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Szubsztituált pirrolidin-2-karboxamidok

Az európai szabadalom ellen, megadásának az Európai Szabadalmi Közlönyben való meghirdetésétől számított kilenc hónapon belül, felszólalást lehet benyújtani az Európai Szabadalmi Hivatalnál. (Európai Szabadalmi Egyezmény 99. cikk(1))

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(54) **SUBSTITUTED PYRROLIDINE-2-CARBOXAMIDES**

SUBSTITUIERTE PYRROLIDIN-2-CARBOXAMIDE

PYRROLIDINE-2-CARBOXAMIDES SUBSTITUÉS

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(56) References cited:

WO-A1-2011/098398

- **NUDELMAN A ET AL: "Prodrugs of butyric acid. Novel derivatives possessing increased aqueous solubility and potential for treating cancer and blood diseases", EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, EDITIONS SCIENTIFIQUE ELSEVIER, PARIS, FR, vol. 36, no. 1, 1 January 2001 (2001-01-01), pages 63-74, XP004372819, ISSN: 0223-5234, DOI: 10.1016/S0223-5234(00)01199-5**

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Description**Background of the Invention**

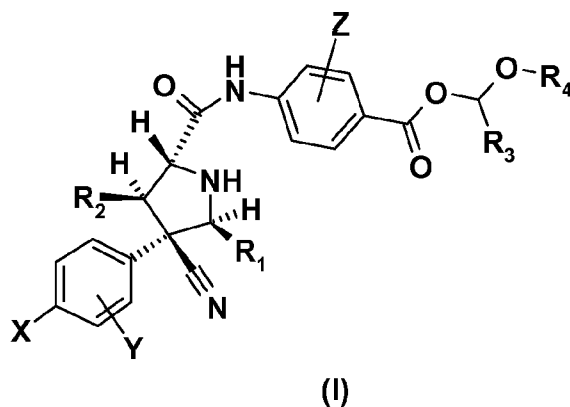
[0001] p53 is a tumor suppresser protein that plays a central role in protection against development of cancer. It guards cellular integrity and prevents the propagation of permanently damaged clones of cells by the induction of growth arrest or apoptosis. At the molecular level, p53 is a transcription factor that can activate a panel of genes implicated in the regulation of cell cycle and apoptosis. p53 is a potent cell cycle inhibitor which is tightly regulated by MDM2 at the cellular level. MDM2 and p53 form a feedback control loop. MDM2 can bind p53 and inhibit its ability to transactivate p53-regulated genes. In addition, MDM2 mediates the ubiquitin-dependent degradation of p53. p53 can activate the expression of the MDM2 gene, thus raising the cellular level of MDM2 protein. This feedback control loop insures that both MDM2 and p53 are kept at a low level in normal proliferating cells. MDM2 is also a cofactor for E2F, which plays a central role in cell cycle regulation.

[0002] The ratio of MDM2 to p53 (E2F) is dysregulated in many cancers. Frequently occurring molecular defects in the p16INK4/p19ARF locus, for instance, have been shown to affect MDM2 protein degradation. Inhibition of MDM2-p53 interaction in tumor cells with wild-type p53 should lead to accumulation of p53, cell cycle arrest and/or apoptosis. MDM2 antagonists, therefore, can offer a novel approach to cancer therapy as single agents or in combination with a broad spectrum of other antitumor therapies. The feasibility of this strategy has been shown by the use of different macromolecular tools for inhibition of MDM2-p53 interaction (e.g. antibodies, antisense oligonucleotides, peptides). MDM2 also binds E2F through a conserved binding region as p53 and activates E2F-dependent transcription of cyclin A, suggesting that MDM2 antagonists might have effects in p53 mutant cells.

[0003] WO2010/031713 and WO2011/098398 disclose compounds as inhibitors of the MDM2p53 interaction, which may sometimes be referred herein as "parent compounds."

Summary of the Invention

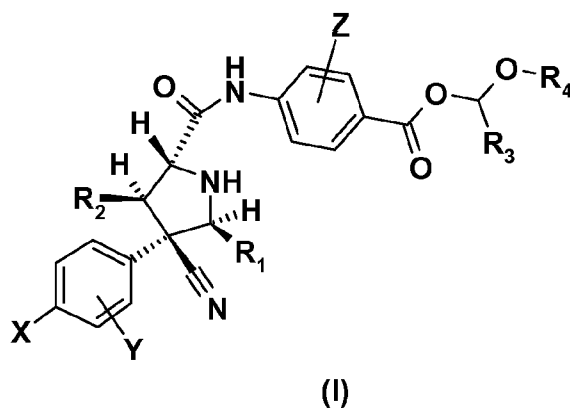
[0004] The present invention relates to pyrrolidine-2-carboxamide derivatives of formula (I) which act as antagonists of MDM2 interactions and hence are useful as potent and selective anticancer agents. The present compounds are of the general formula



wherein X, Y, Z, R₁, R₂, R₃ and R₄ are as described herein and enantiomers and pharmaceutically acceptable salts thereof.

Detailed Description of the Invention

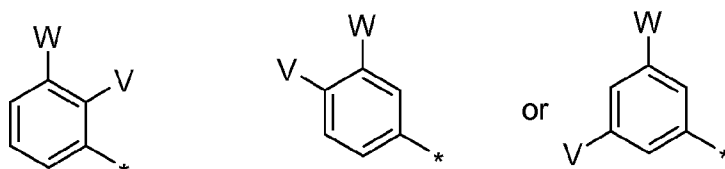
[0005] In one embodiment there are provided compounds of the formula



wherein

X is selected from H, F or Cl,

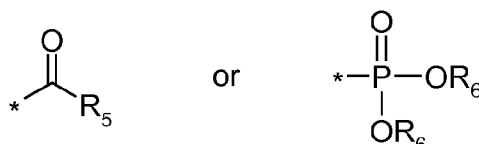
Y is selected from H, F or Cl Z is C1-6 alkoxy R₁ is C1-6 alkyl, or C1-6 alkyl substituted with C1-6 alkoxy or N(C1-6 alkyl)₂, R₂ is a substituted phenyl selected from:



W is F, Cl or Br,

V is H or F,

R₃ is hydrogen or C1-6 alkyl, R₄ is selected from the group consisting of:



R₅ is selected from the group consisting of C1-6 alkyl, C1-6 alkyl substituted with C1-6 alkoxy or N(C1-6 alkyl)₂, natural and unnatural amino acids, -(OCH₂CH₂)_n-OH, -(OCH₂CH₂)_n-OCH₃, -(NCH₂CH₂)_n-OH, -(NCH₂CH₂)_n-OCH₃ and -(OCH₂CH₂)_n-OP(O)(OR₆)₂, wherein n is from 3 to 60, R₆ is hydrogen; or a pharmaceutically acceptable salt thereof.

[0006] In another embodiment, there are provided compounds of formula (I), wherein

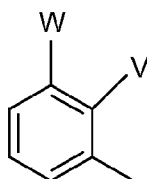
X is selected from H, F or Cl;

Y is selected from H, F or Cl;

Z is C1-6 alkoxy;

R₁ is C1-6 alkyl;

R₂ is



wherein

W is F, Cl or Br;

V is H or F;

R₃ is hydrogen or C1-6 alkyl;

R₄ is -C(O)-R₅; wherein

R₅ is selected from the group consisting of -(OCH₂CH₂)_n-OH; -(OCH₂CH₂)_n-OCH₃; and -(OCH₂CH₂)_n-OP(O)(OR₆)₂, wherein n is from 3 to 60, and R₆ is hydrogen; or

a pharmaceutically acceptable salt thereof.

[0007] In another, more specific embodiment n is from 3 to 55, more preferably n is from 3 to 45. Within this embodiment, compounds wherein R₅ is -(OCH₂CH₂)_n-OCH₃ and n is from 40 to 60 are especially preferred.

[0008] In yet another embodiment, there are provided the compounds selected from

1-(Ethyl(isopropyl)carbamoyloxy)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-phcnyl)-4-(4-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino)-3-methoxy-benzoic acid di-*tert*-butoxy-phosphoryloxymethyl 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-[bis-(2-methoxyethyl)-carbamoyloxy]-ethyl ester,
4-Methyl-piperazine-1-carboxylic acid 1-(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-benzoyloxy)-ethyl ester,
1-Acetoxylethyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate,
Rac-1-(isobutyryloxy)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)-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 acetoxymethyl ester,
1-(Cyclohexyloxycarbonyloxy)ethyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate,
Rac-1-(isopropoxycarbonyloxy)ethyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate,
1-(4-((2R,3S,4R,5S)-3-(3-Chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoyloxy)ethyl morpholine-4-carboxylate,
Morpholine-4-carboxylic acid(R)-1-(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)-ethyl ester,
Morpholine-4-carboxylic acid (S)-1-(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)-ethyl ester,
Rac-1-*tert*-butyl 4-(1-(4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoyloxy)ethyl) piperazine-1,4-dicarboxylate,
Piperazine-1-carboxylic acid 1-(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)-ethyl ester di-hydrochloride,
Rac-1,1-Dioxo-thiomorpholine-4-carboxylic acid 1-(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)-ethyl ester,
4-(((2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-3-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino)-3-methoxy-benzoic acid 1-(2,2-dimethyl-[1,3]dioxolan-4-ylmethylcarbamoyloxy)-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-benzoyloxy)-ethyl ester,
1-(Tetrahydro-2H-pyran-4-ylcarbamoyloxy)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 1-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxycarbonyloxy}-ethyl ester,
4-(((2R,3S,4R,5S)-3-(3-Chloro-2-fluoro-phenyl)-4-(4-chloro-2-fluoro-phenyl)-4-cyano-3-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino)-3-methoxy-benzoic acid 1-(2-[2-(2-methoxy-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-[2-(2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy)-ethoxy]-ethoxy)-ethyl ester

ethoxycarbonyloxy]-ethyl ester,

21-oxo-2,5,8,11,14,17,20,22-octaoxatetracosan-23-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 ester,

1-(2-(Benzyloxy)-2-oxoethylcarbamoxyloxy)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-(((4-((2R,3S,4R,5S)-3-(3-Chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoyloxy)ethoxy)carbonylamino)acetic acid,

(S)-2-[1-(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-benzoyloxy)-ethoxycarbonylamino]-pentanedioic acid,

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-((S)-1-carboxy-ethylcarbamoxyloxy)-ethyl ester,

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)acetic acid,

(S)-Dibenzyl 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)-pentanedioate,

(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,

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,

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,

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,

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-nonaohaheptacosan-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 ,

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,

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 ,

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 amide ,

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 amide ,

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 amide ,

(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)propanoic acid,

Dibenzyl 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-phosphonoxy-ethoxy)-ethoxy]-ethoxy}-ethoxycarbonyloxymethyl 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-phosphonoxy-ethoxy)-ethoxy]-ethoxy}-ethoxycarbonyloxymethyl 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)-pyr-

rolidine-2-carbonyl] -amino} -3 -methoxy-benzoic acid phosphonooxymethyl ester; compound with trifluoro-acetic acid,

1-(((3aR,5R,6S,6aR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[3,2-d][1,3]dioxo-1,6-yloxy)carbonyloxy)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 1-(((2R,3R,4R,5S)-2-((R)-1,2-dihydroxy-ethyl)-4,5-dihydroxy-tetrahydro-furan-3-yloxy)carbonyloxy)-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-(2-{2-[2-(2-dibenzoyloxyphosphoryloxy-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.

[0009] In another embodiment there is provided the compound 2-(((1-(4-((2R,3S,4R,5S)-3-(3-Chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoyloxy)ethoxy)carbon-ylamino)acetic acid.

[0010] In another embodiment there is provided the compound 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)-carbon-ylamino)acetic acid.

[0011] In another embodiment there is provided the compound 3-Oxo-2,4,7,10,13,16,19-heptaaoicaosyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate.

[0012] In another embodiment there is provided the compound 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).

[0013] In another embodiment there is provided the compound 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)

[0014] In another embodiment there is provided the compound 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).

[0015] In another embodiment there is provided the compound 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;

[0016] In another embodiment there is provided the compound 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.

[0017] In another embodiment there is provided the compound 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-(((2R,3R,4R,5S)-2-((R)-1,2-dihydroxy-ethyl)-4,5-dihydroxy-tetrahydro-furan-3-yloxy)carbonyloxy)-ethyl ester.

[0018] In another embodiment there is provided the compound 4-(((2R,3S,4R,5S)-3-(3-Chloro-2-fluoro-phenyl)-4-(4-chloro-2-fluoro-phenyl)-4-cyano-3-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl] -amino} -3 -methoxy-benzoic acid 1-(2-{2-[2-(2-dibenzoyloxyphosphoryloxy-ethoxy)-ethoxy]-ethoxy}-ethoxycarbonyloxy)-ethyl ester.

[0019] In another embodiment there is provided the compound 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.

[0020] The term "mPEG" as used herein means methoxy polyethylene glycol, which is commercially available (e.g. Sigma-Aldrich or ID Biochem (Korea)). The molecular weight distribution of mPEG may vary according to the manufacturer and/or batch. In one embodiment of the present invention, mPEG has an average molecular weight (MW) of about 1500 Da to about 3000 Da. In another embodiment of the present invention mPEG has an average MW of about 2000 Da and about 2200 Da. Average MW is determined by MALDI-TOF mass spectrometry.

[0021] The term "alkyl" refers to straight- or branched-chain saturated hydrocarbon groups having from 1 to about 20 carbon atoms, including groups having from 1 to about 7 carbon atoms. In certain embodiments, alkyl substituents may be lower alkyl substituents. The term "lower alkyl" refers to alkyl groups having from 1 to 6 carbon atoms, and in certain embodiments from 1 to 4 carbon atoms. Examples of alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, and s-pentyl.

[0022] "Alkoxy, alkoxyl or lower alkoxy" refers to any of the above lower alkyl groups attached to an oxygen atom. Typical lower alkoxy groups include methoxy, ethoxy, isopropoxy or propoxy, butyloxy and the like. Further included within the meaning of alkoxy are multiple alkoxy side chains, e.g. ethoxy ethoxy, methoxy ethoxy, methoxy ethoxy ethoxy and the like and substituted alkoxy side chains, e.g., dimethylamino ethoxy, diethylamino ethoxy, dimethoxy-phosphoryl methoxy and the like.

[0023] "Pharmaceutically acceptable," such as pharmaceutically acceptable carrier, excipient, etc., means pharmacologically acceptable and substantially non-toxic to the subject to which the particular compound is administered.

[0024] "Pharmaceutically acceptable salt" refers to conventional acid-addition salts or base-addition salts that retain the biological effectiveness and properties of the compounds of the present invention and are formed from suitable non-toxic organic or inorganic acids or organic or inorganic bases. Sample acid-addition salts include those derived from inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, phosphoric acid and nitric acid, and those derived from organic acids such as p-toluenesulfonic acid, salicylic acid, methanesulfonic acid, oxalic acid, succinic acid, citric acid, malic acid, lactic acid, fumaric acid, trifluoro acetic acid and the like. Sample base-addition salts include those derived from ammonium, potassium, sodium and, quaternary ammonium hydroxides, such as for example, tetramethylammonium hydroxide. Chemical modification of a pharmaceutical compound (i.e. drug) into a salt is a technique well known to pharmaceutical chemists to obtain improved physical and chemical stability, hygroscopicity, flowability and solubility of compounds. See, e.g., Ansel et al., *Pharmaceutical Dosage Forms and Drug Delivery Systems* (6th Ed. 1995) at pp. 196 and 1456- 1457.

[0025] The compounds of formula (I) as well as their salts that have at least one asymmetric carbon atom may be present as racemic mixtures or different stereoisomers. The various isomers can be isolated by known separation methods, e.g., chromatography.

[0026] Compounds disclosed herein and covered by formula (I) above may exhibit tautomerism or structural isomerism. It is intended that the invention encompasses any tautomeric or structural isomeric form of these compounds, or mixtures of such forms, and is not limited to any one tautomeric or structural isomeric form depicted in the formulas above.

[0027] The compounds of the present invention are useful in the treatment or control of cell proliferative disorders, in particular oncological disorders. These compounds and formulations containing said compounds may be particularly useful in the treatment or control of solid tumors, such as, for example, breast, colon, lung and prostate tumors or sarcoma. The compounds may also be useful in the treatment of certain non-solid tumors such as leukemia's and lymphoma's.

[0028] Therefore in another embodiment, the present invention provides a pharmaceutical composition comprising the compounds of formula (I), together with pharmaceutically acceptable excipients.

[0029] In yet another embodiment the present invention provides the compounds of formula (I) for use as medicament.

[0030] In still another embodiment, the present invention provides the compounds of formula (I) for use as medicaments for the treatment of cancer, in particular solid tumors, more particularly breast, colon, lung and prostate tumors or sarcoma.

[0031] In still another embodiment, the present invention provides the compounds of formula (I) for use as medicaments for the treatment of certain non-solid tumors such as leukemia's and lymphoma's, in particular acute myeloid leukemia (AML).

[0032] In yet another embodiment the present invention provides the use of the compounds of formula (I) in the manufacture of medicaments for the treatment of cancer, more particularly solid tumors such as breast, colon, lung and prostate tumors or sarcoma; or alternatively also for the treatment of certain non-solid tumors such as leukemia's and lymphoma's, in particular for the treatment of acute myeloid leukemia (AML).

[0033] A therapeutically effective amount of a compound in accordance with this invention means an amount of compound that is effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated. Determination of a therapeutically effective amount is within the skill in the art.

[0034] The therapeutically effective amount or dosage of a compound according to this invention can vary within wide limits and may be determined in a manner known in the art. Such dosage will be adjusted to the individual requirements in each particular case including the specific compound(s) being administered, the route of administration, the condition being treated, as well as the patient being treated. In general, in the case of oral or parenteral administration to adult humans weighing approximately 70 Kg, a daily dosage of about 10 mg to about 10,000 mg, preferably from about 200 mg to about 1,000 mg, should be appropriate, although the upper limit may be exceeded when indicated. The daily dosage can be administered as a single dose or in divided doses, or for parenteral administration; it may be given as continuous infusion.

[0035] Formulations of the present invention include those suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, as well as the particular mode of administration. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of a formula I compound which produces a

therapeutic effect. Generally, out of one hundred percent, this amount will range from about 1 percent to about ninety-nine percent of active ingredient, preferably from about 5 percent to about 70 percent, most preferably from about 10 percent to about 30 percent.

[0036] Methods of preparing these formulations or compositions include the step of bringing into association a compound of the present invention with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[0037] Another embodiment provides pharmaceutical compositions or medicaments containing the compounds of the invention and a therapeutically inert carrier, diluent or excipient, as well as methods of using the compounds of the invention to prepare such compositions and medicaments. In one example, compounds of formula I may be formulated by mixing at ambient temperature at the appropriate pH, and at the desired degree of purity, with physiologically acceptable carriers, i.e., carriers that are non-toxic to recipients at the dosages and concentrations employed into a galenical administration form. The pH of the formulation depends mainly on the particular use and the concentration of compound, but preferably ranges anywhere from about 3 to about 8. In one example, a compound of formula I is formulated in an acetate buffer, at pH 5. In another embodiment, the compounds of formula I are sterile. The compound may be stored, for example, as a solid or amorphous composition, as a lyophilized formulation or as an aqueous solution. In solution the compounds of the present invention can form micellar structures having a particle size of between 10 to 100 nm (nanometer).

[0038] Compositions are formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The "effective amount" of the compound to be administered will be governed by such considerations, and is the minimum amount necessary to inhibit MDM2 interaction with p53. For example, such amount may be below the amount that is toxic to normal cells, or the mammal as a whole.

[0039] The compounds of the invention may be administered by any suitable means, including oral, topical (including buccal and sublingual), rectal, vaginal, transdermal, parenteral, subcutaneous, intraperitoneal, intrapulmonary, intradermal, intrathecal and epidural and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration. The compounds of the present invention are especially useful when dosed parenterally or infusionally due to their superior solubility and longer plasma half life when compared to their non-esterified/non-amide parent compound. Further the compounds of the present invention exhibit superior PK nonvariability when compared to their parent compounds.

[0040] The compounds of the present invention may be administered in any convenient administrative form, e.g., tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches, etc. Such compositions may contain components conventional in pharmaceutical preparations, e.g., diluents, carriers, pH modifiers, sweeteners, bulking agents, and further active agents.

[0041] A typical formulation is prepared by mixing a compound of the present invention and a carrier or excipient. Suitable carriers and excipients are well known to those skilled in the art and are described in detail in, e.g., Ansel, Howard C., et al., *Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems*. Philadelphia: Lippincott, Williams & Wilkins, 2004; Gennaro, Alfonso R., et al. *Remington: The Science and Practice of Pharmacy*. Philadelphia: Lippincott, Williams & Wilkins, 2000; and Rowe, Raymond C. *Handbook of Pharmaceutical Excipients*. Chicago, Pharmaceutical Press, 2005. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents, diluents and other known additives to provide an elegant presentation of the drug (i.e., a compound of the present invention or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

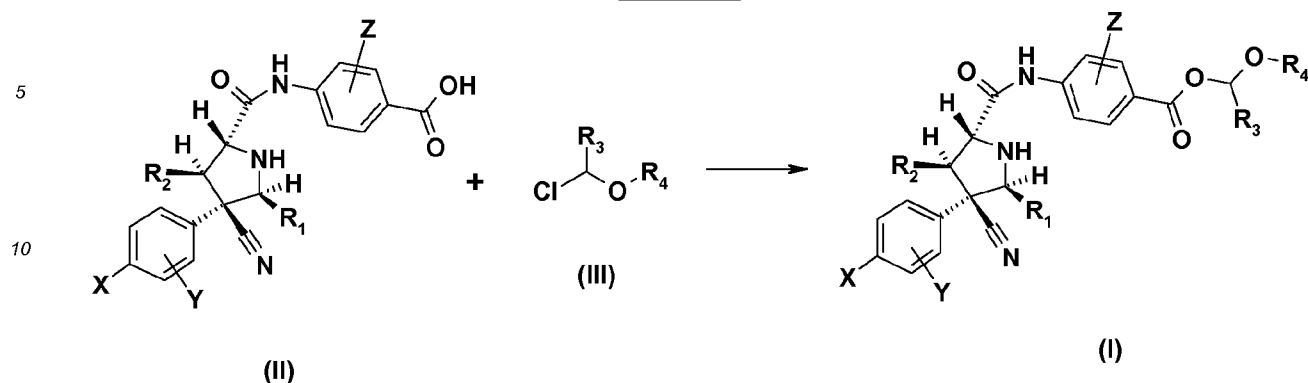
[0042] "Effective amount" means an amount that is effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated.

[0043] "IC₅₀" refers to the concentration of a particular compound required to inhibit 50% of a specific measured activity. IC₅₀ can be measured, *inter alia*, as is described subsequently.

Synthetic Methods

[0044] The general method for the preparation of compounds of formula I is given in Scheme 1. Briefly, the process involves alkylation of the benzoic acid (II) with the chloro compound (III) in the presence of a base such as cesium carbonate. Compounds of Formula II are known in the art, see, for example, US 2010/0152190-A1. The chloro compound (III) is typically prepared by reaction of 1-chloroalkyl chloroformate with alcohol or amine in the presence of a base such as pyridine.

Scheme 1



[0045] The compounds of the invention can be prepared by processes known in the art. Suitable processes for synthesizing these compounds are provided in the examples.

[0046] Therefore, in another embodiment there is provided the method for making the compounds of formula (I) as disclosed in scheme 1.

[0047] The following examples and references are provided to aid the understanding of the present invention. However, the true scope of the invention is set forth in the appended claims.

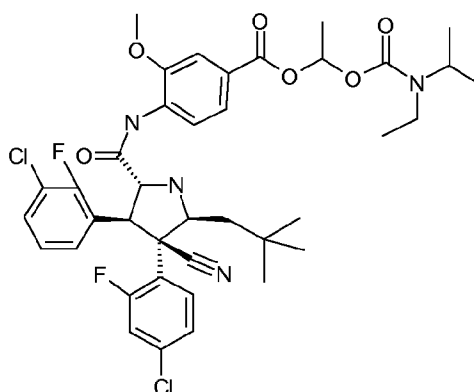
[0048] In the Examples, all abbreviations used have the meanings generally known to the person of skill in the art of chemistry. If not explicitly otherwise stated average molecular weight (MW) is determined using MALDI-TOF mass spectrometry, and is expressed in Daltons (Da).

Examples

Example 1

1-(Ethyl(isopropyl)carbamoyloxy)ethyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate

[0049]



M.W. 773.71, $C_{39}H_{44}Cl_2F_2N_4O_6$

[0050] To a cooled solution of 2-propanol (1.57 g, 2 mL, 26.1 mmol) and N,N-diisopropylethylamine (6.75 g, 9.13 mL, 52.3 mmol) in methylene chloride (15 mL) was added 1-chloroethyl carbonochloridate (Aldrich, 4.11 g, 28.7 mmol) slowly at 0 °C. After addition the reaction mixture was allowed to stir at room temperature overnight. The mixture was concentrated to dryness and the crude material which contained approximately 50% of ethyl-isopropyl-carbamic acid 1-chloro-ethyl ester was used for the next step without further purification.

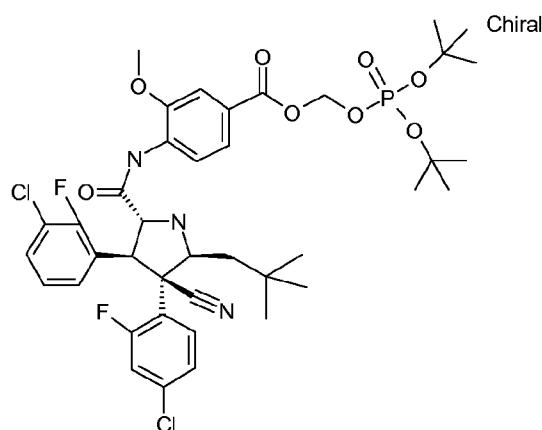
[0051] To a solution of chiral 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid (prepared as described in US20100152190A1, 150 mg, 0.243 mmol) in dimethylformamide (6 mL) was added cesium carbonate (243 mg, 0.746 mmol). After stirring for a few minutes, a solution of the above freshly made ethyl-isopropyl-carbamic acid 1-chloro-ethyl ester (190 mg, 0.491 mmol) in dry

dimethylformamide (1 mL) was added and the reaction mixture was allowed to stir at room temperature overnight. This reaction mixture was diluted with ethyl acetate and washed with water, brine and concentrated to dryness. The crude material was purified by chromatography (hexane/ethyl acetate, 90/10 to 10/90) to give 1-(ethyl(isopropyl)-carbamoyloxy)ethyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate as a white solid (102 mg, 54% yield). LCMS (ES⁺) m/z calcd. for C₃₉H₄₅Cl₂F₂N₄O₆ [(M+H)⁺]: 773, found: 773.

Example 2

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 di-*tert*-butoxy-phosphoryloxymethyl ester

[0052]



M.W.838.72, C₄₀H₄₈Cl₂F₂N₃O₈P

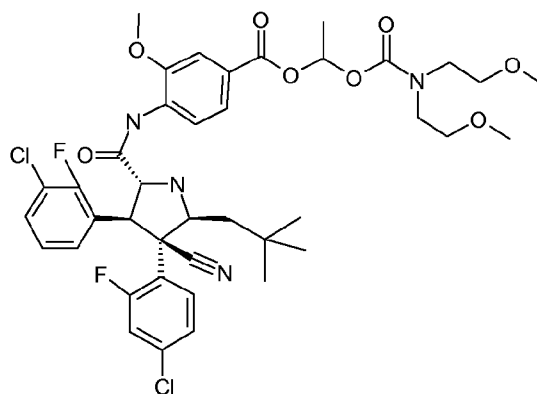
[0053] To a solution of potassium di-*tert*-butylphosphate (2.45 g, 9.51 mmol), sodium bicarbonate (3.19 g, 38.0 mmol) and tetrabutylammonium hydrogen sulfate (340.2 mg, 0.972 mmol) in water (80 mL), was added methylene chloride (50 mL). The mixture was cooled to 0 °C and stirred vigorously under argon for 10 min. Chloromethyl chlorosulfate (1.92 g, 1.2 mL, 11.6 mmol) in methylene chloride (30 mL) was added slowly and the reaction was stirred at room temperature overnight. The organic layer was separated, washed with brine and dried over anhydrous sodium sulfate and concentrated to give di-*tert*-butyl chloromethyl phosphate as a colorless oil (1.46 g, 59% yield).

[0054] To a solution of chiral 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid (prepared as described in US20100152190A1, 200.0 mg, 0.324 mmol) in dimethylformamide (8 mL) was added cesium carbonate (529 mg, 1.62 mmol). The mixture was stirred for ~20 min before di-*tert*-butyl chloromethyl phosphate (TCI, 236 mg, 0.9912 mmol) in dimethylformamide (1 mL) was added. The reaction mixture was allowed to stir at room temperature for 3 h before it was partitioned between ethyl acetate and water, washed with water and dried over anhydrous sodium sulfate and concentrated. The crude product was purified by flash chromatography (hexane/ethyl acetate, 85/15 to 5/95) to give chiral 4-[[[(2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino]-3-methoxy-benzoic acid di-*tert*-butoxy-phosphoryloxymethyl ester as a white solid (192 mg, 70% yield). LCMS (ES⁺) m/z calcd. for C₄₀H₄₉Cl₂F₂N₃O₈P [(M+H)⁺]: 838, found: 838.

Example 3

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-[bis-(2-methoxyethyl)-carbamoyloxy]-ethyl ester

[0055]



MW819.74 $C_{40}H_{46}Cl_2F_2N_4O_8$

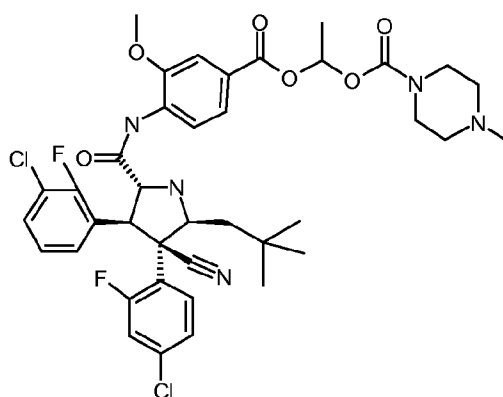
[0056] To a cooled solution of bis(2-methoxyethyl)amine (1.94 g, 14.5 mmol, Aldrich) and pyridine (1.26 g, 1.29 mL, 15.9 mmol) in methylene chloride (18 mL) at -78°C , was added slowly 1-chloroethyl carbonochloridate (1.98 g, 1.5 mL, 13.8 mmol, Aldrich) over ~15 min. The reaction mixture was allowed to stir at -78°C for 3 h, giving a white precipitate. This cold reaction mixture was filtered to remove the solid and the filtrate was concentrated to dryness, giving the crude 1-chloroethyl bis(2-methoxyethyl)carbamate used for the next step without further purification.

[0057] To a solution of chiral 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid (US20100152190A1, 200 mg, 0.324 mmol) in dimethylformamide (8 mL) was added cesium carbonate (846 mg, 2.6 mmol). After stirring for 10 min, a solution of the above freshly made 1-chloroethyl bis(2-methoxyethyl)carbamate (510 mg, 2.13 mmol) in dimethylformamide (3 mL) was added. The reaction mixture was allowed to stir at room temperature overnight. This reaction mixture was taken up in ethyl acetate, washed with water, brine and concentrated to dryness. The crude material was purified by flash chromatography (hexane/ethyl acetate, 90/10 to 10/90) to give 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-[bis-(2-methoxy-ethyl)-carbamoyloxy]-ethyl ester as a white solid (168 mg, 63% yield). LCMS (ES⁺) m/z calcd. for $C_{40}H_{47}Cl_2F_2N_4O_8$ [(M+H)⁺]: 819, found: 819.

Example 4

4-Methyl-piperazine-1-carboxylic acid 1-(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-benzoyloxy]-ethyl ester

[0058]



M.W. 786.71 $C_{39}H_{43}Cl_2F_2N_5O_6$

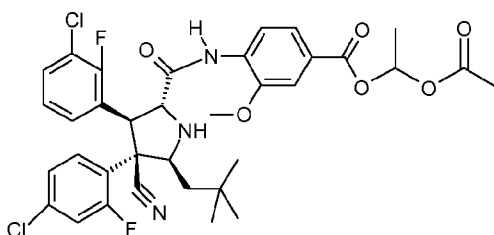
[0059] In a manner similar to the method described in **Example 3**, 1-chloroethyl carbonochloridate was reacted with 1-methylpiperazine and pyridine in methylene chloride at -78°C for 3 h to give 1-chloroethyl 4-methylpiperazine-1-carboxylate hydrochloride salt which was reacted with chiral 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid in the presence of cesium carbonate in dimethylformamide overnight to give, after flash chromatography purification (hexane/ethyl acetate, 80/20 to

20/80), 4-methyl-piperazine-1-carboxylic acid 1-(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-benzoyloxy)-ethyl ester as a white solid. LCMS (ES⁺) m/z calcd. for C₃₉H₄₄Cl₂F₂N₅O₆ [(M+H)⁺]: 786, found: 786.

Example 5

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

[0060]



M.W.702.59 C₃₅H₃₅Cl₂F₂N₃O₆

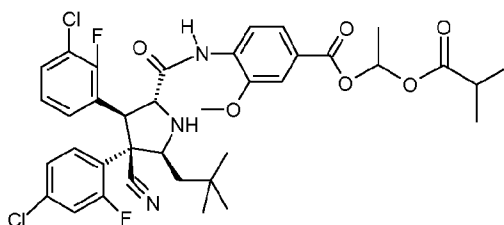
[0061] A mixture of paraldehyde (JT-Baker, 1.39 g, 1.4 mL, 10.5 mmol) and sodium iodide (5.01 g, 33.4 mmol) in methylene chloride (75 mL) were treated with acetyl chloride (2.21 g, 2 mL, 27.8 mmol) in methylene chloride (25 mL) over 20 min and allowed to stir at room temperature in the dark for 18 h. The reaction mixture was filtered and concentrated to give 1-iodoethyl acetate as a brown oil.

[0062] To a mixture of the above 1-iodoethyl acetate (311 mg, 1.457 mmol) and chiral 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid (US20100152190A1, 201.7 mg, 0.327 mmol) in dimethylformamide (6 mL) was added cesium carbonate (659 mg, 2.00 mmol) and the mixture was stirred at room temperature for 16 h. The reaction mixture was taken up in ethyl acetate, washed with water and then brine. The organic layer was dried over sodium sulfate and concentrated to dryness. The crude material was purified by flash chromatography (hexane/ethyl acetate, 80/20 to 20/80) to give 1-acetoxyethyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate (149.4 mg, 65 % yield). MS (ES⁺) m/z calcd. for C₃₅H₃₆Cl₂F₂N₃O₆: [(M+H)⁺]: 702.19, found: 702.4

Example 6

Rac-1-(isobutyryloxy)ethyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate

[0063]



M.W.730.64 C₃₇H₃₉Cl₂F₂N₃O₆

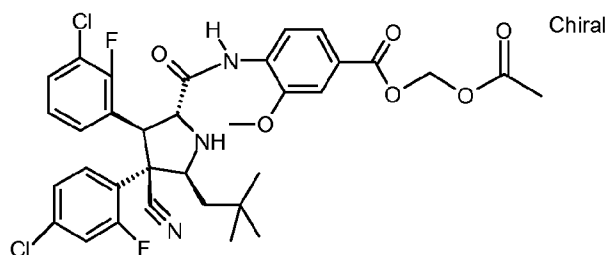
[0064] In a manner similar to the method described in **Example 5**, paraldehyde (JT-Baker, 1.37 g, 10.4 mmol) was reacted with isobutyryl chloride (Aldrich, 2.93 g, 27.5 mmol) and sodium iodide (4.9472 g, 33.0 mmol) in methylene chloride (100 mL) at room temperature for 16 h to give 1-iodoethyl isobutyrate. A portion of this material (400.2 mg, 1.65 mmol) was then reacted with chiral 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid (200.8 mg, 0.332 mmol) and cesium carbonate (653.2 mg, 2.00 mmol) in dimethylformamide (6 mL) at room temperature for 3 h to give 1-(isobutyryloxy)ethyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate.

3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate as an off-white solid (198.8 mg, 83% yield). MS (ES⁺) m/z calcd. for C₃₇H₄₀Cl₂F₂N₃O₆: [(M+H)⁺]: 730, found: 730

Example 7

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 acetoxymethyl ester

[0065]



M.W. 688.56 C₃₄H₃₃Cl₂F₂N₃O₆

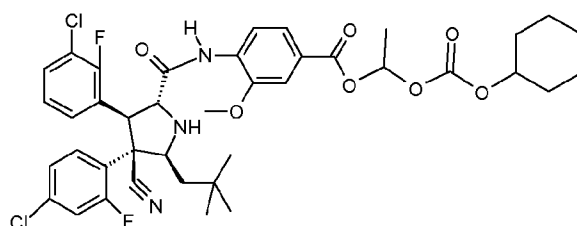
[0066] A mixture of 1,3,5-trioxane (Aldrich, 970.8 mg, 10.8 mmol) and sodium iodide (5.12 g, 34.2 mmol) in methylene chloride (100 mL) was treated with acetyl chloride (2.26 g, 2.1 mL, 28.5 mmol) and stirred at room temperature in the dark for 16 h. The reaction mixture was filtered and concentrated to give crude iodomethyl acetate as a brown oil.

[0067] A portion of this iodomethyl acetate (661 mg, 3.31 mmol) was added to a suspension of chiral 4-[(2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid (200.1 mg, 0.325 mmol) and cesium carbonate (964.4 mg, 2.93 mmol) in dimethylformamide (8 mL) and the reaction was stirred in the dark overnight. It was then taken up in ethyl acetate, washed with water and brine, dried over anhydrous sodium sulfate and concentrated. The crude product was purified by flash chromatography (hexane/ethyl acetate, 80/20 to 10/90) to give chiral 4-[(2R,3S,4R,5S)-4-(4-chloro-2-fluorophenyl)-3-(3-chloro-2-fluorophenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino-3-methoxy-benzoic acid acetoxymethyl ester as a white solid (42.8 mg, 19% yield). MS (ES⁺) m/z calcd. for C₃₄H₃₄Cl₂F₂N₃O₆: [(M+H)⁺]: 688, found: 688

Example 8

1-(Cyclohexyloxycarbonyloxy)ethyl 4-[(2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate

[0068]



M.W. 786.71 C₄₀H₄₃Cl₂F₂N₃O₇

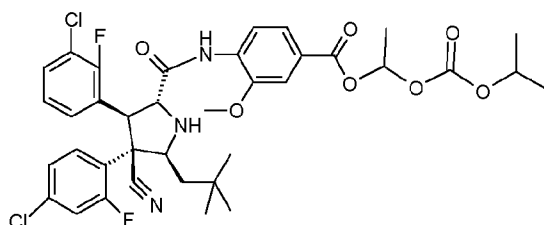
[0069] In a manner similar to the method described in **Example 3**, 1-chloroethyl chloroformate (Oakwood Products, 1.99 g, 1.5 mL, 13.9 mmol) was reacted with cyclohexanol (Alfa Aesar, 1.33 g, 1.4 mL, 13.3 mmol) and pyridine (1.27 g, 1.3 mL, 16.1 mmol) in methylene chloride (11 mL) at -78 °C for 3 h to give 1-chloroethyl cyclohexyl carbonate. A portion of 1-chloroethyl cyclohexyl carbonate (253 mg, 1.22 mmol) was then reacted with chiral 4-[(2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid (150.3 mg, 0.244 mmol) in the presence of cesium carbonate (487.4 mg, 1.5 mmol) in dimethylformamide (5 mL) overnight to give, after flash chromatography purification (hexane/ethyl acetate, 80/20 to 20/80), 1-(cyclohexyloxycarbonyloxy)ethyl 4-[(2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate as a white solid (42.8 mg, 19% yield).

ine-2-carboxamido)-3-methoxybenzoate (135.4 mg, 70% yield). MS (ES⁺) m/z calcd. for C₄₀H₄₄Cl₂F₂N₃O₇ : [(M+H)⁺]: 786, found: 786

Example 9

Rac-1-(isopropoxycarbonyloxy)ethyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate

[0070]



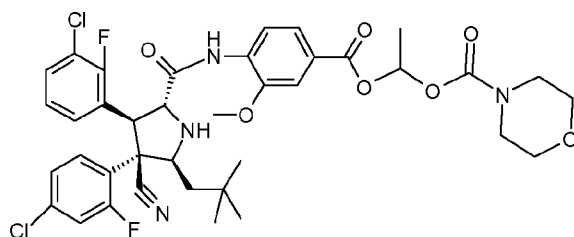
M.W. 746.64 C₃₇H₃₉Cl₂F₂N₃O₇

[0071] In a manner similar to the method described in **Example 3**, 1-chloroethyl chloroformate (Oakwood Products, 1.99 g, 1.5 mL, 13.9 mmol) was reacted with 2-propanol (785 mg, 1 mL, 13.0 mmol) and pyridine (1.27 g, 1.3 mL, 16.1 mmol) in methylene chloride (11 mL) at room temperature for 4 h to give 1-chloroethyl isopropyl carbonate. A portion of 1-chloroethyl isopropyl carbonate (221.6 mg, 1.33 mmol) was then reacted with chiral 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid (150.3 mg, 244 μmol) in the presence of cesium carbonate (478 mg, 1.47 mmol) in dimethylformamide (5 mL) overnight to give, after flash chromatography purification (hexane/ethyl acetate, 80/20 to 20/80), 1-(isopropoxycarbonyloxy)ethyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate (134.4 mg, 73% yield). MS (ES⁺) m/z calcd. for C₃₇H₄₀Cl₂F₂N₃O₇: [(M+H)⁺]: 746, found: 746

Example 10

1-(4-((2R,3S,4R,5S)-3-(3-Chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoyloxy)ethyl morpholine-4-carboxylate

[0072]

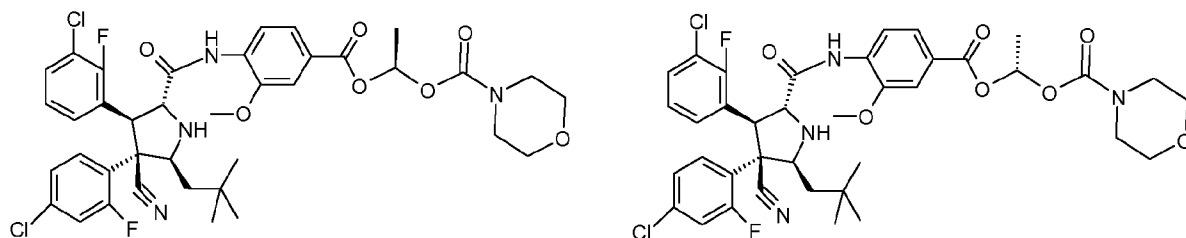


M.W. 773.67 C₃₈H₄₀Cl₂F₂N₄O₇

[0073] In a manner similar to the method described in **Example 3**, 1-chloroethyl chloroformate (2.64 g, 2 mL, 18.5 mmol) was reacted with morpholine (1.69 g, 1.7 mL, 19.4 mmol) and pyridine (1.68 g, 1.72 mL, 21.2 mmol) in methylene chloride (25 mL) at room temperature overnight to give the crude product, 1-chloroethyl morpholine-4-carboxylate. A portion of 1-chloroethyl morpholine-4-carboxylate (670.1 mg, 3.46 mmol) was then reacted with chiral 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid (200.5 mg, 0.325 mmol) in the presence of cesium carbonate (1.094 g, 3.36 mmol) in dimethylformamide (7 mL) overnight to give, 1-(4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoyloxy)ethyl morpholine-4-carboxylate as an off-white solid (186.5 mg, 74 % yield). MS (ES⁺) m/z calcd. for C₃₈H₄₁Cl₂F₂N₄O₇: [(M+H)⁺]: 773, found: 773

Example 11

[0074] Morpholine-4-carboxylic acid (R)-1-(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)-ethyl ester and morpholine-4-carboxylic acid (S)-1-(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)-ethyl ester. The (R) compound is Compound A and (S) is B.



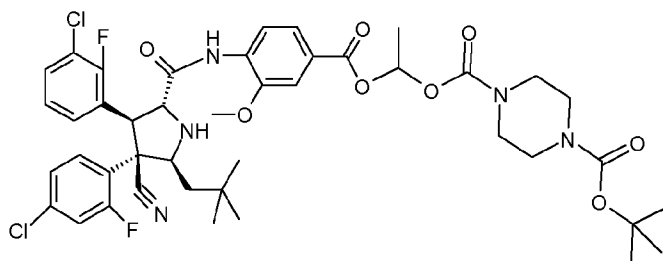
M.W. 773.67 $C_{38}H_{40}Cl_2F_2N_4O_7$

[0075] The title compounds were prepared from supercritical fluid chromatography separation of a mixture of diastereomers of 1-(4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoyloxy)ethyl morpholine-4-carboxylate (**Example 10**). MS (ES⁺) m/z calcd. for $C_{38}H_{41}Cl_2F_2N_4O_7$: [(M+H)⁺]: 773, found: 773

Example 12

Rac-1-tert-butyl 4-(1-(4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoyloxy)ethyl) piperazine-1,4-dicarboxylate

[0076]



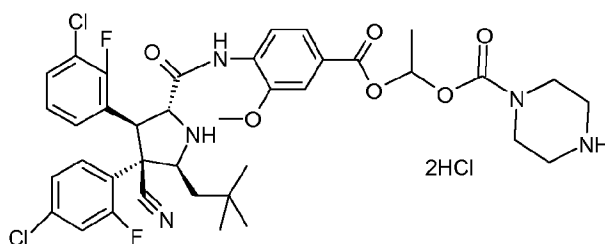
M.W. 872.8 $C_{34}H_{36}Cl_2F_2N_4O_4$

[0077] In a manner similar to the method described in **Example 3**, 1-chloroethyl chloroformate (Oakwood, 1.46 g, 1.1 mL, 10.2 mmol) was reacted with 1-Boc-piperazine (Alfa Aesar, 1.5756 g, 8.37 mmol) and pyridine (870 mg, 0.89 mL, 11.0 mmol) in methylene chloride (10 mL) from -78 °C for 1 h and then at room temperature overnight to give piperazine-1,4-dicarboxylic acid tert-butyl ester 1-chloro-ethyl ester. A portion of piperazine-1,4-dicarboxylic acid tert-butyl ester 1-chloro-ethyl ester (682 mg, 1.67 mmol) was then reacted with chiral 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid (201.4 mg, 0.327 mmol) in the presence of cesium carbonate (743.4 mg, 2.28 mmol) in dimethylformamide (7 mL) overnight to give 1-tert-butyl 4-(1-(4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoyloxy)ethyl) piperazine-1,4-dicarboxylate as an off-white lyophilized solid (259.9 mg, 91% yield). MS (ES⁺) m/z calcd. for $C_{34}H_{36}Cl_2F_2N_4O_4$: [(M+H)⁺]: 872, found: 872

Example 13

Piperazine-1-carboxylic acid 1-(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)-ethyl ester di-hydrochloride

[0078]



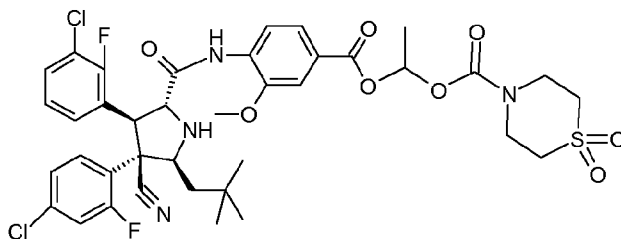
M.W. 845.59 $C_{38}H_{41}Cl_2F_2N_5O_6 \cdot 2 HCl$

[0079] A solution of 1-tert-butyl 4-(1-(4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoyloxy)ethyl) piperazine-1,4-dicarboxylate (**Example 12**, 115.3 mg, 0.132 mmol) in methylene chloride (2 mL) was treated with a solution of hydrochloric acid in 1,4 dioxane (Sigma Aldrich, 4M, 0.33 mL, 1.32 mmol) over 5 min. The reaction mixture was stirred at room temperature for 90 min and concentrated to give piperazine-1-carboxylic acid 1-(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)-ethyl ester dihydrochloride as a white solid (119 mg, 100 % yield). MS (ES⁺) m/z calcd. for $C_{38}H_{42}Cl_2F_2N_5O_6$: [(M+H)⁺]: 772, found: 772

Example 14

rac-1,1-Dioxo-thiomorpholine-4-carboxylic acid 1-(4-(((2R,3S,4R,5S)-4-(4-chloro-2-fluorophenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino)-3-methoxy-benzoyloxy)-ethyl ester

[0080]



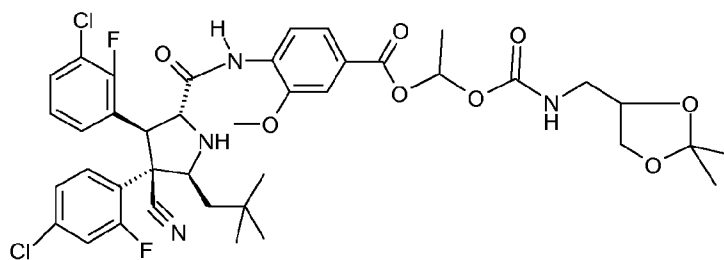
M.W. 821.73 $C_{38}H_{40}Cl_2F_2N_4O_8S$

[0081] In a manner similar to the method described in **Example 3**, 1-chloroethyl chloroformate (Oakwood, 1.32 g, 1 mL, 9.27 mmol) was reacted with thiomorpholine 1,1-dioxide (1.1638 g, 8.61 mmol) and pyridine (783 mg, 801 μ l, 9.9 mmol) in methylene chloride (15 mL) at room temperature for 3 h to give 1,1-dioxo-thiomorpholine-4-carboxylic acid 1-chloro-ethyl ester. A portion of 1,1-dioxo-thiomorpholine-4-carboxylic acid 1-chloro-ethyl ester (577 mg, 1.614 mmol) was then reacted with chiral 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid (150.5 mg, 0.244 mmol) in the presence of cesium carbonate (598.4 mg, 1.84 mmol) in dimethylformamide (7 mL) overnight to give 1,1-dioxo-thiomorpholine-4-carboxylic acid 1-(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)-ethyl ester as an off-white solid (175.3 mg, 87 % yield). MS (ES⁺) m/z calcd. for $C_{38}H_{41}Cl_2F_2N_4O_8S$: [(M+H)⁺]: 821, found: 821

Example 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 1-(2,2-dimethyl-[1,3]dioxolan-4-ylmethylcarbamoyloxy)-ethyl ester

[0082]



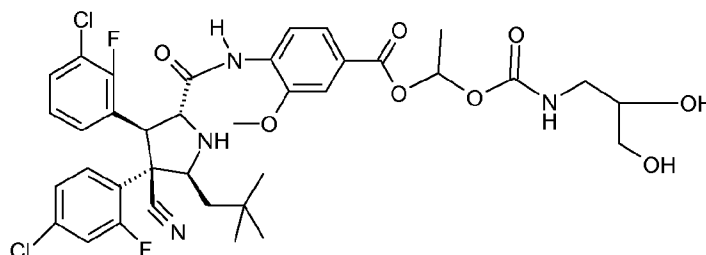
M.W. 817.72 $C_{40}H_{44}Cl_2F_2N_4O_8$

[0083] In a manner similar to the method described in **Example 3**, 1-chloroethyl chloroformate (1.46 g, 1.1 mL, 10.2 mmol) was reacted with (2,2-dimethyl-[1,3]-dioxolan-4-yl)-methylamine (Aldrich, 1.21 g, 1.2 mL, 8.98 mmol) and pyridine (870 mg, 0.89 mL, 11.0 mmol) in methylene chloride (15 mL) at 78 °C for 3 h to give 1-chloroethyl (2,2-dimethyl-1,3-dioxolan-4-yl)methylcarbamate with pyridine hydrochloride (1:1). A portion of this material (622 mg, 1.76 mmol) in dimethylformamide (5 mL) was then reacted with chiral 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid (201 mg, 0.326 mmol) in the presence of cesium carbonate (806.9 mg, 2.48 mmol) in dimethylformamide (7 mL) overnight to give 4-((2R,3S,4R,5S)-4-(4-chloro-2-fluorophenyl)-3-(3-chloro-2-fluorophenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino)-3-methoxybenzoic acid 1-(2,3-dihydroxy-propylcarbamoyloxy)-ethyl ester as a white solid (97.7 mg, 36% yield). MS (ES⁺) m/z calcd. for $C_{40}H_{45}Cl_2F_2N_4O_8$: [(M+H)⁺]: 817, found: 817

Example 16

4-((2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-3-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino)-3-methoxy-benzoic acid 1-(2,3-dihydroxy-propylcarbamoyloxy)-ethyl ester

[0084]



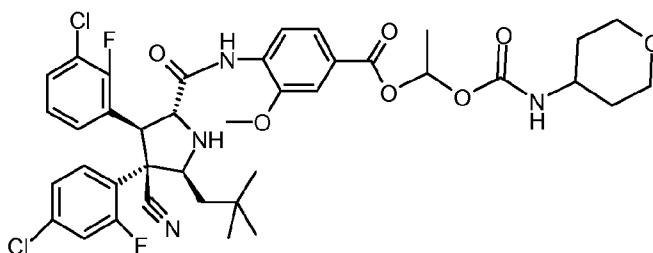
M.W. 777.66 $C_{37}H_{40}Cl_2F_2N_4O_8$

[0085] A solution of 1-((2,2-dimethyl-1,3-dioxolan-4-yl)methylcarbamoyloxy)ethyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate (**Example 15**, 75.7 mg, 0.092 mmol) in acetonitrile (4 mL) was treated with a 2M solution of hydrochloric acid in ether (Sigma Aldrich, 0.5 mL, 1.00 mmol) and stirred for 70 min. The reaction mixture was concentrated, diluted with ethyl acetate and washed with saturated aqueous sodium bicarbonate, brine, dried and concentrated. The crude material was then purified by flash chromatography (methylene chloride/methanol) to give 4-((2R,3S,4R,5S)-4-(4-chloro-2-fluorophenyl)-3-(3-chloro-2-fluorophenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino)-3-methoxy-benzoic acid 1-(2,3-dihydroxy-propylcarbamoyloxy)-ethyl ester as a white solid (36.6 mg, 50 % yield). MS (ES⁺) m/z calcd. for $C_{37}H_{40}Cl_2F_2N_4O_8$: [(M+H)⁺]: 777 found: 777

Example 17

1-(Tetrahydro-2H-pyran-4-ylcarbamoyloxy)ethyl 4-((2R,3S,4R,5 S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate

[0086]



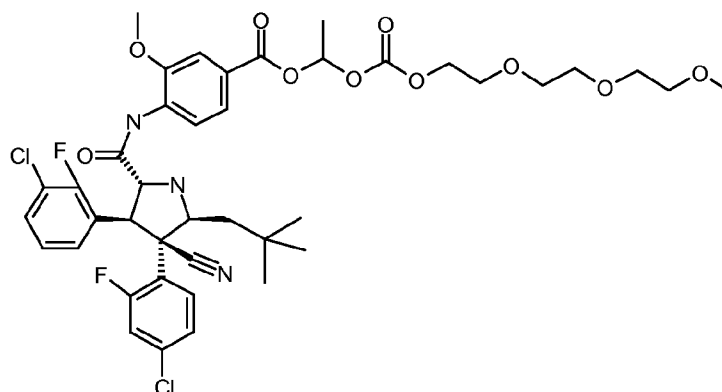
M.W. 787.69 $C_{39}H_{42}Cl_2F_2N_4O_7$

[0087] In a manner similar to the method described in **Example 3**, 1-chloroethyl chloroformate (Oakwood, 1.32 g, 1.0 mL, 9.27 mmol) was reacted with 4-aminotetrahydropyran (Oakwood, 899 mg, 0.92 mL, 8.62 mmol) and pyridine (782 mg, 0.8 mL, 9.89 mmol) in methylene chloride (20 mL) at -78 °C for 3 h to give 1-chloroethyl tetrahydro-2H-pyran-4-ylcarbamate compound with pyridine hydrochloride (1:1). A portion of this material (520 mg, 1.61 mmol) in dimethylformamide (5 mL) was then reacted with chiral 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid (151.4 mg, 0.246 mmol) and cesium carbonate (599.5 mg, 1.84 mmol) in dimethylformamide (4.00 mL) at room temperature for 17 h to give 1-(tetrahydro-2H-pyran-4-ylcarbamate)-4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate as a white solid (145.7 mg, 75% yield). MS (ES⁺) m/z calcd. for $C_{39}H_{42}Cl_2F_2N_4O_7$: [(M+H)⁺]: 787, found: 787

Example 18

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-methoxy-ethoxy)-ethoxy]-ethoxycarbonyloxy}-ethyl ester

[0088]

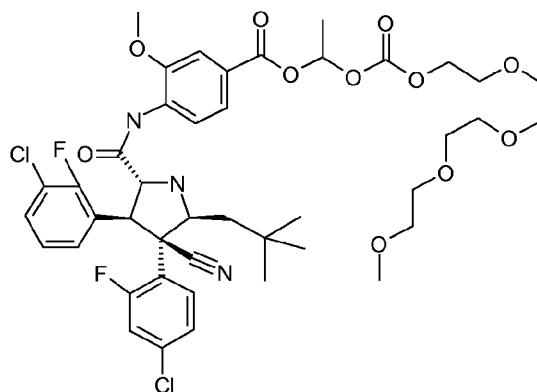


M.W. 850.75 $C_{41}H_{47}Cl_2F_2N_3O_{10}$

[0089] In a manner similar to the method described in **Example 3**, 1-chloroethyl chloroformate was reacted with 2-(2-(2-methoxyethoxy)ethoxy)ethanol (TCI) and pyridine in methylene chloride at -78 °C for 3 h to give 1-chloroethyl 2-(2-(2-methoxyethoxy)ethoxy)ethyl carbonate. This was then reacted with chiral 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid in the presence of cesium carbonate in dimethylformamide overnight to give, after flash chromatography purification (hexane/ethyl acetate, 80/20 to 20/80), 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-methoxy-ethoxy)-ethoxy]-ethoxycarbonyloxy}-ethyl ester as a white solid. LCMS (ES⁺) m/z calcd. for $C_{41}H_{48}Cl_2F_2N_3O_{10}$ [(M+H)⁺]: 850, found: 850.

Example 19

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-methoxy-ethoxy)-ethoxy]-ethoxy}-ethoxy)-ethoxycarbonyloxy)-ethyl ester

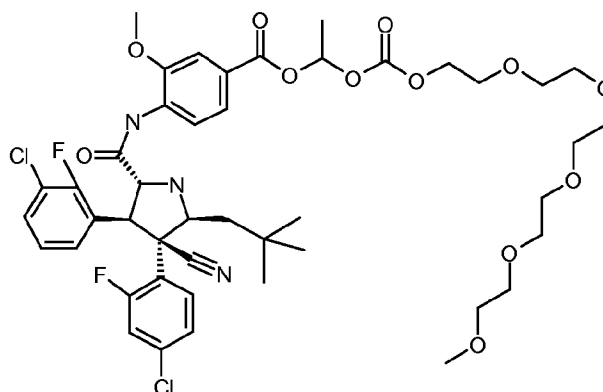
[0090]

M.W. 894.80 $C_{43}H_{51}Cl_2F_2N_3O_{11}$

[0091] In a manner similar to the method described in **Example 3**, 1-chloroethyl chloroformate was reacted with 2,5,8,11-tetraoxatridecan-13-ol (TCI) and pyridine in methylene chloride at -78 °C for 3 h to give 1-chloroethyl 2,5,8,11-tetraoxatridecan-13-yl carbonate. This was then reacted with 4-[(2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido]-3-methoxybenzoic acid in the presence of cesium carbonate in dimethylformamide overnight to give, after flash chromatography purification (hexane/ethyl acetate, 80/20 to 20/80), 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-methoxy-ethoxy)-ethoxy]-ethoxy}-ethoxy)-ethoxycarbonyloxy)-ethyl ester as a white solid. LCMS (ES⁺) m/z calcd. for $C_{43}H_{52}Cl_2F_2N_3O_{11}$ [(M+H)⁺]: 894, found: 894.

Example 20

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-methoxy-ethoxy)-ethoxy]-ethoxy)-ethoxy]-ethoxy)-ethoxycarbonyloxy)-ethyl ester

[0092]

M.W. 938.86 $C_{45}H_{55}Cl_2F_2N_3O_{12}$

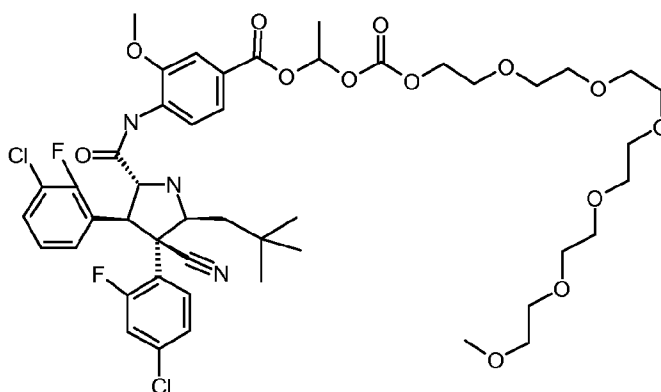
[0093] In a manner similar to the method described in **Example 3**, 1-chloroethyl chloroformate was reacted with pentaethylene glycol monomethyl ether (TCI) and pyridine in methylene chloride at -78 °C for 3 h to give 1-chloroethyl 2,5,8,11,14-pentaohexadecan-16-yl carbonate. This was then reacted with 4-[(2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carboxamido]-3-methoxybenzoic acid in the presence of cesium carbonate in dimethylformamide overnight to give, after flash chromatography purification (hexane/ethyl acetate, 80/20 to 20/80), 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-methoxy-ethoxy)-ethoxy]-ethoxy)-ethoxy]-ethoxy)-ethoxycarbonyloxy)-ethyl ester as a white solid. LCMS (ES⁺) m/z calcd. for $C_{45}H_{56}Cl_2F_2N_3O_{12}$ [(M+H)⁺]: 938, found: 938.

enyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid in the presence of cesium carbonate in dimethylformamide overnight to give, after flash chromatography purification (hexane/ethyl acetate, 80/20 to 20/80), 4-1[(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 as a white solid. LCMS (ES⁺) m/z calcd. for C₄₅H₅₆Cl₂F₂N₃O₁₂ [(M+H)⁺]: 938, found: 938.

Example 21

21-oxo-2,5,8,11,14,17,20,22-octaoxatetracosan-23-yl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate

[0094]



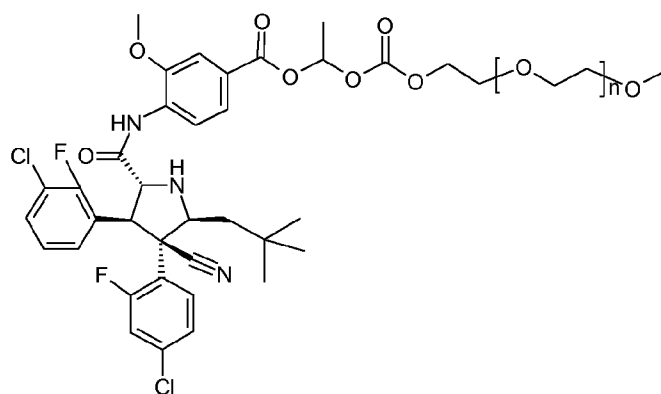
M.W. 982.91, C₄₇H₅₉Cl₂F₂N₃O₁₃

[0095] In a manner similar to the method described in **Example 3**, 1-chloroethyl chloroformate was reacted with 2,5,8,11,14,17-hexaoxonadecan-19-ol (TCl) and pyridine in methylene chloride at -78 °C for 3 h to give 1-chloroethyl 2,5,8,11,14,17-hexaoxonadecan-19-yl carbonate. This was then reacted with 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid in the presence of cesium carbonate in dimethylformamide overnight to give, after flash chromatography purification (hexane/ethyl acetate, 80/20 to 20/80), 21-oxo-2,5,8,11,14,17,20,22-octaoxatetracosan-23-yl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate as a white solid. LCMS (ES⁺) m/z calcd. for C₄₇H₆₀Cl₂F₂N₃O₁₃ [(M+H)⁺]: 982, found: 982.

Example 22

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, ~750)

[0096]



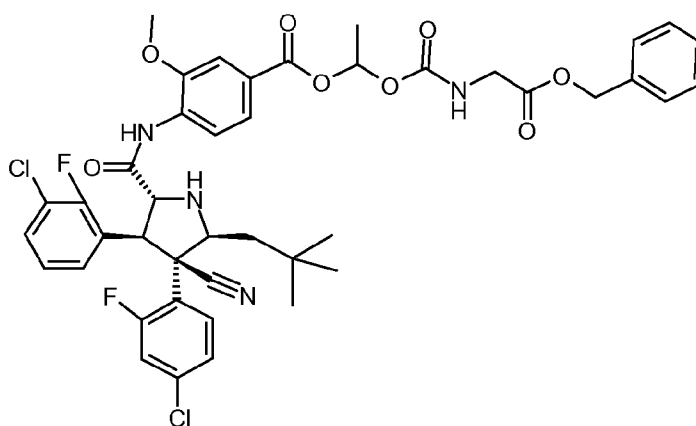
Average MW: 1438

[0097] In a manner similar to the method described in **Example 3**, 1-chloroethyl chloroformate was reacted with poly(ethylene glycol) monomethyl ether (mPEG) (Aldrich, average MW ~750) and pyridine in methylene chloride at -78 °C for 3 h to give the 1-chloroethyl mPEG carbonate. This 1-chloroethyl mPEG carbonate was then reacted with 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid in the presence of cesium carbonate in dimethylformamide overnight to give, after high-performance liquid chromatography purification (10% to 100% acetonitrile in water), 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-methoxybenzoic acid 1-mPEG-carbonyloxy-ethyl ester (mPEG, average MW ~750) as a waxy solid.

Example 23

1-(2-(Benzyloxy)-2-oxoethylcarbamoyloxy)ethyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate

[0098]



M.W.851.74 C₄₃H₄₂Cl₂F₂N₄O₈

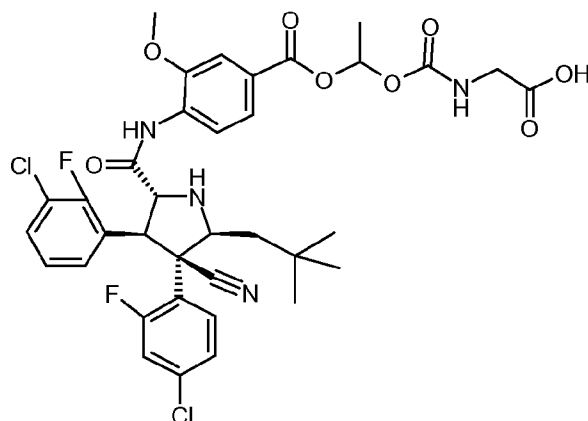
[0099] Benzyl 2-aminoacetate was generated from a treatment of benzyl 2-aminoacetate hydrochloride (Aldrich) in methylene chloride with aqueous sodium bicarbonate solution followed by water wash. To a cooled solution of benzyl 2-aminoacetate (1.837 g, 11.1 mmol) and pyridine (1.1 g, 1.1 mL, 13.9 mmol) in methylene chloride (17 mL) at -78 °C, was added slowly 1-chloroethyl chloroformate (Aldrich, 1.67 g, 11.7 mmol) over ~10 min. The reaction mixture was allowed to stir at -78 °C for 3 h, giving a white precipitate. This cold reaction mixture was filtered to remove the solid and the filtrate was concentrated to dryness, giving the crude benzyl 2-((1-chloroethoxy)carbonylamino)acetate which was used for the next step without further purification.

[0100] To a solution of 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid (215 mg, 0.349 mmol) in dimethylformamide (22 mL) was added cesium carbonate (2.15 g, 6.6 mmol). After stirring for 10 min, a solution of the freshly made benzyl 2-((1-chloroethoxy)carbonylamino)acetate (2.77 g crude, ~5.55 mmol) in dimethylformamide (5 mL) was added. The reaction mixture was allowed to stir at room temperature overnight. This reaction mixture was taken up in ethyl acetate, washed with water, brine and concentrated to dryness. The crude material was purified by flash chromatography (hexane/ethyl acetate, 90/10 to 10/90) to give 1-(2-(benzyloxy)-2-oxoethylcarbamoyloxy)ethyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate as a white solid (191 mg, 64% yield). LCMS (ES⁺) m/z calcd. for C₄₃H₄₃Cl₂F₂N₄O₈ [(M+H)⁺]: 851, found: 851.

Example 24

2-((1-(4-((2R,3S,4R,5S)-3-(3-Chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoyloxy)ethoxy)carbonylamino)acetic acid

[0101]



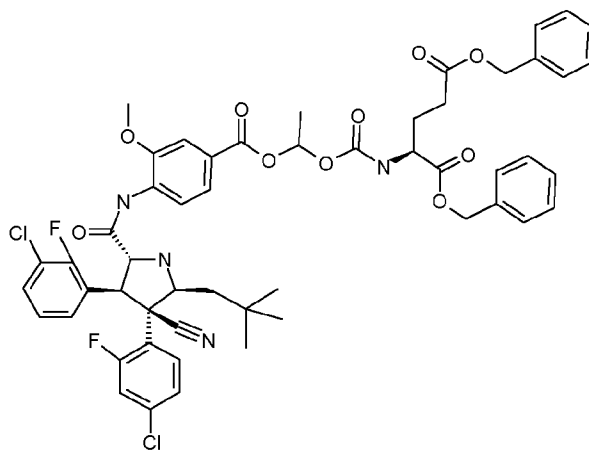
MW: 761.61 $C_{36}H_{36}Cl_2F_2N_4O_8$

[0102] To a solution of 1-(2-(benzyloxy)-2-oxoethylcarbamoyloxy)ethyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate (Example 23, 35.8 mg, 0.042 mmol) in ethyl acetate (8 mL) was added 10% palladium on carbon (12 mg). The content was stirred at room temperature under 1 atm of hydrogen for 2 h. Palladium on carbon solids were filtered off and washed with ethyl acetate. The solution was concentrated to give 2-((1-(4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoyloxy)ethoxy)carbonylamino)acetic acid as a white solid (20.6 mg, 61%). MS (ES⁺) m/z calcd. for $C_{36}H_{37}Cl_2F_2N_4O_8$ [(M+H)⁺]: 761, found: 761.

Example 25

(2S)-Dibenzyl 2-((1-(4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoyloxy)ethoxy)-carbonylamino)pentanedioate

[0103]



M.W. 1013.93, $C_{53}H_{52}Cl_2F_2N_4O_{10}$

[0104] (S)-Dibenzyl 2-aminopentanedioate was generated from a treatment of (S)-glutamic acid dibenzyl ester hydrochloride (Aldrich) in methylene chloride with aqueous sodium bicarbonate solution followed by water wash. To a cooled solution of (S)-dibenzyl 2-aminopentanedioate (6.70 g, 20.5 mmol) and pyridine (2.05 g, 2.1 mL, 26.0 mmol) in methylene chloride (40 mL) at -78 °C, was added slowly 1-chloroethyl chloroformate (Aldrich, 3.07 g, 2.32 mL, 21.5 mmol) over ~10 min. The reaction mixture was allowed to stir at -78 °C for 3 h, giving a white precipitate. The cold reaction mixture was filtered to remove the precipitate and the filtrate was concentrated to dryness, giving crude (2S)-dibenzyl 2-((1-chloroethoxy)carbonylamino)-pentanedioate (11.1 g) which was used for the next step without further purification.

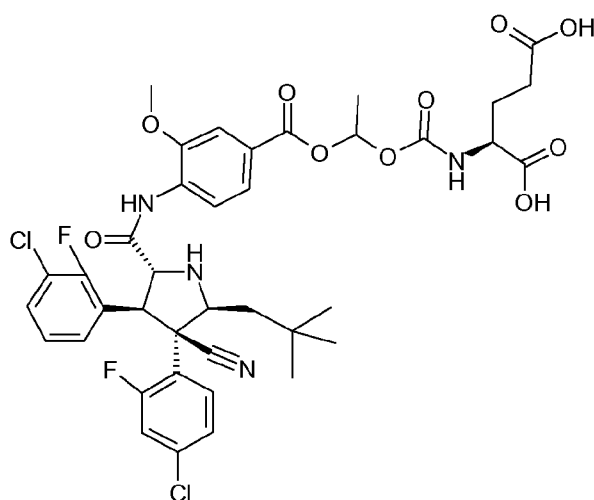
[0105] To a solution of chiral 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid (931 mg, 1.51 mmol) in dimethylformamide (40 mL) was added cesium carbonate (7.80 g, 23.9 mmol). After stirring for 10 min, a solution of the above freshly made (2S)-dibenzyl

2-((1-chloroethoxy)carbonylamino)-pentanedioate (11.10 g crude, ~20 mmole) in dimethylformamide (10 mL) was added and the mixture was allowed to stir at room temperature overnight. This mixture was then taken up in ethyl acetate, washed with water, brine and concentrated to dryness. The crude material was purified by flash chromatography (hexane/ethyl acetate, 90/10 to 10/90) to give (2S)-dibenzyl 2-((1-(4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoyloxy)ethoxy)-carbonylamino)pentanedioate as a white solid (107 mg, 7% yield). MS (ES⁺) m/z calcd. for C₅₃H₅₃Cl₂F₂N₄O₁₀ [(M+H)⁺]: 1013, found: 1013

Example 26

Preparation of (S)-2-[1-(4-((2R,3S,4R,5S)-3-(3-Chloro-2-fluoro-phenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino)-3-methoxy-benzoyloxy)-ethoxycarbonylamino]-pentanedioic acid

[0106]



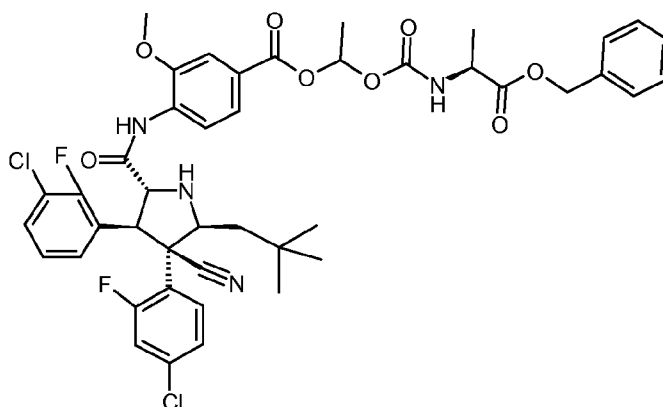
M.W.833.68 C₃₉H₄₀Cl₂F₂N₄O₁₀

[0107] To a solution of (2S)-dibenzyl 2-((1-(4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoyloxy)ethoxy)-carbonylamino)-pentanedioate (**Example 25**, 44 mg, 0.043 mmol) in ethyl acetate (7 mL) was added 10% palladium on carbon (33 mg). The content was stirred at room temperature under 1 atm of hydrogen for 3 h. Palladium on carbon solids were filtered off and washed with ethyl acetate. The solution was concentrated to give (S)-2-[1-(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-benzoyloxy)-ethoxycarbonylamino]-pentanedioic acid as a white solid (18.6 mg, 48%). MS (ES⁺) m/z calcd. for C₃₉H₄₁Cl₂F₂N₄O₁₀ [(M+H)⁺]: 833, found: 833

Example 27

1-((S)-1-(benzyloxy)-1-oxopropan-2-ylcarbamoxyloxy)ethyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate

[0108]



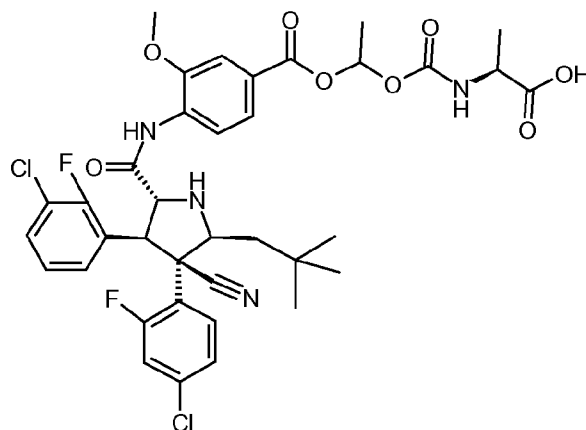
MW: 865.74 $C_{44}H_{44}Cl_2F_2N_4O_8$

[0109] In a manner similar to the method described in **Example 23**, (S)-benzyl 2-((1-chloroethoxy)-carbonylamino)propanoate was prepared from (S)-benzyl 2-aminopropanoate and 1-chloroethyl chloroformate (Aldrich) in the presence of pyridine in methylene chloride. It was then reacted with chiral 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid and cesium carbonate in dimethylformamide to give 1-((S)-1-(benzyloxy)-1-oxopropan-2-ylcarbamoyloxy)ethyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate as a white solid. MS (ES^+) m/z calcd. for $C_{44}H_{45}Cl_2F_2N_4O_8$ [(M+H) $^+$]: 865, found: 865

Example 28

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-((S)-1-carboxy-ethylcarbamoyloxy)-ethyl ester

[0110]

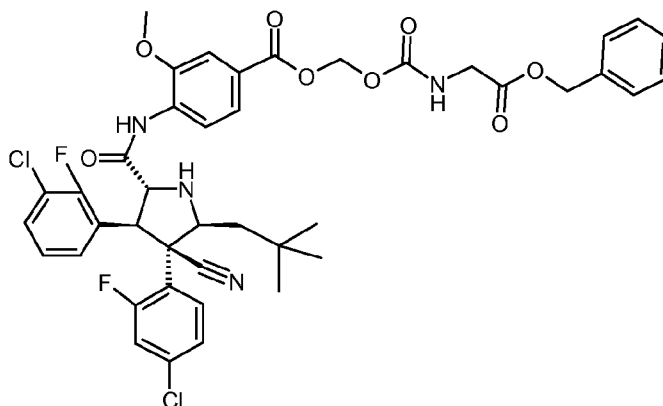


M.W. 775.62 $C_{37}H_{38}Cl_2F_2N_4O_8$

[0111] In a manner similar to the method described in **Example 24**, a solution of 1-((S)-1-(benzyloxy)-1-oxopropan-2-ylcarbamoyloxy)ethyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate (**Example 27**) in ethyl acetate was treated with 10% palladium on carbon under 1 atm of hydrogen to give 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-((S)-1-carboxy-ethylcarbamoyloxy)-ethyl ester as a white solid. MS (ES^+) m/z calcd. for $C_{37}H_{39}Cl_2F_2N_4O_8$ [(M+H) $^+$]: 775, found: 775.

Example 29

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 benzyloxycarbonylmethylcarbamoyloxymethyl ester

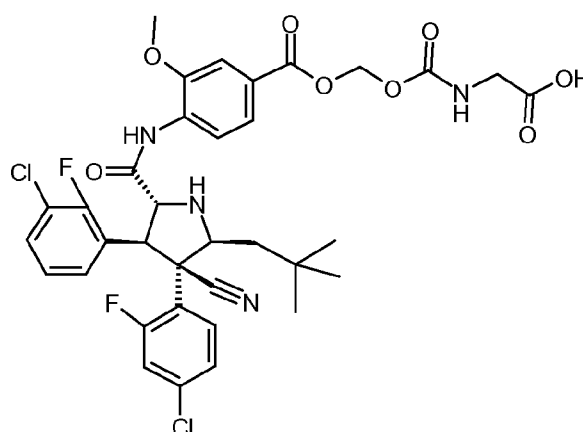
[0112]

M.W. 837.71, $C_{42}H_{40}Cl_2F_2N_4O_8$

[0113] In a manner similar to the method described in **Example 23**, chloromethoxycarbonylamino-acetic acid benzyl ester was prepared from amino-acetic acid benzyl ester and 1-chloroethyl chloroformate (Aldrich) in the presence of pyridine in methylene chloride. It was then reacted with chiral 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid and cesium carbonate in dimethylformamide to give chiral 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 benzyloxycarbonylmethyl-carbamoyloxymethyl ester as a white solid. MS (ES^+) m/z calcd. for $C_{42}H_{41}Cl_2F_2N_4O_8$ $[(M+H)^+]$: 837, found: 837

Example 30

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)acetic acid

[0114]

M.W. 747.57 $C_{35}H_{35}Cl_2F_2N_4O_8$

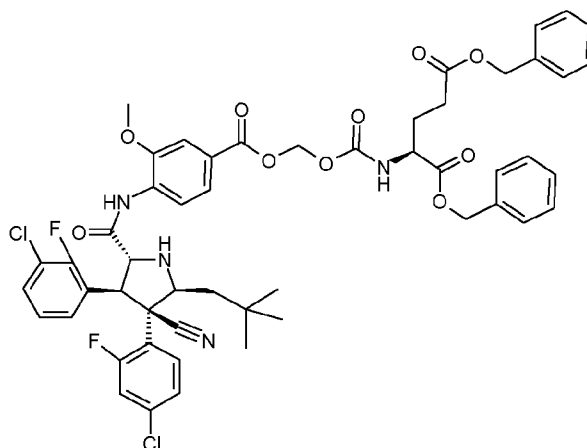
[0115] In a manner similar to the method described in **Example 24**, a solution of 4-[[[(2R,3S,4R,5S)-3-(3-chloro-2-fluoro-phenyl)-4-(4-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino]-3-methoxy-benzoic acid benzyloxycarbonylmethyl-carbamoyloxymethyl ester (**Example 29**) in ethyl acetate was treated with 10% palladium on carbon under 1 atm of hydrogen to give 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)acetic acid as a white solid. MS (ES⁺) m/z calcd. for C₃₅H₃₆Cl₂F₂N₄O₈ [(M+H)⁺]: 747, found: 747.

Example 31

(S)-Dibenzyl 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)-pentanedioate

[0116]



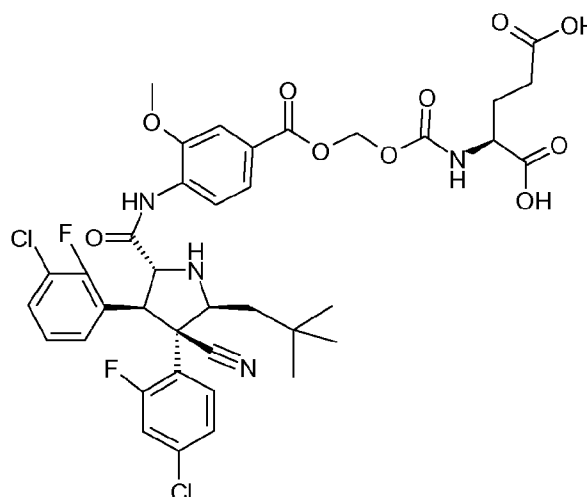
M.W.999.88 C₅₂H₅₀Cl₂F₂N₄O₁₀

[0117] In a manner similar to the method described in **Example 23**, (S)-dibenzyl 2-((chloromethoxy)-carbonylamino)pentanedioate was prepared from (S)-dibenzyl 2-aminopentanedioate and chloromethyl chloroformate in the presence of pyridine in methylene chloride. It was then reacted with chiral 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid and cesium carbonate in dimethylformamide to give chiral (S)-dibenzyl 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)-pentanedioate as a white solid. MS (ES⁺) m/z calcd. for C₅₂H₅₁Cl₂F₂N₄O₁₀ [(M+H)⁺]: 999, found: 999.

Example 32

(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

[0118]



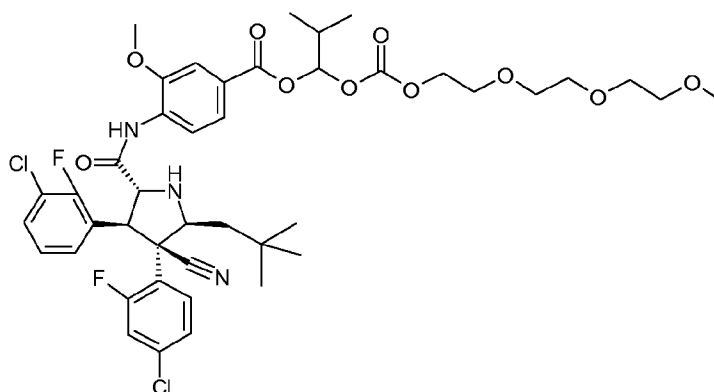
MW: 819.63 $C_{38}H_{39}Cl_2F_2N_4O_{10}$

[0119] In a manner similar to the method described in **Example 24**, a solution of chiral (S)-dibenzyl 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)-pentanedioate (**Example 31**) in ethyl acetate was treated with 10% palladium on carbon under 1 atm of hydrogen to give chiral (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 as a white solid. MS (ES^+) m/z calcd. for $C_{38}H_{39}Cl_2F_2N_4O_{10}$ [(M+H) $^+$]: 819, found: 819.

Example 33

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

[0120]



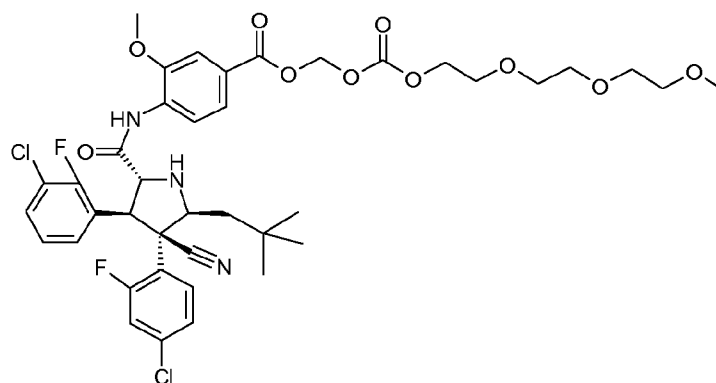
M.W. 878.8 $C_{43}H_{51}Cl_2F_2N_3O_{10}$

[0121] In a manner similar to the method described in **Example 3**, 1-chloro-2-methylpropyl chloroformate (Aldrich) was reacted with 2-(2-(2-methoxyethoxy)ethoxy)ethanol (TCI) and pyridine in methylene chloride at -78 °C for 3 h to give 1-chloro-2-methylpropyl 2-(2-(2-methoxyethoxy)-ethoxy)ethyl carbonate. This material was then reacted with chiral 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid in the presence of cesium carbonate in dimethylformamide overnight to give, after flash chromatography purification (hexane/ethyl acetate, 80/20 to 20/80), 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 as a white solid. MS (ES^+) m/z calcd. for $C_{43}H_{52}Cl_2F_2N_3O_{10}$: [(M+H) $^+$]: 878, found: 878.

Example 34

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

[0122]



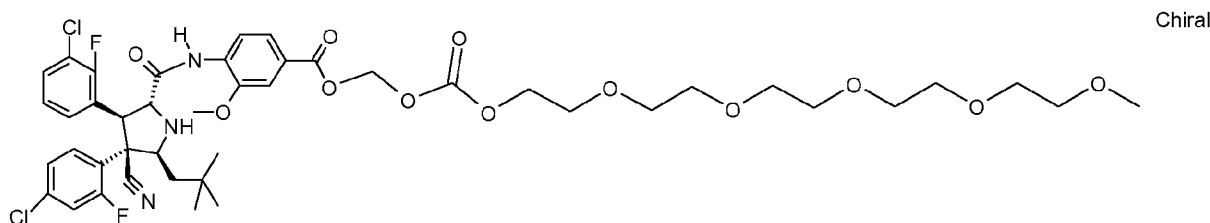
M.W. 836.72 $C_{40}H_{46}Cl_2F_2N_3O_{10}$

[0123] In a manner similar to the method described in **Example 3**, chloromethyl chloroformate (Aldrich) was reacted with 2-(2-(2-methoxyethoxy)ethoxy)ethanol (TEC) and pyridine in methylene chloride at -78°C for 3 h to give chloromethyl 2-(2-(2-methoxyethoxy)ethoxy)ethyl carbonate. This material was then reacted with chiral 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid in the presence of cesium carbonate in dimethylformamide overnight to give, after flash chromatography purification (hexane/ethyl acetate, 80/20 to 20/80), chiral 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 as a white solid. MS (ES⁺) m/z calcd. for $C_{40}H_{47}Cl_2F_2N_3O_{10}$: [(M+H)⁺]: 836, found: 836.

Example 35

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

[0124]



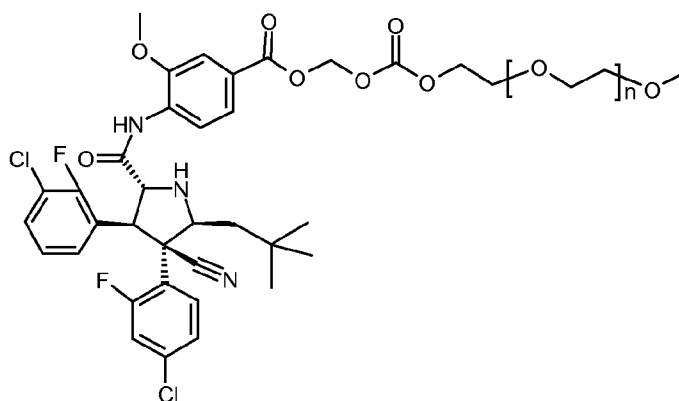
M.W. 924.83 $C_{44}H_{53}Cl_2F_2N_3O_{12}$

[0125] In a manner similar to the method described in **Example 3**, chloromethyl chloroformate (Aldrich) was reacted with pentaerythritol monomethyl ether (TEC) and pyridine in methylene chloride at -78°C for 3 h to give chloromethyl 2,5,8,11,14-pentaaxahexadecan-16-yl carbonate. This material was then reacted with chiral 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid in the presence of cesium carbonate in dimethylformamide overnight to give, after flash chromatography purification (hexane/ethyl acetate, 80/20 to 20/80), chiral 3-oxo-2,4,7,10,13,16,19-heptaooxaicosyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate as a white solid. MS (ES⁺) m/z calcd. for $C_{44}H_{54}Cl_2F_2N_3O_{12}$: [(M+H)⁺]: 924, found: 924.

Example 36

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-carboxyloxy-methyl ester (mPEG, average MW, ~750)

[0126]



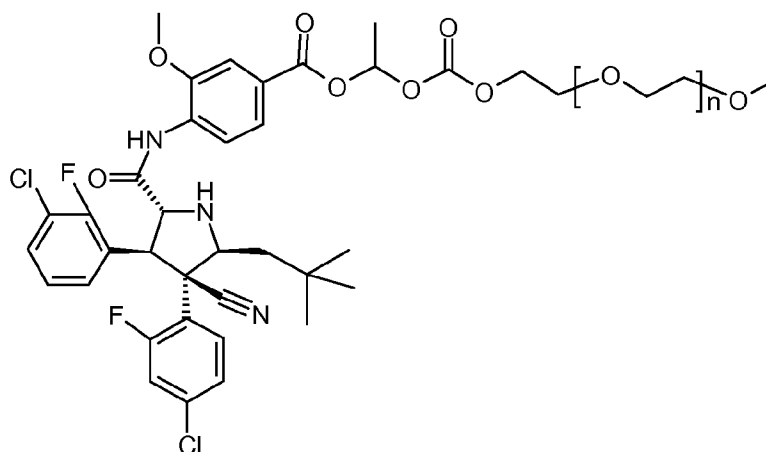
Average MW: ~1431

[0127] In a manner similar to the method described in **Example 3**, chloromethyl chloroformate (594 mg, 410 μ l, 4.43 mmol) was reacted with poly(ethylene glycol) monomethyl ether (mPEG) (Aldrich, average MW ~750, 10.03 g, 13.4 mmol) and pyridine (1.32 g, 1.35 mL, 16.7 mmol) in methylene chloride (6 mL) at -78 °C for 3 h to give 1-chloromethyl mPEG carbonate with pyridine hydrochloride (1:1). This 1-chloromethyl mPEG carbonate (4.67 g, 4.87 mmol) in dimethylformamide (18 mL) was then reacted with 4-[(2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido]-3-methoxybenzoic acid (300 mg, 0.487 mmol) and cesium carbonate (1.92 g, 5.89 mmol) in dimethylformamide (7 mL) overnight to give, after high-performance liquid chromatography purification (10% to 100% acetonitrile in water), chiral 4-[(2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino-3-methoxy-benzoic acid 1-mPEG-carbonyloxy-methyl ester (mPEG, average MW, ~750) as a waxy solid (586.3 mg, 84.5 % yield).

Example 37

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)

[0128]



Average MW: ~2695

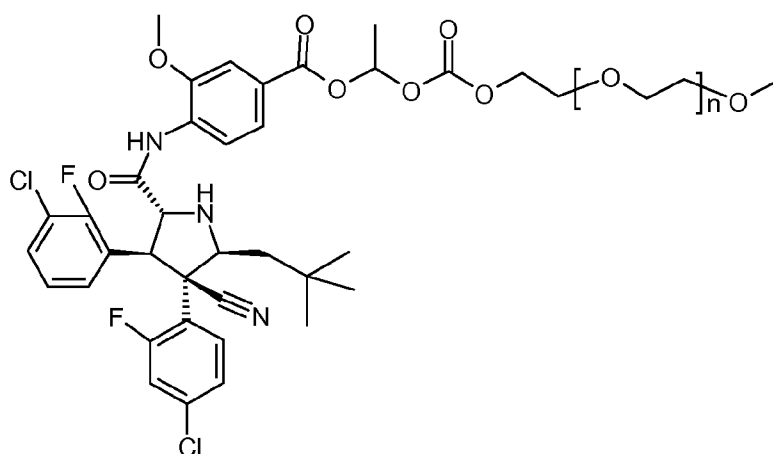
[0129] In a manner similar to the method described in **Example 3**, chloroethyl chloroformate (Oakwood, 1.46 g, 1.1 mL, 10.2 mmol) was reacted with poly(ethylene glycol) monomethyl ether (mPEG) (Aldrich, average MW ~2000, 18.84 g, 9.42 mmol) and pyridine (939 mg, 0.96 mL, 11.9 mmol) in methylene chloride (6 mL) at -78 °C for 3 h to give 1-chloroethyl mPEG carbonate with pyridine hydrochloride (1:1). This 1-chloroethyl mPEG carbonate (4.67 g, 4.87 mmol) in dimethylformamide (25 mL) was then reacted with chiral 4-[(2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido]-3-methoxybenzoic acid (300 mg, 0.487 mmol), as e.g. obtainable via the method disclosed in WO2011/098398, and cesium carbonate (1.97 g, 6.04 mmol) in dimethylformamide (6 mL) overnight to give, after high-performance liquid chromatography purification (10% to 100% acetonitrile in water),

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-carboxyloxy-ethyl ester (mPEG, average MW, ~2000) as a white solid (171.6 mg, 13 % yield).

Example 37a

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-carboxyloxy-ethyl ester (mPEG, average MW, ~2200)

[0130]



Average MW: ~2900

a) 1-Chloroethyl 2-methoxyethyl carbonate-mPEG (average MW ~2300)

[0131] Methoxy-poly(ethylene glycol) (ID Biochem, average MW ~2200 determined by MALDI-TOF MS, 2.5 kg, ~1.14 mol) and lithium carbonate (185 g, 2.5 mol) were charged to a 50-L glass reactor, and dichloromethane (39.8 kg, 30.0 L) was added. The mixture was stirred for 1 hour, and then 1-chloroethyl chloroformate (1.07 kg, 819 mL, 7.5 mol) was added via dropping funnel. With vigorous mixing, a catalytic amount of pyridine (4.94 g, 5.05 mL, 62.5 mmol) was added, and gas evolution was observed. The mixture was stirred at 25 °C under N₂ for 21 hours. HPLC-CAD analysis showed ~3% mPEG-OH remaining. The reaction mixture was filtered to remove insoluble salts, and then the liquors were polish filtered through a 0.4 micron filter. The liquors were concentrated to remove dichloromethane by vacuum distillation and the solvent exchanged to n-heptane. The resulting slurry in n-heptane was cooled to 0 °C and aged for 1 hour prior to filtering the product as a white powder. The solids were washed with n-heptane then dried at 35 °C in a vacuum oven with N₂ purge to yield 2340 g (90%) of 1-chloroethyl 2-methoxyethyl carbonate-mPEG (average MW ~2300).

b) 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-carboxyloxy-ethyl ester (mPEG, average MW, ~2200)

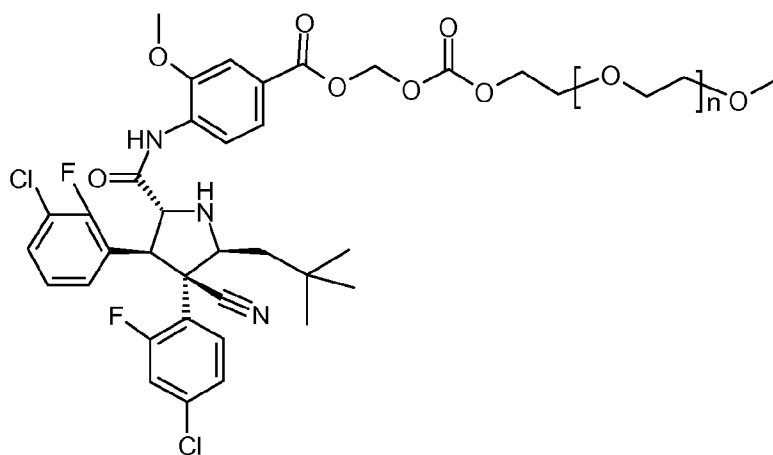
[0132] A 12-L flask was charged with chiral 4-[(2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido]-3-methoxybenzoic acid cesium salt (400 g, 533 mmol), 1-chloroethyl 2-methoxyethyl carbonate-mPEG, (avg MW~2300) (1.51 kg, ~657 mmol), and cesium carbonate (43.4 g, 133 mmol, Eq: 0.25), followed by DMSO (4.00 L). The mixture was stirred and heated to 50 °C for 4 hours. The temperature was adjusted to 30 °C and the reaction stirred for 6 days. Additional 1-chloroethyl 2-methoxyethyl carbonate-mPEG, (avg MW ~2300) (112 g, ~49 mmol) was added, and the mixture heated again to 50 °C for 2 days. HPLC analysis showed ca. 98% conversion. The reaction mixture was cooled to 20 °C, then poured into a prepared solution containing water (8.00 L) and hydrochloric acid (26.7 mL, 320 mmol). The resulting solution was stirred for a few minutes, and then the pH adjusted to ~6.5 by addition of Cs₂CO₃. The solution was stirred until analysis (HPLC-CAD) showed complete hydrolysis of excess 1-chloroethyl 2-methoxyethyl carbonate-mPEG to methoxy-poly(ethylene glycol). The solution was extracted with dichloromethane (10.6 kg, 8.00 L). The dichloromethane fraction was washed with water (8.00 kg, 8.00 L) four (4) times, and then with brine. The organic phase was concentrated under vacuum to give 1.885 kg crude pasty-solid that contained a mixture of the product and mPEG-OH. This residue was dissolved in isopropyl acetate (26.1 kg,

30.0 L) and then washed with 50% brine solution (1.13 L, prepared from 200 g NaCl in 1.13 L water). The mixture was allowed to settle for 1 h, and then the lower aqueous phase was removed. The remaining isopropyl acetate organic phase was polish filtered through diatomaceous earth. This solution was concentrated by vacuum distillation to provide a solid residue that was re-dissolved in isopropyl acetate (4.0 L). Once a clear solution was achieved, it was cooled to 10 °C and then n-heptane (8.0 L) was slowly added with vigorous mixing. After the first ca. 1.0 L was added, the product began to precipitate as a fine, white slurry. The remaining n-heptane was added and the suspension stirred at 6-10 °C for 0.5 h. Filtration provided a white powder that was dried in a vacuum oven at 35 °C with N₂ purge. The title compound 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) Average MW: ~2900, was obtained in 1128 g (73%) yield, 99.5% purity (LC-CAD).

Example 38

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)

[0133]



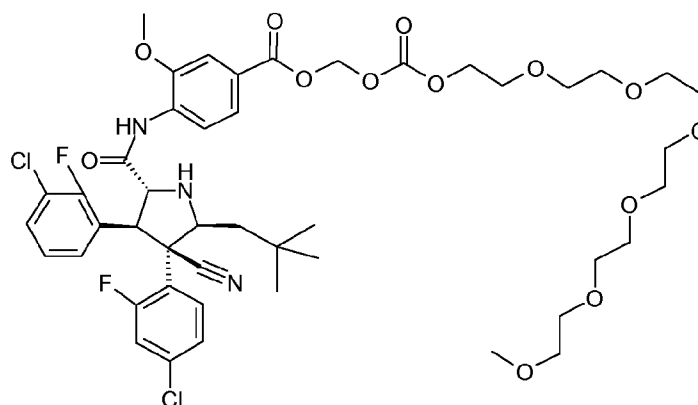
Average MW: ~2674

[0134] In a manner similar to the method described in **Example 3**, chloromethyl chloroformate (Oakwood) was reacted with poly(ethylene glycol) monomethyl ether (mPEG) (Aldrich, average MW ~2000) and pyridine in methylene chloride at -78 °C for 3 h to give 1-chloromethyl mPEG. This 1-chloromethyl mPEG carbonate was then reacted with chiral 4-[(2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido]-3-methoxybenzoic acid and cesium carbonate in dimethylformamide overnight to give, after high-performance liquid chromatography purification (10% to 100% acetonitrile in water), chiral 4-[(2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-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) as a white solid.

Example 39

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

[0135]



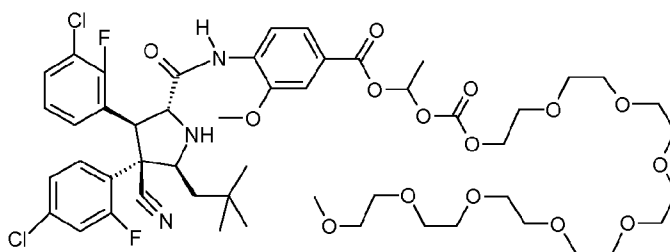
M.W. 968.88 $C_{46}H_{57}Cl_2F_2N_3O_{13}$

[0136] In a manner similar to the method described in **Example 3**, chloromethyl chloroformate (Aldrich) was reacted with 2,5,8,11,14,17-hexaoxonadecan-19-ol (TCI) and pyridine in methylene chloride at $-78^{\circ}C$ for 3 h to give chloromethyl 2,5,8,11,14,17-hexaoxonadecan-19-yl carbonate. This material was then reacted with chiral 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid in the presence of cesium carbonate in dimethylformamide overnight to give, after flash chromatography purification (hexane/ethyl acetate, 80/20 to 20/80), chiral-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 as a white solid. MS (ES⁺) m/z calcd. for $C_{46}H_{58}Cl_2F_2N_3O_{13}$: [(M+H)⁺]: 968, found: 968.

Example 40

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

[0137]



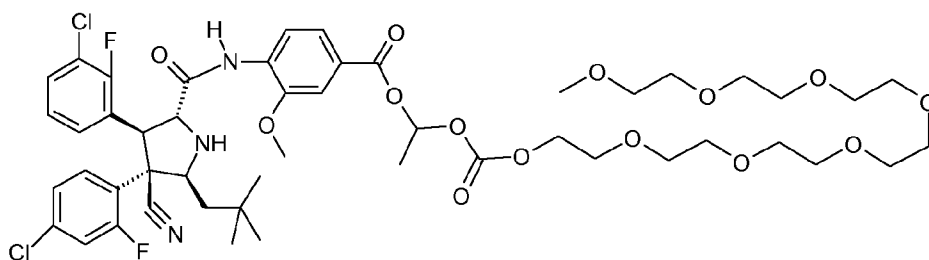
M.W. 1071.02 $C_{51}H_{67}Cl_2F_2N_3O_{15}$

[0138] In a manner similar to the method described in **Example 3**, 1-chloroethyl chloroformate (Aldrich) was reacted with octaethylene glycol monomethyl ether (TCI) and pyridine in methylene chloride at $-78^{\circ}C$ for 3 h to give 1-chloroethyl 2,5,8,11,14,17,20,23-octaoxapentacosan-25-yl carbonate. This was then reacted with chiral 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid in the presence of cesium carbonate in dimethylformamide overnight to give, after flash chromatography purification (hexane/ethyl acetate, 80/20 to 20/80), 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 as a white solid. MS (ES⁺) m/z calcd. for $C_{51}H_{68}Cl_2F_2N_3O_{15}$: [(M+H)⁺]: 1071, found: 1070.

Example 41

24-Oxo-2,5,8,11,14,17,20,23,25-nonaohaheptacosan-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

[0139]



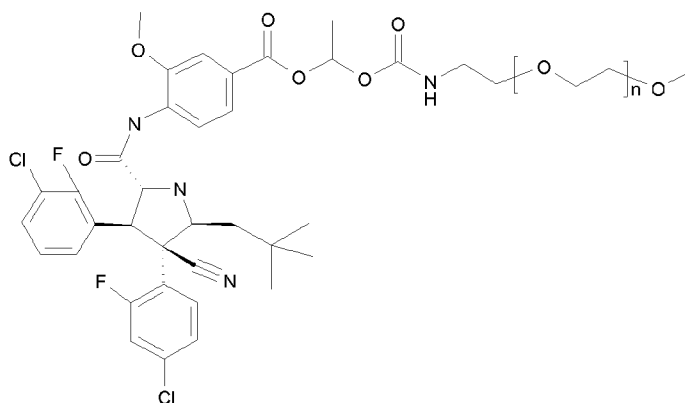
M.W. 1071.02 $C_{51}H_{67}Cl_2F_2N_3O_{15}$

[0140] In a manner similar to the method described in **Example 3**, 1-chloroethyl chloroformate (Aldrich) was reacted with heptaethylene glycol monomethyl ether (TCI) and pyridine in methylene chloride at -78°C for 3 h to give 1-chloroethyl 2,5,8,11,14,17,20,23-octa-oxapentacosan-25-yl carbonate. This was then reacted with chiral 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid in the presence of cesium carbonate in dimethylformamide overnight to give, after flash chromatography purification (hexane/ethyl acetate, 80/20 to 20/80), 24-oxo-2,5,8,11,14,17,20,23,25-nona-oxaheptacosan-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 as a white solid. MS (ES⁺) m/z calcd. for $C_{51}H_{68}Cl_2F_2N_3O_{15}$: [(M+H)⁺]: 1026, found: 1026.

Example 42

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-NH₂, average MW, ~550)

[0141]



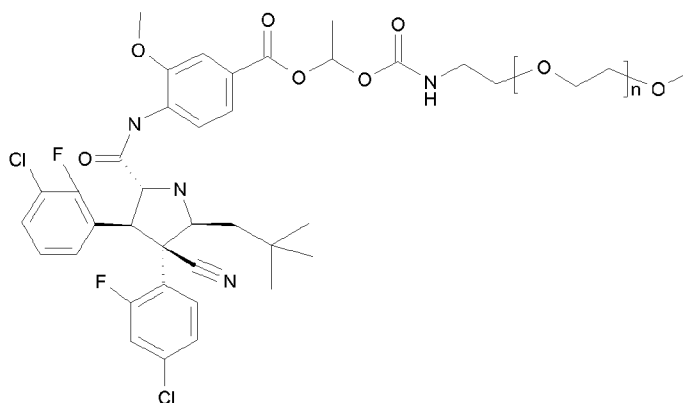
Average MW: ~1240

[0142] In a manner similar to the method described in **Example 3**, 1-chloroethyl chloroformate (Oakwood) was reacted with poly(ethylene glycol)mono amino mono methyl ether (mPEG-NH₂, average MW, ~550, LaySan Bio Inc) and pyridine in methylene chloride at -78°C for 3 h to give 1-chloroethyl mPEG-NH₂ carbamate with pyridine hydrochloride (1:1). This was then reacted with chiral 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid in the presence of cesium carbonate in dimethylformamide overnight to give, after by high-performance liquid chromatography purification (acetonitrile/water), 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, average MW, ~550) as a light brown solid.

Example 43

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-NH₂, average MW, ~1000)

[0143]



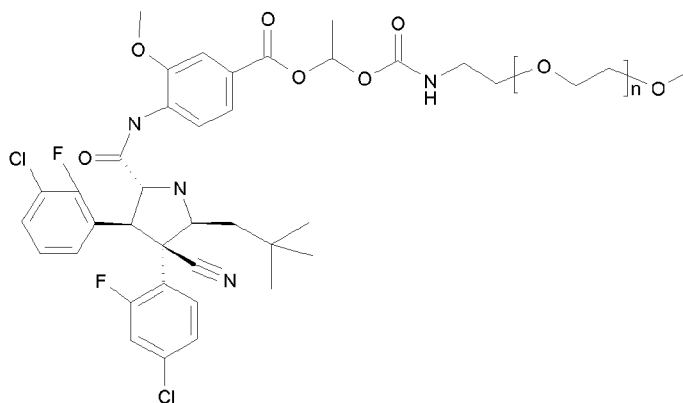
Average MW: ~1687

[0144] In a manner similar to the method described in **Example 3**, 1-chloroethyl chloroformate (Oakwood) was reacted with poly(ethylene glycol)mono amino mono methyl ether (mPEG-NH₂, average MW, ~1000, LaySan Bio Inc.) and pyridine in methylene chloride at -78 °C for 3 h to give 1-chloroethyl mPEG-NH₂ carbamate with pyridine hydrochloride (1:1). This was then reacted with chiral 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid in the presence of cesium carbonate in dimethylformamide overnight to give, after by high-performance liquid chromatography purification (acetonitrile/water), 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino)-3-methoxy-benzoic acid 1-mPEG-carboxyloxy-ethyl amide (mPEG-NH₂, average MW ~1000) as a light brown solid.

Example 44

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-carboxyloxy-ethyl amide (mPEG-NH₂, average MW, ~2000)

[0145]

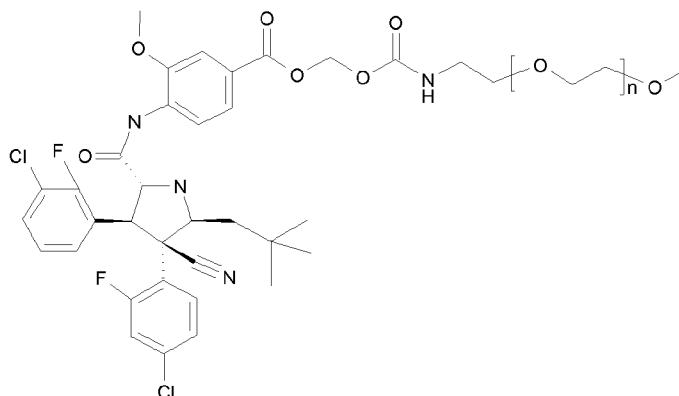


Average MW: ~2687

[0146] In a manner similar to the method described in **Example 3**, 1-chloroethyl chloroformate (Oakwood) was reacted with poly(ethylene glycol)mono amino mono methyl ether (mPEG-NH₂, average MW, ~2000, LaySan Bio Inc.) and pyridine in methylene chloride at -78 °C for 3 h to give 1-chloroethyl mPEG-NH₂ carbamate with pyridine hydrochloride (1:1). This was then reacted with chiral 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid in the presence of cesium carbonate in dimethylformamide overnight to give, after by high-performance liquid chromatography purification (acetonitrile/water), 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino)-3-methoxy-benzoic acid 1-mPEG-carboxyloxy-ethyl amide (mPEG-NH₂, average MW, ~2000) as a white solid.

Example 45

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-carboxyloxy-methyl amide (mPEG-NH₂, average MW ~2000)

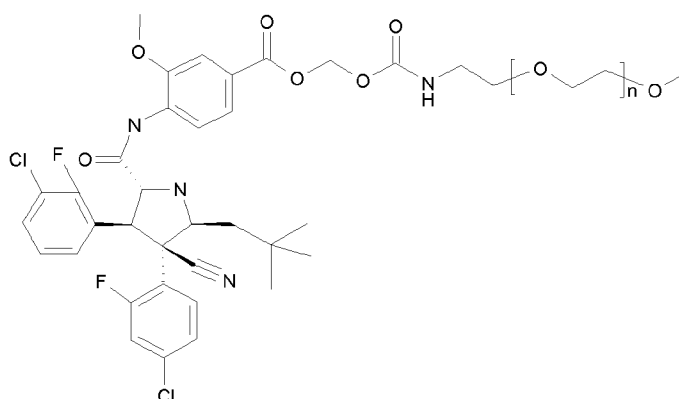
[0147]

Average MW: ~2673

[0148] In a manner similar to the method described in **Example 3**, chloromethyl chloroformate (Oakwood) was reacted with poly(ethylene glycol)mono amino mono methyl ether (mPEG-NH₂, average MW ~2000, LaySan Bio Inc.) and pyridine in methylene chloride at -78 °C for 3 h to give 1-chloromethyl mPEG-NH₂ carbamate with pyridine hydrochloride (1:1). This was then reacted with chiral 4-[(2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido]-3-methoxybenzoic acid in the presence of cesium carbonate in dimethylformamide overnight to give, after by high-performance liquid chromatography purification (acetonitrile/water), chiral 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-carboxyloxy-methyl amide (mPEG-NH₂, average MW ~2000) as a white solid.

Example 46

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-carboxyloxy-methyl amide (mPEG-NH₂, average MW ~1000)

[0149]

Average MW: ~1673

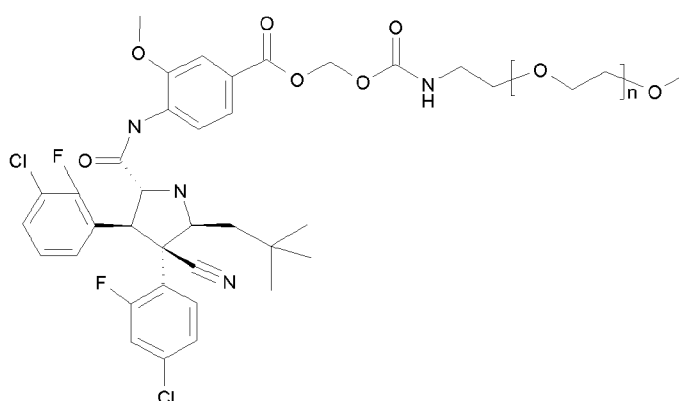
[0150] In a manner similar to the method described in **Example 3**, chloromethyl chloroformate (Oakwood, (160 mg, 110 μl, 1.24 mmol)) was reacted with poly(ethylene glycol)mono amino mono methyl ether (mPEG-NH₂, average MW ~1000, LaySan Bio Inc.) (999.8 mg, 1.00 mmol) and pyridine (53.8 mg, 0.055 mL, 0.68 mmol) in the presence of molecular sieves (~1.74 g, microwave dried, 8-12 mesh) in methylene chloride at -78 °C for 3 h to give 1-chloromethyl mPEG-NH₂

carbamate with pyridine hydrochloride (1:1). This was then reacted with chiral 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid (124 mg, 0.201 mmol) and cesium carbonate (467.3 mg, 1.43 mmol) in dimethylformamide (8 mL) overnight to give, after by high-performance liquid chromatography purification (acetonitrile/water), chiral-4-[[[(2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino]-3-methoxy-benzoic acid 1-mPEG-carboxyloxy-methyl amide (mPEG-NH₂, average MW ~1000) as a white solid (258 mg, 76 % yield).

Example 47

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-carboxyloxy-methyl amide (mPEG-NH₂, average MW ~550)

[0151]



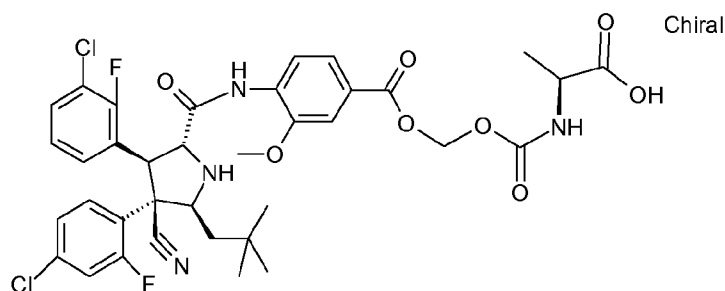
Average MW: ~1223

[0152] In a manner similar to the method described in **Example 46**, chloromethyl chloroformate (Oakwood, 167 mg, 0.11 mL, 1.29 mmol) was reacted with poly(ethylene glycol)mono amino mono methyl ether (mPEG-NH₂, average MW ~550, LaySan Bio Inc.) (576.4 mg, 1.05 mmol) and pyridine (117 mg, 0.12 mL, 1.48 mmol) in the presence of molecular sieves (~0.5 g, microwave dried, 8-12 mesh) in methylene chloride at -78 °C for 3 h to give 1-chloromethyl mPEG-NH₂ carbamate with pyridine hydrochloride (1:1). This was then reacted with chiral 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid (130.4 mg, 0.212 mmol) and cesium carbonate (479 mg, 1.47 mmol) in dimethylformamide (8 mL) overnight to give, after by high-performance liquid chromatography purification (acetonitrile/water), chiral 4-[[[(2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino]-3-methoxy-benzoic acid 1-mPEG-carboxyloxy-methyl amide (mPEG-NH₂, average MW, ~550) as a white solid (173.2 mg, 67.0 % yield).

Example 48

(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)propanoic acid

[0153]



M.W. 761.61 $C_{36}H_{36}Cl_2F_2N_4O_8$

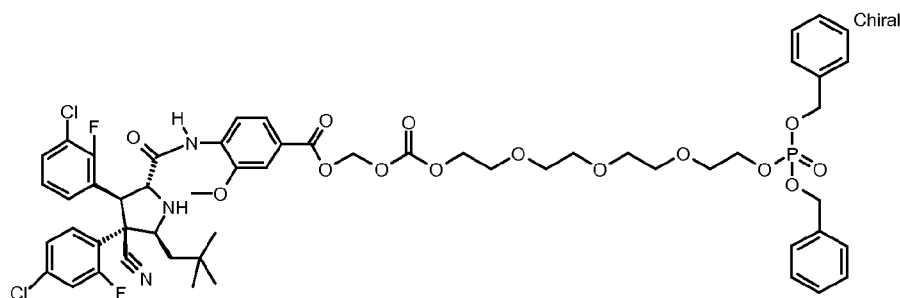
[0154] In a manner similar to the method described in **Example 23**, (S)-benzyl 2-((chloromethoxy)-carbonylamino)propanoate was prepared from (S)-benzyl 2-aminopropanoate (Chem-Impex) and 1-chloromethyl chloroformate (Aldrich) in the presence of pyridine in methylene chloride. It was then reacted with chiral 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid and cesium carbonate in dimethylformamide to give chiral ((S)-1-(benzyloxy)-1-oxopropan-2-ylcarbamoyloxy)methyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate as a white solid.

[0155] In a manner similar to the method described in **Example 24**, a solution of chiral ((S)-1-(benzyloxy)-1-oxopropan-2-ylcarbamoyloxy)methyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate in ethyl acetate was treated with 10% palladium on carbon under 1 atm of hydrogen to give chiral (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)propanoic acid as a white solid. MS (ES⁺) m/z calcd. for $C_{36}H_{36}Cl_2F_2N_4O_8$: [(M+H)⁺]: 761, found: 761.

Example 49

Dibenzyl 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-phosphonooxy-ethoxy)-ethoxy]-ethoxy}-ethoxycarbonyloxymethyl ester

[0156]



M.W. 1126.98 $C_{55}H_{60}Cl_2F_2N_3O_{14}P$

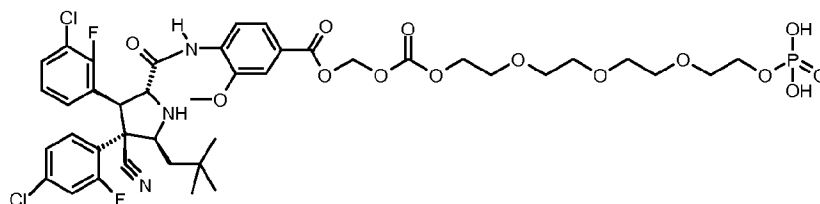
[0157] In a manner similar to the method described in **Example 3**, chloromethyl chloroformate (Oakwood) was reacted with dibenzyl 2-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)ethyl phosphate (**Example 54**) and pyridine in methylene chloride at -78 °C for 3 h to give the corresponding chloromethyl carbonate with pyridine hydrochloride (1:1). This was then reacted with chiral 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid in the presence of cesium carbonate in dimethylformamide overnight to give, after flash chromatography purification, chiral dibenzyl 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-phosphonooxy-ethoxy)-ethoxy]-ethoxy}-ethoxycarbonyloxymethyl ester. MS (ES⁺) m/z calcd. for $C_{55}H_{60}Cl_2F_2N_3O_{14}P$: [(M+H)⁺]: 1126, found: 1126.

Example 50

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-phosphonooxy-ethoxy)-ethoxy]-ethoxy}-ethoxycarbonyloxymethyl ester

[0158]

Chiral



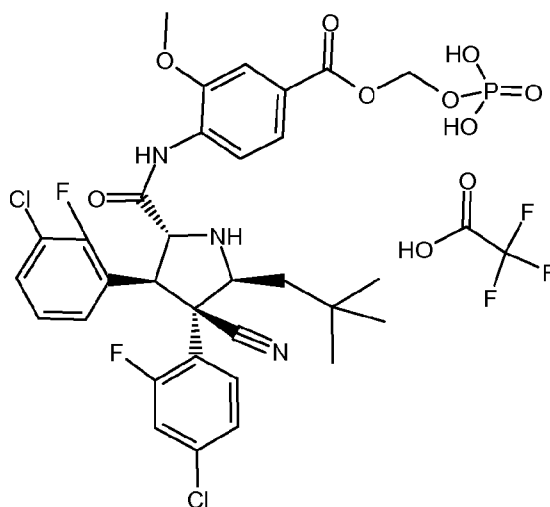
M.W. 946.73 $C_{41}H_{48}Cl_2F_2N_3O_{14}P$

[0159] A solution of chiral dibenzyl 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-phosphonoxy-ethoxy)-ethoxy]-ethoxy}-ethoxycarbonyloxymethyl ester (**Example 49**, 106.7 mg, 0.095 mmol) in ethyl acetate (10 mL) was treated with 10% palladium on carbon (58 mg) under 1 atm of hydrogen for 1 h. The reaction mixture was filtrated and the filtrate was concentrated to give chiral 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-phosphonoxy-ethoxy)-ethoxy]-ethoxy}-ethoxycarbonyloxymethyl ester as a white solid (75 mg, 82% yield). MS (ES^+) m/z calcd. for $C_{41}H_{49}Cl_2F_2N_3O_{14}P$: $[(M+H)^+]$: 946, found: 946.

Example 51

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 phosphonoxyethyl ester; compound with trifluoro-acetic acid

[0160]

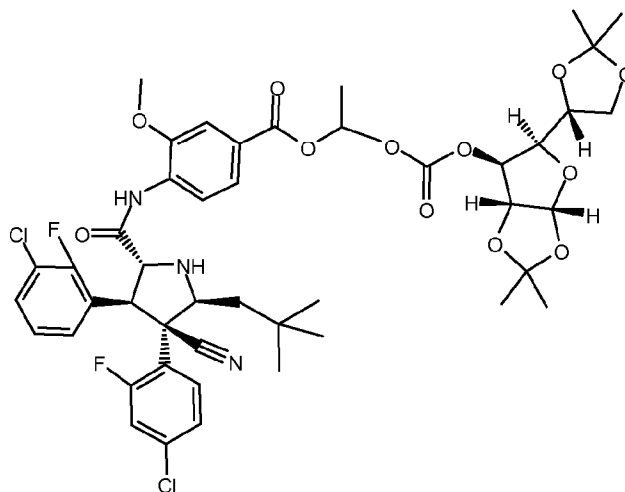


M.W. 840.51 $C_{32}H_{32}Cl_2F_2N_3O_8P.C_2F_3O_2H$

[0161] In a 25 mL pear-shaped flask, (di-tert-butoxyphosphoryloxy)methyl 4-[(2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido]-3-methoxybenzoate (20 mg, 23.8 μ mol, **Example 2**) was combined with dichloromethane (1 mL) to give a colorless solution which was cooled in an ice-water bath. After 5 min trifluoroacetic acid (744 mg, 0.5 mL, 6.53 mmol) was added over 8 min. The reaction mixture was concentrated and dried in vacuo overnight to give 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 phosphonoxyethyl ester, trifluoro-acetate salt, as off-white solids (19.5 mg, 97%).

Example 52

1-(((3aR,5R,6S,6aR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[3,2-d][1,3]dioxo1-6-yloxy)carbonyloxy)ethyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate

[0162]

M.W. 946.82 $C_{46}H_{51}Cl_2F_2N_3O_{12}$

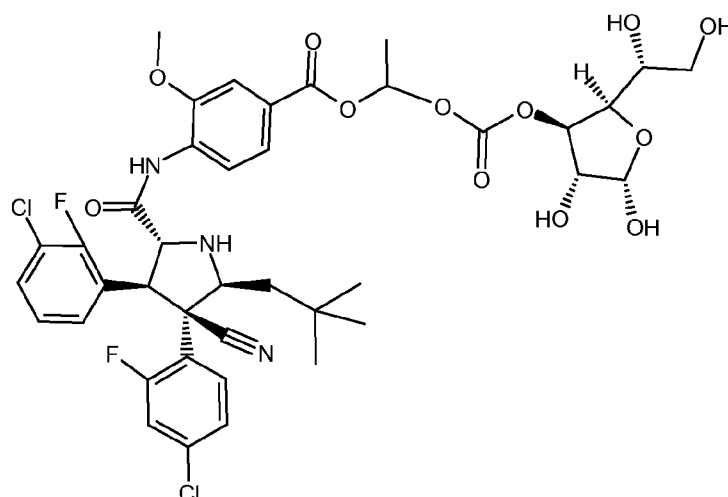
[0163] To a solution of diacetone-D-glucose (1.56 g, 6 mmol) and pyridine (1.09 g, 1.12 mL, 13.8 mmol) in methylene chloride (6 mL) at -78°C was added slowly a solution of 1-chloroethyl chloroformate (970 mg, 732 μ l, 6.78 mmol) in methylene chloride (4 mL). After addition, the reaction mixture was allowed to stir at -78°C for 1.5 h. Then the cold bath was removed and the reaction mixture was warmed up to room temperature. The reaction mixture was concentrated in vacuo and taken up in diethyl ether. The precipitate was filtered and the solid was washed thoroughly with diethyl ether. The filtrate and washing solutions were combined and concentrated to give 2.135 g of 1-chloroethyl (3aS,5S,6R,6aS)-5-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[3,2-d][1,3]dioxol-6-yl carbonate as clear light yellow thick oil, which was used directly without further purification.

[0164] To a solution of 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid (prepared as described in US20100152190A1, 100 mg, 162 μ mol) in dry dimethyl formamide (4 mL) was added cesium carbonate (185 mg, 568 μ mol). The mixture was stirred for 10 min at room temperature. The freshly made solution of 1-chloroethyl (3aS,5S,6R,6aS)-5-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[3,2-d][1,3]dioxol-6-yl carbonate (178 mg, 487 μ mol) in 4 mL of dry dimethyl formamide was added to the above mixture and stirred at room temperature overnight. It was diluted with ethyl acetate and washed with water (2x) and brine. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to give a crude, which was purified with flash chromatography (0-50% ethyl acetate in hexane over 25 min) to give an off-white solid (127 mg, 82% yield). LCMS (ES+) m/z calcd. for $C_{46}H_{51}Cl_2F_2N_3O_{12}$ [(M+H)+]: 946, found: 946.

Example 53

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-((2R,3R,4R,5S)-2-((R)-1,2-dihydroxy-ethyl)-4,5-dihydroxy-tetrahydro-furan-3-yloxy)carbonyloxy]-ethyl ester

[0165]



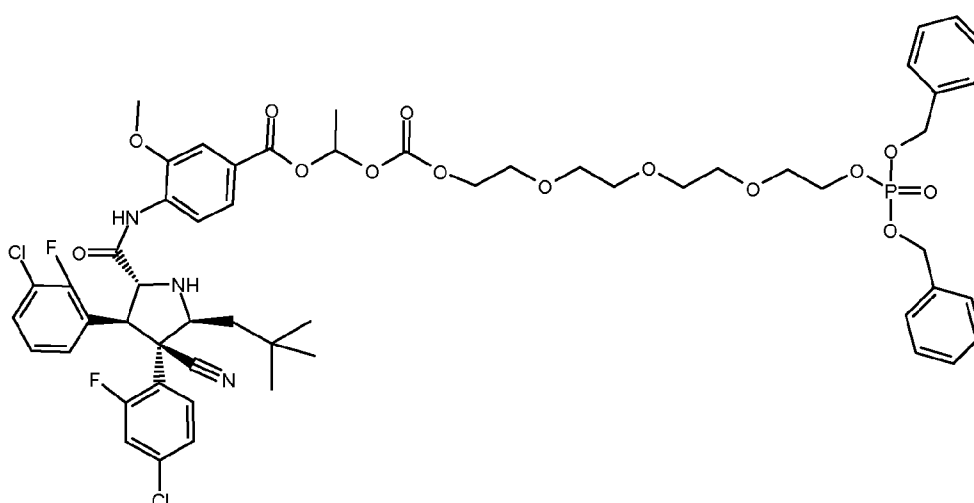
M.W. 866.69 $C_{40}H_{43}Cl_2F_2N_3O_{12}$

[0166] In a 15 mL round-bottomed flask was charged with 1-(((3aR,5R,6S,6aR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[3,2-d][1,3]dioxol-6-yloxy)carbonyloxy)ethyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate (111 mg, 117 μ mol). The mix of trifluoroacetic acid (1.48 g, 1 mL, 13.0 mmol) and water (375 mg, 375 μ L, 20.8 mmol) was added. LC-MS indicated the completion of the reaction after stirring at room temperature for 1 h. The reaction mixture was concentrated in vacuo, and the residue was reconstituted with ethyl acetate. It was washed with water (2x) and brine. The ethyl acetate layer was separated and dried over anhydrous sodium sulfate, then filtered. The filtrate was concentrated to give a crude, which was purified with flash chromatography (24 pre-packed silica gel column, eluted with ethyl acetate over 20min) to yield a white solid (24mg, 23% yield). LCMS (ES+) m/z calcd. for $C_{40}H_{43}Cl_2F_2N_3O_{12}$ [(M+H)+]: 866, found: 866.

Example 54

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-dibenzoyloxyphosphoryloxy-ethoxy)-ethoxy]-ethoxy}-ethoxycarbonyloxy)-ethyl ester

[0167]



M.W. 1140.99 $C_{56}H_{62}Cl_2F_2N_3O_{14}P$

[0168] In a 100 mL three-necked flask equipped with Argon inlet, a solution of potassium t-butoxide (750 mg, 6.69 mmol) in tetrahydrofuran (3 mL) was added to the tetraethylene glycol (5.41 g, 4.81 mL, 27.9 mmol) in anhydrous

tetrahydrofuran (30 mL) at room temperature. The mixture was stirred at room temperature for 20 min. It was cooled down to -40°C. A solution of tetrabenzyl pyrophosphate (3000 mg, 5.57 mmol) in tetrahydrofuran (20 mL) was added to the above cold mixture through a syringe. The reaction mixture was kept stirring at -40°C for 5 min.

[0169] LC-MS analysis of the reaction mixture showed a lot of unreacted tetrabenzyl pyrophosphate, and no improvement was observed after 30 min. Another fresh portion of the mixture of tetraethylene glycol and potassium tert-butoxide in tetrahydrofuran (same amounts, repeated the procedure as aforementioned) was added to the reaction mixture at -40°C. Tetrabenzyl pyrophosphate peak disappeared after 5 min. Acetic acid (5 eq) was added to quench the reaction at -40 °C. The reaction mixture was warmed up to room temperature and concentrated in vacuo. The residue was reconstituted with ethyl acetate. It was washed with water (2x) and brine. The ethyl acetate layer was dried over anhydrous sodium sulfate. The solids were filtered off, and the filtrate was concentrated to give a crude, which was purified with flash column (80 g pre-packed silica gel column, eluted with 0-10% methanol in ethyl acetate) to give 1.14 g of dibenzyl 2-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)ethyl phosphate as clear oil (50% yield). LCMS (ES+) m/z calcd. for C₂₂H₃₁O₈P [(M+H)+]: 455, found:455.

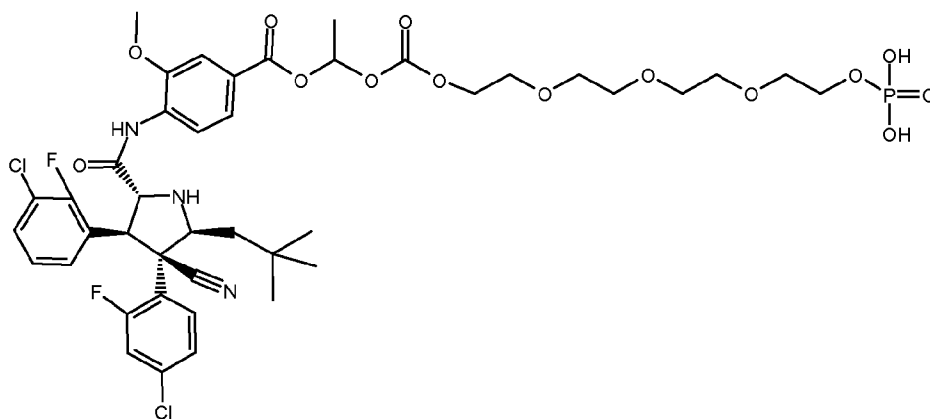
[0170] To a solution of dibenzyl 2-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)ethyl phosphate (500 mg, 1.1 mmol) and pyridine (200 mg, 205 µl, 2.53 mmol) in methylene chloride (6 mL) at -78°C was added slowly 1-chloroethyl chloroformate (178 mg, 134 µl, 1.24 mmol) in methylene chloride (2 mL). After addition, the reaction mixture was allowed to stir at -78°C for 1.5 h. Then the cold bath was removed and the reaction mixture was warmed up to room temperature. ¹H-NMR showed the completion of the reaction. The reaction mixture was concentrated in vacuo. The residue was reconstituted with diethyl ether. The solids in the ethereal solution were filtered off and washed thoroughly with diethyl ether. The filtrate and washing solutions were combined and concentrated to give carbonic acid 2-(2-{2-[2-(bis-benzyloxy-phosphoryloxy)-ethoxy]-ethoxy}-ethoxy)-ethyl ester 1-chloro-ethyl ester as clear light-yellow thick oil. The crude product was used without further purification.

[0171] To a solution of 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoic acid (prepared as described in US20100152190A1, 136mg, 221 µmol) in dry dimethyl formamide (10 mL) was added cesium carbonate (359 mg, 1.1 mmol). It was stirred at room temperature for 10 min. Carbonic acid 2-(2-{2-[2-(bis-benzyloxy-phosphoryloxy)-ethoxy]-ethoxy}-ethoxy)-ethyl ester 1-chloro-ethyl ester, the thick yellow oil got from previous step (617mg, 1.1 mmol), dissolved in 3 mL of dry dimethyl formamide was added to the above mixture and stirred at room temperature overnight. The reaction was completed as shown by LC-MS. The reaction mixture was poured into water. Then it was extracted with ethyl acetate (2x). The ethyl acetate layers were combined and washed with water and brine. It was dried over anhydrous sodium sulfate, filtered and concentrated to give a crude, which was purified with flash chromatography (30-100% ethyl acetate in hexane over 30 min) to give 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-dibenzoyloxyphosphoryloxy-ethoxy)-ethoxy]-ethoxy}-ethoxycarbonyloxy)-ethyl ester as a clear oil (102 mg, 40.5% yield). LCMS (ES+) m/z calcd. for C₅₆H₆₂Cl₂F₂N₃O₁₄P [(M+H)+]: 1140, found: 1140.

Example 55

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

[0172]



M.W. 960.73 C₄₂H₅₀Cl₂F₂N₃O₁₄P

[0173] In a 25 mL three-necked flask, 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-dibenzoyloxyphosphoryloxy-ethoxy)-ethoxy]-ethoxycarbonyloxy)-ethyl ester (100 mg, 87.6 μmol) was combined with isopropyl alcohol (5 mL) at room temperature. Then 10% palladium on carbon (46.6 mg, 43.8 μmol) was added. The flask was flushed with nitrogen, and then replaced with hydrogen. The reaction mixture was stirred at room temperature under hydrogen balloon for 30 min.

[0174] The reaction mixture was filtered through a Celite cake to remove the catalyst. The Celite cake was washed thoroughly with isopropyl alcohol. The filtrate and washing solutions were combined and concentrated to give a crude, which was purified with Gilson reverse phase high-performance liquid chromatography (50-80% gradient of acetonitrile in water over 10 min) to give 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-phosphonoxy-ethoxy)-ethoxy]-ethoxycarbonyloxy)-ethyl ester as white solids (6 mg, 7% yield). LCMS (ES+) m/z calcd. for C₄₂H₅₀Cl₂F₂N₃O₁₄P [(M+H)+]: 960, found: 960.

Example 56

In Vitro Activity Assay

[0175] The ability of the compounds to inhibit the interaction between p53 and MDM2 proteins was measured by an HTRF (homogeneous time-resolved fluorescence) assay in which recombinant GST-tagged MDM2 binds to a peptide that resembles the MDM2-interacting region of p53 (Lane et al.). Binding of GST-MDM2 protein and p53-peptide (biotinylated on its N-terminal end) is registered by the FRET (fluorescence resonance energy transfer) between Europium (Eu)-labeled anti-GST antibody and streptavidin-conjugated Allophycocyanin (APC).

[0176] Test is performed in black flat-bottom 384-well plates (Costar) in a total volume of 40 μL containing: 90 nM biotinylated peptide, 160 ng/ml GST-MDM2, 20 nM streptavidin-APC (PerkinElmerWallac), 2 nM Eu-labeled anti-GST-antibody (PerkinElmerWallac), 0.02% bovine serum albumin (BSA), 1 mM dithiothreitol (DTT) and 20 mM Tris-borate saline (TBS) buffer as follows: Add 10 μL of GST-MDM2 (640 ng/ml working solution) in reaction buffer to each well. Add 10 μL diluted compounds (1:5 dilution in reaction buffer) to each well, mix by shaking. Add 20 μL biotinylated p53 peptide (180 nM working solution) in reaction buffer to each well and mix on shaker. Incubate at 37°C for 1 h. Add 20 μL streptavidin-APC and Eu-anti-GST antibody mixture (6 nM Eu-anti-GST and 60 nM streptavidin-APC working solution) in TBS buffer with 0.02% BSA, shake at room temperature for 30 minutes and read using a TRF-capable plate reader at 665 and 615 nm (Victor 5, Perkin ElmerWallac). If not specified, the reagents were purchased from Sigma Chemical Co.

[0177] Activity data for some of the Example compounds expressed as IC₅₀:bsa:0.02% are as follows:

Example Number	IC ₅₀ (uM, with 0.02% BSA)
1	0.0296
2	0.0108
3	0.0163
4	0.0187
5	0.0104
6	0.0145
7	0.045
8	0.0536
9	0.116
10	0.0536
11 A	0.0101
11 B	0.0194
12	0.0238
13	0.0142
14	0.012
15	0.0128
16	0.0134
17	0.0117
18	0.0131

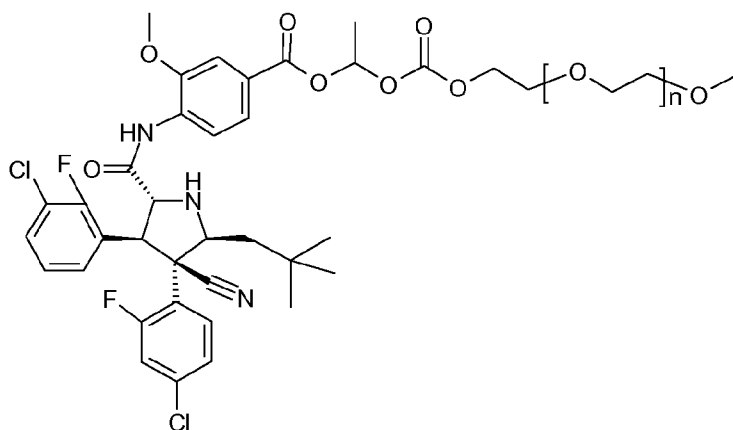
(continued)

	Example Number	IC ₅₀ (uM, with 0.02% BSA)
	19	0.0514
5	20	0.00584
	21	0.0435
	22	0.00713
	23	0.011
	24	0.00439
10	26	0.00582
	28	0.00819
	30	0.0043
	31	0.162
15	33	0.00822
	34	0.00909
	35	0.00525
	36	0.0202
	37	0.00714
20	38	0.00421
	39	0.00506
	40	0.00444
	41	0.00518
25	42	0.00509
	43	0.00569
	44	0.00486
	45	0.00463
	46	0.0408
30	47	0.0303
	48	0.00696
	49	0.0801
	50	0.0265
35	51	0.00514
	52	0.0267
	53	0.0034
	54	0.00421
40	55	0.00475

Example 57Solubility and PK Data

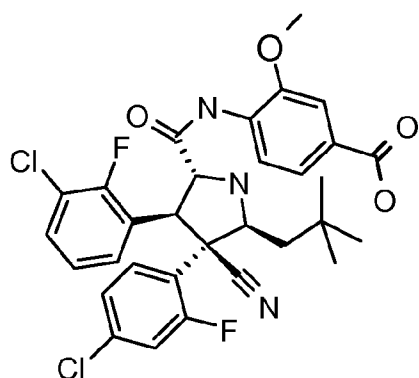
[0178] The compounds of the present invention exhibit superior solubility and PK nonvariability when compared to their non-esterified/non-amide parent compounds.

[0179] With regard to solubility, the compound of Example 37 (Compound A)



(A)

exhibits an aqueous solubility in excess of 30 mg/ml whereas its parent compound (Compound B) having the formula



(B)

has an aqueous solubility of less than 1 $\mu\text{g/ml}$.

PK data:

[0180] Compound A was administered intravenously (iv bolus) at a dose level of 1 mg/kg active drug equivalents (4.37 mg/kg prodrug). Compound A and Compound B were quantified in plasma by selective LC-MS/MS methods with lower limits of quantification of 1 ng/mL and 5 ng/mL, respectively.

[0181] The main results (Mean, N= 2) were the following:

PK data for Compound A (prodrug):

[0182] 4.37 mg/kg iv (corresponding to 1 mg/kg active parent compound) (N = 2): C_{max} = 142000 ng/mL, apparent terminal half-life $t_{1/2}$ = 2.59h, $\text{AUC}(0\text{-}\infty)$ = 108000 (ng•h)/mL, $\text{AUC}(0\text{-t}_{\text{last}})$ = 108000 (ng•h)/mL, CL = 0.709 mL/min•kg and V_{ss} = 0.0235 L/kg.

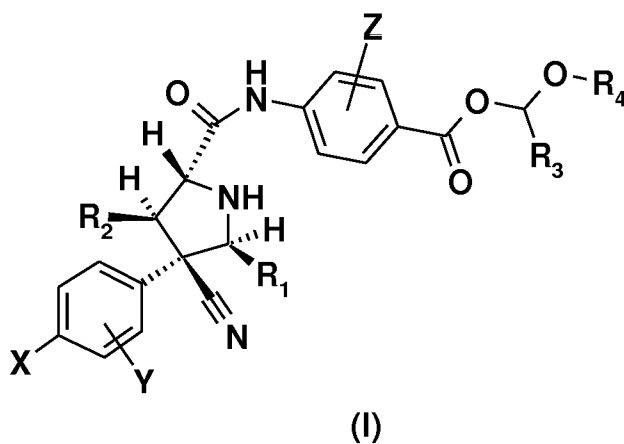
PK data for Compound B (active drug):

[0183] 4.37 mg/kg Compound A iv (corresponding to 1 mg/kg active parent compound) (N = 2): C_{max} = 4390 ng/mL, apparent terminal half-life $t_{1/2}$ = 5.07h, $\text{AUC}(0\text{-}\infty)$ = 21600 (ng•h)/mL and $\text{AUC}(0\text{-t}_{\text{last}})$ = 20900 (ng•h)/mL.

[0184] In conclusion, the prodrug showed very low plasma clearance and volume of distribution, associated with a moderate half-life. Significant conversion to active drug was achieved. Furthermore, only very little prodrug or active drug were recovered into urine.

Claims

1. A compound of the formula



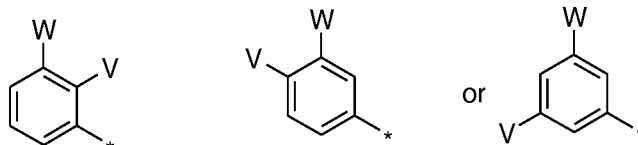
wherein

X is selected from H, F or Cl,

Y is selected from H, F or Cl,

Z is C1-6 alkoxy,

R₁ is C1-6 alkyl or C1-6 alkyl substituted with C1-6 alkoxy or N(C1-6 alkyl)₂, R₂ is a substituted phenyl selected from:

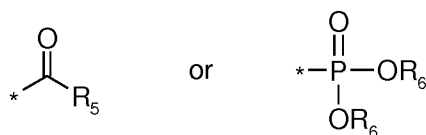


W is F, Cl or Br,

V is H or F,

R₃ is hydrogen or C1-6 alkyl,

R₄ is selected from



R₅ is selected from the group consisting of C1-6 alkyl, C1-6 alkyl substituted with C1-6 alkoxy or N(C1-6 alkyl)₂, natural and unnatural amino acids, -(OCH₂CH₂)_n-OH, -(OCH₂CH₂)_n-OCH₃, -(NCH₂CH₂)_n-OH, -(NCH₂CH₂)_n-OCH₃ and -(OCH₂CH₂)_n-OP(O)(OR₆)₂, wherein n is from 3 to 60,

R₆ is hydrogen; or

a pharmaceutically acceptable salt thereof.

2. The compound of claim 1 wherein

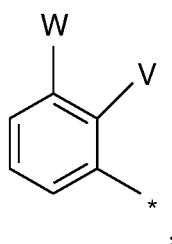
X is selected from H, F or Cl;

Y is selected from H, F or Cl;

Z is C1-6 alkoxy;

R₁ is C1-6 alkyl;

R₂ is



wherein

W is F, Cl or Br;

V is H or F;

R₃ is hydrogen or C1-6 alkyl;

R₄ is -C(O)-R₅; wherein

R₅ is selected from the group consisting of -(OCH₂CH₂)_n-OH; -(OCH₂CH₂)_n-OCH₃; and -(OCH₂CH₂)_n-OP(O)(OR₆)₂, wherein n is from 3 to 60, and R₆ is hydrogen; or

a pharmaceutically acceptable salt thereof.

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

1-(Ethyl(isopropyl)carbamoyloxy)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 di-*tert*-butoxy-phosphoryloxymethyl 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-[bis-(2-methoxy-ethyl)-carbamoyloxy]-ethyl ester,
 4-Methyl-piperazine-1-carboxylic acid 1-(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-benzoyloxy)-ethyl ester,
 1-Acetoxyethyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate,
 Rac-1-(isobutyryloxy)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)-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 acetoxymethyl ester,
 1-(Cyclohexyloxycarbonyloxy)ethyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate,
 Rac-1-(isopropoxycarbonyloxy)ethyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate,
 1-(4-((2R,3S,4R,5S)-3-(3-Chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoyloxy)ethyl morpholine-4-carboxylate and
 Morpholine-4-carboxylic acid (R)-1-(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)-ethyl ester.

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

Morpholine-4-carboxylic acid (S)-1-(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)-ethyl ester,
 Rac-1-*tert*-butyl 4-(1-(4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoyloxy)ethyl) piperazine-1,4-dicarboxylate,
 Piperazine-1-carboxylic acid 1-(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)-ethyl ester di-hydrochloride,
 Rac-1,1-Dioxo-thiomorpholine-4-carboxylic acid 1-(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)-ethyl ester.

loxy)-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-(2,2-dimethyl-[1,3]dioxolan-4-ylmethylcarbamoyloxy)-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-dihydroxy-propylcarbamoyloxy)-ethyl ester, 1-(Tetrahydro-2H-pyran-4-ylcarbamoyloxy)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 1-{2-[2-(2-methoxy-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-(2-{2-[2-(2-methoxy-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-[2-(2-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-ethoxy)-ethoxycarbonyloxy]-ethyl ester and

21-oxo-2,5,8,11,14,17,20,22-octaoxatetracosan-23-yl 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

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, ~750),

1-(2-(Benzyloxy)-2-oxoethylcarbamoyloxy)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-(((1-(4-((2R,3S,4R,5S)-3-(3-Chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoyloxy)ethoxy)carbonylamino)acetic acid,

(S)-2-[1-(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-benzoyloxy)-ethoxycarbonylamino]-pentanedioic acid,

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-((S)-1-carboxy-ethylcarbamoyloxy)-ethyl ester,

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)acetic acid,

(S)-Dibenzyl 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)-pentanedioate and

(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-ethyl ester (mPEG, average MW, ~2200),

pyl)-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-NH₂, 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-mPEG-carbonyloxy-ethyl amide (mPEG-NH₂, average MW, ~1000).

7. 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-mPEG-carbonyloxy-ethyl amide (mPEG-NH₂, 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-methyl amide (mPEG-NH₂, 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-methyl amide (mPEG-NH₂, average MW ~1000),
 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 amide (mPEG-NH₂, average MW ~550),
 (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)propanoic acid,
 Dibenzyl 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-phosphonooxy-ethoxy)-ethoxy]-ethoxy]-ethoxycarbonyloxymethyl 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-phosphonooxy-ethoxy)-ethoxy]-ethoxy]-ethoxycarbonyloxymethyl 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 phosphonooxymethyl ester; compound with trifluoro-acetic acid,
 1-(((3aR,5R,6S,6aR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[3,2-d][1,3]dioxol-6-yloxy)carbonyloxy)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 1-[(2R,3R,4R,5S)-2-((R)-1,2-dihydroxy-ethyl)-4,5-dihydroxy-tetrahydro-furan-3-yloxy]carbonyloxy-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-(2-[2-[2-(2-dibenzoyloxyphosphoryloxy-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-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-[2-[2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy]-ethoxy]-ethoxycarbonyloxy-ethyl ester,

pyl)-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-fluorophe-
 5 nyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate,
 3-Oxo-2,4,7,10,13,16,19-heptaosaicosyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluoroph-
 enyl)-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-pro-
 pyl)-pyrrolidine-2-carbonyl]-amino)-3-methoxy-benzoic acid 1-mPEG-carbonyloxy-ethyl ester,
 10 3-Oxo-2,4,7,10,13-pentaoxatetradecyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophe-
 nyl)-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-nonaohaheptacosan-26-yl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-
 15 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-pro-
 pyl)-pyrrolidine-2-carbonyl]-amino)-3-methoxy-benzoic acid 1-mPEG-carbonyloxy-ethyl amide.

9. The compound according to claim 1, 3-Oxo-2,4,7,10,13,16,19-heptaosaicosyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluor-
 20 ophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate.

10. The compound according to claim 1, 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).

11. The compound according to claim 1, 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)

12. The compound according to claim 1, 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-me-
 30 thyl ester (mPEG, average MW, ~2000).

13. The compound according to claim 1, 3-Oxo-2,4,7,10,13-pentaoxatetradecyl 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluor-
 35 ophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-neopentylpyrrolidine-2-carboxamido)-3-methoxybenzoate.

14. A compound according to any one of claims 1 to 13 for use as a medicament.

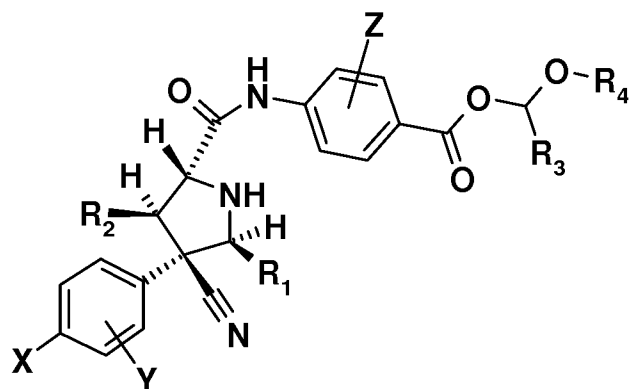
15. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 13 and a thera-
 40apeutically inert carrier.

16. The use of a compound according to any one of claims 1 to 13 for the preparation of a medicament for the treatment
 of cancer.

17. A compound according to any one of claims 1 to 13 for use in the treatment or prophylaxis of cancer.

Patentansprüche

1. Verbindung der Formel



(I)

wobei

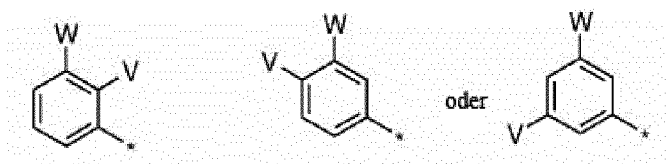
X aus H, F oder Cl ausgewählt ist,

Y aus H, F oder Cl ausgewählt ist,

Z C₁₋₆-Alkoxy ist,

R₁ C₁₋₆-Alkyl oder C₁₋₆-Alkyl substituiert mit C₁₋₆-Alkoxy oder N(C₁₋₆-Alkyl)₂ ist,

R₂ ein substituiertes Phenyl ist, ausgewählt aus:



W F, Cl oder Br ist,

V H oder F ist,

R₃ Wasserstoff oder C₁₋₆-Alkyl ist,

R₄ ausgewählt ist aus



R₅ aus der Gruppe ausgewählt ist, bestehend aus C₁₋₆-Alkyl, C₁₋₆-Alkyl substituiert mit C₁₋₆-Alkoxy oder N(C₁₋₆-Alkyl)₂, natürlichen und unnatürlichen Aminosäuren, -(OCH₂CH₂)_n-OH, - (OCH₂CH₂)_n-OCH₃, -(NCH₂CH₂)_n-OH, -(NCH₂CH₂)_n-OCH₃ und -(OCH₂CH₂)_n-OP(O)(OR₆)₂, wobei n von 3 bis 60 reicht, R₆ Wasserstoff ist; oder

ein pharmazeutisch geeignetes Salz davon.

2. Verbindung nach Anspruch 1, wobei

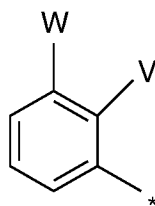
X aus H, F oder Cl ausgewählt ist,

Y aus H, F oder Cl ausgewählt ist,

Z C₁₋₆-Alkoxy ist;

R₁ C₁₋₆-Alkyl ist;

R₂



ist, wobei

W F, Cl oder Br ist,

V H oder F ist;

R₃ Wasserstoff oder C₁₋₆-Alkyl ist,

R₄ -C(O)-R₅ ist; wobei

R₅ aus der Gruppe ausgewählt ist, bestehend aus -(OCH₂CH₂)_n-OH, -(OCH₂CH₂)_n-OCH₃ und -(OCH₂CH₂)_n-OP(O)(OR₆)₂, wobei n von 3 bis 60 reicht, und R₆ Wasserstoff ist; oder

ein pharmazeutisch geeignetes Salz davon.

3. Verbindung nach Anspruch 1, ausgewählt aus der Gruppe bestehend aus

1-(Ethyl(isopropyl)carbamoyloxy)ethyl 4-((2R,3S,4R,5S)-3-(3-chlor-2-fluorphenyl)-4-(4-chlor-2-fluorphenyl)-4-cyano-5-neopentylpyrrolidin-2-carboxamido)-3-methoxybenzoat,
 4-(((2R,3S,4R,5S)-3-(3-Chlor-2-fluor-phenyl)-4-(4-chlor-2-fluor-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidin-2-carbonyl]-amino)-3-methoxy-Benzoesäure di-tert-butoxyphosphoryloxymethylester,
 4-(((2R,3S,4R,5S)-3-(3-Chlor-2-fluor-phenyl)-4-(4-chlor-2-fluor-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidin-2-carbonyl]-amino)-3-methoxy-Benzoesäure 1-[bis-(2-methoxy-ethyl)-carbamoyloxy]-ethylester,
 4-Methyl-piperazin-1-Carboxylsäure 1-(4-(((2R,3S,4R,5S)-3-(3-chlor-2-fluor-phenyl)-4-(4-chlor-2-fluor-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidin-2-carbonyl]-amino)-3-methoxy-benzoyloxy)-ethylester,
 1-Acetoxyethyl 4-((2R,3S,4R,5S)-3-(3-chlor-2-fluorphenyl)-4-(4-chlor-2-fluorphenyl)-4-cyano-5-neopentylpyrrolidin-2-carboxamido)-3-methoxybenzoat,
 Rac-1-(isobutyryloxy)ethyl 4-((2R,3S,4R,5S)-3-(3-chlor-2-fluorphenyl)-4-(4-chlor-2-fluorphenyl)-4-cyano-5-neopentylpyrrolidin-2-carboxamido)-3-methoxybenzoat,
 4-(((2R,3S,4R,5S)-4-(4-Chlor-2-fluor-phenyl)-3-(3-chlor-2-fluor-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidin-2-carbonyl]-amino)-3-methoxy-Benzoesäure-acetoxymethylester,
 1-(Cyclohexyloxycarbonyloxy)ethyl 4-((2R,3S,4R,5S)-3-(3-chlor-2-fluorphenyl)-4-(4-chlor-2-fluorphenyl)-4-cyano-5-neopentylpyrrolidin-2-carboxamido)-3-methoxybenzoat,
 Rac-1-(isopropoxycarbonyloxy)ethyl 4-((2R,3S,4R,5S)-3-(3-chlor-2-fluorphenyl)-4-(4-chlor-2-fluorphenyl)-4-cyano-5-neopentylpyrrolidin-2-carboxamido)-3-methoxybenzoat,
 1-(4-(((2R,3S,4R,5S)-3-(3-Chlor-2-fluorphenyl)-4-(4-chlor-2-fluorphenyl)-4-cyano-5-neopentylpyrrolidin-2-carboxamido)-3-methoxybenzoyloxy)ethyl morpholin-4-carboxylat und
 Morpholin-4-Carboxylsäure (R)-1-(4-(((2R,3S,4R,5S)-4-(4-chlor-2-fluor-phenyl)-3-(3-chlor-2-fluor-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidin-2-carbonyl]-amino)-3-methoxy-benzoyloxy)-ethylester.

4. Verbindung nach Anspruch 1, ausgewählt aus der Gruppe bestehend aus

Morpholin-4-Carboxylsäure (S)-1-(4-(((2R,3S,4R,5S)-4-(4-chlor-2-fluor-phenyl)-3-(3-chlor-2-fluor-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidin-2-carbonyl]-amino)-3-methoxy-benzoyloxy)-ethylester,
 Rac-1-tert-butyl 4-(1-(4-(((2R,3S,4R,5S)-3-(3-chlor-2-fluorphenyl)-4-(4-chlor-2-fluorphenyl)-4-cyano-5-neopentylpyrrolidin-2-carboxamido)-3-methoxybenzoyloxy)ethyl) piperazin-1,4-dicarboxylat,
 Piperazin-1-Carboxylsäure 1-(4-(((2R,3S,4R,5S)-4-(4-chlor-2-fluor-phenyl)-3-(3-chlor-2-fluorphenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidin-2-carbonyl]-amino)-3-methoxy-benzoyloxy)-ethylester di-hydrochlorid,
 Rac-1,1-Dioxo-thiomorpholin-4-Carboxylsäure 1-(4-(((2R,3S,4R,5S)-4-(4-chlor-2-fluor-phenyl)-3-(3-chlor-2-fluor-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidin-2-carbonyl]-amino)-3-methoxy-benzoyloxy)-ethylester,
 4-(((2R,3S,4R,5S)-4-(4-Chlor-2-fluor-phenyl)-3-(3-chlor-2-fluor-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidin-2-carbonyl]-amino)-3-methoxy-Benzoesäure 1-(2,2-dimethyl-[1,3]dioxolan-4-ylmethylcarbamoyloxy)-ethylester,
 4-(((2R,3S,4R,5S)-4-(4-Chlor-2-fluor-phenyl)-3-(3-chlor-2-fluor-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrro-

lidin-2-carbonyl]-amino}-3-methoxy-Benzoesäure 1-(2,3-dihydroxy-propylcarbamoyloxy)-ethylester,
 1-(Tetrahydro-2H-pyran-4-ylcarbamoyloxy)ethyl 4-((2R,3S,4R,5S)-3-(3-chlor-2-fluorphenyl)-4-(4-chlor-2-fluor-
 phenyl)-4-cyano-5-neopentylpyrrolidin-2-carboxamido)-3-methoxybenzoat,
 4-(((2R,3S,4R,5S)-3-(3-Chlor-2-fluor-phenyl)-4-(4-chlor-2-fluor-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrro-
 lidin-2-carbonyl]-amino)-3-methoxy-Benzoesäure 1-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxycarbonylo-
 xy}-ethylester,
 4-(((2R,3S,4R,5S)-3-(3-Chlor-2-fluor-phenyl)-4-(4-chlor-2-fluor-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrro-
 lidin-2-carbonyl]-amino)-3-methoxy-Benzoesäure 1-(2-[2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy]-ethoxy)-ethoxycarbo-
 nyloxy)-ethylester,
 4-(((2R,3S,4R,5S)-3-(3-Chlor-2-fluor-phenyl)-4-(4-chlor-2-fluor-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrro-
 lidin-2-carbonyl]-amino)-3-methoxy-Benzoesäure 1-[2-(2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy)-ethoxy]-etho-
 xy)-ethoxycarbonyloxy]-ethylester und
 21-oxo-2,5, 8,11,14,17,20,22-Octaoxatetracosan-23-yl 4-((2R,3S,4R,5S)-3-(3-chlor-2-fluorphenyl)-4-(4-chlor-
 2-fluorphenyl)-4-cyano-5-neopentylpyrrolidin-2-carboxamido)-3-methoxybenzoat.

5. Verbindung nach Anspruch 1, ausgewählt aus der Gruppe bestehend aus

4-(((2R,3S,4R,5S)-3-(3-Chlor-2-fluor-phenyl)-4-(4-chlor-2-fluor-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrro-
 lidin-2-carbonyl]-amino)-3-methoxy-Benzoesäure 1-mPEG-carbonyloxy-ethylester (mPEG, durchschnittliches
 MG, ~750),
 1-(2-(Benzoyloxy)-2-oxoethylcarbamoyloxy)ethyl 4-((2R,3S,4R,5S)-3-(3-chlor-2-fluorphenyl)-4-(4-chlor-2-fluor-
 phenyl)-4-cyano-5-neopentylpyrrolidin-2-carboxamido)-3-methoxybenzoat,
 2-(((1-(4-((2R,3S,4R,5S)-3-(3-Chlor-2-fluorphenyl)-4-(4-chlor-2-fluorphenyl)-4-cyano-5-neopentylpyrrolidin-2-
 carboxamido)-3-methoxybenzoyloxy)ethoxy)carbonylamino)Essigsäure,
 (S)-2-[1-(4-(((2R,3S,4R,5S)-3-(3-Chlor-2-fluor-phenyl)-4-(4-chlor-2-fluor-phenyl)-4-cyano-5-(2,2-dimethyl-pro-
 pyl)-pyrrolidin-2-carbonyl]-amino)-3-methoxy-benzoyloxy)-ethoxycarbonylamino]-Pentandisäure,
 4-(((2R,3S,4R,5S)-3-(3-Chlor-2-fluor-phenyl)-4-(4-chlor-2-fluor-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrro-
 lidin-2-carbonyl]-amino)-3-methoxy-Benzoesäure 1-((S)-1-carboxy-ethylcarbamoyloxy)-ethylester,
 2-(((4-((2R,3S,4R,5S)-3-(3-Chlor-2-fluorphenyl)-4-(4-chlor-2-fluorphenyl)-4-cyano-5-neopentylpyrrolidin-2-
 carboxamido)-3-methoxybenzoyloxy)methoxy)-carbonylamino)Essigsäure,
 (S)-Dibenzyl 2-(((4-((2R,3S,4R,5S)-3-(3-chlor-2-fluorphenyl)-4-(4-chlor-2-fluorphenyl)-4-cyano-5-neopentyl-
 pyrrolidin-2-carboxamido)-3-methoxybenzoyloxy)methoxy)carbonylamino)-pentandioat und
 (S)-2-(((4-((2R,3S,4R,5S)-3-(3-Chlor-2-fluorphenyl)-4-(4-chlor-2-fluorphenyl)-4-cyano-5-neopentylpyrrolidin-
 2-carboxamido)-3-methoxybenzoyloxy) methoxy)carbonylamino)Pentandisäure.

6. Verbindung nach Anspruch 1, ausgewählt aus der Gruppe bestehend aus

15-Methyl-12-oxo-2,5,8,11,13-pentaoxahexadecan-14-yl 4-((2R,3S,4R,5S)-3-(3-chlor-2-fluorphenyl)-4-(4-
 chlor-2-fluorphenyl)-4-cyano-5-neopentylpyrrolidin-2-carboxamido)-3-methoxybenzoat,
 3-Oxo-2,4,7,10,13-pentaoxatetradecyl 4-((2R,3S,4R,5S)-3-(3-chlor-2-fluorphenyl)-4-(4-chlor-2-fluorphenyl)-4-
 cyano-5-neopentylpyrrolidin-2-carboxamido)-3-methoxybenzoat,
 3-Oxo-2,4,7,10,13,16,19-heptaoxaicosyl 4-((2R,3S,4R,5S)-3-(3-chlor-2-fluorphenyl)-4-(4-chlor-2-fluorphenyl)-
 4-cyano-5-neopentylpyrrolidin-2-carboxamido)-3-methoxybenzoat,
 4-(((2R,3S,4R,5S)-3-(3-Chlor-2-fluor-phenyl)-4-(4-chlor-2-fluor-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrro-
 lidin-2-carbonyl]-amino)-3-methoxy-Benzoesäure 1-mPEG-carbonyloxy-methylester (mPEG, durchschnittli-
 ches MG, ~750),
 4-(((2R,3S,4R,5S)-3-(3-Chlor-2-fluor-phenyl)-4-(4-chlor-2-fluor-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrro-
 lidin-2-carbonyl]-amino)-3-methoxy-Benzoesäure 1-mPEG-carbonyloxy-ethylester (mPEG, durchschnittliches
 MG, ~2000),
 4-(((2R,3S,4R,5S)-3-(3-Chlor-2-fluor-phenyl)-4-(4-chlor-2-fluor-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrro-
 lidin-2-carbonyl]-amino)-3-methoxy-Benzoesäure 1-mPEG-carbonyloxy-ethylester (mPEG, durchschnittliches
 MG, ~2200),
 4-(((2R,3S,4R,5S)-3-(3-Chlor-2-fluor-phenyl)-4-(4-chlor-2-fluor-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrro-
 lidin-2-carbonyl]-amino)-3-methoxy-Benzoesäure 1-mPEG-carbonyloxy-methylester (mPEG, durchschnittli-
 ches MG, ~2000),
 3-Oxo-2,4,7,10,13-pentaoxatetradecyl 4-((2R,3S,4R,5S)-3-(3-chlor-2-fluorphenyl)-4-(4-chlor-2-fluorphenyl)-4-
 cyano-5-neopentylpyrrolidin-2-carboxamido)-3-methoxybenzoat,
 27-Oxo-2,5,8,11,14,17,20,23,26,28-decaoxatriacontan-29-yl 4-((2R,3S,4R,5S)-3-(3-chlor-2-fluorphenyl)-4-(4-

chlor-2-fluorphenyl)-4-cyano-5-neopentylpyrrolidin-2-carboxamido)-3-methoxybenzoat,
 24-Oxo-2,5,8,11,14,17,20,23,25-nonaohaheptacosan-26-yl 4-((2R,3S,4R,5S)-3-(3-chlor-2-fluorphenyl)-4-(4-chlor-2-fluorphenyl)-4-cyano-5-neopentylpyrrolidin-2-carboxamido)-3-methoxybenzoat,
 4-(((2R,3S,4R,5S)-3-(3-Chlor-2-fluor-phenyl)-4-(4-chlor-2-fluor-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrro-
 lidin-2-carbonyl]-amino)-3-methoxy-Benzoesäure 1-mPEG-carbonyloxy-ethylamid (mPEG-NH₂, durchschnitt-
 liches MG, ~550) und
 4-(((2R,3S,4R,5S)-3-(3-Chlor-2-fluor-phenyl)-4-(4-chlor-2-fluor-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrro-
 lidin-2-carbonyl]-amino)-3-methoxy-Benzoesäure 1-mPEG-carbonyloxy-ethylamid (mPEG-NH₂, durchschnitt-
 liches MG, ~1000).

7. Verbindung nach Anspruch 1, ausgewählt aus der Gruppe bestehend aus

4-(((2R,3S,4R,5S)-3-(3-Chlor-2-fluor-phenyl)-4-(4-chlor-2-fluor-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrro-
 lidin-2-carbonyl]-amino)-3-methoxy-Benzoesäure 1-mPEG-carbonyloxy-ethylamid (mPEG-NH₂, durchschnitt-
 liches MG ~2000),
 4-(((2R,3S,4R,5S)-3-(3-Chlor-2-fluor-phenyl)-4-(4-chlor-2-fluor-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrro-
 lidin-2-carbonyl]-amino)-3-methoxy-Benzoesäure 1-mPEG-carbonyloxy-methylamid (mPEG-NH₂, durch-
 schnittliches MG ~2000),
 4-(((2R,3S,4R,5S)-3-(3-Chlor-2-fluor-phenyl)-4-(4-chlor-2-fluor-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrro-
 lidin-2-carbonyl]-amino)-3-methoxy-Benzoesäure 1-mPEG-carbonyloxy-methylamid (mPEG-NH₂, durch-
 schnittliches MG ~1000),
 4-(((2R,3S,4R,5S)-3-(3-Chlor-2-fluor-phenyl)-4-(4-chlor-2-fluor-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrro-
 lidin-2-carbonyl]-amino)-3-methoxy-Benzoesäure 1-mPEG-carbonyloxy-methylamid (mPEG-NH₂, durch-
 schnittliches MG ~550),
 (S)-2-(((4-((2R,3S,4R,5S)-3-(3-Chlor-2-fluorphenyl)-4-(4-chlor-2-fluorphenyl)-4-cyano-5-neopentylpyrrolidin-
 2-carboxamido)-3-methoxybenzoyloxy)methoxy)carbonylamino)Propansäure,
 Dibenzyl 4-(((2R,3S,4R,5S)-4-(4-Chlor-2-fluor-phenyl)-3-(3-chlor-2-fluor-phenyl)-4-cyano-5-(2,2-dimethyl-pro-
 pyl)-pyrrolidin-2-carbonyl]-amino)-3-methoxy-Benzoesäure 2-{2-[2-(2-phosphonoxy-ethoxy)-ethoxy]-ethoxy}-
 ethoxycarbonyloxymethylester,
 4-(((2R,3S,4R,5S)-4-(4-Chlor-2-fluor-phenyl)-3-(3-chlor-2-fluor-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrro-
 lidin-2-carbonyl]-amino)-3-methoxy-Benzoesäure 2-{2-[2-(2-phosphonoxy-ethoxy)-ethoxy]-ethoxy}-ethoxycar-
 bonylloxymethylester,
 4-(((2R,3S,4R,5S)-3-(3-Chlor-2-fluor-phenyl)-4-(4-chlor-2-fluor-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrro-
 lidin-2-carbonyl]-amino)-3-methoxy-Benzoesäure phosphonoxymethylester; Verbindung mit Trifluoressigsäu-
 re,
 1-(((3aR,5R,6S,6aR)-5-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[3,2-d][1,3]dioxol-6-
 yloxy)carbonyloxy)ethyl 4-((2R,3S,4R,5S)-3-(3-chlor-2-fluorphenyl)-4-(4-chlor-2-fluorphenyl)-4-cyano-5-neo-
 pentylpyrrolidin-2-carboxamido)-3-methoxybenzoat,
 4-(((2R,3S,4R,5S)-3-(3-Chlor-2-fluor-phenyl)-4-(4-chlor-2-fluor-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrro-
 lidin-2-carbonyl]-amino)-3-methoxy-Benzoesäure 1-[(2R,3R,4R,5S)-2-((R)-1,2-dihydroxy-ethyl)-4,5-dihydro-
 xy-tetrahydro-furan-3-yloxy]carbonyloxy]-ethylester,
 4-(((2R,3S,4R,5S)-3-(3-Chlor-2-fluor-phenyl)-4-(4-chlor-2-fluor-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrro-
 lidin-2-carbonyl]-amino)-3-methoxy-Benzoesäure 1-(2-{2-[2-(2-dibenzylloxylphosphoryloxy-ethoxy)-ethoxy]-
 ethoxy}-ethoxycarbonyloxy)-ethylester und
 4-(((2R,3S,4R,5S)-3-(3-Chlor-2-fluor-phenyl)-4-(4-chlor-2-fluor-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrro-
 lidin-2-carbonyl]-amino)-3-methoxy-Benzoesäure 1-(2-{2-[2-(2-phosphonoxy-ethoxy)-ethoxy]-ethoxy}-ethoxy)-ethoxycarbonyloxy)-ethylester.

8. Verbindung nach Anspruch 1, ausgewählt aus der Gruppe bestehend aus

4-(((2R,3S,4R,5S)-3-(3-Chlor-2-fluor-phenyl)-4-(4-chlor-2-fluor-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrro-
 lidin-2-carbonyl]-amino)-3-methoxy-Benzoesäure 1-[2-(2-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-ethoxy)-ethoxy]-ethoxycarbonyloxy]-ethylester,
 4-(((2R,3S,4R,5S)-3-(3-Chlor-2-fluor-phenyl)-4-(4-chlor-2-fluor-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrro-
 lidin-2-carbonyl]-amino)-3-methoxy-Benzoesäure 1-mPEG-carbonyloxy-ethylester,
 15-methyl-12-oxo-2,5,8,11,13-pentaohexadecan-14-yl 4-((2R,3S,4R,5S)-3-(3-chlor-2-fluorphenyl)-4-(4-chlor-2-fluorphenyl)-4-cyano-5-neopentylpyrrolidin-2-carboxamido)-3-methoxybenzoat,
 3-Oxo-2,4,7,10,13-pentaohexadecan-14-yl 4-((2R,3S,4R,5S)-3-(3-chlor-2-fluorphenyl)-4-(4-chlor-2-fluorphenyl)-4-

cyano-5-neopentylpyrrolidin-2-carboxamido)-3-methoxybenzoat,
 3-Oxo-2,4,7,10,13,16,19-heptaosaicosyl 4-((2R,3S,4R,5S)-3-(3-chlor-2-fluorphenyl)-4-(4-chlor-2-fluorphenyl)-
 4-cyano-5-neopentylpyrrolidin-2-carboxamido)-3-methoxybenzoat,
 4-(((2R,3S,4R,5S)-3-(3-Chlor-2-fluor-phenyl)-4-(4-chlor-2-fluor-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrro-
 lidin-2-carbonyl]-amino)-3-methoxy-Benzoesäure 1-mPEG-carbonyloxy-ethylester,
 3-Oxo-2,4,7,10,13-pentaoxatetradecyl 4-((2R,3S,4R,5S)-3-(3-chlor-2-fluorphenyl)-4-(4-chlor-2-fluorphenyl)-4-
 cyano-5-neopentylpyrrolidin-2-carboxamido)-3-methoxybenzoat,
 27-Oxo-2,5,8,11,14,17,20,23,26,28-decaoxatriacontan-29-yl 4-((2R,3S,4R,5S)-3-(3-chlor-2-fluorphenyl)-4-(4-
 chlor-2-fluorphenyl)-4-cyano-5-neopentylpyrrolidin-2-carboxamido)-3-methoxybenzoat,
 24-Oxo-2,5,8,11,14,17,20,23,25-nonaohaheptacosan-26-yl 4-((2R,3S,4R,5S)-3-(3-chlor-2-fluorphenyl)-4-(4-
 chlor-2-fluorphenyl)-4-cyano-5-neopentylpyrrolidin-2-carboxamido)-3-methoxybenzoat, und
 4-(((2R,3S,4R,5S)-3-(3-Chlor-2-fluor-phenyl)-4-(4-chlor-2-fluor-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrro-
 lidin-2-carbonyl]-amino)-3-methoxy-Benzoesäure 1-mPEG-carbonyloxy-ethylamid.

9. Verbindung nach Anspruch 1, 3-Oxo-2,4,7,10,13,16,19-heptaosaicosyl 4-((2R,3S,4R,5S)-3-(3-chlor-2-fluorphenyl)-
 4-(4-chlor-2-fluorphenyl)-4-cyano-5-neopentylpyrrolidin-2-carboxamido)-3-methoxybenzoat.

10. Verbindung nach Anspruch 1, 4-(((2R,3S,4R,5S)-3-(3-Chlor-2-fluor-phenyl)-4-(4-chlor-2-fluor-phenyl)-4-cyano-
 5-(2,2-dimethyl-propyl)-pyrrolidin-2-carbonyl]-amino)-3-methoxy-Benzoesäure 1-mPEG-carbonyloxy-ethylester
 (mPEG, durchschnittliches MG, ~2000).

11. Verbindung nach Anspruch 1, 4-(((2R,3S,4R,5S)-3-(3-Chlor-2-fluor-phenyl)-4-(4-chlor-2-fluor-phenyl)-4-cyano-
 5-(2,2-dimethyl-propyl)-pyrrolidin-2-carbonyl]-amino)-3-methoxy-Benzoesäure 1-mPEG-carbonyloxy-ethylester
 (mPEG, durchschnittliches MG, ~2200).

12. Verbindung nach Anspruch 1, 4-(((2R,3S,4R,5S)-3-(3-Chlor-2-fluor-phenyl)-4-(4-chlor-2-fluor-phenyl)-4-cyano-
 5-(2,2-dimethyl-propyl)-pyrrolidin-2-carbonyl]-amino)-3-methoxy-Benzoesäure 1-mPEG-carbonyloxy-methylester
 (mPEG, durchschnittliches MG, ~2000).

13. Verbindung nach Anspruch 1, 3-Oxo-2,4,7,10,13-pentaoxatetradecyl 4-((2R,3S,4R,5S)-3-(3-chlor-2-fluorphenyl)-
 4-(4-chlor-2-fluorphenyl)-4-cyano-5-neopentylpyrrolidin-2-carboxamido)-3-methoxybenzoat.

14. Verbindung nach einem der Ansprüche 1 bis 13 zur Verwendung als Arzneimittel.

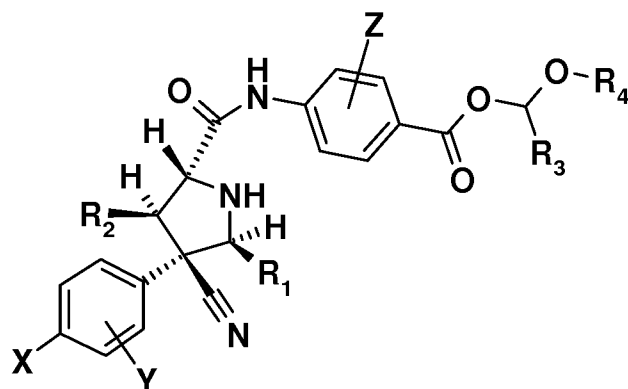
15. Pharmazeutische Zusammensetzung, umfassend eine Verbindung nach einem der Ansprüche 1 bis 13 und einen
 therapeutisch inerten Träger.

16. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 13 für die Herstellung eines Arzneimittels für die
 Behandlung von Krebs.

17. Verbindung nach einem der Ansprüche 1 bis 13 zur Behandlung oder Prophylaxe von Krebs.

Revendications

1. Composé de formule



(I)

dans laquelle

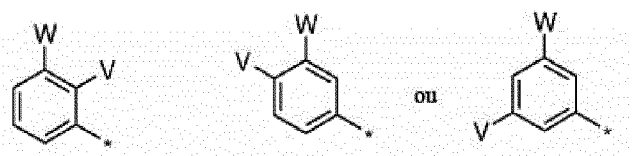
X est choisi parmi H, F ou Cl,

Y est choisi parmi H, F ou Cl,

Z représente un groupe alcoxy en C₁-C₆,

R₁ représente un groupe alkyle en C₁-C₆ ou alkyle en C₁-C₆ substitué par un groupe alcoxy en C₁-C₆ ou N(alkyle en C₁-C₆)₂,

R₂ est un phényle substitué choisi parmi :



W représente F, Cl ou Br,

V représente H ou F,

R₃ représente l'hydrogène ou un groupe alkyle en C₁-C₆,

R₄ est choisi parmi



R₅ est choisi dans le groupe constitué par un groupe alkyle en C₁-C₆, alkyle en C₁-C₆ substitué par un groupe alcoxy en C₁-C₆ ou N(alkyle en C₁-C₆)₂, des acides aminés naturels et non naturels, -(OCH₂CH₂)_n-OH, -(OCH₂CH₂)_n-OCH₃, -(NCH₂CH₂)_n-OH, -(NCH₂CH₂)_n-OCH₃ et -(OCH₂CH₂)_n-OP(O)(OR₆)₂, n valant 3 à 60, R₆ représente l'hydrogène ; ou

sel pharmaceutiquement acceptable de celui-ci.

2. Composé de formule 1, dans lequel

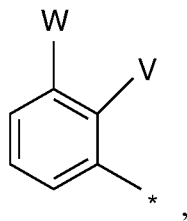
X est choisi parmi H, F ou Cl,

Y est choisi parmi H, F ou Cl,

Z représente un groupe alcoxy en C₁-C₆ ;

R₁ représente un groupe alkyle en C₁-C₆ ;

R₂ représente



dans lequel

W représente F, Cl ou Br,

V représente H ou F ;

R₃ représente l'hydrogène ou un groupe alkyle en C₁-C₆,

R₄ représente -C(O)-R₅; dans lequel

R₅ est choisi dans le groupe constitué par -(OCH₂CH₂)_n-OH, -(OCH₂CH₂)_n-OCH₃ et -(OCH₂CH₂)_n-OP(O)(OR₆)₂, n valant 3 à 60 et R₆ représentant l'hydrogène ; ou

sel pharmaceutiquement acceptable de celui-ci.

3. Composé selon la revendication 1, choisi dans le groupe constitué par :

le 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophényl)-4-(4-chloro-2-fluorophényl)-4-cyano-5-néopentylpyrrolidine-2-carboxamido)-3-méthoxybenzoate de 1-(éthyl(isopropyl)carbamoyloxy)éthyle,

l'ester di-*tert*-butoxy-phosphoryloxyméthyllique de l'acide 4-(((2R,3S,4R,5S)-3-(3-chloro-2-fluoro-phényl)-4-(4-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carbonyl]-amino)-3-méthoxy-benzoïque, l'ester 1-[bis-(2-méthoxy-éthyl)-carbamoyloxy]-éthyllique de l'acide 4-(((2R,3S,4R,5S)-3-(3-chloro-2-fluoro-phényl)-4-(4-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carbonyl]-amino)-3-méthoxy-benzoïque,

l'ester 1-(4-(((2R,3S,4R,5S)-3-(3-chloro-2-fluoro-phényl)-4-(4-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carbonyl]-amino)-3-méthoxy-benzoyloxy)-éthyllique de l'acide 4-méthyl-pipérazine-1-carboxylique,

le 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophényl)-4-(4-chloro-2-fluorophényl)-4-cyano-5-néopentylpyrrolidine-2-carboxamido)-3-méthoxybenzoate de 1-acétoxyéthyle,

le 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophényl)-4-(4-chloro-2-fluorophényl)-4-cyano-5-néopentylpyrrolidine-2-carboxamido)-3-méthoxybenzoate de Rac-1-(isobutyryloxy)éthyle,

l'ester acétoxyméthyllique de l'acide 4-(((2R,3S,4R,5S)-4-(4-chloro-2-fluoro-phényl)-3-(3-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carbonyl]-amino)-3-méthoxy-benzoïque,

le 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophényl)-4-(4-chloro-2-fluorophényl)-4-cyano-5-néopentylpyrrolidine-2-carboxamido)-3-méthoxybenzoate de 1-(cyclohexyloxycarbonyloxy)éthyle,

le 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophényl)-4-(4-chloro-2-fluorophényl)-4-cyano-5-néopentylpyrrolidine-2-carboxamido)-3-méthoxybenzoate de Rac-1-(isopropoxycarbonyloxy)éthyle,

le morpholine-4-carboxylate de 1-(4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophényl)-4-(4-chloro-2-fluorophényl)-4-cyano-5-néopentylpyrrolidine-2-carboxamido)-3-méthoxybenzoyloxy)éthyle et

l'ester (R)-1-(4-(((2R,3S,4R,5S)-4-(4-chloro-2-fluoro-phényl)-3-(3-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carbonyl]-amino)-3-méthoxy-benzoyloxy)-éthyllique de l'acide morpholine-4-carboxylique.

4. Composé selon la revendication 1, choisi dans le groupe constitué par :

l'ester (S)-1-(4-(((2R,3S,4R,5S)-4-(4-chloro-2-fluoro-phényl)-3-(3-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carbonyl]-amino)-3-méthoxy-benzoyloxy)-éthyllique de l'acide morpholine-4-carboxylique,

le 4-(1-(4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophényl)-4-(4-chloro-2-fluorophényl)-4-cyano-5-néopentylpyrrolidine-2-carboxamido)-3-méthoxybenzoyloxy)éthyl)pipérazine-1,4-dicarboxylate de Rac-1-*tert*-butyle,

le dichlorhydrate de l'ester 1-(4-(((2R,3S,4R,5S)-4-(4-chloro-2-fluoro-phényl)-3-(3-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carbonyl]-amino)-3-méthoxy-benzoyloxy)-éthyllique de l'acide pipérazine-1-carboxylique,

l'ester 1-(4-(((2R,3S,4R,5S)-4-(4-chloro-2-fluoro-phényl)-3-(3-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carbonyl]-amino)-3-méthoxy-benzoyloxy)-éthyllique de l'acide morpholine-4-carboxylique.

thyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-méthoxy-benzoyloxy)-éthylque de l'acide Rac-1,1-dioxo-thiomorpholine-4-carboxylique,
 l'ester 1-(2,2-diméthyl-[1,3]dioxolan-4-ylméthylcarbamoxyloxy)-éthylque de l'acide 4-[[[(2R,3S,4R,5S)-4-(4-chloro-2-fluoro-phényl)-3-(3-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carbo-
 5 nyl]-amino}-3-méthoxy-benzoïque,
 l'ester 1-(2,3-dihydroxy-propylcarbamoxyloxy)-éthylque de l'acide 4-[[[(2R,3S,4R,5S)-4-(4-chloro-2-fluoro-phényl)-3-(3-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-méthoxy-benzoïque,
 le 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophényl)-4-(4-chloro-2-fluorophényl)-4-cyano-5-néopentylpyrrolidine-
 10 2-carboxamido)-3-méthoxybenzoate de 1-(tétrahydro-2H-pyran-4-ylcarbamoxyloxy)éthyle,
 l'ester 1-[2-[2-(2-méthoxy-éthoxy)-éthoxy]-éthoxycarbonyloxy]-éthylque de l'acide 4-[[[(2R,3S,4R,5S)-3-(3-chloro-2-fluoro-phényl)-4-(4-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carbo-
 nyl]-amino}-3-méthoxy-benzoïque,
 l'ester 1-(2-[2-[2-(2-méthoxy-éthoxy)-éthoxy]-éthoxy]-éthoxycarbonyloxy)-éthylque de l'acide
 15 4-[[[(2R,3S,4R,5S)-3-(3-chloro-2-fluoro-phényl)-4-(4-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-méthoxy-benzoïque,
 l'ester 1-[2-(2-[2-(2-méthoxy-éthoxy)-éthoxy]-éthoxy)-éthoxy]-éthoxycarbonyloxy]-éthylque de l'acide
 4-[[[(2R,3S,4R,5S)-3-(3-chloro-2-fluoro-phényl)-4-(4-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-méthoxy-benzoïque et
 20 le 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophényl)-4-(4-chloro-2-fluorophényl)-4-cyano-5-néopentylpyrrolidine-2-carboxamido)-3-méthoxybenzoate de 21-oxo-2,5,8,11,14,17,20,22-octaoxatétracosan-23-yle.

5. Composé selon la revendication 1, choisi dans le groupe constitué par :

l'ester 1-mPEG-carbonyloxy-éthylque de l'acide 4-[[[(2R,3S,4R,5S)-3-(3-chloro-2-fluoro-phényl)-4-(4-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-méthoxy-benzoïque (mPEG, poids moléculaire moyen, environ 750),
 le 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophényl)-4-(4-chloro-2-fluorophényl)-4-cyano-5-néopentylpyrrolidine-2-carboxamido)-3-méthoxybenzoate de 1-(2-(benzyloxy)-2-oxoéthylcarbamoxyloxy)éthyle,
 30 l'acide 2-((1-(4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophényl)-4-(4-chloro-2-fluorophényl)-4-cyano-5-néopentylpyrrolidine-2-carboxamido)-3-méthoxybenzoyloxy)éthoxy)carbonylamino)acétique,
 l'acide (S)-2-[1-(4-((2R,3S,4R,5S)-3-(3-chloro-2-fluoro-phényl)-4-(4-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carbonyl]-amino)-3-méthoxy-benzoyloxy)-éthoxycarbonylamino]-pentanedioïque,
 35 l'ester 1-((S)-1-carboxy-éthylcarbamoxyloxy)-éthylque de l'acide 4-[[[(2R,3S,4R,5S)-3-(3-chloro-2-fluoro-phényl)-4-(4-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-méthoxy-benzoïque,
 l'acide 2-(((4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophényl)-4-(4-chloro-2-fluorophényl)-4-cyano-5-néopentylpyrrolidine-2-carboxamido)-3-méthoxybenzoyloxy)méthoxy)-carbonylamino)acétique,
 40 le 2-(((4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophényl)-4-(4-chloro-2-fluorophényl)-4-cyano-5-néopentylpyrrolidine-2-carboxamido)-3-méthoxybenzoyloxy)méthoxy)carbonylamino)-pentanedioate de (S)-dibenzyle et
 l'acide (S)-2-(((4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophényl)-4-(4-chloro-2-fluorophényl)-4-cyano-5-néopentylpyrrolidine-2-carboxamido)-3-méthoxybenzoyloxy) méthoxy)carbonylamino)pentanedioïque.

6. Composé selon la revendication 1, choisi dans le groupe constitué par :

le 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophényl)-4-(4-chloro-2-fluorophényl)-4-cyano-5-néopentylpyrrolidine-2-carboxamido)-3-méthoxybenzoate de 15-méthyl-12-oxo-2,5,8,11,13-pentaoxahexadécane-14-yle,
 le 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophényl)-4-(4-chloro-2-fluorophényl)-4-cyano-5-néopentylpyrrolidine-2-carboxamido)-3-méthoxybenzoate de 3-oxo-2,4,7,10,13-pentaoxatétradécyle,
 50 le 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophényl)-4-(4-chloro-2-fluorophényl)-4-cyano-5-néopentylpyrrolidine-2-carboxamido)-3-méthoxybenzoate de 3-oxo-2,4,7,10,13,16,19-heptaoxaicosyle,
 l'ester 1-mPEG-carbonyloxy-méthylque de l'acide 4-[[[(2R,3S,4R,5S)-3-(3-chloro-2-fluoro-phényl)-4-(4-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-méthoxy-benzoïque
 55 (mPEG, poids moléculaire moyen, environ 750),
 l'ester 1-mPEG-carbonyloxy-éthylque de l'acide 4-[[[(2R,3S,4R,5S)-3-(3-chloro-2-fluoro-phényl)-4-(4-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-méthoxy-benzoïque (mPEG, poids moléculaire moyen, environ 2000),

l'ester 1-mPEG-carboxyloxy-éthylrique de l'acide 4-[(2R,3S,4R,5S)-3-(3-chloro-2-fluoro-phényl)-4-(4-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carboxyl]-amino-3-méthoxy-benzoïque (mPEG, poids moléculaire moyen, environ 2200),

l'ester 1-mPEG-carboxyloxy-méthylrique de l'acide 4-[(2R,3S,4R,5S)-3-(3-chloro-2-fluoro-phényl)-4-(4-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carboxyl]-amino-3-méthoxy-benzoïque (mPEG, poids moléculaire moyen, environ 2000),

le 4-[(2R,3S,4R,5S)-3-(3-chloro-2-fluorophényl)-4-(4-chloro-2-fluorophényl)-4-cyano-5-néopentylpyrrolidine-2-carboxamido]-3-méthoxybenzoate de 3-oxo-2,4,7,10,13-pentaoxatétradécyle,

le 4-[(2R,3S,4R,5S)-3-(3-chloro-2-fluorophényl)-4-(4-chloro-2-fluorophényl)-4-cyano-5-néopentylpyrrolidine-2-carboxamido]-3-méthoxybenzoate de 27-oxo-2,5,8,11,14,17,20,23,26,28-décaoxatriacontan-29-yle,

le 4-[(2R,3S,4R,5S)-3-(3-chloro-2-fluorophényl)-4-(4-chloro-2-fluorophényl)-4-cyano-5-néopentylpyrrolidine-2-carboxamido]-3-méthoxybenzoate de 24-oxo-2,5,8,11,14,17,20,23,25-nonaoxaheptacosan-26-yle,

le 1-mPEG-carboxyloxy-éthylamide de l'acide 4-[(2R,3S,4R,5S)-3-(3-chloro-2-fluoro-phényl)-4-(4-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carboxyl]-amino-3-méthoxy-benzoïque (mPEG-NH₂, poids moléculaire moyen, environ 550) et

le 1-mPEG-carboxyloxy-éthylamide de l'acide 4-[(2R,3S,4R,5S)-3-(3-chloro-2-fluoro-phényl)-4-(4-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carboxyl]-amino-3-méthoxy-benzoïque (mPEG-NH₂, poids moléculaire moyen, environ 1000).

7. Composé selon la revendication 1, choisi dans le groupe constitué par :

le 1-mPEG-carboxyloxy-éthylamide de l'acide 4-[(2R,3S,4R,5S)-3-(3-chloro-2-fluoro-phényl)-4-(4-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carboxyl]-amino-3-méthoxy-benzoïque (mPEG-NH₂, poids moléculaire moyen environ 2000),

le 1-mPEG-carboxyloxy-méthylamide de l'acide 4-[(2R,3S,4R,5S)-3-(3-chloro-2-fluoro-phényl)-4-(4-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carboxyl]-amino-3-méthoxy-benzoïque (mPEG-NH₂, poids moléculaire moyen environ 2000),

le 1-mPEG-carboxyloxy-méthylamide de l'acide 4-[(2R,3S,4R,5S)-3-(3-chloro-2-fluoro-phényl)-4-(4-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carboxyl]-amino-3-méthoxy-benzoïque (mPEG-NH₂, poids moléculaire moyen environ 1000),

le 1-mPEG-carboxyloxy-méthylamide de l'acide 4-[(2R,3S,4R,5S)-3-(3-chloro-2-fluoro-phényl)-4-(4-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carboxyl]-amino-3-méthoxy-benzoïque (mPEG-NH₂, poids moléculaire moyen environ 550),

l'acide (S)-2-(((4-[(2R,3S,4R,5S)-3-(3-chloro-2-fluorophényl)-4-(4-chloro-2-fluorophényl)-4-cyano-5-néopentylpyrrolidine-2-carboxamido]-3-méthoxybenzoyloxy)méthoxy)carbonylamino)propanoïque,

l'ester 2-[2-[2-(2-phosphonooxy-éthoxy)-éthoxy]-éthoxy]-éthoxycarbonyloxyméthylrique de l'acide dibenzyl-4-[(2R,3S,4R,5S)-4-(4-chloro-2-fluoro-phényl)-3-(3-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carboxyl]-amino-3-méthoxy-benzoïque,

l'ester 2-[2-[2-(2-phosphonooxy-éthoxy)-éthoxy]-éthoxy]-éthoxycarbonyloxyméthylrique de l'acide 4-[(2R,3S,4R,5S)-4-(4-chloro-2-fluoro-phényl)-3-(3-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carboxyl]-amino-3-méthoxy-benzoïque,

l'ester phosphonooxyméthylrique de l'acide 4-[(2R,3S,4R,5S)-3-(3-chloro-2-fluoro-phényl)-4-(4-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carboxyl]-amino-3-méthoxy-benzoïque ; composé avec l'acide trifluoro-acétique,

le 4-[(2R,3S,4R,5S)-3-(3-chloro-2-fluorophényl)-4-(4-chloro-2-fluorophényl)-4-cyano-5-néopentylpyrrolidine-2-carboxamido]-3-méthoxybenzoate de 1-(((3aR,5R,6S,6aR)-5-((R)-2,2-diméthyl-1,3-dioxolan-4-yl)-2,2-diméthyl-tétrahydrofuro[3,2-d][1,3]dioxo-1,6-yloxy)carbonyloxy)éthyle,

l'ester 1-[(2R,3R,4R,5S)-2-((R)-1,2-dihydroxy-éthyl)-4,5-dihydroxy-tétrahydro-furan-3-yloxy]carbonyloxy]-éthylrique de l'acide 4-[(2R,3S,4R,5S)-3-(3-chloro-2-fluoro-phényl)-4-(4-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carboxyl]-amino-3-méthoxy-benzoïque,

l'ester 1-(2-[2-[2-(2-dibenzoyloxyphosphoryloxy-éthoxy)-éthoxy]-éthoxy]-éthoxycarbonyloxy)-éthylrique de l'acide 4-[(2R,3S,4R,5S)-3-(3-chloro-2-fluoro-phényl)-4-(4-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carboxyl]-amino-3-méthoxy-benzoïque et

l'ester 1-(2-[2-[2-(2-phosphonooxy-éthoxy)-éthoxy]-éthoxy]-éthoxycarbonyloxy)-éthylrique de l'acide 4-[(2R,3S,4R,5S)-3-(3-chloro-2-fluoro-phényl)-4-(4-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carboxyl]-amino-3-méthoxy-benzoïque,

8. Composé selon la revendication 1, choisi dans le groupe constitué par :

l'ester 1-[2-(2-{2-[2-(2-méthoxy-éthoxy)-éthoxy]-éthoxy}-éthoxy)-éthoxycarbonyloxy]-éthylque de l'acide 4-[[[(2R,3S,4R,5S)-3-(3-chloro-2-fluoro-phényl)-4-(4-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carbonyl]-amino]-3-méthoxy-benzoïque, l'ester 1-mPEG-carbonyloxy-éthylque de l'acide 4-[[[(2R,3S,4R,5S)-3-(3-chloro-2-fluoro-phényl)-4-(4-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carbonyl]-amino]-3-méthoxy-benzoïque, le 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophényl)-4-(4-chloro-2-fluorophényl)-4-cyano-5-néopentylpyrrolidine-2-carboxamido)-3-méthoxybenzoate de 15-méthyl-12-oxo-2,5,8,11,13-pentaoxahexadécan-14-yle, le 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophényl)-4-(4-chloro-2-fluorophényl)-4-cyano-5-néopentylpyrrolidine-2-carboxamido)-3-méthoxybenzoate de 3-oxo-2,4,7,10,13-pentaoxatétradécyle, le 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophényl)-4-(4-chloro-2-fluorophényl)-4-cyano-5-néopentylpyrrolidine-2-carboxamido)-3-méthoxybenzoate de 3-oxo-2,4,7,10,13,16,19-heptaoxaicosyle, l'ester 1-mPEG-carbonyloxy-éthylque de l'acide 4-[[[(2R,3S,4R,5S)-3-(3-chloro-2-fluoro-phényl)-4-(4-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carbonyl]-amino]-3-méthoxy-benzoïque, le 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophényl)-4-(4-chloro-2-fluorophényl)-4-cyano-5-néopentylpyrrolidine-2-carboxamido)-3-méthoxybenzoate de 3-oxo-2,4,7,10,13-pentaoxatétradécyle, le 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophényl)-4-(4-chloro-2-fluorophényl)-4-cyano-5-néopentylpyrrolidine-2-carboxamido)-3-méthoxybenzoate de 27-oxo-2,5,8,11,14,17,20,23,26,28-décaoxatriacontan-29-yle, le 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophényl)-4-(4-chloro-2-fluorophényl)-4-cyano-5-néopentylpyrrolidine-2-carboxamido)-3-méthoxybenzoate de 24-oxo-2,5,8,11,14,17,20,23,25-nonaoxaheptacosan-26-yle et le 1-mPEG-carbonyloxy-éthylamide de l'acide 4-[[[(2R,3S,4R,5S)-3-(3-chloro-2-fluoro-phényl)-4-(4-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carbonyl]-amino]-3-méthoxy-benzoïque.

9. Composé selon la revendication 1, qui est le 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophényl)-4-(4-chloro-2-fluorophényl)-4-cyano-5-néopentylpyrrolidine-2-carboxamido)-3-méthoxybenzoate de 3-oxo-2,4,7,10,13,16,19-heptaoxaicosyle.

10. Composé selon la revendication 1, qui est l'ester 1-mPEG-carbonyloxy-éthylque de l'acide 4-[[[(2R,3S,4R,5S)-3-(3-chloro-2-fluoro-phényl)-4-(4-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carbonyl]-amino]-3-méthoxy-benzoïque (mPEG, poids moléculaire moyen, environ 2000).

11. Composé selon la revendication 1, qui est l'ester 1-mPEG-carbonyloxy-éthylque de l'acide 4-[[[(2R,3S,4R,5S)-3-(3-chloro-2-fluoro-phényl)-4-(4-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carbonyl]-amino]-3-méthoxy-benzoïque (mPEG, poids moléculaire moyen, environ 2200).

12. Composé selon la revendication 1, qui est l'ester 1-mPEG-carbonyloxy-méthylque de l'acide 4-[[[(2R,3S,4R,5S)-3-(3-chloro-2-fluoro-phényl)-4-(4-chloro-2-fluoro-phényl)-4-cyano-5-(2,2-diméthyl-propyl)-pyrrolidine-2-carbonyl]-amino]-3-méthoxy-benzoïque (mPEG, poids moléculaire moyen, environ 2000).

13. Composé selon la revendication 1, qui est le 4-((2R,3S,4R,5S)-3-(3-chloro-2-fluorophényl)-4-(4-chloro-2-fluorophényl)-4-cyano-5-néopentylpyrrolidine-2-carboxamido)-3-méthoxybenzoate de 3-oxo-2,4,7,10,13-pentaoxatétradécyle.

14. Composé selon l'une quelconque des revendications 1 à 13, destiné à une utilisation en tant que médicament.

15. Composition pharmaceutique comprenant un composé selon l'une quelconque des revendications 1 à 13 et un véhicule thérapeutiquement inerte.

16. Utilisation d'un composé selon l'une quelconque des revendications 1 à 13 pour la préparation d'un médicament pour le traitement du cancer.

17. Composé selon l'une quelconque des revendications 1 à 13 pour le traitement ou la prophylaxie du cancer.

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- WO 2010031713 A [0003]
- WO 2011098398 A [0003] [0129]
- US 20100152190 A1 [0044] [0051] [0054] [0057] [0062] [0164] [0171]

Non-patent literature cited in the description

- **ANSEL.** Pharmaceutical Dosage Forms and Drug Delivery Systems. 1995, 196, , 1456-1457 [0024]
- **ANSEL, HOWARD C. et al.** Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. Lippincott, Williams & Wilkins, 2004 [0041]
- **GENNARO, ALFONSO R. et al.** Remington: The Science and Practice of Pharmacy. Lippincott, Williams & Wilkins, 2000 [0041]
- **ROWE, RAYMOND C.** Handbook of Pharmaceutical Excipients. Pharmaceutical Press, 2005 [0041]

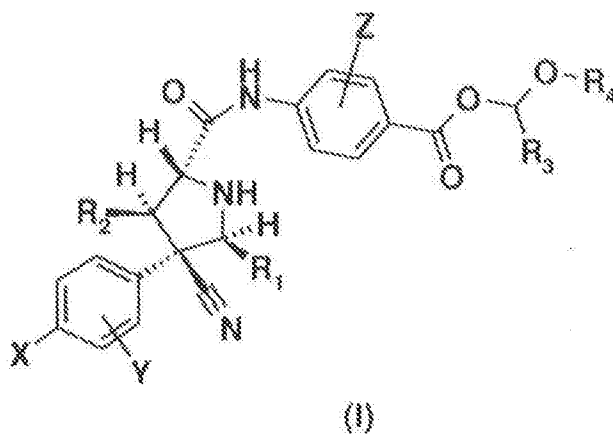


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Szabadalmi igénypontok

1. (I) képletű vegyület,



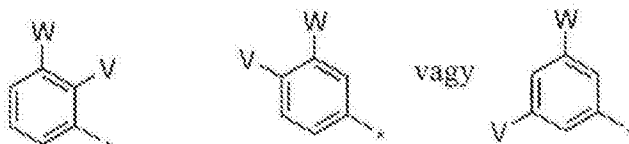
amelyben

X jelentése H, F vagy Cl,

Y jelentése H, F vagy Cl,

Z jelentése 1-6 szénatomos alkoxicsoport,

R₁ jelentése 1-6 szénatomos alkilcsoport vagy 1-6 szénatomos alkoxicsoporttal vagy N(1-6 szénatomos alkil)₂-csoporttal szubsztituált 1-6 szénatomos alkilcsoport,

R₂ jelentése szubsztituált fenilcsoport az alábbiak közül választva:

W jelentése F, Cl vagy Br,

V jelentése H vagy F,

R³ jelentése hidrogénatom vagy 1-6 szénatomos alkilcsoport;

R_4 az alábbiak közül van kiválasztva:



R_5 jelentése a következő csoportból választott: 1–6 szénatomos alkilcsoport, 1–6 szénatomos alkoxicsoporttal vagy $\text{N}(1\text{--}6 \text{ szénatomos alkil})_2$ -csoporttal szubsztituált 1–6 szénatomos alkilcsoport, természetes és nem természetes aminosavak, $-(\text{OCH}_2\text{CH}_2)_n\text{-OH}$, $-(\text{OCH}_2\text{CH}_2)_n\text{-OCH}_3$, $-(\text{NCH}_2\text{CH}_2)_n\text{-OH}$, $-(\text{NCH}_2\text{CH}_2)_n\text{-OCH}_3$ és $-(\text{OCH}_2\text{CH}_2)_n\text{-OP(O)(OR}_6)_2$, ahol n értéke 3–60,

R_6 jelentése hidrogénatom; vagy

ennek gyógyászatiilag elfogadható sója.

2. Az 1. igénypont szerinti vegyület, amelyben

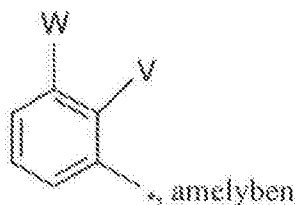
X jelentése H, F vagy Cl;

Y jelentése H, F vagy Cl;

Z jelentése 1–6 szénatomos alkoxicsoport;

R^1 jelentése 1–6 szénatomos alkilcsoport;

R_2 jelentése



W jelentése F, Cl vagy Br;

V jelentése H vagy F;

R^2 jelentése hidrogénatom vagy 1–6 szénatomos alkilcsoport;

R_4 jelentése $-C(O)-R_5$; amelyben

R_5 jelentése a következő csoportból választott: $-(OCH_2CH_2)_n-OH$; $-(OCH_2CH_2)_n-OCH_3$; és $-(OCH_2CH_2)_n-OP(O)(OR_6)_2$, ahol n értéke 3–60, és R_6 jelentése hidrogénatom; vagy ennek gyógyászatiilag elfogadható sója.

3. Az 1. igénypont szerinti vegyület a következő csoportból kiválasztva:

1-(etil(izopropil)karbamoiloxi)etil-4-((2R,3S,4R,5S)-3-(3-klór-2-fluorfenil)-4-(4-klór-2-fluorfenil)-4-ciano-5-neopentil-pirrolidin-2-karboxamido)-3-metoxibenzoát,

4-(((2R,3S,4R,5S)-3-(3-klór-2-fluor-fenil)-4-(4-klór-2-fluor-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino)-3-metoxi-benzoészav-di-*terc*-butoxi-foszforil-oximetil-észter,

4-(((2R,3S,4R,5S)-3-(3-klór-2-fluor-fenil)-4-(4-klór-2-fluor-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino)-3-metoxi-benzoészav-1-[bisz-(2-metoxi-etil)-karbamoiloxi]-etil-észter,

4-metil-piperazin-1-karbonsav-1-(4-(((2R,3S,4R,5S)-3-(3-klór-2-fluor-fenil)-4-(4-klór-2-fluor-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino)-3-metoxi-benzoiloxi)-etil-észter,

1-acetoxietil-4-((2R,3S,4R,5S)-3-(3-klór-2-fluorfenil)-4-(4-klór-2-fluorfenil)-4-ciano-5-neopentil-pirrolidin-2-karboxamido)-3-metoxibenzoát,

Rac-1-(izobutiriloxi)etil-4-((2R,3S,4R,5S)-3-(3-klór-2-fluorfenil)-4-(4-klór-2-fluorfenil)-4-ciano-5-neopentil-pirrolidin-2-karboxamido)-3-metoxibenzoát,

4-(((2R,3S,4R,5S)-4-(4-klór-2-fluor-fenil)-3-(3-klór-2-fluor-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino)-3-metoxi-benzoészav-acetoxi-metilészter,

1-(ciklohexiloxi-karboniloxi)etil-4-((2R,3S,4R,5S)-3-(3-klór-2-fluorfenil)-4-(4-klór-2-fluorfenil)-4-ciano-5-neopentil-pirrolidin-2-karboxamido)-3-metoxibenzoát,

Rac-1-(izopropoxi-karboniloxi)etil-4-((2R,3S,4R,5S)-3-(3-klór-2-fluorfenil)-4-(4-klór-2-fluorfenil)-4-ciano-5-neopentil-pirrolidin-2-karboxamido)-3-metoxibenzoát,

1-(4-((2R,3S,4R,5S)-3-(3-klór-2-fluorfenil)-4-(4-klór-2-fluorfenil)-4-ciano-5-neopentil-pirrolidin-2-karboxamido)-3-metoxibenzoiloxi)etil-morfolin-4-karboxilát és

Morfolin-4-karbonsav-(R)-1-(4-(((2R,3S,4R,5S)-4-(4-klór-2-fluor-fenil)-3-(3-klór-2-fluor-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino)-3-metoxi-benzoiloxi)-etil-észter,

4. Az 1. igénypont szerinti vegyület a következő csoportból kiválasztva:

Morfolin-4-karbonsav-(S)-1-(4-(((2R,3S,4R,5S)-4-(4-klór-2-fluor-fenil)-3-(3-klór-2-fluor-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino)-3-metoxi-benzoiloxi)-etil-észter,

Rac-1-terc-butil-4-(1-(4-((2R,3S,4R,5S)-3-(3-klór-2-fluorfenil)-4-(4-klór-2-fluorfenil)-4-ciano-5-neopentil-pirrolidin-2-karboxamido)-3-metoxibenzoiloxi)etil)piperazin-1,4-dikarboxilát,

Piperazin-1-karbonsav-1-(4-(((2R,3S,4R,5S)-4-(4-klór-2-fluor-fenil)-3-(3-klór-2-fluor-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino)-3-metoxi-benzoiloxi)-etil-észter-dihidroklorid,

Rac-1,1-dioxo-tiomorfolin-4-karbonsav-1-(4-(((2R,3S,4R,5S)-4-(4-klór-2-fluor-fenil)-3-(3-klór-2-fluor-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino)-3-metoxi-benzoiloxi)-etil-észter,

4-(((2R,3S,4R,5S)-4-(4-klór-2-fluor-fenil)-3-(3-klór-2-fluor-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino)-3-metoxi-benzoesav-1-(2,2-dimetil-[1,3]dioxolan-4-ilmetil-karbamoiloxi)-etil-észter,

4-(((2R,3S,4R,5S)-4-(4-klór-2-fluor-fenil)-3-(3-klór-2-fluor-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino)-3-metoxi-benzoesav-1-(2,3-dihidroxi-propil-karbamoiloxi)-etil-észter,

1-(tetrahidro-2H-piran-4-ilkarbamoiloxi)etil-4-((2R,3S,4R,5S)-3-(3-klór-2-fluorfenil)-4-(4-klór-2-fluorfenil)-4-ciano-5-neopentil-pirrolidin-2-karboxamido)-3-metoxibenzoát,

4-(((2R,3S,4R,5S)-3-(3-klór-2-fluor-fenil)-4-(4-klór-2-fluor-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino)-3-metoxi-benzoesav-1-(2-(2-(2-metoxi-etoxi)-

etoxi]-etoxikarboniloxi)-etil-észter,

4-(((2R,3S,4R,5S)-3-(3-klór-2-fluor-fenil)-4-(4-klór-2-fluor-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino)-3-metoxi-benzoészav-1-(2-(2-(2-metoxi-etoxi)-etoxi)-etoxi)-etoxikarboniloxi)-etil-észter,

4-(((2R,3S,4R,5S)-3-(3-klór-2-fluor-fenil)-4-(4-klór-2-fluor-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino)-3-metoxi-benzoészav-1-[2-(2-[2-(2-metoxi-etoxi)-etoxi]-etoxi)-etoxi]-etoxikarboniloxi)-etil-észter-és

21-oxo-2,5,8,11,14,17,20,22-oktaoxatetrakozán-23-íl-4-((2R,3S,4R,5S)-3-(3-klór-2-fluorfenil)-4-(4-klór-2-fluorfenil)-4-ciano-5-neopentil-pirrolidin-2-karboxamido)-3-metoxibenzoát,

5. Az 1. igénypont szerinti vegyület a következő csoportból kiválasztva:

4-(((2R,3S,4R,5S)-3-(3-klór-2-fluor-fenil)-4-(4-klór-2-fluor-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino)-3-metoxi-benzoészav-1-mPEG-karboniloxi-etil-észter (mPEG, átlagos molekulatömeg, ~750),

1-(2-(benziloxi)-2-oxoetil-karbamoiloxi)etil-4-((2R,3S,4R,5S)-3-(3-klór-2-fluorfenil)-4-(4-klór-2-fluorfenil)-4-ciano-5-neopentil-pirrolidin-2-karboxamido)-3-metoxibenzoát,

2-(((1-(4-((2R,3S,4R,5S)-3-(3-klór-2-fluorfenil)-4-(4-klór-2-fluorfenil)-4-ciano-5-neopentil-pirrolidin-2-karboxamido)-3-metoxibenzoiloxi)etoxi)karbonilamino)ecetsav,

(S)-2-[1-(4-(((2R,3S,4R,5S)-3-(3-klór-2-fluor-fenil)-4-(4-klór-2-fluor-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino)-3-metoxi-benzoiloxi)-etoxikarbonil-amino]-glutársav,

4-(((2R,3S,4R,5S)-3-(3-klór-2-fluor-fenil)-4-(4-klór-2-fluor-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino)-3-metoxi-benzoészav-1-((S)-1-karboxi-etilkarbamoiloxi)-etil-észter,

2-(((4-((2R,3S,4R,5S)-3-(3-klór-2-fluorfenil)-4-(4-klór-2-fluorfenil)-4-ciano-5-neopentil-pirrolidin-2-karboxamido)-3-metoxibenzoiloxi)metoxi)-karbonilamino)ecetsav,

(S)-dibenzil-2-(((4-((2R,3S,4R,5S)-3-(3-klór-2-fluorfenil)-4-(4-klór-2-fluorfenil)-4-ciano-5-neopentil-pirrolidin-2-karboxamido)-3-metoxibenzoiloxi)metoxi)karbonilamino)-pentándioát és

(S)-2-(((4-((2R,3S,4R,5S)-3-(3-klór-2-fluorfenil)-4-(4-klór-2-fluorfenil)-4-ciano-5-neopentil-pirrolidin-2-karboxamido)-3-metoxibenzoiloxi)metoxi)karbonilamino)glutársav.

6. Az 1. igénypont szerinti vegyület a következő csoportból kiválasztva:

15-metil-12-oxo-2,5,8,11,13-pentaoxahexadekan-14-il-4-((2R,3S,4R,5S)-3-(3-klór-2-fluorfenil)-4-(4-klór-2-fluorfenil)-4-ciano-5-neopentil-pirrolidin-2-karboxamido)-3-metoxibenzoát,

3-oxo-2,4,7,10,13-pentaoxatetradecil-4-((2R,3S,4R,5S)-3-(3-klór-2-fluorfenil)-4-(4-klór-2-fluorfenil)-4-ciano-5-neopentil-pirrolidin-2-karboxamido)-3-metoxibenzoát,

3-oxo-2,4,7,10,13,16,19-heptaoxaikozil-4-((2R,3S,4R,5S)-3-(3-klór-2-fluorfenil)-4-(4-klór-2-fluorfenil)-4-ciano-5-neopentil-pirrolidin-2-karboxamido)-3-metoxibenzoát,

4-(((2R,3S,4R,5S)-3-(3-klór-2-fluor-fenil)-4-(4-klór-2-fluor-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino)-3-metoxi-benzoészter-1-mPEG-karboniloxi-metil-észter (mPEG, átlagos molekulatömeg, ~750),

4-(((2R,3S,4R,5S)-3-(3-klór-2-fluor-fenil)-4-(4-klór-2-fluor-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino)-3-metoxi-benzoészter-1-mPEG-karboniloxi-etil-észter (mPEG, átlagos molekulatömeg, ~2000),

4-(((2R,3S,4R,5S)-3-(3-klór-2-fluor-fenil)-4-(4-klór-2-fluor-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino)-3-metoxi-benzoészter-1-mPEG-karboniloxi-etil-észter (mPEG, átlagos molekulatömeg, ~2200),

4-(((2R,3S,4R,5S)-3-(3-klór-2-fluor-fenil)-4-(4-klór-2-fluor-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino)-3-metoxi-benzoészter-1-mPEG-karboniloxi-metil-észter (mPEG, átlagos molekulatömeg, ~2000),

3-oxo-2,4,7,10,13-pentaoxatetradecil-4-((2R,3S,4R,5S)-3-(3-klór-2-fluorfenil)-4-(4-klór-2-fluorfenil)-4-ciano-5-neopentil-pirrolidin-2-karboxamido)-3-metoxibenzoát,

27-oxo-2,5,8,11,14,17,20,23,26,28-deksoxatriakontán-29-íl-4-((2R,3S,4R,5S)-3-(3-klór-2-fluorfenil)-4-(4-klór-2-fluorfenil)-4-ciano-5-neopentil-pirrolidin-2-karboxamido)-3-metoxibenzoát,

24-oxo-2,5,8,11,14,17,20,23,25-nonaohaheptakozán-26-íl-4-((2R,3S,4R,5S)-3-(3-klór-2-fluorfenil)-4-(4-klór-2-fluorfenil)-4-ciano-5-neopentil-pirrolidin-2-karboxamido)-3-metoxibenzoát,

4-(((2R,3S,4R,5S)-3-(3-klór-2-fluor-fenil)-4-(4-klór-2-fluor-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino)-3-metoxi-benzoészav-1-mPEG-karboniloxi-etil-amid (mPEG-NH₂, átlagos molekulatömeg, ~550) és

4-(((2R,3S,4R,5S)-3-(3-klór-2-fluor-fenil)-4-(4-klór-2-fluor-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino)-3-metoxi-benzoészav-1-mPEG-karboniloxi-etil-amid (mPEG-NH₂, átlagos molekulatömeg, ~1000).

7. Az 1. igénypont szerinti vegyület a következő csoportból kiválasztva:

4-(((2R,3S,4R,5S)-3-(3-klór-2-fluor-fenil)-4-(4-klór-2-fluor-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino)-3-metoxi-benzoészav-1-mPEG-karboniloxi-etil-amid (mPEG-NH₂, átlagos molekulatömeg ~2000),

4-(((2R,3S,4R,5S)-3-(3-klór-2-fluor-fenil)-4-(4-klór-2-fluor-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino)-3-metoxi-benzoészav-1-mPEG-karboniloxi-metilamid (mPEG-NH₂, átlagos molekulatömeg ~2000),

4-(((2R,3S,4R,5S)-3-(3-klór-2-fluor-fenil)-4-(4-klór-2-fluor-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino)-3-metoxi-benzoészav-1-mPEG-karboniloxi-metilamid (mPEG-NH₂, átlagos molekulatömeg ~1000),

4-(((2R,3S,4R,5S)-3-(3-klór-2-fluor-fenil)-4-(4-klór-2-fluor-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino)-3-metoxi-benzoészav-1-mPEG-karboniloxi-metilamid (mPEG-NH₂, átlagos molekulatömeg ~550),

(S)-2-(((4-((2R,3S,4R,5S)-3-(3-klór-2-fluorfenil)-4-(4-klór-2-fluorfenil)-4-ciano-5-neopentil-pirrolidin-2-karboxamido)-3-metoxibenzoiloxi)metoxi)karbonilamino)propánsav,

Dibenzil-4-(((2R,3S,4R,5S)-4-(4-klór-2-fluor-fenil)-3-(3-klór-2-fluor-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino)-3-metoxi-benzoészav-2-(2-(2-(2-foszfonooxi-etoxi)-etoxi)-etoxi)-etoxikarbonil-oximetil-észter,

4-(((2R,3S,4R,5S)-4-(4-klór-2-fluor-fenil)-3-(3-klór-2-fluor-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino)-3-metoxi-benzoészav-2-(2-(2-(2-foszfonooxi-etoxi)-etoxi)-etoxi)-etoxikarbonil-oximetil-észter,

4-(((2R,3S,4R,5S)-3-(3-klór-2-fluor-fenil)-4-(4-klór-2-fluor-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino)-3-metoxi-benzoészav-foszfonooximetil-észter; trifluorecetsavval alkotott vegyület,

1-(((3aR,5R,6S,6aR)-5-((R)-2,2-dimetil-1,3-dioxolán-4-il)-2,2-dimetil-tetrahidrofuro[3,2-d][1,3]dioxol-6-iloxi)karboniloxi)etil-4-((2R,3S,4R,5S)-3-(3-klór-2-fluor-fenil)-4-(4-klór-2-fluor-fenil)-4-ciano-5-neopentil-pirrolidin-2-karboxamido)-3-metoxibenzoát,

4-(((2R,3S,4R,5S)-3-(3-klór-2-fluor-fenil)-4-(4-klór-2-fluor-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino)-3-metoxi-benzoészav-1-((2R,3R,4R,5S)-2-((R)-1,2-dihidroxi-etil)-4,5-dihidroxi-tetrahidrofuran-3-iloxi-karboniloxi)-etil-észter,

4-(((2R,3S,4R,5S)-3-(3-klór-2-fluor-fenil)-4-(4-klór-2-fluor-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino)-3-metoxi-benzoészav-1-(2-(2-(2-(2-dibenziloxi-foszforiloxi-etoxi)-etoxi)-etoxi)-etoxikarboniloxi)-etil-észter és

4-(((2R,3S,4R,5S)-3-(3-klór-2-fluor-fenil)-4-(4-klór-2-fluor-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino)-3-metoxi-benzoészav-1-(2-(2-(2-(2-foszfonooxi-etoxi)-etoxi)-etoxi)-etoxikarboniloxi)-etil-észter.

8. Az 1. igénypont szerinti vegyület a következő csoportból kiválasztva:

4-(((2R,3S,4R,5S)-3-(3-klór-2-fluor-fenil)-4-(4-klór-2-fluor-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino)-3-metoxi-benzoészav-1-[2-(2-(2-(2-metoxi-etoxi)-etoxi)-etoxi)-etoxi)-etoxikarboniloxi]-etil-észter,

4-(((2R,3S,4R,5S)-3-(3-klór-2-fluor-fenil)-4-(4-klór-2-fluor-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino)-3-metoxi-benzoészav-1-mPEG-karboniloxi-etil-

észter,

15-metil-12-oxo-2,5,8,11,13-pentaoxahexadekan-14-il-4-((2R,3S,4R,5S)-3-(3-klór-2-fluorfenil)-4-(4-klór-2-fluorfenil)-4-ciano-5-neopentil-pirrolidin-2-karboxamido)-3-metoxibenzoát,

3-oxo-2,4,7,10,13-pentaoxatetradecil-4-((2R,3S,4R,5S)-3-(3-klór-2-fluorfenil)-4-(4-klór-2-fluorfenil)-4-ciano-5-neopentil-pirrolidin-2-karboxamido)-3-metoxibenzoát,

3-oxo-2,4,7,10,13,16,19-heptaoxaikozil-4-((2R,3S,4R,5S)-3-(3-klór-2-fluorfenil)-4-(4-klór-2-fluorfenil)-4-ciano-5-neopentil-pirrolidin-2-karboxamido)-3-metoxibenzoát,

4-(((2R,3S,4R,5S)-3-(3-klór-2-fluorfenil)-4-(4-klór-2-fluorfenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino)-3-metoxi-benzoészav-1-mPEG-karboniloxi-etilészter,

3-oxo-2,4,7,10,13-pentaoxatetradecil-4-((2R,3S,4R,5S)-3-(3-klór-2-fluorfenil)-4-(4-klór-2-fluorfenil)-4-ciano-5-neopentil-pirrolidin-2-karboxamido)-3-metoxibenzoát,

27-oxo-2,5,8,11,14,17,20,23,26,28-deksoxatriakontán-29-il-4-((2R,3S,4R,5S)-3-(3-klór-2-fluorfenil)-4-(4-klór-2-fluorfenil)-4-ciano-5-neopentil-pirrolidin-2-karboxamido)-3-metoxibenzoát,

24-oxo-2,5,8,11,14,17,20,23,25-nonaoxaheptakozán-26-il-4-((2R,3S,4R,5S)-3-(3-klór-2-fluorfenil)-4-(4-klór-2-fluorfenil)-4-ciano-5-neopentil-pirrolidin-2-karboxamido)-3-metoxibenzoát, és

4-(((2R,3S,4R,5S)-3-(3-klór-2-fluorfenil)-4-(4-klór-2-fluorfenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino)-3-metoxi-benzoészav-1-mPEG-karboniloxi-etilamid.

9. Az 1. igénypont szerinti vegyület, 3-oxo-2,4,7,10,13,16,19-heptaoxaikozil-4-((2R,3S,4R,5S)-3-(3-klór-2-fluorfenil)-4-(4-klór-2-fluorfenil)-4-ciano-5-neopentil-pirrolidin-2-karboxamido)-3-metoxibenzoát.

10. Az 1. igénypont szerinti vegyület, 4-(((2R,3S,4R,5S)-3-(3-klór-2-fluorfenil)-4-(4-klór-2-fluorfenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil]-amino)-3-metoxi-

benzoesav-1-mPEG-karboniloxi-etilészter (mPEG, átlagos molekulatömeg, ~2000).

11. Az 1. igénypont szerinti vegyület, 4-{{{(2R,3S,4R,5S)-3-(3-klór-2-fluor-fenil)-4-(4-klór-2-fluor-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil}-amino}-3-metoxi-benzoesav-1-mPEG-karboniloxi-etilészter (mPEG, átlagos molekulatömeg, ~2200).

12. Az 1. igénypont szerinti vegyület, 4-{{{(2R,3S,4R,5S)-3-(3-klór-2-fluor-fenil)-4-(4-klór-2-fluor-fenil)-4-ciano-5-(2,2-dimetil-propil)-pirrolidin-2-karbonil}-amino}-3-metoxi-benzoesav-1-mPEG-karboniloxi-etilészter (mPEG, átlagos molekulatömeg, ~2000).

13. Az 1. igénypont szerinti vegyület, 3-oxo-2,4,7,10,13-pentaoxatetradecil-4-(((2R,3S,4R,5S)-3-(3-klór-2-fluorfenil)-4-(4-klór-2-fluorfenil)-4-ciano-5-neopentil-pirrolidin-2-karboxamido)-3-metoxibenzoát.

14. Az 1–13. igénypontok bármelyike szerinti vegyület gyógyszerként történő alkalmazásra.

15. Gyógyszerkészítmény, amely tartalmaz 1–13. igénypontok bármelyike szerinti vegyületet és terápiásan semleges hordozóanyagot.

16. Az 1–13. igénypontok bármelyike szerinti vegyület alkalmazása rák kezelésére szolgáló gyógyszer előállítására.

17. Az 1–13. igénypontok bármelyike szerinti vegyület rák kezelésében vagy megelőzésében történő alkalmazásra.