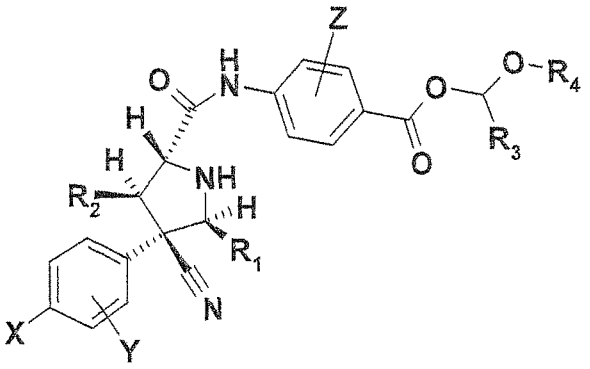
Summary

The present disclosure relates to pyrrolidine-2-carboxamide derivatives of formula (I) which act as antagonists of MDM2 interactions and hence are useful as potent and selective anticancer agents. The present compounds are of the general formula

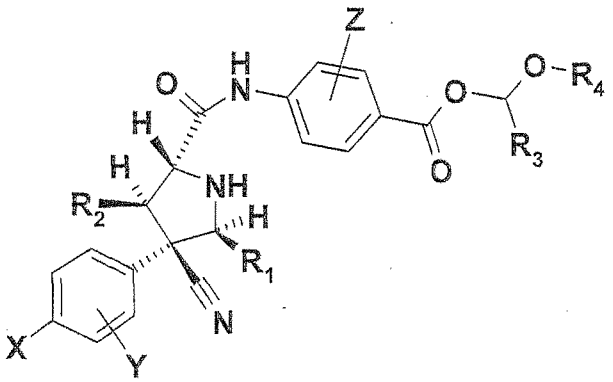


(I)

wherein X, Y, Z, R_1, R_2, R_3 and R_4 are as described herein

and enantiomers and pharmaceutically acceptable salts and esters thereof.

According to a first aspect, there is provided a compound of the formula



(I)

wherein

X is selected from ~~the group consisting of~~ H, F, or Cl, ~~Br, I, cyano, nitro, ethynyl, cyclopropyl, methyl, ethyl, isopropyl, vinyl and methoxy,~~

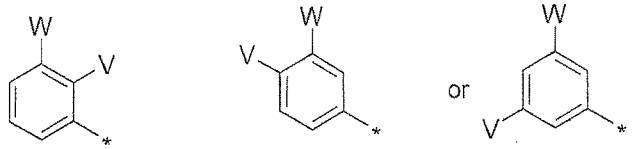
Y is ~~one to four group(s) independently~~ selected from ~~the group consisting of~~ H, F, or Cl, ~~Br, I, CN, OH, nitro, lower alkyl, cycloalkyl, lower alkoxy, lower alkenyl, cycloalkenyl and lower alkynyl,~~

Z is lower alkoxy,

R_1 is ~~selected from the group consisting of~~ lower alkyl, or substituted lower alkyl, ~~lower alkenyl, substituted lower alkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycle,~~

~~substituted heterocycle, cycloalkyl, substituted cycloalkyl, cycloalkenyl and substituted cycloalkenyl,~~

R_2 is a substituted phenyl selected from:



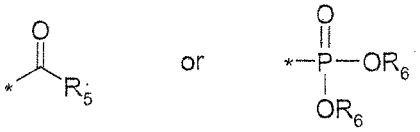
,

W is F, Cl or Br,

V is H or F,

R_3 is selected from the group consisting of hydrogen, lower alkyl and substituted lower alkyl,

R_4 is selected from



R_5 is selected from the group consisting of lower alkyl, substituted lower alkyl, heterocycle, substituted heterocycle, cycloalkyl, substituted cycloalkyl, natural and unnatural amino acids, -$(OCH_2CH_2)_n$-OH, -$(OCH_2CH_2)_n$-OCH_3, -$(NCH_2CH_2)_n$-OH, -$(NCH_2CH_2)_n$-OCH_3 and -$(OCH_2CH_2)_n$-$OP(O)(OR_6)_2$, wherein n is from 3 to 60,

R_6 is hydrogen or benzyl; or

a pharmaceutically acceptable salt or ester thereof.

According to a second aspect, there is provided a compound as defined above for use as a medicament.

According to a third aspect, there is provided a pharmaceutical composition comprising a compound as defined above and a therapeutically inert carrier.According to a fourth aspect, there is provided use of a compound as defined above for the preparation of a medicament for the treatment of cancer.

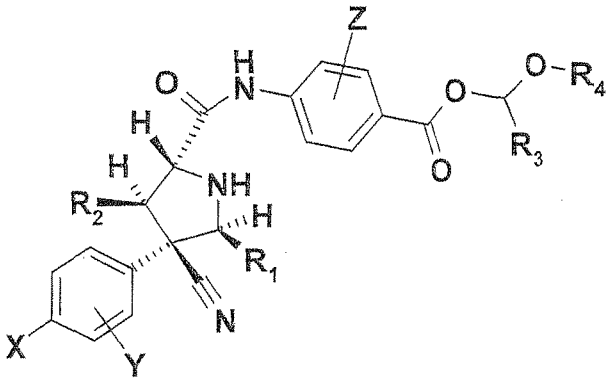
According to a fifth aspect, there is provided a compound as defined above for the treatment or prophylaxis of cancer.

Detailed Description of the Invention

In one embodiment there are provided compounds of the formula

Claims

1. A compound of the formula



(I)

wherein

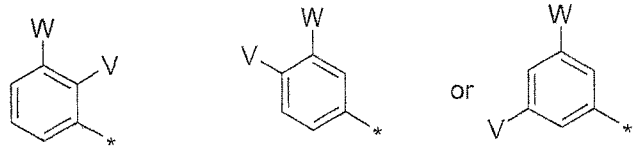
X is selected from ~~the group consisting of~~ H, F, ~~or~~ Cl, ~~Br, I, cyano, nitro, ethynyl, cyclopropyl, methyl, ethyl, isopropyl, vinyl and methoxy,~~

Y is ~~one to four group(s) independently~~ selected from ~~the group consisting of~~ H, F, ~~or~~ Cl, ~~Br, I, CN, OH, nitro, lower alkyl, cycloalkyl, lower alkoxy, lower alkenyl, cycloalkenyl and lower alkynyl,~~

Z is lower alkoxy,

R_1 is ~~selected from the group consisting of~~ lower alkyl, ~~or~~ substituted lower alkyl, ~~lower alkenyl, substituted lower alkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycle, substituted heterocycle, cycloalkyl, substituted cycloalkyl, cycloalkenyl and substituted cycloalkenyl,~~

R_2 is a substituted phenyl selected from:



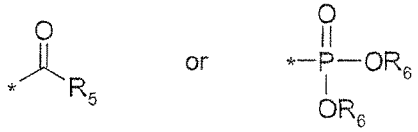
,

W is F, Cl or Br,

V is H or F,

R_3 is selected from the group consisting of hydrogen, lower alkyl and substituted lower alkyl,

R_4 is selected from



R_5 is selected from the group consisting of lower alkyl, substituted lower alkyl, heterocycle, substituted heterocycle, cycloalkyl, substituted cycloalkyl, natural and unnatural amino acids, -

(S)-2-(((4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoyloxy) methoxy)carbonylamino)pentanedioic acid.

6. A compound of claim 1 selected from the group consisting of

15-methyl-12-oxo-2,5,8,11,13-pentaoxahexadecan-14-yl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate,

3-Oxo-2,4,7,10,13-pentaoxatetradecyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate,

3-Oxo-2,4,7,10,13,16,19-heptaoxaicosyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate,

4-{[(2R,3S,4R,5S)-3-(3-Chloro-2-fluoro-phenyl)-4-(4-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid 1-mPEG-carbonyloxy-methyl ester (mPEG, average MW, ~750) ,

4-{[(2R,3S,4R,5S)-3-(3-Chloro-2-fluoro-phenyl)-4-(4-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid 1-mPEG-carbonyloxy-ethyl ester (mPEG, average MW, ~2000) ,

4-{[(2R,3S,4R,5S)-3-(3-Chloro-2-fluoro-phenyl)-4-(4-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid 1-mPEG-carbonyloxy-ethyl ester (mPEG, average MW, ~2200) ,

4-{[(2R,3S,4R,5S)-3-(3-Chloro-2-fluoro-phenyl)-4-(4-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid 1-mPEG-carbonyloxy-methyl ester (mPEG, average MW, ~2000) ,

~~3-Oxo-2,4,7,10,13-pentaoxatetradecyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate,~~

27-Oxo-2,5,8,11,14,17,20,23,26,28-decaoxatriacontan-29-yl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate,

24-Oxo-2,5,8,11,14,17,20,23,25-nonaoxaheptacosan-26-yl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate,

4-{[(2R,3S,4R,5S)-3-(3-Chloro-2-fluoro-phenyl)-4-(4-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid 1-mPEG-carbonyloxy-ethyl amide (mPEG-NH_2, average MW, ~550) and

4-{[(2R,3S,4R,5S)-3-(3-Chloro-2-fluoro-phenyl)-4-(4-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid 1-(2-{2-[2-(2-dibenzyloxyphosphoryloxy-ethoxy)-ethoxy]-ethoxy}-ethoxycarbonyloxy)-ethyl ester and
4-{[(2R,3S,4R,5S)-3-(3-Chloro-2-fluoro-phenyl)-4-(4-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid 1-(2-{2-[2-(2-phosphonooxy-ethoxy)-ethoxy]-ethoxy}-ethoxycarbonyloxy)-ethyl ester.

8. A compound of claim 1 selected from the group consisting of
4-{[(2R,3S,4R,5S)-3-(3-Chloro-2-fluoro-phenyl)-4-(4-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid 1-[2-(2-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-ethoxy)-ethoxycarbonyloxy]-ethyl ester,
4-{[(2R,3S,4R,5S)-3-(3-Chloro-2-fluoro-phenyl)-4-(4-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid 1-mPEG-carbonyloxy-ethyl ester,
15-methyl-12-oxo-2,5,8,11,13-pentaoxahexadecan-14-yl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate,
3-Oxo-2,4,7,10,13-pentaoxatetradecyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate,
3-Oxo-2,4,7,10,13,16,19-heptaoxaicosyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate,
~~4-{[(2R,3S,4R,5S)-3-(3-Chloro-2-fluoro-phenyl)-4-(4-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid 1-mPEG-carbonyloxy-ethyl ester,~~
~~3-Oxo-2,4,7,10,13-pentaoxatetradecyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate,~~
27-Oxo-2,5,8,11,14,17,20,23,26,28-decaoxatriacontan-29-yl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate,
24-Oxo-2,5,8,11,14,17,20,23,25-nonaoxaheptacosan-26-yl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate, and
4-{[(2R,3S,4R,5S)-3-(3-Chloro-2-fluoro-phenyl)-4-(4-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid 1-mPEG-carbonyloxy-ethyl amide.