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(54) Title: A NOVEL HYDROXAMIC ACID DERIVATIVE AS PEPTIDE DEFORMYLASE INHIBITOR AND MANUFACTURING METHOD THEREOF

(57) Abstract: The present invention relates to the novel antibacterial compounds having potent antibacterial activity as inhibitors of peptide deformylase. This invention further relates to pharmaceutically acceptable salts thereof, to processes for their preparation, and to pharmaceutical compositions containing them as an active ingredient.

Description

A NOVEL HYDROXAMIC ACID DERIVATIVE AS PEPTIDE DEFORMYLASE INHIBITOR AND MANUFACTURING METHOD THEREOF

Technical Field

- [1] The present invention relates to the novel antibacterial compounds having potent antibacterial activity as inhibitors of peptide deformylase. This invention further relates to pharmaceutically acceptable salts thereof, to processes for their preparation, and to pharmaceutical compositions containing them as an active ingredient.

Background Art

- [2] Infectious diseases caused by bacteria, fungi and other parasitic organisms affect hundreds of millions of people worldwide and cause millions of deaths each year. In general, bacterial pathogens may be classified as either Gram-positive or Gram-negative pathogens. Antibiotic compounds with effective activity against both Gram-positive and Gram-negative pathogens are generally regarded as having a broad spectrum of activity. The compounds of the present invention are regarded primarily as effective against Gram-positive pathogens because of their particularly potent activity against such pathogens.
- [3] Recently published literature indicate that bacteria are rapidly acquiring resistance to well known antibiotics, including vancomycin and new agent such as linezolid (*Staphylococcus aureus* resistant to vancomycin - United States, 2002. *MMWR* (2002) 51(26): 565-567; Linezolid resistance in a clinical isolate of *Staphylococcus aureus*. *Lancet* (2001) 358 (9277): 207-208).
- [4] Therefore, there is an urgent need to discover antibiotics with new modes of action.
- [5] Peptide deformylase (PDF), an essential enzyme involved in bacterial protein biosynthesis and maturation, is one of the few novel targets that is currently being pursued for antibacterial drug design. PDF is a unique metalloproteinase, which utilizes a ferrous ion (Fe^{2+}) to catalyze the amide bond hydrolysis. In bacteria, protein synthesis starts with an *N*-formyl methionine (fMet), and as a result, all newly synthesized polypeptides carry a formylated *N*-terminus. PDF catalyzes the subsequent removal of the formyl group from the majority of those polypeptides, many of which undergo further *N*-terminal processing by methionine aminopeptidase (MAP) to produce mature proteins. Since protein synthesis in eukaryotic organisms does not depend on *N*-formyl methionine (fMet) for initiation, PDF inhibitors are expected to act as a new class of antimicrobial and antibacterial agents. Numerous PDF inhibitors have been reported in recent years; essentially all of them are metal chelators. On the basis of the chelator

structure, they can be classified into three different types: the thiols, the hydroxamic acids, and the *N*-formyl hydroxylamines.

[6] Several PDF inhibitors have been reported in the literature some of which relevant are given here:

[7] hydroxamic acid derivatives: WO 99/59568, WO 00/44373, WO 01/44178, WO 01/44179, WO 02/28829 and WO 02/081426

[8] *N*-formyl hydroxylamines derivatives: WO 01/85160, WO 01/85170, WO 02/070540, WO 02/070541, WO 02/070653, WO 02/070654, WO 02/098901, WO 03/101442, WO 0035440, WO 99/39704, WO 00/35440, WO 00/58294, WO 00/611134, WO 01/10834, WO 01/10835, WO 03/089412 and WO 2004/033441

[9] Although a wide variety of compounds described in prior art have been developed as inhibitors of peptide deformylase, they did not result in a clinically useful compound.

[10] Though a variety of inhibitors have been prepared, there is a continuing need for potent peptide deformylase inhibitors useful in treating such diseases.

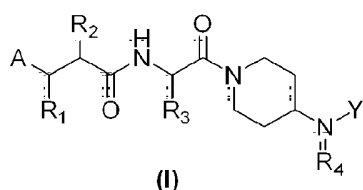
[11] The present invention fulfills this need.

Disclosure of Invention

Technical Solution

[12] The present invention relates to the novel hydroxamic acid derivatives having potent antibacterial activity as inhibitors of peptide deformylase. This invention further relates to processes for their preparation, to intermediates useful in their preparation, and to pharmaceutical compositions containing them as an active ingredient:

[13]



[14] wherein, A is selected from the group of consisting of $-C(=O)NHOH$ or $-N(CHO)OH$;

[15] R_1 represents hydrogen, C_{1-3} alkyl, C_{4-6} cycloalkyl, halogen or hydroxy group;

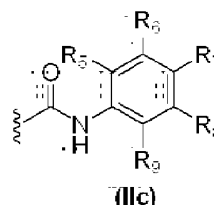
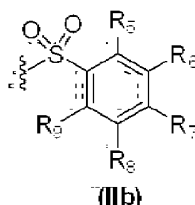
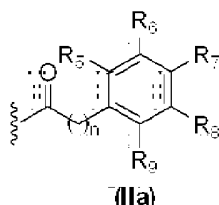
[16] R_2 represents hydrogen, straight or branched C_{1-6} alkyl, straight or branched C_{1-6} alkenyl, C_{4-6} cycloalkyl, C_{4-6} heterocycle including nitrogen or oxygen, or benzyl group;

[17] R_3 represents hydrogen, methyl, straight or branched C_{1-6} alkyl, straight or branched C_{1-6} alkenyl, C_{4-6} cycloalkyl, phenyl or benzyl group;

[18] R_4 represents hydrogen, straight or branched C_{1-4} alkyl, C_{1-4} alkenyl, hydroxy substituted C_{4-6} cycloalkyl group; and

[19] Y represents a group of formula (IIa), or (IIb), or (IIc):

[20]



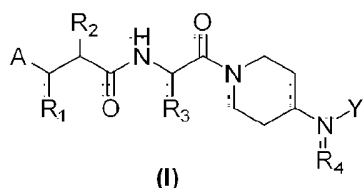
[21] wherein, n is independently 0 or 1;

[22] each of R_5 , R_6 , R_7 , R_8 and R_9 is independently hydrogen, straight or branched C_{1-3} alkyl, hydroxy, alkoxy, acyl, acyloxy, halogen (fluoro, chloro, bromo and iodo) cyano, nitro, amono, *N,N*-dimethylamino, phenyl, morpholinyl, or formyl group.

Best Mode for Carrying Out the Invention

[23] The present invention relates to the novel hydroxamic acid derivatives having potent antibacterial activity as inhibitors of peptide deformylase. This invention further relates to processes for their preparation, to intermediates useful in their preparation, and to pharmaceutical compositions containing them as an active ingredient:

[24]



[25] wherein, A is selected from the group of consisting of $-C(=O)NHOH$ or $-N(CHO)OH$;

[26] R_1 represents hydrogen, C_{1-3} alkyl, C_{4-6} cycloalkyl, halogen or hydroxy group;

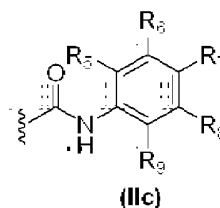
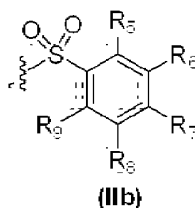
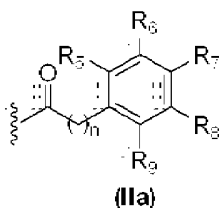
[27] R_2 represents hydrogen, straight or branched C_{1-6} alkyl, straight or branched C_{1-6} alkenyl, C_{4-6} cycloalkyl, C_{4-6} heterocycle including nitrogen or oxygen, or benzyl group;

[28] R_3 represents hydrogen, methyl, straight or branched C_{1-6} alkyl, straight or branched C_{1-6} alkenyl, C_{4-6} cycloalkyl, phenyl or benzyl group;

[29] R_4 represents hydrogen, straight or branched C_{1-4} alkyl, C_{1-4} alkenyl, hydroxy substituted C_{4-6} cycloalkyl group; and

[30] Y represents a group of formula (IIa), or (IIb), or (IIc):

[31]



[32] wherein, n is independently 0 or 1;

[33] each of R_5 , R_6 , R_7 , R_8 and R_9 is independently hydrogen, straight or branched C_{1-3} alkyl, hydroxy, alkoxy, acyl, acyloxy, halogen (fluoro, chloro, bromo and iodo) cyano, nitro, amono, *N,N*-dimethylamino, phenyl, morpholinyl, or formyl group.

[34]

[35] The compounds of this invention may possess one or more asymmetric centers because of the presence of asymmetric carbon atoms. Therefore, the invention includes all such racemic mixtures, optical isomers and diastereoisomers thereof.

[36]

[37] A compounds of the invention may be administered in pharmaceutically acceptable salt forms, hydrate forms or solvate forms. Such salts include acid addition salts, formed with hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, methanesulfonic acid, *p*-toluenesulfonic acid, phosphoric acid, acetic acid, pyruvic acid, citric acid, succinic acid, lactic acid, tartaric acid, fumaric acid, maleic acid, stearic acid and salicylic acid. Salts may also be formed with sodium, potassium, magnesium and calcium salts.

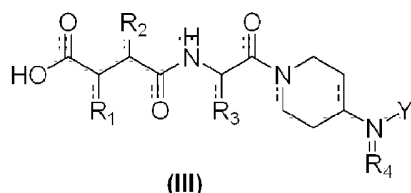
[38]

[39] The present invention provides a process for preparing of formula (I), or pharmaceutically acceptable salt, hydrate or solvate thereof.

[40]

[41] Compounds of the invention wherein A is $-C(=O)NHOH$ group may be prepared by reacting a compound of formula (III) with hydroxylamine or an *N*- and/or *O*-protected hydroxylamine, and thereafter removing any *N*- or *O*-protecting groups:

[42]

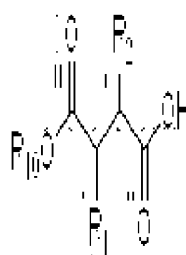


[43] wherein, R_1 , R_2 , R_3 , R_4 and Y are the same as defined above.

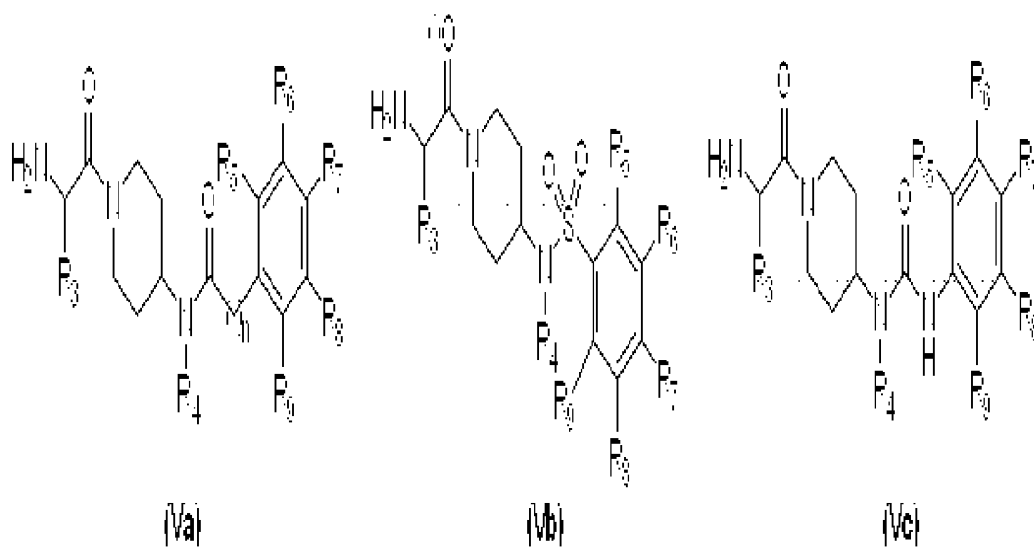
[44]

[45] Reaction of formula (III) with hydroxylamine or an *N*- and/or *O*-protected hydroxylamine may be carried out according to the standard peptide coupling conditions.

- [46] The reaction is typically carried out in the presence of a coupling reagent (e.g. pentafluorophenol, *N,O*-dimethylhydroxylamine, DMAP/EDCI, EDCI/HOBt/NMM, etc.), in an appropriate solvent (e.g. tetrahydrofuran, dichloromethane, *N,N*-dimethylformamide, etc.).
- [47] Deprotection of benzyl group may be carried out in the presence of the hydrogenation catalyst, preferably a palladium catalyst (e.g. palladium on carbon or palladium black). The reaction can be achieved under a hydrogen atmosphere for about 2 to about 24 hours.
- [48] Deprotection of *tert*-butoxycarbonyl group may be carried out in the presence of an appropriate acid, such as hydrochloric acid or trifluoroacetic acid. The reaction can be achieved by stirring for about 2 to about 24 hours.
- [49] Compounds of formula (III) may be prepared by reacting a compound of formula (IV) with a compound of formula (Va) (or Vb, or Vc) or salt thereof.
- [50] Reaction of formula (IV) with a compound of formula (Va) (or Vb, or Vc) or salt thereof may be carried out according to the standard peptide coupling conditions.
- [51] The reaction is typically carried out in the presence of a coupling reagent (e.g. pentafluorophenol, *N,O*-dimethylhydroxylamine, DMAP/EDCI, EDCI/HOBt/NMM, etc.), in an appropriate solvent (e.g. tetrahydrofuran, dichloromethane, *N,N*-dimethylformamide, etc.):
- [52]



(IV)



(Va)

(Vb)

(Vc)

[53] wherein, $R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9$ and n are the same as defined above and R_{10} is a hydroxy protecting group, such as methyl, ethyl, *t*-butyl and benzyl group.

[54]

[55] Carboxylic acids of formula (IV) may be prepared according to any of a variety of methods described in the literature.

[56] Also, compounds of the invention wherein A is -N(CHO)OH group may be prepared by reacting a compound of formula (VI) with a compound of formula (Va) (or Vb, or Vc) or salt thereof.

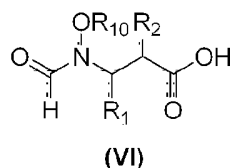
[57] Reaction of formula (VI) with a compound of formula (Va) (or Vb, or Vc) or salt thereof may be carried out according to the standard peptide coupling conditions.

[58] The reaction is typically carried out in the presence of a coupling reagent (e.g. pentafluorophenol, *N,O*-dimethylhydroxylamine, DMAP/EDCI, EDCI/HOBt/NMM, etc.), in an appropriate solvent (e.g. tetrahydrofuran, dichloromethane, *N,N*-dimethylformamide, etc.).

[59] Deprotection of benzyl group may be carried out in the presence of the hydrogenation catalyst, preferably a palladium catalyst (e.g. palladium on carbon or palladium black). The reaction can be achieved under a hydrogen atmosphere for about 2 to about 24 hours.

[60] Deprotection of *tert*-butoxycarbonyl group may be carried out in the presence of an appropriate acid, such as hydrochloric acid or trifluoroacetic acid. The reaction can be achieved by stirring for about 2 to about 24 hours:

[61]



[62] wherein, R_1 , R_2 and R_{10} are the same as defined above.

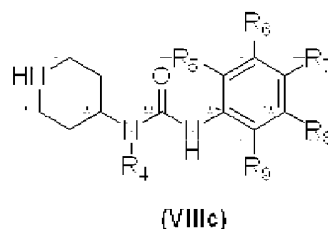
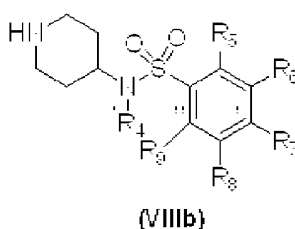
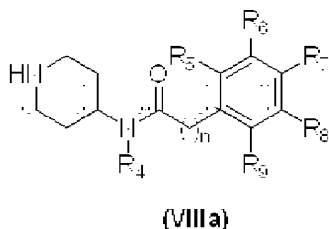
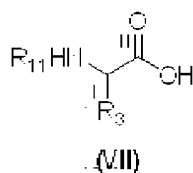
[63]

[64] Carboxylic acids of formula (VI) may be prepared according to any of a variety of methods described in the literature.

[65] The compound of formula (Va) (or Vb, or Vc) or salt thereof may be obtained by reacting a compound of formula (VII) with a compound of (Ia) (or Ib, or Ic) or salt thereof.

[66] The reaction is typically carried out in the presence of a coupling reagent (e.g. pentafluorophenol, *N,O*-dimethylhydroxylamine, DMAP/EDCI, EDCI/HOBt/NMM, etc.), in an appropriate solvent (e.g. tetrahydrofuran, dichloromethane, *N,N*-dimethylformamide, etc.):

[67]



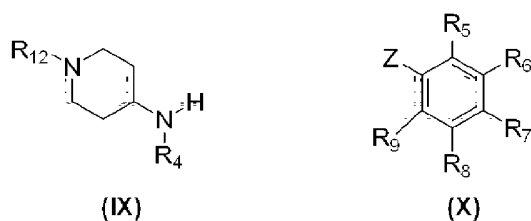
[68] wherein, R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 and n are the same as defined above and R_{11} is an amino protecting group, such as *tert*-butoxycarbonyl, benzyloxycarbonyl or triphenylmethyl group.

[69]

[70] The compound of formula (IIa) (or IIb, or IIc) or salt thereof may be obtained by reacting a compound of formula (IX) or salt thereof with a compound of formula (X) wherein Z is Cl(C=O) group. And also, reacting the compound of formula (IX) or salt thereof with a compound of formula (X) wherein Z is NH₂ group may be carried out in the presence of a reagent such as triphosgen or 1,1'-carbonyldiimidazole.

[71] Preferably, reacting the compound of formula (IX) or salt thereof with a compound of formula (X) may be carried out in an organic solvent such as dichloromethane, acetonitrile, tetrahydrofuran, dimethyl sulfoxide and toluene in the presence of a base such as *N,N*-diisopropylethylamine, triethylamine, *N*-methylmorpholine:

[72]



[73] wherein, R₄, R₅, R₆, R₇, R₈ and R₉ are the same as defined above and R₁₂ is a amino protecting group, such as *tert*-butoxycarbonyl, benzyloxycarbonyl or triphenylmethyl group, and Z is selected from the group of consisting of Cl(C=O), Cl(C=O)CH₂, ClS(=O)₂, NH₂ or O=C=N.

[74]

[75] The examples which follow illustrate embodiments of the invention but are not intended to limit the scope in any way.

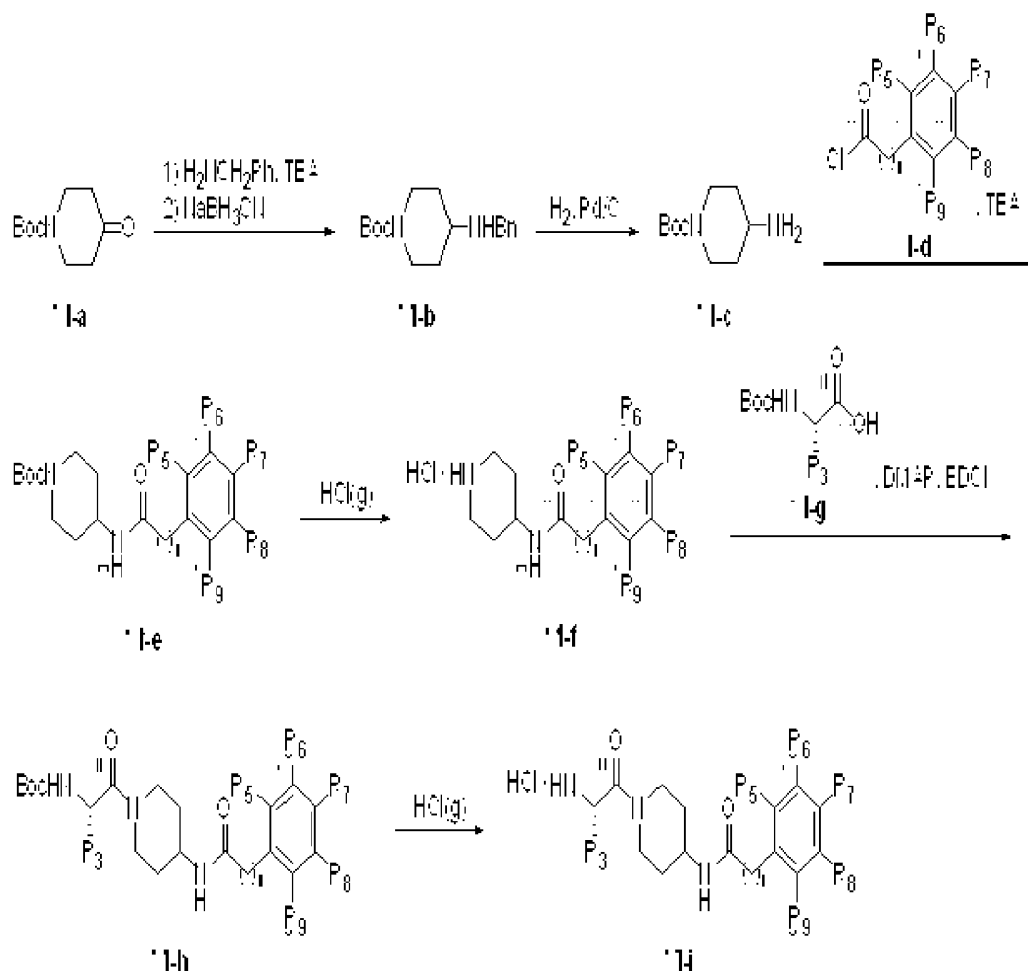
[76]

[77] General procedure I

[78]

[79] Synthesis of *N*-[1-((*S*)-2-Amino-3,3-dimethyl-butyl)-piperidin-4-yl]-4-fluoro-benzamide hydrochloride (Scheme 1)

[81]



[82] Step 1: 4-Benzylamino-piperidine-1-carboxylic acid *tert*-butyl ester (I-b)

[83] To a solution of *tert*-butyl-4-oxo-1-piperidinecarboxylate (25 g, 125.47 mmol) in anhydrous MeOH (600 mL) was added triethylamine (26.23 mL, 188.20 mmol) and benzylamine (20.56 mL, 188.20 mmol). The reaction mixture was heated to 65°C for 5 h before adding sodium cyanoborohydride (15.77 g, 250.94 mmol) portionwise. The mixture was stirred for 48 h and filtered through Celite. The filtrate was evaporated to dryness and ethyl acetate was added. The organic phase was washed with saturated aqueous NaHCO₃, then H₂O, dried over MgSO₄ and evaporated to dryness under reduced pressure. The residue was purified by column chromatography to give the title compound as a pale yellow solid (30 g, 82%).

[84] ¹H-NMR(CDCl₃): δ 7.22-7.35 (m, 5H), 3.95-4.10 (m, 2H), 3.82(s, 2H), 2.75-2.83 (m, 2H), 2.61-2.71 (m, 1H), 1.84-1.88 (m, 2H), 1.45 (s, 9H), 1.24-1.39 (m, 2H).

[85]

[86] Step 2: 4-Amino-piperidine-1-carboxylic acid *tert*-butyl ester (I-c)

- [87] To a solution of compound I-b (25 g, 86.09 mmol) in ethanol (500 mL) was added 10% palladium on charcoal (8.62 g). The mixture was exposed to 7 atm of hydrogen until all of the starting material was consumed. The charcoal was removed by filtration and the filtrate was concentrated to give the title compound as a white crystalline solid (17 g, 98%).
- [88] $^1\text{H-NMR}(\text{CDCl}_3)$: δ 3.90-4.10 (m, 2H), 2.66-2.79 (m, 3H), 1.69-1.73 (m, 2H), 1.38 (s, 9H), 1.10-1.21 (m, 2H).
- [89]
- [90] Step 3: 4-(4-Fluoro-benzoylamino)-piperidine-1-carboxylic acid *tert*-butyl ester (I-e).
- [91] A solution of compound I-c (5 g, 24.96 mmol) and triethylamine (4.7 mL, 33.70 mmol) in CH_2Cl_2 (50 mL) was cooled to 0°C. A solution of compound I-d ($\text{R}_5=\text{R}_6=\text{R}_8=\text{R}_9=\text{H}$, $\text{R}_7=\text{F}$, $n=0$, 5.1 g, 32.1 mmol) in CH_2Cl_2 (30 mL) was slowly added into the above reaction mixture. After stirring for 12 h at room temperature, the mixture was poured into H_2O and extracted with CH_2Cl_2 . The organic layer was washed with aqueous saturated NaHCO_3 and brine and dried over MgSO_4 . After removing the solvent *in vacuo*, the residue was purified by column chromatography to give the title compound as a white crystalline solid (7 g, 87%).
- [92] $^1\text{H-NMR}(\text{CDCl}_3)$: δ 7.75-7.80(m, 2H), 7.07-7.27 (m, 2H), 4.05-4.19 (m, 3H), 2.85-2.93 (m, 2H), 1.97-2.04 (m, 2H), 1.46 (s, 9H), 1.39-1.44 (m, 2H).
- [93]
- [94] Step 4: 4-Fluoro-*N*-piperidin-4-yl-benzamide hydrochloride (I-f)
- [95] Compound I-e (5 g, 15.51 mmol) was dissolved in ethyl acetate (30 mL) and saturated with gaseous HCl, and the reaction mixture stirred until all of the starting material was consumed. The mixture was concentrated to give amine hydrochloride salt as a white crystalline solid which was used in next step without further purification (3.8 g, 95%).
- [96] $^1\text{H-NMR}(\text{D}_2\text{O})$: δ 7.57-7.64 (m, 2H), 7.01-7.11 (m, 2H), 3.93-4.03 (m, 1H), 3.34-3.41 (m, 2H), 2.92-3.07 (m, 2H), 2.02-2.11 (m, 2H), 1.61-1.75 (m, 2H).
- [97]
- [98] Step 5: {(S)-1-[4-(4-Fluoro-benzoylamino)-piperidine-1-carbonyl]-2,2-dimethylpropyl}-carbamic acid *tert*-butyl ester (I-h)
- [99]
- [100] To a solution of I-g ($\text{R}_3=\text{tert-butyl}$, 3 g, 12.97 mmol) in CH_2Cl_2 (60 mL) at 0°C was added successively compound I-f (3.7 g, 14.30 mmol), 4-dimethylaminopyridine (DMAP) (3.32 g, 27.17 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) (2.74 g, 14.30 mmol). The mixture was stirred at room temperature overnight. The mixture was washed with aqueous saturated NaHCO_3 and brine and dried over MgSO_4 . After removing the solvent *in vacuo*, the residue was

purified by column chromatography to give the title compound as a white solid (5 g, 88%).

[101] $^1\text{H-NMR}(\text{CDCl}_3)$: δ 7.76-7.82 (m, 2H), 7.07-7.13 (m, 2H), 4.52-4.68 (m, 2H), 4.09-4.25 (m, 2H), 3.15-3.32 (m, 1H), 2.72-2.85 (m, 1H), 2.02-2.21 (m, 2H), 1.35-1.52 (m, 11H), 0.96-0.98 (d, 9H).

[102]

[103] Step 6: *N*-[1-((*S*)-2-Amino-3,3-dimethyl-butyl)-piperidin-4-yl]-4-fluoro-
[104] benzamide hydrochloride (I-i)

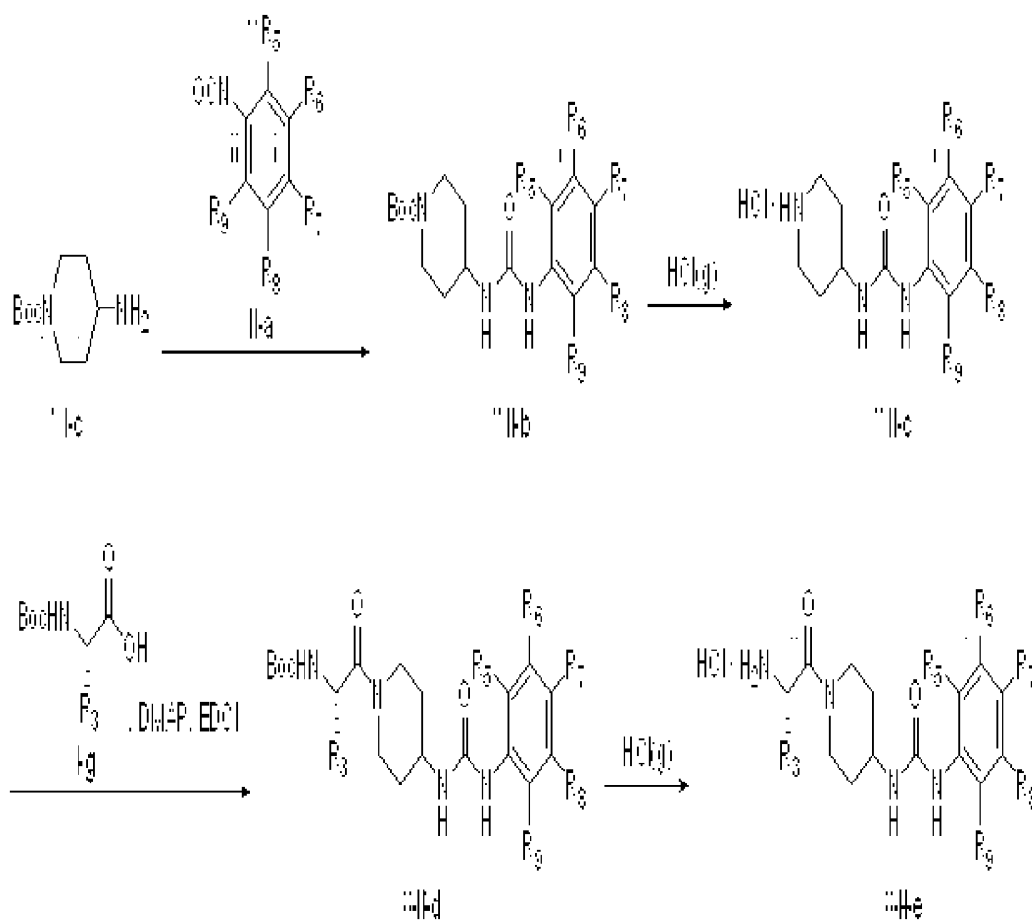
[105] Compound I-h (3 g, 6.936 mmol) was dissolved in ethyl acetate (40 mL) and saturated with gaseous HCl, and the reaction mixture stirred until all of the starting material was consumed. The mixture was concentrated to give amine hydrochloride salt as a white crystalline solid which was used in next step without further purification (2.4 g, 93%).

[106] $^1\text{H-NMR}(\text{D}_2\text{O})$: δ 7.57-7.62 (m, 2H), 7.02-7.09 (m, 2H), 4.20-4.35 (m, 1H), 3.93-4.01 (m, 3H), 3.16-3.30 (m, 1H), 2.77-2.95 (m, 1H), 1.82-1.95 (m, 2H), 1.35-1.53 (m, 2H), 0.93-0.96 (d, 9H).

[107] **General procedure II**

[108] Synthesis of 1-[1-((*S*)-2-Amino-3,3-dimethyl-butyl)-piperidin-4-yl]-3-(4-fluoro-
[109] phenyl)-urea hydrochloride (Scheme II)

[110]



Scheme II

[111] Step 1: 4-[3-(4-Fluoro-phenyl)-ureido]-piperidine-1-carboxylic acid *tert*-butyl ester (II-b)

[112] To a solution of compound I-c (5 g, 24.96 mmol) in THF (60 mL) was added compound II-a ($R_5=R_6=R_8=H$, $R_7=F$, 4.35 g, 27.43 mmol). The reaction mixture was allowed to stir at room temperature for 1-2 hours. After removing the solvent *in vacuo*, the residue was purified by column chromatography to give the title compound as a white solid (6 g, 71%).

[113] $^1\text{H-NMR}(\text{CDCl}_3)$: δ 7.75-7.81(m, 2H), 7.08-7.27 (m, 2H), 4.09-4.22 (m, 3H), 2.85-2.95 (m, 2H), 1.98-2.04 (m, 2H), 1.47 (s, 9H), 1.41-1.45 (m, 2H).

[114]

[115] Step 2: 1-(4-Fluoro-phenyl)-3-piperidin-4-yl-urea hydrochloride (II-c)

[116] Compound II-b (4 g, 11.85 mmol) was dissolved in ethyl acetate (50 mL) and saturated with gaseous HCl, and the reaction mixture stirred until all of the starting material was consumed. The mixture was concentrated to give amine hydrochloride

salt as a white crystalline solid which was used in next step without further purification (3.1 g, 96%).

[117] $^1\text{H-NMR}(\text{D}_2\text{O})$: δ 7.59-7.68 (m, 2H), 7.01-7.13 (m, 2H), 3.98-4.10 (m, 1H), 3.35-3.44 (m, 2H), 2.94-3.07 (m, 2H), 2.05-2.14 (m, 2H), 1.62-1.75 (m, 2H).

[118]

[119] Step 3: ((S)-1-{4-[3-(4-Fluoro-phenyl)-ureido]-piperidine-1-carbonyl}-2,2-dimethyl
[120] -propyl)-carbamic acid *tert*-butyl ester (II-d)

[121] To a solution of I-g ($\text{R}_3 = \text{tert-butyl}$, 2 g, 8.647 mmol) in CH_2Cl_2 (40 mL) at 0°C was added successively compound II-c (2.6 g, 9.498 mmol), 4-dimethylaminopyridine (DMAP) (2.2 g, 18.007 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) (1.8 g, 9.498 mmol). The mixture was stirred at room temperature overnight. The mixture was washed with aqueous saturated NaHCO_3 and brine and dried over MgSO_4 . After removing the solvent *in vacuo*, the residue was purified by column chromatography to give the title compound as a white solid (3.5 g, 90%).

[122] $^1\text{H-NMR}(\text{CDCl}_3)$: δ 7.77-7.85 (m, 2H), 7.09-7.13 (m, 2H), 4.55-4.69 (m, 2H), 4.11-4.26 (m, 2H), 3.18-3.32 (m, 1H), 2.75-2.86 (m, 1H), 2.04-2.22 (m, 2H), 1.35-1.54 (m, 11H), 0.96-0.99 (d, 9H).

[123]

[124] Step 4: 1-[1-((S)-2-Amino-3,3-dimethyl-butyryl)-piperidin-4-yl]-3-(4-fluoro-
[125] phenyl)-urea hydrochloride (II-e)

[126] Compound II-d (2.5 g, 5.549 mmol) was dissolved in ethyl acetate (35 mL) and saturated with gaseous HCl, and the reaction mixture stirred until all of the starting material was consumed. The mixture was concentrated to give amine hydrochloride salt as a white crystalline solid which was used in next step without further purification (2.1 g, 98%).

[127] $^1\text{H-NMR}(\text{D}_2\text{O})$: δ 7.58-7.65 (m, 2H), 7.04-7.09 (m, 2H), 4.25-4.38 (m, 1H), 3.95-4.01 (m, 3H), 3.18-3.32 (m, 1H), 2.79-2.95 (m, 1H), 1.83-1.95 (m, 2H), 1.37-1.54 (m, 2H), 0.94-0.96 (d, 9H).

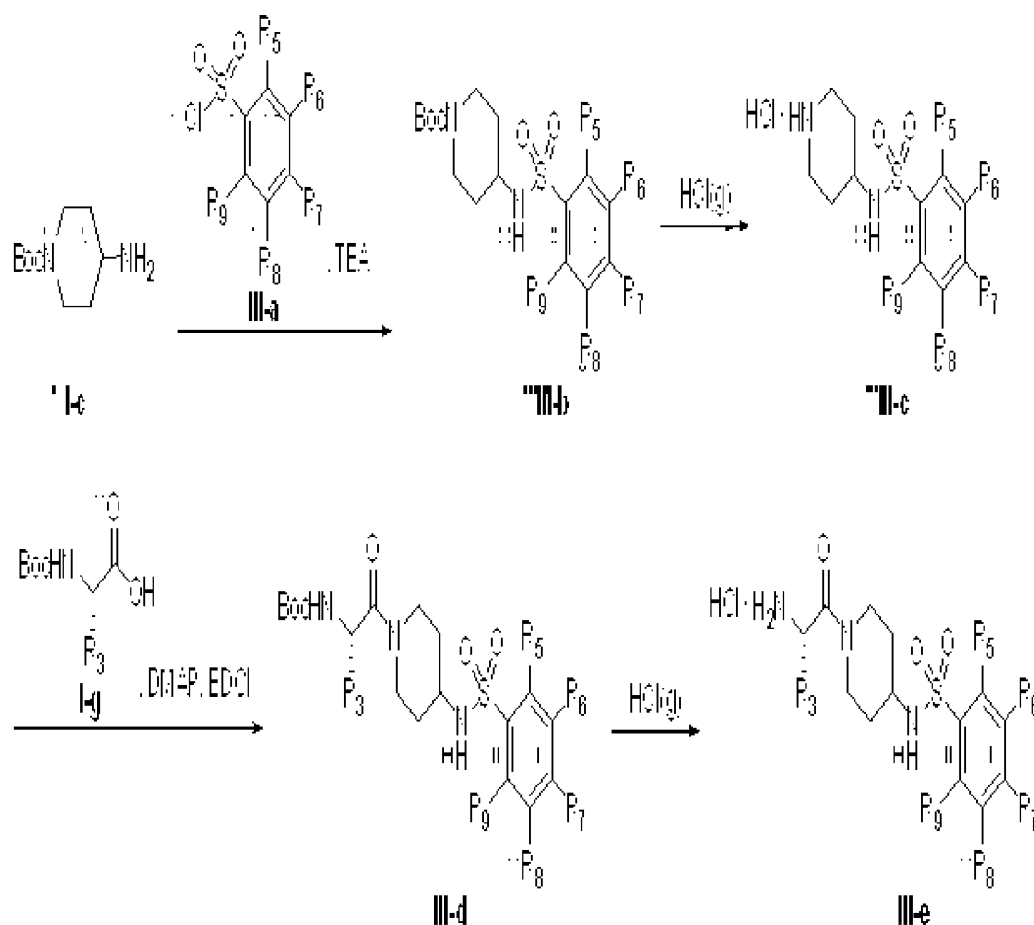
[128]

[129] **General procedure III**

[130]

[131] Synthesis of *N*-[1-((S)-2-Amino-3,3-dimethyl-butyryl)-piperidin-4-yl]-4-fluoro-
[132] benzenesulfonamide hydrochloride (Scheme III)

[133]



Scheme III

[134] Step 1: 4-(4-Fluoro-benzenesulfonylamino)-piperidine-1-carboxylic acid *tert*-butyl ester (III-b)

[135] To a solution of compound I-c (10 g, 49.93 mmol) in acetone/distilled water (4/1, 250 mL) was added compound III-a ($R_5=R_6=R_8=R_9=H$, $R_7=F$, 9.72 g, 49.93 mmol). A solution of triethylamine (6.96 mL, 49.93 mmol) in distilled water was added and the reaction mixture allowed to stir at room temperature for 5 hours. The solvent was removed *in vacuo* and the residue dissolved in ethyl acetate. The organic layer was separated and the aqueous phase extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$, filtered and the solvents removed *in vacuo* to give a crude product. The crude product was purified by column chromatography to give the title compound as a white solid (16 g, 89%).

[136] 1H -NMR($CDCl_3$): δ 7.75-7.81(m, 2H), 7.08-7.19 (m, 2H), 4.09-4.22 (m, 2H), 3.02-3.21 (m, 1H), 2.85-2.95 (m, 2H), 1.98-2.04 (m, 2H), 1.47 (s, 9H), 1.41-1.45 (m, 2H).

[137]

[138] Step 2: 4-Fluoro-*N*-piperidin-4-yl-benzenesulfonamide hydrochloride (III-c)

[139] Compound III-b (10 g, 27.899 mmol) was dissolved in ethyl acetate (120 mL) and saturated with gaseous HCl, and the reaction mixture stirred until all of the starting material was consumed. The mixture was concentrated to give amine hydrochloride salt as a white crystalline solid which was used in next step without further purification (8 g, 97%).

[140] ¹H-NMR(D₂O): δ 7.61-7.68 (m, 2H), 7.10-7.17 (m, 2H), 3.34-3.44 (m, 2H), 3.01-3.15 (m, 1H), 2.93-3.09 (m, 2H), 2.04-2.15 (m, 2H), 1.63-1.75 (m, 2H).

[141]

[142] Step 3: {(S)-1-[4-(4-Fluoro-benzenesulfonylamino)-piperidine-1-carbonyl]-2,2-dimethyl-propyl}-carbamic acid *tert*-butyl ester (III-d)

[143] To a solution of I-g (R₃=*tert*-butyl, 4.5 g, 19.456 mmol) in CH₂Cl₂ (90 mL) at 0°C was added successively compound III-c (5.86 g, 21.407 mmol), 4-dimethylaminopyridine (DMAP) (4.99 g, 40.845 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) (4.1 g, 21.407 mmol). The mixture was stirred at room temperature overnight. The mixture was washed with aqueous saturated NaHCO₃ and brine and dried over MgSO₄. After removing the solvent *in vacuo*, the residue was purified by column chromatography to give the title compound as a white solid (8 g, 87%).

[145] ¹H-NMR(CDCl₃): δ 7.81-7.86 (m, 2H), 7.09-7.14 (m, 2H), 4.56-4.66 (m, 2H), 4.10-4.27 (m, 2H), 3.01-3.12 (m, 1H), 2.74-2.88 (m, 1H), 2.04-2.19 (m, 2H), 1.36-1.54 (m, 11H), 0.95-0.97 (d, 9H).

[146]

[147] Step 4: *N*-[1-((S)-2-Amino-3,3-dimethyl-butyl)-piperidin-4-yl]-4-fluoro-benzenesulfonamide hydrochloride (III-e)

[148] Compound III-d (6 g, 12.723 mmol) was dissolved in ethyl acetate (80 mL) and saturated with gaseous HCl, and the reaction mixture stirred until all of the starting material was consumed. The mixture was concentrated to give amine hydrochloride salt as a white crystalline solid which was used in next step without further purification (5 g, 96%).

[150] ¹H-NMR(D₂O): δ 7.69-7.73 (m, 2H), 7.02-7.05 (m, 2H), 4.19-4.34 (m, 1H), 3.88-4.00 (m, 3H), 3.11-3.31 (m, 1H), 2.74-2.92 (m, 1H), 1.82-1.91 (m, 2H), 1.34-1.51 (m, 2H), 0.93-0.97 (d, 9H).

[151]

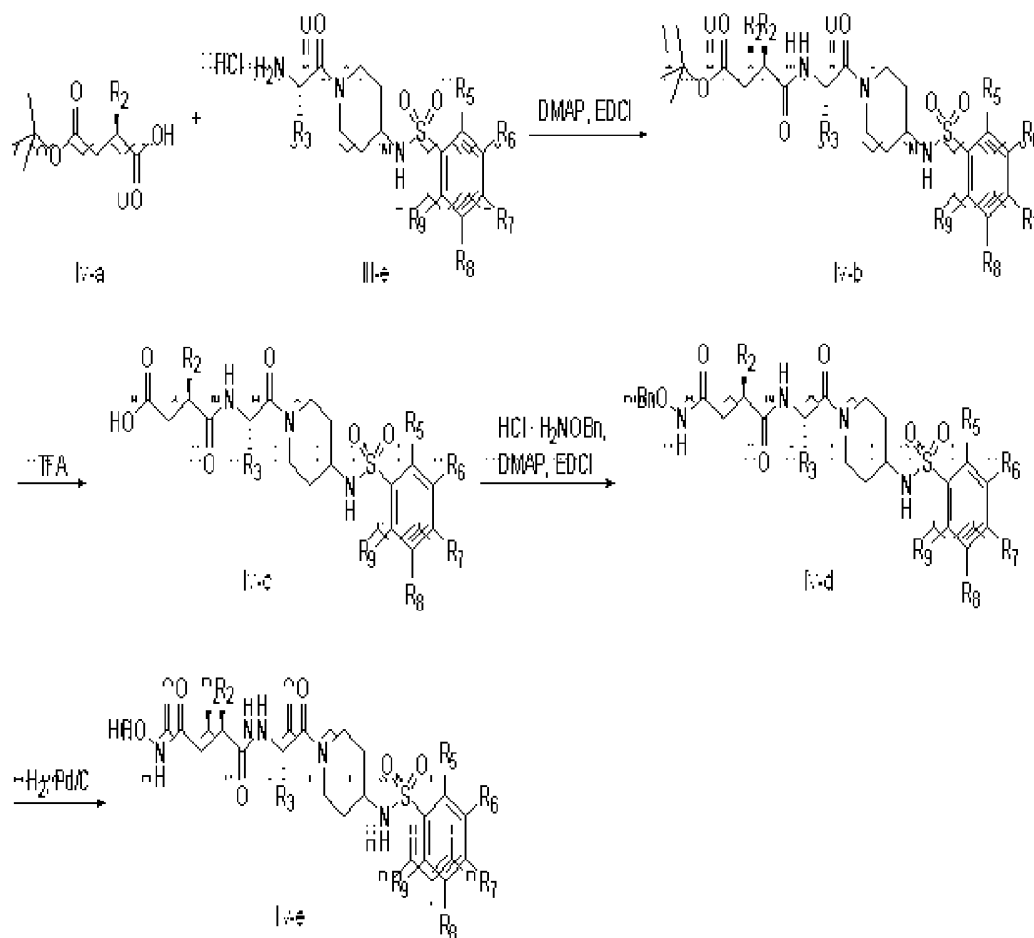
[152] **General procedure IV**

[153] Synthesis of (R)-2-Butyl-*N*¹-

{(S)-1-[4-(4-fluoro-benzenesulfonylamino)-piperidine-

[154] 1-carbonyl]-2,2-dimethyl-propyl]-*N*⁴-hydroxy-succinamide (Scheme IV)

[155]



Scheme IV

[156] Step 1: (R)-3-[(S)-1-[4-(4-Fluoro-benzenesulfonylamino)-piperidine-1-carbonyl]-

[157] 2,2-dimethyl-propylcarbamoyl]-heptanoic acid *tert*-butyl ester (IV-b)

[158] To a solution of IV-a ($R_2 = n$ -butyl, 0.5 g, 2.171 mmol) in CH_2Cl_2 (25 mL) at 0°C was added successively compound III-e ($R_3 = tert$ -butyl, $R_7 = F$, $R_5 = R_6 = R_8 = R_9 = H$, 1.06g, 2.598 mmol), 4-dimethylaminopyridine (DMAP) (0.66 g, 5.402 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) (0.5 g, 2.605 mmol). The mixture was stirred at room temperature overnight. The mixture was washed with 0.5N-HCl, aqueous saturated $NaHCO_3$ and brine, and dried over $MgSO_4$. After removing the solvent *in vacuo*, the residue was purified by column chromatography to give the title compound as a white solid (1 g, 79%).

[159] 1H -NMR($CDCl_3$): δ 7.72-7.79 (m, 2H), 7.07-7.14 (m, 2H), 4.90-4.94 (m, 1H), 4.51-4.70 (m, 1H), 4.19-4.25 (m, 2H), 3.19-3.31 (m, 1H), 2.72-2.81 (m, 1H), 2.53-2.63

(m, 2H), 2.30-2.38 (m, 1H), 2.09-2.23 (m, 2H), 1.25-1.71 (m, 19H), 0.99-1.00 (d, 9H), 0.83-0.89 (m, 3H).

[160]

[161] Step 2: (R)-3-[(S)-1-[4-(4-fluorobenzenesulfonylamino)-piperidin-1-yl]-2,2-dimethylpropyl]-heptanoic acid (IV-c)

[162] Compound IV-b (500 mg, 0.856 mmol) was dissolved in ethyl acetate (10 mL) and saturated with gaseous HCl, and the reaction mixture stirred until all of the starting material was consumed. The mixture was concentrated to give free acid as a white crystalline solid which was used in next step without further purification (430 mg, 96%).

[163] $^1\text{H-NMR}(\text{CDCl}_3)$: δ 7.87-7.93 (m, 2H), 7.23-7.30 (m, 2H), 4.76-4.83 (m, 1H), 4.27-4.40 (m, 1H), 3.91-4.18 (m, 2H), 3.12-3.22 (m, 1H), 2.69-2.81 (m, 2H), 2.46-2.49 (m, 1H), 2.38-2.43 (m, 1H), 2.18-2.25 (m, 1H), 1.75-1.81 (m, 2H), 1.12-1.52 (m, 8H), 0.90-0.94 (d, 9H), 0.77-0.81 (m, 3H).

[165]

[166] Step 3: (R)-*N*⁴-benzyloxy-2-butyl-*N*¹-[(S)-1-[4-(4-fluorobenzenesulfonylamino)-piperidin-1-yl]-2,2-dimethylpropyl]-succinamide (IV-d)

[167] To a solution of IV-c (100 mg, 0.189 mmol) in CH_2Cl_2 (10 mL) at 0°C was added successively *O*-benzylhydroxylamine hydrochloride (36.3 mg, 0.227 mmol), 4-dimethylaminopyridine (DMAP) (57.9 mg, 0.473 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) (43.6 mg, 0.227 mmol). The mixture was stirred at room temperature overnight. The mixture was washed with 0.5N-HCl, aqueous saturated NaHCO_3 and brine, and dried over MgSO_4 . After removing the solvent *in vacuo*, the residue was purified by column chromatography to give the title compound as a white solid (100 mg, 84%).

[168] $^1\text{H-NMR}(\text{CDCl}_3)$: δ 7.74-7.78 (m, 2H), 7.26-7.37 (m, 5H), 7.06-7.14 (m, 2H), 4.81-4.89 (m, 3H), 4.51-4.70 (m, 1H), 4.20-4.25 (m, 2H), 3.11-3.35 (m, 1H), 2.72-2.80 (m, 2H), 1.90-1.31 (m, 4H), 1.25-1.53 (m, 8H), 0.99-1.00 (d, 9H), 0.85-0.89 (m, 3H).

[170]

[171] Step 4: (R)-2-butyl-*N*¹-[(S)-1-[4-(4-fluorobenzenesulfonylamino)-piperidin-1-yl]-2,2-dimethylpropyl]-*N*⁴-hydroxy-succinamide (IV-e)

[172] To a solution of compound IV-d (50 mg, 0.079 mmol) in ethanol (5 mL) was added 10% palladium on charcoal (8.5 mg). A balloon of hydrogen was placed over the reaction mixture, and it was stirred for 8 hours. The charcoal was removed by filtration and the filtrate was concentrated to give a crude product. The crude product was purified by column chromatography to give the title compound as a pale yellow solid (30 mg, 70%).

[173] $^1\text{H-NMR}(\text{DMSO}-d_6)$: δ 7.91 (m, 2H), 7.26 (dt, 2H), 4.78 (t, 1H), 4.37 (m, 1H),

4.10 (m, 2H), 3.15 (t, 1H), 2.74 (m, 2H), 2.02-2.14 (m, 2H), 1.83 (br s, 2H), 1.16-1.38 (m, 8H), 0.77-0.95 (m, 12H).

[175]

[176]

General procedure V

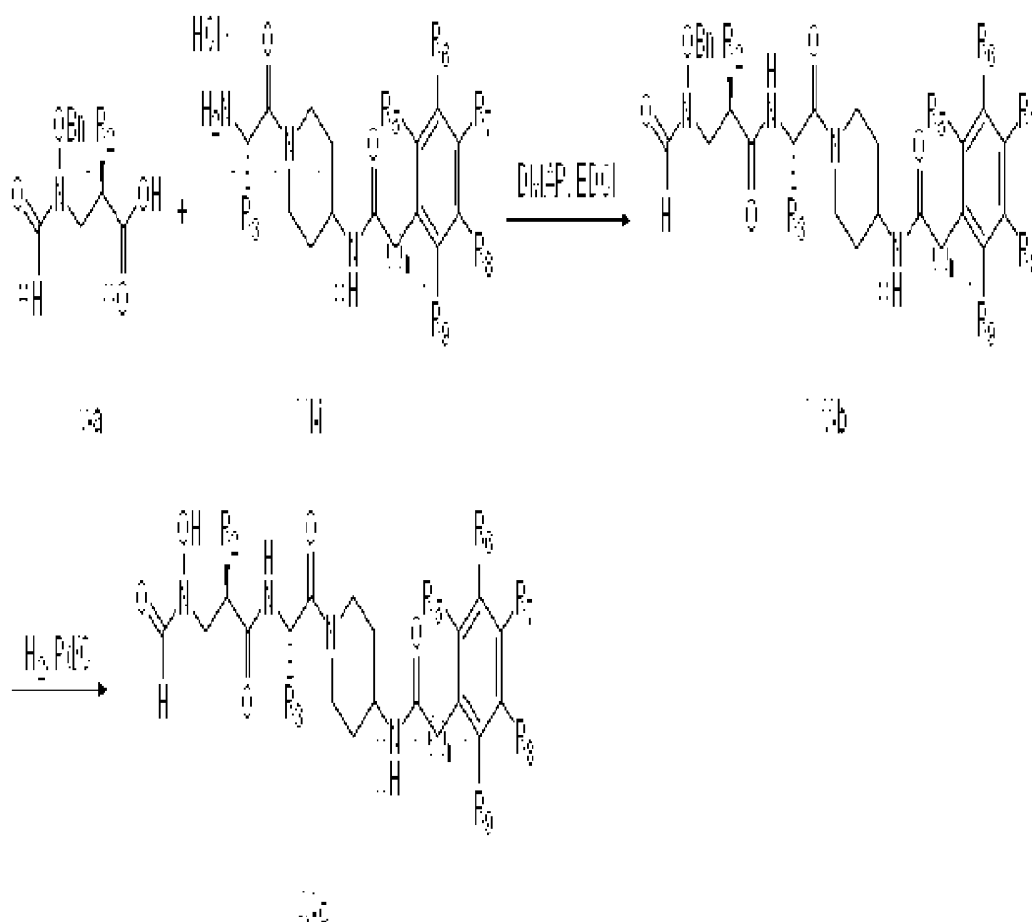
[177]

[178] Synthesis of *N*-(1-[(*S*)-2-[(*R*)-2-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-

[179] propionylamino]-3,3-dimethyl-buteryl]-piperidin-4-yl)-4-fluoro-benzamide

(Scheme V)

[180]



Scheme V

[181] Step 1: *N*-(1-[(*S*)-2-[(*R*)-3-(Benzyloxy-formyl-amino)-2-cyclopentylmethyl-

[182] propionylamino]-3,3-dimethyl-buteryl]-piperidin-4-yl)-4-fluoro-benzamide (V-b)

[183] To a solution of V-a (R_2 =cyclopentylmethyl, 638 mg, 2.090 mmol) in CH₂Cl₂ (25 mL) at 0°C was added successively compound I-i (R_3 =*tert*-butyl, R_5 = R_6 = R_8 = R_9 =H, R_7 =F, n =0, 855 mg, 2.299 mmol), 4-dimethylaminopyridine (DMAP) (562 mg, 4.599

mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) (440 mg, 2.299 mmol). The mixture was stirred at room temperature overnight. The mixture was washed with 0.5N-HCl, aqueous saturated NaHCO_3 and brine, and dried over MgSO_4 . After removing the solvent *in vacuo*, the residue was purified by column chromatography to give the title compound as a white solid (950 mg, 73%).

[184] $^1\text{H-NMR}(\text{CDCl}_3)$: δ 8.11 (s, 0.3H), 7.75-7.79 (m, 2.7H), 7.37 (m, 5H), 7.06-7.13 (m, 2H), 4.78-4.90 (m, 1H), 4.49-4.65 (m, 1H), 4.00-4.15 (m, 3H), 3.56-3.82 (m, 1H), 3.14-3.23 (m, 1H), 2.67-2.85 (m, 2H), 1.23-2.18 (m, 13H), 0.92-1.11 (m, 11H).

[185]

[186] Step 2: *N*-(1-[(*S*)-2-[(*R*)-2-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-
[187] propionylamino]-3,3-dimethyl-butyryl]-piperidin-4-yl)-4-fluoro-benzamide (V-c)

[188] To a solution of compound V-b (100 mg, 0.160 mmol) in ethanol (5 mL) was added 10% palladium on charcoal (17.2 mg). A balloon of hydrogen was placed over the reaction mixture, and it was stirred for 8 hours. The charcoal was removed by filtration and the filtrate was concentrated to give a crude product. The crude product was purified by column chromatography to give the title compound as a pale yellow solid (55 mg, 64%).

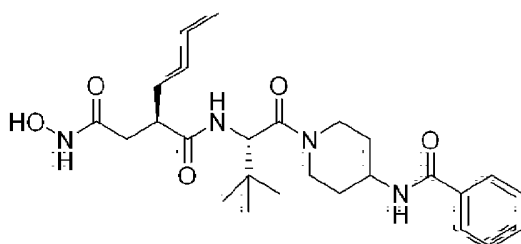
[189] $^1\text{H-NMR}(\text{CDCl}_3)$: δ 8.33 (s, 0.3H), 7.79-7.82 (m, 2.7H), 7.07-7.12 (m, 2H), 4.82-4.96 (m, 1H), 4.61-4.65 (m, 1H), 4.00-4.15 (m, 3H), 3.57-3.81 (m, 1H), 3.16-3.25 (m, 1H), 2.64-2.87 (m, 2H), 1.24-2.18 (m, 13H), 0.97-1.11 (m, 11H).

Mode for the Invention

[190] Example 1

[191] (R)-*N*¹-[(*S*)-1-(4-Benzoylamino-piperidine-1-carbonyl)-2,2-dimethyl-propyl] -
2-butyl-*N*⁴-hydroxy-succinamide

[192]



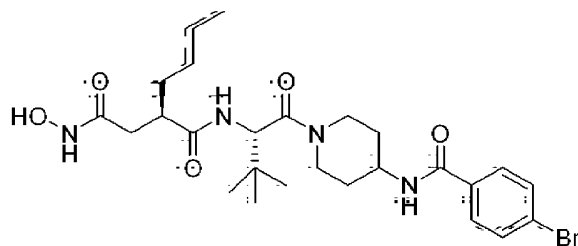
[193] The title compound was prepared from (R)-2-butyl-succinic acid 4-*tert*-butyl ester IV-a ($R_2 = n$ -butyl) and *N*-[1-[(*S*)-2-amino-3,3-dimethyl-butyryl]-piperidin-4-yl] - benzamide hydrochloride I-i ($R_3 = \text{tert-butyl}$, $n=0$, $R_5 = R_6 = R_7 = R_8 = R_9 = \text{H}$) according to General procedure IV.

[194] $^1\text{H-NMR}(\text{DMSO}-d_6)$: δ 7.73-7.83 (m, 2H), 7.43-7.51 (m, 3H), 4.78 (t, 1H), 4.37 (t, 1H), 4.00-4.15 (m, 2H), 3.15 (t, 1H), 2.75 (m, 2H), 1.98-2.20 (m, 2H), 1.82 (br s, 2H), 1.14-1.55 (m, 8H), 0.77-0.95.

[195]

[196] Example 2[197] (R)-N¹-[(S)-1-[4-(4-Bromo-benzoylamino)-piperidine-1-carbonyl]-2,2-dimethyl-propyl]-2-butyl-N⁴-hydroxy-succinamide

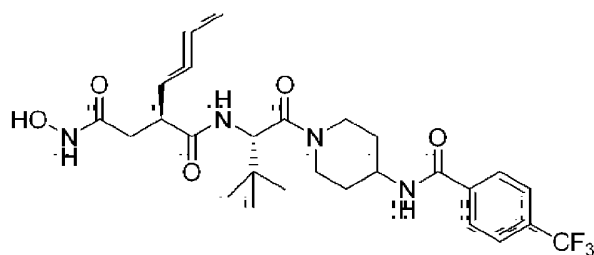
[198]

[199] The title compound was prepared from (R)-2-butyl-succinic acid 4-*tert*-butyl ester IV-a (R₂=*n*-butyl) and N-[1-((S)-2-amino-3,3-dimethyl-butyryl)-piperidin-4-yl]-4-bromo-benzamide hydrochloride I-i (R₃=*tert*-butyl, n=0, R₅=R₆=R₈=R₉=H, R₇=Br) according to General procedure IV.[200] ¹H-NMR(DMSO-d₆): δ 7.73-7.83 (m, 2H), 7.44-7.50 (m, 2H), 4.78 (t, 1H), 4.37 (t, 1H), 4.03-4.11 (m, 2H), 3.14 (t, 1H), 2.75 (m, 2H), 1.98-2.20 (m, 2H), 1.82 (br s, 2H), 1.16-1.34 (m, 8H), 0.77-0.95 (m, 12H).

[201]

[202] Example 3[203] (R)-2-Butyl-N¹-[(S)-2,2-dimethyl-1-[4-(4-trifluoromethyl-benzoylamino)-piperidine-1-carbonyl]-propyl]-N⁴-hydroxy-succinamide

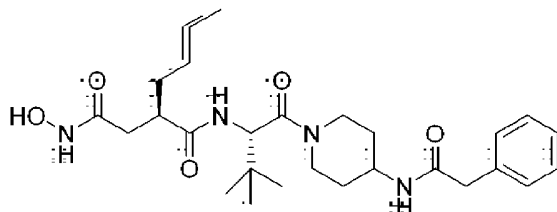
[204]

[205] The title compound was prepared from (R)-2-butyl-succinic acid 4-*tert*-butyl ester IV-a (R₂=*n*-butyl) and N-[1-((S)-2-amino-3,3-dimethyl-butyryl)-piperidin-4-yl]-4-trifluoromethyl-benzamide hydrochloride I-i (R₃=*tert*-butyl, n=0, R₅=R₆=R₈=R₉=H, R₇=CF₃) according to General procedure IV.[206] ¹H-NMR(DMSO-d₆): δ 8.03 (d, 2H), 7.82 (d, 2H), 4.78 (t, 1H), 4.31-4.42 (m, 1H), 4.03-4.11 (m, 2H), 3.13 (t, 1H), 2.71-2.74 (m, 2H), 2.14-2.20 (m, 1H), 1.97-2.04 (m, 1H), 1.85 (br s, 2H), 1.16-1.35 (m, 8H), 0.76-0.95 (m, 12H).

[207]

[208] Example 4[209] (R)-2-Butyl-*N*¹-[(S)-2,2-dimethyl-1-(4-phenylacetyl-amino-piperidine-1-carbonyl)-propyl]-*N*⁴-hydroxy-succinamide

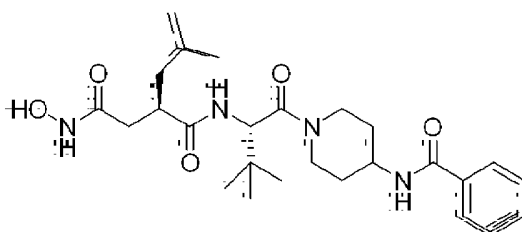
[210]

[211] The title compound was prepared from (R)-2-butyl-succinic acid 4-*tert*-butyl ester IV-a ($R_2 = n$ -butyl) and *N*-[1-((S)-2-amino-3,3-dimethyl-butyryl)-piperidin-4-yl] - 2-phenyl-acetamide hydrochloride I-i ($R_3 = \textit{tert}$ -butyl, $n=1$, $R_5 = R_6 = R_7 = R_8 = R_9 = H$) according to General procedure IV.[212] ¹H-NMR(DMSO-*d*₆): δ 7.22-7.27 (m, 5H), 4.76 (m, 1H), 4.03 (m, 3H), 3.35 (d, 2H), 3.16 (m, 1H), 2.77 (m, 2H), 1.98-2.12 (m, 2H), 1.72 (br s, 2H), 1.16 (m, 8H), 0.76-0.93 (m, 12H).

[213]

[214] Example 5[215] (R)-*N*¹-[(S)-1-(4-Benzoylamino-piperidine-1-carbonyl)-2,2-dimethyl-propyl]-*N*⁴-hydroxy-2-isobutyl-succinamide

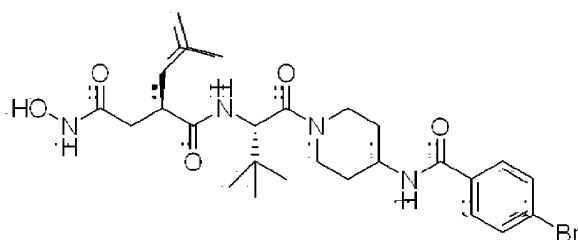
[216]

[217] The title compound was prepared from (R)-2-isobutyl-succinic acid 4-*tert*-butyl ester IV-a ($R_2 = \textit{iso}$ -butyl) and *N*-[1-((S)-2-amino-3,3-dimethyl-butyryl)-piperidin-4-yl] - benzamide hydrochloride I-i ($R_3 = \textit{tert}$ -butyl, $n=0$, $R_5 = R_6 = R_7 = R_8 = R_9 = H$) according to General procedure IV.[218] ¹H-NMR(DMSO-*d*₆): δ 7.69-7.80 (m, 2H), 7.34-7.46 (m, 3H), 4.71 (t, 1H), 4.23-4.35 (m, 1H), 3.91-4.02 (m, 2H), 3.07 (t, 1H), 2.58-2.77 (m, 2H), 1.89-2.15 (m, 2H), 1.74 (m, 2H), 1.28-1.48 (m, 4H), 1.00-1.03 (m, 1H), 0.70-0.88 (m, 15H).

[219]

[220] Example 6[221] (R)-*N*¹-[(S)-1-[4-(4-Bromo-benzoylamino)-piperidine-1-carbonyl] - 2,2-dimethyl-propyl]-*N*⁴-hydroxy-2-isobutyl-succinamide

[222]



[223] The title compound was prepared from (R)-2-isobutyl-succinic acid 4-*tert*-butyl ester IV-a ($R_2 = \text{iso-butyl}$) and *N*-[1-((S)-2-amino-3,3-dimethyl-butyl)-piperidin-4-yl] - 4-bromo-benzamide hydrochloride I-i ($R_3 = \text{tert-butyl}$, $n=0$, $R_5 = R_6 = R_8 = R_9 = H$, $R_7 = Br$) according to General procedure IV.

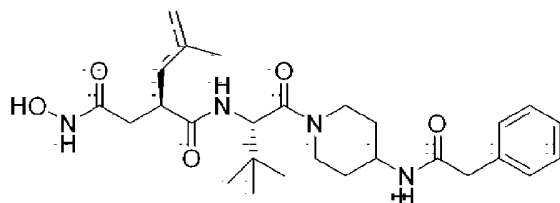
[224] 1H -NMR(DMSO- d_6): δ 7.68-7.79 (m, 2H), 7.34-7.46 (m, 2H), 4.71 (t, 1H), 4.22-4.35 (m, 1H), 3.91-4.02 (m, 2H), 3.07 (m, 1H), 2.59-2.77 (m, 2H), 1.89-2.09 (m, 2H), 1.74-1.83 (m, 2H), 1.15-1.65 (m, 4H), 1.00-1.04 (m, 1H), 0.70-0.88 (m, 15H).

[225]

[226] **Example 7**

[227] (R)-*N*¹-[(S)-2,2-Dimethyl-1-(4-phenylacetyl-amino-piperidine-1-carbonyl)-propyl]-*N*⁴-hydroxy-2-isobutyl-succinamide

[228]



[229] The title compound was prepared from (R)-2-isobutyl-succinic acid 4-*tert*-butyl ester IV-a ($R_2 = \text{iso-butyl}$) and *N*-[1-((S)-2-amino-3,3-dimethyl-butyl)-piperidin-4-yl] - 2-phenyl-acetamide hydrochloride I-i ($R_3 = \text{tert-butyl}$, $n=1$, $R_5 = R_6 = R_7 = R_8 = R_9 = H$) according to General procedure IV.

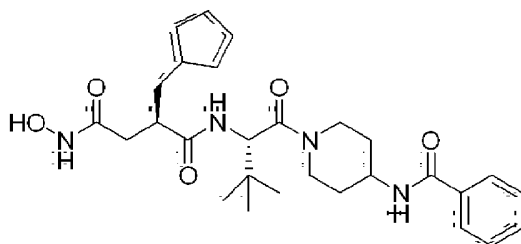
[230] 1H -NMR(DMSO- d_6): δ 7.14-7.20 (m, 5H), 4.67 (t, 1H), 3.93-4.18 (m, 2H), 3.67 (br s, 1H), 3.28 (d, 2H), 3.04 (m, 1H), 2.62-2.74 (m, 2H), 1.91-2.02 (m, 2H), 1.67 (m, 2H), 1.03-1.33 (m, 5H), 0.68-0.86 (m, 15H).

[231]

[232] **Example 8**

[233] (R)-*N*¹-[(S)-1-(4-Benzoylamino-piperidine-1-carbonyl)-2,2-dimethyl-propyl] - 2-cyclopentylmethyl-*N*⁴-hydroxy-succinamide

[234]



[235] The title compound was prepared from (R)-2-cyclopentylmethyl-succinic acid 4-*tert*-butyl ester IV-a (R_2 = cyclopentylmethyl) and *N*-[1-((S)-2-amino-3,3-dimethyl-butyryl)-piperidin-4-yl]-benzamide hydrochloride I-i (R_3 = *tert*-butyl, $n=0$, $R_5=R_6=R_7=R_8=R_9=H$) according to General procedure IV.

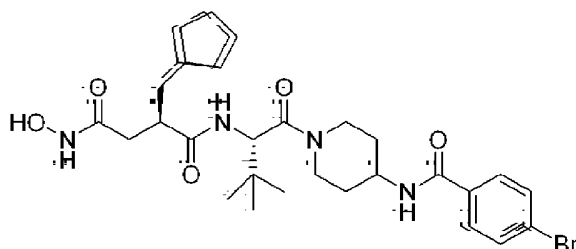
[236] 1H -NMR($CDCl_3$): δ 7.78 (d, 2H), 7.41-7.52 (m, 3H), 4.83-4.90 (m, 1H), 4.56 (dd, 1H), 4.11-4.23 (m, 2H), 3.18-3.30 (m, 1H), 2.70-2.89 (m, 2H), 2.31 (d, 2H), 2.05 (m, 2H), 1.39-1.72 (m, 11H), 1.00 (m, 11H).

[237]

[238] Example 9

[239] (R)-*N*¹-{[(S)-1-[4-(4-Bromo-benzoylamino)-piperidine-1-carbonyl]-2,2-dimethyl-propyl]-2-cyclopentylmethyl-*N*⁴-hydroxy-succinamide

[240]



[241] The title compound was prepared from (R)-2-cyclopentylmethyl-succinic acid 4-*tert*-butyl ester IV-a (R_2 = cyclopentylmethyl) and *N*-[1-((S)-2-amino-3,3-dimethyl-butyryl)-piperidin-4-yl]-4-bromo-benzamide hydrochloride I-i (R_3 = *tert*-butyl, $n=0$, $R_5=R_6=R_8=R_9=H$, $R_7=Br$) according to General procedure IV.

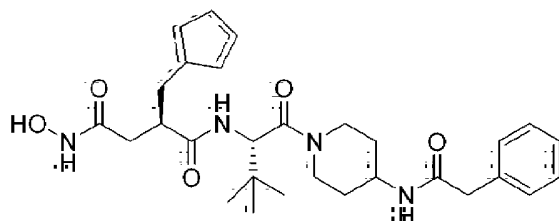
[242] 1H -NMR($CDCl_3$): δ 7.78 (d, 2H), 7.40-7.52 (m, 2H), 4.83-4.90 (m, 1H), 4.56 (dd, 1H), 4.11-4.22 (m, 2H), 3.17-3.30 (m, 1H), 2.70-2.83 (m, 2H), 2.31-2.42 (m, 2H), 2.05 (m, 2H), 1.51-1.72 (m, 11H), 0.99 (m, 11H).

[243]

[244] Example 10

[245] (R)-2-Cyclopentylmethyl-*N*¹-[(S)-2,2-dimethyl-1-(4-phenylacetyl-amino-piperidine-1-carbonyl)-propyl]-*N*⁴-hydroxy-succinamide

[246]



[247] The title compound was prepared from (R)-2-cyclopentylmethyl-succinic acid 4-*tert*-butyl ester IV-a (R_2 = cyclopentylmethyl) and *N*-[1-((S)-2-amino-3,3-dimethyl-butyl)-piperidin-4-yl]-2-phenyl-acetamide hydrochloride I-i (R_3 = *tert*-butyl, $n=1$, $R_5=R_6=R_7=R_8=R_9=H$) according to General procedure IV.

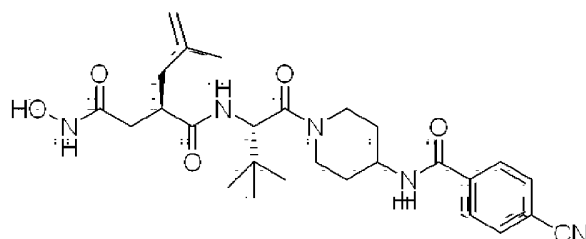
[248] 1H -NMR(DMSO- d_6): δ 7.24-7.27 (m, 5H), 4.79 (t, 1H), 4.03-4.30 (m, 2H), 3.73 (m, 1H), 3.36 (d, 2H), 3.13-3.17 (m, 1H), 2.69-2.80 (m, 2H), 2.02-2.10 (m, 2H), 1.27-1.74 (m, 13H), 0.90-0.94 (m, 11H).

[249]

[250] Example 11

[251] (R)- N^1 -[(S)-1-[4-(4-Cyano-benzoylamino)-piperidine-1-carbonyl]-2,2-dimethyl-propyl]- N^4 -hydroxy-2-isobutyl-succinamide

[252]



[253] The title compound was prepared from (R)-2-isobutyl-succinic acid 4-*tert*-butyl ester IV-a (R_2 = *iso*-butyl) and *N*-[1-((S)-2-amino-3,3-dimethyl-butyl)-piperidin-4-yl]-4-cyano-benzamide hydrochloride I-i (R_3 = *tert*-butyl, $n=0$, $R_5=R_6=R_8=R_9=H$, $R_7=CN$) according to General procedure IV.

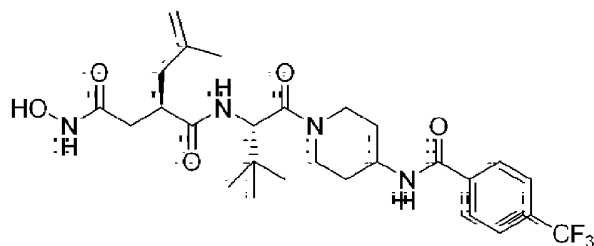
[254] 1H -NMR(DMSO- d_6): δ 7.75 (d, 2H), 7.25 (d, 2H), 4.79 (t, 1H), 4.25-4.50 (m, 1H), 3.90-4.20 (m, 2H), 3.16-3.18 (m, 1H), 2.86 (m, 2H), 1.99-2.13 (m, 2H), 1.81 (m, 2H), 1.42 (m, 4H), 1.10 (m, 1H), 0.79-0.96 (m, 15H).

[255]

[256] Example 12

[257] (R)- N^1 -[(S)-2,2-Dimethyl-1-[4-(4-trifluoromethyl-benzoylamino)-piperidine-1-carbonyl]-propyl]- N^4 -hydroxy-2-isobutyl-succinamide

[258]



[259] The title compound was prepared from (R)-2-isobutyl-succinic acid 4-*tert*-butyl ester IV-a (R_2 = *iso*-butyl) and *N*-[1-((S)-2-amino-3,3-dimethyl-butyryl)-piperidin-4-yl] - 4-trifluoromethyl-benzamide hydrochloride I-i (R_3 = *tert*-butyl, $n=0$, $R_5=R_6=R_8=R_9=H$, $R_7=CF_3$) according to General procedure IV.

[260] 1H -NMR(DMSO- d_6): δ 8.04 (d, 2H), 7.84 (d, 2H), 4.80 (t, 1H), 4.25-4.50 (m, 1H), 3.90-4.20 (m, 2H), 3.16 (m, 1H), 2.72-2.86 (m, 2H), 1.99-2.14 (m, 2H), 1.87 (br s, 2H), 1.40 (m, 4H), 1.10 (m, 1H), 0.79-0.96 (m, 15H).

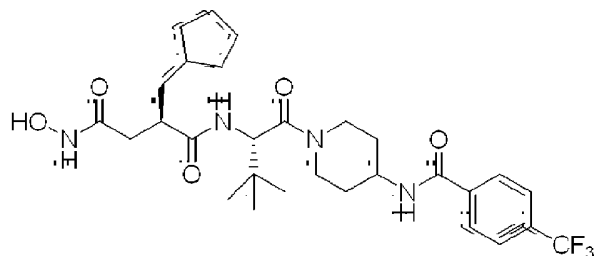
[261]

[262] Example 13

[263] (R)-2-Cyclopentylmethyl-*N*¹ -

{(S)-2,2-dimethyl-1-[4-(4-trifluoromethyl-benzoylamino)-piperidine-1-carbonyl]-propyl}-*N*⁴-hydroxy-succinamide

[264]



[265] The title compound was prepared from (R)-2-cyclopentylmethyl-succinic acid 4-*tert*-butyl ester IV-a (R_2 = cyclopentylmethyl) and *N*-[1-((S)-2-amino-3,3-dimethyl-butyryl)-piperidin-4-yl]-4-trifluoromethyl-benzamide hydrochloride I-i (R_3 = *tert*-butyl, $n=0$, $R_5=R_6=R_8=R_9=H$, $R_7=CF_3$) according to General procedure IV.

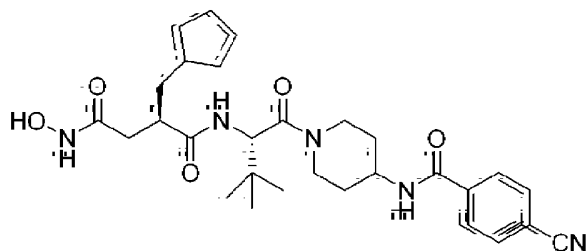
[266] 1H -NMR(CDCl₃): δ 7.82-7.91 (m, 2H), 7.66 (d, 2H), 4.85-4.94 (m, 1H), 4.50-4.67 (m, 1H), 4.11-4.23 (m, 2H), 3.16-3.29 (m, 1H), 2.64-2.89 (m, 2H), 2.34-2.43 (m, 2H), 2.05 (m, 3H), 1.26-1.67 (m, 10H), 0.97 (m, 11H).

[267]

[268] Example 14

[269] (R)-*N*¹-{(S)-1-[4-(4-Cyano-benzoylamino)-piperidine-1-carbonyl] - 2,2-dimethyl-propyl}-2-cyclopentylmethyl-*N*⁴-hydroxy-succinamide

[270]



[271] The title compound was prepared from (R)-2-cyclopentylmethyl-succinic acid 4-*tert*-butyl ester IV-a (R_2 = cyclopentylmethyl) and *N*-[1-((S)-2-amino-3,3-dimethyl-butyryl)-piperidin-4-yl]-4-cyano-benzamide hydrochloride I-i (R_3 = *tert*-butyl, $n=0$, $R_5=R_6=R_8=R_9=H$, $R_7=CN$) according to General procedure IV.

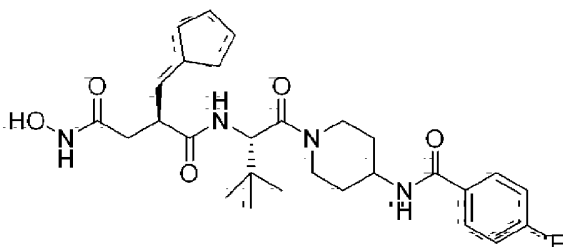
[272] 1H -NMR($CDCl_3$): δ 7.61-7.70 (m, 2H), 7.20 (d, 2H), 4.82-4.94 (m, 1H), 4.57 (dd, 1H), 4.11-4.22 (m, 2H), 3.15-3.33 (m, 1H), 2.64-2.88 (m, 2H), 2.38 (m, 2H), 1.28-2.18 (m, 13H), 0.97 (m, 11H).

[273]

[274] **Example 15**

[275] (R)-2-Cyclopentylmethyl-*N*¹-[1-((S)-1-[4-(4-fluoro-benzoylamino)-piperidine-1-carbonyl]-2,2-dimethyl-propyl)-*N*⁴-hydroxy-succinamide

[276]



[277] The title compound was prepared from (R)-2-cyclopentylmethyl-succinic acid 4-*tert*-butyl ester IV-a (R_2 = cyclopentylmethyl) and *N*-[1-((S)-2-amino-3,3-dimethyl-butyl)-piperidin-4-yl]-4-fluoro-benzamide hydrochloride I-i (R_3 = *tert*-butyl, $n=0$, $R_5=R_6=R_8=R_9=H$, $R_7=F$) according to General procedure IV.

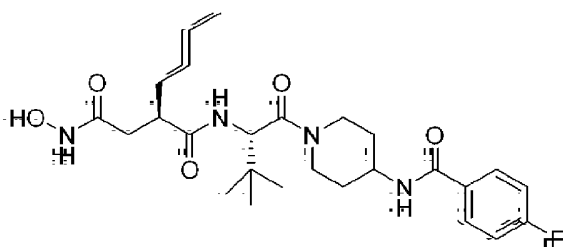
[278] 1H -NMR($CDCl_3$): δ 7.78 (m, 2H), 7.04-7.10 (m, 2H), 4.86-4.89 (m, 1H), 4.48-4.66 (m, 1H), 4.11-4.18 (m, 2H), 3.18-3.23 (m, 1H), 2.64-2.92 (m, 2H), 2.05-2.44 (m, 4H), 1.26-1.68 (m, 11H), 0.96 (m, 11H).

[279]

[280] **Example 16**

[281] (R)-2-Butyl-*N*¹-[1-((S)-1-[4-(4-fluoro-benzoylamino)-piperidine-1-carbonyl]-2,2-dimethyl-propyl)-*N*⁴-hydroxy-succinamide

[282]



[283] The title compound was prepared from (R)-2-butyl-succinic acid 4-*tert*-butyl ester IV-a ($R_2=n$ -butyl) and *N*-[1-((S)-2-amino-3,3-dimethyl-butyryl)-piperidin-4-yl] - 4-fluoro-benzamide hydrochloride I-i ($R_3=tert$ -butyl, $n=0$, $R_5=R_6=R_8=R_9=H$, $R_7=F$) according to General procedure IV.

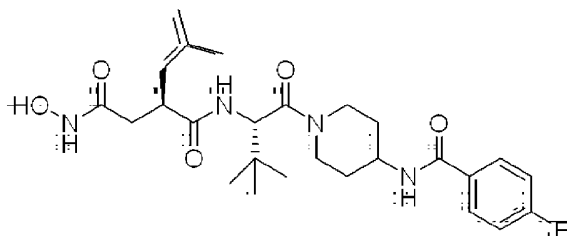
[284] 1H -NMR(DMSO- d_6): δ 7.91 (m, 2H), 7.26 (dt, 2H), 4.78 (t, 1H), 4.37 (m, 1H), 4.10 (m, 2H), 3.15 (t, 1H), 2.74 (m, 2H), 2.02-2.14 (m, 2H), 1.83 (br s, 2H), 1.16-1.38 (m, 8H), 0.77-0.95 (m, 12H).

[285]

[286] Example 17

[287] (R)-*N*¹-[(S)-1-[4-(4-Fluoro-benzoylamino)-piperidine-1-carbonyl] - 2,2-dimethyl-propyl]-*N*⁴-hydroxy-2-isobutyl-succinamide

[288]



[289] The title compound was prepared from (R)-2-isobutyl-succinic acid 4-*tert*-butyl ester IV-a ($R_2=iso$ -butyl) and *N*-[1-((S)-2-amino-3,3-dimethyl-butyryl)-piperidin-4-yl] - 4-fluoro-benzamide hydrochloride I-i ($R_3=tert$ -butyl, $n=0$, $R_5=R_6=R_8=R_9=H$, $R_7=F$) according to General procedure IV.

[290] 1H -NMR(DMSO- d_6): δ 7.91 (m, 2H), 7.26 (t, 2H), 4.78 (t, 1H), 4.37 (m, 1H), 4.11 (m, 2H), 3.14 (t, 1H), 2.70-2.84 (m, 2H), 1.97-2.13 (m, 2H), 1.83 (br s, 2H), 1.39 (m, 4H), 1.09 (m, 1H), 0.77-0.95 (m, 15H).

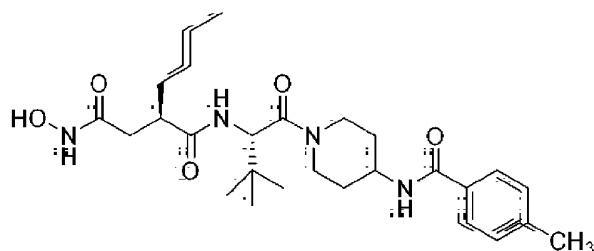
[291]

[292] Example 18

[293] (R)-2-Butyl-*N*¹-[(S)-2,2-dimethyl-1-[4-(4-methyl-benzoylamino)-piperidine-1-carbonyl]-propyl]-*N*⁴-hydroxy-succinamide

[294]

[295]



[296] The title compound was prepared from (R)-2-butyl-succinic acid 4-*tert*-butyl ester IV-a ($R_2=n$ -butyl) and *N*-[1-((S)-2-amino-3,3-dimethyl-butyryl)-piperidin-4-yl] - 4-methyl-benzamide hydrochloride I-i ($R_3=tert$ -butyl, $n=0$, $R_5=R_6=R_8=R_9=H$, $R_7=CH_3$) according to General procedure IV.

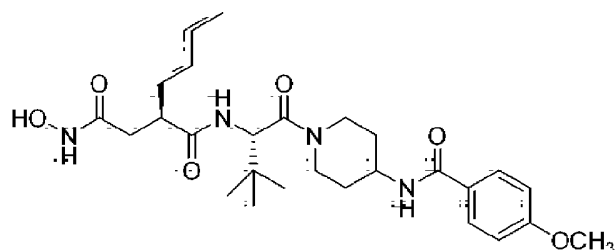
[297] 1H -NMR(CD_3OD): δ 7.72 (t, 2H), 7.25 (d, 2H), 4.89-4.94 (m, 1H), 4.54 (dd, 1H), 4.08-4.26 (m, 2H), 3.21-3.31 (m, 1H), 2.74-2.86 (m, 2H), 2.37 (s, 3H), 2.17-2.41 (m, 2H), 2.01 (t, 2H), 1.21-1.64 (m, 8H), 0.86-1.04 (m, 12H).

[298]

[299] Example 19

[300] (R)-2-Butyl- N^4 -hydroxy- N^1 -
 {(S)-1-[4-(4-methoxy-benzoylamino)-piperidine-1-carbonyl]-2,2-dimethyl-propyl}-succinamide

[301]



[302] The title compound was prepared from (R)-2-butyl-succinic acid 4-*tert*-butyl ester IV-a ($R_2=n$ -butyl) and *N*-[1-((S)-2-amino-3,3-dimethyl-butyryl)-piperidin-4-yl] - 4-methoxy-benzamide hydrochloride I-i ($R_3=tert$ -butyl, $n=0$, $R_5=R_6=R_8=R_9=H$, $R_7=OCH_3$) according to General procedure IV.

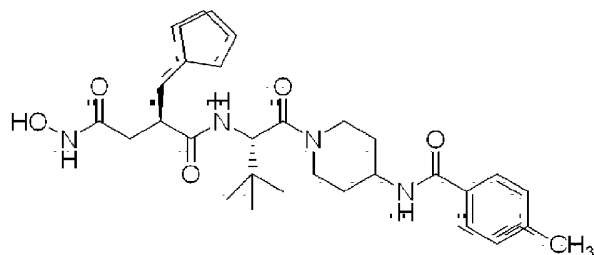
[303] 1H -NMR(CD_3OD): δ 7.79 (t, 2H), 6.96 (d, 2H), 4.88-4.94 (m, 1H), 4.53 (dd, 1H), 4.08-4.26 (m, 2H), 3.83 (s, 3H), 3.21-3.31 (m, 1H), 2.74-2.86 (m, 2H), 2.19-2.40 (m, 2H), 2.01 (t, 2H), 1.21-1.63 (m, 8H), 0.86-1.04 (m, 12H).

[304]

[305] Example 20

[306] (R)-2-Cyclopentylmethyl- N^1 -
 {(S)-2,2-dimethyl-1-[4-(4-methyl-benzoylamino)-piperidine-1-carbonyl]-propyl}- N^4 -hydroxy-succinamide

[307]



[308] The title compound was prepared from (R)-2-cyclopentylmethyl-succinic acid 4-*tert*-butyl ester IV-a (R_2 = cyclopentylmethyl) and *N*-[1-((S)-2-amino-3,3-dimethyl-butyryl)-piperidin-4-yl]-4-methyl-benzamide hydrochloride I-i (R_3 = *tert*-butyl, $n=0$, $R_5=R_6=R_8=R_9=H$, $R_7=CH_3$) according to General procedure IV.

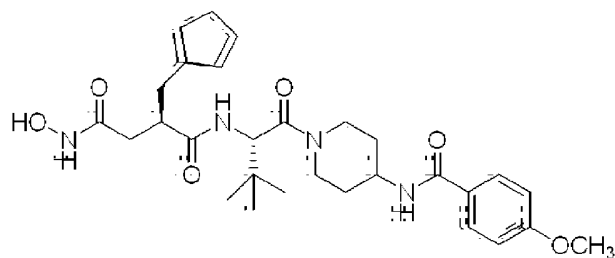
[309] 1H -NMR(DMSO- d_6): δ 7.74 (t, 2H), 7.23 (d, 2H), 4.80 (t, 1H), 4.29-4.42 (m, 2H), 4.00-4.10 (m, 2H), 3.13 (t, 1H), 2.68-2.80 (m, 2H), 2.33 (s, 3H), 1.97-2.12 (m, 2H), 1.08-1.81 (m, 13H), 0.93 (d, 11H).

[310]

[311] Example 21

[312] (R)-2-Cyclopentylmethyl-*N*⁴-hydroxy-*N*¹-[(S)-1-[4-(4-methoxy-benzoylamino)-piperidine-1-carbonyl]-2,2-dimethyl-propyl]-succinamide

[313]



[314] The title compound was prepared from (R)-2-cyclopentylmethyl-succinic acid 4-*tert*-butyl ester IV-a (R_2 = cyclopentylmethyl) and *N*-[1-((S)-2-amino-3,3-dimethyl-butyryl)-piperidin-4-yl]-4-methoxy-benzamide hydrochloride I-i (R_3 = *tert*-butyl, $n=0$, $R_5=R_6=R_8=R_9=H$, $R_7=OCH_3$) according to General procedure IV.

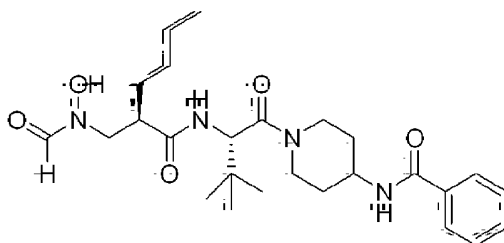
[315] 1H -NMR(DMSO- d_6): δ 7.81 (dd, 2H), 6.96 (dd, 2H), 4.80 (t, 1H), 4.29-4.42 (m, 1H), 4.00-4.10 (m, 2H), 3.78 (s, 3H), 3.13 (t, 1H), 2.67-2.80 (m, 2H), 1.97-2.12 (m, 2H), 1.13-1.81 (m, 13H), 0.93 (d, 11H, $J=11.5$ Hz).

[316]

[317] Example 22

[318] *N*-[1-((*S*)-2-[(*R*)-2-[(Formyl-hydroxy-amino)-methyl]-hexanoylamino]-3,3-dimethyl-butyryl)-piperidin-4-yl]-benzamide

[319]



[320] The title compound was prepared from (*R*)-2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid V-a ($R_2 = n$ -butyl) and *N*-[1-((*S*)-2-amino-3,3-dimethyl-butyryl)-piperidin-4-yl]-benzamide hydrochloride I-i ($R_3 = tert$ -butyl, $n=0$, $R_5 = R_6 = R_7 = R_8 = R_9 = H$) according to General procedure V.

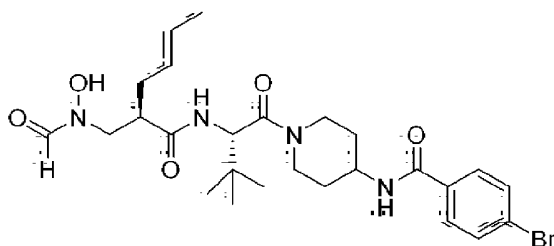
[321] 1H -NMR($CDCl_3$): δ 8.35 (s, 0.3H), 7.75-7.82 (m, 2.7H), 7.40-7.52 (m, 3H), 4.84-4.96 (m, 1H), 4.59 (dd, 1H), 3.96-4.28 (m, 2H), 3.53-3.80 (m, 2H), 3.17-3.26 (m, 1H), 2.70-2.87 (m, 2H), 2.05-2.10 (m, 2H), 1.32-1.59 (m, 8H), 0.85-1.00 (m, 12H).

[322]

[323] **Example 23**

[324] 4-Bromo-*N*-[1-((*S*)-2-[(*R*)-2-[(formyl-hydroxy-amino)-methyl]-hexanoylamino]-3,3-dimethyl-butyryl)-piperidin-4-yl]-benzamide

[325]



[326] The title compound was prepared from (*R*)-2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid V-a ($R_2 = n$ -butyl) and *N*-[1-((*S*)-2-amino-3,3-dimethyl-butyryl)-piperidin-4-yl]-4-bromo-benzamide hydrochloride I-i ($R_3 = tert$ -butyl, $n=0$, $R_5 = R_6 = R_7 = R_8 = R_9 = H$, $R_7 = Br$) according to General procedure V.

[327] 1H -NMR($CDCl_3$): δ 7.75-7.82 (m, 2H), 7.41-7.51 (m, 2H), 4.89-4.96 (m, 1H), 4.62 (dd, 1H), 4.21 (m, 2H), 3.46-3.73 (m, 1H), 3.11-3.30 (m, 2H), 2.59-2.85 (m, 2H), 2.05-2.11 (m, 2H), 1.29-1.58 (m, 8H), 0.85-1.01 (m, 12H).

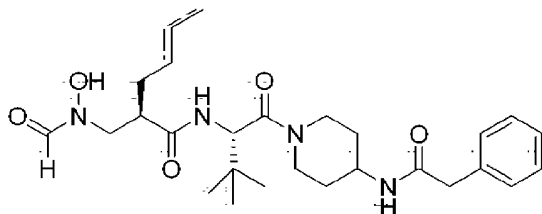
[328]

[329] **Example 24**

[330] (*R*)-2-[(Formyl-hydroxy-amino)-methyl]-hexanoic acid

[(S)-2,2-dimethyl-1-(4-phenylacetyl-amino-piperidine-1-carbonyl)-propyl]-amide

[331]



[332] The title compound was prepared from (R)-2-[(benzyloxy-formyl-amino)-methyl] - hexanoic acid V-a ($R_2 = n$ -butyl) and *N*-[1-((S)-2-amino-3,3-dimethyl-butyryl)-piperidin-4-yl]-2-phenyl-acetamide hydrochloride I-i ($R_3 = \text{tert-butyl}$, $n=1$, $R_5 = R_6 = R_7 = R_8 = R_9 = H$) according to General procedure V.

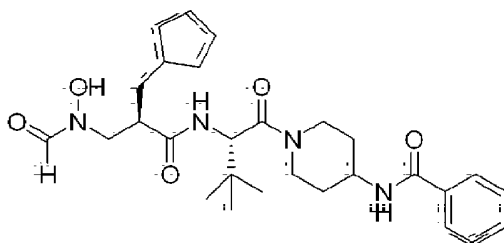
[333] $^1\text{H-NMR}(\text{CDCl}_3)$: δ 8.25 (s, 0.3H), 7.77 (s, 0.7H), 7.22-7.36 (m, 5H), 4.88 (d, 1H), 4.44 (dd, 1H), 4.04 (m, 2H), 3.45-3.75 (m, 4H), 3.08-3.17 (m, 1H), 2.62-2.80 (m, 2H), 1.93 (m, 2H), 1.25-1.55 (m, 8H), 0.79-0.96 (m, 12H).

[334]

[335] Example 25

[336] *N*-(1-{(S)-2-[(R)-2-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionyl-amino]-3,3-dimethyl-butyryl}-piperidin-4-yl)-benzamide

[337]



[338] The title compound was prepared from (R)-3-(Benzyloxy-formyl-amino)-2-cyclopentylmethyl-propionic acid V-a ($R_2 = \text{cyclopentylmethyl}$) and *N*-[1-((S)-2-amino-3,3-dimethyl-butyryl)-piperidin-4-yl] - benzamide hydrochloride I-i ($R_3 = \text{tert-butyl}$, $n=0$, $R_5 = R_6 = R_7 = R_8 = R_9 = H$) according to General procedure V.

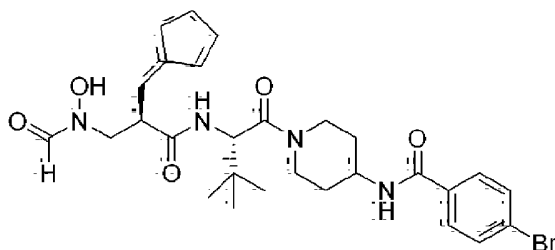
[339] $^1\text{H-NMR}(\text{DMSO}-d_6)$: δ 8.22 (s, 0.3H), 7.75-7.86 (m, 2.7H), 7.44-7.51 (m, 3H), 4.86 (t, 1H), 4.28-4.44 (m, 1H), 3.99-4.13 (m, 2H), 3.54-3.67 (m, 1H), 3.12-3.43 (m, 2H), 2.67-2.92 (m, 2H), 1.15-2.50 (m, 13H), 0.90-0.94 (m, 11H).

[340]

[341] Example 26

[342] 4-Bromo-*N*-(1-{(S)-2-[(R)-2-cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionyl-amino]-3,3-dimethyl-butyryl}-piperidin-4-yl)-benzamide

[343]



[344] The title compound was prepared from (R)-3-(Benzyloxy-formyl-amino)-2-cyclopentylmethyl-propionic acid V-a (R_2 =cyclopentylmethyl) and *N*-[1-((S)-2-amino-3,3-dimethyl-butyryl)-piperidin-4-yl] - 4-bromo-benzamide hydrochloride I-i (R_3 =*tert*-butyl, $n=0$, $R_5=R_6=R_7=R_8=R_9=H$, $R_7=Br$) according to General procedure V.

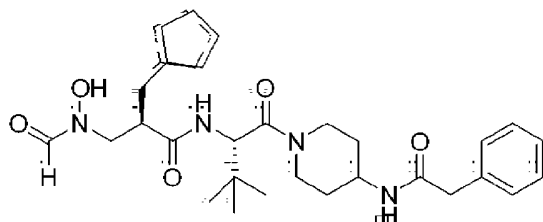
[345] 1H -NMR($CDCl_3$): δ 7.77 (d, 2H), 7.40-7.53 (m, 2H), 4.70 (br s, 1H), 4.43 (m, 1H), 4.08-4.27 (m, 2H), 3.80 (m, 1H), 2.74-3.16 (m, 2H), 2.04-2.18 (m, 4H), 1.43-1.75 (m, 11H), 0.94-1.07 (m, 11H).

[346]

[347] Example 27

[348] (R)-2-Cyclopentylmethyl-*N*-[1-((S)-2,2-dimethyl-1-(4-phenylacetylamino-piperidine-1-carbonyl)-propyl]-3-(formyl-hydroxy-amino)-propionamide

[349]



[350] The title compound was prepared from (R)-3-(Benzyloxy-formyl-amino)-2-cyclopentylmethyl-propionic acid V-a (R_2 =cyclopentylmethyl) and *N*-[1-((S)-2-amino-3,3-dimethyl-butyryl)-piperidin-4-yl] - 2-phenyl-acetamide hydrochloride I-i (R_3 =*tert*-butyl, $n=1$, $R_5=R_6=R_7=R_8=R_9=H$) according to General procedure V.

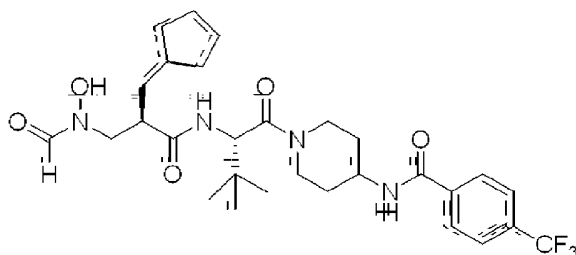
[351] 1H -NMR($CDCl_3$): δ 8.25 (s, 0.4H), 7.77 (s, 0.6H), 7.21-7.37 (m, 5H), 4.78-4.89 (m, 1H), 4.30-4.56 (m, 1H), 4.02 (m, 2H), 3.71-3.79 (m, 1H), 3.50-3.57 (m, 4H), 3.12 (m, 1H), 2.60-2.81 (m, 2H), 1.43-1.79 (m, 11H), 0.92-1.06 (m, 11H).

[352]

[353] Example 28

[354] *N*-(1-((S)-2-[(R)-2-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionylamino]-3,3-dimethyl-butyryl)-piperidin-4-yl)-4-trifluoromethyl-benzamide

[355]



[356] The title compound was prepared from (R)-3-(Benzyloxy-formyl-amino)-2-cyclopentylmethyl-propionic acid V-a (R_2 =cyclopentylmethyl) and N-[1-((S)-2-amino-3,3-dimethyl-butyryl)-piperidin-4-yl] - 4-trifluoromethyl-benzamide hydrochloride I-i (R_3 =*tert*-butyl, $n=0$, $R_5=R_6=R_8=R_9=H$, $R_7=CF_3$) according to General procedure V.

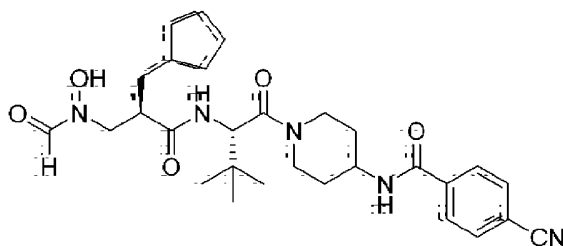
[357] 1H -NMR($CDCl_3$): δ 8.32 (s, 0.3H), 7.86-7.93 (m, 2H), 7.78 (s, 0.7H), 7.68 (d, 2H), 4.82-4.93 (m, 1H), 4.61-4.65 (m, 1H), 3.98-4.31 (m, 3H), 3.58-3.73 (m, 1H), 3.21-3.25 (m, 1H), 2.63-2.90 (m, 2H), 2.04-2.18 (m, 3H), 1.26-1.82 (m, 10H), 0.97-1.11 (m, 11H).

[358]

[359] **Example 29**

[360] 4-Cyano-N-(1-{(S)-2-[(R)-2-cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionylamino]-3,3-dimethyl-butyryl}-piperidin-4-yl)-benzamide

[361]



[362] The title compound was prepared from (R)-3-(Benzyloxy-formyl-amino)-2-cyclopentylmethyl-propionic acid V-a (R_2 =cyclopentylmethyl) and N-[1-((S)-2-amino-3,3-dimethyl-butyryl)-piperidin-4-yl] - 4-cyano-benzamide hydrochloride I-i (R_3 =*tert*-butyl, $n=0$, $R_5=R_6=R_8=R_9=H$, $R_7=CN$) according to General procedure V.

[363] 1H -NMR($CDCl_3$): δ 8.35 (s, 0.3H), 7.80 (s, 0.7H), 7.64-7.73 (m, 2H), 7.21-7.27 (m, 2H), 4.83-4.96 (m, 1H), 4.61 (dd, 1H), 4.16 (m, 3H), 3.54-3.74 (m, 1H), 3.21 (m, 1H), 2.64-2.87 (m, 2H), 1.26-2.06 (m, 13H), 0.96-1.10 (m, 11H).

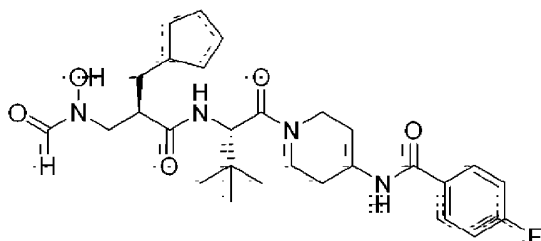
[364]

[365] **Example 30**

[366] N-(1-{(S)-2-[(R)-2-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionylamino]

] -3,3-dimethyl-butyl)-piperidin-4-yl]-4-fluoro-benzamide

[367]



[368] The title compound was prepared from (R)-3-(Benzyloxy-formyl-amino)-2-cyclopentylmethyl-propionic acid V-a (R_2 = cyclopentylmethyl) and *N*-[1-((S)-2-amino-3,3-dimethyl-butyl)-piperidin-4-yl] - 4-fluoro-benzamide hydrochloride I-i (R_3 = *tert*-butyl, $n=0$, $R_5=R_6=R_8=R_9=H$, $R_7=F$) according to General procedure V.

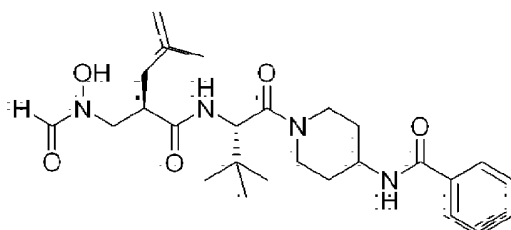
[369] $^1\text{H-NMR}(\text{CDCl}_3)$: δ 8.33 (s, 0.3H), 7.79-7.82 (m, 2.7H), 7.07-7.12 (m, 2H), 4.82-4.96 (m, 1H), 4.61-4.65 (m, 1H), 4.00-4.15 (m, 3H), 3.57-3.81 (m, 1H), 3.16-3.25 (m, 1H), 2.64-2.87 (m, 2H), 1.24-2.18 (m, 13H), 0.97-1.11 (m, 11H).

[370]

[371] Example 31

[372] *N*-[1-((S)-2-{(R)-2-[(Formyl-hydroxy-amino)-methyl] - 4-methyl-pentanoylamino}-3,3-dimethyl-butyl)-piperidin-4-yl]-benzamide

[373]



[374] The title compound was prepared from (R)-2-[(Benzyloxy-formyl-amino)-methyl] - 4-methyl-pentanoic acid V-a (R_2 = *iso*-butyl) and *N*-[1-((S)-2-amino-3,3-dimethyl-butyl)-piperidin-4-yl]-benzamide hydrochloride I-i (R_3 = *tert*-butyl, $n=0$, $R_5=R_6=R_7=R_8=R_9=H$) according to General procedure V.

[375] $^1\text{H-NMR}(\text{DMSO}-d_6)$: δ 8.21 (s, 0.3H), 7.81-7.84 (m, 2H), 7.74 (s, 0.7H), 7.41-7.50 (m, 3H), 4.83 (m, 1H), 4.34 (dd, 1H), 4.11 (m, 2H), 3.54-3.61 (m, 1H), 3.11-3.19 (m, 2H), 2.60-3.00 (m, 2H), 1.81-1.86 (m, 2H), 1.24-1.41 (m, 4H), 1.10 (m, 1H), 0.82-0.93 (m, 15H).

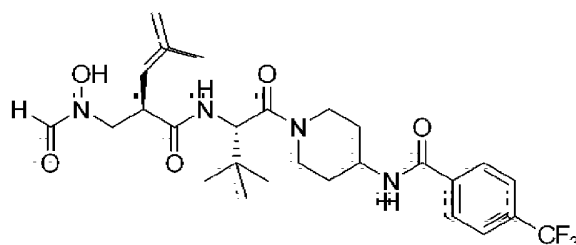
[376]

[377] Example 32

[378] *N*-[1-((S)-2-{(R)-2-[(Formyl-hydroxy-amino)-methyl] -

4-methyl-pentanoylamino}-3,3-dimethyl-buteryl)-piperidin-4-yl]-4-trifluoromethyl-benzamide

[379]



[380] The title compound was prepared from (R)-2-[(Benzyloxy-formyl-amino)-methyl] - 4-methyl-pentanoic acid V-a ($R_2 = \text{iso-butyl}$) and N - [1-((S)-2-amino-3,3-dimethyl-buteryl)-piperidin-4-yl]-4-trifluoromethyl-benzamide hydrochloride I-i ($R_3 = \text{tert-butyl}$, $n=0$, $R_5 = R_6 = R_8 = R_9 = H$, $R_7 = CF_3$) according to General procedure V.

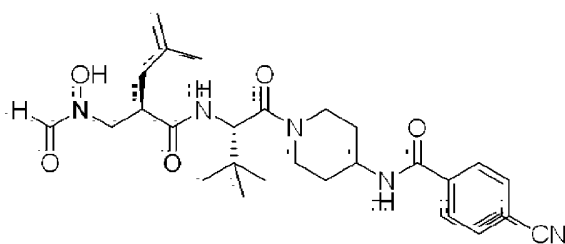
[381] 1H -NMR(DMSO- d_6): δ 8.21 (s, 0.4H), 8.02 (dd, 2H), 7.83 (d, 2H), 7.74 (s, 0.6H), 4.83 (t, 1H), 4.35 (dd, 1H), 4.12 (m, 2H), 3.54-3.61 (m, 1H), 3.12-3.32 (m, 2H), 2.60-3.00 (m, 2H), 1.84-1.98 (m, 2H), 1.00-1.44 (m, 5H), 0.78-0.93 (m, 15H).

[382]

[383] Example 33

[384] 4-Cyano-N-[1-((S)-2-((R)-2-[(formyl-hydroxy-amino)-methyl]-4-methyl-pentanoyl amino)-3,3-dimethyl-buteryl)-piperidin-4-yl]-benzamide

[385]



[386] The title compound was prepared from (R)-2-[(Benzyloxy-formyl-amino)-methyl] - 4-methyl-pentanoic acid V-a ($R_2 = \text{iso-butyl}$) and N - [1-((S)-2-amino-3,3-dimethyl-buteryl)-piperidin-4-yl]-4-cyano-benzamide hydrochloride I-i ($R_3 = \text{tert-butyl}$, $n=0$, $R_5 = R_6 = R_8 = R_9 = H$, $R_7 = CN$) according to General procedure V.

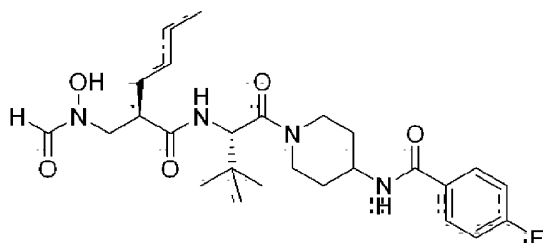
[387] 1H -NMR(DMSO- d_6): δ 8.21 (s, 0.2H), 7.74 (s, 0.8H), 7.74-8.00 (m, 5H), 4.82 (t, 1H), 4.35 (dd, 1H), 4.11 (m, 2H), 3.53-3.69 (m, 1H), 3.16-3.36 (m, 2H), 2.60-3.00 (m, 2H), 1.83-1.93 (m, 2H), 1.06-1.41 (m, 5H), 0.78-0.92 (m, 15H).

[388]

[389] Example 34

[390] 4-Fluoro-*N*-[1-((*S*)-2-((*R*)-2-[(formyl-hydroxy-amino)-methyl]-hexanoylamino)-3,3-dimethyl-butyryl)-piperidin-4-yl]-benzamide

[391]



[392] The title compound was prepared from (*R*)-2-[(benzyloxy-formyl-amino)-methyl] - hexanoic acid V-a ($R_2 = n$ -butyl) and *N*- [1-((*S*)-2-amino-3,3-dimethyl-butyryl)-piperidin-4-yl]-4-fluoro-benzamide hydrochloride I-i ($R_3 = tert$ -butyl, $n=0$, $R_5 = R_6 = R_8 = R_9 = H$, $R_7 = F$) according to General procedure V.

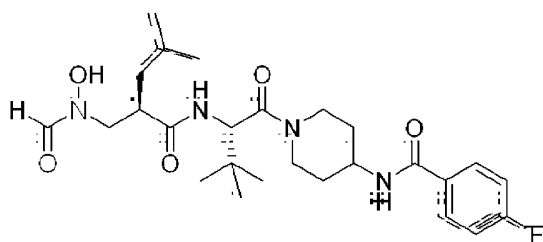
[393] 1H -NMR(DMSO- d_6): δ 8.21 (s, 0.3H), 7.88-7.93 (m, 2H), 7.75 (s, 0.7H), 7.27 (dt, 2H), 4.83 (t, 1H), 4.38 (m, 1H), 4.00-4.13 (m, 2H), 3.49-3.58 (m, 1H), 3.11-3.33 (m, 2H), 2.71-3.00 (m, 2H), 1.83 (m, 2H), 1.18 (m, 8H), 0.81-0.93 (m, 12H).

[394]

[395] **Example 35**

[396] 4-Fluoro-*N*-[1-((*S*)-2-((*R*)-2-[(formyl-hydroxy-amino)-methyl]-4-methyl-pentanoyl amino)-3,3-dimethyl-butyryl)-piperidin-4-yl]-benzamide

[397]



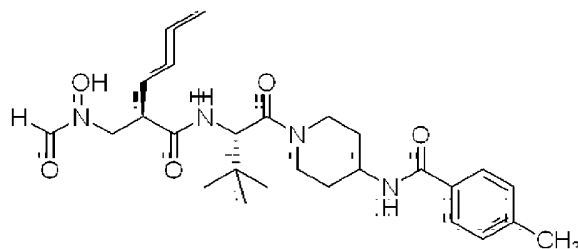
[398] The title compound was prepared from (*R*)-2-[(Benzyloxy-formyl-amino)-methyl] - 4-methyl-pentanoic acid V-a ($R_2 = iso$ -butyl) and *N*- [1-((*S*)-2-amino-3,3-dimethyl-butyryl)-piperidin-4-yl]-4-fluoro-benzamide hydrochloride I-i ($R_3 = tert$ -butyl, $n=0$, $R_5 = R_6 = R_8 = R_9 = H$, $R_7 = F$) according to General procedure V.

[399] 1H -NMR(DMSO- d_6): δ 8.21 (s, 0.3H), 7.88-7.92 (m, 2H), 7.74 (s, 0.7H), 7.27 (dt, 2H), 4.82 (t, 1H), 4.33 (dd, 1H), 4.01-4.12 (m, 2H), 3.54-3.61 (m, 1H), 3.15-3.36 (m, 2H), 2.70-3.00 (m, 2H), 1.82-1.94 (m, 2H), 1.41 (m, 4H), 1.08-1.19 (m, 1H), 0.81-0.93 (m, 15H).

[400]

[401] Example 36[402] *N*-[1-((*S*)-2-{(*R*)-2-[(Formyl-hydroxy-amino)-methyl]-hex-
anoylamino}-3,3-dimethyl-butyryl)-piperidin-4-yl]-4-methyl-benzamide

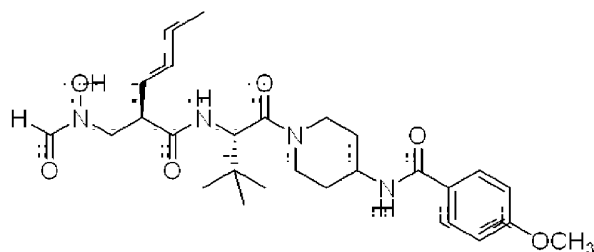
[403]

[404] The title compound was prepared from (*R*)-2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid V-a ($R_2 = n$ -butyl) and *N*-[1-((*S*)-2-amino-3,3-dimethyl-butyryl)-piperidin-4-yl]-4-methyl-benzamide hydrochloride I-i ($R_3 = \text{tert-butyl}$, $n=0$, $R_5 = R_6 = R_8 = R_9 = H$, $R_7 = CH_3$) according to General procedure V.[405] 1H -NMR(DMSO- d_6): δ 8.21 (s, 0.3H), 7.76 (s, 0.7H), 7.74 (dd, 2H), 7.24 (dd, 2H), 4.83 (t, 1H), 4.31-4.42 (m, 1H), 3.98-4.15 (m, 2H), 3.49-3.63 (m, 1H), 3.10-3.33 (m, 2H), 2.66-2.90 (m, 2H), 2.33 (s, 3H), 1.82-1.85 (m, 2H), 1.14-1.38 (m, 8H), 0.81-0.93 (m, 12H).

[406]

[407] Example 37[408] *N*-[1-((*S*)-2-{(*R*)-2-[(Formyl-hydroxy-amino)-methyl]-hex-
anoylamino}-3,3-dimethyl-butyryl)-piperidin-4-yl]-4-methoxy-benzamide

[409]

[410] The title compound was prepared from (*R*)-2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid V-a ($R_2 = n$ -butyl) and *N*-[1-((*S*)-2-amino-3,3-dimethyl-butyryl)-piperidin-4-yl]-4-methoxy-benzamide hydrochloride I-i ($R_3 = \text{tert-butyl}$, $n=0$, $R_5 = R_6 = R_8 = R_9 = H$, $R_7 = OCH_3$) according to General procedure V.[411] 1H -NMR(DMSO- d_6): δ 8.21 (s, 0.3H), 7.81 (dd, 2H), 7.75 (s, 0.7H), 6.96 (dd, 2H), 4.83 (t, 1H), 4.31-4.42 (m, 1H), 3.98-4.11 (m, 2H), 3.49-3.58 (m, 1H), 3.33 (s, 3H), 3.10-3.37 (m, 2H), 2.66-2.88 (m, 2H), 1.81-1.85 (m, 2H), 1.14-1.38 (m, 8H), 0.81-0.93

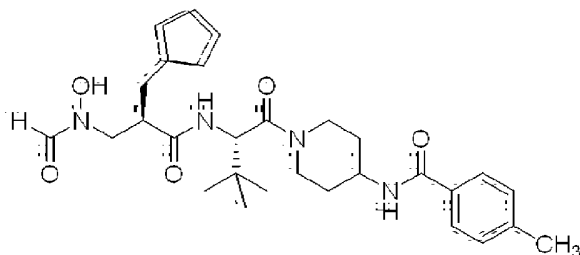
(m, 12H).

[412]

[413] **Example 38**

[414] *N*-(1-((*S*)-2-[(*R*)-2-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionylamino]-3,3-dimethyl-butyryl)-piperidin-4-yl)-4-methyl-benzamide

[415]



[416] The title compound was prepared from (*R*)-3-(Benzyloxy-formyl-amino)-2-cyclopentylmethyl-propionic acid V-a (R_2 = cyclopentylmethyl) and *N*-[1-((*S*)-2-amino-3,3-dimethyl-butyryl)-piperidin-4-yl]-4-methyl-benzamide hydrochloride I-i (R_3 = *tert*-butyl, $n=0$, $R_5=R_6=R_8=R_9=H$, $R_7=CH_3$) according to General procedure V.

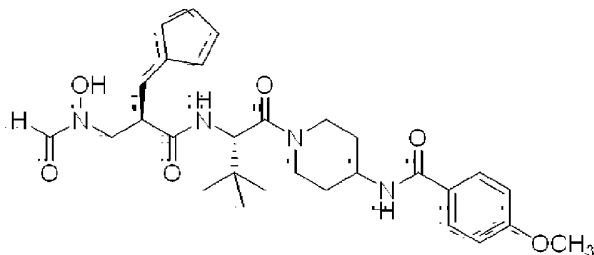
[417] 1H -NMR(DMSO- d_6): δ 8.21 (s, 0.4H), 7.74 (s, 0.6H), 7.71-7.76 (m, 2H), 7.24 (dd, 2H), 4.85 (t, 1H), 4.35 (dd, 1H), 3.98-4.12 (m, 2H), 3.53-3.66 (m, 1H), 3.10-3.43 (m, 2H), 2.65-2.91 (m, 2H), 2.33 (s, 3H), 1.14-1.85 (m, 13H), 0.89-0.92 (m, 11H).

[418]

[419] **Example 39**

[420] *N*-(1-((*S*)-2-[(*R*)-2-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionylamino]-3,3-dimethyl-butyryl)-piperidin-4-yl)-4-methoxy-benzamide

[421]



[422] The title compound was prepared from (*R*)-3-(Benzyloxy-formyl-amino)-2-cyclopentylmethyl-propionic acid V-a (R_2 = cyclopentylmethyl) and *N*-[1-((*S*)-2-amino-3,3-dimethyl-butyryl)-piperidin-4-yl]-4-methoxy-benzamide hydrochloride I-i (R_3 = *tert*-butyl, $n=0$, $R_5=R_6=R_8=R_9=H$, $R_7=OCH_3$) according to General procedure V.

[423] 1H -NMR(DMSO- d_6): δ 8.21 (s, 0.4H), 7.74 (s, 0.6H), 7.81 (dd, 2H), 6.96 (dd, 2H),

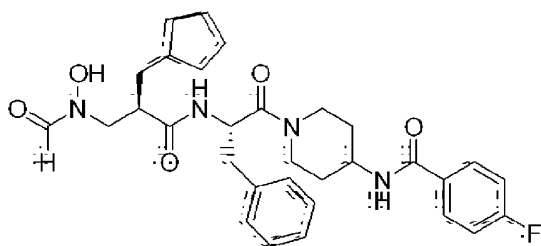
4.85 (t, 1H), 4.35 (dd, 1H), 3.98-4.12 (m, 2H), 3.79 (s, 3H), 3.57 (m, 1H), 3.09-3.33 (m, 2H), 2.65-3.00 (m, 2H), 1.14-1.85 (m, 13H), 0.89-0.93 (m, 11H).

[424]

[425] **Example 40**

[426] *N*-(1-((*S*)-2-[(*R*)-2-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionylamino]-3-phenyl-propionyl)-piperidin-4-yl)-4-fluoro-benzamide

[427]



[428] The title compound was prepared from (*R*)-3-(Benzyloxy-formyl-amino)-2-cyclopentylmethyl-propionic acid V-a (R_2 = cyclopentylmethyl) and *N*-[1-((*S*)-2-amino-3-phenyl-propionyl)-piperidin-4-yl] - 4-fluoro-benzamide hydrochloride I-i (R_3 = benzyl, $n=0$, $R_5=R_6=R_8=R_9=H$, $R_7=F$) according to General procedure V.

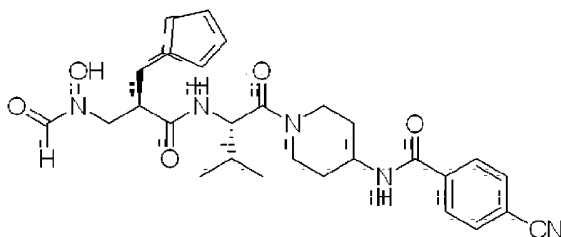
[429] 1H -NMR($CDCl_3$): δ 8.33 (s, 0.3H), 7.79-7.82 (m, 2.7H), 7.35-6.95 (m, 7H), 4.82-4.96 (m, 1H), 4.61-4.65 (m, 1H), 4.00-4.15 (m, 3H), 3.57-3.81 (m, 1H), 3.16-3.25 (m, 1H), 3.11-2.91 (m, 2H), 2.64-2.87 (m, 2H), 1.24-2.18 (m, 13H), 0.97-1.11 (m, 2H).

[430]

[431] **Example 41**

[432] 4-Cyano-*N*-(1-((*S*)-2-[(*R*)-2-cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionylamino]-3-methyl-butyl)-piperidin-4-yl)-benzamide

[433]



[434] The title compound was prepared from (*R*)-3-(Benzyloxy-formyl-amino)-2-cyclopentylmethyl-propionic acid V-a (R_2 = cyclopentylmethyl) and *N*-[1-((*S*)-2-amino-3-methyl-butyl)-piperidin-4-yl] - 4-cyano-benzamide hydrochloride I-i (R_3 = *iso*-propyl, $n=0$, $R_5=R_6=R_8=R_9=H$, $R_7=CN$) according to General procedure V.

[435] 1H -NMR($CDCl_3$): δ 8.35 (s, 0.3H), 7.80 (s, 0.7H), 7.64-7.73 (m, 2H), 7.21-7.27 (m,

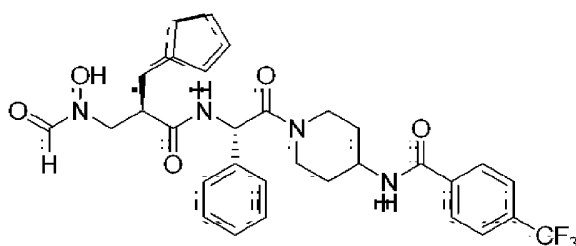
2H), 4.83-4.96 (m, 1H), 4.61 (dd, 1H), 4.16 (m, 3H), 3.54-3.74 (m, 1H), 3.21 (m, 1H), 2.64-2.87 (m, 2H), 1.26-2.06 (m, 13H), 0.96-1.10 (m, 8H).

[436]

[437] Example 42

[438] *N*-(1-((*S*)-2-[(*R*)-2-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionylamino]-2-phenyl-acetyl)-piperidin-4-yl)-4-trifluoromethyl-benzamide

[439]



[440] The title compound was prepared from

(*R*)-3-(Benzyloxy-formyl-amino)-2-cyclopentylmethyl-propionic acid V-a (R_2 = cyclopentylmethyl) and *N*-[1-((*S*)-2-amino-2-phenyl-acetyl)-piperidin-4-yl] - 4-trifluoromethyl-benzamide hydrochloride I-i (R_3 = phenyl, $n=0$, $R_5=R_6=R_8=R_9=H$, $R_7=CF_3$) according to General procedure V.

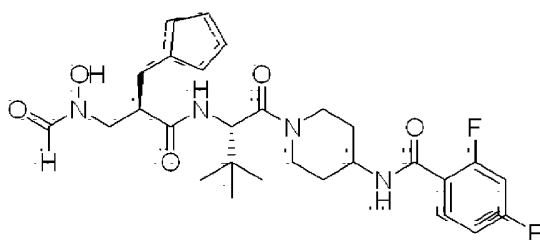
[441] 1H -NMR($CDCl_3$): δ 8.32 (s, 0.3H), 7.86-7.93 (m, 2H), 7.78 (s, 0.7H), 7.68 (d, 2H), 4.82-4.93 (m, 1H), 4.61-4.65 (m, 1H), 3.98-4.31 (m, 3H), 3.58-3.73 (m, 1H), 3.21-3.25 (m, 1H), 2.63-2.90 (m, 2H), 2.04-2.18 (m, 3H), 1.26-1.82 (m, 10H), 0.97-1.11 (m, 2H).

[442]

[443] Example 43

[444] *N*-(1-((*S*)-2-[(*R*)-2-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionylamino]-3,3-dimethyl-butyryl)-piperidin-4-yl)-2,4-difluoro-benzamide

[445]



[446] The title compound was prepared from

(*R*)-3-(Benzyloxy-formyl-amino)-2-cyclopentylmethyl-propionic acid V-a (R_2 = cyclopentylmethyl) and *N*-[1-((*S*)-2-amino-3,3-dimethyl-butyryl)-piperidin-4-yl] - 2,4-difluoro-benzamide hydrochloride I-i (R_3 = *tert*-butyl, $n=0$, $R_6=R_8=R_9=H$, $R_5=R_7=F$) according to General procedure V.

[447] 1H -NMR($CDCl_3$): δ 8.33 (s, 0.3H), 7.81-7.92 (m, 1.7H), 6.99-7.12 (m, 2H),

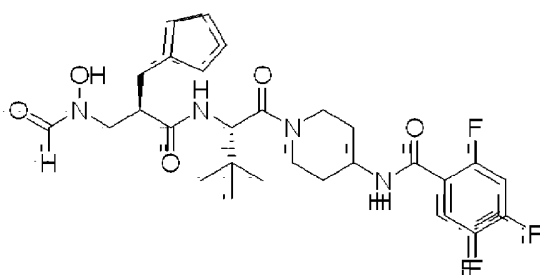
4.82-4.96 (m, 1H), 4.61-4.65 (m, 1H), 4.00-4.15 (m, 3H), 3.57-3.81 (m, 1H), 3.16-3.25 (m, 1H), 2.64-2.87 (m, 2H), 1.24-2.18 (m, 13H), 0.97-1.11 (m, 11H).

[448]

[449] Example 44

[450] *N*-(1-((*S*)-2-[(*R*)-2-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionylamino]-3,3-dimethyl-butyryl)-piperidin-4-yl)-2,4,5-trifluoro-benzamide

[451]



[452] The title compound was prepared from

(*R*)-3-(Benzyloxy-formyl-amino)-2-cyclopentylmethyl-propionic acid V-a (R_2 = cyclopentylmethyl) and *N*-[1-((*S*)-2-amino-3,3-dimethyl-butyryl)-piperidin-4-yl] - 2,4,5-trifluoro-benzamide hydrochloride I-i (R_3 = *tert*-butyl, $n=0$, $R_6=R_9=H$, $R_5=R_7=R_8=F$) according to General procedure V.

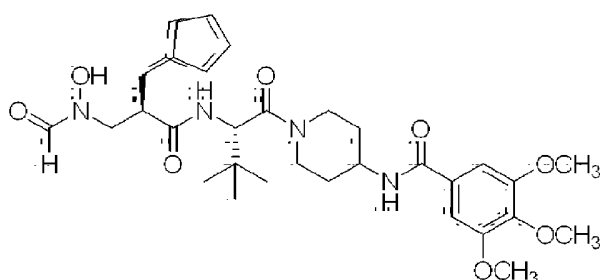
[453] $^1\text{H-NMR}(\text{CDCl}_3)$: δ 8.32 (s, 0.3H), 7.85 (s, 0.7H), 7.69-7.80 (m, 1H), 6.98-7.12 (m, 1H), 4.82-4.96 (m, 1H), 4.61-4.65 (m, 1H), 4.00-4.15 (m, 3H), 3.57-3.81 (m, 1H), 3.16-3.25 (m, 1H), 2.64-2.87 (m, 2H), 1.24-2.18 (m, 13H), 0.97-1.11 (m, 11H).

[454]

[455] Example 45

[456] *N*-(1-((*S*)-2-[(*R*)-2-Cyclopentylmethyl-3-(formyl-hydroxy-amino)-propionylamino]-3,3-dimethyl-butyryl)-piperidin-4-yl)-3,4,5-trimethoxy-benzamide

[457]



[458] The title compound was prepared from

(*R*)-3-(Benzyloxy-formyl-amino)-2-cyclopentylmethyl-propionic acid V-a (R_2 = cyclopentylmethyl) and *N*-[1-((*S*)-2-amino-3,3-dimethyl-butyryl)-piperidin-4-yl] - 3,4,5-trimethoxy-benzamide hydrochloride I-i (R_3 = *tert*-butyl, $n=0$, $R_5=R_9=H$, $R_6=R_7=R_8=\text{OCH}_3$) according to General procedure V.

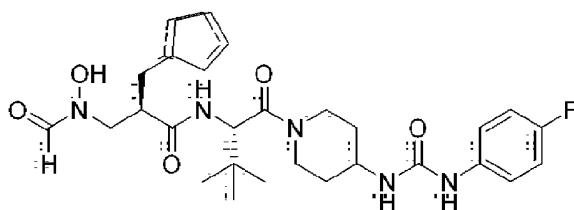
[459] $^1\text{H-NMR}(\text{CDCl}_3)$: δ 8.21 (s, 0.4H), 7.74 (s, 0.6H), 7.11-6.96 (dd, 2H), 4.84 (t, 1H), 4.35 (dd, 1H), 3.99-4.11 (m, 2H), 3.78 (s, 3H), 3.57 (m, 1H), 3.08-3.33 (m, 2H), 2.64-3.00 (m, 2H), 1.14-1.85 (m, 13H), 0.89-0.93 (m, 11H).

[460]

[461] Example 46

[462] (R)-2-Cyclopentylmethyl-N-((S)-1-{4-[3-(4-fluoro-phenyl)-ureido]-piperidine-1-carbonyl}-2,2-dimethyl-propyl)-3-(formyl-hydroxy-amino)-propionamide

[463]



[464] The title compound was prepared from (R)-3-(Benzyloxy-formyl-amino)-2-cyclopentylmethyl-propionic acid V-a (R_2 = cyclopentylmethyl) and 1-[1-((S)-2-amino-3,3-dimethyl-butyryl)-piperidin-4-yl]-3-(4-fluoro-phenyl)-urea hydrochloride II-e (R_3 = *tert*-butyl, $n=0$, $R_5=R_6=R_8=R_9=H$, $R_7=F$) according to General procedure V.

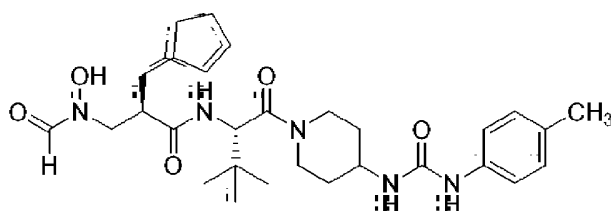
[465] $^1\text{H-NMR}(\text{CDCl}_3)$: δ 8.31 (s, 0.3H), 7.79-7.81 (m, 2.7H), 7.06-7.12 (m, 2H), 4.82-4.94 (m, 1H), 4.60-4.65 (m, 1H), 4.00-4.14 (m, 3H), 3.56-3.81 (m, 1H), 3.15-3.25 (m, 1H), 2.64-2.87 (m, 2H), 1.23-2.18 (m, 13H), 0.97-1.10 (m, 11H).

[466]

[467] Example 47

[468] (R)-2-Cyclopentylmethyl-N-{(S)-2,2-dimethyl-1-[4-(3-*p*-tolyl-ureido)-piperidine-1-carbonyl]-propyl}-3-(formyl-hydroxy-amino)-propionamide

[469]



[470] The title compound was prepared from (R)-3-(Benzyloxy-formyl-amino)-2-cyclopentylmethyl-propionic acid V-a (R_2 = cyclopentylmethyl) and 1-[1-((S)-2-amino-3,3-dimethyl-butyryl)-piperidin-4-yl]-3-*p*-tolyl-urea hydrochloride II-e (R_3 = *tert*-butyl, $n=0$, $R_5=R_6=R_8=R_9=H$, $R_7=CH_3$) according to General procedure V.

[471] $^1\text{H-NMR}(\text{CDCl}_3)$: δ 8.20 (s, 0.4H), 7.73 (s, 0.6H), 7.70-7.75 (m, 2H), 7.24 (dd, 2H), 4.85 (t, 1H), 4.34 (dd, 1H), 3.96-4.11 (m, 2H), 3.53-3.66 (m, 1H), 3.11-3.43 (m,

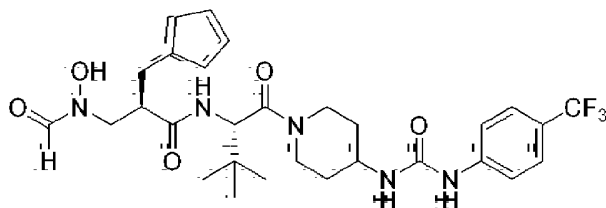
2H), 2.66-2.91 (m, 2H), 2.32 (s, 3H), 1.14-1.84 (m, 13H), 0.89-0.91 (m, 11H).

[472]

[473] **Example 48**

[474] (R)-2-Cyclopentylmethyl-N-((S)-2,2-dimethyl-1-{4-[3-(4-trifluoromethyl-phenyl)-u
reido]-piperidine-1-carbonyl}-propyl)-3-(formyl-hydroxy-amino)-propionamide

[475]



[476] The title compound was prepared from

(R)-3-(Benzyloxy-formyl-amino)-2-cyclopentylmethyl-propionic acid V-a (R_2 =cyclopentylmethyl) and 1-[1-((S)-2-amino-3,3-dimethyl-butyryl)-piperidin-4-yl] - 3-(4-trifluoromethyl-phenyl)-urea hydrochloride II-e (R_3 =*tert*-butyl, $n=0$, $R_5=R_6=R_8=R_9$ =H, R_7 = CF_3) according to General procedure V.

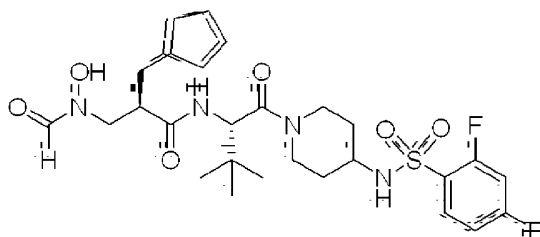
[477] 1H -NMR($CDCl_3$): δ 8.30 (s, 0.3H), 7.88-7.93 (m, 2H), 7.76 (s, 0.7H), 7.62 (d, 2H), 4.81-4.93 (m, 1H), 4.60-4.64 (m, 1H), 3.99-4.31 (m, 3H), 3.56-3.73 (m, 1H), 3.20-3.25 (m, 1H), 2.62-2.90 (m, 2H), 2.03-2.17 (m, 3H), 1.25-1.82 (m, 10H), 0.95-1.11 (m, 11H).

[478]

[479] **Example 49**

[480] (R)-2-Cyclopentylmethyl-N-[(S)-1-[4-(2,4-difluoro-benzenesulfonylamino)-piperid
ine-1-carbonyl]-2,2-dimethyl-propyl]-3-(formyl-hydroxy-amino)-propionamide

[481]



[482] The title compound was prepared from

(R)-3-(Benzyloxy-formyl-amino)-2-cyclopentylmethyl-propionic acid V-a (R_2 =cyclopentylmethyl) and N-[1-((S)-2-amino-3,3-dimethyl-butyryl)-piperidin-4-yl] - 2,4-difluoro-benzenesulfonamide hydrochloride III-e (R_3 =*tert*-butyl, $n=0$, $R_5=R_6=R_8=R_9$ =H, R_7 =F) according to General procedure V.

[483] 1H -NMR($CDCl_3$): δ 8.31 (s, 0.3H), 7.80-7.94 (m, 1.7H), 6.99-7.10 (m, 2H), 4.83-4.95 (m, 1H), 4.60-4.63 (m, 1H), 3.99-4.14 (m, 3H), 3.56-3.81 (m, 1H), 3.15-3.25

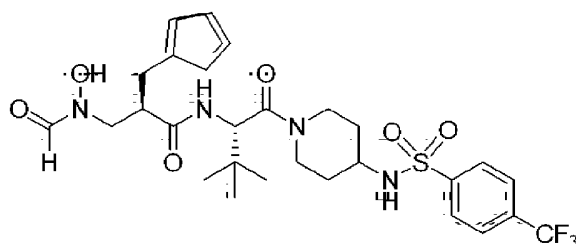
(m, 1H), 2.63-2.87 (m, 2H), 1.23-2.18 (m, 13H), 0.96-1.10 (m, 11H).

[484]

[485] **Example 50**

[486] (R)-2-Cyclopentylmethyl-N-[(S)-2,2-dimethyl-1-[4-(4-trifluoromethyl-benzenesulfonylamino)-piperidine-1-carbonyl]-propyl]-3-(formyl-hydroxy-amino)-propionamide

[487]



[488] The title compound was prepared from

(R)-3-(Benzyloxy-formyl-amino)-2-cyclopentylmethyl-propionic acid V-a (R_2 = cyclopentylmethyl) and N-[1-((S)-2-amino-3,3-dimethyl-butyl)-piperidin-4-yl] - 4-trifluoromethyl-benzenesulfonamide hydrochloride III-e (R_3 = *tert*-butyl, $n=0$, $R_5=R_6=R_7=R_8=R_9=H$, $R_7=CF_3$) according to General procedure V.

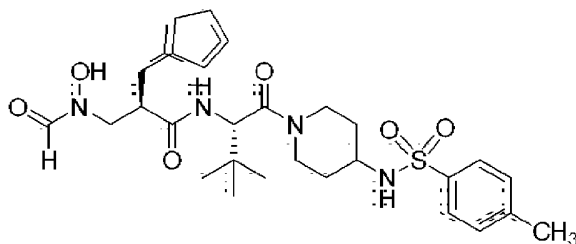
[489] 1H -NMR($CDCl_3$): δ 8.34 (s, 0.3H), 7.84-7.91 (m, 2H), 7.77 (s, 0.7H), 7.67 (d, 2H), 4.83-4.93 (m, 1H), 4.59-4.65 (m, 1H), 3.96-4.31 (m, 3H), 3.57-3.70 (m, 1H), 3.20-3.25 (m, 1H), 2.61-2.89 (m, 2H), 2.02-2.18 (m, 3H), 1.24-1.82 (m, 10H), 0.99-1.12 (m, 11H).

[490]

[491] **Example 51**

[492] (R)-2-Cyclopentylmethyl-N-[(S)-2,2-dimethyl-1-[4-(toluene-4-sulfonylamino)-piperidine-1-carbonyl]-propyl]-3-(formyl-hydroxy-amino)-propionamide

[493]



[494] The title compound was prepared from

(R)-3-(Benzyloxy-formyl-amino)-2-cyclopentylmethyl-propionic acid V-a (R_2 = cyclopentylmethyl) and N-[1-((S)-2-amino-3,3-dimethyl-butyl)-piperidin-4-yl] - 4-methyl-benzenesulfonamide hydrochloride III-e (R_3 = *tert*-butyl, $n=0$, $R_5=R_6=R_7=R_8=R_9=H$, $R_7=CH_3$) according to General procedure V.

[495] 1H -NMR($CDCl_3$): δ 8.19 (s, 0.4H), 7.73 (s, 0.6H), 7.69-7.77 (m, 2H), 7.21 (dd,

2H), 4.81 (t, 1H), 4.31 (dd, 1H), 3.88-4.10 (m, 2H), 3.52-3.65 (m, 1H), 3.11-3.43 (m, 2H), 2.64-2.91 (m, 2H), 2.31 (s, 3H), 1.11-1.83 (m, 13H), 0.88-0.91 (m, 11H).

[496]

[497]

[498] The present invention relates to antibacterial composition comprising a therapeutically effective amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier. The compounds of this invention may be used to treat a subject to treat, prevent, and/or reduce the severity of an infection.

[499]

[500] The present compounds are useful for the treatment of bacterial infection. Therefore, the pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by oral, rectal or parenteral administration. For these purposes the compounds of this invention may be formulated by means known in the art in to the form of, for example, tablets, capsules, aqueous or oily solutions or suspensions, (lipid) emulsions, dispersible powders, suppositories, ointments, creams, aerosols (or sprays), drops and sterile injectable aqueous or oily solutions or suspensions.

[501]

[502] Compounds of formula (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as syrups, tablets, capsules, creams and lozenges.

[503] Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients, disintegrants or glydents. For example, they may be syrup, gelatin, sorbitol, lactose, sugar, maize-starch, calcium phosphate, tableting lubricant, magnesium stearate, polyethylene glycol, potato starch or sodium lauryl sulfate, and, if desired, conventional flavoring or coloring agent.

[504] Typical parenteral compositions consist of a solution or suspension of a compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptably oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil or sesame oil.

[505] Each dosage unit for oral administration contains preferably from 1 mg to 100 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.1 mg to 100 mg/Kg, of a compound of formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid.

[506]

[507] The compounds of this invention, e.g. of formula (I) or a pharmaceutically acceptable salt thereof, may be administered alone or in combination with another

therapeutic agent. Examples of such therapeutic agents include, but are not limited to, penicillins, cephalosporins, carbapenems, fluoroquinolones, clarithromycin, vancomycin, rifamycins, monobactams, licosamides, fosfomycin, glycopeptides, tetracyclines, streptogramins, chloramphenicol, oxazolidinone, corticosteroids, NSAID, narcotic or non-narcotic analgesics.

[508]

[509] **Experimental Example**

[510]

[511] 1. Formulation examples

[512]

[513] The following are representative pharmaceutical formulations containing a compound of formula (I).

[514]

[515] Example 1. Tablet formulation

[516] The following ingredients are mixed and compressed into tablets using suitable punches.

[517] Table 1

Ingredient	Quantity
Compound of this invention	400.0 mg
Cornstarch	40.0 mg
Microcrystalline cellulose	10.0 mg
Croscarmellose sodium	25 mg
Lactose	110 mg
Magnesium stearate	5 mg

[518] Example 2. Capsule formulation

[519] The following ingredients are mixed and filled into hard gelatin capsules of a suitable size.

[520] Table 2

Ingredient	Quantity
Compound of this invention	250 mg
Lactose	148 mg
Magnesium stearate	2 mg

[521] Example 3. Injectable formulation

[522] The following ingredients are mixed and filled into ampoules of a suitable size.

[523] Table 3

Ingredient	Quantity
Compound of this invention	0.2 mg-20 mg
Sodium acetate buffer solution, 0.4 M	20 mL
HCl (1N) or NaOH (1N)	q.s. to suitable pH
Water for injection	q.s. to 20 mL

[524]

[525] 2. Test for antibacterial activity

[526] Minimum inhibitory concentrations (MICs) were determined using the microdilution method in 96-well format plates. Each of the compounds of Examples was dissolved in dimethyl sulfoxide to a concentration of 2 mg/mL and stored at 4°C until used. They were diluted in Mueller-Hinton Broth (MHB) and used for MIC determination. The range of concentrations tested was 64-0.00625 µg/mL final concentration using a two-fold dilution system. Plates were incubated at 37°C and MIC were recorded after 24 hours of incubation for bacteria. MIC was defined as the lowest concentration of compound that does not produce visible growth after incubation.

[527] Linezolid and vancomycin were used as standard antibiotics, respectively.

[528]

[529] Results for some of the compounds of the Examples are reported in Table 4.

[530] Table 4

Comps	MIC (µg/mL)				
	Methicillin-resistant <i>Staphylococcus aureus</i>	Vancomycin-resistant <i>Enterococcus faecalis</i>	<i>Streptococcus pneumoniae</i>	<i>Streptococcus pyogenes</i>	<i>Streptococcus agalactiae</i>
Example 8	12.5	25	6.3	1.6	1.6
Example 10	50	50	50	0.8	0.2
Example 13	12.5	6.3	3.1	0.4	0.2
Example 15	6.3	6.3	6.3	0.2	0.2
Example 20	25	12.5	0.8	0.4	0.4
Example 25	12.5	6.3	6.3	0.4	0.1
Example 28	3.1	6.3	1.6	3.1	0.1
Example 29	3.1	3.1	1.6	0.1	0.1

Example 30	6.3	6.3	1.6	0.2	0.2
Example 38	6.3	3.1	1.6	3.1	0.1
Example 39	12.5	6.3	3.1	0.2	0.2
Example 41	6.3	3.1	1.6	0.4	0.4
Example 44	3.1	3.1	1.6	0.2	0.2
Example 48	6.3	3.1	1.6	0.2	0.2
Example 50	6.3	3.1	1.6	0.4	0.4
Linezolid	1.6	0.8	0.8	0.8	1.6
Vancomycin	3.1	>100	0.8	0.8	1.6

[531]

[532] 3. Acute toxicity

[533] To demonstrate the usefulness of the compounds of this invention as medicaments we have performed acute toxicity study in mice.

[534] The acute toxicity of the compounds of Example 7, 13, 18 and 47 were tested using several groups of ICR mice each of 6 mice. 4,000 mg/kg dose of the medicament was each orally injected into each group of mice, and weight change and death were observed for 14 days after the injection.

[535]

[536] The LD₅₀ values obtained in mice for the compounds of this invention are summarized in Table 5.

[537] Table 5

Compds	LD ₅₀ (mg/kg)
Example 7 Example 13 Example 18 Example 47	>4,000 >4,000 >4,000 >4,000

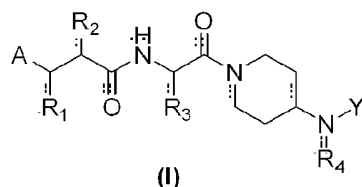
[538] animal: ICR mice (♂, 4 weeks)

Industrial Applicability

[539] The compounds of this invention, e.g. of formula (I) or a pharmaceutically acceptable salt thereof have low toxicity and are antibacterially active against gram-positive organisms, in particular also against those microorganisms which are resistant to various antibiotics. Thus, the compounds of this invention are useful as antibacterial agents for infection with resistant bacteria.

Claims

- [1] A compound of formula (I) or a pharmaceutically acceptable salts thereof:



wherein, A is selected from the group of consisting of -C(=O)NHOH or -N(CHO)OH;

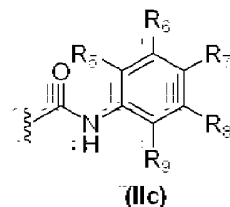
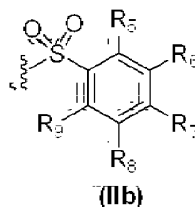
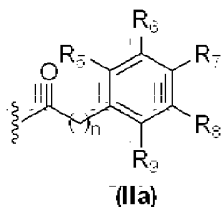
R₁ represents hydrogen, C₁₋₃ alkyl, C₄₋₆ cycloalkyl, halogen or hydroxy group;

R₂ represents hydrogen, straight or branched C₁₋₆ alkyl, straight or branched C₁₋₆ alkenyl, C₄₋₆ cycloalkyl, C₄₋₆ heterocycle including nitrogen or oxygen, or benzyl group;

R₃ represents hydrogen, methyl, straight or branched C₁₋₆ alkyl, straight or branched C₁₋₆ alkenyl, C₄₋₆ cycloalkyl, phenyl or benzyl group;

R₄ represents hydrogen, straight or branched C₁₋₄ alkyl, C₁₋₄ alkenyl, hydroxy substituted C₄₋₆ cycloalkyl group; and

Y represents a group of formula (IIa), or (IIb), or (IIc):



wherein, n is independently 0 or 1;

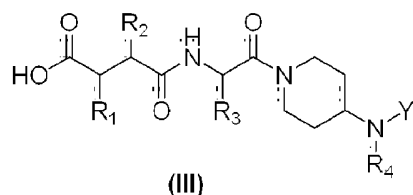
each of R₅, R₆, R₇, R₈ and R₉ is independently hydrogen, straight or branched C₁₋₃ alkyl, hydroxy, alkoxy, acyl, acyloxy, halogen (fluoro, chloro, bromo and iodo) cyano, nitro, amono, *N,N*-dimethylamino, phenyl, morpholinyl, or formyl group.

- [2] The compound of formula (I) according to claim 1, wherein A is -C(=O)NHOH, R₁ is hydrogen, R₂ is *iso*-butyl, *n*-butyl, *n*-pentyl, benzyl or cyclopentylmethyl, R₃ is *tert*-butyl, *iso*-propyl, phenyl or benzyl, R₄ is hydrogen, n is 0 or 1, and R₅, R₆, R₇, R₈ and R₉ is independently hydrogen, methyl, fluoro, chloro, bromo, trifluoromethyl, methoxy, nitro, cyano or amino; or a pharmaceutically acceptable salts thereof.

- [3] The compound of formula (I) according to claim 1, wherein A is -N(CHO)OH, R₁ is hydrogen, R₂ is *iso*-butyl, *n*-butyl, *n*-pentyl, benzyl or cyclopentylmethyl, R₃ is *tert*-butyl, *iso*-propyl, phenyl or benzyl, R₄ is hydrogen, n is 0 or 1, and R₅, R₆, R₇, R₈ and R₉ is independently hydrogen, methyl, fluoro, chloro, bromo, triflu-

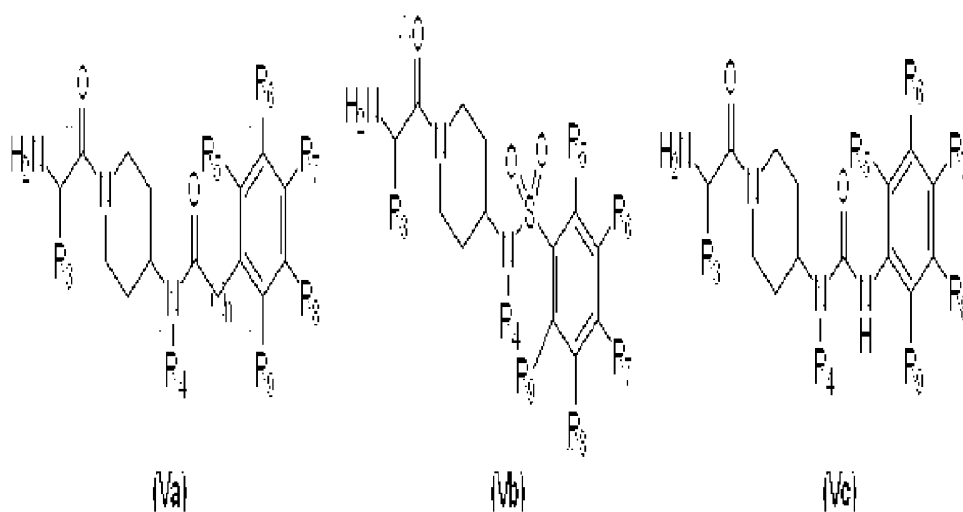
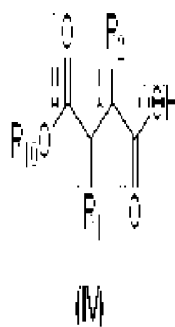
oromethyl, methoxy, nitro, cyano or amino; or a pharmaceutically acceptable salts thereof.

- [4] A process for preparing a compound of formula (I) or a pharmaceutically acceptable salt thereof, which comprises reacting a compound of formula (III) with hydroxylamine or an *N*- and/or *O*-protected hydroxylamine, and thereafter removing any *N*- or *O*-protecting groups:



wherein, R₁, R₂, R₃, R₄ and Y are the same as defined in claim 1.

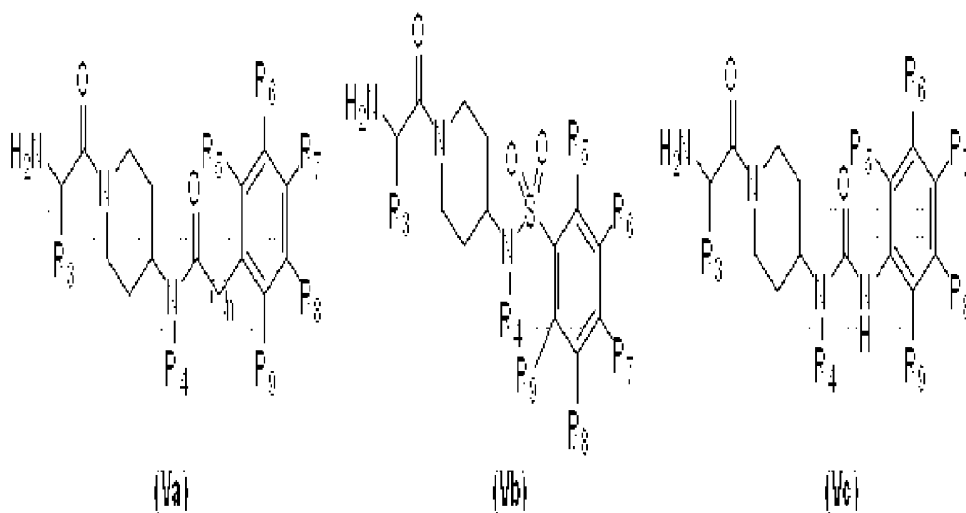
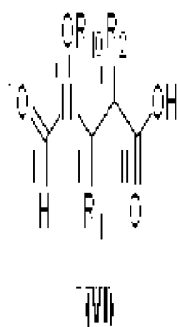
- [5] The method for preparing a compound of formula (III) according to claim 4 which process comprises reacting a compound of formula (IV) with a compound of formula (Va) (or Vb, or Vc) or salt thereof:



wherein, R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉ and n are the same as defined in claim 1

and R_{10} is a hydroxy protecting group, such as methyl, ethyl, *tert*-butyl and benzyl.

- [6] A process for preparing a compound of formula (I) or a pharmaceutically acceptable salt thereof, which comprises reacting a compound of formula (VI) with a compound of formula (Va) (or Vb, or Vc) or salt thereof, and thereafter removing any *N*- or *O*-protecting groups:



wherein, $R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9$ and n are the same as defined in claim 1 and R_{10} is a hydroxy protecting group, such as *tert*-butyl and benzyl.

- [7] An antibacterial composition comprising a therapeutically effective amount of the compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2006/001500

A. CLASSIFICATION OF SUBJECT MATTER

C07D 211/58(2006.01)i, A61K 31/4453(2006.01)i, A61K 31/4468(2006.01)i, A61P 31/04(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC8 as above

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean Patents and applications for inventions since 1975

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN(Registry), eKIPASS (hydroxamic & peptide deformylase inhibitor)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/10834 A2 (BRITISH BIOTECH PHARMACEUTICALS LIMITED) 15 Feb. 2001 See the compound of formula (IID) on p20.	1 - 7
A	WO 00/61134 A1 (BRITISH BIOTECH PHARMACEUTICALS LIMITED) 19 Oct. 2000 See the compound of formula (I).	1 - 7
A	WO 00/44373 A1 (BRITISH BIOTECH PHARMACEUTICALS LIMITED) 3 Aug. 2000 See the compound of formula (I).	1 - 7
A	WO 99/39704 A1 (BRITISH BIOTECH PHARMACEUTICALS LIMITED) 12 Aug. 1999 See the compound of formula (I).	1 - 7



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

13 JUNE 2006 (13.06.2006)

Date of mailing of the international search report

13 JUNE 2006 (13.06.2006)

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2006/001500

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 01/10834 A2	15.02.2001	US 20050065095 A1	24.03.2005
		JP 2003506438 T2	18.02.2003
		EP 1202968 A2	08.05.2002
		CN 1373754 A	09.10.2002
		CA 2379061 AA	15.02.2001
		AU 0063080 A5	05.03.2001
WO 00/61134 A1	19.10.2000	US 6716878 B1	06.04.2004
		JP 2002541197 T2	03.12.2002
		EP 1169031 A1	09.01.2002
		AU 0039792 A5	14.11.2000
WO 00/44373 A1	03.08.2000	US 6545051 B1	08.04.2003
		JP 2002535362 T2	22.10.2002
		EP 1146867 A1	24.10.2001
		AU 0021189 A5	18.08.2000
		AT 0299701 E	15.08.2005
WO 99/39704 A1	12.08.1999	US 20050014702 A1	20.01.2005
		JP 2002502815 T2	29.01.2002
		EP 1052984 A1	22.11.2000
		CN 1298299 A	06.06.2001
		CA 2320476 AA	12.08.1999
		AU 2529299 A1	23.08.1999
		AT 0266394 E	15.05.2004