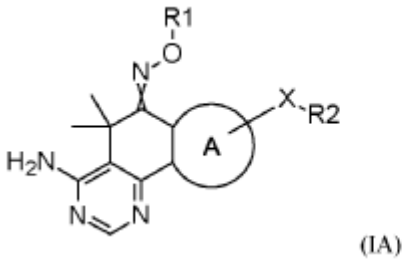
Benzo [h]quinazolin-4-amine and Thieno[3,2-h]quinazolin-4-amine Derivatives for the Treatment of Cancer

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.

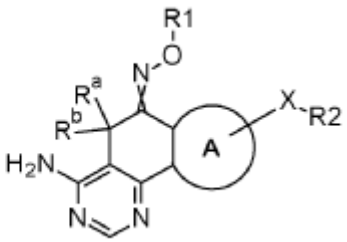
Recurrent mutations in components of the splicing machinery have been reported in diseases like cancer. CLKs belong to the CMGC group of kinases and include four family members: CLK1, -2, -3 and -4. CLKs are known to play a key role in regulating alternative splicing (AS) through phosphorylation of splicing 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. Expression levels of CLKs have been reported to be elevated in a number of cancers and small molecule inhibitors of CLKs have been described to be efficacious in preclinical animal models of cancer (Y oshida 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 one aspect of the present disclosure, there is provided a compound of formula (IA) or a compound of formula (IB)



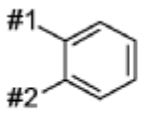
(IA)



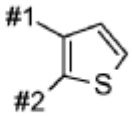
(IB)

or a pharmaceutically acceptable salt thereof; wherein

A is selected from group (A1) and group (A2):



(A1)



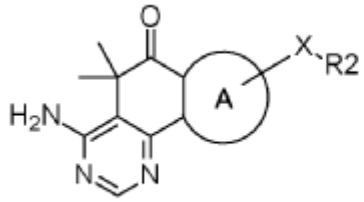
(A2)

wherein #1 is attached to the carbon atom forming the oxime moiety and wherein group (A1) is optionally substituted by one or two R10 and group (A2) is optionally substituted by one R10;
each R10 is independently halogen or $-NH_2$;
X is -O-, -C(=O)-, $-C(=CH_2)-$, $-CH_2-$, -NH- or -N(C1-C4alkyl)- and wherein X is a bond when R2 is halogen or -CN and wherein when X is -C(=O)- R2 is not hydrogen;
or X-R2 is hydrogen;
Ra and Rb together form a $-CH_2-CH_2-CH_2-$ or a $-CH_2-CH_2-CH_2-CH_2-$ bridging moiety;
R1 is -Y-R3;
Y is a bond or C1-C6alkylene wherein one non-terminal $-CH_2-$ moiety may be replaced by -O-;
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), $-C(=O)-N(C1- C4alkylene-R4)_2$, Cycle P, Cycle Q, -O-Cycle P, -O-Cycle Q or $-S(O_2)-C1-C4alkyl$;
R4 is hydrogen, $-NH_2$, -NH(C1-C2alkyl) or $-N(C1-C2alkyl)_2$;
Cycle P is a 5-6-membered saturated or partially unsaturated carbocyclic ring optionally substituted by one to three R5 or is a 5-6-membered saturated or partially unsaturated heterocyclic ring containing one to two heteroatoms selected from N and O optionally substituted by one to three R5;
each R5 is independently $-NH_2$, -OH, -CN, C1-C4alkyl, C1-C4alkylene-R11, -O-C1-C2alkyl or oxo;
each R11 is independently halogen, $-NH_2$, -OH, -CN or -O-C1-C2alkyl;
Cycle Q is phenyl optionally substituted by one to three R6, or is a 5-6-membered heteroaryl containing one to two heteroatoms selected from N, S and O optionally substituted by one to three R6;
each R6 is independently $-NH_2$, -OH, -CN, C1-C2alkyl or -O-C1-C2alkyl;
R2 is hydrogen, halogen, -CN, C1-C4alkyl optionally substituted by one or two R7, or is a 4- to 7-membered saturated carbocyclic ring optionally substituted by one or two R8, or is a 4- to 7-membered saturated heterocyclic ring containing one -N(R9)- moiety as ring member and otherwise containing only carbon atoms as ring members;
each R7 is independently -OH, halogen, $-NH_2$, -NH(C1-C2alkyl), $-N(C1-C2alkyl)_2$ or -NH(-C(=O)-C1-C2alkyl);
each R8 is independently -OH, halogen, $-NH_2$, -NH(C1-C2alkyl), $-N(C1-C2alkyl)_2$, -NH(-C(=O)-C1-C2alkyl) or C1-C2alkyl; and
R9 is hydrogen, C1-C4alkyl or -C(=O)-C1-C2alkyl.

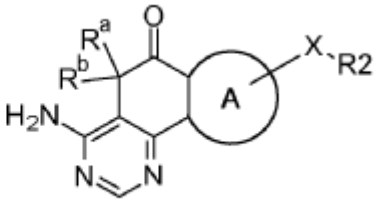
In another aspect of the present disclosure, there is provided a use of a compound of formula (IA) or a compound of formula (IB) disclosed herein or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a neoplastic disease, preferably cancer, in a subject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

In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound of formula (IA) or a compound of formula (IB) disclosed herein or a pharmaceutically acceptable salt thereof and optionally one or more pharmaceutically acceptable excipients.

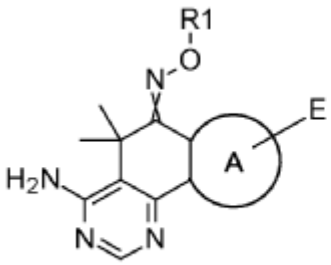
In another aspect of the present disclosure, there is provided a compound of formula (Int-IA), (Int-IB), (Int-IIA) or a compound of formula (Int-IIB)



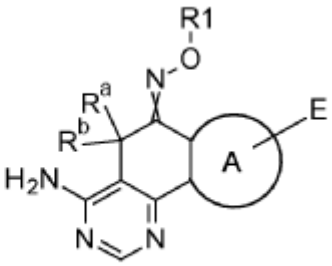
(Int-IA)



(Int-IB)



(Int-IIA)



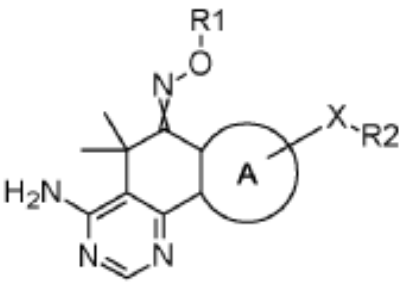
(Int-IIB)

or a salt thereof, wherein A, X, Ra, Rb and R2 are as defined for the compound of formula (IA) or the compound of formula (IB) disclosed herein, and E is halogen or -O-L1, and –O-L1 is a leaving group in which L1 is selected from a perfluoroalkylsulfonyl such as triflyl (trifluoromethansulfonyl) and a sulfonyl such as tosyl (p-toluenesulfonyl) or mesyl (methanesulfonyl).

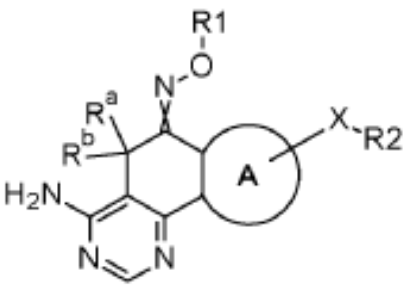
In a further aspect of the present disclosure, there is provided a compound of formula (IA) or a compound of formula (IB) disclosed herein or a pharmaceutically acceptable salt thereof, for use in therapy.

Description

In a first aspect the present invention provides compounds of formula (IA) and formula (IB)



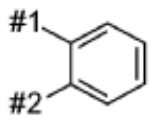
(IA)



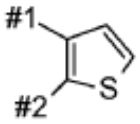
(IB)

and pharmaceutically acceptable salts thereof; wherein

A is selected from group (Al) and group (A2):



(A1)

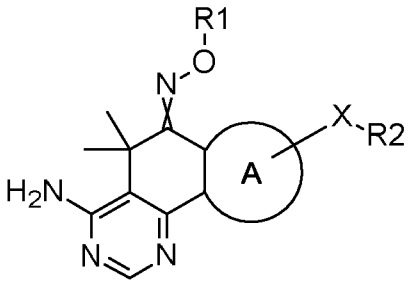


(A2)

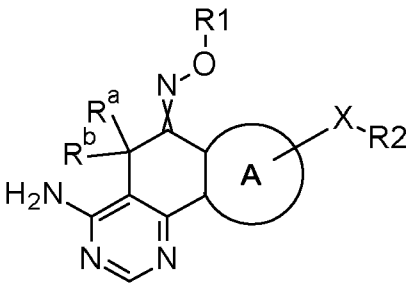
wherein #1 is attached to the carbon atom forming the oxime moiety and wherein group (Al) is optionally substituted by one or two R10 and group (A2) is optionally substituted by one R10;

Claims

1. A compound of formula (IA) or a compound of formula (IB)



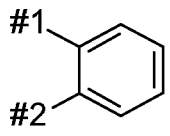
(IA)



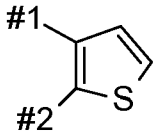
(IB)

or a pharmaceutically acceptable salt thereof; wherein

A is selected from group (A1) and group (A2):



(A1)



(A2)

wherein #1 is attached to the carbon atom forming the oxime moiety and wherein group (A1) is optionally substituted by one or two R10 and group (A2) is optionally substituted by one R10;

each R10 is independently halogen or $-NH_2$;

X is -O-, -C(=O)-, $-C(=CH_2)-$, $-CH_2-$, -NH- or -N(C1-C4alkyl)- and wherein X is a bond when R2 is halogen or -CN and wherein when X is -C(=O)- R2 is not hydrogen;

or X-R2 is hydrogen;

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

R1 is -Y-R3;

Y is a bond or C1-C6alkylene wherein one non-terminal $-CH_2-$ moiety may be replaced by -O-;

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)$_2$, Cycle P, Cycle Q, -O-Cycle P, -O-Cycle Q or $-S(O_2)-C1-C4alkyl$;

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

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

each R5 is independently $-NH_2$, -OH, -CN, C1-C4alkyl, C1-C4alkylene-R11, -O-C1-C2alkyl or oxo;

each R11 is independently halogen, $-NH_2$, -OH, -CN or -O-C1-C2alkyl;

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

each R6 is independently -NH_2, -OH, -CN, C1-C2alkyl or -O-C1-C2alkyl;
R2 is hydrogen, halogen, -CN, C1-C4alkyl optionally substituted by one or two R7, or is a 4- to 7-membered saturated carbocyclic ring optionally substituted by one or two R8, or is a 4- to 7-membered saturated heterocyclic ring containing one -N(R9)- moiety as ring member and otherwise containing only carbon atoms as ring members;
each R7 is independently -OH, halogen, -NH_2, -NH(C1-C2alkyl), -N(C1-C2alkyl)$_2$ or -NH(-C(=O)-C1-C2alkyl);
each R8 is independently -OH, halogen, -NH_2, -NH(C1-C2alkyl), -N(C1-C2alkyl)$_2$, -NH(-C(=O)-C1-C2alkyl) or C1-C2alkyl; and
R9 is hydrogen, C1-C4alkyl or -C(=O)-C1-C2alkyl.

2. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (IA).

3. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (IB)

4. The compound of any one of claims 1 to 3 or a pharmaceutically acceptable salt thereof, wherein when A is group (A1) X is connected to the carbon atom which is at the para position relative to #2 and when A is group (A2) X is connected to the carbon atom adjacent to the S atom.

5. The compound of any one of claims 1 to 4 or a pharmaceutically acceptable salt thereof, wherein A is group (A1).

6. The compound of any one of claims 1 to 4 or a pharmaceutically acceptable salt thereof, wherein A is group (A2).

7. The compound of any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof, wherein X is -O-, -C(=O)-, -C(=CH_2)-, -CH_2-, -NH- or -N(C1-C4alkyl)- and wherein X is a bond when R2 is halogen or -CN and wherein when X is -C(=O)- R2 is not hydrogen.

8. The compound of any one of claims 1 to 7 or a pharmaceutically acceptable salt thereof, wherein R1 is hydrogen or C1-C6alkylene-R3 wherein one non-terminal -CH_2- moiety may be replaced by -O-, or R1 is Cycle P.

9. The compound of any one of claims 1 to 7 or a pharmaceutically acceptable salt thereof, wherein R1 is hydrogen or C1-C3alkylene-R3.

10. The compound of claim 9 or a pharmaceutically acceptable salt thereof, wherein R3 is hydrogen, -CN, -OH, C1-C4haloalkyl, -O-C1-C4alkyl, -O-C1-C4haloalkyl, C2-C4alkynyl, -C(=O)-OH, -C(=O)-O-C1-C4alkyl, -C(=O)-NH_2 or -C(=O)-NH(C1-C4alkyl).

11. The compound of claim 9 or a pharmaceutically acceptable salt thereof, wherein R3 is oxazolidinyl-2-one optionally substituted by one R5, wherein R5 is C1-C4alkyl or C1-C4alkylene-R11.

12. The compound of any one of claims 1 to 9 or a pharmaceutically acceptable salt thereof, wherein R3 is hydrogen, -CN, -OH, C1-C4haloalkyl, C2-C4alkenyl, C2-C4alkynyl, -O-C1-C4alkyl, -O-C1-C4haloalkyl, -NH_2, -C(=O)-OH, -C(=O)-O-C1-C4alkyl, -C(=O)-NH_2, -C(=O)-NH(C1-C4alkylene-R4), Cycle P, Cycle Q, -O-Cycle P, -O-Cycle Q or -S(O_2)-C1-C4alkyl.

13. The compound of any one of claims 1 to 12 or a pharmaceutically acceptable salt thereof, wherein R2 is hydrogen, halogen, C1-C4alkyl optionally substituted by one or two R7, or is a 6-membered saturated carbocyclic ring optionally substituted by one or two R8, or is a 6-membered saturated heterocyclic ring containing one -N(R9)- moiety as ring member and otherwise containing only carbon atoms as ring members.

14. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein
A is selected from group (A1) and group (A2) and wherein group (A1) is optionally substituted by one or two R10 and group (A2) is optionally substituted by one R10;
each R10 is independently fluoro, chloro or -NH_2;
X is -O-, -C(=O)-, -C(=CH_2)-, -CH_2-, -NH- or -N(C1-C4alkyl)- and wherein X is a bond when R2 is halogen or -CN and wherein when X is -C(=O)- R2 is not hydrogen;
Ra and Rb together form a -CH_2-CH_2-CH_2-CH_2- bridging moiety;
R1 is -Y-R3;
Y is a bond or C1-C6alkylene wherein one non-terminal -CH_2- moiety may be replaced by -O-;
R3 is hydrogen, -CN, -OH, C1-C4haloalkyl, C2-C4alkenyl, C2-C4alkynyl, -O-C1-C4alkyl, -O-C1-C4haloalkyl, -NH_2, -C(=O)-OH, -C(=O)-O-C1-C4alkyl, -C(=O)-NH_2, -C(=O)-NH(C1-C4alkylene-R4), Cycle P, Cycle Q, -O-Cycle P, -O-Cycle Q or -S(O_2)-C1-C4alkyl;
R4 is hydrogen, -NH_2 or -NH(CH_3);
Cycle P is a 6-membered saturated carbocyclic ring optionally substituted by one to two R5 or is a 5-membered saturated heterocyclic ring containing one to two heteroatoms selected from N and O optionally substituted by one to two R5;
each R5 is independently -NH_2, -OH, -CN, C1-C2alkyl, -C1-C2alkyl-R11, -O-C1-C2alkyl or oxo;
each R11 is independently halogen, -NH_2, -OH, -CN or -O-C1-C2alkyl;

Cycle Q is phenyl optionally substituted by one or two R6, or is a 6-membered heteroaryl 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, $-CH_3$ or $-OCH_3$;

R2 is hydrogen, halogen, C1-C4alkyl optionally substituted by one or two R7, or is a 6-membered saturated carbocyclic ring optionally substituted by one or two R8 or is a 6-membered saturated heterocyclic ring containing one -N(R9)- moiety as ring member and otherwise containing only carbon atoms as ring members;

each R7 is independently halogen $-NH_2$ or -OH;

each R8 is independently halogen, $-NH_2$ or $-CH_3$; and

R9 is hydrogen or $-CH_3$.

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

A is group (A1) optionally substituted by one R10;

R10 is chloro or $-NH_2$;

X is connected to the carbon atom which is at the para position relative to #2;

X is -O-, -C(=O)-, $-C(=CH_2)-$, $-CH_2-$ or $-N(CH_3)-$ and wherein X is a bond when R2 is halogen and wherein when X is -C(=O)- R2 is not hydrogen;

Ra and Rb together form a $-CH_2-CH_2-CH_2-CH_2-$ bridging moiety;

R1 is hydrogen or C1-C6alkylene-R3;

R3 is hydrogen, -CN, -OH, C1-C4haloalkyl, -O-C1-C4alkyl, -O-C1-C4haloalkyl, C2-C4alkynyl, -C(=O)-OH, -C(=O)-O-C1-C4alkyl, $-C(=O)-NH_2$, -C(=O)-NH(C1-C4alkyl), phenyl, oxazolidinyl-2-one or oxazolidinyl-2-one substituted by one R5;

R5 is C1-C2alkyl or C1-C2alkyl-R11;

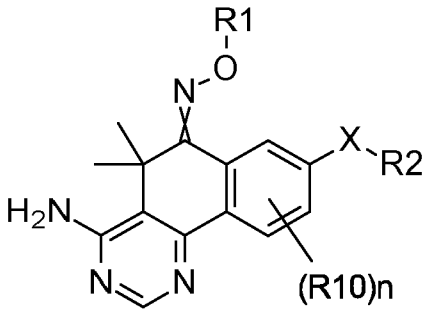
R11 is halogen, $-NH_2$, -OH, -CN or -O-C1-C2alkyl;

R2 is fluoro, chloro, bromo, iodo, $-CH_3$, C1-C4alkyl-R7, a 6-membered saturated carbocyclic ring substituted by one or two R8 wherein at least one R8 is $-NH_2$ and is at the para position with respect to X, or piperidin-4-yl;

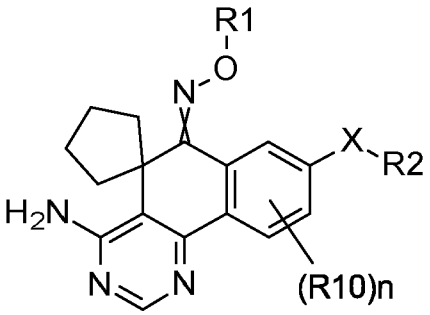
R7 is fluoro, $-NH_2$ or -OH; and

each R8 is independently fluoro, $-NH_2$ or $-CH_3$.

16. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (IAa) or a compound of formula (IBa)



(IAa)



(IBa)

wherein

R10 is chloro or -NH_2;

X is -O-, -C(=O)-, -C(=CH_2)-, -CH_2- or -N(CH_3)- and wherein X is a bond when R2 is halogen and wherein when X is -C(=O)- R2 is not hydrogen;

R1 is hydrogen or C1-C6alkylene-R3;

R3 is hydrogen, -CN, -OH, C1-C4haloalkyl, -O-C1-C4alkyl, -O-C1-C4haloalkyl, C2-C4alkynyl, -C(=O)-OH, -C(=O)-O-C1-C4alkyl, -C(=O)-NH_2, -C(=O)-NH(C1-C4alkyl), phenyl, oxazolidinyl-2-one or oxazolidinyl-2-one substituted by one R5;

R5 is C1-C2alkyl or C1-C2alkyl-R11;

R11 is halogen, -NH_2, -OH, -CN or -O-C1-C2alkyl;

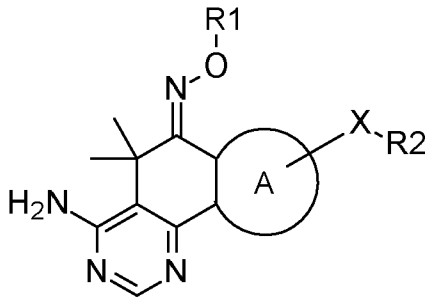
R2 is fluoro, chloro, bromo, iodo, -CH_3, C1-C4alkyl-R7, a 6-membered saturated carbocyclic ring substituted by one or two R8 wherein at least one R8 is -NH_2 and is at the para position with respect to X, or piperidin-4-yl;

R7 is fluoro, -NH_2 or -OH;

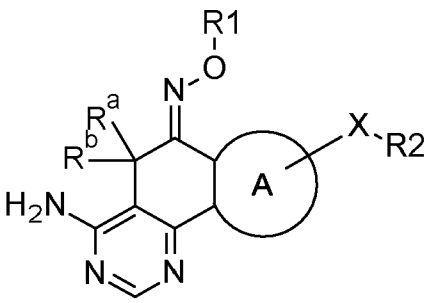
each R8 is independently fluoro, -NH_2 or -CH_3; and

n is 0 or 1.

17. The compound of any one of claims 1 to 16 or a pharmaceutically acceptable salt thereof, wherein the compound of formula (IA) and the compound of formula (IB) is the *Z* isomer of the oxime moiety:

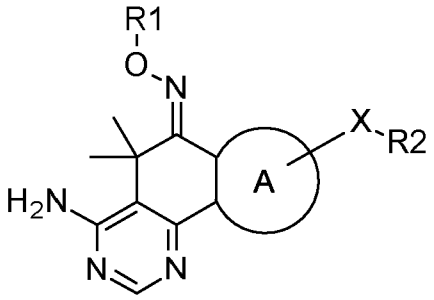


(IA-(*Z*))

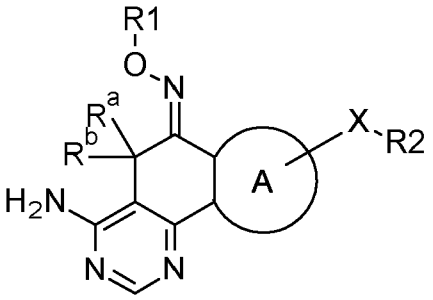


(IB-(*Z*)).

18. The compound of any one of claims 1 to 16 or a pharmaceutically acceptable salt thereof, wherein the compound of formula (IA) and the compound of formula (IB) is the *E* isomer of the oxime moiety:



(IA-(*E*))



(IB-(*E*)).

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

(6*E*)-8-(*trans*-4-aminocyclohexoxy)-6-methoxyimino-5,5-dimethyl-benzo[h]quinazolin-4-amine;

(6*Z*)-8-(*trans*-4-aminocyclohexoxy)-6-benzyloxyimino-5,5-dimethyl-benzo[h]quinazolin-4-amine;

(6*Z*)-8-(*trans*-4-aminocyclohexoxy)-6-methoxyimino-5,5-dimethyl-benzo[h]quinazolin-4-amine;

(6*E*)-4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-benzo[h]quinazolin-6-one oxime;

(6*Z*)-4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-benzo[h]quinazolin-6-one oxime;

methyl 3-[(*Z*)-[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-benzo[h]quinazolin-6-ylidene]amino]oxypropanoate;

3-[(*Z*)-[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-benzo[h]quinazolin-6-ylidene]amino]oxypropan-1-ol;

(6*Z*)-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6-[2-(1-piperidyl)ethoxyimino]benzo[h]quinazolin-4-amine;

(6*Z*)-8-(*trans*-4-aminocyclohexoxy)-6-[3-(diethylamino)propoxyimino]-5,5-dimethyl-benzo[h]quinazolin-4-amine;

(6*Z*)-8-(*trans*-4-aminocyclohexoxy)-6-[2-(diethylamino)ethoxyimino]-5,5-dimethyl-benzo[h]quinazolin-4-amine;

2-[(*Z*)-[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-benzo[h]quinazolin-6-ylidene]amino]oxyethanol;

4-[[(*Z*)-[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-benzo[h]quinazolin-6-ylidene]amino]oxymethyl]benzonitrile;

(6*Z*)-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6-prop-2-ynoxyimino-benzo[h]quinazolin-4-amine;

[(*Z*)-[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-benzo[h]quinazolin-6-ylidene]amino]oxyacetonitrile;

ethyl 3-[(*Z*)-[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-benzo[h]quinazolin-6-ylidene]amino]oxypropanoate;

(6*Z*)-8-(*trans*-4-aminocyclohexoxy)-6-ethoxyimino-5,5-dimethyl-benzo[h]quinazolin-4-amine;

(6*Z*)-8-(*trans*-4-aminocyclohexoxy)-6-[(3,5-dimethylisoxazol-4-yl)methoxyimino]-5,5-dimethyl-benzo[h]quinazolin-4-amine;

(6*Z*)-8-(*trans*-4-aminocyclohexoxy)-6-(3-benzyloxypropoxyimino)-5,5-dimethyl-benzo[h]quinazolin-4-amine;

4-[(*Z*)-[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-benzo[h]quinazolin-6-ylidene]amino]oxybutanenitrile;

(6*Z*)-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-6-(2-pyrrolidin-1-ylethoxyimino)benzo[h]quinazolin-4-amine;

(6*Z*)-8-(*trans*-4-aminocyclohexoxy)-6-(2-methoxyethoxyimino)-5,5-dimethyl-benzo[h]quinazolin-4-amine;

(6*Z*)-8-(*trans*-4-aminocyclohexoxy)-6-isobutoxyimino-5,5-dimethyl-benzo[h]quinazolin-4-amine;

methyl 2-[(*Z*)-[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-benzo[h]quinazolin-6-ylidene]amino]oxyacetate;

2-[(*Z*)-[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-benzo[h]quinazolin-6-ylidene]amino]oxyacetamide;

2-[(*Z*)-[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-benzo[h]quinazolin-6-ylidene]amino]oxy-*N*-methyl-acetamide;

5-[[(*Z*)-[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-benzo[h]quinazolin-6-ylidene]amino]oxymethyl]oxazolidin-2-one;

(6*Z*)-8-(*trans*-4-aminocyclohexoxy)-6-[2-(dimethylamino)ethoxyimino]-5,5-dimethyl-benzo[h]quinazolin-4-amine;

(6*Z*)-8-[1-(*trans*-4-aminocyclohexyl)vinyl]-6-methoxyimino-5,5-dimethyl-benzo[h]quinazolin-4-amine;

(6*E*)-8-[1-(*trans*-4-aminocyclohexyl)vinyl]-6-methoxyimino-5,5-dimethyl-benzo[h]quinazolin-4-amine;

2-[(*Z*)-(4-amino-8-methoxy-5,5-dimethyl-benzo[h]quinazolin-6-ylidene)amino]oxyacetic acid;

(6*Z*)-6-[(*trans*-4-aminocyclohexyl)methoxyimino]-8-methoxy-5,5-dimethyl-benzo[h]quinazolin-4-amine;

(6*Z*)-6-(*cis*-4-aminocyclohexoxy)imino-8-methoxy-5,5-dimethyl-benzo[h]quinazolin-4-amine;

(6*Z*)-6-(*trans*-4-aminocyclohexoxy)imino-8-methoxy-5,5-dimethyl-benzo[h]quinazolin-4-amine;

2-[(*Z*)-(4-amino-8-methoxy-5,5-dimethyl-benzo[h]quinazolin-6-ylidene)amino]oxyacetamide;

4-[(*Z*)-(4-amino-8-methoxy-5,5-dimethyl-benzo[h]quinazolin-6-ylidene)amino]oxybutanenitrile;

N-(2-aminoethyl)-2-[(*Z*)-(4-amino-8-methoxy-5,5-dimethyl-benzo[h]quinazolin-6-ylidene)amino]oxy-acetamide;

(5*S*)-5-[[(*Z*)-[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-benzo[h]quinazolin-6-ylidene]amino]oxymethyl]oxazolidin-2-one;

(5*R*)-5-[[(*Z*)-(4-amino-8-methoxy-5,5-dimethyl-benzo[h]quinazolin-6-ylidene)amino]oxymethyl]oxazolidin-2-one;

(5*S*)-5-[[(*Z*)-(4-amino-8-methoxy-5,5-dimethyl-benzo[h]quinazolin-6-ylidene)amino]oxymethyl]oxazolidin-2-one;

(6*Z*)-8-methoxy-6-methoxyimino-5,5-dimethyl-benzo[h]quinazolin-4-amine;

(6*Z*)-8-(*trans*-4-aminocyclohexoxy)-10-chloro-6-methoxyimino-5,5-dimethyl-benzo[h]quinazolin-4-amine;

(5*R*)-5-[[(*Z*)-[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-benzo[h]quinazolin-6-ylidene]amino]oxymethyl]oxazolidin-2-one;

(6*Z*)-9-chloro-8-methoxy-6-methoxyimino-5,5-dimethyl-benzo[h]quinazolin-4-amine;

(6*E*)-7-chloro-8-methoxy-6-methoxyimino-5,5-dimethyl-benzo[h]quinazolin-4-amine;

(6*E*)-8-methoxy-6-methoxyimino-5,5-dimethyl-benzo[h]quinazoline-4,7-diamine;

(6*Z*)-8-methoxy-6-methoxyimino-5,5-dimethyl-benzo[h]quinazoline-4,9-diamine;

(6*Z*)-7-chloro-8-methoxy-6-methoxyimino-5,5-dimethyl-benzo[h]quinazolin-4-amine;

(6*Z*)-*N*8-(*trans*-4-aminocyclohexyl)-6-methoxyimino-*N*8,5,5-trimethyl-benzo[h]quinazoline-4,8-diamine;

(6*Z*)-8-(*trans*-4-aminocyclohexoxy)-6-methoxyimino-5,5-dimethyl-thieno[3,2-h]quinazolin-4-amine;

(5*S*)-5-[[(*Z*)-(4-amino-8-methoxy-5,5-dimethyl-benzo[h]quinazolin-6-ylidene)amino]oxymethyl]-3-methyl-oxazolidin-2-one;

(5*S*)-5-[[(*Z*)-(4-amino-8-bromo-5,5-dimethyl-benzo[h]quinazolin-6-ylidene)amino]oxymethyl]oxazolidin-2-one;

(5*S*)-5-[[(*Z*)-(4-amino-8-chloro-5,5-dimethyl-benzo[h]quinazolin-6-ylidene)amino]oxymethyl]-3-methyl-oxazolidin-2-one;

(5*S*)-5-[[(*Z*)-(4-amino-8-chloro-5,5-dimethyl-benzo[h]quinazolin-6-ylidene)amino]oxymethyl]-3-methyl-oxazolidin-2-one;

(6*Z*)-8-(*cis*-4-aminocyclohexoxy)-6-methoxyimino-5,5-dimethyl-benzo[h]quinazolin-4-amine

3-[(*Z*)-[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-benzo[h]quinazolin-6-ylidene]amino]oxypropanenitrile;

(5*S*)-5-[[(*Z*)-[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-benzo[h]quinazolin-6-ylidene]amino]oxymethyl]-3-methyl-oxazolidin-2-one;

(6Z)-6-methoxyimino-5,5-dimethyl-8-[-(1*R*,3*S*,4*R*)-4-amino-3-fluoro-cyclohexoxy]benzo[h]quinazolin-4-amine;

(6*Z*)-6-(2-aminoethoxyimino)-8-methoxy-5,5-dimethyl-benzo[h]quinazolin-4-amine;

(6*Z*)-6-(3-aminopropoxyimino)-8-methoxy-5,5-dimethyl-benzo[h]quinazolin-4-amine;

3-[(*E*)-[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-benzo[h]quinazolin-6-ylidene]amino]oxypropanenitrile;

(6*Z*)-4-amino-6-methoxyimino-5,5-dimethyl-benzo[h]quinazolin-8-ol;

(6*Z*)-8-methoxy-5,5-dimethyl-6-[[(3*R*)-pyrrolidin-3-yl]methoxyimino]benzo[h]quinazolin-4-amine;

(6*E*)-8-methoxy-5,5-dimethyl-6-[[(3*R*)-pyrrolidin-3-yl]methoxyimino]benzo[h]quinazolin-4-amine;

(6*Z*)-6-allyloxyimino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-benzo[h]quinazolin-4-amine;

(6*E*)-6-allyloxyimino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-benzo[h]quinazolin-4-amine;

(6*Z*)-6-methoxyimino-5,5-dimethyl-8-(4-piperidyloxy)benzo[h]quinazolin-4-amine;

(6*Z*)-8-(*trans*-4-aminocyclohexoxy)-6-isopropoxyimino-5,5-dimethyl-benzo[h]quinazolin-4-amine;
(6*E*)-8-(*trans*-4-aminocyclohexoxy)-6-isopropoxyimino-5,5-dimethyl-benzo[h]quinazolin-4-amine;
(6*Z*)-6-methoxyimino-*N*8,5,5-trimethyl-*N*8-(4-piperidyl)benzo[h]quinazoline-4,8-diamine;
(6*Z*)-6-methoxyimino-5,5-dimethyl-8-(4-piperidylmethyl)benzo[h]quinazolin-4-amine;
(6*Z*)-8-methoxy-5,5-dimethyl-6-[[(3*S*)-1-methylpyrrolidin-3-yl]methoxyimino]benzo[h]quinazolin-4-amine;
(4*S*)-4-[[(*Z*)-(4-amino-8-methoxy-5,5-dimethyl-benzo[h]quinazolin-6-ylidene)amino]oxymethyl]pyrrolidin-2-one;
(4*R*)-4-[[(*Z*)-(4-amino-8-methoxy-5,5-dimethyl-benzo[h]quinazolin-6-ylidene)amino]oxymethyl]pyrrolidin-2-one;
(6*Z*)-8-[(*trans*-4-aminocyclohexyl)methyl]-6-methoxyimino-5,5-dimethyl-benzo[h]quinazolin-4-amine;
(6*Z*)-8-[(*cis*-4-aminocyclohexyl)methyl]-6-methoxyimino-5,5-dimethyl-benzo[h]quinazolin-4-amine;
(4*S*)-4-[[(*Z*)-(4-amino-8-methoxy-5,5-dimethyl-benzo[h]quinazolin-6-ylidene)amino]oxymethyl]-1-methyl-pyrrolidin-2-one;
(6*Z*)-10-fluoro-8-methoxy-6-methoxyimino-5,5-dimethyl-benzo[h]quinazolin-4-amine;
(2*R*)-1-[(*Z*)-[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-benzo[h]quinazolin-6-ylidene]amino]oxypropan-2-ol;
(2*S*)-1-[(*Z*)-[4-amino-8-(*trans*-4-aminocyclohexoxy)-5,5-dimethyl-benzo[h]quinazolin-6-ylidene]amino]oxypropan-2-ol;
(6*Z*)-8-bromo-6-(2-methoxyethoxyimino)-5,5-dimethyl-benzo[h]quinazolin-4-amine;
3-[(*Z*)-(4-amino-8-bromo-5,5-dimethyl-benzo[h]quinazolin-6-ylidene)amino]oxypropanenitrile;
(6*Z*)-8-(*cis*-4-aminocyclohexoxy)-6-(2-methoxyethoxyimino)-5,5-dimethyl-benzo[h]quinazolin-4-amine;
3-[(*Z*)-[4-amino-8-(*cis*-4-aminocyclohexoxy)-5,5-dimethyl-benzo[h]quinazolin-6-ylidene]amino]oxypropanenitrile;
(*Z*)-4-amino-8-bromo-5,5-dimethyl-benzo[h]quinazolin-6-one oxime;
(*E*)-4-amino-8-bromo-5,5-dimethyl-benzo[h]quinazolin-6-one oxime;
2-[(*Z*)-(4-amino-8-bromo-5,5-dimethyl-benzo[h]quinazolin-6-ylidene)amino]oxyethanol;
2-[(*Z*)-[4-amino-8-(*cis*-4-aminocyclohexoxy)-5,5-dimethyl-benzo[h]quinazolin-6-ylidene]amino]oxyethanol;
(5*S*)-5-[[(*Z*)-[4-amino-8-(*cis*-4-aminocyclohexoxy)-5,5-dimethyl-benzo[h]quinazolin-6-ylidene]amino]oxymethyl]-3-methyl-oxazolidin-2-one;
(6*Z*)-8-bromo-6-methoxyimino-5,5-dimethyl-benzo[h]quinazolin-4-amine;
(5*S*)-5-[[(*Z*)-(4-amino-8-bromo-5,5-dimethyl-benzo[h]quinazolin-6-ylidene)amino]oxymethyl]-3-(2-methoxyethyl)oxazolidin-2-one;
(5*S*)-5-[[(*Z*)-(4-amino-8-bromo-5,5-dimethyl-benzo[h]quinazolin-6-ylidene)amino]oxymethyl]-3-(2-hydroxyethyl)oxazolidin-2-one;

(6*Z*)-4-amino-5,5-dimethyl-6-[[(5*S*)-2-oxooxazolidin-5-yl]methoxyimino]benzo[h]quinazoline-8-carbonitrile;

(5*S*)-5-[[(*Z*)-(4-amino-8-iodo-5,5-dimethyl-benzo[h]quinazolin-6-ylidene)amino]oxymethyl]oxazolidin-2-one;

(5*S*)-5-[[(*Z*)-[4-amino-8-(2-hydroxyethoxy)-5,5-dimethyl-benzo[h]quinazolin-6-ylidene]amino]oxymethyl]oxazolidin-2-one;

(6*Z*)-*N*8-(*trans*-4-aminocyclohexyl)-6-(2-methoxyethoxyimino)-5,5-dimethyl-benzo[h]quinazoline-4,8-diamine;

(6*Z*)-*N*8-(*cis*-4-aminocyclohexyl)-6-(2-methoxyethoxyimino)-5,5-dimethyl-benzo[h]quinazoline-4,8-diamine;

(5*S*)-5-[[(*Z*)-(4-amino-8-iodo-5,5-dimethyl-benzo[h]quinazolin-6-ylidene)amino]oxymethyl]-3-(2-hydroxyethyl)oxazolidin-2-one;

(5*S*)-5-[[(*Z*)-(8-acetyl-4-amino-5,5-dimethyl-benzo[h]quinazolin-6-ylidene)amino]oxymethyl]oxazolidin-2-one;

(6*Z*)-8-(*trans*-4-aminocyclohexoxy)-6-(2-methoxyethoxyimino)spiro[benzo[h]quinazoline-5,1'-cyclopentane]-4-amine;

(6*Z*)-8-(*cis*-4-aminocyclohexoxy)-6-(2-methoxyethoxyimino)spiro[benzo[h]quinazoline-5,1'-cyclopentane]-4-amine;

3-[(*Z*)-[4-amino-8-(*cis*-4-aminocyclohexoxy)spiro[benzo[h]quinazoline-5,1'-cyclopentane]-6-ylidene]amino]oxypropanenitrile;

3-[(*Z*)-[4-amino-8-(*trans*-4-aminocyclohexoxy)spiro[benzo[h]quinazoline-5,1'-cyclopentane]-6-ylidene]amino]oxypropanenitrile;

(6*Z*)-8-(*cis*-4-amino-4-methyl-cyclohexoxy)-6-(2-methoxyethoxyimino)-5,5-dimethyl-benzo[h]quinazoline-4-amine;

4-amino-8-(*cis*-4-aminocyclohexoxy)spiro[benzo[h]quinazoline-5,1'-cyclopentane]-6-one oxime;

(6*Z*)-8-(*cis*-4-aminocyclohexoxy)-5,5-dimethyl-6-[2-(trifluoromethoxy)ethoxyimino]benzo[h]quinazoline-4-amine;

(6*Z*)-8-(*cis*-4-aminocyclohexoxy)-5,5-dimethyl-6-(2-phenylethoxyimino)benzo[h]quinazoline-4-amine;

(6*Z*)-8-(*cis*-4-aminocyclohexoxy)-5,5-dimethyl-6-(2-phenoxyethoxyimino)benzo[h]quinazoline-4-amine;

(6*Z*)-8-(*cis*-4-aminocyclohexoxy)-5,5-dimethyl-6-[3-(3-pyridyl)propoxyimino]benzo[h]quinazoline-4-amine;

(6*Z*)-8-(*cis*-4-aminocyclohexoxy)-6-(2-ethoxyethoxyimino)-5,5-dimethyl-benzo[h]quinazoline-4-amine;

(6*Z*)-8-(*cis*-4-aminocyclohexoxy)-5,5-dimethyl-6-(3-methylsulfonylpropoxyimino)benzo[h]quinazoline-4-amine;

4-[(*Z*)-[4-amino-8-(*cis*-4-aminocyclohexoxy)-5,5-dimethyl-benzo[h]quinazolin-6-ylidene]amino]oxy-2,2-dimethyl-butanenitrile;

(6*Z*)-8-(*cis*-4-aminocyclohexoxy)-5,5-dimethyl-6-[2-(2,2,2-trifluoroethoxy)ethoxyimino]benzo[h]quinazolin-4-amine;
(6*Z*)-8-(*cis*-4-aminocyclohexoxy)-6-(4-fluorobutoxyimino)-5,5-dimethyl-benzo[h]quinazolin-4-amine;
(6*Z*)-8-(*cis*-4-aminocyclohexoxy)-5,5-dimethyl-6-(4,4,4-trifluorobutoxyimino)benzo[h]quinazolin-4-amine;
(6*Z*)-8-(*cis*-4-aminocyclohexoxy)-6-(3,3-difluorobutoxyimino)-5,5-dimethyl-benzo[h]quinazolin-4-amine; and
(6*Z*)-8-(*cis*-4aminocyclohexoxy)-5,5-dimethyl-6-(3,3,3-trifluoropropoxyimino)benzo[h]quinazoline-4-amine.

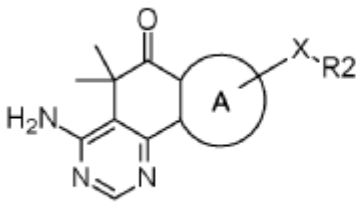
~~20. A compound of formula (IA) or a compound of formula (IB) as defined in any one of claims 1 to 19 or a pharmaceutically acceptable salt thereof, for use in the treatment of a neoplastic disease, preferably cancer, in a subject selected from a mammal, in particular a human.~~

20~~21~~. Use of a compound of formula (IA) or a compound of formula (IB) as defined in any one of claims 1 to 19 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a neoplastic disease, preferably cancer, in a subject selected from a mammal, in particular a human.

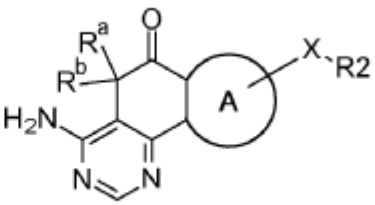
~~22. A method of treating a neoplastic disease, preferably cancer, in a subject selected from a mammal, in particular a human, comprising administering a compound of formula (IA) or a compound of formula (IB) as defined in any one of claims 1 to 19 or a pharmaceutically acceptable salt thereof in a therapeutically acceptable amount to said subject.~~

~~23~~21. A pharmaceutical composition comprising a compound of formula (IA) or a compound of formula (IB) as defined in any one of claims 1 to 19 or a pharmaceutically acceptable salt thereof and optionally one or more pharmaceutically acceptable excipients.

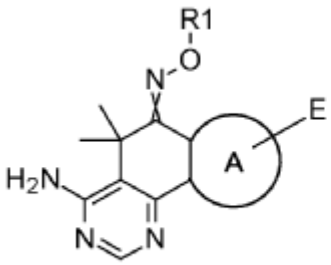
22~~24~~. A compound of formula (Int-IA), (Int-IB), (Int-IIA) or a compound of formula (Int-IIB)



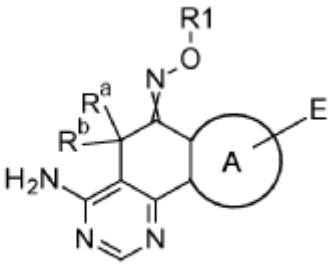
(Int-IA)



(Int-IB)



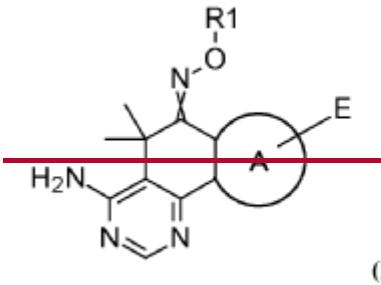
(Int-IIA)



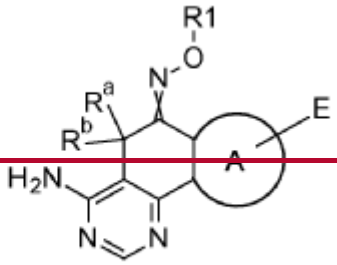
(Int-IIB)

or a salt thereof, wherein A, X, Ra, Rb and R2 are as defined for the compound of formula (IA) or the compound of formula (IB) in any one of claims 1 to 19.

~~25. A compound of formula (Int-IIA) or a compound of formula (Int-IIB)~~



(Int-IIA)



(Int-IIB)

~~or a salt thereof, wherein A, Ra, Rb and R1 are as defined for the compound of formula (IA) or the compound of formula (IB) in any one of claims 1 to 19~~ and E is halogen or -O-L1, and –O-L1 is a leaving group in which L1 is selected from a perfluoroalkylsulfonyl such as triflyl (trifluoromethansulfonyl) and a sulfonyl such as tosyl (p-toluenesulfonyl) or mesyl (methanesulfonyl).

23. A compound of formula (IA) or a compound of formula (IB) as defined in any one of claims 1 to 19 or a pharmaceutically acceptable salt thereof, for use in therapy.