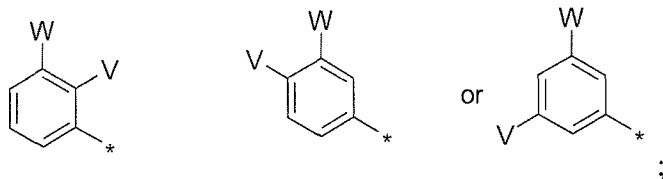


-2a-



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;

and wherein said compound is selected from the group consisting of

2-Hydroxyethyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate,

2-(2-Hydroxyethoxy)ethyl 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 2-((S)-2-tert-butoxycarbonylamino-propionyloxy)-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 2-((S)-2-amino-propionyloxy)-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 2-((R)-2-tert-butoxycarbonylamino-propionyloxy)-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 2-((R)-2-amino-propionyloxy)-ethyl ester,

- 2-(Dimethylamino)ethyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate, (2,2-Dimethyl-1,3-dioxolan-4-yl)methyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate,
- 5 3-Hydroxy-2-(hydroxymethyl)propyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate, 2-Methoxyethyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate,
- 10 2-Iodoethyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate,
- 2-(Di-tert-butoxyphosphoryloxy)ethyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate,
- 2-(Phosphonooxy)ethyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate,
- 15 trifluoroacetate salt,
- (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-carboxylic acid [4-(2-hydroxy-1-methyl-ethylcarbamoyl)-2-methoxy-phenyl]-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 2-diethylamino-ethyl ester,
- 20 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 1-methyl-piperidin-4-yl ester,
- 25 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 1-methyl-piperidin-4-ylmethyl ester,
- 4-{[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid 2-(4-methyl-piperazin-1-yl)-ethyl ester,
- 30 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 [1,2,3]triazolo[4,5-b]pyridin-3-yl 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 1-methyl-2-morpholin-4-yl-ethyl ester,
- 5 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 2-morpholin-4-yl-ethyl ester,
- (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-carboxylic acid [4-(2-diethylamino-ethylcarbamoyl)-2-methoxy-phenyl]-amide, hydrochloride,
- 10 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 dimethylcarbamoylmethyl ester, hydrochloride,
- 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 2-morpholin-4-yl-propyl ester, hydrochloride,
- 15 (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-carboxylic acid {2-methoxy-4-[2-(4-methyl-piperazin-1-yl)-ethylcarbamoyl]-phenyl}-amide, hydrochloride,
- (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-carboxylic acid (4-dimethylcarbamoyl-2-methoxy-phenyl)-amide,
- 20 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 (2S,3R,4R,5R)-2,3,4,5,6-pentahydroxy-hexyl 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 2-(2-tert-butoxycarbonylamino-acetoxy)-ethyl ester,
- 25 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 2-(2-amino-acetoxy)-ethyl 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 2-[2-(tert-butoxycarbonyl-methyl-amino)-acetoxy]-ethyl ester,
- 30 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 2-(2-methylamino-acetoxy)-ethyl ester, hydrochloride,
- 35

- 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 2-[(S)-3-
methyl-2-((S)-2-tert-butoxycarbonyl-methylamino-propionylamino)-butyryloxy]-ethyl ester,
5 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 2-[(S)-3-
methyl-2-((S)-2-methylamino-propionylamino)-butyryloxy]-ethyl ester, hydrochloride,
4-{[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-
(2,2dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid
methoxycarbonylmethyl ester, 4-{[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-
10 2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-
methoxy-benzoic acid 3-carboxy-propyl ester,
4-{[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-
(2,2dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid 2-tert-
butoxycarbonyl-ethyl ester,
15 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 2-carboxy-
ethyl ester,
(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-carboxylic acid (4-hydrazinocarbonyl-2-methoxy-phenyl)-
20 amide,
2S,3S,4S,5R,6S)-6-(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-
benzoyloxy)-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid; compound with trifluoro-
acetic acid,
25 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
(2R,3S,4S,5R,6R)-3,4,5,6-tetrahydroxy-tetrahydro-pyran-2-ylmethyl ester; compound with
trifluoro-acetic acid,
30 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, 2-(2-{2-[2-
(2-{2-[2-(2-hydroxy-ethoxy)-ethoxy]-ethoxy}-ethoxy)-ethoxy]-ethoxy}-ethoxy)-ethyl ester,
trifluoroacetate salt,
4-{[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-
(2,2dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid,
35 dodecaethylene glycol 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, polyethylene glycol-600 ester, trifluoroacetate salt,
- 5 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, polyethylene glycol-200 ester, trifluoroacetate salt,
- 10 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 2-(2-dimethylamino-ethoxy)-ethyl ester, hydrochloride,4-{[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid 2-[2-(2-hydroxy-ethoxy)-ethoxy]-ethyl ester, hydrochloride,
- 15 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 2-[2-(2-methoxy-ethoxy)-ethoxy]-ethyl ester, hydrochloride,
- 20 4-{[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid 2-(2-{2-[2-(2-hydroxy-ethoxy)-ethoxy]-ethoxy}-ethoxy)-ethyl ester, hydrochloride,
- 25 4-{[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid 2-(2-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-ethoxy)-ethyl ester, hydrochloride,
- 30 (R)-2-(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-benzoylamino)-pentanedioic acid dimethyl ester, hydrochloride,
- (R)-2-(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-benzoylamino)-pentanedioic acid, hydrochloride,

- (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-carboxylic acid {2-methoxy-4-[methyl-((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxy-hexyl)-carbamoyl]-phenyl}-amide, hydrochloride,
- 5 (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-carboxylic acid [2-methoxy-4-((2S,3R,4R,5S,6R)-2,4,5-trihydroxy-6-hydroxymethyl-tetrahydro-pyran-3-ylcarbamoyl)-phenyl]-amide, hydrochloride,
- 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 2-{2-[2-(2-hydroxyethoxy)-ethoxy]-ethoxy}-ethyl ester, hydrochloride,
- 10 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-350 ester, trifluoroacetate salt,
- 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-550
- 15 ester, hydrochloride,
- 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, 2-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-ethyl ester, dimer,
- 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 2-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-ethyl ester,
- 20 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 2-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-ethyl ester, PEG-400 ester, hydrochloride salt,
- 25 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 2-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-ethyl ester, mPEG-750 ester, hydrochloride salt,
- 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 2-(4-methyl-
- 30 piperazin-1-yl)-2-oxo-ethyl ester, hydrochloride,
- 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 carbamoylmethyl 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 2-morpholin-4-yl-2-oxo-ethyl ester,
- 5 4-{[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid [(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-carbamoyl]-methyl ester,
- 4-{[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid (2,3-dihydroxy-propylcarbamoyl)-methyl ester,
- 10 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 carboxymethyl ester,
- (S)-2-[2-(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-benzoyloxy)-acetylamino]-pentanedioic acid dibenzyl ester,
- 15 (S)-2-[2-(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-benzoyloxy)-acetylamino]-pentanedioic acid,
- 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 2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxycarbonylmethyl ester,
- 20 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 2-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-ethoxycarbonylmethyl ester,
- 25 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 [2-(2-hydroxy-ethoxy)-ethylcarbamoyl]-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 (2-{2-[2-(2-hydroxy-ethoxy)-ethoxy]-ethoxy}-ethylcarbamoyl)-methyl ester,
- 30 (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-carboxylic acid [4-(2-{2-[2-(2-amino-ethoxy)-ethoxy]-ethoxy}-ethylcarbamoyl)-2-methoxy-phenyl]-amide, dimer,

(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-carboxylic acid [4-(2-{2-[2-(2-amino-ethoxy)-ethoxy]-ethoxy}-ethylcarbamoyl)-2-methoxy-phenyl]-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 ((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.

In a second aspect, there is provided a compound as defined herein for use as a medicament.

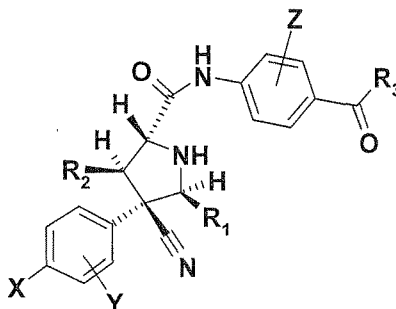
In a third aspect, there is provided a pharmaceutical composition comprising a compound as defined herein, together with pharmaceutically acceptable carriers or excipients.

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;

R₄ is hydrogen or benzyl;

R₅ is selected from the group consisting of heterocycles, substituted heterocycles, dialkylamino, alkylamino and aminoalkyl alcohols; or

5 a pharmaceutically acceptable salt or ester thereof,

and wherein said compound is selected from the group consisting of:

~~2. The compound of claim 1 wherein~~

~~X is selected from H, F or Cl;~~

10 ~~Y is selected from H, F or Cl;~~

~~R₁ is lower alkyl or substituted lower alkyl;~~

~~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-~~

15 ~~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 60;~~

~~R₄ is hydrogen or benzyl;~~

20 ~~R₅ is selected from the group consisting of heterocycles, substituted heterocycles, dialkylamino, alkylamino and aminoalkyl alcohols; or~~

~~a pharmaceutically acceptable salt or ester thereof.~~

~~3. The compound of claim 1 wherein~~

25 ~~X is selected from H, F or Cl;~~

~~Y is selected from H, F or Cl;~~

~~R₁ is lower alkyl or substituted lower alkyl;~~

~~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-~~

30 ~~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 45;~~

35 ~~R₄ is hydrogen or benzyl;~~

R₃ is selected from the group consisting of heterocycles, substituted heterocycles, dialkylamino, alkylamino and aminoalkyl alcohols; or
a pharmaceutically acceptable salt or ester thereof.

- 5 4. A compound of claim 1 selected from the group consisting of
2-Hydroxyethyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-
5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate,
2-(2-Hydroxyethoxy)ethyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-
fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate,
10 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 2-((S)-2-*tert*-
butoxycarbonylamino-propionyloxy)-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 2-((S)-2-amino-
15 propionyloxy)-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 2-((R)-2-*tert*-
butoxycarbonylamino-propionyloxy)-ethyl ester,
4- {[(2R,3S,4R,5S)-3-(3-Chloro-2-fluoro-phenyl)-4-(4-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-
20 dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino }-3-methoxy-benzoic acid 2-((R)-2-amino-
propionyloxy)-ethyl ester,
2-(Dimethylamino)ethyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-
4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate,
(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-
25 2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate,
3-Hydroxy-2-(hydroxymethyl)propyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-
fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate,
2-Methoxyethyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-
5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate,
30 2-Iodoethyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-
neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate, and
2-(Di-*tert*-butoxyphosphoryloxy)ethyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-
fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate.

5. ——— A compound of claim 1 selected from the group consisting of

2-(Phosphonooxy)ethyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate, trifluoroacetate salt,
(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-carboxylic acid [4-(2-hydroxy-1-methyl-ethylcarbamoyl)-2-methoxy-phenyl]-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 2-diethylamino-ethyl 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 1-methyl-piperidin-4-yl 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 1-methyl-piperidin-4-ylmethyl ester ———,

4- {[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino }-3-methoxy-benzoic acid 2-(4-methyl-piperazin-1-yl)-ethyl 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 [1,2,3]triazolo[4,5-b]pyridin-3-yl ester,

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

(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-carboxylic acid [4-(2-diethylamino-ethylcarbamoyl)-2-methoxy-phenyl]-amide, hydrochloride, 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 dimethylcarbamoylmethyl ester, hydrochloride,

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

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 2-morpholin-4-yl-propyl ester, hydrochloride,

5 (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-carboxylic acid {2-methoxy-4-[2-(4-methyl-piperazin-1-yl)-ethylcarbamoyl]-phenyl}-amide, hydrochloride,

(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-carboxylic acid (4-dimethylcarbamoyl-2-methoxy-phenyl)-amide,

10 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 (2S,3R,4R,5R)-2,3,4,5,6-pentahydroxy-hexyl 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 2-(2-tert -

15 butoxycarbonylamino-acetoxy)-ethyl 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 2-(2-amino-acetoxy)-ethyl ester,

20 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 2-[2-(tert-butoxycarbonylmethyl-amino)-acetoxy]-ethyl 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 2-(2-methylamino-acetoxy)-ethyl ester, hydrochloride,

25 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 2-[(S)-3-methyl-2-((S)-2-tert-butoxycarbonyl-methylamino-propionylamino)-butyryloxy]-ethyl 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 2-[(S)-3-methyl-2-((S)-2-methylamino-propionylamino)-butyryloxy]-ethyl ester, hydrochloride, and

30 4-[[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid methoxycarbonylmethyl ester,;

35

7. ~~_____ A compound of claim 1 selected from the group consisting of _____~~

- 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 3-carboxy-propyl ester,
- 5 4- {[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid 2-tert-butoxycarbonyl-ethyl 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 2-carboxy-ethyl ester,
- 10 (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-carboxylic acid (4-hydrazinocarbonyl-2-methoxy-phenyl)-amide,
- 2S,3S,4S,5R,6S)-6-(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-benzoyloxy)-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid; compound with trifluoro-acetic acid,
- 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 (2R,3S,4S,5R,6R)-3,4,5,6-tetrahydroxy-tetrahydro-pyran-2-ylmethyl ester; compound with trifluoro-acetic acid,
- 15 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, 2-(2-{2-[2-(2-{2-(2-hydroxy-ethoxy)-ethoxy}-ethoxy)-ethoxy]-ethoxy}-ethoxy)-ethyl ester, trifluoroacetate salt,
- 20 4- {[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid, dodecaethylene glycol 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, polyethylene glycol-600 ester, trifluoroacetate salt,
- 25 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—, polyethylene glycol-200 ester, trifluoroacetate salt, 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 2-(2-dimethylamino-ethoxy)-ethyl ester, hydrochloride,

- 5 8. ——— A compound of claim 1 selected from the group consisting of
4- {[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid 2-[2-(2-hydroxy-ethoxy)-ethoxy]-ethyl ester, hydrochloride,
4- {[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-
10 dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid 2-[2-(2-methoxy-ethoxy)-ethoxy]-ethyl ester, hydrochloride,
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 2-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-ethyl ester, hydrochloride,
15 4- {[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid 2-(2-{2-[2-(2-hydroxy-ethoxy)-ethoxy]-ethoxy}-ethoxy)-ethyl ester, hydrochloride,
4- {[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid 2-(2-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-ethoxy)-ethyl ester, hydrochloride,
20 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 2-[2-(2-{2-[2-(2-hydroxy-ethoxy)-ethoxy]-ethoxy}-ethoxy)-ethoxy]-ethyl ester, hydrochloride,
(R)-2-(4- {[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-
25 (2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoylamino)-pentanedioic acid dimethyl ester, hydrochloride,
(R)-2-(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-benzoylamino)-pentanedioic acid, hydrochloride,
30 (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-carboxylic acid {2-methoxy-4-[methyl-((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxy-hexyl)-carbamoyl]-phenyl}-amide, hydrochloride,
(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-carboxylic acid [2-methoxy-4-((2S,3R,4R,5S,6R)-2,4,5-

trihydroxy-6-hydroxymethyl-tetrahydro-pyran-3-ylcarbamoyl)-phenyl]-amide, hydrochloride, 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 2-{2-[2-(2-
hydroxyethoxy)-ethoxy]-ethoxy}-ethyl ester, hydrochloride,

5

9. ~~_____ A compound of claim 1 selected from the group consisting of~~

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-350 ester,
trifluoroacetate salt,

10

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-550 ester,
hydrochloride,

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, 2-[4-(2-hydroxy-ethyl)-
piperazin-1-yl]-ethyl ester, dimer,

15

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 2-[4-(2-hydroxy-ethyl)-
piperazin-1-yl]-ethyl 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 2-[4-(2-hydroxy-ethyl)-
piperazin-1-yl]-ethyl ester, PEG-400 ester, hydrochloride salt,

20

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 2-[4-(2-hydroxy-ethyl)-
piperazin-1-yl]-ethyl ester, mPEG-750 ester, hydrochloride salt,

4-[[[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-
(2,2dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino]-3-methoxy-benzoic acid 2-(4-methyl-
piperazin-1-yl)-2-oxo-ethyl ester, hydrochloride,

25

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 carbamoylmethyl 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 2-morpholin-4-yl-2-oxo-
ethyl ester,

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4- {[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid [(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-carbamoyl]-methyl ester, and
4- {[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid (2,3-dihydroxy-propylcarbamoyl)-methyl ester,;

10. ———— A compound of claim 1 selected from the group consisting of

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 carboxymethyl ester,
(S)-2-[2-(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-benzoyloxy)-acetylamino]-pentanedioic acid dibenzyl ester,
(S)-2-[2-(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-benzoyloxy)-acetylamino]-pentanedioic acid,
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 2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxycarbonylmethyl 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 2-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-ethoxycarbonylmethyl 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 [2-(2-hydroxy-ethoxy)-ethylcarbamoyl]-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 (2-{2-[2-(2-hydroxy-ethoxy)-ethoxy]-ethoxy}-ethylcarbamoyl)-methyl ester,
(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-carboxylic acid [4-(2-{2-[2-(2-amino-ethoxy)-ethoxy]-ethoxy}-ethylcarbamoyl)-2-methoxy-phenyl]-amide, dimer,
(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-carboxylic acid [4-(2-{2-[2-(2-amino-ethoxy)-ethoxy]-ethoxy}-ethylcarbamoyl)-2-methoxy-phenyl]-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 ((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.

~~112.~~ A compound according to ~~any one of claims 1 to 10~~ for use as a medicament.

~~123.~~ A pharmaceutical composition comprising a compound in accordance with ~~any one of claims 1 to 10~~, together with pharmaceutically acceptable carriers or excipients.

~~134.~~ The use of a compound according to ~~any one of claims 1 to 10~~ for in the preparation of a medicament for the treatment of cancer, in particular solid tumors, more particularly breast, colon, lung and prostate tumors.

~~145.~~ A compound according to ~~any one of claims 1 to 10~~ for use in the treatment or prophylaxis of cancer, in particular solid tumors, more particularly breast, colon, lung and prostate tumors.