INHIBITORS OF POST-PROLINE CLEAVING PROTEASES

The present invention relates to novel compounds that are inhibitors of post-proline aminopeptidases. The compounds are useful as antiproliferative agents and in the treatment of, *inter alia*, type 2 diabetes and impaired glucose tolerance.

BACKGROUND

The enzyme dipeptidyl peptidase IV, herein abbreviated DP-IV (and elsewhere as DAP-IV or DPP-IV) and also known by the classification EC.3.4.14.5, is a serine protease that cleaves the N-terminal dipeptide from peptides that begin with the sequence H-Xaa-Pro (where Xaa is any amino acid, although preferably a lipophilic one, and Pro is proline). It will also accept as substrates peptides that begin with the sequence H-Xaa-Ala (where Ala is alanine). DP-IV was first identified as a membrane-bound protein. More recently a soluble form has been identified.

Initial interest in DP-IV focussed on its role in the activation of T lymphocytes. DP-IV is identical to the T cell protein CD26. It was proposed that inhibitors of DP-IV would be capable of modulating T cell responsiveness, and so could be developed as novel immunomodulators. It was further suggested that CD26 was a necessary co-receptor for HIV, and thus that DP-IV inhibitors could be useful in the treatment of AIDS.

Attention was given to the role of DP-IV outside the immune system. It was recognised that DP-IV has a key role in the degradation of several peptide hormones, including growth hormone releasing hormone (GHRH) and glucagon-like peptide-1 and -2 (GLP-1 and GLP-2). Since GLP-1 is known to have a potentiating effect on the action of insulin in the control of post-prandial blood glucose levels it is clear that DP-IV inhibitors might also be usefully employed in the treatment of type II diabetes and impaired glucose tolerance. At least two DP-IV inhibitors are currently undergoing clinical trials to explore this possibility.

Several groups have disclosed inhibitors of DP-IV. While some leads have been found from random screening programs, the majority of the work in this field has been directed towards the investigation of substrate analogues. Inhibitors of DP-IV that are substrate analogues are disclosed in, for example, US 5,462,928, US 5,543,396,

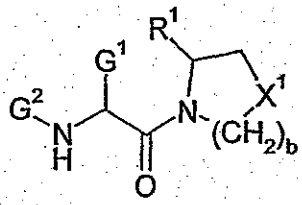
WO95/15309 (equivalent to US 5,939,560 and EP 0731789), WO98/19998 (equivalent to US 6,011,155), WO99/46272 and WO99/61431.

More recently a number of proteins have been found that share some of the enzymatic properties of DP-IV. Some, such as FAP and DPP-8, have sequence homology with DP-IV, while others, such as QPP, have no such homology but nevertheless mimic the aminodipeptidase activity of DP-IV. The physiological function of these newer proteases is still being investigated. FAP has been implicated in invasive processes such as cancer metastasis and endometriosis, and QPP appears to be involved in immune-cell apoptosis. It is also possible that some of these proteases share a common function. This redundancy would allow continuing normal physiological function in the event of a failure in the expression or function of one of the proteases.

In order to further define the roles of these newer proteases it is important to have the tools to manipulate selectively each one or the whole class. Therefore there exists a need for specific and potent inhibitors of each of these proteases, and also for potent non-specific inhibitors of the class of post-proline cleaving aminodipeptidases.

SUMMARY OF THE INVENTION

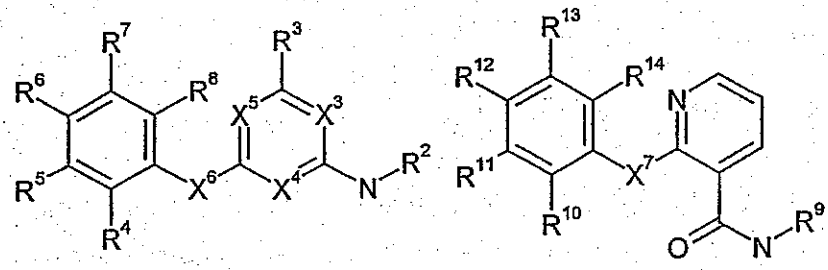
We disclose herein a series of novel compounds that are inhibitors of one or more post-proline cleaving proteases, and specifically compounds according to general formula **1**.



1

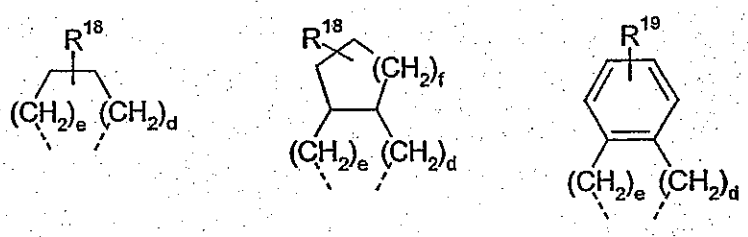
In general formula **1**, R^1 is H or CN, X^1 is O, S, CH_2, CHF, CF_2, $CH(CH_3)$, $C(CH_3)_2$ or CH(CN), and b is 1 or 2. G^1 is H or a group according to the formula $-CH_2-X^2-(CH_2)_a-G^3$ and G^2 is H or a group according to the formula $-CH_2-(CH_2)_a-G^3$, provided that one of G^1 and G^2 is H and the other is not H. X^2 is O, S or CH_2, and a is 0, 1 or 2, provided

that when a is 1 then X^2 is CH_2. G^3 is a group according to one of general formulae **2-4.**



2 **3** **4**

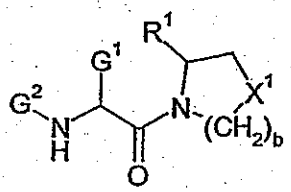
X^3, X^4 and X^5 are either nitrogen N or CH, provided that at least two of X^3, X^4 and X^5 are N. X^6 is either O or NH. R^2 is either H or alkyl. R^3 is selected from H, Cl, OH, O-alkyl, NH_2, NH-alkyl and N(alkyl)$_2$. R^4, R^5, R^6, R^7 and R^8 are selected from H, Br, Cl, F, CF_3, alkyl, acyl, OH, O-alkyl, NH_2, NH-alkyl, N(alkyl)$_2$, NO_2, NH-acyl, CO_2H, CO_2-alkyl, $CONH_2$, CONH-alkyl, CON(alkyl)$_2$ and CN. X^7 is CH_2, O, S or NH. R^9 is either H or alkyl. R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are selected from H, Br, Cl, F, CF_3, alkyl, acyl, OH, O-alkyl, NH_2, NH-alkyl, N(alkyl)$_2$, NO_2, NH-acyl, CO_2H, CO_2-alkyl, $CONH_2$, CONH-alkyl, CON(alkyl)$_2$ and CN. R^{15} and R^{16} are each independently H, alkyl, alkenyl, polyfluoroalkyl, aralkyl, aryl or CH_2-L-R^{17}, where L is a covalent bond, CH=CH, C≡C or -C_6H_4-, and R^{17} is H, alkyl or aryl, or R^{15} and R^{16} together are a group according to one of general formulae **5-7.**



5 **6** **7**

R^{18} is H, alkyl, aryl, OH, O-alkyl, NH_2, NH-alkyl or N(alkyl)$_2$, and R^{19} is H, alkyl, aryl, F, Cl, Br, CF_3, OH, O-alkyl, NH_2, NH-alkyl or N(alkyl)$_2$. The integers d and e are 0, 1, 2 or 3 such that d+e is 3, 4 or 5, and f is 1, 2 or 3. When R^{15} and R^{16} are both H then X^1 may not be S or CH_2 if b is 1.

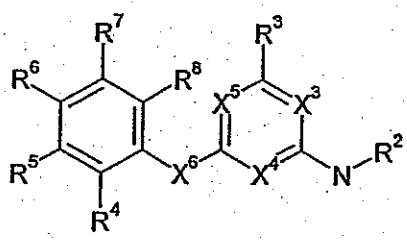
In a first aspect of the present invention, there is provided a compound according to general formula 1, or a pharmaceutically acceptable salt thereof,



1

wherein:

either G^1 is $-CH_2-X^2-(CH_2)_a-G^3$ and G^2 is H, or
G^2 is $-CH_2-(CH_2)_a-G^3$ and G^1 is H;
G^3 is selected from a group according to general formula 2, a group according to general formula 3, and a group according to general formula 4;



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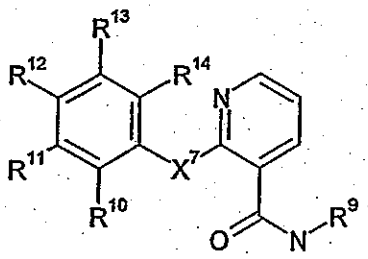

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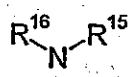


4

a is 0, 1 or 2;
b is 1 or 2;
X^1 is selected from CH_2, S, CF_2, CHF, $CH(CH_3)$, $C(CH_3)_2$, CH(CN) and O;
X^2 is selected from CH_2, O and S, provided that if a is 1 then X^2 is CH_2;
X^3, X^4 and X^5 are selected from N and CH, provided that at least two of X^3, X^4 and X^5 are N;
X^6 is selected from O and NH;
X^7 is selected from CH_2, O, S and NH;
R^1 is selected from H and CN;

R^2 is selected from H and alkyl;

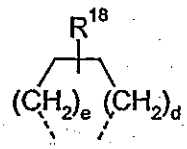
R^3 is selected from H, Cl, OH, O-alkyl, NH_2, NH-alkyl and $N(alkyl)_2$;

R^4, R^5, R^6, R^7 and R^8 are independently selected from H, Br, Cl, F, CF_3, alkyl, acyl, OH, O-alkyl, NH_2, NH-alkyl, $N(alkyl)_2$, NO_2, NH-acyl, CO_2H, CO_2-alkyl, $CONH_2$, CONH-alkyl, $CON(alkyl)_2$ and CN;

R^9 is selected from H and alkyl;

R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are independently selected from H, Br, Cl, F, CF_3, alkyl, acyl, OH, O-alkyl, NH_2, NH-alkyl, $N(alkyl)_2$, NO_2, NH-acyl, CO_2H, CO_2-alkyl, $CONH_2$, CONH-alkyl, $CON(alkyl)_2$ and CN;

R^{15} and R^{16} are independently selected from H, alkyl, alkenyl, polyfluoroalkyl, aralkyl, aryl and $-CH_2-L-R^{17}$, or R^{15} and R^{16} together form a group according to general formula 5, general formula 6 or general formula 7;



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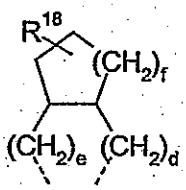

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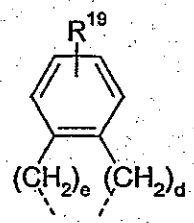


7

R^{17} is selected from H, alkyl and aryl;

R^{18} is selected from H, alkyl, aryl, OH, O-alkyl, NH_2, NH-alkyl and $N(alkyl)_2$;

R^{19} is selected from H, alkyl, aryl, F, Cl, Br, CF_3, OH, O-alkyl, NH_2, NH-alkyl and $N(alkyl)_2$;

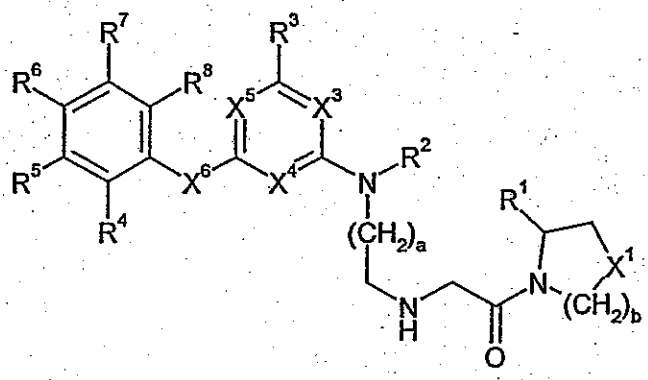
L is selected from a covalent bond, CH=CH, C≡C and $-C_6H_4-$;

d and e are selected from 0, 1, 2 and 3 such that d+e is 3, 4 or 5; and

f is selected from 1, 2 and 3;

provided that when R^{15} and R^{16} are both H and b is 1 then X^1 is not S or CH_2.

In a second aspect of the present invention, there is provided a compound according to general formula 9, or a pharmaceutically acceptable salt thereof,



9

wherein:

a is 1 or 2;

b is 1 or 2;

X^1 is selected from CH_2, S, CF_2, CHF, $CH(CH_3)$, $C(CH_3)_2$, CH(CN) and O;

X^3, X^4 and X^5 are selected from N and CH, provided that at least two of X^3, X^4 and X^5 are N;

X^6 is selected from O and NH;

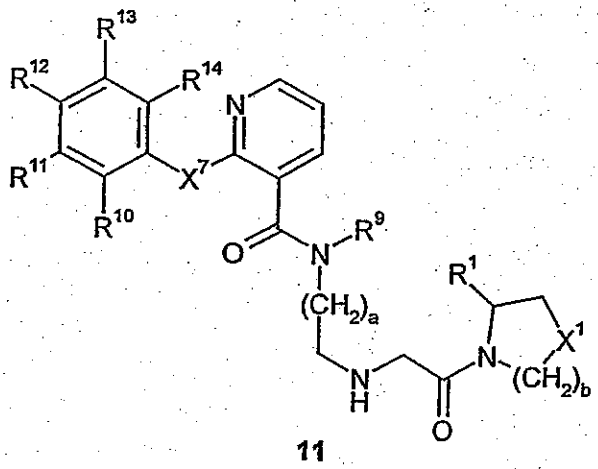
R^1 is selected from H and CN;

R^2 is selected from H and alkyl;

R^3 is selected from H, Cl, OH, O-alkyl, NH_2, NH-alkyl and $N(alkyl)_2$;

R^4, R^5, R^6, R^7 and R^8 are independently selected from H, Br, Cl, F, CF_3, alkyl, acyl, OH, O-alkyl, NH_2, NH-alkyl, $N(alkyl)_2$, NO_2, NH-acyl, CO_2H, CO_2-alkyl, $CONH_2$, CONH-alkyl, $CON(alkyl)_2$ and CN.

In a third aspect of the present invention, there is provided a compound according to general formula 11, or a pharmaceutically acceptable salt thereof,



11

wherein:

a is 1 or 2;

b is 1 or 2;

X^1 is selected from CH_2, S, CF_2, CHF, $CH(CH_3)$, $C(CH_3)_2$, CH(CN) and O;

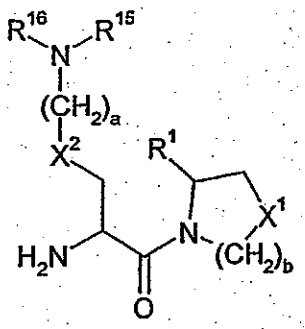
X^7 is selected from O, S, CH_2 and NH;

R^1 is selected from H and CN;

R^9 is selected from H and alkyl;

R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are independently selected from H, Br, Cl, F, CF_3, alkyl, acyl, OH, O-alkyl, NH_2, NH-alkyl, $N(alkyl)_2$, NO_2, NH-acyl, CO_2H, CO_2-alkyl, $CONH_2$, CONH-alkyl, $CON(alkyl)_2$ and CN is selected from H, Cl, OH, O-alkyl, NH_2, NH-alkyl and $N(alkyl)_2$.

In a fourth aspect of the present invention, there is provided a compound according to general formula 12, or a pharmaceutically acceptable salt thereof,



12

wherein:

a is 0, 1 or 2;

b is 1 or 2;

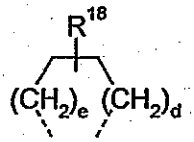
X^1 is selected from CH_2, S, CF_2, CHF, $CH(CH_3)$, $C(CH_3)_2$, CH(CN) and O;

X^2 is selected from CH_2, O and S, provided that if a is 1 then X^2 is CH_2;

R^1 is selected from H and CN;

R^{15} and R^{16} are each independently selected from H, alkyl, alkenyl, polyfluoroalkyl, aralkyl, aryl and CH_2-L-R^{17};

or R^{15} and R^{16} together are a group according to general formula 5, a group according to general formula 6 or a group according to general formula 7;



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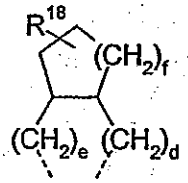

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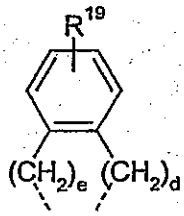


7

R^{17} is selected from H, alkyl and aryl;

R^{18} is selected from H, alkyl, aryl, OH, O-alkyl, NH_2, NH-alkyl and $N(alkyl)_2$;

R^{19} is selected from H, alkyl, aryl, F, Cl, Br, CF_3, OH, O-alkyl, NH_2, NH-alkyl and $N(alkyl)_2$;

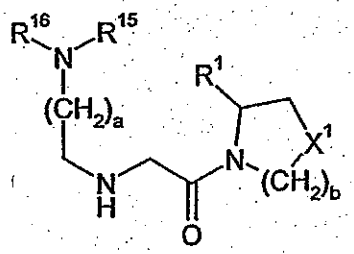
L is selected from a covalent bond, CH=CH, C≡C and -C_6H_4-;

d and e are selected from 0, 1, 2 and 3 such that d+e is 3, 4 or 5; and

f is selected from 1, 2 and 3;

provided that when R^{15} and R^{16} are both H and b is 1 then X^1 is not S or CH_2.

In a fifth aspect of the present invention, there is provided a compound according to general formula 13, or a pharmaceutically acceptable salt thereof,



13

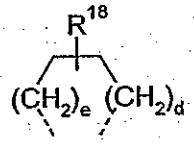
wherein:

X^1 is selected from CH_2, S, CF_2, CHF, $CH(CH_3)$, $C(CH_3)_2$, CH(CN) and O;

R^1 is selected from H and CN;

R^{15} and R^{16} are each independently selected from H, alkyl, alkenyl, polyfluoroalkyl, aralkyl, aryl and CH_2-L-R^{17};

or R^{15} and R^{16} together are a group according to general formula 5, a group according to general formula 6 or a group according to general formula 7;



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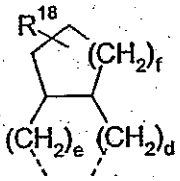

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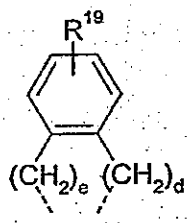


7

R^{17} is selected from H, alkyl and aryl;

R^{18} is selected from H, alkyl, aryl, OH, O-alkyl, NH_2, NH-alkyl and $N(alkyl)_2$;

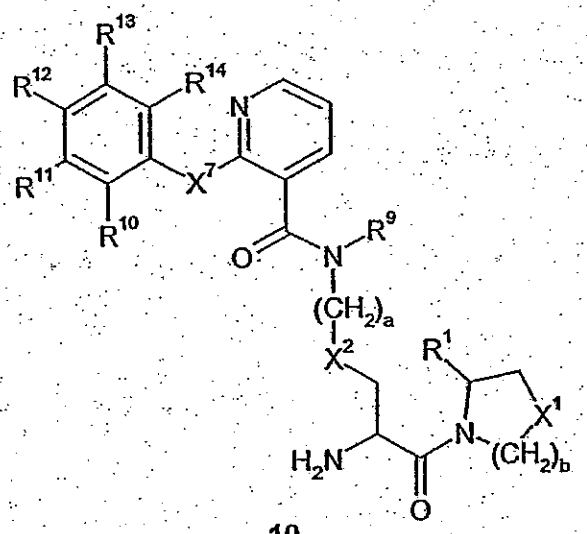
R^{19} is selected from H, alkyl, aryl, F, Cl, Br, CF_3, OH, O-alkyl, NH_2, NH-alkyl and $N(alkyl)_2$;

L is selected from a covalent bond, CH=CH, C≡C and $-C_6H_4-$;

d and e are selected from 0, 1, 2 and 3 such that d+e is 3, 4 or 5; and

f is selected from 1, 2 and 3.

In a sixth aspect of the present invention, there is provided a compound according to general formula 10, or a pharmaceutically acceptable salt thereof,



10

wherein:

a is 0, 1 or 2;
b is 1 or 2;
X^1 is selected from CH_2, S, CF_2, CHF, $CH(CH_3)$, $C(CH_3)_2$, CH(CN) and O;
X^2 is selected from CH_2, O and S, provided that if a is 1 then X^2 is CH_2;
X^7 is selected from O, S, CH_2 and NH;
R^1 is selected from H and CN;
R^9 is selected from H and alkyl;
R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are independently selected from H, Br, Cl, F, CF_3, alkyl, acyl, OH, O-alkyl, NH_2, NH-alkyl, $N(alkyl)_2$, NO_2, NH-acyl, CO_2H, CO_2-alkyl, $CONH_2$, CONH-alkyl, $CON(alkyl)_2$ and CN is selected from H, Cl, OH, O-alkyl, NH_2, NH-alkyl and $N(alkyl)_2$.

In a seventh aspect of the present invention, there is provided a use in the manufacture of a pharmaceutical composition, of a compound as defined above.

In an eighth aspect of the present invention, there is provided a composition as defined in the first or fourth aspect with the proviso that when X^1 = S, b= 1, R^1 = H, G^2 = H; G^1 is -CH_2-X^2-$(CH_2)_a$-G^3; a = 1, X^2 = CH_2, G_3 - $NR^{15}R^{16}$, and one of R^{15}, R^{16} = H, the other of R^{15}, R^{15}, R^{16} is not pyridyl, substituted pyridyl, pyrazinyl or substituted pyrazinyl.

In a ninth aspect of the present invention, there is provided a composition as defined in the first, fourth, fifth or eighth aspect with the proviso that when b=1, R^1 is H and X^1 is S; G^1 = H, G^2 is -CH_2-$(CH_2)_a$-G^3, a = 1, G^3 is $NR^{15}R^{16}$ and one of R^{15} and R^{16} is H the other of R^{15}, R^{16} is not pyridyl, substituted pyridyl, pyrazinyl or substituted pyrazinyl.

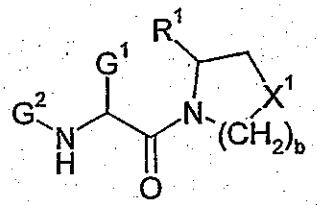
In a tenth aspect of the present invention, there is provided a composition as defined in the first, fourth, fifth, eighth or ninth aspect with the proviso that when b=1, R^1 is is CN and X^1 is CH_2; G^1 = H; G^2 is -CH_2-$(CH_2)_a$-G^3, a = 1; G^3 is $NR^{15}R^{16}$ and one of R^{15} and R^{16} is H, the other of R^{15}, R^{16} is not pyridyl, substituted pyridyl, pyrazinyl or substituted pyrazinyl.

In an eleventh aspect of the present invention, there is provided a composition as defined in the first, fourth, fifth, eighth, ninth or tenth aspect with the proviso that when G^2 = H; G^1 = $-CH_2-X^2-(CH_2)_a-G^3$; X^2 is CH_2; a = 1; G^3 = $NR^{15}R^{16}$ and R^{15} = R^{16} = H; b is not 2 when X^1 is O or CH_2; and b is not 1 when X^1 is CH_2.

Preferred compositions are inhibitors of non-membrane associated post-proline cleaving proteases. The most preferred compositions are selective for non-membrane associated proteases (e.g. for example inhibitors of one or more of QPP, DPP-8 and/or DPP-9).

DETAILED DESCRIPTION OF THE INVENTION

In a first aspect, the present invention relates to a series of novel α-amino acyl derivatives of saturated nitrogen-containing heterocycles according to general formula **1**.

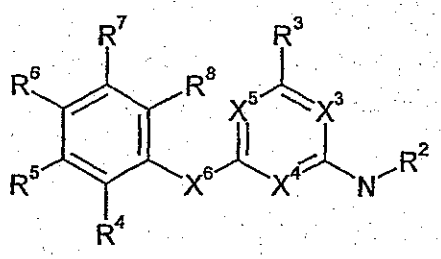


1

In general formula **1**, the group R^1 is either a hydrogen atom H or a nitrile group CN. The group X^1 is selected from an oxygen atom O, a sulphur atom S, a methylene group CH_2, a monofluoromethylene group CHF,a difluoromethylene group CF_2, an ethylidene group $CH(CH_3)$, a 2-propylidene group $C(CH_3)_2$ and a cyanomethylene group CH(CN). The integer b is either 1 or 2, such that the nitrogen-containing ring has 5 or 6 members.

The group G^1 is either H or a group according to the formula $-CH_2-X^2-(CH_2)_a-G^3$ and the group G^2 is either H or a group according to the formula $-CH_2-(CH_2)_a-G^3$, provided that one of G^1 and G^2 is H and the other is not H. The group X^2 is selected from O, S and CH_2. The integer a is **0**, 1 or 2, provided that when a is 1 then X^2 is CH_2.

The group G^3 is selected from a group according to general formula **2**, a group according to general formula **3** and a group according to general formula **4**.



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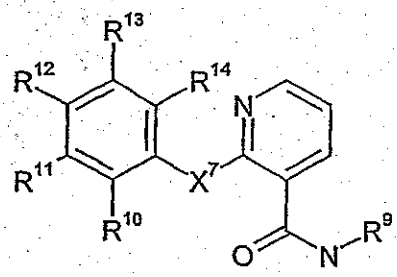

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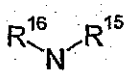
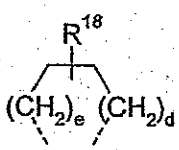


4

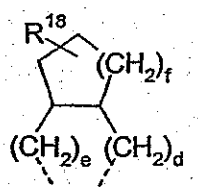
In general formula **2**, the groups X^3, X^4 and X^5 are selected from nitrogen N and methine CH, provided that at least two of X^3, X^4 and X^5 are nitrogen. Preferably X^3, X^4 and X^5 are all nitrogen. The group X^6 is selected from O and NH. R^2 is selected from H and alkyl. R^3 is selected from H, Cl, OH, O-alkyl, NH_2, NH-alkyl and $N(alkyl)_2$. R^4, R^5, R^6, R^7 and R^8 are independently selected from H, Br, Cl, F, CF_3, alkyl, acyl, OH, O-alkyl, NH_2, NH-alkyl, $N(alkyl)_2$, NO_2, NH-acyl, CO_2H, CO_2-alkyl, $CONH_2$, CONH-alkyl, $CON(alkyl)_2$ and CN.

In general formula **3**, the group X^7 is selected from CH_2, O, S and NH. R^9 is selected from H and alkyl. R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are independently selected from H, Br, Cl, F, CF_3, alkyl, acyl, OH, O-alkyl, NH_2, NH-alkyl, $N(alkyl)_2$, NO_2, NH-acyl, CO_2H, CO_2-alkyl, $CONH_2$, CONH-alkyl, $CON(alkyl)_2$ and CN.

In general formula **4**, R^{15} and R^{16} are each independently selected from H, alkyl, alkenyl, polyfluoroalkyl, aralkyl, aryl and CH_2-L-R^{17}, where L is selected from a covalent bond, CH=CH, C≡C and -C_6H_4- and R^{17} is selected from H, alkyl and aryl, or R^{15} and R^{16} together are a group selected from general formula **5**, general formula **6** and general formula **7**.



5



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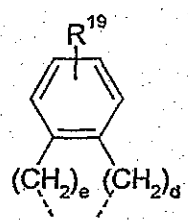


7

In these general formulae, the group R^{18} is selected from H, alkyl, aryl, OH, O-alkyl, NH_2, NH-alkyl and N(alkyl)$_2$, and the group R^{19} is selected from H, alkyl, aryl, F, Cl, Br, CF_3, OH, O-alkyl, NH_2, NH-alkyl and N(alkyl)$_2$. The integers d and e are selected from 0, 1, 2 and 3 such that d+e is 3, 4 or 5, and the integer f is selected from 1, 2 and 3.

When R^{15} and R^{16} are both H then X^1 may not be S or CH_2 if b is 1.

The term alkyl, as used herein, denotes saturated hydrocarbon groups with between 1 and 10 carbon atoms, including straight-chain, branched and mono- and polycycloalkyl groups, such as methyl, ethyl, propyl, isopropyl, *n*-butyl, *tert*-butyl, cyclopentyl, cyclohexylmethyl, 2-cyclohexyl-2-propyl, bicyclo[2.2.2]octyl and the like.

The term alkenyl, as used herein, denotes monounsaturated hydrocarbon groups with between 2 and 10 carbon atoms, including straight-chain, branched and mono- and polycycloalkenyl groups, such as vinyl, allyl, methallyl, cyclohex-3-enyl and the like.

The term aryl, as used herein, denotes monocyclic and fused bicyclic aromatic groups, including carbocyclic groups, such as phenyl and naphthyl, and heteroaryl groups with up to three heteroatoms selected from nitrogen, oxygen and sulphur, such as pyrrolyl, furyl, thienyl, pyrazolyl, imidazolyl, oxazolyl, isothiazolyl, pyridyl, pyrimidinyl, indolyl, quinolinyl and the like. Unless otherwise specified, aryl groups may optionally be substituted with up to three groups independently selected from alkyl, OH, O-alkyl, Cl, F, Br, NH_2, NH-alkyl, N(alkyl)$_2$, CO_2H, CO_2-alkyl, $CONH_2$, CONH-alkyl, CON(alkyl)$_2$, NO_2 and CN.

The term aralkyl, as used herein, denotes alkyl groups that are substituted by, or fused to, one or more aryl groups, including benzyl, phenethyl, indanyl, fluorenyl and the like.

The term acyl, as used herein, denotes a group selected from H-CO, alkyl-CO, aryl-CO and aralkyl-CO, including formyl, acetyl, benzoyl, phenylacetyl and the like.

The term polyfluoroalkyl, as used herein, denotes an alkyl group wherein all the hydrogen atoms on one or more of the carbon atoms are replaced by fluorine atoms, including trifluoromethyl, 2,2,2-trifluoroethyl and the like.

In one preferred embodiment of the invention R^1 is H.

In another preferred embodiment of the invention R^1 is CN.

In another preferred embodiment of the invention X^1 is CH_2.

In another preferred embodiment of the invention X^1 is S.

In another preferred embodiment of the invention b is 1.

In another preferred embodiment of the invention b is 2.

In another preferred embodiment of the invention a is 0.

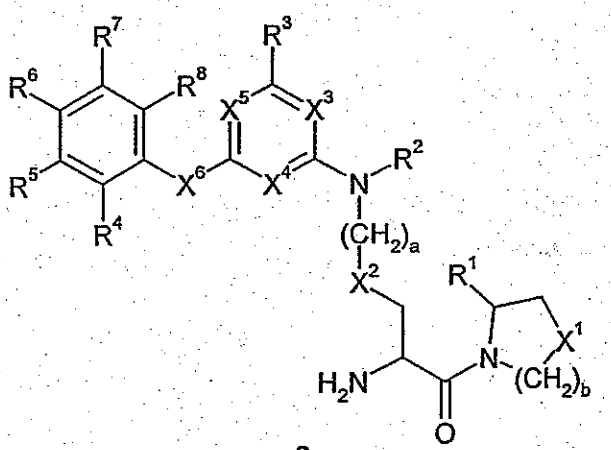
In another preferred embodiment of the invention a is 0 and X^2 is CH_2.

In another preferred embodiment of the invention a is 1.

In another preferred embodiment of the invention a is 1 and X^2 is CH_2.

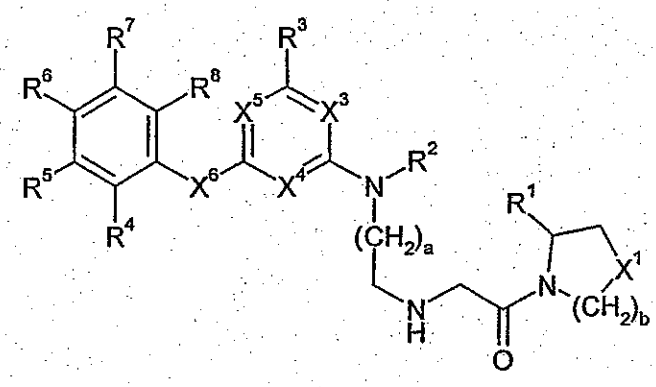
In another preferred embodiment of the invention a is 2 and X^2 is CH_2.

In another preferred embodiment of the invention the compound is a compound according to general formula 8.



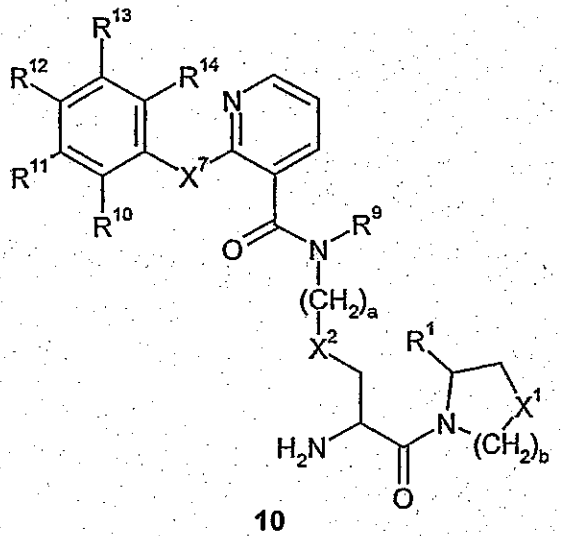
8

In another preferred embodiment of the invention the compound is a compound according to general formula **9**.



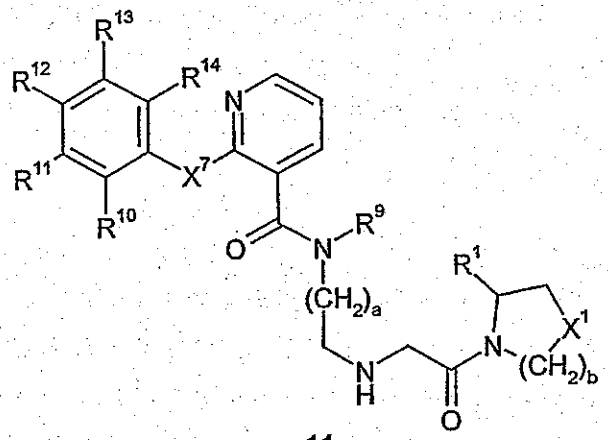
9

In another preferred embodiment of the invention the compound is a compound according to general formula **10**.



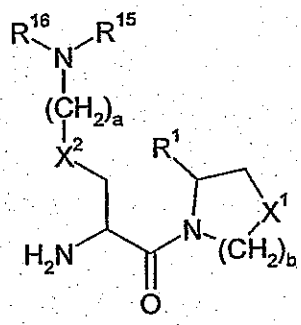
10

In another preferred embodiment of the invention the compound is a compound according to general formula **11**.



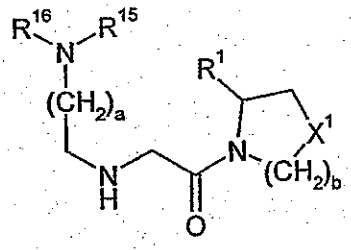
11

In another preferred embodiment of the invention the compound is a compound according to general formula **12**.



12

In another preferred embodiment of the invention the compound is a compound according to general formula **13**.



13

It will be recognised that certain of the compounds within the scope of the present invention are capable of forming salts with suitable acids or bases. To the extent that such salts are pharmaceutically acceptable they are included within the scope of this invention

It will further be recognised that certain of the compounds within the scope of the present invention are capable of existing as optical isomers, such as enantiomers and diastereomers. All such optical isomers and mixtures thereof, including but not limited to racemates, are included within the scope of the invention.

The compounds of the present invention are inhibitors of post-proline cleaving proteases such as DPP-IV, QPP, FAP, DPP-8 (DPRP-1) and DPP-9 (DPRP-2). As such they may be useful in the treatment of diseases in which dysregulation of these enzymes or their endogenous substrates plays a role or the disease is ameliorated by inhibition of such enzymes. Accordingly, in further aspects, the present invention provides for the use of compounds according to the present invention in the preparation of pharmaceutical compositions, and for the use of such compositions a therapeutic agents.

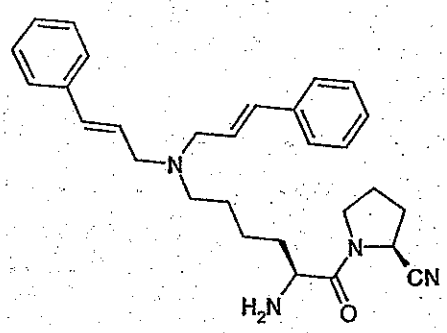
Preferred compositions which are inhibitors for QPP may have G^2=H, b = 1 or 2 and/or a = 0 or 1. Further preferred compositions having b=2 include G1 groups having a=0 or 1 and X^2 is CH_2. Further preferred compositions having b=2 have X^1=CH_2 or S, for example Example 38 of Table 2. Further preferred compositions having b=1 include G1 groups having a=0 or 1 and X^2 is CH_2. . Further preferred compositions having b=1 have X^1= S or CH_2 or CF_2, for example, Example 42 of Table 2.

The compounds of the present invention can be prepared by methods generally known in the art and illustrated in the following non-limiting examples.

EXAMPLES

EXAMPLE 1

(2*S*)-1-[*N*$^{\alpha}$,*N*$^{\alpha}$-(Dicinnamyl)-L-lysinyl]pyrrolidine-2-carbonitrile dihydrochloride



A. (N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysinyl)-L-prolinamide

N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysine (5g, 10.7mmol) was dissolved in CH_2Cl_2 (100mL). The solution was cooled to 0°C, L-prolinamide (1.78g, 11.7mmol) and PyBOP® (6.7g, 12.8mmol) were added, and the pH adjusted to pH9 with triethylamine. After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (200mL). The solution was washed with 0.3M $KHSO_4$ (2 x 50mL), sat. $NaHCO_3$ (2 x 50mL), water (2 x 50mL) and brine (1 x 50mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 2% methanol, 98% chloroform) to give a colourless oil identified as (N^{α}-(*tert*-butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysinyl)-L-prolinamide (4.05g, 7.2mmol, 67%).

B. (2*S*)-1-(N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysinyl)pyrrolidine-2-carbonitrile

(N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysinyl)-L-prolinamide (3.95g, 7.02mmol) was dissolved in dry THF (100mL). The solution was cooled to 0°C, triethylamine (1.4g, 14mmol) was added followed by the slow addition of trifluoroacetic anhydride (2.97g, 14.1mmol). The pH was adjusted to pH9 with triethylamine. After 30min the reaction mixture was diluted with ethyl acetate (100mL), washed with water (1 x 50mL) and brine (1 x 50mL), dried (Na_2SO_4) and evaporated *in vacuo* to give an orange oil. The residue was purified by flash chromatography on silica gel (eluant: 60% pet ether, 40% ethyl acetate) to give a colourless oil identified as (2*S*)-1-(N^{α}-(*tert*-butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysinyl)pyrrolidine-2-carbonitrile (3.3g, 6.11mmol, 87%).

C. (2*S*)-1-(N^{α}-(*tert*-Butyloxycarbonyl)-L-lysinyl)pyrrolidine-2-carbonitrile

(2*S*)-1-(N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysinyl)-pyrrolidine-2-carbonitrile (3.1g, 5.7mmol) was dissolved in THF (80mL). Diethylamine (20mL) was added. After 2h at room temperature the solvent was removed *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 90% chloroform, 7% methanol, 3% triethylamine) to give a colourless oil identified as (2*S*)-1-(N^{α}-(*tert*-butyloxycarbonyl)-L-lysinyl)pyrrolidine-2-carbonitrile (1.63g, 5.03mmol, 89%).

D. (2*S*)-1-(N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω},N^{ω}-(dicinnamyl)-L-lysinyl)pyrrolidine-2-carbonitrile

(2*S*)-1-(N^{α}-(*tert*-Butyloxycarbonyl)-L-lysinyl)pyrrolidine-2-carbonitrile (100mg, 0.31mmol) was dissolved in methanol (25mL). To this solution was added trans-cinnamaldehyde (170mg, 1.18mmol). After 30mins sodium triacetoxyborohydride (330mg, 1.56mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 2% methanol, 98% chloroform) to give a colourless oil identified as (2*S*)-1-(N^{α}-(*tert*-butyloxycarbonyl)-N^{ω},N^{ω}-(dicinnamyl)-L-lysinyl)pyrrolidine-2-carbonitrile (38mg, 0.068mmol, 11%). Further elution with 9% methanol, 90% chloroform and 1% acetic acid gave a colourless oil identified as (2*S*)-1-(N^{α}-(*tert*-butyloxycarbonyl)-N^{ω}-(cinnamyl)-L-lysinyl)pyrrolidine-2-carbonitrile (32mg, 0.073mmol, 12%)

E. (2*S*)-1-[N^{ω},N^{ω}-(Dicinnamyl)-L-lysinyl]pyrrolidine-2-carbonitrile dihydrochloride

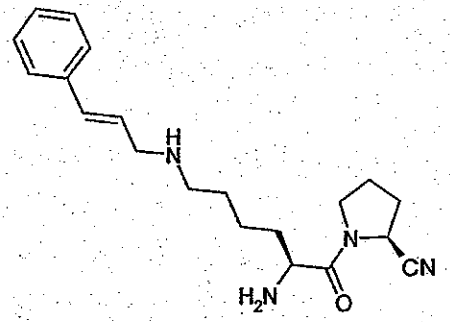
(2*S*)-1-(N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω},N^{ω}-(dicinnamyl)-L-lysinyl)pyrrolidine-2-carbonitrile (32mg, 0.057mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as (2*S*)-1-[N^{ω},N^{ω}-(dicinnamyl)-L-lysinyl]pyrrolidine-2-carbonitrile dihydrochloride (37mg, 0.053mmol, 93%).

$[M+H]^+ = 457.3$

^1H NMR (CD_3OD): δ 1.35-1.55 (2H, m), 1.75-2.00 (2H, m), 2.05-2.23 (6H, m), 3.10-3.29 (4H, m), 3.61-3.68 (2H, m), 4.00-4.03 (4H, m), 4.20-4.30 (1H, m), 4.82-4.93 (1H, m), 6.34-6.39 (2H, m), 6.94 (2H, d, J = 5.8Hz), 7.31-7.37 (6H, m), 7.39-7.53 (4H, m) ppm.

EXAMPLE 2

(2*S*)-1-[*N*$^{\omega}$-(Cinnamyl)-L-lysinyl]pyrrolidine-2-carbonitrile dihydrochloride



A. (2*S*)-1-[*N*$^{\omega}$-(Cinnamyl)-L-lysinyl]pyrrolidine-2-carbonitrile dihydrochloride

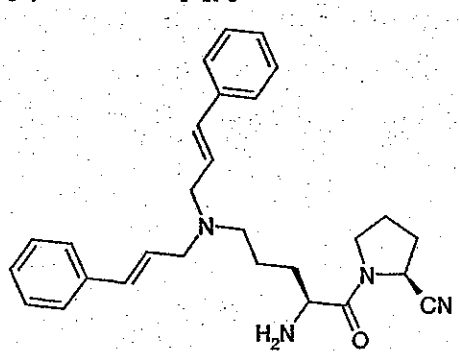
(2*S*)-1-(*N*$^{\alpha}$-(*tert*-Butyloxycarbonyl)-*N*$^{\omega}$-(cinnamyl)-L-lysinyl)pyrrolidine-2-carbonitrile (32mg, 0.057mmol). was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as (2*S*)-1-[*N*$^{\omega}$-(cinnamyl)-L-lysinyl]pyrrolidine-2-carbonitrile dihydrochloride (37mg, 0.053mmol, 93%).

$[M+H]^+ = 341.5$

^{1}H NMR (CD_3OD): δ 1.29-1.55 (2H, m), 1.72-1.80 (2H, m), 1.90-2.11 (2H, m), 2.16-2.29 (6H, m), 3.02-3.09 (2H, m), 3.65-3.69 (2H, m), 3.78-3.82 (2H, m), 4.23-4.27 (1H, m), 4.81-4.82 (1H, m), 4.91-4.99 (1H, m), 6.21-6.32 (1H, m), 6.86 (1H, d, J=6.1Hz), 7.26-7.35 (3H, m), 7.37-7.40 (2H, m) ppm.

EXAMPLE 3

(2*S*)-1-[*N*$^{\omega}$,*N*$^{\omega}$-(Dicinnamyl)-L-ornithinyl]pyrrolidine-2-carbonitrile dihydrochloride



A. (2*S*)-1-(N^{α}-(*tert*-Butyloxycarbonyl)-L-ornithyl)pyrrolidine-2-carbonitrile

(2*S*)-1-(N^{α}-(*tert*-Butyloxycarbonyl)-L-ornithyl)pyrrolidine-2-carbonitrile was prepared by the method described for the lysine derivative in Example 1.

B. (2*S*)-1-(N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω},N^{ω}-(dicinnamyl)-L-ornithinyl)pyrrolidine-2-carbonitrile

(2*S*)-1-(N^{α}-(*tert*-Butyloxycarbonyl)-L-ornithinyl)pyrrolidine-2-carbonitrile (200mg, 0.65mmol) was dissolved in methanol (25mL). To this solution was added trans-cinnamaldehyde (180mg, 1.25mmol). After 30mins sodium triacetoxyborohydride (343mg, 1.63mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography (eluant: 2% methanol, 98% chloroform) to give a colourless oil identified as (2*S*)-1-(N^{α}-(*tert*-butyloxycarbonyl)-N^{ω},N^{ω}-(dicinnamyl)-L-ornithinyl)-pyrrolidine-2-carbonitrile (77mg, 0.14mmol, 22%). Further elution with 9% methanol, 90% chloroform and 1% acetic acid gave a colourless oil identified as (2*S*)-1-(N^{α}-(*tert*-butyloxycarbonyl)-N^{ω}-(cinnamyl)-L-ornithinyl)pyrrolidine-2-carbonitrile (78mg, 0.18mmol, 28%).

C. (2*S*)-1-[N^{ω},N^{ω}-(Dicinnamyl)-L-ornithinyl]pyrrolidine-2-carbonitrile dihydrochloride

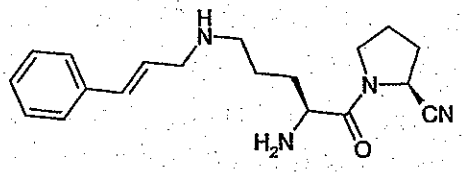
(2*S*)-1-(N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω},N^{ω}-(dicinnamyl)-L-ornithinyl)pyrrolidine-2-carbonitrile (67mg, 0.12mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as (2*S*)-1-[N^{ω},N^{ω}-(dicinnamyl)-L-ornithinyl]pyrrolidine-2-carbonitrile dihydrochloride (82mg, 0.12mmol, 100%).

$[M+H]^+ = 443.3$

^{1}H NMR (CD_3OD): δ 1.98-2.12 (4H, m), 2.22-2.29 (4H, m), 3.27-3.31 (4H, m), 3.62-3.67 (2H, m), 3.96 (4H, d, J=7.5Hz), 4.30-4.40 (1H, m), 4.80-4.83 (1H, m), 6.34-6.41 (2H, m), 6.96 (2H, d, J=15.6Hz), 7.31-7.39 (6H, m), 7.49-7.53 (4H, m) ppm.

EXAMPLE 4

(2*S*)-1-[*N*$^{\omega}$-(Cinnamyl)-L-ornithinyl]pyrrolidine-2-carbonitrile dihydrochloride



A. (2*S*)-1-[*N*$^{\omega}$-(Cinnamyl)-L-ornithinyl]pyrrolidine-2-carbonitrile dihydrochloride

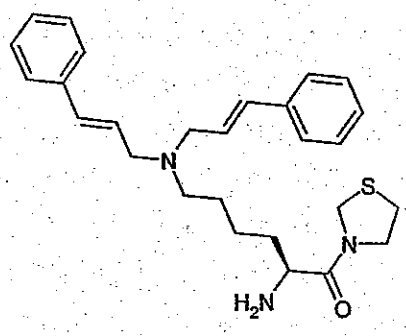
(2*S*)-1-(*N*$^{\alpha}$-(*tert*-Butyloxycarbonyl)-*N*$^{\omega}$-(cinnamyl)-L-ornithinyl)pyrrolidine-2-carbonitrile (71mg, 0.17mmol). was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as (2*S*)-1-[*N*$^{\omega}$-(cinnamyl)-L-ornithinyl]pyrrolidine-2-carbonitrile dihydrochloride (91mg, 0.16mmol, 100%).

$[M+H]^+$ = 327.5

^{1}H NMR (CD_3OD): δ 1.70-1.88 (2H, m), 1.97-2.01 (2H, m), 2.14-2.32 (4H, m), 3.08-3.13 (2H, m), 3.29-3.31 (3H, m), 3.68-3.71 (2H, m), 3.79-3.82 (2H, m), 4.29-4.31 (1H, m), 4.87-4.91 (1H, m), 6.29-6.31 (1H, m), 6.86 (1H, d, J=15.8Hz), 7.29-7.30 (3H, m), 7.44-7.48 (2H, m) ppm.

EXAMPLE 5

3-[*N*$^{\omega}$-*N*$^{\omega}$-(Dicinnamyl)-L-lysinyl]thiazolidine dihydrochloride



A. 3-[N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysinyl]-thiazolidine

N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysine (2.73g, 6mmol) was dissolved in CH_2Cl_2 /DMF (9:1, 100mL). To this solution at 0°C were added 1-hydroxybenzotriazole hydrate (1.53g, 10mmol), water-soluble carbodiimide (1.34g, 7mmol), thiazolidine (1.28g, 18mmol) and N-methylmorpholine (1.0g, 10mmol). After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (100mL). The solution was washed with 0.3M $KHSO_4$ (2 x 25mL), sat. $NaHCO_3$ (2 x 25mL), water (2 x 25mL) and brine (1 x 25mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 75% ethyl acetate, 25% pet. ether) to give a white solid identified as 3-[N^{α}-(*tert*-butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysinyl]thiazolidine (2.55g, 4.85mmol, 81%).

B. 3-[N^{α}-(*tert*-Butyloxycarbonyl)-L-lysinyl]thiazolidine

3-[N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysinyl]thiazolidine (1.15g, 2.13mmol) was dissolved in acetonitrile (20mL). Diethylamine (5mL) was added. After 90min at room temperature the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (eluant: 90% chloroform, 7% methanol, 3% triethylamine) to give a pale yellow oil identified as 3-[N^{α}-(*tert*-butyloxycarbonyl)-L-lysinyl]thiazolidine (530mg, 1.67mmol, 78%).

C. 3-(N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω},N^{ω}-(dicinnamyl)-L-lysinyl)thiazolidine

3-(N^{α}-(*tert*-Butyloxycarbonyl)-L-lysinyl)thiazolidine (200mg, 0.6mmol) was dissolved in methanol (25mL). To this solution was added trans-cinnamaldehyde (400mg, 3.0mmol). After 30mins sodium triacetoxyborohydride (534mg, 2.54mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 2% methanol, 98% chloroform) to give a colourless oil identified as 3-(N^{α}-(*tert*-butyloxycarbonyl)-N^{ω},N^{ω}-(di-cinnamyl)-L-lysinyl)thiazolidine (139mg, 0.25mmol, 40%).

D. 3-[N^{ω},N^{ω}-(Dicinnamyl)-L-lysinyl]thiazolidine dihydrochloride

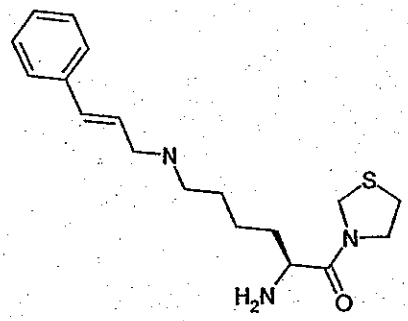
3-(N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω},N^{ω}-(di-cinnamyl)-L-lysinyl)thiazolidine (139mg, 0.25mmol). was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a pale brown solid identified as 3-[N^{ω},N^{ω}-(dicinnamyl)-L-lysinyl]thiazolidine dihydrochloride (127mg, 0.24mmol, 96%).

$[M+H]^+ = 450.2$

^1H NMR (CD_3OD): δ 1.49-1.55 (2H,m), 1.89-1.98 (4H, m), 3.01-3.30 (4H, m), 3.4-3.5 (4H, m), 3.7-3.9 (3H, m), 4.0-4.2 (3H, m), 4.2-4.8 (2H, br m), 6.38-6.44 (2H, m), 6.99-6.93 (2H, m), 7.34-7.37 (5H, m), 7.51-7.60 (4H, m) ppm.

EXAMPLE 6

3-[N^{ω},N^{ω}-(Cinnamyl)-L-lysinyl]thiazolidine dihydrochloride



A. 3-(N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω},N^{ω}-(cinnamyl)-L-lysinyl)thiazolidine

3-(N^{α}-(*tert*-Butyloxycarbonyl)-L-lysinyl)thiazolidine (200mg, 0.6mmol) was dissolved in methanol (25mL). To this solution was added trans-cinnamaldehyde (400mg, 3.0mmol). After 30mins sodium triacetoxyborohydride (534mg, 2.54mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 1% triethylamine, 5% methanol, 94% chloroform) to give a colourless oil identified as 3-(N^{α}-(*tert*-butyloxycarbonyl)-N^{ω},N^{ω}-(cinnamyl)-L-lysinyl)thiazolidine (215mg, 0.50mmol, 83%).

B. 3-[N^{ω},N^{ω}-(Cinnamyl)-L-lysinyl]thiazolidine dihydrochloride

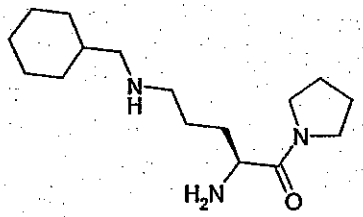
3-(N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω},N^{ω}-(cinnamyl)-L-lysinyl)thiazolidine (215mg, 0.5mmol). was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a pale brown solid identified as 3-[N^{ω},N^{ω}-(cinnamyl)-L-lysinyl]thiazolidine dihydrochloride (160mg, 0.40mmol, 79%).

$[M+H]^+ = 334.4$

^{1}H NMR (CD_3OD): δ 1.28-1.30 (1H, m), 1.51-1.53 (1H, m), 1.79-1.78 (1H, m), 1.93-1.98 (2H, m), 2.9-3.3 (5H, m), 3.6-3.8 (5H, m), 4.30-4.70 (5H, m), 6.2-6.3 (1H, m), 6.85-6.91(1H, m), 7.1-7.7 (5H, m) ppm.

EXAMPLE 7

1-[N^{ω}-(Cyclohexylmethyl)-L-ornithinyl]pyrolidine dihydrochloride



A. 1-[N^{ω}-(Benzyloxycarbonyl)-N^{α}-(*tert*-butyloxycarbonyl)-L-ornithinyl]pyrrolidine

N^{ω}-(Benzyloxycarbonyl)-N^{α}-(*tert*-butyloxycarbonyl)-L-ornithine (5.49g, 15mmol) was dissolved in CH_2Cl_2 /DMF (9:1, 100mL). To this solution at 0°C was added 1-hydroxybenzotriazole hydrate (3.37g, 22mmol), water-soluble carbodiimide (3.46g, 18mmol), pyrrolidine (1.28g, 18mmol) and N-methylmorpholine (2.0g, 20mmol). After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (200mL). The solution was washed with 0.3M $KHSO_4$ (2 x 50mL), sat. $NaHCO_3$ (2 x 50mL), water (2 x 50mL) and brine (1 x 50mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 90% ethyl acetate, 10% pet. ether) to give a colourless oil identified as 1-[N^{ω}-(benzyloxycarbonyl)-N^{α}-(*tert*-butyloxycarbonyl)-L-ornithinyl]pyrrolidine (5.15g, 12.3mmol, 82%).

B. 1-[N^{α}-(*tert*-Butyloxycarbonyl)-L-ornithinyl]pyrrolidine

1-[N^{ω}-(Benzyloxycarbonyl)-N^{α}-(*tert*-butyloxycarbonyl)-L-ornithinyl]pyrrolidine (2.15g, 5.13mmol) was dissolved in methanol (80mL). This solution was hydrogenated over 10% Pd/C (400mg). After 2h the catalyst was filtered off and washed with methanol (50mL). The combined filtrates were evaporated *in vacuo* to give an off white solid identified as 1-[N^{α}-(*tert*-butyloxycarbonyl)-L-ornithinyl]pyrrolidine (1.35g, 4.74mmol, 94%).

C. 1-(N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(cyclohexylmethyl)-L-ornithinyl)pyrrolidine

1-[N^{α}-(*tert*-Butyloxycarbonyl)-L-ornithinyl]pyrrolidine (100mg, 0.35mmol) was dissolved in methanol (25mL). To this solution was added cyclohexanecarboxaldehyde (44mg, 0.39mmol). After 30mins sodium triacetoxyborohydride (148mg, 0.70mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 1% triethylamine, 5% methanol, 94% chloroform) to give a colourless oil identified as 1-(N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(cyclohexylmethyl)-L-ornithinyl)pyrrolidine (51mg, 0.18mmol, 52%).

D. 1-[N^{ω}-(Cyclohexylmethyl)-L-ornithinyl]pyrrolidine dihydrochloride

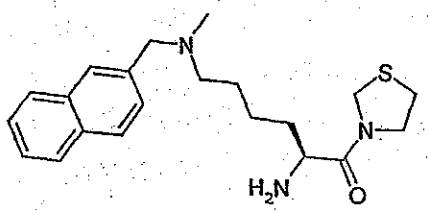
1-(N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(cyclohexylmethyl)-L-ornithinyl)pyrrolidine (215mg, 0.5mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 1-[N^{ω}-(cyclohexylmethyl)-L-ornithinyl]pyrrolidine dihydrochloride (160mg, 0.40mmol, 79%).

$[M+H]^+ = 282.3$

^1H NMR (CD_3OD): δ 0.93-1.24 (3H, m), 1.66-1.81 (15H, m), 2.50-2.70 (2H, m), 2.71-2.88 (2H, m), 3.2-3.48 (6H, m), 4.08 (1H, m), 8.35-8.38 (1H, m), 8.80-8.85 (1H, m) ppm.

EXAMPLE 8

3-[N^{ω}-Me-N^{ω}-(2-napthylmethyl)-L-lysinyl]thiazolidine dihydrochloride



A. N^{α}-(*tert*-Butyloxycarbonyl-N^{ω}-benzyl-L-lysine methyl ester

N^{α}-(*tert*-Butyloxycarbonyl-L-lysine methyl ester (6.1g, 22.2mmol) was dissolved in methanol (100mL). To this solution was added benzaldehyde (1.9g, 17.5mmol). After 2 hours sodium triacetoxyborohydride (5.8g, 27.3mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (200mL). This solution was washed with sat Na HCO_3 (1 x 50mL), water (12 x 50mL) and brine (1 x 50mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 1% acetic acid, 5% methanol, 94% chloroform) to give a colourless oil identified as N^{α}-(*tert*-butyloxycarbonyl-N^{ω}- benzyl-L-lysine methyl ester (5.2g, 14.2mmol, 82%).

B. N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-benzyl-N^{ω}-methyl-L-lysine methyl ester

N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-benzyl-L-lysine methyl ester (5.0g, 14.2mmol) was dissolved in methanol (100mL). To this solution was added formaldehyde (37% solution in water, 10mL). After 2 hours sodium triacetoxyborohydride (3.9g, 18.4mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (200mL). This solution was washed with sat. Na HCO_3 (1 x 50mL), water (12 x 50mL) and brine (1 x 50mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a . colourless oil identified as N^{α}-*tert*-butyloxycarbonyl- N^{ω}-benzyl-N^{ω}-methyl-L-lysine methyl ester (5.2g, 14.2mmol, 100%).

C. N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-methyl-L-lysine methyl ester

N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-benzyl-N^{ω}-methyl-L-lysine methyl ester (5.0g, 14.2mmol) was dissolved in methanol/water (9:1, 100mL). To this solution was added ammonium formate (1.6, 19.3mmol) and 10% palladium on charcoal (2g) . After 3 hours at 60 ^{0}C the catalyst was filtered off through celite and the residue washed with methanol (50mL). The combined filtrates were evaporated *in vacuo* and the residue was taken up in chloroform (200mL). This solution was washed with sat Na HCO_3 (1 x 50mL),

water (12 x 50mL) and brine (1 x 50mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a colourless oil identified as N^{α}-(*tert*-butyloxycarbonyl-N^{ω}-methyl-L-lysine methyl ester (3.48g, 12.5mmol, 93%).

D. N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)-N^{ω}-methyl-L-lysine methyl ester

N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-methyl-L-lysine methyl ester (3.1g, 11.1mmol) was dissolved in dichloromethane (100mL). To this solution was added 1,1-dimethyl-2,2,2-trichloroethyl chloroformate (3.0g, 12.5mmol) and triethylamine (2.3g, 23mmol) . After 18 hours at room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (200mL). This solution was washed with 0.3M $KHSO_4$ (1x 50mL),sat $NaHCO_3$ (1 x 50mL), water (1 x 50mL) and brine (1 x 50mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil purified by flash chromatography on silica gel (eluant: 30% ethyl acetate, 70% pet. ether) to give colourless oil identified as N^{α}-(*tert*-butyloxycarbonyl-N^{ω}-(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)-N^{ω}-methyl-L-lysine methyl ester (3.28g, 6.98mmol, 63%).

E. N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)-N^{ω}-methyl-L-lysine

N^{α}-(*tert*-Butyloxycarbonyl-N^{ω}-(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)-N^{ω}-methyl-L-lysine methyl ester (3.1g, 6.6mmol) was dissolved in tetrahydrofuran (100mL). 1M Lithium hydroxide (7mL, 7.0mmol) was added. After 3 hours at room temperature the reaction mixture was diluted with ethyl acetate (150mL), washed with 1M HCl (1 x 50mL), water (1 x 50mL) and brine (1 x 50mL), dried (Na_2SO_4) and evaporated *in vacuo* to give colourless oil identified as N^{α}-(*tert*-butyloxycarbonyl-N^{ω}-(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)-N^{ω}-methyl-L-lysine (2.94g, 6.45mmol, 98%).

F. 3-(N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)-N^{ω}-methyl-L-lysinyl)thiazolidine

N^{α}-(*tert*-Butyloxycarbonyl-N^{ω}-(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)-N^{ω}-methyl-L-lysine (700mg, 1.51mmol) was dissolved in CH_2Cl_2 /DMF (9:1, 20mL). To this solution at 0°C were added 1-hydroxybenzotriazole hydrate (410mg, 3.0mmol), water-soluble carbodiimide (250mg, 1.3mmol), thiazolidine (170mg, 1.9mmol) and N-methylmorpholine (1.0g, 10mmol). After 18h at 0°C to room temperature the solvent

was removed *in vacuo* and the residue was taken up in ethyl acetate (70mL). The solution was washed with 0.3M $KHSO_4$ (1 x 25mL), sat. $NaHCO_3$ (1 x 25mL), water (1 x 25mL) and brine (1 x 25mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 50% ethyl acetate, 50% pet. ether) to give a white solid identified as 3-(N^{α}-*tert*-butyloxycarbonyl-N^{ω}-(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)-N^{ω}-methyl-L-lysinyl)thiazolidine (758mg, 1.42mmol, 94%).

G. 3-(N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-methyl-L-lysinyl)thiazolidine

3-(N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)-N^{ω}-methyl-L-lysinyl)thiazolidine (730mg, 1.36mmol) was dissolved in acetic acid (30mL). Zinc powder (200mg) was added. After stirring at room temperature for 18 hours the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). The solution was washed with sat. $NaHCO_3$ (1 x 25mL), water (1 x 25mL) and brine (1 x 25mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a colourless oil identified as 3-(N^{α}-*tert*-butyloxycarbonyl-N^{ω}-methyl-L-lysinyl)thiazolidine (438mg, 1.32mmol, 97%).

H. 3-[N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-methyl-N^{ω}-(2-napthylmethyl)-L-lysinyl]thiazolidine

3-(N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-methyl-L-lysinyl)thiazolidine (50mg, 0.15mmol) was dissolved in 1,2-dichloroethane (20mL). To this solution was added 2-naphthaldehyde (26mg, 0.17mmol). After 2 hours sodium triacetoxyborohydride (36mg, 0.17mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 4% methanol, 96% chloroform) to give a colourless oil identified as 3-[N^{α}-*tert*-butyloxycarbonyl-N^{ω}-methyl-N^{ω}-(2-napthylmethyl)-L-lysinyl]thiazolidine (51mg, 0.11mmol, 72%).

I. 3-[N^{ω}-Methyl-N^{ω}-(2-napthylmethyl)-L-lysinyl]thiazolidine dihydrochloride

3-[N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-methyl-N^{ω}-(2-napthylmethyl)-L-lysinyl]thiazolidine (44mg, 0.093mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from

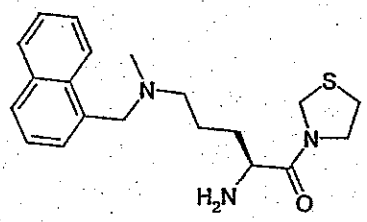
water to give a pale brown solid identified as 3-[N^{ω}-methyl-N^{ω}-(2-napthylmethyl)-L-lysinyl]thiazolidine dihydrochloride (37mg, 0.083mmol, 89%).

$[M+H]^+ = 372.2$

^1H NMR (CD_3OD): δ 1.50-1.53 (2H,m), 1.91-1.98 (4H,m), 2.82 (3H,s), 3.08-3.19 (4H,m), 3.36-3.75 (5H,m), 4.32-4.47 (2H,m), 4.60-4.71 (2H,m), 7.55-7.59 (2H,m), 7.65-7.68 (1H,m), 7.90-8.00 (3H,m), 8.10-8.12 (1H,m) ppm.

EXAMPLE 9

3-[N^{ω}-Methyl-N^{ω}-(1-Napthylmethyl)-L-ornithyl]thiazolidine dihydrochloride



A. 3-[*N*-(*tert*-Butyloxycarbonyl)-O^{ω}-methyl-L-glutamyl]thiazolidine

N-(*tert*-Butyloxycarbonyl)-O^{ω}-methyl-L-glutamic acid (6.28g, 24mmol) was dissolved in CH_2Cl_2/DMF (9:1, 100ml). To this solution at 0°C were added 1-hydroxybenzotriazole hydrate (5.5g, 36mmol), water-soluble carbodiimide (5.38g, 28mmol), thiazolidine (2.48g, 28mmol) and N-methylmorpholine (3.0g, 30mmol). The mixture was stirred for 18h at 0°C to room temperature then the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (150ml). The solution was washed with 0.3M $KHSO_4$ (2 x 30ml), sat. $NaHCO_3$ (2 x 30ml), water (2 x 30ml) and brine (1 x 30ml), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 70% ethyl acetate, 30% pet. ether 60-80) to give a brown oil identified as 3-[*N*-(*tert*-butyloxycarbonyl)-O^{ω}-methyl-L-glutamyl]thiazolidine (4.0g, 12mmol, 50%).

B. 3-[*N,N*-Di-(*tert*-butyloxycarbonyl)-O^{ω}-methyl-L-glutamyl]thiazolidine

3-[*N*-(*tert*-Butyloxycarbonyl)-O^{ω}-methyl-L-glutamyl]thiazolidine (3.2g, 9.6mmol) was dissolved in acetonitrile (20mL). Di-tert-butyl dicarbonate (3.14g, 14.4mmol) and 4-dimethylaminopyridine (235mg, 1.93mmol) were added. After 18 hours at room temperature further di-tert-butyl dicarbonate (3.14g, 14.4mmol) was added. After a further 3 days at room temperature the solvent was evaporated *in vacuo* the residue was purified by flash chromatography on silica gel (eluant: 70% ethyl acetate, 30% pet.

ether 60-80) to give a colourless oil identified as 3-[*N,N*-di-(*tert*-butyloxycarbonyl)-O^{α}-methyl-L-glutamyl]thiazolidine (2.0g, 4.63mmol, 48%).

C. 3-[*N,N*-Di-(*tert*-butyloxycarbonyl)-L-glutamyl]thiazolidine

3-[*N,N*-di-(*tert*-butyloxycarbonyl)-O^{α}-methyl-L-glutamyl]thiazolidine (950mg, 2.22mmol) was dissolved in THF (50ml). 1M Lithium hydroxide (5.5ml, 5.5mmol) was added. The mixture was stirred for 1 hour at room temperature then the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (70ml). The solution was washed with 0.3M $KHSO_4$ (2 x 20ml), water (2 x 20ml) and brine (1 x 20ml), dried (Na_2SO_4) and evaporated *in vacuo* to give a colourless oil identified as 3-[*N,N*-di-(*tert*-butyloxycarbonyl)-L-glutamyl]thiazolidine (912mg, 2.2mmol, 98%).

D. 3-[2-(*N,N*-Di-(*tert*-butyloxycarbonyl)amino)-5-hydroxypentanoyl]thiazolidine

3-[*N,N*-Di-(*tert*-butyloxycarbonyl)-L-glutamyl]thiazolidine (912mg, 2.2mmol) was dissolved in tetrahydrofuran (30 mL). This solution was cooled to –20 ^{0}C, N-methylmorpholine (300mg, 2.96mmol) and isobutyl chloroformate (387mg, 2.83mmol) were added. After 20 mins at –20 ^{0}C the reaction mixture was added to a solution of sodium borohydride (182mg, 4.8mmol) in water (5mL) at 0^{0}C. After 1 hour the reaction mixture was diluted with ethyl acetate (150 mL). This solution was washed with water (1 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a colourless oil identified as 3-[2-(*N,N*-di-(*tert*-butyloxycarbonyl)amino)-5-hydroxy-pentanoyl]thiazolidine (800mg, 2.0mmol, 92%).

E. 3-[2-(*N,N*-Di-(*tert*-butyloxycarbonyl)amino-5-oxopentanoyl]thiazolidine

3-[2-*N,N*-((Di-*tert*-butyloxycarbonyl)amino)-5-hydroxypentanoyl]thiazolidine (800mg, 2.0mmol) was dissolved in dichloromethane (50 mL). Dess-Martin periodinane (933mg,2.2mmol) was added. After 1 hour at room temperature the reaction mixture was diluted with ethyl acetate (150 mL). This solution was washed with water (1 x 20ml) and brine (1 x 20ml), dried (Na_2SO_4) and evaporated *in vacuo* to give a colourless oil. Purified by flash chromatography on silica gel (eluant: 50% ethyl acetate, 50% pet. ether 60-80) to give a colourless oil identified as 3-[2-(*N,N*-di-(*tert*-butyloxycarbonyl)amino-5-oxopentanoyl]thiazolidine (210mg, 0.52mmol, 26%).

F. 3-[*N*,*N*-Di-(*tert*-butyloxycarbonyl-N^{ω}-methyl-N^{ω}-(1-napthylmethyl)-L-ornithyl]-thiazolidine

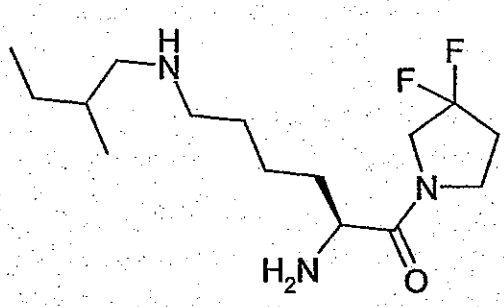
3-[*N*,*N*-Di-(*tert*-butyloxycarbonyl)amino-5-oxopentanoyl]thiazolidine was dissolved in 1,2-dichloroethane (20mL). To this solution was added N-methyl-1-napthylmethylamine. After 2 hours sodium triacetoxyborohydride was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel to give a colourless oil identified as 3-[*N*,*N*-di-(*tert*-butyloxycarbonyl-N^{ω}-methyl-N^{ω}-(1-napthylmethyl)-L-ornithyl]thiazolidine.

G. 3-[N^{ω}-Methyl-N^{ω}-(1-Napthylmethyl)-L-ornithyl]thiazolidine dihydrochloride

3-[*N*,*N*-Di-(*tert*-butyloxycarbonyl-N^{ω}-methyl-N^{ω}-(1-napthylmethyl)-L-ornithyl]thiazolidine was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a pale brown solid identified as 3-[N^{ω}-Me,N^{ω}-(1-napthylmethyl)-L-ornithyl]thiazolidine dihydrochloride.

EXAMPLE 10

3,3-Difluoro-1-[N^{ω}-(2-methylbutyl)-L-lysinyl]pyrrolidine dihydrochloride



A. 1-(*tert*-Butyloxycarbonyl)-3-pyrrolidone

(3*R*)-1-(*tert*-Butyloxycarbonyl)-3-hydroxypyrrolidine (980mg, 5.3mmol) was dissolved in CH_2Cl_2 (40ml). Dess-Martin periodinane (2.5g, 5.8mmol) was added. The mixture was stirred for 3 hours at room temperature then the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (300ml). The solution was washed with sat. $NaHCO_3$, water and brine, dried (Na_2SO_4) and evaporated *in vacuo* to give a

colourless oil. The residue was purified by flash chromatography on silica gel (eluant: 20% ethyl acetate, 80% pet. ether 60-80) to give a colourless oil identified as 1-(*tert*-butyloxycarbonyl)-3-pyrrolidone (842mg, 4.6mmol, 87%).

B. 1-(*tert*-Butyloxycarbonyl)-3,3-difluoropyrrolidine

1-(*tert*-Butyloxycarbonyl)-3-pyrrolidone (810mg, 4.4mmol) was dissolved in CH_2Cl_2 (30ml). (Diethylamino)sulphur trifluoride (2.2g, 13.7mmol) was added to this solution at 0°C. The mixture was stirred for 18 hours at 0°C to room temperature then carefully poured into sat. $NaHCO_3$ (100ml). The mixture was stirred for 15min then extracted with CH_2Cl_2. The organic extract was washed with water and brine, dried (Na_2SO_4) and evaporated *in vacuo* to give an orange oil. The residue was purified by flash chromatography (eluant: 10% ethyl acetate, 90% pet. ether 60-80) to give a colourless oil identified as 1-(*tert*-butyloxycarbonyl)-3,3-difluoropyrrolidine (580mg, 2.8mmol, 64%).

C. 3,3-Difluoropyrrolidine hydrochloride

1-(*tert*-Butyloxycarbonyl)-3,3-difluoropyrrolidine (540mg, 2.6mmol) was dissolved in 4M HCl/dioxan (30ml). The solution was stirred for 1 hour at room temperature then the solvent was removed *in vacuo* to give an off white solid identified as 3,3-difluoropyrrolidine hydrochloride (370mg, 2.6mmol, 100%).

D. 1-[N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysinyl]-3,3-difluoropyrrolidine

N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysine (1.14g, 2.4mmol) was dissolved in CH_2Cl_2 /DMF (9:1, 100ml). To this solution at 0°C were added 1-hydroxybenzotriazole hydrate (394mg, 2.9mmol), water-soluble carbodiimide (680mg, 3.4mmol), 3,3-difluoropyrrolidine hydrochloride (380mg, 2.43mmol) and N-methylmorpholine (400mg, 4mmol). The mixture was stirred for 18h at 0°C to room temperature then the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (200ml). The solution was washed with 0.3M $KHSO_4$, sat. $NaHCO_3$, water and brine, dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 65% ethyl acetate, 35% pet. ether 60-80) to give a white solid identified as 1-[N^{α}-(*tert*-butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysinyl]-3,3-difluoropyrrolidine (1.0g, 1.8mmol, 75%).

E. 1-[N^{α}-(*tert*-Butyloxycarbonyl)-L-lysinyl]-3,3-difluoropyrrolidine

1-[N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysinyl]-3,3-difluoropyrrolidine (1.01g, 1.8mmol) was dissolved in THF (20ml). Diethylamine (5ml) was added. The mixture was stirred for 3 hours at room temperature then the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (eluant: 90% chloroform, 7% methanol, 3% triethylamine) to give a pale yellow oil identified as 1-[N^{α}-(*tert*-butyloxycarbonyl)-L-lysinyl]-3,3-difluoropyrrolidine (598mg, 1.78mmol, 99%).

F. 1-[N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(2-methylbutyl)-L-lysinyl]-3,3-difluoropyrrolidine

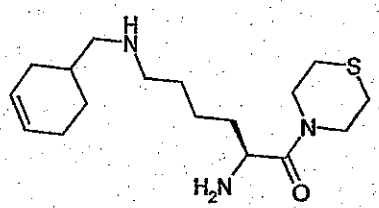
1-[N^{α}-(*tert*-Butyloxycarbonyl)-L-lysinyl]-3,3-difluoropyrrolidine was dissolved in 1,2-dichloroethane (20mL). To this solution was added 2-methylbutanal. After 2 hours sodium triacetoxyborohydride was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel to give a colourless oil identified as 1-[N^{α}-(*tert*-butyloxycarbonyl)-N^{ω}-(2-methylbutyl)-L-lysinyl]-3,3-difluoropyrrolidine.

G. 3,3-Difluoro -1-[N^{ω}-(2-methylbutyl)-L-lysinyl] pyrrolidine dihydrochloride

1-[N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(2-methylbutyl)-L-lysinyl]-3,3-difluoropyrrolidine was dissolved in 4M HCl/dioxan (20ml). The mixture was stirred for 1 hour at room temperature then the solvent was removed *in vacuo* to give a colourless oil identified as 3,3-difluoro-1-[N^{ω}-(2-methylbutyl)-L-lysinyl]pyrrolidine dihydrochloride.

EXAMPLE 11

1-[N^{ω}-(3-Cyclohexenylmethyl)-L-lysinyl]thiomorpholine dihydrochloride



A. 3-[N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysinyl]thiomorpholine

N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysine (2.5g, 5.34mmol) was dissolved in CH_2Cl_2 /DMF (9:1, 100mL). To this solution at 0°C were added 1-hydroxybenzotriazole hydrate (1.44g, 10.6mmol), water-soluble carbodiimide (1.35g, 6.5mmol), thiomorpholine (710mg, 6.9mmol) and N-methylmorpholine (800mg, 8mmol). After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (100mL). The solution was washed with 0.3M $KHSO_4$ (2 x 25mL), sat. $NaHCO_3$ (2 x 25mL), water (2 x 25mL) and brine (1 x 25mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 75% ethyl acetate, 25% pet. ether) to give a white solid identified as 3-[N^{α}-(*tert*-butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysinyl]thiomorpholine (2.70g, 4.88mmol, 91%).

B. 3-[N^{α}-(*tert*-Butyloxycarbonyl)-L-lysinyl]thiomorpholine

3-[N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(9-fluorenylmethyloxycarbonyl)-L-lysinyl]thiomorpholine (2.6g, 4.7mmol) was dissolved in tetrahydrofuran (20mL). Diethylamine (5mL) was added. After 90min at room temperature the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (eluant: 90% chloroform, 7% methanol, 3% triethylamine) to give a pale yellow oil identified as 3-[N^{α}-(*tert*-butyloxycarbonyl)-L-lysinyl]thiomorpholine (1.2g, 3.637mmol, 77%).

C. 3-[N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(3-cyclohexenylmethyl)-L-lysinyl]-thiomorpholine

3-(N^{α}-(*tert*-Butyloxycarbonyl)-L-lysinyl)thiomorpholine (150mg, 0.45mmol) was dissolved in methanol (25mL). To this solution was added 3-cyclohexenecarboxaldehyde (400mg, 0.45mmol). After 30mins sodium triacetoxyborohydride (150mg, 0.71mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 1% acetic acid,9% methanol, 90% chloroform) to give a colourless oil identified as 3-(N^{α}-(*tert*-butyloxycarbonyl)-N^{ω}-(3-cyclohexenylmethyl)-L-lysinyl)thiomorpholine (66mg, 0.12mmol, 26%).

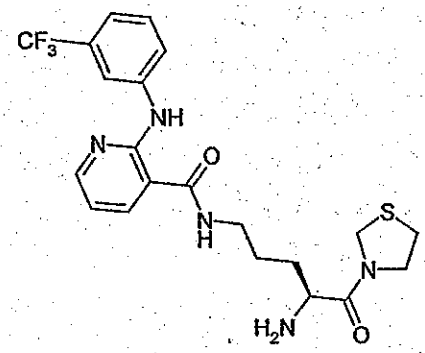
D. 1-[N^{ω}-(3-Cyclohexenylmethyl)-L-lysinyl]thiomorpholine dihydrochloride

3-(N^{α}-(*tert*-Butyloxycarbonyl)-N^{ω}-(3-cyclohexenylmethyl)-L-lysinyl)thiomorpholine (66mg, 0.12mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 1-[N^{ω}-(3-cyclohexenylmethyl)-L-lysinyl]thiomorpholine dihydrochloride (62mg, 0.12mmol, 100%).

$[M+H]^+ = 326.2$

EXAMPLE 12

(2*S*)-1-[N^{ω}-(2-(3'-trifluoromethylanilino)pyridyl-3-carbonyl)-L-ornithyl]thiazolidine dihydrochloride



A. 3-[N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)-L-ornithyl]thiazolidine

N^{α}-(*tert*-Butyloxycarbonyl-N^{ω}-(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)-L-ornithine (2.5g, 5.9mmol) was dissolved in CH_2Cl_2 /DMF (9:1, 30mL). To this solution at 0°C were added 1-hydroxybenzotriazole hydrate (1.6g, 11.9mmol), water-soluble carbodiimide (1.4g, 7.6mmol), thiazolidine (650mg, 7.3mmol) and N-methylmorpholine (2.0g, 20mmol). After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (70mL). The solution was washed with 0.3M $KHSO_4$ (1 x 25mL), sat. $NaHCO_3$ (1 x 25mL), water (1 x 25mL) and brine (1 x 25mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 70% ethyl acetate, 30% pet. ether) to

give a colourless oil identified as 3-[N^{α}-*tert*-butyloxycarbonyl-N^{ω}-(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)-L-ornithyl]thiazolidine (758mg, 1.42mmol, 94%).

B. 3-(N^{α}-*tert*-Butyloxycarbonyl- L-ornithinyl)thiazolidine

3-[N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-(1,1-dimethyl-2,2,2-trichloroethoxycarbonyl)-L-ornithyl]thiazolidine (130mg, 0.26mmol) was dissolved in acetic acid (30mL). Zinc powder (100mg) was added. After stirring at room temperature for 18 hours the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). The solution was washed with sat. $NaHCO_3$ (1 x 25mL), water (1 x 25mL) and brine (1 x 25mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a colourless oil identified as 3-(N^{α}-*tert*-butyloxycarbonyl-L-ornithinyl)thiazolidine (80mg, 0.26mmol, 100%).

C. 3-[N^{α}-*tert*-Butyloxycarbonyl-*N*$^{\omega}$-(2-(3'-trifluoromethylanilino)pyridyl-3-carbonyl)-L-ornithinyl]thiazolidine

3-(N^{α}-*tert*-Butyloxycarbonyl-L-ornithinyl)thiazolidine (80mg, 0.26mmol) was dissolved in CH_2Cl_2 /DMF (9:1, 20mL). To this solution at 0°C was added 1-hydroxybenzotriazole hydrate (80mg, 0.6mmol), water-soluble carbodiimide (65mg, 0.32mmol), niflumic acid (82mg, 0.29mmol) and N-methylmorpholine (100mg, 1.0mmol). After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (70mL). The solution was washed with 0.3M $KHSO_4$ (1 x 20mL), sat. $NaHCO_3$ (1 x 20mL), water (1 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 75% ethyl acetate, 25% pet. ether) to give a yellow oil identified as 3-[N^{α}-*tert*-butyloxycarbonyl-*N*$^{\omega}$-(2-(3'-trifluoromethylanilino)pyridyl-3-carbonyl)-L-ornithinyl]-thiazolidine (60mg, 0.12mmol, 45%).

D. (2*S*)-1-[*N*$^{\omega}$-(2-(3'-Trifluoromethylanilino)pyridyl-3-carbonyl)-L-ornithyl]-thiazolidine dihydrochloride

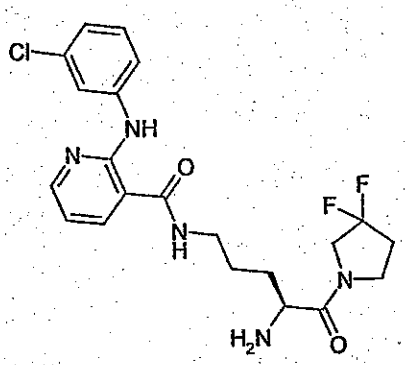
3-[N^{α}-*tert*-Butyloxycarbonyl-*N*$^{\omega}$-(2-(3'-trifluoromethylanilino)pyridyl-3-carbonyl)-L-ornithinyl]thiazolidine (54mg, 0.10mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a pale brown solid identified as (2*S*)-1-[*N*$^{\omega}$-(2-(3'-trifluoromethylanilino)pyridyl-3-carbonyl)-L-ornithyl]thiazolidine dihydrochloride (47mg, 0.10mmol, 100%).

$[M+H]^+$ = 468.0

^{1}H NMR (CD_3OD): δ1.77-1.82 (2H, m), 1.84-2.00 (2H, m), 3.03-3.15 (4H, m), 3.41-3.51 (2H, m), 3.65-3.71 (2H, m), 3.80-3.87 (1H, m), 4.46-4.49 (2H, m), 4.65-4.72 (2H, m), 7.06-7.11 (1H, m), 7.61-7.11 (3H, m), 7.95 (1H, s), 8.09 (1H, d, J=4.7Hz), 8.49 (1H, d, J= 4.2Hz) ppm.

EXAMPLE 13

3,3-Difluoro-1-[*N*$^{\omega}$-(2-(3'-chloroanilino)pyridyl-3-carbonyl)-L-ornithyl]pyrrolidine dihydrochloride



A. 1-[*N*$^{\alpha}$-(*tert*-Butyloxycarbonyl)-L-ornithyl]-3,3-difluoropyrrolidine

1-[*N*$^{\alpha}$-(*tert*-Butyloxycarbonyl)-L-ornithyl]-3,3-difluoropyrrolidine was prepared as described for the lysine derivative in Example 9.

B. 3-Chloroanilinonicotinic acid

3-Chloroaniline was dissolved in xylene. 2-Aminonicotinic acid was added. The reaction mixture was heated at 150 ^{0}C for 18 hours after which time the reaction mixture was diluted with ethyl acetate giving an off-white solid identified as 3-chloroanilinonicotinic acid.

C. 3,3-Difluoro-[N$^{\alpha}$-*tert*-butyloxycarbonyl-*N*$^{\omega}$-(2-(3'-chloroanilino)pyridyl-3-carbonyl)-L-ornithinyl]pyrrolidine

1-[*N*$^{\alpha}$-(*tert*-Butyloxycarbonyl)-L-ornithyl]-3,3-difluoropyrrolidine was dissolved in CH_2Cl_2 /DMF (9:1, 20mL). To this solution at 0°C was added 1-hydroxybenzotriazole hydrate, water-soluble carbodiimide, 3-chloroanilinonicotinic acid and N-methylmorpholine.

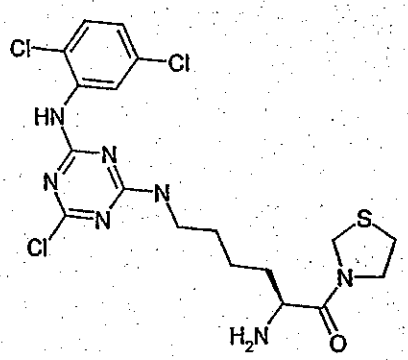
After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (70mL). The solution was washed with 0.3M $KHSO_4$ (1 x 20mL), sat. $NaHCO_3$ (1 x 20mL), water (1 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 75% ethyl acetate, 25% pet. ether) to give a yellow oil identified as 3,3-difluoro-[N^{α}-*tert*-butyloxycarbonyl-N^{ω}-(2-(3'-chloroanilino)pyridyl-3-carbonyl)]-L-ornithinyl)pyrrolidine.

D. 3,3-Difluoro-1-[N^{ω}-(2-(3'-chloroanilino)pyridyl-3-carbonyl)-L-ornithyl]pyrrolidine dihydrochloride

3,3-Difluoro-[N^{α}-*tert*-butyloxycarbonyl-N^{ω}-(2-(3'-chloroanilino)pyridyl-3-carbonyl)]-L-ornithinyl)pyrrolidine was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a pale brown solid identified as 3,3-difluoro-1-[N^{ω}-(2-(3'-chloroanilino)pyridyl-3-carbonyl)-L-ornithyl]pyrrolidine dihydrochloride.

EXAMPLE 14

3-[N^{ω}-6-Chloro-4-(2',5'-dichloroanilino)-1,3,5-triazinyl)-L-lysinyl]thiazolidine dihydrochloride



A. 4,6-Dichloro-2-(2',5'-dichloroanilino)-1,3,5-triazine

Cyanuric chloride (1.844g, 10mmol) was dissolved in acetonitrile (20mL). The solution was cooled to –20 °C. A solution of 2,5-dichloroaniline (1.62g, 10mmol) and triethylamine (1.0g, 10mmol) was slowly added. After 1 hour at –20 °C the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (150mL). The

solution was washed with water (1 x 50mL) and brine (1 x 50mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was recrystallised from ethyl acetate/ hexane to give an off white solid identified as 4,6-dichloro-2-(2',5'-dichloroanilino)-1,3,5-triazine (1.86mg, 6.0mmol, 60%).

B. 3-[N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-6-chloro-4-(2',5'-dichloroanilino)-1,3,5-triazinyl)-L-lysinyl]thiazolidine

3-(N^{α}-(*tert*-Butyloxycarbonyl)-L-lysinyl)thiazolidine (800mg, 2.58mmol) was dissolved in dichloromethane (30mL). To this solution was added 4,6-dichloro-2-(2',5'-dichloroanilino)-1,3,5-triazine (810mg, 2.6mmol) and triethylamine (300mg, 3.0mmol). After 2 hours at room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (150mL). This solution was washed with water (2 x 30mL) and brine (1 x 30mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography (eluant: 60% ethyl acetate, 40% pet. ether) to give a white solid identified as 3-[N^{α}-*tert*-butyloxycarbonyl-N^{ω}-6-chloro-4-(2',5'-dichloroanilino)-1,3,5-triazinyl)-L-lysinyl]thiazolidine (1.33g, 2.23mmol, 86%).

C. 3-[N^{ω}-6-Chloro-4-(2',5'-dichloroanilino)-1,3,5-triazinyl)-L-lysinyl]thiazolidine dihydrochloride

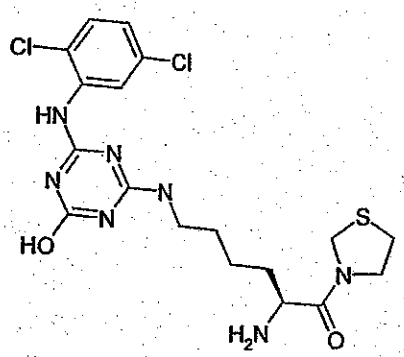
3-[N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-6-chloro-4-(2',5'-dichloroanilino)-1,3,5-triazinyl)-L-lysinyl]thiazolidine (59mg, 0.10mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 3-[N^{ω}-6-chloro-4-(2',5'-dichloroanilino)-1,3,5-triazinyl)-L-lysinyl]thiazolidine dihydrochloride (55mg, 0.098mmol, 98%).

$[M+H]^+$ = 492.2, 494.4

^1H NMR (CD_3OD): δ1.46-1.51 (2H,m), 1.65--1.67 (2H,m), 1.80-1.96 (2H,m), 3.05-3.14 (2H,m), 3.38-3.42 (2H,m), 3.55-3.75 (4H,m), 4.31-4.36 (2H,m0, 4.40-4.52 (1H,m), 4.63-4.95 (2H,m), 7.15-7.18 (1H,m), 7.40-7.45 (1H,m), 8.15-8.25 (1H,m) ppm.

EXAMPLE 15

3-[N^{ω}-4-(2',5'-Dichloroanilino)-6-hydroxy-1,3,5-triazinyl)-L-lysinyl]thiazolidine bis(trifluoroacetate)



A. 3-[N^{ω}-4-(2',5'-Dichloroanilino)-6-hydroxy-1,3,5-triazinyl)-L-lysinyl]thiazolidine bis(trifluoroacetate)

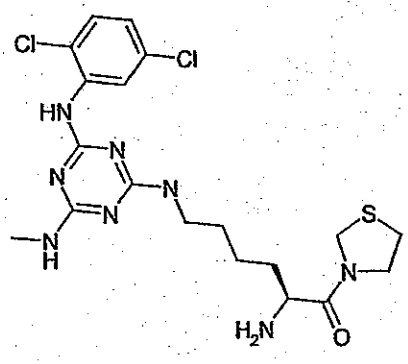
3-[N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-6-chloro-4-(2',5'-dichloroanilino)-1,3,5-triazinyl)]-L-ornithinyl)thiazolidine (54mg, 0.09mmol) was dissolved in trifluoroacetic acid (20mL) and water (2mL). After 2 hours at 70 ^{0}C the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 3-[N^{ω}-4-(2',5'-dichloroanilino)-6-hydroxy-1,3,5-triazinyl)-L-lysinyl]thiazolidine bis(trifluoroacetate) (63mg, 0.089mmol, 97%).

$[M+H]^{+}$ = 472.1, 474.2

^{1}H NMR (CD_3OD): δ1.42-1.47 (2H,m), 1.62-1.67 (2H,m), 1.82-1.89 (2H,m), 3.04-3.16 (4H,m), 3.70-3.75 (2H,m), 3.84-3.91 (1H,m), 4.25-4.32 (2H,m), 4.45-4.54 (2H,m), 4.64-4.70 (2H,m), 7.05-7.15 (1H,m), 7.34-7.38 (1H,m), 7.49-7.55 (1H,m), 7.80-7.92 (1H,m) ppm.

EXAMPLE 16

3-[N^{ω}-4-(2',5'-Dichloroanilino)-6-methylamino-1,3,5-triazinyl)-L-lysinyl]thiazolidine dihydrochloride



A. 3-[N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-4-(2',5'-dichloroanilino)-6-dimethylamino-1,3,5-triazinyl)-L-lysinyl]thiazolidine

3-[N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-3-chloro-5-(2',5'-dichloroanilino)-2,4,6-triazinyl)]-L-ornithinyl)thiazolidine (120mg, 0.20mmol) was dissolved in 1M dimethylamine in tetrahydrofuran (25mL). After 18 hours at room temperature the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (eluant: 70% ethyl acetate, 30% pet. ether) to give a white solid identified as 3-[N^{α}-*tert*-butyloxycarbonyl-N^{ω}-4-(2',5'-dichloroanilino)-6-dimethylamino-1,3,5-triazinyl)-L-lysinyl]thiazolidine (110mg, 0.18mmol, 90%).

B. 3-[N^{ω}-4-(2',5'-Dichloroanilino)-6-dimethylamino-1,3,5-triazinyl)-L-lysinyl]-thiazolidine dihydrochloride

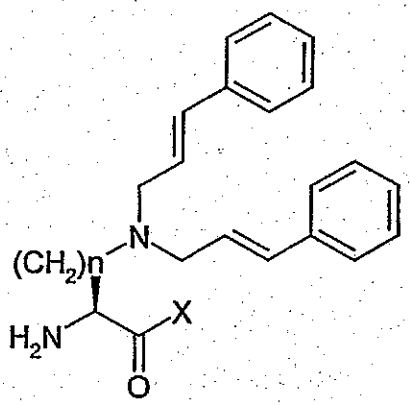
3-[N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-4-(2',5'-dichloroanilino)-6-dimethylamino-1,3,5-triazinyl)-L-lysinyl]thiazolidine (110mg, 0.18mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 3-[N^{ω}-4-(2',5'-dichloroanilino)-6-dimethylamino-1,3,5-triazinyl)-L-lysinyl]thiazolidine dihydrochloride (105mg, 0.18mmol, 100%).

$[M+H]^+$ = 499.1, 501.1

^{1}H NMR (CD_3OD): δ1.52-1.55 (2H,m), 1.69-1.71 (2H,m), 1.90-1.98 (2H,m), 3.13-3.22 (8H,m), 3.48-3.62 (2H,m), 3.65-3.69 (4H,m), 4.37-4.39 (2H,m), 4.46-4.49 (1H,m), 4.57-4.77 (2H,m), 7.20-7.22 (1H,m), 7.45-7.50 (1H,m), 8.09-8.12 (1H,m) ppm.

The following compounds were prepared by analogous methods.

TABLE 1



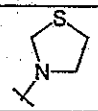
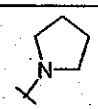
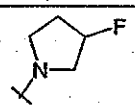
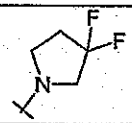
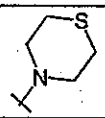
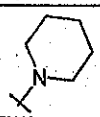
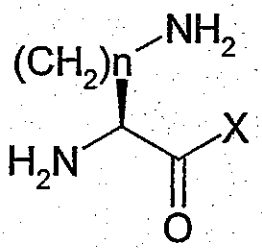
Example No	n	X	Example No	n	X
17	3		22	3	
			23	4	
18	3		24	3	
19	4		25	4	
20	3		26	3	
21	4		27	4	

TABLE 2



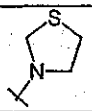
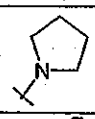
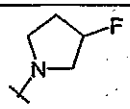
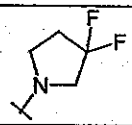
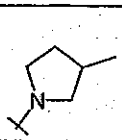
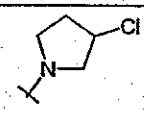
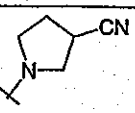
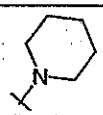
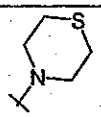
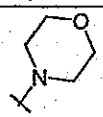
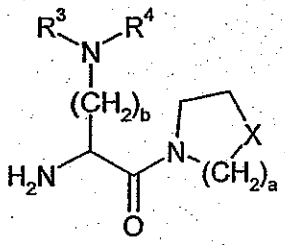
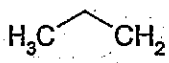
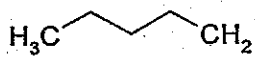
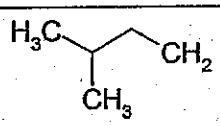
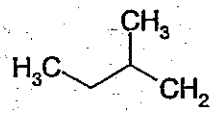
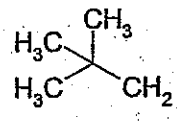
Example No	n	X	Example No	n	X
28	2		41	2	
29	2		42	2	
30	3		43	3	
31	4		45	4	
32	2		46	2	
33	3		47	3	
34	4		48	4	
35	2		49	2	
36	3				
37	4				
38	2		50	2	
39	3		51	3	
40	4		52	4	

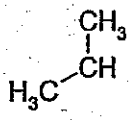
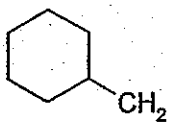
TABLE 3

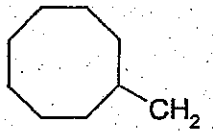
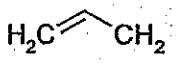


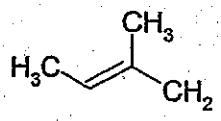
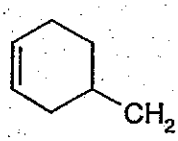
Ex No	a	b	X	R^3	R^4
53	1	3	S	H	
54	1	4		H	
55	1	3	CH_2	H	
56	1	4		H	
57	1	3	CF_2	H	
58	1	4		H	
59	1	4	S	CH_3	
60	1	4		$CH(CH_3)_2$	
61	1	4	CH_2	CH_3	
62	1	4		$CH(CH_3)_2$	

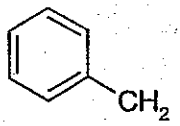
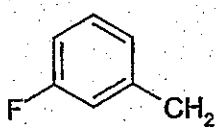
Ex No	a	b	X	R^3	R^4
63	1	3	S	$CH(CH_3)_2$	
64	1	3	CH_2	$CH(CH_3)_2$	
65	2	3	S	H	
66	2	4		H	
67	2	3	CH_2	H	
68	2	4		H	
69	1	3	S	H	
70	1	4		H	
71	1	3	CH_2	H	
72	1	4		H	
73	1	3	CF_2	H	
74	1	4		H	
75	1	4	S	CH_3	
76	1	4		$CH(CH_3)_2$	
77	1	4	CH_2	CH_3	
78	1	4		$CH(CH_3)_2$	
79	1	3	S	$CH(CH_3)_2$	
80	1	3	CH_2	$CH(CH_3)_2$	
81	2	3	S	H	
82	2	4		H	
83	2	3	CH_2	H	
84	2	4		H	
85	1	3	S	H	
86	1	4		H	
87	1	3	CH_2	H	
88	1	4		H	
89	1	3	CF_2	H	
90	1	4		H	
91	1	4	S	CH_3	
92	1	4		$CH(CH_3)_2$	
93	1	4	CH_2	CH_3	
94	1	4		$CH(CH_3)_2$	
95	1	3	S	$CH(CH_3)_2$	

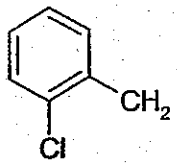
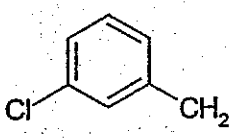
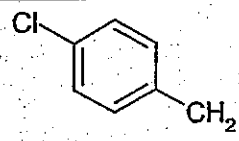
Ex No	a	b	X	R^3	R^4
96	1	3	CH_2	$CH(CH_3)_2$	
97	2	3	S	H	
98	2	4		H	
99	2	3	CH_2	H	
100	2	4		H	
101	1	3	S	H	
102	1	4		H	
103	1	3	CH_2	H	
104	1	4		H	
105	1	3	CF_2	H	
106	1	4	S	CH_3	
107	1	4		$CH(CH_3)_2$	
108	1	4	CH_2	CH_3	
109	1	4		$CH(CH_3)_2$	
110	1	3	S	$CH(CH_3)_2$	
111	1	3	CH_2	$CH(CH_3)_2$	
112	2	3	S	H	
113	2	4		H	
114	2	3	CH_2	H	
115	2	4		H	
116	1	3	S	H	
117	1	4		H	
118	1	3	CH_2	H	
119	1	4		H	
120	1	3	CF_2	H	
121	1	4		H	
122	1	4	S	CH_3	
123	1	4		$CH(CH_3)_2$	
124	1	4	CH_2	CH_3	
125	1	4		$CH(CH_3)_2$	
126	1	3	S	$CH(CH_3)_2$	
127	1	3	CH_2	$CH(CH_3)_2$	
128	2	3	S	H	

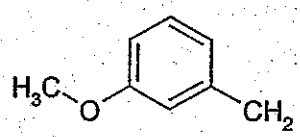
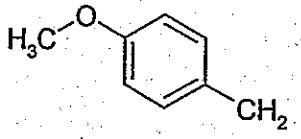
Ex No	a	b	X	R^3	R^4
129	2	4		H	
130	2	3	CH_2	H	
131	2	4		H	
132	1	3	S	H	
133	1	4		H	
134	1	3	CH_2	H	
135	1	4		H	
136	1	3	CF_2	H	
137	1	4		H	
138	1	4	S	CH_3	
139	1	4		$CH(CH_3)_2$	
140	1	4	CH_2	CH_3	
141	1	4		$CH(CH_3)_2$	
142	1	3	S	$CH(CH_3)_2$	
143	1	3	CH_2	$CH(CH_3)_2$	
144	2	3	S	H	
145	2	4		H	
146	2	3	CH_2	H	
147	2	4		H	
148	1	3	S		
149	1	4			
150	1	4	CH_2		
151	1	3	CF_2		
152	1	4			
153	1	4	S	CH_3	
154	1	4		$CH(CH_3)_2$	
155	1	4	CH_2	CH_3	
156	1	4		$CH(CH_3)_2$	
157	1	3	S	$CH(CH_3)_2$	
158	1	3	CH_2	$CH(CH_3)_2$	
159	2	3	S	H	
160	2	4		H	
161	2	3	CH_2	H	

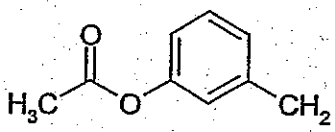
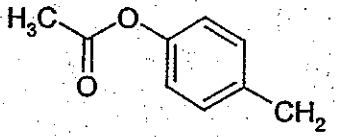
Ex No	a	b	X	R^3	R^4
162	2	4		H	
163	1	3	S	H	
164	1	4		H	
165	1	3	CH_2	H	
166	1	4		H	
167	1	3	CF_2	H	
168	1	4		H	
169	1	4	S	CH_3	
170	1	4		$CH(CH_3)_2$	
171	1	4	CH_2	CH_3	
172	1	4		$CH(CH_3)_2$	
173	1	3	S	$CH(CH_3)_2$	
174	1	3	CH_2	$CH(CH_3)_2$	
175	2	3	S	H	
176	2	4		H	
177	2	3	CH_2	H	
178	2	4		H	
179	1	3	S	H	
180	1	4		H	
181	1	3	CH_2	H	
182	1	4		H	
183	1	3	CF_2	H	
184	1	4		H	
185	1	4	S	CH_3	
186	1	4		$CH(CH_3)_2$	
187	1	4	CH_2	CH_3	
188	1	4		$CH(CH_3)_2$	
189	1	3	S	$CH(CH_3)_2$	
190	1	3	CH_2	$CH(CH_3)_2$	
191	2	3	S	H	
192	2	4		H	
193	2	3	CH_2	H	
194	2	4		H	

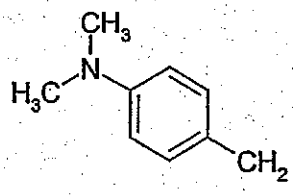
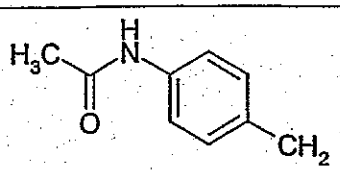
Ex No	a	b	X	R^3	R^4
195	1	3	S	H	
196	1	4		H	
197	1	3	CH_2	H	
198	1	4		H	
199	1	3	CF_2	H	
200	1	4		H	
201	1	4	S	CH_3	
202	1	4		$CH(CH_3)_2$	
203	1	4	CH_2	CH_3	
204	1	4		$CH(CH_3)_2$	
205	1	3	S	$CH(CH_3)_2$	
206	1	3	CH_2	$CH(CH_3)_2$	
207	2	3	S	H	
208	2	4		H	
209	2	3	CH_2	H	
210	2	4		H	
211	1	3	S	H	
212	1	4		H	
213	1	3	CH_2	H	
214	1	4		H	
215	1	3	CF_2	H	
216	1	4		H	
217	1	4	S	CH_3	
218	1	4		$CH(CH_3)_2$	
219	1	4	CH_2	CH_3	
220	1	4		$CH(CH_3)_2$	
221	1	3	S	$CH(CH_3)_2$	
222	1	3	CH_2	$CH(CH_3)_2$	
223	2	3	S	H	
224	2	3	CH_2	H	
225	2	4		H	
226	1	3	S	H	
227	1	4		H	

Ex No	a	b	X	R^3	R^4
228	1	3	CH_2	H	
229	1	4		H	
230	1	3	CF_2	H	
231	1	4		H	
232	1	4	S	CH_3	
233	1	4		$CH(CH_3)_2$	
234	1	4	CH_2	CH_3	
235	1	4		$CH(CH_3)_2$	
236	1	3	S	$CH(CH_3)_2$	
237	1	3	CH_2	$CH(CH_3)_2$	
238	2	3	S	H	
239	2	4		H	
240	2	3	CH_2	H	
241	2	4		H	
242	1	3	S	H	
243	1	4		H	
244	1	3	CH_2	H	
245	1	4		H	
246	1	3	CF_2	H	
247	1	4		H	
248	1	4	S	CH_3	
249	1	4		$CH(CH_3)_2$	
250	1	4	CH_2	CH_3	
251	1	4		$CH(CH_3)_2$	
252	1	3	S	$CH(CH_3)_2$	
253	1	3	CH_2	$CH(CH_3)_2$	
254	2	3	S	H	
255	2	4		H	
256	2	3	CH_2	H	
257	2	4		H	
258	1	3	S	H	
259	1	4		H	
260	1	3	CH_2	H	

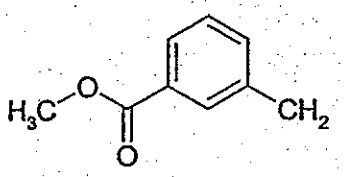
Ex No	a	b	X	R^3	R^4
261	1	4		H	
262	1	3	CF_2	H	
263	1	4		H	
264	1	4	S	CH_3	
265	1	4		$CH(CH_3)_2$	
266	1	4	CH_2	CH_3	
267	1	4		$CH(CH_3)_2$	
268	1	3	S	$CH(CH_3)_2$	
269	1	3	CH_2	$CH(CH_3)_2$	
270	2	3	S	H	
271	2	4		H	
272	2	3	CH_2	H	
273	2	4		H	
274	1	3	S	H	
275	1	4		H	
276	1	3	CH_2	H	
277	1	4		H	
278	1	3	CF_2	H	
279	1	4		H	
280	1	4	S	CH_3	
281	1	4		$CH(CH_3)_2$	
282	1	4	CH_2	CH_3	
283	1	4		$CH(CH_3)_2$	
284	1	3	S	$CH(CH_3)_2$	
285	1	3	CH_2	$CH(CH_3)_2$	
286	2	3	S	H	
287	2	4		H	
288	2	3	CH_2	H	
289	2	4		H	
290	1	3	S	H	
291	1	4		H	
292	1	3	CH_2	H	
293	1	4		H	

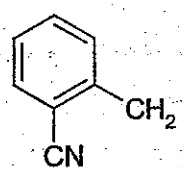
Ex No	a	b	X	R^3	R^4
294	1	3	CF_2	H	
295	1	4		H	
296	1	4	S	CH_3	
297	1	4		$CH(CH_3)_2$	
298	1	4	CH_2	CH_3	
299	1	4		$CH(CH_3)_2$	
300	1	3	S	$CH(CH_3)_2$	
301	1	3	CH_2	$CH(CH_3)_2$	
302	2	3	S	H	
303	2	4		H	
304	2	3	CH_2	H	
305	2	4		H	
306	1	3	S	H	
307	1	4		H	
308	1	3	CH_2	H	
309	1	4		H	
310	1	3	CF_2	H	
311	1	4		H	
312	1	4	S	CH_3	
313	1	4		$CH(CH_3)_2$	
314	1	4	CH_2	CH_3	
315	1	4		$CH(CH_3)_2$	
316	1	3	S	$CH(CH_3)_2$	
317	1	3	CH_2	$CH(CH_3)_2$	
318	2	3	S	H	
319	2	4		H	
320	2	3	CH_2	H	
321	2	4		H	
322	1	3	S	H	
323	1	4		H	
324	1	3	CH_2	H	
325	1	4		H	
326	1	3	CF_2	H	

Ex No	a	b	X	R^3	R^4
327	1	4		H	
328	1	4	S	CH_3	
329	1	4		$CH(CH_3)_2$	
330	1	4	CH_2	CH_3	
331	1	4		$CH(CH_3)_2$	
332	1	3	S	$CH(CH_3)_2$	
333	1	3	CH_2	$CH(CH_3)_2$	
334	2	3	S	H	
335	2	4		H	
336	2	3	CH_2	H	
337	2	4		H	
338	1	3	S	H	
339	1	4		H	
340	1	3	CH_2	H	
341	1	4		H	
342	1	3	CF_2	H	
343	1	4		H	
344	1	4	S	CH_3	
345	1	4		$CH(CH_3)_2$	
346	1	4	CH_2	CH_3	
347	1	4		$CH(CH_3)_2$	
348	1	3	S	$CH(CH_3)_2$	
349	1	3	CH_2	$CH(CH_3)_2$	
350	2	3	S	H	
351	2	4		H	
352	2	3	CH_2	H	
353	2	4		H	
354	1	3	S	H	
355	1	4		H	
356	1	3	CH_2	H	
357	1	4		H	
358	1	3	CF_2	H	
359	1	4		H	

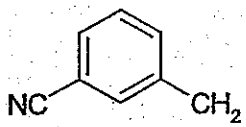
Ex No	a	b	X	R^3	R^4
360	1	4	S	CH_3	
361	1	4		$CH(CH_3)_2$	
362	1	4	CH_2	CH_3	
363	1	4		$CH(CH_3)_2$	
364	1	3	S	$CH(CH_3)_2$	
365	1	3	CH_2	$CH(CH_3)_2$	
366	2	3	S	H	
367	2	4		H	
368	2	3	CH_2	H	
369	2	4		H	
370	1	3	S	H	
371	1	4		H	
372	1	3	CH_2	H	
373	1	4		H	
374	1	3	CF_2	H	
375	1	4		H	
376	1	4	S	CH_3	
377	1	4		$CH(CH_3)_2$	
378	1	4	CH_2	CH_3	
379	1	4		$CH(CH_3)_2$	
380	1	3	S	$CH(CH_3)_2$	
381	1	3	CH_2	$CH(CH_3)_2$	
382	2	3	S	H	
383	2	4		H	
384	2	3	CH_2	H	
385	2	4		H	
386	1	3	S	H	
387	1	4		H	
388	1	3	CH_2	H	
389	1	4		H	
390	1	3	CF_2	H	
391	1	4		H	
392	1	4	S	CH_3	

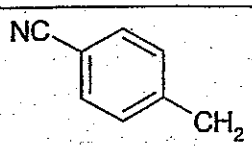
Ex No	a	b	X	R^3	R^4
393	1	4		$CH(CH_3)_2$	
394	1	4	CH_2	CH_3	
395	1	4		$CH(CH_3)_2$	
396	1	3	S	$CH(CH_3)_2$	
397	1	3	CH_2	$CH(CH_3)_2$	
398	2	3	S	H	
399	2	4		H	
400	2	3	CH_2	H	
401	2	4		H	
402	1	3	S	H	
403	1	4		H	
404	1	3	CH_2	H	
405	1	4		H	
406	1	3	CF_2	H	
407	1	4		H	
408	1	4	S	CH_3	
409	1	4		$CH(CH_3)_2$	
410	1	4	CH_2	CH_3	
411	1	4		$CH(CH_3)_2$	
412	1	3	S	$CH(CH_3)_2$	
413	1	3	CH_2	$CH(CH_3)_2$	
414	2	3	S	H	
415	2	4		H	
416	2	3	CH_2	H	
417	2	4		H	
418	1	3	S	H	
419	1	4		H	
420	1	3	CH_2	H	
421	1	4		H	
422	1	3	CF_2	H	
423	1	4		H	
424	1	4	S	CH_3	
425	1	4		$CH(CH_3)_2$	

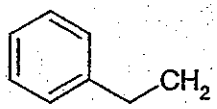
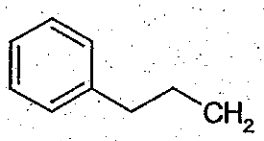


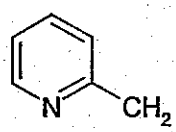
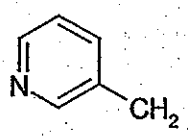


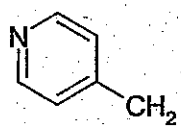
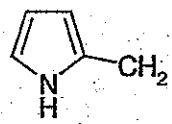
Ex No	a	b	X	R^3	R^4
426	1	4	CH_2	CH_3	
427	1	4		$CH(CH_3)_2$	
428	1	3	S	$CH(CH_3)_2$	
429	1	3	CH_2	$CH(CH_3)_2$	
450	2	3	S	H	
451	2	4		H	
452	2	3	CH_2	H	
453	2	4		H	
454	1	3	S	H	
455	1	4		H	
456	1	3	CH_2	H	
457	1	4		H	
458	1	3	CF_2	H	
459	1	4		H	
460	1	4	S	CH_3	
461	1	4		$CH(CH_3)_2$	
462	1	4	CH_2	CH_3	
463	1	4		$CH(CH_3)_2$	
464	1	3	S	$CH(CH_3)_2$	
465	1	3	CH_2	$CH(CH_3)_2$	
466	2	3	S	H	
467	2	4		H	
468	2	3	CH_2	H	
469	2	4		H	
470	1	3	S	H	
471	1	4		H	
472	1	3	CH_2	H	
473	1	4		H	
474	1	3	CF_2	H	
475	1	4		H	
476	1	4	S	CH_3	
477	1	4		$CH(CH_3)_2$	
478	1	4	CH_2	CH_3	

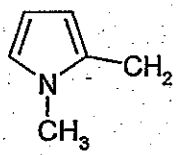
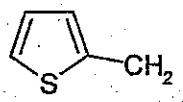


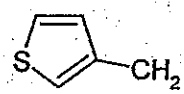
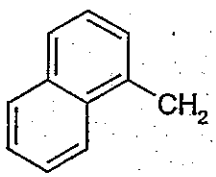


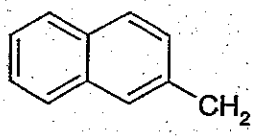
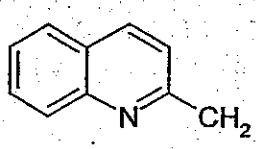
Ex No	a	b	X	R^3	R^4
479	1	4		$CH(CH_3)_2$	
480	1	3	S	$CH(CH_3)_2$	
481	1	3	CH_2	$CH(CH_3)_2$	
482	2	3	S	H	
483	2	4		H	
484	2	3	CH_2	H	
485	2	4		H	
486	1	3	S	H	
487	1	4		H	
488	1	3	CH_2	H	
489	1	4		H	
490	1	3	CF_2	H	
491	1	4		H	
492	1	4	S	CH_3	
493	1	4		$CH(CH_3)_2$	
494	1	4	CH_2	CH_3	
495	1	4		$CH(CH_3)_2$	
496	1	3	S	$CH(CH_3)_2$	
497	1	3	CH_2	$CH(CH_3)_2$	
498	2	3	S	H	
499	2	4		H	
500	2	3	CH_2	H	
501	2	4		H	
502	1	3	S	H	
503	1	4		H	
504	1	3	CH_2	H	
505	1	4		H	
506	1	3	CF_2	H	
507	1	4		H	
508	1	4	S	CH_3	
509	1	4		$CH(CH_3)_2$	
510	1	4	CH_2	CH_3	
511	1	4		$CH(CH_3)_2$	

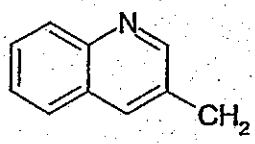
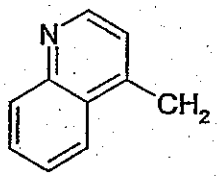
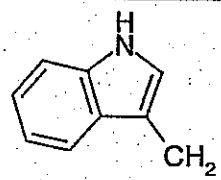
Ex No	a	b	X	R^3	R^4
512	1	3	S	$CH(CH_3)_2$	
513	1	3	CH_2	$CH(CH_3)_2$	
514	2	3	S	H	
515	2	4		H	
516	2	3	CH_2	H	
517	2	4		H	
518	1	3	S	H	
519	1	4		H	
520	1	3	CH_2	H	
521	1	4		H	
522	1	3	CF_2	H	
523	1	4		H	
524	1	4	S	CH_3	
525	1	4		$CH(CH_3)_2$	
526	1	4	CH_2	CH_3	
527	1	4		$CH(CH_3)_2$	
528	1	3	S	$CH(CH_3)_2$	
529	1	3	CH_2	$CH(CH_3)_2$	
530	2	3	S	H	
531	2	4		H	
532	2	3	CH_2	H	
533	2	4		H	
534	1	3	S	H	
535	1	4		H	
536	1	3	CH_2	H	
537	1	4		H	
538	1	3	CF_2	H	
539	1	4		H	
540	1	4	S	CH_3	
541	1	4		$CH(CH_3)_2$	
542	1	4	CH_2	CH_3	
543	1	4		$CH(CH_3)_2$	
544	1	3	S	$CH(CH_3)_2$	

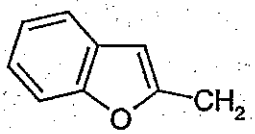
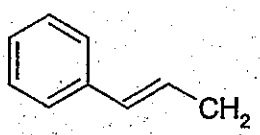
Ex No	a	b	X	R^3	R^4
545	1	3	CH_2	$CH(CH_3)_2$	
546	2	3	S	H	
547	2	4		H	
548	2	3	CH_2	H	
549	2	4		H	
550	1	3	S	H	
551	1	4		H	
552	1	3	CH_2	H	
553	1	4		H	
554	1	3	CF_2	H	
555	1	4		H	
556	1	4	S	CH_3	
557	1	4		$CH(CH_3)_2$	
558	1	4	CH_2	CH_3	
559	1	4		$CH(CH_3)_2$	
560	1	3	S	$CH(CH_3)_2$	
561	1	3	CH_2	$CH(CH_3)_2$	
562	2	3	S	H	
563	2	4		H	
564	2	3	CH_2	H	
565	2	4		H	
566	1	3	S	H	
567	1	4		H	
568	1	3	CH_2	H	
569	1	4		H	
570	1	3	CF_2	H	
571	1	4		H	
572	1	4	S	CH_3	
573	1	4		$CH(CH_3)_2$	
574	1	4	CH_2	CH_3	
575	1	4		$CH(CH_3)_2$	
576	1	3	S	$CH(CH_3)_2$	
577	1	3	CH_2	$CH(CH_3)_2$	

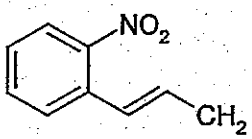
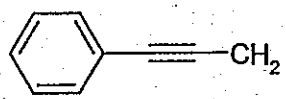
Ex No	a	b	X	R^3	R^4
578	2	3	S	H	
579	2	4		H	
580	2	3	CH_2	H	
581	2	4		H	
582	1	3	S	H	
583	1	4		H	
584	1	3	CH_2	H	
585	1	4		H	
586	1	3	CF_2	H	
587	1	4		H	
588	1	4	S	CH_3	
589	1	4		$CH(CH_3)_2$	
590	1	4	CH_2	CH_3	
591	1	4		$CH(CH_3)_2$	
592	1	3	S	$CH(CH_3)_2$	
593	1	3	CH_2	$CH(CH_3)_2$	
594	2	3	S	H	
595	2	4		H	
596	2	3	CH_2	H	
597	2	4		H	
598	1	3	S	H	
599	1	4		H	
600	1	3	CH_2	H	
601	1	4		H	
602	1	3	CF_2	H	
603	1	4		H	
604	1	4	S	CH_3	
605	1	4		$CH(CH_3)_2$	
606	1	4	CH_2	CH_3	
607	1	4		$CH(CH_3)_2$	
608	1	3	S	$CH(CH_3)_2$	
609	1	3	CH_2	$CH(CH_3)_2$	
610	2	3	S	H	

Ex No	a	b	X	R^3	R^4
611	2	4		H	
612	2	3	CH_2	H	
613	2	4		H	
614	1	3	S	H	
615	1	4		H	
616	1	3	CH_2	H	
617	1	4		H	
618	1	3	CF_2	H	
619	1	4		H	
620	1	4	S	CH_3	
621	1	4		$CH(CH_3)_2$	
622	1	4	CH_2	CH_3	
623	1	4		$CH(CH_3)_2$	
624	1	3	S	$CH(CH_3)_2$	
625	1	3	CH_2	$CH(CH_3)_2$	
626	2	3	S	H	
627	2	4		H	
628	2	3	CH_2	H	
629	2	4		H	
630	1	3	S	H	
631	1	4		H	
632	1	3	CH_2	H	
633	1	4		H	
634	1	3	CF_2	H	
635	1	4		H	
636	1	4	S	CH_3	
637	1	4		$CH(CH_3)_2$	
638	1	4	CH_2	CH_3	
639	1	4		$CH(CH_3)_2$	
640	1	3	S	$CH(CH_3)_2$	
641	1	3	CH_2	$CH(CH_3)_2$	
642	2	3	S	H	
643	2	4		H	

Ex No	a	b	X	R^3	R^4
644	2	3	CH_2	H	
645	2	4		H	
646	1	3	S	H	
647	1	4		H	
648	1	3	CH_2	H	
649	1	4		H	
650	1	3	CF_2	H	
651	1	4		H	
652	1	4	S	$CH(CH_3)_2$	
653	1	4	CH_2	CH_3	
654	1	4		$CH(CH_3)_2$	
655	1	3	S	$CH(CH_3)_2$	
656	1	3	CH_2	$CH(CH_3)_2$	
657	2	3	S	H	
658	2	4		H	
659	2	3	CH_2	H	
660	2	4		H	
661	1	3	S	H	
662	1	4		H	
663	1	3	CH_2	H	
664	1	4		H	
665	1	3	CF_2	H	
666	1	4		H	
667	1	4	S	CH_3	
668	1	4		$CH(CH_3)_2$	
669	1	4	CH_2	CH_3	
670	1	4		$CH(CH_3)_2$	
671	1	3	S	$CH(CH_3)_2$	
672	1	3	CH_2	$CH(CH_3)_2$	
673	2	3	S	H	
674	2	4		H	
675	2	3	CH_2	H	
676	2	4		H	

Ex No	a	b	X	R^3	R^4
677	1	3	S	H	
678	1	4	CH_2	H	
679	1	3	CF_2	H	
680	1	4		H	
681	1	4	S	CH_3	
682	1	4		$CH(CH_3)_2$	
683	1	4	CH_2	CH_3	
684	1	4		$CH(CH_3)_2$	
685	1	3	S	$CH(CH_3)_2$	
686	1	3	CH_2	$CH(CH_3)_2$	
687	2	3	S	H	
688	2	4	CH_2	H	
689	1	3	S	H	
690	1	4		H	
691	1	3	CH_2	H	
692	1	4		H	
693	1	3	CF_2	H	
694	1	4		H	
695	1	4	S	CH_3	
696	1	4		$CH(CH_3)_2$	
697	1	4	CH_2	CH_3	
698	1	4		$CH(CH_3)_2$	
699	1	3	S	$CH(CH_3)_2$	
700	1	3	CH_2	$CH(CH_3)_2$	
701	2	3	S	H	
702	2	4		H	
703	2	3	CH_2	H	
704	2	4		H	
705	1	3	S	H	
706	1	4		H	
707	1	3	CH_2	H	
708	1	4		H	
709	1	3	CF_2	H	

Ex No	a	b	X	R^3	R^4
710	1	4		H	
711	1	4	S	CH_3	
712	1	4		$CH(CH_3)_2$	
713	1	4	CH_2	CH_3	
714	1	4		$CH(CH_3)_2$	
715	1	3	S	$CH(CH_3)_2$	
716	1	3	CH_2	$CH(CH_3)_2$	
717	2	3	S	H	
718	2	4		H	
719	2	3	CH_2	H	
720	2	4		H	
721	1	3	S	H	
722	1	4		H	
723	1	3	CH_2	H	
724	1	4		H	
725	1	3	CF_2	H	
726	1	4		H	
727	1	4	S	CH_3	
728	1	4		$CH(CH_3)_2$	
729	1	4	CH_2	CH_3	
730	1	4		$CH(CH_3)_2$	
731	1	3	S	$CH(CH_3)_2$	
732	1	3	CH_2	$CH(CH_3)_2$	
733	2	3	S	H	
734	2	4		H	
735	2	3	CH_2	H	
736	2	4		H	
737	1	3	S	H	
738	1	3	CH_2	H	
739	1	4		H	
740	1	3	CF_2	H	
741	1	4		H	
742	1	4	S	CH_3	

Ex No	a	b	X	R^3	R^4
743	1	4		$CH(CH_3)_2$	
744	1	4	CH_2	CH_3	
745	1	4		$CH(CH_3)_2$	
746	1	3	S	$CH(CH_3)_2$	
747	1	3	CH_2	$CH(CH_3)_2$	
748	2	3	S	H	
749	2	4		H	
750	2	3	CH_2	H	
751	2	4		H	
752	1	3	S	H	
753	1	4		H	
754	1	3	CH_2	H	
755	1	4		H	
756	1	3	CF_2	H	
757	1	4		H	
758	1	4	S	CH_3	
759	1	4		$CH(CH_3)_2$	
760	1	4	CH_2	CH_3	
761	1	4		$CH(CH_3)_2$	
762	1	3	S	$CH(CH_3)_2$	
763	1	3	CH_2	$CH(CH_3)_2$	
764	2	3	S	H	
765	2	4		H	
766	2	3	CH_2	H	
767	2	4		H	
768	1	3	S	H	
769	1	4		H	
770	1	3	CH_2	H	
771	1	4		H	
772	1	3	CF_2	H	
773	1	4		H	
774	1	4	S	CH_3	
775	1	4		$CH(CH_3)_2$	

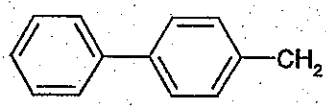
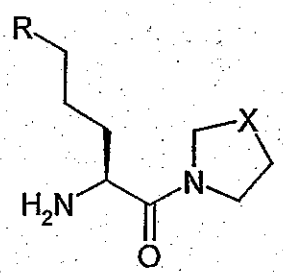
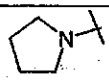
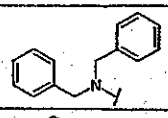
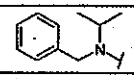
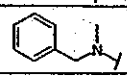
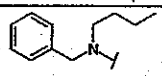
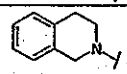
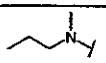
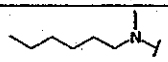
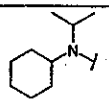
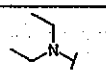
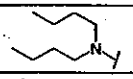
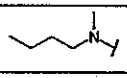
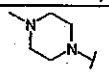
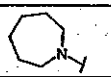
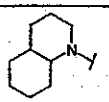
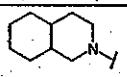
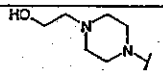
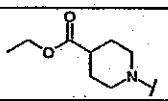
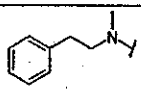
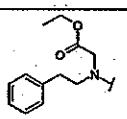
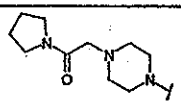
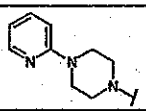
Ex No	a	b	X	R^3	R^4
776	1	4	CH_2	CH_3	
777	1	4		$CH(CH_3)_2$	
778	1	3	S	$CH(CH_3)_2$	
779	1	3	CH_2	$CH(CH_3)_2$	
780	2	3	S	H	
781	2	4		H	
782	2	3	CH_2	H	
783	2	4		H	
784	1	3	S	H	
785	1	4		H	
786	1	3	CH_2	H	
787	1	4		H	
788	1	3	CF_2	H	
789	1	4		H	
790	1	4	S	CH_3	
791	1	4		$CH(CH_3)_2$	
792	1	4	CH_2	CH_3	
793	1	4		$CH(CH_3)_2$	
794	1	3	S	$CH(CH_3)_2$	
795	1	3	CH_2	$CH(CH_3)_2$	
796	2	3	S	H	
797	2	4		H	
798	2	3	CH_2	H	
799	2	4		H	

TABLE 4



Example No	X	R	Example No	X	R
800	S		841	S	
801	CH_2		842	CH_2	
802	S		843	S	
803	CH_2		844	CH_2	
804	S		845	S	
805	CH_2		846	CH_2	
806	S		847	S	
807	CH_2			CH_2	
808	S		848	S	
809	CH_2		849	CH_2	
810	S		850	S	
811	CH_2		851	CH_2	
812	S		852	S	
813	CH_2		853	CH_2	
814	S		854	S	
815	CH_2		855	CH_2	
816	S		856	S	
817	CH_2		857	CH_2	
818	S		858	S	
819	CH_2		859	CH_2	
820	S		860	S	
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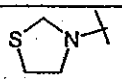
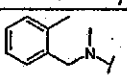
822	S		862	S	
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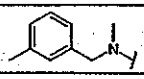
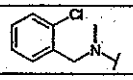
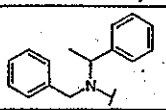
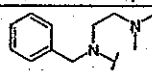
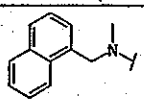
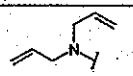
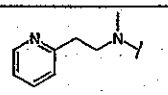
824	S		864	S	
825	CH_2		865	CH_2	
826	S		866	S	
827	CH_2		867	CH_2	
828	CH_2		868	S	
829			869	CH_2	
830	S		870	S	
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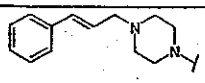
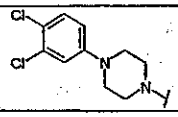
832	S		872	S	
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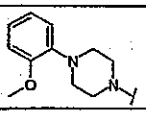
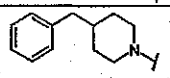
834	S		874	S	
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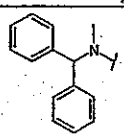
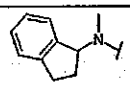
836	S		876	S	
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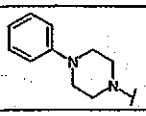
838	S				
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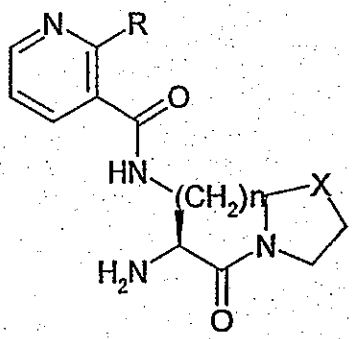
TABLE 5



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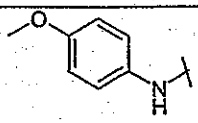
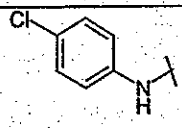
878	3	S		933	3	S	
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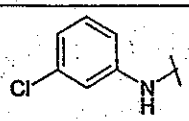
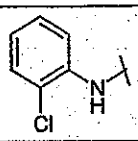
881	4			936	4		
882	3	S		937	3	S	
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884	3	CH_2		939	3	CH_2	
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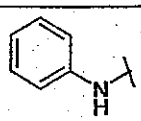
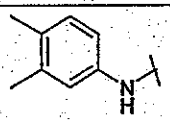
886	3	S		941	3	S	
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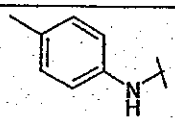
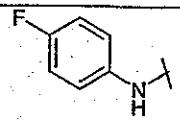
890	3	S		945	3	S	
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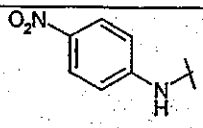
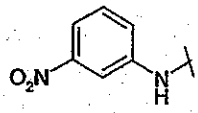
893	4			946	4		
894	3	S		947	3	S	
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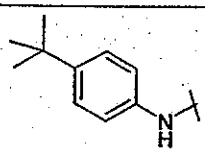
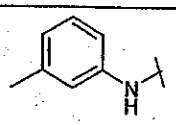
898	3	S		951	3	S	
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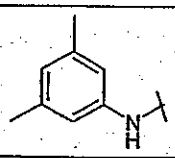
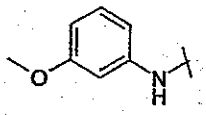
902	3	S		955	3	S	
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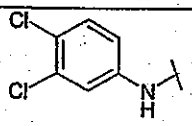
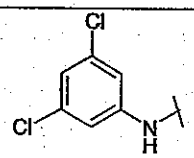
906	3	S		959	3	S	
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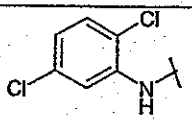
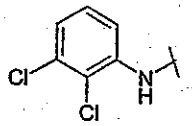
909	4			962	4		
910	3	S		963	3	S	
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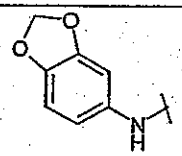
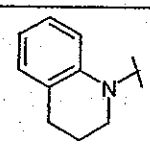
914	3	S		967	3	S	
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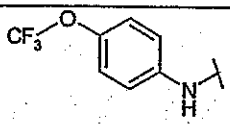
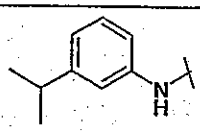
918	3	S		971	3	S	
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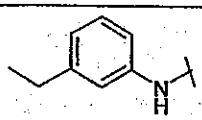
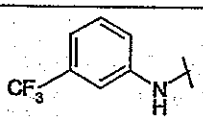
921	3	S		975	4	S	
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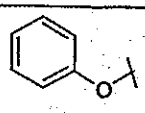
925	3	S		979	3	S	MeS
926	4			980	4		
927	3	CH_2		981	3	CH_2	
928	4			982	4		
929	3	S	Me	983	3	S	MeO
930	4			984	4		
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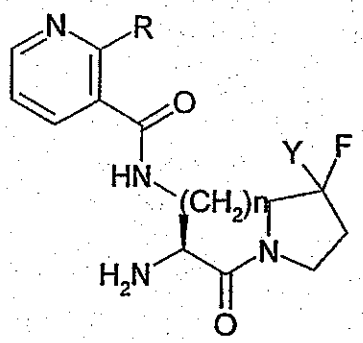
TABLE 6



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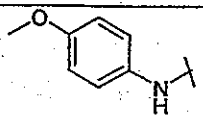
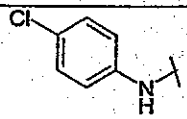
987	3	S		1044	3	S	
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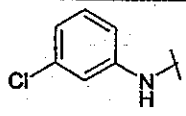
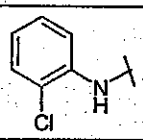
989	3	CH_2		1046	3	CH_2	
990	4			1047	4		
991	4	S		1048	3	S	
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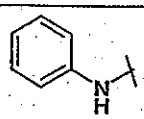
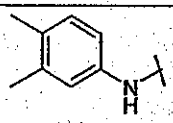
994	4			1051	4		
995	3	S		1052	3	S	
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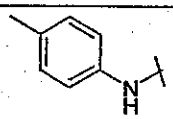
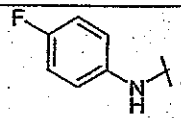
997	3	CH_2		1054	3	CH_2	
998	4			1055	4		
999	3	S		1056	3	S	
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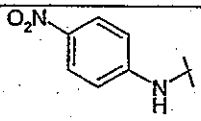
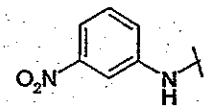
1003	3	S		1058	3	S	
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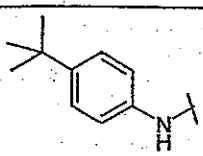
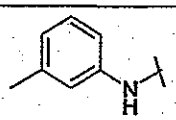
1007	3	S		1062	3	S	
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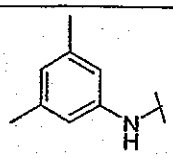
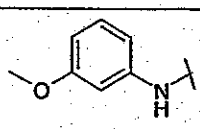
1011	3	S		1066	3	S	
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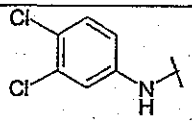
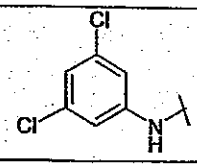
1013	3	CH_2		1068	3	CH_2	
1014	4			1069	4		

1015	3	S		1070	3	S	
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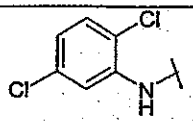
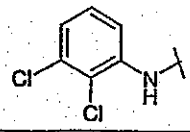
1017	3	CH_2		1072	3	CH_2	
1018	4			1073	4		
1019	3	S		1074	3	S	
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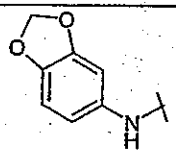
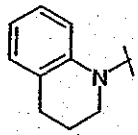
1022	4			1077	4		
1023	3	S		1078	3	S	
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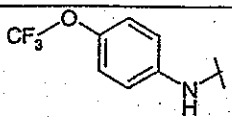
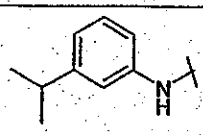
1026	4			1081	4		
1027	3	S		1082	3	S	
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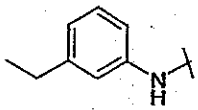
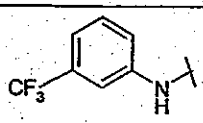
1031	3	S		1086	3	S	
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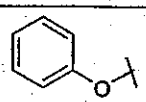
1033	3	CH_2		1088	3	CH_2	
1034	4			1089	4		
1035	3	S		1090	3	S	MeS
1036	4			1091	4		
1037	3	CH_2		1092	3	CH_2	
1038	4			1093	4		
1039	3	S	Me	1094	3	S	MeO
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1041	3	CH_2		1096	3	CH_2	
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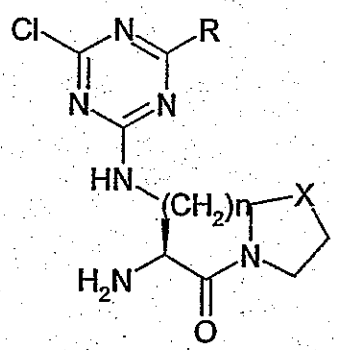
TABLE 7



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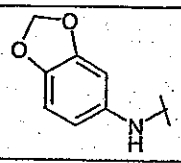
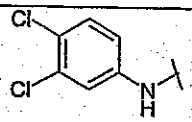
1098	3	S		1145	3	S	
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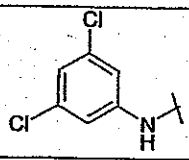
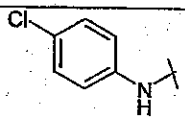
1100	3	CH_2		1147	3	CH_2	
1101	4			1148	4		
1102	3	S		1149	3	S	
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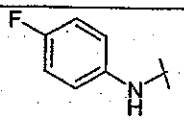
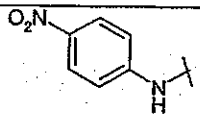
1104	3	CH_2		1151	3	CH_2	
1105	4			1152	4		
1106	3	S		1153	3	S	
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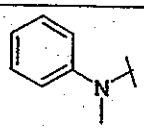
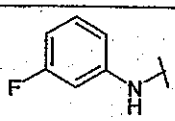
1108	3	CH_2		1155	3	CH_2	
1109	4			1156	4		
1110	3	S		1157	3	S	
1111	4						
1112	3	CH_2				CH_2	
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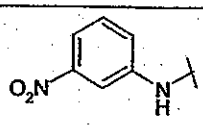
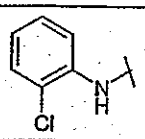
1114	3	S		1159	3	S	
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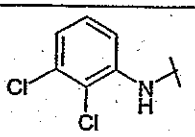
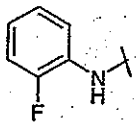
1118	3	S		1163	3	S	
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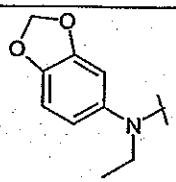
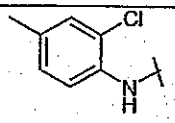
1121	4			1166	4		
1122	3	S		1167	3	S	
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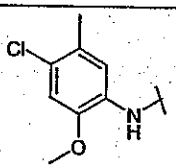
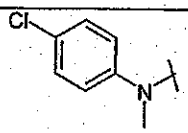
1125	4			1170	4		
1125a	3	S		1171	3	S	
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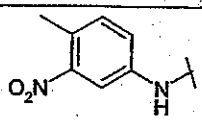
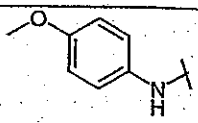
1127	3	CH_2		1173	3	CH_2	
1128	4			1174	4		
1129	3	S		1175	3	S	
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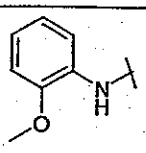
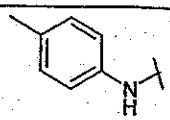
1133	3	S		1179	3	S	
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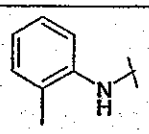
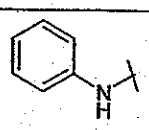
1136	4			1182	4		

1137	3	S		1183	3	S	
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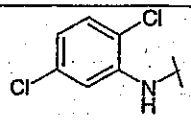
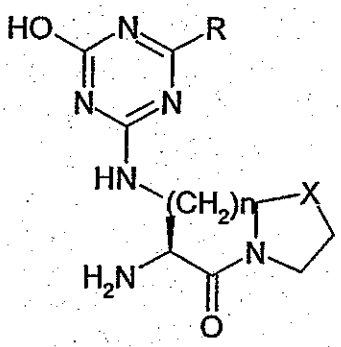
1140	4			1186	4		
1141	3	S					
1142							
1143	3	CH_2					
1144	4						

TABLE 8



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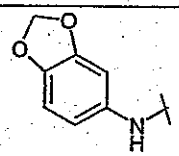
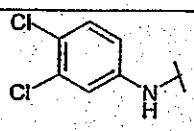
1187	3	S		1235	3	S	
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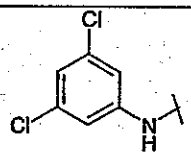
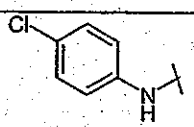
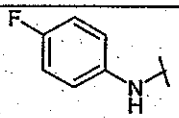
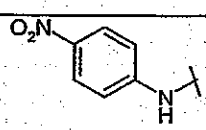
1189	3	CH_2		1237	3	CH_2	
1190	4			1238	4		
1191	3	S		1239	3	S	
1192	4			1240	4		
1193	3	CH_2		1241	3	CH_2	
1194	4			1242	4		
1195	3	S		1243	3	S	
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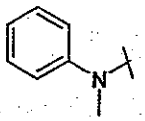
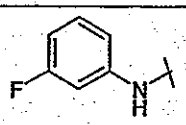
1197	3	CH_2		1245	3	CH_2	
1198	4			1246	4		
1199	3	S		1247	3	S	
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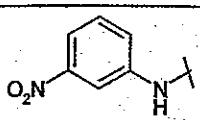
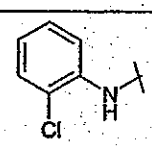
1203	3	S		1249	3	S	
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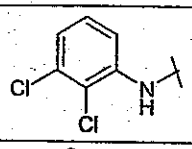
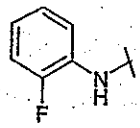
1207	3	S		1253	3	S	
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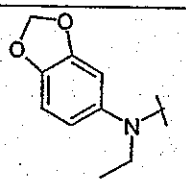
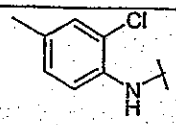
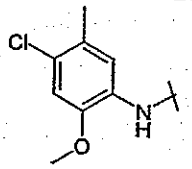
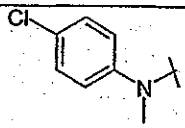
1211	3	S		1257	3	S	
1212	4			1258	4		
1213	3	CH_2		1259	3	CH_2	
1214	4			1260	4		
1215	3	S		1261	3	S	
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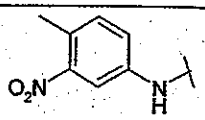
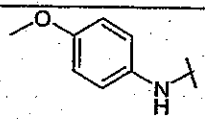
1219	3	S		1265	3	S	
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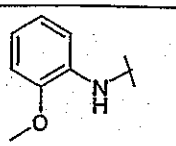
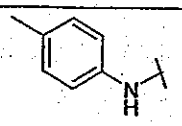
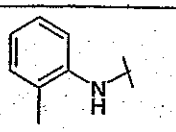
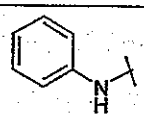
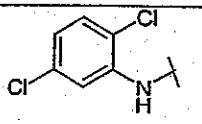
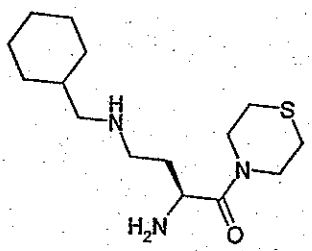
1221	3	CH_2		1267	3	CH_2	
1222	4			1268	4		
1223	3	S		1269	3	S	
1224	4			1270	4		
1225	3	CH_2		1271	3	CH_2	
1226	4			1272	4		
1227	3	S		1273	3	S	
1228	4			1274	4		
1229	3	CH_2		1275	3	CH_2	
1230	4			1276	4		
1231	3	S					
1232							
1233	3	CH_2					
1235	4						

EXAMPLE 1277

1-[2-(S)-Amino-4-(cyclohexylmethylamino)butanoyl]thiomorpholine dihydrochloride



A. 1-[2-(S)-N-(*tert*-Butyloxycarbonyl)amino-4-(9-fluorenylmethyloxycarbonylamino)-butanoyl]thiomorpholine

1-[2-(S)-N-(*tert*-Butyloxycarbonyl)amino-4-(9-fluorenylmethyloxycarbonylamino)-butanoic acid (1.0g, 2.27mmol) was dissolved in CH_2Cl_2 /DMF (9:1, 20mL). To this solution at 0°C were added 1-hydroxybenzotriazole hydrate (461mg, 3.41mmol), water-soluble carbodiimide (521mg, 2.72mmol), thiomorpholine (281mg, 2.72mmol) and triethylamine (340mg, 3.4mmol). After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (100mL). The solution was washed with 0.3M $KHSO_4$ (2 x 25mL), sat. $NaHCO_3$ (2 x 25mL), water (2 x 25mL) and brine (1 x 25mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 75% ethyl acetate, 25% pet. ether) to give a white solid identified as 1-[2-(S)-N-(*tert*-butyloxycarbonyl)amino- 4-(9-fluorenylmethyloxycarbonylamino)-butanoyl]thiomorpholine (516mg, 0.98mmol, 43%).

B. 1-[2-(S)-*N*-(*tert*-Butyloxycarbonyl)-4-amino)-butanoyl]thiomorpholine

1-[2-(S)-N-(*tert*-Butyloxycarbonyl)amino- 4-(9-fluorenylmethyloxycarbonylamino)-butanoyl thiomorpholine (500mg, 0.95mmol) was dissolved in tetrahydrofuran (20mL). Diethylamine (5mL) was added. After 90min at room temperature the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (eluant: 90% chloroform, 7% methanol, 3% triethylamine) to give a pale yellow oil identified as 1-[2-*(S)*-N-(*tert*-butyloxycarbonyl)-4-amino)-butanoyl]thiomorpholine (162mg, 0.54mmol, 56%).

C. 1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-amino-4-(cyclohexylmethylamino)butanoyl] thiomorpholine

1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-4-amino)-butanoyl]thiomorpholine (41mg, 0.135mmol) was dissolved in dichloroethane (10mL). To this solution was added cyclohexanecarboxaldehyde (15mg, 0.135mmol). After 30mins sodium triacetoxyborohydride (32mg, 0.15mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 1% acetic acid,9% methanol, 90% chloroform) to give a colourless oil identified as 1-[2-(S)-N-(*tert*-butyloxycarbonyl)-amino-4-(cyclohexylmethylamino)butanoyl] thiomorpholine (25mg, 0.063mmol, 47%).

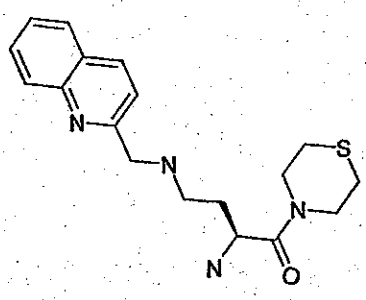
D. 1-[2-(S)-Amino-4-(cyclohexylmethylamino)butanoyl]thiomorpholine dihydrochloride

1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-amino-4-(cyclohexylmethylamino)butanoyl]thiomorpholine (25mg, 0.063mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 1-[2-(S)-amino-4-(cyclohexylmethylamino)butanoyl]thiomorpholine dihydrochloride (23mg, 0.063mmol, 100%).

$[M+H]^+ = 300.3$

EXAMPLE 1278

1-[2-(S)-Amino-4-((quinolin-2-ylmethyl)amino)butanoyl]thiomorpholine dihydrochloride



A. 1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-amino-4-((quinolin-2-ylmethyl)amino)butanoyl thiomorpholine

1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-4-amino)-butanoyl]thiomorpholine (41mg, 0.135mmol) was dissolved in 1,2-dichloroethane (10mL). To this solution was added 2-quinolinecarboxaldehyde (32mg, 0.15mmol). After 30mins sodium triacetoxyborohydride (36mg, 0.17mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 1% acetic acid,9% methanol, 90% chloroform) to give a colourless oil identified as 1-[2-(S)-N-(*tert*-butyloxycarbonyl)-amino-4-((quinolin-2-ylmethyl)amino)butanoyl thiomorpholine (32mg, 0.072mmol, 53%).

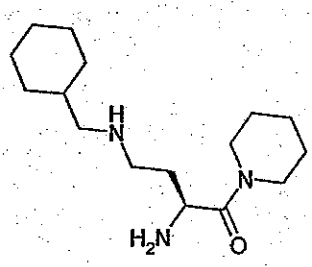
B. 1-[2-(S)-Amino-4-((quinolin-2-ylmethyl)amino)butanoyl]thiomorpholine dihydrochloride

1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-amino-4-((quinolin-2-ylmethyl)amino)butanoyl] thiomorpholine (12mg, 0.027mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 1-[2-(S)-amino-4-((quinolin-2-ylmethyl)amino)butanoyl]thiomorpholine dihydrochloride (11.3mg, 0.027mmol, 100%).

$[M+H]^+ = 345.3$

EXAMPLE 1279

1-[2-(S)-Amino-4-(cyclohexylmethylamino)butanoyl]piperidine dihydrochloride



A. 1-[2-(S)-N-(*tert*-Butyloxycarbonyl)amino-4-(9-fluorenylmethyloxycarbonylamino)-butanoyl] piperidine

1-[2-(S)-N-(*tert*-Butyloxycarbonyl)amino-4-(9-fluorenylmethyloxycarbonylamino)-butanoic acid (947mg, 2.154mmol) was dissolved in CH_2Cl_2 /DMF (9:1, 20mL). To this

solution at 0°C were added 1-hydroxybenzotriazole hydrate (436mg, 3.2mmol), water-soluble carbodiimide (495g, 2.58mmol), piperidine (220g, 2.58mmol) and triethylamine (320mg, 3.2mmol). After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (100mL). The solution was washed with 0.3M $KHSO_4$ (2 x 25mL), sat. $NaHCO_3$ (2 x 25mL), water (2 x 25mL) and brine (1 x 25mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 75% ethyl acetate, 25% pet. ether) to give a white solid identified as 1-[2-(S)-N-(*tert*-butyloxycarbonyl)amino- 4-(9-fluorenylmethyloxycarbonylamino)-butanoyl]piperidine (556mg, 1.1mmol, 51%).

B. 1-[2-*(S)*-*N*-(*tert*-Butyloxycarbonyl)-4-amino)-butanoyl]piperidine

1-[2-(S)-N-(*tert*-Butyloxycarbonyl)amino- 4-(9-fluorenylmethyloxycarbonylamino)-butanoyl] piperidine (540g, 1.1mmol) was dissolved in tetrahydrofuran (20mL). Diethylamine (5mL) was added. After 90min at room temperature the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (eluant: 90% chloroform, 7% methanol, 3% triethylamine) to give a pale yellow oil identified as 1-[2-(S)-N-(*tert*-butyloxycarbonyl)-4-amino)-butanoyl] piperidine (171mg, 0.6mmol, 57%).

C. 1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-amino-4-(cyclohexylmethylamino)butanoyl] piperidine

1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-4-amino)-butanoyl] piperidine (43mg, 0.15mmol) was dissolved in 1,2-dichloroethane (20mL). To this solution was added cyclohexanecarboxaldehyde (17mg, 0.15mmol). After 30mins sodium triacetoxyborohydride (36mg, 0.17mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 1% acetic acid,9% methanol, 90% chloroform) to give a colourless oil identified as 1-[2-(S)-N-(*tert*-butyloxycarbonyl)-amino-4-(cyclohexylmethylamino)butanoyl]piperidine (38mg, 0.1mmol, 66%).

D. 1-[2-(S)-Amino-4-(cyclohexylmethylamino)butanoyl] piperidine dihydrochloride

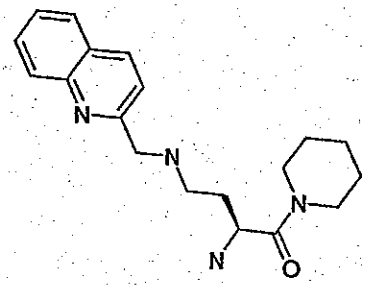
1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-amino-4-(cyclohexylmethylamino)butanoyl]piperidine (38mg, 0.1mmol) was dissolved in 4M HCl/dioxan (2mL). After 1h at room

temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 1-[2-(S)-amino-4-(cyclohexylmethylamino)butanoyl] piperidine dihydrochloride (33mg, 0.093mmol, 93%).

$[M+H]^+ = 282.3$

EXAMPLE 1280

1-[2-(S)-Amino-4-((quinolin-2-ylmethyl)amino)butanoyl]piperidine dihydrochloride



A. 1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-amino-4-((quinolin-2-ylmethyl)amino)butanoyl] piperidine

1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-4-amino)-butanoyl] piperidine (24mg, 0.15mmol) was dissolved in 1,2-dichloroethane (25mL). To this solution was added 2-quinolinecarboxaldehyde (24mg, 0.15mmol). After 30mins sodium triacetoxyborohydride (36mg, 0.17mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 1% acetic acid,9% methanol, 90% chloroform) to give a colourless oil identified as 1-[2-(S)-N-(*tert*-butyloxycarbonyl)-amino-4-((quinolin-2-ylmethyl)amino)butanoyl] piperidine (35mg, 0.082mmol, 55%).

B. 1-[2-(S)-Amino-4-((quinolin-2-ylmethyl)amino)butanoyl] piperidine dihydrochloride

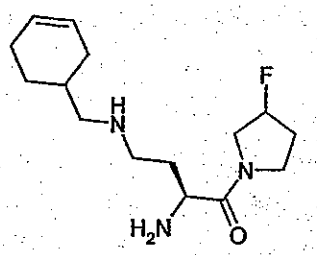
1-[2-(S)-N-(*tert*-Butyloxycarbonyl)-amino-4-((quinolin-2-ylmethyl)amino)butanoyl] piperidine (35mg, 0.082mmol) was dissolved in 4M HCl/dioxan (2mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised

from water to give a white solid identified as 1-[2-(S)-amino-4-((quinolin-2-ylmethyl)amino)butanoyl] piperidine dihydrochloride (26mg, 0.065mmol, 79%).

$[M+H]^+ = 327.3$

EXAMPLE 1281

3-Fluoro-1-[2-(S)-amino-4-(cyclohexenylmethylamino)butanoyl]pyrrolidine dihydrochloride



A. 1-(*tert*-Butyloxycarbonyl)-3-fluoropyrrolidine

N-(*tert*-Butyloxycarbonyl)-3-hydroxypyrrolidine (21.0g, 10.7mmol) was dissolved in CH_2Cl_2 (30ml). (Diethylamino)sulphur trifluoride (1.72g, 10.7mmol) was added to this solution at -78 °C. The mixture was stirred for 18 hours at -78 °C to room temperature then the reaction mixture was carefully poured into sat. $NaHCO_3$ (100ml) and stirred for 15min and extracted with CH_2Cl_2. The organic extract was washed with water and brine, dried (Na_2SO_4) and evaporated *in vacuo* to give an orange oil. The residue was purified by flash chromatography (eluant: 28% ethyl acetate, 72% pet. ether 60-80) to give a colourless oil identified as 1-(*tert*-butyloxycarbonyl)-3-fluoropyrrolidine (1.14g, 5.34mmol, 50%).

B 3-Fluoropyrrolidine hydrochloride

1-(*tert*-Butyloxycarbonyl)-3-fluoropyrrolidine (1.14g, 5.34mmol) was dissolved in 4M HCl/dioxan (30ml). The mixture was stirred for 1 hour at room temperature then the solvent was removed *in vacuo* to give an off-white solid identified as 3-fluoropyrrolidine hydrochloride (640mg, 5.2mmol, 95%).

C. 3-Fluoro-1-[2-(S)-N-(*tert*-butyloxycarbonyl)amino-4-(9-fluorenylmethyloxycarbonylamino)-butanoyl] pyrrolidine

1-[2-(S)-N-(*tert*-Butyloxycarbonyl)amino-4-(9-fluorenylmethyloxycarbonylamino)-butanoic acid (950mg, 2.15mmol) was dissolved in CH_2Cl_2 /DMF (9:1, 20mL). To this

solution at 0°C were added 1-hydroxybenzotriazole hydrate (395mg, 2.6mmol), water-soluble carbodiimide (572mg, 3.0mmol), 3-fluoropyrrolidine hydrochloride (270g, 2.15mmol) and triethylamine (320mg, 3.2mmol). After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (100mL). The solution was washed with 0.3M $KHSO_4$ (2 x 25mL), sat. $NaHCO_3$ (2 x 25mL), water (2 x 25mL) and brine (1 x 25mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 75% ethyl acetate, 25% pet. ether) to give a white solid identified as 3-fluoro1-[2-(S)-N-(*tert*-butyloxycarbonyl)amino- 4-(9-fluorenylmethyloxycarbonylamino)-butanoyl]pyrrolidine (808mg, 1.58mmol, 73%).

D. 3-Fluoro-1-[*2-(S)-N*-(*tert*-butyloxycarbonyl)-4-amino)-butanoyl]pyrrolidine

3-Fluoro-1-[2-(S)-N-(*tert*-butyloxycarbonyl)amino- 4-(9-fluorenylmethyloxycarbonylamino)-butanoyl] pyrrolidine (800mg, 1.58mmol) was dissolved in tetrahydrofuran (20mL). Diethylamine (5mL) was added. After 90min at room temperature the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (eluant: 90% chloroform, 7% methanol, 3% triethylamine) to give a pale yellow oil identified as 3-fluoro-1-[2-(S)-N-(*tert*-butyloxycarbonyl)-4-amino)-butanoyl] pyrrolidine (316mg, 1.04mmol, 66%).

E. 3-Fluoro-1-[2-(S)-N-(*tert*-butyloxycarbonyl)-amino-4-(cyclohexenylmethylamino)butanoyl] pyrrolidine

3-Fluoro-1-[2-(S)-N-(*tert*-butyloxycarbonyl)-4-amino)-butanoyl] pyrrolidine (150mg, 0.52mmol) was dissolved in methanol (20mL). To this solution was added 3-cyclohexenecarboxaldehyde (63mg, 0.57mmol). After 30mins sodium triacetoxyborohydride (220mg, 1.04mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 1% acetic acid,9% methanol, 90% chloroform) to give a colourless oil identified as 3-fluoro-1-[2-(S)-N-(*tert*-butyloxycarbonyl)-amino-4-(cyclohexenylmethylamino)butanoyl]pyrrolidine (176mg, 0.46mmol, 77%).

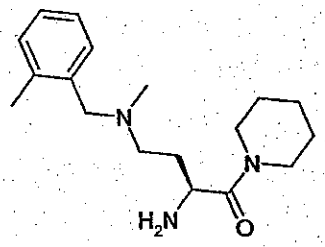
F. 3-Fluoro-1-[2-(S)-amino-4-(cyclohexenylmethylamino)butanoyl] pyrrolidine dihydrochloride

3-Fluoro-1-[2-(S)-N-(*tert*-butyloxycarbonyl)-amino-4-(cyclohexenylmethylamino)butanoyl]pyrrolidine (176mg, 0.46mmol) was dissolved in 4M HCl/dioxan (2mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 3-fluoro-1-[2-(S)-amino-4-(cyclohexenylmethylamino)butanoyl] pyrrolidine dihydrochloride (140mg, 0.39mmol, 963%).

$[M+H]^+ = 284.3$

EXAMPLE 1282

1-[2-(S)-Amino-4-(N-methyl-N-(2-methylbenzyl)amino)butanoyl]piperidine dihydrochloride



A. N-(tert-Butyloxycarbonyl)–L-homoserine lactone

L-Homoserine lactone 1.76g, 12.8mmol) was dissolved in DMF (30 mL). This solution was cooled to 0 ^{0}C, triethylamine (1.41, 14.1 mmol) di-tert-butyl dicarbonate(3.35g, 15.35 mmol) was added. After 18 hours at room temperature the solvent was evaporated *in vacuo,* the residue was taken up in dichloromethane (200 mL). This solution was washed with 1M $KHSO_4$ (2 x 50mL) and brine (1 x 50mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a white solid, recrystallised from EtOAc/pet.ether to give a white solid identified as *N*-(*tert*-butyloxycarbonyl)–L-homoserine lactone (2.25mg, 11.2mmol, 87%).

B. 1-[2-(S)-(*N*-(*tert*-Butyloxycarbonyl)amino)-4-hydroxybutanoyl]piperidine

N-(*tert*-Butyloxycarbonyl)–L-homoserine lactone (100mg, 0.5mmol) was dissolved in tetrahydrofuran (30 mL). Piperidine (42mg, 0.5mmol) was added. After 72 hours at

room temperature the reaction mixture was diluted with ethyl acetate (150 mL). This solution was washed with water (1 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil identified as 1-[2-(S)-(*N*-(*tert*-butyloxycarbonyl)amino)-4-hydroxybutanoyl]piperidine (142mg, 0.5mmol, 100%).

C. 1-[2-(S)-(*N*-(*tert*-Butyloxycarbonyl)amino)-4-oxobutanoyl] piperidine

1-[2-(S)-(*N*-(*tert*-Butyloxycarbonyl)amino)-4-hydroxybutanoyl] piperidine (142mg, 0.5mmol) was dissolved in dichloromethane (50 mL). Dess-Martin periodinane (232mg, 0.5mmol) was added. After 1 hour at room temperature the reaction mixture was diluted with ethyl acetate (150 mL). This solution was washed with water (1 x 20ml) and brine (1 x 20ml), dried (Na_2SO_4) and evaporated *in vacuo* to give a colourless oil. Purified by flash chromatography on silica gel (eluant: 50% ethyl acetate, 50% pet. ether 60-80) to give a colourless oil identified as 1-[2-(S)-(*N*-(*tert*-butyloxycarbonyl)amino)-4-oxobutanoyl] piperidine (40mg, 0.14mmol, 27%).

D. 1-[2-(S)-(*N* -(*tert*-butyloxycarbonyl)amino-4-(N-methyl-N-(2-methylbenzyl)amino) butanoyl]piperidine

1-[2-(S)-(*N*-(*tert*-Butyloxycarbonyl)amino)-4-oxobutanoyl] piperidine (40mg, 14mmol) was dissolved in methanol (20mL). To this solution was added N-methyl-2-methylbenzylamine (19mg, 0.14mmol). After 2 hours sodium triacetoxyborohydride (64mg, 0.3mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel to give a colourless oil identified as 1-[2-(S)-(*N* -(*tert*-butyloxycarbonyl)amino-4-(N-methyl-N-(2-methylbenzyl)amino) butanoyl] piperidine (36mg, 0.09mmol, 64%).

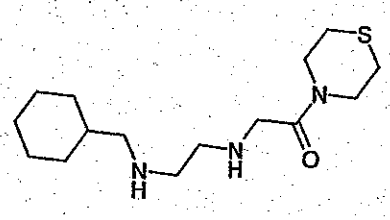
E. 1-[2-(S)-Amino-4-(N-methyl-N-(2-methylbenzyl)amino)butanoyl] piperidine dihydrochloride

1-[2-(S)-(*N*-(*tert*-Butyloxycarbonyl)amino-4-(N-methyl-N-(2-methylbenzyl)amino) butanoyl] piperidine (36mg, 0.09mmol)was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a pale brown solid identified as 1-[2-(S)-amino-4-(N-

methyl-N-(2-methylbenzyl)amino)butanoyl] piperidine dihydrochloride (43mg, 0.09mmol, 100%)

EXAMPLE 1283

1-[N-(2``-(Cyclohexylmethylaminoethyl)glycinyl)]thiomorpholine dihydrochloride



A. 1-[N-2`-(*tert*-Butyloxycarbonyl)-N-(2``-(9-fluorenylmethyloxycarbonyl aminoethyl)-glycinyl]thiomorpholine

N-2`-(*tert*-Butyloxycarbonyl)-N-(2``-(9-fluorenylmethyloxycarbonyl aminoethyl)-glycine (2.5g, 5.7mmol) was dissolved in CH_2Cl_2 /DMF (9:1, 100mL). To this solution at 0°C were added 1-hydroxybenzotriazole hydrate (833mg, 6.3mmol), water-soluble carbodiimide (974mg, 6.3mmol), thiomorpholine (617mg, 6.0mmol) and N-methylmorpholine (800mg, 8mmol). After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (100mL). The solution was washed with 0.3M $KHSO_4$ (2 x 25mL), sat. $NaHCO_3$ (2 x 25mL), water (2 x 25mL) and brine (1 x 25mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 75% ethyl acetate, 25% pet. ether) to give a white solid identified as 1-[N-2`-(*tert*-butyloxycarbonyl)-N-(2``-(9-fluorenylmethyloxycarbonyl aminoethyl)-glycinyl]thiomorpholine (2.7g, 5.1mmol, 90%).

B. 1-[N-2`-(*tert*-Butyloxycarbonyl)-(2``-aminoethyl)-glycinyl] thiomorpholine

1-[N-2`-(*tert*-Butyloxycarbonyl)-N-(2``-(9-fluorenylmethyloxycarbonyl aminoethyl)-glycinyl]thiomorpholine (2.7g, 5.1mmol) was dissolved in tetrahydrofuran (20mL). Diethylamine (5mL) was added. After 90min at room temperature the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (eluant: 90% chloroform, 7% methanol, 3% triethylamine) to give a pale yellow oil identified as 1-[N-2`-(*tert*-butyloxycarbonyl)-(2``-aminoethyl)-glycinyl] thiomorpholine (1.44g, 4.7mmol, 92%).

C. 1-[2`-N-(*tert*-Butyloxycarbonyl *N*-(2``-(cyclohexylmethylaminoethyl)-glycinyl] thiomorpholine

1-[N-2`-(*tert*-Butyloxycarbonyl)-(2``-aminoethyl)-glycinyl] thiomorpholine (100mg, 0.3mmol) was dissolved in methanol (25mL). To this solution was added cyclohexanecarboxaldehyde (34mg, 0.3mmol). After 30mins sodium triacetoxyborohydride (126mg, 0.6mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 1% acetic acid,9% methanol, 90% chloroform) to give a colourless oil identified as 1-[2`-N-(*tert*-Butyloxycarbonyl *N*-(2``-(cyclohexylmethylaminoethyl)-glycinyl] thiomorpholine (33mg, 0.08mmol, 27%).

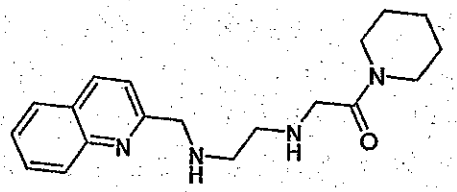
D. 1-[N-(2``-(Cyclohexylmethylaminoethyl)glycinyl)]thiomorpholine dihydrochloride

1-[2`-N-(*tert*-Butyloxycarbonyl-*N*-(2``-(cyclohexylmethylaminoethyl)-glycinyl] thiomorpholine (33mg, 0.081mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 1-[N-(2``-(cyclohexylmethylaminoethyl)glycinyl)]thiomorpholine dihydrochloride (31mg, 0.08mmol, 100%).

$[M+H]^+ = 300.3$

EXAMPLE 1284

1-[N-(2``-((Quinolin-2-ylmethyl)aminoethyl)glycinyl)]pyrrolidine dihydrochloride



A. 1-[N-2`-(*tert*-Butyloxycarbonyl)-N-(2``-(9-fluorenylmethyloxycarbonyl aminoethyl)-glycinyl]piperidine

N-2`-(*tert*-Butyloxycarbonyl)-N-(2``-(9-fluorenylmethyloxycarbonyl aminoethyl)-glycine (2.5g, 5.7mmol) was dissolved in CH_2Cl_2 /DMF (9:1, 100mL). To this solution at 0°C were added 1-hydroxybenzotriazole hydrate (1.5g, 11.1mmol), water-soluble carbodiimide (1.3g, 6.8mmol), piperidine (484mg, 5.69mmol) and N-methylmorpholine (800mg, 8mmol). After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (100mL). The solution was washed with 0.3M $KHSO_4$ (2 x 25mL), sat. $NaHCO_3$ (2 x 25mL), water (2 x 25mL) and brine (1 x 25mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 75% ethyl acetate, 25% pet. ether) to give a white solid identified as 1-[N-2`-(*tert*-butyloxycarbonyl)-N-(2``-(9-fluorenylmethyloxycarbonyl aminoethyl)-glycinyl]piperidine (2.8g, 5.5mmol, 96%).

B. 1-[N-2`-(*tert*-Butyloxycarbonyl)-(2``-aminoethyl)-glycinyl] piperidine

1-[N-2`-(*tert*-Butyloxycarbonyl)-N-(2``-(9-fluorenylmethyloxycarbonyl aminoethyl)-glycinyl]piperidine (2.8g, 5.5mmol) was dissolved in tetrahydrofuran (20mL). Diethylamine (5mL) was added. After 90min at room temperature the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (eluant: 90% chloroform, 7% methanol, 3% triethylamine) to give a pale yellow oil identified as 1-[N-2`-(*tert*-butyloxycarbonyl)-(2``-aminoethyl)-glycinyl] piperidine (1.4g, 4.9mmol, 89%).

C. 1-[2`-N-(*tert*-Butyloxycarbonyl *N*-(2``-((quinolin-2-ylmethyl)aminoethyl)-glycinyl] piperidine

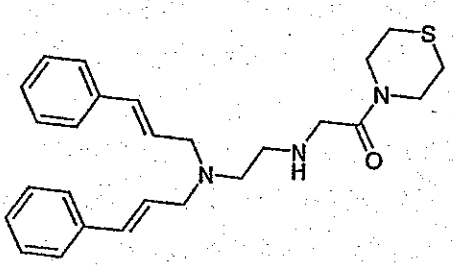
1-[N-2`-(*tert*-Butyloxycarbonyl)-(2``-aminoethyl)-glycinyl] piperidine was dissolved in methanol (25mL). To this solution was added 2-quinolinecarboxaldehyde. After 30mins sodium triacetoxyborohydride was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 1% acetic acid,9% methanol, 90% chloroform) to give a colourless oil identified as 1-[2`-N-(*tert*-butyloxycarbonyl *N*-(2``-((quinolin-2-ylmethyl)aminoethyl)-glycinyl] piperidine.

D. 1-[N-(2``-((Quinolin-2-ylmethyl)aminoethyl)glycinyl)]piperidine dihydrochloride

1-[2`-N-(*tert*-Butyloxycarbonyl-*N*-(2``-((quinolin-2-ylmethyl)aminoethyl)-glycinyl] piperidine was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 1-[N-(2``-((quinolin-2-ylmethyl)aminoethyl)glycinyl)]piperidine dihydrochloride.

EXAMPLE 1285

1-[N,N-(2``,2``-((Dicinnamyl)aminoethyl)glycinyl)]thiomorpholine dihydrochloride



A. 1-[2`-N-(*tert*-Butyloxycarbonyl N,N-(2``,2``-((dicinnamyl)aminoethyl)-glycinyl] thiomorpholine

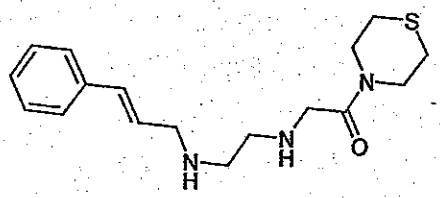
(2*S*)-1-(*N*$^{\alpha}$-(*tert*-Butyloxycarbonyl)-L-lysinyl)-pyrrolidine-2-carbonitrile (250mg, 0.83mmol) was dissolved in dichloroethane (25mL). To this solution was added trans-cinnamaldehyde (108mg, 0.83mmol). After 30mins sodium triacetoxyborohydride (350mg, 1. 6mmol) was added. After 18h at room temperature the solvent was removed *in vacuo* and the residue was taken up in chloroform (70mL). This solution was washed with water (2 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (eluant: 2% methanol, 98% chloroform) to give a colourless oil identified as 1-[2`-N-(*tert*-butyloxycarbonyl N,N-(2``,2``-((dicinnamyl)aminoethyl)-glycinyl] thiomorpholine. Further elution with 9% methanol, 90% chloroform and 1% acetic acid gave a colourless oil identified as 1-[2`-N-(*tert*-butyloxycarbonyl N,-(2``-((cinnamyl)aminoethyl)-glycinyl] thiomorpholine (180mg, 0.43mmol, 52%)

B. 1-[N,N-(2``,2``-((Dicinnamyl)aminoethyl)glycinyl)]thiomorpholine dihydrochloride

1-[2`-N-(*tert*-Butyloxycarbonyl N,N-(2``,2``-((dicinnamyl)aminoethyl)-glycinyl] thiomorpholine was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 1-[N,N-(2``,2``-((dicinnamyl)aminoethyl)glycinyl)]thiomorpholine dihydrochloride.

EXAMPLE 1286

1-[N-(2``-((Cinnamyl)aminoethyl)glycinyl)]thiomorpholine dihydrochloride



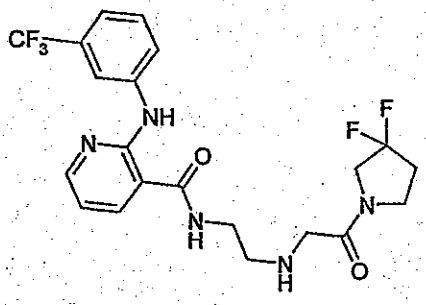
A. 1-[N-(2``-((Cinnamyl)aminoethyl)glycinyl)]thiomorpholine dihydrochloride

1-[2`-N-(*tert*-Butyloxycarbonyl N-(2``-((cinnamyl)aminoethyl)-glycinyl] thiomorpholine (180mg, 0.43mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 1-[N-(2``-((cinnamyl)aminoethyl)glycinyl)]thiomorpholine dihydrochloride (168mg, 0.43mmol, 100%).

$[M+H]^+ = 320.3$

EXAMPLE 1287

3,3-Difluoro-1-[*N*-2``-(3'-trifluoromethylanilino)pyridyl-3-carbonyl aminoethyl)glycinyl)]pyrrolidine dihydrochloride



A. 3,3-Difluoro-1-[N-2`-(*tert*-butyloxycarbonyl)-N-(2``-(9-fluorenylmethyloxycarbonyl aminoethyl)-glycinyl] pyrrolidine

N-2`-(*tert*-Butyloxycarbonyl)-N-(2``-(9-fluorenylmethyloxycarbonyl aminoethyl)-glycine (1.0g, 2.27mmol) was dissolved in CH_2Cl_2 /DMF (9:1, 100mL). To this solution at 0°C were added 1-hydroxybenzotriazole hydrate (620mg, 4.6mmol), water-soluble carbodiimide (560mg, 2.8mmol), 3,3-difluoropyrrolidine hydrochloride (360mg, 2.5mmol) and N-methylmorpholine (800mg, 8mmol). After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (100mL). The solution was washed with 0.3M $KHSO_4$ (2 x 25mL), sat. $NaHCO_3$ (2 x 25mL), water (2 x 25mL) and brine (1 x 25mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 60% ethyl acetate, 40% pet. ether) to give a white solid identified as 3,3-difluoro-1-[N-2`-(*tert*-butyloxycarbonyl)-N-(2``-(9-fluorenylmethyloxycarbonyl aminoethyl)-glycinyl] pyrrolidine (934g, 1.7mmol, 77%).

B.3,3-Difluoro-1-[N-2`-(*tert*-butyloxycarbonyl)aminoethyl)-glycinyl] pyrrolidine

3,3-Difluoro-1-[N-2`-(*tert*-butyloxycarbonyl)-N-(2``-(9-fluorenylmethyloxycarbonyl aminoethyl)-glycinyl] pyrrolidine (890g, 1.68mmol) was dissolved in tetrahydrofuran (20mL). Diethylamine (5mL) was added. After 90min at room temperature the solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (eluant: 90% chloroform, 7% methanol, 3% triethylamine) to give a pale yellow oil identified as 3,3-difluoro-1-[N-2`-(*tert*-butyloxycarbonyl)aminoethyl)-glycinyl] pyrrolidine (470mg, 1.5mmol, 91%).

C. 3,3-Difluoro-1-[N-2`-(*tert*-butyloxycarbonyl)-*N*-2``-(3'-trifluoromethylanilino)pyridyl-3-carbonyl aminoethyl)glycinyl)]pyrrolidine

3,3-Difluoro-1-[N-2`-(*tert*-butyloxycarbonyl)aminoethyl)-glycinyl] pyrrolidine (50mg, 0.16mmol) was dissolved in CH_2Cl_2 /DMF (9:1, 20mL). To this solution at 0°C was

added 1-hydroxybenzotriazole hydrate (46mg, 0.34mmol), water-soluble carbodiimide (40mg, 0.2mmol), niflumic acid (49mg, 0.17mmol) and N-methylmorpholine (40mg, 0.4mmol). After 18h at 0°C to room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (70mL). The solution was washed with 0.3M $KHSO_4$ (1 x 20mL), sat. $NaHCO_3$ (1 x 20mL), water (1 x 20mL) and brine (1 x 20mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant: 75% ethyl acetate, 25% pet. ether) to give a yellow oil identified as 3,3-difluoro-1-[N-2`-(*tert*-butyloxycarbonyl)-*N*-2``-(3'-trifluoromethylanilino)pyridyl-3-carbonyl aminoethyl)glycinyl)]pyrrolidine (63mg, 0.11mmol, 67%).

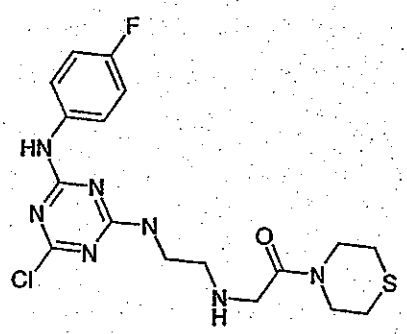
D. 3,3-Difluoro-1-[*N*-2``-(3'-trifluoromethylanilino)pyridyl-3-carbonyl aminoethyl) glycinyl)]pyrrolidine dihydrochloride

3,3-Difluoro-1-[N-2`-(*tert*-butyloxycarbonyl)-*N*-2``-(3'-trifluoromethylanilino)pyridyl-3-carbonyl aminoethyl)glycinyl)]pyrrolidine (55mg, 0.10mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a pale brown solid identified as 3,3-difluoro-1-[*N*-2``-(3'-trifluoromethylanilino)pyridyl-3-carbonyl aminoethyl)glycinyl)]pyrrolidine dihydrochloride (52mg, 0.10mmol, 100%).

$[M+H]^+ = 472.3$

EXAMPLE 1288

3,3-Difluoro-[*N*-2``-(6-Chloro-4-(4'-fluoroanilino)-1,3,5-triazinyl)aminoethyl) glycinyl)]thiomorpholine dihydrochloride



A. 4,6-Dichloro-2-(4'-fluoroanilino)-1,3,5-triazine

Cyanuric chloride (1.844g, 10mmol) was dissolved in acetonitrile (20mL). The solution was cooled to –20 ^{0}C. A solution of 4-fluoroaniline (1.1g, 10mmol) and triethylamine (1.0g, 10mmol) was slowly added. After 1 hour at –20 ^{0}C the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (150mL). The solution was washed with water (1 x 50mL) and brine (1 x 50mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was recrystallised from ethyl acetate/ hexane to give an off white solid identified as 4,6-dichloro-2-(4'-fluoroanilino)-1,3,5-triazine 1.7g, 6.0mmol, 60%).

B. 1-[N-2`-(*tert*-butyloxycarbonyl)-*N*-2``- (6-Chloro-4-(4'-fluoroanilino)-1,3,5-triazinyl aminoethyl)glycinyl)] thiomorpholine

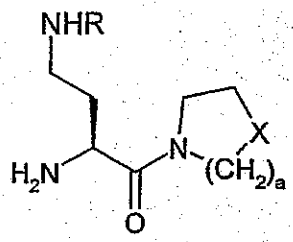
1-[N-2`-(*tert*-butyloxycarbonyl)aminoethyl)-glycinyl] thiomorpholine (100mg, 0.3mmol) was dissolved in dichloromethane (30mL). To this solution was added 4,6-dichloro-2-(4'-fluoroanilino)-1,3,5-triazine (90mg, 0.3mmol) and triethylamine (50mg, 0.5mmol). After 2 hours at room temperature the solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (150mL). This solution was washed with water (2 x 30mL) and brine (1 x 30mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography (eluant: 60% ethyl acetate, 40% pet. ether) to give a white solid identified as 1-[N-2`-(*tert*-butyloxycarbonyl)-*N*-2``- (6-chloro-4-(4'-fluoroanilino)-1,3,5-triazinyl aminoethyl)glycinyl)] thiomorpholine (20mg, 0.032mmol, 11%).

C. 1-[*N*-2``-(6-Chloro-4-(4'-fluoroanilino)-1,3,5-triazinyl)aminoethyl) glycinyl)] thiomorpholine dihydrochloride

1-[N-2`-(*tert*-butyloxycarbonyl)-*N*-2``- (6-chloro-4-(4'-fluoroanilino)-1,3,5-triazinyl aminoethyl)glycinyl)] thiomorpholine (18.8mg, 0.03mmol) was dissolved in 4M HCl/dioxan (20mL). After 1h at room temperature the solvent was removed *in vacuo*. The residue was lyophilised from water to give a white solid identified as 1-[*N*-2``-(6-Chloro-4-(4'-fluoroanilino)-1,3,5-triazinyl)aminoethyl) glycinyl)] thiomorpholine dihydrochloride (18mg, 0.03mmol, 100%).

$[M+H]^+ = 526.4$

TABLE 9



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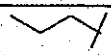
1289	S	1	
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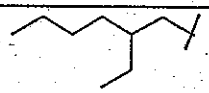
1295	S	1	
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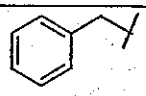
1311	S	1	
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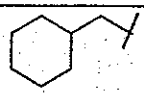
1317	S	1	
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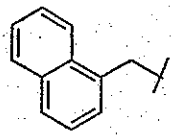
1321	S	1	
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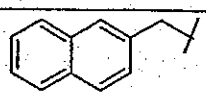
1327	S	1	
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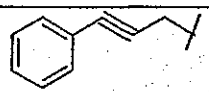
1334	CF_2		
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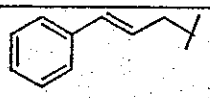
1339	S	1	
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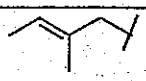
1345	S	1	
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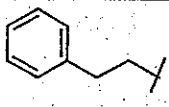
1351	S	1	
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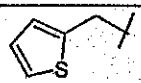
1357	S	1	
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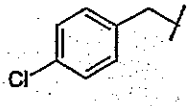
1363	S	1	
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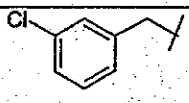
1369	S	1	
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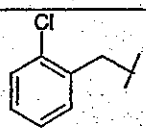
1375	S	1	
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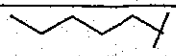
1381	S	1	
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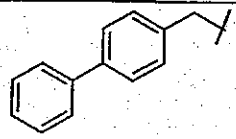
1387	S	1	
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1392	O		
1393	S	1	
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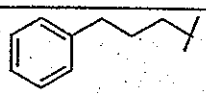
1395	CHF		
1396	S	2	
1397	CH_2		
1398	O		
1399	S	1	
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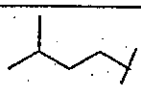
1402	S	2	
1403	CH_2		
1404	O		
1405	S	1	
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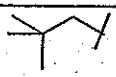
1408	S	2	
1409	CH_2		
1410	O		
1411	S	1	
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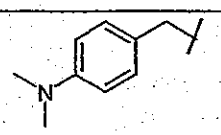
1414	S	2	
1415	CH_2		
1416	O		
1417	S	1	
1418	CF_2		
1419	CHF		
1420	S	2	
1421	CH_2		
1422	O		
1423	S	1	
1424	CF_2		
1425	CHF		

1426	S	2	
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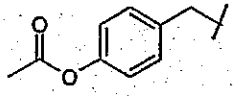
1428	O		
1429	S	1	
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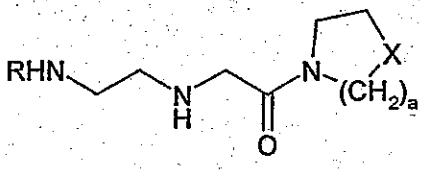
1432	S	2	
1433	CH_2		
1434	O		

TABLE 10



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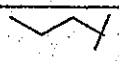
1614	S	1	
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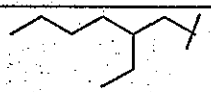
1617	CH_2		
1618	S	1	
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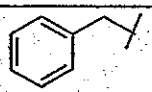
1621	CH_2		
1622	S	1	
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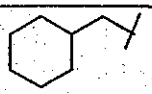
1626	S	1	
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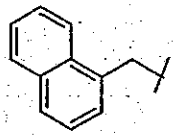
1630	S	1	
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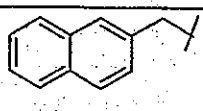
1633	CH_2		
1634	S	1	
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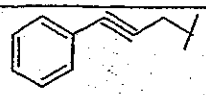
1637	CH_2		
1638	S	1	

1639	CF_2		
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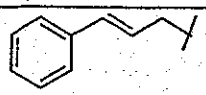
1641	CH_2		
1642	S	1	
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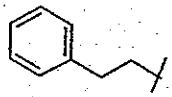
1644	S	2	
1645	CH_2		
1646	S	1	
1647	CF_2		
1648	S	2	
1649	CH_2		
1650	S	1	
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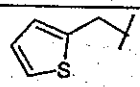
1654	S	1	
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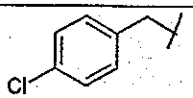
1657	CH_2		
1658	S	1	
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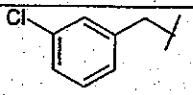
1661	CH_2		
1662	S	1	
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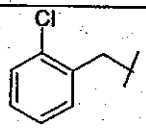
1666	S	1	
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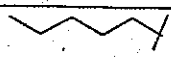
1668	S	2	
1669	CH_2		
1670	S	1	
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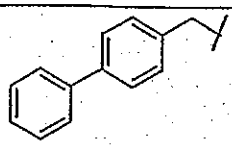
1673	CH_2		
1674	S	1	
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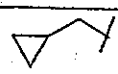
1677	CH_2		
1678	S	1	
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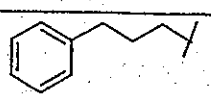
1681	CH_2		
1682	S	1	
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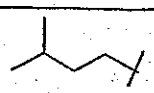
1684	S	2	

1685	CH_2		
1686	S	1	
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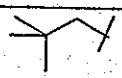
1688	S	2	
1689	CH_2		
1690	S	1	
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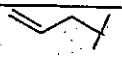
1694	S	1	
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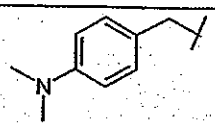
1696	S	2	
1697	CH_2		
1698	S	1	
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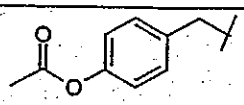
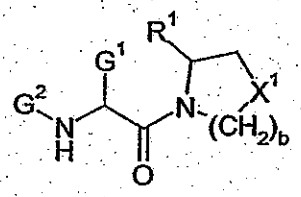
1700	S	2	
1701	CH_2		
1702	S	1	
1703	CF_2		
1704	S	2	
1705	CH_2		

CLAIMS

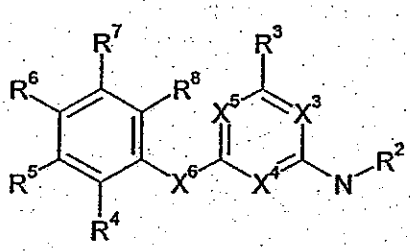
1 A compound according to general formula **1**, or a pharmaceutically acceptable salt thereof,



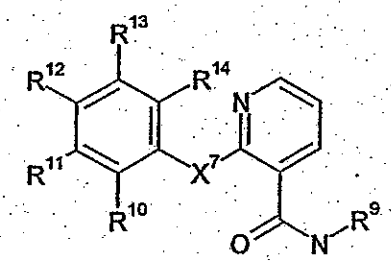
1

wherein:

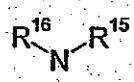
either G^1 is $-CH_2-X^2-(CH_2)_a-G^3$ and G^2 is H, or
G^2 is $-CH_2-(CH_2)_a-G^3$ and G^1 is H;
G^3 is selected from a group according to general formula **2**, a group according to general formula **3**, and a group according to general formula **4**;



2



3



4

a is **0**, 1 or 2;
b is 1 or 2;
X^1 is selected from CH_2, S, CF_2, CHF, $CH(CH_3)$, $C(CH_3)_2$, CH(CN) and O;
X^2 is selected from CH_2, O and S, provided that if a is 1 then X^2 is CH_2;
X^3, X^4 and X^5 are selected from N and CH, provided that at least two of X^3, X^4 and X^5 are N;
X^6 is selected from O and NH;
X^7 is selected from CH_2, O, S and NH;
R^1 is selected from H and CN;

R^2 is selected from H and alkyl;

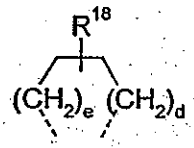
R^3 is selected from H, Cl, OH, O-alkyl, NH_2, NH-alkyl and $N(alkyl)_2$;

R^4, R^5, R^6, R^7 and R^8 are independently selected from H, Br, Cl, F, CF_3, alkyl, acyl, OH, O-alkyl, NH_2, NH-alkyl, $N(alkyl)_2$, NO_2, NH-acyl, CO_2H, CO_2-alkyl, $CONH_2$, CONH-alkyl, $CON(alkyl)_2$ and CN;

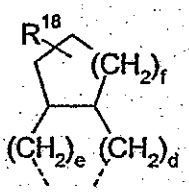
R^9 is selected from H and alkyl;

R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are independently selected from H, Br, Cl, F, CF_3, alkyl, acyl, OH, O-alkyl, NH_2, NH-alkyl, $N(alkyl)_2$, NO_2, NH-acyl, CO_2H, CO_2-alkyl, $CONH_2$, CONH-alkyl, $CON(alkyl)_2$ and CN;

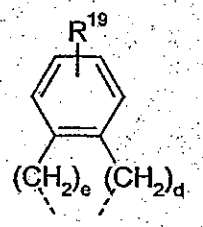
R^{15} and R^{16} are independently selected from H, alkyl, alkenyl, polyfluoroalkyl, aralkyl, aryl and $-CH_2$-L-R^{17}, or R^{15} and R^{16} together form a group according to general formula **5**, general formula **6** or general formula **7**;



5



6



7

R^{17} is selected from H, alkyl and aryl;

R^{18} is selected from H, alkyl, aryl, OH, O-alkyl, NH_2, NH-alkyl and $N(alkyl)_2$;

R^{19} is selected from H, alkyl, aryl, F, Cl, Br, CF_3, OH, O-alkyl, NH_2, NH-alkyl and $N(alkyl)_2$;

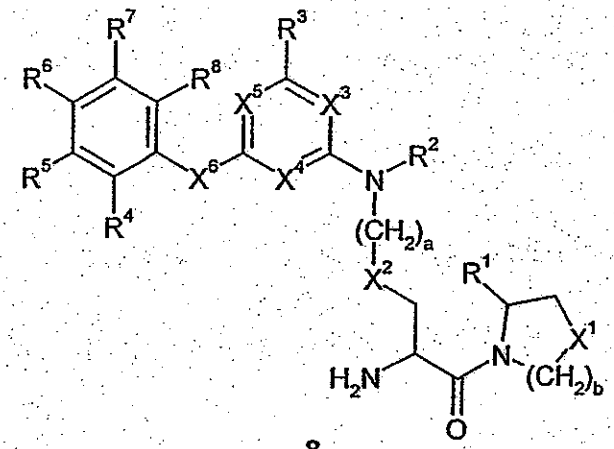
L is selected from a covalent bond, CH=CH, C≡C and $-C_6H_4-$;

d and e are selected from 0, 1, 2 and 3 such that d+e is 3, 4 or 5; and

f is selected from 1, 2 and 3;

provided that when R^{15} and R^{16} are both H and b is 1 then X^1 is not S or CH_2.

2 A compound according to general formula **8**, or a pharmaceutically acceptable salt thereof,



8

wherein:

a is **0**, 1 or 2;

b is 1 or 2;

X^1 is selected from CH_2, S, CF_2, CHF, $CH(CH_3)$, $C(CH_3)_2$, CH(CN) and O;

X^2 is selected from CH_2, O and S, provided that if a is 1 then X^2 is CH_2;

X^3, X^4 and X^5 are selected from N and CH, provided that at least two of X^3, X^4 and X^5 are N;

X^6 is selected from O and NH;

R^1 is selected from H and CN;

R^2 is selected from H and alkyl;

R^3 is selected from H, Cl, OH, O-alkyl, NH_2, NH-alkyl and $N(alkyl)_2$;

R^4, R^5, R^6, R^7 and R^8 are independently selected from H, Br, Cl, F, CF_3, alkyl, acyl, OH, O-alkyl, NH_2, NH-alkyl, $N(alkyl)_2$, NO_2, NH-acyl, CO_2H, CO_2-alkyl, $CONH_2$, CONH-alkyl, $CON(alkyl)_2$ and CN.

3 A compound according to Claim 2 wherein R^1 is H.

4 A compound according to Claim 2 wherein R^1 is CN.

5 A compound according to any of Claims 2 to 4 wherein X^1 is CH_2.

6 A compound according to any of Claims 2 to 4 wherein X^1 is S.

7 A compound according to any of Claims 2 to 6 wherein b is 1.

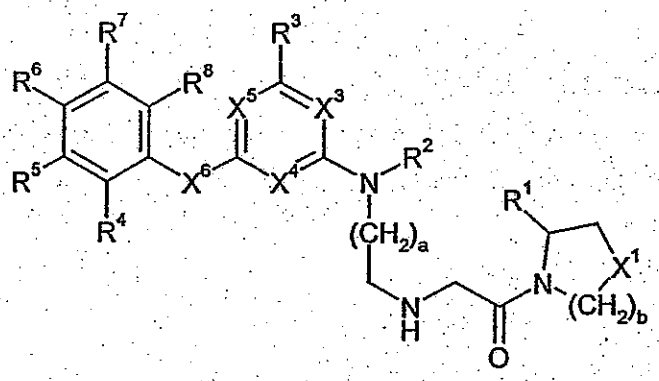
8 A compound according to any of Claims 2 to 6 wherein b is 2.

9 A compound according to any of Claims 2 to 8 wherein a is 1.

10 A compound according to any of Claims 2 to 8 wherein a is 2 and X^2 is CH_2.

11 A compound according to any of Claims 2 to 10 wherein X^3, X^4 and X^5 are all N.

12 A compound according to general formula 9, or a pharmaceutically acceptable salt thereof,



9

wherein:

a is 1 or 2;

b is 1 or 2;

X^1 is selected from CH_2, S, CF_2, CHF, $CH(CH_3)$, $C(CH_3)_2$, CH(CN) and O;

X^3, X^4 and X^5 are selected from N and CH, provided that at least two of X^3, X^4 and X^5 are N;

X^6 is selected from O and NH;

R^1 is selected from H and CN;

R^2 is selected from H and alkyl;

R^3 is selected from H, Cl, OH, O-alkyl, NH_2, NH-alkyl and $N(alkyl)_2$;

R^4, R^5, R^6, R^7 and R^8 are independently selected from H, Br, Cl, F, CF_3, alkyl,

acyl, OH, O-alkyl, NH_2, NH-alkyl, N(alkyl)$_2$, NO_2, NH-acyl, CO_2H, CO_2-alkyl, $CONH_2$, CONH-alkyl, CON(alkyl)$_2$ and CN.

13 A compound according to Claim 12 wherein R^1 is H.

14 A compound according to Claim 12 wherein R^1 is CN.

15 A compound according to any of Claims 12 to 14 wherein X^1 is CH_2.

16 A compound according to any of Claims 12 to 14 wherein X^1 is S.

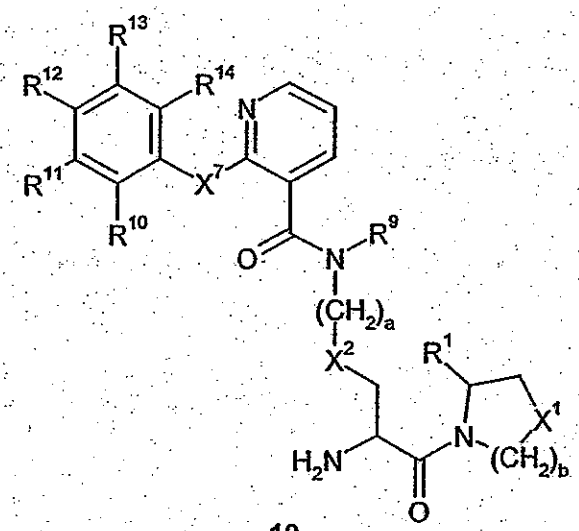
17 A compound according to any of Claims 12 to 16 wherein b is 1.

18 A compound according to any of Claims 12 to 16 wherein b is 2.

19 A compound according to any of Claims 12 to 18 wherein a is 1.

20 A compound according to any of Claims 12 to 19 wherein X^3, X^4 and X^5 are all N.

21 A compound according to general formula **10**, or a pharmaceutically acceptable salt thereof,



10

wherein:

a is **0**, 1 or 2;
b is 1 or 2;
X^1 is selected from CH_2, S, CF_2, CHF, $CH(CH_3)$, $C(CH_3)_2$, CH(CN) and O;
X^2 is selected from CH_2, O and S, provided that if a is 1 then X^2 is CH_2;
X^7 is selected from O, S, CH_2 and NH;
R^1 is selected from H and CN;
R^9 is selected from H and alkyl;
R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are independently selected from H, Br, Cl, F, CF_3, alkyl, acyl, OH, O-alkyl, NH_2, NH-alkyl, $N(alkyl)_2$, NO_2, NH-acyl, CO_2H, CO_2-alkyl, $CONH_2$, CONH-alkyl, $CON(alkyl)_2$ and CN is selected from H, Cl, OH, O-alkyl, NH_2, NH-alkyl and $N(alkyl)_2$.

22 A compound according to Claim 21 wherein R^1 is H.

23 A compound according to Claim 21 wherein R^1 is CN.

24 A compound according to any of Claims 21 to 23 wherein X^1 is CH_2.

25 A compound according to any of Claims 21 to 23 wherein X^1 is S.

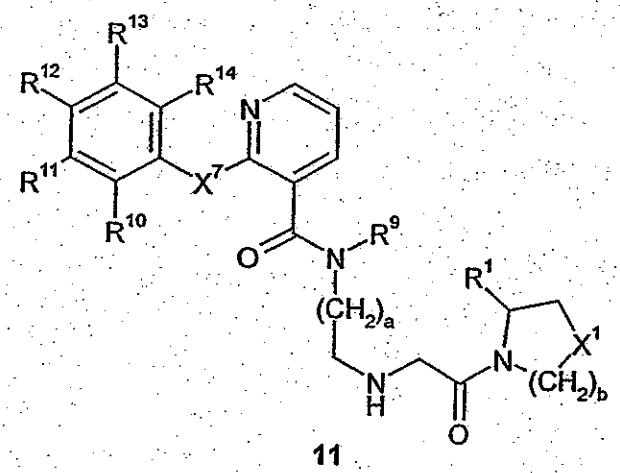
26 A compound according to any of Claims 21 to 25 wherein b is 1.

27 A compound according to any of Claims 21 to 25 wherein b is 2.

28 A compound according to any of Claims 21 to 27 wherein a is 1.

29 A compound according to any of Claims 21 to 27 wherein a is 2 and X^2 is CH_2.

30 A compound according to general formula **11**, or a pharmaceutically acceptable salt thereof,



11

wherein:

a is 1 or 2;

b is 1 or 2;

X^1 is selected from CH_2, S, CF_2, CHF, $CH(CH_3)$, $C(CH_3)_2$, CH(CN) and O;

X^7 is selected from O, S, CH_2 and NH;

R^1 is selected from H and CN;

R^9 is selected from H and alkyl;

R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are independently selected from H, Br, Cl, F, CF_3, alkyl, acyl, OH, O-alkyl, NH_2, NH-alkyl, $N(alkyl)_2$, NO_2, NH-acyl, CO_2H, CO_2-alkyl, $CONH_2$, CONH-alkyl, $CON(alkyl)_2$ and CN is selected from H, Cl, OH, O-alkyl, NH_2, NH-alkyl and $N(alkyl)_2$.

31 A compound according to Claim 30 wherein R^1 is H.

32 A compound according to Claim 30 wherein R^1 is CN.

33 A compound according to any of Claims 30 to 32 wherein X^1 is CH_2.

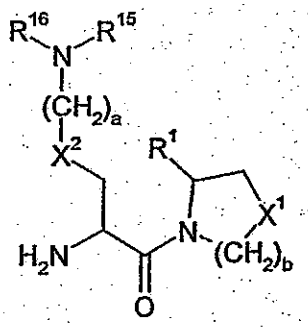
34 A compound according to any of Claims 30 to 32 wherein X^1 is S.

35 A compound according to any of Claims 30 to 34 wherein b is 1.

36 A compound according to any of Claims 30 to 34 wherein b is 2.

37 A compound according to any of Claims 30 to 36 wherein a is 1.

38 A compound according to general formula **12**, or a pharmaceutically acceptable salt thereof,



12

wherein:

a is 0, 1 or 2;

b is 1 or 2;

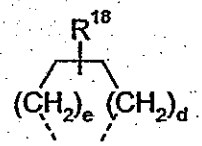
X^1 is selected from CH_2, S, CF_2, CHF, $CH(CH_3)$, $C(CH_3)_2$, CH(CN) and O;

X^2 is selected from CH_2, O and S, provided that if a is 1 then X^2 is CH_2;

R^1 is selected from H and CN;

R^{15} and R^{16} are each independently selected from H, alkyl, alkenyl, polyfluoroalkyl, aralkyl, aryl and CH_2-L-R^{17};

or R^{15} and R^{16} together are a group according to general formula 5, a group according to general formula 6 or a group according to general formula 7;



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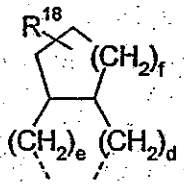

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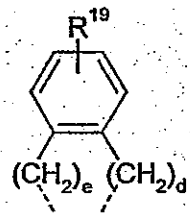


7

R^{17} is selected from H, alkyl and aryl;

R^{18} is selected from H, alkyl, aryl, OH, O-alkyl, NH_2, NH-alkyl and $N(alkyl)_2$;

R^{19} is selected from H, alkyl, aryl, F, Cl, Br, CF_3, OH, O-alkyl, NH_2, NH-alkyl and $N(alkyl)_2$;

L is selected from a covalent bond, CH=CH, C≡C and $-C_6H_4-$;

d and e are selected from 0, 1, 2 and 3 such that d+e is 3, 4 or 5; and
f is selected from 1, 2 and 3;
provided that when R^{15} and R^{16} are both H and b is 1 then X^1 is not S or CH_2.

39 A compound according to Claim 38 wherein R^1 is H.

40 A compound according to Claim 38 wherein R^1 is CN.

41 A compound according to any of Claims 38 to 40 wherein X^1 is CH_2.

42 A compound according to any of Claims 38 to 40 wherein X^1 is S.

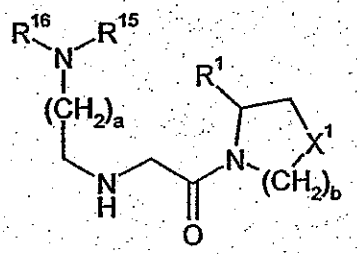
43 A compound according to any of Claims 38 to 42 wherein b is 1.

44 A compound according to any of Claims 38 to 42 wherein b is 2.

45 A compound according to any of Claims 38 to 44 wherein a is 1.

46 A compound according to any of Claims 38 to 44 wherein a is 2 and X^2 is CH_2.

47 A compound according to general formula **13**, or a pharmaceutically acceptable salt thereof,

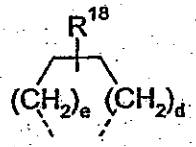


13

wherein:

a is 1 or 2;
b is 1 or 2;

X^1 is selected from CH_2, S, CF_2, CHF, $CH(CH_3)$, $C(CH_3)_2$, CH(CN) and O;
R^1 is selected from H and CN;
R^{15} and R^{16} are each independently selected from H, alkyl, alkenyl, polyfluoroalkyl, aralkyl, aryl and CH_2-L-R^{17};
or R^{15} and R^{16} together are a group according to general formula 5, a group according to general formula 6 or a group according to general formula 7;



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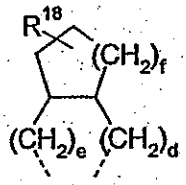

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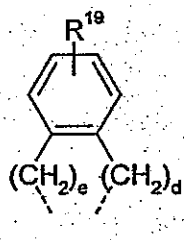

7

R^{17} is selected from H, alkyl and aryl;
R^{18} is selected from H, alkyl, aryl, OH, O-alkyl, NH_2, NH-alkyl and $N(alkyl)_2$;
R^{19} is selected from H, alkyl, aryl, F, Cl, Br, CF_3, OH, O-alkyl, NH_2, NH-alkyl and $N(alkyl)_2$;
L is selected from a covalent bond, CH=CH, C≡C and $-C_6H_4-$;
d and e are selected from 0, 1, 2 and 3 such that d+e is 3, 4 or 5; and
f is selected from 1, 2 and 3.

48 A compound according to Claim 47 wherein R^1 is H.

49 A compound according to Claim 47 wherein R^1 is CN.

50 A compound according to any of Claims 47 to 49 wherein X^1 is CH_2.

51 A compound according to any of Claims 47 to 49 wherein X^1 is S.

52 A compound according to any of Claims 47 to 51 wherein b is 1.

53 A compound according to any of Claims 47 to 51 wherein b is 2.

54 A compound according to any of Claims 47 to 53 wherein a is 1.

55 A pharmaceutical composition comprising a compound according to any of

56 A use, in the manufacture of a pharmaceutical composition, of a compound according to any of Claims 1 to 54

57 The use according to claim 56 wherein the pharmaceutical composition is for the treatment of a disease caused by dysregulation of a post-proline cleaving proteases or their endogenous substrates.

58 The use according to claim 56 wherein the pharmaceutical composition is for the treatment of a disease which is ameliorated by inhibition of a post-proline cleaving proteases.

59 The use according to claim 56 wherein the pharmaceutical composition is for the treatment of a disease which is caused by dysregulation of a post-proline cleaving proteases or its endogenous substrates which is an intracellular protease.

60 A composition according to claim 1 or 38 with the proviso that when X^1 = S, b = 1, R^1 = H; G^2 = H; G^1 is $-CH_2-X^2-(CH_2)_a-G^3$; a = 1, X^2 = CH_2, G^3 = $NR^{15}R^{16}$, and one of R^{15}, R^{16} = H, the other of R^{15}, R^{16} is not pyridyl, substituted pyridyl, pyrazinyl or substituted pyrazinyl.

61 A composition according to claim 1, 38, 47 or 60 with the proviso that when b=1, R^1 is H and X^1 is S; G^1 = H, G^2 is $-CH_2-(CH_2)_a-G^3$; a = 1; G^3 is $NR^{15}R^{16}$ and one of R^{15} and R^{16} is H the other of R^{15}, R^{16} is not pyridyl, substituted pyridyl, pyrazinyl or substituted pyrazinyl

62 A composition according to claim 1, 38, 47, 60 or 61 with the proviso that when b=1, R^1 is CN and X^1 is CH_2; G^1 = H; G^2 is $-CH_2-(CH_2)_a-G^3$; a = 1; G^3 is $NR^{15}R^{16}$ and one of R^{15} and R^{16} is H, the other of R^{15}, R^{16} is not pyridyl, substituted pyridyl, pyrazinyl or substituted pyrazinyl

63 A composition according to claim 1, 38, 47, 60, 61 or 62 with the proviso that when G^2 = H; G^1 = $-CH2-X^2-(CH_2)_a-G^3$; X^2 is CH_2, a = 1, G3 = $NR^{15}R^{16}$ and

$R^{15} = R^{16} = H$, b is not 2 when X^1 is O or CH_2, and b is not 1 when X^1 is CH_2

64 The use according to claim 56 wherein the pharmaceutical composition is for the treatment of a disease which is caused by dysregulation of a non-membrane associated post-proline cleaving proteases such as QPP, DPP-8 and DPP-9 enzymes or their endogenous substrates

65 The use according to claim 56 wherein the pharmaceutical composition is for the treatment of a disease which is ameliorated by inhibition of a non-membrane associated post-proline cleaving proteases such as QPP, DPP-8 and DPP-9 enzymes or their endogenous substrates.

66 The use according to claim 64 or 65 in which the compound is a selective inhibitor of non-membrane associated post-proline cleaving proteases.