

TITLEAN EFFICIENT METHOD FOR THE CONVERSION OF NITRILES TO
AMIDINES

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FIELD OF THE INVENTION

The present invention relates generally to processes for the conversion of cyano groups into amidines for the purpose of producing compounds which are useful as antagonists of the platelet glycoprotein IIb/IIIa fibrinogen receptor complex. These compounds may be used for the inhibition of platelet aggregation, as thrombolytics, and/or for the treatment of thromboembolic disorders.

BACKGROUND

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There are several methods to convert cyano groups into amidine groups (S. Patai, Z. Rappoport, *The Chemistry of Amidines and Imidates*, 1991, John Wiley & Sons Ltd.). One of the most widely used methods for the preparation of amidines is the Pinner synthesis (R. Roger, D. G. Neilson, *Chem. Rev.* **1961**, 61, 179-211), which proceeds in two steps through an imidate intermediate.

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Abood et al, in U.S. Patent No. 5,484,946, discusses formation of the amidine moiety from a nitrile group through an amidoxime intermediate. Jendrall et al, in *Tetrahedron* **1995**, 51, 12047-12068, used a similar process to convert a cyano group into the amidinium functionality. Eloy and Leners, in *Chem. Rev.*, **1962**, 62, 155-183, review the preparation of amidoximes from nitriles. Chio and Shine, in *J. Heterocyclic Chem.*, **1989**, 26, 125-128, reported that these amidoximes can be transformed into 1,2,4-oxadiazole derivatives. Judkins et al, in *Synthetic Commun.* **1996**, 26, 4351, describe formation of amidine moiety from nitrile through an amidoxime intermediate under acetylation or acylation conditions.

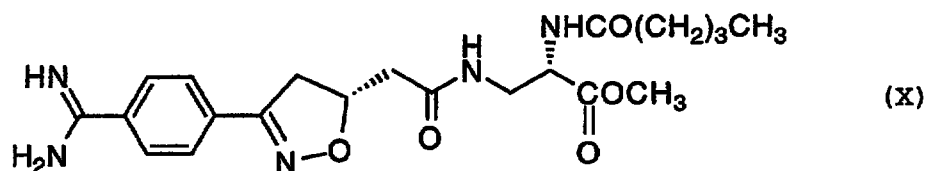
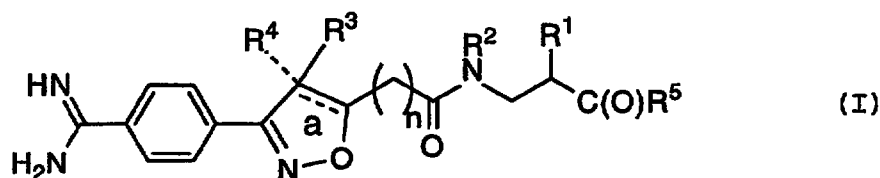
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This literature however, does not disclose any regioselectivity between an amidoxime and an isoxazoline. In fact, Mueller et al, *Angew. Chem.*, **1994**, 106, 1305-1308,

report that hydrogenation with 10%Pd/C will reduce a
isoxazoline ring system. There is also no precedent for the
transformation of a cyano group into an amidine
functionality through a 1,2,4-oxadiazole moiety, and
5 therefore the conversion of a 1,2,4-oxadiazole into amidine
directly through catalytic hydrogenation is not taught.

Compounds of generic form (I) are antagonists of the
platelet glycoprotein IIb/IIIa fibrinogen receptor complex
which are currently being evaluated for the inhibition of
10 platelet aggregation, as thrombolytics, and for the
treatment of thromboembolic disorders. Consequently, large
quantities of these compounds are needed to support drug
development studies.



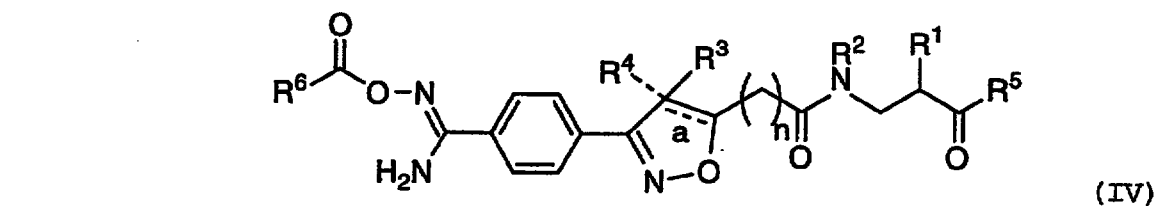
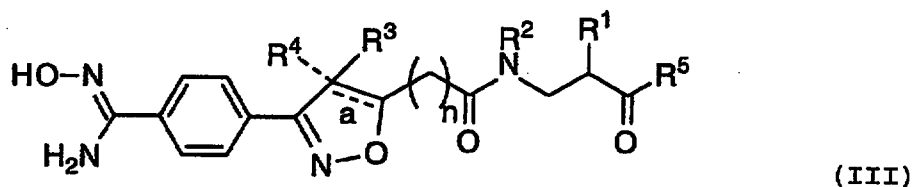
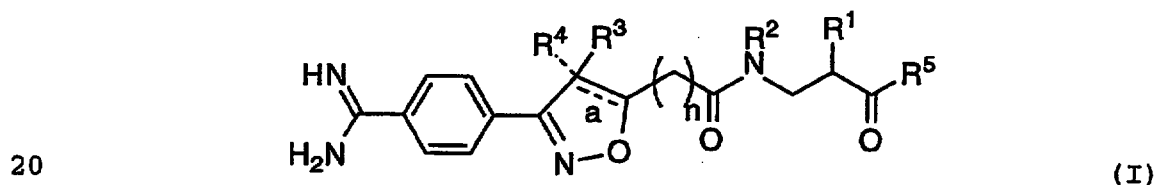
The preparation of compounds of generic form (I) have
been disclosed in U.S. Patent 5,446,056, PCT international
publication WO 95/14683, PCT international publication WO
20 96/38426, pending and commonly owned U.S. Application No.
08/700,906, and in *J. Med. Chem.*, Xue et al, 1997, 40,
2064-2084. The preparation of (X) has been disclosed by
Zhang et al in *Tetrahedron Lett.* 1996, 37, 4455-4458 and *J.*
Org. Chem. 1997, 62, 2466-2470, which describe amidine
25 formation from a nitrile using the Pinner reaction.
Although this process has been able to produce compounds of
formula (X) on a multikilogram scale, employing the Pinner
reaction on a commercial scale poses several disadvantages.
The Pinner approach involves the use of an excess of

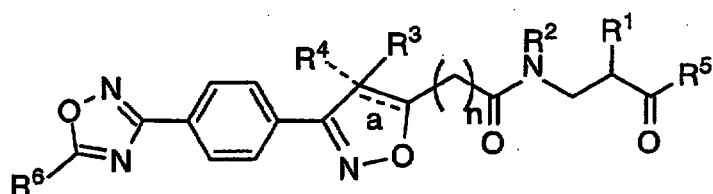
hydrogen chloride gas which is environmentally unfriendly, and removal of the inorganic salts generated during the Pinner process requires extensive purification protocols. It was therefore necessary to develop an efficient, safer process to produce compounds of formula (I) on large scale.

SUMMARY OF THE INVENTION

The present invention relates generally to processes for the conversion of cyano groups into amidines for the purpose of producing compounds, and intermediates therefore, which are useful as antagonists of the platelet glycoprotein IIb/IIIa fibrinogen receptor complex. These compounds may be used for the inhibition of platelet aggregation, as thrombolytics, and/or for the treatment of thromboembolic disorders.

There is provided by this invention a process for the preparation of compounds of formula (I), (III), (IV), (V) and (VI):





(V)

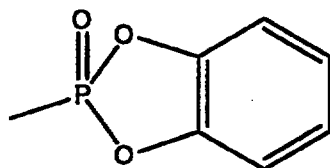
wherein:

R^1 is selected from H or NHR^{1a} ;

5 R^{1a} is selected from the group consisting of:

- C(=O)-O- R^{1b} ,
- C(=O)- R^{1b} ,
- C(=O)N(R^{1b})₂,
- C(=O)NHSO₂ R^{1b} ,
- 10 -C(=O)NHC(=O) R^{1b} ,
- C(=O)NHC(=O)O R^{1b} ,
- C(=O)NHSO₂NH R^{1b} ,
- C(=S)-NH- R^{1b} ,
- NH-C(=O)-O- R^{1b} ,
- 15 -NH-C(=O) R^{1b} ,
- NH-C(=)-NH- R^{1b} ,
- SO₂-O- R^{1b} ,
- SO₂- R^{1b} ,
- SO₂-N(R^{1b})₂,
- 20 -SO₂-NHC(=O)O R^{1b} ,
- P(=S)(O R^{1b})₂,
- P(=O)(O R^{1b})₂,
- P(=S)(R^{1b})₂,
- P(=O)(R^{1b})₂, and

25



R^{1b} is selected from the group consisting of:

- 30 C₁-C₈ alkyl substituted with 0-2 R^{1c} ,
- C₂-C₈ alkenyl substituted with 0-2 R^{1c} ,
- C₂-C₈ alkynyl substituted with 0-2 R^{1c} ,

C₃-C₈ cycloalkyl substituted with 0-2 R^{1c},
aryl substituted with 0-4 R^{1c},
aryl(C₁-C₆ alkyl)-substituted with 0-4 R^{1c},
a 5-10 membered heterocyclic ring system having 1-3
5 heteroatoms selected independently from O, S, and
N, said heterocyclic ring being substituted with
0-4 R^{1c}, and
C₁-C₆ alkyl substituted with a 5-10 membered
heterocyclic ring system having 1-3 heteroatoms
10 selected independently from O, S, and N, said
heterocyclic ring being substituted with 0-4 R^{1c};
R^{1c} is H, halogen, CF₃, CN, NO₂, C₁-C₈ alkyl, C₂-C₆ alkenyl,
C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl,
aryl(C₁-C₆ alkyl)-, C₁-C₆ alkoxy, and C₂-C₅
15 alkoxy carbonyl;
R² is selected from H or C₁-C₁₀ alkyl;
R³ and R⁴ are independently selected from the group
consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆
alkynyl, C₃-C₇ cycloalkyl, and aryl substituted with
20 0-2 R^{3a};
R^{3a} is selected from the group consisting of C₁-C₄ alkyl,
C₁-C₄ alkoxy, halo, CF₃, NO₂, and NR^{3b}R^{3c};
R^{3b} and R^{3c} are each independently selected from the group
consisting of H, C₁-C₁₀ alkyl, C₂-C₁₀ alkoxy carbonyl,
25 C₂-C₁₀ alkyl carbonyl, C₁-C₁₀ alkyl sulfonyl,
heteroaryl(C₁-C₄ alkyl) sulfonyl,
aryl(C₁-C₁₀ alkyl) sulfonyl, aryl sulfonyl, aryl,
heteroaryl carbonyl, heteroaryl sulfonyl, and
heteroaryl alkyl carbonyl, wherein said aryl and
30 heteroaryl are optionally substituted with 0-3 R^{3d};
R^{3d} is selected from the group consisting of C₁-C₄ alkyl,
C₁-C₄ alkoxy, halo, CF₃, and NO₂;
R⁵ is selected from the group consisting of:
hydroxy, C₁-C₁₀ alkyloxy, C₃-C₁₁ cycloalkyloxy,
35 C₆-C₁₀ aryloxy, C₇-C₁₁ arylalkyloxy,
C₃-C₁₀ alkyl carbonyloxyalkyloxy,
C₃-C₁₀ alkoxy carbonyloxyalkyloxy,

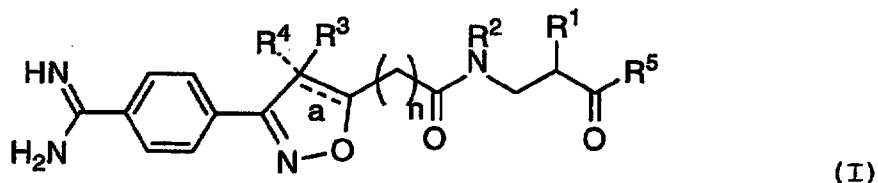
- C₃-C₁₀ alkoxy carbonylalkyloxy,
C₅-C₁₀ cycloalkylcarbonyloxyalkyloxy,
C₅-C₁₀ cycloalkoxy carbonyloxyalkyloxy,
C₅-C₁₀ cycloalkoxy carbonylalkyloxy,
5 C₈-C₁₁ aryloxy carbonylalkyloxy,
C₈-C₁₂ aryloxy carbonyloxyalkyloxy,
C₈-C₁₂ arylcarbonyloxyalkyloxy,
C₅-C₁₀ alkoxyalkylcarbonyloxyalkyloxy,
5-(C₅-C₁₀ alkyl)-1,3-dioxo-cyclopenten-2-one-yl)-
10 methyloxy,
(5-aryl-1,3-dioxo-cyclopenten-2-one-yl)-methyloxy, and
(R^{5a})HN-(C₁-C₁₀ alkoxy)-;
- R^{5a} is selected from the group consisting of H, C₁-C₄ alkyl,
aryl(C₁-C₁₀ alkoxy)carbonyl, C₂-C₁₀ alkoxy carbonyl, and
15 C₃-C₆ alkenyl;
- R⁶ is selected from the group consisting of H, CF₃, CF₂CF₃,
CF₂CF₂CF₃, CF₂CF₂CF₂CF₃, C₁-C₈ alkyl, C₁-C₈
perfluoroalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₁₁
cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl(C₁-C₆ alkyl)-,
20 C₁-C₆ alkoxy, C₇-C₁₀ arylalkyloxy, aryloxy and aryl
substituted with 0-5 R^{6c};
- R^{6c} is selected from the group consisting of H, halo, CF₃,
CN, NO₂, NR^{6d}R^{6e}, C₁-C₈ alkyl, C₂-C₆ alkenyl, C₃-C₁₁
cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl, aryl(C₁-C₆
25 alkyl)-, C₁-C₆ alkoxy, and C₂-C₅ alkoxy carbonyl;
- R^{6d} and R^{6e} are independently selected from the group
consisting of H, C₁-C₁₀ alkyl, C₂-C₁₀ alkoxy carbonyl,
C₂-C₁₀ alkylcarbonyl, C₁-C₁₀ alkylsulfonyl, aryl,
aryl(C₁-C₁₀ alkyl)sulfonyl, arylsulfonyl,
30 heteroaryl(C₁-C₄ alkyl)sulfonyl, heteroarylcarbonyl,
heteroarylsulfonyl, or heteroarylalkylcarbonyl, wherein
said aryl and heteroaryl are optionally substituted
with 0-3 substituents selected from the group
consisting of C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, CF₃, and
35 NO₂;
- n is 0-4; and

a is a single or double bond, with the proviso that if a is a double bond, it is not simultaneously substituted with R³ and R⁴;

- 5 said process comprising one or more of the steps of:
- step (1): contacting a compound of formula (II) with a salt of hydroxyl amine in the presence of a suitable base to form a compound of formula (III);
- step (2): contacting a compound of formula (III) with an acylating agent of formula R⁶CO-O-COR⁶ or R⁶COX, wherein X is fluorine, bromine, chlorine or imidazole, in a suitable solvent to form a compound of formula (IV) or a salt thereof; and
- step (3): contacting a compound of formula (IV) with hydrogen under a suitable pressure in the presence of a hydrogenation catalyst to form a compound of formula (I) or a pharmaceutically acceptable salt form thereof.

DETAILED DESCRIPTION OF THE INVENTION

- 20 In a first embodiment, the present invention provides a process for the preparation of compounds of formula (I):



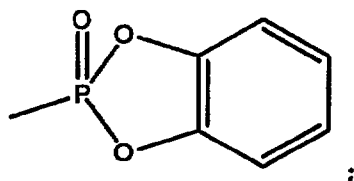
- 25 or a pharmaceutically acceptable salt form thereof; wherein:

R¹ is selected from H or NHR^{1a};

R^{1a} is selected from the group consisting of:

- 30 -C(=O)-O-R^{1b},
 -C(=O)-R^{1b},
 -C(=O)N(R^{1b})₂,
 -C(=O)NHSO₂R^{1b},
 -C(=O)NHC(=O)R^{1b},
 -C(=O)NHC(=O)OR^{1b},

- C(=O)NHSO₂NHR^{1b},
 -C(=S)-NH-R^{1b},
 -NH-C(=O)-O-R^{1b},
 -NH-C(=O)R^{1b},
 5 -NH-C(=)-NH-R^{1b},
 -SO₂-O-R^{1b},
 -SO₂-R^{1b},
 -SO₂-N(R^{1b})₂,
 -SO₂-NHC(=O)OR^{1b},
 10 -P(=S)(OR^{1b})₂,
 -P(=O)(OR^{1b})₂,
 -P(=S)(R^{1b})₂,
 -P(=O)(R^{1b})₂, and



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R^{1b} is selected from the group consisting of:

- C₁-C₈ alkyl substituted with 0-2 R^{1c},
 C₂-C₈ alkenyl substituted with 0-2 R^{1c},
 20 C₂-C₈ alkynyl substituted with 0-2 R^{1c},
 C₃-C₈ cycloalkyl substituted with 0-2 R^{1c},
 aryl substituted with 0-4 R^{1c},
 aryl(C₁-C₆ alkyl)-substituted with 0-4 R^{1c},
 a 5-10 membered heterocyclic ring system having 1-3
 25 heteroatoms selected independently from O, S, and
 N, said heterocyclic ring being substituted with
 0-4 R^{1c}, and
 C₁-C₆ alkyl substituted with a 5-10 membered
 heterocyclic ring system having 1-3 heteroatoms
 30 selected independently from O, S, and N, said
 heterocyclic ring being substituted with 0-4 R^{1c};

R^{1c} is H, halogen, CF₃, CN, NO₂, C₁-C₈ alkyl, C₂-C₆ alkenyl,
 C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl.

- aryl(C₁-C₆ alkyl)-, C₁-C₆ alkoxy, and C₂-C₅ alkoxy carbonyl;
- R² is selected from H or C₁-C₁₀ alkyl;
- R³ and R⁴ are independently selected from the group
- 5 consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, and aryl substituted with 0-2 R^{3a};
- R^{3a} is selected from the group consisting of C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, CF₃, NO₂, and NR^{3b}R^{3c};
- 10 R^{3b} and R^{3c} are each independently selected from the group consisting of H, C₁-C₁₀ alkyl, C₂-C₁₀ alkoxy carbonyl, C₂-C₁₀ alkyl carbonyl, C₁-C₁₀ alkyl sulfonyl, heteroaryl(C₁-C₄ alkyl) sulfonyl, aryl(C₁-C₁₀ alkyl) sulfonyl, aryl sulfonyl, aryl,
- 15 heteroaryl carbonyl, heteroaryl sulfonyl, and heteroaryl alkyl carbonyl, wherein said aryl and heteroaryl are optionally substituted with 0-3 R^{3d};
- R^{3d} is selected from the group consisting of C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, CF₃, and NO₂;
- 20 R⁵ is selected from the group consisting of: hydroxy, C₁-C₁₀ alkyloxy, C₃-C₁₁ cycloalkyloxy, C₆-C₁₀ aryloxy, C₇-C₁₁ arylalkyloxy, C₃-C₁₀ alkyl carbonyloxyalkyloxy, C₃-C₁₀ alkoxy carbonyloxyalkyloxy,
- 25 C₃-C₁₀ alkoxy carbonylalkyloxy, C₅-C₁₀ cycloalkyl carbonyloxyalkyloxy, C₅-C₁₀ cycloalkoxy carbonyloxyalkyloxy, C₅-C₁₀ cycloalkoxy carbonylalkyloxy, C₈-C₁₁ aryloxy carbonylalkyloxy,
- 30 C₈-C₁₂ aryloxy carbonyloxyalkyloxy, C₈-C₁₂ aryl carbonyloxyalkyloxy, C₅-C₁₀ alkoxy alkyl carbonyloxyalkyloxy, 5-(C₅-C₁₀ alkyl)-1,3-dioxo-cyclopenten-2-one-yl)-methyloxy,
- 35 (5-aryl-1,3-dioxo-cyclopenten-2-one-yl)-methyloxy, and (R^{5a})HN-(C₁-C₁₀ alkoxy)-;

R^{5a} is selected from the group consisting of H, C₁-C₄ alkyl, aryl(C₁-C₁₀ alkoxy)carbonyl, C₂-C₁₀ alkoxy carbonyl, and C₃-C₆ alkenyl;

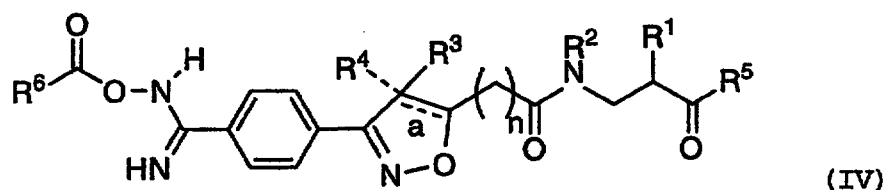
n is 0-4;

5 a is a single or double bond, with the proviso that if a is a double bond, it is not simultaneously substituted with R³ and R⁴;

said process comprising:

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contacting a compound of formula (IV):



15 wherein:

R⁶ is selected from the group consisting of H, CF₃, CF₂CF₃, CF₂CF₂CF₃, CF₂CF₂CF₂CF₃, C₁-C₈ alkyl, C₁-C₈ perfluoroalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl(C₁-C₆ alkyl)-, C₁-C₆ alkoxy, C₇-C₁₀ arylalkyloxy, C₁-C₆ alkyloxy, aryloxy and aryl substituted with 0-5 R^{6c};

R^{6C} is selected from the group consisting of H, halo, CF₃, CN, NO₂, NR^{6D}R^{6E}, C₁-C₈ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl, aryl(C₁-C₆ alkyl)-, C₁-C₆ alkoxy, and C₂-C₅ alkoxycarbonyl;

R^{6d} and R^{6e} are independently selected from the group consisting of H, C₁-C₁₀ alkyl, C₂-C₁₀ alkoxy carbonyl, C₂-C₁₀ alkyl carbonyl, C₁-C₁₀ alkyl sulfonyl, aryl, aryl(C₁-C₁₀ alkyl)sulfonyl, arylsulfonyl, heteroaryl(C₁-C₄ alkyl)sulfonyl, heteroaryl carbonyl, heteroarylsulfonyl, or heteroarylalkyl carbonyl, wherein said aryl and heteroaryl are optionally substituted with 0-3 substituents selected from the group

consisting of C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, CF₃, and NO₂;

5 with hydrogen under a suitable pressure in the presence of a hydrogenation catalyst to form a compound of formula (I) or a pharmaceutically acceptable salt form thereof.

In a preferred embodiment, the present invention provides a process for the preparation of a compound of
10 formula (I), wherein:

said suitable pressure is up to 100 psi, and

said hydrogenation catalyst is selected from the group
15 consisting of palladium on carbon, palladium hydroxide on carbon, palladium on calcium carbonate and platinum on carbon.

In a more preferred embodiment, the present invention provides a process for the preparation of a compound of
20 formula (I), wherein:

R¹ is selected from H or NHR^{1a};

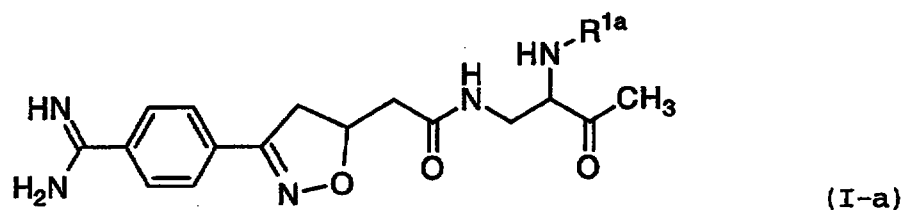
R^{1a} is -C(=O)-O-R^{1b} or -SO₂-R^{1b};

R^{1b} is selected from the group consisting of:

- 25 C₁-C₈ alkyl substituted with 0-1 R^{1c},
C₂-C₈ alkenyl substituted with 0-1 R^{1c},
C₂-C₈ alkynyl substituted with 0-1 R^{1c},
C₃-C₈ cycloalkyl substituted with 0-1 R^{1c},
aryl substituted with 0-3 R^{1c},
30 aryl(C₁-C₆ alkyl)-substituted with 0-3 R^{1c},
a 5-10 membered heterocyclic ring system having 1-3
heteroatoms selected independently from O, S, and
N, said heterocyclic ring being substituted with
0-4 R^{1c}, and
35 C₁-C₆ alkyl substituted with a 5-10 membered
heterocyclic ring system having 1-3 heteroatoms

- selected independently from O, S, and N, said heterocyclic ring being substituted with 0-4 R^{1c} ;
- R^{1c} is selected from the group consisting of H, halogen, CF_3 , CN, NO_2 , C_1-C_8 alkyl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylalkyl, aryl, aryl(C_1-C_6 alkyl)-, C_1-C_6 alkoxy and C_2-C_5 alkoxycarbonyl;
- R^2 is H or C_1-C_{10} alkyl;
- R^3 and R^4 are H or C_1-C_6 alkyl;
- R^5 is selected from the group consisting of hydroxy, C_1-C_{10} alkyloxy, C_3-C_{11} cycloalkyloxy, C_6-C_{10} aryloxy and C_7-C_{11} arylalkyloxy;
- R^6 is selected from the group consisting of H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, C_1-C_8 perfluoroalkyl, C_7-C_{10} arylalkyloxy, C_1-C_6 alkyloxy, aryloxy, aryl substituted with 0-2 R^{6c} ;
- R^{6c} is H, halogen, CF_3 , CN, NO_2 , $NR^{6d}R^{6e}$, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylalkyl, aryl, aryl(C_1-C_6 alkyl)-, C_1-C_6 alkoxy, and C_2-C_5 alkoxycarbonyl; and
- R^{6d} and R^{6e} are independently selected from H or C_1-C_{10} alkyl;
- n is 1;
- a is a single or double bond, with the proviso that if a is a double bond, it is not simultaneously substituted with R^3 and R^4 .

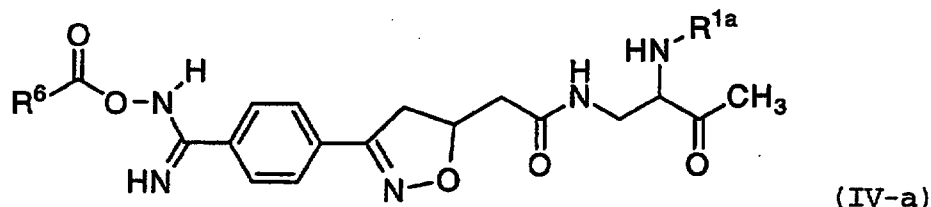
In an even more preferred embodiment, the present invention provides a process for the preparation of a compound of formula (I-a):



or a pharmaceutically acceptable salt form thereof, wherein:

R^{1a} is -C(=O)OCH₂(CH₂)₂CH₃ or 3,5-dimethyloxazol-4-yl-sulfonyl;

comprising contacting a compound of formula (IV-a):

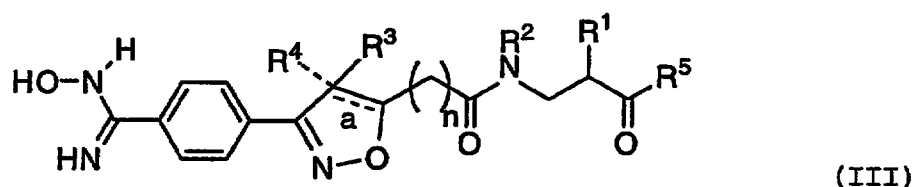


wherein R⁶ is H, methyl, ethyl, propyl, butyl, pentyl, hexyl
C₇-C₈ arylalkyloxy, C₁-C₅ alkyloxy, aryloxy or aryl;

10 with hydrogen under a suitable pressure from about 20 to
about 50 psi in the presence of palladium on carbon, in the
range of about 1% to about 10% by weight of compound (IV),
to form a compound of formula (I) or a pharmaceutically
15 acceptable salt form thereof.

In a second embodiment, the present invention provides
a process for the preparation of compounds of formula (IV)
or a salt thereof comprising:

20 contacting a compound of formula (III):



25 with an acylating agent of formula R⁶CO-O-COR⁶ or R⁶COX,
wherein X is fluorine, bromine, chlorine or imidazole, in
a suitable solvent to form a compound of formula (IV) or a
salt thereof.

In a preferred second embodiment, the present invention provides a process for the preparation of a compound of formula (IV), wherein:

X is chlorine;

5 R^1 is NHR^{1a} ;

R^{1a} is $-C(=O)OCH_2(CH_2)_2CH_3$ or 3,5-dimethyloxazol-4-yl-sulfonyl;

R^2 is H;

R^3 and R^4 are H;

10 R^5 is methyl;

R^6 is CH_3 ;

n is 1;

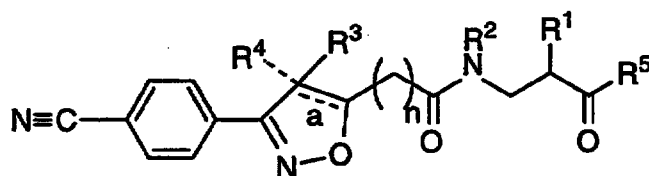
a is a single bond; and

15 said suitable solvent is acetic acid.

In a third embodiment, the present invention provides a process for the preparation of compounds of formula (III), comprising:

20

contacting a compound of formula (II):



(II)

25 with a salt of hydroxyl amine in the presence of a suitable base to form a compound of formula (III).

In a preferred third embodiment, the present invention provides a process for the preparation of a compound of formula (III), wherein said salts of hydroxyl amine are hydroxylamine hydrochloride and hydroxylamine sulfate.

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In a more preferred third embodiment, the present invention provides a process for the preparation of a compound of formula (III), wherein:

X is chlorine;

5 R^1 is NHR^{1a} ;

R^{1a} is $-C(=O)-O-CH_2(CH_2)_2CH_3$ or 3,5-dimethyloxazol-4-yl-sulfonyl;

R^2 is H;

R^3 and R^4 are H;

10 R^5 is methyl;

R^6 is selected from the group consisting of:

H, C_1-C_6 alkyl, C_7-C_8 arylalkyloxy, C_1-C_5 alkyloxy, aryloxy and aryl;

n is 1;

15 a is a single bond;

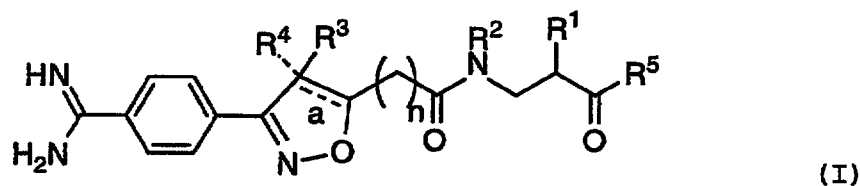
said suitable salt of hydroxylamine is hydroxylamine hydrochloride; and

the suitable base is selected from the group consisting of:

20 triethylamine, diisopropylethylamine and 4-methylmorpholine.

In a fourth embodiment, the present invention provides a process for the preparation of compounds of formula (I):

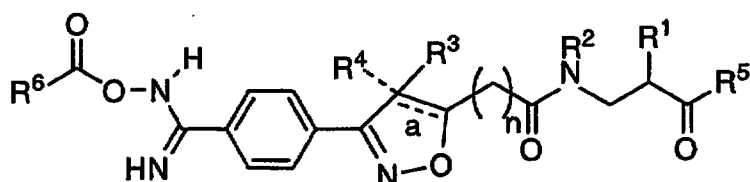
25



or a pharmaceutically acceptable salt form thereof,

30 said process comprising:

(a) heating a compound of the formula (IV):



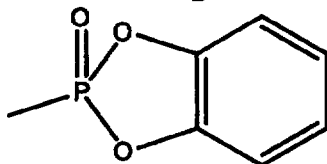
(IV)

wherein:

R^1 is selected from H or NHR^{1a} ;

R^{1a} is selected from the group consisting of:

- 5 $-C(=O)-O-R^{1b}$,
 $-C(=O)-R^{1b}$,
 $-C(=O)N(R^{1b})_2$,
 $-C(=O)NHSO_2R^{1b}$,
 $-C(=O)NHC(=O)R^{1b}$,
 10 $-C(=O)NHC(=O)OR^{1b}$,
 $-C(=O)NHSO_2NHR^{1b}$,
 $-C(=S)-NH-R^{1b}$,
 $-NH-C(=O)-O-R^{1b}$,
 $-NH-C(=O)R^{1b}$,
 15 $-NH-C(=O)-NH-R^{1b}$,
 $-SO_2-O-R^{1b}$,
 $-SO_2-R^{1b}$,
 $-SO_2-N(R^{1b})_2$,
 $-SO_2-NHC(=O)OR^{1b}$,
 20 $-P(=S)(OR^{1b})_2$,
 $-P(=O)(OR^{1b})_2$,
 $-P(=S)(R^{1b})_2$,
 $-P(=O)(R^{1b})_2$, and



25

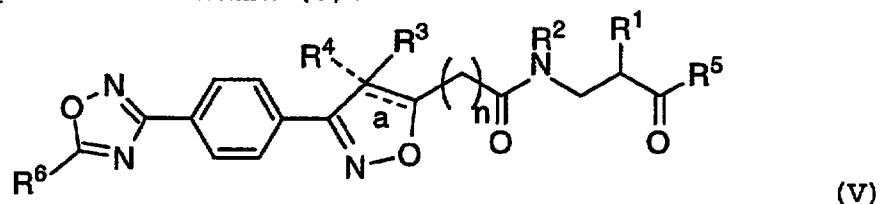
R^{1b} is selected from the group consisting of:

- 30 C₁-C₈ alkyl substituted with 0-2 R^{1c},
C₂-C₈ alkenyl substituted with 0-2 R^{1c},
C₂-C₈ alkynyl substituted with 0-2 R^{1c},
C₃-C₈ cycloalkyl substituted with 0-2 R^{1c},
aryl substituted with 0-4 R^{1c},

- aryl(C₁-C₆ alkyl)-substituted with 0-4 R^{1c},
a 5-10 membered heterocyclic ring system having 1-3
heteroatoms selected independently from O, S, and
N, said heterocyclic ring being substituted with
0-4 R^{1c}, and
C₁-C₆ alkyl substituted with a 5-10 membered
heterocyclic ring system having 1-3 heteroatoms
selected independently from O, S, and N, said
heterocyclic ring being substituted with 0-4 R^{1c};
- 10 R^{1c} is H, halogen, CF₃, CN, NO₂, C₁-C₈ alkyl, C₂-C₆ alkenyl,
C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl,
aryl(C₁-C₆ alkyl)-, C₁-C₆ alkoxy, and C₂-C₅
alkoxycarbonyl;
- R² is selected from H or C₁-C₁₀ alkyl;
- 15 R³ and R⁴ are independently selected from the group
consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆
alkynyl, C₃-C₇ cycloalkyl, and aryl substituted with
0-2 R^{3a};
- R^{3a} is selected from the group consisting of C₁-C₄ alkyl,
C₁-C₄ alkoxy, halo, CF₃, NO₂, and NR^{3b}R^{3c};
- 20 R^{3b} and R^{3c} are each independently selected from the group
consisting of H, C₁-C₁₀ alkyl, C₂-C₁₀ alkoxycarbonyl,
C₂-C₁₀ alkylcarbonyl, C₁-C₁₀ alkylsulfonyl,
heteroaryl(C₁-C₄ alkyl)sulfonyl,
25 aryl(C₁-C₁₀ alkyl)sulfonyl, arylsulfonyl, aryl,
heteroarylcarbonyl, heteroarylsulfonyl, and
heteroarylalkylcarbonyl, wherein said aryl and
heteroaryl are optionally substituted with 0-3 R^{3d};
- R^{3d} is selected from the group consisting of C₁-C₄ alkyl,
C₁-C₄ alkoxy, halo, CF₃, and NO₂;
- 30 R⁵ is selected from the group consisting of:
hydroxy, C₁-C₁₀ alkyloxy, C₃-C₁₁ cycloalkyloxy,
C₆-C₁₀ aryloxy, C₇-C₁₁ arylalkyloxy,
C₃-C₁₀ alkylcarbonyloxyalkyloxy,
35 C₃-C₁₀ alkoxycarbonyloxyalkyloxy,
C₃-C₁₀ alkoxycarbonylalkyloxy,
C₅-C₁₀ cycloalkylcarbonyloxyalkyloxy,

- C₅-C₁₀ cycloalkoxycarbonyloxyalkyloxy,
 C₅-C₁₀ cycloalkoxycarbonylalkyloxy,
 C₈-C₁₁ aryloxycarbonylalkyloxy,
 C₈-C₁₂ aryloxycarbonyloxyalkyloxy,
 5 C₈-C₁₂ arylcarbonyloxyalkyloxy,
 C₅-C₁₀ alkoxyalkylcarbonyloxyalkyloxy,
 5-(C₅-C₁₀ alkyl)-1,3-dioxo-cyclopenten-2-one-yl)-
 methyloxy,
 (5-aryl-1,3-dioxo-cyclopenten-2-one-yl)-methyloxy, and
 10 (R^{5a})HN-(C₁-C₁₀ alkoxy)-;
- R^{5a} is selected from the group consisting of H, C₁-C₄ alkyl,
 aryl(C₁-C₁₀ alkoxy)carbonyl, C₂-C₁₀ alkoxy carbonyl, and
 C₃-C₆ alkenyl;
- R⁶ is selected from the group consisting of H, CF₃, CF₂CF₃,
 15 CF₂CF₂CF₃, CF₂CF₂CF₂CF₃, C₁-C₈ alkyl, C₁-C₈
 perfluoroalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₁₁
 cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl(C₁-C₆ alkyl)-,
 C₁-C₆ alkoxy, C₇-C₁₀ arylalkyloxy, aryloxy and aryl
 substituted with 0-5 R^{6c};
- 20 R^{6c} is selected from the group consisting of H, halo, CF₃,
 CN, NO₂, NR^{6d}R^{6e}, C₁-C₈ alkyl, C₂-C₆ alkenyl, C₃-C₁₁
 cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl, aryl(C₁-C₆
 alkyl)-, C₁-C₆ alkoxy, and C₂-C₅ alkoxy carbonyl;
- R^{6d} and R^{6e} are independently selected from the group
 25 consisting of H, C₁-C₁₀ alkyl, C₂-C₁₀ alkoxy carbonyl,
 C₂-C₁₀ alkylcarbonyl, C₁-C₁₀ alkylsulfonyl, aryl,
 aryl(C₁-C₁₀ alkyl)sulfonyl, arylsulfonyl,
 heteroaryl(C₁-C₄ alkyl)sulfonyl, heteroarylcarbonyl,
 heteroarylsulfonyl, or heteroarylalkylcarbonyl, wherein
 30 said aryl and heteroaryl are optionally substituted
 with 0-3 substituents selected from the group
 consisting of C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, CF₃, and
 NO₂;
- n is 0-4;
- 35 a is a single or double bond, with the proviso that if a is
 a double bond, it is not simultaneously substituted
 with R³ and R⁴;

for a time sufficient, and to a temperature sufficient to form a compound of formula (V):



5

and (b) contacting said compound of formula (V) with hydrogen under a suitable pressure in the presence of a hydrogenation catalyst to form a compound of formula (I) or a salt thereof.

10

In a preferred fourth embodiment, the present invention provides a process for the preparation of a compound of formula (I), wherein:

15 said suitable pressure is up to 100 psi;

said hydrogenation catalyst is selected from the group consisting of palladium on carbon, palladium hydroxide on carbon, palladium on calcium carbonate and platinum on carbon;

20

said sufficient temperature is from about 30°C to about 120°C;

25 said sufficient time is from about 10 minutes to about 24 hours;

wherein an amount of catalyst loaded on carbon is from about 1% to about 10% by weight; and

30

wherein an amount of a hydrogenation catalyst is from about 1% to about 30% by weight of compound (IV).

In a more preferred fourth embodiment, the present invention provides a process for the preparation of a compound of formula (I), wherein:

R¹ is NHR^{1a};

5 R^{1a} is -C(=O)-O-CH₂(CH₂)₂CH₃ or 3,5-dimethyloxazol-4yl-sulfonyl;

R² is H;

R³ and R⁴ are H;

R⁵ is methyl;

10 R⁶ is selected from the group consisting of:

H, methyl, ethyl, propyl, butyl, pentyl, hexyl, C₇-C₈ arylalkyloxy, aryloxy, C₁-C₅ alkoxy and aryl;

n is 1, and

a is a single bond;

15

said suitable pressure is from about 20 to about 50 psi;

said sufficient temperature is from about 50°C to about 120°C;

20

said sufficient time is from about 10 minutes to about 3 hours;

said hydrogenation catalyst is palladium on carbon;

25

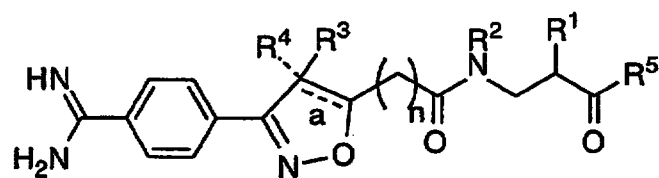
wherein an amount of catalyst loaded on carbon is from about 3% to about 5% by weight; and

wherein an amount of palladium on carbon is from about 3% to about 7% by weight of compound (IV).

30

In a fifth embodiment, the present invention provides a process for the preparation of compounds of the formula (I):

35



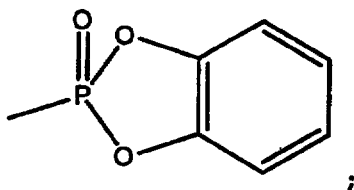
(I)

or a pharmaceutically acceptable salt form thereof;
wherein:

5 R^1 is selected from H or NHR^{1a} ;

R^{1a} is selected from the group consisting of:

- C(=O)-O- R^{1b} ,
- C(=O)- R^{1b} ,
- C(=O)N(R^{1b})₂,
- 10 -C(=O)NHSO₂ R^{1b} ,
- C(=O)NHC(=O) R^{1b} ,
- C(=O)NHC(=O)O R^{1b} ,
- C(=O)NHSO₂NH R^{1b} ,
- C(=S)-NH- R^{1b} ,
- 15 -NH-C(=O)-O- R^{1b} ,
- NH-C(=O) R^{1b} ,
- NH-C(=)-NH- R^{1b} ,
- SO₂-O- R^{1b} ,
- SO₂- R^{1b} ,
- 20 -SO₂-N(R^{1b})₂,
- SO₂-NHC(=O)O R^{1b} ,
- P(=S)(O R^{1b})₂,
- P(=O)(O R^{1b})₂,
- P(=S)(R^{1b})₂,
- 25 -P(=O)(R^{1b})₂, and



R^{1b} is selected from the group consisting of:

- 30 C₁-C₈ alkyl substituted with 0-2 R^{1c} ,
- C₂-C₈ alkenyl substituted with 0-2 R^{1c} ,

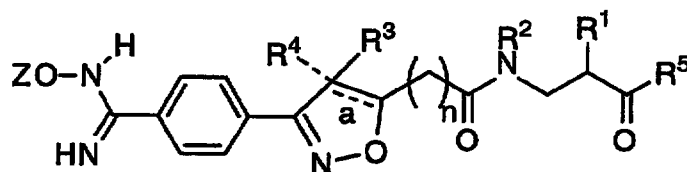
- C₂-C₈ alkynyl substituted with 0-2 R^{1c},
C₃-C₈ cycloalkyl substituted with 0-2 R^{1c},
aryl substituted with 0-4 R^{1c},
aryl(C₁-C₆ alkyl)-substituted with 0-4 R^{1c},
5 a 5-10 membered heterocyclic ring system having 1-3
heteroatoms selected independently from O, S, and
N, said heterocyclic ring being substituted with
0-4 R^{1c}, and
C₁-C₆ alkyl substituted with a 5-10 membered
10 heterocyclic ring system having 1-3 heteroatoms
selected independently from O, S, and N, said
heterocyclic ring being substituted with 0-4R^{1c};
R^{1c} is H, halogen, CF₃, CN, NO₂, C₁-C₈ alkyl, C₂-C₆ alkenyl,
C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl,
15 aryl(C₁-C₆ alkyl)-, C₁-C₆ alkoxy, and C₂-C₅
alkoxycarbonyl;
R² is selected from H or C₁-C₁₀ alkyl;
R³ and R⁴ are independently selected from the group
consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆
20 alkynyl, C₃-C₇ cycloalkyl, and aryl substituted with
0-2 R^{3a};
R^{3a} is selected from the group consisting of C₁-C₄ alkyl,
C₁-C₄ alkoxy, halo, CF₃, NO₂, and NR^{3b}R^{3c};
R^{3b} and R^{3c} are each independently selected from the group
25 consisting of H, C₁-C₁₀ alkyl, C₂-C₁₀ alkoxycarbonyl,
C₂-C₁₀ alkylcarbonyl, C₁-C₁₀ alkylsulfonyl,
heteroaryl(C₁-C₄ alkyl)sulfonyl,
aryl(C₁-C₁₀ alkyl)sulfonyl, arylsulfonyl, aryl,
heteroarylcarbonyl, heteroarylsulfonyl, and
30 heteroarylalkylcarbonyl, wherein said aryl and
heteroaryl are optionally substituted with 0-3 R^{3d};
R^{3d} is selected from the group consisting of C₁-C₄ alkyl,
C₁-C₄ alkoxy, halo, CF₃, and NO₂;
R⁵ is selected from the group consisting of:
35 hydroxy, C₁-C₁₀ alkyloxy, C₃-C₁₁ cycloalkyloxy,
C₆-C₁₀ aryloxy, C₇-C₁₁ arylalkyloxy,
C₃-C₁₀ alkylcarbonyloxyalkyloxy,

- C₃-C₁₀ alkoxy carbonyloxyalkyloxy,
 C₃-C₁₀ alkoxy carbonylalkyloxy,
 C₅-C₁₀ cycloalkyl carbonyloxyalkyloxy,
 C₅-C₁₀ cycloalkoxy carbonyloxyalkyloxy,
 5 C₅-C₁₀ cycloalkoxy carbonylalkyloxy,
 C₈-C₁₁ aryloxy carbonylalkyloxy,
 C₈-C₁₂ aryloxy carbonyloxyalkyloxy,
 C₈-C₁₂ aryl carbonyloxyalkyloxy,
 C₅-C₁₀ alkoxy alkyl carbonyloxyalkyloxy,
 10 5-(C₅-C₁₀ alkyl)-1,3-dioxo-cyclopenten-2-one-yl)-
 methyloxy,
 (5-aryl-1,3-dioxo-cyclopenten-2-one-yl)-methyloxy, and
 (R^{5a})HN-(C₁-C₁₀ alkoxy)-;
- R^{5a} is selected from the group consisting of H, C₁-C₄ alkyl,
 15 aryl(C₁-C₁₀ alkoxy)carbonyl, C₂-C₁₀ alkoxy carbonyl, and
 C₃-C₆ alkenyl;
- n is 0-4;
- a is a single or double bond, with the proviso that if a is
 a double bond, it is not simultaneously substituted
 20 with R³ and R⁴;

said process comprising:

contacting a compound of formula (VI):

25



(VI)

wherein:

- Z is selected from R⁶SO₂- or (R⁷)₃Si-;
- 30 R⁶ is selected from the group consisting of H, CF₃, CF₂CF₃,
 CF₂CF₂CF₃, CF₂CF₂CF₂CF₃, C₁-C₈ alkyl, C₁-C₈
 perfluoroalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₁₁
 cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl(C₁-C₆ alkyl)-,

C₁-C₆ alkoxy, C₇-C₁₀ arylalkyloxy, aryloxy and aryl substituted with 0-5 R^{6c};

R^{6c} is selected from the group consisting of H, halo, CF₃, CN, NO₂, NR^{6d}R^{6e}, C₁-C₈ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl, aryl(C₁-C₆ alkyl)-, C₁-C₆ alkoxy, and C₂-C₅ alkoxycarbonyl;

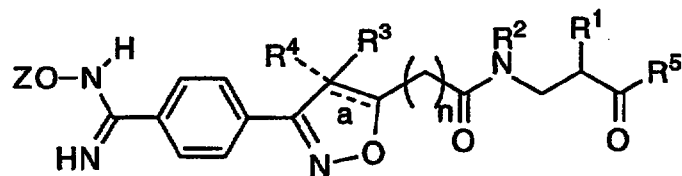
R^{6d} and R^{6e} are independently selected from the group consisting of H, C₁-C₁₀ alkyl, C₂-C₁₀ alkoxycarbonyl, C₂-C₁₀ alkylcarbonyl, C₁-C₁₀ alkylsulfonyl, aryl, aryl(C₁-C₁₀ alkyl)sulfonyl, arylsulfonyl, heteroaryl(C₁-C₄ alkyl)sulfonyl, heteroarylcarbonyl, heteroarylsulfonyl, or heteroarylalkylcarbonyl, wherein said aryl and heteroaryl are optionally substituted with 0-3 substituents selected from the group consisting of C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, CF₃, and NO₂;

R⁷ is selected independently from C₁-C₁₀ alkyl or aryl substituted 0-3 R^{7a}; and

R^{7a} is C₁-C₁₀ alkyl;

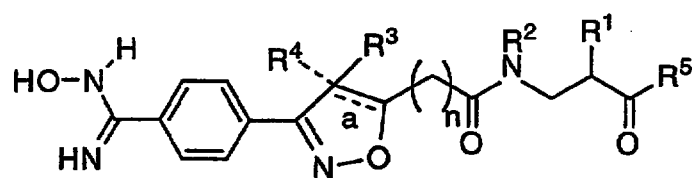
with hydrogen under a suitable pressure in the presence of a hydrogenation catalyst to form a compound of formula (I) or a pharmaceutically acceptable salt form thereof.

In a sixth embodiment, the present invention provides a process for the preparation of compounds of formula (VI):



(VI)

comprising: contacting a compound of formula (III):



(III)

with an agent of formula Z-X, wherein:

X is fluorine, bromine or chlorine;

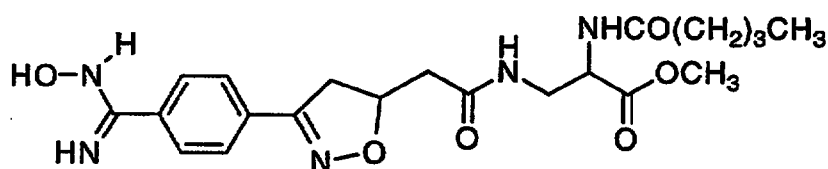
5 Z is R^6SO_2- or $(R^7)_3Si-$;

R^7 is selected independently from C_1-C_{10} alkyl or aryl
substituted 0-3 R^{7a} ; and

R^{7a} is C_1-C_{10} alkyl;

10 in the presence of a suitable acid scavenger in a suitable
solvent to form a compound of formula (IV) or a salt
thereof.

In a seventh embodiment, the present invention provides
15 a compound of formula (III-i):

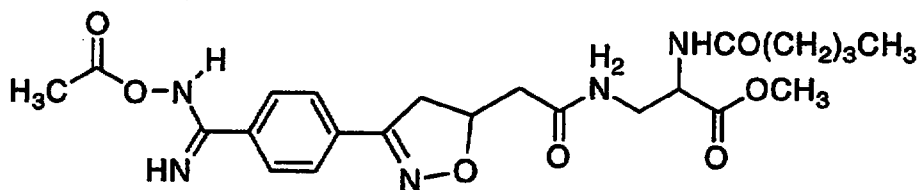


(III-i)

and salt forms thereof.

20

In a eighth embodiment, the present invention provides
a compound of formula (IV-i):

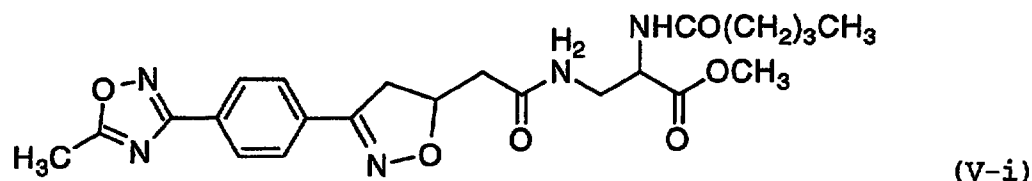


(IV-i)

25

and salt forms thereof.

In a ninth embodiment, the present invention provides a compound of formula (V-i):



5

and salt forms thereof.

The reactions of the synthetic methods claimed herein are carried out in suitable solvents which may be readily selected by one of skill in the art of organic synthesis, said suitable solvents generally being any solvent which is substantially nonreactive with the starting materials (reactants), the intermediates, or products at the temperatures at which the reactions are carried out, i.e., temperatures which may range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction may be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step may be selected.

Suitable halogenated solvents include: carbon tetrachloride, bromodichloromethane, dibromochloromethane, bromoform, chloroform, bromochloromethane, dibromomethane, butyl chloride, dichloromethane, tetrachloroethylene, trichloroethylene, 1,1,1-trichloroethane, 1,1,2-trichloroethane, 1,1-dichloroethane, 2-chloropropane, hexafluorobenzene, 1,2,4-trichlorobenzene, o-dichlorobenzene, chlorobenzene, fluorobenzene, fluorotrichloromethane, chlorotrifluoromethane, bromotrifluoromethane, carbon tetrafluoride, dichlorofluoromethane, chlorodifluoromethane, trifluoromethane, 1,2-dichlorotetrafluoroethane and hexafluoroethane.

Suitable ether solvents include: dimethoxymethane, tetrahydrofuran, 1,3-dioxane, 1,4-dioxane, furan, diethyl

ether, ethylene glycol dimethyl ether, ethylene glycol diethyl ether, diethylene glycol dimethyl ether, diethylene glycol diethyl ether, triethylene glycol dimethyl ether, anisole, or t-butyl methyl ether.

5 Suitable protic solvents may include, by way of example and without limitation, water, methanol, ethanol, 2-nitroethanol, 2-fluoroethanol, 2,2,2-trifluoroethanol, ethylene glycol, 1-propanol, 2-propanol, 2-methoxyethanol, 1-butanol, 2-butanol, i-butyl alcohol, t-butyl alcohol, 2-
10 ethoxyethanol, diethylene glycol, 1-, 2-, or 3- pentanol, neo-pentyl alcohol, t-pentyl alcohol, diethylene glycol monomethyl ether, diethylene glycol monoethyl ether, cyclohexanol, benzyl alcohol, phenol, or glycerol.

 Suitable aprotic solvents may include, by way of
15 example and without limitation, tetrahydrofuran (THF), dimethylformamide (DMF), dimethylacetamide (DMAC), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), 1,3-dimethyl-2-imidazolidinone (DMI), N-methylpyrrolidinone (NMP), formamide, N-methylacetamide, N-methylformamide,
20 acetonitrile, dimethyl sulfoxide, propionitrile, ethyl formate, methyl acetate, hexachloroacetone, acetone, ethyl methyl ketone, ethyl acetate, sulfolane, N,N-dimethylpropionamide, tetramethylurea, nitromethane, nitrobenzene, or hexamethylphosphoramide.

25 Suitable hydrocarbon solvents include: benzene, cyclohexane, pentane, hexane, toluene, cycloheptane, methylcyclohexane, heptane, ethylbenzene, m-, o-, or p-xylene, octane, indane, nonane, or naphthalene.

 Suitable carboxylic acid solvents include acetic acid,
30 trifluoroacetic acid, ethanoic acid, propionic acid, propiolic acid, butyric acid, 2-butyric acid, vinyl acetic acid, pentanoic acid, hexanoic acid, heptanoic acid, octanoic acid, nonanoic acid and decanoic acid.

 Suitable pressures range from atmospheric to any
35 pressure obtainable in a laboratory or industrial plant.

 Suitable hydrogenation catalysts are those which

facilitate the delivery of hydrogen to the N-O bond of an N-acylated hydroxylamine. Such hydrogenation catalysts by way of example and without limitation are palladium on carbon, palladium hydroxide on carbon, palladium on calcium carbonate poisoned with lead and platinum on carbon.

As used herein, suitable acid scavengers include those compounds capable of accepting a proton from a hydroxyamidine during either an acylation, sulfonation or silation reaction without reacting with the agent reacting with the oxygen of the hydroxyamidine. Examples include, but are not limited to tertiary bases such as N,N-diisopropylethylamine, 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, 3,5-lutidine, triethylamine, 2-, 3-, or 4-picoline, pyrrole, pyrrolidine, N-methyl morpholine, pyridine and pyrimidine.

As used herein, suitable bases include those soluble in the reaction solvent and capable of free-basing hydroxylamine. Examples include, but are not limited to: lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium carbonate, sodium carbonate, potassium carbonate, imidazole, ethylene diamine, N,N-diisopropylethylamine, 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, 3,5-lutidine, triethylamine, 2-, 3-, or 4-picoline, pyrrole, pyrrolidine, N-methyl morpholine, pyridine, pyrimidine or piperidine.

As used herein, acylating agent refers to an acid halide or anhydride, which, when reacted with a hydroxyamidine results in O-acylation of the hydroxyl amidine. Such acylating agents by way of example and without limitation are of the general structure R^6COX or $R^6CO-O-COR^6$, as defined above in the specification. By way of further example, and without limitation, where X is fluorine, chlorine, bromine or imidazole, R^6 is H, CF_3 , CF_2CF_3 , $CF_2CF_2CF_3$, $CF_2CF_2CF_2CF_3$, methyl, ethyl, propyl, butyl, ethenyl, allyl, ethynyl, cyclopropyl, phenyl, benzyl, C₇-C₁₀ arylalkyloxy, C₁-C₁₀ alkyloxy or aryloxy.

As used herein, agent refers to a compound of the formula Z-X, which, when reacted with a hydroxyamidine

results in placement of the Z group on the oxygen of the hydroxyamidine. By way of further example, and without limitation, where X is fluorine, chlorine, bromine or imidazole, Z is either R^6SO_2- or $(R^7)_3Si-$, R^6 is H, CF_3 ,
5 CF_2CF_3 , $CF_2CF_2CF_3$, $CF_2CF_2CF_2CF_3$, methyl, ethyl, propyl, butyl, ethenyl, allyl, ethynyl, cyclopropyl, phenyl, benzyl, C_7-C_{10} arylalkyloxy, or aryloxy, and R^7 is independently selected from C_1-C_{10} alkyl or aryl substituted with 0-3 R^{7a} , and R^{7a} is C_1-C_{10} alkyl.

10 The compounds described herein may have asymmetric centers. Unless otherwise indicated, all chiral, diastereomeric and racemic forms are included in the present invention. Many geometric isomers of olefins, C=N double
15 bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. It will be appreciated that compounds of the present invention that contain asymmetrically substituted carbon atoms may be
20 isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically active starting materials are known in the art, such as by resolution of racemic forms or by synthesis. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended.

25 When any variable (for example but not limited to R^{1b} , R^{1c} , R^{3a} , R^{3b} , R^{3c} , R^{6c} , etc.) occurs more than one time in any constituent or in any formula, its definition on each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be
30 substituted with 0-2 R^{3a} , then said group may optionally be substituted with up to two R^{3a} and R^{3a} at each occurrence is selected independently from the defined list of possible R^{3a} .

35 Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By stable compound or stable structure it is meant herein a compound that is sufficiently robust to

survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

5 The term "substituted", as used herein, means that any one or more hydrogen on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound.

10 As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms; for example, C₁-C₄ alkyl includes methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, and t-butyl; for example C₁-C₁₀ alkyl includes C₁-C₄ alkyl, pentyl, hexyl, 15 heptyl, octyl, nonyl, decyl, and isomer thereof.

As used herein, any carbon range such as "C_x-C_y" is intended to mean a minimum of "x" carbons and a maximum of "y" carbons representing the total number of carbons in the substituent to which it refers. For example, "C₃-C₁₀ 20 alkylcarbonyloxyalkyloxy" could contain one carbon for "alkyl", one carbon for "carbonyloxy" and one carbon for "alkyloxy" giving a total of three carbons, or a larger number of carbons for each alkyl group not to exceed a total of ten carbons.

25 "Alkenyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1,3-butadienyl 30 and the like. "Alkynyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl, propynyl, butynyl and the like. "Aryl" is intended to mean phenyl or 35 naphthyl. The term "arylalkyl" represents an aryl group attached through an alkyl bridge; for example aryl(C₁-

C₂)alkyl is intended to mean benzyl, phenylethyl and the like.

As used herein, "cycloalkyl" is intended to include saturated ring groups, including mono-, bi-, or poly-cyclic ring systems, such as cyclopropyl, cyclobutyl, cyclopentyl, 5 cyclohexyl, cycloheptyl, cyclooctyl, and adamantyl.

As used herein, "alkyloxy" or "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge, for example methoxy, ethoxy, 10 propoxy, i-propoxy, butoxy, i-butoxy, s-butoxy and t-butoxy. The term "aryloxy" is intended to mean phenyl or naphthyl attached through an oxygen bridge;

As used herein, "carbonyl" means a carbon double bonded to oxygen and additionally substituted with two groups 15 through single bonds; "carbonyloxy" means a carbon double bonded to oxygen and additionally bonded through a single bonds to two groups, one of which is an oxygen. As used herein, "sulfonyl" is intended to mean a sulfur bonded through double bonds to two oxygens and bonded to two 20 additional groups through single bonds. As used herein, "hydroxy" means a group consisting of an oxygen and a hydrogen bonded to another group through the oxygen.

"Halo" or "halogen" as used herein refers to fluoro, chloro, bromo and iodo.

25 As used herein, the term "heterocycle" or "heterocyclic" is intended to mean a stable 5- to 10-membered monocyclic or bicyclic or 5- to 10-membered bicyclic heterocyclic ring which may be saturated, partially unsaturated, or aromatic, and which consists of carbon atoms 30 and from 1 to 3 heteroatoms independently selected from the group consisting of N, O and S and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen may optionally be quaternized, and including any bicyclic group in which any of the above-defined 35 heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom which results in a stable

structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. Examples of such heterocycles include, but are not limited to, pyridyl (pyridinyl), pyrimidinyl, 5 furanyl (furyl), thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, benzothiophenyl, indolyl, indolenyl, isoxazoliny, quinoliny, isoquinoliny, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrroliny, tetrahydrofuranyl, 10 tetrahydroquinoliny, tetrahydroisoquinoliny, decahydroquinoliny or octahydroisoquinoliny, azociny, triazinyl, 6H-1,2,5-thiadiaziny, 2H,6H-1,5,2-dithiaziny, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathiiny, 2H-pyrrolyl, pyrrolyl, 15 imidazolyl, pyrazolyl, isothiazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyridazinyl, indoliziny, isoindolyl, 3H-indolyl, 1H-indazolyl, puriny, 4H-quinoliziny, phthalazinyl, naphthyridiny, quinoxaliny, quinazoliny, cinnoliny, pteridinyl, 4aH-carbazole, carbazole, β -carboliny, 20 phenanthridiny, acridiny, perimidiny, phenanthroliny, phenazinyl, phenarsazinyl, phenothiaziny, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidiny, imidazoliny, pyrazolidiny, pyrazoliny, piperazinyl, indoliny, isoindoliny, quinuclidiny, morpholiny or 25 oxazolidiny. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

As used herein, the term "heteroaryl" refers to aromatic heterocyclic groups. Such heteroaryl groups are preferably 5-6 membered monocyclic groups or 8-10 membered 30 fused bicyclic groups. Examples of such heteroaryl groups include, but are not limited to pyridyl (pyridinyl), pyrimidinyl, furanyl (furyl), thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, indolyl, isoxazolyl, oxazolyl, pyrazinyl, pyridazinyl, benzofuranyl, benzothienyl, 35 benzimidazolyl, quinoliny, or isoquinoliny.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the

intermediates or final compound are modified by making acid or base salts of the intermediates or final compounds.

Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic
5 residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like.

The pharmaceutically acceptable salts of the intermediates or final compounds include the conventional non-toxic salts or the quaternary ammonium salts from non-
10 toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic,
15 succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

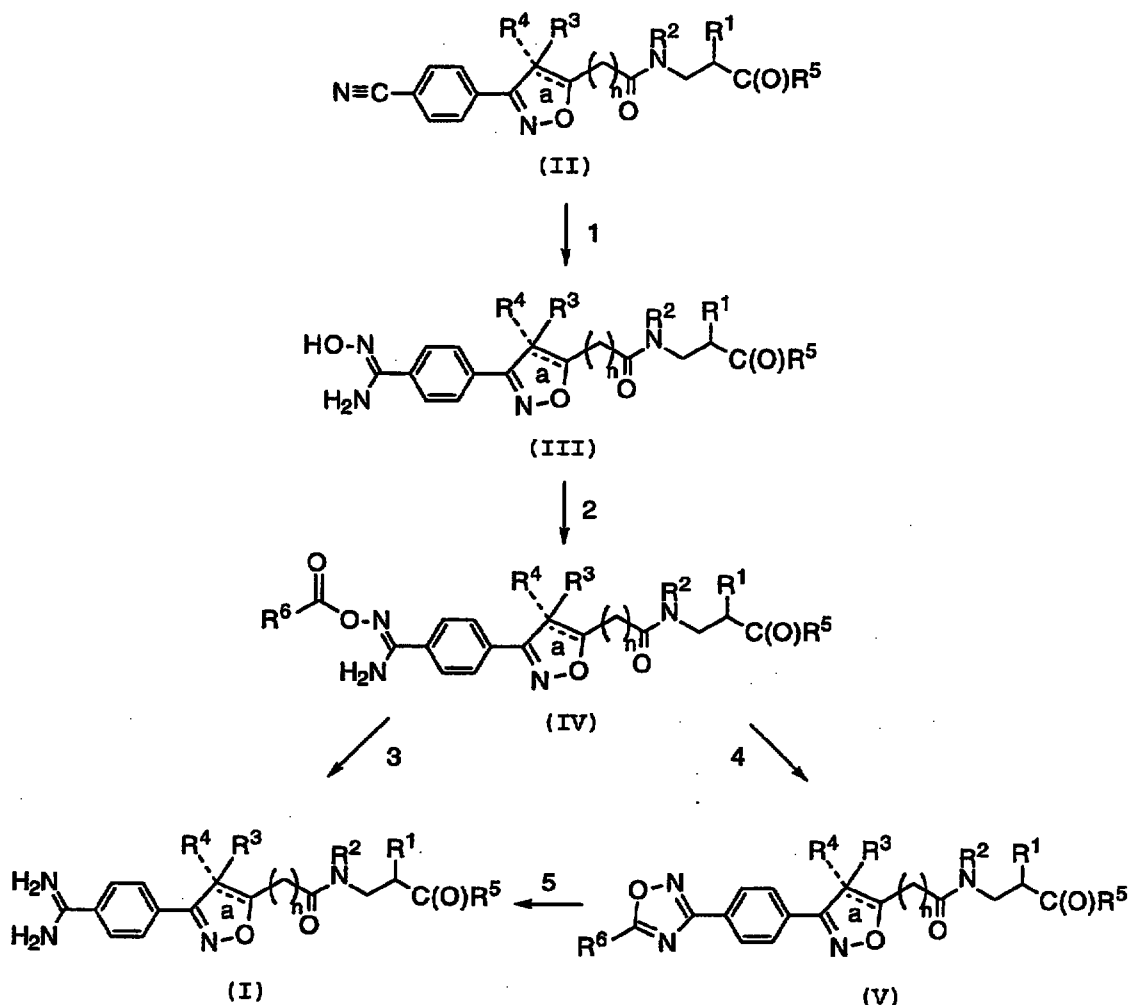
20 The pharmaceutically acceptable salts are generally prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base in a suitable solvent or various combinations of solvents.

25 The pharmaceutically acceptable salts of the acids of the intermediates or final compounds are prepared by combination with an appropriate amount of a base, such as an alkali or alkaline earth metal hydroxide e.g. sodium, potassium, lithium, calcium, or magnesium, or an organic
30 base such as an amine, e.g., dibenzylethylenediamine, trimethylamine, piperidine, pyrrolidine, benzylamine and the like, or a quaternary ammonium hydroxide such as tetramethylammonium hydroxide and the like.

As discussed above, pharmaceutically acceptable salts
35 of the compounds of the invention can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid,

respectively, in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's
5 Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference. The present invention is contemplated to be practiced on at least a multigram scale, kilogram scale, multikilogram scale, or industrial scale.
10 Multigram scale, as used herein, is preferably the scale wherein at least one starting material is present in 10 grams or more, more preferably at least 50 grams or more, even more preferably at least 100 grams or more. Multikilogram scale, as used herein, is intended to mean the
15 scale wherein more than one kilogram of at least one starting material is used. Industrial scale as used herein is intended to mean a scale which is other than a laboratory scale and which is sufficient to supply product sufficient for either clinical tests or distribution to consumers.
20 The methods of the present invention, by way of example and without limitation, may be further understood by reference to Scheme 1. Scheme 1 details the general synthetic method for synthesis of compounds of formula (I). Compound (II) can be prepared by methods described in
25 J. Org. Chem. **1997**, *62*, 2466-2470, and Tetrahedron Lett. **1996**, *37*, 4455-4458. It is understood to one skilled in the art that the anhydride or acid chlorides used in the acylation step can be prepared by conversion of carboxylic acid derivatives as described in Advanced Organic Chemistry,
30 March, 4th edition, John Wiley and Sons, Inc., 1992, p. 401-402 and p. 437-438.

SCHEME 1



- 5 In Step 1, a compound of formula (II) is dissolved in about 10 liters of suitable solvent per kilogram of compound (II). A suitable salt of hydroxyl amine is added. While a wide range of solvents such as halogenated, protic, aprotic, hydrocarbon, or ethers can be used, protic
- 10 solvents such as methanol, ethanol and isopropanol are preferred, of which methanol is most preferred. Suitable salts of hydroxyl amine include phosphate, sulfate, nitrate and hydrochloride salts; a most preferred salt is hydroxyl amine hydrochloride. The hydroxyl amine salt is free-based
- 15 with about 1.0 to about 2.0 equivalents of an appropriate base. Preferable bases are tertiary amines; most

preferred is triethyl amine. The reaction mixture can then be heated for a time sufficient to form a compound of form (III). By way of general guidance, compound (II) may be contacted with free-based hydroxyl amine at about 40°C to about 65°C for about 1 to about 5 hours to produce compound (III). Preferred temperatures are from about 55°C to about 65°C. Preferred reaction times are from about 2 to about 4 hours. The product precipitates as a white solid during the course of the reaction. The solids can then be filtered and the cake washed with a solvent, the choice of which is readily understood by one skilled in the art. The product is dried to afford pure compound (III).

In Step 2, a vessel is charged with compound (III). The solids are dissolved in a suitable solvent followed by the slow charging of the vessel with a second solution made by dissolving a suitable acylating agent in the solvent being used for the reaction. Preferably, the addition of the acylating agent solution should be done over a period of about 15 minutes to about one hour. While a wide range of reaction solvents such as halogenated, aprotic, hydrocarbon, ether, or organic acids are possible, preferred solvents are acetic acid, trifluoroacetic acid, pyridine, chloroform, dichloromethane, dichlorobenzene, acetonitrile, and tetrahydrofuran. Most preferred are carboxylic acids which are structural derivatives of the acylating agent being used. By way of general example, acetic acid would preferably be used as the solvent when acetic anhydride is the acylating agent, whereas trifluoroacetic acid would be preferably used when trifluoroacetic anhydride is the acylating agent. Certain solvents such as aprotic, ether, halogenated and hydrocarbon solvents may require the addition of an acid scavenger. Preferred acid scavengers include tertiary bases such as triethyl amine, diisopropyl ethylamine, N-methyl morpholine and pyridine. Most preferred is triethyl amine. Solvents capable of reacting with the acylating agent, such as alcohols, water and the like are not preferred as is readily understood by one

skilled in the art. Preferred acylating agents are anhydrides. Most preferred is acetic anhydride. Further, the acylating agent (and preferable solvent) can be strategically chosen to form the desired salt of the
5 reaction product. By way of general example, acetic anhydride would be selected as the acylating agent if the acetate salt of the product is desired. The choice of acylating agent and solvent in this regard is readily understood by one skilled in the art.

10 After the addition of the acylating agent, the reaction progression can be monitored by HPLC analysis performed on an aliquot of the reaction solution. The acylation reaction is considered finished when compound (III) is completely consumed. Typical reaction times are in the range of about
15 5 minutes to about 24 hours. Preferred reaction times are about 5 minutes to about 3 hours. The product can be isolated by the removal of the solvent via distillation and precipitation of the product through the addition of a suitable aprotic solvent. Preferred aprotic solvents are
20 ethers. The choice of precipitation solvent and the methods of isolation are readily understood by one skilled in the art. Preferably, the product is carried forward without isolation.

Step 3, comprises the hydrogenation of the O-
25 substituted hydroxyamidine. This reaction can be carried out without isolation of compound (IV), by the addition of a slurry of a suitable hydrogenation catalyst in the solvent used in the preceding reaction. If compound (IV) is isolated, the hydrogenation can be carried out in protic,
30 aprotic, hydrocarbon, ether, or organic acid solvents. The preferred solvents are methanol, ethanol, 2-propanol, dimethylformamide, ethyl acetate, anisole, acetic acid and trifluoroacetic acid. Most preferred is a mixture of methanol and acetic acid. While numerous hydrogenation
35 catalysts are possible, palladium on carbon is most preferred. The amount of catalyst loaded on the carbon ranges from about 0.5% to about 30%. The preferred amount

of catalyst on carbon is about 1% to about 10%. Most preferred is about 3% to 5%. The total weight of the catalyst and carbon per gram of starting material is preferably about 1% to about 10%. Most preferred is about 3% to 7%. The total weight of catalyst and carbon is based on the weight of the O-alkylated hydroxyamidine. The reaction solution is then subjected to a hydrogen atmosphere under a suitable pressure. Preferred pressures range from about 1 psi to 100 psi. Most preferred is 20 psi to 50 psi.

10 The reaction time of the hydrogenation is dependent on cumulative factors, including the amount of catalyst present, the reaction temperature and the hydrogen pressure. By way of general example, an acetylation reaction containing 10.0 kilograms of compound (III) required the use of 0.5 kilograms of 3% palladium on carbon, under 5 psi of hydrogen at room temperature to reach completion in about 5 hours. Varying any one of these conditions will effect reaction time which is readily understood by one skilled in the art.

20 Reaction completion can be monitored by HPLC analysis performed on aliquots of the reaction mixture. The reaction is considered complete when compound (IV) has been completely consumed. After the reaction is judged complete, the catalyst is filtered off and washed with reaction solvent. The filtrate is concentrated, and the product precipitated by the addition of a suitable aprotic solvent. The most preferred solvent for precipitation is acetone. The choice of precipitation solvent and the methods of isolation are readily understood by one skilled in the art.

25 The product is then filtered and dried to give pure compound (I).

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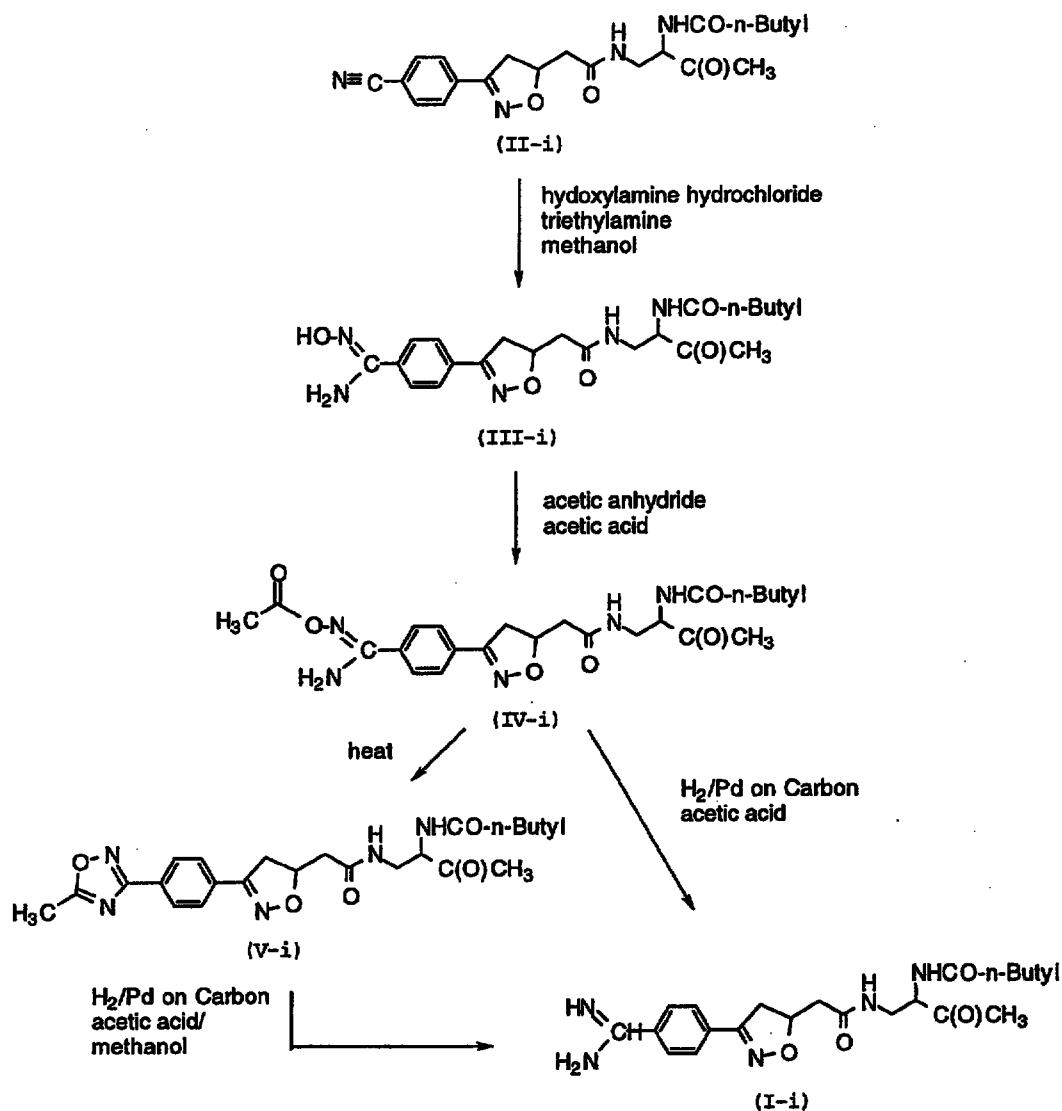
In Step 4, the resultant reaction solution of Step 2 is heated to form compound (V). The heating range is from about 30°C to the reflux temperature of the solvent.

35 Preferred temperatures are from about 30°C to about 120°C. Preferred solvents for the cyclization are acetic acid, trifluoroacetic acid, pyridine, chloroform,

dichloromethane, dichlorobenzene, acetonitrile, and tetrahydrofuran. The most preferred solvent for the cyclization is acetic acid. The preferred time of reflux is solvent dependent due to the limitations of boiling points.

- 5 By way of general example, the use of acetic acid as the solvent required a heating time of about 3 hours. The product can be isolated by the removal of the solvent via distillation followed by the drying of the solids. Preferably, compound (V) is carried forward without
10 isolation.

In Step 4, compound (V) is hydrogenated under the identical conditions of Step 3 to give compound (I). The present invention may be further exemplified without
15 limitation by reference to Scheme 2.

SCHEME 2

5 The following examples are meant to be illustrative of the present invention. These examples are presented to exemplify the invention and are not to be construed as limiting the inventors scope.

10

EXAMPLE 1

(R)-Methyl-3-[[[3[4[amino(hydroxyimino)methyl]phenyl]-4,5-dihydro-5-isoxazolyl]acetyl]amino]-N(butoxy-carbonyl)-L-alanine: Compound (III-i)

A 100 gal stainless steel reactor was charged with methanol (87 Kg), compound (II-i) (11 Kg), hydroxylamine hydrochloride (3.6 Kg), and triethylamine (5.2 Kg). The reaction mixture was heated at 60°C for 3 h and a large amount of solid precipitated during the reaction. After cooling to 0-5°C, the solid was filtered through a Nutsche filter and the cake was washed with a mixture of methanol and water (made from 20 Kg of methanol and 25 Kg of water). After dried the cake, the product (11.8 Kg) was obtained.

10

EXAMPLE 2

(R)-Methyl-3-[[[3-[4-(aminoiminomethyl)phenyl]-4,5-dihydro-5-isoxazolyl]acetyl]amino]-N(butoxy carbonyl)-L-alanine monoacetate: Compound (I-i)

15

A 50 gal stainless steel reactor was charged with acetic acid (63 Kg) and (R)-Methyl-3[[[3[4[amino(hydroxyimino)methyl]phenyl]-4,5-dihydro-5-isoxazolyl]acetyl]amino]-N(butoxy-carbonyl)-L-alanine (Batch 1: 10.0 Kg; Batch 2: 10.0 Kg.) A solution of acetic anhydride (Batch 1: 2205 g; Batch 2: 1983 g) in acetic acid (21 Kg) was charged into the reactor slowly over 30 min from a pressure cylinder using nitrogen pressure at rt (22°C). Additional 5.3 Kg of acetic acid was then used to rinse the cylinder. After stirring at 22°C for 30 min or until a clear solution was attained, a small sample was taken for HPLC analysis. After the reaction was complete as determined by HPLC. A slurry of Pd/C (Batch 1: 3%Pd/C, 0.5 Kg; Batch 2: 5%Pd/C, 0.4 Kg) in acetic acid (5 L) was added and the resulting mixture was hydrogenated under 5 psi hydrogen pressure for 4-5 h. After the reaction was complete as determined by HPLC, the catalyst was filtered off and washed with acetic acid (21 Kg) to give a solution of the product. Anisole (80 Kg) was then added to the filtrate and the resulting mixture was concentrated at about 70°C under vacuum (40 mm Hg or lower) in a 100 gal reactor. The distillation was stopped until that the distillate was about 148 L or the solid became

35

visible in the batch. Cooled the reactor to 40°C, 72 Kg of acetone was added over 30-90 min. The slurry was stirred at ambient temperature for 1 h and the 0-5°C for another 1 h. The solid was collected on a Rosenmund filter/dryer and the cake was washed with 10% methanol in acetone (made from 6 Kg of methanol and 57 Kg of acetone). The solid cake was dried until LOD < 1%. A hot (80°C) mixture of acetonitrile (27 Kg) and acetic acid (18 Kg) was charged into the filter to dissolve the cake and the hot solution was then transfer back to 100 gal reactor. The transfer line was washed with a mixture of acetic acid (0.9 Kg) and acetonitrile (1.4 Kg). After the solution was cooled to 40-45°C, acetone (65 Kg) was added within 10 min. The resulting slurry was stirred gently at 25°C for 1 h and then 0-5°C for another 1 h. The solid was filtered by the Rosenmund filter/dryer and the cake was washed with 10% methanol in acetone (prepared from 5.5 Kg methanol and 50 Kg of acetone). After drying the cake until LOD < 0.1%, the product was obtained (Batch 1: 6.3 Kg. Batch 2: 6.8 Kg). Heels from both batches in the Rosenmund filter/dryer were dissolved in acetonitrile and acetic acid and combined, which was crystallized in the Kilo lab to give additional 2.86 Kg of product.

EXAMPLE 3

(R)-methyl-3-[[[3-[4-[(acetyloxyimino)aminomethyl]phenyl]-4,5-dihydro-5-isoxazolyl]acetyl]amino]-N-(butoxycarbonyl)-L-alanine: Compound (IV-i)

To a suspension of (R)-Methyl-3-[[[3-[4-[amino(hydroxyimino)methyl]phenyl]-4,5-dihydro-5-isoxazolyl]acetyl]amino]-N-(butoxycarbonyl)-L-alanine (11.76 g) in acetic acid (50 mL) was added acetic anhydride (3.6 g) dropwise. After the completion of addition, the reaction mixture was stirred at room temperature 15 min. The reaction mass became clear. Ether (200 mL) was added slowly and a thick slurry formed. The resulting mixture was then stirred for another 1.5 h at room temperature and the solid

was filtered. The cake was washed with ether (50 mL) and dried to give (R)-methyl-3-[[[3-[4-[(acetyloxyimino)aminomethyl] phenyl]-4,5-dihydro-5-isoxazolyl]acetyl]amino]-N-(butoxycarbonyl)-L-alanine (12.3 g).

5

EXAMPLE 4

(R)-methyl-N-(butoxycarbonyl)-3-[[[4,5-dihydro-3-[4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-5-isoxazolyl]acetyl] amino]-L-alanine: Compound (V-i)

10

To a suspension of (R)-Methyl-3-[[[3-[4-[amino(hydroxyimino)methyl]phenyl]-4,5-dihydro-5-isoxazolyl]acetyl]amino]-N-(butoxycarbonyl)-L-alanine (1.05 g) in acetic acid (7 mL) was added acetic anhydride (0.35 g) dropwise. After the completion of addition, the reaction mixture was refluxed for 3 h. The solvent was distilled under vacuum and the solid was dried to give (R)-methyl-N-(butoxycarbonyl)-3-[[[4,5-dihydro-3-[4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-5-isoxazolyl]acetyl]amino]-L-alanine (1.05 g).

15

20

EXAMPLE 5

(R)-Methyl-3-[[[3-[4-(aminoiminomethyl)phenyl]-4,5-dihydro-5-isoxazolyl]acetyl]amino]-N-(butoxycarbonyl)-L-alanine monoacetate: Compound (I-i)

25

Method B:

A mixture of (R)-methyl-N-(butoxycarbonyl)-3-[[[4,5-dihydro-3-[4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-5-isoxazolyl]acetyl]amino]-L-alanine (70 mg) and 3%Pd/C (30 mg) in methanol (3 mL) and acetic acid (0.5 mL) was stirred under hydrogen atmosphere for 3 h. The catalyst was filtered off and washed with methanol (4 mL). The combined filtrate and wash was concentrated to small volume. Acetone (2 mL) was added slowly and a slurry was formed. After stirred for 30 min, the solid was filtered and the cake was

30

35

washed with 10% methanol in acetone (4 mL) and dried to give the product (25 mg).

HPLC CONDITIONS

5

Column: Eclipse XDB-C8 4.6 x 250 mm

Mobile Phase: A: 0.1% trifluoroacetic acid/0.1%

triethylamine in HPLC grade water

10

B: tetrahydrofuran (unstabilized-suitable for liquid chromatography)/0.1% trifluoroacetic acid

Gradient: t = 0 min 85% A 15% B

15

t = 10 min 85% A 15% B

t = 32 min 50% A 50% B

t = 40 min 50% A 50% B

Flow Rate: 1.5 mL/min

20

Injection Volume: 10 microliters

Stop Time: 40 minutes

Post Time: 10 minutes

Oven Temp.: 40°C

Detector: UV (280 nm, 230 nm, 260 nm)

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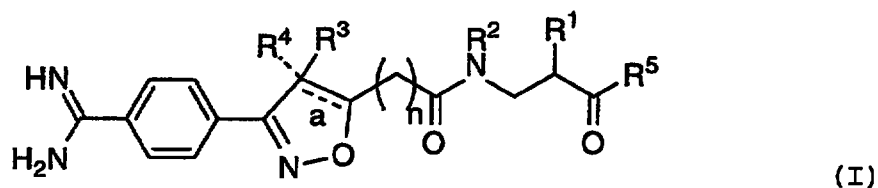
Sample Prep.: Dissolve approximately 0.5 mg of sample (dry solids weight) per mL in 50% tetrahydrofuran 49.9% H₂O/0.1% acetic acid. Filter any undissolved solids through an Acrodisc 0.45 micron Nylon filter.

30

CLAIMS

What is claimed is:

1. A process for the formation of a compound of the
5 formula (I):



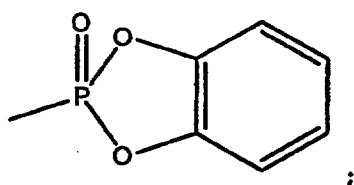
or a pharmaceutically acceptable salt form thereof;
10 wherein:

R¹ is selected from H or NHR^{1a};

R^{1a} is selected from the group consisting of:

- C(=O)-O-R^{1b},
- 15 -C(=O)-R^{1b},
- C(=O)N(R^{1b})₂,
- C(=O)NHSO₂R^{1b},
- C(=O)NHC(=O)R^{1b},
- C(=O)NHC(=O)OR^{1b},
- 20 -C(=O)NHSO₂NHR^{1b},
- C(=S)-NH-R^{1b},
- NH-C(=O)-O-R^{1b},
- NH-C(=O)R^{1b},
- NH-C(=)-NH-R^{1b},
- 25 -SO₂-O-R^{1b},
- SO₂-R^{1b},
- SO₂-N(R^{1b})₂,
- SO₂-NHC(=O)OR^{1b},
- P(=S)(OR^{1b})₂,
- 30 -P(=O)(OR^{1b})₂,
- P(=S)(R^{1b})₂,
- P(=O)(R^{1b})₂, and





R^{1b} is selected from the group consisting of:

- 5 C₁-C₈ alkyl substituted with 0-2 R^{1c},
 C₂-C₈ alkenyl substituted with 0-2 R^{1c},
 C₂-C₈ alkynyl substituted with 0-2 R^{1c},
 C₃-C₈ cycloalkyl substituted with 0-2 R^{1c},
 aryl substituted with 0-4 R^{1c},
 aryl(C₁-C₆ alkyl)-substituted with 0-4 R^{1c},
 10 a 5-10 membered heterocyclic ring system having 1-3
 heteroatoms selected independently from O, S, and
 N, said heterocyclic ring being substituted with
 0-4 R^{1c}, and
 C₁-C₆ alkyl substituted with a 5-10 membered
 15 heterocyclic ring system having 1-3 heteroatoms
 selected independently from O, S, and N, said
 heterocyclic ring being substituted with 0-4R^{1c};
 R^{1c} is H, halogen, CF₃, CN, NO₂, C₁-C₈ alkyl, C₂-C₆ alkenyl,
 C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl,
 20 aryl(C₁-C₆ alkyl)-, C₁-C₆ alkoxy, and C₂-C₅
 alkoxycarbonyl;

R² is selected from H or C₁-C₁₀ alkyl;

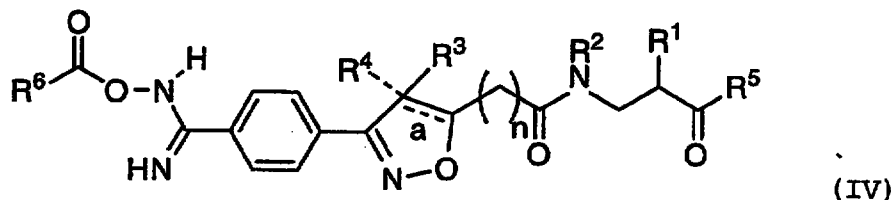
- R³ and R⁴ are independently selected from the group
 consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆
 25 alkynyl, C₃-C₇ cycloalkyl, and aryl substituted with
 0-2 R^{3a};

R^{3a} is selected from the group consisting of C₁-C₄ alkyl,
 C₁-C₄ alkoxy, halo, CF₃, NO₂, and NR^{3b}R^{3c};

- R^{3b} and R^{3c} are each independently selected from the group
 consisting of H, C₁-C₁₀ alkyl, C₂-C₁₀ alkoxycarbonyl,
 30 C₂-C₁₀ alkylcarbonyl, C₁-C₁₀ alkylsulfonyl,
 heteroaryl(C₁-C₄ alkyl)sulfonyl,
 aryl(C₁-C₁₀ alkyl)sulfonyl, arylsulfonyl, aryl,
 heteroarylcarbonyl, heteroarylsulfonyl, and

- heteroarylalkylcarbonyl, wherein said aryl and heteroaryl are optionally substituted with 0-3 R^{3d} ; R^{3d} is selected from the group consisting of C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halo, CF_3 , and NO_2 ;
- 5 R^5 is selected from the group consisting of:
 hydroxy, C_1 - C_{10} alkyloxy, C_3 - C_{11} cycloalkyloxy,
 C_6 - C_{10} aryloxy, C_7 - C_{11} arylalkyloxy,
 C_3 - C_{10} alkylcarbonyloxyalkyloxy,
 C_3 - C_{10} alkoxy carbonyloxyalkyloxy,
 10 C_3 - C_{10} alkoxy carbonylalkyloxy,
 C_5 - C_{10} cycloalkylcarbonyloxyalkyloxy,
 C_5 - C_{10} cycloalkoxy carbonyloxyalkyloxy,
 C_5 - C_{10} cycloalkoxy carbonylalkyloxy,
 C_8 - C_{11} aryloxy carbonylalkyloxy,
 15 C_8 - C_{12} aryloxy carbonyloxyalkyloxy,
 C_8 - C_{12} arylcarbonyloxyalkyloxy,
 C_5 - C_{10} alkoxyalkylcarbonyloxyalkyloxy,
 5-(C_5 - C_{10} alkyl)-1,3-dioxo-cyclopenten-2-one-yl)-
 methyloxy,
 20 (5-aryl-1,3-dioxo-cyclopenten-2-one-yl)-methyloxy, and
 (R^{5a})HN-(C_1 - C_{10} alkoxy)-;
- R^{5a} is selected from the group consisting of H, C_1 - C_4 alkyl,
 aryl(C_1 - C_{10} alkoxy)carbonyl, C_2 - C_{10} alkoxy carbonyl, and
 C_3 - C_6 alkenyl;
- 25 n is 0-4;
 a is a single or double bond, with the proviso that if a is
 a double bond, it is not simultaneously substituted
 with R^3 and R^4 ;
- 30 said process comprising:

contacting a compound of formula (IV):



wherein:

R⁶ is selected from the group consisting of H, CF₃, CF₂CF₃,
CF₂CF₂CF₃, CF₂CF₂CF₂CF₃, C₁-C₈ alkyl, C₁-C₈
5 perfluoroalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₁₁
cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl(C₁-C₆ alkyl)-,
C₁-C₆ alkoxy, C₇-C₁₀ arylalkyloxy, C₁-C₆ alkyloxy,
aryloxy and aryl substituted with 0-5 R^{6c};

10 R^{6c} is selected from the group consisting of H, halo, CF₃,
CN, NO₂, NR^{6d}R^{6e}, C₁-C₈ alkyl, C₂-C₆ alkenyl, C₃-C₁₁
cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl, aryl(C₁-C₆
alkyl)-, C₁-C₆ alkoxy, and C₂-C₅ alkoxycarbonyl;

15 R^{6d} and R^{6e} are independently selected from the group
consisting of H, C₁-C₁₀ alkyl, C₂-C₁₀ alkoxycarbonyl,
C₂-C₁₀ alkylcarbonyl, C₁-C₁₀ alkylsulfonyl, aryl,
20 aryl(C₁-C₁₀ alkyl)sulfonyl, arylsulfonyl,
heteroaryl(C₁-C₄ alkyl)sulfonyl, heteroarylcarbonyl,
heteroarylsulfonyl, or heteroarylalkylcarbonyl, wherein
said aryl and heteroaryl are optionally substituted
with 0-3 substituents selected from the group
consisting of C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, CF₃, and
NO₂;

25 with hydrogen under a suitable pressure in the presence of a
hydrogenation catalyst to form a compound of formula (I) or
a pharmaceutically acceptable salt form thereof.

2. The process of Claim 1, wherein:
said suitable pressure is up to 100 psi, and



30 said hydrogenation catalyst is selected from the group
consisting of palladium on carbon, palladium hydroxide on
carbon, palladium on calcium carbonate and platinum on
carbon.

35 3. The process of Claim 1, wherein:
R¹ is selected from H or NHR^{1a};

R^{1a} is -C(=O)-O-R^{1b} or -SO₂-R^{1b};

R^{1b} is selected from the group consisting of:

- 5 C₁-C₈ alkyl substituted with 0-1 R^{1c},
C₂-C₈ alkenyl substituted with 0-1 R^{1c},
C₂-C₈ alkynyl substituted with 0-1 R^{1c},
C₃-C₈ cycloalkyl substituted with 0-1 R^{1c},
aryl substituted with 0-3 R^{1c},
aryl(C₁-C₆ alkyl)-substituted with 0-3 R^{1c},
a 5-10 membered heterocyclic ring system having 1-3
10 heteroatoms selected independently from O, S, and
N, said heterocyclic ring being substituted with
0-4 R^{1c}, and
C₁-C₆ alkyl substituted with a 5-10 membered
heterocyclic ring system having 1-3 heteroatoms
15 selected independently from O, S, and N, said
heterocyclic ring being substituted with 0-4 R^{1c};
R^{1c} is selected from the group consisting of H, halogen,
CF₃, CN, NO₂, C₁-C₈ alkyl, C₂-C₆ alkenyl, C₃-C₁₁
cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl, aryl(C₁-C₆
20 alkyl)-, C₁-C₆ alkoxy and C₂-C₅ alkoxycarbonyl;
R² is H or C₁-C₁₀ alkyl;
R³ and R⁴ are H or C₁-C₆ alkyl;
R⁵ is selected from the group consisting of hydroxy, C₁-C₁₀
alkyloxy, C₃-C₁₁ cycloalkyloxy, C₆-C₁₀ aryloxy and
25 C₇-C₁₁ arylalkyloxy;
R⁶ is selected from the group consisting of H, C₁-C₆ alkyl,
C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, C₁-C₈
perfluoroalkyl, C₇-C₁₀ arylalkyloxy, C₁-C₆ alkyloxy,
aryloxy, aryl substituted with 0-2 R^{6c};
30 R^{6c} is H, halogen, CF₃, CN, NO₂, NR^{6d}R^{6e}, C₁-C₈ alkyl, C₂-C₆
alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl,
aryl, aryl(C₁-C₆ alkyl)-, C₁-C₆ alkoxy, and C₂-C₅
alkoxycarbonyl; and
R^{6d} and R^{6e} are independently selected from H or C₁-C₁₀
35 alkyl;
n is 1;



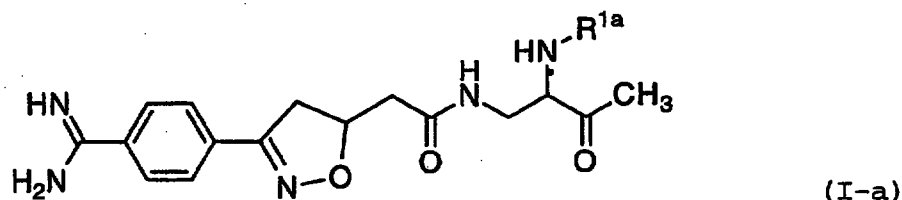
a is a single or double bond, with the proviso that if a is a double bond, it is not simultaneously substituted with R³ and R⁴.

5 4. The process according to Claim 3, wherein:

said suitable pressure is up to 100 psi; and

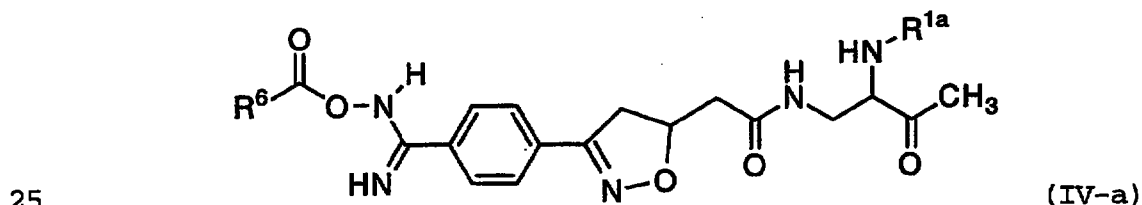
10 said hydrogenation catalyst is selected from the group consisting of palladium on carbon, palladium hydroxide on carbon, palladium on calcium carbonate and platinum on carbon.

15 5. The process of Claim 1 for the preparation of a compound of formula (I-a):



20 or a pharmaceutically acceptable salt form thereof, wherein: R^{1a} is -C(=O)OCH₂(CH₂)₂CH₃ or 3,5-dimethyloxazol-4-yl-sulfonyl;

comprising contacting a compound of formula (IV-a):



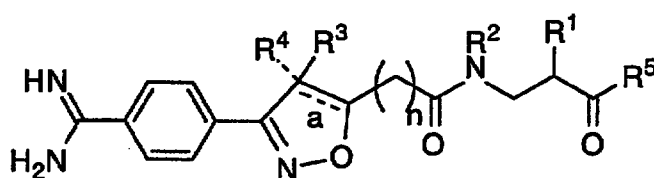
25 wherein R⁶ is H, methyl, ethyl, propyl, butyl, pentyl, hexyl C₇-C₈ arylalkyloxy, C₁-C₅ alkyloxy, aryloxy or aryl;

with hydrogen under a suitable pressure from about 20 to about 50 psi in the presence of palladium on carbon, in the range of about 1% to about 10% by weight of compound (IV), to form a compound of formula (I) or a pharmaceutically acceptable salt form thereof.

6. A process for the formation of a compound of the formula (I):



10



(I)

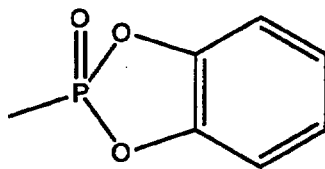
or a pharmaceutically acceptable salt form thereof;
wherein:

15 R^1 is selected from H or NHR^{1a} ;

R^{1a} is selected from the group consisting of:

- C(=O)-O- R^{1b} ,
- C(=O)- R^{1b} ,
- C(=O)N(R^{1b})₂,
- 20 -C(=O)NHSO₂ R^{1b} ,
- C(=O)NHC(=O) R^{1b} ,
- C(=O)NHC(=O)O R^{1b} ,
- C(=O)NHSO₂NH R^{1b} ,
- C(=S)-NH- R^{1b} ,
- 25 -NH-C(=O)-O- R^{1b} ,
- NH-C(=O) R^{1b} ,
- NH-C(=)-NH- R^{1b} ,
- SO₂-O- R^{1b} ,
- SO₂- R^{1b} ,
- 30 -SO₂-N(R^{1b})₂,
- SO₂-NHC(=O)O R^{1b} ,
- P(=S)(O R^{1b})₂,
- P(=O)(O R^{1b})₂,
- P(=S)(R^{1b})₂,

$-P(=O)(R^{1b})_2$, and



- 5 R^{1b} is selected from the group consisting of:
 C_1 - C_8 alkyl substituted with 0-2 R^{1c} ,
 C_2 - C_8 alkenyl substituted with 0-2 R^{1c} ,
 C_2 - C_8 alkynyl substituted with 0-2 R^{1c} ,
 C_3 - C_8 cycloalkyl substituted with 0-2 R^{1c} ,
 10 aryl substituted with 0-4 R^{1c} ,
 aryl(C_1 - C_6 alkyl)-substituted with 0-4 R^{1c} ,
 a 5-10 membered heterocyclic ring system having 1-3
 heteroatoms selected independently from O, S, and
 N, said heterocyclic ring being substituted with
 15 0-4 R^{1c} , and
 C_1 - C_6 alkyl substituted with a 5-10 membered
 heterocyclic ring system having 1-3 heteroatoms
 selected independently from O, S, and N, said
 heterocyclic ring being substituted with 0-4 R^{1c} ;
- 20 R^{1c} is H, halogen, CF_3 , CN, NO_2 , C_1 - C_8 alkyl, C_2 - C_6 alkenyl,
 C_3 - C_{11} cycloalkyl, C_4 - C_{11} cycloalkylalkyl, aryl,
 aryl(C_1 - C_6 alkyl)-, C_1 - C_6 alkoxy, and C_2 - C_5
 alkoxycarbonyl;
- R^2 is selected from H or C_1 - C_{10} alkyl;
- 25 R^3 and R^4 are independently selected from the group
 consisting of H, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6
 alkynyl, C_3 - C_7 cycloalkyl, and aryl substituted with
 0-2 R^{3a} ;
- R^{3a} is selected from the group consisting of C_1 - C_4 alkyl,
 30 C_1 - C_4 alkoxy, halo, CF_3 , NO_2 , and $NR^{3b}R^{3c}$;
- R^{3b} and R^{3c} are each independently selected from the group
 consisting of H, C_1 - C_{10} alkyl, C_2 - C_{10} alkoxycarbonyl,
 C_2 - C_{10} alkylcarbonyl, C_1 - C_{10} alkylsulfonyl,
 heteroaryl(C_1 - C_4 alkyl)sulfonyl,

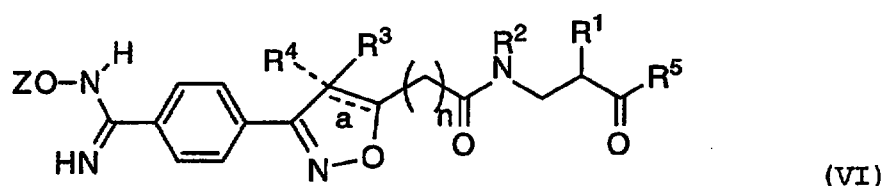
- aryl(C₁-C₁₀ alkyl)sulfonyl, arylsulfonyl, aryl,
heteroarylcarbonyl, heteroarylsulfonyl, and
heteroarylalkylcarbonyl, wherein said aryl and
heteroaryl are optionally substituted with 0-3 R^{3d};
5 R^{3d} is selected from the group consisting of C₁-C₄ alkyl,
C₁-C₄ alkoxy, halo, CF₃, and NO₂;
R⁵ is selected from the group consisting of:
hydroxy, C₁-C₁₀ alkyloxy, C₃-C₁₁ cycloalkyloxy,
C₆-C₁₀ aryloxy, C₇-C₁₁ arylalkyloxy,
10 C₃-C₁₀ alkylcarbonyloxyalkyloxy,
C₃-C₁₀ alkoxy carbonyloxyalkyloxy,
C₃-C₁₀ alkoxy carbonylalkyloxy,
C₅-C₁₀ cycloalkylcarbonyloxyalkyloxy,
C₅-C₁₀ cycloalkoxy carbonyloxyalkyloxy,
15 C₅-C₁₀ cycloalkoxy carbonylalkyloxy,
C₈-C₁₁ aryloxy carbonylalkyloxy,
C₈-C₁₂ aryloxy carbonyloxyalkyloxy,
C₈-C₁₂ arylcarbonyloxyalkyloxy,
C₅-C₁₀ alkoxyalkylcarbonyloxyalkyloxy,
20 5-(C₅-C₁₀ alkyl)-1,3-dioxo-cyclopenten-2-one-yl)-
methyloxy,
(5-aryl-1,3-dioxo-cyclopenten-2-one-yl)-methyloxy, and
(R^{5a})HN-(C₁-C₁₀ alkoxy)-;
R^{5a} is selected from the group consisting of H, C₁-C₄ alkyl,
25 aryl(C₁-C₁₀ alkoxy)carbonyl, C₂-C₁₀ alkoxy carbonyl, and
C₃-C₆ alkenyl;
n is 0-4;
a is a single or double bond, with the proviso that if a is
a double bond, it is not simultaneously substituted
30 with R³ and R⁴;

said process comprising:

contacting a compound of formula (VI):

35





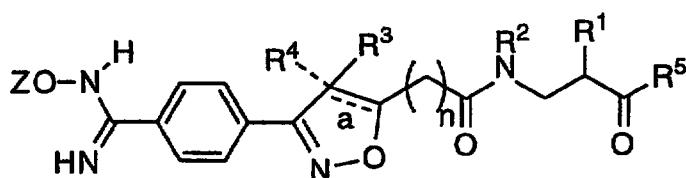
wherein:

Z is selected from R^6SO_2- or $(R^7)_3Si-$;

- 5 R^6 is selected from the group consisting of H, CF_3 , CF_2CF_3 , $CF_2CF_2CF_3$, $CF_2CF_2CF_2CF_3$, C_1-C_8 alkyl, C_1-C_8 perfluoroalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylalkyl, aryl(C_1-C_6 alkyl)-, C_1-C_6 alkoxy, C_7-C_{10} arylalkyloxy, aryloxy and aryl
- 10 substituted with 0-5 R^{6c} ;
- R^{6c} is selected from the group consisting of H, halo, CF_3 , CN, NO_2 , $NR^{6d}R^{6e}$, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylalkyl, aryl, aryl(C_1-C_6 alkyl)-, C_1-C_6 alkoxy, and C_2-C_5 alkoxycarbonyl;
- 15 R^{6d} and R^{6e} are independently selected from the group consisting of H, C_1-C_{10} alkyl, C_2-C_{10} alkoxycarbonyl, C_2-C_{10} alkylcarbonyl, C_1-C_{10} alkylsulfonyl, aryl, aryl(C_1-C_{10} alkyl)sulfonyl, arylsulfonyl, heteroaryl(C_1-C_4 alkyl)sulfonyl, heteroarylcarbonyl,
- 20 heteroarylsulfonyl, or heteroarylalkylcarbonyl, wherein said aryl and heteroaryl are optionally substituted with 0-3 substituents selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, CF_3 , and NO_2 ;
- 25 R^7 is selected independently from C_1-C_{10} alkyl or aryl substituted 0-3 R^{7a} ; and
- R^{7a} is C_1-C_{10} alkyl;

- 30 with hydrogen under a suitable pressure in the presence of a hydrogenation catalyst to form a compound of formula (I) or a pharmaceutically acceptable salt form thereof.

7. The process of Claim 6, wherein the compound of formula (VI):

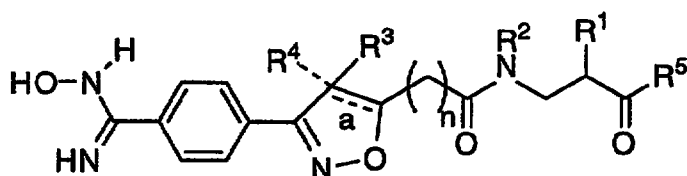
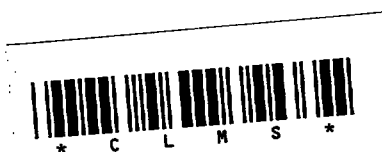


(VI)

or a salt thereof is prepared by a process comprising:

5

contacting a compound of formula (III):



(III)

10 with an agent of formula Z-X, wherein:

X is fluorine, bromine or chlorine;

Z is R^6SO_2- or $(R^7)_3Si-$;

R^7 is selected independently from C_1 - C_{10} alkyl or aryl substituted 0-3 R^{7a} ; and

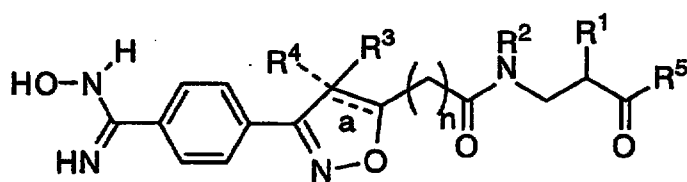
15 R^{7a} is C_1 - C_{10} alkyl;

in the presence of a suitable acid scavenger in a suitable solvent to form a compound of formula (IV) or a salt thereof.

20

8. The process of Claim 1, wherein the compound of formula (IV) or a salt thereof is prepared by a process comprising:

25 contacting a compound of formula (III):



(III)

with an acylating agent of formula $R^6CO-O-COR^6$ or R^6COX , wherein X is fluorine, bromine, chlorine or imidazole, in a suitable solvent to form a compound of formula (IV) or a salt thereof.

5

9. The process according to Claim 8, wherein:

R^1 is selected from H or NHR^{1a} ;

R^{1a} is $-C(=O)-O-R^{1b}$ or $-SO_2-R^{1b}$;

R^{1b} is selected from the group consisting of:

- 10 C_1-C_8 alkyl substituted with 0-1 R^{1c} ,
 C_2-C_8 alkenyl substituted with 0-1 R^{1c} ,
 C_2-C_8 alkynyl substituted with 0-1 R^{1c} ,
 C_3-C_8 cycloalkyl substituted with 0-1 R^{1c} ,
aryl substituted with 0-3 R^{1c} ,
15 aryl(C_1-C_6 alkyl)-substituted with 0-3 R^{1c} ,
a 5-10 membered heterocyclic ring system having 1-3
heteroatoms selected independently from O, S, and
N, said heterocyclic ring being substituted with
0-4 R^{1c} , and
20 C_1-C_6 alkyl substituted with a 5-10 membered
heterocyclic ring system having 1-3 heteroatoms
selected independently from O, S, and N, said
heterocyclic ring being substituted with 0-4 R^{1c} ;
 R^{1c} is H, halogen, CF_3 , CN, NO_2 , C_1-C_8 alkyl, C_2-C_6 alkenyl,
25 C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylalkyl, aryl,
aryl(C_1-C_6 alkyl)-, C_1-C_6 alkoxy and C_2-C_5
alkoxycarbonyl;
 R^2 is selected from H or C_1-C_{10} alkyl;
 R^3 and R^4 are H or C_1-C_6 alkyl;
30 R^5 is selected from the group consisting of hydroxy, C_1-C_{10}
alkyloxy, C_3-C_{11} cycloalkyloxy, C_6-C_{10} aryloxy and C_7-
 C_{11} arylalkyloxy;
 R^6 is selected from the group consisting of H, CF_3 , CF_2CF_3 ,
 $CF_2CF_2CF_3$, $CF_2CF_2CF_2CF_2$, C_1-C_8 alkyl, C_1-C_8
35 perfluoroalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{11}
cycloalkyl, C_4-C_{11} cycloalkylalkyl, aryl(C_1-C_6 alkyl)-,



C₁-C₆ alkoxy, C₇-C₁₀ arylalkyloxy, aryloxy and aryl substituted with 0-5 R^{6c};

R^{6c} is selected from the group consisting of H, halo, CF₃, CN, NO₂, NR^{6d}R^{6e}, C₁-C₈ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl, aryl(C₁-C₆ alkyl)-, C₁-C₆ alkoxy, and C₂-C₅ alkoxycarbonyl;

R^{6d} and R^{6e} are independently selected from the group consisting of H, C₁-C₁₀ alkyl, C₂-C₁₀ alkoxycarbonyl, C₂-C₁₀ alkylcarbonyl, C₁-C₁₀ alkylsulfonyl, aryl, aryl(C₁-C₁₀ alkyl)sulfonyl, arylsulfonyl, heteroaryl(C₁-C₄ alkyl)sulfonyl, heteroarylcarbonyl, heteroarylsulfonyl, or heteroarylalkylcarbonyl, wherein said aryl and heteroaryl are optionally substituted with 0-3 substituents selected from the group consisting of C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, CF₃, and NO₂;

n is 1;

a is a single or double bond, with the proviso that if a is a double bond, it is not simultaneously substituted with R³ and R⁴; and

X is chlorine.

10. The process of Claim 8, wherein:

X is chlorine;

R⁶ is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, C₁-C₈ perfluoroalkyl, C₇-C₁₀ arylalkyloxy, C₁-C₆ alkyloxy, aryloxy, aryl substituted with 0-2 R^{6c};

R^{6c} is H, halogen, CF₃, CN, NO₂, NR^{6d}R^{6e}, C₁-C₈ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl, aryl(C₁-C₆ alkyl)-, C₁-C₆ alkoxy, and C₂-C₅ alkoxycarbonyl, and

R^{6d} and R^{6e} are independently selected from H, C₁-C₁₀ alkyl and aryl.

11. The process of Claim 8, wherein:



X is chlorine;

R¹ is NHR^{1a};

R^{1a} is -C(=O)OCH₂(CH₂)₂CH₃ or 3,5-dimethyloxazol-4-yl-sulfonyl;

5 R^2 is H;

R^3 and R^4 are H;

R⁵ is methyl;

R^6 is CH_3 ;

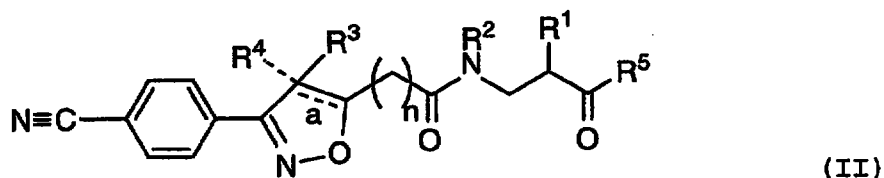
n is 1;

10 a is a single bond; and

said suitable solvent is acetic acid.

12. The process of Claim 8, wherein the compound of
15 formula (III) is prepared by a process comprising:

contacting a compound of formula (II):



20

with a salt of hydroxyl amine in the presence of a suitable base to form a compound of formula (III).

13. The process of Claim 12, wherein said salt of
25 hydroxyl amine is hydroxylamine hydrochloride.

14. The process of Claim 12, wherein:

X is chlorine;

R¹ is selected from H or NHR^{1a};

30 R^{1a} is -C(=O)-O-R^{1b} or -SO₂-R^{1b};

R^{1b} is selected from the group consisting of:

C₁-C₈ alkyl substituted with 0-1R¹C,

C₂-C₈ alkenyl substituted with 0-1R^{1c},

C₂-C₈ alkynyl substituted with 0-1R^{1c},

C₃-C₈ cycloalkyl substituted with 0-1R^{1c},
aryl substituted with 0-3R^{1c},
aryl(C₁-C₆ alkyl)-substituted with 0-3R^{1c},
a 5-10 membered heterocyclic ring system having 1-3
5 heteroatoms selected independently from O, S, and
N, said heterocyclic ring being substituted with 0-
4 R^{1c}, and
C₁-C₆ alkyl substituted with a 5-10 membered
heterocyclic ring system having 1-3 heteroatoms
10 selected independently from O, S, and N, said
heterocyclic ring being substituted with 0-4R^{1c};
R^{1c} is selected from the group consisting of H, halogen,
CF₃, CN, NO₂, C₁-C₈ alkyl C₂-C₆ alkenyl, C₃-C₁₁
cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl, aryl(C₁-C₆
15 alkyl)-, C₁-C₆ alkoxy and C₂-C₅ alkoxycarbonyl;
R² is selected from H or C₁-C₁₀ alkyl;
R³ and R⁴ are H or C₁-C₆ alkyl,
R⁵ is selected from the group consisting of hydroxy, C₁-C₁₀
alkyloxy, C₃-C₁₁ cycloalkyloxy, C₆-C₁₀ aryloxy and
20 C₇-C₁₁ arylalkyloxy;
n is 1;
a is a single or double bond, with the proviso that if a is
a double bond, it is not simultaneously substituted
with R³ and R⁴.

25

15. The process according to Claim 12, wherein:

R¹ is selected from H or NHR^{1a};
R^{1a} is -C(=O)-O-R^{1b} or -SO₂-R^{1b};
R^{1b} is selected from the group consisting of:
30 C₁-C₈ alkyl substituted with 0-1R^{1c},
C₂-C₈ alkenyl substituted with 0-1R^{1c},
C₂-C₈ alkynyl substituted with 0-1R^{1c},
C₃-C₈ cycloalkyl substituted with 0-1R^{1c},
aryl substituted with 0-3R^{1c},
35 aryl(C₁-C₆ alkyl)-substituted with 0-3R^{1c},
a 5-10 membered heterocyclic ring system having 1-3,
heteroatoms selected independently from O, S, and



N, said heterocyclic ring being substituted with 0-4 R^{1C}, and
C₁-C₆ alkyl substituted with a 5-10 membered
heterocyclic ring system having 1-3 heteroatoms
5 selected independently from O, S, and N, said
heterocyclic ring being substituted with 0-4 R^{1C};
R^{1C} is selected from the group consisting of H, halogen,
CF₃, CN, NO₂, C₁-C₈ alkyl C₂-C₆ alkenyl, C₃-C₁₁
cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl, aryl(C₁-C₆
10 alkyl)-, C₁-C₆ alkoxy and C₂-C₅ alkoxy carbonyl;
R² is selected from H or C₁-C₁₀ alkyl;
R³ and R⁴ are independently selected from H, methyl, ethyl,
propyl, butyl, pentyl or hexyl;
R⁵ is selected from the group consisting of hydroxy, C₁-C₁₀
15 alkyloxy, C₃-C₁₁ cycloalkyloxy, C₆-C₁₀ aryloxy and
C₇-C₁₁ arylalkyloxy;
n is 1;
a is a single or double bond, with the proviso that if a is
a double bond, it is not simultaneously substituted
20 with R³ and R⁴, and

said salt of hydroxyl amine is hydroxylamine hydrochloride
or hydroxylamine sulfate.

25 16. The process of Claim 12, wherein:

X is chlorine;

R¹ is NHR^{1a};

R^{1a} is -C(=O)-O-CH₂(CH₂)₂CH₃ or 3,5-dimethyloxazol-4yl-
sulfonyl;

30 R² is H;

R³ and R⁴ are H;

R⁵ is methyl;

R⁶ is selected from the group consisting of:

H, C₁-C₆ alkyl, C₇-C₈ arylalkyloxy, C₁-C₅ alkyloxy,
35 aryloxy and aryl;
n is 1;
a is a single bond;



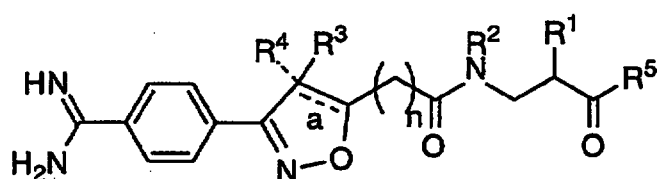
said suitable salt of hydroxylamine is hydroxlyamine hydrochloride; and

the suitable base is selected from the group consisting of:
 5 triethylamine, diisopropylethylamine and 4-methylmorpholine.

17. A process for the preparation of compound (I)



10



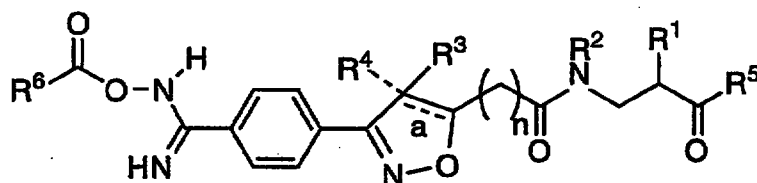
(I)

or a pharmaceutically acceptable salt form thereof,

said process comprising:

15

(a) heating a compound of the formula (IV):



(IV)

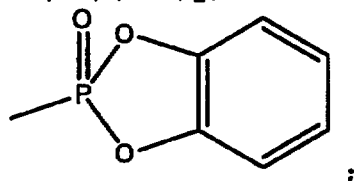
wherein:

20 R¹ is selected from H or NHR^{1a};

R^{1a} is selected from the group consisting of:

- C(=O)-O-R^{1b},
- C(=O)-R^{1b},
- C(=O)N(R^{1b})₂,
- 25 -C(=O)NHSO₂R^{1b},
- C(=O)NHC(=O)R^{1b},
- C(=O)NHC(=O)OR^{1b},
- C(=O)NHSO₂NHR^{1b},
- C(=S)-NH-R^{1b},
- 30 -NH-C(=O)-O-R^{1b},
- NH-C(=O)R^{1b},

$-\text{NH}-\text{C}(=\text{O})-\text{NH}-\text{R}^{1b}$,
 $-\text{SO}_2-\text{O}-\text{R}^{1b}$,
 $-\text{SO}_2-\text{R}^{1b}$,
 $-\text{SO}_2-\text{N}(\text{R}^{1b})_2$,
 $-\text{SO}_2-\text{NHC}(=\text{O})\text{OR}^{1b}$,
 $-\text{P}(=\text{S})(\text{OR}^{1b})_2$,
 $-\text{P}(=\text{O})(\text{OR}^{1b})_2$,
 $-\text{P}(=\text{S})(\text{R}^{1b})_2$,
 $-\text{P}(=\text{O})(\text{R}^{1b})_2$, and



R^{1b} is selected from the group consisting of:

C_1-C_8 alkyl substituted with 0-2 R^{1c} ,
 C_2-C_8 alkenyl substituted with 0-2 R^{1c} ,
 C_2-C_8 alkynyl substituted with 0-2 R^{1c} ,
 C_3-C_8 cycloalkyl substituted with 0-2 R^{1c} ,
 aryl substituted with 0-4 R^{1c} ,
 aryl(C_1-C_6 alkyl)-substituted with 0-4 R^{1c} ,
 a 5-10 membered heterocyclic ring system having 1-3

heteroatoms selected independently from O, S, and
 N, said heterocyclic ring being substituted with
 0-4 R^{1c} , and

C_1-C_6 alkyl substituted with a 5-10 membered
 heterocyclic ring system having 1-3 heteroatoms
 selected independently from O, S, and N, said
 heterocyclic ring being substituted with 0-4 R^{1c} ;

R^{1c} is H, halogen, CF_3 , CN, NO_2 , C_1-C_8 alkyl, C_2-C_6 alkenyl,
 C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylalkyl, aryl,
 aryl(C_1-C_6 alkyl)-, C_1-C_6 alkoxy, and C_2-C_5
 alkoxycarbonyl;

R^2 is selected from H or C_1-C_{10} alkyl;

R^3 and R^4 are independently selected from the group
 consisting of H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6

alkynyl, C₃-C₇ cycloalkyl, and aryl substituted with 0-2 R^{3a};

R^{3a} is selected from the group consisting of C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, CF₃, NO₂, and NR^{3b}R^{3c};

5 R^{3b} and R^{3c} are each independently selected from the group consisting of H, C₁-C₁₀ alkyl, C₂-C₁₀ alkoxycarbonyl, C₂-C₁₀ alkylcarbonyl, C₁-C₁₀ alkylsulfonyl, heteroaryl(C₁-C₄ alkyl)sulfonyl,

10 aryl(C₁-C₁₀ alkyl)sulfonyl, arylsulfonyl, aryl, heteroarylcarbonyl, heteroarylsulfonyl, and heteroarylalkylcarbonyl, wherein said aryl and heteroaryl are optionally substituted with 0-3 R^{3d};

R^{3d} is selected from the group consisting of C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, CF₃, and NO₂;

15 R⁵ is selected from the group consisting of:

hydroxy, C₁-C₁₀ alkyloxy, C₃-C₁₁ cycloalkyloxy,

C₆-C₁₀ aryloxy, C₇-C₁₁ arylalkyloxy,

C₃-C₁₀ alkylcarbonyloxyalkyloxy,

C₃-C₁₀ alkoxycarbonyloxyalkyloxy,

20 C₃-C₁₀ alkoxycarbonylalkyloxy,

C₅-C₁₀ cycloalkylcarbonyloxyalkyloxy,

C₅-C₁₀ cycloalkoxycarbonyloxyalkyloxy,

C₅-C₁₀ cycloalkoxycarbonylalkyloxy,

C₈-C₁₁ aryloxy carbonylalkyloxy,

25 C₈-C₁₂ aryloxy carbonyloxyalkyloxy,

C₈-C₁₂ arylcarbonyloxyalkyloxy,

C₅-C₁₀ alkoxyalkylcarbonyloxyalkyloxy,

5-(C₅-C₁₀ alkyl)-1,3-dioxo-cyclopenten-2-one-yl)-methyloxy,

30 (5-aryl-1,3-dioxo-cyclopenten-2-one-yl)-methyloxy, and (R^{5a})HN-(C₁-C₁₀ alkoxy)-;

R^{5a} is selected from the group consisting of H, C₁-C₄ alkyl, aryl(C₁-C₁₀ alkoxy)carbonyl, C₂-C₁₀ alkoxycarbonyl, and C₃-C₆ alkenyl;

35 R⁶ is selected from the group consisting of H, CF₃, CF₂CF₃, CF₂CF₂CF₃, CF₂CF₂CF₂CF₃, C₁-C₈ alkyl, C₁-C₈ perfluoroalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₁₁



cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl(C₁-C₆ alkyl)-, C₁-C₆ alkoxy, C₇-C₁₀ arylalkyloxy, aryloxy and aryl substituted with 0-5 R^{6c};

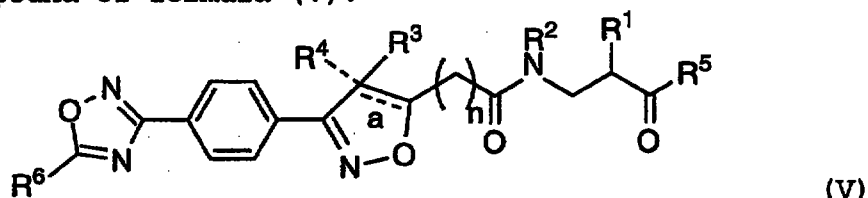
R^{6c} is selected from the group consisting of H, halo, CF₃, CN, NO₂, NR^{6d}R^{6e}, C₁-C₈ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl, aryl(C₁-C₆ alkyl)-, C₁-C₆ alkoxy, and C₂-C₅ alkoxycarbonyl;

R^{6d} and R^{6e} are independently selected from the group consisting of H, C₁-C₁₀ alkyl, C₂-C₁₀ alkoxycarbonyl, C₂-C₁₀ alkylcarbonyl, C₁-C₁₀ alkylsulfonyl, aryl, aryl(C₁-C₁₀ alkyl)sulfonyl, arylsulfonyl, heteroaryl(C₁-C₄ alkyl)sulfonyl, heteroarylcarbonyl, heteroarylsulfonyl, or heteroarylalkylcarbonyl, wherein said aryl and heteroaryl are optionally substituted with 0-3 substituents selected from the group consisting of C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, CF₃, and NO₂;

n is 0-4;

a is a single or double bond, with the proviso that if a is a double bond, it is not simultaneously substituted with R³ and R⁴;

for a time sufficient, and to a temperature sufficient to form a compound of formula (V):



and (b) contacting said compound of formula (V) with hydrogen under a suitable pressure in the presence of a hydrogenation catalyst to form a compound of formula (I) or a salt thereof.

18. The process of Claim 17, wherein:
said suitable pressure is up to 100 psi;



said hydrogenation catalyst is selected from the group consisting of palladium on carbon, palladium hydroxide on carbon, palladium on calcium carbonate and platinum on carbon;

5

said sufficient temperature is from about 30°C to about 120°C;

said sufficient time is from about 10 minutes to about 24
10 hours;

wherein an amount of catalyst loaded on carbon is from about 1% to about 10% by weight; and

15 wherein an amount of a hydrogenation catalyst is from about 1% to about 30% by weight of compound (IV).

19. The process of Claim 17, wherein:

R¹ is selected from H or NHR^{1a};

20 R^{1a} is -C(=O)-O-R^{1b} or -SO₂-R^{1b};

R^{1b} is selected from the group consisting of:

C₁-C₈ alkyl substituted with 0-1 R^{1c},

C₂-C₈ alkenyl substituted with 0-1 R^{1c},

C₂-C₈ alkynyl substituted with 0-1 R^{1c},

25 C₃-C₈ cycloalkyl substituted with 0-1 R^{1c},

aryl substituted with 0-3 R^{1c},

aryl(C₁-C₆ alkyl)-substituted with 0-3 R^{1c},

a 5-10 membered heterocyclic ring system having 1-3

30 heteroatoms selected independently from O, S, and N, said heterocyclic ring being substituted with 0-4 R^{1c}, and

C₁-C₆ alkyl substituted with a 5-10 membered

heterocyclic ring system having 1-3 heteroatoms

selected independently from O, S, and N, said

35 heterocyclic ring being substituted with 0-4 R^{1c};

R^{1c} is selected from the group consisting of H, halogen,

CF₃, CN, NO₂, C₁-C₈ alkyl, C₂-C₆ alkenyl, C₃-C₁₁



- cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl, aryl(C₁-C₆ alkyl)-, C₁-C₆ alkoxy and C₂-C₅ alkoxycarbonyl;
 R² is H or C₁-C₁₀ alkyl;
 R³ and R⁴ are independently selected from H, methyl, ethyl,
 5 propyl, butyl, pentyl or hexyl;
 R⁵ is selected from the group consisting of hydroxy, C₁-C₁₀ alkyloxy, C₃-C₁₁ cycloalkyloxy, C₆-C₁₀ aryloxy and C₇-C₁₁ arylalkyloxy;
 R⁶ is selected from the group consisting of H, C₁-C₆ alkyl,
 10 C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, C₁-C₈ perfluoroalkyl, C₇-C₁₀ arylalkyloxy, C₁-C₆ alkoxy, aryloxy, and aryl substituted with 0-2 R^{6c};
 R^{6c} is H, halogen, CF₃, CN, NO₂, NR^{6d}R^{6e}, C₁-C₈ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl,
 15 aryl, aryl(C₁-C₆ alkyl)-, C₁-C₆ alkoxy, and C₂-C₅ alkoxycarbonyl; and
 R^{6d} and R^{6e} are independently selected from H or C₁-C₁₀ alkyl;
 n is 1; and
 20 a is a single or double bond, with the proviso that if a is a double bond, it is not simultaneously substituted with R³ and R⁴.

20. The process of Claim 17, wherein:

- 25 R¹ is selected from H or NHR^{1a};
 R^{1a} is -C(=O)-O-R^{1b} or -SO₂-R^{1b};
 R^{1b} is selected from the group consisting of:
 C₁-C₈ alkyl substituted with 0-1 R^{1c},
 C₂-C₈ alkenyl substituted with 0-1 R^{1c},
 30 C₂-C₈ alkynyl substituted with 0-1 R^{1c},
 C₃-C₈ cycloalkyl substituted with 0-1 R^{1c},
 aryl substituted with 0-3 R^{1c},
 aryl(C₁-C₆ alkyl)-substituted with 0-3 R^{1c},
 a 5-10 membered heterocyclic ring system having 1-3
 35 heteroatoms selected independently from O, S, and N, said heterocyclic ring being substituted with 0-4 R^{1c}, and



- C₁-C₆ alkyl substituted with a 5-10 membered heterocyclic ring system having 1-3 heteroatoms selected independently from O, S, and N, said heterocyclic ring being substituted with 0-4 R^{1c};
- 5 R^{1c} is selected from the group consisting of H, halogen, CF₃, CN, NO₂, C₁-C₈ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl, aryl(C₁-C₆ alkyl)-, C₁-C₆ alkoxy and C₂-C₅ alkoxycarbonyl;
- R² is H or C₁-C₁₀ alkyl;
- 10 R³ and R⁴ are independently selected from H, methyl, ethyl, propyl, butyl, pentyl or hexyl;
- R⁵ is selected from the group consisting of hydroxy, C₁-C₁₀ alkyloxy, C₃-C₁₁ cycloalkyloxy, C₆-C₁₀ aryloxy and C₇-C₁₁ arylalkyloxy;
- 15 R⁶ is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, C₁-C₈ perfluoroalkyl, C₇-C₁₀ arylalkyloxy, C₁-C₆ alkoxy, aryloxy and aryl substituted with 0-2 R^{6c};
- R^{6c} is H, halogen, CF₃, CN, NO₂, NR^{6d}R^{6e}, C₁-C₈ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl, aryl(C₁-C₆ alkyl)-, C₁-C₆ alkoxy, and C₂-C₅ alkoxycarbonyl; and
- 20 R^{6d} and R^{6e} are independently selected from H or C₁-C₁₀ alkyl;
- 25 n is 1;
- a is a single or double bond, with the proviso that if a is a double bond, it is not simultaneously substituted with R³ and R⁴;

- 30 said suitable pressure is up to 100 psi;



- said hydrogenation catalyst is selected from the group consisting of palladium on carbon, palladium hydroxide on carbon, palladium on calcium carbonate and platinum on
- 35 carbon;

said sufficient temperature is from about 50°C to about 120°C;

said sufficient time is from about 10 minutes to about 3
5 hours;

wherein an amount of catalyst loaded on carbon is from about 3% to about 5% by weight; and

10 wherein an amount of a hydrogenation catalyst is from about 3% to about 7% by weight of compound (IV).

21. The process of Claim 17, wherein:

R¹ is NHR^{1a};

15 R^{1a} is -C(=O)-O-CH₂(CH₂)₂CH₃ or 3,5-dimethyloxazol-4yl-sulfonyl;

R² is H;

R³ and R⁴ are H;

R⁵ is methyl;

20 R⁶ is selected from the group consisting of:

H, methyl, ethyl, propyl, butyl, pentyl, hexyl, C₇-C₈ arylalkyloxy, aryloxy, C₁-C₅ alkoxy and aryl;

n is 1, and

a is a single bond;

25

said suitable pressure is from about 20 to about 50 psi;

said sufficient temperature is from about 50°C to about 120°C;

30

said sufficient time is from about 10 minutes to about 3 hours;

said hydrogenation catalyst is palladium on carbon;

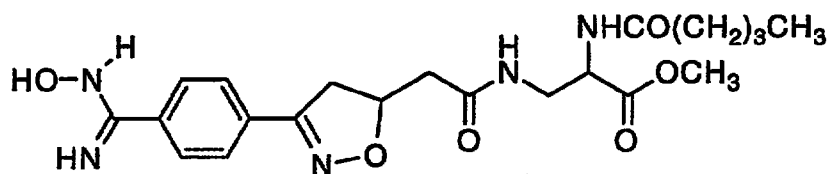
35

wherein an amount of catalyst loaded on carbon is from about 3% to about 5% by weight; and



wherein an amount of palladium on carbon is from about 3% to about 7% by weight of compound (IV).

- 5 22. A compound of the formula:

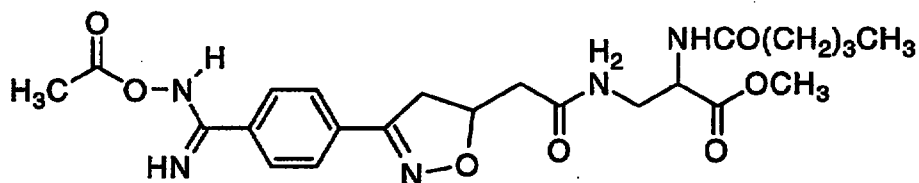


(III-i)

and salt forms thereof.

10

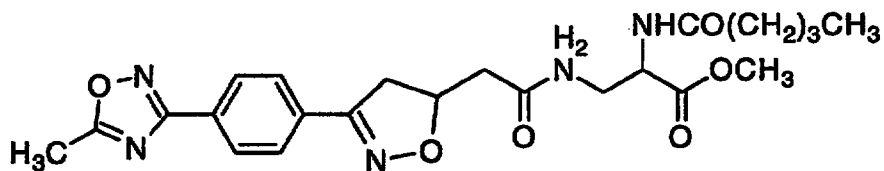
23. A compound of the formula:



(IV-i)

15 and salt forms thereof.

24. A compound of the formula:



(V-i)

20

and salt forms thereof.