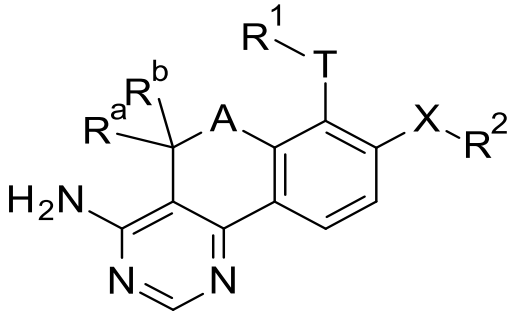
Benzo[h]quinazoline-4-amine Derivatives for the Treatment of Cancer

The present invention relates to compounds targeting the family of CDC2-like kinases (CLKs) and their use in the treatment of neoplastic diseases such as cancer.

Recurrent mutations in components of the splicing machinery have been reported in diseases like cancer. CLKs belong to the CMGC group of kinases and include four family members: CLK1, -2, -3 and -4. CLKs are known to play a key role in regulating alternative splicing (AS) through phosphorylation of splicing factors of the serine-arginine-rich (SR) family. Alternative splicing of transcripts is an important regulatory mechanism in eukaryotes that allows a single gene to generate multiple protein isoforms with distinct functions. CLK-mediated phosphorylation of SR proteins is implicated in their redistribution from speckles to a diffuse nucleoplasmic distribution pattern (Colwill et al., EMBO J. 1996, 15(2):265-75). SR protein phosphorylation has to be tightly regulated for nuclear import, spliceosome assembly, and ultimately for correct splicing, in particular to promote exon inclusion. Small molecule inhibitors of CLKs have been described to be efficacious in preclinical animal models of cancer (Yoshida T et al., Cancer Res. 2015, 75(7):1516-26; Iwai K et al., EMBO Mol Med. 2018 10(6):e8289; Zhu D et al., Mol Cancer Ther. 2018, 17(8):1727-1738). Therefore, targeting of CLKs offers potential for anti-cancer therapy, for instance in splicing factor mutant cancers, where there is a compelling rationale to exploit aberrant splicing as a vulnerability and therapeutic opportunity.

Summary

In a first aspect of the present disclosure, there is provided a compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof; wherein

Ra and Rb are both -CH_3 or Ra and Rb together form a -CH_2-CH_2-CH_2- or a -CH_2-CH_2-CH_2-CH_2- bridging moiety;

A is -CH_2- or -C(=O)-;

T is -N(R11)-, -N(R11)-C(=O)-, -N(R11)-S(O_2)-, -O-, -C(R12)(R13)-, -C=C(R12)$_2$, -S-, -S(O)-, -S(O_2)-, -S(O_2)-N(R14)- or -C(=O)-N(R14)-;

R11, when not forming a ring with R1 or R2, is hydrogen, C1-C4alkylene-R11a, C1-C4haloalkylene-R11a or C3-C6cycloalkyl, wherein the cycloalkyl is optionally substituted by one or two R11b;

each R12, when not forming a ring with R2, is independently hydrogen, C1-C4alkylene-R12a, C1-C4haloalkylene-R12a or C3-C6cycloalkyl, wherein the cycloalkyl is optionally substituted by one or two R12b;

R14, when not forming a ring with R1 or R2, is hydrogen, C1-C4alkylene-R14a, C1-C4haloalkylene-R14a or C3-C6cycloalkyl, wherein the cycloalkyl is optionally substituted by one or two R14b;

each R11a, R12a and R14a are independently hydrogen, halogen, -OH, -CN, $-NH_2$, -O-C1-C2alkyl, -O-C1-C2haloalkyl, -NH(C1-C2alkyl) or $-N(C1\text{-}C2alkyl)_2$;

each R11b, R12b and R14b are independently halogen, -OH, -CN, $-NH_2$, -O-C1-C2alkyl, -O-C1-C2haloalkyl, -NH(C1-C2alkyl) or $-N(C1\text{-}C2alkyl)_2$;

R13 is hydrogen, C1-C4alkyl or C1-C4haloalkyl;

R2 and R11, R2 and R12 or R2 and R14 may together form a partially unsaturated 6- to 7-membered heterocyclic ring containing no additional heteroatoms, wherein the heterocyclic ring is optionally substituted by one or two R2a;

each R2a is independently halogen, -OH, -CN, $-NH_2$, -O-C1-C2alkyl, -O-C1-C2haloalkyl, -NH(C1-C2alkyl) or $-N(C1\text{-}C2alkyl)_2$;

R1 and R11 or R1 and R14 may together form a saturated or partially unsaturated 4- to 7-membered heterocyclic ring optionally containing one or two additional heteroatoms as ring members selected from N, O and S, wherein the heterocyclic ring is optionally substituted by one to three R1a, or R1 and R11 or R1 and R14 may together form a 5- to 6-membered heteroaryl ring optionally containing one to three additional heteroatoms as ring members selected from N and O, wherein the heteroaryl ring is optionally substituted by one to three R1b;

each R1a is independently halogen, -OH, -CN, $-NH_2$, C1-C4alkylene-R1c, C1-C4haloalkylene-R1c, -O-C1-C4alkyl, -O-C1-C4haloalkyl, -NH(C1-C4alkyl), $-N(C1\text{-}C4alkyl)_2$, $-C(=O)NH_2$, -C(=O)NH(C1-C4alkyl), $-C(=O)N(C1\text{-}C4alkyl)_2$ or oxo;

each R1b is independently halogen, -OH, -CN, $-NH_2$, C1-C4alkylene-R1c, C1-C4haloalkylene-R1c, -O-C1-C4alkyl, -O-C1-C4haloalkyl, -NH(C1-C4alkyl) or $-N(C1\text{-}C4alkyl)_2$, $-C(=O)NH_2$, -C(=O)NH(C1-C4alkyl) or $-C(=O)N(C1\text{-}C4alkyl)_2$;

each R1c is independently hydrogen, halogen, -OH, -CN, $-NH_2$, -O-C1-C2alkyl, -O-C1-C2haloalkyl, -NH(C1-C2alkyl) or $-N(C1\text{-}C2alkyl)_2$;

R1, when not forming a ring with R11 or R14, is hydrogen or -Y-R3;

Y is a bond or C1-C6alkylene wherein one non-terminal $-CH_2-$ moiety may be replaced by -O- and wherein the alkylene moiety may be substituted by one or two moieties independently selected from -OH, -O-C1-C4alkyl and -O-C1-C4haloalkyl and wherein the alkylene moiety may include a 3- to 5-membered saturated or partially unsaturated carbocyclic ring as part of the moiety;

R3 is hydrogen, -CN, -OH, C1-C4haloalkyl, C2-C4alkenylene-R4, C2-C4alkynylene-R4, -O-C1-C4alkylene-R4, -O-C1-C4haloalkyl, $-NH_2$, -NH(C1-C4alkylene-R4), $-N(C1\text{-}C4alkylene\text{-}R4)_2$, -C(=O)-OH, -C(=O)-O-C1-C4alkylene-R4, $-C(=O)-NH_2$, -C(=O)-NH(C1-C4alkylene-R4), -C(=O)-N(C1-

C4alkylene-R4)$_2$, -NH-C(=O)-C1-C4alkylene-R4, -N(C1-C4alkyl)-C(=O)-C1-C4alkylene-R4, Cycle P, Cycle Q, -O-Cycle P, -O-Cycle Q, -NH-S(O_2)-C1-C4alkylene-R4, -N(C1-C4alkyl)-S(O_2)-C1-C4alkylene-R4, -S-C1-C4alkylene-R4 or -S(O_2)-C1-C4alkyl-R4, providing that the atom in R3 connected to Y is not a heteroatom when (i) Y is a bond and (ii) T is not -N(R11)-, -C(R12)(R13)- or -C=C(R12)$_2$;

R4 is hydrogen, halogen, -NH_2, -NH(C1-C2alkyl) or -N(C1-C2alkyl)$_2$;

Cycle P is a 3- to 6-membered saturated or partially unsaturated carbocyclic ring optionally substituted by one to three R5 or is a 3- to 6-membered saturated or partially unsaturated heterocyclic ring containing one or two heteroatoms selected from N and O optionally substituted by one to three R5;

each R5 is independently halogen, -NH_2, -OH, -CN, C1-C4alkylene-R5a, -O-C1-C4alkylene-R5a or oxo;

each R5a is independently hydrogen, halogen, -NH_2, -OH, -CN or -O-C1-C2alkyl;

Cycle Q is phenyl optionally substituted by one to three R6, or is a 5- to 6-membered heteroaryl ring containing one or two heteroatoms selected from N, S and O optionally substituted by one to three R6;

each R6 is independently halogen, -NH_2, -OH, -CN, C1-C4alkylene-R6a or -O-C1-C4alkylene-R6a;

each R6a is independently hydrogen, halogen, -NH_2, -OH, -CN or -O-C1-C2alkyl;

X is -O-, -C(=O)-, -C(=CH_2)-, -N(R10a)- or -CH(R10b)- and wherein X is a bond when R2 is halogen or -CN and wherein when X is -C(=O)- then R2 is not hydrogen, or wherein X-R2 is hydrogen;

R10a, when not forming a ring with R2, is hydrogen or C1-C4alkyl;

R10b is hydrogen or C1-C4alkyl;

R2 and R10a may together form a 4- to 7-membered saturated or partially unsaturated heterocyclic ring optionally containing an -N(R9)- moiety as ring member in addition to the nitrogen atom of X and otherwise containing only carbon atoms as ring members optionally substituted by one or two R8;

R2 and R10b may together form a 4- to 7-membered saturated or partially unsaturated carbocyclic ring or a 4- to 7-membered saturated or partially unsaturated heterocyclic ring containing an -N(R9)- moiety as ring member and otherwise containing only carbon atoms as ring members optionally substituted by one or two R8;

R2, when not forming a ring with R10a, R10b, R11, R12 or R14, is hydrogen, halogen, -CN, C1-C4alkyl optionally substituted by one or two R7, or is a 4- to 7-membered saturated or partially unsaturated carbocyclic ring optionally substituted by one or two R8, or is a 4- to 7-membered saturated or partially unsaturated heterocyclic ring containing one -N(R9)- moiety as a ring member and otherwise containing only carbon atoms as ring members;

each R7 is independently -CN, -OH, halogen, -N(R7a)R7b or -NH(-C(=O)-C1-C4alkyl);

each R7a and R7b, when not together forming a ring, is independently hydrogen, C1-C4alkylene-R7c or C1-C4haloalkylene-R7c;

each R7c is independently hydrogen, halogen, -O-C1-C2alkyl or -O-C1-C2haloalkyl;

R7a and R7b may together form a 4- to 7-membered saturated or partially unsaturated heterocyclic ring optionally containing one or two additional heteroatoms as ring members selected from N, O and S, and wherein the heterocyclic ring is optionally substituted by one or two R7d;

each R7d is independently halogen, -OH, -CN, -NH_2, C1-C2alkyl, C1-C2haloalkyl, -O-C1-C2alkyl, -O-C1-C2haloalkyl, -NH(C1-C2alkyl) or -N(C1-C2alkyl)$_2$;

each R8 is independently -CN, -OH, halogen, -N(R8a)R8b, -NH(-C(=O)-C1-C4alkyl), C1-C4alkyl or C1-C4haloalkyl;

each R8a and R8b, when not together forming a ring, is independently hydrogen, C1-C4alkylene-R8c or C1-C4haloalkylene-R8c;

R8c is hydrogen, halogen, -O-C1-C2alkyl or -O-C1-C2haloalkyl;

R8a and R8b may together form a 4- to 7-membered saturated or partially unsaturated heterocyclic ring optionally containing one or two additional heteroatoms as ring members selected from N, O and S, and wherein the heterocyclic ring is optionally substituted by one or two R8d;

each R8d is independently halogen, -OH, -CN, -NH_2, C1-C2alkyl, C1-C2haloalkyl, -O-C1-C2alkyl, -O-C1-C2haloalkyl, -NH(C1-C2alkyl) or -N(C1-C2alkyl)$_2$;

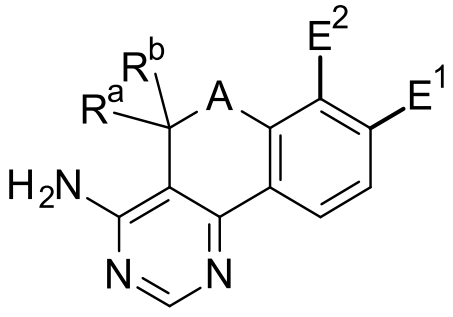
R9 is hydrogen, C1-C4alkylene-R9a, C1-C4haloalkylene-R9a or -C(=O)-C1-C4alkyl; and

R9a is hydrogen, halogen, -O-C1-C2alkyl or -O-C1-C2haloalkyl.

In another aspect of the present disclosure, there is provided a use of a compound of formula (I) as disclosed herein or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a neoplastic disease, e.g. cancer, in a subject selected from a mammal, in particular a human.

In yet another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound of formula (I) as disclosed herein or a pharmaceutically acceptable salt thereof and optionally a pharmaceutically acceptable excipient.

In a further aspect of the present disclosure, there is provided a compound of formula (B)



(B)

or a salt thereof, wherein

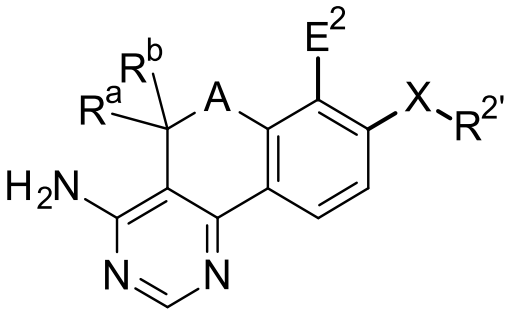
A, Ra and Rb are as defined for the compound of formula (I) in any one of claims 1 to 20;

E1 is -OH, -halogen, -O-C1-C4alkyl, boronic acid, a boronic ester or O-L1;

L1 is methanesulfonyl, *p*-toluenesulfonyl or trifluoromethanesulfonyl; and

E2 is -OH, halogen, -NO_2 or -SO_2Cl; or

a compound of formula (C)



(C)

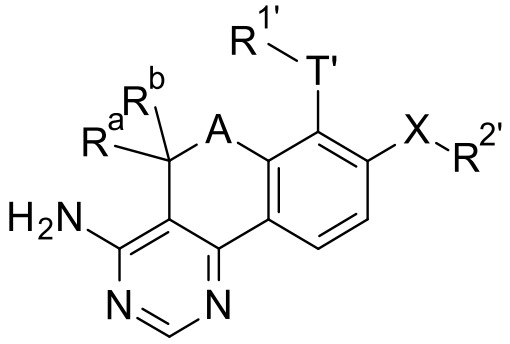
or a salt thereof, wherein

A, X, Ra and Rb are as defined for the compound of formula (I) in any one of claims 1 to 20;

E2 is -OH, halogen, $-NO_2$ or $-SO_2Cl$; and

R2' is as defined for R2 for the compound of formula (I) in any one of claims 1 to 20, wherein any functional group within R2 is optionally protected with a suitable protecting group; or

a compound of formula (D)



(D)

or a salt thereof, wherein

A, Ra and Rb are as defined for the compound of formula (I) in any one of claims 1 to 20;

T' is -N(R11')-, -N(R11')-C(=O)-, -N(R11')-$S(O_2)$-, -O-, -C(R12')(R13)-, -C=$C(R12')_2$, -S-, -S(O)-, -$S(O_2)$-, -$S(O_2)$-N(R14')- or -C(=O)-N(R14')-;

R11' is as defined for R11 in the compound of formula (I) in any one of claims 1 to 20, wherein any functional group within R11 is optionally protected with a suitable protecting group;

R12' is as defined for R12 in the compound of formula (I) in any one of claims 1 to 20, wherein any functional group within R12 is optionally protected with a suitable protecting group;

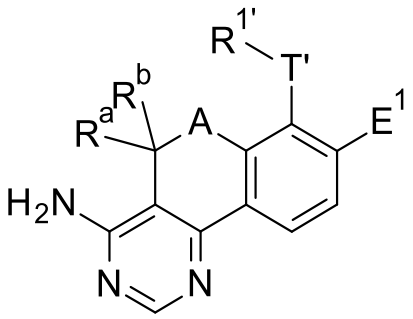
R13 is as defined for the compound of formula (I) in any one of claims 1 to 20;

R14' is as defined for R14 in the compound of formula (I) in any one of claims 1 to 20, wherein any functional group within R14 is optionally protected with a suitable protecting group;

R1' is as defined for R1 in the compound of formula (I) in any one of claims 1 to 20, wherein any functional group within R1 is optionally protected with a suitable protecting group; and

R2’ is as defined for R2 in the compound of formula (I) in any one of claims 1 to 20, wherein any functional group within R2 is optionally protected with a suitable protecting group; or

a compound of formula (E)



(E)

or a salt thereof, wherein

A, Ra and Rb are as defined for the compound of formula (I) in any one of claims 1 to 20;

T’ is -N(R11’)-, -N(R11’)-C(=O)-, -N(R11’)-S(O_2)-, -O-, -C(R12’)(R13)-, -C=C(R12’)$_2$, -S-, -S(O)-, -S(O_2)-, -S(O_2)-N(R14’)- or -C(=O)-N(R14’)-;

R11’ is as defined for R11 in the compound of formula (I) in any one of claims 1 to 20, wherein any functional group within R11 is optionally protected with a suitable protecting group;

R12’ is as defined for R12 in the compound of formula (I) in any one of claims 1 to 20, wherein any functional group within R12 is optionally protected with a suitable protecting group;

R13 is as defined for the compound of formula (I) in any one of claims 1 to 20;

R14’ is as defined for R14 in the compound of formula (I) in any one of claims 1 to 20, wherein any functional group within R14 is optionally protected with a suitable protecting group;

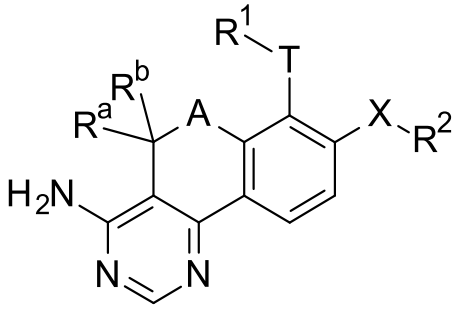
R1’ is as defined for R1 in the compound of formula (I) in any one of claims 1 to 20, wherein any functional group within R1 is optionally protected with a suitable protecting group; and

E1 is -OH, -halogen, -O-C1-C4alkyl, boronic acid, a boronic ester or O-L1; and

L1 is methanesulfonyl, *p*-toluenesulfonyl or trifluoromethanesulfonyl.

Description

In a first aspect the present invention provides compounds of formula (I)



(I)

and pharmaceutically acceptable salts thereof; wherein

Ra and Rb are both $-CH_3$ or Ra and Rb together form a $-CH_2-CH_2-CH_2-$ or a $-CH_2-CH_2-CH_2-CH_2-$ bridging moiety;

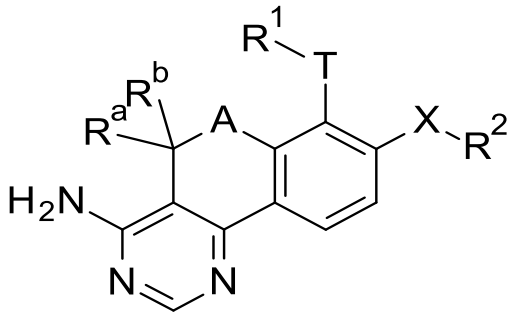
A is $-CH_2-$ or -C(=O)-;

T is -N(R11)-, -N(R11)-C(=O)-, -N(R11)-$S(O_2)$-, -O-, -C(R12)(R13)-, -C=$C(R12)_2$, -S-, -S(O)-, -$S(O_2)$-, -$S(O_2)$-N(R14)- or -C(=O)-N(R14)-;

R11, when not forming a ring with R1 or R2, is hydrogen, C1-C4alkylene-R11a, C1-C4haloalkylene-R11a or C3-C6cycloalkyl, wherein the cycloalkyl is optionally substituted by one or two R11b;

Claims

1. A compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof; wherein

Ra and Rb are both -CH_3 or Ra and Rb together form a -CH_2-CH_2-CH_2- or a -CH_2-CH_2-CH_2-CH_2- bridging moiety;

A is -CH_2- or -C(=O)-;

T is -N(R11)-, -N(R11)-C(=O)-, -N(R11)-S(O_2)-, -O-, -C(R12)(R13)-, -C=C(R12)$_2$, -S-, -S(O)-, -S(O_2)-, -S(O_2)-N(R14)- or -C(=O)-N(R14)-;

R11, when not forming a ring with R1 or R2, is hydrogen, C1-C4alkylene-R11a, C1-C4haloalkylene-R11a or C3-C6cycloalkyl, wherein the cycloalkyl is optionally substituted by one or two R11b;

each R12, when not forming a ring with R2, is independently hydrogen, C1-C4alkylene-R12a, C1-C4haloalkylene-R12a or C3-C6cycloalkyl, wherein the cycloalkyl is optionally substituted by one or two R12b;

R14, when not forming a ring with R1 or R2, is hydrogen, C1-C4alkylene-R14a, C1-C4haloalkylene-R14a or C3-C6cycloalkyl, wherein the cycloalkyl is optionally substituted by one or two R14b;

each R11a, R12a and R14a are independently hydrogen, halogen, -OH, -CN, -NH_2, -O-C1-C2alkyl, -O-C1-C2haloalkyl, -NH(C1-C2alkyl) or -N(C1-C2alkyl)$_2$;

each R11b, R12b and R14b are independently halogen, -OH, -CN, -NH_2, -O-C1-C2alkyl, -O-C1-C2haloalkyl, -NH(C1-C2alkyl) or -N(C1-C2alkyl)$_2$;

R13 is hydrogen, C1-C4alkyl or C1-C4haloalkyl;

R2 and R11, R2 and R12 or R2 and R14 may together form a partially unsaturated 6- to 7-membered heterocyclic ring containing no additional heteroatoms, wherein the heterocyclic ring is optionally substituted by one or two R2a;

each R2a is independently halogen, -OH, -CN, -NH_2, -O-C1-C2alkyl, -O-C1-C2haloalkyl, -NH(C1-C2alkyl) or -N(C1-C2alkyl)$_2$;

R1 and R11 or R1 and R14 may together form a saturated or partially unsaturated 4- to 7-membered heterocyclic ring optionally containing one or two additional heteroatoms as ring members selected from N, O and S, wherein the heterocyclic ring is optionally substituted by one to three R1a, or R1 and R11 or R1 and R14 may together form a 5- to 6-membered heteroaryl ring optionally containing one to three

additional heteroatoms as ring members selected from N and O, wherein the heteroaryl ring is optionally substituted by one to three R1b;

each R1a is independently halogen, -OH, -CN, -NH_2, C1-C4alkylene-R1c, C1-C4haloalkylene-R1c, -O-C1-C4alkyl, -O-C1-C4haloalkyl, -NH(C1-C4alkyl), -N(C1-C4alkyl)$_2$, -C(=O)NH_2, -C(=O)NH(C1-C4alkyl), -C(=O)N(C1-C4alkyl)$_2$ or oxo;

each R1b is independently halogen, -OH, -CN, -NH_2, C1-C4alkylene-R1c, C1-C4haloalkylene-R1c, -O-C1-C4alkyl, -O-C1-C4haloalkyl, -NH(C1-C4alkyl) or -N(C1-C4alkyl)$_2$, -C(=O)NH_2, -C(=O)NH(C1-C4alkyl) or -C(=O)N(C1-C4alkyl)$_2$;

each R1c is independently hydrogen, halogen, -OH, -CN, -NH_2, -O-C1-C2alkyl, -O-C1-C2haloalkyl, -NH(C1-C2alkyl) or -N(C1-C2alkyl)$_2$;

R1, when not forming a ring with R11 or R14, is hydrogen or -Y-R3;

Y is a bond or C1-C6alkylene wherein one non-terminal -CH_2- moiety may be replaced by -O- and wherein the alkylene moiety may be substituted by one or two moieties independently selected from -OH, -O-C1-C4alkyl and -O-C1-C4haloalkyl and wherein the alkylene moiety may include a 3- to 5-membered saturated or partially unsaturated carbocyclic ring as part of the moiety;

R3 is hydrogen, -CN, -OH, C1-C4haloalkyl, C2-C4alkenylene-R4, C2-C4alkynylene-R4, -O-C1-C4alkylene-R4, -O-C1-C4haloalkyl, -NH_2, -NH(C1-C4alkylene-R4), -N(C1-C4alkylene-R4)$_2$, -C(=O)-OH, -C(=O)-O-C1-C4alkylene-R4, -C(=O)-NH_2, -C(=O)-NH(C1-C4alkylene-R4), -C(=O)-N(C1-C4alkylene-R4)$_2$, -NH-C(=O)-C1-C4alkylene-R4, -N(C1-C4alkyl)-C(=O)-C1-C4alkylene-R4, Cycle P, Cycle Q, -O-Cycle P, -O-Cycle Q, -NH-S(O_2)-C1-C4alkylene-R4, -N(C1-C4alkyl)-S(O_2)-C1-C4alkylene-R4, -S-C1-C4alkylene-R4 or -S(O_2)-C1-C4alkyl-R4, providing that the atom in R3 connected to Y is not a heteroatom when (i) Y is a bond and (ii) T is not -N(R11)-, -C(R12)(R13)- or -C=C(R12)$_2$;

R4 is hydrogen, halogen, -NH_2, -NH(C1-C2alkyl) or -N(C1-C2alkyl)$_2$;

Cycle P is a 3- to 6-membered saturated or partially unsaturated carbocyclic ring optionally substituted by one to three R5 or is a 3- to 6-membered saturated or partially unsaturated heterocyclic ring containing one or two heteroatoms selected from N and O optionally substituted by one to three R5;

each R5 is independently halogen, -NH_2, -OH, -CN, C1-C4alkylene-R5a, -O-C1-C4alkylene-R5a or oxo;

each R5a is independently hydrogen, halogen, -NH_2, -OH, -CN or -O-C1-C2alkyl;

Cycle Q is phenyl optionally substituted by one to three R6, or is a 5- to 6-membered heteroaryl ring containing one or two heteroatoms selected from N, S and O optionally substituted by one to three R6;

each R6 is independently halogen, -NH_2, -OH, -CN, C1-C4alkylene-R6a or -O-C1-C4alkylene-R6a;

each R6a is independently hydrogen, halogen, -NH_2, -OH, -CN or -O-C1-C2alkyl;

X is -O-, -C(=O)-, -C(=CH_2)-, -N(R10a)- or -CH(R10b)- and wherein X is a bond when R2 is halogen or -CN and wherein when X is -C(=O)- then R2 is not hydrogen, or wherein X-R2 is hydrogen;

R10a, when not forming a ring with R2, is hydrogen or C1-C4alkyl;

R10b is hydrogen or C1-C4alkyl;

R2 and R10a may together form a 4- to 7-membered saturated or partially unsaturated heterocyclic ring optionally containing an -N(R9)- moiety as ring member in addition to the nitrogen atom of X and otherwise containing only carbon atoms as ring members optionally substituted by one or two R8;

R2 and R10b may together form a 4- to 7-membered saturated or partially unsaturated carbocyclic ring or a 4- to 7-membered saturated or partially unsaturated heterocyclic ring containing an -N(R9)- moiety as ring member and otherwise containing only carbon atoms as ring members optionally substituted by one or two R8;

R2, when not forming a ring with R10a, R10b, R11, R12 or R14, is hydrogen, halogen, -CN, C1-C4alkyl optionally substituted by one or two R7, or is a 4- to 7-membered saturated or partially unsaturated carbocyclic ring optionally substituted by one or two R8, or is a 4- to 7-membered saturated or partially unsaturated heterocyclic ring containing one -N(R9)- moiety as a ring member and otherwise containing only carbon atoms as ring members;

each R7 is independently -CN, -OH, halogen, -N(R7a)R7b or -NH(-C(=O)-C1-C4alkyl);

each R7a and R7b, when not together forming a ring, is independently hydrogen, C1-C4alkylene-R7c or C1-C4haloalkylene-R7c;

each R7c is independently hydrogen, halogen, -O-C1-C2alkyl or -O-C1-C2haloalkyl;

R7a and R7b may together form a 4- to 7-membered saturated or partially unsaturated heterocyclic ring optionally containing one or two additional heteroatoms as ring members selected from N, O and S, and wherein the heterocyclic ring is optionally substituted by one or two R7d;

each R7d is independently halogen, -OH, -CN, -NH_2, C1-C2alkyl, C1-C2haloalkyl, -O-C1-C2alkyl, -O-C1-C2haloalkyl, -NH(C1-C2alkyl) or -N(C1-C2alkyl)$_2$;

each R8 is independently -CN, -OH, halogen, -N(R8a)R8b, -NH(-C(=O)-C1-C4alkyl), C1-C4alkyl or C1-C4haloalkyl;

each R8a and R8b, when not together forming a ring, is independently hydrogen, C1-C4alkylene-R8c or C1-C4haloalkylene-R8c;

R8c is hydrogen, halogen, -O-C1-C2alkyl or -O-C1-C2haloalkyl;

R8a and R8b may together form a 4- to 7-membered saturated or partially unsaturated heterocyclic ring optionally containing one or two additional heteroatoms as ring members selected from N, O and S, and wherein the heterocyclic ring is optionally substituted by one or two R8d;

each R8d is independently halogen, -OH, -CN, -NH_2, C1-C2alkyl, C1-C2haloalkyl, -O-C1-C2alkyl, -O-C1-C2haloalkyl, -NH(C1-C2alkyl) or -N(C1-C2alkyl)$_2$;

R9 is hydrogen, C1-C4alkylene-R9a, C1-C4haloalkylene-R9a or -C(=O)-C1-C4alkyl; and

R9a is hydrogen, halogen, -O-C1-C2alkyl or -O-C1-C2haloalkyl.

2. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein Ra and Rb are both -CH_3 and A is -CH_2-.

3. The compound of claim 1 or claim 2 or a pharmaceutically acceptable salt thereof, wherein T is -N(R11)-, -N(R11)-S(O_2)-, -O-, -C(R12)(R13)-, -C=C(R12)$_2$, -S- or -C(=O)-N(R14)-.

4. The compound of any one of claim 1 to 3 or a pharmaceutically acceptable salt thereof, wherein the substituent R1 is not hydrogen.

5. The compound of any one of claims 1 to 4 or a pharmaceutically acceptable salt thereof, wherein R2 and R11, R2 and R12, R2 and R14, R1 and R11, and R1 and R14 do not together form a heterocyclic ring.

6. The compound of claim 1 or claim 2, or a pharmaceutically acceptable salt thereof, wherein T is -N(R11)-, -N(R11)-C(=O)- or -N(R11)-S(O_2)- and R1 and R11 together form a saturated or partially unsaturated 4- to 7-membered heterocyclic ring optionally containing one or two additional heteroatoms as ring members selected from N, O and S, wherein the heterocyclic ring is optionally substituted by one to three R1a, or R1 and R11 together form a 5- to 6-membered heteroaryl ring optionally containing one to three additional heteroatoms as ring members selected from N and O, wherein the heteroaryl ring is optionally substituted by one to three R1b.

7. The compound of any one of claims 1 to 3 or claim 5, or a pharmaceutically acceptable salt thereof, wherein R1, when not forming a ring with R11 or R14, is hydrogen or C1-C6alkylene-R3, wherein the alkylene moiety may be substituted by one -OH, wherein the alkylene moiety may include a 3-membered saturated carbocyclic ring as part of the moiety, and wherein there are no more than three carbon atom spacers between the connection to T and the connection to R3, or wherein R1 is Cycle P or Cycle Q.

8. The compound of any one of claims 1 to 7 or a pharmaceutically acceptable salt thereof, wherein R3 is hydrogen, -CN, -OH, C1-C4haloalkyl, -O-C1-C4alkylene-R4, -O-C1-C4haloalkyl, -NH_2, -NH(C1-C4alkylene-R4), -N(C1-C4alkylene-R4)$_2$, -C(=O)-OH, -C(=O)-NH_2, Cycle P or Cycle Q.

9. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein T is -N(R11)-, -N(R11)-C(=O)- or -N(R11)-S(O_2)-;
R1, when not forming a ring with R11, is -Y-R3;
or wherein R1 and R11 may together form a saturated or partially unsaturated 4- to 7-membered heterocyclic ring optionally containing one or two additional heteroatoms as ring members selected from N, O and S, wherein the heterocyclic ring is optionally substituted by one to three R1a, or R1 and R11 may together form a 5- to 6-membered heteroaryl ring optionally containing one to three additional

heteroatoms as ring members selected from N and O, wherein the heteroaryl ring is optionally substituted by one to three R1b; and

R11 is C1-C4alkylene-R11a, C1-C4haloalkylene-R11a or C3-C6cycloalkyl, wherein the cycloalkyl is optionally substituted by one or two R11b.

10. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein T is -N(R11)-, -N(R11)-C(=O)- or -N(R11)-S(O_2)-;

R1, when not forming a ring with R11, is -Y-R3;

Y is C1-C6alkylene wherein one non-terminal -CH_2- moiety may be replaced by -O- and wherein the alkylene moiety may be substituted by one or two moieties independently selected from -OH, -O-C1-C4alkyl and -O-C1-C4haloalkyl and wherein the alkylene moiety may include a 3- to 5-membered saturated or partially unsaturated carbocyclic ring as part of the moiety;

or wherein R1 and R11 may together form a saturated or partially unsaturated 4- to 7-membered heterocyclic ring optionally containing one or two additional heteroatoms as ring members selected from N, O and S, wherein the heterocyclic ring is optionally substituted by one to three R1a, or R1 and R11 or may together form a 5- to 6-membered heteroaryl ring optionally containing one to three additional heteroatoms as ring members selected from N and O, wherein the heteroaryl ring is optionally substituted by one to three R1b; and

R11 is C1-C4alkylene-R11a, C1-C4haloalkylene-R11a or C3-C6cycloalkyl, wherein the cycloalkyl is optionally substituted by one or two R11b.

11. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein

T is -N(R11)- or -N(R11)-S(O_2)-;

R11, when not forming a ring with R1, is C1-C4alkylene-R11a, C1-C4haloalkylene-R11a or C3-C4cycloalkyl;

R11a is hydrogen, halogen, -CN or -OH;

R1 and R11 may together form a 5- to 6-membered saturated heterocyclic ring containing no additional heteroatoms as ring members, wherein the heterocyclic ring is optionally substituted by one R1a, or R1 and R11 may together form a 5-membered heteroaryl ring containing no additional heteroatoms as ring members, and wherein the heteroaryl ring is optionally substituted by one R1b;

R1a is halogen, -OH or -CN;

R1b is halogen, -OH or -CN;

R1, when not forming a ring with R11, is C1-C3alkylene-R3, Cycle P or Cycle Q;

R3 is hydrogen, -CN, -OH, C1-C4haloalkyl, -O-C1-C4alkylene-R4, -O-C1-C4haloalkyl, -NH_2, -NH(C1-C4alkylene-R4) or -N(C1-C4alkylene-R4)$_2$, -C(=O)-OH, -C(=O)-NH_2, Cycle P or Cycle Q;

Cycle P is oxazolidinyl optionally substituted by one or two R5;

each R5 is independently C1-C2alkyl, -C1-C2alkyl-R5a or oxo, wherein Cycle P is not substituted by two oxo;

Cycle Q is phenyl optionally substituted by one R6, or is a 5- to 6-membered heteroaryl ring containing one to two heteroatoms selected from N and O optionally substituted by one R6;

each R6 is independently -NH_2, -OH, -CN, C1-C2alkylene-R6a or -O-C1-C2alkyl; and

each R6a is independently hydrogen, halogen or -CN.

12. The compound of any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof, wherein R2, when not forming a ring with R10a, R10b, R11, R12 or R14, is C1-C4alkyl or is a 4- or 7-membered saturated carbocyclic ring optionally substituted by one R8, or is a 4- or 7-membered saturated heterocyclic ring containing one -N(R9)- moiety as a ring member and otherwise containing only carbon atoms as ring members, or wherein X-R2 is halogen or hydrogen.

13. The compound of any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof, wherein R2 is C1-C4alkyl or is a 6-membered saturated carbocyclic ring substituted by one R8 at the 3 ("*para*") position with respect to X and R8 is -N(R8a)R8b, or wherein X-R2 is bromine.

14. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein

Ra and Rb are both -CH_3 or together form a -CH_2-CH_2-CH_2-CH_2- bridging moiety;

A is -CH_2- or -C(=O)-;

T is -N(R11)-, -N(R11)-S(O_2)-, -O-, -C(R12)(R13)-, -C=C($R12)_2$, -S-, -S(O_2)-, -S(O_2)-N(R14)- or -C(=O)-N(R14)-;

R11, when not forming a ring with R1 or R2, is hydrogen, C1-C4alkylene-R11a, C1-C4haloalkylene-R11a or C3-C6cycloalkyl;

R11a is hydrogen, halogen, -CN or -OH;

each R12 is independently hydrogen or C1-C4alkylene-R12a;

each R12a is independently hydrogen, halogen, -CN or -OH;

R13 is hydrogen;

R14 is hydrogen or C1-C4alkyl;

R2 and R11 may together form a partially unsaturated 6-membered heterocyclic ring containing no additional heteroatoms when T is -N(R11)- and X is -O-;

R1 and R11 may together form a 4- to 6-membered saturated or partially unsaturated heterocyclic ring optionally containing one additional heteroatom as a ring member selected from N and O, wherein the heterocyclic ring is optionally substituted by one or two R1a, or R1 and R11 may together form a 5-membered heteroaryl ring optionally containing one additional heteroatom as a ring member selected from N, and wherein the heteroaryl ring is optionally substituted by one or two R1b;

each R1a is independently halogen, -OH, -CN, C1-C4alkylene-R1c, -O-C1-C4haloalkyl, -C(=O)NH_2 or oxo;

each R1b is independently halogen, -OH, -CN, C1-C4alkylene-R1c or -O-C1-C4haloalkyl;

each R1c is independently hydrogen or -OH;

R1, when not forming a ring with R11, is -Y-R3;

Y is a bond or C1-C6alkylene wherein the alkylene moiety may be substituted by one -OH, wherein the alkylene moiety may include a 3-membered saturated carbocyclic ring as part of the moiety and wherein there are no more than three carbon atom spacers between the connection to T and the connection to R3;

R3 is hydrogen, -CN, -OH, C1-C4haloalkyl, -O-C1-C4alkylene-R4, -O-C1-C4haloalkyl, -NH_2, -NH(C1-C4alkylene-R4), -N(C1-C4alkylene-R4)$_2$, -C(=O)-NH_2, -C(=O)-NH(C1-C4alkylene-R4), -C(=O)-OH, -C(=O)-O-C1-C4alkylene-R4, -C(=O)-N(C1-C4alkylene-R4)$_2$, -NH-C(=O)-C1-C4alkylene-R4, -N(C1-C4alkyl)-C(=O)-C1-C4alkylene-R4, Cycle P, Cycle Q, -NH-S(O_2)-C1-C4alkylene-R4, -N(C1-C4alkyl)-S(O_2)-C1-C4alkylene-R4, -S-C1-C4alkylene-R4 or -S(O_2)-C1-C4alkyl-R4;

R4 is hydrogen;

Cycle P is a 3- to 6-membered saturated carbocyclic ring optionally substituted by one to two R5 or is a 5- or 6-membered saturated heterocyclic ring containing one heteroatom selected from N and O optionally substituted by one to two R5;

each R5 is independently -NH_2, C1-C2alkyl, -C1-C2alkyl-R5a or oxo;

each R5a is independently hydrogen, halogen, -NH_2, -OH, -CN or -O-C1-C2alkyl;

Cycle Q is phenyl optionally substituted by one or two R6, or is a 5- to 6-membered heteroaryl ring containing one to two heteroatoms selected from N, S and O optionally substituted by one or two R6;

each R6 is independently -NH_2, -OH, -CN, C1-C2alkylene-R6a or -O-C1-C2alkyl;

each R6a is independently hydrogen, halogen or -CN;

X is -O- or -N(R10a)- or X-R2 is halogen or hydrogen;

R10a is hydrogen or -CH_3 or R2 and R10a may together form a 4- to 7-membered saturated heterocyclic ring optionally containing an -N(R9)- moiety as ring member in addition to the nitrogen atom of X and otherwise containing only carbon atoms as ring members and wherein when not containing an -N(R9)- moiety the heterocyclic ring is optionally substituted by one R8;

R2, when not forming a ring with R10a or R11, is C1-C4alkyl optionally substituted by R7 or is a 4- or 7-membered saturated carbocyclic ring optionally substituted by one R8, or is a 6- or 7-membered saturated heterocyclic ring containing one -N(R9)- moiety as a ring member and otherwise containing only carbon atoms as ring members, or X-R2 is halogen or hydrogen;

R7 is -N(R7a)R7b;

R7a is hydrogen or C1-C4alkyl;

R7b is hydrogen or C1-C4alkyl;

R8 is -N(R8a)R8b;

R8a, when not forming a ring with R8b, is hydrogen or C1-C4alkyl;

R8b when not forming a ring with R8a, is hydrogen or C1-C4alkyl;

R8a and R8b may together form a 6-membered saturated heterocyclic ring optionally containing one or two additional heteroatoms as ring members selected from N and O; and

R9 is hydrogen or C1-C4alkyl.

15. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein

Ra and Rb are both $-CH_3$;

A is $-CH_2-$;

T is -N(R11)-, -N(R11)-S(O_2)-, -C=C($R12)_2$, -S- or -C(=O)-N(R14)-;

R11, when not forming a ring with R1, is hydrogen, C1-C4alkylene-R11a, C1-C4haloalkylene-R11a or C3-C4cycloalkyl;

R11a is hydrogen, halogen, -CN or -OH;

each R12 is independently hydrogen or C1-C4alkylene-R12a;

each R12a is independently hydrogen, halogen, -CN or -OH;

R14 is hydrogen or C1-C4alkyl;

R1 and R11 may together form a 5- to 6-membered saturated heterocyclic ring containing no additional heteroatoms as ring members, wherein the heterocyclic ring is optionally substituted by one R1a, or R1 and R11 may together form a 5-membered heteroaryl ring containing no additional heteroatoms as ring members, and wherein the heteroaryl ring is optionally substituted by one R1b;

R1a is halogen, -OH or -CN;

R1b is halogen, -OH or -CN;

R1, when not forming a ring with R11, is hydrogen, C1-C3alkylene-R3, Cycle P or Cycle Q;

R3 is hydrogen, -CN, -OH, C1-C4haloalkyl, -O-C1-C4alkylene-R4, -O-C1-C4haloalkyl, $-NH_2$, -NH(C1-C4alkylene-R4) or -N(C1-C4alkylene-R4)$_2$, -C(=O)-OH, -C(=O)-NH_2, Cycle P or Cycle Q;

R4 is hydrogen;

Cycle P is oxazolidinyl optionally substituted by one or two R5;

each R5 is independently C1-C2alkyl, -C1-C2alkyl-R5a or oxo, wherein Cycle P is not substituted by two oxo;

Cycle Q is phenyl optionally substituted by one R6, or is a 5- to 6-membered heteroaryl ring containing one to two heteroatoms selected from N and O optionally substituted by one R6;

R6 is independently $-NH_2$, -OH, -CN, C1-C2alkylene-R6a or -O-C1-C2alkyl;

R6a is independently hydrogen, halogen or -CN;

X is -O- or -N(R10a)- or X-R2 is halogen;

R10a is hydrogen or $-CH_3$ or R2 and R10a may together form a 6- to 7-membered saturated heterocyclic ring containing one -N(R9)- moiety as a ring member at the 3 position with respect to the nitrogen atom of X and otherwise containing only carbon atoms as ring members and wherein when not containing an -

N(R9)- moiety the heterocyclic ring is substituted by one R8 at the 3 position with respect to the nitrogen atom of X;

R2, when not forming a ring with R10a, is C1-C4alkyl optionally substituted by R7, or is a 6- to 7-membered saturated carbocyclic ring substituted by one R8 at the 3 position with respect to X or R2 is a 6- to 7-membered saturated heterocyclic ring containing one -N(R9)- moiety as a ring member at the 3 position with respect to X and otherwise containing only carbon atoms as ring members, or wherein X-R2 is halogen or hydrogen;

R7 is -N(R7a)R7b;

R7a is hydrogen or C1-C4alkyl-R7c;

R7b is hydrogen or C1-C4alkyl;

R7c is hydrogen, halogen, -O-C1-C2alkyl or -O-C1-C2haloalkyl;

R8is -N(R8a)R8b;

R8a, when not forming a ring with R8b, is hydrogen or C1-C4alkyl-R8c;

R8b, when not forming a ring with R8a, is hydrogen or C1-C4alkyl;

R8a and R8b may together form a 6-membered saturated heterocyclic ring optionally containing one or two additional heteroatoms as ring members selected from N and O;

R8c is hydrogen, halogen, -O-C1-C2alkyl or -O-C1-C2haloalkyl; and

R9 is hydrogen or C1-C4alkyl.

16. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein the compound is selected from one of the following compounds:

8-methoxy-5,5,7-trimethyl-6*H*-benzo[h]quinazolin-4-amine;

8-methoxy-5,5-dimethyl-6*H*-benzo[h]quinazoline-4,7-diamine;

6,6-dimethyl-2,3,4,5-tetrahydroquinazolino[7,8-f][1,4]benzoxazin-7-amine;

4,6,6-trimethyl-3,5-dihydro-2*H*-quinazolino[7,8-f][1,4]benzoxazin-7-amine;

8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazoline-4,7-diamine;

N-[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]acetamide;

8-(*trans*-4-aminocyclohexoxy)-*N*7,*N*7-diethyl-5,5-dimethyl-6*H*-benzo[h]quinazoline-4,7-diamine;

8-(*trans*-4-aminocyclohexoxy)-*N*7-ethyl-5,5-dimethyl-6*H*-benzo[h]quinazoline-4,7-diamine;

8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-7-(1-piperidyl)-6*H*-benzo[h]quinazolin-4-amine;

8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-7-morpholino-6*H*-benzo[h]quinazolin-4-amine;

2-[[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]-(2-hydroxyethyl)amino]ethanol;

2-[[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]-methyl-amino]ethanol;

8-(*trans*-4-aminocyclohexoxy)-*N*7-(2-methoxyethyl)-*N*7,5,5-trimethyl-6*H*-benzo[h]quinazoline-4,7-diamine;

2-[[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]amino]ethanol;
1-[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]pyrrolidin-3-ol – isomer 1;
1-[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]pyrrolidin-3-ol – isomer 2;
8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-7-pyrrol-1-yl-6*H*-benzo[h]quinazolin-4-amine;
8-(*trans*-4-aminocyclohexoxy)-*N*7-(2-methoxyethyl)-5,5-dimethyl-6*H*-benzo[h]quinazoline-4,7-diamine;
8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-7-propoxy-6*H*-benzo[h]quinazolin-4-amine;
8-(*trans*-4-aminocyclohexoxy)-*N*7,*N*7,5,5-tetramethyl-6*H*-benzo[h]quinazoline-4,7-diamine;
1-(4-amino-8-methoxy-5,5-dimethyl-6*H*-benzo[h]quinazolin-9-yl)piperidin-4-ol;
2-[[4-amino-8-(*cis*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]-ethyl-amino]ethanol;
2-[[4-amino-8-(*cis*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]-propyl-amino]ethanol;
2-[[4-amino-8-(*cis*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]-methyl-amino]ethanol;
1-(4-amino-8-methoxy-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl)azetidin-3-ol;
2-[[4-amino-8-(*cis*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]-methyl-amino]-*N*-methyl-acetamide;
3-[(4-amino-8-methoxy-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl)amino]propane-1,2-diol;
[1-(4-amino-8-methoxy-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl)azetidin-3-yl]methanol;
8-(*cis*-4-aminocyclohexoxy)-*N*7,5,5-trimethyl-*N*7-(tetrahydropyran-4-ylmethyl)-6*H*-benzo[h]quinazoline-4,7-diamine;
2-[[4-amino-8-(*cis*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]-methyl-amino]acetonitrile;
8-(*cis*-4-aminocyclohexoxy)-*N*7,5,5-trimethyl-*N*7-(2-methylsulfanylethyl)-6*H*-benzo[h]quinazoline-4,7-diamine;
8-(*cis*-4-aminocyclohexoxy)-*N*7,5,5-trimethyl-*N*7-(2-methylsulfonylethyl)-6*H*-benzo[h]quinazoline-4,7-diamine;
2-[[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]-methyl-amino]acetonitrile;
4,7-diamino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-benzo[h]quinazolin-6-one;
2-[[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]amino]acetonitrile;
8-(*trans*-4-aminocyclohexoxy)-*N*7-(2-ethoxyethyl)-*N*7,5,5-trimethyl-6*H*-benzo[h]quinazoline-4,7-diamine;
8-(*trans*-4-aminocyclohexoxy)spiro[6*H*-benzo[h]quinazoline-5,1'-cyclopentane]-4,7-diamine;

N-[2-[[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]-methyl-amino]ethyl]acetamide;

N-[2-[[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]-methyl-amino]ethyl]methanesulfonamide;

1-[[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]-methyl-amino]-2-methyl-propan-2-ol;

N-[4-amino-8-*(trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]-2-hydroxy-*N*-methyl-acetamide;

N-[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]-2-hydroxy-ethanesulfonamide;

8-(*trans*-4-aminocyclohexoxy)-*N*7,5,5-trimethyl-*N*7-(3,3,3-trifluoropropyl)-6*H*-benzo[h]quinazoline-4,7-diamine;

N-[4-amino-8-(4-*trans*-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]-2-hydroxy-*N*-methyl-ethanesulfonamide;

N-[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]-2-hydroxy-acetamide;

3-[[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]-methyl-amino]propanenitrile;

8-(*trans*-4-aminocyclohexoxy)-*N*7,5,5-trimethyl-*N*7-[2-(trifluoromethoxy)ethyl]-6*H*-benzo[h]quinazoline-4,7-diamine;

1-[[[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]-methyl-amino]methyl]cyclopropanecarbonitrile;

1-[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]pyrrolidine-3-carbonitrile – isomer 1;

1-[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]pyrrolidine-3-carbonitrile – isomer 2;

3-[[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]-cyclopropyl-amino]propanenitrile;

3-[[4-amino-5,5-dimethyl-8-(*trans*-4-morpholinocyclohexoxy)-6*H*-benzo[h]quinazolin-7-yl]-methyl-amino]propanenitrile;

3-[[4-amino-8-[*trans*-4-(2-methoxyethylamino)cyclohexoxy]-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]-methyl-amino]propanenitrile;

8-(*trans*-4-aminocyclohexoxy)-*N*7-but-3-ynyl-*N*7,5,5-trimethyl-6*H*-benzo[h]quinazoline-4,7-diamine;

1-(4-amino-8-methoxy-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl)pyrrolidine-3-carbonitrile;

1-[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]-2*H*-pyrrol-5-one;

8-(*trans*-4-aminocyclohexoxy)-7-(3-methoxypyrrol-1-yl)-5,5-dimethyl-6*H*-benzo[h]quinazolin-4-amine;

4-[[4-amino-8-(4-*trans*-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]-methyl-amino]butanenitrile;

2-[[4-amino-8-(4-*trans*-aminocyclohexoxy)spiro[6*H*-benzo[h]quinazoline-5,1'-cyclopentane]-7-yl]-methyl-amino]ethanol;

2-[[4-amino-8-(4-*trans*-aminocyclohexoxy)spiro[6*H*-benzo[h]quinazoline-5,1'-cyclopentane]-7-yl]amino]ethanol;

8-methoxy-7-(3-methoxypropyl)-5,5-dimethyl-6*H*-benzo[h]quinazolin-4-amine;

8-(*trans*-4-aminocyclohexoxy)-*N*7-(2-methoxyethyl)spiro[6*H*-benzo[h]quinazoline-5,1'-cyclopentane]-4,7-diamine;

8-(*trans*-4-aminocyclohexoxy)-7-(3-methoxypyrrolidin-1-yl)-5,5-dimethyl-6*H*-benzo[h]quinazolin-4-amine – isomer 1;

N-[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]-2-methoxy-*N*-methyl-ethanesulfonamide;

ethyl 2-[[4-amino-8-(*cis*-4-aminocyclohexoxy)spiro[6*H*-benzo[h]quinazoline-5,1'-cyclopentane]-7-yl]amino]acetate;

1-[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]pyrrolidine-3-carbonitrile;

8-(*trans*-4-aminocyclohexoxy)-*N*7-ethyl-*N*7,5,5-trimethyl-6*H*-benzo[h]quinazoline-4,7-diamine;

8-(*trans*-4-aminocyclohexoxy)-*N*7,5,5-trimethyl-6*H*-benzo[h]quinazoline-4,7-diamine;

3-[[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]-methyl-sulfamoyl]propanoic acid;

2-[[4-amino-8-(*cis*-4-aminocyclohexoxy)spiro[6*H*-benzo[h]quinazoline-5,1'-cyclopentane]-7-yl]amino]ethanol;

3-[[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]oxy]propanenitrile;

8-(*trans*-4-aminocyclohexoxy)-*N*7-(2-methoxyethyl)-*N*7-methyl-spiro[6*H*-benzo[h]quinazoline-5,1'-cyclopentane]-4,7-diamine;

8-(*trans*-4-aminocyclohexoxy)-7-(3-methoxypyrrolidin-1-yl)-5,5-dimethyl-6*H*-benzo[h]quinazolin-4-amine – isomer 2;

N-[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]-2-cyano-*N*-methyl-ethanesulfonamide;

8-(*cis*-4-aminocyclohexoxy)-*N*7-(2-methoxyethyl)-*N*7-methyl-spiro[6*H*-benzo[h]quinazoline-5,1'-cyclopentane]-4,7-diamine;

1-[[[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]amino]methyl]cyclopropanecarbonitrile;

1-[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]pyrrolidine-3-carboxamide;

3-[[4-amino-8-(azepan-4-yloxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]-methyl-amino]propanenitrile;
2-[[4-amino-8-(*cis*-4-aminocyclohexoxy)spiro[6*H*-benzo[h]quinazoline-5,1'-cyclopentane]-7-yl]amino]acetic acid;
8-(*trans*-4-aminocyclohexoxy)-*N*7-(2-aminoethyl)-*N*7,5,5-trimethyl-6*H*-benzo[h]quinazoline-4,7-diamine;
4-[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]butanenitrile;
(5*R*)-5-[[(4-amino-8-methoxy-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl)amino]methyl]oxazolidin-2-one;
2-[[4-amino-8-(*cis*-4-aminocyclohexoxy)spiro[6*H*-benzo[h]quinazoline-5,1'-cyclopentane]-7-yl]-methyl-amino]ethanol;
8-(*trans*-4-aminocyclohexoxy)-*N*7-cyclopropyl-5,5-dimethyl-6*H*-benzo[h]quinazoline-4,7-diamine;
3-[[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]-methyl-amino]propanoic acid;
3-[[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]-methyl-sulfamoyl]propanamide;
8-(*cis*-4-aminocyclohexoxy)-*N*7-(2-methoxyethyl)spiro[6*H*-benzo[h]quinazoline-5,1'-cyclopentane]-4,7-diamine;
3-[[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]-methyl-amino]-2,2-dimethyl-propanamide;
(5*R*)-5-[2-[(4-amino-8-methoxy-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl)amino]ethyl]oxazolidin-2-one;
4-amino-8-(*trans*-4-aminocyclohexoxy)-*N*-(cyanomethyl)-5,5-dimethyl-6*H*-benzo[h]quinazoline-7-carboxamide;
3-[[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]-methyl-amino]-2,2-dimethyl-propanenitrile;
3-[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]butan-1-ol;
3-[[4-amino-5,5-dimethyl-8-(4-piperidyloxy)-6*H*-benzo[h]quinazolin-7-yl]-methyl-amino]propanenitrile;
4-amino-8-(*trans*-4-aminocyclohexoxy)-*N*-(cyanomethyl)-*N*,5,5-trimethyl-6*H*-benzo[h]quinazoline-7-carboxamide;
3-[(4-amino-8-methoxy-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl)-methyl-amino]propanenitrile;
3-[[4-amino-8-*trans*-4-(dimethylamino)cyclohexoxy]-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]-methyl-amino]propanenitrile;
4-[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]pentanenitrile;
(*E*)-3-[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]but-2-en-1-ol;
3-[[4-amino-5,5-dimethyl-8-[*trans*-4-(methylamino)cyclohexoxy]-6*H*-benzo[h]quinazolin-7-yl]-methyl-amino]propanenitrile;
8-(*trans*-4-aminocyclohexoxy)-*N*7-butyl-*N*7,5,5-trimethyl-6*H*-benzo[h]quinazoline-4,7-diamine;

8-(*trans*-4-aminocyclohexoxy)-*N*7,5,5-trimethyl-*N*7-(4-pyridylmethyl)-6*H*-benzo[h]quinazoline-4,7-diamine;

8-(*trans*-4-aminocyclohexoxy)-*N*7-isopropyl-*N*7,5,5-trimethyl-6*H*-benzo[h]quinazoline-4,7-diamine;

8-(*trans*-4-aminocyclohexoxy)-*N*7-(1*H*-imidazol-4-ylmethyl)-*N*7,5,5-trimethyl-6*H*-benzo[h]quinazoline-4,7-diamine;

8-(*trans*-4-aminocyclohexoxy)-*N*7-isopentyl-*N*7,5,5-trimethyl-6*H*-benzo[h]quinazoline-4,7-diamine;

8-(*trans*-4-aminocyclohexoxy)-*N*7,5,5-trimethyl-*N*7-(oxazol-4-ylmethyl)-6*H*-benzo[h]quinazoline-4,7-diamine;

8-(*trans*-4-aminocyclohexoxy)-*N*7-isobutyl-*N*7,5,5-trimethyl-6*H*-benzo[h]quinazoline-4,7-diamine;

8-(*trans*-4-aminocyclohexoxy)-*N*7,5,5-trimethyl-*N*7-(3-pyridylmethyl)-6*H*-benzo[h]quinazoline-4,7-diamine;

3-[[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]sulfanyl]propanenitrile;

3-[(4-amino-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl)-methyl-amino]propanenitrile;

3-[[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]-methyl-amino]-2,2-dimethyl-propan-1-ol;

4-[[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]-methyl-amino]-2-methyl-butan-2-ol;

3-[[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]sulfonyl]propanenitrile;

4-amino-8-(*trans*-4-aminocyclohexoxy)-*N*-(cyanomethyl)-*N*,5,5-trimethyl-6*H*-benzo[h]quinazoline-7-sulfonamide;

N-[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]-4-fluoro-*N*-methyl-benzenesulfonamide;

3-[(4-amino-8-bromo-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl)-methyl-amino]propanenitrile;

4-amino-8-(*trans*-4-aminocyclohexoxy)-*N*-(cyanomethyl)-5,5-dimethyl-6*H*-benzo[h]quinazoline-7-sulfonamide;

3-(7-amino-6,6-dimethyl-3,5-dihydro-2*H*-quinazolino[7,8-f][1,4]benzoxazin-4-yl)propanenitrile;

3-[[4-amino-5,5-dimethyl-8-(4-methylpiperazin-1-yl)-6*H*-benzo[h]quinazolin-7-yl]-methyl-amino]propanenitrile;

8-(*trans*-4-aminocyclohexoxy)-7-(1,1-dioxo-1,2-thiazolidin-2-yl)-5,5-dimethyl-6*H*-benzo[h]quinazolin-4-amine;

1-(4-amino-8-bromo-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl)pyrrolidine-3-carbonitrile;

(5*R*)-5-[[(4-amino-8-bromo-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl)amino]methyl]oxazolidin-2-one;

*N*7-[[5-(1-fluoroethyl)-1,3,4-oxadiazol-2-yl]methyl]-8-methoxy-5,5-dimethyl-6*H*-benzo[h]quinazoline-4,7-diamine;

3-[[4-amino-8-[2-(dimethylamino)ethoxy]-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]-methyl-amino]propanenitrile;

3-[(4-amino-8-methoxy-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl)-[[5-(1-fluoroethyl)-1,3,4-oxadiazol-2-yl]methyl]amino]propanenitrile;

3-[(4-amino-5,5-dimethyl-8-piperazin-1-yl-6*H*-benzo[h]quinazolin-7-yl)-methyl-amino]propanenitrile;

(5*S*)-5-[[(4-amino-8-bromo-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl)-methyl-amino]methyl]oxazolidin-2-one;

(5*R*)-5-[[(4-amino-8-bromo-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl)amino]methyl]-3-(2-hydroxyethyl)oxazolidin-2-one;

(5*R*)-5-[[[4-amino-8-(*cis*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]amino]methyl]oxazolidin-2-one;

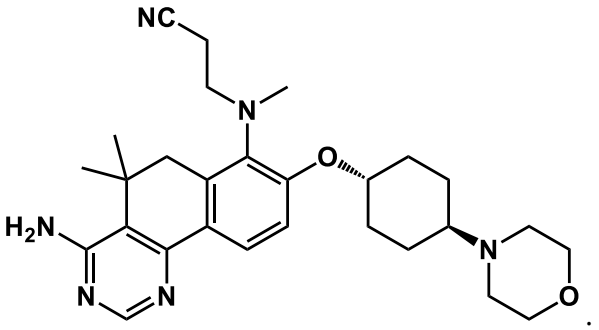
(5*R*)-5-[[[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl]amino]methyl]oxazolidin-2-one;

(5*R*)-5-[[[4-amino-5,5-dimethyl-8-(*cis*-4-morpholinocyclohexoxy)-6*H*-benzo[h]quinazolin-7-yl]amino]methyl]oxazolidin-2-one;

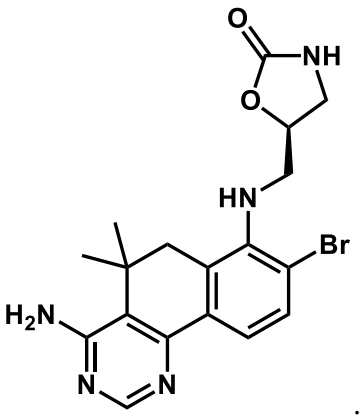
(5*R*)-5-[[[4-amino-5,5-dimethyl-8-(*trans*-4-morpholinocyclohexoxy)-6*H*-benzo[h]quinazolin-7-yl]amino]methyl]oxazolidin-2-one; and

3-[(4-amino-8-bromo-5,5-dimethyl-6*H*-benzo[h]quinazolin-7-yl)-[[(5*S*)-2-oxooxazolidin-5-yl]methyl]amino]propanenitrile.

17. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein the compound is represented by the structure:

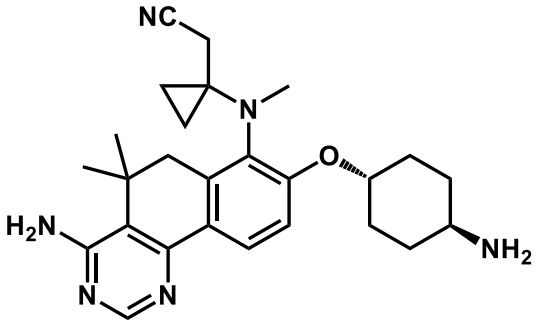


18. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein the compound is represented by the structure:



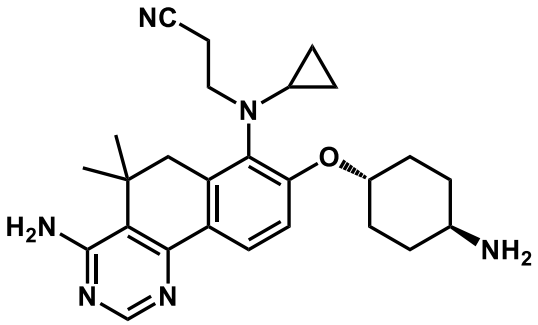
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19. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein the compound is represented by the structure:



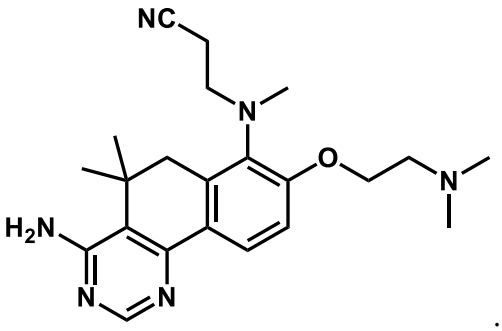
.

20. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein the compound is represented by the structure:



.

21. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein the compound is represented by the structure:

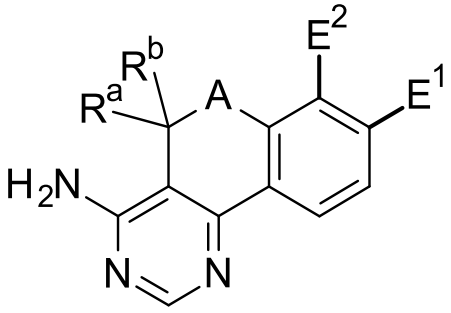


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22. Use of a compound of formula (I) as defined in any one of claims 1 to 21 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a neoplastic disease, e.g. cancer, in a subject selected from a mammal, in particular a human.

23. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of claims 1 to 21 or a pharmaceutically acceptable salt thereof and optionally a pharmaceutically acceptable excipient.

24. A compound of formula (B)



(B)

or a salt thereof, wherein

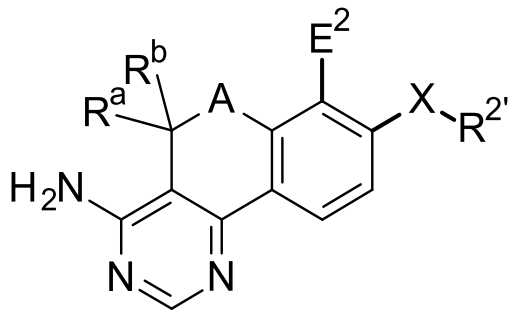
A, Ra and Rb are as defined for the compound of formula (I) in any one of claims 1 to 20;

E1 is -OH, -halogen, -O-C1-C4alkyl, boronic acid, a boronic ester or O-L1;

L1 is methanesulfonyl, *p*-toluenesulfonyl or trifluoromethanesulfonyl; and

E2 is -OH, halogen, $-NO_2$ or $-SO_2Cl$; or

a compound of formula (C)



(C)

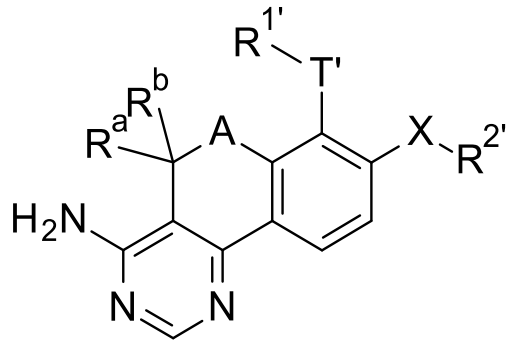
or a salt thereof, wherein

A, X, Ra and Rb are as defined for the compound of formula (I) in any one of claims 1 to 20;

E2 is -OH, halogen, $-NO_2$ or $-SO_2Cl$; and

R2' is as defined for R2 for the compound of formula (I) in any one of claims 1 to 20, wherein any functional group within R2 is optionally protected with a suitable protecting group; or

a compound of formula (D)



(D)

or a salt thereof, wherein

A, Ra and Rb are as defined for the compound of formula (I) in any one of claims 1 to 20;

T' is $-N(R11')-$, $-N(R11')-C(=O)-$, $-N(R11')-S(O_2)-$, $-O-$, $-C(R12')(R13)-$, $-C=C(R12')_2$, $-S-$, $-S(O)-$, $-S(O_2)-$, $-S(O_2)-N(R14')-$ or $-C(=O)-N(R14')-$;

R11' is as defined for R11 in the compound of formula (I) in any one of claims 1 to 20, wherein any functional group within R11 is optionally protected with a suitable protecting group;

R12' is as defined for R12 in the compound of formula (I) in any one of claims 1 to 20, wherein any functional group within R12 is optionally protected with a suitable protecting group;

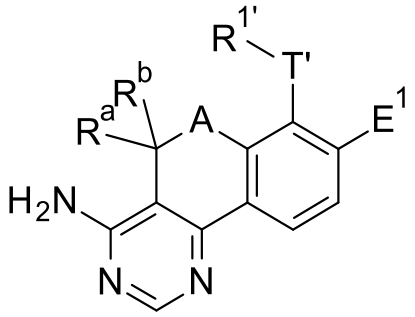
R13 is as defined for the compound of formula (I) in any one of claims 1 to 20;

R14' is as defined for R14 in the compound of formula (I) in any one of claims 1 to 20, wherein any functional group within R14 is optionally protected with a suitable protecting group;

R1' is as defined for R1 in the compound of formula (I) in any one of claims 1 to 20, wherein any functional group within R1 is optionally protected with a suitable protecting group; and

R2' is as defined for R2 in the compound of formula (I) in any one of claims 1 to 20, wherein any functional group within R2 is optionally protected with a suitable protecting group; or

a compound of formula (E)



(E)

or a salt thereof, wherein

A, Ra and Rb are as defined for the compound of formula (I) in any one of claims 1 to 20;

T' is -N(R11')-, -N(R11')-C(=O)-, -N(R11')-S(O_2)-, -O-, -C(R12')(R13)-, -C=C(R12')$_2$, -S-, -S(O)-, -S(O_2)-, -S(O_2)-N(R14')- or -C(=O)-N(R14')-;

R11' is as defined for R11 in the compound of formula (I) in any one of claims 1 to 20, wherein any functional group within R11 is optionally protected with a suitable protecting group;

R12' is as defined for R12 in the compound of formula (I) in any one of claims 1 to 20, wherein any functional group within R12 is optionally protected with a suitable protecting group;

R13 is as defined for the compound of formula (I) in any one of claims 1 to 20;

R14' is as defined for R14 in the compound of formula (I) in any one of claims 1 to 20, wherein any functional group within R14 is optionally protected with a suitable protecting group;

R1' is as defined for R1 in the compound of formula (I) in any one of claims 1 to 20, wherein any functional group within R1 is optionally protected with a suitable protecting group; and

E1 is -OH, -halogen, -O-C1-C4alkyl, boronic acid, a boronic ester or O-L1; and

L1 is methanesulfonyl, *p*-toluenesulfonyl or trifluoromethanesulfonyl.