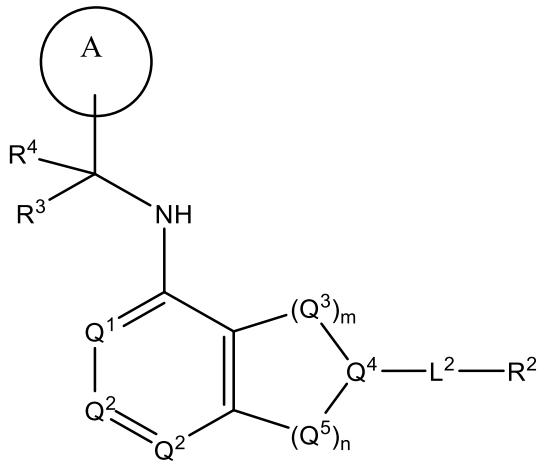
Natl. Acad. Sci. 2014, 111(9):3401-6). However, binding of these molecules seems to lead to increased nucleotide exchange and thereby activation of RAS instead of deactivation.

[0010] In an effort to stabilize the protein-protein-interaction of RAS-family proteins with SOS1 and to prevent reloading of RAS-family proteins with GTP, several different fragments were subsequently identified (Winter et al., J. Med. Chem. 2015, 58(5):2265-74). However, reversible binding of fragments to SOS1 did not translate into a measurable effect on the nucleotide exchange and only a weak effect was observed for fragments covalently bound to RAS.

[0011] Also recently, studies have been conducted to combine rational design and screening platforms to identify small molecule inhibitors of SOS1 (Evelyn et al., Chem. Biol. 2014, 21 (12):1618-28; Evelyn et al., J. Biol. Chem. 2015, 290(20):12879-98; Zheng et al., WO 2016/077793), i.e. compounds which bind to SOS1 and inhibit protein-protein interaction with RAS-family proteins. Although compounds with a slight inhibitory effect on SOS1 have been identified, the effects on guanine nucleotide exchange and cellular signal transduction modulation (e.g., ERK phosphorylation) are weak.

BRIEF SUMMARY

[0011a] In an aspect of the present disclosure, there is provided a compound having the structure of Formula (I),



(I)

or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein:

Q^1 is CH or N;

Q^4 is CH, C, or N;

each Q^2 is independently C-R^1 or N, wherein one Q^2 is N and the other Q^2 is C-R^1;

each Q^3 and Q^5 are independently $C(R^{QC})_2$, NR^{QN}, CO, O, S, or SO_2, wherein each R^{QC} is independently H, F, Cl, Br, or 6-10 membered aryl, and wherein each R^{QN} is independently H, C_{1-6} alkyl, or 6-10 membered aryl;

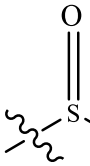
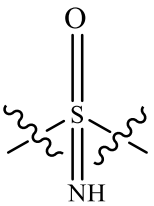
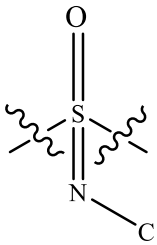
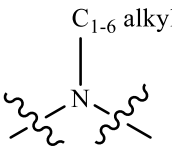
wherein at least one of Q^1, Q^2, Q^3, Q^4, and Q^5 is N, NR^{QN}, O, or SO_2;

m is 0, 1, 2, or 3;

n is 0, 1, 2, or 3;

wherein when m is 0, then n is not 0;

R^1 is selected from the group consisting of H, C_{1-6} alkyl, halogen, -$CONHR^{1a}$, -NHR^{1a}, –OR^{1a}, cyclopropyl, azetidinyl, and –CN; wherein each C_{1-6} alkyl and azetidinyl is optionally substituted with halogen, R^{1a}, -NHR^{1a}, or –OR^{1a}; wherein R^{1a} is H, C_{1-6} alkyl, cyclopropyl, 3-6 membered heterocyclyl, or C_{1-6} haloalkyl;

L^2 is selected from the group consisting of a bond, –C(O)–, –C(O)O–, –$C(O)NH(CH_2)_o$–, –$S(O)_2$–, , , , , –$C(O)(CH_2)_p$–, –$(CH_2)_p$–, and –O–; wherein o is 0, 1, or 2; and wherein p is a number from 1 to 6;

R^2 is selected from the group consisting of H, C_{1-6} alkyl, -$NR^{2b}R^{2c}$, -OR^{2a}, 3-14 membered cycloalkyl, 3-14 membered cycloalkenyl, 3-14 membered heterocyclyl, 6-10 membered aryl, and 5-10 membered heteroaryl; wherein each C_{1-6} alkyl, 3-14 membered cycloalkyl, 3-14 membered cycloalkenyl, 3-14 membered heterocyclyl, 6-10 membered aryl, and 5-10 membered heteroaryl are independently optionally substituted with C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} methoxyalkyl, –OH, –OR^{2a}, oxo, =N, halogen,

–C(O)R^{2a}, –C(O)OR^{2a}, –C(O)N$R^{2b}R^{2c}$, -SO_2R^{2a}, –CN, -N$R^{2b}R^{2c}$, 3-6 membered cycloalkyl, 3-7 membered heterocyclyl, 6-10 membered aryl, or 5-10 membered heteroaryl;

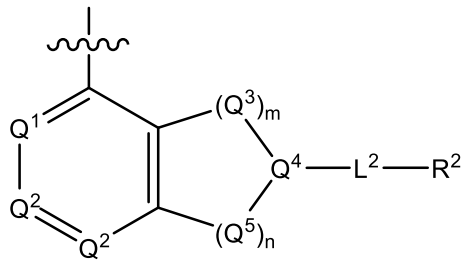
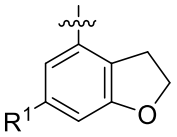
wherein R^{2a} is H, C_{1-6} alkyl, C_{1-6} haloalkyl, 3-7 membered heterocyclyl, or –$(CH_2)_rOCH_3$, wherein r is 1, 2, or 3;

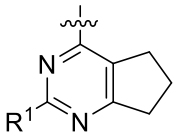
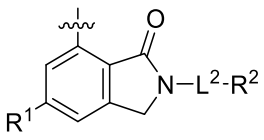
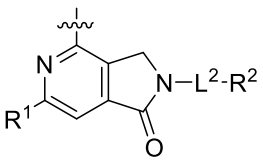
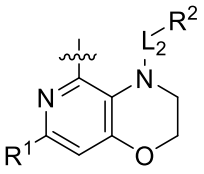
wherein R^{2b} is H or C_{1-6} alkyl;

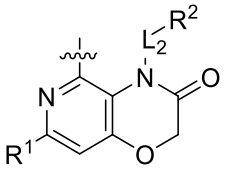
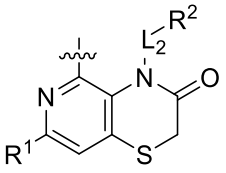
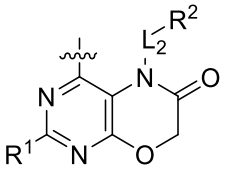
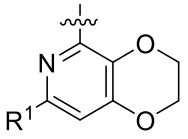
wherein R^{2c} is H or C_{1-6} alkyl;

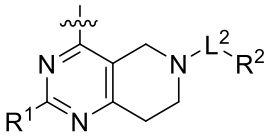
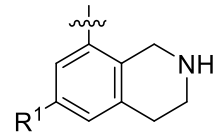
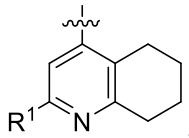
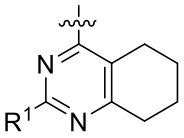
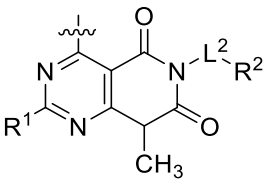
R^3 and R^4 are independently H or C_{1-6} alkyl optionally substituted with halo or -OH; wherein at least one of R^3 and R^4 is H or wherein R^3 and R^4 together with the atom to which they are attached combine to form a 3-6 membered cycloalkyl; and

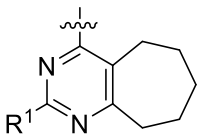
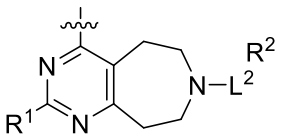
A is an optionally substituted 6-membered aryl or an optionally substituted 5-6 membered heteroaryl;

with the proviso that when  is ,

, , , ,

, , , ,

, , , , ,

, or ;

then R^1 is not H.

[0011b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, and a pharmaceutically acceptable carrier.

[0011c] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, in the manufacture of a medicament for inhibiting SOS1 in a subject.

[0011d] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, hydate, tautomer, or isomer thereof, in the manufacture of a medicament for inhibiting the interaction of SOS1 and a RAS-family protein in a cell or inhibiting the interaction of SOS1 and RAC1 in a cell.

[0011e] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, in the manufacture of a medicament for treating or preventing a disease, wherein treating or preventing the disease is characterized by inhibition of the interaction of SOS1 and a RAS-family protein or by inhibition of the interaction of SOS1 and RAC1.

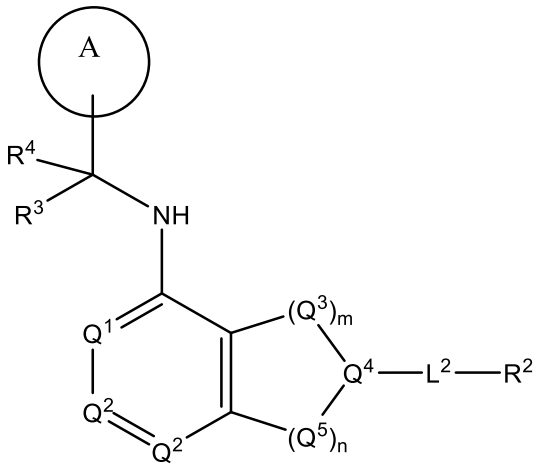
[0011f] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, in the manufacture of a medicament for treating or preventing cancer in a subject in need thereof.

[0011g] In a further aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, for use in inhibiting SOS1 in a subject, or for use in inhibiting the interaction of SOS1 and a RAS-family protein in a cell or inhibiting the interaction of SOS1 and RAC1 in a cell, or for use in treating or preventing a disease, wherein treating or preventing the disease is characterized by inhibition of the interaction of SOS1 and a RAS-

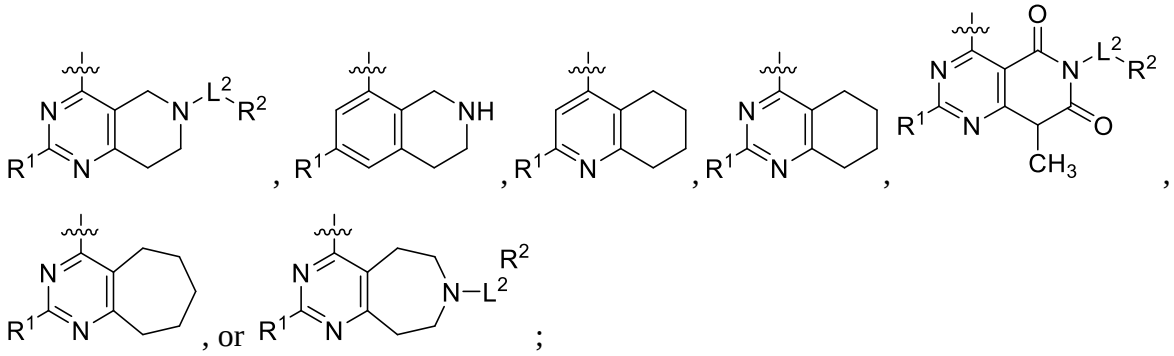
family protein or by inhibition of the interaction of SOS1 and RAC1, or for use in treating or preventing cancer in a subject in need thereof.

[0012] The present disclosure relates to compounds capable of inhibiting the activity of SOS1. The present disclosure further provides a process for the preparation of compounds, pharmaceutical preparations comprising such compounds and methods of using such compounds and compositions in the management of diseases or disorders associated with the aberrant activity of SOS1.

[0013] One example of the present disclosure relates to compounds of Formula (I):

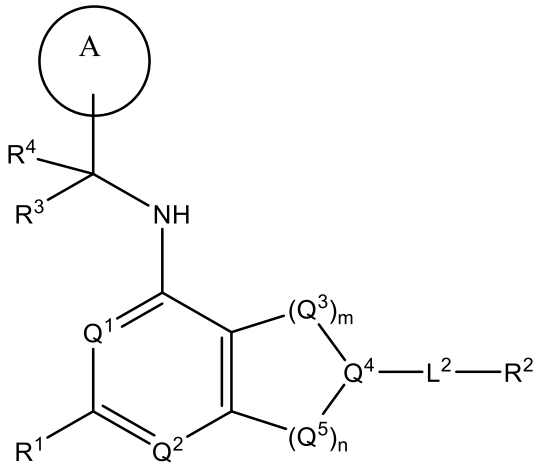


(I)



then R^1 is not H.

[0014] One example of the present disclosure relates to compounds of Formula (I-a):



(I-a)

or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein:

Q^1, Q^3, Q^4, Q^5, m, n and A are as defined in Formula (I);

Q^2 is CH or N;

wherein at least one of Q^1, Q^2, Q^3, Q^4, and Q^5 is N, NR^{QN}, O, or SO_2;

R^1 is selected from the group consisting of H, halogen, C_{1-6} alkyl, cyclopropyl, –CN, and $–OR^{1a}$; wherein R^{1a} is H or C_{1-6} alkyl;

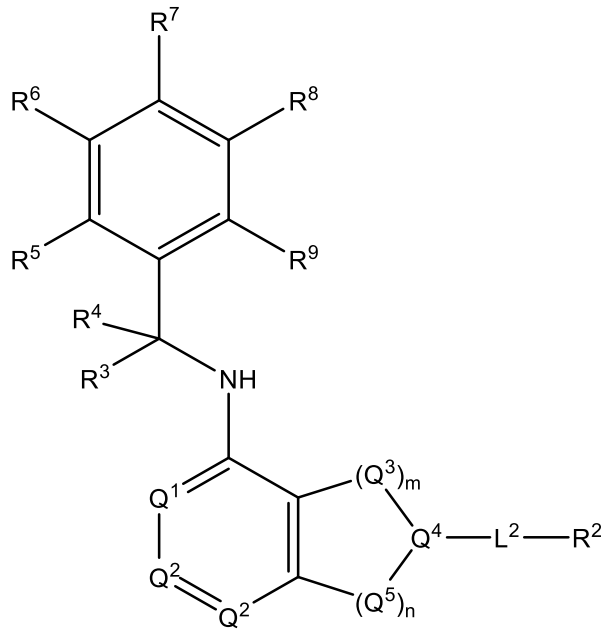
L^2 is selected from the group consisting of a bond, –C(O)–, –C(O)O–, $–C(O)NH(CH_2)_o–$, $–S(O)_2–$, $–C(O)(CH_2)_p–$, $–(CH_2)_p–$, or –O–; wherein o is 0, 1, or 2; and wherein p is a number from 1 to 6;

R^2 is selected from the group consisting of H, $–(CH_2)_qCH_3$, 3-14 membered cycloalkyl, 3-14 membered cycloalkenyl, 3-14 membered heterocyclyl, 6-10 membered aryl, and 5-10 membered heteroaryl; wherein q is a number from 1 to 5; wherein each 3-14 membered cycloalkyl, 3-14 membered cycloalkenyl, 3-14 membered heterocyclyl, 6-10 membered aryl, or 5-10 membered heteroaryl is optionally substituted with C_{1-6} alkyl, –OH, halogen, $–C(O)R^{2a}$, or $–C(O)NR^{2b}R^{2c}$; wherein R^{2a} is C_{1-6} alkyl or $–(CH_2)_rOCH_3$, wherein r is 1, 2, or 3; wherein R^{2b} is H or C_{1-6} alkyl; and wherein R^{2c} is H or C_{1-6} alkyl; and

R^3 and R^4 are independently H or C_{1-6} alkyl; wherein at least one of R^3 and R^4 is not H; or R^3 and R^4 together with the atom to which they are attached combine to form a 3-6 membered cycloalkyl; and

wherein the proviso of Formula (I) also applies to Formula (I-a).

[0015] Another example of the present disclosure relates to compounds of Formula (V):



(V)

or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein:

L^2, Q^1, Q^2, Q^3, Q^4, Q^5, m, n, R^1, R^2, R^3 and R^4 are as defined in Formula (I);

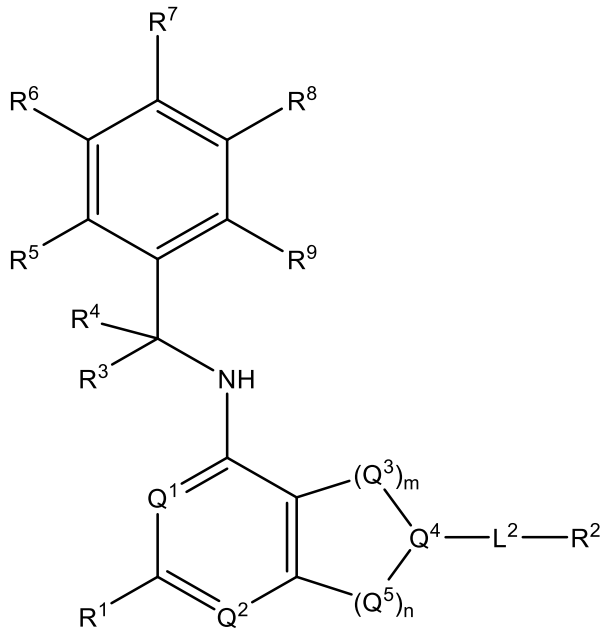
R^5, R^6, R^7, R^8, and R^9 are independently selected from the group consisting of H, D, C_{1-6} alkyl, C_{2-6} alkenyl, 4-8 membered cycloalkenyl, C_{2-6} alkynyl, 3-8 membered cycloalkyl, 3-14 membered heterocyclyl, -OH, halogen, $–NO_2$, –CN, $–NR^{11}R^{12}$, $–SR^{10}$, $–S(O)_2NR^{11}R^{12}$, $–S(O)_2R^{10}$, $–NR^{10}S(O)_2NR^{11}R^{12}$, $–NR^{10}S(O)_2R^{11}$, $–S(O)NR^{11}R^{12}$, $–S(O)R^{10}$, $–NR^{10}S(O)NR^{11}R^{12}$, $–NR^{10}S(O)R^{11}$, $–C(O)R^{10}$, and $–CO_2R^{10}$, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, 4-8 membered cycloalkenyl, C_{2-6} alkynyl, 3-8 membered cycloalkyl, and 3-14 membered heterocyclyl are independently optionally substituted with –OH, halogen, $–NO_2$, oxo, –CN, $−R^{10}$, $–OR^{10}$, $–NR^{11}R^{12}$, $−SR^{10}$, $–S(O)_2NR^{11}R^{12}$, $–S(O)_2R^{10}$, $–NR^{10}S(O)_2NR^{11}R^{12}$, $–NR^{10}S(O)_2R^{11}$, $–S(O)NR^{11}R^{12}$, $–S(O)R^{10}$, $–NR^{10}S(O)NR^{11}R^{12}$, $–NR^{10}S(O)R^{11}$, 3-8 membered cycloalkyl, 3-14 membered heterocyclyl, 6-10 membered aryl, or 5-10 membered heteroaryl, or any two adjacent R^5, R^6, R^7, R^8, and R^9 form a 3-14 membered fused ring;

R^{10}, R^{11}, and R^{12} are at each occurrence independently selected from H, D, C_{1-6} alkyl, C_{2-6} alkenyl, 4-8 membered cycloalkenyl, C_{2-6} alkynyl, 3-8 membered cycloalkyl, 3-14 membered heterocyclyl, $–OR^{13}$, $–SR^{13}$, halogen, $–NR^{13}R^{14}$, $–NO_2$, and –CN; and

R^{13} and R^{14} are at each occurrence independently selected from H, D, C_{1-6} alkyl, C_{2-6} alkenyl, 4-8 membered cycloalkenyl, C_{2-6} alkynyl, 3-8 membered cycloalkyl, and 3-14 membered heterocyclyl, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, 4-8 membered cycloalkenyl, C_{2-6} alkynyl, 3-8 membered cycloalkyl, and 3-14 membered heterocyclyl are independently optionally substituted with –OH, –SH, $–NH_2$, $–NO_2$, or –CN; and

wherein the proviso of Formula (I) also applies to Formula (V).

[0016] Another example of the present disclosure relates to compounds of Formula (V-a):



(V-a)

or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein:

Q^1, Q^3, Q^4, Q^5, m, n, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are as defined in Formula (V);

Q^2 is CH or N;

wherein at least one of Q^1, Q^2, Q^3, Q^4, and Q^5 is N, NR^{QN}, O, or SO_2;

R^1 is selected from the group consisting of H, halogen, $C_{1\text{-}6}$ alkyl, cyclopropyl, –CN, and $–OR^{1a}$; wherein R^{1a} is H or $C_{1\text{-}6}$ alkyl; and

L^2 is selected from the group consisting of a bond, –C(O)–, –C(O)O–, $–C(O)NH(CH_2)_o–$, $–S(O)_2–$, $–C(O)(CH_2)_p–$, $–(CH_2)_p–$, or –O–; wherein o is 0, 1, or 2; and wherein p is a number from 1 to 6; and

wherein the proviso of Formula (I) also applies to Formula (V-a).

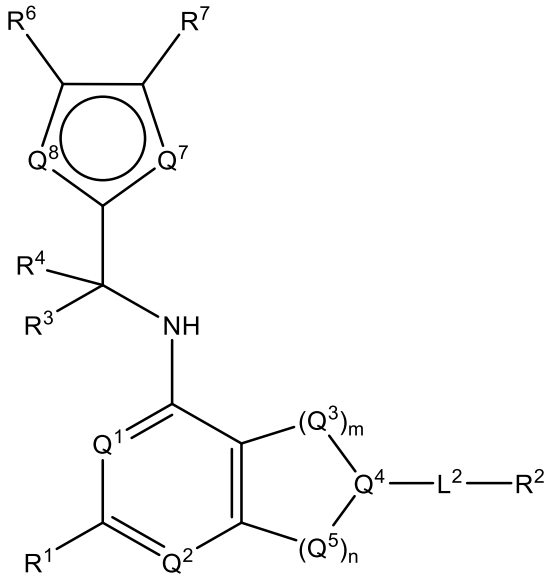
[0017] Another example of the present disclosure relates to compounds of Formula (VI):

R^{10}, R^{11}, and R^{12} are at each occurrence independently selected from H, D, C_{1-6} alkyl, C_{2-6} alkenyl, 4-8 membered cycloalkenyl, C_{2-6} alkynyl, 3-8 membered cycloalkyl, 3-14 membered heterocyclyl, $–OR^{13}$, $–SR^{13}$, halogen, $–NR^{13}R^{14}$, $–NO_2$, and –CN; and

R^{13} and R^{14} are at each occurrence independently selected from H, D, C_{1-6} alkyl, C_{2-6} alkenyl, 4-8 membered cycloalkenyl, C_{2-6} alkynyl, 3-8 membered cycloalkyl, and 3-14 membered heterocyclyl, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, 4-8 membered cycloalkenyl, C_{2-6} alkynyl, 3-8 membered cycloalkyl, and 3-14 membered heterocyclyl are independently optionally substituted with –OH, –SH, $–NH_2$, $–NO_2$, or –CN; and

wherein the proviso of Formula (I) also applies to Formula (VI).

[0018] Another example of the present disclosure relates to compounds of Formula (VI-a):



(VI-a)

wherein L^2, Q^1, Q^2, Q^3, Q^4, Q^5, Q^7, Q^8, R^1, R^2, R^3, R^4, R^6, and R^7 are as defined in Formula (VI), and wherein the proviso of Formula (I) also applies to Formula (VI-a).

[0019] Another example of the present disclosure relates to a pharmaceutical composition comprising a compound, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, as set forth above and a pharmaceutically acceptable carrier.

[0020] Another example of the present disclosure relates to a method of inhibiting SOS1 in a subject, comprising administering to the subject a compound, or a pharmaceutically

acceptable salt, solvate, hydrate, tautomer, or isomer thereof, or a pharmaceutical composition, as set forth above.

[0021] Another example of the present disclosure relates to a method of inhibiting the interaction of SOS1 and a RAS-family protein in a cell or inhibiting the interaction of SOS1 and RAC1 in a cell, comprising administering to the cell a compound, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, or a pharmaceutical composition, as set forth above.

[0022] Another example of the present disclosure relates to a method of treating or preventing a disease, wherein treating or preventing the disease is characterized by inhibition of the interaction of SOS1 and a RAS-family protein or by inhibition of the interaction of SOS1 and RAC1, the method comprising administering to a subject in need thereof an effective amount of a compound, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, or a pharmaceutical composition, as set forth above.

[0023] Another example of the present disclosure relates to a method of treating or preventing cancer in a subject in need thereof, comprising administering to the subject an effective amount of a compound, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, or a pharmaceutical composition, as set forth above.

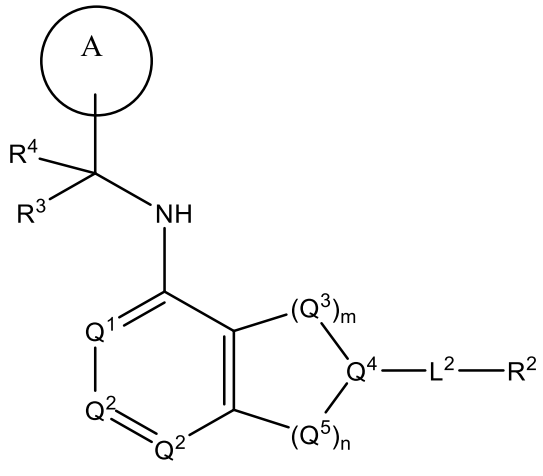
[0024] Another example of the present disclosure relates to a compound, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, or a pharmaceutical composition, as set forth above for use as a medicament.

[0025] Another example of the present disclosure relates to the use of the compound, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, or a pharmaceutical composition, as set forth above in the manufacture of a medicament for use in inhibiting the binding of hSOS1 to H- or N- or K-RAS including their clinically known mutations and which inhibits the nucleotide exchange reaction catalyzed by hSOS1 in the presence of a concentration of 20 μM or lower, but which are substantially inactive against EGFR-kinase at concentrations of 20 μM or lower.

[0026] Another example of the present disclosure relates to the use the compound, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, or a pharmaceutical composition, as set forth above in the manufacture of a medicament for use inhibiting the binding of hSOS1 specifically to K-RAS G12C protein and which inhibits

We claim:

1. A compound having the structure of Formula (I),



(I)

or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein:

Q^1 is CH or N;

Q^4 is CH, C, or N;

each Q^2 is independently C-R^1 or N, wherein one Q^2 is N and the other Q^2 is C-R^1;

each Q^3 and Q^5 are independently $C(R^{QC})_2$, NR^{QN}, CO, O, S, or SO_2, wherein each R^{QC} is independently H, F, Cl, Br, or 6-10 membered aryl, and wherein each R^{QN} is independently H, C_{1-6} alkyl, or 6-10 membered aryl;

wherein at least one of Q^1, Q^2, Q^3, Q^4, and Q^5 is N, NR^{QN}, O, or SO_2;

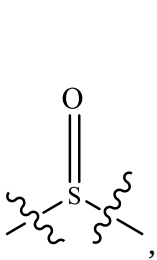
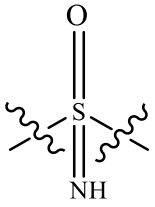
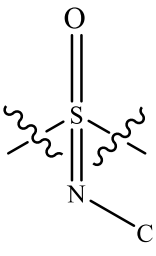
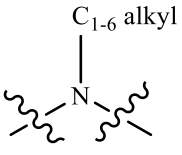
m is 0, 1, 2, or 3;

n is 0, 1, 2, or 3;

wherein when m is 0, then n is not 0;

R^1 is selected from the group consisting of H, C_{1-6} alkyl, halogen, -$CONHR^{1a}$, -NHR^{1a}, –OR^{1a}, cyclopropyl, azetidinyl, and –CN; wherein each C_{1-6} alkyl and azetidinyl is

optionally substituted with halogen, R^{1a}, -NHR^{1a}, or –OR^{1a}; wherein R^{1a} is H, C_{1-6} alkyl, cyclopropyl, 3-6 membered heterocyclyl, or C_{1-6} haloalkyl;

L^2 is selected from the group consisting of a bond, –C(O)–, –C(O)O–, –C(O)$NH(CH_2)_o$–, –$S(O)_2$–, , , , , –$C(O)(CH_2)_p$–, –$(CH_2)_p$–, and –O–; wherein o is 0, 1, or 2; and wherein p is a number from 1 to 6;

R^2 is selected from the group consisting of H, C_{1-6} alkyl, -$NR^{2b}R^{2c}$, -OR^{2a}, 3-14 membered cycloalkyl, 3-14 membered cycloalkenyl, 3-14 membered heterocyclyl, 6-10 membered aryl, and 5-10 membered heteroaryl; wherein each C_{1-6} alkyl, 3-14 membered cycloalkyl, 3-14 membered cycloalkenyl, 3-14 membered heterocyclyl, 6-10 membered aryl, and 5-10 membered heteroaryl are independently optionally substituted with C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} methoxyalkyl, –OH, –OR^{2a}, oxo, =N, halogen, –$C(O)R^{2a}$, –$C(O)OR^{2a}$, –$C(O)NR^{2b}R^{2c}$, -SO_2R^{2a}, –CN, -$NR^{2b}R^{2c}$, 3-6 membered cycloalkyl, 3-7 membered heterocyclyl, 6-10 membered aryl, or 5-10 membered heteroaryl;

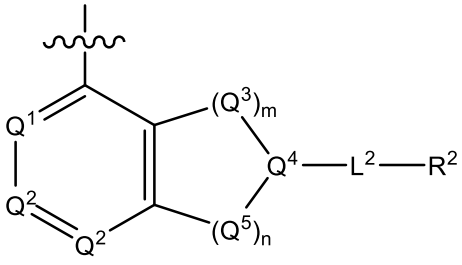
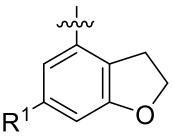
wherein R^{2a} is H, C_{1-6} alkyl, C_{1-6} haloalkyl, 3-7 membered heterocyclyl, or –$(CH_2)_rOCH_3$, wherein r is 1, 2, or 3;

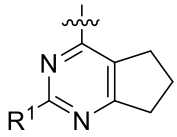
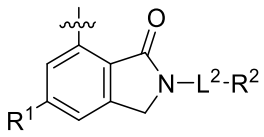
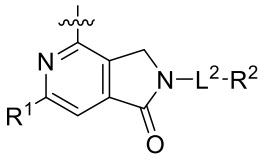
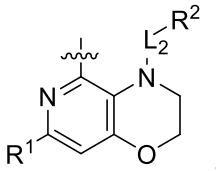
wherein R^{2b} is H or C_{1-6} alkyl;

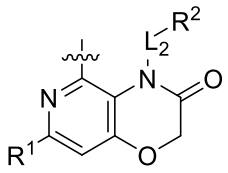
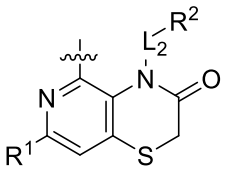
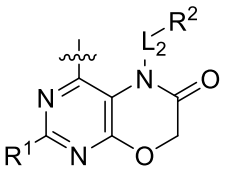
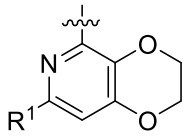
wherein R^{2c} is H or C_{1-6} alkyl;

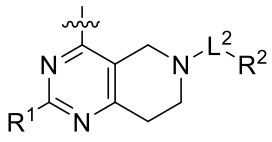
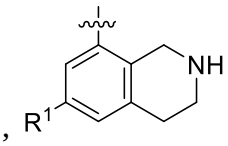
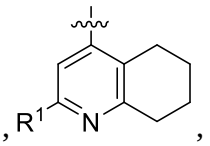
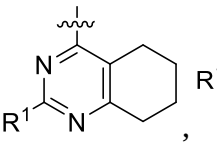
R^3 and R^4 are independently H or C_{1-6} alkyl optionally substituted with halo or -OH; wherein at least one of R^3 and R^4 is H or wherein R^3 and R^4 together with the atom to which they are attached combine to form a 3-6 membered cycloalkyl; and

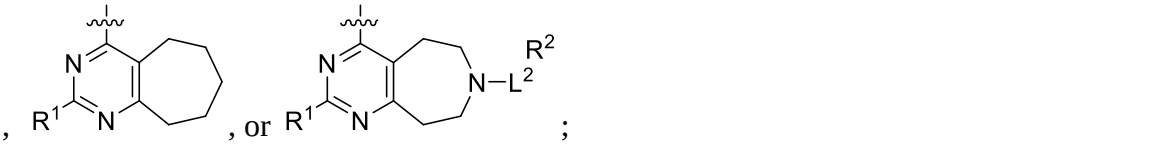
A is an optionally substituted 6-membered aryl or an optionally substituted 5-6 membered heteroaryl;

with the proviso that when  is ,

, , , ,

, , , ,

, , , ,



or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein:

Q^1, Q^3, Q^4, Q^5, m, n and A are as defined in claim 1;

Q^2 is CH or N;

wherein at least one of Q^1, Q^2, Q^3, Q^4, and Q^5 is N, NR^{QN}, O, or SO_2;

R^1 is selected from the group consisting of H, halogen, C_{1-6} alkyl, cyclopropyl, –CN, and $–OR^{1a}$; wherein R^{1a} is H or C_{1-6} alkyl;

L^2 is selected from the group consisting of a bond, –C(O)–, –C(O)O–, $–C(O)NH(CH_2)_o–$, $–S(O)_2–$, $–C(O)(CH_2)_p–$, $–(CH_2)_p–$, or –O–; wherein o is 0, 1, or 2; and wherein p is a number from 1 to 6;

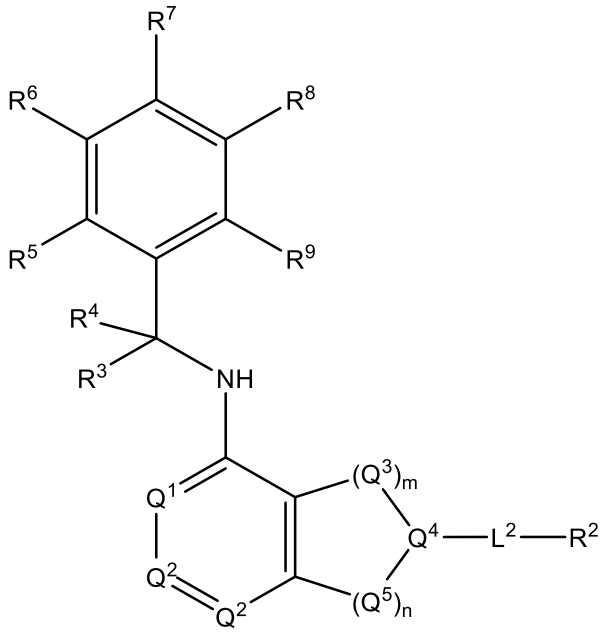
R^2 is selected from the group consisting of H, $–(CH_2)_qCH_3$, 3-14 membered cycloalkyl, 3-14 membered cycloalkenyl, 3-14 membered heterocyclyl, 6-10 membered aryl, and 5-10 membered heteroaryl; wherein q is a number from 1 to 5; wherein each 3-14 membered cycloalkyl, 3-14 membered cycloalkenyl, 3-14 membered heterocyclyl, 6-10 membered aryl, or 5-10 membered heteroaryl is optionally substituted with C_{1-6} alkyl, –OH, halogen, $–C(O)R^{2a}$, or $–C(O)NR^{2b}R^{2c}$; wherein R^{2a} is C_{1-6} alkyl or $–(CH_2)_rOCH_3$, wherein r is 1, 2, or 3; wherein R^{2b} is H or C_{1-6} alkyl; and wherein R^{2c} is H or C_{1-6} alkyl; and

R^3 and R^4 are independently H or C_{1-6} alkyl; wherein at least one of R^3 and R^4 is not H; or R^3 and R^4 together with the atom to which they are attached combine to form a 3-6 membered cycloalkyl.

3. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein A is an optionally substituted 6-membered aryl.

4. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein A is an optionally substituted 5-6 membered heteroaryl.

5. The compound of claim 1 having the structure of Formula (V),



(V)

or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein:

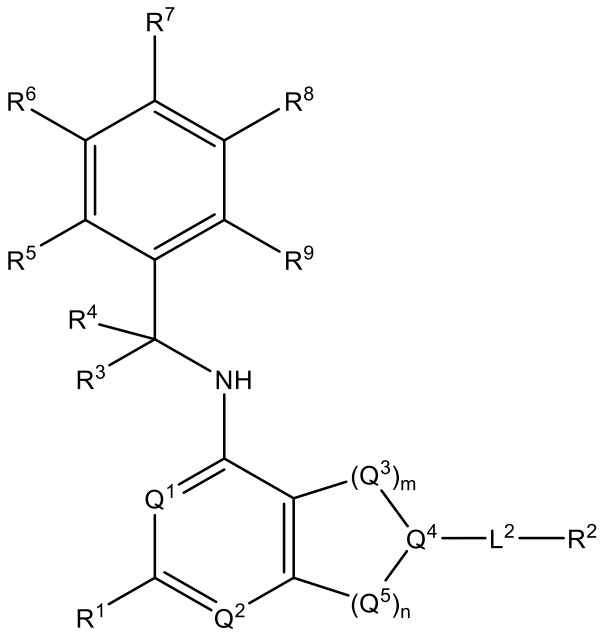
L^2, Q^1, Q^2, Q^3, Q^4, Q^5, m, n, R^1, R^2, R^3 and R^4 are as defined in claim 1;

R^5, R^6, R^7, R^8, and R^9 are independently selected from the group consisting of H, D, C_{1-6} alkyl, C_{2-6} alkenyl, 4-8 membered cycloalkenyl, C_{2-6} alkynyl, 3-8 membered cycloalkyl, 3-14 membered heterocyclyl, -OH, halogen, $–NO_2$, –CN, $–NR^{11}R^{12}$, $–SR^{10}$, $–S(O)_2NR^{11}R^{12}$, $–S(O)_2R^{10}$, $–NR^{10}S(O)_2NR^{11}R^{12}$, $–NR^{10}S(O)_2R^{11}$, $–S(O)NR^{11}R^{12}$, $–S(O)R^{10}$, $–NR^{10}S(O)NR^{11}R^{12}$, $–NR^{10}S(O)R^{11}$, $–C(O)R^{10}$, and $–CO_2R^{10}$, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, 4-8 membered cycloalkenyl, C_{2-6} alkynyl, 3-8 membered cycloalkyl, and 3-14 membered heterocyclyl are independently optionally substituted with –OH, halogen, $–NO_2$, oxo, –CN, $–R^{10}$, $–OR^{10}$, $–NR^{11}R^{12}$, $–SR^{10}$, $–S(O)_2NR^{11}R^{12}$, $–S(O)_2R^{10}$, $–NR^{10}S(O)_2NR^{11}R^{12}$, $–NR^{10}S(O)_2R^{11}$, $–S(O)NR^{11}R^{12}$, $–S(O)R^{10}$, $–NR^{10}S(O)NR^{11}R^{12}$, $–NR^{10}S(O)R^{11}$, 3-8 membered cycloalkyl, 3-14 membered heterocyclyl, 6-10 membered aryl, or 5-10 membered heteroaryl, or any two adjacent R^5, R^6, R^7, R^8, and R^9 forms a 3-14 membered fused ring;

R^{10}, R^{11}, and R^{12} are at each occurrence independently selected from H, D, C_{1-6} alkyl, C_{2-6} alkenyl, 4-8 membered cycloalkenyl, C_{2-6} alkynyl, 3-8 membered cycloalkyl, 3-14 membered heterocyclyl, $–OR^{13}$, $–SR^{13}$, halogen, $–NR^{13}R^{14}$, $–NO_2$, and –CN; and

R^{13} and R^{14} are at each occurrence independently selected from H, D, C_{1-6} alkyl, C_{2-6} alkenyl, 4-8 membered cycloalkenyl, C_{2-6} alkynyl, 3-8 membered cycloalkyl, and 3-14 membered heterocyclyl, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, 4-8 membered cycloalkenyl, C_{2-6} alkynyl, 3-8 membered cycloalkyl, and 3-14 membered heterocyclyl are independently optionally substituted with –OH, –SH, $–NH_2$, $–NO_2$, or –CN.

6. The compound of claim 5 having the structure of Formula (V-a),



(V-a)

or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein:

Q^1, Q^3, Q^4, Q^5, m, n, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are as defined in claim 5;

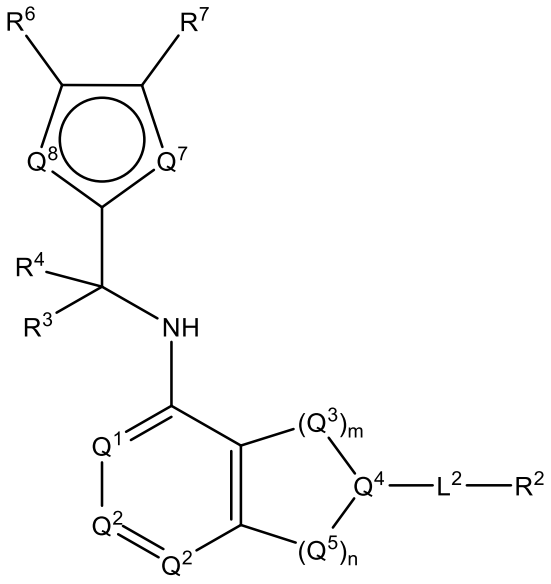
Q^2 is CH or N;

wherein at least one of Q^1, Q^2, Q^3, Q^4, and Q^5 is N, NR^{QN}, O, or SO_2;

R^1 is selected from the group consisting of H, halogen, C_{1-6} alkyl, cyclopropyl, –CN, and $–OR^{1a}$; wherein R^{1a} is H or C_{1-6} alkyl; and

L^2 is selected from the group consisting of a bond, –C(O)–, –C(O)O–, $–C(O)NH(CH_2)_o–$, $–S(O)_2–$, $–C(O)(CH_2)_p–$, $–(CH_2)_p–$, or –O–; wherein o is 0, 1, or 2; and wherein p is a number from 1 to 6.

7. The compound of claim 1 having the structure of Formula (VI),



(VI)

or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein:

L^2, Q^1, Q^2, Q^3, Q^4, Q^5, m, n, R^1, R^2, R^3, and R^4 are as defined in claim 1;

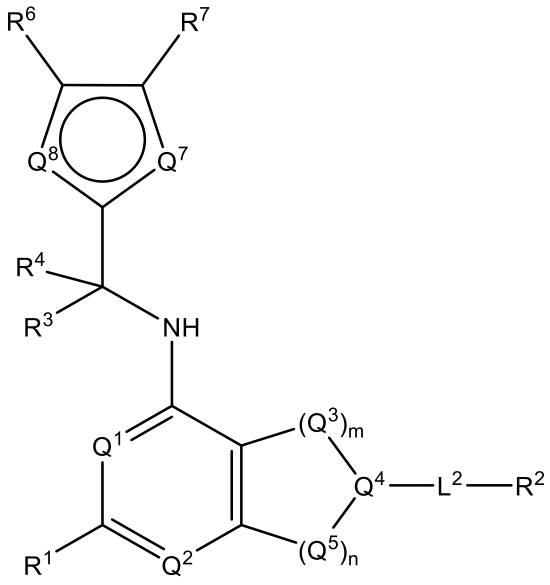
Q^7 and Q^8 are each independently CH, N, NH, O, or S, provided at least one of Q^7 and Q^8 is N, NH, O, or S;

R^6 and R^7 are independently selected from the group consisting of H, D, C_{1-6} alkyl, C_{2-6} alkenyl, 4-8 membered cycloalkenyl, C_{2-6} alkynyl, 3-8 membered cycloalkyl, 3-14 membered heterocyclyl, -OH, halogen, $–NO_2$, –CN, $–NR^{11}R^{12}$, $–SR^{10}$, $–S(O)_2NR^{11}R^{12}$, $–S(O)_2R^{10}$, $–NR^{10}S(O)_2NR^{11}R^{12}$, $–NR^{10}S(O)_2R^{11}$, $–S(O)NR^{11}R^{12}$, $–S(O)R^{10}$, $–NR^{10}S(O)NR^{11}R^{12}$, $–NR^{10}S(O)R^{11}$, $–C(O)R^{10}$, and $–CO_2R^{10}$, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, 4-8 membered cycloalkenyl, C_{2-6} alkynyl, 3-8 membered cycloalkyl, and 3-14 membered heterocyclyl are independently optionally substituted with –OH, halogen, $–NO_2$, oxo, –CN, $–R^{10}$, $–OR^{10}$, $–NR^{11}R^{12}$, $–SR^{10}$, $–S(O)_2NR^{11}R^{12}$, $–S(O)_2R^{10}$, $–NR^{10}S(O)_2NR^{11}R^{12}$, $–NR^{10}S(O)_2R^{11}$, $–S(O)NR^{11}R^{12}$, $–S(O)R^{10}$, $–NR^{10}S(O)NR^{11}R^{12}$, $–NR^{10}S(O)R^{11}$, 3-8 membered cycloalkyl, 3-14 membered heterocyclyl, 6-10 membered aryl, or 5-10 membered heteroaryl,

R^{10}, R^{11}, and R^{12} are at each occurrence independently selected from H, D, C_{1-6} alkyl, C_{2-6} alkenyl, 4-8 membered cycloalkenyl, C_{2-6} alkynyl, 3-8 membered cycloalkyl, 3-14 membered heterocyclyl, $–OR^{13}$, $–SR^{13}$, halogen, $–NR^{13}R^{14}$, $–NO_2$, and –CN; and

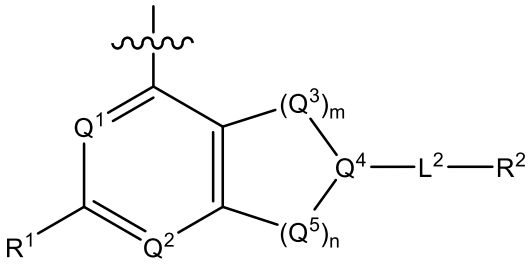
R^{13} and R^{14} are at each occurrence independently selected from H, D, C_{1-6} alkyl, C_{2-6} alkenyl, 4-8 membered cycloalkenyl, C_{2-6} alkynyl, 3-8 membered cycloalkyl, and 3-14 membered heterocyclyl, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, 4-8 membered cycloalkenyl, C_{2-6} alkynyl, 3-8 membered cycloalkyl, and 3-14 membered heterocyclyl are independently optionally substituted with –OH, –SH, $–NH_2$, $–NO_2$, or –CN.

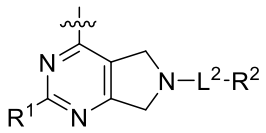
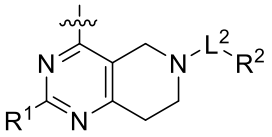
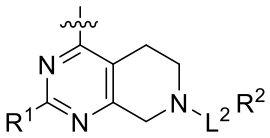
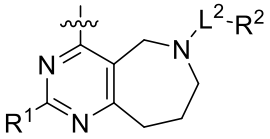
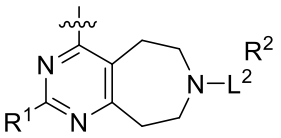
8. The compound of claim 7, or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, having the structure (VI-a),

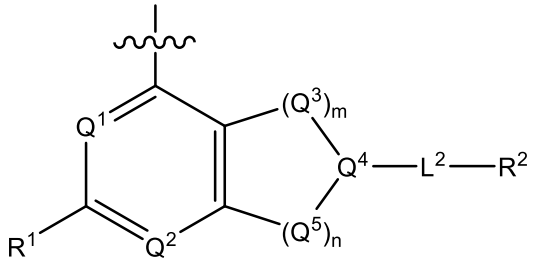
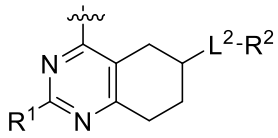
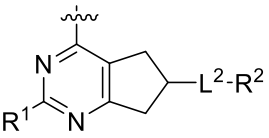


(VI-a)

wherein L^2, Q^1, Q^2, Q^3, Q^4, Q^5, Q^7, Q^8, R^1, R^2, R^3, R^4, R^6, and R^7 are as defined in claim 7.

9. The compound of claim 2, or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein  is

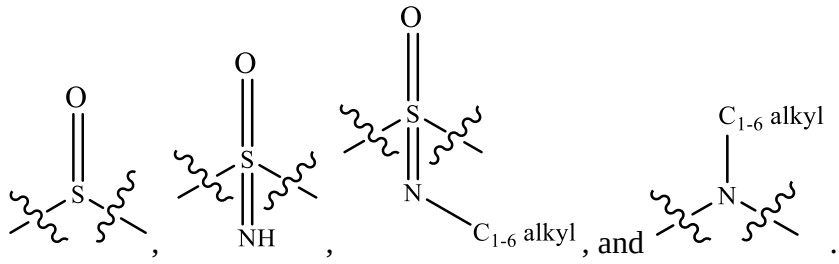
selected from the group consisting of , , , , and .

10. The compound of claim 2, or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein  is selected from the group consisting of  and .

11. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein R^1 is selected from the group consisting of H, C_{1-6} alkyl, halogen, -NHR^{1a}, –OR^{1a}, cyclopropyl, and –CN; wherein C_{1-6} alkyl is optionally substituted with halogen, -NHR^{1a}, or –OR^{1a}; wherein R^{1a} is H, C_{1-6} alkyl, 3-6 membered heterocyclyl, or C_{1-6} haloalkyl.

12. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein R^1 is H, halogen, C_{1-6} alkyl, cyclopropyl, –CN, or –OR^{1a}; wherein R^{1a} is H or C_{1-6} alkyl.

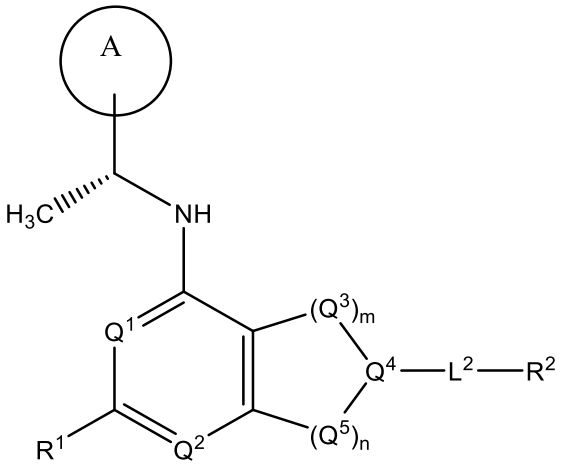
13. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein L^2 is selected from the group consisting of a bond, –C(O)–, –C(O)O–, –C(O)$NH(CH_2)_o$–, –$S(O)_2$–, –$C(O)(CH_2)_p$–, –$(CH_2)_p$–, and –O–; wherein o is 0, 1, or 2; and wherein p is a number from 1 to 6.

14. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein L^2 is selected from the group consisting of .

15. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein R^2 is selected from the group consisting of H, C_{1-6} alkyl, $-NR^{2b}R^{2c}$, $-OR^{2a}$, 3-14 membered cycloalkyl, 3-14 membered cycloalkenyl, 3-14 membered heterocyclyl, 6-10 membered aryl, and 5-10 membered heteroaryl; wherein each C_{1-6} alkyl, 3-14 membered cycloalkyl, 3-14 membered cycloalkenyl, 3-14 membered heterocyclyl, 6-10 membered aryl, and 5-10 membered heteroaryl are independently optionally substituted with C_{1-6} alkyl, –OH, $–OR^{2a}$, oxo, =N, halogen, $–C(O)R^{2a}$, $–C(O)OR^{2a}$, $–C(O)NR^{2b}R^{2c}$, –CN, $-NR^{2b}R^{2c}$, 3-6 membered cycloalkyl, 3-7 membered heterocyclyl, 6-10 membered aryl, or 5-10 membered heteroaryl.

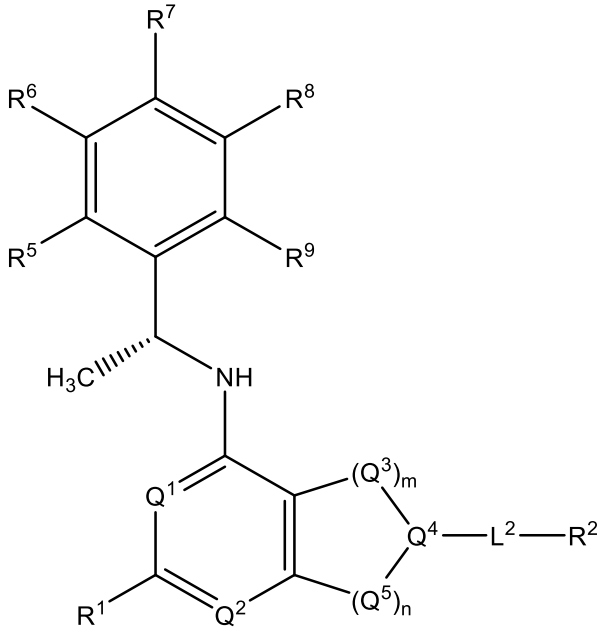
16. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein R^2 is 3-14 membered heterocyclyl, wherein the 3-14 membered heterocyclyl is optionally substituted with C_{1-6} alkyl optionally substituted with halogen or $–OR^{2a}$, –OH, $–OR^{2a}$, oxo, =N, halogen, $–C(O)R^{2a}$, $–C(O)OR^{2a}$, $–C(O)NR^{2b}R^{2c}$, $-SO_2R^{2a}$, –CN, $-NR^{2b}R^{2c}$, 3-6 membered cycloalkyl, 3-7 membered heterocyclyl, 6-10 membered aryl, or 5-10 membered heteroaryl; wherein R^{2a} is H, C_{1-6} alkyl, C_{1-6} haloalkyl, 3-7 membered heterocyclyl, or $–(CH_2)_rOCH_3$, wherein r is 1, 2, or 3; wherein R^{2b} is H or C_{1-6} alkyl; and wherein R^{2c} is H or C_{1-6} alkyl.

17. The compound of claim 2, or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein R^3 is H and R^4 is $–CH_3$ and the compound is of the following formula:



wherein A, L^2, Q^1, Q^2, Q^3, Q^4, Q^5, R^1, R^2, m and n are as defined in claim 2.

18. The compound of claim 5, or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein R^3 is H and R^4 is $–CH_3$ and the compound is of the following formula:



wherein L^2, Q^1, Q^2, Q^3, Q^4, Q^5, R^1, R^2, R^4, R^5, R^6, R^7, R^8, R^9, m and n are as defined in claim 5.

19. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, selected from the group consisting of compounds of Collection 1.

20. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, selected from the group consisting of compounds of Collection 2.

21. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, selected from the group consisting of compounds of Collection 3.

22. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, selected from the group consisting of compounds of Table A.

23. A pharmaceutical composition comprising a compound of any one of claims 1-22, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, and a pharmaceutically acceptable carrier.

24. Use of a compound of any one of claims 1-22, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, in the manufacture of a medicament for inhibiting SOS1 in a subject.

25. Use of a compound of any one of claims 1-22, or a pharmaceutically acceptable salt, solvate, hydate, tautomer, or isomer thereof, in the manufacture of a medicament for inhibiting the interaction of SOS1 and a RAS-family protein in a cell or inhibiting the interaction of SOS1 and RAC1 in a cell.

26. Use of a compound of any one of claims 1-22, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, in the manufacture of a medicament for treating or preventing a disease, wherein treating or preventing the disease is characterized by inhibition of the interaction of SOS1 and a RAS-family protein or by inhibition of the interaction of SOS1 and RAC1.

27. Use of a compound of any one of claims 1-22, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, in the manufacture of a medicament for treating or preventing cancer in a subject in need thereof.

28. A compound of any one of claims 1-22, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof, for use in inhibiting SOS1 in a subject,

or for use in inhibiting the interaction of SOS1 and a RAS-family protein in a cell or inhibiting the interaction of SOS1 and RAC1 in a cell, or for use in treating or preventing a disease, wherein treating or preventing the disease is characterized by inhibition of the interaction of SOS1 and a RAS-family protein or by inhibition of the interaction of SOS1 and RAC1, or for use in treating or preventing cancer in a subject in need thereof.

29. The use of claim 26 or 27, or the compound for use of claim 28, wherein the disease or cancer is selected from the group consisting of pancreatic cancer, lung cancer, colorectal cancer, hematological cancer, cholangiocarcinoma, multiple myeloma, melanoma, uterine cancer, endometrial cancer, thyroid cancer, acute myeloid leukemia, bladder cancer, urothelial cancer, gastric cancer, cervical cancer, head and neck squamous cell carcinoma, diffuse large B cell lymphoma, esophageal cancer, chronic lymphocytic leukemia, hepatocellular cancer, breast cancer, ovarian cancer, prostate cancer, glioblastoma, renal cancer and sarcomas.

30. The use or compound for use of claim 29, wherein the disease is a RASopathy.

31. The use or compound for use of claim 30, wherein the RASopathy is selected from the group consisting of Neurofibromatosis type 1 (NF1), Noonan Syndrome (NS), Noonan Syndrome with Multiple Lentigines (NSML), Capillary Malformation-Arteriovenous Malformation Syndrome (CM-AVM), Costello Syndrome (CS), Cardio-Facio-Cutaneous Syndrome (CFC), Legius Syndrome, and Hereditary gingival fibromatosis.