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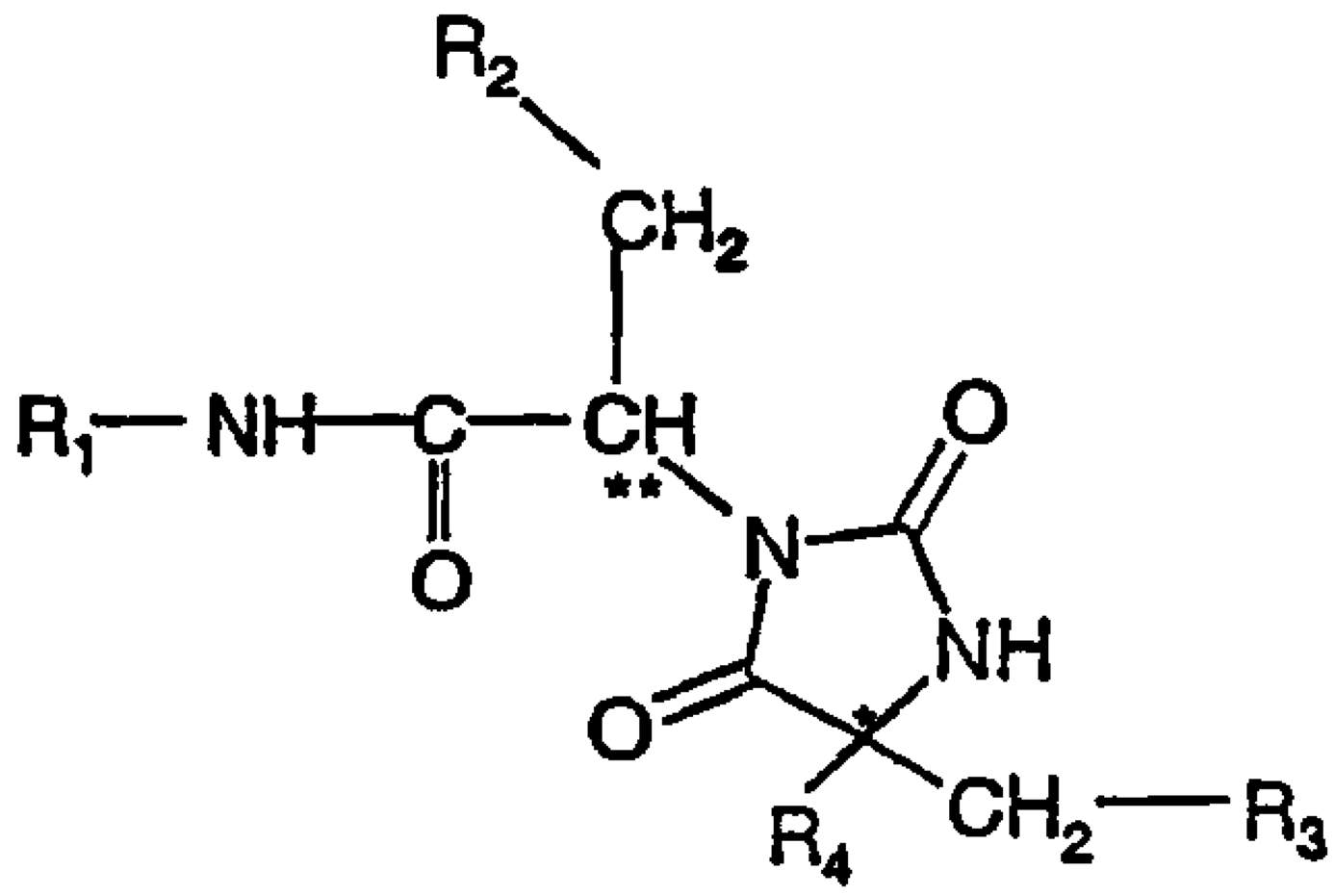

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(57) Abrégé/Abstract:
Hydantoin compounds of the formula: wherein R^1 is a five-or-six-membered aromatic heterocyclic ring having one to three heteroatoms selected from nitrogen, oxygen, and sulfur, which ring is unsubstituted or substituted with halo, amino, hydroxylamino, nitro, cyano, sulfonamido, lower alkyl, perfluoro lower alkyl, lower alkyl thio, perfluoro-lower alkyl thio, lower alkyl sulfonyl, perfluoro-lower alkyl sulfonyl, lower alkyl sulfinyl, or-$(R_5)_n$-C(O)-OR_6; R_2 is a cycloalkyl ring containing from 5 to 7 carbon atoms; which are active as glucokinase activators to increase insulin secretion which makes them useful for treating type II diabetes.

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(54) Title: HYDANTOIN-CONTAINING GLUCOKINASE ACTIVATORS

(I)

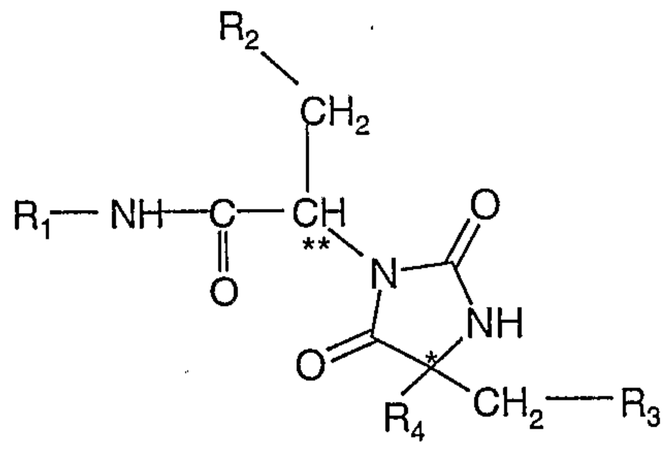
(57) Abstract: Hydantoin compounds of the formula: wherein R^1 is a five-or-six-membered aromatic heterocyclic ring having one to three heteroatoms selected from nitrogen, oxygen, and sulfur, which ring is unsubstituted or substituted with halo, amino, hydroxylamino, nitro, cyano, sulfonamido, lower alkyl, perfluoro lower alkyl, lower alkyl thio, perfluoro-lower alkyl thio, lower alkyl sulfonyl, perfluoro-lower alkyl sulfonyl, lower alkyl sulfinyl, or-$(R_5)_n$-C(O)-OR_6; R_2 is a cycloalkyl ring containing from 5 to 7 carbon atoms; which are active as glucokinase activators to increase insulin secretion which makes them useful for treating type II diabetes.

Hydantoin-Containing Glucokinase Activators

Glucokinase (GK) is one of four hexokinases found in mammals [Colowick, S.P., in *The Enzymes*, Vol. 9 (P. Boyer, ed.) Academic Press, New York, NY, pages 1-48, 1973]. The hexokinases catalyze the first step in the metabolism of glucose, i.e., the conversion of glucose to glucose-6-phosphate. Glucokinase has a limited cellular distribution, being found principally in pancreatic β-cells and liver parenchymal cells. In addition, GK is a rate-controlling enzyme for glucose metabolism in these two cell types that are known to play critical roles in whole-body glucose homeostasis [Chipkin, S.R., Kelly, K.L., and Ruderman, N.B. in *Joslin's Diabetes* (C.R. Khan and G.C. Wier, eds.), Lea and Febiger, Philadelphia, PA, pages 97-115, 1994]. The concentration of glucose at which GK demonstrates half-maximal activity is approximately 8 mM. The other three hexokinases are saturated with glucose at much lower concentrations (<1 mM). Therefore, the flux of glucose through the GK pathway rises as the concentration of glucose in the blood increases from fasting (5 mM) to postprandial (≈10-15 mM) levels following a carbohydrate-containing meal [Printz, R.G., Magnuson, M.A., and Granner, D.K. in *Ann. Rev. Nutrition* Vol. 13 (R.E. Olson, D.M. Bier, and D.B. McCormick, eds.), Annual Review, Inc., Palo Alto, CA, pages 463-496, 1993]. These findings contributed over a decade ago to the hypothesis that GK functions as a glucose sensor in β-cells and hepatocytes (Meglasson, M.D. and Matschinsky, F.M. *Amer. J. Physiol.* **246**, E1-E13, 1984). In recent years, studies in transgenic animals have confirmed that GK does indeed play a critical role in whole-body glucose homeostasis. Animals that do not express GK die within days of birth with severe diabetes while animals overexpressing GK have improved glucose tolerance (Grupe, A., Hultgren, B., Ryan, A. et al., *Cell* **83**, 69-78, 1995; Ferrie, T., Riu, E., Bosch, F. et al., *FASEB J.*, **10**, 1213-1218, 1996). An increase in glucose exposure is coupled through GK in β-cells to increased insulin secretion and in hepatocytes to increased glycogen deposition and perhaps decreased glucose production.

The finding that type II maturity-onset diabetes of the young (MODY-2) is caused by loss of function mutations in the GK gene suggests that GK also functions as a glucose sensor in humans (Liang, Y., Kesavan, P., Wang, L. et al., *Biochem. J.* **309**, 167-173, 1995). Additional evidence supporting an important role for GK in the regulation of glucose metabolism in humans was provided by the identification of patients that express a mutant form of GK with increased enzymatic activity. These patients exhibit a fasting hypoglycemia associated with an inappropriately elevated level of plasma insulin (Glaser, B., Kesavan, P., Heyman, M. et al., *New England J. Med.* **338**, 226-230, 1998). While mutations of the GK gene are not found in the majority of patients with type II diabetes, compounds that activate GK and, thereby, increase the sensitivity of the GK sensor system will still be useful in the treatment of the hyperglycemia characteristic of all type II diabetes. Glucokinase activators will increase the flux of glucose metabolism in β-cells and hepatocytes, which will be coupled to increased insulin secretion. Such agents would be useful for treating type II diabetes.

This invention provides a compound, comprising a substituted hydantoin of the formula:



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wherein

R_1 is a five- or six- membered aromatic heterocyclic ring having one to three heteroatoms selected from nitrogen, oxygen, and sulfur, which ring is unsubstituted or substituted with halo, amino, hydroxylamino, nitro, cyano, sulfonamido, lower alkyl, perfluoro lower alkyl, lower alkyl thio, perfluoro-lower alkyl thio, lower alkyl sulfonyl, perfluoro-lower alkyl sulfonyl, lower alkyl sulfinyl, or $-(R_5)_n$-C(O)-OR_6;

R_2 is a cycloalkyl ring containing from 5 to 7 carbon atoms;

R_3 is hydrogen, lower alkyl, a cycloalkyl ring containing from 5 to 7 carbon atoms, unsubstituted aryl, aryl substituted with halo or hydroxy, or an unsubstituted five- or six-

membered aromatic heterocyclic ring having one or two heteroatoms selected from nitrogen, oxygen, and sulfur;

R_4 is hydrogen, lower alkyl, or R_3 and R_4 together with the carbon atom to which they are attached form a cycloalkyl ring containing 5 to 7 carbon atoms;

R_5 is -C(O)- or lower alkyl;

R_6 is lower alkyl;

n is 0 or 1; * and ** each designate an asymmetric center,

and pharmaceutically acceptable salts thereof.

The compounds of Formula I have been found to activate glucokinase. Glucokinase activators are useful for increasing insulin secretion in the treatment of type II diabetes. Therefore compounds of this invention are useful to increase insulin secretion in view of their activity as glucokinase activators.

The present invention also relates to a pharmaceutical composition comprising a compound of formula I and a pharmaceutically acceptable carrier and/or adjuvant. Furthermore, the present invention relates to the use of such compounds as therapeutic active substances as well as to their use for the preparation of medicaments for the treatment or prophylaxis of type II diabetes. The present invention further relates to processes for the preparation of the compounds of formula I. In addition, the present invention relates to a method for the prophylactic or therapeutic treatment of type II diabetes, which method comprises administering a compound of formula I to a human being or an animal.

In more detail, this invention is directed to compounds of Formula I above. The invention is particularly directed to compounds as follows, where:

R_2 and R_3 are both cyclohexyl, or

R_3, when it is lower alkyl, is methyl, ethyl, propyl, or butyl, or

R_4, when it is lower alkyl, is methyl or ethyl (especially compounds where R_3 and R_4 are both so defined), or

R_1, when substituted, is substituted with halo, lower alkyl, or $-(R_5)_n$-C(O)-OR_6,

or compounds where any two or more, or all, of these conditions are met. For any compound of this invention where R_1, R_2, or R_3 are not specified, it is preferred that the variable is as described in this paragraph.

Certain preferred compounds of Formula I include a compound where R_1 is substituted or unsubstituted thiazolyl (Compound A). Among the embodiments of Compound A are those compounds where R_1 is thiazolyl substituted with halo, lower alkyl, or $-(R_5)_n$-C(O)-OR_6, and especially with -$(R_5)_n$-C(O)-OR_6. (Compound A-1). In Compound A-1, it is preferred that R_2 is cyclopentyl or cyclohexyl. It is also preferred that R_3 is cyclopentyl or cyclohexyl. It is preferred that R_4 is hydrogen. It is especially preferred that R_2 and R_3 are cyclohexyl.

In preferred embodiments of Compound A-1, R_2 and R_3 are cyclopentyl or cyclohexyl, and R_4 is hydrogen (Compound A-1a). In one embodiment of Compound A-1a, n is 0 (e.g., the thiazolyl is substituted with –C(O)-OR_6). Examples of such compounds are

(S,S)-2-[[3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl]propanoyl]amino]thiazole-4-carboxylic acid methyl ester.

(S,S)-2-[[2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl)-3-cyclopentylpropanoyl]amino]thiazole-4-carboxylic acid methyl ester .

(S,S)-2-[[3-cyclopentyl-2-[4-(cyclopentyl)methyl-2,5-dioxoimidazolidin-1-yl]propanoyl]amino]thiazole-4-carboxylic acid methyl ester.

(S,S)-2-[[3-cyclohexyl-2-[4-(cyclopentyl)methyl-2,5-dioxoimidazolidin-1-yl]propanoyl]amino]thiazole-4-carboxylic acid methyl ester.

In such a compound, R_2 and R_3 may both be cyclohexyl, for example (S,S)-2-[[3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl]propanoyl] amino] thiazole-4-carboxylic acid methyl ester.

In another embodiment of Compound A-1a, R_5 is –C(O)- or lower alkyl (e.g., the thiazolyl is substituted with –C(O)-C(O)-OR_6 or –lower alkyl-C(O)-OR_6). In addition, in such compounds R_2 and R_3 may be cyclohexyl. Examples of such compounds are

(S,S)-[2-[[3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl]propanoyl]amino]thiazole-4-yl]oxoacetic acid ethyl ester and

(S,S)-[2-[[3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl]propanoyl]amino]thiazole-4-yl]acetic acid ethyl ester.

In another embodiment of Compound A1, R_2 is cyclopentyl or cyclohexyl (Compound A-1b). In one embodiment of Compound A-1b, R_3 is substituted or unsubstituted phenyl and R_4 is hydrogen. Examples of these compounds are

(S,S)-2-[[2-(4-benzyl-2,5-dioxoimidazolidin-1-yl)-3-cyclohexylpropanoyl]amino]thiazole-4-carboxylic acid methyl ester.

2-[[(S)-2-[(R)-4-(4-chlorobenzyl)-2,5-dioxoimidazolidin-1-yl]-3-cyclohexylpropanoyl]amino]thiazole-4-carboxylic acid methyl ester.

(S,S)-2-[[3-cyclohexyl-2-[2,5-dioxo-4-(4-hydroxybenzyl)imidazolidin-1-yl]propanoyl]amino]thiazole-4-carboxylic acid methyl ester.

(S,S)-2-[[3-cyclohexyl-2-[2,5-dioxo-4-(3-hydroxybenzyl)imidazolidin-1-yl]propanoyl]amino]thiazole-4-carboxylic acid methyl ester, and

2-[[(S)-3-cyclohexyl-2-[(R,S)-2,5-dioxo-4-(4-fluorobenzyl)imidazolidin-1-yl]propanoyl]amino]thiazole-4-carboxylic acid methyl ester.

In another embodiment of Compound A-1b, at least one of R_3 and R_4 are lower alkyl. Examples of such compounds are

(S)-2-[[3-cyclohexyl-2-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)propanoyl]amino]thiazole-4-carboxylic acid methyl ester, and

2-[[(S)-3-cyclohexyl-2-[(R)-2,5-dioxo-4-propylimidazolidin-1-yl]propanoyl]amino]thiazole-4-carboxylic acid methyl ester.

In yet another embodiment of Compound A-1b, R_3 is naphthyl and R_4 is hydrogen. An example of such a compound is (S,S)-2-[[3-cyclohexyl-2-[2,5-dioxo-4-(naphthalen-2-yl)methylimidazolidin-1-yl]propanoyl]amino]thiazole-4-carboxylic acid methyl ester.

In another embodiment of Compound A-1b, R_3 and R_4 together with the carbon atoms to which they are attached form a cycloalkyl ring containing 5 to 7 carbon atoms. An example of such a compound is (S)-2-[[3-cyclohexyl-2-(2,4-dioxo-1,3-diazaspiro[4.4]non-3-yl)propanoyl]amino]thiazole-4-carboxylic acid methyl ester.

And in another embodiment of Compound A-1b, R_3 is an unsubstituted five- or six-membered aromatic heterocyclic ring having one or two heteroatoms selected from nitrogen, oxygen, and sulfur. An example of such a compound is (S,S)-2-[[3-cyclohexyl-2-[2,5-dioxo-4-(thiophen-2-yl)methylimidazolidin-1-yl]propanoyl]amino]thiazole-4-carboxylic acid methyl ester.

In one embodiment of Compound A (a compound of Formula I wherein R_1 is substituted or unsubstituted thiazolyl), R_1 is unsubstituted thiazolyl (Compound A-2). It is preferred that R_2 and R_3 are cyclohexyl and R_4 is hydrogen. An example of such a Compound A-2 is (S,S)-3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl]-N-(thiazole-2-yl)propanamide.

In other preferred compounds of Formula I, R_1 is substituted or unsubstituted pyridine (Compound B). It is preferred that R_2 is cyclopentyl or cyclohexyl, especially cyclohexyl. It is also preferred that R_3 is cyclopentyl or cyclohexyl, especially cyclohexyl. It is preferred that R_4 is hydrogen.

In one embodiment of Compound B, R_2 is cyclohexyl. In such a compound where R_2 is cyclohexyl, it is preferred that R_3 is cyclohexyl and R_4 is hydrogen (Compound B-1).

In one embodiment of Compound B-1, R_1 is substituted pyridine. Preferably the pyridine is substituted with $-(R_5)_n-C(O)-OR_6$, especially where n is 0 and R_6 is lower alkyl, such as methyl (e.g., methoxycarbonyl). Examples of such compounds are

(S,S)- 3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl]-N-(5-methylpyridin-2-yl)propanamide.

(S,S)-6-[[3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl]propanoyl]amino]nicotinic acid methyl ester, and

(S,S)-N-(5-chloropyridin-2-yl)-3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl]propanamide.

In another embodiment of Compound B-1, R_1 is unsubstituted pyridine. An example of such a compound is (S,S)- 3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl]-N-(pyridin-2-yl)propanamide.

In the compound of Formula I the "*" and "**" illustrate the two separate asymmetric centers. The (S) enantiomer at the position designated by "**" is preferred. However the compounds of this invention may be pure (R)(R), pure (S)(S), pure (R)(S), pure (S)(R) or any mixture of pure enantiomers.

As used throughout this application unless otherwise specified, the term "lower alkyl" includes both straight chain and branched chain alkyl groups having from 1 to 6 or 1 to 7 carbon atoms, such as methyl, ethyl, propyl, isopropyl, preferably methyl and ethyl. Unless otherwise specified, propyl is taken to include both forms of propyl (e.g., isopropyl, n-propyl) and butyl is taken to include all forms of butyl (e.g., isobutyl, n-butyl, tert-butyl). Preferred at R_3 is methyl, ethyl, propyl, or butyl. Preferred at R_4 is methyl or ethyl.

The term "cycloalkyl ring" may be a ring of from three to seven carbon atoms, but preferably from five to seven carbon atoms, especially cyclopentyl, cyclohexyl, cyclobutyl and

cyclopropyl. The more preferable cycloalkyl groups contain from 5 to 6 carbon atoms, e.g., cyclopentyl and cyclohexyl, and cyclohexyl is most preferable. Thus, in one embodiment of the present invention for example, cycloalkyl residue R_2 is cyclopentyl or cyclohexyl. In another embodiment, cycloalkyl residue R_2 is cyclopentyl. In still another embodiment , cycloalkyl residue R_2 is cyclohexyl.

As used herein, "perfluoro-lower alkyl" means any lower alkyl group wherein all of the hydrogens of the lower alkyl group are substituted or replaced by fluoro. Among the preferred perfluoro-lower alkyl groups are trifluoromethyl, pentafluoroethyl, heptafluoropropyl, etc.

As used herein, "lower alkyl thio" means a lower alkyl group as defined above where a thio group is bound to the rest of the molecule. Similarly "perfluoro-lower alkyl" thio means a perfluoro-lower alkyl group as defined above where a thio group is bound to the rest of the molecule. As used herein, "lower alkyl sulfonyl" or "lower alkyl sulfinyl" means a lower alkyl group as defined above where a sulfonyl or sulfinyl group is bound to the rest of the molecule. Similarly "perfluoro-lower alkyl sulfonyl" means a perfluoro-lower alkyl group as defined above where a sulfonyl group is bound to the rest of the molecule.

When R_3 and R_4 together with the carbon atom to which they are attached form a cycloalkyl ring containing five to seven carbon atoms, this includes the ring carbon atom and the methylene linking the ring carbon atom and R_4 such that if R_3 and R_4 are each methylene, cyclobutyl is formed. If R_3 is methylene and R_4 is ethylene, cyclopentyl is formed , etc. Preferable cycloalkyl ring formed by R_3 and R_4 together with the carbon atom to which they are attached is cyclopentyl.

As used herein, the terms "halogen" or "halo" unless otherwise specified, designates all four halogens, i.e. fluorine, chlorine, bromine and iodine.

R_1 is, and R_3 can be any five- or six-membered aromatic heterocyclic ring containing from one to three, preferably from one to two, heteroatoms selected from the group consisting

of sulfur, oxygen or nitrogen. Any such five- or six-membered aromatic heterocyclic ring can be used in accordance with this invention. Among the preferred rings for R_1 are thiazole and pyridine (especially pyridine), and a preferred ring for R_3 is thiophene. R_1, and R_3 when R_3 is a heterocyclic ring, is connected to the remainder of the molecule of Formula I through a ring carbon atom. Above residues R_1, such as for example thiazolyl or pyridyl, may optionally be substituted on a ring carbon atom with halo, amino, hydroxylamino, nitro, cyano, sulfonamido, lower alkyl, perfluoro lower alkyl, lower alkyl thio, perfluoro-lower alkyl thio, lower alkyl sulfonyl, perfluoro-lower alkyl sulfonyl, lower alkyl sulfinyl, or $-(R_5)_n$-C(O)-OR_6, wherein n, R_5 and R_6 are as defined in above Formula I. Preferable substituents of a thiazolyl residue R_1 are substituents of the formula -$(R_5)_n$-C(O)-OR_6, wherein n, R_5 and R_6 are as defined in above Formula I. Preferable substituents of a pyridyl residue R_1 are halo, lower alkyl, or $-(R_5)_n$-C(O)-OR_6, wherein n, R_5 and R_6 are as defined in above Formula I. R_1 is preferably monosubstituted, but may be di or tri substituted. A preferred substituent, especially for pyridine, is lower alkoxy (preferably methoxy) carbonyl.

As used herein the term "aryl" signifies an aromatic hydrocarbon ring having six or ten carbon atoms such as phenyl or naphthyl.

Preferable residues R_3 are selected from hydrogen, lower alkyl, cyclopentyl, cyclohexyl, phenyl, naphthyl, thiophenyl, phenyl substituted with halo or phenyl substituted with hydroxy. In one embodiment, R_3 is hydrogen or lower alkyl. In another embodiment, R_3 is cyclopentyl or cyclohexyl. In still another embodiment, R_3 is thiophenyl. In still another embodiment, R_3 is naphthyl. In still another embodiment, R_3 is is phenyl, optionally substituted with halo or hydroxy. Preferable residues R_4 are hydrogen and lower alkyl. In one embodiment, R_5 is -C(O)-. In another embodiment, R_5 is lower alkyl. In one embodiment, n is 0. In another embodiment, n is 1.

Preferable compounds in accordance with the present invention are those wherein R_1 is unsubstituted thiazolyl or pyridyl; or thiazolyl or pyridyl substituted with halo, lower alkyl or -$(R_5)_n$-C(O)-OR_6; R_2 is cyclopentyl or cyclohexyl; R_3 is hydrogen, lower alkyl, cyclopentyl, cyclohexyl, phenyl, naphthyl, thiophenyl, phenyl substituted with halo or phenyl substituted with hydroxy; R_4 is hydrogen, lower alkyl, or R_3 and R_4 together with the carbon atom to

which they are attached form a cyclopentyl ring; R_5 is -C(O)- or lower alkyl; R_6 is lower alkyl; and n is 0 or 1.

Especially preferred compounds in accordance with the present invention are:

(S,S)-2-[[2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl)-3-cyclopentylpropanoyl]amino]thiazole-4-carboxylic acid methyl ester,

(S,S)-2-[[3-cyclopentyl-2-[4-(cyclopentyl)methyl-2,5-dioxoimidazolidin-1-yl]propanoyl]amino]thiazole-4-carboxylic acid methyl ester,

(S,S)-2-[[3-cyclohexyl-2-[4-(cyclopentyl)methyl-2,5-dioxoimidazolidin-1-yl]propanoyl]amino]thiazole-4-carboxylic acid methyl ester,

(S,S)-2-[[3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl]propanoyl]amino]thiazole-4-carboxylic acid methyl ester,

(S,S)-[2-[[3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl]propanoyl]amino]thiazol-4-yl]oxoacetic acid ethyl ester,

(S,S)-[2-[[3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl]propanoyl]amino]thiazol-4-yl]acetic acid ethyl ester,

(S,S)-2-[[2-(4-benzyl-2,5-dioxoimidazolidin-1-yl)-3-cyclohexylpropanoyl]amino]thiazole-4-carboxylic acid methyl ester,

2-[[(S)-2-[(R)-4-(4-chlorobenzyl)-2,5-dioxoimidazolidin-1-yl]-3-cyclohexylpropanoyl]amino]thiazole-4-carboxylic acid methyl ester,

(S,S)-2-[[3-cyclohexyl-2-[2,5-dioxo-4-(4-hydroxybenzyl)imidazolidin-1-yl]propanoyl]amino]thiazole-4-carboxylic acid methyl ester,

(S,S)-2-[[3-cyclohexyl-2-[2,5-dioxo-4-(3-hydroxybenzyl)imidazolidin-1-yl]propanoyl]amino]thiazole-4-carboxylic acid methyl ester,

2-[[(S)-3-cyclohexyl-2-[(R,S)-2,5-dioxo-4-(4-fluorobenzyl)imidazolidin-1-yl]propanoyl]amino]thiazole-4-carboxylic acid methyl ester,

(S)-2-[[3-cyclohexyl-2-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)propanoyl]amino]thiazole-4-carboxylic acid methyl ester,

2-[[(S)-3-cyclohexyl-2-[(R)-2,5-dioxo-4-propylimidazolidin-1-yl]propanoyl]amino]thiazole-4-carboxylic acid methyl ester,

(S,S)-2-[[3-cyclohexyl-2-[2,5-dioxo-4-(naphthalen-2-yl)methylimidazolidin-1-yl]propanoyl]amino]thiazole-4-carboxylic acid methyl ester,

(S)-2-[[3-cyclohexyl-2-(2,4-dioxo-1,3-diazaspiro[4.4]non-3-yl)propanoyl]amino]thiazole-4-carboxylic acid methyl ester,

(S,S)-2-[[3-cyclohexyl-2-[2,5-dioxo-4-(thiophen-2-yl)methylimidazolidin-1-yl]propanoyl]amino]thiazole-4-carboxylic acid methyl ester,

(S,S)-3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl]-N-(thiazole-2-yl)propanamide,

(S,S)-6-[[3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl]propanoyl]amino]nicotinic acid methyl ester,

(S,S)-3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl]-N-(5-methylpyridin-2-yl)propanamide,

(S,S)-N-(5-chloropyridin-2-yl)-3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl]propanamide, and

(S,S)-3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl]-N-(pyridin-2-yl)propanamide.

The compounds of this invention may be produced by the reaction schemes provided below.

The term "resin" designates any conventional polymer resin which has suitable characteristics for use in solid phase peptide synthesis. A resin with the suitable characteristics is inert, physically stable, insoluble in inorganic solvents, and has a linker functionality which is labile under known chemical conditions. Preferred are polystyrene resins having chemically labile functional linkers such as trityl resins and especially Wang resins.

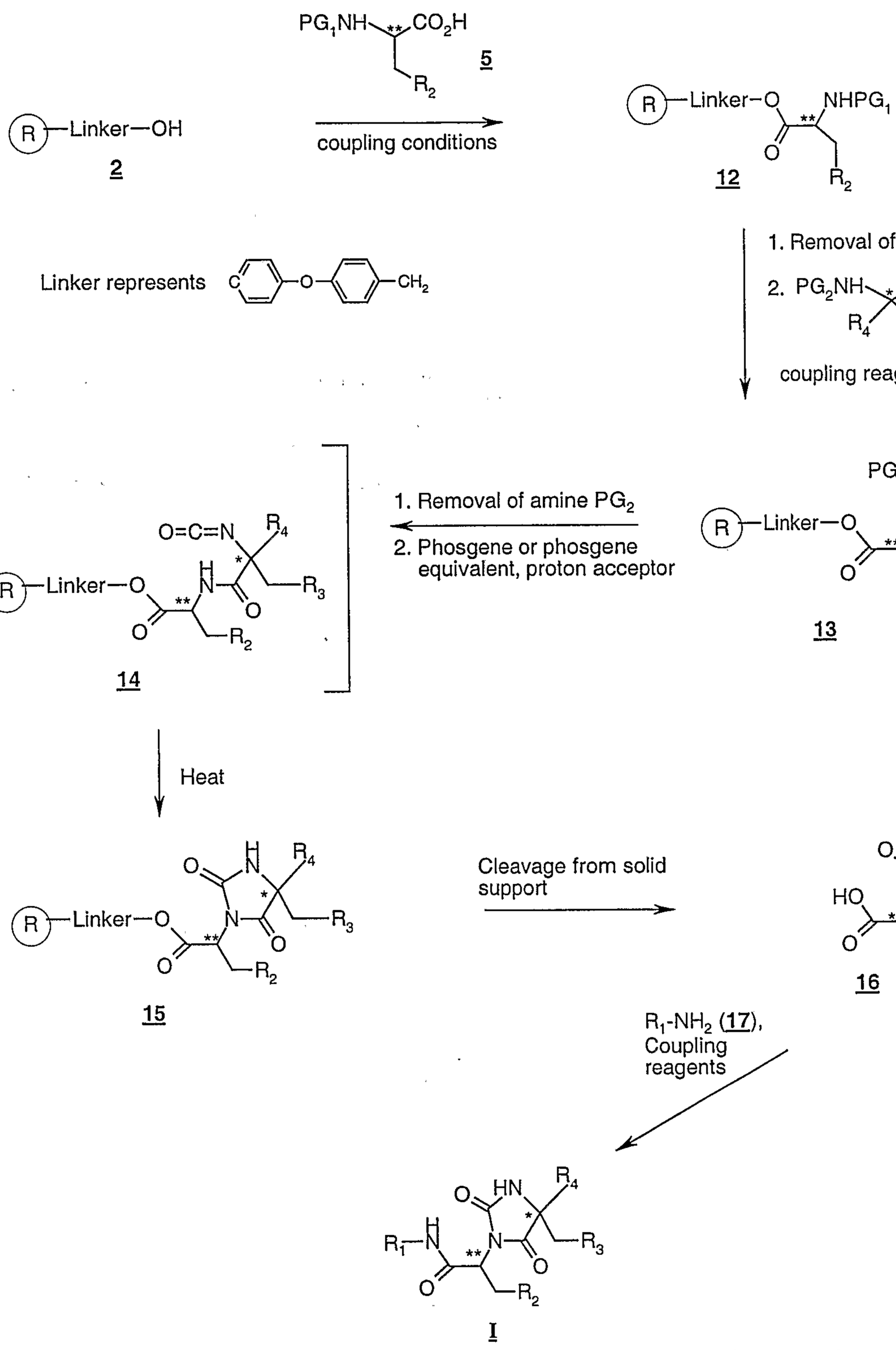
The term "amino protecting group" designates any conventional amino protecting group which can be cleaved to yield the free amino group. The preferred protecting groups are the conventional amino protecting groups utilized in peptide synthesis. Especially preferred are those amino protecting groups which are cleavable under treatment with secondary dialkyl amines. A particularly preferred amino protecting group is 9H-fluoren-9-ylmethoxy carbamate.

"Orthogonal" is the term used to describe the relationship of the amino protecting group to the resin. The resin and the amino protecting group must be compatible, in that the resin-peptide bond and the amino protecting group should not labile under the same conditions. During synthesis of a given compound, one should be able to cleave the amino protecting groups off the compound while leaving the compound attached to the resin. In other words, the conditions under which the amino protecting group comes off the compound should not also cause the compound to come off the resin. It is preferred that the amino protecting group be cleavable under basic or weakly acidic conditions, because the preferred Wang-type resins are cleavable under strongly acidic conditions (i.e. about pH 0 to about pH 1) A skilled person will readily be able to determine the necessary conditions to select an orthogonal amino protecting group – resin set.

The term "pharmaceutically acceptable salts" as used herein include any salt with both inorganic or organic pharmaceutically acceptable acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulfonic acid, *para*-toluene sulfonic acid and the like. The term "pharmaceutically acceptable salts" also includes any pharmaceutically acceptable base salt such as amine salts, trialkyl amine salts and the like. Such salts can be formed quite readily by those skilled in the art using standard techniques.

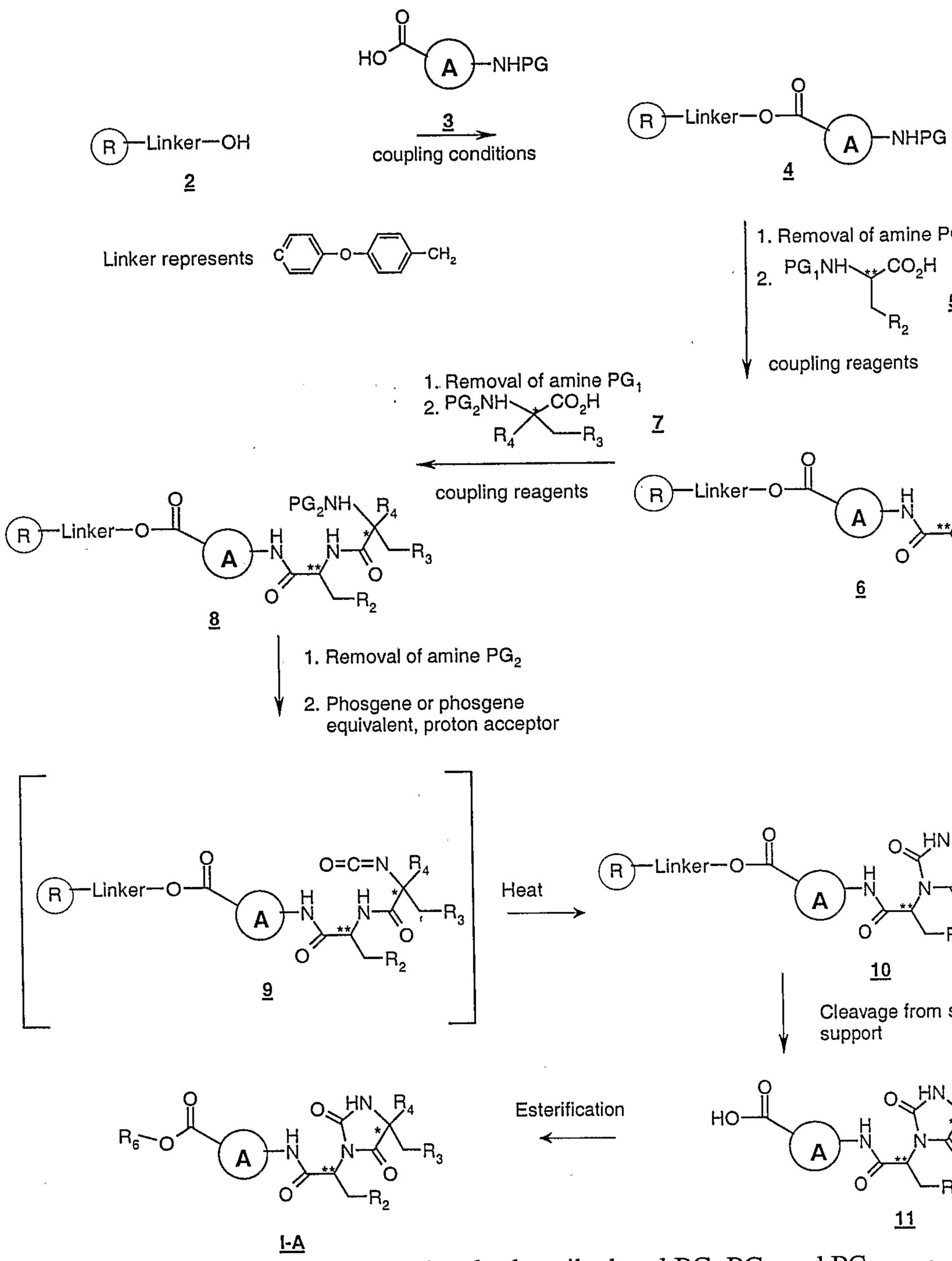
In accordance with this invention, the compounds of Formula I are produced by the following reaction schemes. Any compound of Formula I may be produced as shown in Reaction Scheme 1. The compounds of Formula I-A are produced as shown in Reaction Scheme 2. Reaction Scheme 3 shows how to produce N-Fmoc-aminothiazole-4-carboxylic acid, which is compound 3 of Scheme 2 where PG is the protecting group Fmoc.

Reaction Scheme 1



wherein R_1, R_2, R_3 and R_4 are as previously described and PG_1 and PG_2 are amine protecting groups which may or may not be equivalent, that are removable under conditions compatible with the Linker-O bond.

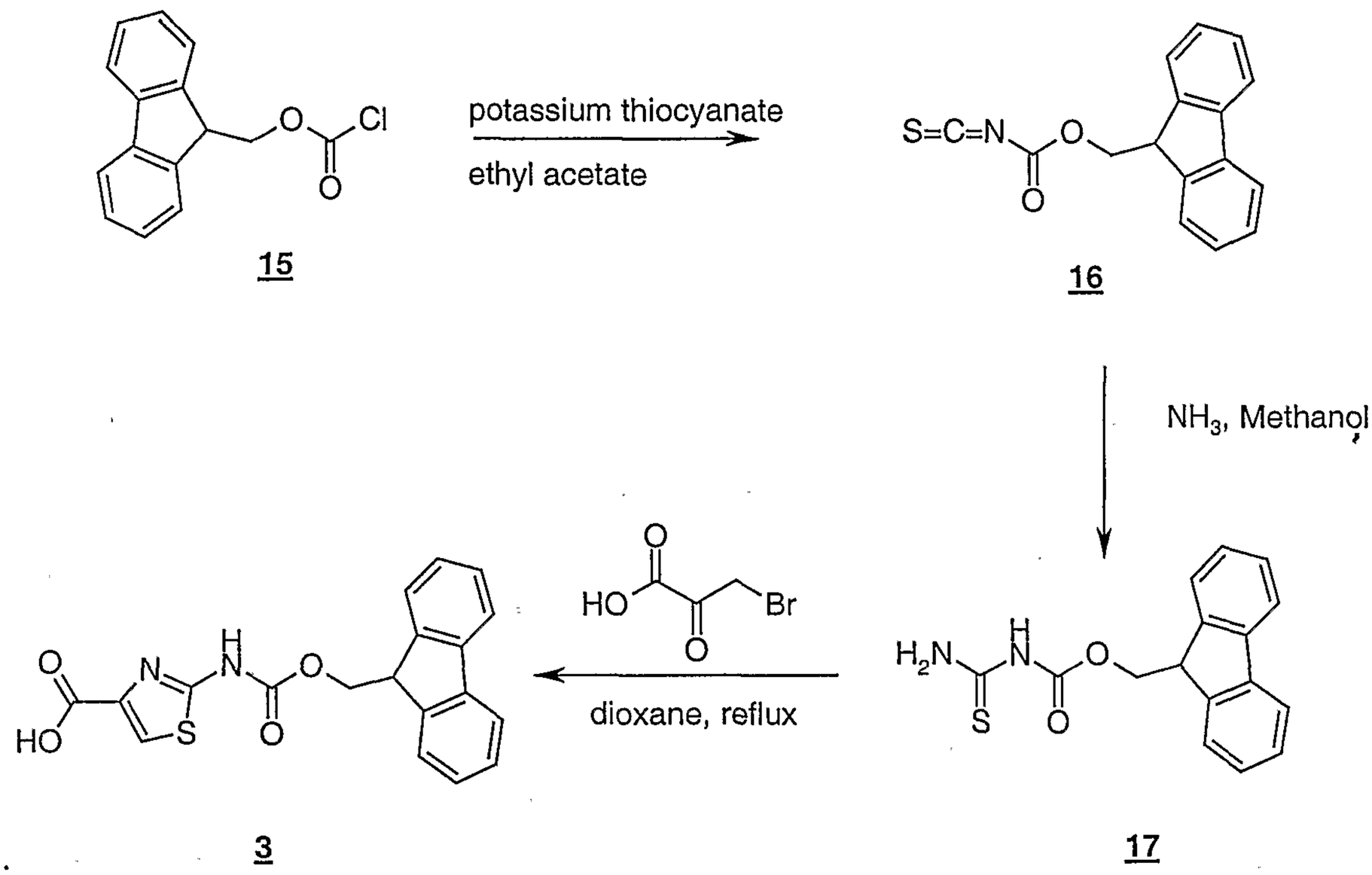
Reaction Scheme 2



I-A

wherein R_2, R_3, R_4 and R_6 are as previously described and PG, PG_1 and PG_2 are amine protecting groups which may or may not be equivalent, that are removable under conditions compatible with the linker-O bond and where the ring A represents a five or six membered heteroaromatic ring having one, two or three hetero atoms selected from nitrogen, oxygen or sulfur.

Reaction Scheme 3



The synthesis of the compounds of this invention may be carried out by a procedure whereby each amino acid in the desired sequence is added one at a time in succession to another amino acid or residue thereof or by a procedure whereby peptide fragments with the desired amino acid sequence are first synthesized conventionally and then condensed to provide the compound.

Such conventional procedures for synthesizing the novel compounds of the present invention include for example any solid phase peptide synthesis method. In such a method the synthesis of the novel compounds can be carried out by sequentially incorporating the desired amino acid residues one at a time into the growing peptide chain according to the general principles of solid phase methods [Merrifield, R. B., *J. Amer. Chem. Soc.* **1963**, *85*, 2149-2154; Barany *et al.*, The Peptides, Analysis, Synthesis and Biology, Vol. 2, Gross, E. and Meienhofer, J., Eds. Academic Press 1-284 (1980); Bunin, B., Combinatorial Index, Academic Press (1998)].

Common to chemical syntheses of peptides is the protection of reactive side chain groups of the various amino acid moieties with suitable protecting groups, which will prevent a chemical reaction from occurring at that site until the protecting group is ultimately removed. Usually also common is the protection of the alpha amino group of an amino acid or fragment while that entity reacts at the carboxyl group, followed by the selective removal of the alpha amino protecting group and allow a subsequent reaction to take place at that site. While specific protecting groups are mentioned below in regard to the solid phase synthesis method, it should be noted that each amino acid can be protected by any protective group conventionally used for the respective amino acid in solution phase synthesis.

For example, alpha amino groups may be protected by a suitable protecting group selected from aromatic urethane-type protecting groups, such as benzyloxycarbonyl (Z) and substituted benzyloxycarbonyl, such as *p*-chlorobenzyloxycarbonyl, *p*-nitrobenzyloxycarbonyl, *p*-bromobenzyloxycarbonyl, *p*-biphenyl-isopropoxycarbonyl, 9-fluorenylmethoxycarbonyl (Fmoc) and *p*-methoxybenzyloxycarbonyl (Moz); aliphatic urethane-type protecting groups, such as *t*-butyloxycarbonyl (Boc), diisopropylmethoxycarbonyl, isopropoxycarbonyl, and allyloxycarbonyl. In the present case, Fmoc is the most preferred for alpha amino protection. Guanidino groups may be protected by a suitable protecting group selected from nitro, p-toluenesulfonyl (Tos), Z, pentamethylchromanesulfonyl (Pmc), adamantyloxycarbonyl, and Boc. Pmc is the most preferred for arginine (Arg).

The solvents dichloromethane, dimethylformamide (DMF) and N-methylpyrrolidinone and toluene may be purchased from Fisher or Burdick and Jackson and may be used without additional distillation. Trifluoroacetic acid was purchased from Halocarbon or Fluka and used without further purification. Diisopropylcarbodiimide and diisopropylethylamine (DIPEA) was purchased from Fluka or Aldrich and used without further purification. 1-Hydroxybenzotriazole (HOBT) may be purchased from Sigma Chemical Co. and used without further purification. Protected amino acids, unless otherwise specified, are generally preferably of the L configuration and may be obtained commercially from Bachem, Advanced ChemTech, or Neosystem. Such amino acids may also be chemically synthesized using any

one of several well known methods of amino acid synthesis. The configuration of the amino acids 5 and 7 used to prepare a given compound of this invention will determine the configuration of the ** and * positions respectively of Formula I. Therefore, it is useful to select the amino acid configuration with the desired final configuration in mind. L amino acids have the (S) absolute configuration and D amino acids have the (R) absolute configuration.

Compounds of this invention may be prepared using solid phase synthesis following the principles and general methods described by Merrifield or by Bunin, although other equivalent chemical synthesis known in the art could be used as previously mentioned. Solid phase synthesis is commenced from the C-terminal end of the peptide by coupling a N-protected amino acid to a suitable resin. Such a starting material can be prepared by attaching an N-protected amino acid by an ester linkage to a p-benzyloxybenzyl alcohol (Wang) resin, or by an amide bond between an Fmoc-Linker, such as p-[(R,S)-α-[1-(9H-fluoren-9-yl)-methoxyformamido]-2,4-dimethyloxybenzyl]-phenoxyacetic acid (Rink linker) to a benzhydrylamine (BHA) resin. Preparation of the hydroxymethyl resin is well known in the art. Wang resin supports are commercially available and generally used when the desired peptide being synthesized has an ester or a substituted amide at the C-terminus. To form the starting resin bound amino acid, a Fmoc N-protected amino acid is activated by the formation of a mixed anhydride which in turn couples with the hydroxymethyl resin though an ester bond. Several reagents are used to form mixed anhydrides in which the carbonyl group originating from the C-terminal amino acid is preferentially activated to nucleophilic attack by the hydroxymethyl residues in the Wang resin, through either electronic or steric effects. For example, appropriate compounds used in the formation of the mixed anhydrides are trimethylacetyl chloride, 2,6-dichlorobenzoyl chloride and 2,4,6-trichlorobenzoyl chloride, preferably 2,6-dichlorobenzoyl chloride.

Subsequently, the amino acids or mimetics are then coupled onto the Wang resin using the Fmoc protected form of the amino acid or mimetic, with 2 - 5 equivalents of amino acid and a suitable coupling reagent. After each coupling, the resin may be washed and dried under

vacuum. Loading of the amino acid onto the resin may be determined by amino acid analysis of an aliquot of Fmoc-amino acid resin or by determination of Fmoc groups by UV analysis.

The resins are carried through one or two cycles to add amino acids sequentially. In each cycle, the N-terminal Fmoc protecting group is removed under basic conditions from the resin bound amino acid. A secondary amine base such as piperidine, piperazine or morpholine, preferably piperidine (20-40% v/v) in an inert solvent, for example, N,N-dimethylformamide is particularly useful for this purpose. Following the removal of the alpha amino protecting group, the subsequent protected amino acids are coupled stepwise in the desired order to obtain an N-Fmoc protected peptide-resin. The activating reagents used for coupling of the amino acids in the solid phase synthesis of the peptides are well known in the art. For example, appropriate coupling reagents for such syntheses are [(benzotriazol-1-yl)oxy]tris(dimethylamino) phosphonium hexafluorophosphate (BOP), [(benzotriazol-1-yl)oxy]tris(pyrrolidino)-phosphonium hexafluorophosphate (PyBOP), O-(1H-benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU), and diisopropylcarbodiimide (DIC), preferably HBTU and DIC. Other activating agents as described by Barany and Merrifield [The Peptides, Vol. 2, J. Meienhofer, ed., Academic Press, 1979, pp 1-284] may be utilized. The couplings are conveniently carried out in an inert solvent, such as N,N-dimethylformamide or N-methylpyrrolidinone, preferably N-methylpyrrolidinone, optionally in the presence of a substance that minimizes racemization and increases the rate of reaction. Among such substances are 1-hydroxybenzotriazole (HOBT), 3,4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazine (HOOBT), 1-hydroxy-7-azabenzotriazole (HOAT), and N-hydroxysuccinimide (HOSu). In the present instance, HOBT is preferred.

The protocol for a typical coupling cycle is as follows (Method B):

Step	Reagent	Time
1	20% piperidine/DMF	30 min
2	DMF	3 x 30 sec
3	methanol	3 x 30 sec

4	dichloromethane	3 x 30 sec
5	coupling	overnight
6	DMF	3 x 30 sec
7	methanol	3 x 30 sec
8	dichloromethane	3 x 30 sec

Solvents for all washings and couplings may be measured to volumes of, for example, 10 - 20 ml/g resins. Coupling reactions throughout the synthesis may be monitored by assays, such as the Kaiser ninhydrin test, to determine extent of completion [Kaiser *et at. Anal. Biochem.* **1970**, *34*, 595-598].

When the requisite number of amino acid units have been assembled on the resin, the N-terminal Fmoc group may be cleaved using Steps 1-4 of Method B and the deprotected amine is reacted with phosgene or a phosgene equivalent to form an isocyanate. The reagent of choice in this transformation is trichloromethyl chloroformate (diphosgene). The reaction is carried out in an inert solvent, for example dichloromethane, in the presence of a proton acceptor. When a suspension of the resin bound isocyanate is heated, cyclization occurs wherein the isocyanate moiety condenses with the nitrogen of the neighboring amide group to form a 2,5-dioxoimidazolidine ring.

The compounds may be cleaved from the resin by the following procedure, conditions which also remove other protecting groups if they are present. The peptide-resins are shaken in a mixture (1:1) of trifluoroacetic acid in dichloromethane, optionally in the presence of a cation scavanger, for example ethanedithiol, dimethylsulfide, anisole or triethylsilane, at room temperature for 60 min. The cleavage solution may be filtered free from the resin, concentrated to dryness, and the product then used *per se* in subsequent transformations as shown in Reaction Scheme 1 and Reaction Scheme 2.

Compounds of Formula 1 can be prepared by the methods outlined in Reaction Scheme 1 and Reaction Scheme 2. Reaction Scheme 2 is a general procedure that can be used

to prepare all compounds embodied by Formula 1, but in the present case, it is particularly useful in the preparation of compounds where R_1 is varied while R_2 and R_3 are limited to cycloalkyl and R_4 is hydrogen. Reaction Scheme 1 is used in the preparation of compounds of Formula I-A.

In Reaction Scheme 2, an N-protected-amino acid **3** (see Reaction Scheme 3) is converted to a mixed anhydride on treatment with 2,6-dichlorobenzoyl chloride in the presence of Wang resin **2** and a proton acceptor, such as triethylamine, diisopropylethylamine or pyridine, preferably pyridine to give the resin bound amino acid of structure **4** . The reaction is conveniently carried out in an inert solvent for example N,N-dimethylformamide or N-methylpyrrolidinone, preferably N-methylpyrrolidinone at from zero degrees to room temperature, most conveniently at room temperature. The conversiono of **4** to the resin bound compound of structure **6** can be achieved by using the protocol outlined in method B. Thus after N-deprotection of the resin bound amino acid of structure **4** with piperidine in N,N-dimethylformamide, the product is then acylated with the N^{α}–protected amino acid of structure **5** in the presence of diisopropylcarbodiimide and HOBT in N-methylpyrrolidinone. The deprotection and N-acylation is carried out at a temperature between about zero degrees and about room temperature, preferably at about room temperature. By using the coupling cycle described above for the conversion of **4** to **6** the N^{α}–protected amino acids of structure **7** is incorporated into the resin bound compound of structure **6**. Thus compounds of structure **6** are sequentially deprotected with piperidine in N,N-dimethylformamide and then coupled with compounds of structure **7** in the presence of diisopropylcarbodiimide and 1-hydroxybenzotriazole in N-methylpyrrolidinone at a temperature between about zero degrees and about room temperature, preferably at about room temperature to afford the resin bound compounds of structure **8**.

The N-terminus protecting group PG_2 in the compounds of structure **8** was removed on treatment with a secondary amine base, preferably piperidine in an inert solvent (preferably N,N-dimethylformamide) and then was reacted with phosgene or a phosgene equivalent reagent, to ultimately yield in a two step sequence, the 2,5-dioxoimidazolidines of structure **10**. The reaction to give the intermediate isocyanate **9** is conveniently carried out using

trichloromethyl chloroformate (diphosgene) in an inert solvent, for example, a halogenated hydrocarbon in the presence of a proton acceptor, for example, pyridine, triethylamine or diisopropylethylamine, preferably diisopropylethylamine at a temperature between about zero degrees and about room temperature, preferably at about room temperature. The thermally induced cyclization of the intermediate isocyanates is performed by heating a suspension of the resin bound isocyanates of structure **9** in an inert solvent, for example toluene, at a temperature of from between 50 °C and the reflux temperature of the mixture, preferably at about 70 °C to give the resin bound compounds of structure **10**.

Cleavage of the assembled peptidic residue **10** from the solid support to give the acids of structure **11** is achieved by shaking a suspension of **10** in a strong acid, for example methanesulfonic acid, hydrofluoric acid or trifluoroacetic acid, preferably trifluoroacetic acid optionally in the presence of a cation scavenger and an inert co-solvent, for example dichloromethane. The reaction is conveniently run at a temperature between about zero degrees and about room temperature, preferably at about room temperature.

To complete the synthesis, the acid of structure **11** is reacted with an alcohol (R_6OH) to form the ester **1**. The esterification can be accomplished using many of the methods well known to those of average skill in the field of organic chemistry. The conversion is conveniently carried out using a coupling reagent, for example one of the many useful carbodiimides, preferably the water soluble 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, optionally using R_6OH or a mixture of R_6OH and a inert co-solvent, e.g., dichloromethane, as the reaction medium. The reaction is run at a temperature between about zero degrees and about room temperature, preferably at about room temperature.

In a similar fashion, Reaction Scheme 1, the N^{α}–protected amino acids of structure **5** is converted to a mixed anhydride on treatment with 2,6-dichlorobenzoyl chloride in the presence of Wang resin **2** and a proton acceptor, such as triethylamine, diisopropylethylamine or pyridine, preferably pyridine to give the resin bound amino acid of structure **12**. The reaction is conveniently carried out in an inert solvent for example N,N-dimethylformamide or N-methylpyrrolidinone, preferably N-methylpyrrolidinone at from zero degrees to room temperature, most conveniently at room temperature. The conversion of **12** to the resin bound

compound of structure **13** can be achieved by using the protocol outlined in method B. Thus after N-deprotection of the resin bound amino acid of structure **12** with piperidine in N,N-dimethylformamide, the product is then acylated with the N^{α}–protected amino acid of structure **7** in the presence of diisopropylcarbodiimide and HOBT in N-methylpyrrolidinone. The deprotection and N-acylation is carried out at a temperature between about zero degrees and about room temperature, preferably at about room temperature.

The N-terminus protecting group PG_2 in the compounds of structure **13** was removed on treatment with a secondary amine base, preferably piperidine in an inert solvent, preferably N,N-dimethylformamide and then was reacted with phosgene or a phosgene equivalent reagent, to ultimately yield in a two step sequence, the 2,5-dioxoimidazolidines of structure **15**. The reaction to give the intermediate isocyanate **14** is conveniently carried out using trichloromethyl chloroformate (diphosgene) in an inert solvent, for example, a halogenated hydrocarbon in the presence of a proton acceptor, for example, pyridine, triethylamine or diisopropylethylamine, preferably diisopropylethylamine at a temperature between about zero degrees and about room temperature, preferably at about room temperature. The thermally induced cyclization of the intermediate isocyanates is accomplished by heating a suspension of the resin bound isocyanates of structure **14** in an inert solvent, for example toluene, at a temperature of from between 50 °C and the reflux temperature of the mixture, preferably at about 70 °C to give the resin bound compounds of structure **15**.

Cleavage of the peptidic residue **15** from the solid support to give the acids of structure **16** is achieved by shaking a suspension of **15** in a strong acid, for example methanesulfonic acid, hydrofluoric acid or trifluoroacetic acid, preferably trifluoroacetic acid optionally in the presence of a cation scavenger and an inert co-solvent, for example dichloromethane. The reaction is conveniently run at a temperature of between about zero degrees and about room temperature, preferably at about room temperature.

Reaction of the acid **16** with R_1-NH_2 to form the amide of Formula **1** can be carried out under the coupling conditions previously described. The preferred coupling reagent in this instance is HBTU. The reaction is carried out in the presence of a tertiary amine base, such as

triethylamine or diisopropylethylamine, preferably diisopropylethylamine in an inert solvent, for example N,N-dimethylformamide or N-methylpyrrolidinone, preferably N-methylpyrrolidinone at from zero degrees to room temperature, most conveniently at room temperature.

Reaction Scheme 3 outlines the preparation of the intermediate N-Fmoc-2-aminothiazole-4-carboxylic acid **3**. Initially 9-fluorenylmethoxycarbonyl chloride (**18**) is reacted with potassium thiocyanate in an inert solvent, preferably ethyl acetate at a temperature of between zero degrees and 5 °C. Then the reaction is allowed to proceed at a temperature of from zero degrees to 40 °C, preferably at room temperature to furnish N-Fmoc-thiocyanate (**19**). Treatment of **19** with a solution of ammonia in an inert solvent, for example methanol or ethanol, preferably methanol at a temperature of from zero degrees to room temperature, preferably zero degrees afforded N-Fmoc-thiourea **20**. In the final step, the thiourea **20** is then reacted with bromopyruvic acid to form the thiazole of structure 3. The reaction is conveniently carried out if an inert solvent, such as a cyclic ether, for example tetrahydrofuran or dioxane, preferably dioxane at a temperature of from 40 °C to the reflux temperature of the mixture preferably at about 70 °C.

All of the compounds of Formula I which include the compounds set forth in the Examples, activated glucokinase *in vitro* by the procedure of Example A. In this manner, they increase the flux of glucose metabolism which causes increased insulin secretion. Therefore, the compounds of Formula I are glucokinase activators useful for increasing insulin secretion.

On the basis of their capability of activating glucokinase, the compounds of above formula I can be used as medicaments for the treatment of type II diabetes. Therefore, as mentioned earlier, medicaments containing a compound of formula I are also an object of the present invention, as is a process for the manufacture of such medicaments, which process comprises bringing one or more compounds of formula I and, if desired, one or more other therapeutically valuable substances into a galenical administration form, e.g. by combining a compound of formula I with a pharmaceutically acceptable carrier and/or adjuvant.

The pharmaceutical compositions may be administered orally, for example in the form of tablets, coated tablets, dragées, hard or soft gelatine capsules, solutions, emulsions or suspensions. Administration can also be carried out rectally, for example using suppositories; locally or percutaneously, for example using ointments, creams, gels or solutions; or parenterally, e.g. intravenously, intramuscularly, subcutaneously, intrathecally or transdermally, using for example injectable solutions. Furthermore, administration can be carried out sublingually or as an aerosol, for example in the form of a spray. For the preparation of tablets, coated tablets, dragées or hard gelatine capsules the compounds of the present invention may be admixed with pharmaceutically inert, inorganic or organic excipients. Examples of suitable excipients for tablets, dragées or hard gelatine capsules include lactose, maize starch or derivatives thereof, talc or stearic acid or salts thereof. Suitable excipients for use with soft gelatine capsules include for example vegetable oils, waxes, fats, semi-solid or liquid polyols etc.; according to the nature of the active ingredients it may however be the case that no excipient is needed at all for soft gelatine capsules. For the preparation of solutions and syrups, excipients which may be used include for example water, polyols, saccharose, invert sugar and glucose. For injectable solutions, excipients which may be used include for example water, alcohols, polyols, glycerine, and vegetable oils. For suppositories, and local or percutaneous application, excipients which may be used include for example natural or hardened oils, waxes, fats and semi-solid or liquid polyols. The pharmaceutical compositions may also contain preserving agents, solubilising agents, stabilising agents, wetting agents, emulsifiers, sweeteners, colorants, odorants, salts for the variation of osmotic pressure, buffers, coating agents or antioxidants. As mentioned earlier, they may also contain other therapeutically valuable agents. It is a prerequisite that all adjuvants used in the manufacture of the preparations are non-toxic.

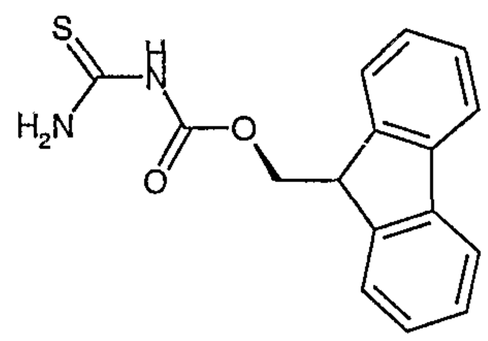
Preferred forms of use are intravenous, intramuscular or oral administration, most preferred is oral administration. The dosages in which the compounds of formula (I) are administered in effective amounts depend on the nature of the specific active ingredient, the age and the requirements of the patient and the mode of application. In general, dosages of about 1-100 mg/kg body weight per day come into consideration.

This invention will be better understood from the following examples, which are for purposes of illustration and are not intended to limit the invention defined in the claims which follow thereafter.

Analytical high performance liquid chromatography was (HPLC) was conducted on a Hewlett-Packard 1090 system with ultraviolet (UV) detection system at 214 nm using an ES Industries C_{18} column (30 x 3.2 mm). Preparative HPLC separations were carried out using a Shimazu VP series system interfaced with a Perkin-Elmer Sciex Mass Spectrometer detector (PE Sciex 150EX) using a YMC C_{18} column (2 x 5 cm).

Example 1

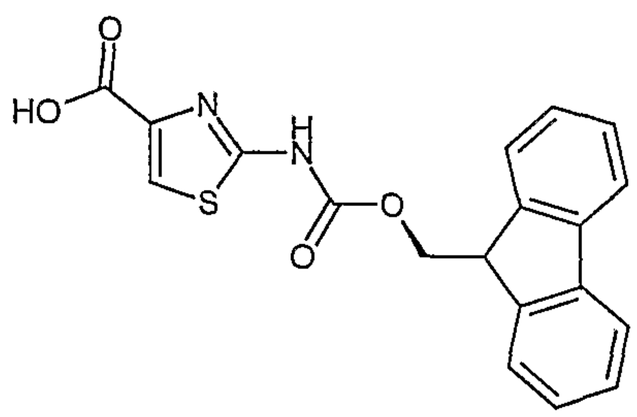
Preparation of N-Fmoc-thiourea.



To a suspension of potassium thiocyanate (8.55 g, 88 mmol) in ethyl acetate (100 mL) cooled to 0 °C was added dropwise a solution of 9-fluorenylmethoxycarbonyl chloride (20.7 g, 80 mmol) in ethyl acetate (100 mL) over a period of 15 min. The resulting suspension was allowed to warm to ambient temperature overnight with stirring. The formed solid was filtered off and the filtrate was concentrated *in vacuo* to afford an orange oil. Without further purification, the oil was dissolved in ethanol (50 mL) and treated by dropwise addition with a cold solution of ammonia in ethanol (7N, 91 mL, 637 mmol). A precipitate formed upon addition of the ammonia solution. The suspension was stirred vigorously at 0 °C for 15 min and then the solids were filtered off, washed with cold ethanol (3 x 20 mL) and dried to afford N-Fmoc-thiourea (16.8g, 70%) as an off-white solid: EI-HRMS m/e calcd for $C_{16}H_{14}N_2O_2S$ (M^+) 298.0776, found 298.0770.

Example 2

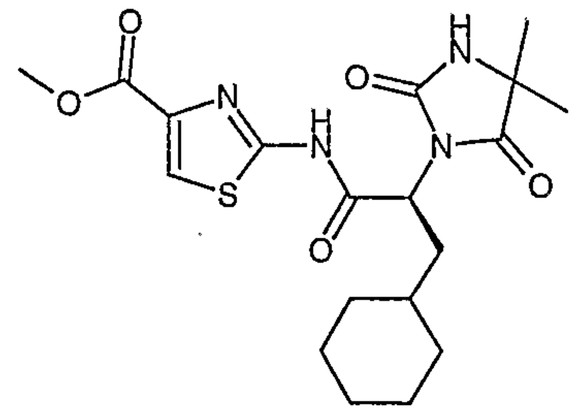
Preparation of N-Fmoc-2-aminothiazole-4-carboxylic acid.



A solution of N-Fmoc-thiourea (5.96g, 20 mmol) in dioxane (40 mL) was treated with bromopyruvic acid (3.34g, 20 mmol). The reaction mixture was refluxed for 1 h, then the precipitated solids were recovered by filtration and washed with diethyl ether (3 x 20 mL) to afford N-Fmoc-2-aminothiazole-4-carboxylic acid (7.1g, 97%) as a white solid: EI-HRMS m/e calcd for $C_{19}H_{14}N_2O_4S$ (M^+) 366.0674, found 366.0679.

Example 3

Preparation of (S)-2-[[3-cyclohexyl-2-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)propanoyl]amino]thiazole-4-carboxylic acid methyl ester.



Step (i). A mixture of N-Fmoc-2-aminothiazole-4-carboxylic acid (6.0 g, 16.5 mmol), 2,6-dichlorobenzoyl chloride (7.9mL, 55 mmol) in N-methylpyrrolidinone (50 mL) was added into a fritted polypropylene column charged with Wang resin (Midwest Bio-Tech, 10 g, 11mmol). After the suspension was shaken for 5 min, pyridine (6.2 mL, 77 mmol) was added slowly and the resulting dark mixture was shaken overnight at ambient temperature. The mixture was then filtered and the resin was washed with N,N-dimethylformamide (3 x 100 mL), methanol (3 x 100 mL), dichloromethane (3 x 100 mL) and dried *in vacuo*.

Step (ii). To the resin product of the previous step (3 g, 2.31 mmol) was added 20% piperidine in N,N-dimethylformamide (25 mL). The reaction mixture was shaken at ambient temperature for 30 min. The mixture was filtered and the resin was washed with N,N-dimethylformamide (3 x 30 mL), methanol (3 x 30 mL), dichloromethane (3 x 30 mL). The resin was then suspended in N-methylpyrrolidinone (10 mL) and N-Fmoc-3-cyclohexyl-L-alanine (2.7 g, 6.93 mmol), diisopropylcarbodiimide (1.09 mL, 6.93 mmol) and HOBT (0.936 g, 6.93 mmol) were added. The resulting mixture was shaken at ambient temperature overnight and filtered. The resin was washed with N,N-dimethylformamide (3 x 100 mL), methanol (3 x 100 mL), dichloromethane (3 x 100 mL) and dried *in vacuo*.

Step (iii). To the resin product of the previous step (200 mg, 0.14 mmol) was added 20% piperidine in N,N-dimethylformamide (5 mL) and the reaction mixture was shaken at ambient temperature for 30 min. The mixture was filtered and the resin was washed with N,N-dimethylformamide (3 x 10 mL), methanol (3 x 10 mL), dichloromethane (3 x 10 mL). The resin was then suspended in N-methylpyrrolidinone (2 mL) N-Fmoc-2-amino-2-

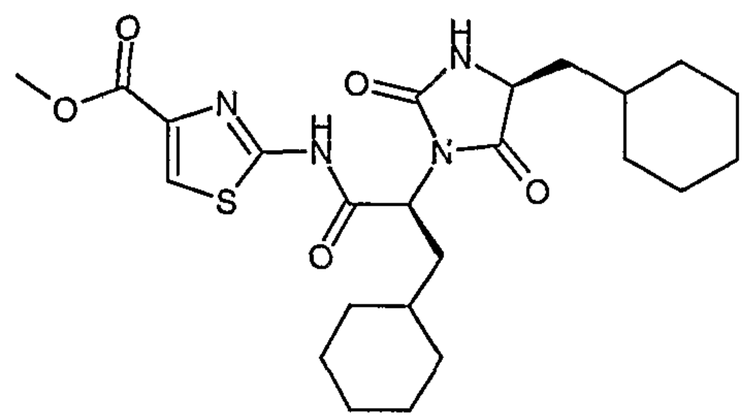
methylpropanoic acid (136 mg, 0.42 mmol), diisopropylcarbodiimide (65 μL, 0.42 mmol) and HOBT (57 mg, 0.42 mmol) were added. The resulting mixture was shaken at ambient temperature overnight and filtered. The resin was washed with N,N-dimethylformamide (3 x 10 mL), methanol (3 x 10 mL), dichloromethane (3 x 10 mL) and dried *in vacuo*.

Step (iv). To the product of the previous step (0.14 mmol) was added 20% piperidine in N,N-dimethylformamide (5 mL) and the reaction mixture was shaken at ambient temperature for 30 min. The mixture was filtered and the resin was washed with N,N-dimethylformamide (3 x 10 mL), methanol (3 x 10 mL), dichloromethane (3 x 10 mL). The resin was then suspended in dichloromethane (2 mL) and treated with diisopropylethylamine (73 μL, 0.42 mmol). The reaction mixture was then cooled to 0 °C and diphosgene (50 μL, 0.42 mmol) was added dropwise. The resulting mixture was allowed to warm to the ambient temperature and was stirred for 3 h. The mixture was filtered and the resin was washed with dichloromethane (3 x 10 mL) and dried *in vacuo*. The resin was then suspended in toluene (2 mL) and stirred reaction mixture was heated at 70 °C for 4 h. The cooled resin mixture was filtered and the resin was washed with dichloromethane (3 x 10 mL). Cleavage from the support was effected by treatment with 50% trifluoroacetic acid in dichloromethane (3 mL) for 1 hr. Concentration of the filtrate yielded a brown solid.

Step (v). Without further purification, the solid from Step (iv) was dissolved in methanol (1 mL) and then treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (40 mg, 0.21 mmol). The mixture was stirred at ambient temperature overnight and then was concentrated *in vacuo*. The resulting oil was triturated with 99/1 dichloromethane/methanol (3 x 5 mL) and filtered through a silica gel plug. The filtrate was concentrated *in vacuo* to afford (S)-2-[[3-cyclohexyl-2-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)propanoyl]amino]thiazole-4-carboxylic acid methyl ester (18 mg) as a white foam: EI-HRMS m/e calcd for $C_{19}H_{26}N_4O_5S$ (M^+) 423.1702, found 423.1701.

Example 4

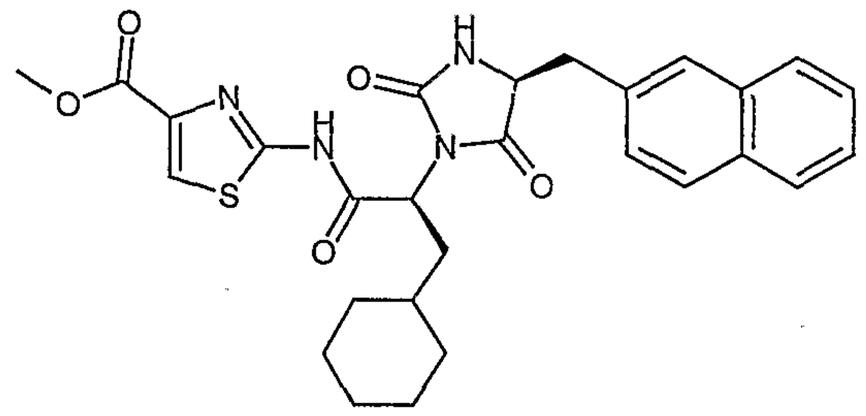
Preparation of (S,S)-2-[[3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl]propanoyl]amino]thiazole-4-carboxylic acid methyl ester.



The compound was prepared as described in Example 3, except N-Fmoc-3-cyclohexyl-L-alanine was the amino acid incorporated in Step (iii) of the procedure. The title compound was obtained as a white foam: EI-HRMS m/e calcd for $C_{24}H_{34}N_4O_5S$ (M^+) 491.2328, found 491.2323.

Example 5

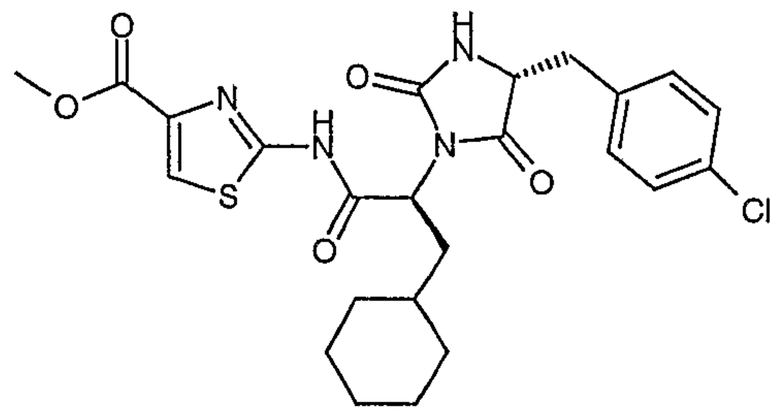
Preparation of (S,S)-2-[[3-cyclohexyl-2-[2,5-dioxo-4-(naphthalen-2-yl)methylimidazolidin-1-yl]propanoyl]amino]thiazole-4-carboxylic acid methyl ester.



The compound was prepared as described in Example 3, except N-Fmoc-3-(naphthalen-2-yl)-L-alanine was the amino acid incorporated in Step (iii) of the procedure. The title compound was obtained as a white foam: EI-HRMS m/e calcd for $C_{28}H_{30}N_4O_5S$ (M^+) 535.2015, found 535.2035.

Example 6

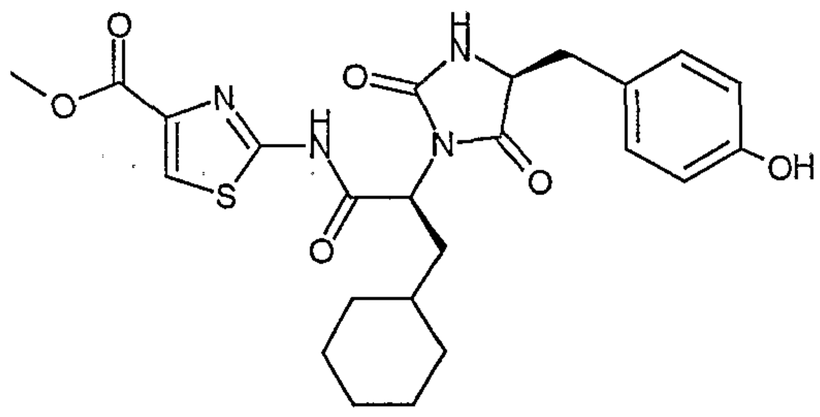
Preparation of 2-[[(S)-2-[(R)-4-(4-chlorobenzyl)-2,5-dioxoimidazolidin-1-yl]-3-cyclohexylpropanoyl]amino]thiazole-4-carboxylic acid methyl ester.



The compound was prepared as described in Example 3, except N-Fmoc-3-(4-chlorophenyl)-D-alanine was the amino acid incorporated in Step (iii) of the procedure. The title compound was obtained as a white foam: EI-HRMS m/e calcd for $C_{24}H_{27}N_4O_5SCl$ (M^+) 519.1469, found 519.1466.

Example 7

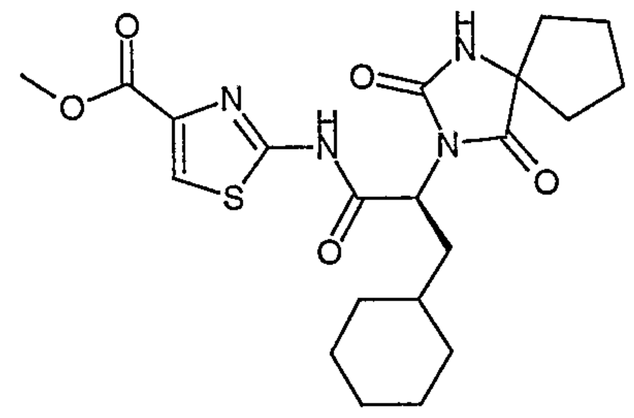
Preparation of (S,S)-2-[[3-cyclohexyl-2-[2,5-dioxo-4-(4-hydroxybenzyl)imidazolidin-1-yl]propanoyl]amino]thiazole-4-carboxylic acid methyl ester.



The compound was prepared as described in Example 3, except N-Fmoc-L-tyrosine was the amino acid incorporated in Step (iii) of the procedure. The title compound was obtained as a white foam: EI-HRMS m/e calcd for $C_{24}H_{28}N_4O_6S$ (M^+) 501.1808, found 501.1815.

Example 8

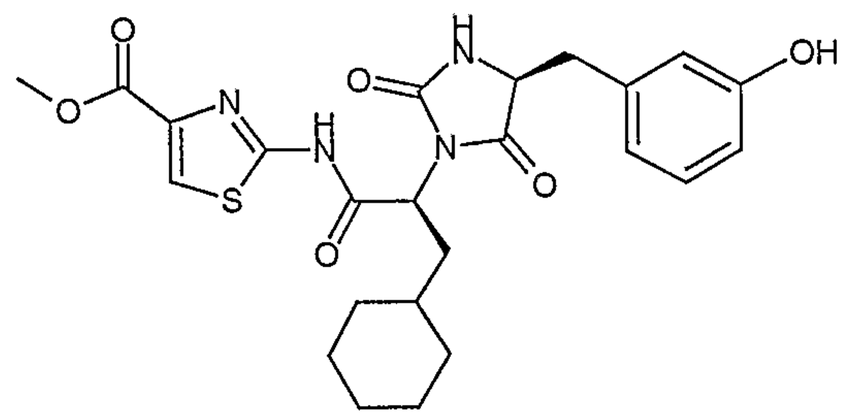
Preparation of (S)-2-[[3-cyclohexyl-2-(2,4-dioxo-1,3-diazaspiro[4.4]non-3-yl)propanoyl]amino]thiazole-4-carboxylic acid methyl ester.



The compound was prepared as described in Example 3, except N-Fmoc-1-aminocyclopentanecarboxylic acid was the amino acid incorporated in Step (iii) of the procedure: EI-HRMS m/e calcd for $C_{21}H_{28}N_4O_5S$ (M^+) 449.1859, found 449.1853.

Example 9

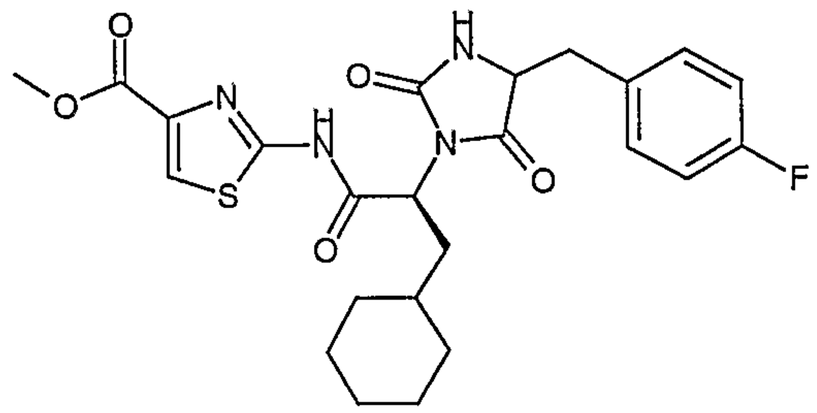
Preparation of (S,S)-2-[[3-cyclohexyl-2-[2,5-dioxo-4-(3-hydroxybenzyl)imidazolidin-1-yl]propanoyl]amino]thiazole-4-carboxylic acid methyl ester.



The compound was prepared as described in Example 3, except N-Fmoc-3-(3-hydroxyphenyl)-L-alanine was the amino acid incorporated in Step (iii) of the procedure: EI-HRMS m/e calcd for $C_{24}H_{28}N_4O_6S$ (M^+) 501.1808, found 501.1816.

Example 10

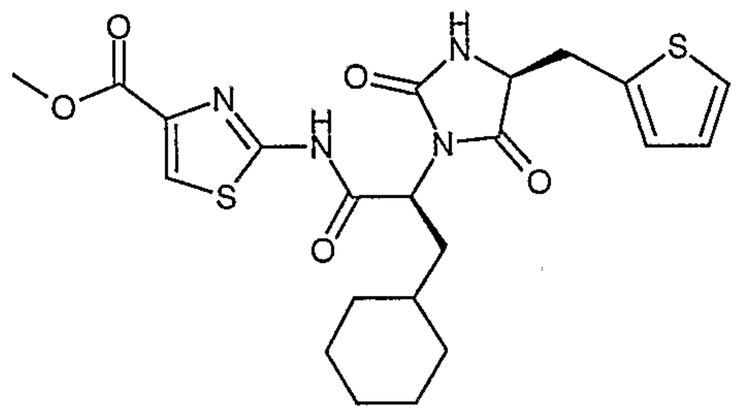
Preparation of 2-[[(S)-3-cyclohexyl-2-[(R,S)-2,5-dioxo-4-(4-fluorobenzyl)imidazolidin-1-yl]propanoyl]amino]thiazole-4-carboxylic acid methyl ester.



The compound was prepared as described in Example 3, except N-Fmoc-3-(4-fluorophenyl)-DL-alanine was the amino acid incorporated in Step (iii) of the procedure: EI-HRMS m/e calcd for $C_{24}H_{27}N_4O_5SF$ (M^+) 503.1764, found 503.1776.

Example 11

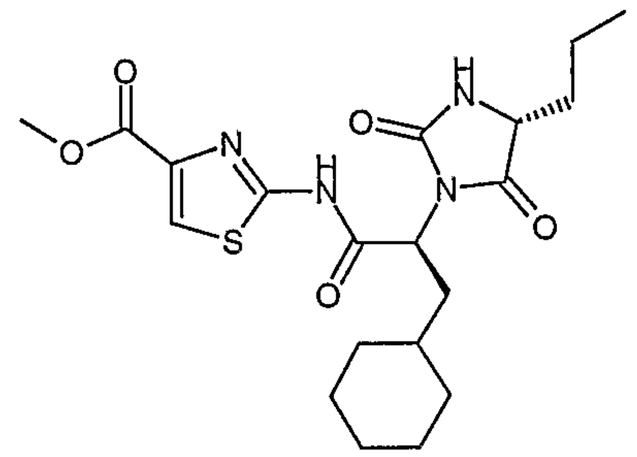
Preparation of (S,S)-2-[[3-cyclohexyl-2-[2,5-dioxo-4-(thiophen-2-yl)methylimidazolidin-1-yl]propanoyl]amino]thiazole-4-carboxylic acid methyl ester.



The compound was prepared as described in Example 3, except N-Fmoc-3-(thiophen-2-yl)-L-alanine was the amino acid incorporated in Step (iii) of the procedure: EI-HRMS m/e calcd for $C_{22}H_{26}N_4O_5S_2$ (M^+) 491.1423, found 491.1425.

Example 12

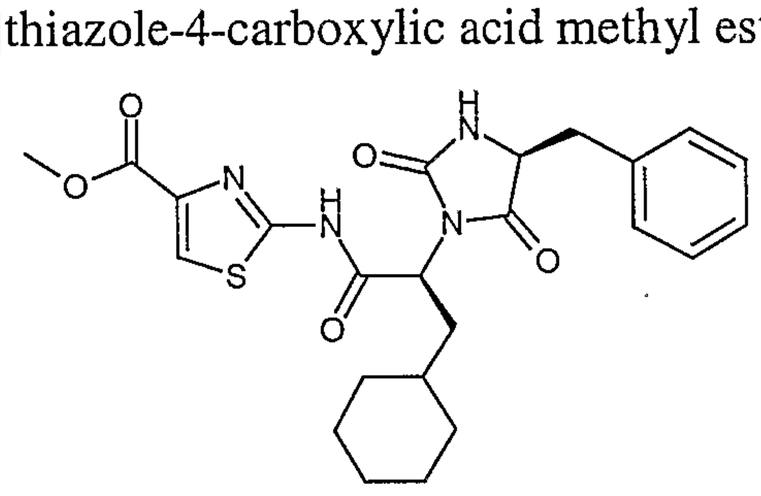
Preparation of 2-[[(S)-3-cyclohexyl-2-[(R)-2,5-dioxo-4-propylimidazolidin-1-yl]propanoyl]amino]thiazole-4-carboxylic acid methyl ester



The compound was prepared as described in Example 3, except (R)-N-Fmoc-2-aminopentanoic acid was the amino acid incorporated in Step (iii) of the procedure: EI-HRMS m/e calcd for $C_{20}H_{28}N_4O_5S$ (M^+) 437.1859, found 437.1850.

Example 13

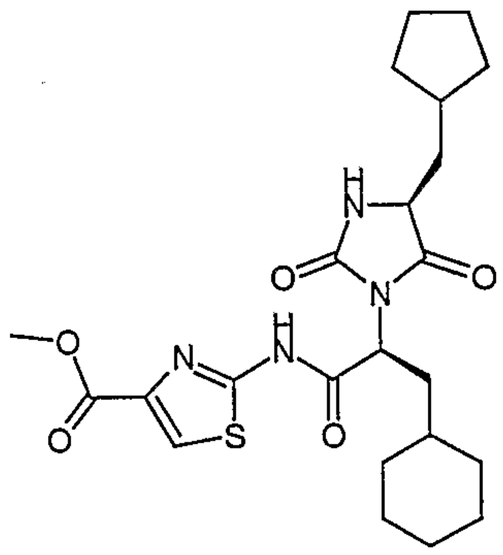
Preparation of (S,S)-2-[[2-(4-benzyl-2,5-dioxoimidazolidin-1-yl)-3-cyclohexylpropanoyl]amino]thiazole-4-carboxylic acid methyl ester.



The compound was prepared as described in Example 3, except N-Fmoc-L-phenylalanine was the amino acid incorporated in Step (iii) of the procedure: EI-HRMS m/e calcd for $C_{24}H_{28}N_4O_5S$ (M^+) 485.1859, found 485.1857.

Example 14

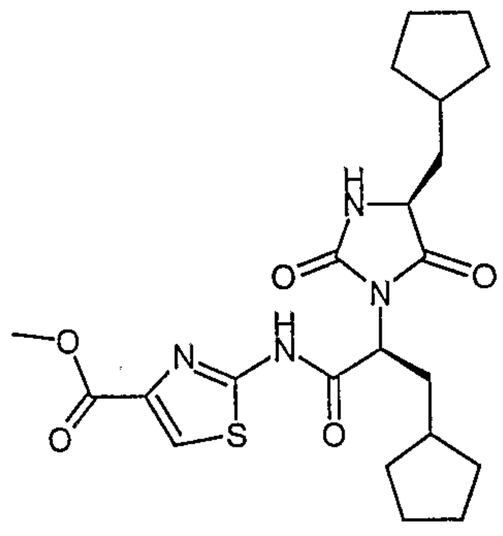
Preparation of (S,S)-2-[[3-cyclohexyl-2-[4-(cyclopentyl)methyl-2,5-dioxoimidazolidin-1-yl]propanoyl]amino]thiazole-4-carboxylic acid methyl ester.



The compound was prepared as described in Example 3, except N-Fmoc-3-cyclopentyl-L-alanine was the amino acid incorporated in Step (iii) of the procedure: EI-HRMS m/e calcd for $C_{23}H_{32}N_4O_5S$ (M^+) 477.2172, found 477.2170.

Example 15

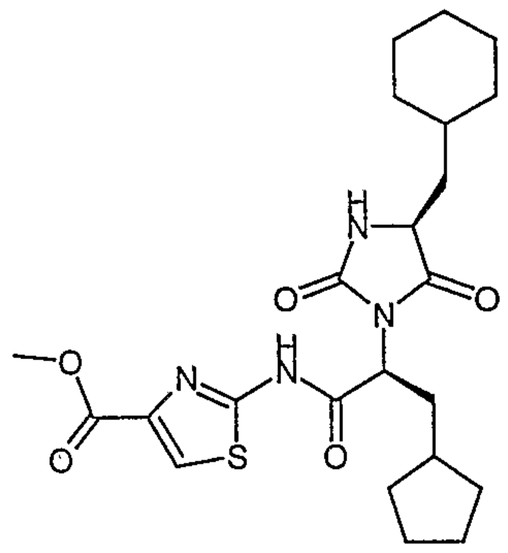
Preparation of (S,S)-2-[[3-cyclopentyl-2-[4-(cyclopentyl)methyl-2,5-dioxoimidazolidin-1-yl]propanoyl]amino]thiazole-4-carboxylic acid methyl ester.



The compound was prepared as described in Example 3, except N-Fmoc-3-cyclopentyl-L-alanine was the amino acid incorporated in both Step (ii) and Step (iii) of the procedure. The title compound was obtained as a white foam: EI-HRMS m/e calcd for $C_{22}H_{30}N_4O_5S$ (M^+) 463.2015, found 463.2023.

Example 16

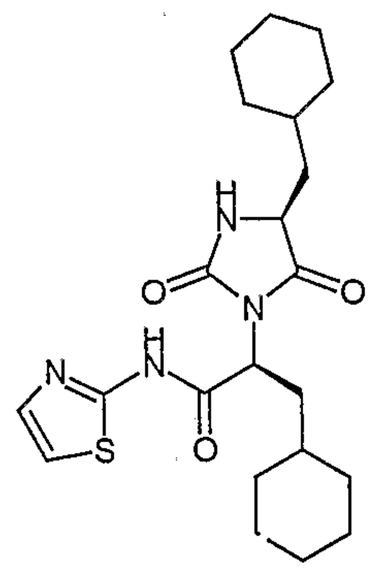
Preparation of (S,S)-2-[[2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl]-3-cyclopentylpropanoyl]amino]thiazole-4-carboxylic acid methyl ester.



The compound was prepared as described in Example 3, except N-Fmoc-3-cyclopentyl-L-alanine and N-Fmoc-3-cyclohexyl-L-alanine were the amino acids incorporated in Step (ii) and Step (iii) of the procedure respectively: EI-HRMS m/e calcd for $C_{23}H_{32}N_4O_5S$ (M^+) 477.2172, found 477.2164.

Example 17

Preparation of (S,S)-3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl]-N-(thiazol-2-yl)propanamide:



Step (i). A mixture of N-Fmoc-3-cyclohexyl-L-alanine (3.47g, 8.8 mmol), 2,6-dichlorobenzoyl chloride (3.2 mL, 22 mmol) in N-methylpyrrolidinone (20 mL) was added into a fritted polypropylene column charged with Wang resin (Midwest Bio-Tech, 4 g, 4.4 mmol). The suspension was shaken for 5 min, then pyridine (2.5 mL, 30.8 mmol) was then added slowly and the resulting dark mixture was shaken overnight at ambient temperature. The mixture was then filtered and the resin was washed with N,N-dimethylformamide (3 x 30 mL), methanol (3 x 30 mL), dichloromethane (3 x 30 mL) and dried *in vacuo*.

Step (ii). To the resin product of step (i) was added 20% piperidine in N,N-dimethylformamide (25 mL) and the reaction mixture was shaken at ambient temperature for 30 min. The mixture was filtered and the resin was washed with N,N-dimethylformamide (3 x 30 mL), methanol (3 x 30 mL), dichloromethane (3 x 30 mL). The resin was then suspended in N-methylpyrrolidinone (10 mL) and N-Fmoc-3-cyclohexyl–L-alanine (5.2 g, 13.2 mmol), diisopropylcarbodiimide (2.1 mL, 13.2 mmol) and HOBT (1.8 g, 13.2 mmol) were added. The resulting mixture was shaken at ambient temperature overnight and filtered. The resin was washed with N,N-dimethylformamide (3 x 30 mL), methanol (3 x 30 mL), dichloromethane (3 x 30 mL) and dried *in vacuo*.

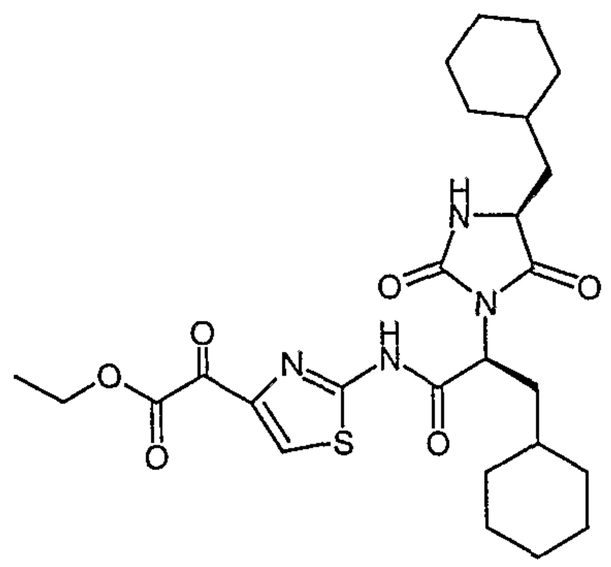
Step (iii). To the resin product of Step (ii) was added 20% piperidine in N,N-dimethylformamide (25 mL) and the reaction mixture was shaken at ambient temperature for 30 min. The mixture was filtered and the resin was washed with N,N-dimethylformamide (3 x 30 mL), methanol (3 x 30 mL), dichloromethane (3 x 30 mL). The resin was then suspended in dichloromethane (20 mL) and treated with diisopropylethylamine (2.3 mL, 13.2 mmol). The reaction mixture was then cooled to 0 °C and diphosgene (1.6 mL, 13.2 mmol) was added dropwise. The mixture was allowed to warm to room temperature with stirring for 5 h, then was filtered and the resin was washed with dichloromethane (3 x 30 mL) and dried *in vacuo*. The resin was then suspended in toluene (20 mL) and the stirred mixture was heated at 70 °C for 4 h. The cooled resin mixture was filtered and the resin was washed with dichloromethane (3 x 30 mL). Cleavage from the support was effected by treatment with 50% trifluoroacetic acid in dichloromethane (30 mL) for 1 hr. Concentration of the filtrate yielded a brown solid. It was then purified by reversed phase HPLC to afford (S,S)-3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl]propanoic acid (850 mg) as a white foam: EI-HRMS m/e calcd for $C_{19}H_{30}N_2O_4$ (M^+) 350.2205, found 350.2204.

Step (iv). A solution of (S,S)-3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl]propanoic acid [Step (iii); 25 mg, 0.071 mmol] in N-methylpyrrolidinone (1 mL) was treated with diisopropylethylamine (19 µL, 1.065 mmol) and HBTU (29.3 mg, 0.078 mmol). The reaction mixture was then treated with 2-aminothiazole (7.2 mg, 0.071 mmol) and stirred

at ambient temperature overnight. The reaction mixture was then diluted with water (2 mL) and extracted with ethyl acetate (2 x 3 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The product was purified by using flash chromatography (Merck Silica gel 60, 230-400 mesh, 99/1 dichloromethane/methanol) to furnish (*S*,*S*)-3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl]-N-(thiazol-2-yl)propanamide (27 mg, 88%) as a white foam: EI-HRMS m/e calcd. for $C_{22}H_{32}N_4O_3S$ (M^+) 433.2273, found 433.2270.

Example 18

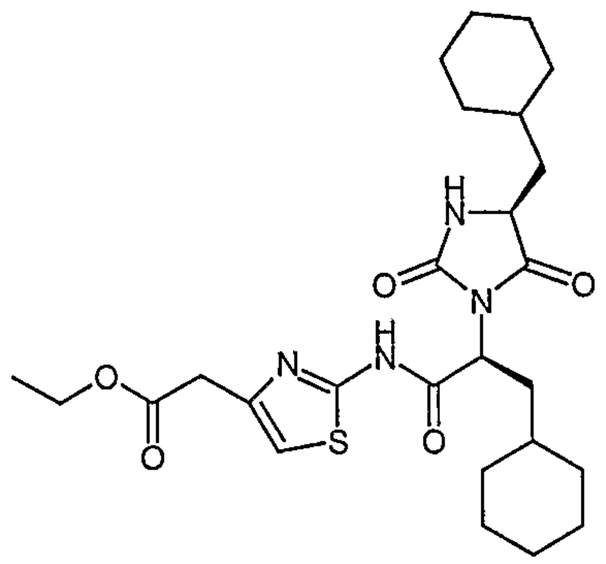
Preparation of (S,S)-[2-[[3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl]propanoyl]amino]thiazol-4-yl]oxoacetic acid ethyl ester.



By using the conditions described in Step (iv) of Example 17, ethyl 2-amino-4-thiazoleglyoxylate was condensed with (S,S)-3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidinyl]propanoic acid [Example 17, Step (iii)] to give the title compound as a colorless foam: EI-HRMS m/e calcd. for $C_{26}H_{36}N_4O_6S$ (M^+) 533.2434, found 533.2431.

Example 19

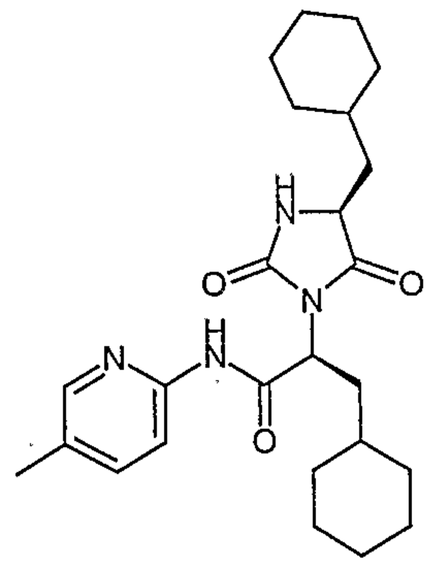
Preparation of (S,S)-[2-[[3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl]propanoyl]amino]thiazol-4-yl]acetic acid ethyl ester.



By using the conditions described in Step (iv) of Example 17, ethyl 2-amino-4-thiazoleacetate was condensed with (S,S)-3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidinyl]propanoic acid [Example 17, Step (iii)] to give the title compound as a colorless foam: EI-HRMS m/e calcd. for $C_{26}H_{38}N_4O_5S$ (M^+) 519.2641, found 519.2620.

Example 20

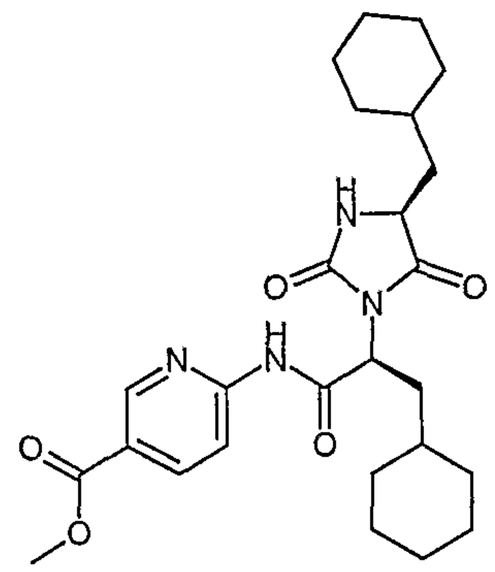
Preparation of (S,S)- 3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl]-N-(5-methylpyridin-2-yl)propanamide.



By using the conditions described in Step (iv) of Example 17, 2-amino-5-methylpyridine was condensed with (S,S)-3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidinyl]propanoic acid [Example 17, Step (iii)] to give the title compound as a colorless foam: EI-HRMS m/e calcd. for $C_{25}H_{36}N_4O_3$ (M^+) 441.2866, found 441.2869.

Example 21

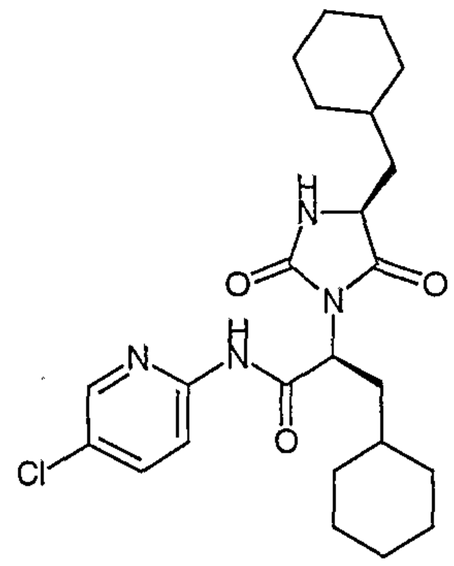
Preparation of (S,S)-6-[[3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl]propanoyl]amino]nicotinic acid methyl ester.



By using the conditions described in Step (iv) of Example 17, methyl 6-aminonicotinate was condensed with (S,S)-3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidinyl]propanoic acid [Example 17, Step (iii)] to give the title compound as a colorless foam: EI-HRMS m/e calcd for $C_{26}H_{36}N_4O_5$ (M^+) 485.2764, found 485.2768.

Example 22

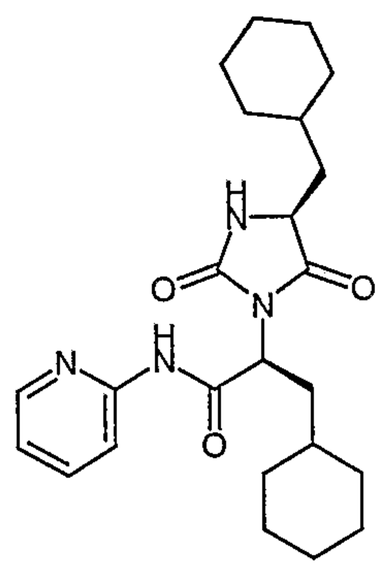
Preparation of (S,S)-N-(5-chloropyridin-2-yl)-3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl]propanamide.



By using the conditions described in Step (iv) of Example 17, 2-amino-5-chloropyridine was condensed with (S,S)-3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidinyl]propanoic acid [Example 17, Step (iii)] to give the title compound as a colorless foam: EI-HRMS m/e calcd for $C_{24}H_{33}N_4O_3Cl$ (M^+) 461.2319, found 461.2321.

Example 23

Preparation of (S,S)-3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl]-N-(pyridin-2-yl)propanamide.



By using the conditions described in Step (iv) of Example 17, 2-aminopyridine was condensed with (S,S)-3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidinyl]propanoic acid [Example 17, Step (iii)] to give the title compound as a colorless foam: EI-HRMS m/e calcd for $C_{24}H_{34}N_4O_3$ (M^+) 427.2709, found 427.2706.

Example A

Tablets containing the following ingredients can be produced in a conventional manner:

Ingredients	mg per tablet
Compound of formula (I)	10.0 - 100.0
Lactose	125.0
Corn starch	75.0
Talc	4.0
Magnesium stearate	1.0

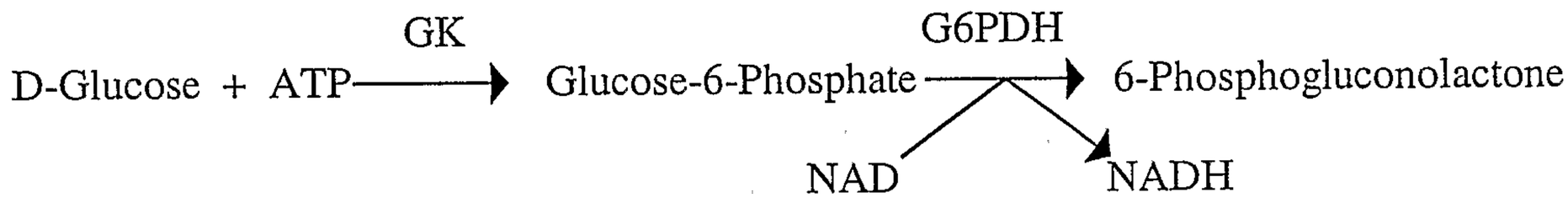
Example B

Capsules containing the following ingredients can be produced in a conventional manner:

Ingredients	mg per capsule
Compound of formula (I)	25.0
Lactose	150.0
Corn starch	20.0
Talc	5.0

Biological Activity Example: **Glucokinase Activity**

Glucokinase Assay: Glucokinase (GK) was assayed by coupling the production of glucose-6-phosphate to the generation of NADH with glucose-6-phosphate dehydrogenase (G6PDH, 0.75-1 k units/mg; Boehringer Mannheim, Indianapolis, IN) from *Leuconostoc mesenteroides* as the coupling enzyme (Scheme 2).



Scheme 2

Recombinant human liver GK1 was expressed in *E. coli* as a glutathione S-transferase fusion protein (GST-GK) [Liang, Y., Kesavan, P., Wang, L., Niswender, K., Tanizawa, Y., Permut, M. A., Magnuson, M., and Matschinsky, F. M. Variable effects of maturity-onset-diabetes-of-youth (MODY)-associated glucokinase mutations on the substrate interactions and stability of the enzyme. *Biochem. J.* 309: 167-173, 1995] and was purified by chromatography over a glutathione-Sepharose 4B affinity column using the procedure provided by the manufacturer (Amersham Pharmacia Biotech, Piscataway, NJ). Previous studies have demonstrated that the enzymatic properties of native GK and GST-GK are essentially identical (Liang et al, 1995; Neet, K., Keenan, R. P., and Tippett, P.S. Observation of a kinetic slow transition in monomeric glucokinase. *Biochemistry* 29;770-777, 1990).

The assay was conducted at 25° C in a flat bottom 96-well tissue culture plate from Costar (Cambridge, MA) with a final incubation volume of 120 µl. The incubation mixture contained: 25 mM Hepes buffer (pH, 7.1), 25 mM KCl, 5 mM D-glucose, 1mM ATP, 1.8 mM NAD, 2 mM $MgCl_2$, 1 µM sorbitol-6-phosphate, 1 mM dithiothreitol, test drug or 10% DMSO, 1.8 unit/mL G6PDH, and GK (see below). All organic reagents were >98 % pure and were from Boehringer Mannheim with the exceptions of D-glucose and Hepes that were from Sigma Chemical Co, St Louis, MO. Test compounds were dissolved in DMSO and were added to the incubation mixture minus GST-GK in a volume of 12 µl to yield a final DMSO concentration of 10%. This mix was preincubated in the temperature controlled chamber of a SPECTRAmax 250 microplate spectrophotometer (Molecular Devices Corporation,

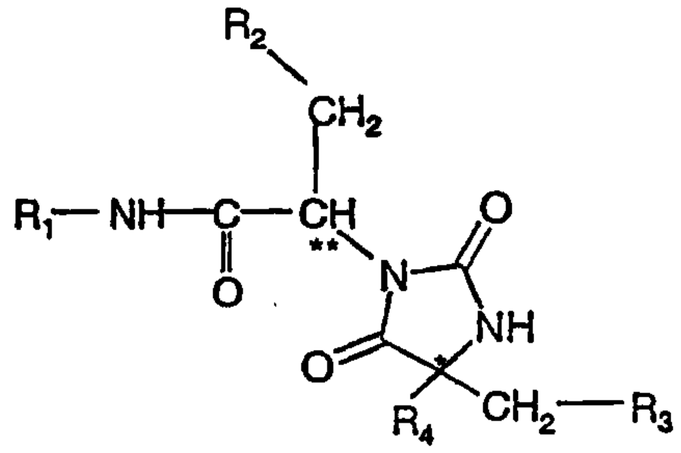
Sunnyvale, CA) for 10 minutes to allow temperature equilibrium and then the reaction was started by the addition of 20 µl GST-GK.

After addition of enzyme, the increase in optical density (OD) at 340 nm was monitored over a 10 minute incubation period as a measure of GK activity. Sufficient GST-GK was added to produce an increase in OD_{340} of 0.08 to 0.1 units over the 10 minute incubation period in wells containing 10% DMSO, but no test compound. Preliminary experiments established that the GK reaction was linear over this period of time even in the presence of activators that produced a 5-fold increase in GK activity. The GK activity in control wells was compared with the activity in wells containing test GK activators, and the concentration of activator that produced a 50% increase in the activity of GK, i.e., the $SC_{1.5}$, was calculated.

All of the compounds of Formula I described in the Synthesis Examples had an $SC_{1.5}$ less than or equal to 30 µM.

Claims:

1. A compound of the formula:



I

wherein

R_1 is a five- or six- membered aromatic heterocyclic ring having one to three heteroatoms selected from nitrogen, oxygen, and sulfur, which ring is unsubstituted or substituted with halo, amino, hydroxylamino, nitro, cyano, sulfonamido, lower alkyl, perfluoro lower alkyl, lower alkyl thio, perfluoro-lower alkyl thio, lower alkyl sulfonyl, perfluoro-lower alkyl sulfonyl, lower alkyl sulfinyl, or $-(R_5)_n-C(O)-OR_6$;

R_2 is a cycloalkyl ring containing from 5 to 7 carbon atoms;

R_3 is hydrogen, lower alkyl, a cycloalkyl ring containing from 5 to 7 carbon atoms, unsubstituted aryl, aryl substituted with halo or hydroxy, or an unsubstituted five- or six-membered aromatic heterocyclic ring having one or two heteroatoms selected from nitrogen, oxygen, and sulfur;

R_4 is hydrogen, lower alkyl, or R_3 and R_4 together with the carbon atom to which they are attached form a cycloalkyl ring containing 5 to 7 carbon atoms;

R_5 is $-C(O)-$ or lower alkyl;

R_6 is lower alkyl;

n is 0 or 1;

wherein * and ** each designate an asymmetric center; and

wherein "lower alkyl" is a straight chain or branched chain alkyl group having from 1 to 6 or 1 to 7 carbon atoms;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1 wherein R_1 is unsubstituted thiazolyl or pyridyl; or thiazolyl or pyridyl substituted with halo, amino, hydroxylamino, nitro, cyano, sulfonamido, lower alkyl, perfluoro lower alkyl, lower alkyl thio, perfluoro-lower alkyl thio, lower alkyl

sulfonyl, perfluoro-lower alkyl sulfonyl, lower alkyl sulfinyl, or $-(R_5)_n-C(O)-OR_6$; and n, R_5 and R_6 are as defined in claim 1.

3. The compound of claim 1 or 2 wherein R_1 is thiazolyl substituted with halo, amino, hydroxylamino, nitro, cyano, sulfonamido, lower alkyl, perfluoro lower alkyl, lower alkyl thio, perfluoro-lower alkyl thio, lower alkyl sulfonyl, perfluoro-lower alkyl sulfonyl, lower alkyl sulfinyl, or $-(R_5)_n-C(O)-OR_6$; and n, R_5 and R_6 are as defined in claim 1.

4. The compound of claim 1 or 2 wherein R_1 is thiazolyl substituted with $-(R_5)_n-C(O)-OR_6$; and n, R_5 and R_6 are as defined in claim 1.

5. The compound of claim 1 or 2 wherein R_1 is pyridyl substituted with halo, amino, hydroxylamino, nitro, cyano, sulfonamido, lower alkyl, perfluoro lower alkyl, lower alkyl thio, perfluoro-lower alkyl thio, lower alkyl sulfonyl, perfluoro-lower alkyl sulfonyl, lower alkyl sulfinyl, or $-(R_5)_n-C(O)-OR_6$; and n, R_5 and R_6 are as defined in claim 1.

6. The compound of claim 1 or 2 wherein R_1 is pyridyl substituted with halo, lower alkyl, or $-(R_5)_n-C(O)-OR_6$; and n, R_5 and R_6 are as defined in claim 1.

7. The compound of any one of claims 1 to 6 wherein R_2 is cyclopentyl or cyclohexyl.

8. The compound of any one of claims 1 to 6 wherein R_2 is cyclopentyl.

9. The compound of any one of claims 1 to 6 wherein R_2 is cyclohexyl.

10. The compound of any one of claims 1 to 9 wherein R_3 is hydrogen, lower alkyl, cyclopentyl, cyclohexyl, phenyl, naphthyl, thiophenyl, phenyl substituted with halo or phenyl substituted with hydroxy.

11. The compound of any one of claims 1 to 9 wherein R_3 is hydrogen or lower alkyl.

12. The compound of any one of claims 1 to 9 wherein R_3 is cyclopentyl or cyclohexyl.

13. The compound of any one of claims 1 to 9 wherein R_3 is thiophenyl.

14. The compound of any one of claims 1 to 9 wherein R_3 is naphthyl.

15. The compound of any one of claims 1 to 9 wherein R_3 is phenyl, optionally substituted with halo or hydroxy.

16. The compound of any one of claims 1 to 15 wherein R_4 is hydrogen or lower alkyl.

17. The compound of any one of claims 1 to 15 wherein R_3 and R_4 together with the carbon atom to which they are attached form a cyclopentyl ring.

18. The compound of any one of claims 1 to 17 wherein R_5 is –C(O)-.

19. The compound of any one of claims 1 to 17 wherein R_5 is lower alkyl.

20. The compound of any one of claims 1 to 19 wherein n is 0.

21. The compound of any one of claims 1 to 19 wherein n is 1.

22. The compound of claim 1 wherein R_1 is unsubstituted thiazolyl or pyridyl; or thiazolyl or pyridyl substituted with halo, lower alkyl or $-(R_5)_n-C(O)-OR_6$; R_2 is cyclopentyl or cyclohexyl; R_3 is hydrogen, lower alkyl, cyclopentyl, cyclohexyl, phenyl, naphthyl, thiophenyl, phenyl substituted with halo or phenyl substituted with hydroxy; R_4 is hydrogen, lower alkyl, or R_3 and R_4 together with the carbon atom to which they are attached form a cyclopentyl ring; R_5 is -C(O)- or lower alkyl; R_6 is lower alkyl; and n is 0 or 1.

23. A compound of any one of claims 1 to 22 selected from the group consisting of:

(S,S)-2-[[2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl)-3-cyclopentylpropanoyl]amino]thiazole-4-carboxylic acid methyl ester,

(S,S)-2-[[3-cyclopentyl-2-[4-(cyclopentyl)methyl-2,5-dioxoimidazolidin-1-yl]propanoyl]amino]thiazole-4-carboxylic acid methyl ester,

(S,S)-2-[[3-cyclohexyl-2-[4-(cyclopentyl)methyl-2,5-dioxoimidazolidin-1-yl]propanoyl]amino]thiazole-4-carboxylic acid methyl ester,

(S,S)-2-[[3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl]propanoyl]amino]thiazole-4-carboxylic acid methyl ester,

(S,S)-[2-[[3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl]propanoyl]amino]thiazol-4-yl]oxoacetic acid ethyl ester,

(S,S)-[2-[[3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl]propanoyl]amino]thiazol-4-yl]acetic acid ethyl ester,

(S,S)-2-[[2-(4-benzyl-2,5-dioxoimidazolidin-1-yl)-3-cyclohexylpropanoyl]amino]thiazole-4-carboxylic acid methyl ester,

2-[[(S)-2-[(R)-4-(4-chlorobenzyl)-2,5-dioxoimidazolidin-1-yl]-3-cyclohexylpropanoyl]amino]thiazole-4-carboxylic acid methyl ester,

(S,S)-2-[[3-cyclohexyl-2-[2,5-dioxo-4-(4-hydroxybenzyl)imidazolidin-1-yl]propanoyl]amino]thiazole-4-carboxylic acid methyl ester,

(S,S)-2-[[3-cyclohexyl-2-[2,5-dioxo-4-(3-hydroxybenzyl)imidazolidin-1-yl]propanoyl]amino]thiazole-4-carboxylic acid methyl ester,

2-[[(S)-3-cyclohexyl-2-[(R,S)-2,5-dioxo-4-(4-fluorobenzyl)imidazolidin-1-yl]propanoyl]amino]thiazole-4-carboxylic acid methyl ester,

(S)-2-[[3-cyclohexyl-2-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)propanoyl]amino]thiazole-4-carboxylic acid methyl ester,

2-[[(S)-3-cyclohexyl-2-[(R)-2,5-dioxo-4-propylimidazolidin-1-yl]propanoyl]amino]thiazole-4-carboxylic acid methyl ester,

(S,S)-2-[[3-cyclohexyl-2-[2,5-dioxo-4-(naphthalen-2-yl)methylimidazolidin-1-yl]propanoyl]amino]thiazole-4-carboxylic acid methyl ester,

(S)-2-[[3-cyclohexyl-2-(2,4-dioxo-1,3-diazaspiro[4.4]non-3-yl)propanoyl]amino]thiazole-4-carboxylic acid methyl ester,

(S,S)-2-[[3-cyclohexyl-2-[2,5-dioxo-4-(thiophen-2-yl)methylimidazolidin-1-yl]propanoyl]amino]thiazole-4-carboxylic acid methyl ester,

(S,S)-3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl]-N-(thiazole-2-yl)propanamide,

(S,S)-6-[[3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl]propanoyl]amino]nicotinic acid methyl ester,

(S,S)-3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl]-N-(5-methylpyridin-2-yl)propanamide,

(S,S)-N-(5-chloropyridin-2-yl)-3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl]propanamide, and

(S,S)-3-cyclohexyl-2-[4-(cyclohexyl)methyl-2,5-dioxoimidazolidin-1-yl]-N-(pyridin-2-yl)propanamide.

24. A pharmaceutical composition comprising the compound of any one of claims 1 to 23 and a pharmaceutically acceptable carrier and/or adjuvant.

25. A process for the preparation of the pharmaceutical composition of claim 24 comprising combining the compound of formula I defined in any one of claims 1 to 23 with a pharmaceutically acceptable carrier and/or adjuvant.

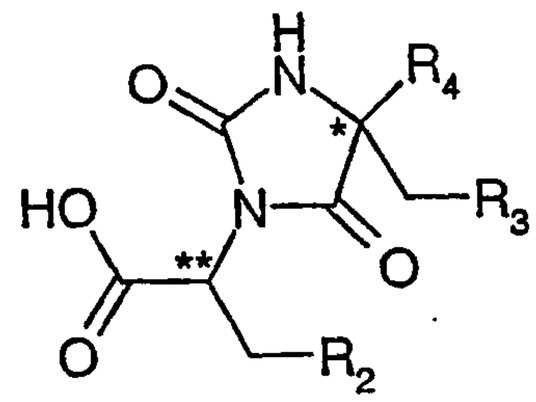
26. The compound according to any one of claims 1 to 23 for use in the treatement or prophylaxis of type II diabetes.

27. A use of the compound defined in any one of claims 1 to 23 for the treatment or prophylaxis of type II diabetes.

28. A use of the compound defined in any one of claims 1 to 23 for the preparation of a medicament for the treatment or prophylaxis of type II diabetes.

29. A process for the preparation of the compound of formula I defined in claim 1, which process comprises:

(a) coupling a compound of formula



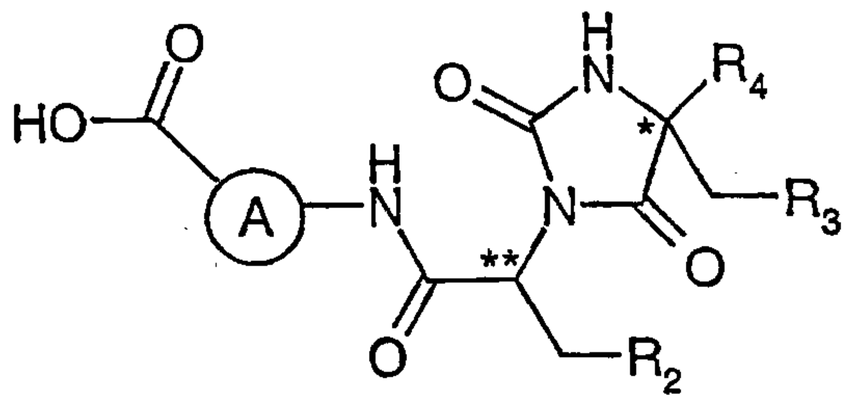
wherein R_2, R_3 and R_4 are as defined in claim 1;

with a compound of the formula

R_1-NH_2

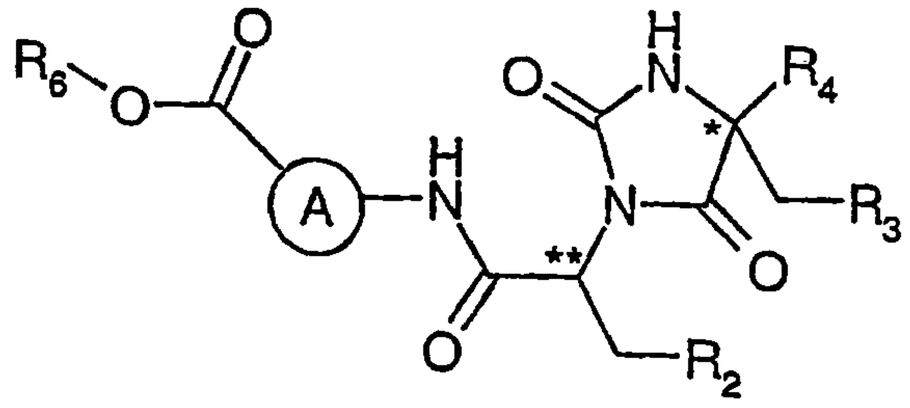
wherein R_1 is as defined in claim 1; or

(b) esterification of a compound of formula

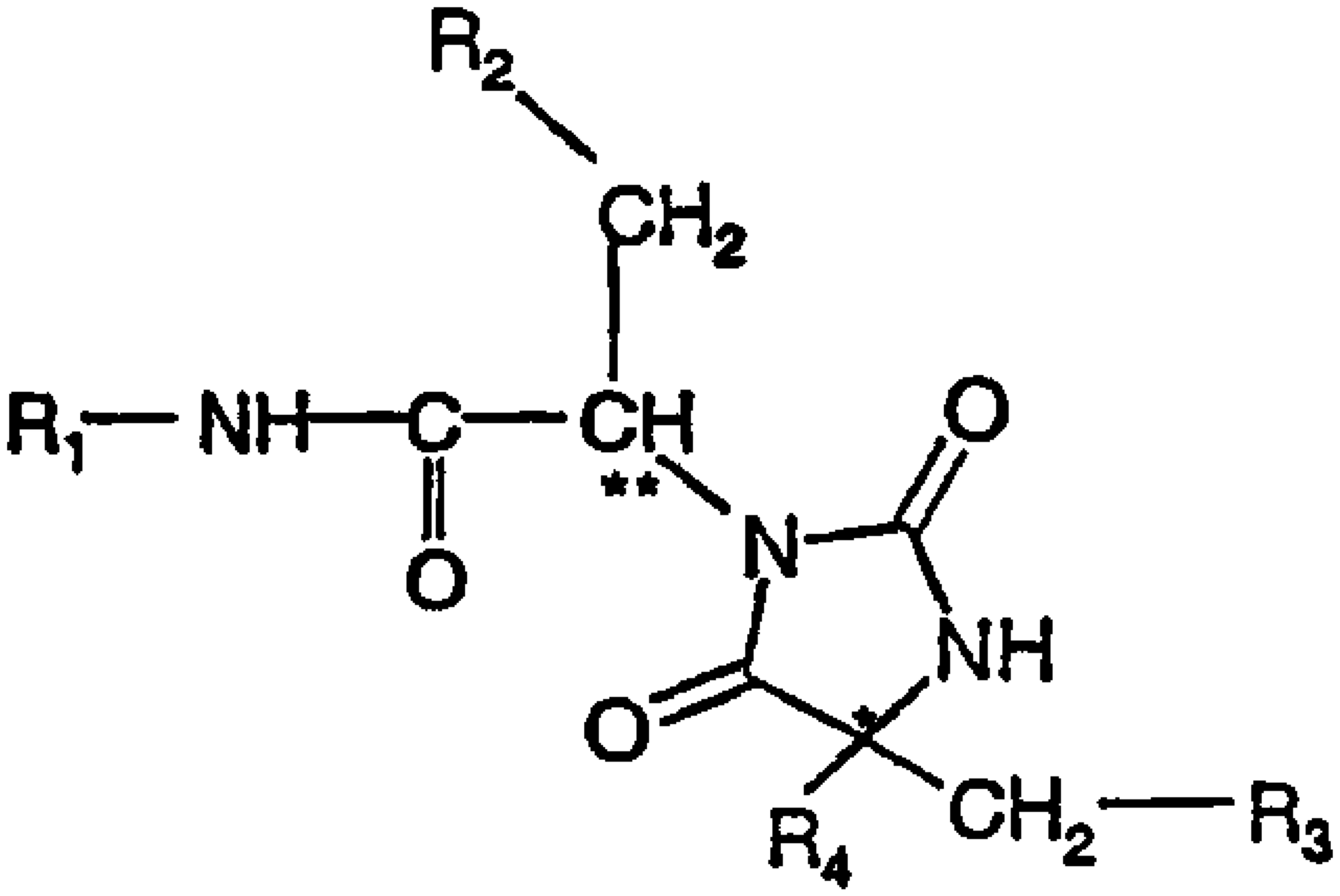


wherein A represents a five or six membered heteroaromatic ring having one, two or three hetero atoms selected from nitrogen, oxygen and sulfur, and R_2, R_3, and R_4 are as defined in claim 1;

to a compound of the formula I-A



wherein A represents a five or six membered heteroaromatic ring having one, two or three hetero atoms selected from nitrogen, oxygen and sulfur, and R_2, R_3, R_4 and R_6 are as defined in claim 1.



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