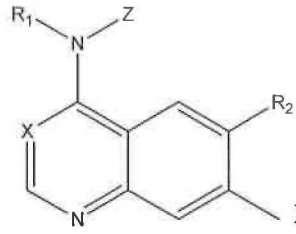
CLAIMS

1. A compound of formula (I):



Linker - IAP inhibitor

(I)

wherein

X represents N or CH;

L is a linking group comprising a length of 4-16 atoms in shortest length,

R^1 is H, $-SO_2(C_1-C_4)$alkyl, $-CO(C_1-C_4)$alkyl, or (C_1-C_4)alkyl;

R^2 is $-SR^a$, $-SOR^a$, $-SO_2R^a$, $-SO_2NH_2$, or $-SO_2NR^bR^c$,
wherein R^a is (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, 4-7 membered heterocycloalkyl, aryl, or heteroaryl, wherein:

said (C_1-C_6)alkyl is optionally substituted by one or two groups each independently selected from the group consisting of cyano, hydroxyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_2-C_6)alkoxy, $-CO_2H$, $-CO_2(C_1-C_4)$alkyl, $-SO_2(C_1-C_4)$alkyl, (C_3-C_7)cycloalkyl, phenyl, 5-6 membered heteroaryl, 9-10 membered heteroaryl, 4-7 membered heterocycloalkyl and (phenyl)(C_1-C_4 alkyl)amino-, wherein said (C_3-C_7)cycloalkyl, phenyl, (phenyl)(C_1-C_4 alkyl)amino-, 5-6 membered heteroaryl, 9-10 membered heteroaryl or 4-7 membered heterocycloalkyl is optionally substituted by 1-3 groups each independently selected from the group consisting of halogen, $-CF_3$, hydroxyl, amino, $((C_1-C_4)$alkyl)amino-, $((C_1-C_4)$alkyl)$((C_1-C_4)$alkyl)amino-, (C_1-C_4)alkyl, phenyl(C_1-C_4)alkyl-, hydroxy(C_1-C_4)alkyl and (C_1-C_4)alkoxy,

said (C_3-C_7)cycloalkyl or 4-7 membered heterocycloalkyl is optionally substituted by 1-3 groups each independently selected from the group consisting of halogen, $-CF_3$, hydroxyl, amino, $((C_1-C_4)$alkyl)amino-, $((C_1-C_4)$alkyl)$((C_1-C_4)$alkyl)amino-, (C_1-C_4)alkyl, phenyl(C_1-C_4)alkyl-, hydroxy(C_1-C_4)alkyl-, oxo and (C_1-C_4)alkoxy, and

said aryl or heteroaryl is optionally substituted by 1-3 groups each independently selected from the group consisting of halogen, $-CF_3$, hydroxyl, amino, $((C_1\text{-}C_4)$alkyl)amino-, $((C_1\text{-}C_4)$alkyl)$((C_1\text{-}C_4)$alkyl)amino-, $(C_1\text{-}C_4)$alkyl, phenyl$(C_1\text{-}C_4)$alkyl-, hydroxy$(C_1\text{-}C_4)$alkyl- and $(C_1\text{-}C_4)$alkoxy;

R^b is $(C_1\text{-}C_6)$alkyl or 4-7 membered heterocycloalkyl, wherein:

said $(C_1\text{-}C_6)$alkyl is optionally substituted by one or two groups each independently selected from the group consisting of hydroxyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxy$(C_2\text{-}C_6)$alkoxy, $-CO_2H$, $-CO_2(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4$ alkyl)amino-, $(C_1\text{-}C_4$ alkyl$)(C_1\text{-}C_4$ alkyl)amino-, 5-6 membered heteroaryl, and 4-7 membered heterocycloalkyl, wherein said 5-6 membered heteroaryl or 4-7 membered heterocycloalkyl is optionally substituted by 1-3 groups each independently selected from the group consisting of halogen, $(C_1\text{-}C_4)$alkyl, hydroxy$(C_1\text{-}C_4)$alkyl and $(C_1\text{-}C_4)$alkoxy,

said 4-7 membered heterocycloalkyl is optionally substituted by 1-3 groups each independently selected from the group consisting of hydroxyl, amino, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxycarbonyl-, hydroxy$(C_1\text{-}C_4)$alkyl-, oxo and $(C_1\text{-}C_4)$alkoxy, and

R^c is H, $(C_1\text{-}C_4)$alkoxy or $(C_1\text{-}C_6)$alkyl;

or R^b and R^c taken together with the nitrogen atom to which they are attached form a 3-7 membered heterocycloalkyl group, optionally containing one or two additional ring heteroatoms each independently selected from nitrogen and oxygen, wherein said 3-7 membered heterocycloalkyl is optionally substituted by 1-3 groups each independently selected from the group consisting of $(C_1\text{-}C_4)$alkyl, hydroxy, $-CO_2H$ and $-CO(C_1\text{-}C_4)$alkyl;

Z is phenyl or aryl$(C_1\text{-}C_4)$alkyl-, wherein in the phenyl group or the aryl moiety of the aryl$(C_1\text{-}C_4)$alkyl- group is substituted by R^4, R^5, R^6 and R^7, wherein:

R^4 is H, halogen, cyano, $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, phenoxy, phenyl$(C_1\text{-}C_4)$alkoxy, hydroxyl, hydroxy$(C_1\text{-}C_4)$alkyl-, or aminocarbonyl, wherein the phenyl moiety of said phenoxy or phenyl$(C_1\text{-}C_4)$alkoxy- is optionally substituted by 1-3 substituents each independently selected from the group consisting of halogen, $-CF_3$, $(C_1\text{-}C_4)$alkyl and $(C_1\text{-}C_4)$alkoxy; and

each of R^5, R^6 and $R^7$is independently selected from the group consisting of H, hydroxyl, halogen, $-CF_3$, hydroxy$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkyl and $(C_1\text{-}C_4)$alkoxy; or

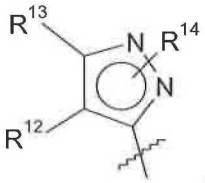
Z is phenyl or pyridyl, substituted by R^8, R^9 and R^{10}, wherein:

R^8 and R^9 are located on adjacent atoms and taken together with the atoms to which they are attached form a 5-membered ring containing 1, 2 or 3 heteroatoms each independently selected from N, O and S, which 5-membered ring is substituted by R^{11};

wherein one of R^{10} or R^{11} is H, halogen, cyano, $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, phenoxy, phenyl$(C_1\text{-}C_4)$alkoxy, hydroxyl, hydroxy$(C_1\text{-}C_4)$alkyl-, or aminocarbonyl,

where the phenyl moiety of said phenoxy or phenyl(C_1-C_4)alkoxy is optionally substituted by 1-3 substituents each independently selected from the group consisting of halogen, -CF_3, (C_1-C_4)alkyl and (C_1-C_4)alkoxy; and

the other of R^{10} or R^{11} is H, hydroxyl, halogen, -CF_3, hydroxy(C_1-C_4)alkyl, (C_1-C_4)alkyl or (C_1-C_4)alkoxy; or

Z is pyrazolyl, having the formula:  wherein:

R^{12} is H, methyl or hydroxymethyl;

R^{13} is methyl, trifluoromethyl or hydroxymethyl;

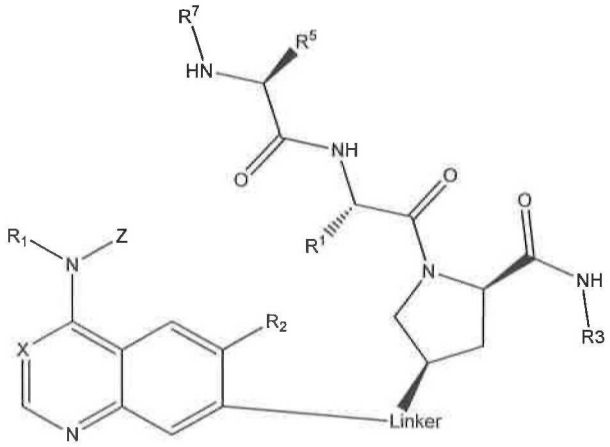
R^{14} is H, OH, or (C_1-C_3)alkyl; or

R^{12} and R^{13}, taken together with the atoms to which they are attached, form a 6-membered ring substituted by R^{15} and R^{16}, wherein the 6-membered ring optionally contains 1 nitrogen atom;

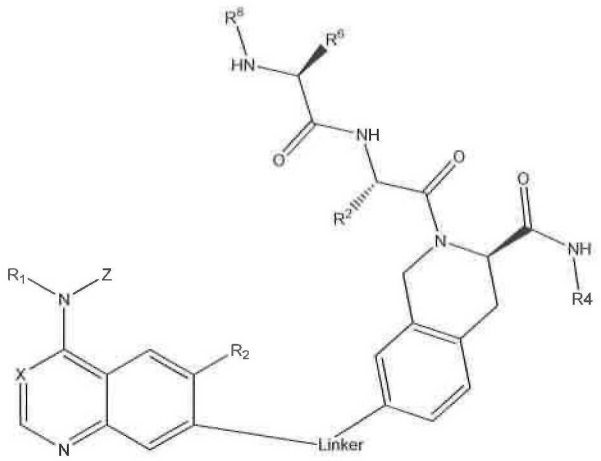
wherein R^{15} and R^{16} are each independently selected from the group consisting of H, halogen, cyano, (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, (C_1-C_4)alkoxy, phenoxy, phenyl(C_1-C_4)alkoxy, hydroxyl, hydroxy(C_1-C_4)alkyl-, and aminocarbonyl, wherein the phenyl moiety of said phenoxy or phenyl(C_1-C_4)alkoxy is optionally substituted by 1-3 substituents each independently selected from the group consisting of halogen, -CF_3, (C_1-C_4)alkyl and (C_1-C_4)alkoxy;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 which is a compound of Formula (II), (III), or (IV):



(II)



(III)

wherein the definitions of R^1, Z, X and R^2 in the RIP2 inhibitor moiety in the compounds of formula (II) and (III) are as defined in claim 1,

the linker is as defined in claim 1,

for the IAP binding moiety, in formula (II) and (III),

R^1 and R^2 are independently optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted arylalkyl, optionally substituted aryl, or

R^1 and R^2 are independently optionally substituted thioalkyl wherein the substituents attached to the S atom of the thioalkyl are optionally substituted alkyl, optionally substituted branced alkyl, optionally substituted heterocyclyl, $-(CH_2)vCOR_{20}$,$-CH_2CHR_{21}COR_{22}$ or $-CH_2R_{23}$, wherein

v-1-3,

R_{20} and R_{22} are independently selected from OH, $NR_{24}R_{25}$ or OR_{26},

R_{21} is $NR_{24}R_{25}$,

R_{23} is optionally substituted aryl or optionally substituted heterocyclyl, where the optional substituents include alkyl and halogen,

R_{24} is hydrogen or optionally substituted alkyl,

R_{25} is hydrogen, optionally substituted alkyl, optionally substituted branched alkyl, optionally substituted arylalkyl, optionally substituted heterocyclyl, $-CH_2(OCH_2CH_2O)_mCH_3$, or a

polyamine chain,

R_{26} is optionally substituted alkyl,

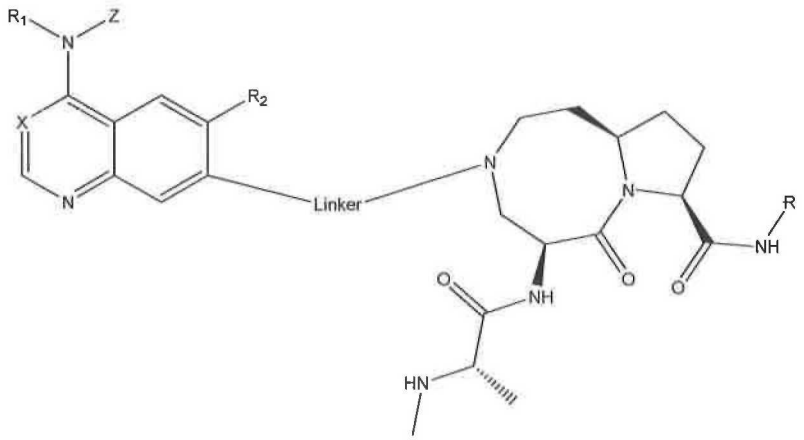
w=1-8,

where the optional substituents are OH, halogen or NH_2;

R^3 and R^4 are independently optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted arylalkoxy, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted heteroarylalkyl or optionally substituted hetercycloalkyl, wherein the substitutents are alkyl, halogen or OH;

R^5, R^6, R^7 and R^8 are independently hydrogen, optionally substituted alkyl or optionally substituted cycloalkyl;

R^9 is hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl or CO alkyl;

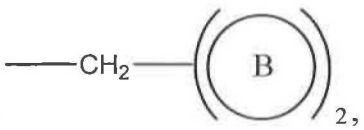


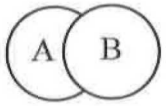
(IV)

wherein the definitions of R^1, Z, X and R^2 in the RIP2 inhibitor moiety in the compounds of formula (IV) are as defined in claim 1,

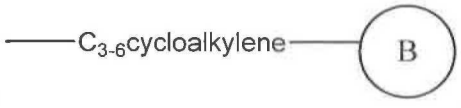
the linker is as defined in claim 1,

for the IAP binding moiety, in formula (IV),

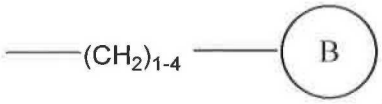
R is selected from the group consisting of 

, 

, wherein

ring A is C_{4-8} aliphatic ring, 

, and



, wherein the B ring is aryl or nitrogen atom-containing heteroaryl and the B rings are optionally substituted;
or a pharmaceutically acceptable salt thereof.

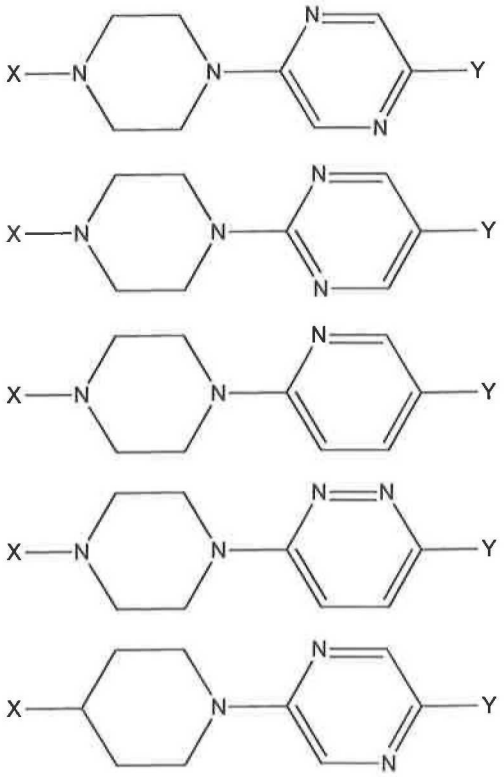
3. A compound according to claim 2 wherein in formula IV ring B is phenyl, napthyl, pyridinyl, pyrazonyl or pyrimidinyl.

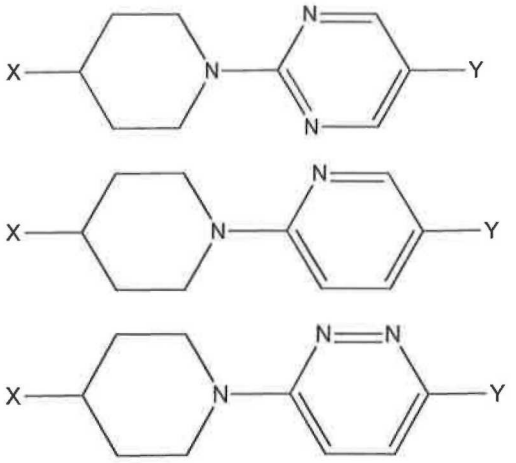
4. A claim according to claim 3 wherein the linker is a straight chain alkyline group of 4-20 carbon atoms wherein one or more carbo atoms one replaced by a group each independently selected from -O-, -NH, -N(CH_3), -CO-, piperidine, piperazine, pyrimidine, pyridine, phenyl.

5. A compound according to claims 1-4 wherein the linker is (in the direction RIP2 Kinase inhibitor – IAP inhibitor–):

$-O(CH_2CH_2O)_{3-4}$

$-O(CH_2CH_2)_4OCH_2CONH$





wherein X is $O(CH_2CH_2)_{0-4}$

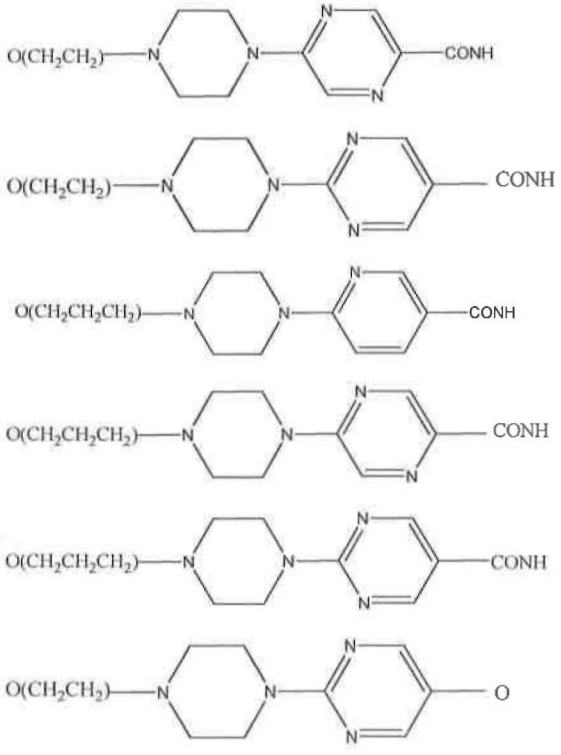
and Y is CONH, O or CO.

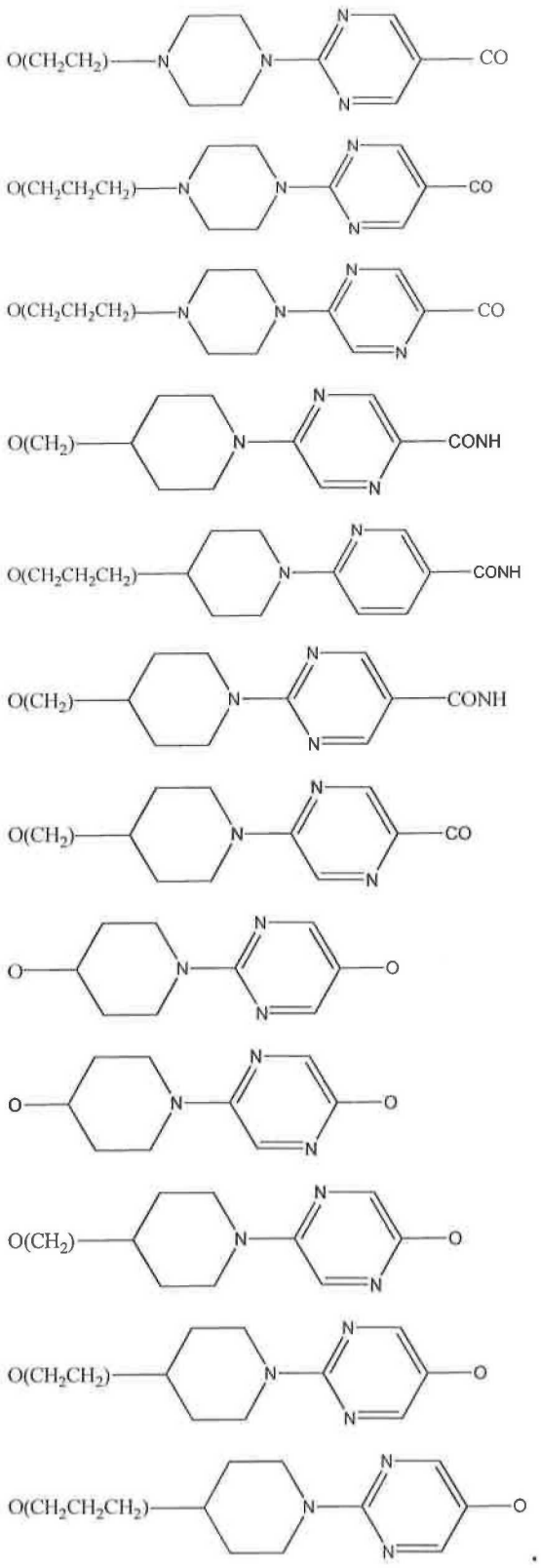
6. A compound according to claims 1-5 wherein the linker is (in the one linker RIP2 Kinase inhibitor – IAP inhibitor):

$-(OCH_2CH_2)_4O-$

$-(OCH_2CH_2)_3O-$

$-(OCH_2CH_2)_4OCH_2CONH$





7. A compound according to claim 1 which is

(S)-7-(2-(2-(2-(2-((4-(Benzo[d]thiazol-5-ylamino)-6-(tert-butylsulfonyl)quinolin-7-yl)oxy)ethoxy)ethoxy)ethoxy)ethoxy)-2-((S)-3,3-dimethyl-2-((S)-2-

methylamino)propanamido)butanoyl)-N-((R)-1,2,3,4-tetrahydronaphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;

(S)-7-(2-(2-(2-(2-((4-(Benzo[d]thiazol-5-ylamino)-6-(tert-butylsulfonyl)quinolin-7-yl)oxy)ethoxy)ethoxy)ethoxy)ethoxy)-2-((S)-3,3-dimethyl-2-((S)-2-(methylamino)propanamido)butanoyl)-N-((S)-1,2,3,4-tetrahydronaphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;

(S)-7-(2-(2-(2-(2-((6-(Tert-butylsulfonyl)-4-((4,5-dimethyl-1H-pyrazol-3-yl)amino)quinazolin-7-yl)oxy)ethoxy)ethoxy)ethoxy)ethoxy)-2-((S)-3,3-dimethyl-2-((S)-2-(methylamino)propanamido)butanoyl)-N-((R)-1,2,3,4-tetrahydronaphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;

(2S,4S)-4-(14-((4-(benzo[d]thiazol-5-ylamino)-6-(tert-butylsulfonyl)quinolin-7-yl)oxy)-3,6,9,12-tetraoxatetradecanamido)-1-((S)-3,3-dimethyl-2-((S)-2-(methylamino)propanamido)butanoyl)-N-((R)-3-methylbutan-2-yl)pyrrolidine-2-carboxamide;

(2S,4S)-4-(14-((4-(benzo[d]thiazol-5-ylamino)-6-(tert-butylsulfonyl)quinolin-7-yl)oxy)-3,6,9,12-tetraoxatetradecanamido)-1-((S)-3,3-dimethyl-2-((S)-2-(methylamino)propanamido)butanoyl)-N-((R)-1,2,3,4-tetrahydronaphthalen-1-yl)pyrrolidine-2-carboxamide;

(2S,4S)-4-(14-((4-(benzo[d]thiazol-5-ylamino)-6-(tert-butylsulfonyl)quinolin-7-yl)oxy)-3,6,9,12-tetraoxatetradecanamido)-N-((R)-2,3-dihydro-1H-inden-1-yl)-1-((S)-3,3-dimethyl-2-((S)-2-(methylamino)propanamido)butanoyl)pyrrolidine-2-carboxamide;

(2S,4S)-4-(14-((4-(benzo[d]thiazol-5-ylamino)-6-(tert-butylsulfonyl)quinolin-7-yl)oxy)-3,6,9,12-tetraoxatetradecanamido)-1-((S)-3,3-dimethyl-2-((S)-2-(methylamino)propanamido)butanoyl)-N-((R)-1-phenylpropyl)pyrrolidine-2-carboxamide;

(2S,4S)-4-(14-((4-(benzo[d]thiazol-5-ylamino)-6-(tert-butylsulfonyl)quinolin-7-yl)oxy)-3,6,9,12-tetraoxatetradecanamido)-N-(2,6-difluorophenyl)-1-((S)-3,3-dimethyl-2-((S)-2-(methylamino)propanamido)butanoyl)pyrrolidine-2-carboxamide;

(2S,4S)-4-(2-(2-(2-(2-((6-(Tert-butylsulfonyl)-4-((5-fluoro-1H-indazol-3-yl)amino)quinolin-7-yl)oxy)ethoxy)ethoxy)ethoxy)ethoxy)-1-((S)-3,3-dimethyl-2-((S)-2-(methylamino)propanamido)butanoyl)-N-((R)-1,2,3,4-tetrahydronaphthalen-1-yl)pyrrolidine-2-

carboxamide;

(2S,4S)-4-(2-(2-(2-((6-(Tert-butylsulfonyl)-4-((5-fluoro-1H-indazol-3-yl)amino)quinolin-7-yl)oxy)ethoxy)ethoxy)ethoxy)-1-((S)-3,3-dimethyl-2-((S)-2-(methylamino)propanamido)butanoyl)-N-((R)-1,2,3,4-tetrahydronaphthalen-1-yl)pyrrolidine-2-carboxamide;

5-(4-(2-((6-(Tert-butylsulfonyl)-4-((4,5-dimethyl-1H-pyrazol-3-yl)amino)quinazolin-7-yl)oxy)ethyl)piperazin-1-yl)-N-((3S,5S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)-5-(((R)-1,2,3,4-tetrahydronaphthalen-1-yl)carbamoyl)pyrrolidin-3-yl)pyrazine-2-carboxamide;

2-(4-(2-((6-(tert-butylsulfonyl)-4-((4,5-dimethyl-1H-pyrazol-3-yl)amino)quinazolin-7-yl)oxy)ethyl)piperazin-1-yl)-N-((3S,5S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)-5-(((R)-1,2,3,4-tetrahydronaphthalen-1-yl)carbamoyl)pyrrolidin-3-yl)pyrimidine-5-carboxamide;

5-(4-(((6-(tert-butylsulfonyl)-4-((4,5-dimethyl-1H-pyrazol-3-yl)amino)quinazolin-7-yl)oxy)methyl)piperidin-1-yl)-N-((3S,5S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)-5-(((R)-1,2,3,4-tetrahydronaphthalen-1-yl)carbamoyl)pyrrolidin-3-yl)pyrazine-2-carboxamide;

6-(4-(3-((6-(tert-butylsulfonyl)-4-((4,5-dimethyl-1H-pyrazol-3-yl)amino)quinazolin-7-yl)oxy)propyl)piperidin-1-yl)-N-((3S,5S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)-5-(((R)-1,2,3,4-tetrahydronaphthalen-1-yl)carbamoyl)pyrrolidin-3-yl)nicotinamide;

2-(4-(((6-(tert-butylsulfonyl)-4-((4,5-dimethyl-1H-pyrazol-3-yl)amino)quinazolin-7-yl)oxy)methyl)piperidin-1-yl)-N-((3S,5S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)-5-(((R)-1,2,3,4-tetrahydronaphthalen-1-yl)carbamoyl)pyrrolidin-3-yl)pyrimidine-5-carboxamide;

6-(4-(3-((6-(tert-butylsulfonyl)-4-((4,5-dimethyl-1H-pyrazol-3-yl)amino)quinazolin-7-yl)oxy)propyl)piperazin-1-yl)-N-((3S,5S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)-5-(((R)-1,2,3,4-tetrahydronaphthalen-1-yl)carbamoyl)pyrrolidin-3-yl)nicotinamide;

5-(4-(3-((6-(tert-butylsulfonyl)-4-((4,5-dimethyl-1H-pyrazol-3-yl)amino)quinazolin-7-yl)oxy)propyl)piperazin-1-yl)-N-((3S,5S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)-5-(((R)-1,2,3,4-tetrahydronaphthalen-1-yl)carbamoyl)pyrrolidin-3-yl)pyrazine-2-carboxamide;

2-(4-(3-((6-(tert-butylsulfonyl)-4-((4,5-dimethyl-1H-pyrazol-3-yl)amino)quinazolin-7-yl)oxy)propyl)piperazin-1-yl)-N-((3S,5S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)-5-(((R)-1,2,3,4-tetrahydronaphthalen-1-yl)carbamoyl)pyrrolidin-3-yl)pyrimidine-5-carboxamide;

5-(4-(3-((6-(tert-butylsulfonyl)-4-((4,5-dimethyl-1H-pyrazol-3-yl)amino)quinazolin-7-yl)oxy)propyl)piperazin-1-yl)-N-((3S,5S)-1-((S)-3,3-dimethyl-2-((S)-2-(methylamino)propanamido)butanoyl)-5-(((R)-1,2,3,4-tetrahydronaphthalen-1-yl)carbamoyl)pyrrolidin-3-yl)pyrazine-2-carboxamide;

(2S,4S)-4-((2-(4-(2-((6-(tert-butylsulfonyl)-4-((4,5-dimethyl-1H-pyrazol-3-yl)amino)quinazolin-7-yl)oxy)ethyl)piperazin-1-yl)pyrimidin-5-yl)oxy)-1-((S)-3,3-dimethyl-2-((S)-2-(methylamino)propanamido)butanoyl)-N-((R)-1,2,3,4-tetrahydronaphthalen-1-yl)pyrrolidine-2-carboxamide;

2-(4-(3-((6-(tert-butylsulfonyl)-4-((4,5-dimethyl-1H-pyrazol-3-yl)amino)quinazolin-7-yl)oxy)propyl)piperazin-1-yl)-N-((3S,5S)-5-((2,6-difluorophenyl)carbamoyl)-1-((S)-3,3-dimethyl-2-((S)-2-(methylamino)propanamido)butanoyl)pyrrolidin-3-yl)pyrimidine-5-carboxamide;

2-(4-(2-((6-(tert-butylsulfonyl)-4-((4,5-dimethyl-1H-pyrazol-3-yl)amino)quinazolin-7-yl)oxy)ethyl)piperazin-1-yl)-N-((3S,5S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)-5-((3-methyl-1-phenyl-1H-pyrazol-5-yl)carbamoyl)pyrrolidin-3-yl)pyrimidine-5-carboxamide;

2-(4-(3-((6-(tert-butylsulfonyl)-4-((4,5-dimethyl-1H-pyrazol-3-yl)amino)quinazolin-7-yl)oxy)propyl)piperazin-1-yl)-N-((3S,5S)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)-5-((3-methyl-1-phenyl-1H-pyrazol-5-yl)carbamoyl)pyrrolidin-3-yl)pyrimidine-5-carboxamide;

(S)-7-((6-(4-((6-(Tert-butylsulfonyl)-4-((4,5-dimethyl-1H-pyrazol-3-yl)amino)quinazolin-7-yl)oxy)piperidin-1-yl)pyrimidin-4-yl)oxy)-2-((S)-3,3-dimethyl-2-((S)-2-(methylamino)propanamido)butanoyl)-N-((R)-1,2,3,4-tetrahydronaphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;

(S)-7-((6-(4-(((6-(Tert-butylsulfonyl)-4-((4,5-dimethyl-1H-pyrazol-3-yl)amino)quinazolin-7-yl)oxy)methyl)piperidin-1-yl)pyrimidin-4-yl)oxy)-2-((S)-3,3-dimethyl-2-((S)-2-(methylamino)propanamido)butanoyl)-N-((R)-1,2,3,4-tetrahydronaphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide;

(2S,4S)-4-((2-(4-(((6-(Tert-butylsulfonyl)-4-((4,5-dimethyl-1H-pyrazol-3-yl)amino)quinazolin-7-yl)oxy)methyl)piperidin-1-yl)pyrimidin-5-yl)oxy)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)-N-((R)-1,2,3,4-tetrahydronaphthalen-1-yl)pyrrolidine-2-carboxamide;

(2S,4S)-4-((2-(4-((6-(tert-butylsulfonyl)-4-((4,5-dimethyl-1H-pyrazol-3-yl)amino)quinazolin-7-yl)oxy)piperidin-1-yl)pyrimidin-5-yl)oxy)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)-N-((R)-1,2,3,4-tetrahydronaphthalen-1-yl)pyrrolidine-2-carboxamide;

(2S,4S)-4-((2-(4-(2-((6-(tert-butylsulfonyl)-4-((4,5-dimethyl-1H-pyrazol-3-yl)amino)quinazolin-7-yl)oxy)ethyl)piperazin-1-yl)pyrimidin-5-yl)oxy)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)-N-((R)-1,2,3,4-tetrahydronaphthalen-1-yl)pyrrolidine-2-carboxamide;

(2S,4S)-4-((2-(4-(2-((6-(tert-butylsulfonyl)-4-((4,5-dimethyl-1H-pyrazol-3-yl)amino)quinazolin-7-yl)oxy)ethyl)piperidin-1-yl)pyrimidin-5-yl)oxy)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)-N-((R)-1,2,3,4-tetrahydronaphthalen-1-yl)pyrrolidine-2-carboxamide;

(2S,4S)-4-((2-(4-(3-((6-(tert-butylsulfonyl)-4-((4,5-dimethyl-1H-pyrazol-3-yl)amino)quinazolin-7-yl)oxy)propyl)piperidin-1-yl)pyrimidin-5-yl)oxy)-1-((S)-2-cyclohexyl-2-((S)-2-(methylamino)propanamido)acetyl)-N-((R)-1,2,3,4-tetrahydronaphthalen-1-yl)pyrrolidine-2-carboxamide;

(2S,4S)-4-((2-(4-(2-((6-(tert-butylsulfonyl)-4-((4,5-dimethyl-1H-pyrazol-3-yl)amino)quinazolin-7-yl)oxy)ethyl)piperazin-1-yl)pyrimidin-5-yl)oxy)-1-((S)-3,3-dimethyl-2-((S)-2-

(methylamino)propanamido)butanoyl)-N-((R)-1,2,3,4-tetrahydronaphthalen-1-yl)pyrrolidine-2-carboxamide;

(2S,4S)-4-((2-(4-(2-((6-(tert-butylsulfonyl)-4-((4,5-dimethyl-1H-pyrazol-3-yl)amino)quinazolin-7-yl)oxy)ethyl)piperazin-1-yl)pyrimidin-5-yl)oxy)-N-(2,6-difluorophenyl)-1-((S)-3,3-dimethyl-2-((S)-2-(methylamino)propanamido)butanoyl)pyrrolidine-2-carboxamide;

2-(4-(2-((6-(Tert-butylsulfonyl)-4-((4,5-dimethyl-1H-pyrazol-3-yl)amino)quinazolin-7-yl)oxy)ethyl)piperazin-1-yl)-N-((3S,5S)-5-((2,6-difluorophenyl)carbamoyl)-1-((S)-3,3-dimethyl-2-((S)-2-(methylamino)propanamido)butanoyl)pyrrolidin-3-yl)pyrimidine-5-carboxamide;

5-(4-(3-((6-(Tert-butylsulfonyl)-4-((4,5-dimethyl-1H-pyrazol-3-yl)amino)quinazolin-7-yl)oxy)propyl)piperazin-1-yl)-N-((3S,5S)-5-((2,6-difluorophenyl)carbamoyl)-1-((S)-3,3-dimethyl-2-((S)-2-(methylamino)propanamido)butanoyl)pyrrolidin-3-yl)pyrazine-2-carboxamide;

(S)-1-((S)-2-(1-(2-(4-(2-((6-(Tert-butylsulfonyl)-4-((4,5-dimethyl-1H-pyrazol-3-yl)amino)quinazolin-7-yl)oxy)ethyl)piperazin-1-yl)pyrimidine-5-carbonyl)piperidin-4-yl)-2-((S)-2-(methylamino)propanamido)acetyl)-N-((R)-1,2,3,4-tetrahydronaphthalen-1-yl)pyrrolidine-2-carboxamide;

(S)-1-((S)-2-(1-(2-(4-(3-((6-(tert-butylsulfonyl)-4-((4,5-dimethyl-1H-pyrazol-3-yl)amino)quinazolin-7-yl)oxy)propyl)piperazin-1-yl)pyrimidine-5-carbonyl)piperidin-4-yl)-2-((S)-2-(methylamino)propanamido)acetyl)-N-((R)-1,2,3,4-tetrahydronaphthalen-1-yl)pyrrolidine-2-carboxamide;

(5S,8S,10aR)-N-Benzhydryl-3-(5-(4-(((6-(tert-butylsulfonyl)-4-((4,5-dimethyl-1H-pyrazol-3-yl)amino)quinazolin-7-yl)oxy)methyl)piperidin-1-yl)pyrazine-2-carbonyl)-5-((S)-2-(methylamino)propanamido)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocine-8-carboxamide;

(5S,8S,10aR)-3-(5-(4-(((6-(tert-butylsulfonyl)-4-((4,5-dimethyl-1H-pyrazol-3-yl)amino)quinazolin-7-yl)oxy)methyl)piperidin-1-yl)pyrazine-2-carbonyl)-5-((S)-2-(methylamino)propanamido)-6-oxo-N-((R)-1,2,3,4-tetrahydronaphthalen-1-yl)decahydropyrrolo[1,2-a][1,5]diazocine-8-carboxamide;

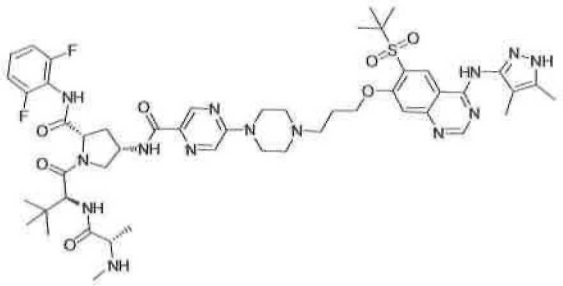
(5S,8S,10aR)-3-(5-(4-(3-((6-(tert-butylsulfonyl)-4-((4,5-dimethyl-1H-pyrazol-3-yl)amino)quinazolin-7-yl)oxy)propyl)piperazin-1-yl)pyrazine-2-carbonyl)-5-((S)-2-

(methylamino)propanamido)-6-oxo-N-((R)-1,2,3,4-tetrahydronaphthalen-1-yl)decahydropyrrolo[1,2-a][1,5]diazocine-8-carboxamide;

(5S,8S,10aR)-3-(2-(4-(3-((6-(tert-butylsulfonyl)-4-((4,5-dimethyl-1H-pyrazol-3-yl)amino)quinazolin-7-yl)oxy)propyl)piperazin-1-yl)pyrimidine-5-carbonyl)-5-((S)-2-(methylamino)propanamido)-6-oxo-N-((R)-1,2,3,4-tetrahydronaphthalen-1-yl)decahydropyrrolo[1,2-a][1,5]diazocine-8-carboxamide;

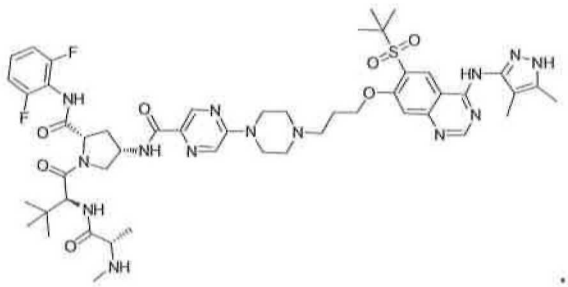
and pharmaceutically acceptable salts thereof.

8. A compound according to claim 1 which is 5-(4-(3-((6-(Tert-butylsulfonyl)-4-((4,5-dimethyl-1H-pyrazol-3-yl)amino)quinazolin-7-yl)oxy)propyl)piperazin-1-yl)-N-((3S,5S)-5-((2,6-difluorophenyl)carbamoyl)-1-((S)-3,3-dimethyl-2-((S)-2-(methylamino)propanamido)butanoyl)pyrrolidin-3-yl)pyrazine-2-carboxamide:



or a pharmaceutically acceptable salt thereof.

9. A compound according to claim 8 which is 5-(4-(3-((6-(Tert-butylsulfonyl)-4-((4,5-dimethyl-1H-pyrazol-3-yl)amino)quinazolin-7-yl)oxy)propyl)piperazin-1-yl)-N-((3S,5S)-5-((2,6-difluorophenyl)carbamoyl)-1-((S)-3,3-dimethyl-2-((S)-2-(methylamino)propanamido)butanoyl)pyrrolidin-3-yl)pyrazine-2-carboxamide:



10. A compound according to claims 1-9 or a pharmaceutically acceptable salt thereof for use in therapy.

11. A compound according to claims 1-9 or a pharmaceutically acceptable salt thereof for use in the treatment of diseases conditions mediated by RIP2 Kinase.

12. A pharmaceutical composition comprising a compound according to claims 1-9 or a pharmaceutically acceptable salt thereof and one or more of pharmaceutically acceptable carriers, diluents and excipients.

13. The use of a compound according to claims 1-9, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in treating diseases and conditions mediated by the RIP2 Kinase.

14. A combination comprising a compound of according to claims 1-9, or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent.

15. A combination comprising a compound according to claims 1-9 or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent for use in therapy, particularly for treating diseases and conditions mediated by the RIP2 Kinase.

16. A combination comprising compound according to claims 1-9 or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent for use in treating diseases and conditions mediated by the RIP2 Kinase.

17. The use of a combination comprising compound according to claims 1-9 or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent in the manufacture of a medicament for treating diseases and conditions mediated by the RIP2 Kinase.