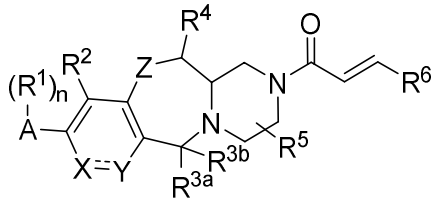
Claims

1) A compound of Formula (A):



(A)

wherein:

A is phenyl or a bicyclic heteroaryl group;

X and Y are connected by a double bond and i) X is CR^7 and Y is CR^8, ii) X is N and Y is CR^8, or iii) X is CR^7 and Y is N; or

X and Y together are $C(O)NR^9$; or

X and Y are adjacent ring atoms of an optionally substituted 5- or 6-membered N-heterocycle fused to the aromatic ring substituted with Z, and X and Y are both C or are C and N;

Z is O, NH, or NMe;

R^1 is independently selected from F, Cl, Br, OH, CH_2OH, OMe, CH_2OMe, C_1-C_3alkyl and C_1-C_3fluoroalkyl;

n is 0, 1, 2 or 3;

R^2 is H, F, Cl, CCH, CCMe, CN, Br, C_1-C_3alkyl, C_1-C_3fluoroalkyl, OMe or OEt;

R^{3a} and R^{3b} together are =O or R^{3a} and R^{3b} are H;

R^4 is H or Me;

R^5 is H or Me;

R^6 is H or CH_2NMe_2;

R^7 and R^8 are independently selected from H, F, Cl, CCH, CC(C_1-C_3alkyl), $CCCH_2NMe_2$, $CCCH_2O$(C_1-C_3alkyl), CN, Me, C_1-C_6alkyl, OH, OMe, O(C_1-C_3alkyl), O(C_1-C_3deuteroalkyl), O(C_1-C_3fluoroalkyl), O(C_3-C_6cycloalkyl), C_1-C_3fluoroalkyl, $OCH_2CH_2NMe_2$, OCH_2CH_2OMe, CH_2OMe, $OCH_2CH_2N(CH_2CH_2)_2CH$, $OCH_2CH_2N(CH_2CH_2)_2O$, OCH_2CH_2(2-pyridyl) or an optionally substituted 3-, 4-, 5- or 6-membered carbocycle or heterocycle; or

R^7 and R^8 combine to form an optionally substituted 5- or 6-membered carbocycle or heterocycle;

R^9 is selected from H, Me, Et, C_3H_7 and C_1-C_3fluoroalkyl;

or a pharmaceutically acceptable salt thereof.

2) Compound according to claim 1, wherein i) X is CR^7 and Y is CR^8, ii) X is N and Y is CR^8 or iii) X is CR^7 and Y is N.

3) Compound according to claim 1 or claim 2 wherein Z is O.

4) Compound according to any preceding claim wherein R^{3a} and R^{3b} are H.

5) Compound according to any preceding claim wherein R^4 is H.

6) Compound according to any preceding claim wherein R^6 is H.

7) Compound according to any preceding claim wherein A is phenyl.

8) Compound according to claim 1 selected from:
(12*aS*)-2-Acryloyl-10-chloro-9-(5-methyl-1*H*-indazol-4-yl)-1,2,3,4,12,12a-hexahydro-6*H*-benzo[f]pyrazino[2,1-c][1,4]oxazepin-6-one;
1-((12*aS*)-10-Chloro-9-(5-methyl-1*H*-indazol-4-yl)-3,4,12,12a-tetrahydro-6*H*-benzo[f]pyrazino[2,1-c][1,4]oxazepin-2(1*H*)-yl)prop-2-en-1-one;
1-[(12aR)-10-Chloro-9-(2-fluoro-6-hydroxyphenyl)-7-methoxy-3,4,12,12a-tetrahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepin-2(1*H*)-yl]prop-2-en-1-one;
(12a*R*)-10-chloro-9-(2-fluoro-6-hydroxyphenyl)-7-hydroxy-2-(prop-2-enoyl)-1,2,3,4,12,12a-hexahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepin-6-one;
(12aR)-10-Chloro-9-(5-methyl-1*H*-indazol-4-yl)-2-(prop-2-enoyl)-1,2,3,4,12,12a-hexahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepin-6-one;
1-((12a*R*)-10-Chloro-9-(5-methyl-1*H*-indazol-4-yl)-3,4,12,12a-tetrahydro-6*H*-benzo[*f*]pyrazino[2,1-*c*][1,4]oxazepin-2(1*H*)-yl)prop-2-en-1-one;
(12aR)-10-Chloro-8-fluoro-9-(2-fluoro-6-hydroxyphenyl)-2-(prop-2-enoyl)-1,2,3,4,12,12a-hexahydro-6H-pyrazino[2,1-c][1,4]benzoxazepin-6-one;
1-[(12aR)-8,10-dichloro-9-(2-fluoro-6-hydroxyphenyl)-7-hydroxy-3,4,12,12a-tetrahydro-6H-pyrazino[2,1-c][1,4]benzoxazepin-2(1H)-yl]prop-2-en-1-one;
1-[(12aR)-10-Chloro-9-(2-fluoro-6-hydroxyphenyl)-7-(1H-imidazol-1-yl)-3,4,12,12a-tetrahydro-6H-pyrazino[2,1-c][1,4]benzoxazepin-2(1H)-yl]prop-2-en-1-one;
(12a*R*)-10-Chloro-9-(2-fluoro-6-hydroxyphenyl)-2-(prop-2-enoyl)-1,2,3,4,12,12a-hexahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepine-7-carbonitrile;
1-[(12a*R*)-10-Chloro-9-(2-fluoro-6-hydroxyphenyl)-7-(1*H*-pyrazol-1-yl)-3,4,12,12a-tetrahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepin-2(1*H*)-yl]prop-2-en-1-one;
1-((12aR)-10-Chloro-8-fluoro-9-(5-methyl-1*H*-benzo[*d*]imidazol-4-yl)-3,4,12,12a-tetrahydro-6*H*-benzo[*f*]pyrazino[2,1-*c*][1,4]oxazepin-2(1*H*)-yl)prop-2-en-1-one;
(12a*R*)-8,10-Dichloro-9-(2-fluoro-6-hydroxyphenyl)-2-(prop-2-enoyl)-1,2,3,4,12,12a-hexahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepin-6-one;

(12a*R*)-10-Chloro-9-(2-fluoro-6-hydroxyphenyl)-2-(prop-2-enoyl)-1,2,3,4,12,12a-hexahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepine-8-carbonitrile;

(12a*R*)-10-Chloro-9-(2-fluoro-6-hydroxyphenyl)-8-methyl-2-(prop-2-enoyl)-1,2,3,4,12,12a-hexahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepin-6-one;

1-[(12a*R*)-8,10-Dichloro-9-(2-fluoro-6-hydroxyphenyl)-3,4,12,12a-tetrahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepin-2(1*H*)-yl]prop-2-en-1-one;

8-[(12a*R*)-10-Chloro-8-fluoro-2-(prop-2-enoyl)-1,2,3,4,12,12a-hexahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepin-9-yl]-7-methylisoquinolin-1(2*H*)-one;

1-[(12a*R*)-10-chloro-9-(2-fluoro-6-hydroxyphenyl)-8-methoxy-3,4,12,12a-tetrahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepin-2(1*H*)-yl]prop-2-en-1-one;

(12a*S*)-10-Chloro-9-(5-methyl-1*H*-indazol-4-yl)-2-(prop-2-enoyl)-1,3,4,11,12,12a-hexahydropyrazino[2,1-*c*][1,4]benzodiazepin-6(2*H*)-one;

1-[(12a*R*)-10-chloro-9-(2-chloro-6-hydroxyphenyl)-8-fluoro-3,4,12,12a-tetrahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepin-2(1*H*)-yl]prop-2-en-1-one;

(12a*S*)-10-Chloro-11-methyl-9-(5-methyl-1*H*-indazol-4-yl)-2-(prop-2-enoyl)-1,3,4,11,12,12a-hexahydropyrazino[2,1-*c*][1,4]benzodiazepin-6(2*H*)-one;

1-[(12a*R*)-10-Chloro-9-(2,3-difluoro-6-hydroxyphenyl)-8-fluoro-3,4,12,12a-tetrahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepin-2(1*H*)-yl]prop-2-en-1-one;

(12a*R*)-10-Chloro-9-(2-hydroxy-6-methylphenyl)-2-(prop-2-enoyl)-1,2,3,4,12,12a-hexahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepine-8-carbonitrile;

1-[(12a*R*)-9-(2-Chloro-6-hydroxyphenyl)-8,10-difluoro-3,4,12,12a-tetrahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepin-2(1*H*)-yl]prop-2-en-1-one;

1-[(12a*R*)-8,10-Difluoro-9-(2-hydroxy-6-methylphenyl)-3,4,12,12a-tetrahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepin-2(1*H*)-yl]prop-2-en-1-one;

1-[(12a*R*)-8,10-Difluoro-9-[2-fluoro-6-(hydroxymethyl)phenyl]-3,4,12,12a-tetrahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepin-2(1*H*)-yl]prop-2-en-1-one;

1-[(12a*R*)-8,10-Difluoro-9-[2-hydroxy-6-(trifluoromethyl)phenyl]-3,4,12,12a-tetrahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepin-2(1*H*)-yl]prop-2-en-1-one;

1-[(12a*R*)-9-(2-Ethyl-6-hydroxyphenyl)-8,10-difluoro-3,4,12,12a-tetrahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepin-2(1*H*)-yl]prop-2-en-1-one;

1-[(12a*R*)-9-[2-(Difluoromethyl)-6-hydroxyphenyl]-8,10-difluoro-3,4,12,12a-tetrahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepin-2(1*H*)-yl]prop-2-en-1-one;

(12a*R*)-9-(2-Chloro-6-hydroxyphenyl)-10-fluoro-2-(prop-2-enoyl)-1,2,3,4,12,12a-hexahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepine-8-carbonitrile;

(12a*R*)-10-Chloro-9-(2-chloro-6-hydroxyphenyl)-2-(prop-2-enoyl)-1,2,3,4,12,12a-hexahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepine-8-carbonitrile;

1-[(12a*R*)-9-(2-Bromo-6-hydroxyphenyl)-8,10-difluoro-3,4,12,12a-tetrahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepin-2(1*H*)-yl]prop-2-en-1-one;

1-[(12a*R*)-8-Chloro-10-fluoro-9-(2-hydroxy-6-methylphenyl)-3,4,12,12a-tetrahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepin-2(1*H*)-yl]prop-2-en-1-one;

1-[(12a*R*)-8-Chloro-10-ethynyl-9-(2-hydroxy-6-methylphenyl)-3,4,12,12a-tetrahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepin-2(1*H*)-yl]prop-2-en-1-one;

1-[(12a*R*)-10-Ethynyl-8-fluoro-9-(2-hydroxy-6-methylphenyl)-3,4,12,12a-tetrahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepin-2(1*H*)-yl]prop-2-en-1-one;

(6a*R*)-4-Chloro-3-(2-fluoro-6-hydroxyphenyl)-2-methyl-8-(prop-2-enoyl)-2,6,6a,7,8,9,10,12-octahydro-1*H*-pyrazino[2,1-*c*]pyrido[3,4-*f*][1,4]oxazepin-1-one;

1-[(6a*R*)-1,4-Dichloro-3-(2-fluoro-6-hydroxyphenyl)-6a,7,9,10-tetrahydro-12*H*-pyrazino[2,1-*c*]pyrido[3,4-*f*][1,4]oxazepin-8(6*H*)-yl]prop-2-en-1-one;

(6a*R*)-4-Chloro-3-(2-fluoro-6-hydroxyphenyl)-8-(prop-2-enoyl)-2,6,6a,7,8,9,10,12-octahydro-1*H*-pyrazino[2,1-*c*]pyrido[3,4-*f*][1,4]oxazepin-1-one;

1-[(8a*R*)-6-Chloro-5-(2-fluoro-6-hydroxyphenyl)-8a,9,11,12-tetrahydro-14*H*-pyrazino[2,1-*c*][1,2,4]triazolo[4',3':1,2]pyrido[3,4-*f*][1,4]oxazepin-10(8*H*)-yl]prop-2-en-1-one;

1-[(7a*R*)-5-chloro-4-(2-fluoro-6-hydroxyphenyl)-1-methyl-1,7a,8,10,11,13-hexahydropyrazino[2',1':3,4][1,4]oxazepino[7,6-*g*]indazol-9(7*H*)-yl]prop-2-en-1-one; and

1-[(7aR)-5-Chloro-4-(2-fluoro-6-hydroxyphenyl)-2-methyl-2,7a,8,10,11,13-hexahydropyrazino[2',1':3,4][1,4]oxazepino[7,6-g]indazol-9(7H)-yl]prop-2-en-1-one;

1-[(12a*R*)-9-(2-chloro-6-hydroxyphenyl)-8-ethynyl-10-fluoro-3,4,12,12a-tetrahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepin-2(1*H*)-yl]prop-2-en-1-one;

1-[(12aR)-10-Chloro-9-(2-chloro-6-hydroxyphenyl)-8-ethynyl-3,4,12,12a-tetrahydro-6H-pyrazino[2,1-c][1,4]benzoxazepin-2(1H)-yl]prop-2-en-1-one;

1-((12a*R*)-10-chloro-8-ethynyl-9-(2-fluoro-6-hydroxyphenyl)-3,4,12,12a-tetrahydro-6*H*-benzo[*f*]pyrazino[2,1-*c*][1,4]oxazepin-2(1*H*)-yl)prop-2-en-1-one;

1-[(7a*R*)-5-Chloro-4-(2-chloro-6-hydroxyphenyl)-1-methyl-1,7a,8,10,11,13-hexahydroimidazo[4,5-*g*]pyrazino[2,1-*c*][1,4]benzoxazepin-9(7*H*)-yl]prop-2-en-1-one ;

1-[(12a*R*)-8-Chloro-9-(2-chloro-6-hydroxyphenyl)-10-fluoro-3,4,12,12a-tetrahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepin-2(1*H*)-yl]prop-2-en-1-one;

1-[(12a*R*)-9-(2-Chloro-6-hydroxyphenyl)-10-fluoro-8-(prop-1-yn-1-yl)-3,4,12,12a-tetrahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepin-2(1*H*)-yl]prop-2-en-1-one;

1-[(6a*R*)-4-Chloro-3-(2-chloro-6-hydroxyphenyl)-2-ethynyl-6a,7,9,10-tetrahydro-12*H*-pyrazino[2,1-*c*]pyrido[2,3-*f*][1,4]oxazepin-8(6*H*)-yl]prop-2-en-1-one;
1-[(12a*R*)-9-(2-Chloro-6-hydroxyphenyl)-8-ethynyl-10-methyl-3,4,12,12a-tetrahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepin-2(1*H*)-yl]prop-2-en-1-one;
1-[(12a*R*)-10-chloro-9-(2-chloro-6-hydroxyphenyl)-7,8-difluoro-3,4,12,12a-tetrahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepin-2(1*H*)-yl]prop-2-en-1-one;
1-[(12a*R*)-9-(2-chloro-6-hydroxyphenyl)-8-(difluoromethoxy)-10-fluoro-3,4,12,12a-tetrahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepin-2(1*H*)-yl]prop-2-en-1-one;
1-[(12a*R*)-9-(2-chloro-6-hydroxyphenyl)-8-ethynyl-7,10-difluoro-3,4,12,12a-tetrahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepin-2(1*H*)-yl]prop-2-en-1-one;
1-[(12a*R*)-10-Chloro-9-(2-chloro-6-hydroxyphenyl)-8-(difluoromethoxy)-3,4,12,12a-tetrahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepin-2(1*H*)-yl]prop-2-en-1-one;
1-[(12a*R*)-9-(2-chloro-6-hydroxyphenyl)-8-(cyclopropyloxy)-10-fluoro-3,4,12,12a-tetrahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepin-2(1*H*)-yl]prop-2-en-1-one;
1-((12a*R*)-9-(2-Chloro-6-hydroxyphenyl)-8-(3-(dimethylamino)prop-1-yn-1-yl)-10-fluoro-3,4,12,12a-tetrahydro-6*H*-benzo[*f*]pyrazino[2,1-*c*][1,4]oxazepin-2(1*H*)-yl)prop-2-en-1-one;
1-[(12a*R*)-9-(2-chloro-6-hydroxyphenyl)-10-fluoro-8-[(pyridin-4-yl)methoxy]-3,4,12,12a-tetrahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepin-2(1*H*)-yl]prop-2-en-1-one;
1-[(12a*R*)-10-chloro-9-(2-chloro-6-hydroxyphenyl)-8-(2-methoxyethoxy)-3,4,12,12a-tetrahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepin-2(1*H*)-yl]prop-2-en-1-one;
1-[(12a*R*)-9-(2-Chloro-6-hydroxyphenyl)-10-fluoro-8-[2-(piperidin-1-yl)ethoxy]-3,4,12,12a-tetrahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepin-2(1*H*)-yl]prop-2-en-1-one;
1-[(12a*R*)-10-Chloro-9-(2-chloro-6-hydroxyphenyl)-8-(prop-1-yn-1-yl)-3,4,12,12a-tetrahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepin-2(1*H*)-yl]prop-2-en-1-one;
1-[(6a*R*)-4-Chloro-3-(2-chloro-6-hydroxyphenyl)-2-[($^2H_3$)methyloxy]-6a,7,9,10-tetrahydro-12*H*-pyrazino[2,1-*c*]pyrido[2,3-*f*][1,4]oxazepin-8(6*H*)-yl]prop-2-en-1-one;
1-[(12a*R*)-10-Chloro-9-(2-chloro-6-hydroxyphenyl)-8-(methoxymethyl)-3,4,12,12a-tetrahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepin-2(1*H*)-yl]prop-2-en-1-one; and
1-[(12a*R*)-9-(2-Chloro-6-hydroxyphenyl)-7-[2-(dimethylamino)ethoxy]-10-fluoro-3,4,12,12a-tetrahydro-6*H*-pyrazino[2,1-*c*][1,4]benzoxazepin-2(1*H*)-yl]prop-2-en-1-one;
1-[(6aR)-4-Chloro-3-(2-chloro-6-hydroxyphenyl)-1-(prop-1-yn-1-yl)-6a,7,9,10-tetrahydro-12H-pyrazino[2,1-c]pyrido[3,4-f][1,4]oxazepin-8(6H)-yl]prop-2-en-1-one; and
1-((6aR)-4-Chloro-3-(2-chloro-6-hydroxyphenyl)-1-ethynyl-6a,7,9,10-tetrahydro-12H-pyrazino[2,1-c]pyrido[3,4-f][1,4]oxazepin-8(6H)-yl)prop-2-en-1-one;

or a pharmaceutically acceptable salt thereof.

9) A compound, or a pharmaceutically acceptable salt thereof, according to claim 1 that is 1-[(12a*R*)-9-(2-chloro-6-hydroxyphenyl)-8-ethynyl-10-fluoro-3,4,12,12a-tetrahydro-6H-pyrazino[2,1-c][1,4]benzoxazepin-2(1H)-yl]prop-2-en-1-one.

10) A compound, or a pharmaceutically acceptable salt thereof, according to claim 1 that is 1-[(12a*R*)-9-(2-chloro-6-hydroxyphenyl)-10-fluoro-8-(prop-1-yn-1-yl)-3,4,12,12a-tetrahydro-6H-pyrazino[2,1-c][1,4]benzoxazepin-2(1H)-yl]prop-2-en-1-one.

11) A pharmaceutical composition comprising a compound, or a pharmaceutically acceptable salt thereof, according to any preceding claim and a pharmaceutically acceptable excipient.

12) A compound, or a pharmaceutically acceptable salt thereof, according to any of claims 1 to 10, for use as a medicament.

13) Compound for use according to claim 12, for use in the treatment of a cancer mediated by KRAS, NRAS or HRAS G12C mutations.

14) Compound for use according to claim 12 for use in the treatment of cancer.

15) Use of a compound according to any of claims 1 to 10, or a pharmaceutical acceptable salt thereof, for the manufacture of a medicament for the treatment of a cancer mediated by KRAS, NRAS or HRAS G12C mutations.

16) Use of a compound according to any of claims 1 to 10, or a pharmaceutical acceptable salt thereof, for the manufacture of a medicament for the treatment of cancer.