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Cheng et al.

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(54) **SUBSTITUTED HETEROCYCLIC DERIVATIVES USEFUL AS ANTIDIABETIC AND ANTIOBESITY AGENTS AND METHOD**

(75) Inventors: **Peter T. W. Cheng**, Princeton, NJ (US); **Sean Chen**, Princeton, NJ (US); **Charles Z. Ding**, Plano, TX (US); **Timothy F. Herpin**, Princeton, NJ (US)

(73) Assignee: **Bristol-Myers Squibb Company**, Princeton, NJ (US)

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(65) **Prior Publication Data**

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Related U.S. Application Data

(60) Provisional application No. 60/394,553, filed on Jul. 9, 2002.

(51) **Int. Cl.**[7] **A61K 31/4245**; A61K 31/4192; C07D 271/06; C07D 249/04

(52) **U.S. Cl.** **514/364**; 548/131; 548/255; 514/359

(58) **Field of Search** 514/364, 359; 548/131, 255

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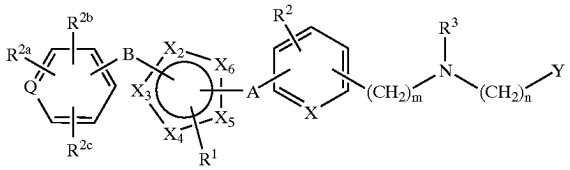
Primary Examiner—Charanjit S. Aulakh
(74) *Attorney, Agent, or Firm*—Burton Rodney

(57) **ABSTRACT**

Compounds are provided which are useful as antidiabetic agents and antiobesity agents and have the structure



wherein m is 0, 1 or 2; n is 0, 1 or 2;

Q is C or N;

A is $(CH_2)_x$ where x is 1 to 5, or A is $(CH_2)_x{}^1$ where x^1 is 1 to 5 with an alkenyl bond or an alkynyl bond embedded anywhere in the chain, or A is —$(CH_2)_x{}^2$—O—$(CH_2)_x{}^3$— where x^2 is 0 to 5 and x^3 is 0 to 5, provided that at least one of x^2 and x^3 is other than 0;

B is a bond or is $(CH_2)_x{}^4$ where x^4 is 1 to 5;

X is CH or N;

X_2 is C, N, O or S;

X_3 is C, N, O or S;

X_4 is C, N, O or S;

X_5 is C, N, O or S;

X_6 is C, N, O or S;

and A, R^1, R^2, R^{2a}, R^{2b}, R^{2c}, R^3 and Y are as defined herein.

15 Claims, No Drawings

SUBSTITUTED HETEROCYCLIC DERIVATIVES USEFUL AS ANTIDIABETIC AND ANTIOBESITY AGENTS AND METHOD

This application claims priority from U.S. Provisional Application 60/394,553, filed Jul. 9, 2002 which is incorporated herein by reference.

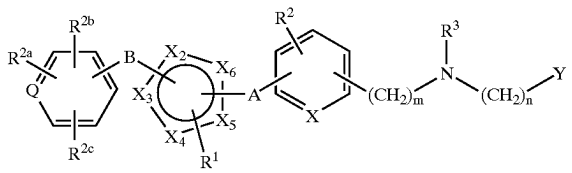
FIELD OF THE INVENTION

The present invention relates to novel substituted heterocyclic derivatives which modulate blood glucose levels, triglyceride levels, insulin levels and non-esterified fatty acid (NEFA) levels, and thus are particularly useful in the treatment of diabetes and obesity, and to a method for treating diabetes, especially Type 2 diabetes, as well as hyperglycemia, hyperinsulinemia, hyperlipidemia, obesity, atherosclerosis and related diseases employing such substituted heterocyclic derivatives alone or in combination with another antidiabetic agent and/or a hypolipidemic agent and/or other therapeutic agents.

DESCRIPTION OF THE INVENTION

In accordance with the present invention, substituted heterocyclic derivatives are provided which have the structure I:

I



wherein m is 0, 1 or 2; n is 0, 1 or 2;

Q is C or N;

A is $(CH_2)_x$ where x is 1 to 5, or A is $(CH_2)_x^1$ where x^1 is 1 to 5 with an alkenyl bond or an alkynyl bond embedded anywhere in the chain, or A is —$(CH_2)_x^2$—O—$(CH_2)_x^3$— where x^2 is 0 to 5 and x^3 is 0 to 5, provided that at least one of x^2 and x^3 is other than 0;

B is a bond or is $(CH_2)_x^4$ where X^4 is 1 to 5;

X is CH or N;

X_2 is C, N, O or S;

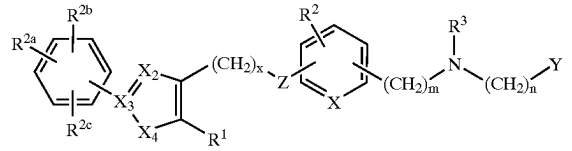
X_3 is C, N, O or S;

X_4 is C, N, O or S;

X_5 is C, N, O or S;

X_6 is C, N, O or S;

provided that at least one of X_2, X_3, X_4 X_5 and X_6 is N; and at least one of X_2, X_3, X_4 X_5 and X_6 is C, and specifically excluding the structure(s) as shown below:



where X_2=N, X_3=C, X_4=O or S, Z=O or a bond

In each of X through X_6, as defined above, C may include CH.

R^1 is H or alkyl;

R^{2a}, R^{2b} and R^{2c} may be the same or different and are selected from H, alkyl, alkoxy, halogen, amino, substituted amino or cyano;

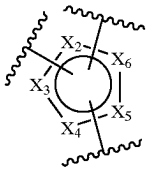
R^3 is selected from H, alkyl, arylalkyl, aryloxycarbonyl, alkyloxycarbonyl, alkynyloxycarbonyl, alkenyloxycarbonyl, arylcarbonyl, alkylcarbonyl, aryl, heteroaryl, cycloheteroalkyl, heteroarylcarbonyl, heteroaryl-heteroarylalkyl, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, alkoxycarbonylamino, aryloxycarbonylamino, heteroaryloxycarbonylamino, heteroaryl-heteroarylcarbonyl, alkylsulfonyl, alkenylsulfonyl, heteroaryloxycarbonyl, cycloheteroalkyloxycarbonyl, heteroarylalkyl, aminocarbonyl, substituted aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylalkenyl, cycloheteroalkyl-heteroarylalkyl; hydroxyalkyl, alkoxy, alkoxyaryloxycarbonyl, arylalkyloxycarbonyl, alkylaryloxycarbonyl, arylheteroarylalkyl, arylalkylarylalkyl, aryloxyarylalkyl, haloalkoxyaryloxycarbonyl, alkoxycarbonylaryloxycarbonyl, aryloxyaryloxycarbonyl, arylsulfinylarylcarbonyl, arylthioarylcarbonyl, alkoxycarbonylaryloxycarbonyl, arylalkenyloxycarbonyl, heteroaryloxyarylalkyl, aryloxyarylcarbonyl, aryloxyarylalkyloxycarbonyl, arylalkenyloxycarbonyl, arylalkylcarbonyl, aryloxyalkyloxycarbonyl, arylalkylsulfonyl, arylthiocarbonyl, arylalkenylsulfonyl, heteroarylsulfonyl, arylsulfonyl, alkoxyarylalkyl, heteroarylalkoxycarbonyl, arylheteroarylalkyl, alkoxyarylcarbonyl, aryloxyheteroarylalkyl, heteroarylalkyloxyarylalkyl, arylarylalkyl, arylalkenylarylalkyl, arylalkoxyarylalkyl, arylcarbonyl-arylalkyl, alkylaryloxyarylalkyl, arylalkoxycarbonylheteroarylalkyl, heteroarylarylalkyl, arylcarbonylheteroarylalkyl, heteroaryloxyarylalkyl, arylalkenylheteroarylalkyl, arylaminoarylalkyl, aminocarbonylarylarylalkyl;

Y is CO_2R^4 (where R^4 is H or alkyl, or a prodrug ester) or Y is a C-linked 1-tetrazole, a phosphinic acid of the structure $P(O)(OR^{4a})R^5$, (where R^{4a} is H or a prodrug ester, R^5 is alkyl or aryl) or a phosphonic acid of the structure $P(O)(OR^{4a})_2$;

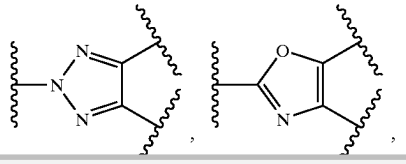
$(CH_2)_x$, $(CH_2)_x^1$, $(CH_2)_x^2$, $(CH_2)_x^3$, $(CH_2)_x^4$, $(CH_2)_m$, and $(CH_2)_n$ may be optionally substituted with 1, 2 or 3 substituents;

including all stereoisomers thereof, prodrug esters thereof, and pharmaceutically acceptable salts thereof.

Examples of



which are present in the compounds of the invention include, but are not limited to,



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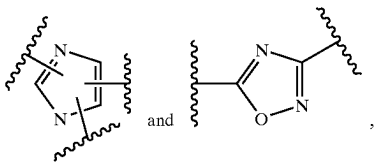
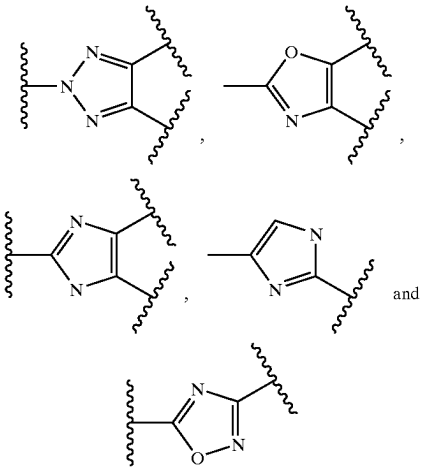
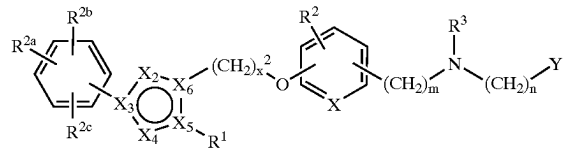


as well as the five-membered rings covered under the definition of heteroaryl set out hereinafter, preferably



Preferred are compounds of formula I of the invention having the structure IA:

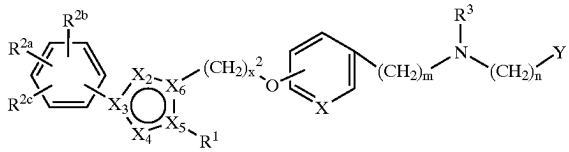
IA



where X is CH

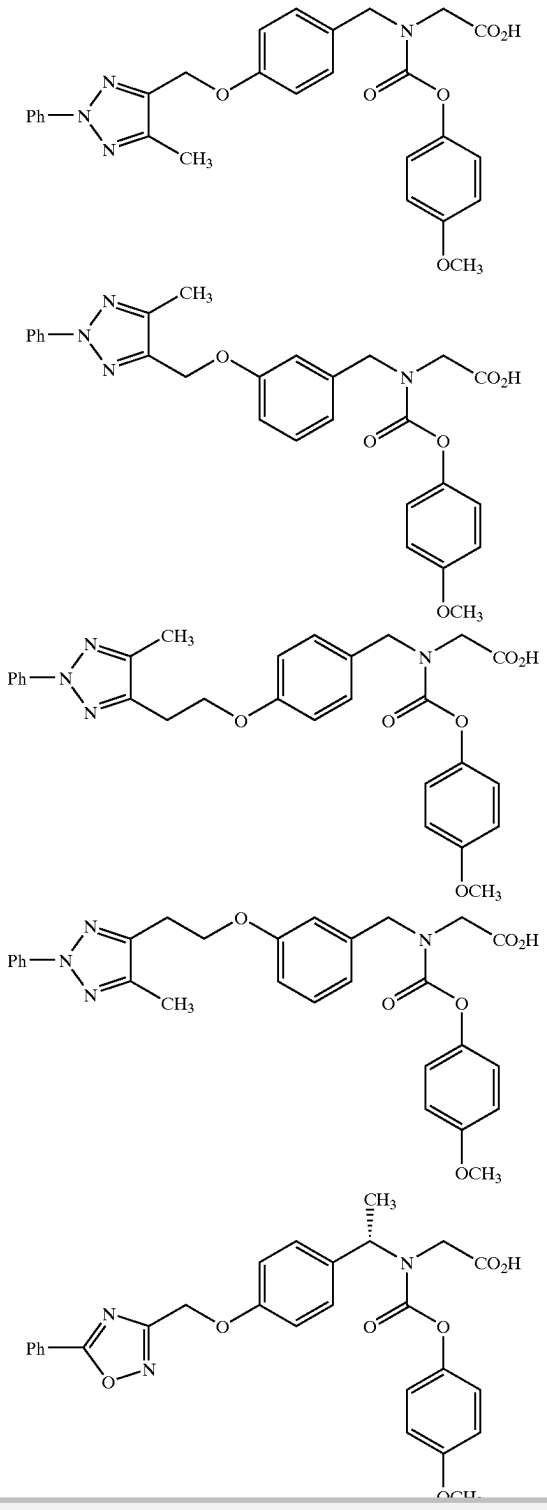
More preferred are compounds of formula I of the invention having the structure IB:

IB



In the above compounds, it is most preferred that R^{2a}, R^{2b} and R^{2c} are each H; R^1 is alkyl, preferably CH_3; x^2 is 1 to 3; R^2 is H; m is 0 or $(CH_2)_m$ is CH_2 or CHOH or CH-alkyl, X_2, X_3, X_4, X_5 and X_6 represent a total of 1, 2 or 3 nitrogens; $(CH_2)_n$ is a bond or CH_2, R^3 is arylalkyloxycarbonyl, arylheteroarylalkyl, aryloxyarylalkyl, arylalkyl, aryloxycarbonyl, haloaryloxycarbonyl, alkoxyaryloxycarbonyl, alkylaryloxycarbonyl, aryloxyaryloxycarbonyl, heteroaryloxyarylalkyl, heteroaryloxycarbonyl, aryloxyarylcarbonyl, arylalkenyloxycarbonyl, cycloalkylaryloxycarbonyl, arylalkylarylcarbonyl, heteroaryl-heteroarylalkyl, cycloalkyloxyaryloxycarbonyl, cycloheteroalkylalkyloxycarbonyl, cycloheteroalkyloxycarbonyl, or polyhaloalkylaryloxycarbonyl, which may be optionally substituted, more preferably alkoxyaryloxycarbonyl.

Preferred compounds of the invention include the following:



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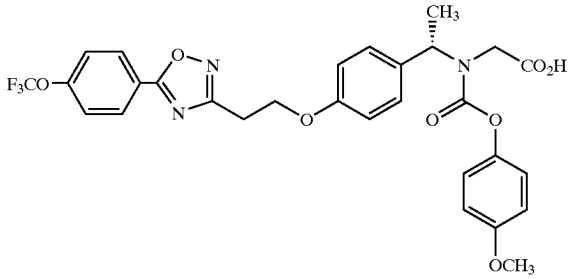

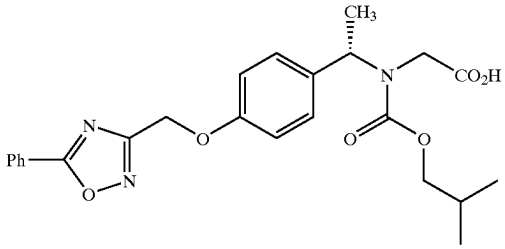

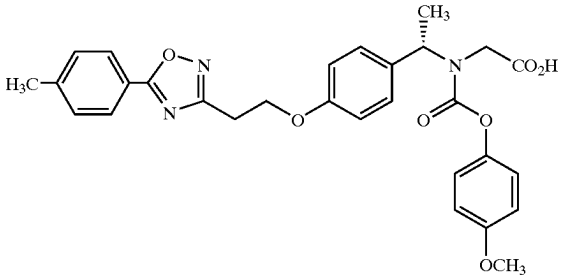

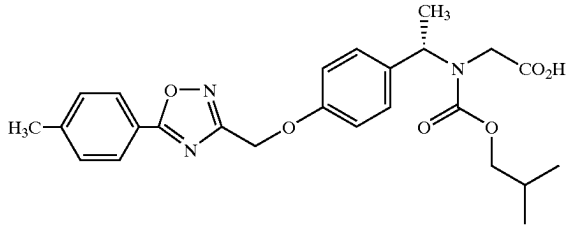

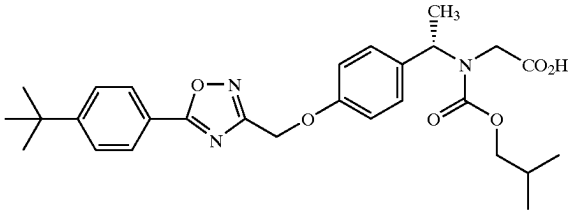

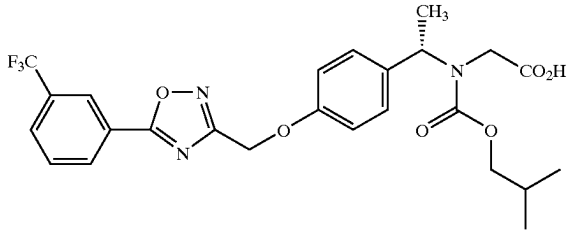

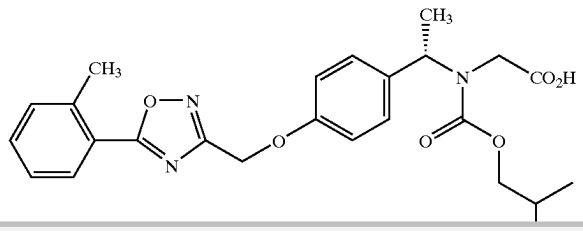

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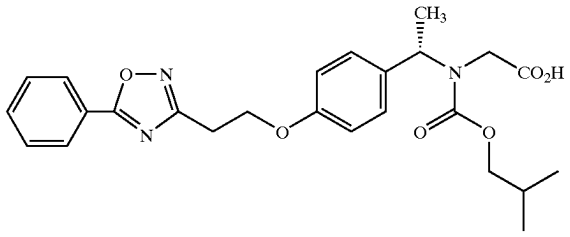

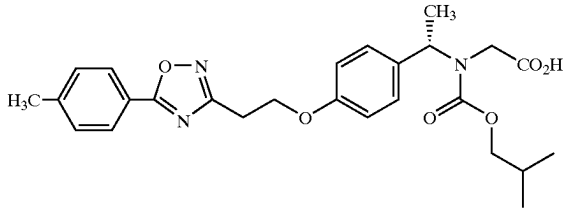

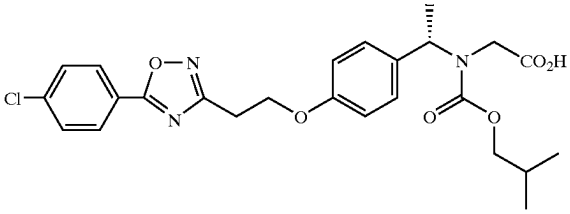

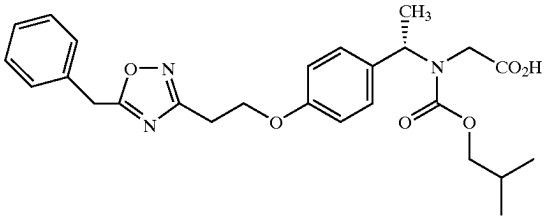

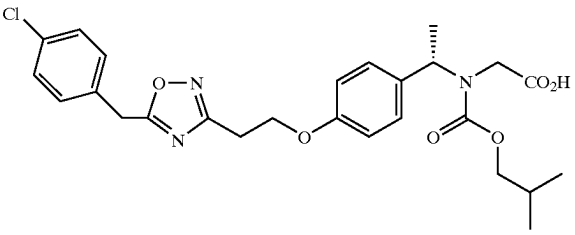

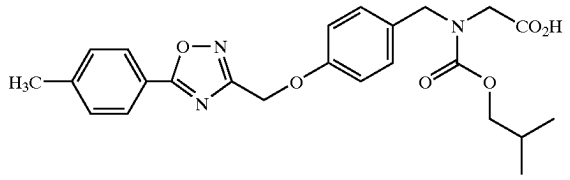

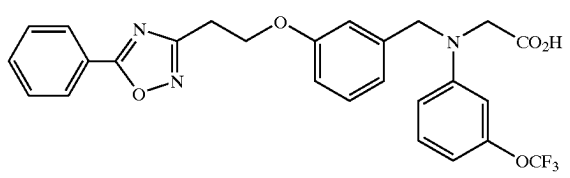

In addition, in accordance with the present invention, a method is provided for treating diabetes, especially Type 2 diabetes, and related diseases such as Type I diabetes, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, hyperlipidemia, obesity, hypertriglyceridemia, inflammation, Syndrome X, diabetic

of a compound of structure I is administered to a patient in need of treatment.

In addition, in accordance with the present invention, a method is provided for treating early malignant lesions (such as ductal carcinoma in situ of the breast and lobular carcinoma in situ of the breast), premalignant lesions (such as fibroadenoma of the breast and prostatic intraepithelial neoplasia (PIN), liposarcomas and various other epithelial tumors (including breast, prostate, colon, ovarian, gastric and lung), irritable bowel syndrome, Crohn's disease, gastric ulceritis, and osteoporosis and proliferative diseases such as psoriasis, wherein a therapeutically effective amount of a compound of structure I is administered to a patient in need of treatment.

In addition, in accordance with the present invention, a method is provided for treating diabetes and related diseases as defined above and hereinafter, wherein a therapeutically effective amount of a combination of a compound of structure I and another type antidiabetic agent and/or a hypolipidemic agent, and/or lipid modulating agent and/or other type of therapeutic agent, is administered to a human patient in need of treatment.

In the above method of the invention, the compound of structure I will be employed in a weight ratio to the antidiabetic agent (depending upon its mode of operation) within the range from about 0.01:1 to about 100:1, preferably from about 0.5:1 to about 10:1.

The conditions, diseases, and maladies collectively referenced to as "Syndrome X" or Dysmetabolic Syndrome (as detailed in Johanson, *J. Clin. Endocrinol. Metab.,* 1997, 82, 727–734, and other publications) include hyperglycemia and/or prediabetic insulin resistance syndrome, and is characterized by an initial insulin resistant state generating hyperinsulinemia, dyslipidemia, and impaired glucose tolerance, which can progress to Type II diabetes, characterized by hyperglycemia, which can progress to diabetic complications.

The term "diabetes and related diseases" refers to Type II diabetes, Type I diabetes, impaired glucose tolerance, obesity, hyperglycemia, Syndrome X, dysmetabolic syndrome, diabetic complications and hyperinsulinemia.

The conditions, diseases and maladies collectively referred to as "diabetic complications" include retinopathy, neuropathy and nephropathy, and other known complications of diabetes.

The term "other type(s) of therapeutic agents" as employed herein refers to one or more antidiabetic agents (other than compounds of formula I), one or more anti-obesity agents, and/or one or more lipid-lowering agents, one or more lipid modulating agents (including anti-atherosclerosis agents), and/or one or more antiplatelet agents, one or more agents for treating hypertension, one or more anti-cancer drugs, one or more agents for treating arthritis, one or more anti-osteoporosis agents, one or more anti-obesity agents, one or more agents for treating immunomodulatory diseases, and/or one or more agents for treating anorexia nervosa.

The term "lipid-modulating" agent as employed herein refers to agents which lower LDL and/or raise HDL and/or lower triglycerides and/or lower total cholesterol and/or other known mechanisms for therapeutically treating lipid disorders.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the formula I of the present invention

thetic schemes, as well as relevant published literature procedures that are used by one skilled in the art. Exemplary reagents and procedures for these reactions appear hereinafter and in the working Examples. Protection and deprotection in the Schemes below may be carried out by procedures generally known in the art (see, for example, T. W. Greene & P. G. M. Wuts, Protecting Groups in Organic Synthesis, 3rd Edition, 1999 [Wiley]).

Scheme 1 describes a general synthesis of the amino acids described in this invention. An alcohol 1 ($R^5(CH_2)_x{}^2OH$) is coupled with a hydroxy aryl- or heteroaryl-aldehyde 2 (preferably 3- or 4-hydroxybenzaldehyde) under standard Mitsunobu reaction conditions (e.g. Mitsunobu, O., *Synthesis,* 1981, 1). The resulting aldehyde 3 is then subjected to reductive amination using procedures known in the literature (e.g. Abdel-Magid et al, *J. Org. Chem.* 1996, 61, 3849) with an α-amino ester hydrochloride 4. PG in Scheme 1 denotes a preferred carboxylic acid-protecting group, such as a methyl or tert-butyl ester. The resulting secondary amino-ester 5 is then subjected to a second reductive amination using methods known in the literature (e.g. Abdel-Magid et al, *J. Org. Chem.* 1996, 61, 3849) with an R^{3a} aldehyde 6. Final deprotection of the carboxylic acid ester under standard conditions known in the literature (reference: Greene et al supra) utilizing basic conditions (for methyl esters) or acidic conditions (for tert-butyl esters) then furnishes the desired amino acid products II.

An alternative route to the aldehyde 3 is shown in Scheme 1A. Alcohol 1 ($R^5(CH_2)_xOH$) is treated with methanesulfonyl chloride to give the corresponding mesylate 7. The mesylate 7 is then alkylated under standard basic conditions with a hydroxyaryl or hydroxyheteroaryl aldehyde 2 to furnish the aldehyde 3.

A route to the amino acids III is shown in Scheme 2. The secondary amine-ester 5 is deprotected under standard conditions (basic conditions if the protecting group (PG) is methyl; acidic conditions if PG is tert-butyl; ref. Greene et al supra) to furnish the corresponding amino acid 8. Reductive amination with aldehyde 9 under analogous conditions as described in Scheme 1 provides the desired tertiary amino acid products III.

Alternatively, as shown in Scheme 3, reaction of the secondary amine-ester 5 with an alkylating agent 10 (with an appropriate leaving group (LG) such as halide, mesylate, or tosylate) under standard conditions followed by deprotection of the carboxylic acid ester 11 provides the desired tertiary amino acids III.

As shown in Scheme 4, the tertiary amino acid III may also be assembled through reductive amination first of the R^{3a} aldehyde 12 with an appropriate amine ester hydrochloride 4. The resulting secondary amine-ester 13 then is subjected to reductive amination with appropriate alkyl, aryl or heteroaryl aldehydes 3 (as in Scheme 1) followed by deprotection of the carboxylic acid ester to give the desired amino acid analogs III.

An alternative general synthesis of amino acid analogs II is shown in Scheme 5. A hydroxyaryl or heteroaryl aldehyde 2 is subjected to the usual reductive amination conditions with an appropriate amine-ester hydrochloride 4. The resulting secondary amine-ester 14 is functionalized, in this case by a second reductive amination with aldehyde 6 to furnish the corresponding hydroxy tertiary amine-ester 15. Phenol 15 now undergoes a Mitsunobu reaction with a preferred alcohol 1 (R^5—$(CH_2)_nOH$) which is followed by the deprotection of the product ester 16 to furnish the desired amino

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