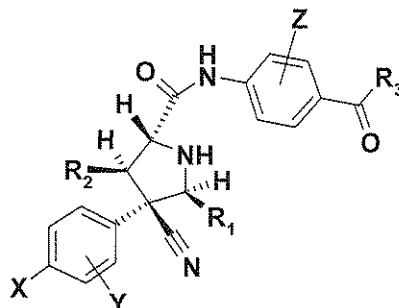


Summary of the Invention

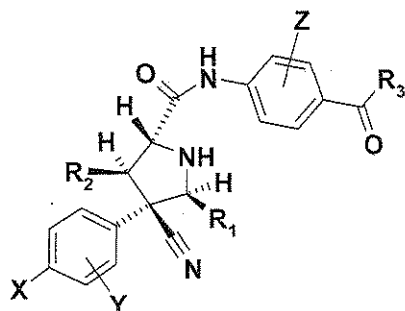
The present ~~invention~~ disclosure relates to pyrrolidine-2-carboxamide derivatives I which act as antagonists of mdm2 interactions and hence are useful as potent and selective anticancer agents. The present compounds are of the general formula



(I)

wherein X, Y, Z, R₁, R₂ and R₃ are as described herein and enantiomers and pharmaceutically acceptable salts and esters thereof.

In a first aspect, there is provided a compound of the formula



(II)

wherein

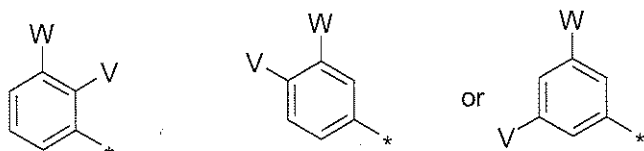
X is selected from the group consisting of H, F, Cl, Br, I, cyano, nitro, ethynyl, cyclopropyl, methyl, ethyl, isopropyl, vinyl and methoxy;

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

Z is lower alkoxy;

R₁ is selected from the group consisting of lower alkyl, substituted lower alkyl, lower alkenyl, substituted lower alkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycle, substituted heterocycle, cycloalkyl, substituted cycloalkyl, cycloalkenyl, and substituted cycloalkenyl;

R₂ is a substituted phenyl selected from:



W is -F, -Cl or -Br;

V is -H or -F,

R₃ is selected from the group consisting of lower alkoxy, substituted lower alkoxy, alkylamino, dialkylamino, glucuronic acid, hexoses, aminohexoses, pyranoses, aminoglycosides, natural and unnatural amino acids, -OCH₂C(O)N(CH₃)₂, -(OCH₂CH₂)_n-OH, -(OCH₂CH₂)_n-OCH₃, -(OCH₂CH₂)_n-OP(O)(OR₄)₂, -OCH₂C(O) -(OCH₂CH₂)_n-OH, -OCH₂C(O) -(OCH₂CH₂)_n-OCH₃, -NH(CH₂CH₂O)_n-CH₃, -NH(CH₂CH₂O)_n-H, -OCH₂C(O)NH(CH₂CH₂O)_n-CH₃, -O-R₅, -OCH₂-R₅, OCH₂CH₂-R₅, -OCH₂C(O) -R₅, -NH(OCH₂CH₂)_n-NH₂ and -OCH₂CH₂-amino acid, wherein n is from 3 to 80;

R₄ is hydrogen or benzyl;

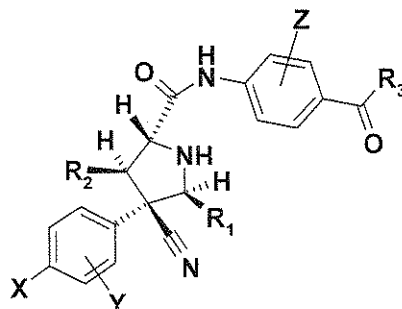
R₅ is selected from the group consisting of heterocycles, substituted heterocycles, dialkylamino, alkylamino and aminoalkyl alcohols; or a pharmaceutically acceptable salt or ester thereof.

In a second aspect, there is provided a compound as defined herein for use as a medicament.
In a third aspect, there is provided a pharmaceutical composition comprising a compound as defined herein, together with pharmaceutically acceptable carriers or excipients.
In a fourth aspect, there is provided use of a compound as defined herein for the preparation of a medicament for the treatment of cancer, in particular solid tumors, more particularly breast, colon, lung and prostate tumors.

In a fifth aspect, there is provided a compound as defined herein for the treatment or prophylaxis of cancer, in particular solid tumors, more particularly breast, colon, lung and prostate tumors.

Detailed Description of the Invention

There are provided compounds of the formula



(I)

wherein

5 X is selected from the group consisting of -H, -F, -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, -Cl, -Br, -I, -CN, -OH, nitro, lower alkyl, cycloalkyl, lower alkoxy, lower alkenyl, cycloalkenyl and lower alkynyl;

10 Z is lower alkoxy;

R₁ is selected from the group consisting of lower alkyl, substituted lower alkyl, lower alkenyl, substituted lower alkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycle, substituted heterocycle, cycloalkyl, substituted cycloalkyl, cycloalkenyl and substituted cycloalkenyl;

4- {[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino }-3-methoxy-benzoic acid ((S)-1-allyloxycarbonyl-5-tert-butoxycarbonylamino-pentylcarbamoyl)-methyl ester,

4- {[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino }-3-methoxy-benzoic acid, mPEG-1000 amide,

4- {[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino }-3-methoxy-benzoic acid, mPEG-1000 ester,

4- {[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino }-3-methoxy-benzoic acid, mPEG-2000 amide, and

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

11. A compound according to any one of claims 1 to 10 for use as a medicament.

12. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 10, together with pharmaceutically acceptable carriers or excipients.

~~13. The use of a compound according to any one of claims 1 to 10 for the treatment of cancer, in particular solid tumors, more particularly breast, colon, lung and prostate tumors.~~

~~13.~~ 13. The use of a compound according to any one of claims 1 to 10 for the preparation of a medicament for the treatment of cancer, in particular solid tumors, more particularly breast, colon, lung and prostate tumors.:-

~~14.~~ 14. A compound according to any one of claims 1 to 10 for the treatment or prophylaxis of cancer, in particular solid tumors, more particularly breast, colon, lung and prostate tumors.:-