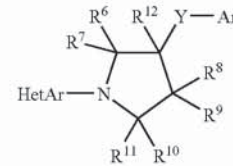




US 20090093527A1

(19) **United States**(12) **Patent Application Publication****Li et al.**(10) **Pub. No.: US 2009/0093527 A1**(43) **Pub. Date: Apr. 9, 2009**(54) **AZACYCLOPENTANE DERIVATIVES AS  
INHIBITORS OF STEAROYL-COENZYME A  
DELTA-9 DESATURASE**(76) Inventors: **Chun Sing Li,**  
Dollard-des-Ormeaux (CA);  
**Yeeman K. Ramtobul,** Pierrefonds  
(CA)Correspondence Address:  
**MERCK AND CO., INC**  
**P O BOX 2000**  
**RAHWAY, NJ 07065-0907 (US)**(21) Appl. No.: **12/227,549**(22) PCT Filed: **Jun. 8, 2007**(86) PCT No.: **PCT/CA2007/001027**§ 371 (c)(1),  
(2), (4) Date: **Nov. 20, 2008****Related U.S. Application Data**(60) Provisional application No. 60/813,091, filed on Jun.  
13, 2006.**Publication Classification**(51) **Int. Cl.**  
*A61K 31/433* (2006.01)  
*C07D 413/14* (2006.01)  
*C07D 417/04* (2006.01)  
*C07D 417/14* (2006.01)  
*A61P 3/10* (2006.01)  
*A61P 3/04* (2006.01)  
*C07D 413/04* (2006.01)  
*A61K 31/427* (2006.01)  
*A61K 31/4245* (2006.01)  
(52) **U.S. Cl. .... 514/363; 548/131; 514/364; 548/194;**  
**514/370; 548/138; 548/143**(57) **ABSTRACT**

Azacyclopentane derivatives of structural formula (I) are selective inhibitors of stearoyl-coenzyme A delta-9 desaturase (SCD1) relative to other known stearoyl-coenzyme A desaturases. The compounds of the present invention are useful for the prevention and treatment of conditions related to abnormal lipid synthesis and metabolism, including cardiovascular disease; atherosclerosis; obesity; diabetes; neurological disease; metabolic syndrome; insulin resistance; liver steatosis; and non-alcoholic steatohepatitis.



(I)

**AZACYCLOPENTANE DERIVATIVES AS  
INHIBITORS OF STEAROYL-COENZYME A  
DELTA-9 DESATURASE**

FIELD OF THE INVENTION

**[0001]** The present invention relates to azacyclopentane derivatives which are inhibitors of stearoyl-coenzyme A delta-9 desaturase (SCD) and the use of such compounds to control, prevent and/or treat conditions or diseases mediated by SCD activity. The compounds of the present invention are useful for the control, prevention and treatment of conditions and diseases related to abnormal lipid synthesis and metabolism, including cardiovascular disease; atherosclerosis; obesity; diabetes; neurological disease; metabolic syndrome; insulin resistance; cancer; liver steatosis; and non-alcoholic steatohepatitis.

BACKGROUND OF THE INVENTION

**[0002]** At least three classes of fatty acyl-coenzyme A (CoA) desaturases (delta-5, delta-6 and delta-9 desaturases) are responsible for the formation of double bonds in mono- and polyunsaturated fatty acyl-CoAs derived from either dietary sources or de novo synthesis in mammals. The delta-9 specific stearoyl-CoA desaturases (SCDs) catalyze the rate-limiting formation of the cis-double bond at the C9-C10 position in monounsaturated fatty acyl-CoAs. The preferred substrates are stearoyl-CoA and palmitoyl-CoA, with the resulting oleoyl and palmitoleoyl-CoA as the main components in the biosynthesis of phospholipids, triglycerides, cholesterol esters and wax esters (Dobryzn and Natami, *Obesity Reviews*, 6: 169-174 (2005)).

**[0003]** The rat liver microsomal SCD protein was first isolated and characterized in 1974 (Strittmatter et al., *PNAS*, 71: 4565-4569 (1974)). A number of mammalian SCD genes have since been cloned and studied from various species. For example, two genes have been identified from rat (SCD1 and SCD2, Thiede et al., *J. Biol. Chem.*, 261, 13230-13235 (1986)), Mihara, K., *J. Biochem. (Tokyo)*, 108: 1022-1029 (1990); four genes from mouse (SCD1, SCD2, SCD3 and SCD4) (Miyazaki et al., *J. Biol. Chem.*, 278: 33904-33911 (2003)); and two genes from human (SCD1 and ACOD4 (SCD2)), (Zhang, et al., *Biochem. J.*, 340: 255-264 (1991); Beiraghi, et al., *Gene*, 309: 11-21 (2003); Zhang et al., *Biochem. J.*, 388: 135-142 (2005)). The involvement of SCDs in fatty acid metabolism has been known in rats and mice since the 1970's (Oshino, N., *Arch. Biochem. Biophys.*, 149: 378-387 (1972)). This has been further supported by the biological studies of a) Asebia mice that carry the natural mutation in the SCD1 gene (Zheng et al., *Nature Genetics*, 23: 268-270 (1999)), b) SCD1-null mice from targeted gene deletion (Ntambi, et al., *PNAS*, 99: 11482-11486 (2002), and c) the suppression of SCD1 expression during leptin-induced weight loss (Cohen et al., *Science*, 297: 240-243 (2002)). The potential benefits of pharmacological inhibition of SCD activity has been demonstrated with anti-sense oligonucleotide inhibitors (ASO) in mice (Jiang, et al., *J. Clin. Invest.*, 115: 1030-1038 (2005)). ASO inhibition of SCD activity reduced fatty acid synthesis and increased fatty acid oxidation in primary mouse hepatocytes. Treatment of mice with SCD-ASOs resulted in the prevention of diet-induced obesity, reduced body adiposity, hepatomegaly, steatosis, post-

and increased expression of genes promoting energy expenditure in liver and adipose tissues. Thus, SCD inhibition represents a novel therapeutic strategy in the treatment of obesity and related metabolic disorders.

**[0004]** There is compelling evidence to support that elevated SCD activity in humans is directly implicated in several common disease processes. For example, there is an elevated hepatic lipogenesis to triglyceride secretion in non-alcoholic fatty liver disease patients (Diraison, et al., *Diabetes Metabolism*, 29: 478-485 (2003)); Donnelly, et al., *J. Clin. Invest.*, 115: 1343-1351 (2005)). The postprandial de novo lipogenesis is significantly elevated in obese subjects (Marques-Lopes, et al., *American Journal of Clinical Nutrition*, 73: 252-261 (2001)). There is a significant correlation between a high SCD activity and an increased cardiovascular risk profile including elevated plasma triglycerides, a high body mass index and reduced plasma HDL (Attie, et al., *J. Lipid Res.*, 43: 1899-1907 (2002)). SCD activity plays a key role in controlling the proliferation and survival of human transformed cells (Scaglia and Igal, *J. Biol. Chem.*, (2005)).

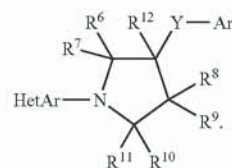
**[0005]** Other than the above mentioned anti-sense oligonucleotides, inhibitors of SCD activity include non-selective thia-fatty acid substrate analogs [B. Behrouzian and P. H. Buist, *Prostaglandins, Leukotrienes, and Essential Fatty Acids*, 68: 107-112 (2003)], cyclopropenoid fatty acids (Raju and Reiser, *J. Biol. Chem.*, 242: 379-384 (1967)), certain conjugated long-chain fatty acid isomers (Park, et al., *Biochim. Biophys. Acta*, 1486: 285-292 (2000)) and a series of pyridazine derivatives disclosed in published international patent applications WO 2005/011653, 2005/011654, 2005/011656, 2005/011656, and 2005/011657, all assigned to Xenon Pharmaceuticals, Inc.

**[0006]** The present invention is concerned with novel azacyclopentane derivatives as inhibitors of stearoyl-CoA delta-9 desaturase which are useful in the treatment and/or prevention of various conditions and diseases mediated by SCD activity including those related, but not limited, to elevated lipid levels, as exemplified in non-alcoholic fatty liver disease, cardiovascular disease, obesity, diabetes, metabolic syndrome, and insulin resistance.

**[0007]** The role of stearoyl-coenzyme A desaturase in lipid metabolism has been described by M. Miyazaki and J. M. Ntambi, *Prostaglandins, Leukotrienes, and Essential Fatty Acids*, 68: 113-121 (2003). The therapeutic potential of the pharmacological manipulation of SCD activity has been described by A. Dobryzn and J. M. Ntambi, in "Stearoyl-CoA desaturase as a new drug target for obesity treatment" *Obesity Reviews*, 6: 169-174 (2005).

SUMMARY OF THE INVENTION

**[0008]** The present invention relates to azacyclopentane derivatives of structural formula I:



(I)

[0009] These azacyclopentane derivatives are effective as inhibitors of SCD. They are therefore useful for the treatment, control or prevention of disorders responsive to the inhibition of SCD, such as diabetes, insulin resistance, lipid disorders, obesity, atherosclerosis, and metabolic syndrome.

[0010] The present invention also relates to pharmaceutical compositions comprising the compounds of the present invention and a pharmaceutically acceptable carrier.

[0011] The present invention also relates to methods for the treatment, control, or prevention of disorders, diseases, or conditions responsive to inhibition of SCD in a subject in need thereof by administering the compounds and pharmaceutical compositions of the present invention.

[0012] The present invention also relates to methods for the treatment, control, or prevention of Type 2 diabetes, insulin resistance, obesity, lipid disorders, atherosclerosis, and metabolic syndrome by administering the compounds and pharmaceutical compositions of the present invention.

[0013] The present invention also relates to methods for the treatment, control, or prevention of obesity by administering the compounds of the present invention in combination with a therapeutically effective amount of another agent known to be useful to treat the condition.

[0014] The present invention also relates to methods for the treatment, control, or prevention of Type 2 diabetes by administering the compounds of the present invention in combination with a therapeutically effective amount of another agent known to be useful to treat the condition.

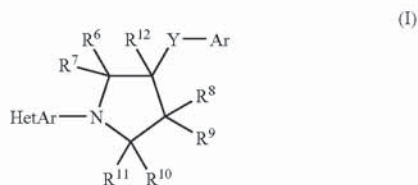
[0015] The present invention also relates to methods for the treatment, control, or prevention of atherosclerosis by administering the compounds of the present invention in combination with a therapeutically effective amount of another agent known to be useful to treat the condition.

[0016] The present invention also relates to methods for the treatment, control, or prevention of lipid disorders by administering the compounds of the present invention in combination with a therapeutically effective amount of another agent known to be useful to treat the condition.

[0017] The present invention also relates to methods for treating metabolic syndrome by administering the compounds of the present invention in combination with a therapeutically effective amount of another agent known to be useful to treat the condition.

#### DETAILED DESCRIPTION OF THE INVENTION

[0018] The present invention is concerned with azacyclopentane derivatives useful as inhibitors of SCD. Compounds of the present invention are described by structural formula I:



or a pharmaceutically acceptable salt thereof; wherein

Y is O, S(O)<sub>p</sub>, or CR<sup>1</sup>R<sup>2</sup>;

[0019] Ar is phenyl, benzyl, naphthyl, or pyridyl each of

HetAr is an heteroaromatic ring selected from the group consisting of:

- [0020] oxazolyl,
- [0021] thiazolyl,
- [0022] imidazolyl,
- [0023] pyrazolyl,
- [0024] isoxazolyl,
- [0025] isothiazolyl,
- [0026] 1,2,4-oxadiazolyl,
- [0027] 1,3,4-oxadiazolyl,
- [0028] 1,2,5-oxadiazolyl,
- [0029] 1,2,3-oxadiazolyl,
- [0030] 1,2,4-thiadiazolyl,
- [0031] 1,2,5-thiadiazolyl,
- [0032] 1,3,4-thiadiazolyl,
- [0033] 1,2,3-thiadiazolyl,
- [0034] 1,2,4-triazolyl,
- [0035] 1,2,3-triazolyl,
- [0036] tetrazolyl,
- [0037] benzthiazolyl,
- [0038] benzoxazolyl,
- [0039] benzimidazolyl,
- [0040] benzisoxazolyl, and
- [0041] benzisothiazolyl;

in which the heteroaromatic ring is optionally substituted with one to two substituents independently selected from R<sup>5</sup>; R<sup>1</sup> and R<sup>2</sup> are each independently hydrogen or C<sub>1-3</sub> alkyl, wherein alkyl is optionally substituted with one to three substituents independently selected from fluorine and hydroxy; each R<sup>3</sup> is independently selected from the group consisting of:

- [0042] C<sub>1-6</sub> alkyl,
- [0043] (CH<sub>2</sub>)<sub>n</sub>OR<sup>4</sup>,
- [0044] (CH<sub>2</sub>)<sub>n</sub>-phenyl,
- [0045] (CH<sub>2</sub>)<sub>n</sub>-naphthyl,
- [0046] (CH<sub>2</sub>)<sub>n</sub>-heteroaryl,
- [0047] (CH<sub>2</sub>)<sub>n</sub>-heterocyclyl,
- [0048] (CH<sub>2</sub>)<sub>n</sub>C<sub>3-7</sub> cycloalkyl,
- [0049] halogen,
- [0050] (CH<sub>2</sub>)<sub>n</sub>N(R<sup>4</sup>)<sub>2</sub>,
- [0051] (CH<sub>2</sub>)<sub>n</sub>C≡N,
- [0052] (CH<sub>2</sub>)<sub>n</sub>CO<sub>2</sub>R<sup>4</sup>,
- [0053] (CH<sub>2</sub>)<sub>n</sub>COR<sup>4</sup>,
- [0054] NO<sub>2</sub>,
- [0055] (CH<sub>2</sub>)<sub>n</sub>NR<sup>4</sup>SO<sub>2</sub>R<sup>4</sup>,
- [0056] (CH<sub>2</sub>)<sub>n</sub>SO<sub>2</sub>N(R<sup>4</sup>)<sub>2</sub>,
- [0057] (CH<sub>2</sub>)<sub>n</sub>S(O)<sub>p</sub>R<sup>4</sup>,
- [0058] (CH<sub>2</sub>)<sub>n</sub>NR<sup>4</sup>C(O)N(R<sup>4</sup>)<sub>2</sub>,
- [0059] (CH<sub>2</sub>)<sub>n</sub>C(O)N(R<sup>4</sup>)<sub>2</sub>,
- [0060] (CH<sub>2</sub>)<sub>n</sub>C(O)N(OR<sup>4</sup>)<sub>2</sub>R<sup>4</sup>,
- [0061] (CH<sub>2</sub>)<sub>n</sub>C(O)N(NH<sub>2</sub>)R<sup>4</sup>,
- [0062] (CH<sub>2</sub>)<sub>n</sub>NR<sup>4</sup>C(O)R<sup>4</sup>,
- [0063] (CH<sub>2</sub>)<sub>n</sub>NR<sup>4</sup>CO<sub>2</sub>R<sup>4</sup>,
- [0064] O(CH<sub>2</sub>)<sub>n</sub>C(O)N(R<sup>4</sup>)<sub>2</sub>,
- [0065] (CH<sub>2</sub>)<sub>n</sub>P(=O)(OR<sub>4</sub>)<sub>2</sub>,
- [0066] (CH<sub>2</sub>)<sub>n</sub>OP(=O)(OR<sub>4</sub>)<sub>2</sub>,
- [0067] (CH<sub>2</sub>)<sub>n</sub>O(CH<sub>2</sub>)<sub>n</sub>P(=O)(OR<sub>4</sub>)<sub>2</sub>,
- [0068] CF<sub>3</sub>,
- [0069] CH<sub>2</sub>CF<sub>3</sub>,
- [0070] OCF<sub>3</sub>, and
- [0071] OCH<sub>2</sub>CF<sub>3</sub>;

in which phenyl, naphthyl, heteroaryl, cycloalkyl, and het-

alkoxy, C<sub>3-6</sub> cycloalkyl, and C<sub>1-4</sub> alkyl wherein alkyl is optionally substituted with hydroxy or one to three fluorines; and wherein any methylene (CH<sub>2</sub>) carbon atom in R<sup>3</sup> is optionally substituted with one to two groups independently selected from fluorine, hydroxy, and C<sub>1-4</sub> alkyl optionally substituted with one to five fluorines; or two substituents when on the same methylene (CH<sub>2</sub>) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

each R<sup>4</sup> is independently selected from the group consisting of

- [0072] hydrogen,
- [0073] C<sub>1-6</sub> alkyl,
- [0074] (CH<sub>2</sub>)<sub>m</sub>-phenyl,
- [0075] (CH<sub>2</sub>)<sub>m</sub>-heteroaryl,
- [0076] (CH<sub>2</sub>)<sub>m</sub>-naphthyl, and
- [0077] (CH<sub>2</sub>)<sub>m</sub>C<sub>3-7</sub> cycloalkyl;

wherein alkyl, phenyl, heteroaryl, and cycloalkyl are optionally substituted with one to three groups independently selected from halogen, C<sub>1-4</sub> alkyl, and C<sub>1-4</sub> alkoxy, wherein alkyl and alkoxy are optionally substituted with one to five fluorines; or two R<sup>4</sup> groups together with the atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and NC<sub>1-4</sub> alkyl; each R<sup>5</sup> is independently selected from the group consisting of

- [0078] C<sub>1-6</sub> alkyl,
- [0079] C<sub>2-4</sub> alkenyl,
- [0080] (CH<sub>2</sub>)<sub>n</sub>OR<sup>4</sup>,
- [0081] (CH<sub>2</sub>)<sub>n</sub>-phenyl,
- [0082] (CH<sub>2</sub>)<sub>n</sub>-naphthyl,
- [0083] (CH<sub>2</sub>)<sub>n</sub>-heteroaryl,
- [0084] (CH<sub>2</sub>)<sub>n</sub>-heterocyclyl,
- [0085] (CH<sub>2</sub>)<sub>n</sub>C<sub>3-7</sub> cycloalkyl,
- [0086] halogen,
- [0087] (CH<sub>2</sub>)<sub>n</sub>N(R<sup>4</sup>)<sub>2</sub>,
- [0088] (CH<sub>2</sub>)<sub>n</sub>C=N,
- [0089] (CH<sub>2</sub>)<sub>n</sub>CO<sub>2</sub>R<sup>4</sup>,
- [0090] (CH<sub>2</sub>)<sub>n</sub>OC(O)R<sup>4</sup>,
- [0091] (CH<sub>2</sub>)<sub>n</sub>COR<sup>4</sup>,
- [0092] NO<sub>2</sub>,
- [0093] (CH<sub>2</sub>)<sub>n</sub>NR<sup>4</sup>SO<sub>2</sub>R<sup>4</sup>,
- [0094] (CH<sub>2</sub>)<sub>n</sub>SO<sub>2</sub>N(R<sup>4</sup>)<sub>2</sub>,
- [0095] (CH<sub>2</sub>)<sub>n</sub>S(O)<sub>p</sub>R<sup>4</sup>,
- [0096] (CH<sub>2</sub>)<sub>n</sub>NR<sup>4</sup>C(O)N(R<sup>4</sup>)<sub>2</sub>,
- [0097] (CH<sub>2</sub>)<sub>n</sub>C(O)N(R<sup>4</sup>)<sub>2</sub>,
- [0098] (CH<sub>2</sub>)<sub>n</sub>C(O)N(OR<sup>4</sup>)<sub>2</sub>R<sup>4</sup>,
- [0099] (CH<sub>2</sub>)<sub>n</sub>C(O)N(NH<sub>2</sub>)R<sup>4</sup>,
- [0100] (CH<sub>2</sub>)<sub>n</sub>C(O)NR<sup>4</sup>NC(O)R<sup>4</sup>,
- [0101] (CH<sub>2</sub>)<sub>n</sub>NR<sup>4</sup>C(O)R<sup>4</sup>,
- [0102] (CH<sub>2</sub>)<sub>n</sub>NR<sup>4</sup>CO<sub>2</sub>R<sup>4</sup>,
- [0103] (CH<sub>2</sub>)<sub>n</sub>P(=O)(OR<sub>4</sub>)<sub>2</sub>,
- [0104] (CH<sub>2</sub>)<sub>n</sub>OP(=O)(OR<sub>4</sub>)<sub>2</sub>,
- [0105] (CH<sub>2</sub>)<sub>n</sub>O(CH<sub>2</sub>)<sub>n</sub>P(=O)(OR<sub>4</sub>)<sub>2</sub>,
- [0106] O(CH<sub>2</sub>)<sub>n</sub>C(O)N(R<sup>4</sup>)<sub>2</sub>,
- [0107] CF<sub>3</sub>,
- [0108] CH<sub>2</sub>CF<sub>3</sub>,
- [0109] OCF<sub>3</sub>, and
- [0110] OCH<sub>2</sub>CF<sub>3</sub>;

in which phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are optionally substituted with one to three substituents independently selected from halogen, hydroxy, C<sub>1-4</sub>

hydroxy, or one to three fluorines; and wherein any methylene (CH<sub>2</sub>) carbon atom in R<sup>5</sup> is optionally substituted with one to two groups independently selected from fluorine, hydroxy, and C<sub>1-4</sub> alkyl optionally substituted with one to five fluorines; or two substituents when on the same methylene (CH<sub>2</sub>) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

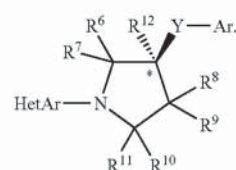
R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, and R<sup>12</sup> are each independently hydrogen or C<sub>1-3</sub> alkyl, wherein alkyl is optionally substituted with one to three substituents independently selected from fluorine and hydroxyl;

each n is independently 0, 1 or 2;

each m is independently 0, 1, or 2;

p is 0, 1, or 2.

[0111] In one embodiment of the compounds of the present invention, there are provided compounds of structural formula Ia having the indicated absolute stereochemical configuration at the stereogenic azacyclopentane carbon atom marked with an \*:



(Ia)

[0112] In a class of this embodiment of the compounds of the present invention, Y is O. In a subclass of this class, HetAr is 2-thiazolyl or 1,3,4-thiadiazol-2-yl monosubstituted at the C-5 position of the thiazole or 1,3,4-thiadiazole ring with R<sup>5</sup> as defined above. In another subclass of this class, Ar is phenyl or pyridyl optionally substituted with one to three R<sup>3</sup> substituents as defined above. In yet another subclass of this class, Ar is phenyl or pyridyl optionally substituted with one to three R<sup>3</sup> substituents as defined above, and HetAr is 2-thiazolyl or 1,3,4-thiadiazol-2-yl monosubstituted at the C-5 position of the thiazole or 1,3,4-thiadiazole ring with R<sup>5</sup> as defined above.

[0113] In a second class of this embodiment of the compounds of the present invention, Y is S(O)<sub>p</sub>. In a subclass of this class, HetAr is 2-thiazolyl or 1,3,4-thiadiazol-2-yl monosubstituted at the C-5 position of the thiazole or 1,3,4-thiadiazole ring with R<sup>5</sup> as defined above. In another subclass of this class, Ar is phenyl or pyridyl optionally substituted with one to three R<sup>3</sup> substituents as defined above. In yet another subclass of this class, p is 0, Ar is phenyl or pyridyl optionally substituted with one to three R<sup>3</sup> substituents as defined above, and HetAr is 2-thiazolyl or 1,3,4-thiadiazol-2-yl monosubstituted at the C-5 position of the thiazole or 1,3,4-thiadiazole ring with R<sup>5</sup> as defined above.

[0114] In a third class of this embodiment of the compounds of the present invention, Y is CR<sup>1</sup>R<sup>2</sup>. In a subclass of this class, HetAr is 2-thiazolyl or 1,3,4-thiadiazol-2-yl monosubstituted at the C-5 position of the thiazole or 1,3,4-thiadiazole ring with R<sup>5</sup> as defined above. In another subclass of this class, Ar is phenyl or pyridyl optionally substituted with one to three R<sup>3</sup> substituents as defined above. In yet another subclass of this class, R<sup>1</sup> and R<sup>2</sup> are hydrogen, Ar is phenyl or

thiadiazol-2-yl monosubstituted at the C-5 position of the thiazole or 1,3,4-thiadiazole ring with R<sup>5</sup> as defined above.

[0115] In a second embodiment of the compounds of the present invention, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, and R<sup>12</sup> hydrogen.

[0116] In a third embodiment of the compounds of the present invention, each R<sup>3</sup> is independently selected from the group consisting of halogen, C<sub>1-4</sub> alkyl, trifluoromethyl, C<sub>1-4</sub> alkylsulfonyl, cyano, and C<sub>1-4</sub> alkoxy.

[0117] In a fourth embodiment of the compounds of the present invention, each R<sup>5</sup> is independently selected from the group consisting of:

[0118] halogen,

[0119] cyano,

[0120] C(O)N(R<sup>4</sup>)<sub>2</sub>,

[0121] C(O)R<sup>4</sup>,

[0122] CO<sub>2</sub>R<sup>4</sup>,

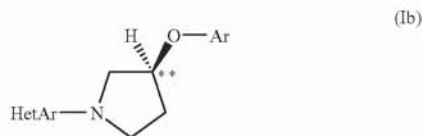
[0123] CH<sub>2</sub>OR<sup>4</sup>, wherein CH<sub>2</sub> is optionally substituted with one to substituents independently from hydroxy, fluorine, and methyl,

[0124] NR<sup>4</sup>C(O)R<sup>4</sup>,

[0125] SO<sub>2</sub>N(R<sup>4</sup>)<sub>2</sub>, and

[0126] heteroaryl which is selected from the group consisting of 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl, 2-thiazolyl, and 2H-tetrazol-5-yl, wherein heteroaryl is optionally substituted with one to two substituents independently selected from halogen, hydroxy, C<sub>1-4</sub> alkoxy, C<sub>3-6</sub> cycloalkyl, and C<sub>1-4</sub> alkyl wherein alkyl is optionally substituted with hydroxy or one to three fluorines.

[0127] In a fifth embodiment, there are provided compounds of structural formula (Ib) having the indicated absolute stereochemical configuration at the stereogenic azacyclopentane carbon atom marked with an \*\*:



wherein Ar and HetAr are as defined above.

[0128] In a class of this embodiment, Ar is phenyl optionally substituted with one to three R<sup>3</sup> substituents and HetAr is 2-thiazolyl or 1,3,4-thiadiazol-2-yl monosubstituted at the C-5 position of the thiazole or 1,3,4-thiadiazole ring with R<sup>5</sup>; each R<sup>3</sup> is independently selected from the group consisting of halogen, C<sub>1-4</sub> alkyl, trifluoromethyl, C<sub>1-4</sub> alkylsulfonyl, cyano, and C<sub>1-4</sub> alkoxy; and each R<sup>5</sup> is independently selected from the group consisting of:

[0129] halogen,

[0130] cyano,

[0131] C(O)N(R<sup>4</sup>)<sub>2</sub>,

[0132] C(O)R<sup>4</sup>,

[0133] CO<sub>2</sub>R<sup>4</sup>,

[0134] CH<sub>2</sub>OR<sup>4</sup>, wherein CH<sub>2</sub> is optionally substituted with one to substituents independently from hydroxy, fluorine, and methyl,

[0135] NR<sup>4</sup>C(O)R<sup>4</sup>,

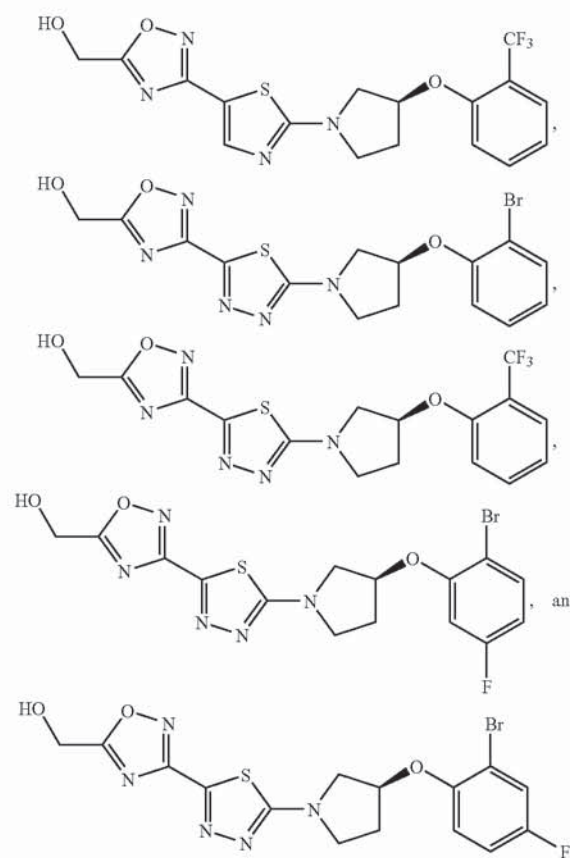
[0136] SO<sub>2</sub>N(R<sup>4</sup>)<sub>2</sub>, and

[0137] heteroaryl which is selected from the group consisting of 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-oxa-

independently selected from halogen, hydroxy, C<sub>1-4</sub> alkoxy, C<sub>3-6</sub> cycloalkyl, and C<sub>1-4</sub> alkyl wherein alkyl is optionally substituted with hydroxy or one to three fluorines.

[0138] In a subclass of this class, R<sup>5</sup> is heteroaryl optionally substituted with one to three substituents independently selected from halogen, hydroxy, hydroxymethyl, C<sub>1-3</sub> alkyl, trifluoromethyl, and C<sub>1-3</sub> alkoxy. In a subclass of this subclass, heteroaryl is 1,3,4-oxadiazol-2-yl or 1,2,4-oxadiazol-3-yl each of which is optionally substituted with one substituent independently selected from halogen, hydroxy, hydroxymethyl, C<sub>1-3</sub> alkyl, trifluoromethyl, and C<sub>1-3</sub> alkoxy.

[0139] Illustrative, but nonlimiting examples, of compounds of the present invention that are useful as inhibitors of SCD are the following:



and pharmaceutically acceptable salts thereof.

[0140] As used herein the following definitions are applicable.

[0141] "Alkyl", as well as other groups having the prefix "alk", such as alkoxy and alkanoyl, means carbon chains which may be linear or branched, and combinations thereof, unless the carbon chain is defined otherwise. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl, and the like. Where the specified number of carbon atoms permits, e.g., from C<sub>3-10</sub>, the term alkyl also includes cycloalkyl groups, and combinations of linear or branched alkyl chains

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