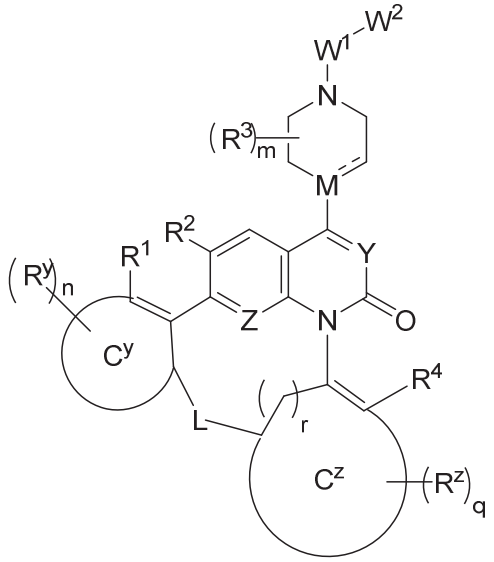
most, 70-75%, to cancer cases having the KRAS G12C mutation. *See* Lindsay, C.R., *et al.*, *Br J Cancer* 121, 197–198 (2019).

Accordingly, while progress has been made in this field, there remains a need in the art for improved compounds and methods for treatment of cancer, for example, by inhibition of a mutant KRAS, HRAS or NRAS protein (*e.g.*, KRAS G12C). Embodiments of the present disclosure fulfill this need and provide further related advantages.

SUMMARY OF THE DISCLOSURE

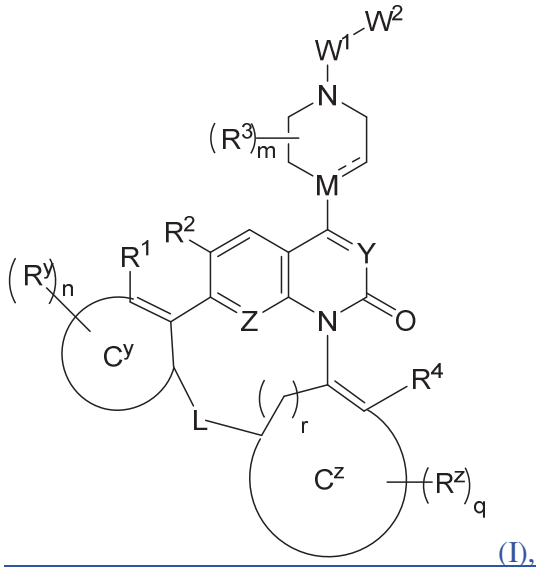
The present disclosure provides compounds which modulate mutant KRAS, HRAS, and/or NRAS proteins and may be valuable pharmaceutically active compounds for the treatment of cancer. In some embodiments the disclosed compounds selectively inhibit the KRAS (G12C) protein. The compounds of Formula (I)



(I)

and their pharmaceutically acceptable salts, can modulate the activity of KRAS, HRAS and/or NRAS activity and thereby effect the signaling pathway which regulates cell growth, differentiation, and proliferation associated with oncological disorders. In certain embodiments, the compounds of Formula (I) can inhibit the KRAS (G12C) protein. The disclosure furthermore provides processes for preparing compounds of Formula (I), methods for using such compounds to treat oncological disorders, and pharmaceutical compositions which comprise compounds of Formula (I).

In one aspect, provided herein is a compound of Formula (I)



(I),

wherein:

Y is N or C(H);

Z is N or C(R^5);

M is C or N;

the dashed line in the illustrated ring containing M indicates an optional double bond;

L is C_1-C_7 alkylene or C_1-C_7 heteroalkylene,

wherein said alkylene or heteroalkylene is unsubstituted or substituted by 1 to 5 substituents which are independently selected from oxo, fluoro, C_1-C_3 alkyl, C_1-C_3 fluoroalkyl, amino, and hydroxy;

or alternatively, two geminal, vicinal or hominal substitutions of said alkylene or heteroalkylene can, together with the carbon atoms to which they are attached, form a ring C^L, wherein said ring C^L is C_3-C_6 cycloalkyl, and wherein said ring C^L is unsubstituted or substituted by 1 to 3 fluoro;

R^1 is halo, H, C_1-C_4 alkyl, C_1-C_4 fluoroalkyl, or C_1-C_4 hydroxyalkyl;

R^2 is H, CH_3, or halo;

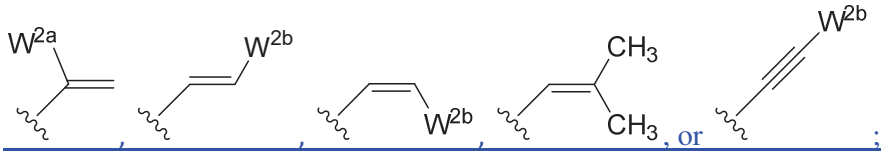
each R^3 is independently:

(a) C_1-C_4 alkyl, C_1-C_4 cyanoalkyl, C_1-C_4 fluoroalkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 alkylphenyl, oxo, or carboxy;

(b) or, alternatively, two R^3 substituents, together with the carbon atoms to which they are attached, can form a 3- to 6-membered bicyclo- or spirocyclic ring system with the illustrated ring containing M;

W^1 is -C(O)- or -$S(O)_2$-;

W^2 is a group of the formula:

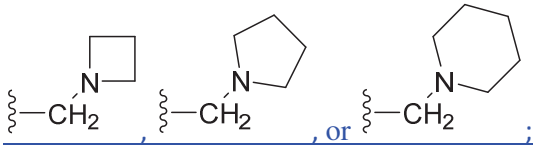


, , , , , or ;

wherein

W^{2a} is H, CH_3, F, cyano, CH_2OH, CH_2CH_2OH, or CH_2Br;

W^{2b} is CH_3, CH_2NH_2, $CH_2N(H)CH_3$, $CH_2N(CH_3)_2$, CH_2-NH-cyclopropyl,



, , or ;

R^4 is H, C_1-C_4 alkyl, or C_3-C_5 cycloalkyl;

R^5 is H or halo;

ring C^Y is:

(a) phenyl,

(b) a 5- to 6-membered monocyclic heteroaryl containing one to three heteroatoms selected from N, O, and S; or

(c) a 9- to 10-membered bicyclic heteroaryl containing one to four heteroatoms selected from N, O, and S;

each R^Y is independently halo, hydroxy, C_1-C_3 alkyl, C_1-C_3 fluoroalkyl, C_1-C_3 alkoxy, cyano, hydroxy, or C_1-C_3 hydroxyalkyl;

ring C^Z is:

(a) phenyl, or

(b) a 5- to 6-membered heteroaryl containing one to three heteroatoms selected from N, O, and S;

each R^Z is independently halo, hydroxy, C_1-C_3 alkyl, C_1-C_3 fluoroalkyl, C_1-C_3 alkoxy, cyano, or C_1-C_3 hydroxyalkyl;

the subscript m is 0, 1, 2, or 3;

the subscript n is 0, 1, 2, 3, or 4;

the subscript q is 0, 1, 2, 3, or 4; and

the subscript r is 0 or 1;

or a pharmaceutically acceptable salt thereof.

In one aspect, provided herein is a pharmaceutical composition comprising the compound as described herein, or the pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In one aspect, provided herein is a method of inhibiting KRAS G12C protein comprising contacting KRAS G12C protein with the compound as described herein, or the pharmaceutically acceptable salt thereof, to inhibit the activity of the KRAS G12C protein.

In one aspect, provided herein is a use of the compound as described herein, or the pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer, wherein the medicament is to be administered to a subject in need of such treatment.

In one aspect, provided herein is a compound as described herein, or the pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising the compound as described herein, or the pharmaceutically acceptable salt thereof, for use in therapy.

In one aspect, provided herein is a compound as described herein, or the pharmaceutically acceptable salt thereof, for use in treating cancer.

In one aspect, provided herein is a use of the compound as described herein, or the pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment of cancer.

In one aspect, provided herein is the compound as described herein, or the pharmaceutically acceptable salt thereof, and an additional anti-cancer agent, for use in therapy or for use in the treatment of cancer.

In one aspect, provided herein is a use of the compound as described herein, or the pharmaceutically acceptable salt thereof, and an additional anti-cancer agent, for the preparation of a medicament for the treatment of cancer.

In one aspect, provided herein is a pharmaceutical composition comprising the compound as described herein, or the pharmaceutically acceptable salt thereof, for use in the treatment of cancer, or use of the pharmaceutical composition comprising the compound as described herein, or the pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer.

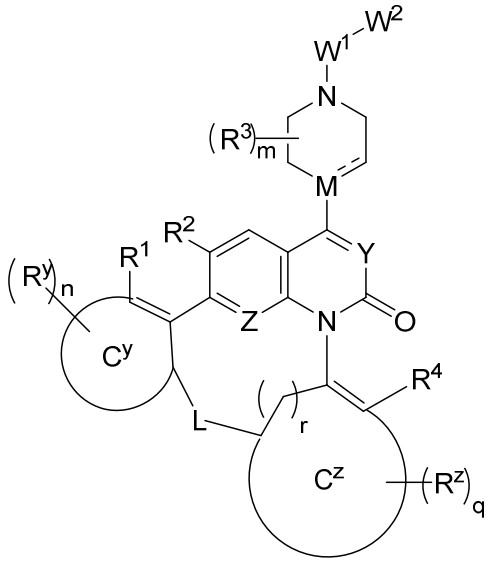
In one aspect, provided herein is a pharmaceutical composition comprising the compound as described herein, or the pharmaceutically acceptable salt thereof, and an additional anti-cancer agent, for use in therapy or for use in the treatment of cancer, or use of the pharmaceutical composition comprising the compound as described herein, or the pharmaceutically acceptable salt thereof, and an additional anti-cancer agent in the manufacture of a medicament, for treating cancer.

DETAILED DESCRIPTION OF THE INVENTION

CLAIMS

We claim:

1. A compound of Formula (I)



(I),

wherein:

Y is N or C(H);

Z is N or C(R^5);

M is C or N;

the dashed line in the illustrated ring containing M indicates an optional double bond;

L is C_1-C_7 alkylene or C_1-C_7 heteroalkylene,

wherein said alkylene or heteroalkylene is unsubstituted or substituted by 1 to 5 substituents which are independently selected from oxo, fluoro, C_1-C_3 alkyl, C_1-C_3 fluoroalkyl, amino, and hydroxy;

or alternatively, two geminal, vicinal or hominal substitutions of said alkylene or heteroalkylene can, together with the carbon atoms to which they are attached, form a ring C^L, wherein said ring C^L is C_3-C_6 cycloalkyl, and wherein said ring C^L is unsubstituted or substituted by 1 to 3 fluoro;

R^1 is halo, H, C_1-C_4 alkyl, C_1-C_4 fluoroalkyl, or C_1-C_4 hydroxyalkyl;

R^2 is H, CH_3, or halo;

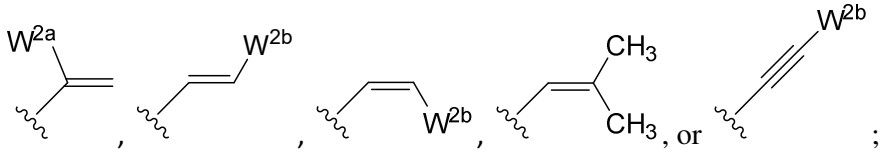
each R^3 is independently:

(a) C_1-C_4 alkyl, C_1-C_4 cyanoalkyl, C_1-C_4 fluoroalkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 alkylphenyl, oxo, or carboxy;

(b) or, alternatively, two R^3 substituents, together with the carbon atoms to which they are attached, can form a 3- to 6-membered bicyclo- or spirocyclic ring system with the illustrated ring containing M;

W^1 is -C(O)- or -$S(O)_2$-;

W^2 is a group of the formula:

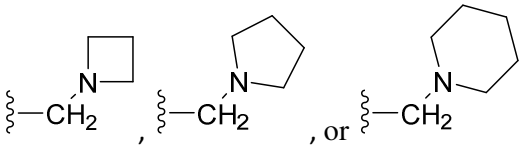


, , , , or ;

wherein

W^{2a} is H, CH_3, F, cyano, CH_2OH, CH_2CH_2OH, or CH_2Br;

W^{2b} is CH_3, CH_2NH_2, $CH_2N(H)CH_3$, $CH_2N(CH_3)_2$, CH_2-NH-cyclopropyl,



, , or ;

R^4 is H, C_1-C_4 alkyl, or C_3-C_5 cycloalkyl;

R^5 is H or halo;

ring C^y is:

(a) phenyl,

(b) a 5- to 6-membered monocyclic heteroaryl containing one to three heteroatoms selected from N, O, and S; or

(c) a 9- to 10-membered bicyclic heteroaryl containing one to four heteroatoms selected from N, O, and S;

each R^y is independently halo, hydroxy, C_1-C_3 alkyl, C_1-C_3 fluoroalkyl, C_1-C_3 alkoxy, cyano, hydroxy, or C_1-C_3 hydroxyalkyl;

ring C^z is:

(a) phenyl, or

(b) a 5- to 6-membered heteroaryl containing one to three heteroatoms selected from N, O, and S;

each R^z is independently halo, hydroxy, C_1-C_3 alkyl, C_1-C_3 fluoroalkyl, C_1-C_3 alkoxy, cyano, or C_1-C_3 hydroxyalkyl;

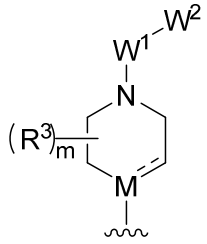
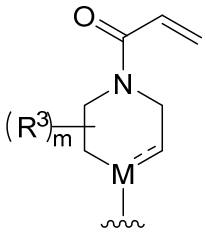
the subscript m is 0, 1, 2, or 3;

the subscript n is 0, 1, 2, 3, or 4;

the subscript q is 0, 1, 2, 3, or 4; and

the subscript r is 0 or 1;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1 or the pharmaceutically acceptable salt thereof, wherein the group  is ;

each R^3 is independently:

(a) C_1-C_4 alkyl, C_1-C_4 cyanoalkyl, C_1-C_4 fluoroalkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 alkylphenyl, oxo, or carboxy;

(b) or, alternatively, two R^3 substituents, together with the carbon atoms to which they are attached, can form a 3- to 6-membered bicyclo- or spirocyclic ring system with the illustrated ring containing M; and

each R^y is independently halo, hydroxy, C_1-C_3 alkyl, C_1-C_3 fluoroalkyl, C_1-C_3 alkoxy, cyano, hydroxy, or C_1-C_3 hydroxyalkyl.

3. The compound of claim 1 or 2 or the pharmaceutically acceptable salt thereof, wherein L is a group -X^1-X^2-X^5-X^4-X^3-, wherein:

X^1 and X^3 are independently -CH_2-, -O-, -S-, -C(O)-, -C(H)(CH_3)-, or -N(H)-;

X^2 is -CH_2-, -CF_2-, -C(H)(F)-, -C(H)(OH)-, -C(H)(CH_3)-, -O-, -S-, -N(H)-, or -C(O)-;

X^4 is absent, -CF_2-, -C(H)(F)-, -C(H)(OH)-, -C(H)(CH_3)-, -CH_2-, -O-, -S-, -N(H)-, or -C(O)-;

X^5 is absent, -CH_2-, -CF_2-, -C(H)(F)-, -O-, -S-, -N(H)-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -O-CH_2-, -CH_2-O-;

wherein:

when X^1 is -O-, -S-, or -N(H)-, then X^2 is -CH_2- or -C(O)-;

when X^2 is -O-, -S-, or -N(H)-, then X^1 is -CH_2- or –C(O)- and X^5, if present, is -CH_2-, -CF_2-, -CH_2CH_2-, or -$CH_2CH_2CH_2$-;

when X^3 is -O-, -S-, or -N(H)-, then X^4 is $-CH_2-$ or -C(O)-;

when X^4 is -O-, -S-, or -N(H)- then X^3 is $-CH_2-$ and X^5, if present, is $-CH_2-$, $-CH_2CH_2-$, or $-CH_2CH_2CH_2-$; and

when X^5 is -O-, -S-, or -N(H)-, then X^2 and X^4 are both $-CH_2-$.

4. The compound of claim 3 or the pharmaceutically acceptable salt thereof, wherein the group $-X^1-X^2-X^5-X^4-X^3-$ is:

$-O-CH_2CH_2CH_2-O-$;

$-CH_2CH_2CH_2-O-$;

$-O-CH_2CH_2CH_2-$;

$-O-C(H)(CH_3)CH_2CH_2-$;

$-O-CH_2CH_2CH_2CH_2-$;

$-O-CH_2CF_2CH_2CH_2-$;

$-CH_2CH_2CH_2CH_2-O-$;

$-CH_2CH_2CH_2CH_2-$;

$-CH_2CH_2CH_2-$;

$-CH_2CH_2C(H)(OH)CH_2-$;

$-CH_2C(H)(OH)CH_2CH_2-$;

$-O-CH_2CH_2-$;

$-CH_2CH_2-O-$;

$-O-CH_2CH_2-O-$;

$-O-CH_2C(H)(CH_3)-O-$;

$-O-C(H)(CH_3)\ CH_2-O-$;

$-O-CH_2CF_2CH_2-O-$;

$-CH_2CH_2-O-CH_2CH_2-$;

$-O-CH_2CH_2-O-CH_2CH_2-O-$;

$-CH_2-O-CH_2CH_2-$;

$-CH_2CH_2-O-CH_2-$;

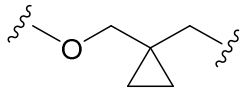
$-N(H)-CH_2CH_2CH_2-$;

$-O-CH_2CH_2-O-CH_2-$;

$-C(O)-N(H)-CH_2CH_2CH_2-$;

-$CH_2CH_2CH_2$-N(H)-C(O)-;

-N(H)-CH_2CH_2-O-CH_2-;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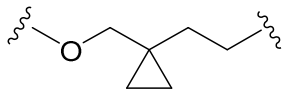

.

5. The compound of claim 4 or the pharmaceutically acceptable salt thereof, wherein the group -X^1-X^2-X^5-X^4-X^3- is:

-O-$CH_2CH_2CH_2$-O-;

-$CH_2CH_2CH_2$-O-;

-O-$CH_2CH_2CH_2$-;

-O-$CH_2CH_2CH_2CH_2$-;

-$CH_2CH_2CH_2CH_2$-;

-O-CH_2CH_2-;

-O-CH_2CH_2-O-;

-O-$CH_2CF_2CH_2$-O-;

-CH_2CH_2-O-CH_2CH_2-;

-C(O)-N(H)-$CH_2CH_2CH_2$-; or

-CH_2-O-CH_2CH_2-.

6. The compound of claim 4 or the pharmaceutically acceptable salt thereof, wherein the group -X^1-X^2-X^5-X^4-X^3- is:

-O-$CH_2CH_2CH_2$-;

-O-$CH_2CH_2CH_2CH_2$-;

-O-CH_2CH_2-O-; or

-O-$CH_2CF_2CH_2CH_2$-.

7. The compound of any one of claims 1-6 or the pharmaceutically acceptable salt thereof, wherein R^1 is fluoro.

8. The compound of any one of claims 1-7 or the pharmaceutically acceptable salt thereof, wherein R^2 is fluoro or chloro.

9. The compound of any one of claims 1-8 or the pharmaceutically acceptable salt thereof, wherein R^4 is H or isopropyl.

10. The compound of any one of claims 1-9 or the pharmaceutically acceptable salt thereof, wherein the subscript m is 1 or 2, and R^3 is methyl or -CH_2-CN.

11. The compound of any one of claims 1-10 or the pharmaceutically salt thereof, wherein M is N.

12. The compound of any one of claims 1-11 or the pharmaceutically acceptable salt thereof, wherein C^y is phenyl.

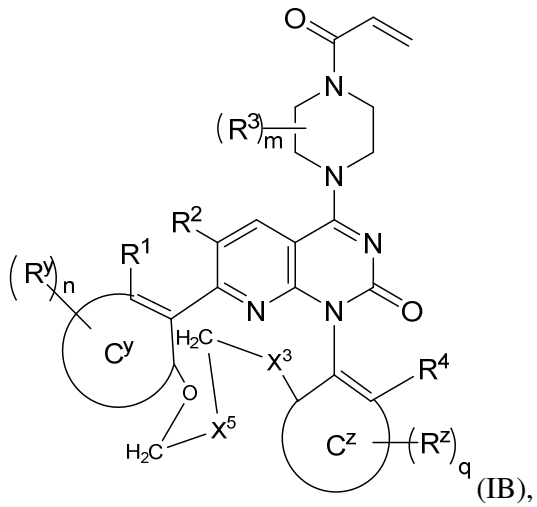
13. The compound of any one of claims 1-12 or the pharmaceutically acceptable salt thereof, wherein C^z is phenyl or pyridine.

14. The compound of any one of claims 1-13 or the pharmaceutically acceptable salt thereof, wherein Y is N.

15. The compound of any one of claims 1-14 or the pharmaceutically acceptable salt thereof, wherein Z is N.

16. The compound of any one of claims 1-15 or the pharmaceutically acceptable salt thereof, wherein the subscript r is 0.

17. The compound of claim 1 or the pharmaceutically acceptable salt thereof, wherein the compound of Formula (I) has Formula (IB)



(IB),

wherein:

C^y is phenyl;

C^z is pyridyl;

X^3 is $-CH_2-$ or $-O-$;

X^5 is absent, $-CH_2-$, $-CF_2-$, or $-C(H)(F)-$;

R^1 is fluoro or chloro;

R^2 is fluoro or chloro; and

R^4 is C_1-C_4 alkyl.

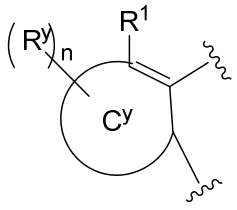
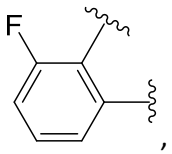
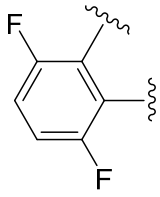
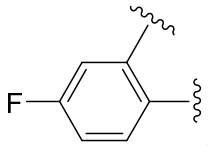
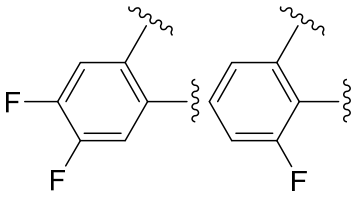
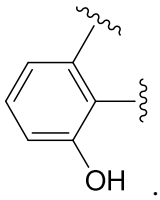
18. The compound of claim 17 or the pharmaceutically acceptable salt thereof, wherein the group $-O-CH_2-X^5-CH_2-X^3-$ is:

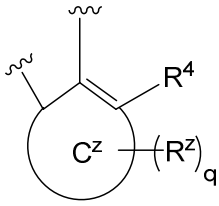
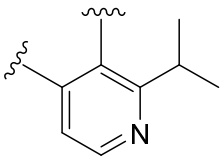
$-O-CH_2CH_2CH_2-$;

$-O-CH_2CH_2CH_2CH_2-$;

$-O-CH_2CH_2-O-$; or

$-O-CH_2CF_2CH_2CH_2-$.

19. The compound of claim 17 or 18 or the pharmaceutically acceptable salt thereof, wherein the group  is , , , , or .

20. The compound of any one of claims 17-19 or the pharmaceutically acceptable salt thereof, wherein the group  is .

21. The compound of claim 1, wherein the compound is:

18,21-difluoro-2-[(2*S*)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]-6-(propan-2-yl)-12,13-dihydro-4*H*,11*H*-1,19-ethenopyrido[4,3-*f*]pyrimido[1,6-*h*][1,5,8,10]benzodioxadiazacyclotridecin-4-one;

21-fluoro-2-[(2*S*)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]-6-(propan-2-yl)-12,13-dihydro-4*H*,11*H*-1,19-(ethanediylidene)dipyrido[4,3-*b*:3',2'-*h*]pyrimido[1,6-*d*][1,10,4,6]dioxadiazacyclotridecin-4-one;

22-fluoro-2-[(2*S*)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]-6-(propan-2-yl)-12,13-dihydro-4*H*,11*H*-1,20-ethenopyrido[4',3':2,3]pyrimido[1',6':4,5][1,4,6,10]oxatriazacyclotridecino[8,9,10-*hi*]indazol-4-one;

18,21-difluoro-2-[(2*S*)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]-6-(propan-2-yl)-10,11,12,13-tetrahydro-4*H*-1,19-ethenopyrido[4,3-*f*]pyrimido[1,6-*h*][1,8,10]benzoxadiazacyclotridecin-4-one;

20-fluoro-2-[(2*S*)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]-6-(propan-2-yl)-10,11,12,13-tetrahydro-4*H*-1,18-(ethanediylidene)pyrazolo[5,1-*e*]pyrido[4,3-*k*]pyrimido[1,6-*a*][1,3,6]triazacyclododecin-4-one;

22-fluoro-2-[(2*S*)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]-6-(propan-2-yl)-10,11,12,13-tetrahydro-4*H*-1,20-(ethanediylidene)pyrido[4',3':12,13]pyrimido[1',6':1,2][1,3,7]triazacyclotridecino[5,6,7-*hi*]indazol-4-one;

2-[(3*R*,5*S*)-3,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-18,21-difluoro-6-(propan-2-yl)-10,11,12,13-tetrahydro-4*H*-1,19-ethenopyrido[4,3-*f*]pyrimido[1,6-*h*][1,8,10]benzoxadiazacyclotridecin-4-one**;**

2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-18,21-difluoro-6-(propan-2-yl)-10,11,12,13-tetrahydro-4*H*-1,19-ethenopyrido[4,3-*f*]pyrimido[1,6-*h*][1,8,10]benzoxadiazacyclotridecin-4-one;

19-Chloro-16-fluoro-2-[(2*S*)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]-10,11-dihydro-4*H*-1,17-ethenodibenzo[*b*,*h*]pyrimido[6,1-*f*][1,5,7]oxadiazacycloundecin-4-one;

17,20-difluoro-2-[(2*S*)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]-6-(propan-2-yl)-11,12-dihydro-4*H*,10*H*-1,18-ethenopyrido[4,3-*e*]pyrimido[1,6-*g*][1,7,9]benzoxadiazacyclododecin-4-one;

[(2*S*)-4-[17,20-difluoro-4-oxo-6-(propan-2-yl)-11,12-dihydro-4*H*,10*H*-1,18-ethenopyrido[4,3-*e*]pyrimido[1,6-*g*][1,7,9]benzoxadiazacyclododecin-2-yl]-1-(prop-2-enoyl)piperazin-2-yl]acetonitrile;

17,20-difluoro-2-[(2*S*)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]-6-(propan-2-yl)-11,12-dihydro-4*H*-1,18-(ethanediylidene)pyrido[4,3-*e*]pyrimido[1,6-*g*][1,4,7,9]benzodioxadiazacyclododecin-4-one;

2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-12,12,18,21-tetrafluoro-6-(propan-2-yl)-12,13-dihydro-4*H*,11*H*-1,19-(ethanediylidene)pyrido[4,3-*f*]pyrimido[1,6-*h*][1,5,8,10]benzodioxadiazacyclotridecin-4-one;

[(2*S*)-4-[17,20-difluoro-4-oxo-6-(propan-2-yl)-11,12-dihydro-4*H*-1,18-(ethanediylidene)pyrido[4,3-*e*]pyrimido[1,6-*g*][1,4,7,9]benzodioxadiazacyclododecin-2-yl]-1-(prop-2-enoyl)piperazin-2-yl]acetonitrile;

2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-17,20-difluoro-6-(propan-2-yl)-11,12-dihydro-4*H*-1,18-(ethanediylidene)pyrido[4,3-*e*]pyrimido[1,6-*g*][1,4,7,9]benzodioxadiazacyclododecin-4-one;

19,22-Difluoro-2-[(2*S*)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]-7-(propan-2-yl)-11,12,13,14-tetrahydro-4*H*-1,20-(ethanediylidene)-6,10-(metheno)pyrimido[1,6-*k*][1,8,11,13]benzoxatriazacyclohexadecin-4-one;

18,21-Difluoro-2-[(2*S*)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]-6-(propan-2-yl)-10,11,13,14-tetrahydro-4*H*-1,19-ethenopyrido[3,4-*e*]pyrimido[6,1-*c*][9,2,4]benzoxadiazacyclotridecin-4-one;

17,20-difluoro-2-[(2*S*)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]-6-(propan-2-yl)-10,11-dihydro-1,18-ethenopyrido[3,4-*e*]pyrimido[6,1-*c*][9,2,4]benzoxadiazacyclododecin-4(13*H*)-one;

18,21-Difluoro-2-[(2*S*)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]-6-(propan-2-yl)-10,11,12,13-tetrahydro-1,19-ethenopyrido[3,4-*e*]pyrimido[6,1-*c*][2,4,10]benzotriazacyclotridecine-4,14-dione;

17,20-Difluoro-2-[(2*S*)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]-6-(propan-2-yl)-12,13-dihydro-1,18-ethenopyrido[3,4-*e*]pyrimido[6,1-*c*][7,2,4]benzoxadiazacyclododecin-4(11*H*)-one;

(5aS_a,17aR_a)-20-chloro-2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-14,17-difluoro-6-(propan-2-yl)-11,12-dihydro-4*H*-1,18-(ethanediylidene)pyrido[4,3-*e*]pyrimido[1,6-*g*][1,4,7,9]benzodioxadiazacyclododecin-4-one;

(5aS_a,17aR_a)-20-Chloro-2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-14,17-difluoro-6-(propan-2-yl)-11,12-di[(^{2}H)hydro](11,12-$^2H_2$)-4*H*-1,18-(ethanediylidene)pyrido[4,3-*e*]pyrimido[1,6-*g*][1,4,7,9]benzodioxadiazacyclododecin-4-one;

(5aR_a,18aR_a)-2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-12,12,18,21-tetrafluoro-6-(propan-2-yl)-10,11,12,13-tetrahydro-4*H*-1,19-(ethanediylidene)pyrido[4,3-*f*]pyrimido[1,6-*h*][1,8,10]benzoxadiazacyclotridecin-4-one;

(5aR_a,18aR_a)-2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-12,12,17,18,21-pentafluoro-6-(propan-2-yl)-10,11,12,13-tetrahydro-4*H*-1,19-(ethanediylidene)pyrido[4,3-*f*]pyrimido[1,6-*h*][1,8,10]benzoxadiazacyclotridecin-4-one**;**

(5aR_a,18aR_a)-2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-12,12,15,18,21-pentafluoro-6-(propan-2-yl)-10,11,12,13-tetrahydro-4*H*-1,19-(ethanediylidene)pyrido[4,3-*f*]pyrimido[1,6-*h*][1,8,10]benzoxadiazacyclotridecin-4-one;

(5aR_a,18aR_a)-2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-12,12,16,18,21-pentafluoro-6-(propan-2-yl)-10,11,12,13-tetrahydro-4*H*-1,19-(ethanediylidene)pyrido[4,3-*f*]pyrimido[1,6-*h*][1,8,10]benzoxadiazacyclotridecin-4-one;

(5aS_a,17aR_a)-20-chloro-2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-16,17-difluoro-6-(propan-2-yl)-11,12-di[(^{2}H)hydro](11,12-$^2H_2$)-4*H*-1,18-(ethanediylidene)pyrido[4,3-*e*]pyrimido[1,6-*g*][1,4,7,9]benzodioxadiazacyclododecin-4-one;

2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-12,12,17,18,21-pentafluoro-6-(propan-2-yl)-10,11,12,13-tetrahydro-4*H*-1,19-(ethanediylidene)dipyrimido[4,5-*f*:1',6'-*h*][1,8,10]benzoxadiazacyclotridecin-4-one;

21-chloro-2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-12,12,18-trifluoro-6-(propan-2-yl)-12,13-dihydro-4*H*,11*H*-1,19-(ethanediylidene)pyrido[4,3-*f*]pyrimido[1,6-*h*][1,5,8,10]benzodioxadiazacyclotridecin-4-one;

2'-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-18',21'-difluoro-6'-(propan-2-yl)-10',11'-dihydro-4'*H*,13'*H*-spiro[cyclopropane-1,12'-[14]oxa[3,5,7,20]tetraaza[1,19](ethanediylidene)pyrido[4,3-*f*]pyrimido[1,6-*h*][1,8,10]benzoxadiazacyclotridecin]-4'-one;

2'-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-15',18',21'-trifluoro-6'-(propan-2-yl)-10',11'-dihydro-4'*H*,13'*H*-spiro[cyclopropane-1,12'-[14]oxa[3,5,7,20]tetraaza[1,19](ethanediylidene)pyrido[4,3-*f*]pyrimido[1,6-*h*][1,8,10]benzoxadiazacyclotridecin]-4'-one;

2'-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-17',18',21'-trifluoro-6'-(propan-2-yl)-10',11'-dihydro-4'*H*,13'*H*-spiro[cyclopropane-1,12'-[14]oxa[3,5,7,20]tetraaza[1,19](ethanediylidene)pyrido[4,3-*f*]pyrimido[1,6-*h*][1,8,10]benzoxadiazacyclotridecin]-4'-one;

20-chloro-2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-17-fluoro-6-(propan-2-yl)-11,12-dihydro-4*H*,10*H*-1,18-(ethanediylidene)pyrido[4,3-*e*]pyrimido[1,6-*g*][1,7,9]benzoxadiazacyclododecin-4-one;

2-[(2*S*,5*R*)-2,5-Dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-16,17,20-trifluoro-6-(propan-2-yl)-11,12-di[(^{2}H)hydro](11,12-$^2H_2$)-4*H*-1,18-(ethanediylidene)pyrido[4,3-*e*]pyrimido[1,6-*g*][1,4,7,9]benzodioxadiazacyclododecin-4-one;

12,12,17,18,21-pentafluoro-6-(propan-2-yl)-2-[4-(prop-2-enoyl)piperazin-1-yl]-10,11,12,13-tetrahydro-4*H*-1,19-(ethanediylidene)pyrido[4,3-*f*]pyrimido[1,6-*h*][1,8,10]benzoxadiazacyclotridecin-4-one;

12,12,17,18,21-pentafluoro-2-[(3*R*)-3-methyl-4-(prop-2-enoyl)piperazin-1-yl]-6-(propan-2-yl)-10,11,12,13-tetrahydro-4*H*-1,19-(ethanediylidene)pyrido[4,3-*f*]pyrimido[1,6-*h*][1,8,10]benzoxadiazacyclotridecin-4-one;

2-[(2*S*,5*R*)-2,5-Dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-14,17,20-trifluoro-6-(propan-2-yl)-11,12-di[(^{2}H)hydro](11,12-$^2H_2$)-4*H*-1,18-(ethanediylidene)pyrido[4,3-*e*]pyrimido[1,6-*g*][1,4,7,9]benzodioxadiazacyclododecin-4-one;

2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-22-fluoro-6-(propan-2-yl)-10,11,12,13-tetrahydro-4*H*-1,20-(ethanediylidene)pyrido[4',3':12,13]pyrimido[1',6':1,2][1,3,7]triazacyclotridecino[5,6,7-*hi*]indazol-4-one;

9-chloro-2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-17,20-difluoro-6-(propan-2-yl)-11,12-dihydro-4*H*-1,18-(ethanediylidene)pyrido[4,3-*e*]pyrimido[1,6-*g*][1,4,7,9]benzodioxadiazacyclododecin-4-one;

2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-20-fluoro-6-(propan-2-yl)-17-(trifluoromethyl)-11,12-dihydro-4*H*-1,18-(ethanediylidene)pyrido[4,3-*e*]pyrimido[1,6-*g*][1,4,7,9]benzodioxadiazacyclododecin-4-one;

20-chloro-2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-16,17-difluoro-6-(propan-2-yl)-11,12-dihydro-4*H*,10*H*-1,18-ethenodipyrimido[4,5-*e*:1',6'-*g*][1,7,9]benzoxadiazacyclododecin-4-one;

2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-17,20-difluoro-6-(propan-2-yl)-11,12-dihydro-4*H*,10*H*-1,18-ethenopyrido[4,3-*e*]pyrimido[1,6-*g*][1,7,9]benzoxadiazacyclododecin-4-one;

17-chloro-2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-20-fluoro-6-(propan-2-yl)-11,12-dihydro-4*H*,10*H*-1,18-ethenopyrido[4,3-*e*]pyrimido[1,6-*g*][1,7,9]benzoxadiazacyclododecin-4-one;

2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-14,16,17,20-tetrafluoro-6-(propan-2-yl)-11,12-dihydro-4*H*,10*H*-1,18-ethenopyrido[4,3-*e*]pyrimido[1,6-*g*][1,7,9]benzoxadiazacyclododecin-4-one;

2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-16,17,20-trifluoro-6-(propan-2-yl)-11,12-dihydro-4*H*,10*H*-1,18-ethenopyrido[4,3-*e*]pyrimido[1,6-*g*][1,7,9]benzoxadiazacyclododecin-4-one;

15,18,21-trifluoro-2-[(2*S*)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]-6-(propan-2-yl)-10,11,12,13-tetrahydro-4*H*-1,19-(ethanediylidene)pyrido[4,3-*f*]pyrimido[1,6-*h*][1,8,10]benzoxadiazacyclotridecin-4-one;

2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-15,16,17,20-tetrafluoro-6-(propan-2-yl)-11,12-dihydro-4*H*,10*H*-1,18-ethenopyrido[4,3-*e*]pyrimido[1,6-*g*][1,7,9]benzoxadiazacyclododecin-4-one;

2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-17,20-difluoro-12-methyl-6-(propan-2-yl)-11,12-dihydro-4*H*,10*H*-1,18-ethenopyrido[4,3-*e*]pyrimido[1,6-*g*][1,7,9]benzoxadiazacyclododecin-4-one;

20-chloro-2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-14,16-difluoro-6-(propan-2-yl)-11,12-dihydro-4*H*,10*H*-1,18-ethenopyrido[4,3-*e*]pyrimido[1,6-*g*][1,7,9]benzoxadiazacyclododecin-4-one;

17-chloro-2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-20-fluoro-6-(propan-2-yl)-11,12-dihydro-4*H*-1,18-(ethanediylidene)pyrido[4,3-*e*]pyrimido[1,6-*g*][1,4,7,9]benzodioxadiazacyclododecin-4-one;

2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-15,16,20-trifluoro-6-(propan-2-yl)-11,12-dihydro-4*H*-1,18-(ethanediylidene)pyrido[4,3-*e*]pyrimido[1,6-*g*][1,4,7,9]benzodioxadiazacyclododecin-4-one;

18,21-difluoro-2-[(2*S*)-4-(2-fluoroprop-2-enoyl)-2-methylpiperazin-1-yl]-6-(propan-2-yl)-10,11,12,13-tetrahydro-4*H*-1,19-ethenopyrido[4,3-*f*]pyrimido[1,6-*h*][1,8,10]benzoxadiazacyclotridecin-4-one;

2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-20-fluoro-6-(propan-2-yl)-16-(trifluoromethyl)-11,12-dihydro-4*H*-1,18-(ethanediylidene)pyrido[4,3-*e*]pyrimido[1,6-*g*][1,4,7,9]benzodioxadiazacyclododecin-4-one;

6-chloro-2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-14,17,20-trifluoro-11,12-dihydro-4*H*-1,18-ethenopyrido[4,3-*e*]pyrimido[1,6-*g*][1,4,7,9]benzodioxadiazacyclododecin-4-one;

2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-19,22-difluoro-24-methyl-7-(propan-2-yl)-11,12,13,14-tetrahydro-4*H*-1,20-etheno-6,10-(metheno)pyrimido[1,6-*k*][1,8,11,13]benzoxatriazacyclohexadecin-4-one;

2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-16,17,20-trifluoro-10-methyl-6-(propan-2-yl)-11,12-dihydro-4*H*,10*H*-1,18-ethenopyrido[4,3-*e*]pyrimido[1,6-*g*][1,7,9]benzoxadiazacyclododecin-4-one;

2'-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-16',17',20'-trifluoro-6'-(propan-2-yl)-4'*H*,10'*H*,12'*H*-spiro[cyclopropane-1,11'-[13]oxa[3,5,7,19]tetraaza[1,18]ethenopyrido[4,3-*e*]pyrimido[1,6-*g*][1,7,9]benzoxadiazacyclododecin]-4'-one;

2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-14,17,20-trifluoro-6-(propan-2-yl)-11,12-dihydro-4*H*-1,18-(ethanediylidene)pyrido[4,3-*e*]pyrimido[1,6-*g*][1,4,7]benzodioxazacyclododecin-4-one;

(11*S*)-2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-14,17,20-trifluoro-11-methyl-6-(propan-2-yl)-11,12-dihydro-4*H*-1,18-ethenopyrido[4,3-*e*]pyrimido[1,6-*g*][1,4,7,9]benzodioxadiazacyclododecin-4-one;

2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-14,17,20-trifluoro-6-(propan-2-yl)-11,12-dihydro-4*H*,10*H*-1,18-(ethanediylidene)pyrido[4,3-*e*]pyrimido[1,6-*g*][1,7,9]benzoxadiazacyclododecin-4-one;

2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-16,19-difluoro-6-(propan-2-yl)-10,11-dihydro-4*H*-1,17-ethenopyrido[4,3-*d*]pyrimido[1,6-*f*][1,6,8]benzoxadiazacycloundecin-4-one;

12,12,17,18,21-pentafluoro-2-[(2*S*)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]-6-(propan-2-yl)-10,11,12,13-tetrahydro-4*H*-1,19-(ethanediylidene)pyrido[4,3-*f*]pyrimido[1,6-*h*][1,8,10]benzoxadiazacyclotridecin-4-one;

2-[(2*S*)-2-ethyl-4-(prop-2-enoyl)piperazin-1-yl]-17,20-difluoro-6-(propan-2-yl)-11,12-dihydro-4*H*,10*H*-1,18-(ethanediylidene)pyrido[4,3-*e*]pyrimido[1,6-*g*][1,7,9]benzoxadiazacyclododecin-4-one;

2-[2-(difluoromethyl)-4-(prop-2-enoyl)piperazin-1-yl]-17,20-difluoro-6-(propan-2-yl)-11,12-dihydro-4*H*,10*H*-1,18-ethenopyrido[4,3-*e*]pyrimido[1,6-*g*][1,7,9]benzoxadiazacyclododecin-4-one;

2-[2-benzyl-4-(prop-2-enoyl)piperazin-1-yl]-17,20-difluoro-6-(propan-2-yl)-11,12-dihydro-4*H*,10*H*-1,18-ethenopyrido[4,3-*e*]pyrimido[1,6-*g*][1,7,9]benzoxadiazacyclododecin-4-one;

17,20-difluoro-6-(propan-2-yl)-2-[4-(prop-2-enoyl)-2-(2,2,2-trifluoroethyl)piperazin-1-yl]-11,12-dihydro-4*H*,10*H*-1,18-(ethanediylidene)pyrido[4,3-*e*]pyrimido[1,6-*g*][1,7,9]benzoxadiazacyclododecin-4-one;

2-[2,2-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-17,20-difluoro-6-(propan-2-yl)-11,12-dihydro-4*H*,10*H*-1,18-ethenopyrido[4,3-*e*]pyrimido[1,6-*g*][1,7,9]benzoxadiazacyclododecin-4-one;

2-[(3*S*)-3-ethyl-4-(prop-2-enoyl)piperazin-1-yl]-17,20-difluoro-6-(propan-2-yl)-11,12-dihydro-4*H*,10*H*-1,18-ethenopyrido[4,3-*e*]pyrimido[1,6-*g*][1,7,9]benzoxadiazacyclododecin-4-one;

18,21-difluoro-6-(propan-2-yl)-2-[(1*S*,4*S*)-5-(prop-2-enoyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-10,11,12,13-tetrahydro-4H-1,19-ethenopyrido[4,3-*f*]pyrimido[1,6-*h*][1,8,10]benzoxadiazacyclotridecin-4-one;

17,20-difluoro-6-(propan-2-yl)-2-[5-(prop-2-enoyl)-2,5-diazabicyclo[2.2.2]octan-2-yl]-11,12-dihydro-4*H*,10*H*-1,18-ethenopyrido[4,3-*e*]pyrimido[1,6-*g*][1,7,9]benzoxadiazacyclododecin-4-one;

17,20-difluoro-4-oxo-6-(propan-2-yl)-2-[5-(prop-2-enoyl)-2,5-diazabicyclo[2.2.2]octan-2-yl]-11,12-dihydro-4*H*,10*H*-1,18-ethenopyrido[4,3-*e*]pyrimido[1,6-*g*][1,7,9]benzoxadiazacyclododecin-4-one;

2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-19,22-difluoro-6-(propan-2-yl)-10,11,12,13-tetrahydro-4*H*-1,20-(ethanediylidene)pyrido[4',3':12,13]pyrimido[1',6':1,2][1,3,7]triazacyclotridecino[5,6,7-*hi*]indazol-4-one;

2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-18,22-difluoro-6-(propan-2-yl)-10,11,12,13-tetrahydro-4*H*-1,20-(ethanediylidene)pyrido[4',3':12,13]pyrimido[1',6':1,2][1,3,7]triazacyclotridecino[5,6,7-*hi*]indazol-4-one;

20-chloro-2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-17-fluoro-6-(propan-2-yl)-10,11-dihydro-1,18-ethenopyrido[3,4-*e*]pyrimido[6,1-*c*][9,2,4]benzoxadiazacyclododecin-4(13*H*)-one;

2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-14,17-difluoro-20-methyl-6-(propan-2-yl)-11,12-dihydro-4*H*-1,18-ethenopyrido[4,3-*e*]pyrimido[1,6-*g*][1,4,7,9]benzodioxadiazacyclododecin-4-one;

6-cyclopropyl-2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-14,17,20-trifluoro-11,12-dihydro-4*H*-1,18-ethenopyrido[4,3-*e*]pyrimido[1,6-*g*][1,4,7,9]benzodioxadiazacyclododecin-4-one;

17,20-difluoro-2-[(2*S*)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]-6-(propan-2-yl)-10,11,12,13-tetrahydro-4*H*-1,18-ethenopyrido[4,3-*e*]pyrimido[1,6-*g*][1,7,9]benzotriazacyclododecin-4-one;

2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-20-fluoro-14-hydroxy-6-(propan-2-yl)-11,12-dihydro-4*H*,10*H*-1,18-(ethanediylidene)pyrido[4,3-*e*]pyrimido[1,6-*g*][1,7,9]benzoxadiazacyclododecin-4-one;

2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-14,20-difluoro-6-(propan-2-yl)-11,12-dihydro-4*H*-1,18-(ethanediylidene)pyrido[4,3-*e*]pyrimido[1,6-*g*][1,4,7,9]benzodioxadiazacyclododecin-4-one;

2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-17,20-difluoro-6-(propan-2-yl)-10,11-dihydro-1,18-ethenopyrido[3,4-*e*]pyrimido[6,1-*c*][9,2,4]benzoxadiazacyclododecin-4(13*H*)-one;

2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-20-fluoro-6-(propan-2-yl)-14-(trifluoromethyl)-11,12-dihydro-4*H*-1,18-ethenopyrido[4,3-*e*]pyrimido[1,6-*g*][1,4,7,9]benzodioxadiazacyclododecin-4-one;

22-fluoro-9-[(2*S*)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]-13-(propan-2-yl)-18,19-dihydro-11*H*,17*H*-6,8-ethenopyrido[4',3':11,12]pyrimido[1',6':1,2][1,3,7]triazacyclododecino[5,6,7-*hi*]indazol-11-one;

17,20-difluoro-12-hydroxy-2-[(2*S*)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]-6-(propan-2-yl)-10,11,12,13-tetrahydro-4*H*-1,18-ethenopyrido[3,4-e]pyrimido[6,1-*c*][2,4]benzodiazacyclododecin-4-one;

17,20-difluoro-11-hydroxy-2-[(2*S*)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]-6-(propan-2-yl)-10,11,12,13-tetrahydro-4*H*-1,18-ethenopyrido[3,4-*e*]pyrimido[6,1-*c*][2,4]benzodiazacyclododecin-4-one;

19-chloro-2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-16-fluoro-6-(propan-2-yl)-10,11-dihydro-4*H*-1,17-ethenopyrido[4,3-*d*]pyrimido[1,6-*f*][1,6,8]benzoxadiazacycloundecin-4-one;

2-[(2*S*,5*R*)-2,5-dimethyl-4-(prop-2-enoyl)piperazin-1-yl]-14,17-difluoro-20-methyl-6-(propan-2-yl)-11,12-dihydro-4*H*,10*H*-1,18-ethenopyrido[4,3-*e*]pyrimido[1,6-*g*][1,7,9]benzoxadiazacyclododecin-4-one;

2-{(2*R*,5*S*)-4-[20-chloro-14,17-difluoro-4-oxo-6-(propan-2-yl)-11,12-dihydro-4*H*,10*H*-1,18-ethenopyrido[4,3-*e*]pyrimido[1,6-*g*][1,7,9]benzoxadiazacyclododecin-2-yl]-2,5-dimethylpiperazine-1-carbonyl}prop-2-enenitrile;

2-{(2*S*,5*R*)-4-[4-(dimethylamino)but-2-ynoyl]-2,5-dimethylpiperazin-1-yl}-12,12,17,18,21-pentafluoro-6-(propan-2-yl)-10,11,12,13-tetrahydro-4*H*-1,19-(ethanediylidene)pyrido[4,3-*f*]pyrimido[1,6-*h*][1,8,10]benzoxadiazacyclotridecin-4-one;

2-[(2*S*,5*R*)-4-(but-2-ynoyl)-2,5-dimethylpiperazin-1-yl]-12,12,17,18,21-pentafluoro-6-(propan-2-yl)-10,11,12,13-tetrahydro-4*H*-1,19-(ethanediylidene)pyrido[4,3-*f*]pyrimido[1,6-*h*][1,8,10]benzoxadiazacyclotridecin-4-one;

2-[(2*S*,5*R*)-2,5-dimethyl-4-(2-methylprop-2-enoyl)piperazin-1-yl]-12,12,17,18,21-pentafluoro-6-(propan-2-yl)-10,11,12,13-tetrahydro-4*H*-1,19-(ethanediylidene)pyrido[4,3-*f*]pyrimido[1,6-*h*][1,8,10]benzoxadiazacyclotridecin-4-one;

2-{(2*S*,5*R*)-4-[(2*E*)-4-(dimethylamino)but-2-enoyl]-2,5-dimethylpiperazin-1-yl}-12,12,17,18,21-pentafluoro-6-(propan-2-yl)-10,11,12,13-tetrahydro-4*H*-1,19-(ethanediylidene)pyrido[4,3-*f*]pyrimido[1,6-*h*][1,8,10]benzoxadiazacyclotridecin-4-one;

2-[(2*S*,5*R*)-4-(ethenesulfonyl)-2,5-dimethylpiperazin-1-yl]-12,12,17,18,21-pentafluoro-6-(propan-2-yl)-10,11,12,13-tetrahydro-4*H*-1,19-(ethanediylidene)pyrido[4,3-*f*]pyrimido[1,6-*h*][1,8,10]benzoxadiazacyclotridecin-4-one; or

a pharmaceutically acceptable salt thereof.

22. A pharmaceutical composition comprising the compound of any one of claims 1-21, or the pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

23. A method of inhibiting KRAS G12C protein comprising contacting KRAS G12C protein with the compound of any one of claims 1-21, or the pharmaceutically acceptable salt thereof, to inhibit the activity of the KRAS G12C protein.

24. ~~A method of treating cancer comprising administering~~ Use of ~~a therapeutically effective amount of~~ the compound of any one of claims 1-21, or the pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer, wherein the medicament is to be administered to a subject in need of such treatment.

25. The ~~method~~ use of claim 24, ~~further comprising administering~~ wherein an additional active agent is to be administered to the subject.

26. The compound of any one of claims 1-21, or the pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising the compound of any one of claims 1-21, or the pharmaceutically acceptable salt thereof, for use in therapy~~, or use of the compound of any one of claims 1-21, or the pharmaceutically acceptable salt thereof, in therapy~~.

27. The compound of any one of claims 1-21, or the pharmaceutically acceptable salt thereof, for use in treating cancer~~, or use of a compound of any one of claims 1-21, or the pharmaceutically acceptable salt thereof, for treating cancer~~.

28. ~~The compound of any one of claims 1-21, or the pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment of cancer, or use~~ Use of the compound of any one of claims 1-21, or the pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment of cancer.

29. The compound of any one of claims 1-21, or the pharmaceutically acceptable salt thereof, and an additional anti-cancer agent, for use in therapy or for use in the treatment of cancer~~, or use~~

~~of the compound of any one of claims 1-21, or the pharmaceutically acceptable salt thereof, and the additional anti-cancer agent for treating cancer~~.

30. ~~The compound of any one of claims 1-21, or the pharmaceutically acceptable salt thereof, and an additional anti-cancer agent, for the preparation of a medicament for the treatment of cancer, or use~~ Use of the compound of any one of claims 1-21, or the pharmaceutically acceptable salt thereof, and an~~the~~ additional anti-cancer agent, for the preparation of a medicament for the treatment of cancer.

31. A pharmaceutical composition comprising the compound of any one of claims 1-21, or the pharmaceutically acceptable salt thereof, for use in the treatment of cancer, or use of the pharmaceutical composition comprising the compound of any one of claims 1-21, or the pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer.

32. A pharmaceutical composition comprising the compound of any one of claims 1-21, or the pharmaceutically acceptable salt thereof, and an additional anti-cancer agent, for use in therapy or for use in the treatment of cancer, or use of the pharmaceutical composition comprising the compound of any one of claims 1-21, or the pharmaceutically acceptable salt thereof, and ~~the~~ an additional anti-cancer agent in the manufacture of a medicament, for treating cancer.