Title: SUBSTITUTED PYRROLIDINONES AS INHIBITORS OF 11-BETA-HYDROX YSTEROID DEHYDROGENASE 1

Abstract: The present invention discloses novel compounds of Formula I: (1) possessing 11\textbeta\text{-HSD type 1 antagonist activity, as well as methods for preparing such compounds. In another embodiment, the invention discloses pharmaceutical compositions comprising compounds of Formula I, as well as methods of using the compounds and compositions to treat diabetes, hyperglycemia, obesity, hypertension, hyperlipidemia, metabolic syndrome, cognitive disorders, and other conditions associated with 11\textbeta\text{-HSD type 1 activity.
This application claims the benefit of U.S. Provisional Application No. 60/745,467 filed April 24, 2006.

This invention relates to compounds that are inhibitors of 11-β-hydroxysteroid dehydrogenase type 1 ("11-β-HSD1"), and to pharmaceutical compositions thereof, and the uses of these compounds and compositions in the treatment of the human or animal body, and to novel intermediates useful in preparation of the inhibitors. The present compounds show potent and selective inhibition of 11-β-HSD1, and as such are useful in the treatment of disorders responsive to the modulation of 11-β-HSD1, such as diabetes, metabolic syndrome, cognitive disorders, and the like.

Glucocorticoids acting in the liver, adipose tissue, and muscle, are important regulators of glucose, lipid, and protein metabolism. Chronic glucocorticoid excess is associated with insulin resistance, visceral obesity, hypertension, and dyslipidemia, which also represent the classical hallmarks of metabolic syndrome. 11-β-HSD1 catalyses the conversion of inactive cortisone to active Cortisol, and has been implicated in the development of metabolic syndrome. Evidence in rodents and humans links 11-β-HSD1 to metabolic syndrome. Evidence suggests that a drug which specifically inhibits 11-β-HSD1 in type 2 diabetic patients will lower blood glucose by reducing hepatic gluconeogenesis, reduce central obesity, improve atherogenic lipoprotein phenotypes, lower blood pressure, and reduce insulin resistance. Insulin effects in muscle will be enhanced, and insulin secretion from the beta cells of the islet may also be increased. Evidence from animal and human studies also indicates that an excess of glucocorticoids impair cognitive function. Recent results indicate that inactivation of 11-β-HSD1 enhances memory function in both men and mice. The 11-β-HSD inhibitor carbenoxolone was shown to improve cognitive function in healthy elderly men and type 2 diabetics, and inactivation of the 11-β-HSD1 gene prevented aging-induced impairment in mice. Selective inhibition of 11-β-HSD1 with a pharmaceutical agent has recently been shown to improve memory retention in mice.

A number of publications have appeared in recent years reporting agents that inhibit 11-β-HSD1. See International Application WO2004/056744 which discloses adamantyl acetamides as inhibitors of 11-β-HSD, International Application
WO2005/108360 which discloses pyrrolidin-2-one and piperidin-2-one derivatives as inhibitors of 11-β-HSD, and International Application WO2005/108361 which discloses adamantyl pyrrolidin-2-one derivatives as inhibitors of 11-β-HSD. In spite of the number of treatments for diseases that involve 11-β-HSD, the current therapies suffer from one or more inadequacies, including poor or incomplete efficacy, unacceptable side effects, and contraindications for certain patient populations. Thus, there remains a need for an improved treatment using alternative or improved pharmaceutical agents that inhibit 11-β-HSD and treat the diseases that could benefit from 11-β-HSD inhibition. The present invention provides such a contribution to the art based on the finding that a novel class of compounds has a potent and selective inhibitory activity on 11-β-HSD. The present invention is distinct in the particular structures and their activities. There is a continuing need for new methods of treating diabetes, metabolic syndrome, and cognitive disorders, and it is an object of this invention to meet these and other needs.

The present invention provides a compound structurally represented by formula I:

\[ \text{Formula I} \]

or a pharmaceutically acceptable salt thereof, wherein

\( R^{1a} \) is -halogen;
\( R^{1b} \) is -H or -halogen;
\( R^2 \) is

- H, -halogen, -CH\(_3\) (optionally substituted with 1 to 3 halogens), or -O-CH\(_3\) (optionally substituted with 1 to 3 halogens);
\( R^3 \) is

- halogen, -CH\(_3\) (optionally substituted with 1 to 3 halogens), or -O-CH\(_3\) (optionally substituted with 1 to 3 halogens);
\( R^4 \) is -H or -halogen;
\( R^5 \) is
wherein the dashed line represents the point of attachment to the R₅ position in formula I;

wherein n is 0, 1, or 2, and wherein when n is 0, then "(CH₂)ₙ" is a bond;

wherein m is 1 or 2;

R₆ is

- H, -(C₆H₅)alkyl(optionally substituted with 1 to 3 halogens), -(C₆H₅)alkyl-O-R²⁰, -(C₆H₅)alkyl-pyrrolidinyl, phenyl, -HET¹, -HET², -CH₂-phenyl, -CH₂-HET¹, -CH₂-HET²,
-(C₆H₅)alkyl-N(R²⁰)(R²⁰), -(C₆H₅)alkyl-N⁺(O')(CH₃)₂,
-(C₆H₅)alkyl-C(O)N(R₄¹)(R₄¹), -CH(C(O)OH)(CH₂OR²⁰),
-CH(C(O)OH)(CH₂N(R²⁰)(R²⁰)), -(C₆H₅)alkyl-C(O)O-R²⁰,
HET$^1$ is

HET$^2$ is
R$^7$ is
-H, -(Ci-C$_3$)alkyl(optionally substituted with 1 to 3 halogens), or
-(Ci-C$_3$)alkyl-O-R$_{20}$.

R$^8$ is
5 -H, -OH, -(Ci-C6)alkyl(optionally substituted with 1 to 3 halogens),
-(C$_2$-C$_3$)alkyl-O-R$_{20}$, -(O)(Ci-C$_6$)alkyl(optionally substituted with 1 to 3 halogens),
-C(O)-(Ci-C$_3$)alkyl or -(Ci-C$_3$)alkyl-O-C(O)-(Ci-C$_6$)alkyl,
-S(O$_2$)-(Ci-C$_6$)alkyl,
-S(O$_2$)-(Ci-C$_3$)alkyl(optionally substituted with 1 to 3 halogens) or
-C(O)-N(R$_{20}$)(R$_{20}$);

R$^9$ is
-H, -halogen, -CH$_3$ (optionally substituted with 1 to 3 halogens), or
-0-CH$_3$ (optionally substituted with 1 to 3 halogens);

R$^{10}$ is independently at each occurrence -H, or -halogen;

R$^{20}$ is independently at each occurrence -H, or -(Ci-C$_3$)alkyl(optionally substituted with 1 to 3 halogens);

R$^{21}$ is independently at each occurrence -H, -halogen, or -(Ci-C$_3$)alkyl;

R$^{22}$ is independently at each occurrence -H or -(Ci-C6)alkyl(optionally substituted with 1 to 3 halogens);

R$^{23}$ is independently at each occurrence -H, -(Ci-C$_3$)alkyl, or -C(O)(Ci-C$_6$)alkyl;

R$^{24}$ is independently at each occurrence -H, -halogen, or -(Ci-C$_3$)alkyl(optionally substituted with 1 to 3 halogens);

R$^{31}$ is independently at each occurrence -H, -halogen, or -(Ci-C$_3$)alkyl; and

R$^{41}$ is independently at each occurrence -H, or -CH$_3$.

The present invention provides compounds of formula I that are useful as potent and selective inhibition of 11-β-HSDL. The present invention further provides a pharmaceutical composition which comprises a compound of Formula I, or a pharmaceutical salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient. In addition, the present invention provides a method for the treatment of metabolic syndrome, and related disorders, which comprise administering to a patient in need thereof an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.
In one embodiment, the present invention provides compounds of Formula I or a pharmaceutically acceptable salt thereof as described in detail above. While all of the compounds of the present invention are useful, certain of the compounds are particularly interesting and are preferred. The following listings set out several groups of preferred compounds.

In another embodiment the invention provides a compound structurally represented by formula I, or a pharmaceutically acceptable salt thereof, wherein $R_{1a}$ is -halogen; $R_{1b}$ is -H or -halogen; $R_{2}$ is -halogen; $R_{3}$ is -halogen; $R_{4}$ is -H or -halogen; $R_{5}$ is
or herein the dashed line represents the point of attachment to the R⁵ position in formula I;

R⁶ is
-H, -(C₅-C₇)alkyl optionally substituted with 1 to 3 halogens,
-(C₁-C₃)alkyl-O-R²⁰, -(C₁-C₃)alkyl-pyrrolidinyl,
-(C₁-C₃)alkyl-N(R₂₀)(R₂₀), -(C₁-C₃)alkyl-N⁺(O)(CH₃)₂,
-(C₅-C₇)alkyl-C(O)N(R₄₁)(R₄₁), -CH(C(O)OH)(CH₂OR₂⁰),
-CH(C(O)OH)(CH₂N(R²⁰)(R²⁰)), -(C₁-C₃)alkyl-C(O)O-R²⁰,

wherein the dashed line indicates the point of attachment to the position indicated by R⁶;

R⁷ is
-H, -(C₅-C₇)alkyl optionally substituted with 1 to 3 halogens, or
-(C₁-C₃)alkyl-O-R²⁰;

R⁸ is
-H, -OH, -(C₁-C₇)alkyl optionally substituted with 1 to 3 halogens,
-(C₂-C₈)alkyl-O-R²⁰, -(C₅-C₇)alkyl optionally substituted with 1 to 3 halogens,
-C(O)-O-(C₅-C₇)alkyl, -(C₅-C₇)alkyl, -(C₂-C₆)cycloalkyl, -(C₂-C₆)cycloalkyl,
-S(O)₂-(C₁-C₇)alkyl optionally substituted with 1 to 3 halogens or
-S(O)₂-(C₁-C₇)alkyl optionally substituted with 1 to 3 halogens or
-C(O)-N(R²⁰)(R²⁰);

R⁹ is
-H, -halogen, -CH₃ optionally substituted with 1 to 3 halogens, or
-0-CH₃ optionally substituted with 1 to 3 halogens;

R¹₀ is independently at each occurrence -H or -halogen;
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R_{20}^{20} is independently at each occurrence -H or -(C_i-C_3)alkyl (optionally substituted with 1 to 3 halogens);
R_{21}^{21} is independently at each occurrence -H, -halogen, or -(C_i-C_3)alkyl;
R_{22}^{22} is independently at each occurrence -H or -(C_i-C_6)alkyl (optionally substituted with 1 to 3 halogens);
R_{23}^{23} is independently at each occurrence -H, -(C_i-C_4)alkyl, or -C(O)O-(C_i-C_4)alkyl;
R_{24}^{24} is independently at each occurrence -H, -halogen, or -(C_i-C_2)alkyl (optionally substituted with 1 to 3 halogens); and
R_{41}^{41} is independently at each occurrence -H or -CH_3.

In another embodiment the invention provides a compound structurally represented by formula I, or a pharmaceutically acceptable salt thereof, wherein
R_{1a}^{1a} is -halogen; R_{1b}^{1b} is -H or -halogen;
R_{2}^{2} is -fluorine, -chlorine, or -bromine;
R_{3}^{3} is -fluorine, -chlorine, or -bromine;
R_{4}^{4} is -H or -halogen;
R_{5}^{5} is
or wherein the dashed line represents the point of attachment to the R^5 position in formula I:

R^6 is

5 -H, -(Ci-C_3)alkyl(optionally substituted with 1 to 3 halogens),
-((Ci-C_3)alkyl-O-R^{20}), -(Ci-C_3)alkyl-pyrrolidinyl,
-(C_1-C_3)alkyl-N(R^{20})(R^{20}), -(C_1-C_3)alkyl-N^+(O)(CH_3)_2,
-(Ci-C_3)alkyl-C(O)N(R^{41})(R^{41}), -CH(C(O)OH)(CH_3OR^{20}),
-CH(C(O)OH)(CH_2N(R^{20})(R^{20})), -(Ci-C_3)alkyl-C(O)O-R^{20},

10 wherein the dashed line indicates the point of attachment to the position indicated by R^6;

R^7 is

-H, -(Ci-C_3)alkyl(optionally substituted with 1 to 3 halogens), or

15 -(Ci-C_3)alkyl-O-R^{20};

R^8 is

-H, -OH, -(Ci-C_6)alkyl(optionally substituted with 1 to 3 halogens),
-(C_2-C_3)alkyl-O-R^{20}, -(C(O)(C_1-C_6)alkyl(optionally substituted with 1 to 3 halogens),
-((C_1-C_3)alkyl optionally substituted with 1 to 3 halogens),
-C(O)-O-(Ci-C_3)alkyl(optionally substituted with 1 to 3 halogens),

20 -C(O)-(C_3-C_6)cycloalkyl, -S(O)(O)-(C_3-C_8)cycloalkyl,
-S(O)(O)-(Ci-C_3)alkyl(optionally substituted with 1 to 3 halogens) or
-C(O)-N(R^{20})(R^{20});

R^9 is
In another embodiment the invention provides a compound structurally represented by formula I, or a pharmaceutically acceptable salt thereof, wherein

R₁ is -halogen; R₂ is -H or -halogen; R₃ is -fluorine, -chlorine, or -bromine; R₄ is -H; R₅ is

R⁸ is

-H, -OH, -(Cᵩ-C₆)alkyl(optionally substituted with 1 to 3 halogens), -(C₂-C₃)alkyl-O-R²₀, -C(O)(Cᵩ-C₆)alkyl(optionally substituted with 1 to 3 halogens), -C(O)O-(Cᵩ-C₃)alkyl(optionally substituted with 1 to 3 halogens),
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-C(O)-(C₃-C₈) cycloalkyl, -S(O₂)-(C₃-C₈) cycloalkyl,
-S(θ₂)-(Ci-C₃) alkyl (optionally substituted with 1 to 3 halogens) or
-C(O)-N(R²₀)(R²₀);

R⁹ is

- H, -halogen, -CH₃ (optionally substituted with 1 to 3 halogens), or
- O-CH₃ (optionally substituted with 1 to 3 halogens);

R¹⁰ is independently at each occurrence -H or -halogen;

R²⁰ is independently at each occurrence -H, or -(Ci-C₃) alkyl (optionally substituted with 1 to 3 halogens);

R²¹ is independently at each occurrence -H, -halogen, or -(Ci-C₃) alkyl;

R²² is independently at each occurrence -H or -(Ci-C₆) alkyl (optionally substituted with 1 to 3 halogens); and

R²³ is independently at each occurrence -H, -(Ci-C₄) alkyl, or -C(O)O-(Ci-C₄) alkyl.

Other embodiments of the invention are provided wherein each of the embodiments described herein above is further narrowed as described in the following preferences. Specifically, each of the preferences below is independently combined with each of the embodiments above, and the particular combination provides another embodiment in which the variable indicated in the preference is narrowed according to the preference.

Preferably embodiments of the invention are structurally represented by the formula:

![Chemical Structure](image)

wherein R¹ᵃ is -fluorine, -chlorine, or -bromine. Preferably R¹ᵃ is -fluorine. Preferably R¹ᵇ is -H. Preferably R¹ᵇ is -fluorine, -chlorine, -bromine. Preferably R¹ᵇ is -fluorine. Preferably R² is -halogen, -CH₃ (optionally substituted with 1 to 3 halogens), or -O-CH₃ (optionally substituted with 1 to 3 halogens). Preferably R² is -halogen. Preferably R² is -CH₃ (optionally substituted with 1 to 3 halogens). Preferably R² is -O-CH₃ (optionally substituted with 1 to 3 halogens).
Preferably $R^2$ is -chlorine, -fluorine, or -bromine. Preferably $R^2$ is -chlorine. Preferably $R^3$ is -halogen, -CH$_3$ (optionally substituted with 1 to 3 halogens), or -O-CH$_3$ (optionally substituted with 1 to 3 halogens). Preferably $R^3$ is -halogen. Preferably $R^3$ is -CH$_3$ (optionally substituted with 1 to 3 halogens). Preferably $R^3$ is -O-CH$_3$ (optionally substituted with 1 to 3 halogens). Preferably $R^3$ is -chlorine, -fluorine, or -bromine. Preferably $R^3$ is -chlorine. Preferably $R^2$ is -chlorine, -fluorine, or -bromine, and $R^3$ is -chlorine, -fluorine, or -bromine. Preferably $R^4$ is -H. Preferably $R^4$ is -halogen. Preferably $R^4$ is -fluorine or -chlorine.

Preferably $R^5$ is . Preferably $R^5$ is . Preferably $R^5$ is

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Preferably $R^5$ is . Preferably $R^5$ is . Preferably $R^5$ is
R<sup>5</sup> is ⍟. Preferably R<sup>5</sup> is

or

wherein R<sup>8</sup> is -(Ci-C<sub>4</sub>)alkyl optionally substituted with 1 to 3 halogens; R<sup>9</sup> is -H-halogen, or -CH<sub>3</sub> optionally substituted with 1 to 3 halogens; and

R<sup>10</sup> is independently at each occurrence -H or -halogen. Preferably R<sup>5</sup> is

Preferably R<sup>5</sup> is

Preferably R<sup>6</sup> is -(C<sub>1</sub>-C<sub>3</sub>)alkyl optionally substituted with 1 to 3 halogens), -(Ci-C<sub>4</sub>)alkyl-O-R<sup>20</sup>, -(C<sub>1</sub>-C<sub>3</sub>)alkyl-pyrrolidinyl, phenyl, -HET<sup>1</sup>, -HET<sup>2</sup>, -CH<sub>2</sub>-phenyl, -CH<sub>2</sub>HET<sup>1</sup>, -CH<sub>2</sub>HET<sup>2</sup>, -(Ci-C<sub>3</sub>)alkyl-N(R<sup>20</sup>)<sup>(R<sup>20</sup>)</sup>, -(Ci-C<sub>3</sub>)alkyl-N<sup>+</sup>(O'(CH<sup>3</sup>))<sub>2</sub>, -(Ci-C<sub>3</sub>)alkyl-C(O)N(R<sup>4</sup>1)<sup>(R<sup>4</sup>1)</sup>, -CH(C(O)OH)(CH<sub>2</sub>O R<sup>20</sup>),

-CH(C(O)OH)(CH<sub>2</sub>N(R<sup>20</sup>)<sup>(R<sup>20</sup>)</sup>), -(Ci-C<sub>3</sub>)alkyl-C(O)-O-R<sup>20</sup>, R<sup>5</sup> is ⍟. Preferably R<sup>6</sup> is -(C<sub>1</sub>-C<sub>3</sub>)alkyl optionally substituted with 1 to 3 halogens), -(Ci-C<sub>4</sub>)alkyl-O-R<sup>20</sup>, -(Ci-C<sub>3</sub>)alkyl-pyrrolidinyl, -(C<sub>1</sub>-C<sub>3</sub>)alkyl-N(R<sup>20</sup>)<sup>(R<sup>20</sup>)</sup>, -(Ci-C<sub>3</sub>)alkyl-N<sup>+</sup>(O'(CH<sup>3</sup>))<sub>2</sub>, -(Ci-C<sub>3</sub>)alkyl-C(O)N(R<sup>4</sup>1)<sup>(R<sup>4</sup>1)</sup>, -CH(C(O)OH)(CH<sub>2</sub>OR<sup>20</sup>),

-CH(C(O)OH)(CH<sub>2</sub>N(R<sup>20</sup>)<sup>(R<sup>20</sup>)</sup>), -(Ci-C<sub>3</sub>)alkyl-C(O)-O-R<sup>20</sup>, R<sup>6</sup> is -(Ci-C<sub>3</sub>)alkyl optionally substituted with 1 to 3 halogens), -(Ci-C<sub>3</sub>)alkyl-O-R<sup>20</sup>, -(Ci-C<sub>3</sub>)alkyl-pyrrolidinyl, -(C<sub>1</sub>-C<sub>3</sub>)alkyl-N(R<sup>20</sup>)<sup>(R<sup>20</sup>)</sup>, -(Ci-C<sub>3</sub>)alkyl-N<sup>+</sup>(O'(CH<sup>3</sup>))<sub>2</sub>, -(Ci-C<sub>3</sub>)alkyl-C(O)N(R<sup>4</sup>1)<sup>(R<sup>4</sup>1)</sup>, -CH(C(O)OH)(CH<sub>2</sub>OR<sup>20</sup>),

-CH(C(O)OH)(CH<sub>2</sub>N(R<sup>20</sup>)<sup>(R<sup>20</sup>)</sup>),
Preferably $R^7$ is -H. Preferably $R^7$ is -(C$_1$-C$_3$)alkyl optionally substituted with 1 to 3 halogens. Preferably $R^7$ is -(C$_2$-C$_3$)alkyl-O-R$^{20}$.

Preferably $R^8$ is -H. Preferably $R^8$ is -(C$_1$-C$_4$)alkyl optionally substituted with 1 to 3 halogens, -(C$_2$-C$_3$)alkyl-O-R$^{20}$, -(C)-(C$_1$-C$_4$)alkyl, -(C)-(C$_1$-C$_4$)alkyl, or -(C)-(C$_1$-C$_4$)alkyl, or -(C)-(C$_1$-C$_4$)alkyl, or -(C)-(C$_1$-C$_4$)alkyl, or -(C)-(C$_1$-C$_4$)alkyl, or -(C)-(C$_1$-C$_4$)alkyl, or -(C)-(C$_1$-C$_4$)alkyl, or -(C)-(C$_1$-C$_4$)alkyl, or -(C)-(C$_1$-C$_4$)alkyl. Preferably $R^8$ is -(C$_2$-C$_3$)alkyl optionally substituted with 1 to 3 halogens. Preferably $R^8$ is -(C$_2$-C$_3$)alkyl-O-R$^{20}$, -(C)-(C$_1$-C$_4$)alkyl, -(C)-(C$_1$-C$_4$)alkyl, or -(C)-(C$_1$-C$_4$)alkyl, or -(C)-(C$_1$-C$_4$)alkyl, or -(C)-(C$_1$-C$_4$)alkyl, or -(C)-(C$_1$-C$_4$)alkyl, or -(C)-(C$_1$-C$_4$)alkyl. Preferably $R^8$ is -(C$_2$-C$_3$)alkyl-O-R$^{20}$.

Preferably $R^9$ is -H. Preferably $R^9$ is -halogen. Preferably $R^9$ is -CH$_3$ optionally substituted with 1 to 3 halogens, or -0-CH$_3$ optionally substituted with 1 to 3 halogens. Preferably $R^9$ is -H. Preferably $R^{10}$ is -halogen. Preferably $R^9$ is -H and $R^{10}$ is -H.

Preferably $R^9$ is -halogen and $R^{10}$ is -halogen.

Preferred embodiments of the invention are compounds of the formula (R)-3-[3,5-Dichloro-4'-((4-trifluoromethyl-piperidine-1-carbonyl)-biphenyl-4-ylmethyl]-1-(4,4-difluoro-cyclohexyl)-pyrrolidin-2-one and (R)-3-[3,5-Dichloro-4'-((1,1-dioxo-llamda*6*-thiomorpholine-4-carbonyl)-biphenyl-4-ylmethyl]-1-(4,4-difluoro-cyclohexyl)-pyrrolidin-2-one. A further embodiment of the invention are the novel intermediate preparations described herein which are useful for preparing the 11-β-HSDI inhibitors according to formula I and the embodiments described herein. A further embodiment of the invention are the novel intermediate preparations described herein which are useful for preparing (R)-3-[3,5-Dichloro-4'-((4-trifluoromethyl-piperidine-1-carbonyl)-biphenyl-4-ylmethyl]-1-(4,4-difluoro-cyclohexyl)-pyrrolidin-2-one and (R)-3-[3,5-Dichloro-4'-((1,1-dioxo-llamda*6*-thiomorpholine-4-carbonyl)-biphenyl-4-ylmethyl]-1-(4,4-difluoro-cyclohexyl)-pyrrolidin-2-one or a pharmaceutically acceptable salt thereof.

Patients with type 2 diabetes often develop "insulin resistance" which results in abnormal glucose homeostasis and hyperglycemia leading to increased morbidity and
premature mortality. Abnormal glucose homeostasis is associated with obesity, hypertension, and alterations in lipid, lipoprotein, and apolipoprotein metabolism. Type 2 diabetics are at increased risk of developing cardiovascular complications, e.g., atherosclerosis, coronary heart disease, stroke, peripheral vascular disease, hypertension, nephropathy, neuropathy, and retinopathy. Therefore, therapeutic control of glucose homeostasis, lipid metabolism, obesity, and hypertension are important in the management and treatment of diabetes mellitus. Many patients who have insulin resistance but have not developed type 2 diabetes are also at risk of developing "Syndrome X" or "Metabolic syndrome". Metabolic syndrome is characterized by insulin resistance along with abdominal obesity, hyperinsulinemia, high blood pressure, low HDL, high VLDL, hypertension, atherosclerosis, coronary heart disease, and chronic renal failure. These patients are at increased risk of developing the cardiovascular complications listed above whether or not they develop overt diabetes mellitus.

Due to their inhibition of 11-β-HSD1, the present compounds are useful in the treatment of a wide range of conditions and disorders in which inhibition of 11-β-HSD1 is beneficial. These disorders and conditions are defined herein as "diabetic disorders" and "metabolic syndrome disorders". One of skill in the art is able to identify "diabetic disorders" and "metabolic syndrome disorders" by the involvement of 11-β-HSD1 activity either in the pathophysiology of the disorder, or in the homeostatic response to the disorder. Thus, the compounds may find use for example to prevent, treat, or alleviate, diseases or conditions or associated symptoms or sequelae, of "Diabetic disorders" and "metabolic syndrome disorders".

"Diabetic disorders" and "metabolic syndrome disorders" include, but are not limited to, diabetes, type 1 diabetes, type 2 diabetes, hyperglycemia, hyper insulinemia, beta-cell rest, improved beta-cell function by restoring first phase response, prandial hyperglycemia, preventing apoptosis, impaired fasting glucose (IFG), metabolic syndrome, hypoglycemia, hyper-/hypokalemia, normalizing glucagon levels, improved LDL/HDL ratio, reducing snacking, eating disorders, weight loss, polycystic ovarian syndrome (PCOS), obesity as a consequence of diabetes, latent autoimmune diabetes in adults (LADA), insulitis, islet transplantation, pediatric diabetes, gestational diabetes, diabetic late complications, micro-/macroalbuminuria, nephropathy, retinopathy, neuropathy, diabetic foot ulcers, reduced intestinal motility due to glucagon
administration, short bowel syndrome, antidiarrheic, increasing gastric secretion, decreased blood flow, erectile dysfunction, glaucoma, post surgical stress, ameliorating organ tissue injury caused by reperfusion of blood flow after ischemia, ischemic heart damage, heart insufficiency, congestive heart failure, stroke, myocardial infarction, arrhythmia, premature death, anti-apoptosis, wound healing, impaired glucose tolerance (IGT), insulin resistance syndromes, metabolic syndrome, syndrome X, hyperlipidemia, dyslipidemia, hypertriglyceridemia, hyperlipoproteinemia, hypercholesterolemia, arteriosclerosis including atherosclerosis, glucagonomas, acute pancreatitis, cardiovascular diseases, hypertension, cardiac hypertrophy, gastrointestinal disorders, obesity, diabetes as a consequence of obesity, diabetic dyslipidemia, etc. Thus the present invention also provides a method of treatment of "Diabetic disorders" and "metabolic syndrome disorders" while reducing and or eliminating one or more of the unwanted side effects associated with the current treatments.

In addition, the present invention provides a compound of Formula I, or a pharmaceutical salt thereof, or a pharmaceutical composition which comprises a compound of Formula I, or a pharmaceutical salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient: for use in inhibiting 11-β-HSD1 activity; for use in inhibiting a 11-β-HSD1 activity mediated cellular response in a mammal; for use in reducing the glycemic level in a mammal; for use in treating a disease arising from excessive 11-β-HSD1 activity; for use in treating diabetic and other metabolic syndrome disorders in a mammal; and for use in treating diabetes, metabolic syndrome, obesity, hyperglycemia, atherosclerosis, ischemic heart disease, stroke, neuropathy, and wound healing. Thus, the methods of this invention encompass a prophylactic and therapeutic administration of a compound of Formula I.

The present invention further provides the use of a compound of Formula I, or a pharmaceutical salt thereof for the manufacture of a medicament for inhibiting 11-β-HSD1 activity; for the manufacture of a medicament for inhibiting 11-β-HSD1 activity mediated cellular response in a mammal; for the manufacture of a medicament for reducing the glycemic level in a mammal; for the manufacture of a medicament for treating a disease arising from excessive 11-β-HSD1 activity; for the manufacture of a medicament for treating diabetic and other metabolic syndrome disorders in a mammal;
and for the manufacture of a medicament for preventing or treating diabetes, metabolic syndrome, obesity, hyperglycemia, atherosclerosis, ischemic heart disease, stroke, neuropathy, and improper wound healing.

The present invention further provides a method of treating conditions resulting from excessive 11-β-HSD1 activity in a mammal; a method of inhibiting 11-β-HSD1 activity in a mammal; a method of inhibiting a 11-β-HSD1 activity mediated cellular response in a mammal; a method of reducing the glycemic level in a mammal; a method of treating diabetic and other metabolic syndrome disorders in a mammal; a method of preventing or treating diabetes, metabolic syndrome, obesity, hyperglycemia, atherosclerosis, ischemic heart disease, stroke, neuropathy, and improper wound healing; said methods comprising administering to a mammal in need of such treatment a 11-β-HSD1 activity inhibiting amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition which comprises a compound of Formula I, or a pharmaceutical salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

In addition, the present invention provides a pharmaceutical composition which comprises a compound of Formula I, or a pharmaceutical salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient: adapted for use in inhibiting 11-β-HSD1 activity; adapted for use in inhibiting 11-β-HSD1 activity mediated cellular responses; adapted for use in reducing the glycemic level in a mammal; adapted for use in treating diabetic and other metabolic syndrome disorders in a mammal; and adapted for use in preventing or treating diabetes, metabolic syndrome, obesity, hyperglycemia, atherosclerosis, ischemic heart disease, stroke, neuropathy, and wound healing.

In a further aspect of the invention the present compounds are administered in combination with one or more further active substances in any suitable ratios. Such further active substances may for example be selected from antidiabetics, antiobesity agents, antihypertensive agents, agents for the treatment of complications resulting from or associated with diabetes and agents for the treatment of complications and disorders resulting from or associated with obesity. The following listing sets out several groups of combinations. It will be understood that each of the agents named may be combined with other agents named to create additional combinations.
Thus, in a further embodiment of the invention the present compounds may be administered in combination with one or more antidiabetics.

Suitable antidiabetic agents include insulin, insulin analogues and derivatives such as those disclosed in EP 792 290 (Novo Nordisk A/S), for example N\textsuperscript{εB29}-tetradecanoyl des (B30) human insulin, EP 214 826 and EP 705 275 (Novo Nordisk A/S), for example Asp\textsuperscript{B28} human insulin, US 5,504,188 (Eli Lilly), for example Lys\textsuperscript{B28} Pro\textsuperscript{B29} human insulin, EP 368 187 (Aventis), for example Lantus®, GLP-I and GLP-I derivatives such as those disclosed in WO 98/08871 (Novo Nordisk A/S), as well as orally active hypoglycemic agents.

The orally active hypoglycemic agents preferably comprise imidazolines, sulphonylureas, biguanides, meglinitides, oxadiazolidinediones, thiazolidinediones, insulin sensitizers, insulin secretagogues, such as glimepiride, α-glucosidase inhibitors, agents acting on the ATP-dependent potassium channel of the β-cells for example potassium channel openers such as those disclosed in WO 97/26265, WO 99/03861 and WO 00/37474 (Novo Nordisk A/S), or mitiglinide, or a potassium channel blocker, such as BTS-67582, nateglinide, glucagon antagonists such as those disclosed in WO 99/01423 and WO 00/39088 (Novo Nordisk A/S and Agouron Pharmaceuticals, Inc.), GLP-I antagonists, DPP-IV (dipeptidyl peptidase-IV) inhibitors, PTPase (protein tyrosine phosphatase) inhibitors, inhibitors of hepatic enzymes involved in stimulation of gluconeogenesis and/or glycogenosis, glucose uptake modulators, activators of glucokinase (GK) such as those disclosed in WO 00/58293, WO 01/44216, WO 01/83465, WO 01/83478, WO 01/85706, WO 01/85707, and WO 02/08209 (Hoffman-La Roche) or those disclosed in WO 03/00262, WO 03/00267 and WO 03/15774 (AstraZeneca), GSK-3 (glycogen synthase kinase-3) inhibitors, compounds modifying the lipid metabolism such as antilipidemic agents such as HMG CoA inhibitors (statins), compounds lowering food intake, PPAR (Perxisome proliferator-activated receptor) ligands including the PPAR-alpha, PPAR-gamma and PPAR-delta subtypes, and RXR (retinoid X receptor) agonists, such as ALRT-268, LG-1268 or LG-1069.

In another embodiment, the present compounds are administered in combination with insulin or an insulin analogue or derivative, such as N\textsuperscript{εB29}-tetradecanoyl des (B30) human insulin, Asp\textsuperscript{B28} human insulin, Lys\textsuperscript{B28} Pro\textsuperscript{B29} human insulin, Lantus®, or a mix-preparation comprising one or more of these.
In a further embodiment of the invention the present compounds are administered in combination with a sulphonylurea such as glibenclamide, glipizide, tolbutamide, chloropamide, tolazamide, glimepride, glicazide and glyburide.

In another embodiment of the invention the present compounds are administered in combination with a sulphonylurea such as glibenclamide, glipizide, tolbutamide, chloropamide, tolazamide, glimepride, glicazide and glyburide.

In another embodiment of the invention the present compounds are administered in combination with a biguanide, for example, metformin.

In yet another embodiment of the invention the present compounds are administered in combination with a meglitinide, for example, repaglinide or nateglinide.

In still another embodiment of the invention the present compounds are administered in combination with a thiazolidinedione insulin sensitizer, for example, troglitazone, ciglitazone, pioglitazone, rosiglitazone, darglitazone.

In still another embodiment of the invention the present compounds may be administered in combination with an α-glucosidase inhibitor, for example, voglibose, emiglitate, miglitol or acarbose.

In another embodiment of the invention the present compounds are administered in combination with an agent acting on the ATP-dependent potassium channel of the β-cells, for example, tolbutamide, glibenclamide, glipizide, glicazide, BTS-67582 or repaglinide.

In yet another embodiment of the invention the present compounds may be administered in combination with nateglinide.
In still another embodiment of the invention the present compounds are administered in combination with an antilipemic agent or antihyperlipidemic agent for example cholestyramine, colestipol, clofibrate, gemfibrozil, lovastatin, pravastatin, simvastatin, pitavastatin, rosuvastatin, probucol, dextrothyroxine, fenofibrate or atorvastatin.

In still another embodiment of the invention the present compounds are administered in combination with compounds lowering food intake.

In another embodiment of the invention, the present compounds are administered in combination with more than one of the above-mentioned compounds for example in combination with metformin and a sulphonylurea such as glyburide; a sulphonylurea and acarbose; nateglinide and metformin; repaglinide and metformin, acarbose and metformin; a sulfonylurea, metformin and troglitazone; insulin and a sulfonylurea; insulin and metformin; insulin, metformin and a sulfonylurea; insulin and troglitazone; insulin and lovastatin; etc.

General terms used in the description of compounds herein described bear their usual meanings.

As used herein, the terms "(C₁-C₃)alkyl", "(C₄-C₆)alkyl" or "(C₁-C₆)alkyl" refer to straight-chain or branched-chain saturated aliphatic groups of the indicated number of carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, and the like. The term "(C₄-C₆)alkoxy" represents a C₄-C₆ alkyl group attached through an oxygen and include moieties such as, for example, methoxy, ethoxy, n-propoxy, isopropoxy, and the like. The term "halogen" refers to fluoro, chloro, bromo, and iodo. The term "(Cs-C₈) cycloalkyl" refers to a saturated or partially saturated carbocycle ring of from 3 to 8 carbon atoms, typically 3 to 7 carbon atoms. Examples of (C₃-C₈) cycloalkyl include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like.

The term "optionally substituted," or "optional substituents," as used herein, means that the groups in question are either unsubstituted or substituted with one or more of the substituents specified. When the groups in question are substituted with more than one substituent, the substituents may be the same or different. Furthermore, when using the terms "independently," "independently are," and "independently selected from" mean that the groups in question may be the same or different. Certain of the herein defined
terms may occur more than once in the structural formulae, and upon such occurrence each term shall be defined independently of the other.

It is understood that guinea pigs, dogs, cats, rats, mice, hamsters, and primates, including humans, are examples of patients within the scope of the meaning of the term "patient". Preferred patients include humans. The term "patient" includes livestock animals. Livestock animals are animals raised for food production. Ruminants or "cud-chewing" animals such as cows, bulls, heifers, steers, sheep, buffalo, bison, goats and antelopes are examples of livestock. Other examples of livestock include pigs and avians (poultry) such as chickens, ducks, turkeys and geese. The patient to be treated is preferably a mammal, in particular a human being.

The terms "treatment", "treating" and "treat", as used herein, include their generally accepted meanings, i.e., the management and care of a patient for the purpose of preventing, reducing the risk in incurring or developing a given condition or disease, prohibiting, restraining, alleviating, ameliorating, slowing, stopping, delaying, or reversing the progression or severity, and holding in check and/or treating existing characteristics, of a disease, disorder, or pathological condition, described herein, including the alleviation or relief of symptoms or complications, or the cure or elimination of the disease, disorder, or condition. The present method includes both medical therapeutic and/or prophylactic treatment, as appropriate.

As used herein, the term "therapeutically effective amount" means an amount of compound of the present invention that is capable of alleviating the symptoms of the various pathological conditions herein described. The specific dose of a compound administered according to this invention will, of course, be determined by the particular circumstances surrounding the case including, for example, the compound administered, the route of administration, the state of being of the patient, and the pathological condition being treated.

"Composition" means a pharmaceutical composition and is intended to encompass a pharmaceutical product comprising the active ingredient(s) including compound(s) of Formula I, and the inert ingredient(s) that make up the carrier. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier.
The term "substantially pure" refers to pure crystalline form of a compound comprising greater than about 90% of the desired crystalline form, and preferably, greater than about 95% of the desired crystal form.

The term "suitable solvent" refers to any solvent, or mixture of solvents, inert to the ongoing reaction that sufficiently solubilizes the reactants to afford a medium within which to effect the desired reaction.

The term "unit dosage form" means physically discrete units suitable as unitary dosages for human subjects and other non-human animals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier.

The compounds of the present invention may have one or more chiral centers and may exist in a variety of stereoisomeric configurations. As a consequence of these chiral centers the compounds of the present invention can occur as racemates, as individual enantiomers or mixtures of enantiomers, as well as diastereomers and mixtures of diastereomers. All such racemates, enantiomers, diastereomers and mixtures are within the scope of the present invention, whether pure, partially purified, or unpurified mixtures. For the examples provided herein, when a molecule which contains a chiral center or centers of known configuration is presented, its stereochemistry is designated in the name and in the structural representation of the molecule. If the stereochemistry is unknown or undefined its stereochemistry is not designated in the name or in the structural representation of the molecule. Embodiments of the invention include the Examples provided herein, and although the Example provided may be of one chiral or conformational form, or a salt thereof, further embodiments of the invention include all other stereoisomeric and or conformational forms of the examples described, as well as pharmaceutically acceptable salts thereof. These embodiments include any isolated enantiomers, diastereomers, and or conformers of these structures, as well as any mixtures containing more than one form.

Furthermore, when a double bond or a fully or partially saturated ring system or more than one center of asymmetry or a bond with restricted rotatability is present in the molecule diastereomers may be formed. It is intended that any diastereomers, as separated, pure or partially purified diastereomers or mixtures thereof are included within the scope of the invention. Furthermore, some of the compounds of the present invention
may exist in different tautomeric forms and it is intended that any tautomeric forms which
the compounds are able to form are included within the scope of the present invention.

The term "enantiomeric enrichment" as used herein refers to the increase in the
amount of one enantiomer as compared to the other. A convenient method of expressing
the enantiomeric enrichment achieved is the concept of enantiomeric excess, or "ee",
which is found using the following equation:

\[
ee = \frac{E^1 - E^2}{E^1 + E^2} \times 100
\]

wherein \(E^1\) is the amount of the first enantiomer and \(E^2\) is the amount of the second
enantiomer. Thus, if the initial ratio of the two enantiomers is 50:50, such as is present in
a racemic mixture, and an enantiomeric enrichment sufficient to produce a final ratio of
70:30 is achieved, the ee with respect to the first enantiomer is 40%. However, if the
final ratio is 90:10, the ee with respect to the first enantiomer is 80%. An ee of greater
than 90% is preferred, an ee of greater than 95% is most preferred and an ee of greater
than 99% is most especially preferred. Enantiomeric enrichment is readily determined by
one of ordinary skill in the art using standard techniques and procedures, such as gas or
high performance liquid chromatography with a chiral column. Choice of the appropriate
chiral column, eluent and conditions necessary to effect separation of the enantiomeric
pair is well within the knowledge of one of ordinary skill in the art. In addition, the
specific stereoisomers and enantiomers of compounds of formula I can be prepared by
one of ordinary skill in the art utilizing well known techniques and processes, such as
those disclosed by J. Jacques, et al., "Enantiomers, Racemates, and Resolutions", John
838448, published April 29, 1998. Examples of resolutions include recrystallization
techniques or chiral chromatography.

The compounds of Formula I, can be prepared by one of ordinary skill in the art
following a variety of procedures, some of which are illustrated in the procedures and
schemes set forth below. The particular order of steps required to produce the
compounds of Formula I is dependent upon the particular compound to being
synthesized, the starting compound, and the relative lability of the substituted moieties.
The reagents or starting materials are readily available to one of skill in the art, and to the
extent not commercially available, are readily synthesized by one of ordinary skill in the art following standard procedures commonly employed in the art, along with the various procedures and schemes set forth below.

The following Schemes, Preparations, Examples and Procedures are provided to better elucidate the practice of the present invention and should not be interpreted in any way as to limit the scope of the same. Those skilled in the art will recognize that various modifications may be made while not departing from the spirit and scope of the invention. All publications mentioned in the specification are indicative of the level of those skilled in the art to which this invention pertains.

The optimal time for performing the reactions of the Schemes, Preparations, Examples and Procedures can be determined by monitoring the progress of the reaction via conventional chromatographic techniques. Furthermore, it is preferred to conduct the reactions of the invention under an inert atmosphere, such as, for example, argon, nitrogen. Choice of solvent is generally not critical so long as the solvent employed is inert to the ongoing reaction and sufficiently solubilizes the reactants to effect the desired reaction. The compounds are preferably isolated and purified before their use in subsequent reactions. Some compounds may crystallize out of the reaction solution during their formation and then collected by filtration, or the reaction solvent may be removed by extraction, evaporation, or decantation. The intermediates and final products of Formula I may be further purified, if desired by common techniques such as recrystallization or chromatography over solid supports such as silica gel or alumina.

The skilled artisan will appreciate that not all substituents are compatible with all reaction conditions. These compounds may be protected or modified at a convenient point in the synthesis by methods well known in the art.

The terms and abbreviations used in the instant Schemes, Preparations, Examples and Procedures have their normal meanings unless otherwise designated. For example, as used herein, the following terms have the meanings indicated: "psi" refers to pounds per square inch; "TLC" refers to thin layer chromatography; "HPLC" refers to high performance liquid chromatography; "R_t" refers to retention factor; "R_f" refers to retention time; "δ" refers to part per million down-field from tetramethylsilane; "MS" refers to mass spectrometry, Observed Mass indicates [M+H] unless indicated otherwise. "MS(APCi)" refers to atmospheric pressure chemical ionization mass spectrometry, "UV"
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refers to ultraviolet spectrometry, "\(^1\)H NMR" refers to proton nuclear magnetic resonance spectrometry, "LCMS" refers to liquid chromatography-mass spectrometry, "GC/MS" refers to gas chromatography/mass spectrometry. "IR" refers to infra red spectrometry, and the absorption maxima listed for the IR spectra are only those of interest and not all of the maxima observed. "RT" refers to room temperature.

"THF" refers to tetrahydrofuran, "LAH" refers to lithium aluminum hydride, "LDA" refers to lithium diisopropylamide, "DMSO" refers to dimethylsulfoxide, "DMF" refers to dimethylforamide, "EtOAc" refers to ethyl acetate, "Pd-C" refers to palladium on carbon, "DCM" refers to dichloromethane, "DMAP" refers to dimethylaminopyridine, "TBAF" refers to Lithium Hexamethydisilisilane, "TFA" refers to trifluoroacetic acid, "EDAC" refers to N-EAyI-\(\Lambda\)-(S-dimethylaminopropyl)carbodiimide hydrochloride, "HOBT" refers to 1-Hydroxy benzotriazole, "Bn-9-BBN" refers to Benzyl -9-borabicyclo[3.3.1]nonane, "Ph" refers to phenyl, "Me" refers to methyl, "Pd(dppf)Cl_2" refers to tetrakis(triphenylphoshine)palladium, "Bn" refers to tert-butyl, "TsOH" refers to p-toluenesulfonic acid, "DCE" refers to dichloroethane, "DAST" refers to (Diethylamino)sulfur trifluoride, "EA/H" refers to ethyl acetate/hexanes mixture, "Pd_{2}(dba)_{3}" refers to Bis(dibenzylideneacetone)palladium, "BINAP" refers to 2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene, "NMP" refers to N-Methylpyrrolidinone, "TMSCN" refers to Trimethylsilyl cyanide, "TBAF" refers to Tetrabutylammonium fluoride, "Tf_{2}O" refers to trifluoromethanesulfonic fluoride, "TBSO" refers to tert-butyldimethylsilanyloxy, "OTf" refers to trifluoromethanesulfonate, MeTi(Oi-Pr)$_3$ refers to methyltitanium triisopropoxide, "BBr$_3$" refers to boron tribromide, "PBr$_3$" refers to phosphorous tribromide, "Pd(PPh$_3$)$_4$" refers to tetrakis(triphenylphoshine)palladium (0), "OAc" refers to acetate, "DME" refers to dimethylethane, "Et$_2$O" refers to diethyl ether, "(Ph$_3$P)$_4$Pd" refers to tetrakis(triphenylphoshine)palladium (0), "DMF DMA" refers to N,N-dimethylformamide dimethyl acetal, "Et$_3$N" refers to triethylamine, "tBu" refers to tert-butyl, "DIPEA" refers to diisopropylethyl amine, "EDC" refers to -(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, "HOAc" refers to acetic acid, "boc" refers to t-butoxycarbonyl. In a structure, "Ph" refers to phenyl, "Me" refers to methyl.
methyl, "Et" refers to ethyl, "Bn" refers to benzyl, "MeOH" refers to methanol, "OTf" refers to trifluoromethanesulfonate, "TIPS" refers to triisopropylsilanyloxy, "TBSO" refers to tert-butyl-dimethyl-silanyloxy.

The Examples provided herein are illustrative of the invention claimed herein and are not intended to limit the scope of the claimed invention in any way. The preparations and examples are named using AutoNom 2.2 in ChemDraw Ultra, or AutoNom 2000 in MDL ISIS/Draw version 2.5 from MDL Information Systems, Inc., or are provided by Chemical Abstracts Services.

A Varian INOVA 400 MHz spectrometer is used to obtain 1H NMR Spectra in the solvent indicated. An Agilent HPLC 100 instrument equipped with a Mass Spectrometer (Agilent MSD SL) is used to obtain LCMS. A Waters Xterra C18 (2.1x50 mm, 3.5 micron) is used as stationary phase and a standard method is a gradient of 5-100% acetonitrile/methanol (50:50) with 0.2% ammonium formate over 3.5 minutes then held at 100% B for 0.5 minutes at a column temperature of 50°C and a flow rate of 1.0 mL/min. Another standard method is a gradient of 5-100% acetonitrile/methanol (50:50) with 0.2% ammonium formate over 7.0 minutes then held at 100% B for 1.0 minutes at a column temperature of 50°C and a flow rate of 1.0 mL/min. Additional MS analysis via Agilent MSD (loop machine) is standard Flow injection Analysis (FIA), no column is present and flow is 0.5 mL/min of 80% MeOH with 6.5mM Ammonium Acetate

Additional 30secs run time.

In Scheme A, an optionally substituted phenol (1) is protected (e.g., with TBSCI) to form compound 2, and then compound 2 is converted to the aldehyde (3). Compound 3 is reacted with a compound containing a protecting group (Pg) and leaving group (Lg) to give the ether compound 4. Pg can be -CH3 or -CH2-phenyl and Lg can be mesylate.
or halo. Preferably, the Lg-Pg compound is I-CH₃ or Br-CH₂-phenyl. The aldehyde is reduced to form the alcohol (5) and then converted to compound 6. Preferably, compound 5 is halogenated with PBr₃ to give the 2-bromo-methyl compound.

Protection and deprotection of the compounds to form compounds of formula I and others are well known to the skilled artisan and are described in the literature. (For example, see: Greene and Wuts, Protective Groups in Organic Synthesis, Third Edition, John Wiley and Sons Inc., 1999).

Scheme B

Scheme B shows the stereo selective synthesis to form the intermediate compound 10. Compound 8 is formed by acylating commercially available (R)-4-benzyl-oxazolidin-2-one with 4-pentenoyl chloride. It is then alkylated with an optionally substituted compound 6 (see Scheme A) to give compound of 9. Compound 9 is oxidized to form the aldehyde intermediate compound 10 using ozone and triphenylphosphine or osmium tetroxide and an oxidant such as sodium metaperiodate.

Preparation 1

2,6-dichloro-4-hydroxy-benzaldehyde

Dissolve 3,5 dichlorophenol (1 kg, 6.13 mol) in 3 L dimethylformamide (DMF) and cool to 0°C. Add imidazole (918.74 g, 6.75 mol), followed by tertbutyldimethylsilyl chloride (1017.13g, 6.75 mol). Warm the mixture to room temperature and stir for 15 minutes. Pour into water (6 L) and extract with ether (4 L). Wash the organic layer with
water 2 times, 10% aqueous lithium chloride solution then brine before drying over sodium sulfate. Filter and concentrate under vacuum to obtain tert-butyl-(3,5-dichlorophenoxy)-dimethyl-silane (1700 g) as an oil.

Dissolve tert-butyl-(3,5-dichlorophenoxy)-dimethyl-silane (425 g, 1.5 mol) in 4 L dry tetrahydrofuran and cool to -68°C. Slowly add 1.1 equivalents of sec-butyl lithium (103.1 g, 1.61 mol) at -68°C (-1.75 hr). After addition is complete stir the reaction at -70°C for 30 min. Add dimethylformamide (168.5 g, 2.3 mol) and stir the reaction at -70°C for 1 hr. Add 1 M hydrochloric acid in water (3.5 L) and allow the reaction to warm to room temperature.

Pour the reaction mixture into ether (5 L), wash with water then brine. Dry over sodium sulfate and concentrate under vacuum to an orange solid. Triturate with cold dichloromethane and filter to recover 250 g (80 %) pale yellow solid.

Preparation 2
2,6-dichloro-4-methoxy-benzaldehyde

Combine 2,6-dichloro-4-hydroxy-benzaldehyde (120 g, 628.24 mmol) and potassium carbonate (173.65 g, 1256.5 mmol) in 900 mL dimethylformamide and treat with iodomethane (107 g, 753.9 mmol). Stir the reaction at room temperature for 3 hours. Filter off solids and pour into 6 L of water. Filter solids, wash several times with water, air dry and dissolve in ethyl acetate. Wash with water, followed by brine and then dry over sodium sulfate. Filter and concentrate under vacuum to -100 mL volume, at which point, solids start to crash out. Filter then concentrate down the filtrate to yield a second crop. Wash with hexane, combine all solids and vacuum dry to yield 112.3 g of off-white, solid: 1HNMR (400 MHz, CDCl3) δ 10.41 (s, 1H), 6.90 (s, 2H), 3.87 (s, 3H).

Preparation 3
2,6-dichloro-4-benzyloxy-benzaldehyde

Treat a mixture of 2,6-dichloro-4-hydroxy-benzaldehyde (250 g, 1.3 mol) and potassium carbonate (361.8 g, 2.62 mol) in 2 L dimethylformamide with benzyl bromide (268.64 g, 1.57 mol). Stir the reaction at room temperature for 1 hour. Filter off solids and pour into 12 L of water. Filter off solid, wash several times with water, air dry and dissolve in ethyl acetate. Dry over magnesium sulfate, filter and concentrate under vacuum to -1.5 L. Allow to sit overnight then filter. Wash solid with minimal amount of
hexane and vacuum dry. Concentrate the filtrate under vacuum and triturate with hexane to yield a second crop of product which when combined with the first crop equals 245 g white crystals. Repeat to obtain a 3rd crop of 80 g as a light-tan powder (88% overall yield): IH NMR (400 MHz, DMSO-d6) δ 10.26 (s, 1H), 7.43 (m, 5H), 7.28 (s, 2H), 5.25 (s, 2H).

Preparation 4

(2,6-dichloro-4-methoxy-phenyl)-methanol

Suspend 2,6-dichloro-4-methoxy-benzaldehyde (112 g, 546 mmol) in 1500 mL ethanol and cool in an ice bath to 7°C. Add sodium borohydride (20.67, 546 mmol) portionwise to obtain a solution. Remove the ice bath and stir for 2 hours. Carefully add reaction mixture to saturated ammonium chloride solution (~4L) and stir until fully quenched. Extract with dichloromethane (3 x 1L) and dry the combined organic extracts over sodium sulfate. Filter and concentrate under vacuum to yield 113 g of a light-tan solid: IH NMR (400 MHz, CDCl₃) δ 6.86 (s, 2H), 4.86 (s, 2H), 3.78 (s, 3H), 2.07 (s, 1H).

Preparation 5

(2,6-dichloro-4-benzyloxy-phenyl)-methanol

Prepare the title compound essentially as prepared by the method of Preparation 4. NMR (DMSO-d₆) δ 7.38 (m, 4H), 7.33 (m, 1H), 7.12 (s, 2H), 5.14 (s, 2H), 5.05 (t, 1H), 4.59 (d, 2H).

Preparation 6

2-bromomethyl-1, 3-dichloro-5-methoxy-benzene

Dissolve (2,6-dichloro-4-methoxy-phenyl)-methanol (113 g, 545.76 mmol) in 1200 mL dry THF and cool to 0 deg under nitrogen. Add PBr₃ (59.1 g, 218.3 mmol) under nitrogen and stir at 0°C for 30 minutes. Pour into saturated aqueous NaHCO₃ and extract with EtOAc. Dry and concentrate under vacuum to obtain 129.4 g product as an off-white solid. NMR (CDCl₃) δ 6.88 (s, 2H), 4.73 (s, 2H), 3.79 (s, 3H).

Preparation 7

2-bromomethyl-1, 3-dichloro-5-benzyloxy-benzene

Prepare the title compound essentially as prepared by the method of Preparation 6 in an 89% yield. ESM (m/z): 347 (M + 1).
(R)-4-benzyl-3-pent-4-enoyl-oxazolidin-2-one

Flush with nitrogen a 12 L 3-neck round bottom flask equipped with a mechanical stirrer, internal temperature probe/N2 inlet, and 1L addition funnel for 20 min and then add (R)-4-benzyl-2-oxazolidinone (250 g, 1.41 mol). Dilute with tetrahydrofuran (THF) (1.8 L) and cool in a dry ice/acetone bath until the internal temperature is -74°C. Transfer a 1.6M hexanes solution of n-butyllithium (970 mL, 1.552 mol) to the addition funnel via cannula, and add to the oxazolidinone solution at a rate such that the internal temperature does not reach above -65°C. After the addition is complete, allow the reaction to stir in the cooling bath 30 min. Transfer 4-pentenoyl chloride (175 mL, 1.585 mol) to the addition funnel and add dropwise to the anion solution over a 25 min period. Stir the reaction for 45 min in the cooling bath. Remove the cooling bath and stir the reaction 18 hr as it slowly reaches room temperature. Dilute the mixture with IN aqueous hydrochloric acid (1.5L) and diethyl ether (1 L). Separate the layers and wash the organic phase with water (2X IL) then brine (1 L). Extract the combined aqueous washes with ether (1 L). Dry the combined organic phases over anhydrous magnesium sulfate, filter, and concentrate to 390 g of a light tan oil. Purify this material by silica gel chromatography using hexanes:ethyl acetate to obtain 345 g (94.5%) of a clear, yellow oil.

Preparation 9

(R)-4-benzyl-3-[(S)-2-(4-benzyloxy-2,6-dichloro-benzyl)-pent-4-enoyl]-oxazolidin-2-one

Stir a mixture of (R)-4-benzyl-3-pent-4-enoyl-oxazolidin-2-one (345 g, 1.33 mol) and THF (1.8 L) in a 12 L 3-neck round bottom flask, with internal temperature probe/nitrogen inlet and addition funnel, under a nitrogen atmosphere and cool to -75°C. Transfer 1 M LiHMDS (1.6 L) to the addition funnel and add at a rate such that the internal temperature does not reach above -60°C. After the addition is complete, allow the reaction to stir at -25°C for 30 min then cool to about -60°C. At this point add solid 2-bromomethyl-1,3-dichloro-5-benzyloxy-benzene portionwise over 5 min. After the addition is complete, transfer the reaction vessel to a -10°C acetone bath and maintain the internal reaction temperature below 10°C for 1 hr. Cool the mixture to 0°C then quench with 2 L aqueous IN hydrochloric acid. Transfer the mixture to a 22 L separatory funnel and dilute with 2.5 L water and 2 L ether. Separate the layers and extract the aqueous
layer with ether. Dry the combined organic phase over anhydrous magnesium sulfate, filter and concentrate to 800 g of a thick oil. Purify by silica gel chromatography using hexanes:ethyl acetate to obtain 597 g, (86%) of a colorless oil.

Preparation 10

(R)-4-((R)-4-benzyl-2-oxo-oxazolidin-3-yl)-3-(4-benzyloxy-2,6-dichloro-benzyl)-4-oxo-butyraldehyde

Cool a mixture of (R)-4-benzyl-3-[(S)-2-(4-benzyloxy-2,6-dichloro-benzyl)-pent-4-enoyl]-oxazolidin-2-one (100 g, 190.68 mmol) and dichloromethane (800 mL) to -74°C. Bubble ozone, produced via the A-1 ozone generator at a rate of 75%, through the reaction via carrier air at a rate of 5 CFM until the solution takes on a blue color (approx 3 hr). Add triphenylphosphine (60 g, 228.8 mmol) as a solution in 200 mL dichloromethane and allow the reaction to stir while reaching room temperature overnight. Concentrate the solution under vacuum and purify by silica gel chromatography using a gradient of 20-50% ethyl acetate in hexanes to obtain 82.1 g (82%) of the product as a white foam: MS (m/z): 526 (M+).

Alternate procedure for making (R)-4-((R)-4-benzyl-2-oxo-oxazolidin-3-yl)-3-(4-benzyloxy-2,6-dichloro-benzyl)-4-oxo-butyraldehyde:

Treat a mixture of (R)-4-benzyl-3-[(S)-2-(4-benzyloxy-2,6-dichloro-benzyl)-pent-4-enoyl]-oxazolidin-2-one (0.96 g, 1.8 mmol), THF (21 mL) and water (7 mL) with 2.5% osmium tetroxide in t-butanol (46 mg, 0.18 mmol). Add sodium periodate (1.17 g, 5.5 mmol) and stir the reaction 4 hr at room temperature. Quench the reaction with water and extract with ethyl acetate. Wash the organic phase with aqueous IN sodium thiosulfate then brine. Dry the organic layer over magnesium sulfate, filter, and concentrate under vacuum. Purify the crude material by silica gel chromatography using hexanes: ethyl acetate to elute the pure product. Concentrate the fractions containing product under vacuum to afford 0.46 g (48%) of desired product. MS (m/z): 526 (M+).
Preparation 1

R-3-(4-Benzyloxy-2,6-difluoro-benzyl)-l-(4,4-difluoro-cyclohexyl)-pyrrolidin-2-one

Treat a solution of (R)-4-((R)-4-Benzyl-2-oxo-oxazolidin-3-yl)-3-(4-benzyloxy-2,6-dichloro-benzyl)-4-oxo-butyraldehyde (4.2 g, 8.0 mmol) and 4,4-Difluorocyclohexylamine hydrochloride (1.4 g, 8.4 mmol) in CH$_2$Cl$_2$ (100 mL) with HOAc (0.4 mL, 8.0 mmol). The reaction stirs 1 hr at room temperature. Treat the reaction with sodium triacetoxyborohydride (6.8 g, 32 mmol) and stir for an additional 4
hr at room temperature. Quench the reaction with water and separate the organic layer. Wash the organic with brine, dry over MgSO₄, filter, and remove the solvent. Purify the crude by silica gel column chromatography using Hexanes:EtOAc to elute the pure product. Remove the solvent to afford 1.8 g (48%) of desired product. MS (m/e): 468 (M+1).

**Preparation 12**

(R)-3-(2,6-Dichloro-4-hydroxy-benzyl)-l-(4,4-difluoro-cyclohexyl)-pyrrolidin-2-one

Treat a solution of 3-(4-Benzylxy-2,6-difluoro-benzyl)-l-(4,4-difluoro-cyclohexyl)-pyrrolidin-2-one (1.8 g, 3.8 mmol) in EtOAc (30 mL) with Palladium Hydroxide on carbon (0.2 g) and purge the solution with Hydrogen. Stir the reaction overnight under 1 atm of hydrogen. Filter the reaction through celite to remove catalyst. Remove the solvent to afford 1.4 g (97%) of desired product. MS (m/e): 378 (M+1).

**Preparation 13**

Trifluoro-methanesulfonic acid 3,5-dichloro-4-[l-(4,4-difluoro-cyclohexyl)-2-oxo-pyrrolidin-3-ylmethyl]-phenyl ester

Cool a solution of l-(4,4-Difluoro-cyclohexyl)-3-(2,6-difluoro-4-hydroxy-benzyl)-pyrrolidin-2-one (1.4 g, 3.7 mmol) in pyridine (15 mL) 0°C and treat with Trifluoromethanesulfonic anhydride (0.9 mL, 5.6 mmol). Allow the reaction to warm to room temperature. After stirring for 2 hr at room temperature, quench the reaction with 1N HCl and extract with EtOAc. Wash the organic with brine, dry over MgSO₄, and filter. Purify the crude by silica gel column chromatography.

**Preparation 14**

3',5'-Dichloro-4'-[(R)-l-(4,4-difluoro-cyclohexyl)-2-oxo-pyrrolidin-3-ylmethyl]-biphenyl-4-carboxylic acid methyl ester

Treat a solution of Trifluoro-methanesulfonic acid 3,5-dichloro-4-[l-(4,4-difluoro-cyclohexyl)-2-oxo-pyrrolidin-3-ylmethyl]-phenyl ester (1.8 g, 3.5 mmol), 4-Methoxycarbonylphenylboronic acid (1.3 g, 7.0 mmol), and Tetrakis(triphenylphosphine)palladium(0) (0.4 g, 0.4 mmol) in DME (20 mL) with 2M aqueous K₂CO₃ (5.2 mL). Heat the reaction to 80°C and stir overnight. Cool the reaction and quench with 1N HCl. Extract the aqueous with EtOAc. Wash the organic with brine, dried over MgSO₄, and filter. Purify the crude by silica gel column chromatography.
using Hexanes:EtOAc to elute the pure product. Remove the solvent to afford 1.0 g (57%) of desired product. MS (m/e): 498 (M+1).

**Preparation 15**

3',5'-Dichloro-4'-(R)-l-(4,4-difluoro-cyclohexyl)-2-oxo-pyrrolidin-3-ylmethyl]-biphenyl-4-carboxylic acid

Treat a solution of 3',5'-Dichloro-4'-[(R)-l-(4,4-difluoro-cyclohexyl)-2-oxo-pyrrolidin-3-ylmethyl]-biphenyl-4-carboxylic acid methyl ester (Preparation 14) (1.0 g, 2.0 mmol) in THF/water (15 mL/5 mL) with 2M aqueous LiOH (3.0 mL). Stir the reaction overnight at room temperature. Quench the reaction with IN HCl and extract with EtOAc. Wash the organic with brine, dry over MgSO₄, and filter. Remove the solvent to afford 0.97 g (100%) of desired product. MS (m/e): 482 (M+1).
In Scheme D, compound 10 reacts with π-4-amino-cyclohexanol to form the π-4-hydroxy-cyclohexyl lactam (17). The trans configuration is retained to compound 24.
In Scheme E, compound 24 is reacted with methanesulfonyl chloride to form compound 25. In 25, the mesylate group is in the trans configuration. Compound 25 is reacted with TBAF 5H₂O to form the cis-4-fluoro-cyclohexyl compound 26.

**Preparation 16**

(R)-3-(4-Benzyl-2,6-dichloro-benzyl)-fr aαs-l-(4-hydroxy-cyclohexyl)-pyrrolidin-2-one

Mix (R)-4-((R)-4-benzyl-2-oxo-oxazolidin-3-yl)-3-(4-benzyl-2,6-dichloro-benzyl)-4-oxo-butyrilate (Preparation 10) (3.054 g, 5.8 mmol), trans-A-zmno-cyclohexanol (1.35, 11.6 mmol), NaBH(OAc)₃ (5.18 g, 23.21 mmol) and acetic acid (0.63 mL, 11.2 mmol) in 50 mL of 1,2-dichloroethane. Stir for 12 hours at room temperature. Quench with saturated solution of NaHCO₃ and extract with ethyl acetate. Wash the extract with brine. Dry over magnesium sulfate, filter, and concentrate. After flash column chromatography receive 1.39 g (54%) of the title compound: Mass spectrum (apci) m/z=448 (M+H).

**Preparation 17**

(R)-3-(4-Benzyl-2,6-dichloro-benzyl)-fr aαs-l-(4-triisopropylsilanyloxy-cyclohexyl)-pyrrolidin-2-one

Mix (R)-3-(4-Benzyl-2,6-dichloro-benzyl)-fr aαs-l-(4-hydroxy-cyclohexyl)-pyrrolidin-2-one (Preparation 16) (1.37 g, 3.07 mmol) and imidazole (0.527g, 8.08
mmol) in 10 ml of dry DMF. Add triisopropylsilylchloride (0.81ml, 3.07 mmol) dropwise and stir at room temperature for 5 hours. Quench with IN HCl and extract with ethyl acetate. Wash the extract with NaHCO₃ and brine. Dry over magnesium sulfate, filter, and concentrate. After flash column chromatography, receive 1.83 g (99%) of the title compound: Mass spectrum (apci) m/z=604 (M+H).

Preparation 18

(R)-3-(2,6-Dichloro-4-hydroxy-benzyl)-L-raws-l-(4-triisopropylsilanyloxy-cyclohexyl)pyrrolidin-2-one

Stir (R)-3-(4-Benzyl-2,6-dichloro-benzyl)-L-arø-l-(4-triisopropylsilanyloxy-cyclohexyl)-pyrrolidin-2-one (Preparation 17) (1.83 g, 3.03 mmol) and palladium hydroxide (20% on carbon) (0.200g, 10% by weight) in 100 ml of Ethyl Acetate. Bubble hydrogen gas through the solution while stirring at room temperature for 5 minutes. Stir the mixture under the hydrogen gas atmosphere for 5 hours. Filter through celite and strip the solvent to receive 1.42 g of the title compound (91%). Mass spectrum (apci) m/z=514 (M+H).

Preparation 19

Trifluoro-methanesulfonic acid 3,5-dichloro-4-[(R)-2-oxo-L-arø-l-(4-triisopropylsilanyloxy-cyclohexyl)-pyrrolidin-3-ylmethyl]-phenyl ester

Dissolve (R)-3-(2,6-Dichloro-4-hydroxy-benzyl)-L-arø-l-(4-triisopropylsilanyloxy-cyclohexyl)pyrrolidin-2-one (Preparation 18) (1.42 g, 2.78 mmol) in 10 ml of dry pyridine at 0°C. Add trifluoromethanesulfonic anhydride (0.71ml, 4.17 mmol) dropwise. Stir at room temperature for 2 hours. Quench with IN HCl and extract with ethyl acetate. Wash the extract with IN HCl, NaHCO₃ and brine. Dry over magnesium sulfate, filter, and concentrate. After flash column chromatography receive 1.70 g (96%) of the title compound: Mass spectrum (apci) m/z=646 (M+H).

Preparation 20

3',5'-Dichloro-4'-(R)-2-oxo-L-arø-l-(4-triisopropylsilanyloxy-cyclohexyl)-pyrrolidin-3-ylmethyl]-biphenyl-4-carboxylic acid methyl ester

Mix Trifluoro-methanesulfonic acid 3,5-dichloro-4-[(R)-2-oxo-L-arø-l-(4-triisopropylsilanyloxy-cyclohexyl)-pyrrolidin-3-ylmethyl]-phenyl ester (Preparation 19) (1.70 g, 2.64 mmol), (4-methoxycarbonylphenyl)boronic acid (0.576 g, 3.17 mmol),
tetrakis(triphenylphosphine)palladium(0) (0.305 g, 0.26 mmol) and 1.32 ml of 2 M solution of \( \text{K}_2\text{CO}_3 \) in DME (10 mL). Stir for 12 hours at 80°C. Quench the reaction with water and extract with ethyl acetate. Wash the extract with brine and dry over magnesium sulfate. Flash chromatography affords 1.32 g (80%) of the title compound:

5 Mass spectrum (apci) \( m/z=632 \) (M+H).

**Preparation 21**

3',5'-Dichloro-4'-(R)-2-oxo-\( \text{L} \)-(4-triisopropylsilanyloxy-cyclohexyl)-pyrrolidin-3-ylmethyl]-biphenyl-4-carboxylic acid

Place 3',5'-Dichloro-4'-(R)-2-oxo-\( \text{L} \)-(4-triisopropylsilanyloxy-cyclohexyl)-pyrrolidin-3-ylmethyl]-biphenyl-4-carboxylic acid methyl ester (Preparation 20) (1.32 g, 2.09 mmol) in MeOH (10 mL) and IN NaOH solution (10 mL). Stir for 3 hours at reflux. Strip most of the solvent and quench with IN HCl. Filter white precipitate and rinse with water on the filter. After drying receive 0.95 g (74%) of the title compound: Mass spectrum (apci) \( m/z=617 \) (M+H).

**Preparation 22**

(R)-3-[3,5-Dichloro-4'-(4-trifluoromethyl-piperidine-1-carbonyl)-biphenyl-4-ylmethyl]-\( \text{t} \)rans-1-(4-hydroxy-cyclohexyl)-pyrrolidin-2-one

Mix (R)-3-[3,5-Dichloro-4'-(4-trifluoromethyl-piperidine-1-carbonyl)-biphenyl-4-ylmethyl]-\( \text{t} \)rans-1-(4-hydroxy-cyclohexyl)-pyrrolidin-2-one (Preparation 21) (0.94 g, 1.52 mmol), EDCI (0.358 g, 1.83 mmol), N-methylmorpholine (0.50 mL, 4.57 mmol), HOBT (0.51 g, 1.52 mmol) and 4-trifluoromethyl-piperidine hydrochloride (0.466 g, 3.05 mmol) in CH\(_2\)Cl\(_2\) (15 mL). Stir for 12 hours at room temperature. Quench with IN HCl and extract with ethyl acetate. Wash the extract with NaHCO\(_3\) brine. Dry over magnesium sulfate, filter, and concentrate. After flash column chromatography receive 0.586 g (51%) of the title compound: Mass spectrum (apci) \( m/z=753 \) (M+H).

**Preparation 23**

(R)-3-[3,5-Dichloro-4'-(4-trifluoromethyl-piperidine-1-carbonyl)-biphenyl-4-ylmethyl]-\( \text{t} \)rans-1-(4-hydroxy-cyclohexyl)-pyrrolidin-2-one

Mix (R)-3-[3,5-Dichloro-4'-(4-trifluoromethyl-piperidine-1-carbonyl)-biphenyl-4-ylmethyl]-\( \text{t} \)rans-1-(4-hydroxy-cyclohexyl)-pyrrolidin-2-one (Preparation 22) (0.548 g, 0.78 mmol) and TBAF (1.55 ml, 1.55 mmol) in 15 ml of dry THF. Stir at room temperature for 2 hours. Quench with saturated NaHCO\(_3\) extract with ethyl acetate.
Wash with brine. Dry over magnesium sulfate, filter, and concentrate. After flash column chromatography receive 0.448 g (97%) of the title compound: Mass spectrum (apci) m/z=596 (M+H).

**Preparation 24**

5 Methanesulfonic acid *trans*-4-{(R)-3-[3,5-dichloro-4'-(4-trifluoromethyl-piperidine-1-carbonyl)-biphenyl-4-ylmethyl]-2-oxo-pyrrolidin-1-yl}-cyclohexyl ester

Dissolve (R)-3-[3,5-Dichloro-4'-(4-trifluoromethyl-piperidine-1-carbonyl)-biphenyl-4-ylmethyl]-a -trans-4-(4-hydroxy-cyclohexyl)-pyrrolidin-2-one (Preparation 23) (0.419 g, 0.70 mmol) in 10 ml of dry dichloromethane at 0°C. Add triethylamine (0.18 ml, 1.41 mmol) followed by methanesulfonyl chloride (0.06ml, 0.77 mmol). Stir at room temperature for 5 hours. Quench with IN HCl and extract with ethyl acetate. Wash the extract with IN HCl, NaHCO₃ and brine. Dry over magnesium sulfate, filter, and concentrate. Filter through a short silica plug to receive 0.45 g (95%) of the title compound: Mass spectrum (apci) m/z=675 (M+H).

**Example 1**

(R)-3-{3,5-Dichloro-4'-[4-(2-fluoro-ethyl)-piperazine-1-carbonyl]-biphenyl-4-ylmethyl}-1-(4,4-difluoro-cyclohexyl)-pyrrolidin-2-one

Stir a solution of 3',5'-Dichloro-4'-(R)-1-(4,4-difluoro-cyclohexyl)-2-oxo-pyrrolidin-3-ylmethyl]-biphenyl-4-carboxylic acid (Preparation 15) (0.2 g, 0.4 mmol), 1-(2-Fluoro-ethyl)-piperazine ditrifluorooacetic acid (0.18 g, 0.5 mmol), N-(3-Dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride (0.09 g, 0.5 mmol), 1-Hydroxybenzotriazole (0.17 g, 0.5 mmol) and 4-Methylmorpholine (0.18 mL, 1.7 mmol) in CH₂Cl₂ (10 mL) at room temperature overnight. Quench the reaction with IN HCl and extract with EtOAc. Wash the organic with brine, dry over MgSO₄, and filter. Purify the crude by silica gel column chromatography using Hexanes:EtOAc to elute the pure product. Remove the solvent to afford 0.09 g (39%) of desired product. MS (m/e): 596 (M+1).
Table 1: Prepare the Examples of Table 1 essentially by the method of Example 1 except that 1-(2-Fluoro-ethyl)-piperazine ditrifluoroacetic acid is replaced by the reagent as indicated in column 3.

<table>
<thead>
<tr>
<th>Example</th>
<th>Structure and Chemical name</th>
<th>Reagent</th>
<th>Data m/z (M+1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td><img src="#" alt="Structure" /> (R)-3-[3,5-Dichloro-4'-(morpholine-4-carbonyl)-biphenyl-4-ylmethyl]-1-(4,4-difluoro-cyclohexyl)-pyrrolidin-2-one</td>
<td>Morpholine</td>
<td>MS (m/z): 551 (M+1)</td>
</tr>
<tr>
<td>3</td>
<td><img src="#" alt="Structure" /> (R)-3-[3,5-Dichloro-4'-(4-trifluoromethyl-piperidine-1-carbonyl)-biphenyl-4-ylmethyl]-1-(4,4-difluoro-cyclohexyl)-pyrrolidin-2-one</td>
<td>4-trifluoromethyl-piperidine</td>
<td>MS (m/z): 617 (M+1)</td>
</tr>
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<td><img src="#" alt="Structure" /> (R)-3-[3,5-Dichloro-4'-(1,1-dioxo-llamda<em>6</em>-thiomorpholine-4-carbonyl)-biphenyl-4-ylmethyl]-1-(4,4-difluoro-cyclohexyl)-pyrrolidin-2-one</td>
<td>thiomorpholine 1,1-dioxide</td>
<td>MS (m/z): 599 (M+1)</td>
</tr>
<tr>
<td>Example</td>
<td>Structure and Chemical name</td>
<td>Reagent</td>
<td>Data m/z (M+1)</td>
</tr>
<tr>
<td>---------</td>
<td>----------------------------</td>
<td>-------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>4-tert-butyl-piperidine</td>
<td>MS (m/z): 606 (M+1)</td>
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<tr>
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<td><img src="image" alt="Chemical Structure" /></td>
<td>4,4-difluoro-piperidine</td>
<td>MS (m/z): 585 (M+1)</td>
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<tr>
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<td>1-adamantan-2-yl-piperazine</td>
<td>MS (m/z): 684 (M+1)</td>
</tr>
</tbody>
</table>
Example 9

(R)-3-{3,5-Dichloro-4'-(4-trifluoromethyl-piperidine-1-carbonyl)-biphenyl-4-ylmethyl}-
cis-1-(4-fluoro-cyclohexyl)-pyrrolidin-2-one

Dissolve TBAF 3H₂O (0.436g, 1.36 mmol) in 5 ml of acetonitrile. Add water (0.05ml, 2.72mmol) and stir for 10 minutes. Add Methanesulfonic acid tetrakis-4-[(R)-3-[3,5-dichloro-4'-(4-trifluoromethyl-piperidine-1-carbonyl)-biphenyl-4-ylmethyl]-2-oxo-pyrrolidin-1-yl]-cyclohexyl ester (Preparation 24) (0.458 g, 0.68 mmol). Stir at 80°C for 12 hours. Quench with saturated NaHCO₃ and extract with ethyl acetate. Wash the extract with brine. Dry over magnesium sulfate, filter, and concentrate. After flash column chromatography receive 0.036 g (9%) of the title compound: Mass spectrum (apci) m/z=599 (M+H).
In the following section enzyme and functional assays are described which are useful for evaluating the compounds of the invention.

**11β-HSD type 1 enzyme assay**

Human 11β-HSD type 1 activity is measured by assaying NADPH production by fluorescence assay. Solid compounds are dissolved in DMSO to a concentration of 10 mM. Twenty microliters of each are then transferred to a column of a 96-well polypropylene Nunc plate where they are further diluted 50-fold followed by subsequent two-fold titration, ten times across the plate with additional DMSO using a Tecan Genesis 200 automated system. Plates are then transferred to a Tecan Freedom 200 system with an attached Tecan Temo 96-well head and an Ultra 384 plate reader. Reagents are supplied in 96-well polypropylene Nunc plates and are dispensed individually into black 96-well Molecular Devices High Efficiency assay plates (40 µL/well capacity) in the following fashion: 9 µL/well of substrate (2.22 mM NADP, 55.5 µM Cortisol, 10 mM Tris, 0.25% Prionex, 0.1% Triton X100), 3 µL/well of water to compound wells or 3 µL to control and standard wells, 6 µL/well recombinant human 11β-HSD type 1 enzyme, 2 µL/well of compound dilutions. For ultimate calculation of percent inhibition, a series of wells are added that represent assay minimum and maximum: one set containing substrate with 667 µM carbenoxolone (background), and another set containing substrate and enzyme without compound (maximum signal). Final DMSO concentration is 0.5% for all compounds, controls and standards. Plates are then placed on a shaker by the robotic arm of the Tecan for 15 seconds before being covered and stacked for a three hour incubation period at room temperature. Upon completion of this incubation, the Tecan robotic arm removes each plate individually from the stacker and places them in position for addition of 5 µL/well of a 250 µM carbenoxolone solution to stop the enzymatic reaction. Plates are then shaken once more for 15 seconds then placed into an Ultra 384 microplate reader (355EX/460EM) for detection of NADPH fluorescence.

Data for example compounds in the 11-βHSD1 assay are shown below:
Compounds of the invention can also be tested for selectivity against 11-βHSD2 in an assay similar to that described for 11-βHSD1, but using the 11-βHSD2 enzyme. The assay using the 11-βHSD2 enzyme can be carried out by the methods described herein and supplemented by methods known in the art.

Human aortic smooth muscle cell assay

Primary human aortic smooth muscle cells (AoSMC) are cultured in 5% FBS growth medium to a passage number of 6, then pelleted by centrifugation and resuspended at a density of 9x10⁴ cells/mL in 0.5% FBS assay medium containing 12 ng/mL hTNFα to induce expression of 11β-HSD1. Cells are seeded into 96-well tissue culture assay plates at 100 μL/well (9x10³ cells/well) and incubated for 48 hours at 37°C, 5% CO₂. Following induction, cells are incubated for 4 hours at 37°C, 5% CO₂ in assay medium containing test compounds then treated with 10 μL/well of 10 μM cortisone solubilized in assay medium, and incubated for 16 hours at 37°C, 5% CO₂. Medium from each well is transferred to a plate for subsequent analysis of Cortisol using a competitive fluorescence resonance time resolved immunoassay. In solution, an allophycocyanin
(APC)-cortisol conjugate and free Cortisol analyte compete for binding to a mouse anti-cortisol antibody/Europium (Eu)-anti mouse IgG complex. Higher levels of free Cortisol result in diminishing energy transfer from the Europium-IgG to the APC-cortisol complex resulting in less APC fluorescence. Fluorescent intensities for Europium and APC are measured using a LIL Analyst AD. Europium and APC excitation is measured using 360 nm excitation and 615 nm and 650 nm emission filters respectively. Time resolved parameters for Europium were 1000 µs integration time with a 200 µs delay. APC parameters are set at 150 µs integration time with a 50 µs delay. Fluorescent intensities measured for APC are modified by dividing by the Eu fluorescence (APC/Eu). This ratio is then used to determine the unknown Cortisol concentration by interpolation using a Cortisol standard curve fitted with a 4-parameter logistic equation. These concentrations are then used to determine compound activity by plotting concentration versus % inhibition, fitting with a 4-parameter curve and reporting the IC50.

All of the examples disclosed herein demonstrate activity in the human aortic smooth muscle cell assay with IC50 of less than 300 nM. Data for example compounds in the human aortic smooth muscle cell assay are shown below:

<table>
<thead>
<tr>
<th>Example</th>
<th>Structure</th>
<th>IC50 (nM)</th>
</tr>
</thead>
<tbody>
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<td><img src="image" alt="Structure" /></td>
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<tr>
<td>9</td>
<td><img src="image" alt="Structure" /></td>
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</tbody>
</table>

**Acute In Vivo Cortisone Conversion Assay**

In general, compounds are dosed orally into mice, the mice are challenged with a subcutaneous injection of cortisone at a set timepoint after compound injection, and the blood of each animal is collected some time later. Separated serum is then isolated and analyzed for levels of cortisone and Cortisol by LC-MS/MS, followed by calculation of mean Cortisol and percent inhibition of each dosing group. Specifically, male C57BL/6
mice are obtained from Harlan Sprague Dawley at average weight of 25 grams. Exact weights are taken upon arrival and the mice randomized into groups of similar weights. Compounds are prepared in 1% w-w HEC, 0.25% w-w polysorbate 80, 0.05% w-w Dow Corning antifoam #15 10-US at various doses based on assumed average weight of 25 grams. Compounds are dosed orally, 200 µl per animal, followed by a subcutaneous dose, 200 µl per animal, of 30 mg/kg cortisone at 1 to 24 hours post compound dose. At 10 minutes post cortisone challenge, each animal is euthanized for 1 minute in a CO₂ chamber, followed by blood collection via cardiac puncture into serum separator tubes. Once fully clotted, tubes are spun at 2500 x g, 4°C for 15 minutes, the serum transferred to wells of 96-well plates (Corning Inc, Costar #4410, cluster tubes, 1.2 ml, polypropylene), and the plates are frozen at -20°C until analysis by LC-MS/MS. For analysis, serum samples are thawed and the proteins are precipitated by the addition of acetonitrile containing d₄-cortisol internal standard. Samples are vortex mixed and centrifuged. The supernatant is removed and dried under a stream of warm nitrogen. Extracts are reconstituted in methanol/water (1:1) and injected onto the LC-MS/MS system. The levels of cortisone and Cortisol are assayed by selective reaction monitoring mode following positive ACPI ionization on a triple quadrupole mass spectrophotometer. Data for example compounds in the acute in vivo cortisone conversion assay are shown below:

<table>
<thead>
<tr>
<th>Example</th>
<th>Structure</th>
<th>% Inhibition after 16 hours (dose of 10 (mg/kg))</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
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<td>60.7</td>
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<tr>
<td>4</td>
<td><img src="image" alt="Structure 4" /></td>
<td>50.2</td>
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</tbody>
</table>

Pharmaceutically acceptable salts and common methodology for preparing them are well known in the art. See, e.g., P. Stahl, et al, HANDBOOK OF

The particular dosage of a compound of formula (I) or a pharmaceutically acceptable salt thereof required to constitute an effective amount according to this invention will depend upon the particular circumstances of the conditions to be treated. Considerations such as dosage, route of administration, and frequency of dosing are best decided by the attending physician. Generally, accepted and effective dose ranges for oral or parenteral administration will be from about 0.1 mg/kg/day to about 10 mg/kg/day which translates into about 6 mg to 600 mg, and more typically between 30 mg and 200 mg for human patients. Such dosages will be administered to a patient in need of treatment from one to three times each day or as often as needed to effectively treat a disease selected from those described herein.

One skilled in the art of preparing formulations can readily select the proper form and mode of administration depending upon the particular characteristics of the compound selected, the disorder or condition to be treated, the stage of the disorder or condition, and other relevant circumstances. (Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing Co. (1990)). The compounds claimed herein can be administered by a variety of routes. In effecting treatment of a patient afflicted with or at risk of developing the disorders described herein, a compound of formula (I) or a pharmaceutically acceptable salt thereof can be administered in any form or mode that makes the compound bioavailable in an effective amount, including oral and parenteral routes. For example, the active compounds can be administered rectally, orally, by inhalation, or by the subcutaneous, intramuscular, intravenous, transdermal, intranasal, rectal, occular, topical, sublingual, buccal, or other routes. Oral administration may be preferred for treatment of the disorders described herein. In those instances where oral administration is impossible or not preferred, the composition may be made available in a
form suitable for parenteral administration, e.g., intravenous, intraperitoneal or intramuscular.
WE CLAIM:

1. A compound structurally represented by the formula:

\[
\begin{align*}
\text{wherein} & \\
R_1^a & \text{is } -\text{halogen;} \\
R_1^b & \text{is } -\text{H or } -\text{halogen;} \\
R_2 & \text{is } -\text{H, } -\text{halogen, } -\text{CH}_3 \text{ (optionally substituted with 1 to 3 halogens), or } -\text{O-CH}_3 \text{ (optionally substituted with 1 to 3 halogens);} \\
R_3 & \text{is } -\text{halogen, } -\text{CH}_3 \text{ (optionally substituted with 1 to 3 halogens), or } -\text{O-CH}_3 \text{ (optionally substituted with 1 to 3 halogens);} \\
R_4 & \text{is } -\text{H or } -\text{halogen;} \\
R_5 & \text{is }
\end{align*}
\]
wherein the dashed line represents the point of attachment to the R⁵ position;

wherein n is 0, 1, or 2, and wherein when n is 0, then "(CH₂)ⁿ" is a bond;

wherein m is 1 or 2;

R⁶ is

-H, -(C₁-C₃)alkyl optionally substituted with 1 to 3 halogens),

-(C₁-C₃)alkyl-O-R²₀, -(C₁-C₃)alkyl-pyrrolidinyl, phenyl, -HET¹,

-HET², -CH₂-phenyl, -CH₂-HET¹, -CH₂-HET²,

-(C₁-C₃)alkyl-N(R²₀)(R²₀), -(C₁-C₃)alkyl-N⁺(O⁻)(CH₃)₂,

-(C₁-C₃)alkyl-C(O)N(R⁴¹)(R⁴¹), -CH(C(O)OH)(CH₂OR²₀),

-CH(C(O)OH)(CH₂N(R²₀)(R²₀)), -(C₁-C₃)alkyl-C(O)-R²₀,

N, or

NH₂, or

wherein the dashed line indicates the point of attachment to the position indicated by R⁶;
HET\textsuperscript{1} is
\begin{align*}
\begin{array}{c}
\begin{array}{c}
\text{HET}\textsuperscript{1} \\
\text{HET}\textsuperscript{2}
\end{array}
\end{array}
\end{align*}

wherein the dashed line indicates the point of attachment to the position indicated by HET\textsuperscript{1};

HET\textsuperscript{2} is
\begin{align*}
\begin{array}{c}
\begin{array}{c}
\text{HET}\textsuperscript{2}
\end{array}
\end{array}
\end{align*}

wherein the dashed line indicates the point of attachment to the position indicated by HET\textsuperscript{2};

R\textsuperscript{7} is
\begin{align*}
\text{R}\textsuperscript{7} & = -\text{H}, -(\text{Ci-C3})\text{alkyl}(\text{optionally substituted with 1 to 3 halogens}), \text{ or } \\
& -(\text{Ci-C3})\text{alkyl-O-R}\textsuperscript{20};
\end{align*}

R\textsuperscript{8} is
\begin{align*}
\text{R}\textsuperscript{8} & = -\text{H}, -\text{OH}, -(\text{Ci-C}_6)\text{alkyl}(\text{optionally substituted with 1 to 3 halogens}),
\end{align*}
-52-

\[-(C_2\text{C}_3)\text{alkyl-O-}R^{20}, -(C(O)(C_1-C_6)\text{alkyl(optionally substituted with 1 to 3 halogens}), -(C(O)(C_1-C_6)\text{alkyl(optionally substituted with 1 to 3 halogens}), -(C(O)(C_3-C_8)\text{cycloalkyl, } -S(O_2)-(C_3-C_8)\text{cycloalkyl, } -S(\theta_2)-(C_i-C_3)\text{alkyl(optionally substituted with 1 to 3 halogens) or } \]

R^9 is

-H, -halogen, -CH_3 (optionally substituted with 1 to 3 halogens), or
-0-CH_3 (optionally substituted with 1 to 3 halogens);

R^{10} is independently at each occurrence -H, or -halogen;

R^{20} is independently at each occurrence -H, or -(Ci-C_3)alkyl(optionally substituted with 1 to 3 halogens);

R^{21} is independently at each occurrence -H, -halogen, or -(Ci-C_3)alkyl;

R^{22} is independently at each occurrence -H or -(Ci-C_6)alkyl(optionally substituted with 1 to 3 halogens);

R^{23} is independently at each occurrence -H, -(Ci-C_3)alkyl, or
-C(O)O-(Ci-C_4)alkyl;

R^{24} is independently at each occurrence -H, -halogen, or -(Ci-C_3)alkyl(optionally substituted with 1 to 3 halogens);

R^{25} is independently at each occurrence -H, -halogen, or -(Ci-C_3)alkyl; and

R^{41} is independently at each occurrence -H, or -CH_3,

or a pharmaceutically acceptable salt thereof.

2. A compound of Claim 1 wherein R^{1a} is fluorine and R^{1b} is -H, or a pharmaceutically acceptable salt thereof.

3. A compound of Claim 1 wherein R^{1a} is fluorine and R^{1b} is fluorine, or a pharmaceutically acceptable salt thereof.

4. A compound as claimed by any one of Claims 1 through 3 wherein R^2 and R^3 are chlorine, or a pharmaceutically acceptable salt thereof.

5. A compound as claimed by any one of Claims 1 through 4 wherein R^4 is hydrogen, or a pharmaceutically acceptable salt thereof.
6. A compound as claimed by any one of Claims 1 through 8 wherein R⁵ is

RX3

wherein

R⁸ is -(Ci-C⁴)alkyl optionally substituted with 1 to 3 halogens;
R⁹ is -H, -halogen, or -CH₃ optionally substituted with 1 to 3 halogens; and
R¹⁰ is independently at each occurrence -H or -halogen;
or a pharmaceutically acceptable salt thereof.

7. A compound as claimed by any one of Claims 1 through 6 wherein R⁵ is

SO

, or a pharmaceutically acceptable salt thereof.

8. A compound as claimed by any one of Claims 1 through 6 wherein R⁵ is

RX3

wherein R⁸ is -(Ci-C³)alkyl optionally substituted with 1 to 3 halogens), or a pharmaceutically acceptable salt thereof.

9. A compound as claimed by any one of Claims 1 through 6 wherein R⁵ is

RX3

, or a pharmaceutically acceptable salt thereof.

10. A compound as claimed by any one of Claims 1 through 6 wherein R⁵ is

RX3

, or a pharmaceutically acceptable salt thereof.

11. A compound as claimed by any one of Claims 1 through 6 wherein R⁵ is

RX3

, or a pharmaceutically acceptable salt thereof.

12. A compound that is (R)-3-[3,5-Dichloro-4'- (4-trifluoromethyl-piperidine-1-carbonyl)-biphenyl-4-ylmethyl]-l-(4,4-difluoro-cyclohexyl)-pyrrolidin-2-one, or a pharmaceutically acceptable salt thereof.
13. A compound that is (R)-3-[3,5-Dichloro-4'-(1,1-dioxo-lamda*6*-
thiomorpholine-4-carbonyl)-biphenyl-4-ylmethyl]-1-(4,4-difluoro-cyclohexyl)-
pyrrolidin-2-one, or a pharmaceutically acceptable salt thereof.

14. A pharmaceutical composition which comprises a compound or salt as claimed by
any one of Claims 1 through 13, or a pharmaceutically acceptable salt thereof, and
a pharmaceutically acceptable carrier.

15. A compound as claimed by any one of Claims 1 through 13, or a pharmaceutically
acceptable salt thereof, for use in the preparation of a medicament.

16. A method of selectively reducing the glycemic level in a mammal comprising
administering to a mammal in need thereof an 11-beta hydroxysteroid
dehydrogenase 1 inhibiting dose of a compound or salt as described in any of
claims 1 to 13.

17. A method for treating type 2 diabetes in a patient in need thereof which comprises
administering to said patient an effective amount of a compound as claimed by
any one of Claims 1 through 13, or a stereoisomer thereof, or a pharmaceutically
acceptable salt thereof.

18. An intermediate for preparing a compound of claim 12 or 13 wherein the

intermediate is
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. C07D207/27  C07D401/10  A61K31/4015  A61P3/00

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

C07D  A61K  A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
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<th>Category</th>
<th>Citation of document with indication where appropriate, of the relevant passages</th>
<th>Relevant to claim No</th>
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<td>A</td>
<td>WO 2005/108361 A (JANSSEN PHARMACEUTICA NV [BE]; JAROSKOVA LIBUSE [BE]; LINDERS JOANNE) 17 November 2005 (2005-11-17) cited in the application abstract examples claims</td>
<td>1-18</td>
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</table>

* Special categories of cited documents

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

'S' document member of the same patent family

**D. Further documents are listed in the continuation of Box C**

[X] See patent family annex

Date of the actual completion of the international search: 25 September 2007

Date of mailing of the international search report: 02/10/2007

Name and mailing address of the ISA/

European Patent Office

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Fax (+31-70) 340-3016

Authorized officer: Six-Mal aim, Elke

Form PCT/ISA/21 0 (second sheet) (April 2005)
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos because they relate to subject matter not required to be searched by this Authority, namely although claims 16 and 17 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically.

3. [ ] Claims Nos because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant this International Search Report covers only those claims for which fees were paid specifically claims Nos.

4. [ ] No required additional search fees were timely paid by the applicant Consequently, this International Search Report is restricted to the invention first mentioned in the claims it is covered by claims Nos.

Remark on Protest

- [ ] The additional search fees were accompanied by the applicant's protest
- [ ] No protest accompanied the payment of additional search fees
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