13 DEC 2005

N-FORMYL HYDROXYLAMINE COMPOUNDS AS INHIBITORS OF PDF

This invention is directed to novel N-formyl hydroxylamine compounds, to the uses of these compounds in various medicinal applications, including treating disorders amenable to treatment by peptidyl deformylase inhibitors such as treatment of bacterial infections, and to pharmaceutical compositions comprising these compounds.

Treatment of microbial infection in host organisms requires an effective means to kill the microbe while doing as little harm to the host as possible. Accordingly, agents which target characteristics unique to a pathology-causing microorganism are desirable for treatment. Penicillin is an extremely well known example of such an agent. Penicillin acts by inhibiting biosynthesis of bacterial cell walls. Since mammalian cells do not require cell walls for survival, administration of penicillin to a human infected with bacteria may kill the bacteria without killing human cells.

However, the use of antibiotics and antimicrobials has also resulted in increased resistance to these agents. As bacteria become resistant to older, more widely used antimicrobial agents, new antimicrobials must be developed in order to provide effective treatments for human and non-human animals suffering from microbial infection.

Peptide deformylase is a metallopeptidase found in prokaryotic organisms such as bacteria. Protein synthesis in prokaryotic organisms begins with N-formyl methionine (fMet). After initiation of protein synthesis, the formyl group is removed by the enzyme peptide deformylase (PDF); this activity is essential for maturation of proteins. It has been shown that PDF is required for bacterial growth (Chang et al., J. Bacteriol., Vol. 171, pp. 4071-4072 (1989); Meinnel et al., J. Bacteriol., Vol. 176, No. 23, pp. 7387-7390 (1994); Mazel et al., EMBO J., Vol. 13, No. 4, pp. 914-23 (1994)). Since protein synthesis in eukaryotic organisms does not depend on fMet for initiation, agents that will inhibit PDF are attractive candidates for development of new antimicrobial and antibacterial drugs. Prokaryotic organisms, including disease-causing prokaryotes, are described in Balows A, Truper HG, Dworkin M, Harder W and Schleifer K-H (eds.), "The Prokaryotes", 2nd ed., New York: Springer-Verlag (1992); and Holt JG (editor-in-chief), "Bergey's Manual of Systematic Bacteriology", Vols. 1-4, Baltimore: Williams & Wilkins (1982, 1986, 1989).

PDF is part of the metalloproteinase superfamily. While PDF clearly shares many of the features which characterize metalloproteinases, it differs from other members of the

superfamily in several important respects. First, the metal ion in the active enzyme appears to be Fe (II), or possibly another divalent cationic metal, instead of the zinc ion more commonly encountered (Rajagopalan et al., J. Am. Chem. Soc., Vol. 119, pp. 12418-12419 (1997)). Second, the divalent ion appears to play an important role, not only in catalysis, but also in the structural integrity of the protein. Third, the third ligand of the divalent ion is a cysteine, rather than a histidine or a glutamate, as in other metalloproteinases and is not located at the C-terminal side of the HEXXH motif but far away along the amino acid sequence and N-terminal to the motif. Finally, the solution structure shows significant differences in the secondary and tertiary structure of PDF compared to other prototypical metalloproteinases (see Meinnel et al., J. Mol. Biol., Vol. 262, pp. 375-386 (1996)). PDF from *E. coli*, *Bacillus stearothermophilus*, and *Thermus thermophilus* have been characterized (see Meinnel et al., J. Mol. Biol., Vol. 267, pp. 749-761 (1997)). The enzyme studied by Meinnel et al. contained a zinc ion as the divalent ion and the structural features summarized above were obtained from zinc-containing proteins. The structure of the protein has also been determined by NMR (see O'Connell et al., J. Biomol. NMR, Vol. 13, No. 4, pp. 311-324 (1999)).

Metalloproteinases are critical to many aspects of normal metabolism. The class known as matrix metalloproteinases (MMPs) are involved in tissue remodeling, such as degradation of the extracellular matrix. These enzymes are believed to play a role in normal or beneficial biological events such as the formation of the corpus luteum during pregnancy (see Liu et al., Endocrinology, Vol. 140, No. 11, pp. 5330-5338 (1999)), wound healing (Yamagiwa et al., Bone, Vol. 25, No. 2, pp. 197-203 (1999)), and bone growth in healthy children (Bord et al., Bone, Vol. 23, No. 1, pp. 7-12 (1998)). Disorders involving metalloproteinases have been implicated in several diseases such as cancer, arthritis, and autoimmune diseases.

Because of the importance of MMPs in normal physiological processes, it would be preferable to develop agents that inhibit PDF, a metalloproteinase present only in prokaryotes, while avoiding significant inhibition of MMPs. Alternatively, PDF inhibitors which also inhibit MMPs may be of use where the therapeutic benefits of inhibiting PDF outweigh the risk of side effects from MMP inhibition.

A wide variety of compounds have been developed as candidate inhibitors of MMPs and other metalloproteinases, and much effort has also been directed at synthetic methods for these compounds and related compounds (see Izquierdo-Martin et al., J. Am. Chem. Soc., Vol. 114, pp. 325-331 (1992); Cushman et al., Chapter 5, "Specific Inhibitors of Zinc

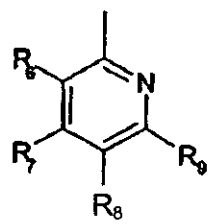
Metallopeptidases", Topics in Molecular Pharmacology, Burgen & Roberts, eds. (1981); Mohler et al., Nature, Vol. 370, pp. 218-220 (1994); Gearing et al., Nature, Vol. 370, pp. 555-557 (1994); McGeehan et al., Nature, Vol. 370, pp. 558-561 (1994); U.S. Patent Nos. 4,052,511, 4,303,662, 4,311,705, 4,321,383, 4,599,361, 4,804,676, 5,128,346, 5,256,657, 5,268,384, 5,447,929, 5,453,423, 5,552,419, 5,614,625, 5,643,908, 5,712,300, and 5,869,518; European patent publications EP 236872, EP 274453, EP 334244, EP 423943, EP 489577, EP 489579, EP 497192, EP 574758; and International PCT Patent Applications Publication Nos. WO 90/05716, WO 90/05719, WO 91/02716, WO 92/13831, WO 92/22523, WO 93/09090, WO 93/09097, WO 93/20047, WO 93/24449, WO 93/24475, WO 94/02446, WO 94/02447, WO 94/21612, WO 94/25434, WO 94/25435, WO 95/33731, WO 96/25156, WO 96/26918 WO 97/30707, WO 97/49674, WO 98/55449, and WO 99/02510).

Research on inhibitors of PDF is much less extensive than that for inhibitors of MMPs. N-formyl hydroxylamine derivatives are described in International Patent Application WO 99/39704. Peptide aldehyde inhibitors of PDFs are described in Durand et al., Arch. Biochem. Biophys., Vol. 367, No. 2, pp. 297-302 (1999). The PDF inhibitor (S)-2-0-(H-phosphonoxy)-L-caproyl-L-leucyl-p-nitroanilide is described in Hao et al., Biochemistry, Vol. 38, pp. 4712-4719 (1999), and peptidyl H-phosphonate inhibitors of PDF are discussed in Hu et al., Bioorg. Med. Chem. Left., Vol. 8, pp. 2479-2482 (1998). Formylated peptides and pseudopeptides are described in Meinnel et al., Biochemistry, Vol. 38, No. 14, pp. 4288-4295 (1999) as inhibitors of PDF.

In view of the importance of identifying new antibiotics to treat bacteria resistant to existing antibiotics, it is desirable to develop novel inhibitors of PDF for evaluation and use as antibacterial and antimicrobial agents. The present invention fulfills this need.

In particular, the present invention provides a N-[1-oxo-2-alkyl-3-(N-hydroxyformamido)-propyl]-(carbonylamino-aryl or -heteroaryl)-azacyclo $_{\phi 7}$ alkane or thiazacyclo $_{\phi 7}$ alkane or imidazacyclo $_{\phi 7}$ alkane (referred to herein collectively as "compounds of the invention"), or a salt thereof which is characterized by formula (I).

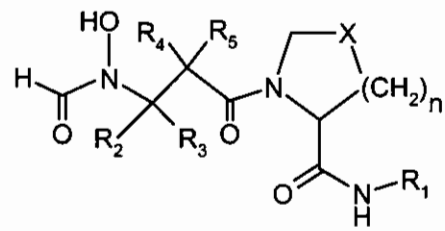
In another embodiment, R, is preferably a heteroaryl of formula (II.1)



wherein R_6, R_7, R_8 and R_9 are as defined above for formula (II);

e.g. wherein

A compound of formula (I)



Wherein X is -CH_2-, S-, -CH(OH)-, -CH(OR)-, -CH)-(SH)- or –CH(F)-; wherein R is C_{1-7} alkyl;

R is C_{1-7} alkyl;

R_1 is aryl or heteroaryl;

Each of R_2, R_3, R_4, R_5 independently is hyfrogen or C_{1-7} alkyl, or (R_2 or R_3) and (R_4 or R_5) collectively form a C_{4-7} cycloalkyl; and

N is 0 to 3, procided that when n is 0, X is –CH_2-;

Or a salt thereof,

Wherein aryl refers to an aromatic carbocyclic group of 6 to 13 carbon atoms having a single ring or multiple condensed rings, and

Wherein heteroaryl refers to a 4- to 7-membered, monocyclic aromatic heterocycle or a bicycle that is composed of a 4- to 7-membered, monocyclic aromatic heterocycle and a fused-on benzene ring, and wherein said heteroaryl has at least one hetero atom.

Wherein each of R_6, R_7, R_8 and R_9 independently is hydrogen, C_{1-7} alkyl, substituted C_{1-7} alkyl, hydroxy, C_{1-7} alkoxy, acyl being –(O_CR where R is C_{1-7} alkyl, acyloxy being –OC(O)R where R is C_{1-7} alkyl, SCN, halogen, cyano, nitro, thio-C_{1-7} alkoxy, phenyl, hetero C_{1-7} alkylaryl, C_{1-7} alkylsulfonyl, or formyl;

a.) R_6 is nitro, C_{1-7}alkyl, substituted C_{1-7}alkyl, phenyl, hydroxy, formyl, hetero C_{1-7}alkylaryl, C_{1-7}alkoxy, -(O)CR wherein R_2C_{1-7} alkyl or -OC(O)R wherein R_2C_{1-7} , especially C_{1-7} alkyl; hydroxyl; or a C_{1-7} alkoxy; and R_7, R_8, and R_9 are hydrogen; or

b.) R_6, R_8 and R_9 are hydrogen, and R_7 is C_{1-7}alkyl, substituted C_{1-7}alkyl, phenyl, halogen, C_{1-7}alkoxy or cyano, especially C_{1-7} alkyl; especially substituted C_{1-7} alkyl such as $-CF_3$; or especially C_{1-7} alkoxy; or

c.) R_6, R_7, R_9 are hydrogen and R_8 is C_{1-7}alkyl, substituted C_{1-7}alkyl, halogen, nitro, cyano, thio C_{1-7}alkoxy, -(O)CR wherein R_2C_{1-7} alkyl, phenyl, alkylsulfonyl or carboxy C_{1-7}alkyl, , especially C_{1-7}
alkyl; substituted C_{1-7v}alkyl, especially $-CF_3$; halogen; or carboxy C_{1-7}alkyl; or

d.) R_6, R_7, R_8 are hydrogen and R_9 is C_{1-7}alkyl, halogen or hydroxy; or

e.) R_7 and R_9 are hydrogen, and each of R_6 and R_8 independently is halogen, C_{1-7}alkyl, substituted C_{1-7}alkyl, phenyl or cyano; or

f.) each of R_7 and R_9 is C_{1-7}alkyl or substituted C_{1-7}alkyl and R_6 and R_8 are hydrogen;

or

g.) R_6 and R_9 are hydrogen, R_7 is C_{1-7}alkyl or substituted C_{1-7}alkyl and R_8 is nitro; or

h.) R_8 and R_9 are hydrogen, R_6 is cyano, and R_7 is C_{1-7}alkoxy; or

i.) R_7 and R_8 are hydrogen and R_6 is C_{1-7}alkyl, substituted C_{1-7}alkyl, C_{1-7}alkoxy or SCN and R_9 is C_{1-7}alkyl or substituted C_{1-7}alkyl; or

j.) R_6 and R_7 are hydrogen, R_8 is nitro or halogen and R_9 is C_{1-7}alkyl or substituted C_{1-7}alkyl; or

k.) R_6, R_7, R_e and R_9 are hydrogen; or

l.) R_6 and R_7 together with the carbon atoms to which they are attached form a phenyl group, preferably substituted with hydroxy, and R_8 and R_9 are hydrogen; or

m.) R_6 and R_7 are hydrogen and R_8 and R_9 together with the carbon atoms to which they are attached form a phenyl group; or

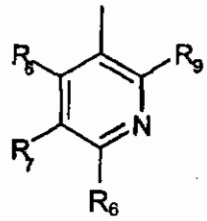
n.) n is 0; or

o.) n is 0, and each of R_6, R_7, R_8 and R_9 independently is hydrogen, C_{1-7}alkyl or halogen and more particularly R_6, R_7, R_8 and R_9 are hydrogen; or

p.) n is 0, and R_6, R_8 and R_9 are hydrogen and R_7 is C_{1-7}alkyl; or

q.) n is 0, and R_6, R_7 and R_9 are hydrogen and R_8 is C_{1-7}alkyl or halogen.

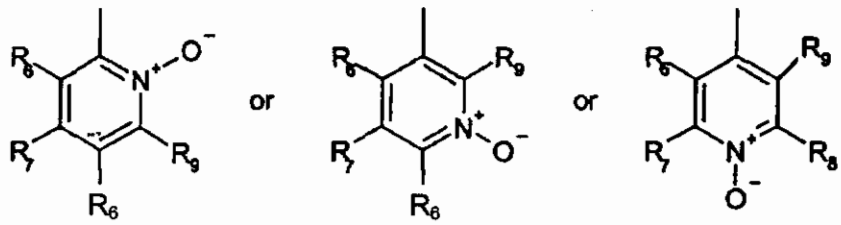
In another embodiment, R_1 is of formula (II.2)



(II.2)

wherein R_6, R_7, R_6 and R_9 are as defined above for formula (II); in particular, R_7 and R_6 together with the carbon atoms to which they are attached form a phenyl group and R_6 and R_9 are hydrogen.

In yet another embodiment, the R, is of formula (III)



wherein each of R_6, R_7, R_6 and R_9 independently is hydrogen, C_{1-7}alkyl, substituted C_{1-7}alkyl, phenyl, halogen, hydroxy or alkoxy,

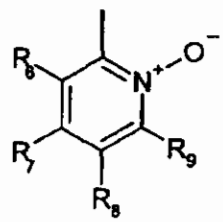
e.g. wherein

a.) R_6 and R_6 are hydrogen, R_9 is hydrogen or C_{1-7}alkyl and R7 is C_{1-7}alkyl, substituted C_{1-7}alkyl or phenyl;

b.) R_6, R_7 and R_9 are hydrogen and R_6 is halogen, alkyl or substituted C_{1-7}alkyl

c.) R_7, R_8 and R_9 are hydrogen and R_6 is hydroxy.

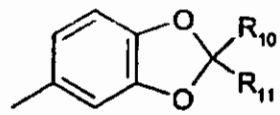
In a particularly useful embodiment the heteroaryl is of the formula (III.1)



wherein R_6, R_7, R_8 and R_9 are as defined above for formula (III).

In another embodiment, R, is an unsubstituted phenyl or the phenyl is substituted with alkoxy, e.g. methoxy, or aryloxy, e.g. phenoxy.

In another embodiment, the R, is of formula (IV)



wherein each of R_{10} and R_{11} independently is hydrogen or halogen. In particular, R_{10} and R_{11} are both either hydrogen or both halogen.

Unless otherwise stated, the following terms as used in the specification have the following meaning.

The term "cycloalkane" or cycloalkyl" contains from 3- to 7-ring carbon atoms, and is, e.g. cyclopropyl,-cyclobutyl, cyclopentyl, and cyclohexyl.

The term "azacyclo 4-7 alkane" contains 1-ring heteroatom which is a nitrogen. It contains from 4 to 7, and especially 4- or 5-ring atoms including the heteroatom.

The term "thiazacyclo $_{4_7}$ alkane" contains 2-ring heteroatoms, nitrogen and sulfur. It contains from 4 to 7, and especially 5-ring atoms including the heteroatoms.

The term "imidazacyclo 4_7 alkane" contains 2-ring heteroatoms which are both nitrogen. It contains from 4 to 7, and especially 5-ring atoms including the heteroatoms.

The term "alkyl" refers to saturated or unsaturated aliphatic groups such as alkenyl or alkynyl, cycloalkyl, or substituted alkyl including straight-chain, branched chain and cyclic groups having from 1 to 7 carbons atoms. Preferably "alkyl" or "alk", whenever it occurs, is a saturated aliphatic group or cycloalkyl, particularly $C_{1\text{-}4}$alkyl. Examples of "alkyl" or "alk" include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, nbutyl, isobutyl, sec-butyl, t-butyl, n-pentyl, neopentyl, n-hexyl or n-heptyl, cyclopropyl, and especially n-butyl.

The term "substituted alkyl" refers to an alkyl group that is substituted with one or more substitutents preferably 1 to 3 substitutents including, but not limited to substituents such as halogen, lower alkoxy, hydroxy, mercapto, carboxy, cycloalkyl, aryl, heteroaryl, and the like. Examples of substituted alkyl groups include, but are not limited to, -CF3, -CFrCF3,

hydroxymethyl, 1- or 2-hydroxyethyl, methoxymethyl, 1- or 2-ethoxyethyl, carboxymethyl, for 2-carboxyethyl, and the like.

The term "aryl" or "Ar" refers to an aromatic carbocyclic group of 6 to 14 carbon atoms having a single ring (including, but not limited to, groups such as phenyl) or multiple condensed rings (including, but not limited to, groups such as naphthyl or anthryl), and is especially phenyl.

The term "heteroaryl" or "HetAr" refers to a 4- to 7-membered, monocyclic aromatic heterocycle or a bicycle that is composed of a 4- to 7-membered, monocyclic aromatic heterocycle and a fused-on benzene ring. The heteroaryl has at least one hetero atom, preferably one or two heteroatoms including, but not limited to, heteroatoms such as N, 0 and S, within the ring. A preferred heteroaryl group is pyridinyl, pyrimidinyl or benzdioxolanyl.

The aryl or heteroaryl may be unsubstituted or substituted by one or more substituents including, but not limited to C_1_7 alkyl, particularly C1.4 alkyl such as methyl, hydroxy, alkoxy, acyl, acyloxy, SCN, halogen, cyano, nitro, thioalkoxy, phenyl, heteroalkylaryl, alkylsulfonyl, and formyl.

The term "carbonylamine" as used herein refers to a -NHC(O)- group wherein the amino portion of the group is linked to the aryl/heteroaryl and the carbonyl portion of the group is linked to the azacyclo 4_7 alkane, thiazacyclo $_{4_7}$ alkane or imidazacyclo 4_7 alkane.

The term "heteroalkyl" refers to saturated or unsaturated C_{1-7} alkyl as defined above, and especially C_{1-4} heteroalkyl which contain one or more heteroatoms, as part of the main, branched, or cyclic chains in the group. Heteroatoms may independently be selected from the group consisting of -NR- where R is hydrogen or alkyl, -5-, -0-, and -P-; preferably -NRwhere R is hydrogen or alkyl, and/or -0-. Heteroalkyl groups may be attached to the remainder of the molecule either at a heteroatom (if a valence is available) or at a carbon atom. Examples of heteroalkyl groups include, but are not limited to, groups such as -0-CH_3,

-CH_2-0-CH_3, -CH_2-CH_2-O-CH_3, -S-CH_2-CH_2-CH_3, -CH_2-CH(CH_3)-S-CH_3, and -CH_2-CH_2-NHCH_2-CH_2-.

The heteroalkyl group may be unsubstituted or substituted with one or more substituents, preferably one to three substituents, including but not limited to, alkyl, halogen, alkoxy, hydroxyl, mercapto, carboxy, and especially phenyl. The heteroatom(s) as well as the carbon atoms of the group may be substituted. The heteroatom(s) may also be in oxidized form.

The term "alkoxy" as used herein refers to a C_{1-7} alkyl linked to an oxygen atom, preferably C_{1-4} alkoxy. Examples of alkoxy groups include, but are not limited to, groups such as methoxy, ethoxy, n-butoxy, tert-butoxy, and allyloxy.

The term "aryl" as used herein refers to the group -(O)CR where R is C_{1-7} alkyl such as methyl. Examples of acyl groups include, but are not limited to, acetyl, propanoyl and butanoyl.

The term "acyloxy" as used herein refers to the group -OC(O)R, wherein R is hydrogen, C_{1-7} alkyl such as methyl or ethyl, or phenyl or substituted alkyl as defined above.

The term "alkoxycarbonyl" as used herein refers to the group -COOR, wherein R is C_{1-7} alkyl such as methyl or ethyl.

The term "halogen" or "halo" as used herein refer to chlorine, bromine, fluorine, iodine, and is especially fluorine.

The term "thioalkoxy" as used herein means a group -SR where R is an alkyl as defined above, e.g. methylthio, ethylthio, propylthio, butylthio, and the like.

The term "heteroalkylaryl" as used herein means a heteroalkyl group, e.g. -O-CH_2- substituted with an aryl group, especially phenyl. The phenyl group itself may also be substituted with one or more substituents such as halogen, especially fluoro and chloro, and alkoxy such as methoxy.

The term "alkylsulfonyl" as used herein means a group -SO_2R wherein R is C_{1-7} alkyl, such as methyl sulfonyl.

"Protecting group" refers to a chemical group that exhibits the following characteristics: 1) reacts selectively with the desired functionality in good yield to give a protected substrate that is stable to the projected reactions for which protection is desired; 2) is selectively removable from the protected substrate to yield the desired functionality; and 3) is removable in good yield by reagents compatible with the other functional group(s) present or generated in such projected reactions. Examples of suitable protecting groups may be found in Greene et al., "Protective Groups in Organic Synthesis", 2nd Ed., John Wiley & Sons, Inc., New York (1991). Preferred amino protecting groups include, but are not limited to, benzyloxycarbonyl (CBz), t-butyl-oxycarbonyl (Boc), t-butyldimethylsilyl (TBDMS), 9-fluorenylmethyl-oxycarbonyl (Fmoc), or suitable photolabile protecting groups such as 6-nitroveratryloxy carbonyl (Nvoc),

nitropiperonyl, pyrenylmethoxycarbonyl, nitrobenzyl, dimethyl dimethoxybenzyl, 5-bromo-7-nitroindolinyl, and the like. Preferred hydroxy protecting groups include Fmoc, TBDMS, photolabile protecting groups (such as nitroveratryl oxymethyl ether (Nvom)), Mom (methoxy methyl ether), and Mem (methoxy ethoxy methyl ether). Particularly preferred protecting groups include NPEOC (4-nitrophenethyloxycarbonyl) and NPEOM (4-nitrophenethyloxy-methyloxycarbonyl).

It will be appreciated that the compounds of formula (I) may exist in the form of optical isomers, racemates or diastereoisomers. For example, a compound of formula (I) wherein R_2 and R_3 are different residues or wherein R_4 and R_5 are different residues, is asymmetric and may have the R- or S- configuration. It is to be understood that the present invention embraces all enantiomers and their mixtures. Similar considerations apply in relation to starting materials exhibiting asymetric carbon atoms as mentioned.

The compounds of the invention, e.g. the compounds of formula (I), may exist in free form or in salt form, e.g. in form of a pharmaceutically acceptable salt. A "pharmaceutically acceptable salt" of a compound means a physiologically and pharmaceutically acceptable salt that possesses the desired pharmacological activity of the parent compound and does not impart undesired toxicological effects. Such salts include:

(1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzene-sulfonic acid, 2-napthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynapthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or

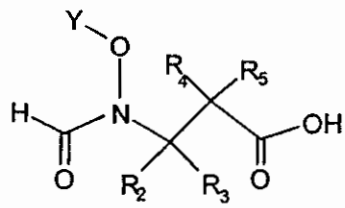
(2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g. an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanol-amine, tromethamine, N-methylglucamine, and the like.

A compound of the invention, e.g. the compounds of formula (I), may act as a pro-drug. "Prodrug" means any compound which releases an active parent drug according to formula (I) *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of a compound of formula (I) are prepared by modifying functional groups present in the compound of formula (I) in such a way that the modifications may be cleaved *in vivo* to release the parent compound. Prodrugs include compounds of formula (I) wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that may be cleaved *in vivo* to regenerate the free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to esters (e.g. acetate, formate, and benzoate derivatives), carbamates (e.g. N, N-dimethylamino-carbonyl) of hydroxy functional groups in compounds of formula (I), and the like.

In the compounds of formula (I), the following significances are preferred individually or in any sub-combination:

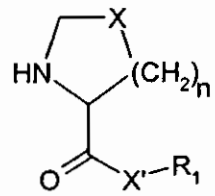
1. R_1 is a heteroaryl of formula (II.1) wherein R_6, R_7 and R_9 are hydrogen and R_8 is methyl or trifluoromethyl; or R_6, R_7 and R_8 are hydrogen and R_9 is fluoro; or R_6, R_8 and R_9 are hydrogen and R_7 is ethyl or methoxy; or R_7, R_8 and R_9 are hydrogen and R_6 is hydroxy; or R_7 and R_8 are hydrogen, R_6 is methoxy and R_9 is methyl; or R_1 is a heteroaryl of formula (III.1) wherein R_6, R_7 and R_9 are hydrogen and R_8 is fluoro or trifluoromethyl; or R_6, R_8 and R_9 are hydrogen and R_7 is ethyl; preferably R_1 is a heteroaryl of formula (II.1) wherein R_6, R_8 and R_9 are hydrogen and R_7 is ethyl or a heteroaryl of formula (III.1) wherein R_6, R_7 and R_9 are hydrogen and R_8 is fluoro.
2. X is $-CH_2-$, -CH(OH)-, -CH(OR)-, $-CF_2-$ or -CH(F)-, preferably X is $-CH_2-$;
3. R_2, R_3, R_4 are hydrogen;
4. R_5 is alkyl, preferably C_{1-7} alkyl such as n-butyl;
5. n is 1.

The present invention also provides a process for preparing a compound of the invention, e.g. a compound of formula (I) which process comprises reacting a compound of formula (V)



(V)

wherein R_2, R_3, R_4 and R_5 are as defined above and Y is a hydroxy protecting group, or a functional derivative thereof, with a compound of formula (VI)



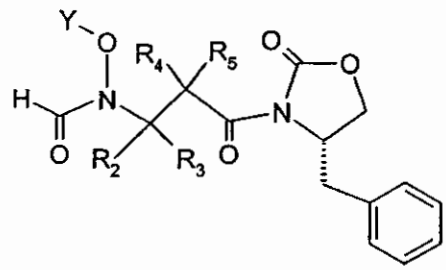
(VI)

wherein R_1, X and n are as defined above, and X' is NH or O, and where required, converting the resulting compounds obtained in free form into salt forms or vice versa.

Functional derivatives of compounds of formula (V) include e.g. halogenides, e.g. acid chloride, acid anhydride or an activated ester.

Above reactions may be carried out according to methods known in the art or as disclosed in the Examples below. The reaction may conveniently be carried out in the presence of a base and then followed by hydrogenation, prefereably in the presence of a hydrogenation catalyst. Suitable bases include e.g. Hunig base (i.e. diisopropylethylamine) and inorganic bases such as sodium bicarbonate. The hydrogenation catalyst, preferably a palladium catalyst, e.g. palladium on carbon or palladium black, may then be added to the resulting product, e.g. after concentration and stirred under a hydrogen atmosphere e.g. for about 16 to about 24 hours. The palladium catalyst may be added preferably from about 5 mol% to about 10 mol% of the concentrated product.

Compounds of formula (V), used as starting materials, may be prepared e.g. by reacting a compound of formula (VII)

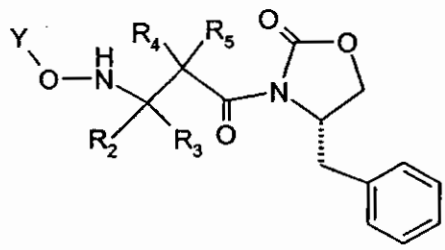


(VII)

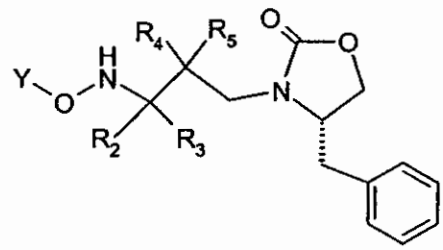
wherein R_2, R_3, R_4, R_5, and Y are as defined above, e.g. under mild basic conditions e.g. as known in the art. Typically, this reaction may be carried out by dissolving the compound of formula (VII) e.g. in a mixture of an inert solvent, such as THF, DMF, toluene, dioxane or

CH_2Cl_2, and water, and adding hydrogen peroxide and then an aqueous solution of the base in water to the cooled mixture. Examples of base include, e.g. sodium bicarbonate, lithium hydroxide, sodium hydroxide and the like. The base may be used preferably at from about 1.1 to about 1.5 equivalents to the compound of formula (VII).

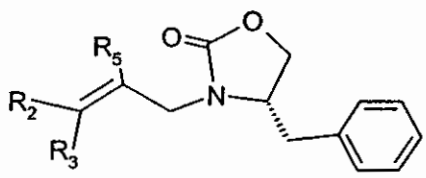
Compounds of formula (VII) may be produced e.g. by reacting a compound of formula (VIII) wherein R_2, R_3, R_4, R_5 and Y are as defined above, with formic acid as known in the art. The reaction may typically be carried out, e.g. at 0°C, by adding a solution of acetic anhydride in formic acid to a solution of a compound of formula (VIII) in formic acid.



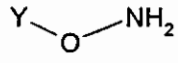
(VIII)



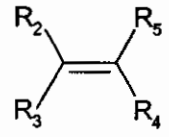
(IX)



(X)



(XI)



(XII)

Compounds of formula (VIII) may be prepared e.g. by reacting a compound of formula (IX) wherein R_2, R_3, R_4 and R_5 are as defined above, with a solution of p-toluenesulfonic acid in an inert organic solvent, and a solution of Na_2CO_3, e.g. 1M, as known in the art.

Compounds of formula (IX) may be prepared e.g. by reacting a compound of formula (X) wherein R_2, R_3 and R_5 are as defined above, with a hydroxy protected compound of formula (XI) wherein Y is aryl, alkyl, aralkyl or silyl, as known in the art.

The compound of formula (X) may be produced e.g. by reacting a compound of formula (XII) with pivaloyl chloride, wherein R_4 is as defined above, as known in the art.

Insofar as the production of starting materials is not particularly described, the compounds are known or may be prepared analogously to methods known in the art or as disclosed in the examples hereinafter.

The following abbreviations are used:

DIEA = diisopropylethylamine
DMF = dimethylformamide
DMSO = dimethylsulfoxide
EtOAc = ethyl acetate
FC = flash chromatography
HATU = O-(7-aza-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
MCPBA = meta-chloroperoxy-benzoic acid
PFP = pentafluorophenyl
p-TSA = p-toluenesulfonic acid
rt = room temperature
TFA = trifluoroacetic acid
THF = tetrahydrofuran

General Procedure A : Synthesis of 1-{2(R)-[(formylhydroxyamino)-methyl]-alkanoyl}-pyrrolidine-2(S)-carboxylic acid amide (Scheme)

Step 1: 2-*n*-butyl acrylic acid (A-2)

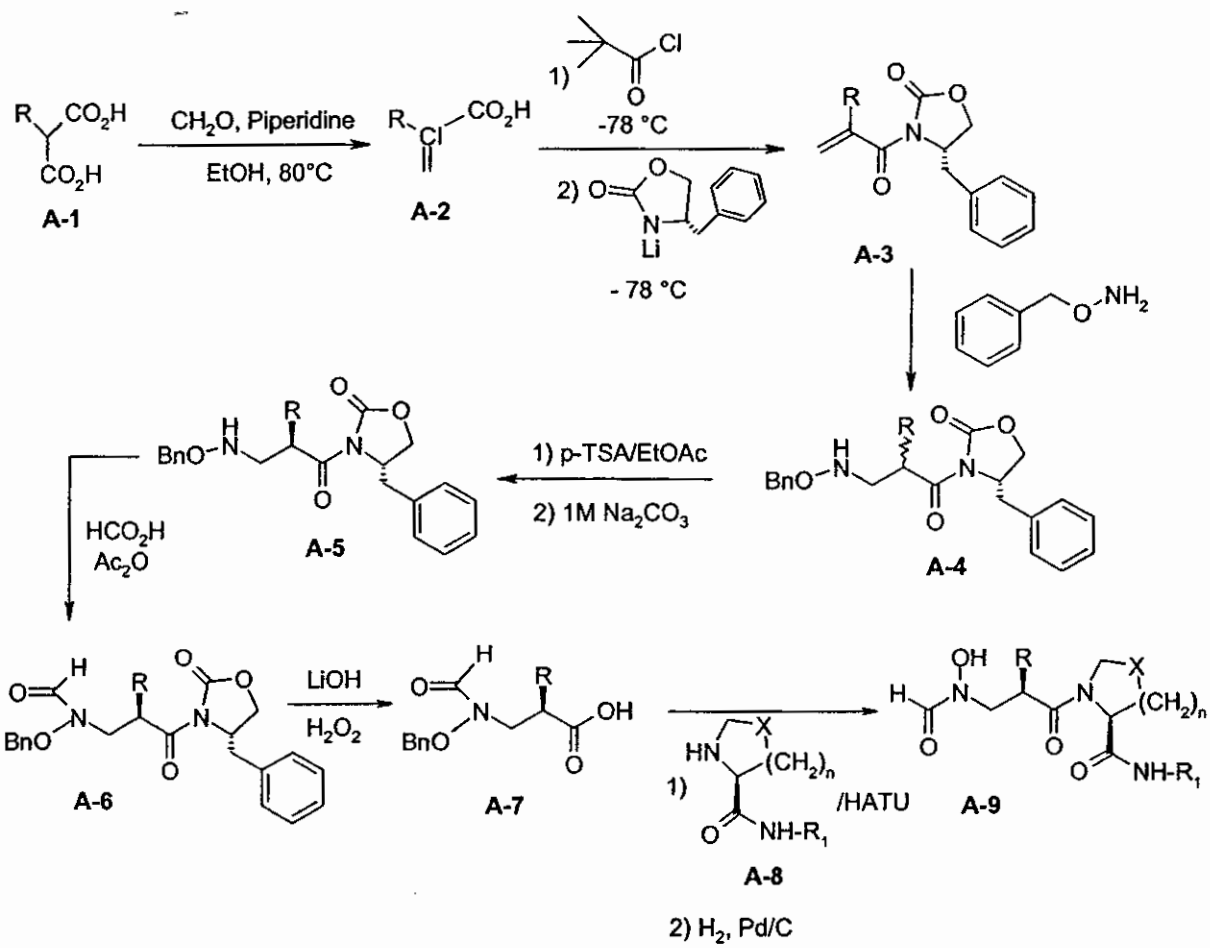
To a solution of alkyl malonic acid **A-1** (R = *n*-butyl (107.4 mmol) in ethanol (200 ml) is added piperidine (12.7 ml, 128.8 mmol, 1.2 equiv.) and 37% aqueous formaldehyde (40.0 ml, 536.9 mmol, 5 equiv.). The solution is heated to 80°C during which time a precipitate appears, and then gradually re-dissolves over 1 h. The reaction mixture is stirred at 80°C overnight then cooled to rt. The solvents are removed under reduced pressure, and the residue is dissolved in EtOAc, washed successively with 1M HCl and brine, dried over anhydrous Na_2SO_4, and filtered. The filtrate is concentrated to give the title compound **A-2** as a clear oil.

Step 2: 4-benzyl-3-(2-butyl-acryloyl)-oxazolidin-2-one (A-3)

2-*n*-Butyl acrylic acid (9.90 g, 77.2 mmol, and 1 equiv.) is dissolved in dry THF (260 ml) and cooled to -78°C under nitrogen. Hunig's base (17.5 ml, 100.4 mmol, 1.3 equiv.) and pivaloyl chloride (9.5 ml, 77.2 mmol, 1 equiv.) are added at such a rate that the temperature remains below -60°C. The mixture is stirred at -78°C for 30 min, warmed to rt for 2 h, and finally

cooled back to -78°C. In a separate flask, (*S*)-(-)-4-benzyl-2-oxazolidinone (13.49 g, 77.24 mmol) is dissolved in dry THF (150 ml) and cooled to -78°C under nitrogen. *n*-Butyllithium (2.5M solution in hexanes, 30.9 ml, 77.2 mmol, 1 equiv.) is added slowly at -78°C, and the mixture is stirred for 30 min at rt. The resulting anion is slowly transferred via a cannula into the original reaction vessel. The mixture is allowed to warm to rt and is stirred overnight at rt. The reaction is quenched with 1M $KHCO_3$, and the solvents are removed under reduced pressure. The residue is partitioned between EtOAc and water. The organic layer is washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to give a yellow oil which is purified by FC (hexane:EtOAc = 4:1) to yield the title compound **A-3** as a white solid.

1H NMR ($CDCl_3$): δ 7.39-7.20 (m, 5H), 5.42-5.40 (d, J = 7.14 Hz, 2H), 4.76-4.68 (m, 1H), 4.29-4.16 (m, 2H), 3.40-3.35 (dd, J = 3.57, 13.46 Hz, 1H), 2.86-2.79 (dd, J = 9.34, 13.46 Hz, 1H), 2.42-2.37 (t, J = 7.69 Hz, 2H), 1.55-1.30 (m, 4H), 0.95-0.90 (t, J = 7.14 Hz, 3H). ES-MS: calcd. For $C_{17}H_{21}NO_3$ (287.35); found: 288.5 [M+H].



X = CH_2, -S-, -CH(OH)-, -CH(OR)-, -CH(SH)-, -CH(SR)-, -CF_2-, -C=N(OR)- or -CH(F)-; n = 0 to 3

Step 3: 4-benzyl-3-[2-(benzyloxyamino-methyl)-hexanoyl]-oxazolidin-2-one (*p*-toluene-sulfonic acid salt)

Compound **A-3** (8.25 g, 28.7 mmol) is mixed with *O*-benzylhydroxylamine (7.07 g, 57.4 mmol, 2 equiv.) and stirred for 40 h at rt under nitrogen. The mixture is dissolved in EtOAc and p-TSA (21.84 g, 114.8 mmol, and 4 equiv.) is added to precipitate excess *O*-benzylhydroxylamine as a white solid. The white solid is filtered off, and the filtrate is concentrated to give a crude yellow oil (HPLC analysis indicated a small trace of starting material). Charging the crude yellow oil with excess diethyl ether and cooling to 0°C for 30 min gives a solid which is collected by filtration and dried in vacuo to afford the title compound as a white crystalline solid (single diastereomer).

1H NMR ($CDCl_3$): δ 8.07-8.04 (d, J = 8.24 Hz, 2H), 7.59-7.39 (m, 10H), 7.18-7.15 (d, J = 7.69 Hz, 2H), 5.49-5.40 (q, J = 8.61 Hz, 2H), 4.65-4.56 (m, 1H), 4.25-4.08 (m, 3H), 3.83-3.79 (d, J = 13.46 Hz, 1H), 3.15-3.11 (d, J = 13.46 Hz, 1H), 2.56 (s, 3H), 1.83-1.67 (m, 4H), 1.40 (bs, 4H), 1.00-0.951 (t, J = 6.87, 3H). ES-MS: calcd. For $C_{24}H_{30}N_2O_4{}^*C_7H_8O_3S$ (582.71); found: 411.7 [M+H] free base.

Step 4: 4-benzyl-3-[2-(benzyloxyamino-methyl)-hexanoyl]-oxazolidin-2-one (A-5)

To a solution of p-TSA (22.9 g, 39 3 mmol) dissolved in EtOAc (400 ml), is added 1M Na_2CO_3 (200 ml, 5 equiv.) and stirred at rt for 30 min. The layers are separated, and the aqueous layer extracted with EtOAc. The combined organic layers are dried over anhydrous Na_2SO_4, filtered, and concentrated to give the title compound as a pale opaque oil.

1H NMR ($CDCl_3$): δ 7.57-7.38 (m, 10H), 4.98-4.90 (m, 2H), 4.87-4.79 (m, 1H), 4.38-4.28 (m, 3H), 3.64-3.57 (dd, J = 9.21, 12.64 Hz, 1H), 3.46-3.36 (td, J = 3.76, 13.05 Hz, 2H), 2.68-2.60 (dd, J = 10.03, 13.46 Hz, 1H), 1.90-1.88 (m, 1H), 1.78-1.71 (m, 1H), 1.51-1.44 (m, 4H), 1.10-1.06 (t, J = 6.73 Hz, 3H). ES-MS: calcd. For $C_{24}H_{30}N_2O_4$ (410.51); found: 411.7 [M+H].

Step 5: *N*-[2-(4-benzyl-2-oxo-oxazolidine-3-carbonyl)-hexyl]-*N*-benzyloxy-formamide (A-6)

A solution of compound **A-5** (5.38 g, 13.1 mmol, 1 equiv.) in formic acid (7.4 ml, 196.6 mmol, 15 equiv.) is cooled to 0°C under nitrogen. In a separate flask, formic acid (7.4 ml, 196.6 mmol, 15 equiv.) is cooled to 0°C under nitrogen, and acetic anhydride (2.47 ml, 26.2 mmol, 2 equiv.) is added dropwise. The solution is stirred at 0°C for 15 min. The resulting mixed anhydride is slowly transferred via syringe into the original reaction vessel. The mixture is stirred at 0°C for 1 h, then at rt for 3 h. The mixture is concentrated, taken up in CH_2Cl_2, and washed successively with saturated $NaHCO_3$ and brine. The organic layer is dried over

anhydrous Na_2SO_4, filtered, and concentrated to give an opaque oil which is purified by FC (hexane:EtOAc = 2:1 then CH_2Cl_2:acetone = 9:1) to yield the title compound as a colorless oil.

1H NMR ($CDCl_3$, rotamers): δ 8.38 (s, 0.7H), 8.21 (s, 0.3H), 7.54-7.35 (m, 10H), 5.0-5.00 (m, 2H), 4.88-4.81 (m, 1H), 4.39-4.29 (m, 4H), 4.07-4.03 (m, 1H), 3.43-3.39 (m, 1H), 2.66-2.58 (m, 1H), 1.89 (bs, 1H), 1.73 (bs, 1H), 1.49-1.44 (m, 3H), 1.10-1.06 (t, J = 6.73 Hz, 3H). ES-MS: calcd. For $C_{25}H_{30}N_2O_5$ (438.52); found: 439.7 [M+H].

Step 6: 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid (A-7)

Compound **A-6** (0.163 g, 0.372 mmol, 1 equiv.) is dissolved in THF (4.5 ml) and water (1.5 ml) and cooled to 0°C. Hydrogen peroxide (30% in water, 228 µl, 2.23 mmol, 6 equiv.) is added dropwise followed by the slow addition of a solution of lithium hydroxide (0.019 g, 0.446 mmol, 1.2 equiv.) in water (350 µl). The resulting mixture is stirred at 0°C for 1.5 h. The basic reaction mixture is quenched with Amberlite IR-120 resin (H^+) to pH 4-5 at 0°C. The resin is filtered off and rinsed with EtOAc. The mixture is concentrated to remove THF, and then taken up in EtOAc. The aqueous layer is separated, and the organic layer dried over anhydrous Na_2SO_4, filtered, and concentrated to give an opaque oil which is purified by FC (CH_2Cl_2:acetone = 4:1 then acetone: methanol = 99:1) to yield the title compound **A-7** as a colorless oil.

1H NMR (DMSO-d_6, rotamers): δ 11.2 (s, 1H), 8.20 (s, 0.2H), 7.95 (s, 0.8H), 7.33-7.41 (m, 5H), 4.87 (s, 2H), 3.71 (bs, 2H), 2.50 (bs, 1H), 1.35-1.45 (m, 2H), 1.14-1.28 (m, 4H), 0.857-0.813 (t, J = 13.1 Hz, 3H). ES-MS: calcd. For $C_{15}H_{21}NO_4$ (279.33); found: 278.5 (M-H], 302.5 [M+Na].

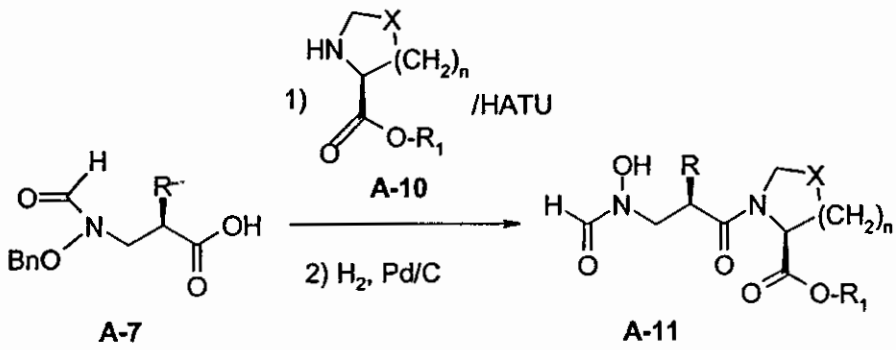
Step 7: 1-{2-[(benzyloxy-formyl-amino)-methyl]-hexanoyl}-pyrrolidine-2-carboxylic acid amide

To a solution of compound **A-7** (0.190 g, 0.680 mmol, 1 equiv.) in dry dioxane (4 ml) at rt under nitrogen is added successively Hunig's base (391 µl, 2.24 mmol, 3.3 equiv.), amine **A-8** (0.748 mmol, 1.1 equiv.) and HATU (0.284 g, 0.748 mmol, 1.1 equiv.). The resulting mixture is stirred at rt for 22 h. The mixture is partitioned between EtOAc and 10% citric acid. The organic layer is washed with brine and saturated $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue is purified by FC (CH_2Cl_2:acetone = 3:1) to give the title compound as a colorless oil.

Step 8: 1-{2-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-carboxylic acid amide (A-9)

Pd-C (0.059 g, 0.1 equiv.) is added to a solution of above compound (0.550 mmol, 1 equiv.) in a 1:1 EtOAc/ethanol solution (12 ml) under nitrogen. The mixture is stirred under hydrogen atmosphere for 36 h. The catalyst is removed by filtration through a pad of Celite. The filtrate is concentrated, and the residue is purified by preparative TLC (CH_2Cl_2:acetone = 2:1) to give the title compound as an amorphous solid.

General Procedure B : Synthesis of 1-{2(R)-[(formylhydroxyamino)-methyl]-alkanoyl}-pyrrolidine-2(S)-carboxylate ester



A-7 A-11

X = CH_2, S
n = 0, 1, 2

X = CH_2, -S-, -CH(OH)-, -CH(OR)-, -CH(SH)-, -CH(SR)-, -CF_2-, -C=N(OR)- or -CH(F)-; n = 0 to 3

Step 1: 1-{2-[(benzyloxy-formyl-amino)-methyl]-hexanoyl}-pyrrolidine-2-carboxylic acid ester

To a solution of compound **A-7** (0.680 mmol, 1 equiv.) in dry dioxane (4 ml) at rt under nitrogen is added successively Hunig's base (391 µl, 2.24 mmol, 3.3 equiv.), amine **A-10** (0.748 mmol, 1.1 equiv.) and HATU (0.284 g, 0.748 mmol, 1.1 equiv.). Usual work-up and purification provides the title compound.

Step 8: 1{2-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-carboxylic acid ester (A-11)

Pd-C (0.059 g, 0.1 equiv.) is added to a solution of above compound (0.550 mmol) in a 1:1 EtOAc/ethanol solution (12 ml) under nitrogen. The mixture is stirred under hydrogen atmosphere for 36 h. By following the same procedure as disclosed above, the title compound is obtained.

Example 1: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid pyridin-2-ylamide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and pyrrolidine-2-carboxylic acid pyridin-2-ylamide **A-8** (X = CH_2, n = 1, R_1 = 2-pyridyl).

1H NMR (DMSO-d_6): δ 10.7 (s, 1H), 9.89 (s, 1H), 8.50-8.44 (m, 1H), 8.23-8.17 (m, 1H), 7.97-7.92 (m, 2H), 7.29-7.25 (m, 1H), 4.83-4.71 (m, 1H), 3.91-3.51 (m, 4H), 3.30-3.15 (m, 1H), 2.46-1.83 (m, 4H), 1.52-1.31 (m, 6H), 1.11-0.93 (m, 3H). ES-MS: calcd. for $C_{18}H_{26}N_4O_4$ (362.42); found: 363.6 [M+H], 385.5 [M+Na].

Preparation of pyrrolidine-2-S-carboxylic acid (pyridin-2-yl) amide A-8 (X = CH_2, n = 1, R_1 = 2-pyridyl)

2-S-(pyridin-2-ylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester

A solution of 2-S-(chlorocarbonyl)-pyrrolidine-1-carboxylic acid benzyl ester (5.0 g, 18.7 mmol, 1 equiv.) in pyridine (40 ml) is cooled to 0°C under nitrogen. 2-Aminopyridine (5.27 g, 56.0 mmol, 3 equiv.) in pyridine (10 ml) is added dropwise. The resulting mixture is stirred at rt for 4 h, then concentrated. The residual oil is dissolved in EtOAc and washed successively with water, 10% citric acid, saturated $NaHCO_3$, and brine. The organic layer is dried over anhydrous Na_2SO_4, filtered, and concentrated to give the title compound as an opaque solid.

1H NMR (DMSO-d_6): δ 10.8-10.7 (d, J = 15.6 Hz, 1H), 8.51-8.49 (m, 1H), 8.29-8.24 (m, 1H), 8.01-7.93 (m, 1H), 7.57-7.48 (m, 3H), 7.40-7.25 (m, 3H), 5.31-.22 (m, 2H), 4.76-4.68 (m, 1H), 3.72-3.58 (m, 2H), 2.50-2.31 (m, 1H), 2.14-1.95 (m, 3H).

Pyrrolidine-2-S-carboxylic acid (pyridin-2-yl) amide hydrobromic acid salt

A solution of above compound (4.21 g, 13.0 mmol, 1 equiv.) in AcOH (65 ml) at rt is treated with HBr (5.7M, 33% in AcOH, 110 ml, 649 mmol, 50 equiv.), and the mixture is stirred at rt for 2 h. Charging the reaction mixture with excess diethyl ether and cooling to 0°C for 30 min gives a solid which is collected by filtration and dried in vacuo to afford the title compound as a brownish powder.

1H NMR (DMSO-d_6): δ 11.3 (s, 1H), 8.89 (bs, 1H), 8.57-8.5 (m, 1H), 8.24-8.22 (m, 1H), 8.08-8.03 (m, 1H), 7.40-7.36 (m, 1H), 4.61 (bs, 1H), 3.47-3.45 (m, 2H), 2.65-2.55 (m, 1H), 2.21-2.07 (m, 3H). ES-MS: calcd. for $C_{10}H_{13}N_3O$*2HBr (353.05); found: 192.4 [M+H] free base.

Example 2: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid-(3-methyl-pyridin-2-yl)-amide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and pyrrolidine-2-carboxylic acid (3-methyl-pyridin-2-yl)-amide **A-8** [X = CH_2, n = 1, R_1 = 2-(3-methyl)pyridyl]. **A-8** is prepared from 2-chlorocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester and 3-picoline as described for the synthesis of pyrrolidine-2-carboxylic acid pyridin-2-yl-amide (hydrobromic acid salt) in Example 1.

1H NMR (DMSO-d_6): δ 8.45-8.42 (m, 1H), 8-7.8 (m, 1H), 7.4-7.36 (dd, 1H), 4.7 (bs, 1H), 3.8 (m, 4H), 3.15-3.3 (m, 1H), 2.37-2.3 (bs, 3H), 2.12 (bs, 4H), 1.65-1.43 (m, 6H), 1.03-1 (d, J = 6.2 Hz, 3H). ES-MS: calcd. for $C_{19}H_{28}N_4O_4$ (376.45); found: 377.7 [M+H].

Example 3: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid-(6-methyl-pyridin-2-yl)-amide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and pyrrolidine-2-carboxylic acid (6-methyl-pyridin-2-yl)-amide **A-8** (X = CH_2, n = 1, R_1 = 2-(6-methyl)pyridyl). **A-8** is prepared from 2-chlorocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester and 6-picoline as described for the synthesis of pyrrolidine-2-carboxylic acid pyridin-2-yl-amide (hydrobromic acid salt) in Example 1.

1H NMR (DMSO-d_6): δ 8.04-7.8 (m, 1H), 7.2-7.12 (d, J = 7.42 Hz, 1H), 4.75-4.73 (d, J = 4.4 Hz, 1H), 3.85-3.71 (m, 4H), 3.21 (bs, 1H), 2.58 (bs, 3H), 2.3-2.1 (m, 4H), 1.67-1.42 (m, 6H), 1.06-1.04 (d, J = 6.3 Hz, 3H). ES-MS: calcd. for $C_{19}H_{28}N_4O_4$ (376.45); found: 377.7 [M+H].

Example 4: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid-(4-methyl-pyridin-2-yl)-amide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and pyrrolidine-2-carboxylic acid (4-methyl-pyridin-2-yl)-amide **A-8** (X = CH_2, n = 1, R_1 = 2-(4-methyl)pyridyl).

1H NMR (DMSO-d_6): δ 8.35-8.34 (d, J = 4.67 Hz, 1H), 8.08-7.98 (d, 1H), 4.75-4.73 (d, J = 4.67 Hz, 1H), 4.74 (bs, 1H), 3.73 (bs, 2H), 3.52 (bs, 2H), 2.49 (bs, 3H), 2.27-2.05 (m, 4H), 1.66-1.46 (m, 6H), 1.05 (bs, 3H). ES-MS: calcd. for $C_{19}H_{28}N_4O_4$ (376.46); found: 377.7 [M+H].

A-8 is prepared from 2-chlorocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester and 4-picoline as described for the synthesis of pyrrolidine-2-carboxylic acid pyridin-2-yl-amide (hydrobromic acid salt) in Example 1.

2-S-(4-methyl-pyridin-2-ylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester

1H NMR (DMSO-d_6): δ 8.33 (bs, 1H), 8.17-8.13 (m, 1H), 7.81-7.77 (m, 1H),7.6-7.3 (m, 4H), 5.9-5.11 (m, 2H), 4.72-4.66 (m, 1H), 3.68-3.61 (m, 2H), 2.44 (bs, 3H), 2.34-1.98 (m, 4H). ES-MS: calcd. for $C_{19}H_{21}N_3O_3$ (339.39); found: 340.6 [M+H].

Pyrrolidine-2-S-carboxylic acid (4-methyl-pyridin-2-yl) amide hydrobromic acid salt

1H NMR (DMSO-d_6): δ 8.45-8.43 (d, 1H, J = 5.2 Hz), 8.03 (bs, 1H), 7.29-7.28 (d, J = 5.2 Hz, 1H), 4.64 (bs, 1H), 3.47 (bs, 2H), 2.63 (bs, 3H), 2.56-2.07 (m, 4H). ES-MS: calcd. for $C_{11}H_{15}N_3O$ (205.12); found: 206.4 [M+H].

Example 5: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid-(5-fluoro-pyridin-2-yl)-amide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and pyrrolidine-2-carboxylic acid (5-fluoro-pyridin-2-yl)-amide **A-8** (X = CH_2, n = 1, R_1 = 2-(5-fluoro)pyridyl).

1H NMR (DMSO-d_6): δ 8.51-8.44 (m, 1H), 8.3-8.25 (m, 1H), 7.97-7.88 (m, 1H), 4.75 (bs, 1H), 3.82-3.72 (m, 2H), 3.65-3.52 (m, 2H), 3.21 (bs, 1H), 2.7-2.68 (m, 4H), 2.3-1.45 (m, 6H), 1.04 (d, 3H). ES-MS: calcd. for $C_{18}H_{25}FN_4O_4$ (380.42); found: 381.7 [M+H].

A-8 is prepared from 2-chlorocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester and 5-fluoro-pyridin-2-ylamine as described for the synthesis of pyrrolidine-2-carboxylic acid pyridin-2-yl-amide (hydrobromic acid salt) in Example 1.

Pyrrolidine-2-S-carboxylic acid (5-fluoro-pyridin-2-yl) amide hydrobromic acid salt

1H NMR (DMSO-d_6): δ 8.58-8.57 (d, J = 3.02 Hz, 1H), 8.3-8.25 (m, 1H), 8.05-7.83 (m, 1H), 4.62-4.59 (d, J = 7.87 Hz, 1H), 3.46 (bs, 2H), 2.69-2.55 (m, 1H), 2.21-2.06 (m, 3H). ES-MS: calcd. for $C_{10}H_{12}FN_3O$ (209.1); found: 210.4 [M+H].

Example 6: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid-(5-methyl-pyridin-2-yl)-amide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and pyrrolidine-2-carboxylic acid (5-methyl-pyridin-2-yl)-amide **A-8** (X = CH_2, n = 1, R_1 = 2-(5-methyl)pyridyl).

1H NMR (DMSO-d_6): δ 7.95-7.92 (d, J = 8.52 Hz, 1H), 7.78 (bs, 1H), 7.6-7.58 (m, 1H), 4.55 (bs, 1H), 3.88-3.54 (bs, 2H), 3.33-3.29 (bs, 2H), 3.1-2.9 (m, 1H), 2.24 (bs, 3H), 2.11-1.87 (m, 4H), 1.48-1.26 (m, 6H), 0.87-0.85 (d, 3H). ES-MS: calcd. for $C_{19}H_{28}N_4O_4$ (376.46); found: 377.7 [M+H].

A-8 is prepared from 2-chlorocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester and 5-methyl-pyridin-2-ylamine as described for the synthesis of pyrrolidine-2-carboxylic acid pyridine-2-yl-amide (hydrobromic acid salt) in Example 1.

2-S-(5-methyl-pyridin-2-ylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester

1H NMR (DMSO-d_6): δ 8.36-8.35 (d, J = 4.7 Hz, 1H), 8.12 (bs, 1H), 7.57-7.14 (m, 5H), 5.3-5.11 (m, 2H), 4.74-4.68 (t, J = 9.34 Hz, 1H), 3.7-3.62 (m, 2H), 2.5 2 (bs, 3H), 2.41-2.06 (m, 4H). ES-MS: calcd. for $C_{19}H_{21}N_3O_3$ (339.39); found: 340.6 [M+H].

Pyrrolidine-2-S-carboxylic acid (5-methyl-pyridin-2-yl) amide hydrobromic acid salt

1H NMR (DMSO-d_6): δ 8.45-8.43 (d, 1H, J = 5.2 Hz), 8.03 (bs, 1H), 7.29-7.28 (d, J = 5.2 Hz, 1H), 4.64 (bs, 1H), 3.47 (bs, 2H), 2.63 (bs, 3H), 2.56-2.07 (m, 4H). ES-MS: calcd. for $C_{11}H_{15}N_3O$ (205.12); found: 206.4 [M+H].

Example 7: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid-(6-ethyl-pyridin-2-yl)-amide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and pyrrolidine-2-carboxylic acid (6-ethyl-pyridin-2-yl)-amide **A-8** [X = CH_2, n = 1, R_1 = 2-(6-ethyl)pyridyl].

1H NMR (DMSO-d_6): δ 8.06-7.83 (m, 2H), 7.17-7.14 (d, J = 7.69 Hz, 1H), 4.77 (bs, 1H), 3.83-3.78 (m, 2H), 3.58-3.32 (m, 2H), 3.05 (bs, 1H), 2.87-2.83 (m, 2H), 2.3-2.07 (m, 3H), 1.65-1.38 (m, 10H), 1.04 (bs, 3H). ES-MS: calcd. for $C_{20}H_{30}N_4O_4$ (390.48); found: 391.4 [M+H].

A-8 is prepared from 2-chlorocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester and 6-ethyl-pyridin-2-ylamine as described for the synthesis of pyrrolidine-2-carboxylic acid pyridine-2-yl-amide (hydrobromic acid salt) in Example 1.

Pyrrolidine-2-S-carboxylic acid (6-ethyl-pyridin-2-ylamide (hydrobromic acid salt)

1H NMR (DMSO-d_6): δ 8.07-7.94 (m, 2H), 7.27-7.25 (d, J = 7.42 Hz, 1H), 4.61 (bs, 1H), 3.46 (bs, 2H), 2.93-2.85 (m, 2H), 2.61-2.56 (m, 1H), 2.18-2.09 (m, 3H), 1.44-1.39 (m, 3H). ES-MS: calcd. for $C_{12}H_{17}N_3O$ (219.1); found: 220.2 [M+H].

Example 8: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid-(5-trifluoromethyl-pyridin-2-yl)-amide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and pyrrolidine-2-carboxylic acid (5-trifluoromethyl-pyridin-2-yl)-amide **A-8** [X = CH_2, n = 1, R_1 = 2-(5-trifluoromethyl)pyridyl].

1H NMR (DMSO-d_6): δ 8.45-8.35 (m, 2H), 7.98 (bs, 1H), 4.8-4.78 (d, J = 4.4 Hz, 1H), 3.84-3.73 (m, 2H), 3.54 (bs, 2H), 3.2 (bs, 1H), 2.34-2.1 (m, 4H), 1.65-1.46 (m, 6H), 1.05 (bs, 3H). ES-MS: calcd. for $C_{19}H_{25}F_3N_4O_4$ (430.43); found: 431.3 [M+H].

A-8 is prepared from 2-chlorocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester and 5-trifluoromethyl-pyridin-2-ylamine as described for the synthesis of pyrrolidine-2-carboxylic acid pyridine-2-yl-amide (hydrobromic acid salt) in Example 1.

Pyrrolidine-2-S-carboxylic acid (5-trifluoromethyl-pyridin-2-ylamide (hydrobromic acid salt)

1H NMR (DMSO-d_6): δ 8.98 (bs, 1H), 8.49-8.40 (m, 2H), 4.67 (bs, 1H), 3.49-3.47 (d, 2H), 2.64-2.57 (m, 1H), 2.22-2.09 (m, 3H). ES-MS: calcd. for $C_{11}H_{12}F_3N_3O$ (259.1); found: 260.2 [M+H].

Example 9: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid-(6-fluoro-pyridin-2-yl)-amide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R-n-butyl) and pyrrolidine-2-carboxylic acid (6-fluoro-pyridin-2-yl)-amide **A-8** [X = CH_2, n = 1, R_1 = 2-(5-trifluoromethyl)pyridyl].

1H NMR (DMSO-d_6): δ 8.14 (bs, 1H), 8.04-7.97 (m, 1H), 7.04-7.02 (m, 1H), 4.70 (bs, 1H), 3.85-3.78 (m, 2H), 3.72-3.47 (m, 2H), 3.24 (bs, 1H), 2.3-2.06 (m, 4H), 1.64-1.45 (m, 6H), 1.04 (d, 3H). ES-MS: calcd. for $C_{18}H_{25}FN_4O_4$ (380.42); found: 381.3 [M+H].

A-8 is prepared from 2-chlorocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester and 6-fluoro-pyridin-2-ylamine as described for the synthesis of pyrrolidine-2-carboxylic acid pyridine-2-yl-amide (hydrobromic acid salt) in Example 1.

(6-fluoro-pyridin-2-yl)-(4-methoxy-benzyl)-amine

To a solution of 2,6-di-fluoro-pyridine (2.2 g, 1 equiv.) in DMF (20 ml) is added 4-methoxy-benzylamine (5.6 g, 2.2 equiv.) and potassium carbonate (12 g, 4.4 equiv.). After heating at 50°C for 16 h, the solution is cooled to rt and filtered through Celite. The filtrate is concentrated under reduced pressure. The residue is purified by silica gel column chromatography using a gradient of hexane:EtOAc (19:1→4:1) to give the title compound.

1H NMR ($CDCl_3$): δ 7.49-7.41 (dd, J = 7&8 Hz, 1H), 7.24-7.28 (m, 2H), 6.90-6.85 (m, 2H), 6.19-6.13 (m, 2H), 4.40 (d, J = 6 Hz, 2H), 3.80 (s, 3H). ES-MS: calcd. for $C_{13}H_{13}FN_2O$ (232.25); found: 233.4 [M+H].

2-S-(6-fluoro-pyridin-2-yl-carbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester

2-chlorocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester and (3-fluoro-phenyl)-(4-methoxy-benzyl)-amine is reacted to give amide intermediate as described for the synthesis of 2-S-(pyridin-2-yl-carbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester in Example 1. This intermediate is treated with 90% aq. TFA to give the title compound.

1H NMR ($CDCl_3$): δ 8.06 (d, J = 8.2 Hz, 1H), 7.82-7.74 (dd, J = 8 Hz, 1H), 7.38-7.26 (m, 5H), 6.66 (d, J = 7.5 Hz, 1H), 5.30-5.18 (m, 3H), 3.60-3.59 (m, 2H), 2.05-1.92 (m, 4H). ES-MS: calcd. for $C_{18}H_{18}FN_3O_3$ (343.35); found: 344.3 [M+H].

Pyrrolidine-2-S-carboxylic acid (6-fluoro-pyridin-2-yl) amide hydrobromic acid salt

Title compound is prepared from above intermediate as described for the synthesis of pyrrolidine-2-carboxylic acid pyridine-2-yl-amide (hydrobromic acid salt) in Example 1.

1H NMR (DMSO-d_6): δ 7.4-7.3 (m, 1H), 6.21-6.17 (m, 1H), 4.88-4.87 (d, 1H), 3.86 (bs, 1H), 2.89-2.69 (m, 2H), 1.99-1.91 (m, 1H), 1.58-1.45 (m, 3H). ES-MS: calcd. for $C_{10}H_{12}FN_3O$ (209.1); found: 242.3 [M+K].

Example 10: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid-(4,6-di-methyl-1-oxy-pyridin-2-yl)-amide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and pyrrolidine-2-carboxylic acid (4,6-di-methyl-1-oxy-pyridin-2-yl)-amide **A-8** [X = CH_2, n = 1, R_1 = 2-(4,6-di-methyl-1-oxy)-pyridyl].

1H NMR (DMSO-d_6): δ 8.29 (bs, 1H), 7.99 (bs, 1H), 7.24 (bs, 1H), 4.86-4.83 (d, J = 7.692 Hz, 1H), 3.82-3.70 (m, 2H), 3.53-3.5 (m, 2H), 3.24 (bs, 1H), 2.57 (bs, 3H), 2.47 (bs, 3H), 2.3-2.12 (m, 4H), 1.97-1.43 (m, 6H), 1.01 (bs, 3H). ES-MS: calcd. for $C_{20}H_{30}N_4O_5$ (406.48); found: 407.3 [M+H].

Pyrrolidine-2-S-carboxylic acid (4,6-di-methyl-1-oxy-pyridin-2-yl) amide hydrobromic acid salt

2-chlorocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester and 4,6-di-methyl-pyridin-2-ylamine is reacted to give amide intermediate as described for the synthesis of 2-S-(pyridin-2-yl-carbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester in Example 1. This intermediate on oxidation with MCPBA followed by treatment with HBr-AcOH provides the title compound.

1H NMR (DMSO-d_6): δ 8.2-8.19 (d, J = 1.92 Hz, 1H), 7.34-7.33 (d, J = 1.92 Hz, 1H), 4.98-4.96 (d, J = 9.87 Hz, 1H), 3.48-3.46 (d, J = 6.49 Hz, 2H), 2.60 (bs, 4H), 2.55 (bs, 3H), 2.2-2.09 (m, 3H). ES-MS: calcd. for $C_{12}H_{17}N_3O$ (235.13); found: 258.3 [M+Na].

Example 11: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid-(4-methyl-1-oxy-pyridin-2-yl)-amide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and pyrrolidine-2-carboxylic acid (4-methyl-1-oxy-pyridin-2-yl)-amide **A-8** [X = CH_2, n = 1, R_1 = 2-(4-methyl-1-oxy)-pyridyl].

1H NMR (DMSO-d_6): δ 8.45-8.42 (d, J = 6.32 Hz, 1H), 8.3 (bs, 1H), 7.17-7.15 (d, J = 6.7 Hz, 1H), 4.91-4.89 (d, J = 7.42 Hz, 1H), 3.87-3.66 (m, 2H), 3.53 (bs, 2H), 3.22 (bs, 1H), 2.5 (bs, 3H), 2.34-2.33 (d, J = 4.5 Hz, 2H), 2.13-2.12 (d, J = 3.3 Hz, 2H), 1.68-1.45 (m, 6H), 1.02 (bs, 3H). ES-MS: calcd. for $C_{19}H_{28}N_4O_5$ (392.46); found: 393.3 [M+H].

Pyrrolidine-2-S-carboxylic acid (4-methyl-1-oxy-pyridin-2-yl) amide hydrobromic acid salt

2-chlorocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester and 4-methyl-pyridin-2-ylamine is reacted to give amide intermediate as described for the synthesis of 2-S-(pyridin-2-yl-carbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester in Example 1. This intermediate on oxidation with MCPBA followed by treatment with HBr-AcOH provides the title compound.

1H NMR (DMSO-d_6): δ 8.54-8.53 (d, J = 6.6 Hz, 1H), 8.32-8.315 (d, J = 2.2 Hz, 1H), 7.31-7.28 (m, 1H), 4.98-4.96 (d, J = 6.77 Hz, 1H), 3.48-3.46 (d, J = 4.39 Hz, 2H), 2.62-2.54 (m, 4H), 2.2-2.07 (m, 3H). ES-MS: calcd. for $C_{11}H_{15}N_3O_2$ (221.12); found: 222.3 [M+H].

Example 12: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-azetidine-2-S-carboxylic acid-pyridin-2-ylamide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and azetidine-2-carboxylic acid (pyridin-2-yl)-amide **A-8** [X = CH_2, n = 1, R_1 = 2-pyridyl].

1H NMR (DMSO-d_6): δ 10.74 (bs, 1H), 8.52 (bs, 1H), 8.29 (bs, 1H), 8.01 (bs, 1H), 7.32 (bs, 1H), 5.11 (bs, 1H), 4.35 (bs, 1H), 3.75-3.55 (m, 4H), 2.71-2.44 (m, 2H), 1-46 (bs, 6H), 1.06 (bs, 3H). ES-MS: calcd. for $C_{17}H_{24}N_4O_4$ (348.40); found: 349.3 [M+H].

A-8 is prepared from azetidine-1,2-dicarboxylic acid 1-tert butyl ester and pyridin-2-ylamine as described below.

2-S-(pyridin-2-ylcarbamoyl)-azetidine-1-carboxylic acid tert butyl ester

Boc-protected azetidine carboxylic acid is prepared by reacting the free amino acid with Boc-anhydride in the presence of $NaHCO_3$, THF:water (1:1 v/v). The protected amino acid is coupled to 2-amino pyridine using HATU/DIEA/DMF to yield the protected amide.

1H NMR ($CDCl_3$): δ 8.52-8.49 (m, 2H), 8.02-7 96 (m, 1H), 7.32-7.28 (dd, 1H), 5.02-4.97 (t, J = 8.42 & 8.24 Hz, 1H), 4.2-4.06 (m, 2H), 2.75-2.7 (t, J = 6.04 & 8.24 Hz, 2H), 1.73-1.63 (m, 9H). ES-MS: calcd. for $C_{14}H_{19}N_3O_3$ (277.32); found: 278.5 [M+H].

Azetidine-2-S-carboxylic acid pyridin-2-yl-amide hydrochloric acid salt

The protected amide is treated with 4.0M HCl-dioxane to give HCl salt of **A-8**.

1H NMR (DMSO-d_6): δ 8.56-8.54 (dd, 1H), 8.29-8.26 (d, J = 7.97 Hz, 1H), 8.10-8.05 (dd, 1H), 7.41-7.37 (dd, 1H), 5.32 (s, 1H), 4.17-3.9 (m, 2H), 2.94-2.85 (m, 2H). ES-MS: calcd. for $C_9H_{11}N_3O$ (177.2); found: 178.4 [M+H].

Example 13: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid-(4,6-di-methyl-pyridin-2-yl)-amide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and pyrrolidine-2-carboxylic acid (4,6-di-methyl-pyridin-2-yl)-amide **A-8** [X = CH_2, n = 1, R_1 = 2-(5-trifluoromethyl)pyridyl].

1H NMR (DMSO-d_6, rotamers): δ 10.5 (s, 1H), 10.3 (s, 0.4H), 9.87 (s, 0.6H), 8.44 (s, 0.5H), 7.97 (s, 0.5H), 7.89 (s, 1H), 6.98 (s, 1H), 4.74-4.72 (m, 1H), 3.84-3.45 (m, 4H), 3.32 (bs, 1H), 2.54 (s, 3H), 2.43 (s, 3H), 2.29-2.05 (m, 4H), 1.64-1.46 (m, 6H), 1.11-0.925 (m, 3H). ES-MS: calcd. for $C_{20}H_{30}N_4O_4$ (390.48); found: 391.4 [M+H].

Pyrrolidine-2-S-carboxylic acid (4,6-di-methyl-pyridin-2-yl) amide hydrobromic acid salt

2-Chlorocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester and 4,6-di-methyl-pyridin-2-ylamine are reacted to give amide intermediate as described for the synthesis of 2-S-(pyridin-2-yl-carbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester in Example 1. This intermediate on with treatment with HBr-AcOH provides the title compound.

1H NMR (DMSO-d_6): δ 11.3 (s, 1H), 10.2 (bs, 1H), 7.87 (s, 1H), 7.17 (s, 1H), 4.61 (s, 1H), 2.60 (s, 3H), 2.58 (bs, 1H), 2.50 (s, 3H), 2.17-2.06 (m, 3H). ES-MS: calcd. for $C_{12}H_{17}N_3O$*2HBr (219.28); found: 220.5 [M+H] free base.

Example 14: Synthesis of 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid-(4-ethyl-pyridin-2-yl)-amide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and pyrrolidine-2-carboxylic acid (4-ethyl-pyridin-2-yl)-amide **A-8** [X = CH_2, n = 1, R_1 = 2-(4-ethyl)pyridyl].

1H NMR (DMSO-d_6, rotamers): δ 10.6 (bs, 1H), 10.23 (s, 0.4H), 9.87 (s, 0.6H), 8.38-8.36 (m, 1H), 8.12 (bs, 1H), 7.99 (bs, 1H), 7.16-7.14 (m, 1H), 4.75 (bs, 1H), 3.75 (bs, 4H), 3.20 (bs, 1H), 2.82-2.75 (q, J = 7.56Hz, 2H), 2.05 (bs, 4H), 1.65-1.45 (m, 6H), 1.38-1.33 (t, J = 7.56Hz, 3H), 1.04 (bs, 3H). ES-MS: calcd. for $C_{20}H_{30}N_4O_4$ (390.48); found: 391.4 [M+H].

A-8 is prepared from 2-chlorocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester and 4-ethyl-pyridin-2-ylamine as described for the synthesis of pyrrolidine-2-carboxylic acid pyridine-2-yl-amide (hydrobromic acid salt) in Example 1.

2-S-(4-ethyl-pyridin-2-ylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester

1H NMR (DMSO-d_6): δ 10.8-10.7 (d, J = 15.1 Hz, 1H), 8.39-8.36 (M, 1H), 8.16 (S, 1H), 7.57-7.25 (m, 5H), 7.18-7.17 (m, 1H), 5.27-5.25 (m, 2H), 4.74-4.68 (m, 1H), 3.68-3.61 (m, 2H), 2.83-2.77 (q, J = 6.50 Hz, 2H), 2.43-2.29 (m, 1H), 2.13-1.98 (m, 3H), 1.40-1.35 (t, J = 7.55 Hz, 3H). ES-MS: calcd. for $C_{20}H_{23}N_3O_3$ (353.42); found: 354.2 [M+H].

Pyrrolidine-2-S-carboxylic acid (4-ethyl-pyridin-2-yl)-amide hydrobromic acid salt

1H NMR (DMSO-d_6): δ 11.43 (s, 1H), 8.47-8.45 (m, 1H), 8.24 (bs, 1H), 8.08 (s 1H), 7.33-7.30 (m, 1H), 4.64 (s, 1H), 3.49-3.47 (m, 2H), 2.89-2.82 (q, J = 7.51 Hz, 2H), 2.65-2.55 (m, 1H), 2.33-2.07 (m, 3H), 1.40-1.35 (t, J = 7.56 Hz, 3H). ES-MS: calcd. for $C_{12}H_{17}N_3O$*2HBr (219.28); found: 220.3 [M+H] free base.

Example 15: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid (3-hydroxy-pyridin-2-yl)-amide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and pyrrolidine-2-carboxylic acid (3-benzyloxy-pyridin-2-yl)-amide **A-8** [X = CH_2, n = 1, R_1 = 2-(3-benzyloxy)pyridyl].

1H NMR (DMSO-d_6, rotamers): δ 10.94 (bs, 1H), 10.34 (bs, 1H), 9.88 (bs, 1H), 8.10-8.09 (m, 1H), 7.99 (s, 1H), 7.49-7.47 (m, 1H), 7.37-7.33 (m, 1H), 4.85 (bs, 1H), 3.87-3.74 (m, 4H), 3.21 (s, 1H), 2.29 (bs, 1H), 2.19-211 (m, 3H), 1.65-1.44 (m, 6H), 1.03 (bs, 3H). ES-MS: calcd. for $C_{18}H_{26}N_4O_5$ (378.42); found: 379.2 [M+H].

A-8 is prepared from 2-chlorocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester and 3-benzyloxy-pyridin-2-ylamine as described for the synthesis of pyrrolidine-2-carboxylic acid pyridine-2-yl-amide (hydrobromic acid salt) in Example 1.

2-S-(3-benzyloxy-pyridin-2-ylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester

1H NMR (DMSO-d_6): δ 10.1-10.0 (d, J = 18.1 Hz, 1H), 8.21-8.16 (m, 1H), 7.73-7.40 (m, 12H), 5.32-5.26 (m, 4H), 4.66-.4.64 (m, 1H), 3.67-3.54 (m, 2H), 2.38-2.23 (m, 1H), 2.06-1.93 (m, 3H). ES-MS: calcd. for $C_{25}H_{25}N_3O_4$ (431.48); found: 432.3 [M+H].

Pyrrolidine-2-S-carboxylic acid (3-benzyloxy-pyridin-2-yl)-amide hydrobromic acid salt

1H NMR (DMSO-d_6): δ 10.9 (bs, 1H), 8.88 (s, 1H), 8.24-8.21 (m, 1H), 7.91-7.88 (m, 1H), 7.68-7.51 (m, 6H), 5.42 (s, 2H), 4.71 (bs, 1H), 3.51-3.40 (m, 2H), 2.65-2.47 (m, 1H), 2.19-1.93 (m, 3H). ES-MS: calcd. for $C_{17}H_{19}N_3O_2$*2HBr (297.35); found: 298.3 [M+H] free base.

1-{2-R-[(benzyloxy-formyl-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid (3-benzyloxy-pyridin-2-yl)-amide

1H NMR (DMSO-d_6): δ 9.95 (bs, 1H), 8.42 (bs, 1H), 8.16-8.14 (m, 2H), 7.76-7.39 (m, 10H), 5.33 (bs, 2H), 5.06 (bs, 2H), 3.88-3.85 (m, 2H), 3.65-3.63 (m, 2H), 3.15-3.09 (m, 1H), 2.01-1.89 (m, 4H), 1.49-1.39 (m, 6H), 1.03-0.976 (m, 3H). ES-MS: calcd. for $C_{32}H_{38}N_4O_5$ (558.67); found: 559.3 [M+H].

Example 16: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid isoquinolin-1-ylamide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and pyrrolidine-2-carboxylic acid (isoquinolin-1-ylamide **A-8** [X = CH_2, n = 1, R_1 = 1-isoquinolinyl].

1H NMR (DMSO-d_6, rotamers): δ 10.78 (bs, 1H), 10.26 (s, 0.4H), 9.90 (s, 0.6H), 8.51-9.49 (m, 1H), 8.29-8.26 (m, 1H), 8.17-8.14 (m, 1H), 8.03 (s, 1H), 7.98-7.91 (m, 2H), 7.79-7.74 (m, 1H), 4.82 (bs, 1H), 3.20 (bs, 1H), 2.28-2.12 (m, 4H), 1.53-1.40 (m, 6H), 0.944 (bs, 3H). ES-MS: calcd. for $C_{22}H_{28}N_4O_4$ (412.48); found: 413.4 [M+H].

A-8 is prepared from 2-chlorocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester and 1-amino-isoquinoline as described for the synthesis of pyrrolidine-2-carboxylic acid pyridine-2-yl-amide (hydrobromic acid salt) in Example 1.

Pyrrolidine-2-S-carboxylic acid isoquinolin-1-yl) amide hydrobromic acid salt

1H NMR (DMSO-d_6): δ 8.97 (bs, 1H), 8.72-8.68 (d, J = 8.241 Hz, 1H), 8.48-8.46 (d, J = 6.044 Hz, 1H), 8.32-8.2 (t, J = 8.24 and 8.93 Hz, 1H), 8.18-8.15 (d, J = 7.98 Hz, 1H), 8.07-8.0 (m, 1H), 4.92 (bs, 1H), 3.52 (bs, 2H), 2.4-2.31 (m, 1H), 2.23-2.1 (m, 3H). ES-MS: calcd. for $C_{14}H_{15}N_3O$ (241.12); found: 242.3 [M+H].

1-{2-R-[(benzyloxy-formyl-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylicacid isoquinolin-1-ylamide

1H NMR (DMSO-d_6): δ 10.8 (S, 1H), 8.50 (S, 1H), 8.49 (S, 1H), 8.28-8.25 (m, 1H), 8.16-8.14 (m, 1H), 7.97-7.91 (m, 2H), 7.79-7.74 (m, 1H), 7.63-7.59 (m, 5H), 5.08 (bs, 2H), 4,81 (bs, 1H), 3.90 (bs, 2H), 3.78 (bs, 2H), 3.14 (s, 1H), 2.35-2.26 (m, 2H), 2.19-2.10 (m, 2H), 1.51-

1.36 (m, 6H), 0.946-0.901 (t, J = 6.87 Hz, 3H). ES-MS: calcd. for $C_{29}H_{34}N_4O_4$ (502.60); found: 503.4 [M+H].

Example 17: **1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid quinolin-3-ylamide**

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and pyrrolidine-2-carboxylic acid quinolin-3-yl-amide **A-8** [X = CH_2, n = 1, R_1 = 3-quinolinyl].

1H NMR (DMSO-d_6, rotamers): δ 10.82 (bs, 1H), 10.25 (s, 0.3H), 9.98 (s, 0.7H), 9.34 (s, 1H), 8.61(s, 1H), 8.26-8.23 (m, 1H), 8.09-8.06 (m, 1H), 7.99 (s, 1H), 7.92-7.87 (m, 1H), 7.74-7.79 (m, 1H), 4.84 (bs, 1H), 3.83-3.72 (m, 4H), 3.24 (s, 1H), 2.25-2.10 (m, 4H), 1.67-1.48 (m, 6H), 1.06 (bs, 3H). ES-MS: calcd. for $C_{22}H_{28}N_4O_4$ (412.48); found: 413.3 [M+H].

A-8 is prepared from 2-chlorocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester and 3-amino-quinoline as described for the synthesis of pyrrolidine-2-carboxylic acid pyridine-2-yl-amide (hydrobromic acid salt) in Example 1.

2-S-(quinolin-3-ylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester

1H NMR (DMSO-d_6): δ 11.0-10.9 (d, J = 15.9 Hz, 1H), 9.34-9.33 (m, 1H), 8.66-8.65 (m, 1H), 8.27-8.24 (m, 1H), 8.10-8.05 (m, 1H), 7.94-7.88 (m, 1H), 7.77-7.70 (m, 1H), 7.58-7.49 (m, 2H), 7.41-7.39 (m, 1H), 7.29-7.17 (m, 2H), 5.28-5.27 (m, 2H), 4.82-4.74 (m, 1H), 3.76-3.64 (m, 2H), 2.55-2.33 (m, 1H), 2.15-2.01 (m, 3H). ES-MS: calcd. for $C_{22}H_{21}N_3O_3$ (375.42); found: 376.3 [M+H].

Pyrrolidine-2-S-carboxylic acid quinolin-3-yl) amide hydrobromic acid salt

1H NMR (DMSO-d_6): δ 11.4 (s, 1H), 9.40 (s, 1H), 8.93-8.92 (bs, 1H), 8.63 (s, 1H), 8.30-8.28 (s, 1H), 8.15-8.12 (s, 1H), 8.01-7.92 (m, 1H), 7.80-7.75 (m, 1H), 4.68-4.66 (m, 1H), 3.53-3.48 (m, 2H), 2.66-2.59 (m, 1H), 2.26-2.09 (m, 3H). ES-MS: calcd. for $C_{14}H_{15}N_3O$*2HBr (241.29); found: 242.2 [M+H] free base.

1-{2-R-[(benzyloxy-formyl-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylicacid quinolin-3-ylamide

1H NMR (DMSO-d_6): δ 10.82 (bs, 1H), 9.33 (bs, 1H), 8.60 (bs, 1H), 8.42 (bs, 1H), 8.25-8.22 (m, 1H), 8.08-8.05 (m, 1H), 7.91-7.86 (m, 1H), 7.73-7.69 (m, 1H), 7.63 (bs, 5H), 5.07 (bs, 2H), 4.84 (bs, 1H), 3.92-3.82 (m, 2H), 3.76-3.67 (m, 2H), 3.14(bs, 1H), 2.33-2.17 (m, 2H), 2.12-2.06 (m, 2H), 1.67-1.45 (m, 6H), 1.04 (m, 3H). ES-MS: calcd. for $C_{29}H_{34}N_4O_4$ (502.60); found: 503.4 [M+H].

Example 18: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-azetidine-2-S-carboxylic acid-4-methyl-pyridin-2-ylamide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and azetidine-2-carboxylic acid (4-methyl-pyridin-2-yl)-amide **A-8** [X = CH_2, n = 1, R_1 = 2-(4-Me-pyridyl)].

1H NMR (DMSO-d_6): δ 8.36-8.35 (d, J = 4.12 Hz, 1H), 8.14-8.03 (d, J = 23 Hz, 1H), 7.16-7.15 (d, J = 3.85 Hz, 1H), 5.06 (bs, 1H), 4.39-4.30 (m, 2H), 3.75-3.72 (d, J = 7.42 Hz, 1H), 3.53 (bs, 2H), 2.51 (bs, 3H), 2.41 (bs, 2H), 1.44 (bs, 6H), 1.03 (bs, 3H). ES-MS: calcd. for $C_{18}H_{26}N_4O_4$ (362.43); found: 363.3 [M+H].

A-8 is prepared from azetidine-1,2-dicarboxylic acid 1-tert butyl ester and 4-methyl-pyridin-2-ylamine as described below.

Azetidine 2-S-(4-methyl-pyridin-2-ylcarbamoyl)amide

The N-Boc protected amino acid is coupled to 2-amino pyridine using HATU/DIEA/DMF to yield the protected amide. The protected amide is treated with 4.0M HCl-dioxane to give HCl salt of **A-8**.

1H NMR (DMSO-d_6): δ 8.41 (bs, 1H), 8.17-8.14 (d, J = 8.24 Hz, 1H), 7.99-7.96 (d, J = 8.24 Hz, 1H), 5.33 (bs, 1H), 4.2-4.12 (m, 1H), 3.99-3.95 (m, 1H), 2.93-2.84 (m, 2H), 2.47 (s, 3H). ES-MS: calcd. for $C_{10}H_{13}N_3O$ (191.11); found: 192.3 [M+H].

Example 19: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-azetidine-2-S-carboxylic acid-5-methyl-pyridin-2-ylamide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and azetidine-2-carboxylic acid (5-methyl-pyridin-2-yl)-amide **A-8** [X = CH_2, n = 1, R_1 = 2-(5-Me-pyridyl)].

1H NMR (DMSO-d_6): δ 8.07 (bs, 1H), 7.94-7.91 (d, J = 8.24 Hz, 1H), 7.56-7.53 (d, J = 8.52 Hz, 1H), 4.79 (bs, 1H), 4.13-4.04 (m, 2H), 3.48 (bs, 1H), 3.37 (bs, 2H), 2.28 (bs, 1H), 2.17 (bs, 4H), 1.18 (bs, 6H), 0.77 (bs, 3H). ES-MS: calcd. for $C_{18}H_{26}N_4O_4$ (362.43); found: 363.3 [M+H].

A-8 is prepared from azetidine-1,2-dicarboxylic acid 1-tert butyl ester and 5-methyl-pyridin-2-ylamine as described below.

Azetidine 2-S-(5-methyl-pyridin-2-ylcarbamoyl)amide

The N-Boc protected amino acid is coupled to 2-amino pyridine using HATU/DIEA/DMF to yield the protected amide. The protected amide is treated with 4.0M HCl-dioxane to give HCl salt of **A-8**.

1H NMR (DMSO-d_6): δ 8.41 (bs, 1H), 8.17-8.14 (d, J = 8.24 Hz, 1H), 7.99-7.96 (d, J = 8.24 Hz, 1H), 5.33 (bs, 1H), 4.2-4.12 (m, 1H), 3.99-3.95 (m, 1H), 2.93- 2.84 (m, 2H), 2.47 (s, 3H). ES-MS: calcd. for $C_{10}H_{13}N_3O$ (191.11); found: 192.3 [M+H].

Example 20: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-azetidine-2-S-carboxylic acid-5-fluoro-pyridin-2-ylamide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and azetidine-2-carboxylic acid (5-fluoro-pyridin-2-yl)-amide **A-8** [X = CH_2, n = 1, R_1 = 2-(5-F-pyridyl)].

1H NMR (DMSO-d_6): δ 8.52 (bs, 1H), 8.36-8.33 (t, J = 3.3 & 5.2 Hz, 1H), 8.01-7.93 (dd, J = 4.95 & 8.52 Hz, 1H), 5.08 (bs, 1H), 4.33 (bs, 2H), 3.74 (bs, 1H), 3.53 (bs, 2H), 2.41 (bs, 2H), 1.42 (bs, 6H), 1.03 (bs, 3H). ES-MS: calcd. for $C_{17}H_{23}FN_4O_4$ (366.69); found: 367.2 [M+H].

A-8 is prepared from azetidine-1,2-dicarboxylic acid 1-tert butyl ester and 5-methyl-pyridin-2-ylamine as described below.

Azetidine 2-S-(5-fluoro-pyridin-2-ylcarbamoyl)amide

The N-Boc protected amino acid is coupled to 2-amino pyridine using HATU/DIEA/DMF to yield the protected amide. The protected amide is treated with 4.0M HCl-dioxane to give HCl salt of the free amine.

1H NMR (DMSO-d_6): δ 8.58-8.57 (d, J = 3.02 Hz, 1H), 8.32 (bs, 1H), 8.06-7.9 (m, 1H), 5.32 (bs, 1H), 4.17-3.98 (m, 2H), 2.93-2.74 (m, 2H). ES-MS: calcd. for $C_9H_{10}FN_3O$ (195.08); found: 196.2 [M+H].

Example 21: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid-(5-trifluoromethyl-1-oxy-pyridin-2-yl)-amide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and pyrrolidine-2-carboxylic acid (5-trifluoromethyl-1-oxy-pyridin-2-yl)-amide **A-8** [X = CH_2, n = 1, R_1 = 2-(5-trifluoromethyl-1-oxy)-pyridyl].

1H NMR (DMSO-d_6): δ 9.15 (bs, 1H), 8.64-8.62 (d, J = 8.79 Hz, 1H), 7.98-7.96 (d, J = 9.34 Hz, 1H), 5.04-5.0 (m, 1H), 3.87-3.73 (m, 2H), 3.65 (bs, 2H), 3.49-3.48 (m, 1H), 2.34 (bs, 2H), 2.13-2.12 (d, J = 2.47 Hz, 2H), 1.67-1.45 (m, 6H), 1.03 (bs, 3H). ES-MS: calcd. for $C_{19}H_{25}F_3N_4O_5$ (446.43); found: 447.3 [M+H].

A-8 is prepared from 2-chlorocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester and 3-amino-quinoline as described for the synthesis of pyrrolidine-2-carboxylic acid pyridine-2-yl-amide (hydrobromic acid salt) in Example 1.

2-S-(5-trifluoromethyl-1-oxy-pyridin-2-ylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester

2-chlorocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester and 5-trifluoromethyl-pyridin-2-ylamine is reacted to give amide intermediate as described for the synthesis of 2-S-(pyridin-2-yl-carbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester in Example 1. This intermediate on oxidation with MCPBA provides the title compound.

1H NMR (DMSO-d_6): δ 9.15 (bs, 1H), 8.67-8.58 (dd, J = 8.79 & 9.07 Hz, 1H), 7.98 (bs, 1H), 7.57 (bs, 2H), 7.37-7.34 (d, J = 8.065 Hz, 2H), 5.29-5.26 (d, J = 9.9 Hz, 2H), 5.1-5.0 (m, 1H), 3.68-3.53 (m, 2H), 2.63-2.57 (m, 2H), 2.2-2.05 (m, 2H). ES-MS: calcd. for $C_{19}H_{18}F_3N_3O_4$ (409.12); found: 410.2 [M+H].

Pyrrolidine-2-S-carboxylic acid (5-trifluoromethyl-1-oxy-pyridin-2-yl) amide hydrobromic acid salt

The treatment of the above N-protected intermediate with HBr-AcOH provides the title compound.

1H NMR (DMSO-d_6): δ 9.21 (bs, 1H), 8.66-8.63 (d, J = 8.79 Hz, 1H), 8.06-8.02 (dd, J = 1.37 Hz, 1H), 5.05-5.0 (t, J = 6.58 & 7.14 Hz, 1H), 3.58-3.47 (m, 2H), 2.63-2.57 (m, 2H), 2.23-2.1 (m, 2H). ES-MS: calcd. for $C_{11}H_{12}F_3N_3O_2$ (275.09); found: 276.1 [M+H].

Example 22: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid-(4-ethyl-1-oxy-pyridin-2-yl)-amide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and pyrrolidine-2-carboxylic acid (4-ethyl-1-oxy-pyridin-2-yl)-amide **A-8** [X = CH_2, n = 1, R_1 = 2-(4-ethyl-1-oxy)-pyridyl].

1H NMR (DMSO-d_6): δ 8.47-8.45 (d, J = 6.593 Hz, 1H), 8.35-8.34 (d, J = 2.2 Hz, 1H), 7.22-7.20 (m, 1H), 4.92-4.89 (t, J = 4.7 & 3.02 Hz, 1H), 3.85-3.80 (t, J = 6.49 & 8.24 Hz, 2H), 3.53 (bs, 2H), 3.22 (bs, 1H), 2.85-2.71 (m, 2H), 2.35-2.13 (m, 4H), 1.68-1.36 (m, 6H), 1.02 (bs, 3H). ES-MS: calcd. for $C_{20}H_{30}N_4O_5$ (406.48); found: 407.3 [M+H].

2-S-(4-ethyl-1-oxy-pyridin-2-ylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester

2-chlorocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester and 4-ethyl-pyridin-2-ylamine is reacted to give amide intermediate as described for the synthesis of 2-S-(pyridin-2-yl-

carbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester in Example 1. This intermediate on oxidation with MCPBA provides the title compound.

1H NMR ($CDCl_3$): δ 8.8-8.12 (m, 1H), 7.4-7.2 (m, 1H), 6.85-6.83 (d, J = 6.59 Hz, 1H), 5.3-5.1 (m, 2H), 4.57 (bs, 1H), 3.71-3.54 (m, 2H), 2.7-2.63 (dd, J = 7.42 Hz, 2H), 2.24-1.73 (m, 4H), 1.3-1.2 (m, 3H). ES-MS: calcd. for $C_{20}H_{23}N_3O_4$ (369.17); found: 370.2 [M+H].

Pyrrolidine-2-S-carboxylic acid (4-ethyl-1-oxy-pyridin-2-yl) amide hydrobromic acid salt

The treatment of the above N-protected intermediate with HBr-AcOH provides the title compound.

1H NMR (DMSO-d_6): δ 8.56 -8.53 (d, J = 6.6 Hz, 1H), 8.36-8.35 (d, J = 2.3 Hz, 1H), 7.33-7.3 (dd, J = 2.37 & 2.47 Hz, 1H), 5.0-4.96 (t, J = 8.24 & 5.49 Hz, 1H), 3.39-3.42 (m, 2H), 2.88-2.81 (dd, J = 7.7 Hz, 2H), 2.64-2.55 (m, 1H), 2.2-2.05 (m, 3H), 1.29-1.25 (t, J = 7.14 & 6.87 Hz, 3H). ES-MS: calcd. for $C_{12}H_{17}N_3O_2$ (235.13); found: 236.2 [M+H].

Example 23: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid-(4-phenyl-pyridin-2-yl)-amide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and pyrrolidine-2-carboxylic acid (4-phenyl-pyridin-2-yl)-amide **A-8** [X = CH_2, n = 1, R_1 = 2-(4-phenyl)pyridyl].

1H NMR (DMSO-d_6): δ 8.6-8.45 (m, 1H), 8.3-7.6 (m, 5H), 4.8 (bs, 1H), 3.85-3.71 (m, 2H), 3.31 (bs, 1H), 2.32-1.98 (m, 4H), 1.76-1.43 (m, 6H), 1.04 (bs, 3H). ES-MS: calcd. for $C_{24}H_{30}N_4O_4$ (438.53); found: 439.4 [M+H].

A-8 is prepared from 2-chlorocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester and 4-phenyl-pyridin-2-ylamine as described for the synthesis of pyrrolidine-2-carboxylic acid pyridine-2-yl-amide (hydrobromic acid salt) in Example 1.

2-S-(4-phenyl-pyridin-2-yl-carbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester

1H NMR ($CDCl_3$): δ 8.8-8.12 (m, 1H), 7.4-7.2 (m, 1H), 6.85-6.83 (d, J = 6.59 Hz, 1H), 5.3-5.1 (m, 2H), 4.57 (bs, 1H), 3.71-3.54 (m, 2H), 2.7-2.63 (dd, J = 7.42 Hz, 2H), 2.24-1.73 (m, 4H), 1.3-1.2 (m, 3H). ES-MS: calcd. for $C_{20}H_{23}N_3O_4$ (369.17); found: 370.2 [M+H].

Pyrrolidine-2-S-carboxylic acid (4-phenyl-pyridin-2-yl) amide hydrobromic acid salt

1H NMR (DMSO-d_6): δ 8.64-8.63 (d, J = 5.22 Hz, 1H), 8.53 (s, 1H), 7.94-7.91 (dd, J = 1.65 & 1.1 Hz, 1H), 7.78-7.67 (m, 5H), 4.68 (bs, 1H), 3.5-3.46 (m, 2H), 2.65-2.58 (m, 1H), 2.24-2.09 (m, 3H). ES-MS: calcd. for $C_{16}H_{17}N_3O$ (267.14); found: 268.3 [M+H].

Example 24: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid-(4-phenyl-1-oxy-pyridin-2-yl)-amide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and pyrrolidine-2-carboxylic acid (4-phenyl-1-oxy-pyridin-2-yl)-amide **A-8** [X = CH_2, n = 1, R_1 = 2-(4-phenyl-1-oxy)-pyridyl].

1H NMR (DMSO-d_6): δ 8.78-8.79 (d, J = 2.47 Hz, 1H), 8.64-8.62 (d, J = 6.87 Hz, 1H), 7.9-7.6 (m, 5H), 4.99-4.96 (t, J = 4.67 & 3.3 Hz, 1H), 3.88-3.76 (m, 1H), 3.53 (bs, 2H), 3.24 (bs, 1H), 2.35-2.15 (m, 4H), 1.68-1.45 (m, 6H), 1.05-1.03 (d, J = 6.59 Hz, 3H). ES-MS: calcd. for $C_{24}H_{30}N_4O_5$ (454.53); found: 455.3 [M+H].

2-S-(4-phenyl-1-oxy-pyridin-2-ylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester

2-chlorocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester and 4-phenyl-pyridin-2-ylamine is reacted to give amide intermediate as described for the synthesis of 2-S-(pyridin-2-yl-carbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester in Example 1. This intermediate on oxidation with MCPBA provides the title compound.

1H NMR ($CDCl_3$): δ 8.3-8.2 (m, 1H), 7.96-7.13 (m, 12H), 5.73-5.12 (m, 2H), 4.7-4.4 (m, 1H), 3.8-3.5 (m, 2H), 2.5-2.01 (m, 4H). ES-MS: calcd. for $C_{24}H_{23}N_3O_4$ (417.17); found: 418.1 [M+H].

Pyrrolidine-2-S-carboxylic acid (4-phenyl-1-oxy-pyridin-2-yl) amide hydrobromic acid salt

The treatment of the above N-protected intermediate with HBr-AcOH provides the title compound.

1H NMR (DMSO-d_6): δ 8.79-8.78 (d, J = 2.47 Hz, 1H), 8.7-8.67 (d, J = 6.87 Hz, 1H), 7.94-7.89 (m, 1H), 7.79-7.64 (m, 5H), 5.03-4.97 (dd, J = 6.59 Hz, 1H), 3.53-3.44 (m, 2H), 2.64-2.55 (m, 1H), 2.28-2.09 (m, 3H). ES-MS: calcd. for $C_{16}H_{17}N_3O_2$ (283.13); found: 284.2 [M+H].

Example 25: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid-(4-trifluoromethyl-pyridin-2-yl)-amide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and pyrrolidine-2-carboxylic acid (4-trifluoromethyl-pyridin-2-yl)-amide **A-8** [X = CH_2, n = 1, R_1 = 2-(4-trifluoromethyl)pyridyl].

1H NMR (DMSO-d_6): δ 8.8-8.78 (d, J = 5.22 Hz, 1H), 7.97 (bs, 1H), 7.66-7.65 (d, J = 4.67 Hz, 1H), 4.8-4.77 (t, J = 4.12 & 4.4 Hz, 1H), 3.86-3.7 (m, 2H), 3.52 (bs, 2H), 3.2 (bs, 1H), 2.33-2.1 (m, 4H), 1.64-1.45 (m, 6H), 1.06-1.04 (d, J = 6.32 Hz, 3H). ES-MS: calcd. for $C_{19}H_{25}F_3N_4O_4$ (430.43); found: 431.3 [M+H].

A-8 is prepared from 2-chlorocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester and 4-trifluoromethyl-pyridin-2-ylamine as described for the synthesis of pyrrolidine-2-carboxylic acid pyridine-2-yl-amide (hydrobromic acid salt) in Example 1.

Pyrrolidine-2-S-carboxylic acid (4-trifluoromethyl-pyridin-2-yl) amide hydrobromic acid salt

1H NMR (DMSO-d_6): δ 8.93-8.85 (m, 2H), 7.77-7.75 (m, 1H), 4.67-4.65 (d, J = 6.593 Hz, 1H), 3.49-3.44 (m, 2H), 2.65-2.56 (m, 1H), 2.24-2.09 (m, 3H). ES-MS: calcd. for $C_{11}H_{12}F_3N_3O$ (259.1); found: 260.2 [M+H].

Example 26: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid-(4-trifluoromethyl-1-oxy-pyridin-2-yl)-amide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and pyrrolidine-2-carboxylic acid (4-trifluoromethyl-1-oxy-pyridin-2-yl)-amide **A-8** [X = CH_2, n = 1, R_1 = 2-(4-trifluoromethyl-1-oxy)-pyridyl].

1H NMR (DMSO-d_6): δ 8.79-8.76 (m, 1H), 7.98 (bs, 1H), 7.73-7.65 (m, 1H), 5.04-5.0 (m, 1H), 3.84-3.72 (m, 2H), 3.52 (bs, 2H), 3.3 (bs, 1H), 2.32-2.13 (m, 2H), 1.77-1.44 (m, 6H), 1.04-1.02 (d, J = 6.04 Hz, 3H). ES-MS: calcd. for $C_{19}H_{25}F_3N_4O_5$ (446.43); found: 447.3 [M+H].

Pyrrolidine-2-S-carboxylic acid (4-trifluoromethyl-1-oxy-pyridin-2-yl) amide hydrobromic acid salt

2-chlorocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester and 4-trifluoromethyl-pyridin-2-ylamine is reacted to give amide intermediate as described for the synthesis of 2-S-(pyridin-2-yl-carbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester in Example 1. This intermediate on oxidation with MCPBA followed by the removal of N-benzyloxycarbonyl group with HBr-AcOH provides the title compound.

1H NMR (DMSO-d_6): δ 8.94-8.74 (m, 2H), 7.83-7.8 (m, 1H), 5.02-4.97 (t, J = 6.22 & 8.52 Hz, 1H), 3.5-3.42 (m, 2H), 2.61-2.52 (m, 1H), 2.27-2.06 (m, 3H). ES-MS: calcd. for $C_{11}H_{12}F_3N_3O_2$ (275.09); found: 276.1 [M+H].

Example 27: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid-(8-hydroxy-quinolin-2-yl)-amide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and pyrrolidine-2-carboxylic acid (8-benzyloxy-quinolin-2-yl)-amide **A-8** [X = CH_2, n = 1, R_1= 2-(8-benzyloxy)quinolinyl].

1H NMR (DMSO-d_6): δ 8.5-8.35 (m, 2H), 7.98 (bs, 1H), 7.55-7.46 (m, 1H), 7.28-7.26 (m, 1H), 4.83-4.82 (d, J = 4.4 Hz, 1H), 3.86-3.68 (m, 4H), 3.27 (bs, 1H), 2.38 - 2.06 (m, 4H), 1.68-1.42 (bs, 6H), 1.06-1.04 (d, J = 6.32 Hz, 3H). ES-MS: calcd. for $C_{22}H_{28}N_4O_5$ (428.48); found: 429.3 [M+H].

2-S-(8-benzyloxy-quinolin-2-ylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester

2-chlorocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester and 8-hydroxy-quinolin-2-ylamine is reacted to give bis-proline intermediate as described for the synthesis of 2-S-(pyridin-2-yl-carbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester in Example 1. This intermediate on treatment with lithium hydroxide in THF:water (4:1) provides the corresponding 8-hydroxy derivative which on O-benzylation with benzyl bromide in DMF-K_2CO_3 yields the desired compound.

1H NMR (DMSO-d_6): δ 11.2-11.1 (m, 1H), 8.49 (s, 1H), 7.73-7.23 (m, 14H), 5.50 (s, 2H), 5.31-5.22 (m, 2H), 4.83 (bs, 1H), 3.73-3.61 (m, 2H), 2.52-2.36 (m, 1H), 2.18-2.03 (m, 3H). ES-MS: calcd. for $C_{29}H_{27}N_3O_4$ (481.54); found: 482.2 [M+H].

Pyrrolidine-2-S-carboxylic acid (8-benzyloxy-quinolin-2-yl)-amide hydrobromic acid salt

1H NMR (DMSO-d_6): δ 11.6 (bs, 1H), 8.91 (bs, 1H), 8.60-8.57 (m, 1H), 7.73-7.31 (m, 9H), 5.52 (s, 2H), 4.68 (bs, 1H), 3.55-3.46 (m, 2H), 2. 68-2.63 (m, 1H), 2.18-2.09 (m, 3H). ES-MS: calcd. for $C_{21}H_{21}N_3O_2$*2HBr (347.41); found: 348.3 [M+H].

<u>Example 28:</u> 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid-(3-methoxy-6-methyl-pyridin-2-yl)-amide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and pyrrolidine-2-carboxylic acid (3-methoxy-6-methyl-pyridin-2-yl)-amide **A-8** [X = CH_2, n = 1, R_1 = 2-(3-methoxy-6-methyl)pyridyl].

1H NMR (DMSO-d_6): δ 7.54-7.51 (d, J = 8.24 Hz, 1H), 7.24-7.21 (d, J = 8.24 Hz, 1H), 4.79 (bs, 1H), 3.94 (bs, 3H), 3.86-3.52 (m, 2H), 3.51 (bs, 2H), 3.27 (bs, 1H), 2.69 (bs, 3H), 2.26-2.01 (m, 4H), 1.64-1.42 (bs, 6H), 1.04-1.0 (t, J = 5.77 & 6.04 Hz, 3H). ES-MS: calcd. for $C_{20}H_{30}N_4O_5$ (406.48); found: 407.3 [M+H].

A-8 is prepared from 2-chlorocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester and 3-methoxy-6-methyl-pyridin-2-ylamine as described for the synthesis of pyrrolidine-2-carboxylic acid pyridine-2-yl-amide (hydrobromic acid salt) in Example 1.

Pyrrolidine-2-S-carboxylic acid (3-methoxy-6-methyl-pyridin-2-yl) amide hydrobromic acid salt

1H NMR (DMSO-d_6): δ 7.79-7.76 (d, J = 8.24 Hz, 1H), 7.45-7.42 (d, J = 8.24 Hz, 1H), 4.68 (bs, 1H), 4.01 (bs, 3H), 3.47-3.43 (t, J = 5.49 Hz, 2H), 2.7 (bs, 3H), 2.2-2.08 (m, 4H). ES-MS: calcd. for $C_{12}H_{17}N_3O_2$ (235.13); found: 236.2 [M+H].

Example 29: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid (4-methoxy-pyridin-2-yl)-amide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and pyrrolidine-2-carboxylic acid (4-methoxy-pyridin-2-yl)-amide **A-8** [X = CH_2, n = 1, R_1 = 2-(4-methoxy)pyridyl].

1H NMR (DMSO-d_6, rotamers): δ 10.7 (bs, 1H), 10.2 (s, 0.3H), 9.87 (s, 0.7H), 8.44 (s, 0.6H), 8.32-8.30 (d, J = 5.77 Hz, 1H), 7.98 (s, 0.4H), 7.86 (s, 1H), 6.91-6.88 (m, 1H), 4.75-4.73 (m, 1H), 3.99 (s, 3H), 3.87-3.67 (m, 4H), 3.30-3.10 (bs, 1H), 2.30-2.06 (m, 4H), 1.65-1.36 (m, 6H), 1.11-0.926 (m, 3H). ES-MS: calcd. for $C_{19}H_{28}N_4O_5$ (392.45); found: 393.3 [M+H].

A-8 is prepared from 2-chlorocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester and 4-methoxy-pyridin-2-ylamine as described for the synthesis of pyrrolidine-2-carboxylic acid pyridine-2-yl-amide (hydrobromic acid salt) in Example 1.

2-S-(4-methoxy-pyridin-2-ylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester

1H NMR (DMSO-d_6): δ 10.8-10.7 (d, J = 15.9 Hz, 1H), 8.32-8.31 (d, J = 5.7 Hz, 1H), 7.91 (s, 1H), 7.58-7.27 (m, 5H), 6.92-6.89 (m, 1H), 5.32-5.16 (m, 2H), 4.75-4.68 (m, 1H), 4.00 (s, 3H), 3.76-3.53 (m, 2H), 2.44-1.98 (m, 4H). ES-MS: calcd. for $C_{19}H_{21}N_3O_4$ (355.39); found: 356.3 [M+H].

Pyrrolidine-2-S-carboxylic acid (4-methoxy-pyridin-2-yl)-amide hydrobromic acid salt

1H NMR (DMSO-d_6): □11.9 (bs, 1H), 8.98 (bs, 1H), 8.48-8.47 (d, J = 6.32 Hz, 1H), 7.67 (bs, 1H), 7.22-7.19 (m, 1H), 4.70-4.69 (m, 1H), 4.12 (s, 3H), 3.51-3.47 (m, 2H), 2.66-2.57 (m, 1H), 2.28-2.10 (m, 3H). ES-MS: calcd. for $C_{11}H_{15}N_3O_2$*2HBr (221.26); found: 222.2 [M+H] free base.

1-{2-R-[(benzyloxy-formyl-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid (4-methoxy-pyridin-2-yl)-amide

1H NMR (DMSO-d_6, rotamers): δ 10.7 (s, 1H), 8.41 (s, 0.5H), 8.33-8.31 (m, 1H), 8.06 (s, 0.5H), 7.85 (s, 1H), 7.62-7.59 (m, 5H), 6.91-6.88 (m, 1H), 5.06 (s, 2H), 4.77 (s, 1H), 3.99 (s, 3H), 3.85-3.67 (m, 4H), 3.10 (bs, 1H), 2.28-2.06 (m, 4H), 1.65-1.44 (m, 6H), 1.05-1.01 (m, 3H). ES-MS: calcd. for $C_{26}H_{34}N_4O_5$ (482.57); found: 483.3 [M+H].

Example 30: **1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid (3-methoxy-pyridin-2-yl)-amide**

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and pyrrolidine-2-carboxylic acid (3-methoxy-pyridin-2-yl)-amide **A-8** [X = CH_2, n = 1, R_1 = 2-(3-methoxy)pyridyl].

1H NMR (DMSO-d_6): δ 9.83 (s, 1H), 8.45 (s, 1H), 8.13-8.11 (m, 1H), 7.98 (s, 1H), 7.65-7.62 (m, 1H), 7.40-7.36 (m, 1H), 4.83 (bs, 1H), 4.00 (s, 3H), 3.70-3.83 (m, 4H), 3.20 (bs, 1H), 2.35-2.205 (m, 4H), 1.75-1.43 (m, 6H), 1.15-1.00 (m, 3H). ES-MS: calcd. for $C_{19}H_{28}N_4O_5$ (392.45); found: 393.3 [M+H].

A-8 is prepared from 2-chlorocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester and 3-methoxy-pyridin-2-ylamine as described for the synthesis of pyrrolidine-2-carboxylic acid pyridine-2-yl-amide (hydrobromic acid salt) in Example 1.

2-S-(3-methoxy-pyridin-2-ylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester

1H NMR (DMSO-d_6): δ 9.96-9.90 (d, J = 17.8 Hz, 1H), 8.17-8.13 (m, 1H), 7.66-7.39 (m, 7H), 5.28-5.19 (m, 2H), 4.72 (bs, 1H), 3.94 (s, 3H), 3.69-3.53 (m, 2H), 2.49-2.31 (m, 1H), 2.18-2.04 (m, 3H)s. ES-MS: calcd. for $C_{19}H_{21}N_3O_4$ (355.39); found: 356.3 [M+H].

Pyrrolidine-2-S-carboxylic acid (3-methoxy-pyridin-2-yl)-amide hydrobromic acid salt

1H NMR (DMSO-d_6): δ 10.8 (bs, 1H), 8.89 (bs, 1H), 8.23-8.21 (m, 1H), 7.87-7.85 (m, 1H), 7.60-7.56 (m, 1H), 4.73 (bs, 1H), 4.07 (s, 3H), 3.54-3.45 (m, 2H), 2.64-2.57 (m, 1H), 2.24-2.14 (m, 3H). ES-MS: calcd. for $C_{11}H_{15}N_3O_2$*2HBr (221.26); found: 222.2 [M+H] free base.

1-{2-R-[(benzyloxy-formyl-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid (3-methoxy-pyridin-2-yl)-amide

1H NMR (DMSO-d_6): δ 9.82 (s, 1H), 8.42 (s, 1H), 8.13-8.11 (m, 1H), 7.65-7.59 (m, 6H), 7.40-7.36 (m, 1H), 5.06 (s, 2H), 4.81 (bs, 1H), 4.00 (s, 3H), 3.88-3.70 (m, 4H), 3.10 (bs, 1H), 2.13-2.01 (m, 4H), 1.65-1.41 (m, 6H), 1.03-0.968 (m, 3H). ES-MS: calcd. for $C_{26}H_{34}N_4O_5$ (482.57); found: 483.3 [M+H].

Example 31: **1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid (6-hydroxy-pyridin-2-yl)-amide**

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and pyrrolidine-2-carboxylic acid (6-benzyloxy-pyridin-2-yl)-amide **A-8** [X = CH_2, n = 1, R_1 = 2-(3-benzyloxy)pyridyl].

1H NMR (DMSO-d_6, rotamers): δ 10.4 (bs, 1H), 10.24 (s, 1H), 9.87 (s, 1H), 8.44 (s, 1H), 7.97 (s, 1H), 7.74-7.69 (m, 1H), 6.43 (bs, 1H), 4.70 (bs, 1H), 3.85-3.70 (m, 4H), 3.21 (bs, 1H),

2.27-2.06 (m, 4H), 1.65-1.43 (m, 6H), 1.03 (bs, 3H). ES-MS: calcd. for $C_{18}H_{26}N_4O_5$ (378.42); found: 379.2 [M+H].

A-8 is prepared from 2-chlorocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester and 6-hydroxy-pyridin-2-ylamine to give bis-proline derivative which on basic hydrolysis followed by O-benzylation provides the desired amine as described for the synthesis of pyrrolidine-2-carboxylic acid pyridine-2-yl-amide (hydrobromic acid salt) in Example 1.

2-S-(6-hydroxy-pyridin-2-ylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester

1H NMR (DMSO-d_6): δ 10.9 (bs, 1H), 10.5 (bs, 1H), 7.77-7.70 (m, 1H), 7.56-7.30 (m, 6H), 6.48-6.46 (m, 1H), 5.27-5.26 (m, 2H), 4.67-4.62 (m, 1H), 3.72-3.57 (m, 2H), 2.47-1.98 (m, 4H). ES-MS: calcd. for $C_{18}H_{19}N_3O_4$ (341.36); found: 342.3 [M+H].

2-S-(6-benzyloxy-pyridin-2-ylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester

The hydroxy compound (0.920 g, 2.70 mmol, 1 equiv.) is dissolved in DMF (9 ml) and cooled to 0°C. K_2CO_3 (1.12 g, 8.09 mmol, 3 equiv.) is added followed by benzyl bromide (385 µl, 3.23 mmol, 1.2 equiv.). The resulting mixture is stirred at 0°C for 1 h, then at rt for 3 h. The reaction mixture is diluted with EtOAc, washed with brine, and saturated $NaHCO_3$. The organic layer is dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by FC (hexane:EtOAc = 2:1) gives the title compound as a colorless oil.

1H NMR (DMSO-d_6): δ 10.6-10.5 (m, 1H), 7.92-7.86 (m, 1H), 7.69-7.52 (m, 9H), 7.41-7.26 (m, 2H), 6.81-6.75 (m, 1H), 5.54-5.51 (m, 2H), 5.28-5.24 (m, 2H), 4.79-4.68 (m, 1H), 3.69-3.59 (m, 2H), 2.46-2.07 (m, 4H). ES-MS: calcd. for $C_{25}H_{25}N_3O_4$ (431.48); found: 432.3 [M+H].

Pyrrolidine-2-S-carboxylic acid (6-benzyloxy-pyridin-2-yl)-amide hydrobromic acid salt

1H NMR (DMSO-d_6, rotamers): δ 11.1 (s, 0.6H), 11.0 (s, 0.4H), , 8.88 (bs, 1H), 7.99-7.94 (m, 0.4H), 7.86-7.80 (m, 0.6H), 7.67-7.47 (m, 6H), 6.85-6.83 (m, 0.6H), 6.63-6.60 (m, 0.4H), 5.54-5.53 (s, 2H), 4.67-4.62 (m, 1H), 3.51-3.46 (m, 2H), 2.65-2.53 (m, 1H), 2.21-2.03 (m, 3H). ES-MS: calcd. for $C_{17}H_{19}N_3O_2$*2HBr (297.35); found: 298.3 [M+H] free base.

1-{2-R-[(benzyloxy-formyl-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid (6-benzyloxy-pyridin-2-yl)-amide

1H NMR (DMSO-d_6): δ 10.5 (s, 1H), 8.05 (s, 1H), 7.88-7.80 (m, 2H), 7.64-7.52 (m, 10H), 6.76-6.74 (m, 1H), 5.53 (s, 2H), 5.06 (s, 2H), 4.79 (bs, H), 3.84-3.74 (m, 4H), 3.13 (bs, 1H), 2.22-1.92 (m, 4H), 1.65-1.43 (m, 6H), 1.04-0.976 (m, 3H). ES-MS: calcd. for $C_{32}H_{38}N_4O_5$ (558.67); found: 559.3 [M+H].

Example 32: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-s-carboxylic acid (3-hydroxy-1-oxy-pyridin-2-yl)-amide

The title compound is prepared according to General Procedure A described below from PFP ester of 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and pyrrolidine-2-carboxylic acid (3-benzyloxy-1-oxy-pyridin-2-yl)-amide **A-8** [X = CH_2, n = 1, R_1 = 2-(3-benzyloxy-1-oxy)-pyridyl].

1H NMR (DMSO-d_6): δ 10.2-10.2 (m, 1H), 9.62 (s, 1H), 8.17 (s, 1H), 7.86-7.82 (m, 1H), 7.73 (s, 1H), 7.09-7.03 (m, 1H), 6.85-6.82 (m, 1H), 4.65-4.61 (m, 1H), 3.56-3.45 (m, 4H), 2.96 (bs, 1H), 2.20-1.85 (m, 4H), 1.39-1.17 (m, 6H), 0.753 (bs, 3H). ES-MS: calcd. for $C_{18}H_{26}N_4O_6$ (394.42); found: 395.2 [M+H].

2-S-(3-benzyloxy-1-oxy-pyridin-2-ylcarbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester

2-chlorocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester and 3-benzyloxy-pyridin-2-ylamine is reacted to give amide intermediate as described for the synthesis of 2-S-(pyridin-2-yl-carbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester in Example 1. This intermediate on oxidation with MCPBA provides the title compound.

1H NMR (DMSO-d_6): δ 10.2-10.1 (m, 1H), 8.21-8.16 (m, 1H), 7.65-7.35 (m, 12H), 5.37-5.21 (m, 4H), 4.78-4.70 (m, 1H), 3.63-3.60 (m, 2H), 2.30-1.84 (m, 4H). ES-MS: calcd. for $C_{25}H_{25}N_3O_5$ (447.46); found: 448.2 [M+H].

Pyrrolidine-2-S-carboxylic acid (3-benzyloxy-1-oxy-pyridin-2-yl)-amide hydrobromic acid salt

The removal of N-benzyloxycarbonyl group with HBr-AcOH from above intermediate furnished the desired compound.

1H NMR (DMSO-d_6): δ 10.8 (s, 1H), 8.90-8.88 (m, 1H), 8.26-8.23 (m, 1H), 7.65-7.45 (m, 7H), 5.39 (s, H), 4.72-4.67 (m, 1H), 3.46-3.34 (m, 2H), 2. 54-1.75 (m, 4H). ES-MS: calcd. for $C_{17}H_{19}N_3O_3$*2HBr (313.35); found: 314.3 [M+H] free base.

1-{2-R-[(benzyloxy-formyl-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid (3-benzyloxy-1-oxy-pyridin-2-yl)-amide

To a solution of pentafluorophenyl ester of **A-7** (0.920 g, 2.13 mmol, 1 equiv.) in dry DMF (11 ml) at 0°C under nitrogen is added Hunig's base (1.9 ml, 10.7 mmol, 5.0 equiv.) followed by amine (1.52 g, 3.20 mmol, 1.5 equiv.). The resulting mixture is stirred at rt for 23 h. The reaction mixture is partitioned between EtOAc and 10% citric acid. The organic layer is washed with brine and saturated $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue is purified by FC (CH_2Cl_2:methanol = 100:0 to 96:4) to give the title compound as a white solid.

1H NMR (DMSO-d_6): δ 10.08 (s, 1H), 8.19-8.16 (m, H), 7.65-7.36 (m, 13H), 5.32 (s, 2H), 5.06-5.05 (m, 2H), 3.88-3.59 (m, 4H), 3.07 (bs, 1H), 2.10-1.78 (m, 4H), 1.65-1.39 (m, 6H), 1.03-0.945 (m, 3H). ES-MS: calcd. for $C_{32}H_{38}N_4O_6$ (574.67); found: 575.4 [M+H].

Example 33: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid (benzo[1,3]dioxol-5-yl)-amide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and pyrrolidine-2-carboxylic acid (benzo[1,3]dioxol-5-yl)-amide **A-8** [X = CH_2, n = 1, R_1 = 5-(benzo[1,3]dioxol)].

1H NMR (DMSO-d_6): δ 7.47-7.46 (d, J = 1.65 Hz, 1H), 7.15-7.02 (m, 2H), 6.17-6.16 (d, J = 3.85 Hz, 2H), 4.54 (bs, 1H), 3.86-3.7 (m, 2H), 3.52 (bs, 2H), 2.28-2.05 (m, 4H), 1.64-1.45 (m, 6H), 1.06-1.04 (d, J = 6.32 Hz, 3H). ES-MS: calcd. for $C_{20}H_{27}N_3O_6$ (405.45); found: 406.3 [M+H].

A-8 is prepared from 2-chlorocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester and 5-amino-(benzo[1,3]dioxol as described for the synthesis of pyrrolidine-2-carboxylic acid pyridine-2-yl-amide (hydrobromic acid salt) in Example 1.

2-S-(benzo[1,3]dioxol-5-yl-carbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester

1H NMR (DMSO-d_6): δ 7.6-7.3 (m, 6H), 7.2-7.02 (m, 2H), 6.17-6.16 (d, J = 1.47 Hz, 2H), 5.31-5.11 (m, 2H), 4.5-4.45 (m, 1H), 3.7-3.6 (m, 2H), 2.5-2.34 (m, 1H), 2.14-1.98 (m, 3H). ES-MS: calcd. for $C_{20}H_{20}N_2O_5$ (368.14); found: 369.2 [M+H].

Pyrrolidine-2-S-carboxylic acid (benzo[1,3]dioxol-5-yl)-amide hydrobromic acid salt

1H NMR (DMSO-d_6): δ 7.49-7.48 (d, J = 2.2 Hz, 1H), 7.2-7.17 (m, 1H), 7.11-7.08 (d, J= 8.24 Hz, 1H), 6.2 (bs, 2H), 4.5-4.48 (t, J = 7.1 & 6.3 Hz, 1H), 3.46-3.45 (d, J = 5.22 Hz, 2H), 2.58-2.54 (t, J = 8.24 & 6.6 Hz, 1H), 2.18-2.1 (m, 3H). ES-MS: calcd. for $C_{12}H_{14}N_2O_3$ (234.1); found: 235.2 [M+H].

Example 34: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid (2,2-difluoro-benzo[1,3]dioxol-5-yl)-amide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and pyrrolidine-2-carboxylic acid (2,2-difluoro-benzo[1,3]dioxol-5-yl)-amide **A-8** [X = CH_2, n = 1, R_1 = 5-((2,2-difluoro-benzo[1,3]dioxol].

1H NMR (DMSO-d_6): δ 7.96-7.93 (m, 1H), 7.56-7.42 (m, 2H, 4.56-4.55 (d, J = 3.57 Hz, 1H), 3.86-3.6 (m, 2H), 3.53 (bs, 2H), 3.28 (bs, 1H), 2.31-2.02 (m, 4H), 1.63-1.45 (m, 6H), 1.04 (bs, 3H). ES-MS: calcd. for $C_{20}H_{25}F_2N_3O_6$ (441.43); found: 442.3 [M+H].

A-8 is prepared from 2-chlorocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester and 5-amino-(2,2-difluoro-benzo[1,3]dioxol) as described for the synthesis of pyrrolidine-2-carboxylic acid pyridine-2-yl-amide (hydrobromic acid salt) in Example 1.

2-S-(2,2-difluoro-benzo[1,3]dioxol-5-yl-carbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester

1H NMR (DMSO-d_6): δ 7.97-7.87 (dd, 1H), 7.57-7.3 (m, 7H), 5.31-5.10 (m, 2H), 4.6-4.48 (m, 1H), 3.73-3.6 (m, 2H), 2.46-2.38 (m, 1H), 2.15-2.02 (m, 3H). ES-MS: calcd. for $C_{20}H_{18}F_2N_2O_5$ (404.12); found: 427.2 [M+Na].

Pyrrolidine-2-S-carboxylic acid (2,2-difluoro-benzo[1,3]dioxol-5-yl)-amide (hydrobromic acid salt)

1H NMR (DMSO-d_6): δ 7.63-7.33 (m, 3H), 4.56 (bs, 1H), 3.59 (bs, 2H), 2.63-2.56 (m, 1H), 2.2-2.13 (m, 3H). ES-MS: calcd. for $C_{12}H_{12}F_2N_2O_3$ (270.08); found: 271.2 [M+H].

Example 35: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid (phenoxy-phenyl-3-yl)-amide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and pyrrolidine-2-carboxylic acid 3-phenoxy-phenyl-3-yl)-amide **A-8** [X = CH_2, n = 1, R_1 = 3-(phenoxy-phenyl).

1H NMR (DMSO-d_6): δ 7.95 (bs, 1H), 7.60-7.19 (m, 7H), 6.89 (bs, 1H), 4.55 (bs, 1H), 3.8-3.71 (m, 2H), 3.53 (bs, 2H), 3.27 (bs, 1H), 2.27-2.05 (m, 4H), 1.42 (bs, 6H), 1.01 (bs, 3H). ES-MS: calcd. for $C_{25}H_{31}N_3O_5$ (453.54); found: 454.3 [M+H].

A-8 is prepared from 2-chlorocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester and 3-phenoxy-aniline as described for the synthesis of pyrrolidine-2-carboxylic acid pyridine-2-yl-amide (hydrobromic acid salt) in Example 1.

2-S-(phenoxy-phenyl-3-yl-carbamoyl)-pyrrolidine-1-carboxylic acid benzyl ester

1H NMR (DMSO-d_6): δ 7.62-7.19 (m, 13H), 6.95-6.9 (m, 1H), 5.28 - 5.09 (m, 2H), 4.54-4.46 (m, 1H), 4.2-3.58 (m, 2H), 2.42-2.39 (m, 1H), 2.12-1.99 (m, 3H). ES-MS: calcd. for $C_{25}H_{24}N_2O_4$ (416.17); found: 417.3 [M+H].

Pyrrolidine-2-S-carboxylic acid (phenoxy-phenyl-3-yl)-amide hydrobromic acid salt

1H NMR (DMSO-d_6): δ 7.64-7.21 (m, 8H), 7.01-6.97 (m, 1H), 4.51 (bs, 1H), 3.60-3.43 (m, 2H), 2.61-2.52 (m, 1H), 2.16-2.05 (m, 3H). ES-MS: calcd. for $C_{17}H_{18}N_2O_2$ (282.14); found: 283.3 [M+H].

Example 36: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid (5-fluoro-1-oxy-pyridin-2-yl)-amide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and pyrrolidine-2-carboxylic acid (5-fluoro-pyridin-2-yl)-amide **A-8** [X = CH_2, n = 1, R_1 = 2-(5-fluoro)-pyridyl] followed by the oxidation with with MCPBA.

1H NMR (DMSO-d_6): δ 10.6 (s, 1H), 9.85 (s, 1H), 8.71 (s, 1H), 8.28 (m, 1H), 7.80 (s, 1H), 7.45 (m, 1H), 4.75 (m, 1H), 3.52-3.80 (m, 2H), 3.32 (m, 2H), 3.05 (m, 1H), 2.14 (m, 1H), 1.94 (m, 3H), 1.50 (m, 1H), 1.35 (m, 2H), 1.26 (m, 3H), d 0.84 (m, 3H). ES-MS calcd. for $C_{18}H_{25}FN_4O_5$ (396.42); found: 397.2 [M+H].

A-8 is prepared from 2-chlorocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester and 5-fluoro-pyridin-2-ylamine as described for the synthesis of pyrrolidine-2-carboxylic acid pyridine-2-yl-amide (hydrobromic acid salt) in Example 1.

1-{2-R-[(benzyloxy-formyl-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid (5-fluoro-pyridin-2-yl)-amide

1H NMR (DMSO-d_6): δ 10.66 (s, 1H), 8.33 (m, 1H), 8.10 (m, 1H), d 7.75 (m, 1H), 7.44 (m, 5H), 7.14 (m, 1H), 4.88 (s, 2H), 4.59 (m, 1H), 3.67 (m, 2H), 3.55 (m, 2H), 2.94 (m, 1H), 1.72-2.12 (m, 4H), 1.48 (m, 1H), 1.34 (m, 1H), 1.26 (m, 4H), 0.86 (m, 3H). ES-MS calcd. for $C_{25}H_{31}FN_4O_4$ (470.55); found 471.4 [M+H].

1-{2-R-[(benzyloxy-formyl-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid (5-fluoro-1-oxy-pyridin-2-yl)-amide

1H NMR (DMSO-d_6): δ 10.61 (s, 1H), 8.73 (m, 1H), 8.26 (m, 1H), 7.90 (m, 1H), d 7.42 (m, 5H), 7.11-7.30 (m, 1H), 4.86 (s, 2H), 4.78 (m, 1H), 3.67 (m, 2H), 3.56 (m, 2H), 2.92 (m, 1H), d 2.01 (m, 1H), 1.91 (m, 2H), 1.82 (m, 1H), 1.48 (m, 1H), 1.36 (m, 1H), 1.24 (m, 4H), d 0.83 (m, 3H). ES-MS calcd. for $C_{25}H_{31}FN_4O_5$ (486.55); found: 487.4 [M+H].

Example 37: 6-[1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-S-pyrrolidine-2-carbonyl)-amino] nicotinic acid methyl ester

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and 6-[(pyrrolidine-2-S-carbonyl)-

amino]-nicotinic acid methyl ester **A-8** [X = CH_2, n = 1, R_1= 6-amino-nicotinic acid methyl ester].

1H NMR (DMSO-d_6): δ 10.60 (s,1H), 8.83 (s, 1H), 8.26 (1, d), 8.13 (d, 1H), 4.65 (1, m), 3.88 (s, 3H), 3.70 (m, 1H), 3.62 (m, 2H), 3.43 (m, 1H), 3.06 (m, 1H), 2.14 (m, 1H), 1.86-2.04 (m, 3H), 1.54 (m, 1H), 1.43 (m, 1H), 1.22-1.38 (m, 4H), 0.86 (t, 3H). ES-MS calcd. for $C_{20}H_{28}N_4O_6$ (420.46); found: 421.4 [M+H].

Example 38: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-4-R-hydroxypyrrolidine-2-S-carboxylic acid (5-methyl-pyridine-2-yl)-amide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and 4-R-benzyloxy-pyrrolidine-2-carboxylic acid (5-methyl-pyridin-2-yl)-amide **A-8** [X = (R)-CH-OH, n = 1, R_1 = 2-(5-methyl)pyridyl].

1H NMR (DMSO-d_6): δ 8.4-8.3 (m, 1H), 8.17-8.01 (m, 1H), 7.86-7.75 (m, 1H), 5.36 (bs, 1H), 4.83-4.78 (t, J = 8.42 & 7.67 Hz, 1H), 4.56 (bs, 1H), 3.89-3.73 (m, 2H), 3.52 (bs, 2H), 3.14 (bs, 1H), 2.69 (bs, 3H), 2.26-2.09 (m, 4H), 1.63-1.44 (m, 6H), 1.03 (bs, 3H). ES-MS: calcd. for $C_{19}H_{28}N_4O_5$ (392.46); found: 393.5 [M+H].

A-8 is prepared from 4-R-benzyloxy-pyrrolidine-1-carboxylic acid tert-butyl ester and 5-methyl-pyridin-2-ylamine under HATU condition to give proline amide derivative which on treatment with 4M HCl in dioxane provides the desired amine as described for the synthesis of azetidine-2-S-(4-methyl-pyridin-2-yl)-amide hydrochloric acid salt in Example 18.

4-R-benzyloxy-pyrrolidine-2-S-carboxylic acid (5-methyl-pyridine-2-yl)-amide

1H NMR (DMSO-d_6): δ 8.42 (bs, 1H), 8.15-8.12 (d, J = 8.24 Hz, 1H), 7.96-7.92 (m, 1H), 7.61-7.47 (m, 5H), 4.77-4.56 (m, 4H), 3.68-3.58 (m, 2H), 2.97-2.90 (m, 1H), 2.69 (bs, 3H), 2.27-2.17 (m, 1H). ES-MS: calcd. for $C_{18}H_{21}N_3O_2$ (311.38); found: 312.5 [M+H].

4-R-benzyloxy-1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid (5-methyl-pyridine-2-yl)-amide

1H NMR (DMSO-d_6): δ 8.4-8.3 (m, 1H), 8.14-8.01 (m, 1H), 7.8-7.76 (d, J = 8.52 Hz, 1H), 7.56-7.48 (m, 5H), 4.85-4.8 (t, J = 7.42 & 7.69 Hz, 1H), 4.75-4.46 (m, 2H), 4.05 (bs, 1H), 4.0-3.68 (m, 2H), 3.54 (bs, 2H), 3.16 (bs, 1H), 2.69 (bs, 3H), 2.49-2.23 (m, 4H), 1.64-1.44 (m, 6H), 1.04 (bs, 3H). ES-MS: calcd. for $C_{26}H_{34}N_4O_5$ (482.57); found: 483.5 [M+H].

Example 39: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-4-S-hydroxypyrrolidine-2-S-carboxylic acid (5-methyl-pyridine-2-yl)-amide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and 4-S-O-benzoyl-pyrrolidine-2-carboxylic acid (5-methyl-pyridin-2-yl)-amide **A-8** [X = (R)-CH-OH, n = 1, R_1 = 2-(5-methyl)pyridyl].

1H NMR (DMSO-d_6): δ 8.31-8.38 (d, J = 7.42 Hz, 1H), 8.16-8.11 (m, 1H), 7.8-7.76 (m, 1H), 5.51-5.5 (d, J = 4.95 Hz, 1H), 4.63 (bs, 1H), 4.52-4.35 (d, J = 4.95 Hz, 1H), 4.02-3.68 (m, 2H), 3.52 (bs, 2H), 2.70 (bs, 1H), 2.69 (bs, 3H), 2.21-1.97 (m, 4H), 1.64-1.42 (m, 6H), 1.05-1.03 (d, J = 6.04 Hz, 3H). ES-MS: calcd. for $C_{19}H_{28}N_4O_5$ (392.46); found: 393.5 [M+H].

4-S-O-benzoyl-pyrrolidine-2-S-carboxylic acid (5-methyl-pyridine-2-yl)-amide

A-8 is prepared by the inversion of 4-R-hydroxy-pyrrolidine-1-carboxylic acid butyl (5-methyl-pyridin-2-yl)-amide under Mitsunobu condition to give 4-S-O-benzyloxy proline amide derivative which on treatment with 4M HCl in dioxane provides the desired amine as described for the synthesis of azetidine-2-S-(4-methyl-pyridin-2-yl)-amide hydrochloric acid salt in Example 18.

1H NMR (DMSO-d_6): δ 8.38 (bs, 1H), 8.15-8.06 (m, 2H), 7.92-7.8 (m, 4H), 7.66-7.61 (t, J = 7.69 Hz, 1H), 5.74 (bs, 1H), 4.89 (bs, 1H), 3.83 (bs, 2H), 3.03-2.94 (m, 1H), 2.7-2.45 (m, 4H). ES-MS: calcd. for $C_{18}H_{19}N_3O_3$ (325.37); found: 326.4 [M+H].

Example 40: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-4-R-hydroxypyrrolidine-2-S-carboxylic acid (4-ethyl-pyridine-2-yl)-amide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and pyrrolidine-2-carboxylic acid (4-ethyl-pyridin-2-yl)-amide **A-8** [X = (R)-CH-OH, n = 1, R_1 = 2-(4-ethyl)pyridyl].

1H NMR (DMSO-d_6): δ 8.38-8.36 (d, J = 4.945 Hz, 1H), 8.12-8.01 (m, 1H), 7.16-7.14 (m, 1H), 5.37-5.36(d, J = 2.3 Hz, 1H), 4.85-4.8 (t, J = 7.69 Hz, 1H), 4.57 (bs, 1H), 3.89-3.55 (m, 2H), 3.52 (bs, 2H), 3.14 (bs, 1H), 2.82-2.6 (m, 2H), 2.26-2.09 (m, 4H), 1.63-1.33 (m, 9H), 1.04 (bs, 3H). ES-MS: calcd. for $C_{20}H_{30}N_4O_5$ (406.48); found: 407.5 [M+H].

A-8 is prepared from 4-R-benzyloxy-pyrrolidine-1-carboxylic acid tert-butyl ester and 4-ethyl-pyridin-2-ylamine under HATU condition to give proline amide derivative which on treatment with 4M HCl in dioxane provides the desired amine as described for the synthesis of azetidine-2-S-(4-methyl-pyridin-2-yl)- amide hydrochloric acid salt in Example 18.

4-R-benzyloxy-pyrrolidine-2-S-carboxylic acid (4-ethyl-pyridine-2-yl)-amide

1H NMR (DMSO-d_6): δ 8.48-8.46 (d, J = 5.22 Hz, 1H), 8.11 (bs, 1H), 7.62-7.34 (m, 8H), 4.81-4.56 (m, 4H), 3.69-3.59 (m, 2H), 2.98-2.83 (m, 3H), 2.29-2.19 (m, 1H), 1.41-1.38 (t, J = 5.49 & 2.2 Hz, 3H). ES-MS: calcd. for $C_{19}H_{23}N_3O_2$ (325.41); found: 326.3 [M+H].

Example 41: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-4-R-hydroxypyrrolidine-2-S-carboxylic acid (5-trifluoromethyl-pyridine-2-yl)-amide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and pyrrolidine-2-carboxylic acid (5-trifluoromethyl-pyridin-2-yl)-amide **A-8** [X = (R)-CH-OH, n = 1, R_1 = 2-(5-trifluomethylethyl)-pyridyl.

1H NMR (DMSO-d_6): δ 8.44-8.3 (m, 2H), 8.01 (bs, 1H), 4.88-4.83 (t, J = 7.69 Hz, 1H), 4.57 (bs, 1H), 3.91-3.66 (m, 4H), 3.15 (bs, 1H), 2.3-2.13 (m, 2H), 1.63-1.45 (m, 6H), 1.03 (bs, 3H). ES-MS: calcd. for $C_{19}H_{25}F_3N_4O_5$ (446.43); found: 447.3 [M+H].

A-8 is prepared from 4-R-benzyloxy-pyrrolidine-1-carboxylic acid tert-butyl ester and 5-trifluoromethyl-pyridin-2-ylamine under HATU condition to give proline amide derivative which on treatment with 4M HCl in dioxane provides the desired amine as described for the synthesis of azetidine-2-S-(4-methyl-pyridin-2-yl)-amide hydrochloric acid salt in Example 18.

4-R-benzyloxy-pyrrolidine-2-S-carboxylic acid (5-trifluoromethyl-pyridine-2-yl)-amide

1H NMR (DMSO-d_6): δ 8.98 (bs, 1H), 8.5-8.42 (m, 2H), 7.62-7.47 (m, 5H), 4.84-4.56 (m, 4H), 3.69-3.61 (m, 2H), 2.97-2.91 (m, 1H), 2.3-2.21 (m, 1H). ES-MS: calcd. for $C_{18}H_{18}F_3N_3O_2$ (365.36); found: 366.3 [M+H].

Example 42: 4-S-fluoro-1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid (5-methyl-pyridine-2-yl)-amide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and 4-S-fluoro-pyrrolidine-2-carboxylic acid (5-methyl-pyridin-2-yl)-amide **A-8** [X = (S)-CH-F, n = 1, R_1 = 2-(5-methyl)-pyridyl.

1H NMR (DMSO-d_6): δ 8.34-8.32 (bs, 1H), 8.1-8.05 (m, 1H), 7.83-7.80 (d, J = 8.52 Hz, 1H), 5.63-5.45 (d, J = 54.1 Hz, 1H), 4.9-4.86 (d, J = 9.89 Hz, 1H), 4.22-3.5 (m, 4H), 3.18 (bs, 1H), 2.69 (bs, 3H), 2.59-2.44 (m, 2H), 1.69-1.32 (m, 6H), 1.08-1.03 (t, J = 6.87 Hz, 3H). ES-MS: calcd. for $C_{19}H_{27}FN_4O_4$ (394.44); found: 395.4 [M+H].

4-R-hydroxy-pyrrolidine-2-S-carboxylic acid (5-methyl-pyridine-2-yl)-amide

The coupling of O-tert butyl protected proline (1 mmol) with 5-picoline (1.5 mmol) in DMF (5 ml) under HATU (1.3 mmol) and N,N-diisopropylethyl amine (5 mmol) condition followed by removal of O-tert butyl with TFA-dichloroethane (1:1) provides the title compound.

1H NMR (DMSO-d_6): δ 8.34-8.32 (t, J = 1.5 & 3.3 Hz, 1H), 8.18-8.14 (m, 1H), 7.82-7.77 (m, 1H), 7.57-7.24 (m, 5H), 5.95-5.1 (m, 3H), 4.83-4.72 (m, 1H), 4.5 (bs, 1H), 3.75-3.59 (m, 4H), 2.7-2.67 (m, 3H), 2.38-2.31 (m, 1H), 2.18-2.1 (m, 1H). ES-MS: calcd. for $C_{19}H_{21}N_3O_4$ (355.15); found: 356.4 [M+H].

4-S-fluoro-pyrrolidine-2-S-carboxylic acid (5-methyl-pyridine-2-yl)-amide

The above hydroxy compound (2 mmol) in methylenechloride (20 ml) is treated with N'N-diethylamino sulphur trifluoride (DAST; 4 mmol) at -70°C. Then, reaction mixture is stirred at rt for 16 h and washed with cold aq. $NaHCO_3$ solution, dried and concentrated under reduced pressure. It is purified on silica gel column chromatography to give N-protected derivative which on treatment with HBr-AcOH provides amino compound.

1H NMR (DMSO-d_6): δ 8.41 (bs, 1H), 8.11-8.09 (d, J = 8.24 Hz, 1H), 7.92-7.05 (m, 1H), 5.71-5.53 (d, J = 52.47 Hz, 1H), 4.8 (bs, 1H), 3.84-3.67 (m, 2H), 3.04-2.81 (m, 1H), 2.69 (bs, 3H), 2.68-2.09 (m, 1H). ES-MS: calcd. for $C_{11}H_{14}FN_3O$ (223.25); found: 224.4 [M+H].

Example 43: 4-R-fluoro-1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid (5-methyl-pyridine-2-yl)-amide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and 4-R-fluoro-pyrrolidine-2-carboxylic acid (5-methyl-pyridin-2-yl)-amide **A-8** [X = (R)-CH-F, n = 1, R_1 = 2-(5-methyl)-pyridyl.

1H NMR (DMSO-d_6): δ 8.34-8.31 (d, J = 7.42 Hz, 1H), 8.15-8.12 (d, J = 8.51 Hz, 1H), 7.99-7.73 (m, 1H), 5.66-5.48 (d, J = 52.7 Hz, 1H), 4.87-4.81 (t, J = 8.52 & 8.24 Hz, 1H), 4.26-3.56 (m, 2H), 3.52 (bs, 2H), 3.14 (bs, 1H), 2.69-2.68 (t, J = 1.92 & 1.65 Hz, 3H), 2.49-2.17 (m, 2H), 1.64-1.42 (m, 6H), 1.08-1.04 (bs, 3H). ES-MS: calcd. for $C_{19}H_{27}FN_4O_4$ (394.44); found: 395.4 [M+H].

4-S-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester-2-methyl ester

To a solution of trans-4-hydroxy compound (1mmol), triphenyl phosphine (1.5 mmol) and benzoic acid (1.5 mmol) in THF (10 ml) is added N,N-diisopropyl-azo dicarboxylate (1.5 mmol) in THF (5 ml) dropwise at 0°C. It is stirred at rt for 16 h. The solvent is removed under reduced pressure and residue is dissolved in ether. It is ice cooled to precipitate phosphine oxide which is removed by filtration and filtrate is concentrated under reduced

pressure. The crude material is treated with methanolic sodium methoxide for 2 h at 0°C to give title cis-hydroxy compound.

1H NMR (DMSO-d_6) δ 4.43-4.35 (m, 2H), 3.80 (bs, 3H), 3.69 (m, 1H), 3.34-3.26 (m, 1H), 2.54-2.50 (m, 1H), 2.04-1.97 (m, 1H), 1.55 (bs, 9H). ES-MS: calcd. for $C_{11}H_{17}NO_5$ (245.44); found: 246.3 [M+H].

4-R-fluoro-pyrrolidine-2-S-carboxylic acid (5-methyl-pyridine-2-yl)-amide

The fluorination of the above cis-hydroxy under similar reaction condition as described in Example 42 provides the trans-4-fluoro derivative which on saponification gives the corresponding acid. The amide is prepared from 4-R-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester and 5-methyl-pyridin-2-ylamine under HATU condition to give proline amide derivative which on treatment with 4M HCl in dioxane provides the desired amine as described for the synthesis of azetidine-2-S-(4-methyl-pyridin-2-yl)-amide hydrochloric acid salt in Example 18.

1H NMR (DMSO-d_6): δ 8.418-8.416 (t, J = 0.82 Hz, 1H), 8.14-8.11 (d, J = 8.52 Hz, 1H), 7.97-7.94 (m, 1H), 5.78-5.59 (d, J = 55.77 Hz, 1H), 4.83 (bs, 1H), 3.89-3.69 (m, 2H), 3.04-2.91 (m, 1H), 2.68 (bs, 3H), 2.44-2.29 (m, 1H). ES-MS: calcd. for $C_{11}H_{14}FN_3O$ (223.25); found: 224.4 [M+H].

Example 44: 4,4-difluoro-1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-pyrrolidine-2-S-carboxylic acid (5-methyl-pyridine-2-yl)-amide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and 4-difluoro-pyrrolidine-2-carboxylic acid (5-methyl-pyridin-2-yl)-amide **A-8** [X = CF_2, n = 1, R_1 = 2-(5-methyl)-pyridyl.

1H NMR (DMSO-d_6): δ 8.34 (bs, 1H), 8.13-8.1 (d, J = 8.24 Hz, 1H), 7.87-7.78 (m, 1H), 4.94-4.91 (d, J = 8.24 Hz, 1H), 4.49-4.16 (m, 1H), 3.75-3.3 (m, 3H), 2.97 (bs, 1H), 2.94-2.88 (m, 1H), 2.75-2.66 (m, 4H), 1.65-1.45 (m, 6H), 1.06-1.04 (d, J = 6.04 Hz, 3H). ES-MS: calcd. for $C_{19}H_{26}F_2N_4O_4$ (412.44); found: 413.5 [M+H].

4-oxo-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester-2-methyl ester

To a solution of oxalyl chloride (1.3 mmol) in methylene chloride (5 ml) is added DMSO (2.6 mmol) dropwise at -70°C. After 20 min, a solution of trans-hydroxy compound (1 mmol) in methylene chloride (5 ml) is added to reaction mixture. The reaction mixture is warmed to -60°C and triethylamine is added to it. The reaction mixture is warmed up to 0°C and diluted with more methylene chloride. It is washed with saline, 10% aq. citric acid, dried and

concentrated under reduced pressure. The purification over silica gel with 20-30% EtOAc in hexane gives the 4-oxo compound.

1H NMR ($CDCl_3$): δ 4.83-4.71 (m, 1H), 3.91-3.79 (m, 2H), 3.77 (bs, 3H), 2.98-2.88 (m, 1H), 2.62-2.56 (m, 1H), 1.48 (bs, 9H). ES-MS: calcd. for $C_{11}H_{17}NO_5$ (243.44); found: 244.3 [M+H].

4-Di-fluoro-pyrrolidine-2-S-carboxylic acid (5-methyl-pyridine-2-yl)-amide

The fluorination of the above 4-oxo compound under similar reaction condition as described in Example 42 provides the 4-di-fluoro derivative which on saponification gives the corresponding acid. **A-8** is prepared from 4-di-fluoro-pyrrolidine-1-carboxylic acid tert-butyl ester and 5-methyl-pyridin-2-ylamine under HATU condition to give proline amide derivative which on treatment with 4 M HCl in dioxane provides the desired amine as described for the synthesis of azetidine-2-S-(4-methyl-pyridin-2-yl)-amide hydrochloric acid salt in Example 18.

1H NMR (DMSO-d_6): δ 8.41-8.407 (t, J = 0.82 Hz, 1H), 8.13-8.10 (d, J = 8.52 Hz, 1H), 7.94-7.91 (m, 1H), 4.98-4.93 (t, J = 8.24 Hz, 1H), 4.02-3.93 (m, 2H), 3.26-3.2 (m, 1H), 2.94-2.84 (m, 1H), 2.69-2.68 (t, J = 1.92 & 1.65 Hz, 3H). ES-MS: calcd. for $C_{11}H_{13}F_2N_3O$ (241.24); found: 242.4 [M+H].

Example 45: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-4-R-methoxy-pyrrolidine-2-S-carboxylic acid (5-methyl-pyridin-2-yl)-amide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and 4-trans-methoxy-pyrrolidine-2-carboxylic acid (5-methyl-pyridin-2-yl)-amide **A-8** [X = 4-trans-CH-OMe, n = 1, R_1 = 2-(5-methyl)-pyridyl.

1H NMR (DMSO-d_6): δ 10.6 (s, 1H), 9.90 (s, 1H), 8.33-8.32 (m, 1H), 8.14-8.11 (m, 1H), 7.79-7.77 (m, 1H), 4.78-4.72 (m, 1H), 4.24 (bs, 1H), 3.97-3.78 (m, 2H), 3.69-3.67 (m, 1H), 3.52-3.34 (m, 4H), 3.15 (bs, 1H), 2.49-2.36 (m, 4H), 2.24-2.12 (m, 1H), 1.64-1.44 (m, 6H), 1.10-0.993 (m, 3H). ES-MS: calcd. for $C_{20}H_{30}N_4O_5$ (406.48); found: 407.5 [M+H].

A-8 is prepared from 4-R-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester and 5-methyl-pyridin-2-ylamine as described below.

4-R-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester

To a DMF solution (70 ml) of 4-R-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (5.0 g, 20.4 mmol, 1 equiv.) are successively added Ag_2O (14.2 g, 61 mmol, 3 equiv.) and methyl iodide (7.0 ml, 102 mmol, 5 equiv.) at 0°C. The reaction mixture is allowed to come to rt overnight. The reaction mixture is diluted with excess EtOAc, and the insoluble salts are

removed by filtration through Celite. The reaction mixture is washed with water, sat. $NaHCO_3$, and 10% sodium thiosulfate. The organic layer is dried over anhydrous Na_2SO_4, filtered, and concentrated to give a light yellow oil.

1H NMR (DMSO-d_6): δ 4.37-4.30 (m, 1H), 4.15-4.11 (m, 1H), 3.85-3.82 (m, 3H), 3.60-3.58 (m, 2H), 3.40 (s, 3H), 2.54-2.47 (m, 1H), 2.18-2.08 (m, 1H), 1.58 (s, 3H), 1.51 (m, 6H). ES-MS: calcd. for $C_{12}H_{21}NO_5$ (259.30); found: 282.4 [M+Na].

4-R-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester

The above methyl ester (5.0 g, 19.2 mmol, 1 equiv.) is taken in a 3:1 solution of THF/water (180 ml/60 ml) and cooled to 0°C. A solution of lithium hydroxide (1M solution in water, 38 ml, 38 mmol, 2 equiv.) is added, and the resulting mixture is stirred at 0°C for 2 h and at rt for 2 h. The basic reaction mixture is quenched with Amberlite IR-120 resin (H^+) to pH 4-5 at 0°C. The resin is filtered off and rinsed with EtOAc, and the mixture is concentrated to remove solvents. The residual oil is co-evaporated twice with toluene, and concentrated to give a light yellow oil.

1H NMR (DMSO-d_6): δ 12.8 (bs, 1H), 4.32-4.20 (m, 1H), 4.13 (bs, 1H), 3.59-3.33 (m, 5H), 2.52-2.42 (m, 1H), 2.17-2.06 (m, 1H), 1.58-1.53 (m, 9H). ES-MS: calcd. for $C_{11}H_{19}NO_5$ (245.27); found: 2.44 [M-H].

4-R-methoxy-2-S-(5-methyl-pyridin-2-ylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester

To a DMF solution (35 ml) of above carboxylic acid (4.20 g, 17.1 mmol, 1 equiv.) are successively added Hunig's base (15 ml, 86 mmol, 5 equiv.), 2-amino-5-picoline (2.78 g, 26 mmol, 1.5 equiv.), and HATU (9.77 g, 26 mmol, 1.5 equiv.) at 0°C. The resulting mixture is stirred at rt for 18 h. The mixture is partitioned between excess EtOAc and 10% citric acid. The organic layer is washed with brine and saturated $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue is purified by FC (hexane:EtOAc = 100% to 50%:50%) to give the title compound as a white solid.

1H NMR (DMSO-d_6): δ 10.7-10.6 (m, 1H), 8.33 (s, 1H), 8.21-8.14 (m, 1H), 7.82-7.77 (m, 1H), 4.63-4.54 (m, 1H), 4.15 (bs, 1H), 3.65-3.61 (m, 2H), 3.41 (s, 3H), 2.52-2.43 (m, 4H), 2.18-2.08 (m, 1H), 1.58-1.42 (m, 9H). ES-MS: calcd. for $C_{17}H_{25}N_3O_4$ (335.40); found: 336.5 [M+H].

4-R-methoxy-pyrrolidine-2-S-carboxylic acid (5-methyl-pyridin-2-yl)-amide (hydrochloric acid salt)

The Boc-prolineaminopicoline (2.78 g, 8.29 mmol, 1 equiv.) is charged with 4N HCl/dioxane (21 ml, 83 mmol, 10 equiv.) at rt and allowed to stir for 18 h. The mixture is concentrated, and the residue is co-evaporated twice with toluene, and concentrated to give a pink solid.

1H NMR (DMSO-d_6): δ 11.4 (bs, 1H), 10.4 (bs, 1H), 8.41-8.40 (m, 1H), 8.15-8.12 (m, 1H), 7.92-7.88 (m, 1H), 4.69-4.63 (m, 1H), 4.36-4.33 (m, 1H), 3.69-3.56 (m, 1H), 3.53-3.44 (m, 4H), 2.87-2.80 (m, 1H), 2.46 (s, 1H), 2.20-2.11 (m, 1H). ES-MS: calcd. for $C_{12}H_{17}N_3O_2$*2HCl (235.28); found: 236.4 [M+H] free base.

1-{2-R-[(benzyloxy-formyl-amino)-methyl]-hexanoyl}-4-R-methoxy-pyrrolidine-2-S-carboxylic acid (5-methyl-pyridin-2-yl)-amide

To a DMF solution (6 ml) of trans-methoxyprolineaminopicoline HCl salt (679 mg, 2.20 mmol, 1.5 equiv.), are successively added Hunig's base (1.3 ml, 7.34 mmol, 5 equiv.), Versiacid VRI 172 (410 mg, 1.47 mmol, 1 equiv.), and HATU (837 mg, 2.20 mmol, 1.5 equiv) at 0°C. The resulting mixture is stirred at rt for 18 h. The mixture is partitioned between excess EtOAc and 10% citric acid. The organic layer is washed with brine and saturated $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue is purified by FC (CH_2Cl_2:ACE = 100% to 50%:50%) to give the title compound as a colorless oil.

1H NMR (DMSO-d_6): δ 10.6 (s, 1H), 8.37-8.33 (m, 1H), 8.14-8.05 (m, 1H), 7.79-7.76 (m, 1H), 7.61-7.57 (m, 6H), 5.06 (s. 2H), 4.79-4.70 (m, 1H), 4.21 (m, 1H), 3.85-3.83 (m, 2H), 3.65-3.45 (m, 2H), 3.36 (bs, 3H), 4.14 (bs, 1H), 2.49-2.40 (m, 4H), 2.19-2.11 (m, 1H), 1.63-1.33 (m, 6H), 1.05-0.992 (m, 3H). ES-MS: calcd. for $C_{27}H_{36}N_4O_5$ (496.60); found: 497.7 [M+H].

Example 46: 1-{2-R-[(formyl-hydroxy-amino)-methyl]-hexanoyl}-4-S-methoxy-pyrrolidine-2-S-carboxylic acid (5-methyl-pyridin-2-yl)-amide

The title compound is prepared according to General Procedure A from 2-[(benzyloxy-formyl-amino)-methyl]-hexanoic acid **A-7** (R=n-butyl) and 4-cis-methoxy-pyrrolidine-2-carboxylic acid (5-methyl-pyridin-2-yl)-amide **A-8** [X = 4-cis-CH-OMe, n = 1, R_1 = 2-(5-methyl)-pyridyl].

1H NMR (DMSO-d_6): δ 10.3 (bs, 1H), 9.89 (bs, 1H), 8.30 (bs, 1H), 8.13-8.10 (m, 1H), 7.99 (bs, 1H), 7.80-7.77 (m, 1H), 4.66 (bs, 1H), 4.44-4.14 (m, 2H), 3.74-3.52 (m, 5H), 3.41-3.28 (m, 2H), 2.56-2.42 (m, 4H), 2.24-2.12 (m, 1H), 1.66-1.46 (m, 6H), 1.05-1.03 (m, 3H). ES-MS: calcd. for $C_{20}H_{30}N_4O_5$ (406.48); found: 407.5 [M+H].

A-8 is prepared from 4-S-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester and 5-methyl-pyridin-2-ylamine as described for the corresponding trans methoxy compound (Example 45).

4-S-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester

1H NMR ($CDCl_3$): δ 4.45-4.33 (m, 2H), 3.96-3.91 (m, 1H), 3.73 (s, 3H), 3.68-3.45 (m, 1H), 3.28 (s, 3H), 2.33-2.22 (m, 2H), 1.481.42 (m, 9H). ES-MS: calcd. for $C_{12}H_{21}NO_5$ (259.30); found: 282.4 [M+Na].

4-S-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester

1H NMR (DMSO-d_6): δ 12.8 (bs, 1H), 4.36-4.29 (m, 1H), 4.10-4.07 (m, 1H), 3.75-3.68 (m, 1H), 341.3.35 (m, 4H), 2.58-2.49 (m, 1H), 2.21-2.14 (m, 1H), 1.58-1.53 (m, 9H). ES-MS: calcd. for $C_{11}H_{19}NO_5$ (245.27); found: 2.44 [M-H].

4-S-methoxy-2-S-(5-methyl-pyridin-2-ylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester

1H NMR (DMSO-d_6): δ 10.3-10.2 (m, 1H), 8.32-8.31 (m, 1H), 8.18-8.15 (m, 1H), 7.81-7.78 (m, 1H), 4.51-4.46 (m, 1H), 4.18-4.11 (m, 1H), 3.52 (s, 3H), 3.47-3.35 (m, 1H), 2.64-2.56 (m, 1H), 2.43 (s, 3H), 2.20-2.05 (m, 1H), 1.59-1.44 (m, 9H). ES-MS: calcd. for $C_{17}H_{25}N_3O_4$ (335.40); found: 336.5 [M+H].

4-S-methoxy-pyrrolidine-2-S-carboxylic acid (5-methyl-pyridin-2-yl)-amide (hydrochloric acid salt)

1H NMR (DMSO-d_6): δ 11.3 (bs, 1H), 10.6 (bs, 1H), 8.40-8.39 (m, 1H), 8.11-8.08 (m, 1H), 7.92-7.88 (m, 1H), 4.65-4.57 (m, 1H), 4.29-4.25 (m, 1H), 3.52-3.39 (m, 2H), 3.37 (s, 3H), 2.81-2.71 (m, 1H), 2.59-2.33 (m, 4H). ES-MS: calcd. for $C_{12}H_{17}N_3O_2$*2HCl (235.28); found: 236.4 [M+H] free base.

1-{2-R-[(benzyloxy-formyl-amino)-methyl]-hexanoyl}-4-S-methoxy-pyrrolidine-2-S-carboxylic acid (5-methyl-pyridin-2-yl)-amide

1H NMR (DMSO-d_6): δ 10.1 (bs, 1H), 8.43(bs, 1H), 8.34-8.31 (m, 1H), 8.11-8.09 (m, 1H), 7.79-7.76 (m, 1H), 7.62 (m, 6H), 5.05 (s. 2H), 4.79 (bs, 1H), 4.62 (bs, 1H), 4.01-3.98 (m, 1H), 3.90-3.83 (m, 1H), 3.54-3.34 (m, 5H), 3.17 (bs, 1H), 2.46-2.42 (m, 4H), 2.13-2.09 (m, 1H), 1.50-1.39 (m, 6H), 1.15-0.992 (m, 3H). ES-MS: calcd. for $C_{27}H_{36}N_4O_5$ (496.60); found: 497.7 [M+H].

Preferred compounds according to the invention are e.g. the compounds of Examples 6, 8, 9, 14, 15, 21, 22, 28, 29, or 36. Even more preferred are those of Examples 14 or 36.

The compounds of the invention, e.g. the compounds of formula (I), in free form or in pharmaceutically acceptable salt from or a prodrug thereof, exhibit valuable pharmacological properties, e.g. as anti-infectious agents, e.g. as indicated in *in vitro* and *in vivo* tests and are therefore indicated for therapy.

A. Inhibition of Peptide Deformylase Activity

The PDF/FDH coupled assay (Lazennec et al., Anal. Biochem., Vol. 224, pp. 180-182 (1997)) is used. In this coupled assay, the formate released by PDF from its substrate fMAS is oxidized by the coupling enzyme FDH, reducing one molecule of NAD^+ to NADH, which causes an increase in absorption at 340 nM. All assays are carried out at rt in a buffer of 50 mM HEPES, pH 7.2, 10 mM NaCl, 0.2 mg/ml BSA, in half-area 96-well microtiter plates (Corning). The reaction is initiated by adding a mixture of 0.5 Unit/ml FDH, 1 mM NAD^+, and fMAS at the desired concentration. To determine IC_{50} (the concentration needed to inhibit 50% of enzyme activity) values, PDF is pre-incubated for 10 minutes with varying concentrations of the inhibitor, and the deformylation reaction is initiated by the addition of reaction mixture containing 4 mM fMAS. The initial reaction velocity, y, is measured as the initial rate of absorption increase at 340 nM using a SpectraMax plate reader (Molecular Devices, Sunnyvale, CA). The inhibitor concentration [In] at which 50% of the enzyme activity is inhibited, IC_{50}, is calculated using the following formula:

$$y = y_o/(1 + [In]/IC_{50})$$

where y_o is the reaction velocity in the absence of inhibitor. Solving this equation for IC_{50} at the [In] when $y = y_o/2$ yields IC_{50}. The IC_{50} is calculated based on a nonlinear least-square regression fit using a commercial software package (Deltapoint, Inc., Chicago, IL.).

Using this assay, the IC_{50} of various compounds of the invention is determined. The IC_{50} for the various compounds is determined against deformylase enzyme containing nickel and zinc as the metal ion. The IC_{50} values of preferred compounds of formula (I) determined for the zinc-containing deformylase range from about 0.001 μM to about 0.2 μM. The IC_{50} values of preferred compounds of formula (I) determined for the nickel-containing deformylase ranged from about 0.005 μM to about 3 μM.

B. Assay for Testing Antimicrobial Activity

Minimum inhibitory concentrations (MICs) are determined using the microdilution method in 96-well format plates. Compounds are suspended in DMSO at 5 or 10 mg/ml and stored at 4°C until used. They are diluted in Mueller-Hinton Broth (MHB) or Trypticase Soy Broth (TSB) and used for MIC determination. The range of concentrations tested is 64-0.0625 μg/ml final concentration using a two-fold dilution system.

The inoculum is prepared from cells grown on Trypticase Soy Agar (TSA) and incubated overnight at 35°C, 5-10 colonies are used to inoculate MHB or TSB broths, and the culture is incubated overnight at 35°C. The overnight culture is diluted 1:10, incubated for 1 hour at 35°C, diluted to the appropriate inoculum size and applied to the wells containing broth and test compound. Inoculum sizes are 2×10^4 CFU/ml.

Plates are incubated at 35°C for 48 hours and MIC are recorded after 18 hours of incubation for bacteria. MIC is defined as the lowest concentration of a compound of the invention that does not produce visible growth after incubation.

Minimum inhibitory concentration for various preferred compounds of formula (I) ranges from about 0.25 µg/ml to about 32 µg/ml against *H.* influenza (four strains), from about 0.001 µg/ml to greater than 8 µg/ml against *S. aureus* (four strains), from about 0.016 µg/ml to about 16 µg/ml against *S. pneumonia* (four strains), and from about 0.008 µg/ml to about 16 µg/ml against *M. catarrhalis*. The deformylase enzyme is obtained from *E. coli*.

C. Demonstration of Selective Inhibition of PDF Compared to MMP-7 (Matrilysin)

As noted previously, inhibitors which are selective for peptidyl deformylase over MMPs are desirable in order to avoid side effects.

In order to test the compounds of the invention for possible inhibitory effects on MMPs, the following assay for MMP-7 (matrilysin) is used.

MMP-7 (Matrilysin) Assay:

Matrilysin activity is assayed using a thio-peptide (Pro-Leu-Gly-S-Leu-Leu-Gly) as substrate. Upon enzyme hydrolysis, the thiolate is released as a product. The thiolate thus generated reacts with DTNB (dithionitrobenzene), giving rise to a yellow color which is monitored at 405 nM. The assay is carried out at rt; the assay buffer contains 50 mM Tricine, pH 7.5, 0.2 M NaCl, 10 mM $CaCl_2$, and 0.05% Brij, in a half-area 96-well microtiter plate. The reaction is initiated by adding a mixture of 200 TM DTNB and 100 TM thiopeptide in buffer. To determine IC_{50} (the concentration needed to inhibit 50% of enzyme activity) values, MMP-7 is preincubated for 10 minutes with varying concentrations of compounds of the invention, and the hydrolysis initiated by the addition of reaction mixture containing thiopeptide and DTNB. The reaction rate is recorded as the absorbance increase in OD_{405} over 30 minutes

using a SpectraMax plate reader (Molecular Devices, Sunnyvale, CA). The inhibitor concentration [In] at which 50% of the enzyme activity is inhibited, IC_{50}, is calculated using the following formula:

$$y = y_o/(1 + [In]/IC_{50})$$

where y_o is the reaction velocity in the absence of inhibitor. Solving this equation for IC_{50} at the [In] when $y = y_o/2$ yields IC_{50}.

Using this assay, the IC_{50} of various compounds of the invention are determined. The IC_{50} of various preferred compounds of formula (I) against MMP-7 ranges from greater than 10 μM to greater than 100 μM, whereas the IC_{50} of these same compounds against zinc-containing PDF ranges from about 0.005 μM to about 5 μM, and against nickel-containing PDF ranged from about 0.001 μM to about 0.3 μM. Accordingly, compounds of the invention have superior selectivity for PDF as compared to their activity against MMP-7. Similar selectivity of the compounds for peptidyl deformylase over MMP-1, MMP-2, MMP-3, MMP-9, MMP-13, MT-MMP-1, and tissue necrosis factor converting enzyme is observed. Similar selectivity is also observed over other metalloproteinases such as angiotensin converting enzyme.

D. Mouse Septicemia Model for Determining *In Vivo* Efficacy

CD1 female out-bred mice (Charles River Laboratories) weighing 18-22 g each are injected intraperitoneally with 0.5 ml of a suspension containing 5 x 10^7 cfu of *S. aureus* (Smith strain) in 7% hog gastric mucosa (mucin). The mice are treated, either subcutaneously (s.c.), intravenously (i.v.) or orally (p.o.), 1 hour and 5 hours after infection. Six groups of six mice each are given different dosage levels representing two-fold dilutions of each compound to be tested (range of 100-0.1 mg/kg). Vancomycin is used as the control antibiotic and is administered s.c. Compounds of the invention are formulated in PBS and untreated controls are dosed with vehicle alone.

Deaths in each group are monitored daily for 6 days and cumulative mortality is used to determine the 50% protective doses (PD_{50}), which are calculated using the method of Reed and Muench. The PD_{50} (s.c.) in mice against *S. aureus* for several preferred compound of formula (I) ranges from about 0.1 mg/kg to greater than 12 mg/kg. The PD_{50} (p.o.) in mice against *S. aureus* for these same compounds of formula (I) ranges from 1 mg/ml to greater than 12 mg/kg.

E. Pharmacokinetics Study of PDF Inhibitors in Mice

The pharmacokinetics of PDF compounds are determined in CD1 female out-bred mice (Charles River Laboratories) weighing 20-25 g. PDF compounds are formulated in 20% cyclodextrin (Aldrich) and filtered through 0.22 μm filter for sterilization. Either single compound or mixtures of 4-6 compounds as a cassette are administered i.v. and p.o. at 10 ml/kg. The dose ranged from 3-15 mg/kg for each compound. At 0.083, 0.25, 0.5, 1, 2, 4 and 7 hours after dosing, serum samples are collected via cardiac puncture under anesthesia. Groups of four mice are used for each time point. The serum samples are stored at -80°C until analysis.

The serum protein is precipitated by addition of acetonitrile. The samples after protein precipitation are analyzed by LC/MS/MS method. Standard curve is obtained for each compound and used for determination of compound concentration in serum. The pharmacokinetics parameters including T_{max} (time of maximum concentration), C_{max} (maximum concentration), $t_{1/2}$ (terminal half-life), and AUC (area under the curve), are calculated according to standard method. The oral bioavailability is calculated as the ratio of AUC of p.o. administration vs. the AUC administered i.v. The preferred compounds of formula (I) exhibit oral bioavailability greater than 70%.

The compounds of the present invention are, therefore, useful for the treatment and/or prevention of infectious disorders caused by a variety of bacterial or prokaryotic organisms. Examples include, but are not limited to, Gram positive and Gram negative aerobic and anaerobic bacteria, including *Staphylococci*, e.g. *S. aureus* and *S. epidermidis*; *Enterococci*, e.g. *E. faecalis* and *E. faecium*; *Streptococci*, e.g. *S. pneumoniae*; *Haemophilus*, e.g. *H. influenza*; *Moraxella*, e.g. *M. catarrhalis*; *Bacteroides*, e.g., *Bacteroides fragilis*, *Clostridium*, e.g., *Clostridium difficile*, *Niesseria*, e.g., *N. meningitidis* and *N. gonorrhoae*, *Legionella*, and *Escherichia*, e.g. *E. coli*. Other examples include *Mycobacteria*, e.g. *M. tuberculosis*; intercellular microbes, e.g. *Chlamydia* and *Rickettsiae*; and *Mycoplasma*, e.g. *M. pneumoniae*; and *Pseudomonas*, e.g. *P. aeruginosa*; *Helicobacter pylori*; and *parasites*, e.g. *Plasmodium falciparum*.

As used herein, an "infectious disorder" is any disorder characterized by the presence of a microbial infection, such as the presence of bacteria. Such infectious disorders include, for example, central nervous system infections, external ear infections, infections of the middle ear, such as acute otitis media, infections of the cranial sinuses, eye infections, infections of the oral cavity, such as infections of the teeth, gums and mucosa, upper respiratory tract

infections, lower respiratory tract infections, genitourinary infections, gastrointestinal infections, gynecological infections, septicemia, bone and joint infections, skin and skin structure infections, bacterial endocarditis, burns, antibacterial prophylaxis of surgery, antibacterial prophylaxis in immunosuppressed patients, such as patients receiving cancer chemotherapy, or organ transplant patients and chronic diseases caused by infectious organisms, e.g. arteriosclerosis.

The compounds may be used to treat a subject to treat, prevent, and/or reduce the severity of an infection. Subjects include animals, plants, blood products, cultures and surfaces such as those of medical or research equipment, such as glass, needles, surgical equipment and tubing, and objects intended for temporary or permanent implantation into an organism. Preferred animals include mammals, e.g. mice, rats, cats, dogs, cows, sheep, pigs, horses, swine, primates, such as rhesus monkeys, chimpanzees, gorillas, and most preferably humans. Treating a subject includes, but is not limited to, preventing, reducing, and/or eliminating the clinical symptoms caused by an infection of a subject by a microorganism; preventing, reducing, and/or eliminating an infection of a subject by a microorganism; or preventing, reducing, and/or eliminating contamination of a subject by a microorganism. The microorganism involved is preferably a prokaryote, more preferably a bacterium.

For the above uses the required dosage will of course vary depending on the mode of administration, the particular condition to be treated and the effect desired. The compositions may contain, for example, from about 0.1% by weight to about 99% by weight, e.g. from about 10-60% by weight, of the active material, depending on the method of administration. Where the compositions comprise dosage units, each unit will contain, for example, from about 1-1000 mg, e.g. 1-500 mg, of the active ingredient. The dosage as employed for adult human treatment will range, for example, from about 1-3000 mg per day, for instance 1500 mg per day depending on the route and frequency of administration. Such a dosage corresponds to about 0.015-50 mg/kg per day. Suitably the dosage is, for example, from about 5-20 mg/kg per day. Suitable unit dosage forms for oral administration comprise ca. 0.25-1500 mg active ingredient.

A "pharmaceutically acceptable carrier" means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes an excipient that is acceptable for veterinary use as well

as human pharmaceutical use. A "pharmaceutically acceptable carrier" as used in the specification and claims includes both one and more than one such carriers.

The compounds may be administered by any conventional route, e.g. locally or systemically e.g. orally, topically, parenterally, subdermally, or by inhalation and may be used for the treatment of bacterial infection in a subject such as animals, preferably, mammals, more preferably, humans.

The compounds of the invention may be formulated for administration in any convenient way for use in human or veterinary medicine, by analogy with other antibiotics. Such methods are known in the art (see, e.g. Remington's Pharmaceutical Sciences, Easton, PA: Mack Publishing Co.) and are not described in detail herein.

The compositions may be in any form known in the art, including but not limited to tablets, capsules, wafers, fast melts (without wafers), powders, granules, lozenges, creams or liquid preparations, such as oral or sterile parenteral solutions or suspensions. The compounds may also be administered in liposomal, micellar or microemulsion formulations. The compounds may also be administered as prodrugs, where the prodrug administered undergoes biotransformation in the treated mammal to a form which is biologically active.

The topical formulations of the present invention may be presented as, for instance, ointments, creams or lotions, solutions, salves, emulsions, plasters, eye ointments and eye or ear drops, impregnated dressings, transdermal patches, sprays and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams.

The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present, for example, from about 1% up to about 99% of the formulation. For example, they may form up to about 80% of the formulation.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example, syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrollidone; fillers, for example, lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example, magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example, potato starch; or

acceptable wetting agents, such as sodium lauryl sulphate. The tablets may be coated according to methods well-known in standard pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or another suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example, sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example, methyl or propyl p-hydroxybenzoate or sorbic acid, and, if desired, conventional flavoring or coloring agents.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, may be either suspended or dissolved in the vehicle or other suitable solvent. In preparing solutions, the compound may be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampule and sealing. Advantageously, agents such as a local anesthetic preservative and buffering agents may be dissolved in the vehicle. To enhance the stability, the composition may be frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The compound may be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compounds of the invention, e.g. the compounds of formula (I), may be administered in free form or in pharmaceutically acceptable salt form e.g. as indicated above. Such salts may be prepared in conventional manner and exhibit the same order of activity as the free compounds.

In accordance with the foregoing the present invention further provides:

1.1 Use of a compound of formula I in the manufacture of a medicament for treating and/or preventing an infectious disorder in a subject, such as a human or other animal subject, comprising administering to the subject an effective amount of a compound of the invention, of formula (I), a pharmaceutically acceptable salt thereof.

1.2 Use of a compound of formula I in the manufacture of a medicament for inhibiting peptidyl deformylase in a subject comprising administering to the subject an effective peptidyl deformylase inhibiting amount of a compound of the invention, of formula (I), a pharmaceutically acceptable salt thereof.

2. A compound of the invention, of formula (I), in free form or in a pharmaceutically acceptable salt form for use as a pharmaceutical, e.g. in any method as indicated under 1.1 or 1.2 above.

3. A pharmaceutical composition, e.g. for use in any of the methods as in 1.1 or 1.2 above comprising a compound of the invention, e.g. of formula (I), in free form or pharmaceutically acceptable salt form e.g. in association with a pharmaceutically acceptable diluent or carrier therefor.

4. A compound of the invention, of formula (1), a pharmaceutically acceptable salt for use as a pharmaceutical or in the preparation of a pharmaceutical composition for use in any method as indicated under 1.1 or 1.2 above.

"Treating" or "treatment" of a disease includes:

(1) preventing the disease, i.e. causing the clinical symptoms of the disease not to develop in a subject, e.g. a mammal, that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease,

(2) inhibiting the disease, i.e. arresting or reducing the development of the disease or its clinical symptoms, or

(3) relieving the disease, i.e. causing regression of the disease or its clinical symptoms.

An "effective peptidyl deformylase inhibiting amount" means the amount of a compound, a pharmaceutically acceptable salt thereof or a prodrug thereof, that when administered to a subject for treating an infectious disorder responsive to inhibition of peptidyl deformylase or for inhibiting peptidyl deformylase, is sufficient to inhibit peptidyl deformylase. The "effective peptidyl deformylase inhibiting amount" will vary depending on the compound, salt thereof or prodrug thereof, employed, the microorganism that is inhibited in the subject, the age,

weight, sex, medical condition, species, disorder and its severity, of the subject to be treated, and the route of administration, but may nevertheless be readily determined by one skilled in the art.

The compounds of the invention, e.g. of formula (I), a pharmaceutically acceptable salt thereof or prodrug thereof, may be administered alone or in combination with another therapeutic agent. Examples of such therapeutic agents include, but are not limited to, other antibacterial agents such as β-lactams e.g. penicillins; cephalosporins; carbapenems; ketolides; quinolones e.g. fluoroquinolones; macrolides e.g. clarithromycin, azithromycin or vancomycin; rifamycins; monobactams; isoniazid; licosamides; mupirocin; sulfonamides; phenicols; fosfomycin; glycopeptides; tetracyclines; streptogramins; chloramphenicol; and oxazolidinone, anti-inflammatory agents, e.g. corticosteroids or NSAID, analgesics, e.g. narcotic or non-opioic analgesics.

In accordance with the foregoing the present invention provides in a yet further aspect:

5. A method as defined above comprising co-administration, e.g. concomitantly or in sequence, of a therapeutically effective amount of a compound of the invention, e.g. of formula (I), a pharmaceutically acceptable salt thereof or a prodrug thereof, and a second therapeutic agent.

6. A therapeutic combination, e.g. a kit, comprising a) a compound of the invention, e.g. of formula (I), a pharmaceutically acceptable salt thereof or a prodrug thereof, and b) at least one second therapeutic agent. Component a) and component b) may be used concomitantly or in sequence. The kit may comprise instructions for its administration.

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

Example 1: Tablet Formulation

The following ingredients are mixed intimately and pressed into single scored tablets:

Quantity per Ingredient	Tablet (mg)
Compound of this invention	400
Cornstarch	50
Croscarmellose sodium	25
Lactose	120

Magnesium stearate	5

Example 2: Capsule Formulation

The following ingredients are mixed intimately and loaded into a hard-shell gelatin capsule:

Quantity per	Ingredient Capsule (mg)
Compound of this invention	200
Lactose, spray -- dried	148
Magnesium stearate	2

Example 3: Suspension Formulation

The following ingredients are mixed to form a suspension for oral administration:

Ingredient	Amount
Compound of this invention	1.0 g
Fumaric acid	0.5 g
Sodium chloride	2.0 g
Methyl paraben	0.15 g
Propyl paraben	0.05 g
Granulated sugar	25.0 g
Sorbitol (70% solution)	13.00 g
Veegum K (Vanderbilt Co.)	1.0 g
Flavoring	0.035 ml
Colorings	0.5 mg
Distilled water	q.s. to 100 ml

Example 4: Injectable Formulation

The following ingredients are mixed to form an injectable formulation:

Ingredient	Amount
Compound of this invention	0.2-20 mg
Sodium acetate buffer solution, 0.4 M	20 ml
HCl (1 N) or NaOH (1 N)	q.s. to suitable pH
Water (distilled, sterile)	q.s. to 20 ml

Example 5: Suppository Formulation

A suppository of total weight 2.5 g is prepared by mixing the compound of the invention with Witepsol® H-5 (triglycerides of saturated vegetable fatty acid; Riches-Nelson, Inc., New York), and has the following composition:

Compound of the invention	500 mg
Witepsol® H-15	2000 mg

The present invention is not limited to the clinical use of the compounds of the invention, i.e, in the treatment of infection in a subject. The compounds of the invention are useful to inhibit bacteria wherever it is desired to inhibit bacteria by contacting the bacteria with one or more compounds of the invention. Because of their ability to inhibit bacteria, the compounds of the invention are particularly useful to prevent contamination of cell cultures. As used in this context, the term "inhibit" means the suppression, control, stasis, or kill of bacteria. Eukaryotic cells, in particular animal cells, are often cultured for various reasons such as for their ability to produce substances such as proteins. Examples of such cells include Chinese hamster ovary cells (CHO cells), African green monkey kidney cells, hybridomoas constructed by fusing a parent cell (myeloma, etc.) with a useful substance-producing normal cell (lymphocyte, etc.), and the like. Typically, the compounds of the invention are incorporated into cell culture media at a bacteria inhibiting amount, e.g., a concentration of about 0.0001 to about 10 microgram/ml, preferably about 0.0001 to about 1 microgram/ml, and more preferably about 0.001 to about 0.1 microgram/ml. Any conventional cell culture medium known in the art can be used.

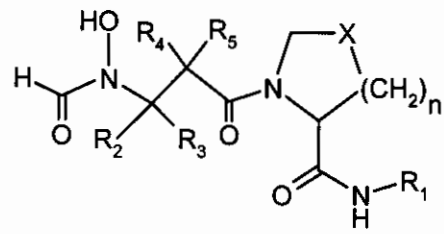
In accordance with the foregoing the present invention provides in a yet further aspect:

7. A method for preventing bacterial contamination of a cell culture medium comprising incorporating into said cell culture medium a bacteria inhibiting amount of a compound of the invention, e.g. of formula (I), or a pharmaceutically acceptable salt thereof.
8. A cell culture medium comprising. a bacteria inhibiting amount of a compound of the invention, e.g. of formula (I), or a pharmaceutically acceptable salt thereof.

The foregoing invention has been described in some detail by way of illustration and example. It will be obvious to one of skill in the art that changes and modifications may be practiced within the scope of the appended claims. All patents, patent applications and publications cited in this application are hereby incorporated by reference in their entirety.

CLAIMS:

1. A compound of formula (I)



(I)

wherein X is $-CH_2-$, -S-, -CH(OH)-, -CH(OR)-, -CH(SH)-, -CH(SR)-or -CH(F)-; wherein R is C_{1-7} alkyl;

R_1 is aryl or heteroaryl;

each of R_2, R_3, R_4 and R_5 independently is hydrogen or C_{1-7} alkyl, or (R_2 or R_3) and (R_4 or R_5) collectively form a C_{4-7} cycloalkyl; and

n is 0 to 2, provided that when n is 0, X is $-CH_2-$;

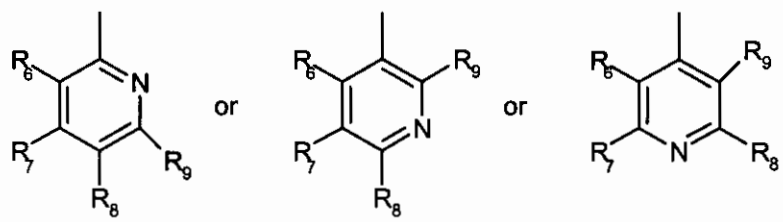
or a salt thereof,

wherein aryl refers to an aromatic carbocyclic group of 6 to 14 carbon atoms having a single ring or multiple condensed rings, and

wherein heteroaryl refers to a 4- to 7-membered, monocyclic aromatic heterocycle or a bicycle that is composed of a 4- to 7-membered, monocyclic aromatic heterocycle and a fused-on benzene ring, and wherein said heteroaryl has at least one hetero atom.

2. A compound according to claim 1, wherein X is $-CH_2$; R_1 is heteroaryl; R_2, R_3 and R_4 are hydrogen; R_5 is n-butyl and n is 1; or a salt thereof.

3. A compound according to claim 1 or 2, wherein heteroaryl is a residue of formula (II)

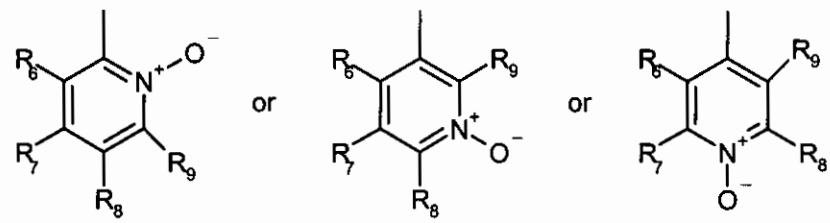


(II)

wherein each of R_6, R_7, R_8 and R_9 independently is hydrogen, C_{1-7}alkyl, substituted C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, acyl being –(O)CR where R is C_{1-7}alkyl, acyloxy being –

OC(O)R where R is C_{1-7}alkyl, SCN, halogen, cyano, nitro, thio-C_{1-7}alkoxy, phenyl, hetero C_{1-7}alkylaryl, C_{1-7}alkylsulfonyl, or formyl; or a salt thereof.

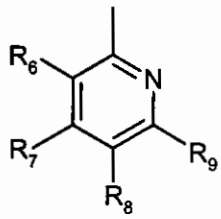
4. A compound according to claim 1 or 2, wherein heteroaryl is a residue of formula (III)



(III)

wherein each of R_6, R_7, R_8 and R_9 independently is hydrogen, C_{1-7}alkyl, substituted C_{1-7}alkyl, phenyl, halogen, hydroxy or C_{1-7}alkoxy.

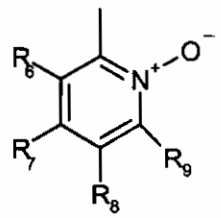
5. A compound according to any one of claims 1 to 3, wherein R_1 is a heteroaryl of formula (II.1)



(II.1)

wherein R_6, R_8 and R_9 are hydrogen and R_7 is ethyl or methoxy.

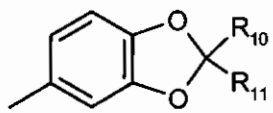
6. A compound according to any one of claims 1, 2, or 4, wherein R_1 is a heteroaryl of formula (III.1)



(III.1)

wherein R_6, R_7 and R_9 are hydrogen and R_8 is fluoro or trifluoromethyl.

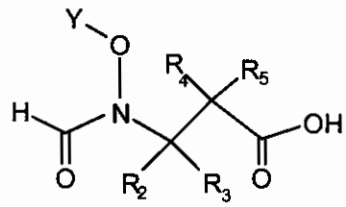
7. A compound according to claim 1, wherein R_1 is of formula (IV)



(IV)

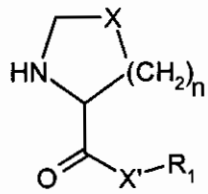
wherein each of R_{10} and R_{11} independently is hydrogen or halogen.

8. A process for preparing a compound of formula (I) according to claim 1 which process comprises reacting a compound of formula (V)



(V)

wherein R_2, R_3, R_4 and R_5 are as defined in claim 1 and Y is a hydroxy protecting group, or a functional derivative thereof, with a compound of formula (VI)



(VI)

wherein R_1, X and n are as defined in claim 1, and X' is NH or O, and where required, converting the resulting compounds obtained in free form into salt forms or vice versa.

9. A pharmaceutical composition comprising a compound of formula I according to claim 1, or a pharmaceutically acceptable salt, in association with a pharmaceutically acceptable diluent or carrier therefor.

10. A compound of formula I according to claim 1, or a pharmaceutically acceptable salt thereof for use as a pharmaceutical.

11. Use of a compound of formula I according to claim 1 in the manufacture of a medicament for treating and/or preventing an infectious disorder in a subject.

12. A cell culture medium comprising a bacteria inhibiting amount of a compound of formula I, or a pharmaceutically acceptable salt thereof.