R^3 is independently in each occurrence selected from substituted or unsubstituted C_{1-8}alkyl, C_{3-8}cycloalkyl, C_{4-8}heterocycloalkyl, C_{6-10}aryl and C_{5-10}heteroaryl;

X^1 is halo or an electron-withdrawing group;

X^2 is selected from H, halo, and an electron-withdrawing group;

X^3 and X^4 are each selected from H, halo, an electron-withdrawing group, C_{1-3}alkyl, C_{3-4}cycloalkyl, and OC_{1-3}alkyl ;

or a pharmaceutically acceptable salt or solvate thereof.

The compounds of Formula I are also defined according to any of the examples~~embodiments~~, alone or in combination, and examples described throughout the present document.

In another aspect, there is provided a pharmaceutical composition comprising a compound as defined above, together with a pharmaceutically acceptable carrier, diluent or excipient.

According to another ~~aspect~~example, the present technology relates to a pharmaceutical composition for a use as defined in any one of the aforementioned ~~embodiments~~examples, the composition comprising a compound as herein defined together with a pharmaceutically acceptable carrier, diluent or excipient.

In a further example~~aspect~~, the present technology relates to the use of a compound as herein defined for the treatment of a disease or disorder selected from a proliferative disease or disorder, a developmental anomaly caused by dysregulation of the RAS-ERK signaling cascade (RASopathies), or an inflammatory disease or an immune system disorder.

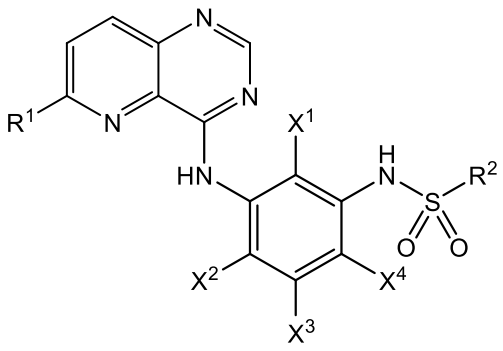
In another aspect, there is provided the use of a compound as defined above in the manufacture of a medicament for the treatment of a disease or disorder selected from a proliferative disease or disorder, a developmental anomaly caused by dysregulation of the RAS-ERK signaling cascade (RASopathies), or an inflammatory disease or an immune system disorder.

The present technology also further relates to a method for the treatment of a disease or disorder selected from a proliferative disease or disorder, a developmental anomaly caused by dysregulation of the RAS-ERK signaling cascade (RASopathies), or an inflammatory disease or an immune system disorder, comprising administering a compound as herein defined to a subject in need thereof. A method for inhibiting abnormal proliferation of cells, comprising contacting the cells with a compound as defined herein is also contemplated.

In one ~~embodiment~~ example of the above uses and methods, the disease or disorder is selected from a neoplasm and a developmental anomaly, for instance, a disease or disorder associated with a RAF gene mutation (e.g. ARAF, BRAF, or CRAF), a disease or disorder associated with a RAS gene mutation (e.g. KRAS), or a disease or disorder associated with both a RAF gene mutation and a RAS gene mutation. In one ~~embodiment~~example, the disease or disorder is associated with a receptor tyrosine kinase mutation or amplification (e.g. EGFR, HER2) or a mutation in a regulator of RAS downstream of the receptor (e.g. SOS1 gain of function, NF1 loss of function).

CLAIMS

1. A compound of Formula I:



Formula I

wherein:

R^1 is selected from substituted or unsubstituted OR^3, SR^3, NH_2, NHR^3, $N(R^3)_2$, C_{3-8}cycloalkyl, C_{4-8}heterocycloalkyl, C_{6-10}aryl and C_{5-10}heteroaryl, for example, selected from substituted or unsubstituted C_{6-10}aryl and C_{5-10}heteroaryl;

R^2 is selected from substituted C_6aryl or C_{5-10}heteroaryl, substituted or unsubstituted C_{4-8}heterocycloalkyl, and $N(R^3)_2$;

R^3 is independently in each occurrence selected from substituted or unsubstituted C_{1-8}alkyl, C_{3-8}cycloalkyl, C_{4-8}heterocycloalkyl, C_{6-10}aryl and C_{5-10}heteroaryl;

X^1 is halo or an electron-withdrawing group;

X^2 is selected from H, halo, and an electron-withdrawing group;

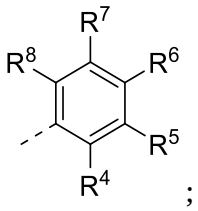
X^3 and X^4 are each selected from H, halo, an electron-withdrawing group, C_{1-3}alkyl, C_{3-4}cycloalkyl, and OC_{1-3}alkyl;

or a pharmaceutically acceptable salt or solvate thereof.

~~2. The compound of claim 1, wherein R^2 is a substituted C_6aryl or C_{5-10}heteroaryl.~~

~~3. The compound of claim 2, wherein R^2 is a C_6aryl substituted with at least one group selected from F, Cl, Br, CN, NO_2, and a substituted or unsubstituted C_{1-3}alkyl, C_{3-4}cycloalkyl or OC_{1-3}alkyl.~~

~~4.~~2. The compound of claim 1~~2~~, wherein R^2 is a group of the formula:



;

wherein:

R^4 is selected from H, F, Cl, Br, CN, and a substituted or unsubstituted C_{1-3}alkyl, C_{3-4}cycloalkyl or OC_{1-3}alkyl;

R^5 is selected from H, F, Cl, CN, and a substituted or unsubstituted C_{1-3}alkyl, C_{3-4}cycloalkyl or OC_{1-3}alkyl;

R^6 is selected from H, F, Cl, Br, NO_2, NH_2, and a substituted or unsubstituted C_{1-3}alkyl, C_{3-4}cycloalkyl or OC_{1-3}alkyl;

R^7 is selected from H, F, Cl, and a substituted or unsubstituted C_{1-3}alkyl;

R^8 is selected from H, F, and a substituted or unsubstituted C_{1-3}alkyl;

or R^4 and R^5 or R^5 and R^6 are taken together with their adjacent carbon atoms to form a substituted or unsubstituted carbocycle or heterocycle provided that the heterocycle is not a benzoxazolinone; and

(---) represents a bond;

wherein when R^4 is H or F, then at least one of R^5, R^6, R^7 or R^8 is other than H or F; and

wherein when R^5 is CN, then at least one of R^4, R^6, R^7 or R^8 is other than H.

~~5. The compound of claim 4, wherein R^4 is selected from H, F, Cl, Br, Me, Et, CN, CHF_2, and CF_3.~~

~~6. The compound of claim 4 or 5, wherein R^5 is selected from H, F, Me, CF_3, CN, and Cl.~~

~~7. The compound of any one of claims 4 to 6, wherein R^6 is selected from H, F, Cl, Br, and a substituted or unsubstituted C_{1-3}alkyl, C_{3-4}cycloalkyl or OC_{1-3}alkyl.~~

~~8. The compound of any one of claims 4 to 7, wherein R^6 is selected from H, F, Cl, Me, Et, and OMe.~~

~~9. The compound of any one of claims 4 to 8, wherein R^7 is selected from H, Me, F, and Cl.~~

~~10. The compound of any one of claims 4 to 9, wherein R^8 is selected from H, Me and F.~~

~~11.~~3. The compound of claim ~~4~~2, wherein:

R^4 is selected from Cl and a substituted or unsubstituted $C_{1\text{-}3}$alkyl;

R^5 is selected from H, F, Cl, and a substituted or unsubstituted $C_{1\text{-}3}$alkyl;

R^6 is selected from H, F, Cl, a substituted or unsubstituted $C_{1\text{-}3}$alkyl, and a substituted or unsubstituted $OC_{1\text{-}3}$alkyl; and

R^7 and R^8 are each H.

~~12. The compound of claim 11, wherein R^4 is selected from Cl and CH_3.~~

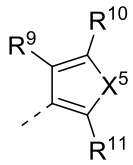
~~13. The compound of claim 11 or 12, wherein R^5 is selected from F, Cl and CH_3.~~

~~14. The compound of any one of claims 11 to 13, wherein R^6 is H or F.~~

~~15. The compound of any one of claims 11 to 13, wherein R^6 is Cl or a substituted or unsubstituted $C_{1\text{-}3}$alkyl or substituted or unsubstituted $OC_{1\text{-}3}$alkyl.~~

~~16. The compound of claim 15, wherein R^6 is CH_3 or OCH_3.~~

~~17.~~4. The compound of claim ~~2~~1, wherein R^2 is a group of the formula:



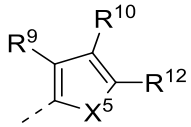
wherein:

X^5 is selected from NH, $NC_{1\text{-}3}$alkyl, $NC_{3\text{-}4}$cycloalkyl, O and S;

R^9, R^{10}, R^{11} are each independently selected from H, F, Cl, CN, and a substituted or unsubstituted $C_{1\text{-}3}$alkyl, $C_{3\text{-}4}$cycloalkyl, $C(O)OC_{1\text{-}3}$alkyl or $OC_{1\text{-}3}$alkyl, provided that one of R^9 and R^{11} is H and the other is different from H; and

(---) represents a bond.

~~18.~~5. The compound of claim ~~2~~1, wherein R^2 is a group of the formula:



wherein:

X^5 is selected from NH, NC_{1-3}alkyl, NC_{3-4}cycloalkyl, O and S;

R^9 is selected from F, Cl, CN, and a substituted or unsubstituted C_{1-3}alkyl, C_{3-4}cycloalkyl, $C(O)OC_{1-3}$alkyl or OC_{1-3}alkyl;

R^{10} and R^{12} are each independently selected from H, F, Cl, CN, and a substituted or unsubstituted C_{1-3}alkyl, C_{3-4}cycloalkyl, $C(O)OC_{1-3}$alkyl or OC_{1-3}alkyl; and

(---) represents a bond.

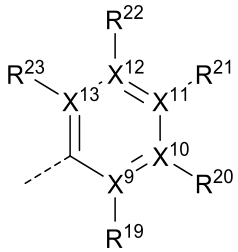
~~19. The compound of claim 17 or 18, wherein R^9 and R^{10} are each independently selected from F, Cl, CN, and a substituted or unsubstituted C_{1-3}alkyl, C_{3-4}cycloalkyl, $C(O)OC_{1-3}$alkyl or OC_{1-3}alkyl.~~

~~20. The compound of claim 19, wherein R^9 and R^{10} are each independently selected from Cl and a substituted or unsubstituted C_{1-3}alkyl.~~

~~21. The compound of claim 19, wherein R^9 and R^{10} are both Cl.~~

~~22. The compound of any one of claims 17 to 21, wherein X^5 is O or S, preferably S.~~

~~23.~~6. The compound of claim ~~2~~1, wherein R^2 is a group of the formula:



wherein:

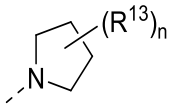
X^9, X^{10}, X^{11}, X^{12}, and X^{13} are independently selected from N and C, wherein at least one and at most two of X^9, X^{10}, X^{11}, X^{12}, and X^{13} are N; and

R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are selected from H, F, Cl, Br, CN, NO_2, NH_2, and a substituted or unsubstituted $C_{1\text{-}3}$alkyl, $C_{3\text{-}4}$cycloalkyl or $OC_{1\text{-}3}$alkyl, or are absent when their attached X^9, X^{10}, X^{11}, X^{12}, or X^{13} is N;

wherein at least one of X^9 and X^{13} is not N; and

wherein when one of X^9 and X^{13} is N, then the other is not N or CH.

~~24.~~7. The compound of claim 1, wherein R^2 is a group of the formula:



wherein:

R^{13} is independently in each occurrence selected from F, Cl, and a substituted or unsubstituted $C_{1\text{-}3}$alkyl, $C_{3\text{-}4}$cycloalkyl, or $C_{1\text{-}3}$alkoxy;

n is an integer selected from 0 to 8; or

n is between 2 and 8 and two R^{13} are taken together with their adjacent carbon atoms to form a $C_{3\text{-}4}$cycloalkyl;

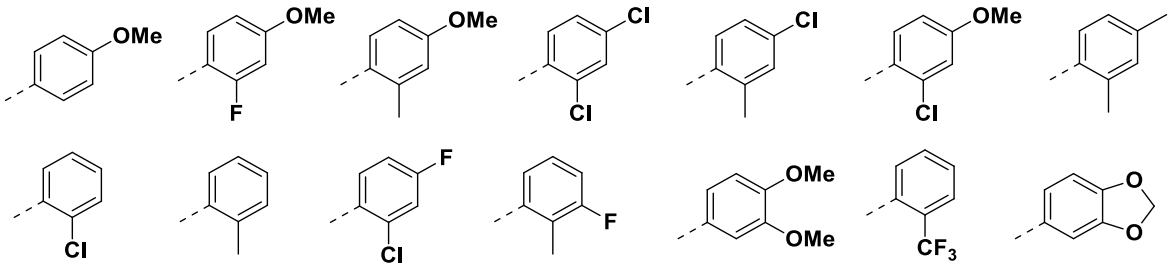
(---) represents a bond.

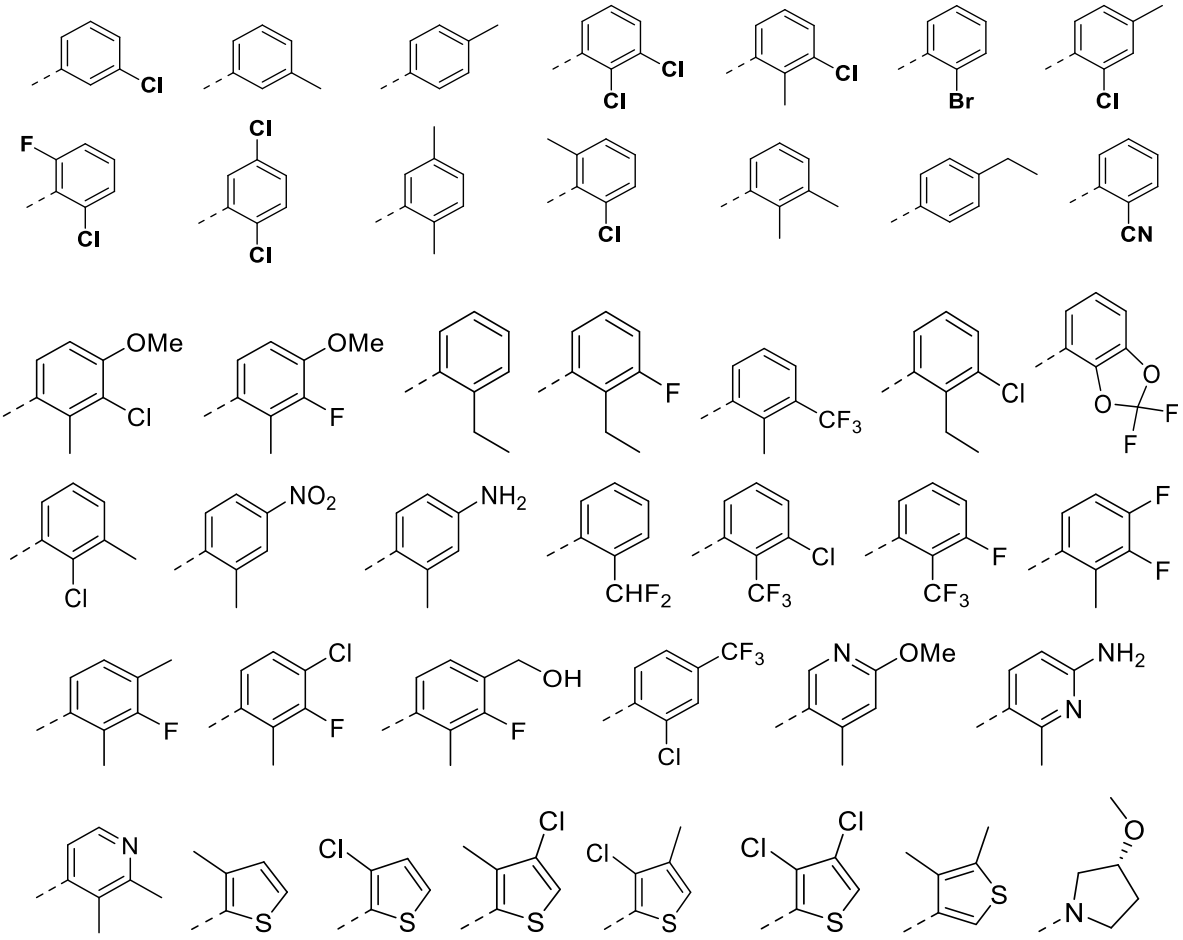
~~25. The compound of claim 24, wherein R^{13} is methoxy and n is 1.~~

~~26. The compound of claim 1, wherein R^2 is $N(R^3)_2$.~~

~~27. The compound of claim 26, wherein R^3 is selected from substituted or unsubstituted $C_{1\text{-}8}$alkyl or $C_{3\text{-}8}$cycloalkyl.~~

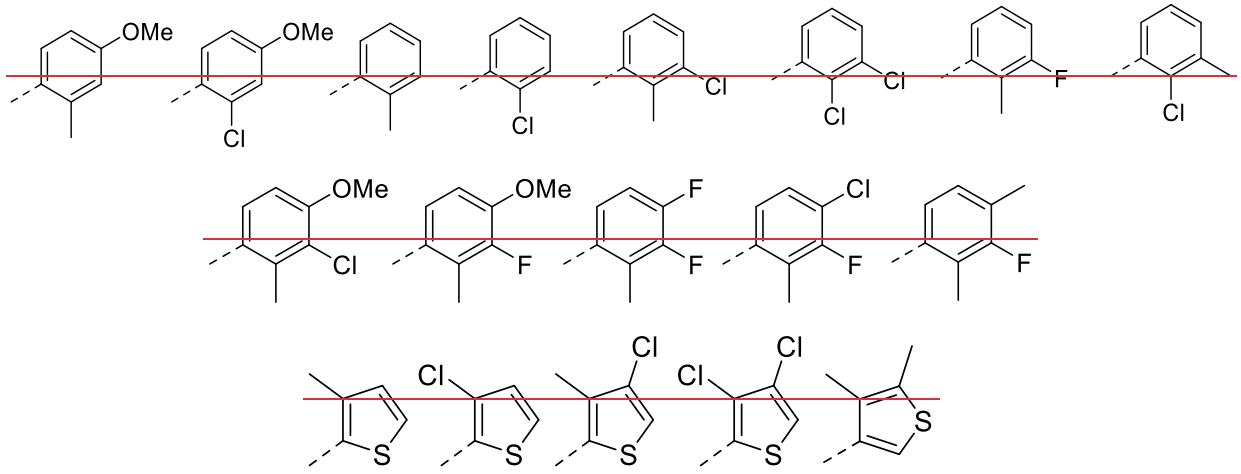
~~28.~~8. The compound of claim 1, wherein R^2 is a group selected from:





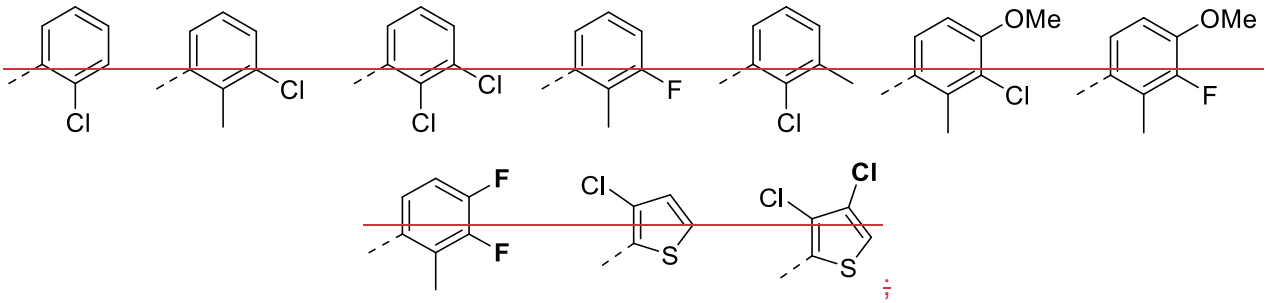
wherein (---) represents a bond.

~~29. The compound of claim 28, wherein R^2 is a group selected from:~~



~~wherein (- - -) represents a bond.~~

~~30. The compound of claim 29, wherein R^2 is a group selected from:~~



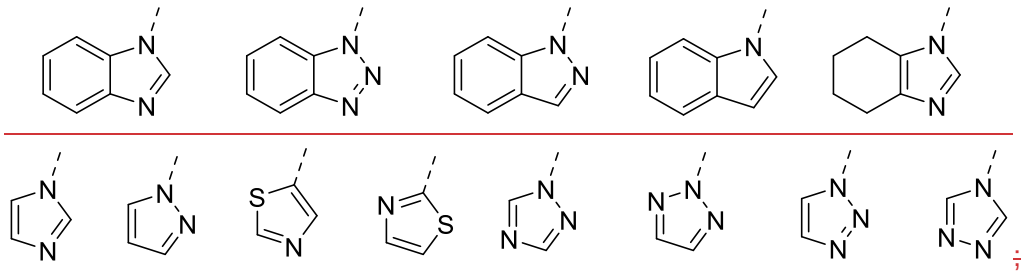
wherein (---) represents a bond.

31. The compound of any one of claims 1 to 30, wherein R^1 is a substituted or unsubstituted C_{5-6}heteroaryl group.

32. The compound of any one of claims 1 to 30, wherein R^1 is a substituted or unsubstituted C_9heteroaryl group.

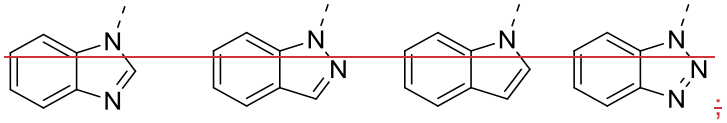
33.9. The compound of any one of claims 1 to 830, wherein R^1 is a substituted or unsubstituted group selected from thienyl, imidazolyl, pyrazolyl, triazolyl, thiazolyl, pyridyl, pyrimidinyl, indolyl, indazolyl, benzimidazolyl, benzotriazolyl, pyrrolopyridinyl (e.g. pyrrolo[3,2-b]pyridinyl or pyrrolo[3,2-c]pyridinyl), pyrazolopyridinyl (e.g. pyrazolo[1,5-a]pyridinyl), purinyl, imidazopyrazinyl (e.g. imidazo[4,5-b]pyrazinyl), and quinolyl (quinolinyl).

34. The compound of any one of claims 1 to 30, wherein R^1 is a substituted or unsubstituted group selected from:



wherein (---) represents a bond.

35. The compound of claim 34, wherein R^1 is a substituted or unsubstituted group selected from:



wherein (---) represents a bond.

~~36. The compound of any one of claims 1 to 35, wherein R^1 is substituted with at least one substituent selected from OH, halo, CN, NO_2, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, OC_{1-6}alkyl, C_{5-10}heteroaryl, C_{3-10}cycloalkyl, C_{4-10}heterocycloalkyl, $C(O)R^{15}$, $C(O)N(R^{14})_2$, SO_2R^{15}, $SO_2N(R^{14})_2$, $N(R^{16})C(O)R^{15}$, $N(R^{16})SO_2R^{15}$, $N(R^{16})C(O)N(R^{14})_2$, $N(R^{16})SO_2N(R^{14})_2$, $N(R^{14})_2$, $P(O)(R^{15})_2$, $CH_2C(O)R^{15}$, $CH_2C(O)N(R^{14})_2$, $CH_2SO_2R^{15}$, $CH_2SO_2N(R^{14})_2$, $CH_2N(R^{16})C(O)R^{15}$, $CH_2N(R^{16})SO_2R^{15}$, $CH_2N(R^{16})C(O)N(R^{14})_2$, $CH_2N(R^{16})SO_2N(R^{14})_2$, and $CH_2N(R^{14})_2$;~~

~~wherein:~~

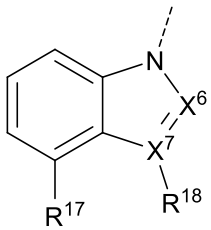
~~R^{14} is independently in each occurrence selected from H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{4-10}heterocycloalkyl, C_6aryl, and C_{5-10}heteroaryl, or two R^{14} are taken together with their adjacent nitrogen atom to form a C_{4-10}heterocycloalkyl group;~~

~~R^{15} is independently in each occurrence selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_6aryl, and C_{5-10}heteroaryl; and~~

~~R^{16} is independently in each occurrence selected from H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_6aryl, and C_{5-10}heteroaryl;~~

~~wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group is optionally further substituted.~~

~~37.~~10. The compound of any one of claims 1 to ~~8~~30, wherein R^1 is a group of the formula:



wherein:

R^{17} is selected from H, OH, halo, CN, NO_2, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, OC_{1-6}alkyl, C_{5-10}heteroaryl, C_{3-10}cycloalkyl, C_{4-10}heterocycloalkyl, $C(O)R^{15}$, $C(O)N(R^{14})_2$, SO_2R^{15}, $SO_2N(R^{14})_2$, $N(R^{16})C(O)R^{15}$, $N(R^{16})SO_2R^{15}$, $N(R^{16})C(O)N(R^{14})_2$, $N(R^{16})SO_2N(R^{14})_2$, $N(R^{14})_2$, $P(O)(R^{15})_2$, $CH_2C(O)R^{15}$, $CH_2C(O)N(R^{14})_2$, $CH_2SO_2R^{15}$, $CH_2SO_2N(R^{14})_2$, $CH_2N(R^{16})C(O)R^{15}$, $CH_2N(R^{16})SO_2R^{15}$, $CH_2N(R^{16})C(O)N(R^{14})_2$, $CH_2N(R^{16})SO_2N(R^{14})_2$, and $CH_2N(R^{14})_2$;

X^6 is N or CH; and

X^7 is N and R^{18} is absent; or

X^7 is C and R^{18} is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, OC_{1-6}alkyl, C_{5-10}heteroaryl, C_{3-10}cycloalkyl, C_{4-10}heterocycloalkyl, $C(O)R^{15}$, $C(O)N(R^{14})_2$, SO_2R^{15}, $SO_2N(R^{14})_2$, $N(R^{16})C(O)R^{15}$, $N(R^{16})SO_2R^{15}$, $N(R^{16})C(O)N(R^{14})_2$, $N(R^{16})SO_2N(R^{14})_2$, $N(R^{14})_2$, $P(O)(R^{15})_2$, $CH_2C(O)R^{15}$, $CH_2C(O)N(R^{14})_2$, $CH_2SO_2R^{15}$, $CH_2SO_2N(R^{14})_2$, $CH_2N(R^{16})C(O)R^{15}$, $CH_2N(R^{16})SO_2R^{15}$, $CH_2N(R^{16})C(O)N(R^{14})_2$, $CH_2N(R^{16})SO_2N(R^{14})_2$, and $CH_2N(R^{14})_2$;

wherein ~~R^{14}, R^{15}, and R^{16} are as defined in claim 32~~;

R^{14} is independently in each occurrence selected from H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{4-10}heterocycloalkyl, C_6aryl, and C_{5-10}heteroaryl, or two R^{14} are taken together with their adjacent nitrogen atom to form a C_{4-10}heterocycloalkyl group;

R^{15} is independently in each occurrence selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_6aryl, and C_{5-10}heteroaryl; and

R^{16} is independently in each occurrence selected from H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_6aryl, and C_{5-10}heteroaryl;

wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group is optionally further substituted; and

wherein (---) represents a bond.

~~38. The compound of claim 37, wherein X^6 is N.~~

~~39. The compound of claim 37, wherein X^6 is CH.~~

~~40.~~11. The compound of ~~any one of~~ claim~~s 37 to 39~~10, wherein X^7 is N, R^{17} is selected from H, OH, CN, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, OC_{1-6}alkyl, C_{5-10}heteroaryl, C_{3-10}cycloalkyl, C_{4-10}heterocycloalkyl, $C(O)R^{15}$, $C(O)N(R^{14})_2$, SO_2R^{15}, $SO_2N(R^{14})_2$, $N(R^{16})C(O)R^{15}$, $N(R^{16})SO_2R^{15}$, $N(R^{16})C(O)N(R^{14})_2$, $N(R^{16})SO_2N(R^{14})_2$, $N(R^{14})_2$, $P(O)(R^{15})_2$, $CH_2C(O)R^{15}$, $CH_2C(O)N(R^{14})_2$, $CH_2SO_2R^{15}$, $CH_2SO_2N(R^{14})_2$, $CH_2N(R^{16})C(O)R^{15}$, $CH_2N(R^{16})SO_2R^{15}$, $CH_2N(R^{16})C(O)N(R^{14})_2$, $CH_2N(R^{16})SO_2N(R^{14})_2$, and $CH_2N(R^{14})_2$, and R^{18} is absent, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, or heteroaryl is optionally further substituted.

41. The compound of claim 40, wherein R^{17} is selected from C_{1-6}alkyl, C_{5-10}heteroaryl, C_{4-10}heterocycloalkyl, $N(R^{14})_2$, $N(R^{16})C(O)R^{15}$, $N(R^{16})SO_2R^{15}$, $C(O)N(R^{14})_2$, and $SO_2N(R^{14})_2$, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, or heteroaryl is optionally further substituted.

42. The compound of claim 40, wherein R^{17} is selected from R^{17} is H, NH_2, and an optionally substituted C_{5-10}heteroaryl or C_{4-10}heterocycloalkyl, preferably an optionally substituted C_{5-10}heteroaryl or C_{4-10}heterocycloalkyl.

43. The compound of any one of claims 37 to 39, wherein R^{17} is an optionally substituted C_{4-10}heterocycloalkyl, wherein said heterocycloalkyl is a mono or bicyclic and include from 1 to 3 heteroatoms, preferably wherein X^7 is N.

44. The compound of claim 43, wherein the heterocycloalkyl is substituted with at least one group selected from F, OH, oxo, CN, C_{1-4}alkyl and OC_{1-4}alkyl, wherein said C_{1-4}alkyl is optionally further substituted (e.g. with F, OH, OC_{1-3}alkyl, etc.).

45. The compound of any one of claims 42 or 44, wherein the heterocycloalkyl is selected from piperidine, piperazine, thiomorpholine and morpholine groups, or a bicyclic structure (bridged or spiro) containing a piperidine, piperazine, thiomorpholine or morpholine ring.

46. The compound of any one of claims 37 to 39, wherein X^7 is C.

47. The compound of claim 46, wherein X^7 is C and R^{18} is selected from C_{1-6}alkyl, C_{5-10}heteroaryl, C_{3-10}cycloalkyl, C_{4-10}heterocycloalkyl, $C(O)R^{15}$, $C(O)N(R^{14})_2$, SO_2R^{15}, $SO_2N(R^{14})_2$, $N(R^{16})C(O)R^{15}$, $N(R^{16})SO_2R^{15}$, $N(R^{16})C(O)N(R^{14})_2$, $N(R^{16})SO_2N(R^{14})_2$, $N(R^{14})_2$, $CH_2C(O)R^{15}$, $CH_2C(O)N(R^{14})_2$, $CH_2SO_2R^{15}$, $CH_2SO_2N(R^{14})_2$, $CH_2N(R^{16})C(O)R^{15}$, $CH_2N(R^{16})SO_2R^{15}$, $CH_2N(R^{16})C(O)N(R^{14})_2$, $CH_2N(R^{16})SO_2N(R^{14})_2$, and $CH_2N(R^{14})_2$, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally further substituted.

48. The compound of claim 47, wherein R^{18} is selected from $C(O)N(R^{14})_2$, SO_2R^{15}, and $SO_2N(R^{14})_2$.

49. The compound of any one of claims 46 to 48, wherein R^{17} is selected from H, OH, C_{1-6}alkyl, $N(R^{14})_2$, and an optionally substituted C_{5-10}heteroaryl.

~~50. The compound of claim 49, wherein R^{17} is selected from H, NH_2, and an optionally substituted C_{5-10}heteroaryl, preferably H or NH_2.~~

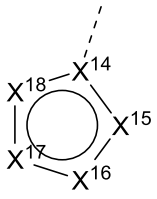
~~51. The compound of any one of claims 38 to 50, wherein R^{14} is independently in each occurrence selected from H, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-10}cycloalkyl, optionally substituted C_{4-10}heterocycloalkyl, and optionally substituted C_{5-6}heteroaryl, or two R^{14} are taken together with their adjacent nitrogen atom to form an optionally substituted C_{4-10}heterocycloalkyl group.~~

~~52. The compound of claim 51, wherein two R^{14} are taken together with their adjacent nitrogen atom to form an optionally substituted C_{4-10}heterocycloalkyl group, wherein said heterocycloalkyl is a mono or bicyclic and include from 1 to 3 heteroatoms.~~

~~53. The compound of claim 52, wherein the heterocycloalkyl is substituted with at least one group selected from F, OH, oxo, CN, C_{1-4}alkyl and OC_{1-4}alkyl, wherein said C_{1-4}alkyl is optionally further substituted (e.g. with F, OH, OC_{1-3}alkyl, etc.).~~

~~54. The compound of any one of claims 51 to 53, wherein the heterocycloalkyl is selected from piperidine, piperazine, thiomorpholine and morpholine groups, or a bicyclic structure (bridged or spiro) containing a piperidine, piperazine, thiomorpholine or morpholine ring.~~

~~55.~~12. The compound of any one of claims 1 to ~~30~~8, wherein R^1 is a group of the formula:



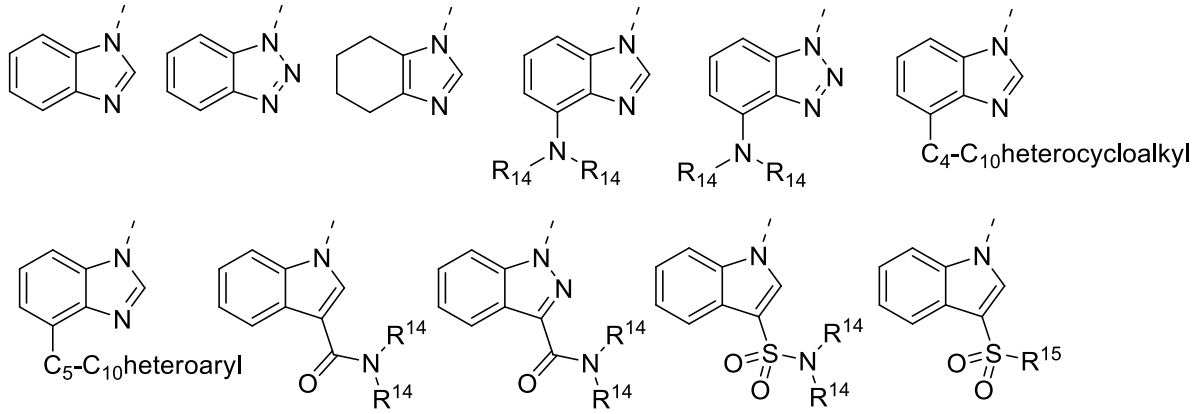
wherein:

X^{14} is selected from C and N;

X^{15}, X^{16}, X^{17}, and X^{18} are independently selected from O, N, S, and CR^{17}, wherein R^{17} is as previously defined;

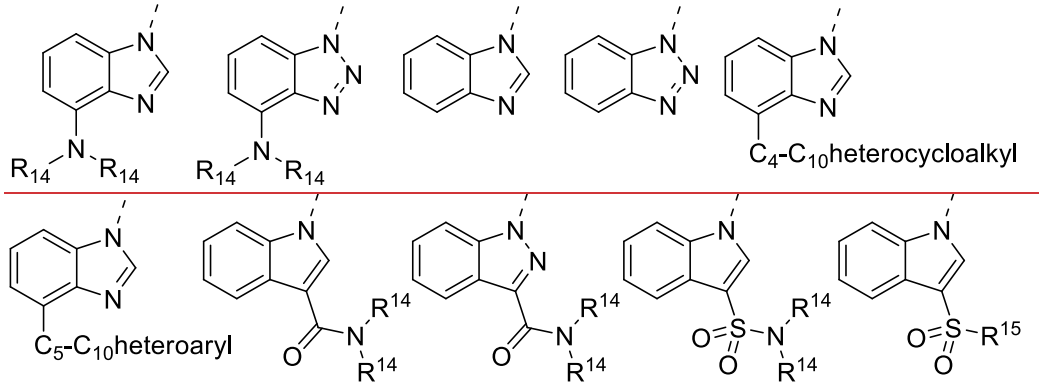
wherein at least one and at most three of X^{14}, X^{15}, X^{16}, X^{17}, and X^{18} are O, N, or S, and two double bonds and present in the cycle in order for aromaticity to be maintained.

~~56.~~13. The compound of any one of claims 1 to ~~30~~8, wherein R^1 is selected from:



wherein R^{14} is as previously defined herein and (---) represents a bond.

~~57. The compound of claim 56, wherein R^1 is selected from:~~



~~wherein R^{14} is as defined herein and (---) represents a bond.~~

~~58. The compound of any one of claims 1 to 30, wherein R^1 is selected from groups A1 to A514.~~

~~59. The compound of any one of claims 1 to 58, wherein X^1 is Cl and X^2 is F.~~

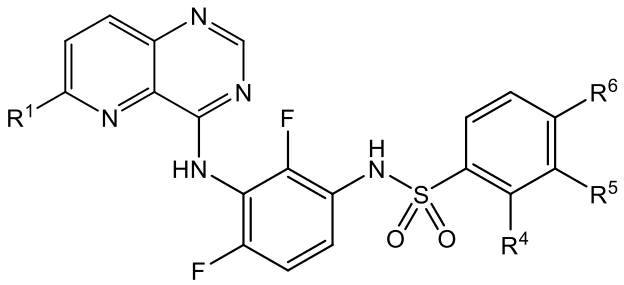
~~60. The compound of any one of claims 1 to 58, wherein X^1 is F and X^2 is H.~~

~~61. The compound of any one of claims 1 to 58, wherein both X^1 and X^2 are F.~~

~~62. The compound of any one of claims 1 to 61, wherein X^3 and X^4 are each H.~~

~~63. The compound of any one of claims 1 to 61, wherein X^3 is F and X^4 is H.~~

~~64.~~14. The compound of claim ~~61~~1, wherein said compound is of Formula II:

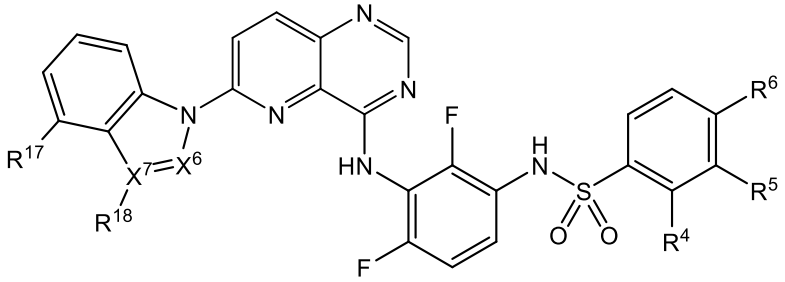


Formula II

wherein R^1, R^4, R^5, and R^6 are each independently as defined herein, preferably R^4 is selected from Cl, Br and Me, R^5 is selected from H, F, Cl or methyl, and R^6 is selected from H, F, Cl, Me and OMe;

or a pharmaceutically acceptable salt or solvate thereof.

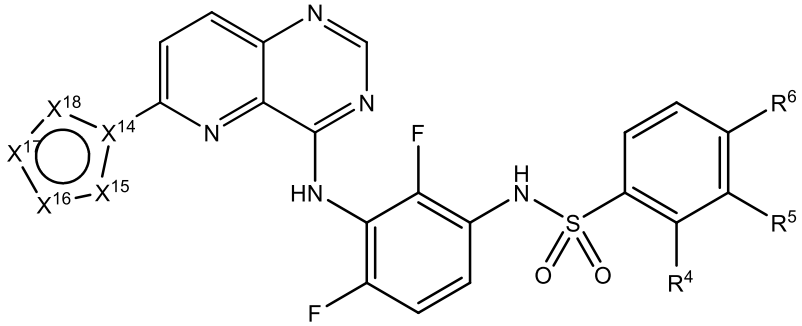
~~65.~~15. The compound of claim ~~64~~14, wherein said compound if a compound of Formula IV:



Formula IV

wherein X^6, X^7, R^4, R^5, R^6, R^{17}, and R^{18} are each independently as previously defined.

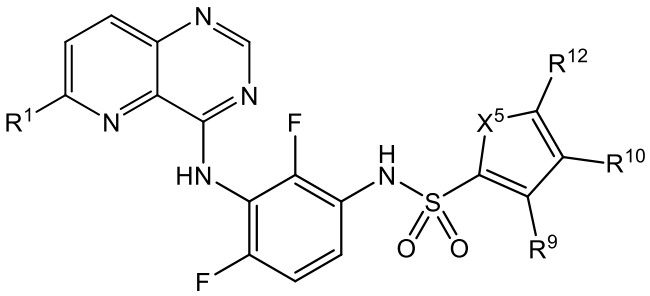
~~66.~~16. The compound of claim ~~64~~14, wherein said compound if a compound of Formula V:



Formula V

wherein R^4, R^5, R^6, X^{14}, X^{15}, X^{16}, X^{17}, and X^{18} are each independently as previously defined.

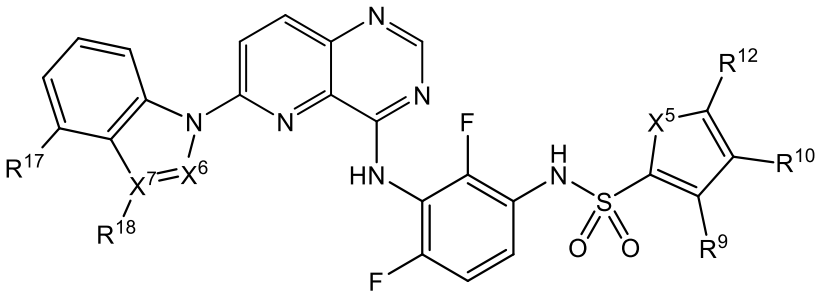
~~67.~~17. The compound of claim ~~61~~1, wherein said compound is of Formula III:



Formula III

wherein R^1, R^9, R^{10}, R^{12}, and X^5 are each independently as previously defined.

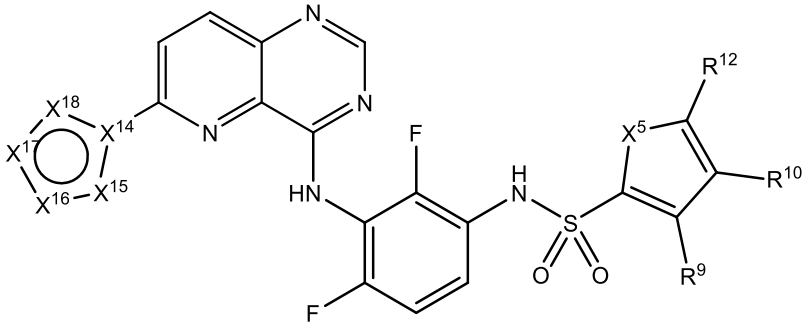
~~68.~~18. The compound of claim ~~67~~17, wherein said compound is of Formula VI:



Formula VI

wherein R^9, R^{10}, R^{12}, R^{17}, R^{18}, X^5, X^6, and X^7, are each independently as previously defined.

~~69.~~19. The compound of claim ~~67~~17, wherein said compound is of Formula VII:



Formula VII

wherein R^9, R^{10}, R^{12}, X^5, X^{14}, X^{15}, X^{16}, X^{17} and X^{18} are each independently as previously defined.

~~70.~~20. The compound of claim 1, wherein said compound is selected from Examples 1 to 691 as defined herein, or a salt and/or solvate thereof.

~~71. The compound of claim 70, wherein said compound is selected from Examples 3, 6, 8, 19, 20-22, 30, 31, 43, 46, 48, 68, 76, 83, 84, 91-93, 99-102, 111, 113-115, 123, 124-128, 131, 139-141, 168, 171, 176, 177, 180, 188-190, 198, 202-206, 240, 244, 247, 248, 250-253, 261, 262, 264-275, 277-280, 282, 284-286, 290, 292, 294-299, 304, 305, 307-310, 312-315, 317-319, 321-323, 325, 328, 331, 333-337, 342, 346, 347, 350, 351, 354, 355, 356, 359, 361, 364-367, 370, 372, 377, 378, 381, 385-389, 395-398, 400, 401, 403, 408-412, 416-419, 421-423, 426-429, 431-433, 435-439, 441-445, 447-453, 454, 456, 458, 461, 462, 464, 466-469, 484, 486, 488, 490, 497, 502, 509, 511, 514, 517, 520, 524, 529, 530, 533, 538-543, 546, 548, 552-554, 556, 557, 560, 561, 562, 568, 569, 571, 572, 574, 575, 578, 580-583, 585, 586, 588-590, 592, 596-600, 602, 604, 605, 608-612, 614-617, 619-621, 623, 625-630, 632, 636, 638, 640, 641, 643-652, 654-660, 665 and 667-691 as defined herein, or a salt and/or solvate thereof.~~

~~72. The compound of claim 70, wherein said compound is selected from Examples 3, 6, 20-22, 43, 46, 48, 68, 76, 84, 91-93, 99-102, 123, 125, 168, 171, 177, 188, 202, 205, 206, 251, 266, 272, 296-299, 304, 305, 307-310, 312, 318, 321, 331, 342, 354, 355, 359, 364, 366, 377, 378, 381, 385-387, 389, 395, 397, 400, 401, 403, 411, 412, 416-419, 421-423, 426-429, 431-433, 435-438, 441, 443-445, 451-454, 456, 458, 462, 466-469, 486, 497, 502, 509, 517, 520, 524, 527, 529, 530, 538-540, 546, 552, 554, 556, 558, 560, 562, 571, 572, 578, 580-583, 585, 586, 588, 589, 592, 597, 599, 600, 604, 605, 608-610, 615, 617, 619-621, 623, 625-628, 630, 632-638, 640, 641, 643, 645-649, 665, 671-680, 682, 683, 685 and 688-690 as defined herein, or a salt and/or solvate thereof.~~

~~73. The compound of claim 70, wherein said compound is selected from Examples 20, 84, 99-102, 123, 205, 251, 266, 296 - 299, 308, 312, 318, 321, 342, 355, 385, 387, 412, 421, 432 462, 509, 517, 520, 524, 529, 530, 538, 539, 546, 554, 556, 560, 562, 568, 571, 572, 578, 580-583, 586, 588, 592, 597, 600, 605, 608, 609, 615, 617,621, 628, 630, 632, 633, 636, 637, 641, 643, 648, 649, 665, 672-675, 679, 682 and 688 as defined herein, or a salt and/or solvate thereof.~~

~~74.~~21. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 20~~73~~, together with a pharmaceutically acceptable carrier, diluent or excipient.

~~75.~~22. Use of a compound as defined in any one of claims 1 to 20~~73~~ in the manufacture of a medicament for the treatment of a disease or disorder selected from a proliferative disease or disorder, a developmental anomaly caused by dysregulation of the RAS-ERK signaling cascade (RASopathies), or an inflammatory disease or an immune system disorder.

~~76. The use of claim 75, wherein the disease or disorder is selected from a neoplasm and a developmental anomaly.~~

~~77.~~23. The use of claim ~~75 or 76~~22, wherein said disease or disorder is associated with a RAF gene mutation (e.g. ARAF, BRAF, or CRAF).

~~78. The use of any one of claims 75 to 77, wherein said disease or disorder is associated with a RAS gene mutation (e.g. KRAS).~~

~~79. The use of any one of claims 75 to 78, wherein said disease or disorder is associated with a receptor tyrosine kinase mutation or amplification (e.g. EGFR, HER2) or a mutation in a regulator of RAS downstream of the receptor (e.g. SOS1 gain of function, NF1 loss of function).~~

~~80. The use of any one of claims 75 to 79, wherein said disease of disorder is a neoplasm.~~

~~81.~~24. The use of claim ~~80~~23, wherein said disease is a neoplasm ~~is~~ selected from melanoma, thyroid carcinoma (e.g. papillary thyroid carcinoma), colorectal, ovarian, breast cancer, endometrial cancer, liver cancer, sarcoma, stomach cancer, pancreatic carcinoma, Barret's adenocarcinoma, glioma (e.g. ependymoma), lung cancer (e.g. non-small cell lung cancer), head and neck cancer, acute lymphoblastic leukemia, acute myelogenous leukemia, non-Hodgkin's lymphoma, and hairy-cell leukemia.

~~82. The use of claim 80, wherein said neoplasm is selected from colon or colorectal cancer, lung cancer, pancreatic cancer, thyroid cancer, breast cancer and melanoma.~~

~~83. The use of any one of claims 75 to 82, wherein said treatment comprises inhibiting the RAS-ERK signaling pathway without substantial induction of a paradoxical pathway.~~

~~84. A method for the treatment of a disease or disorder selected from a proliferative disease or disorder, a developmental anomaly caused by dysregulation of the RAS-ERK signaling cascade (RASopathies), or an inflammatory disease or an immune system disorder,~~

comprising administering a compound as defined in any one of claims 1 to 73 to a subject in need thereof.

85. The method of claim 84, wherein the disease or disorder is selected from a neoplasm and a developmental anomaly.

86. The method of claim 84 or 85, wherein said disease or disorder is associated with a RAF gene mutation (e.g. ARAF, BRAF, or CRAF).

87. The method of any one of claims 84 to 86, wherein said disease or disorder is associated with a RAS mutation (e.g. KRAS).

88. The method of any one of claims 84 to 87, wherein said disease or disorder is associated with a receptor tyrosine kinase mutation or amplification (e.g. EGFR, HER2) or a mutation in a regulator of RAS downstream of the receptor (e.g. SOS1 gain of function, NF1 loss of function).

89. The method of any one of claims 84 to 88, wherein said disease or disorder is a neoplasm.

90. The method of claim 89, wherein said neoplasm is selected from melanoma, thyroid carcinoma (e.g. papillary thyroid carcinoma), colorectal, ovarian, breast cancer, endometrial cancer, liver cancer, sarcoma, stomach cancer, pancreatic carcinoma, Barret's adenocarcinoma, glioma (e.g. ependymoma), lung cancer (e.g. non-small cell lung cancer), head and neck cancer, acute lymphoblastic leukemia, acute myelogenous leukemia, non-Hodgkin's lymphoma, and hairy-cell leukemia.

91. The method of claim 89, wherein said neoplasm is selected from colon or colorectal cancer, lung cancer, pancreatic cancer, thyroid cancer, breast cancer and melanoma.

92. The method of any one of claims 84 to 91, wherein said method comprises inhibiting the RAS-ERK signaling pathway without substantial induction of a paradoxical pathway.

93. A method for inhibiting abnormal proliferation of cells, comprising contacting the cells with a compound as defined in any one of claims 1 to 73.

94. The method of claim 93, wherein said cells comprise a mutated RAF protein kinase (e.g. a mutated ARAF, BRAF, or CRAF).

95. The method of claim 93 or 94, wherein said cells comprise a mutated RAS gene (e.g. mutated KRAS).

96. The method of any one of claims 93 to 95, wherein said abnormal proliferation is associated with a receptor tyrosine kinase mutation or amplification (e.g. EGFR, HER2) or a mutation in a regulator of RAS downstream of the receptor (e.g. SOS1 gain of function, NF1 loss of function).

97. The method of any one of claims 93 to 96, wherein said cells are selected from melanoma cells, thyroid carcinoma cells (e.g. papillary thyroid carcinoma cells), colorectal, ovarian, breast cancer cells, endometrial cancer cells, liver cancer cells, sarcoma cells, stomach cancer cells, pancreatic carcinoma cells, Barret's adenocarcinoma cells, glioma cells (e.g. ependymoma cells), lung cancer cells (e.g. non-small cell lung cancer cells), head and neck cancer cells, acute lymphoblastic leukemia cells, acute myelogenous leukemia cells, non-Hodgkin's lymphoma cells, and hairy-cell leukemia cells.

98. The method of any one of claims 93 to 97, wherein said cells are selected from colon or colorectal cancer cells, lung cancer cells, pancreatic cancer cells, thyroid cancer cells, breast cancer cells and melanoma cells.

99. The method of any one of claims 93 to 98, wherein said method comprises inhibiting the RAS-ERK signaling pathway without substantially inducing a paradoxical pathway.

100. The method of any one of claims 93 to 99, wherein said contacting is done *in vivo*.

101. The method of any one of claims 93 to 99, wherein said contacting is done *ex vivo*.