selected review see: Lu et al., ChemMedChem. 2016, 11(8):814-21), have been made with limited success.

[0009] Recently, small activating molecules have been identified, which bind to a lipophilic pocket of SOS1 in close proximity to the RAS binding site (Burns et al., Proc. 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.

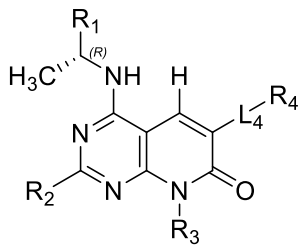
[0010] In an effort to stabilize the protein-protein-interaction of RAS-family proteins with SOS1 and to prevent reloading of RAS-family proteins with GTP, several different fragments were subsequently identified (Winter et al., J. Med. Chem. 2015, 58(5):2265-74). However, reversible binding of fragments 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

[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.

[0012a] In an aspect of the present disclosure, there is provided a compound having the structure of Formula (I),



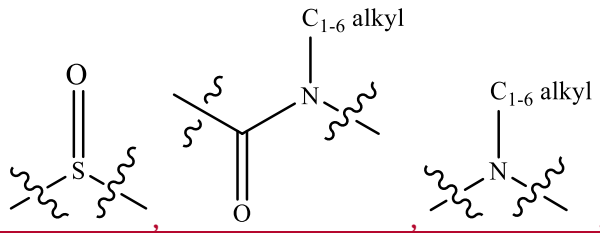
(I)

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

R_1 is selected from the group consisting of optionally substituted 3-6 membered cycloalkyl, optionally substituted 3-6 membered heterocyclyl, optionally substituted 6-membered aryl, and optionally substituted 5-6 membered heteroaryl;

R_2 is selected from the group consisting of H, C_{1-6} alkyl, halogen, -NHR_{2a}, –OR_{2a}, cyclopropyl, and –CN; wherein C_{1-6} alkyl is optionally substituted with halogen, -NHR_{2a}, –OR_{2a}, or 5-6 membered heterocyclyl, and further wherein R_{2a} is selected from the group consisting of H, C_{1-6} alkyl, 3-6 membered heterocyclyl, and C_{1-6} haloalkyl;

R_3 is selected from the group consisting of H, C_{1-3} alkyl, –OR_{3a}, cyclopropyl, and 3-6 membered heterocyclyl, wherein each of C_{1-3} alkyl, cyclopropyl, and 3-6 membered heterocyclyl is optionally substituted with R_{3a}, and further wherein R_{3a} is selected from the group consisting of C_{1-3} alkyl, halogen, –OH, or –CN;

L_4 is selected from the group consisting of bond, –C(O)–, –C(O)O–, –C(O)NH$(CH_2)_o$–, –NH–, –S–, –$S(O)_2$–, 

, –$(CH_2)_p$–, and –O–; wherein o is 0, 1, or 2; and wherein p is a number from 1 to 6; and

R_4 is selected from the group consisting of H, 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; 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 is optionally substituted with C_{1-6} alkyl, –R_{4a}, –OR_{4a}, –O–C_{1-6} alkyl–R_{4a}, =O, halogen, –C(O)R_{4a}, –C(OO)R_{4a}, –C(O)$NR_{4b}R_{4c}$, –NR_{4b}C(O)R_{4c}, –CN, =NR_{4a}, –$NR_{4b}R_{4c}$, –SO_2R_{4a}, 3-6 membered cycloalkyl optionally substituted with R_{4a}, 3-7 membered heterocyclyl optionally substituted with R_{4a}, 6-10 membered aryl optionally substituted with R_{4a},, or 5-10 membered heteroaryl optionally substituted with R_{4a},;

wherein R_{4a} is H, C_{1-6} alkyl, C_{1-6} haloalkyl, $–C(O)R_{4b}$, $–C(O)NR_{4b}R_{4c}$, =O, 3-6 membered cycloalkyl, 6-10 membered aryl optionally substituted with $–OR_{4b}$, –CN, =N-3-6 membered cycloalkyl, 3-7 membered heterocyclyl, $–(CH_2)_rOCH_3$, or $–(CH_2)_rOH$, wherein r is 1, 2, or 3;

wherein each R_{4b} is independently H, C_{1-6} alkyl; and

wherein each R_{4c} is independently H or C_{1-6} alkyl.

[0012b] 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 stereoisomer thereof, and a pharmaceutically acceptable carrier.

[0012c] In a further aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, for use in therapy.

[0012d] 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 stereoisomer thereof, in the manufacture of a medicament for treating or preventing cancer in a subject in need thereof.

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

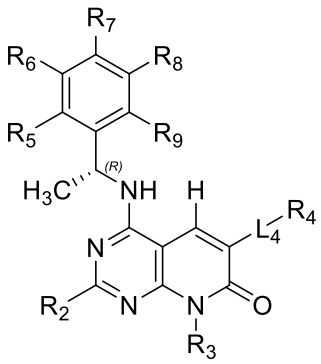
heteroaryl is optionally substituted with C_{1-6} alkyl, $–R_{4a}$, $–OR_{4a}$, $–O–C_{1-6}$ alkyl$–R_{4a}$, =O, halogen, $–C(O)R_{4a}$, $–C(OO)R_{4a}$, $–C(O)NR_{4b}R_{4c}$, $–NR_{4b}C(O)R_{4c}$, –CN, $=NR_{4a}$, $–NR_{4b}R_{4c}$, $–SO_2R_{4a}$, 3-6 membered cycloalkyl optionally substituted with R_{4a}, 3-7 membered heterocyclyl optionally substituted with R_{4a}, 6-10 membered aryl optionally substituted with R_{4a}, or 5-10 membered heteroaryl optionally substituted with R_{4a};

wherein R_{4a} is H, C_{1-6} alkyl, C_{1-6} haloalkyl, $–C(O)R_{4b}$, $–C(O)NR_{4b}R_{4c}$, =O, 3-6 membered cycloalkyl, 6-10 membered aryl optionally substituted with $–OR_{4b}$, –CN, =N-3-6 membered cycloalkyl, 3-7 membered heterocyclyl, $–(CH_2)_rOCH_3$, or $–(CH_2)_rOH$, wherein r is 1, 2, or 3;

wherein each R_{4b} is independently H, C_{1-6} alkyl; and

wherein each R_{4c} is independently H or C_{1-6} alkyl.

[0014] Another example~~aspect~~ of the present disclosure relates to compounds of Formula (II):



(II)

or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein R_2, R_3, L_4, and R_4 are as defined in Formula (I);

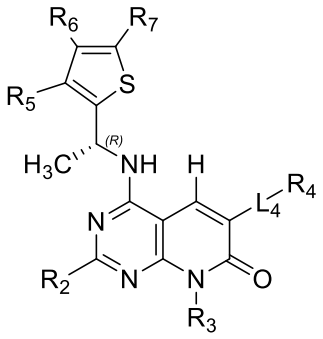
R_5, R_6, R_7, R_8, and R_9 are independently selected from the group consisting of H, D, C_{1-6} alkyl, C_{2-6} alkenyl, 4-8 membered cycloalkenyl, C_{2-6} alkynyl, 3-8 membered cycloalkyl, 3-14 membered heterocyclyl, –OH, halogen, $–NO_2$, –CN, $–NR_{11}R_{12}$, $–SR_{10}$, $–S(O)_2NR_{11}R_{12}$, $–S(O)_2R_{10}$, $–NR_{10}S(O)_2NR_{11}R_{12}$, $–NR_{10}S(O)_2R_{11}$, $–S(O)NR_{11}R_{12}$, $–S(O)R_{10}$, $–NR_{10}S(O)NR_{11}R_{12}$, $–NR_{10}S(O)R_{11}$, $–C(O)R_{10}$, $–CO_2R_{10}$, 6-10 membered aryl, and 5-10 membered heteroaryl, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, 4-8 membered cycloalkenyl, C_{2-6} alkynyl, 3-8 membered cycloalkyl, 3-14 membered heterocyclyl, 6-10 membered aryl, and 5-10 membered heteroaryl is optionally substituted with –OH, C_{1-6} alkyl, 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 an optionally substituted 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.

[0015] Another example~~aspect~~ of the present disclosure relates to compounds of Formula (III),



(III)

or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein R_2, R_3, L_4, and R_4 are as defined in Formula (I);

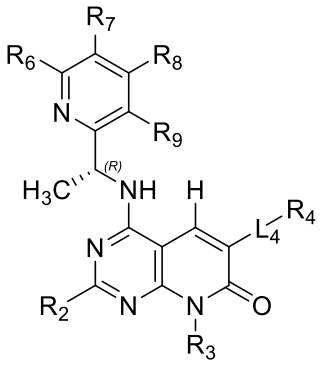
R_5, R_6, R_7, R_8, and R_9 are independently selected from the group consisting of H, D, C_{1-6} alkyl, C_{2-6} alkenyl, 4-8 membered cycloalkenyl, C_{2-6} alkynyl, 3-8 membered cycloalkyl, 3-14 membered heterocyclyl, –OH, halogen, $–NO_2$, –CN, $–NR_{11}R_{12}$, $–SR_{10}$, $–S(O)_2NR_{11}R_{12}$, $–S(O)_2R_{10}$, $–NR_{10}S(O)_2NR_{11}R_{12}$, $–NR_{10}S(O)_2R_{11}$, $–S(O)NR_{11}R_{12}$, $–S(O)R_{10}$, $–NR_{10}S(O)NR_{11}R_{12}$, $–NR_{10}S(O)R_{11}$, $–C(O)R_{10}$, $–CO_2R_{10}$, 6-10 membered aryl, and 5-10 membered heteroaryl, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, 4-8 membered cycloalkenyl, C_{2-6} alkynyl, 3-8 membered cycloalkyl, 3-14 membered heterocyclyl, 6-10 membered aryl,

and 5-10 membered heteroaryl is optionally substituted with –OH, C_{1-6} alkyl, 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 an optionally substituted 3-14 membered fused ring;

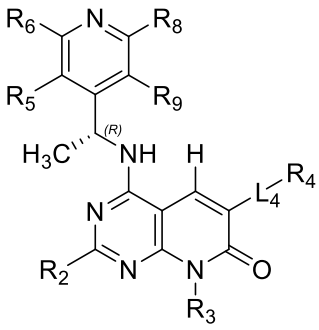
R_{10}, R_{11}, and R_{12} are at each occurrence independently selected from H, D, C_{1-6} alkyl, C_{2-6} alkenyl, 4-8 membered cycloalkenyl, C_{2-6} alkynyl, 3-8 membered cycloalkyl, 3-14 membered heterocyclyl, –OR_{13}, –SR_{13}, halogen, –$NR_{13}R_{14}$, –NO_2, and –CN; and

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.

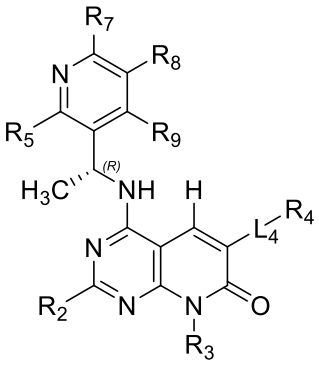
[0016] Another example~~aspect~~ of the present disclosure relates to compounds of Formula (IV-a), (IV-b), or (IV-c),



(IV-a)



(IV-b)



(IV-c)

or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein R_2, R_3, L_4, 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}, –

$S(O)_2NR_{11}R_{12}$, $–S(O)_2R_{10}$, $–NR_{10}S(O)_2NR_{11}R_{12}$, $–NR_{10}S(O)_2R_{11}$, $–S(O)NR_{11}R_{12}$, $–S(O)R_{10}$, $–NR_{10}S(O)NR_{11}R_{12}$, $–NR_{10}S(O)R_{11}$, $–C(O)R_{10}$, $–CO_2R_{10}$, 6-10 membered aryl, and 5-10 membered heteroaryl, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, 4-8 membered cycloalkenyl, C_{2-6} alkynyl, 3-8 membered cycloalkyl, 3-14 membered heterocyclyl, 6-10 membered aryl, and 5-10 membered heteroaryl is optionally substituted with –OH, C_{1-6} alkyl, 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 an optionally substituted 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.

[0017] One example~~aspect~~ of the present disclosure relates to a method of inhibiting SOS1 in a subject in need thereof, comprising administering to the subject a SOS1 inhibitor of the present ~~invention~~disclosure, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof.

[0018] Another example~~aspect~~ of the present disclosure relates to methods of treating or preventing a disease that is effected by inhibition of the interaction of SOS1 and a RAS-family protein and/or RAC1 in a subject in need thereof, comprising administering to the subject an effective amount of a compound of any one of Formula (I)-(IV), and pharmaceutically acceptable salts, prodrugs, solvates, hydrates, tautomers, and isomers thereof.

[0019] Another example~~aspect~~ of the present disclosure relates to methods of treating or preventing cancer in a subject in need thereof, comprising administering to the subject an

effective amount of a compound of any one of Formula (I)-(IV), and pharmaceutically acceptable salts, prodrugs, solvates, hydrates, tautomers, and isomers thereof.

[0020] Another exampleaspect of the present disclosure relates to methods of inhibiting SOS1. The method comprises administering to a patient in need thereof, an effective amount of a compound of any one of Formula (I)-(IV), and pharmaceutically acceptable salts, prodrugs, solvates, hydrates, tautomers, and isomers thereof.

[0021] Another exampleaspect of the present disclosure is directed to pharmaceutical compositions comprising a compound of any one of Formula (I)-(IV), and pharmaceutically acceptable salts, prodrugs, solvates, hydrates, tautomers, and isomers thereof, and a pharmaceutically acceptable carrier. The pharmaceutically acceptable carrier can further comprise an excipient, diluent, or surfactant. The pharmaceutical composition can be effective for treating or preventing a disease associated with SOS1 modulation in a subject in need thereof. The pharmaceutical composition can be effective for treating or preventing a cancer in a subject in need thereof.

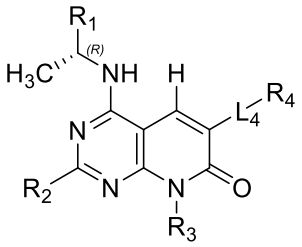
[0022] Another exampleaspect of the present disclosure relates to a compound of any one of Formula (I)-(IV), and pharmaceutically acceptable salts, prodrugs, solvates, hydrates, tautomers, and isomers thereof, for use in treating or preventing a disease associated with SOS1 modulation. Another exampleaspect of the present disclosure relates to a compound of any one of Formula (I)-(IV), and pharmaceutically acceptable salts, prodrugs, solvates, hydrates, tautomers, and isomers thereof, for use in treating or preventing a disease cancer.

[0023] Another exampleaspect of the present disclosure relates to the use of a compound of any one of Formula (I)-(IV), and pharmaceutically acceptable salts, prodrugs, solvates, hydrates, tautomers, and isomers thereof, in the manufacture of a medicament for treating or preventing a disease associated with SOS1 modulation. Another exampleaspect of the present disclosure relates to the use of a compound of any one of Formula (I)-(IV) and pharmaceutically acceptable salts, prodrugs, solvates, hydrates, tautomers, and isomers thereof, in the manufacture of a medicament for treating or preventing cancer.

[0024] The present disclosure also provides compounds that are useful in inhibiting SOS1.

We Claim:

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



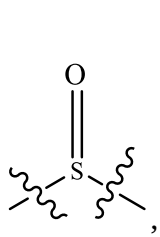
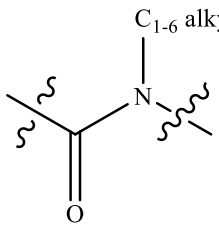
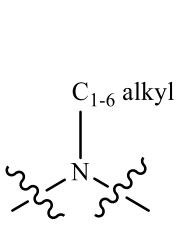
(I)

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

R_1 is selected from the group consisting of optionally substituted 3-6 membered cycloalkyl, optionally substituted 3-6 membered heterocyclyl, optionally substituted 6-membered aryl, and optionally substituted 5-6 membered heteroaryl;

R_2 is selected from the group consisting of H, C_{1-6} alkyl, halogen, -NHR_{2a}, –OR_{2a}, cyclopropyl, and –CN; wherein C_{1-6} alkyl is optionally substituted with halogen, -NHR_{2a}, –OR_{2a}, or 5-6 membered heterocyclyl, and further wherein R_{2a} is selected from the group consisting of H, C_{1-6} alkyl, 3-6 membered heterocyclyl, and C_{1-6} haloalkyl;

R_3 is selected from the group consisting of H, C_{1-3} alkyl, –OR_{3a}, cyclopropyl, and 3-6 membered heterocyclyl, wherein each of C_{1-3} alkyl, cyclopropyl, and 3-6 membered heterocyclyl is optionally substituted with R_{3a}, and further wherein R_{3a} is selected from the group consisting of C_{1-3} alkyl, halogen, –OH, or –CN;

L_4 is selected from the group consisting of bond, –C(O)–, –C(O)O–, –C(O)NH$(CH_2)_o$–, –NH–, –S–, –S(O)$_2$–, , , , –$(CH_2)_p$–, and –O–; wherein o is 0, 1, or 2; and wherein p is a number from 1 to 6; and

R_4 is selected from the group consisting of H, 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; 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 is optionally substituted with C_{1-6} alkyl, $–R_{4a}$, $–OR_{4a}$, $–O–C_{1-6}$ alkyl$–R_{4a}$, =O, halogen, $–C(O)R_{4a}$, $–C(OO)R_{4a}$, $–C(O)NR_{4b}R_{4c}$, $–NR_{4b}C(O)R_{4c}$, –CN, $=NR_{4a}$, $–NR_{4b}R_{4c}$, $–SO_2R_{4a}$, 3-6 membered cycloalkyl optionally substituted with R_{4a}, 3-7 membered heterocyclyl optionally substituted with R_{4a}, 6-10 membered aryl optionally substituted with R_{4a},, or 5-10 membered heteroaryl optionally substituted with R_{4a},;

wherein R_{4a} is H, C_{1-6} alkyl, C_{1-6} haloalkyl, $–C(O)R_{4b}$, $–C(O)NR_{4b}R_{4c}$, =O, 3-6 membered cycloalkyl, 6-10 membered aryl optionally substituted with $–OR_{4b}$, –CN, =N-3-6 membered cycloalkyl, 3-7 membered heterocyclyl, $–(CH_2)_rOCH_3$, or $–(CH_2)_rOH$, wherein r is 1, 2, or 3;

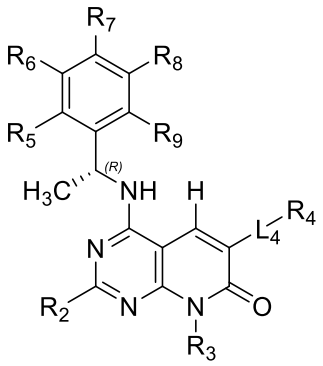
wherein each R_{4b} is independently H, C_{1-6} alkyl; and

wherein each R_{4c} is independently H or C_{1-6} alkyl.

2. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, hydrate, ~~isomer, prodrug, or~~ tautomer, or stereoisomer thereof, wherein R_1 is optionally substituted 6-membered aryl.

3. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, hydrate, ~~isomer, prodrug, or~~ tautomer, or stereoisomer thereof, wherein R_1 is optionally substituted 5-6 membered heteroaryl.

4. The compound of claim 1, having the structure of Formula (II),



(II)

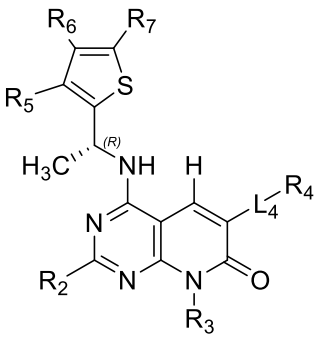
or a pharmaceutically acceptable salt, solvate, hydrate, ~~isomer, prodrug, or~~ tautomer, or stereoisomer thereof, wherein R_2, R_3, L_4, and R_4 are as defined in claim 1;

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, $–NR_{11}R_{12}$, $–SR_{10}$, $–S(O)_2NR_{11}R_{12}$, $–S(O)_2R_{10}$, $–NR_{10}S(O)_2NR_{11}R_{12}$, $–NR_{10}S(O)_2R_{11}$, $–S(O)NR_{11}R_{12}$, $–S(O)R_{10}$, $–NR_{10}S(O)NR_{11}R_{12}$, $–NR_{10}S(O)R_{11}$, $–C(O)R_{10}$, $–CO_2R_{10}$, 6-10 membered aryl, and 5-10 membered heteroaryl, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, 4-8 membered cycloalkenyl, C_{2-6} alkynyl, 3-8 membered cycloalkyl, 3-14 membered heterocyclyl, 6-10 membered aryl, and 5-10 membered heteroaryl is optionally substituted with –OH, C_{1-6} alkyl optionally substituted with $-R_{10}$, 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 optionally substituted with R_{10}, 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 an optionally substituted 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.

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



(III)

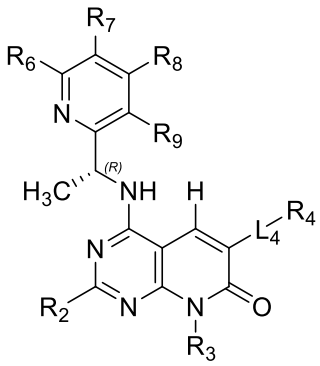
or a pharmaceutically acceptable salt, solvate, hydrate, ~~isomer, prodrug, or~~ tautomer, or stereoisomer thereof, wherein R_2, R_3, L_4, and R_4 are as defined in claim 1;

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, $–NR_{11}R_{12}$, $–SR_{10}$, $–S(O)_2NR_{11}R_{12}$, $–S(O)_2R_{10}$, $–NR_{10}S(O)_2NR_{11}R_{12}$, $–NR_{10}S(O)_2R_{11}$, $–S(O)NR_{11}R_{12}$, $–S(O)R_{10}$, $–NR_{10}S(O)NR_{11}R_{12}$, $–NR_{10}S(O)R_{11}$, $–C(O)R_{10}$, $–CO_2R_{10}$, 6-10 membered aryl, and 5-10 membered heteroaryl, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, 4-8 membered cycloalkenyl, C_{2-6} alkynyl, 3-8 membered cycloalkyl, 3-14 membered heterocyclyl, 6-10 membered aryl, and 5-10 membered heteroaryl is optionally substituted with –OH, C_{1-6} alkyl optionally substituted with $-R_{10}$, 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 optionally substituted with R_{10}, 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 an optionally substituted 3-14 membered fused ring;

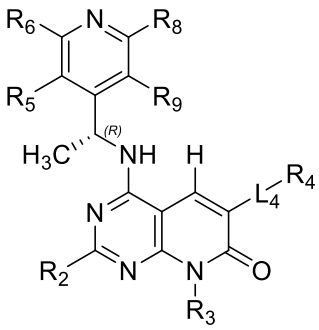
R_{10}, R_{11}, and R_{12} are at each occurrence independently selected from H, D, C_{1-6} alkyl, C_{2-6} alkenyl, 4-8 membered cycloalkenyl, C_{2-6} alkynyl, 3-8 membered cycloalkyl, 3-14 membered heterocyclyl, $–OR_{13}$, $–SR_{13}$, halogen, $–NR_{13}R_{14}$, $–NO_2$, and –CN; and

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.

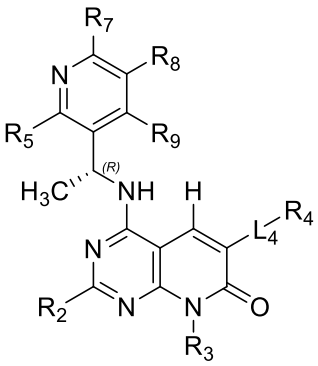
6. The compound of claim 1, having the structure of Formula (IV-a), (IV-b), or (IV-c),



(IV-a)



(IV-b)



(IV-c)

or a pharmaceutically acceptable salt, solvate, hydrate, ~~isomer, prodrug, or~~ tautomer, or stereoisomer thereof, wherein R_2, R_3, L_4, 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, $–NR_{11}R_{12}$, $–SR_{10}$, $–S(O)_2NR_{11}R_{12}$, $–S(O)_2R_{10}$, $–NR_{10}S(O)_2NR_{11}R_{12}$, $–NR_{10}S(O)_2R_{11}$, $–S(O)NR_{11}R_{12}$, $–S(O)R_{10}$, $–NR_{10}S(O)NR_{11}R_{12}$, $–NR_{10}S(O)R_{11}$, $–C(O)R_{10}$, $–CO_2R_{10}$, 6-10 membered aryl, and 5-10 membered heteroaryl, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, 4-8 membered cycloalkenyl, C_{2-6} alkynyl, 3-8 membered cycloalkyl, 3-14 membered heterocyclyl, 6-10 membered aryl, and 5-10 membered heteroaryl is optionally substituted with –OH, C_{1-6} alkyl optionally substituted with $-R_{10}$, 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 optionally substituted with R_{10}, 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 an optionally substituted 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.

~~7. The compound of any one of claims 4-6, or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein one to three of R_5, R_6, R_7, R_8, and R_9 is C_{1-6} alkyl substituted with halogen.~~

~~8. The compound of any one of claims 4-6, or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein one to three of R_5, R_6, R_7, R_8, and R_9 is C_{1-6} alkyl substituted with halogen and –OH.~~

~~9. The compound of any one of claims 4-6, or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein one to three of R_5, R_6, R_7, R_8, and R_9 is halogen, and one to three of R_5, R_6, R_7, R_8, and R_9 is C_{1-6} alkyl substituted with halogen.~~

~~10. The compound of any one of claims 4-6, or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein one to three of R_5, R_6, R_7, R_8, and R_9 is $–NH_2$.~~

~~11. The compound of any one of claims 4-6, or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein one of R_5, R_6, R_7, R_8, and R_9 is $–NH_2$; and one of R_5, R_6, R_7, R_8, and R_9 is C_{1-6} alkyl substituted with halogen.~~

~~12~~7. The compound of any one of claims 4-6, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer~~, prodrug, or tautomer~~ thereof, wherein any two adjacent R^5, R^6, R^7, R^8, and R^9 forms a 3-14 membered fused ring, wherein the fused ring is substituted with halogen.

8~~13~~. The compound of any one of claims 1-7~~12~~, or a pharmaceutically acceptable salt, solvate, hydrate, ~~isomer, prodrug, or~~ tautomer, or stereoisomer thereof, wherein R_2 is H.

9~~14~~. The compound of any one of claims 1-7~~12~~, or a pharmaceutically acceptable salt, solvate, hydrate, ~~isomer, prodrug, or~~ tautomer, or stereoisomer thereof, wherein R_2 is C_{1-6} alkyl.

~~15. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein R_2 is C_{1-6} alkyl substituted with 5-6 membered heterocyclyl.~~

~~16. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein R_2 is C_{1-6} alkyl substituted with -NHR_{2a}, wherein R_{2a} is C_{1-6} alkyl or 3-6 membered heterocyclyl.~~

~~17. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein R_2 is C_{1-6} alkyl substituted with -OR_{2a}, wherein R_{2a} is C_{1-6} alkyl.~~

~~18. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein R_2 is -NHR_{2a}, wherein R_{2a} is C_{1-6} alkyl.~~

~~19. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein R_2 is -OR_{2a}, wherein R_{2a} is C_{1-6} alkyl.~~

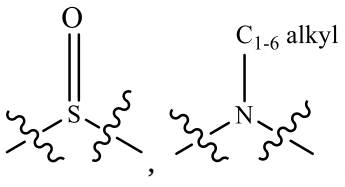
~~20~~10. The compound of any one of claims 1-~~1~~9, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer~~, prodrug, or tautomer~~ thereof, wherein R_3 is C_{1-3} alkyl.

~~21. The compound of any one of claims 1-19, or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein R_3 is C_{1-3} alkyl substituted with -OH.~~

~~22~~11. The compound of any one of claims 1-~~1~~9, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer~~, prodrug, or tautomer~~ thereof, wherein R_3 is H~~.~~

~~23. The compound of any one of claims 1-19, or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein R_3 is,~~ cyclopropyl~~.~~

~~24. The compound of any one of claims 1-19, or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein R_3 is,~~ or 3-6 membered heterocyclyl.

~~25~~12. The compound of any one of claims 1-~~24~~11, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer~~, prodrug, or tautomer~~ thereof, wherein L_4 is selected from the group consisting of bond, –C(O)–, –C(O)O–, –C(O)NH$(CH_2)_o$–,–NH–, –S–, –S(O)$_2$–, 

, –$(CH_2)_p$–, and –O–; wherein o is 0, 1, or 2; and wherein p is a number from 1 to 6.

13~~26~~. The compound of any one of claims 1-11~~24~~, or a pharmaceutically acceptable salt, solvate, hydrate, ~~isomer, prodrug, or~~ tautomer, or stereoisomer thereof, wherein L_4 is a bond.

~~27. The compound of any one of claims 1-24, or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein L_4 is –C(O)–.~~

~~28. The compound of any one of claims 1-24, or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein L_4 is –$(CH_2)_p$–.~~

~~29~~14. The compound of any one of claims 1-~~28~~13, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer~~, prodrug, or tautomer~~ thereof, wherein R_4 is selected from the group consisting of H, 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; 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 is optionally substituted with C_{1-6} alkyl –OR_{4a}, =O, halogen, –C(O)R_{4a}, –C(OO)R_{4a}, –C(O)N$R_{4b}R_{4c}$, –CN, –N$R_{4b}R_{4c}$,3-6 membered cycloalkyl, 3-7 membered heterocyclyl, 6-10 membered aryl, or 5-10 membered heteroaryl.

~~30. The compound of any one of claims 1-28, or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein R_4 is 3-14 membered heterocyclyl.~~

~~31. The compound of any one of claims 1-28, or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein R_4 is 3-14 membered heterocyclyl substituted with 3-6 membered heterocyclyl.~~

~~32. The compound of any one of claims 1-28, or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein R_4 is 3-14 membered heterocyclyl substituted with C_{1-6} alkyl.~~

~~33. The compound of any one of claims 1-28, or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein R_4 is 3-14 membered heterocyclyl substituted with 3-6 membered cycloalkyl.~~

~~34. The compound of any one of claims 1-28, or a pharmaceutically acceptable salt, solvate, isomer, prodrug, or tautomer thereof, wherein R_4 is 3-14 membered heterocyclyl substituted with =O.~~

~~35~~15. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, selected from the group consisting of compounds of Collection 1, Collection 2, Collection 3, Collection 4, or Collection 5.

~~36. 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.~~

~~37. 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.~~

~~38. 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 4.~~

~~39. 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 5.~~

~~40~~16. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, selected from the group consisting of compounds of Table A.

17~~41~~. A pharmaceutical composition comprising a compound of any one of claims 1-16~~40~~, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, and a pharmaceutically acceptable carrier.

~~42. A method of inhibiting SOS1 in a subject, comprising administering to the subject a compound of any one of claims 1-40, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof.~~

~~43. 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 of any one of claims 1-40, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof.~~

~~44. 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 of any of claims 1-40, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof.~~

18. A compound of any of claims 1-16, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, for use in therapy.

~~45~~19. Use of a compound of any of claims 1-16, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, in the manufacture of a medicament for~~A method of~~ treating or preventing cancer in a subject in need thereof~~, comprising administering to the subject an effective amount of a compound of any of claims 1-40, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or isomer thereof~~.

~~46. The method of claim 44 or 45, 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.~~

~~47. The method of claim 44, wherein the disease is a RASopathy.~~

~~48. The method of claim 47, 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.~~

~~49. The method of claim 45 or 46, wherein the cancer comprises a Ras^{MUT} or an $NF1^{LOF}$ mutation.~~