, $C(=NR^{e11})NR^{c11}R^{d11}$, $NR^{c11}C(=NR^{e11})NR^{c11}R^{d11}$, $S(O)R^{b11}$, $S(O)NR^{c11}R^{d11}$, $S(O)_2R^{b11}$, $NR^{c11}S(O)_2R^{b11}$, $S(O)_2NR^{c11}R^{d11}$ and oxo;

each R^{14} is independently selected from H and C_{1-6} alkyl;

R^{15} is selected from H, R^{13}, C_{1-6} alkyl and OH;

a pair of R^{14} groups attached to adjacent carbon atoms, or a pairing of R^{14} and R^{15} groups attached to adjacent carbon atoms, may, independently of other occurrences of R^{14}, together be replaced a bond connecting the adjacent carbon atoms to which the pair of R^{14} groups or pairing of R^{14} and R^{15} groups is attached, such that the adjacent carbon atoms are connected by a double bond; or

a pair of R^{14} groups attached to the same carbon atom, or a pairing of R^{13} and R^{15} groups attached to the same carbon atom, may, independently of other occurrences of R^{14}, and together with the carbon atom to which the pair of R^{14} groups or pairing of R^{13} and R^{15} groups is attached together form a spiro-fused C_{3-10} cycloalkyl or 4-10 membered heterocycloalkyl ring, wherein the ring atoms of the 4-10 membered heterocycloalkyl ring formed consist of carbon atoms and 1, 2, or 3 heteroatoms selected from O, N and S, wherein the spiro-fused C_{3-10} cycloalkyl or 4-10 membered heterocycloalkyl ring formed is optionally further substituted with 1, 2 or 3 substituents independently selected from halogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, haloalkyl, CN, OR^{a11}, SR^{a11}, $C(O)R^{b11}$, $C(O)NR^{c11}R^{d11}$, $C(O)OR^{a11}$, $OC(O)R^{b11}$, $OC(O)NR^{c11}R^{d11}$, $NR^{c11}R^{d11}$, $NR^{c11}C(O)R^{b11}$, $NR^{c11}C(O)NR^{c11}R^{d11}$, $NR^{c11}C(O)OR^{a11}$, $C(=NR^{e11})NR^{c11}R^{d11}$, $NR^{c11}C(=NR^{e11})NR^{c11}R^{d11}$, $S(O)R^{b11}$, $S(O)NR^{c11}R^{d11}$, $S(O)_2R^{b11}$, $NR^{c11}S(O)_2R^{b11}$, $S(O)_2NR^{c11}R^{d11}$ and oxo; or

pairs of R^{14} groups attached to adjacent carbon atoms, or a pairing of R^{14} and R^{15} groups attached to adjacent carbon atoms, may, independently of other occurrences of R^{14}, together with the adjacent carbon atoms to which the pair of R^{14} groups or pairing of R^{14} and R^{15} groups is attached, form a fused C_{3-10} cycloalkyl or 4-10 membered heterocycloalkyl ring, wherein the ring atoms of the 4-10 membered heterocycloalkyl ring formed consist of carbon atoms and 1, 2, or 3 heteroatoms selected from O, N and S, wherein the fused C_{3-10} cycloalkyl or 4-10 membered heterocycloalkyl ring formed is optionally further substituted with 1, 2 or 3 substituents independently selected from halogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, haloalkyl, CN, OR^{a11}, SR^{a11}, $C(O)R^{b11}$, $C(O)NR^{c11}R^{d11}$, $C(O)OR^{a11}$, $OC(O)R^{b11}$, $OC(O)NR^{c11}R^{d11}$, $NR^{c11}R^{d11}$, $NR^{c11}C(O)R^{b11}$, $NR^{c11}C(O)NR^{c11}R^{d11}$, $NR^{c11}C(O)OR^{a11}$, $C(=NR^{e11})NR^{c11}R^{d11}$, $NR^{c11}C(=NR^{e11})NR^{c11}R^{d11}$, $S(O)R^{b11}$, $S(O)NR^{c11}R^{d11}$, $S(O)_2R^{b11}$, $NR^{c11}S(O)_2R^{b11}$, $S(O)_2NR^{c11}R^{d11}$ and oxo; or

a grouping of four R^{14} groups attached to two adjacent carbon atoms, or a grouping of two R^{14} , one R^{13} and one R^{15} groups attached to two adjacent carbon atoms, may, independently of other occurrences of R^{14}, together with the two adjacent carbon atoms to which the grouping of four R^{14} groups or grouping of two R^{14} , one R^{13} and one R^{15} groups are attached, form a fused C_{6-10} aryl or 5-10 membered heteroaryl, C_{3-10} cycloalkyl or 4-10 membered heterocycloalkyl ring, wherein the ring atoms of the 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl ring formed consist of carbon atoms and 1, 2, or 3 heteroatoms selected from O, N and S, and wherein the fused C_{6-10} aryl or 5-10 membered heteroaryl, C_{3-10} cycloalkyl or 4-10 membered heterocycloalkyl ring formed is optionally further substituted with 1, 2 or 3 substituents independently selected from halogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, haloalkyl, CN, OR^{a11}, SR^{a11}, $C(O)R^{b11}$, $C(O)NR^{c11}R^{d11}$, $C(O)OR^{a11}$, $OC(O)R^{b11}$, $OC(O)NR^{c11}R^{d11}$, $NR^{c11}R^{d11}$, $NR^{c11}C(O)R^{b11}$, $NR^{c11}C(O)NR^{c11}R^{d11}$, $NR^{c11}C(O)OR^{a11}$, $C(=NR^{e11})NR^{c11}R^{d11}$, $NR^{c11}C(=NR^{e11})NR^{c11}R^{d11}$, $S(O)R^{b11}$, $S(O)NR^{c11}R^{d11}$, $S(O)_2R^{b11}$, $NR^{c11}S(O)_2R^{b11}$, $S(O)_2NR^{c11}R^{d11}$ and oxo;

n1 is 1 or 2;

n2 is 0, 1 or 2;

provided that the sum of n1 and n2 is 1, 2 or 3;

provided that if n1 is 1 or n2 is 0, then A^{11} is $CR^{13}R^{15}$;

n3 is 0, 1 or 2;

each R^{13A} is independently H or C_{1-6} alkyl;

each R^{13B} is independently H or C_{1-6} alkyl; or

or R^{13A} and R^{13B} attached to the same carbon atom, independently of any other R^{13A} and R^{13B} groups, together may form $–(CH_2)_{2-5}$-, thereby forming a 3-6 membered cycloalkyl ring;

Cy^{1B} is unsubstituted or substituted C_{6-10} aryl, unsubstituted or substituted 5-10 membered heteroaryl, unsubstituted or substituted C_{3-10} cycloalkyl, or unsubstituted or substituted 4-10 membered heterocycloalkyl; wherein the ring atoms of the 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl forming Cy^{1B} consist of carbon atoms and 1, 2 or 3 heteroatoms selected from O, N and S; and

wherein the substituted C_{6-10} aryl, substituted 5-10 membered heteroaryl, substituted C_{3-10} cycloalkyl or substituted 4-10 membered heterocycloalkyl forming Cy^{1B} are substituted with 1, 2, 3, 4 or 5 substituents each independently selected from R^{Cy1B}, halogen, C_{1-6} haloalkyl, CN, OR^{a11}, S^{Ra11}, $C(O)R^{b11}$, $C(O)NR^{c11}R^{d11}$, $C(O)OR^{a11}$, $OC(O)R^{b11}$, $OC(O)NR^{c11}R^{d11}$, $NR^{c11}R^{d11}$, $NR^{c11}C(O)R^{b11}$, $NR^{c11}C(O)NR^{c11}R^{d11}$, $NR^{c11}C(O)OR^{a11}$, $C(=NR^{e11})NR^{c11}R^{d11}$, $C(=NOR^{a11})NR^{c11}R^{d11}$, $C(=NOC(O)R^{b11})NR^{c11}R^{d11}$, $C(=NR^{e11})NR^{c11}C(O)OR^{a11}$, $NR^{c11}C(=NR^{e11})NR^{c11}R^{d11}$, $S(O)R^{b11}$, $S(O)NR^{c11}R^{d11}$, $S(O)_2R^{b11}$, $NR^{c11}S(O)_2R^{b11}$, $S(O)_2NR^{c11}R^{d11}$ and oxo;

wherein each R^{Cy1B} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, wherein the ring atoms of the 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl forming R^{Cy1B} consist of carbon atoms and 1, 2 or 3 heteroatoms selected from O, N and S; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl forming R^{Cy1B} is independently unsubstituted or substituted with 1, 2 or 3 substituents independently selected from halogen, CN, OR^{a11}, SR^{a11}, $C(O)R^{b11}$, $C(O)NR^{c11}R^{d11}$, $C(O)OR^{a11}$, $OC(O)R^{b11}$, $OC(O)NR^{c11}R^{d11}$, $NR^{c11}R^{d11}$, $NR^{c11}C(O)^{Rb11}$, $NR^{c11}C(O)NR^{c11}R^{d11}$, $NR^{c11}C(O)OR^{a11}$, $C(=NR^{e11})NR^{c11}R^{d11}$, $NR^{c11}C(=NR^{e11})NR^{c11}R^{d11}$, $S(O)R^{b11}$, $S(O)NR^{c11}R^{d11}$, $S(O)_2R^{b11}$, $NR^{c11}S(O)_2R^{b11}$, $S(O)_2NR^{c11}R^{d11}$ and oxo; and wherein each C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl forming R^{Cy1B} is independently unsubstituted or substituted with 1, 2 or 3 substituents independently selected from halogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, OR^{a11}, SR^{a11}, $C(O)R^{b11}$, $C(O)NR^{c11}R^{d11}$, $C(O)OR^{a11}$, $OC(O)R^{b11}$, $OC(O)NR^{c11}R^{d11}$, $NR^{c11}R^{d11}$, $NR^{c11}C(O)^{Rb11}$, $NR^{c11}C(O)NR^{c11}R^{d11}$, $NR^{c11}C(O)OR^{a11}$, $C(=NR^{e11})NR^{c11}R^{d11}$,

$NR^{c11}C(=NR^{e11})NR^{c11}R^{d11}$, $S(O)R^{b11}$, $S(O)NR^{c11}R^{d11}$, $S(O)_2R^{b11}$, $NR^{c11}S(O)_2R^{b11}$, $S(O)_2NR^{c11}R^{d11}$ and oxo;

R^{16} is H, Cy^{1C}, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl forming R^{16} is unsubstituted or substituted by 1, 2, 3, 4 or 5 substituents selected from the group consisting of Cy^{1C}, halogen, CN, OR^{a11}, SR^{a11}, $C(O)R^{b11}$, $C(O)NR^{c11}R^{d11}$, $C(O)OR^{a11}$, $OC(O)R^{b11}$, $OC(O)NR^{c11}R^{d11}$, $NR^{c11}R^{d11}$, $NR^{c11}C(O)R^{b11}$, $NR^{c11}C(O)NR^{c11}R^{d11}$, $NR^{c11}C(O)OR^{a11}$, $C(=NR^{e11})NR^{c11}R^{d11}$, $NR^{c11}C(=NR^{e11})NR^{c11}R^{d11}$, $S(O)R^{b11}$, $S(O)NR^{c11}R^{d11}$, $S(O)_2R^{b11}$, $NR^{c11}S(O)_2R^{b11}$, $S(O)_2NR^{c11}R^{d11}$ and oxo, provided that no more than one of the substituents of R^{16} is Cy^{1C};

Cy^{1C} is unsubstituted or substituted C_{6-10} aryl, unsubstituted or substituted 5-10 membered heteroaryl, unsubstituted or substituted C_{3-10} cycloalkyl, or unsubstituted or substituted 4-10 membered heterocycloalkyl; wherein the ring atoms of the 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl forming Cy^{1C} consist of carbon atoms and 1, 2 or 3 heteroatoms selected from O, N and S; and

wherein the substituted C_{6-10} aryl, substituted 5-10 membered heteroaryl, substituted C_{3-10} cycloalkyl or substituted 4-10 membered heterocycloalkyl forming Cy^{1C} are substituted with 1, 2, 3, 4 or 5 substituents each independently selected from R^{Cy1C}, halogen, C_{1-6} haloalkyl, CN, OR^{a11}, S^{Ra11}, $C(O)R^{b11}$, $C(O)NR^{c11}R^{d11}$, $C(O)OR^{a11}$, $OC(O)R^{b11}$, $OC(O)NR^{c11}R^{d11}$, $NR^{c11}R^{d11}$, $NR^{c11}C(O)R^{b11}$, $NR^{c11}C(O)NR^{c11}R^{d11}$, $NR^{c11}C(O)OR^{a11}$, $C(=NR^{e11})NR^{c11}R^{d11}$, $C(=NOR^{a11})NR^{c11}R^{d11}$, $C(=NOC(O)R^{b11})NR^{c11}R^{d11}$, $C(=NR^{e11})NR^{c11}C(O)OR^{a11}$, $NR^{c11}C(=NR^{e11})NR^{c11}R^{d11}$, $S(O)R^{b11}$, $S(O)NR^{c11}R^{d11}$, $S(O)_2R^{b11}$, $NR^{c11}S(O)_2R^{b11}$, $S(O)_2NR^{c11}R^{d11}$ and oxo;

wherein each R^{Cy1C} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, wherein the ring atoms of the 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl forming R^{Cy1C} consist of carbon atoms and 1, 2 or 3 heteroatoms selected from O, N and S; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl forming R^{Cy1C} is independently unsubstituted or substituted with 1, 2 or 3 substituents independently selected from halogen, CN, OR^{a11}, SR^{a11}, $C(O)R^{b11}$, $C(O)NR^{c11}R^{d11}$, $C(O)OR^{a11}$, $OC(O)R^{b11}$, $OC(O)NR^{c11}R^{d11}$, $NR^{c11}R^{d11}$, $NR^{c11}C(O)^{Rb11}$, $NR^{c11}C(O)NR^{c11}R^{d11}$, $NR^{c11}C(O)OR^{a11}$, $C(=NR^{e11})NR^{c11}R^{d11}$, $NR^{c11}C(=NR^{e11})NR^{c11}R^{d11}$, $S(O)R^{b11}$, $S(O)NR^{c11}R^{d11}$, $S(O)_2R^{b11}$, $NR^{c11}S(O)_2R^{b11}$, $S(O)_2NR^{c11}R^{d11}$ and oxo; and wherein each C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-}

$_{10}$ cycloalkyl and 4-10 membered heterocycloalkyl forming R^{Cy1C} is independently unsubstituted or substituted with 1, 2 or 3 substituents independently selected from halogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, OR^{a11}, SR^{a11}, $C(O)R^{b11}$, $C(O)NR^{c11}R^{d11}$, $C(O)OR^{a11}$, $OC(O)R^{b11}$, $OC(O)NR^{c11}R^{d11}$, $NR^{c11}R^{d11}$, $NR^{c11}C(O)^{Rb11}$, $NR^{c11}C(O)NR^{c11}R^{d11}$, $NR^{c11}C(O)OR^{a11}$, $C(=NR^{e11})NR^{c11}R^{d11}$, $NR^{c11}C(=NR^{e11})NR^{c11}R^{d11}$, $S(O)R^{b11}$, $S(O)NR^{c11}R^{d11}$, $S(O)_2R^{b11}$, $NR^{c11}S(O)_2R^{b11}$, $S(O)_2NR^{c11}R^{d11}$ and oxo;

R^{a11}, R^{b11}, R^{c11} and R^{d11} are each independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-7} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-3} alkyl, 5-10 membered heteroaryl-C_{1-3} alkyl, C_{3-7} cycloalkyl-C_{1-3} alkyl and 4-10 membered heterocycloalkyl-C_{1-3} alkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-7} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-3} alkyl, 5-10 membered heteroaryl-C_{1-3} alkyl, C_{3-7} cycloalkyl-C_{1-3} alkyl and 4-10 membered heterocycloalkyl-C_{1-3} alkyl forming R^{a11}, R^{b11}, R^{c11} and R^{d11} are each optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from C_{1-6} alkyl, halo, CN, OR^{a12}, SR^{a12}, $C(O)R^{b12}$, $C(O)NR^{c12}R^{d12}$, $C(O)OR^{a12}$, $OC(O)R^{b12}$, $OC(O)NR^{c12}R^{d12}$, $NR^{c12}R^{d12}$, $NR^{c12}C(O)R^{b12}$, $NR^{c12}C(O)NR^{c12}R^{d12}$, $NR^{c12}C(O)OR^{a12}$, $C(=NR^{e12})NR^{c12}R^{d12}$, $NR^{c12}C(=NR^{e12})NR^{c12}R^{d12}$, $S(O)R^{b12}$, $S(O)NR^{c12}R^{d12}$, $S(O)_2R^{b12}$, $NR^{c12}S(O)_2R^{b12}$, $S(O)_2NR^{c12}R^{d12}$ and oxo;

or R^{c11} and R^{d11} attached to the same N atom, together with the N atom to which they are both attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group or 5-membered heteroaryl group, each optionally substituted with 1, 2 or 3 substituents independently selected from C_{1-6} alkyl, halo, CN, OR^{a12}, SR^{a12}, $C(O)R^{b12}$, $C(O)NR^{c12}R^{d12}$, $C(O)OR^{a12}$, $OC(O)R^{b12}$, $OC(O)NR^{c12}R^{d12}$, $NR^{c12}R^{d12}$, $NR^{c12}C(O)R^{b12}$, $NR^{c12}C(O)NR^{c12}R^{d12}$, $NR^{c12}C(O)OR^{a12}$, $C(=NR^{e12})NR^{c12}R^{d12}$, $NR^{c12}C(=NR^{e12})NR^{c12}R^{d12}$, $S(O)R^{b12}$, $S(O)NR^{c12}R^{d12}$, $S(O)_2R^{b12}$, $NR^{c12}S(O)_2R^{b12}$, $S(O)_2NR^{c12}R^{d12}$ and oxo;

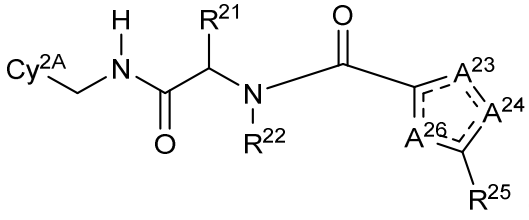
R^{a12}, R^{b12}, R^{c12} and R^{d12} are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-3} alkyl, 5-6 membered heteroaryl-C_{1-3} alkyl, C_{3-7} cycloalkyl-C_{1-3} alkyl and 4-7 membered heterocycloalkyl-C_{1-3} alkyl, wherein said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-}

$_3$ alkyl, 5-6 membered heteroaryl-C_{1-3} alkyl, C_{3-7} cycloalkyl-C_{1-3} alkyl and 4-7 membered heterocycloalkyl-C_{1-3} alkyl forming R^{a12}, R^{b12}, R^{c12} and R^{d12} are each optionally substituted with 1, 2 or 3 substituents independently selected from OH, CN, amino, NH(C_{1-6} alkyl), N(C_{1-6} alkyl)$_2$, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy and oxo;

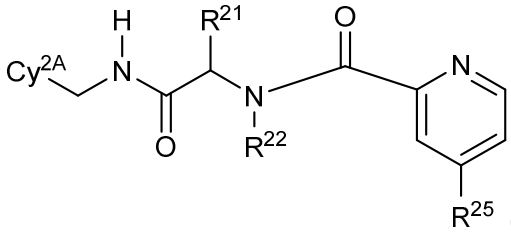
or R^{c12} and R^{d12} attached to the same N atom, together with the N atom to which they are both attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group or 5-membered heteroaryl group, each of which is unsubstituted or substituted with 1, 2 or 3 substituents independently selected from OH, CN, amino, NH(C_{1-6} alkyl), N(C_{1-6} alkyl)$_2$, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy and oxo; and

R^{e11} and Re^{12} are each, independently, H, CN or NO_2.

The present disclosure provides, *inter alia*, compounds of Formulae (**IIA**) and (**IIB**):



(**IIA**)



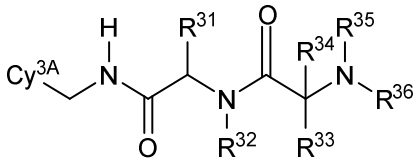
(**IIB**)

or a salt thereof; wherein the variables are as defined below. Various examples of the compounds of Formula (**IIA**) or (**IIB**), are also described.

The present disclosure also provides a pharmaceutical composition comprising a compound of Formula (**IIA**) or (**IIB**), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier or excipient.

The compounds of Formula (**IIA**) or (**IIB**) 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. The present disclosure also provides methods of treating a MASP-2-associated disease and disorder comprising administering to a patient a therapeutically effective amount of a compound of Formula (**IIA**) or (**IIB**), or a salt thereof.

The present disclosure provides, *inter alia*, compounds of Formula (**III**):



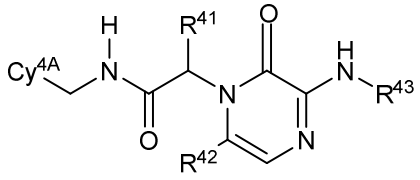
(**III**)

or a salt thereof; wherein the variables are as defined below. Various examples of the compounds of Formula (**III**), are also described.

The present disclosure also provides a pharmaceutical composition comprising a compound of Formula (**III**), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier or excipient.

The compounds of Formula (**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. The present disclosure also provides methods of treating a MASP-2-associated disease and disorder comprising administering to a patient a therapeutically effective amount of a compound of Formula (**III**), or a salt thereof.

The present disclosure provides, *inter alia*, compounds of Formulae (**IV**):



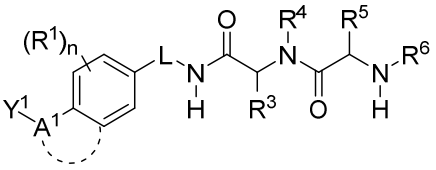
(**IV**)

or a salt thereof; wherein the variables are as defined below. Various examples of the compounds of Formula (**IV**), are also described.

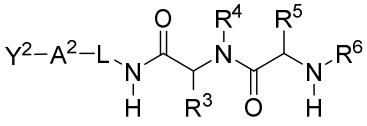
The present disclosure also provides a pharmaceutical composition comprising a compound of Formula (**IV**), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier or excipient.

The compounds of Formula (**IV**) are useful as MASP-2 inhibitors. The compounds of Formula (**IV**) are useful in therapy. The compounds of Formula (**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. The present disclosure also provides methods of treating a MASP-2-associated disease and disorder comprising administering to a patient a therapeutically effective amount of a compound of Formula (**IV**), or a salt thereof.

The present disclosure provides, *inter alia*, compounds of Formulae (**VA**) or (**VB**):



(**VA**),



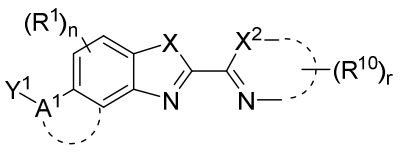
(**VB**)

or a salt thereof; wherein the variables are as defined below. Various examples of the compounds of Formula (**VA**) or (**VB**) are also described.

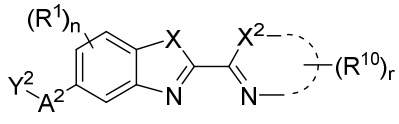
The present disclosure also provides a pharmaceutical composition comprising a compound of Formula (**VA**) or (**VB**), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier or excipient.

The compounds of Formula (**VA**) and (**VB**) are useful as MASP-2 inhibitors. The compounds of Formula (**VA**) and (**VB**) are useful in therapy. The compounds of Formula (**VA**) and (**VB**) 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. The present disclosure also provides methods of treating a MASP-2-associated disease and disorder comprising administering to a patient a therapeutically effective amount of a compound of Formula (**VA**) or (**VB**), or a salt thereof.

The present disclosure provides, *inter alia*, compounds of Formulae (**VIA**) or (**VIB**):



(**VIA**)



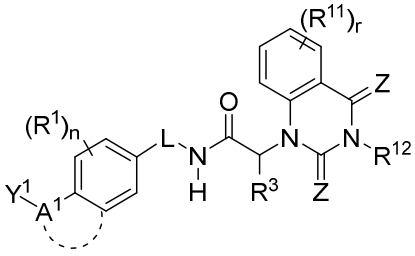
(**VIB**)

or a salt thereof; wherein the variables are as defined below. Various examples of the compounds of Formula (**VIA**) or (**VIB**) are also described.

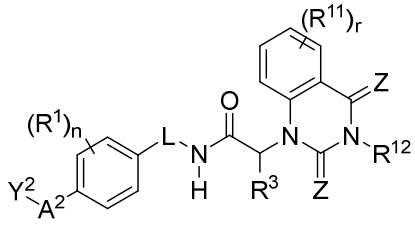
The present disclosure also provides a pharmaceutical composition comprising a compound of Formula (**VIA**) or (**VIB**), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier or excipient.

The compounds of Formula (**VIA**) and (**VIB**) are useful as MASP-2 inhibitors. The compounds of Formula (**VIA**) and (**VIB**) are useful in therapy. The compounds of Formula (**VIA**) and (**VIB**) 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. The present disclosure also provides methods of treating a MASP-2-associated disease and disorder comprising administering to a patient a therapeutically effective amount of a compound of Formula (**VIA**) or (**VIB**), or a salt thereof.

The present disclosure provides, *inter alia*, compounds of Formulae (**VIIA**) or (**VIIB**):



(**VIIA**),



(**VIIB**),

or a salt thereof; wherein the variables are as defined below. Various examples of the compounds of Formula (**VIIA**) or (**VIIB**) are also described.

The present disclosure also provides a pharmaceutical composition comprising a compound of Formula (**VIIA**) or (**VIIB**), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier or excipient.

The compounds of Formula (**VIIA**) and (**VIIB**) are useful as MASP-2 inhibitors. The compounds of Formula (**VIIA**) and (**VIIB**) are useful in therapy. The compounds of Formula (**VIIA**) and (**VIIB**) 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. The present disclosure also provides methods of treating a MASP-2-associated disease and disorder comprising administering to a patient a therapeutically effective amount of a compound of Formula (**VIIA**) or (**VIIB**), or a salt thereof.

The present disclosure provides, *inter alia*, small molecule compounds having MASP-2 inhibitory activity, especially for therapeutic use. The small molecule compound with MASP-2 inhibitory activity interacts with the MASP-2 serine protease domain in an enzyme-inhibitor complex with a plurality of intermolecular interactions. In certain examples, the small molecule is described with complete specificity and description by the number and type(s) of intermolecular interactions within a MASP-2 binding site, using an empirically derived rule set. The inhibitors follow one or more of the interaction rules.

In certain examples, the present disclosure provides a small molecule compound with MASP-2 inhibitory activity, for therapeutic use, wherein the compound has one or more such as 1, 2, 3, 4, or 5 of the following interactions (a) to (e):

a) the compound binds via H-bonds with one or more of PRO 606, ASP 627, SER 628, ARG 630, SER 633, SER 654, GLY 656, SER 657, CYS 660 and GLN 665 in MASP-2;

b) the compound binds via ionic or electrostatic interactions or hydrogen bonding to one or more of ASP 627 and ARG 630 in MASP-2;

c) the compound interacts via a water molecule in MASP-2 to one or more of TYR 602, TYR 607, ASP 627, SER 628, SER 657, ASN 659, GLU 662, TRP 655, GLY656, CYS660, GLN 665, TYR 666, VAL 668, and ARG 630 in MASP-2;

d) the compound interacts via π-π interactions with one or more of PHE 529, TYR 607, and TRP 655 in MASP-2; and

e) the compound interacts via van der Waals contacts to one or more of ALA 468, ALA 469, HIS 483, ASP 526, ALA 527, GLY 528, PHE 529, LEU 575, PRO 606, TYR 607, PRO 608, SER 611, ASP 627, SER 628, CYS 629, ARG 630, GLY 631, ASP 632, SER 633, GLY 634, GLY 635, VAL 653, SER 654, TRP 655, GLY656, SER 657, MET 658, ASN 659, CYS 660, GLN 665, GLY 667, and TYR 669 in MASP-2,

In some examples, the compound is not an endogenous MASP-2 ligand.

In one aspect, the present disclosure refers to use of a small molecule compound with MASP-2 inhibitory activity, in the manufacture of a medicament for the treatment of a MASP-2-associated disease or disorder, wherein the compound has one or more of the following interactions (a) to (e):

a) the compound binds via H-bonds with one or more of PRO 606, ASP 627, SER 628, ARG 630, SER 633, SER 654, GLY 656, SER 657, CYS 660 and GLN 665 in MASP-2;

b) the compound binds via ionic or electrostatic interactions or hydrogen bonding to one or more of ASP 627 and ARG 630 in MASP-2;

c) the compound interacts via a water molecule in MASP-2 to one or more of TYR 602, TYR 607, ASP 627, SER 628, SER 657, ASN 659, GLU 662, TRP 655, GLY656, CYS660, GLN 665, TYR 666, VAL 668, and ARG 630 in MASP-2;

d) the compound interacts via π-π interactions with one or more of PHE 529, TYR 607, and TRP 655 in MASP-2; and

e) the compound interacts via van der Waals contacts to one or more of ALA 468, ALA 469, HIS 483, ASP 526, ALA 527, GLY 528, PHE 529, LEU 575, PRO 606, TYR 607, PRO 608, SER 611, ASP 627, SER 628, CYS 629, ARG 630, GLY 631, ASP 632, SER 633, GLY 634, GLY 635, VAL 653, SER 654, TRP 655, GLY656, SER 657, MET 658, ASN 659, CYS 660, GLN 665, GLY 667, and TYR 669 in MASP-2,

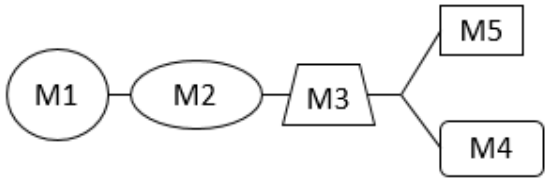
wherein the compound is not an endogenous MASP-2 ligand.

In some examples, the compound is a synthetic small molecule MASP-2 inhibitor.

In some examples, the compound selectively inhibits MASP-2 as compared to thrombin.

Various examples of the compounds defined by interaction rules are described. The disclosure provides a composition comprising such a compound, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier or excipient. The compounds are useful as MASP-2 inhibitors. The compounds are useful in therapy. The compounds 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. The present disclosure also provides methods of treating a MASP-2-associated disease and disorder comprising administering to a patient a therapeutically effective amount of a compound of defined by interaction rules set forth herein.

The present disclosure provides, *inter alia*, compounds of Formula (**VIII**):



(**VIII**).

or a salt thereof; wherein the elements of the Formula may have values as described below. Various examples of the compounds of Formula (**VIII**) are also described. The present disclosure also provides a pharmaceutical composition comprising a compound of Formula (**VIII**), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier or excipient. The compounds of Formula (**VIII**) are useful as MASP-2 inhibitors. The compounds of Formula (**VIII**) are useful in therapy. The compounds of Formula (**VIII**) 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. The present disclosure also provides methods of treating a MASP-2-associated disease and disorder comprising administering to a patient a therapeutically effective amount of a compound of Formula (**VIII**), or a salt thereof.

The present disclosure provides, *inter alia*, a pharmacophore model for describing small molecule compounds including synthetic compounds that inhibit MASP-2 and compounds defined with specificity by reference to such a pharmacophore model.

In some examples, the compounds that are active as inhibitors of MASP-2 may include one or combinations of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20,

21, or 22 of the pharmacophore elements, preferably combinations of 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 of the pharmacophore elements listed in Table 1. In some examples, the compounds may have pharmacophore elements corresponding to those listed in Table 1, wherein the (x, y, z) coordinates of the pharmacophore elements are within four standard deviations, preferably within three standard deviations, more preferably within two standard deviations and most preferably within one standard deviation as listed in Table 1.

In some examples, a compound is provided that comprises a combination of pharmacophore elements comprising:

(a) an S1 pharmacophore group comprising CA1 and N1 pharmacophore elements or CA1 and C5 pharmacophore elements; and/or

(b) an S2 pharmacophore group comprising H4 and O2 pharmacophore elements; and/or

(c) an S3 pharmacophore group comprising a C2 pharmacophore element and an N2 or H3 pharmacophore element;

wherein:

C2 and C5 are hydrophobic groups;

CA1 is an aromatic ring;

H3 and H4 are hydrogen bond donors;

N1 and N2 are positive ionizable groups; and

O2 is a hydrogen bond acceptor;

wherein C2, C5, CA1, H3, H4, N1, N2, and O2 have coordinates in the ranges given in Table 3, 4 or 5 below.

In one aspect, the present disclosure refers to use of a small molecule compound in the manufacture of a medicament for the treatment of MASP-2-associated diseases or disorders, wherein the compound comprises a combination of pharmacophore elements comprising:

(a) an S1 pharmacophore group comprising CA1 and N1 pharmacophore elements or CA1 and C5 pharmacophore elements;

(b) an S2 pharmacophore group comprising H4 and O2 pharmacophore elements; and

(c) an S3 pharmacophore group comprising a C2 pharmacophore element and an N2 or H3 pharmacophore element;

wherein:

C2 and C5 are hydrophobic groups;

CA1 is an aromatic ring;

H3 and H4 are hydrogen bond donors;

N1 and N2 are positive ionizable groups; and

O2 is a hydrogen bond acceptor;

wherein C2, C5, CA1, H3, H4, N1, N2, and O2 have coordinates in the ranges given in Table 3.

In some examples, a compound is provided that comprises a combination of pharmacophore elements comprising:

(a) an S1 pharmacophore group comprising CA1 and N1 pharmacophore elements or CA1 and C5 pharmacophore elements;

(b) an S2 pharmacophore group comprising H4 and O2 pharmacophore elements; and

(c) an S3 pharmacophore group comprising a C2 pharmacophore element and an N2 or H3 pharmacophore element.

Various examples of the small molecule compounds defined by the pharmacophore model are described. The disclosure provides a composition comprising such a compound, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier or excipient. The compounds are useful as MASP-2 inhibitors. The compounds are useful in therapy. The compounds 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. The present disclosure also provides methods of treating a MASP-2-associated disease and disorder comprising administering to a patient a therapeutically effective amount of a compound of defined by the pharmacophore model.

The present disclosure also provides small molecule compounds with MASP-2 inhibitory activity, wherein the compound interacts with a binding site of MASP-2, wherein the compounds are defined by reference to "binding rules" or "rule sets" derived using virtual docking models of crystallographically-derived MASP-2 enzyme co-crystal structures and binding sites within the MASP-2 enzyme. In certain examples, the amino acids and their respective atoms of the MASP-2 binding site that are accessible to small molecule MASP-2 inhibitors are described. By using a variety of compounds and their intermolecular interactions, it is possible to design a set of "binding rules" or "rule set" by which MASP-2 inhibitors are specifically described.

In certain examples, an small molecule MASP-2 inhibitor is described by a rule set. The compound with MASP-2 inhibitory activity interacts with a binding site of MASP-2 such as an enzyme-inhibitor complex, with a plurality of intermolecular interactions. In certain examples, the molecule is described with complete specificity and a complete description by the number and type(s) of *in silico* intermolecular interactions between atoms of the MASP-2 amino acid residues of the binding site and atoms of the inhibitor molecule. These rules are empirically derived using virtual docking models of crystallographically-derived MASP-2 enzyme co-crystal structures and binding sites within the MASP-2 enzyme. In certain instances, a plurality of MASP-2 enzyme-inhibitor models can be used such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 or even more protein models to generate a set of rules.

In some examples, the present disclosure provides a compound with MASP-2 inhibitory activity, wherein the compound interacts with a binding site, the interactions being one or more of (a) to (e):

a) the compound interacts via H-bonds with one or more amino acid residues in the binding site of MASP-2 (SEQ ID NO: 1);

b) the compound interacts via ionic or electrostatic interactions or hydrogen bonding in the binding site of SEQ ID NO: 1;

c) the compound interacts via a water molecule in a binding site of SEQ ID NO: 1;

d) the compound interacts via π-π interactions with one or more amino acid residues in the binding site of SEQ ID NO: 1; and/or

e) the compound interacts via van der Waals contacts to one or more amino acid residues in the binding site of SEQ ID NO: 1, wherein the compound is not an endogenous ligand or substrate.

In one aspect, the present disclosure refers to use of a small molecule compound with MASP-2 inhibitory activity in the manufacture of a medicament for the treatment of a MASP-2-associated disease or disorder, wherein the compound interacts with a binding site, the interactions being one or more of (a) to (e):

a) the compound interacts via H-bonds with one or more amino acid residues in the binding site of MASP-2 (SEQ ID NO: 1);

b) the compound interacts via ionic or electrostatic interactions or hydrogen bonding in the binding site of SEQ ID NO: 1;

c) the compound interacts via a water molecule in a binding site of SEQ ID NO: 1;

d) the compound interacts via π-π interactions with one or more amino acid residues in the binding site of SEQ ID NO: 1; and/or

e) the compound interacts via van der Waals contacts to one or more amino acid residues in the binding site of SEQ ID NO: 1, wherein the compound is not an endogenous MASP-2 ligand.

In certain examples, the compound has 1, 2, 3, 4, or 5 of the interactions (a)-(e).

In another example, the present disclosure provides a method for identifying a small molecule capable of inhibiting MASP-2, comprising:

a) screening small molecule libraries using *in silico* docking for candidate small molecules that are selectively identified for their ability to target and bind to MASP-2 at a binding site of a MASP-2 model; and

b) testing/evaluating the candidate agents identified in step (a) through one or more *in vitro* assays for their ability to target and bind to a MASP-2 binding site, to thereby identify the small molecule capable of inhibiting MASP-2.

In certain examples, the candidate small molecules comprise unique chemical scaffolds as identified in step (b) and are optimized for their ability to inhibit MASP-2.

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

BRIEF DESCRIPTION OF THE FIGURES

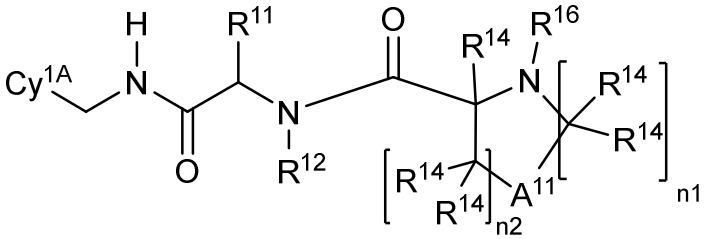
FIG. 1 is a plot illustrating a schematic of one embodiment of the atoms of an inhibitory compound (1129) with those of MASP-2 amino acids as computed by LigPlot+ software settings for hydrogen-bond calculation parameters (3.35 Å for maximum distance between hydrogen bond donor and acceptor; and non-bonded contact parameters between hydrophobic to any contacts, such as van der Waals interactions with maximum contact distance of 3.90 Å) employing models derived from the corresponding crystallographic MASP-2-compound co-structures.

FIG. 2 is a plot illustrating a schematic of one embodiment of the atoms of an inhibitory compound (1034) with those of MASP-2 amino acids as computed by LigPlot+ software settings for hydrogen-bond calculation parameters (3.35 Å for maximum distance between hydrogen bond donor and acceptor; and non-bonded contact parameters between hydrophobic to any contacts, such as van der Waals interactions with maximum contact distance of 3.90 Å) employing models derived from the corresponding crystallographic MASP-2-compound co-structures.

FIG. 3 is a plot illustrating a schematic of one embodiment of the atoms of an inhibitory compound (1024) with those of MASP-2 amino acids as computed by LigPlot+

What is claimed is:

1. A compound of Formula (**I-1**):



(**I-1**)

or a salt thereof, wherein:

Cy^{1A} is unsubstituted or substituted C_{6-10} aryl or unsubstituted or substituted 5-10 membered heteroaryl; wherein the ring atoms of the 5-10 membered heteroaryl forming Cy^{1A} consist of carbon atoms and 1, 2, or 3 heteroatoms selected from O, N and S; wherein the substituted C_{6-10} aryl or substituted 5-10 membered heteroaryl forming Cy^{1A} are substituted with 1, 2, 3, 4 or 5 substituents each independently selected from R^{Cy1A}, halogen, C_{1-6} haloalkyl, CN, OR^{a11}, S^{Ra11}, $C(O)R^{b11}$, $C(O)NR^{c11}R^{d11}$, $C(O)OR^{a11}$, $OC(O)R^{b11}$, $OC(O)NR^{c11}R^{d11}$, $NR^{c11}R^{d11}$, $NR^{c11}C(O)R^{b11}$, $NR^{c11}C(O)NR^{c11}R^{d11}$, $NR^{c11}C(O)OR^{a11}$, $C(=NR^{e11})NR^{c11}R^{d11}$, $C(=NOR^{a11})NR^{c11}R^{d11}$, $C(=NOC(O)R^{b11})NR^{c11}R^{d11}$, $C(=NR^{e11})NR^{c11}C(O)OR^{a11}$, $NR^{c11}C(=NR^{e11})NR^{c11}R^{d11}$, $S(O)R^{b11}$, $S(O)NR^{c11}R^{d11}$, $S(O)_2R^{b11}$, $NR^{c11}S(O)_2R^{b11}$, $S(O)_2NR^{c11}R^{d11}$ and oxo;

each R^{Cy1A} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, wherein the ring atoms of the 5-10 membered heteroaryl or 4-10-membered heterocycloalkyl forming R^{Cy1A} consist of carbon atoms and 1, 2, 3 or 4 heteroatoms selected from O, N and S, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl forming R^{Cy1A} is independently unsubstituted or substituted with 1, 2 or 3 substituents independently selected from halogen, CN, OR^{a11}, SR^{a11}, $C(O)R^{b11}$, $C(O)NR^{c11}R^{d11}$, $C(O)OR^{a11}$, $OC(O)R^{b11}$, $OC(O)NR^{c11}R^{d11}$, $NR^{c11}R^{d11}$, $NR^{c11}C(O)R^{b11}$, $NR^{c11}C(O)NR^{c11}R^{d11}$, $NR^{c11}C(O)OR^{a11}$, $C(=NR^{e11})NR^{c11}R^{d11}$, $NR^{c11}C(=NR^{e11})NR^{c11}R^{d11}$, $S(O)R^{b11}$, $S(O)NR^{c11}R^{d11}$, $S(O)_2R^{b11}$, $NR^{c11}S(O)_2R^{b11}$, $S(O)_2NR^{c11}R^{d11}$ and oxo, and wherein each C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl forming R^{Cy1A} is independently unsubstituted or substituted with 1, 2 or 3 substituents independently selected from halogen, C_{1-6} alkyl, C_{2-6}

alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, OR^{a11}, SR^{a11}, $C(O)R^{b11}$, $C(O)NR^{c11}R^{d11}$, $C(O)OR^{a11}$, $OC(O)R^{b11}$, $OC(O)NR^{c11}R^{d11}$, $NR^{c11}R^{d11}$, $NR^{c11}C(O)R^{b11}$, $NR^{c11}C(O)NR^{c11}R^{d11}$, $NR^{c11}C(O)OR^{a11}$, $C(=NR^{e11})NR^{c11}R^{d11}$, $NR^{c11}C(=NR^{e11})NR^{c11}R^{d11}$, $S(O)R^{b11}$, $S(O)NR^{c11}R^{d11}$, $S(O)_2R^{b11}$, $NR^{c11}S(O)_2R^{b11}$, $S(O)_2NR^{c11}R^{d11}$ and oxo;

R^{11} is H or C_{1-6} alkyl, C_{6-10} aryl-C_{1-6} alkyl or 5-10 membered heteroaryl-C_{1-6} alkyl, wherein the C_{1-6} alkyl forming R^{11} is unsubstituted or substituted by 1, 2 or 3 substituents independently selected from halogen, CN, OR^{a11}, SR^{a11}, $C(O)R^{b11}$, $C(O)NR^{c11}R^{d11}$, $C(O)OR^{a11}$, $OC(O)R^{b11}$, $OC(O)NR^{c11}R^{d11}$, $NR^{c11}R^{d11}$, $NR^{c11}C(O)R^{b11}$, $NR^{c11}C(O)NR^{c11}R^{d11}$, $NR^{c11}C(O)OR^{a11}$, $C(=NR^{e11})NR^{c11}R^{d11}$, $NR^{c11}C(=NR^{e11})NR^{c11}R^{d11}$, $S(O)R^{b11}$, $S(O)NR^{c11}R^{d11}$, $S(O)_2R^{b11}$, $NR^{c11}S(O)_2R^{b11}$, $S(O)_2NR^{c11}R^{d11}$ and oxo, and wherein the C_{6-10} aryl-C_{1-6} alkyl or 5-10 membered heteroaryl-C_{1-6} alkyl forming R^{11} is unsubstituted or substituted by 1, 2 or 3 substituents independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, OR^{a11}, SR^{a11}, $C(O)R^{b11}$, $C(O)NR^{c11}R^{d11}$, $C(O)OR^{a11}$, $OC(O)R^{b11}$, $OC(O)NR^{c11}R^{d11}$, $NR^{c11}R^{d11}$, $NR^{c11}C(O)R^{b11}$, $NR^{c11}C(O)NR^{c11}R^{d11}$, $NR^{c11}C(O)OR^{a11}$, $C(=NR^{e11})NR^{c11}R^{d11}$, $NR^{c11}C(=NR^{e11})NR^{c11}R^{d11}$, $S(O)R^{b11}$, $S(O)NR^{c11}R^{d11}$, $S(O)_2R^{b11}$, $NR^{c11}S(O)_2R^{b11}$, $S(O)_2NR^{c11}R^{d11}$ and oxo;

R^{12} is H or C_{1-6} alkyl; or

R^{11} and R^{12}, together with the groups to which they are attached, form a 4-6 membered heterocycloalkyl ring;

A^{11} is $CR^{13}R^{15}$ or N;

each R^{13} is independently Cy^{1B}, $(CR^{13A}R^{13B})_{n3}Cy^{1B}$, ($C_{1-6}$ alkylene)Cy^{1B}, (C_{2-6} alkenylene)Cy^{1B}, (C_{2-6} alkynylene)Cy^{1B} or OCy^{1B}, wherein the C_{1-6} alkylene, C_{2-6} alkenylene, or C_{2-6} alkynylene component of R^{13} is unsubstituted or substituted by 1, 2, 3, 4 or 5 substituents each independently selected from the group consisting of halogen, CN, OR^{a11}, SR^{a11}, $C(O)R^{b11}$, $C(O)NR^{c11}R^{d11}$, $C(O)OR^{a11}$, $OC(O)R^{b11}$, $OC(O)NR^{c11}R^{d11}$, $NR^{c11}R^{d11}$, $NR^{c11}C(O)R^{b11}$, $NR^{c11}C(O)NR^{c11}R^{d11}$, $NR^{c11}C(O)OR^{a11}$, $C(=NR^{e11})NR^{c11}R^{d11}$, $NR^{c11}C(=NR^{e11})NR^{c11}R^{d11}$, $S(O)R^{b11}$, $S(O)NR^{c11}R^{d11}$, $S(O)_2R^{b11}$, $NR^{c11}S(O)_2R^{b11}$, $S(O)_2NR^{c11}R^{d11}$ and oxo;

each R^{14} is independently selected from H and C_{1-6} alkyl;

R^{15} is selected from H, R^{13}, C_{1-6} alkyl and OH;

a pair of R^{14} groups attached to adjacent carbon atoms, or a pairing of R^{14} and R^{15} groups attached to adjacent carbon atoms, may, independently of other occurrences of R^{14},

together be replaced a bond connecting the adjacent carbon atoms to which the pair of R^{14} groups or pairing of R^{14} and R^{15} groups is attached, such that the adjacent carbon atoms are connected by a double bond; or

a pair of R^{14} groups attached to the same carbon atom, or a pairing of R^{13} and R^{15} groups attached to the same carbon atom, may, independently of other occurrences of R^{14}, and together with the carbon atom to which the pair of R^{14} groups or pairing of R^{13} and R^{15} groups is attached together form a spiro-fused C_{3-10} cycloalkyl or 4-10 membered heterocycloalkyl ring, wherein the ring atoms of the 4-10 membered heterocycloalkyl ring formed consist of carbon atoms and 1, 2, or 3 heteroatoms selected from O, N and S, wherein the spiro-fused C_{3-10} cycloalkyl or 4-10 membered heterocycloalkyl ring formed is optionally further substituted with 1, 2 or 3 substituents independently selected from halogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, haloalkyl, CN, OR^{a11}, SR^{a11}, $C(O)R^{b11}$, $C(O)NR^{c11}R^{d11}$, $C(O)OR^{a11}$, $OC(O)R^{b11}$, $OC(O)NR^{c11}R^{d11}$, $NR^{c11}R^{d11}$, $NR^{c11}C(O)R^{b11}$, $NR^{c11}C(O)NR^{c11}R^{d11}$, $NR^{c11}C(O)OR^{a11}$, $C(=NR^{e11})NR^{c11}R^{d11}$, $NR^{c11}C(=NR^{e11})NR^{c11}R^{d11}$, $S(O)R^{b11}$, $S(O)NR^{c11}R^{d11}$, $S(O)_2R^{b11}$, $NR^{c11}S(O)_2R^{b11}$, $S(O)_2NR^{c11}R^{d11}$ and oxo; or

pairs of R^{14} groups attached to adjacent carbon atoms, or a pairing of R^{14} and R^{15} groups attached to adjacent carbon atoms, may, independently of other occurrences of R^{14}, together with the adjacent carbon atoms to which the pair of R^{14} groups or pairing of R^{14} and R^{15} groups is attached, form a fused C_{3-10} cycloalkyl or 4-10 membered heterocycloalkyl ring, wherein the ring atoms of the 4-10 membered heterocycloalkyl ring formed consist of carbon atoms and 1, 2, or 3 heteroatoms selected from O, N and S, wherein the fused C_{3-10} cycloalkyl or 4-10 membered heterocycloalkyl ring formed is optionally further substituted with 1, 2 or 3 substituents independently selected from halogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, haloalkyl, CN, OR^{a11}, SR^{a11}, $C(O)R^{b11}$, $C(O)NR^{c11}R^{d11}$, $C(O)OR^{a11}$, $OC(O)R^{b11}$, $OC(O)NR^{c11}R^{d11}$, $NR^{c11}R^{d11}$, $NR^{c11}C(O)R^{b11}$, $NR^{c11}C(O)NR^{c11}R^{d11}$, $NR^{c11}C(O)OR^{a11}$, $C(=NR^{e11})NR^{c11}R^{d11}$, $NR^{c11}C(=NR^{e11})NR^{c11}R^{d11}$, $S(O)R^{b11}$, $S(O)NR^{c11}R^{d11}$, $S(O)_2R^{b11}$, $NR^{c11}S(O)_2R^{b11}$, $S(O)_2NR^{c11}R^{d11}$ and oxo; or

a grouping of four R^{14} groups attached to two adjacent carbon atoms, or a grouping of two R^{14} , one R^{13} and one R^{15} groups attached to two adjacent carbon atoms, may, independently of other occurrences of R^{14}, together with the two adjacent carbon atoms to which the grouping of four R^{14} groups or grouping of two R^{14} , one R^{13} and one R^{15} groups are attached, form a fused C_{6-10} aryl or 5-10 membered heteroaryl, C_{3-10} cycloalkyl or 4-10

membered heterocycloalkyl ring, wherein the ring atoms of the 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl ring formed consist of carbon atoms and 1, 2, or 3 heteroatoms selected from O, N and S, and wherein the fused C_{6-10} aryl or 5-10 membered heteroaryl, C_{3-10} cycloalkyl or 4-10 membered heterocycloalkyl ring formed is optionally further substituted with 1, 2 or 3 substituents independently selected from halogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, haloalkyl, CN, OR^{a11}, SR^{a11}, $C(O)R^{b11}$, $C(O)NR^{c11}R^{d11}$, $C(O)OR^{a11}$, $OC(O)R^{b11}$, $OC(O)NR^{c11}R^{d11}$, $NR^{c11}R^{d11}$, $NR^{c11}C(O)R^{b11}$, $NR^{c11}C(O)NR^{c11}R^{d11}$, $NR^{c11}C(O)OR^{a11}$, $C(=NR^{e11})NR^{c11}R^{d11}$, $NR^{c11}C(=NR^{e11})NR^{c11}R^{d11}$, $S(O)R^{b11}$, $S(O)NR^{c11}R^{d11}$, $S(O)_2R^{b11}$, $NR^{c11}S(O)_2R^{b11}$, $S(O)_2NR^{c11}R^{d11}$ and oxo;

n1 is 1 or 2;

n2 is 0, 1 or 2;

provided that the sum of n1 and n2 is 1, 2 or 3;

provided that if n1 is 1 or n2 is 0, then A^{11} is $CR^{13}R^{15}$;

n3 is 0, 1 or 2;

each R^{13A} is independently H or C_{1-6} alkyl;

each R^{13B} is independently H or C_{1-6} alkyl; or

or R^{13A} and R^{13B} attached to the same carbon atom, independently of any other R^{13A} and R^{13B} groups, together may form $–(CH_2)_{2-5}$-, thereby forming a 3-6 membered cycloalkyl ring;

Cy^{1B} is unsubstituted or substituted C_{6-10} aryl, unsubstituted or substituted 5-10 membered heteroaryl, unsubstituted or substituted C_{3-10} cycloalkyl, or unsubstituted or substituted 4-10 membered heterocycloalkyl; wherein the ring atoms of the 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl forming Cy^{1B} consist of carbon atoms and 1, 2 or 3 heteroatoms selected from O, N and S; and

wherein the substituted C_{6-10} aryl, substituted 5-10 membered heteroaryl, substituted C_{3-10} cycloalkyl or substituted 4-10 membered heterocycloalkyl forming Cy^{1B} are substituted with 1, 2, 3, 4 or 5 substituents each independently selected from R^{Cy1B}, halogen, C_{1-6} haloalkyl, CN, OR^{a11}, S^{Ra11}, $C(O)R^{b11}$, $C(O)NR^{c11}R^{d11}$, $C(O)OR^{a11}$, $OC(O)R^{b11}$, $OC(O)NR^{c11}R^{d11}$, $NR^{c11}R^{d11}$, $NR^{c11}C(O)R^{b11}$, $NR^{c11}C(O)NR^{c11}R^{d11}$, $NR^{c11}C(O)OR^{a11}$, $C(=NR^{e11})NR^{c11}R^{d11}$, $C(=NOR^{a11})NR^{c11}R^{d11}$, $C(=NOC(O)R^{b11})NR^{c11}R^{d11}$, $C(=NR^{e11})NR^{c11}C(O)OR^{a11}$, $NR^{c11}C(=NR^{e11})NR^{c11}R^{d11}$, $S(O)R^{b11}$, $S(O)NR^{c11}R^{d11}$, $S(O)_2R^{b11}$, $NR^{c11}S(O)_2R^{b11}$, $S(O)_2NR^{c11}R^{d11}$ and oxo;

wherein each R^{Cy1B} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, wherein the ring atoms of the 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl forming R^{Cy1B} consist of carbon atoms and 1, 2 or 3 heteroatoms selected from O, N and S; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl forming R^{Cy1B} is independently unsubstituted or substituted with 1, 2 or 3 substituents independently selected from halogen, CN, OR^{a11}, SR^{a11}, $C(O)R^{b11}$, $C(O)NR^{c11}R^{d11}$, $C(O)OR^{a11}$, $OC(O)R^{b11}$, $OC(O)NR^{c11}R^{d11}$, $NR^{c11}R^{d11}$, $NR^{c11}C(O)^{Rb11}$, $NR^{c11}C(O)NR^{c11}R^{d11}$, $NR^{c11}C(O)OR^{a11}$, $C(=NR^{e11})NR^{c11}R^{d11}$, $NR^{c11}C(=NR^{e11})NR^{c11}R^{d11}$, $S(O)R^{b11}$, $S(O)NR^{c11}R^{d11}$, $S(O)_2R^{b11}$, $NR^{c11}S(O)_2R^{b11}$, $S(O)_2NR^{c11}R^{d11}$ and oxo; and wherein each C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl forming R^{Cy1B} is independently unsubstituted or substituted with 1, 2 or 3 substituents independently selected from halogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, OR^{a11}, SR^{a11}, $C(O)R^{b11}$, $C(O)NR^{c11}R^{d11}$, $C(O)OR^{a11}$, $OC(O)R^{b11}$, $OC(O)NR^{c11}R^{d11}$, $NR^{c11}R^{d11}$, $NR^{c11}C(O)^{Rb11}$, $NR^{c11}C(O)NR^{c11}R^{d11}$, $NR^{c11}C(O)OR^{a11}$, $C(=NR^{e11})NR^{c11}R^{d11}$, $NR^{c11}C(=NR^{e11})NR^{c11}R^{d11}$, $S(O)R^{b11}$, $S(O)NR^{c11}R^{d11}$, $S(O)_2R^{b11}$, $NR^{c11}S(O)_2R^{b11}$, $S(O)_2NR^{c11}R^{d11}$ and oxo;

R^{16} is H, Cy^{1C}, C_{1}-$_6$ alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein the C_{1}-$_6$ alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl forming R^{16} is unsubstituted or substituted by 1, 2, 3, 4 or 5 substituents selected from the group consisting of Cy^{1C}, halogen, CN, OR^{a11}, SR^{a11}, $C(O)R^{b11}$, $C(O)NR^{c11}R^{d11}$, $C(O)OR^{a11}$, $OC(O)R^{b11}$, $OC(O)NR^{c11}R^{d11}$, $NR^{c11}R^{d11}$, $NR^{c11}C(O)R^{b11}$, $NR^{c11}C(O)NR^{c11}R^{d11}$, $NR^{c11}C(O)OR^{a11}$, $C(=NR^{e11})NR^{c11}R^{d11}$, $NR^{c11}C(=NR^{e11})NR^{c11}R^{d11}$, $S(O)R^{b11}$, $S(O)NR^{c11}R^{d11}$, $S(O)_2R^{b11}$, $NR^{c11}S(O)_2R^{b11}$, $S(O)_2NR^{c11}R^{d11}$ and oxo, provided that no more than one of the substituents of R^{16} is Cy^{1C};

Cy^{1C} is unsubstituted or substituted C_{6-10} aryl, unsubstituted or substituted 5-10 membered heteroaryl, unsubstituted or substituted C_{3-10} cycloalkyl, or unsubstituted or substituted 4-10 membered heterocycloalkyl; wherein the ring atoms of the 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl forming Cy^{1C} consist of carbon atoms and 1, 2 or 3 heteroatoms selected from O, N and S; and

wherein the substituted C_{6-10} aryl, substituted 5-10 membered heteroaryl, substituted C_{3-10} cycloalkyl or substituted 4-10 membered heterocycloalkyl forming Cy^{1C} are substituted with 1, 2, 3, 4 or 5 substituents each independently selected from R^{Cy1C}, halogen, C_{1-6}

haloalkyl, CN, OR^{a11}, S^{Ra11}, $C(O)R^{b11}$, $C(O)NR^{c11}R^{d11}$, $C(O)OR^{a11}$, $OC(O)R^{b11}$, $OC(O)NR^{c11}R^{d11}$, $NR^{c11}R^{d11}$, $NR^{c11}C(O)R^{b11}$, $NR^{c11}C(O)NR^{c11}R^{d11}$, $NR^{c11}C(O)OR^{a11}$, $C(=NR^{e11})NR^{c11}R^{d11}$, $C(=NOR^{a11})NR^{c11}R^{d11}$, $C(=NOC(O)R^{b11})NR^{c11}R^{d11}$, $C(=NR^{e11})NR^{c11}C(O)OR^{a11}$, $NR^{c11}C(=NR^{e11})NR^{c11}R^{d11}$, $S(O)R^{b11}$, $S(O)NR^{c11}R^{d11}$, $S(O)_2R^{b11}$, $NR^{c11}S(O)_2R^{b11}$, $S(O)_2NR^{c11}R^{d11}$ and oxo;

wherein each R^{Cy1C} is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, wherein the ring atoms of the 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl forming R^{Cy1C} consist of carbon atoms and 1, 2 or 3 heteroatoms selected from O, N and S; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl forming R^{Cy1C} is independently unsubstituted or substituted with 1, 2 or 3 substituents independently selected from halogen, CN, OR^{a11}, SR^{a11}, $C(O)R^{b11}$, $C(O)NR^{c11}R^{d11}$, $C(O)OR^{a11}$, $OC(O)R^{b11}$, $OC(O)NR^{c11}R^{d11}$, $NR^{c11}R^{d11}$, $NR^{c11}C(O)^{Rb11}$, $NR^{c11}C(O)NR^{c11}R^{d11}$, $NR^{c11}C(O)OR^{a11}$, $C(=NR^{e11})NR^{c11}R^{d11}$, $NR^{c11}C(=NR^{e11})NR^{c11}R^{d11}$, $S(O)R^{b11}$, $S(O)NR^{c11}R^{d11}$, $S(O)_2R^{b11}$, $NR^{c11}S(O)_2R^{b11}$, $S(O)_2NR^{c11}R^{d11}$ and oxo; and wherein each C_{6-10} aryl, 5-10 membered heteroaryl, C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl forming R^{Cy1C} is independently unsubstituted or substituted with 1, 2 or 3 substituents independently selected from halogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, CN, OR^{a11}, SR^{a11}, $C(O)R^{b11}$, $C(O)NR^{c11}R^{d11}$, $C(O)OR^{a11}$, $OC(O)R^{b11}$, $OC(O)NR^{c11}R^{d11}$, $NR^{c11}R^{d11}$, $NR^{c11}C(O)^{Rb11}$, $NR^{c11}C(O)NR^{c11}R^{d11}$, $NR^{c11}C(O)OR^{a11}$, $C(=NR^{e11})NR^{c11}R^{d11}$, $NR^{c11}C(=NR^{e11})NR^{c11}R^{d11}$, $S(O)R^{b11}$, $S(O)NR^{c11}R^{d11}$, $S(O)_2R^{b11}$, $NR^{c11}S(O)_2R^{b11}$, $S(O)_2NR^{c11}R^{d11}$ and oxo;

R^{a11}, R^{b11}, R^{c11} and R^{d11} are each independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-7} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-3} alkyl, 5-10 membered heteroaryl-C_{1-3} alkyl, C_{3-7} cycloalkyl-C_{1-3} alkyl and 4-10 membered heterocycloalkyl-C_{1-3} alkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-7} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-3} alkyl, 5-10 membered heteroaryl-C_{1-3} alkyl, C_{3-7} cycloalkyl-C_{1-3} alkyl and 4-10 membered heterocycloalkyl-C_{1-3} alkyl forming R^{a11}, R^{b11}, R^{c11} and R^{d11} are each optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from C_{1-6} alkyl, halo, CN, OR^{a12}, SR^{a12}, $C(O)R^{b12}$, $C(O)NR^{c12}R^{d12}$, $C(O)OR^{a12}$, $OC(O)R^{b12}$, $OC(O)NR^{c12}R^{d12}$, $NR^{c12}R^{d12}$, $NR^{c12}C(O)R^{b12}$, $NR^{c12}C(O)NR^{c12}R^{d12}$, $NR^{c12}C(O)OR^{a12}$,

$C(=NR^{e12})NR^{c12}R^{d12}$, $NR^{c12}C(=NR^{e12})NR^{c12}R^{d12}$, $S(O)R^{b12}$, $S(O)NR^{c12}R^{d12}$, $S(O)_2R^{b12}$, $NR^{c12}S(O)_2R^{b12}$, $S(O)_2NR^{c12}R^{d12}$ and oxo;

or R^{c11} and R^{d11} attached to the same N atom, together with the N atom to which they are both attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group or 5-membered heteroaryl group, each optionally substituted with 1, 2 or 3 substituents independently selected from C_{1-6} alkyl, halo, CN, OR^{a12}, SR^{a12}, $C(O)R^{b12}$, $C(O)NR^{c12}R^{d12}$, $C(O)OR^{a12}$, $OC(O)R^{b12}$, $OC(O)NR^{c12}R^{d12}$, $NR^{c12}R^{d12}$, $NR^{c12}C(O)R^{b12}$, $NR^{c12}C(O)NR^{c12}R^{d12}$, $NR^{c12}C(O)OR^{a12}$, $C(=NR^{e12})NR^{c12}R^{d12}$, $NR^{c12}C(=NR^{e12})NR^{c12}R^{d12}$, $S(O)R^{b12}$, $S(O)NR^{c12}R^{d12}$, $S(O)_2R^{b12}$, $NR^{c12}S(O)_2R^{b12}$, $S(O)_2NR^{c12}R^{d12}$ and oxo;

R^{a12}, R^{b12}, R^{c12} and R^{d12} are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-3} alkyl, 5-6 membered heteroaryl-C_{1-3} alkyl, C_{3-7} cycloalkyl-C_{1-3} alkyl and 4-7 membered heterocycloalkyl-C_{1-3} alkyl, wherein said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, phenyl-C_{1-3} alkyl, 5-6 membered heteroaryl-C_{1-3} alkyl, C_{3-7} cycloalkyl-C_{1-3} alkyl and 4-7 membered heterocycloalkyl-C_{1-3} alkyl forming R^{a12}, R^{b12}, R^{c12} and R^{d12} are each optionally substituted with 1, 2 or 3 substituents independently selected from OH, CN, amino, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy and oxo;

or R^{c12} and R^{d12} attached to the same N atom, together with the N atom to which they are both attached, form a 4-, 5-, 6- or 7-membered heterocycloalkyl group or 5-membered heteroaryl group, each of which is unsubstituted or substituted with 1, 2 or 3 substituents independently selected from OH, CN, amino, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy and oxo; and

R^{e11} and Re^{12} are each, independently, H, CN or NO_2.

2. Use of a small molecule compound with MASP-2 inhibitory activity, in the manufacture of a medicament for the treatment of a MASP-2-associated disease or disorder, wherein the compound has one or more of the following interactions (a) to (e):

a) the compound binds via H-bonds with one or more of PRO 606, ASP 627, SER 628, ARG 630, SER 633, SER 654, GLY 656, SER 657, CYS 660 and GLN 665 in MASP-2;

b) the compound binds via ionic or electrostatic interactions or hydrogen bonding to one or more of ASP 627 and ARG 630 in MASP-2;

c) the compound interacts via a water molecule in MASP-2 to one or more of TYR 602, TYR 607, ASP 627, SER 628, SER 657, ASN 659, GLU 662, TRP 655, GLY656, CYS660, GLN 665, TYR 666, VAL 668, and ARG 630 in MASP-2;

d) the compound interacts via π-π interactions with one or more of PHE 529, TYR 607, and TRP 655 in MASP-2; and

e) the compound interacts via van der Waals contacts to one or more of ALA 468, ALA 469, HIS 483, ASP 526, ALA 527, GLY 528, PHE 529, LEU 575, PRO 606, TYR 607, PRO 608, SER 611, ASP 627, SER 628, CYS 629, ARG 630, GLY 631, ASP 632, SER 633, GLY 634, GLY 635, VAL 653, SER 654, TRP 655, GLY656, SER 657, MET 658, ASN 659, CYS 660, GLN 665, GLY 667, and TYR 669 in MASP-2,

wherein the compound is not an endogenous MASP-2 ligand.

3. The use of claim 2, wherein the compound binds via H-bonds with one or more of the following: PRO 606, ASP 627, SER 628, SER 633, SER 654, GLY 656, SER 657, CYS 660 and GLN 665 in MASP-2.

4. The use of claim 2, wherein the compound binds via ionic or electrostatic interactions or hydrogen bonding to one or both of ASP 627 and ARG 630 in MASP-2.

5. The use of claim 2, wherein the compound binds via a water molecule in MASP-2 to one or more of TYR 602, TYR 607, ASP 627, SER 628, SER 657, ASN 659, GLU 662, TRP 655, GLY656, CYS660, GLN 665, TYR 666, VAL 668, and ARG 630 in MASP-2.

6. The use of claim 2, wherein the compound interacts via π-π interactions with one or more of PHE 529, TYR 607, and TRP 655 in MASP-2.

7. The use of claim 2, wherein the compound interacts via van der Waals contacts to one or more of ALA 468, ALA 469, HIS 483, ASP 526, ALA 527, GLY 528, PHE 529, LEU 575, PRO 606, TYR 607, PRO 608, SER 611, ASP 627, SER 628, CYS 629, ARG 630, GLY 631, ASP 632, SER 633, GLY634, GLY 635, VAL 653, SER 654, TRP 655, GLY 656, SER 657, MET 658, ASN 659, CYS 660, GLN 665, GLY 667, and TYR 669 in MASP-2.

8. Use of a small molecule compound in the manufacture of a medicament for the treatment of MASP-2-associated diseases or disorders, wherein the compound comprises a combination of pharmacophore elements comprising:

(a) an S1 pharmacophore group comprising CA1 and N1 pharmacophore elements or CA1 and C5 pharmacophore elements;

(b) an S2 pharmacophore group comprising H4 and O2 pharmacophore elements; and

(c) an S3 pharmacophore group comprising a C2 pharmacophore element and an N2 or H3 pharmacophore element;

wherein:

C2 and C5 are hydrophobic groups;

CA1 is an aromatic ring;

H3 and H4 are hydrogen bond donors;

N1 and N2 are positive ionizable groups; and

O2 is a hydrogen bond acceptor;

wherein C2, C5, CA1, H3, H4, N1, N2, and O2 have coordinates in the ranges given in Table 3.

9. The use of claim 8, wherein the S1 pharmacophore group comprises CA1 and N1 pharmacophore elements, CA1 and C5 pharmacophore elements, a C7 pharmacophore element, an H2 pharmacophore element, an O4 pharmacophore element, or combinations thereof.

10. The use of claim 8, wherein the S2 pharmacophore group further comprises 1 or 2 pharmacophore elements selected from the group consisting of CA6 and O1, wherein:

CA6 is an aromatic ring;

O1 is a hydrogen bond acceptor;

wherein CA6 and O1 have coordinates in the ranges given in Table 12.

11. The use of claim 8, wherein the S3 pharmacophore group comprises C2 and N2 pharmacophore elements.

12. The use of claim 8, wherein the compound further comprises an S4 pharmacophore group; wherein

the S4 pharmacophore group comprises a C4, CA2, CA4 or CA5 pharmacophore element; wherein

C4 is a hydrophobic group; and

CA2, CA4, and CA5 are aromatic rings; and

wherein C4, CA2, CA4, and CA5 have coordinates in the ranges given in Table 15.

13. The use of claim 12, wherein the S4 pharmacophore group comprises a C6 pharmacophore element, a C7 pharmacophore element, a CA4 pharmacophore element, a CA5 pharmacophore element, or combinations thereof.

14. The use of claim 8, wherein the compound further comprises an RM pharmacophore group; wherein the RM pharmacophore group comprises a CA3 pharmacophore element, wherein CA3 is an aromatic ring that has coordinates in the ranges given in Table 21.

15. Use of a small molecule compound with MASP-2 inhibitory activity in the manufacture of a medicament for the treatment of a MASP-2-associated disease or disorder, wherein the compound interacts with a binding site, the interactions being one or more of (a) to (e):

a) the compound interacts via H-bonds with one or more amino acid residues in the binding site of MASP-2 (SEQ ID NO: 1);

b) the compound interacts via ionic or electrostatic interactions or hydrogen bonding in the binding site of SEQ ID NO: 1;

c) the compound interacts via a water molecule in a binding site of SEQ ID NO: 1;

d) the compound interacts via π-π interactions with one or more amino acid residues in the binding site of SEQ ID NO: 1; and/or

e) the compound interacts via van der Waals contacts to one or more amino acid residues in the binding site of SEQ ID NO: 1, wherein the compound is not an endogenous MASP-2 ligand.

16. The use of claim 15, wherein the compound binds via 1-10 H-bonds to one or more amino acid residues in the binding site of SEQ ID NO: 1.

17. The use of claim 15, wherein the compound binds via 1-20 water molecule(s) in the binding site of SEQ ID NO: 1.

18. The use of claim 15, wherein the compound interacts via van der Waals contacts in the binding site to one or more amino acid residues of SEQ ID NO: 1.