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(54) Title: SPIROCYCLIC COMPOUNDS AS STEAROYL COA DESATURASE INHIBITORS

(57) Abstract: The present invention provides Stearoyl CoA Desaturase (SCD) inhibitors. In particular, compounds described herein are useful for treating or preventing diseases, conditions and/or disorders modulated by Stearoyl CoA Desaturase 1 (SCDl). Also provided herein are processes for preparing compounds described herein, intermediates used in their synthesis, pharmaceutical compositions thereof, and methods for treating or preventing diseases, conditions and/or disorders modulated by Stearoyl CoA Desaturase (SCD).

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SPIROCYCLIC COMPOUNDS AS STEAROYL CoA DESATURASE INHIBITORS

This application claims the benefit of Indian Patent Application No. 1842/MUM/2007 filed on September 20, 2007, and 669/MUM/2008 filed on March 28, 2008, and U.S. Provisional Application No. 61/015,329, filed on December 20, 2007, all of which are hereby incorporated by reference.

Field of the Invention

The present invention provides spirocyclic compounds, which are used as Stearoyl CoA Desaturase (SCD) inhibitors. In particular, compounds described herein are used for treating or preventing diseases, conditions and/or disorders modulated by Stearoyl CoA Desaturasel (SCD1). Also, provided herein are processes for preparing the described compounds, and the intermediates used in their synthesis, pharmaceutical compositions thereof, and methods for treating or preventing diseases, conditions and/or disorders modulated by Stearoyl CoA Desaturase (SCD1) inhibitors.

Background of the Invention

Metabolic energy balance which is important for well-being, is maintained by appropriate adjustment between energy intake and energy expenditure. Primary defects in energy balance produce obesity. Over the past few years there has been a sharp increase in obesity in many countries. Obesity is a principal cause of morbidity and mortality mainly because it increases risk for other conditions that shorten life, including diabetes, insulin resistance, coronary artery disease, hypertension and non-alcoholic fatty liver disease collectively known as metabolic syndrome (*J. Am. Med. Assoc.*, 288, 1723-1727 (2002)). Obesity has been identified as an independent risk factor for the development of Type 2 diabetes.

Although, the exact etiology of many events underlying obesity is not very well known, typically obesity is manifested by increase in plasma free fatty acids and excessive lipid accumulation in some organs. Abnormal lipid metabolism in obese subjects results in accumulation of significant amounts of fat in liver, adipose tissue, muscle and other peripheral tissues, which sets in insulin resistance (*Obesity Reviews*, 6, 169-174 (2005)). In the liver, fatty acids accumulate causing an increase in hepatic lipid content or get packaged into the very low density lipoprotein for export to other peripheral tissues. Liver steatosis associated with obesity can also result from an enhanced rate of *de novo* fatty acid synthesis

and/or dysregulation of intracellular lipid partitioning in which fatty acid oxidation is impaired and its esterification enhanced. Lipid abnormalities in obese subjects, in particular hypertriglyceridemia, low HDL cholesterol and altered LDL cholesterol particle size, are atherogenic. The dyslipidemic state initiates a cascade of events including release of proinflammatory adipokines which induces a proinflammatory state that drives pathogenesis of atherosclerosis. Increased release of proinflammatory adipokines also increases fibrinogen and plasminogen activator inhibitor levels thereby increasing risk for arterial thrombosis. Several studies show that even modest weight gain can precipitate the onset of hypertension (*Ann. Rev. Med.,* 56, 45-62 (2005)). Hence obesity alone can drive all aspects of the metabolic syndrome. It is believed that effective treatment of obesity could lead to prevention and control of metabolic syndrome (*Obesity Reviews,* 6, 169-174 (2005)).

Stearoyl CoA desaturase1 (SCD1) is shown to be a key enzyme that plays crucial role in lipid metabolism and body weight control (*Science,* 297, 240-243 (2002); *Obesity Reviews,* 6, 169-174 (2005); *J. Clinical Investigation,* 1-9 (2005)). SCD1 is a central lipogenic enzyme catalyzing the biosynthesis of monounsaturated fatty acids from saturated fatty acids by addition of a cis double bond between carbon 9 and carbon 10 (*PNAS,* 71, 4565-4569 (1974); *J Biol Chem.,* 251, 5095-5103 (1976)). SCD1 has two preferred substrates palmitoyl CoA and stearoyl CoA, which are desaturated to palmitoleoyl and oleoyl CoA respectively (*J Biol Chem.,* 251, 5095-5103 (1976)). Oleate is found to be the major monounsaturated fatty acid of membrane phospholipids, triglycerides, cholesterol esters, wax esters and alkyl-1, 2-diacylglycerol. The ratio of stearate to oleate is one of the factors influencing membrane fluidity and its alteration is important in diseases like aging, cancer, diabetes, obesity, and neurological, vascular and heart diseases (*Biochem. Biophys. Acta.,* 431, 469-480 (1976); *J. Biol. Chem.,* 268, 6823-6826 (1993); *Diabetes,* 40, 280-289 (1991); *Neurochem Res.,* 26, 771-782 (1994); *Arthritis Rheum.,* 43, 894-900 (2000); *Cancer Lett.,* 173, 139-144 (2001)).

The role of SCD1 in regulation of body weight is well discussed in the literature. Robust up-regulation of SCD1 expression and/or activity is observed in obese experimental animals (*Science,* 297, 240-243 (2002)), fat chickens (*Am Soc Nutri Scie.,* 249-256 (1997)) and obese human subjects (*Cell Metab.,* 2, 251-61 (2005)) compared to their lean counterparts. In chickens, the fat chickens have higher hepatic delta-9 desaturase activity and higher plasma triglyceride compared to lean birds. Inhibition of delta-9 (δ-9) desaturase by a mixture of cyclopropenic fatty acids resulted in reduced triglyceride formation *in vitro* in hepatocytes isolated from the fat chickens (*Am Soc Nutri Scie.,* 249-256 (1997)). SCD1 over activity leads to weight gain and its deficiency leads to leanness. SCD1 deficiency either

directly or indirectly induces a signal that partitions fatty acids towards oxidation rather than synthesis. Asebia mice with natural mutation in the SCD1 gene manifest defective cholesterol ester and triglyceride synthesis and are lean and hypermetabolic (*J. Biol. Chem.*, 275, 30132-30138 (2000); *Science,* 297, 240-243 (2002)). Laboratory mice with targeted disruption in the SCD1 gene are resistant to diet-induced obesity and have reduced body adiposity, liver lipid accumulation and postprandial plasma insulin and glucose levels, with concomitant increase in the metabolic rate, thermogenesis and insulin sensitivity (*J Nutr.*, 131, 2260-2268 (2001); *PNAS,* 99, 11482-11486 (2002)). SCD1 is documented as a key enzyme in regulating hepatic lipogenesis, lipid oxidation and therapeutic manipulation of SCD can be of benefit in treatment of obesity and metabolic syndrome (*Obesi Reviews,* 6, 169-174 (2005); *Curr Drug Targets Immune Endocr Metabol Disord.*, 3, 271-280 (2003)). Several studies report inhibition of SCD1 expression and activity by different agents such as thia-fatty acids like 9-thiastearic acid, cyclopropenoid fatty acids like sterculic acid and certain conjugated linoleic acid isomers. Trans-10, cis-12 isomer of conjugated linolenic acid inhibits SCD1 expression as well as desaturase activity in *vitro* (*Biochim Biophys Acta.*, 1486 (2-3), 285-292 (2000); *Biochem Biophys Res Commun.*, 284(3), 689-693 (2001)). Conjugated linoleic acid (CLA) administration through feed reduces body fat and increases lean body mass in several animal species (*Lipids,* 32, 853-858 (1997); *FASEB,* 12, A836 (1998); *Lipids,* 34, 243- 248 (1999)). Sterculic acid (8-(2-octylcyclopropenyl) octanoic acid) and malvalic acid (7-(2-octylcyclopropenyl)heptanoic acid) are C18 and C16 derivatives of sterculoyl- and malvaloyl fatty acids, respectively and inhibit SCD enzymatic activity by direct interaction with the enzyme. However all these agents are weak and non-specific inhibitors of SCD1. SCD1 antisense oligonucleotide inhibitors specifically reduce SCD1 expression thereby reducing fatty acid synthesis and secretion, body adiposity, hepatomegaly, steatosis and prevent obesity in mice by improving energy balance (*J Clinical Investigation*, F 1-9 (2005)).

U.S. Publication No. 2004/0209865 and PCT Publication No. WO 2003/9780 disclose certain alkyne compounds with MCH antagonistic activity. PCT Publication No. WO 2004/092179 discloses certain spiro derivatives as antioxidant. PCT Publication No. WO 2006/129826 discloses certain novel piperidine derivatives as histamine H_3 receptors.

U.S. Publication Nos. 2006/009459 and PCT Publication Nos. WO 2005/011653, 2005/01164, 2005/011655, 2005/011656 and 2005/011657 disclose certain pyridazine derivatives, pyridyl derivatives, and piperazine derivatives and their use for inhibiting human stearoyl-CoA desaturase (hSCD) activity. U.S. Publication No. 2004/072877 is directed to a

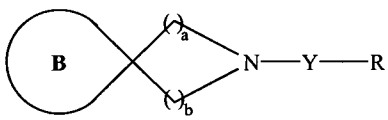
method for increasing insulin sensitivity by reducing stearoyl CoA desaturase 1 (SCD1) activity in a subject sufficiently to increase insulin sensitivity.

There is still a need for safer and more effective therapeutic treatments for diseases, conditions and/or disorders modulated by SCD enzyme. In particular, there is a need for novel compounds that are used for treating obesity, diabetes, cardiovascular disease and complications thereof.

Summary of the Invention

The present invention provides spirocyclic compounds as SCD inhibitors, which are used in the treatment of diseases, conditions or disorders modulated by SCD enzyme (and in particular SCD1) and processes for the synthesis of these compounds, Pharmaceutically acceptable salts, pharmaceutically acceptable solvates, stereoisomers, metabolites, polymorphs or N-oxides of these compounds having the same type of activity, and are also provided Pharmaceutical compositions containing compounds described herein optionally together with one or more pharmaceutically acceptable excipients (e.g., carriers or diluents), which are used for treating diseases, conditions or disorders modulated by SCD, are further provided.

Accordingly, in one aspect, this invention is related to spirocyclic compounds of the formula (I):

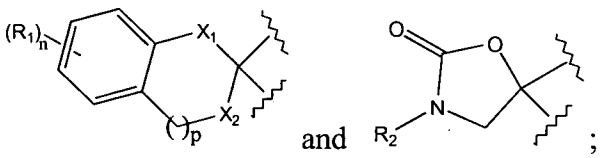


Formula I

wherein

ring B is substituted or unsubstituted heterocyclyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl; or

a mono or bicyclic ring selected from



;

X_1 and X_2 are independently selected from $-CR_aR_b$, $-CR_aR_b-CR_aR_b$, $-CR_aR_bC(O)-$, $-C(O)CR_aR_b-$, $-NR_c-$, -S- or -O;

Y is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or

unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,or substituted or unsubstituted heterocyclyl;

R is -L-R_d or R';

R' is $C(O)NR^xR^y$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocyclyl;

L is $-(CR_aR_b)_n-$, $-C(R_a)=C(R_a)-$, or $-C\equiv C-$;

R_d is selected from H, halogen, nitro, cyano, $-COOR^x$, $-C(O)R^x$, $-C(S)R^x$, $-C(O)NR^xR^y$, $-C(O)ONR^xR^y$, $-NR^xCONR^yR^z$, $-N(R^x)SOR^y$, $-N(R^x)SO_2R^y$, $-NR^xC(O)OR^y$, $-NR^xR^y$, $-NR^xC(O)R^y$, $-NR^xC(S)R^y$, $-NR^xC(S)NR^yR^z$, $-SONR^xR^y$, $-SO_2NR^xR^y$, $-OR^x$, $-OC(O)R^x$, $-OC(O)NR^xR^y$, $-SR^x$, $-SOR^x$, $-SO_2R^x$, $-ONO_2$, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each occurrence of R_1 is selected from H, halogen, nitro, cyano, $-COOR^x$, $-C(O)R^x$, $-C(S)R^x$, $-C(O)NR^xR^y$, $-C(O)ONR^xR^y$, $-NR^xCONR^yR^z$, $-N(R^x)SOR^y$, $-N(R^x)SO_2R^y$, $-NR^xC(O)OR^y$, $-NR^xR^y$, $-NR^xC(O)R^y$, $-NR^xC(S)R^y$, $-NR^xC(S)NR^yR^z$, $-SONR^xR^y$, $-SO_2NR^xR^y$, $-OR^x$, $-OC(O)R^x$, $-OC(O)NR^xR^y$, $-R^xNR^yC(O)R^z$, $-R^xOR^y$, $-R^xC(O)OR^y$, $-R^xC(O)NR^yR^z$, $-R^xC(O)R^y$, $-R^xOC(O)R^y$, $-SR^x$, $-SOR^x$, $-SO_2R^x$, $-ONO_2$, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocycle, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R_2 is selected from H, $-COOR^x$, $-C(O)R^x$, $-C(S)R^x$, $-C(O)NR^xR^y$, $-C(O)ONR^xR^y$, $-NR^xCONR^yR^z$, $-N(R^x)SOR^y$, $-N(R^x)SO_2R^y$, $-NR^xC(O)OR^y$, $-NR^xR^y$, $-NR^xC(O)R^y$, $-NR^xC(S)R^y$, $-NR^xC(S)NR^yR^z$, $-SONR^xR^y$, $-SO_2NR^xR^y$, substituted or unsubstituted alkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocyclyl;

R^x, R^y and R^z are independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or

unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclylalkyl, or substituted or unsubstituted amino;

R_a,R_b, and R_c are independently selected from hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclylalkyl, or substituted or unsubstituted amino;

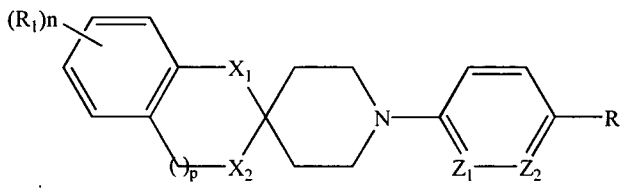
'a' and 'b' are independently an integer selected from1, 2 or 3;

'n' is an integer selected from 0, 1, 2, 3 or 4;

'p' is an integer selected from 0 or 1.

or a pharmaceutically acceptable salt thereof, solvate thereof, an ester thereof, a stereoisomers thereof, a polymorph thereof, a prodrug thereof, a metabolite thereof or an N-oxide thereof.

Another preferred embodiment of the present invention is a compound of Formula (II),



Formula (II)

Z_1 and Z_2 are selected from N or CR_1;

X_1 and X_2 are independently selected from $-CR_aR_b$, $-CR_aR_b-CR_aR_b$, $-CR_aR_bC(O)-$, $-C(O)CR_aR_b-$, $-NR_c-$, -S- or -O;

R is $-L-R_d$ or R';

R' is $C(O)NR^xR^y$, substituted or unsubstituted alkyl or substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl,

substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocyclyl;

L is $-(CR_aR_b)_n-$, $-C(R_a)=C(R_a)-$, or $-C\equiv C-$;

R_d is selected from H, halogen, nitro, cyano, $-COOR^x$, $-C(O)R^x$, $-C(S)R^x$, $-C(O)NR^xR^y$, $-C(O)ONR^xR^y$, $-NR^xCONR^yR^z$, $-N(R^x)SOR^y$, $-N(R^x)SO_2R^y$, $-NR^xC(O)OR^y$, $-NR^xR^y$, $-NR^xC(O)R^y$, $-NR^xC(S)R^y$, $-NR^xC(S)NR^yR^z$, $-SONR^xR^y$, $-SO_2NR^xR^y$, $-OR^x$, $-OC(O)R^x$, $-OC(O)NR^xR^y$, $-R^xNR^yC(O)R^z$, $-R^xOR^y$, $-R^xC(O)OR^y$, $-R^xC(O)NR^yR^z$, $-R^xC(O)R^y$, $-R^xOC(O)R^y$, $-SR^x$, $-SOR^x$, $-SO_2R^x$, $-ONO_2$, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocycle, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each occurrence of R_1 is selected from H, halogen, nitro, cyano, $-COOR^x$, $-C(O)R^x$, $-C(S)R^x$, $-C(O)NR^xR^y$, $-C(O)ONR^xR^y$, $-NR^xCONR^yR^z$, $-N(R^x)SOR^y$, $-N(R^x)SO_2R^y$, $-NR^xC(O)OR^y$, $-NR^xR^y$, $-NR^xC(O)R^y$, $-NR^xC(S)R^y$, $-NR^xC(S)NR^yR^z$, $-SONR^xR^y$, $-SO_2NR^xR^y$, $-OR^x$, $-OC(O)R^x$, $-OC(O)NR^xR^y$, $-R^xNR^yC(O)R^z$, $-R^xOR^y$, $-R^xC(O)OR^y$, $-R^xC(O)NR^yR^z$, $-R^xC(O)R^y$, $-R^xOC(O)R^y$, $-SR^x$, $-SOR^x$, $-SO_2R^x$, $-ONO_2$, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocycle, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^x, R^y and R^z are independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclylalkyl, or substituted or unsubstituted amino;

R_a,R_b, and R_c are independently selected from hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted

cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclylalkyl, or substituted or unsubstituted amino;

'n' is an integer selected from 0, 1, 2, 3 or 4;

'p' is an integer selected from 0 or 1.

or a pharmaceutically acceptable salt thereof, solvate thereof, an ester thereof, a stereoisomers thereof, a polymorph thereof, a prodrug thereof, a metabolite thereof or an N-oxide thereof.

Another preferred embodiment is a compound of formula (I), wherein p is 0.

Another preferred embodiment is a compound of formula (I), wherein p is 1.

Another preferred embodiment is a compound of formula (II), wherein Z_1 is N; and Z_2 is CR_1. In this embodiment R_1 is hydrogen.

Another preferred embodiment is a compound of formula (II), wherein Z_1 and Z_2 are N.

Another preferred embodiment is a compound of formula (II), wherein R_1 is halogen; and 'n' is 0, 1 or 2.

Another preferred embodiment is a compound of formula (II), wherein X_1 and X_2 are oxygen; and 'p' is 0.

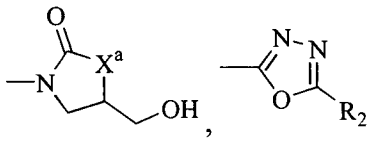
Another preferred embodiment is a compound of formula (II), wherein X_1 is oxygen; X_2 is $-CR_aR_b-CR_aR_b$, $-CR_aR_bC(O)-$, or $-C(O)\ CR_aR_b-$. In this embodiment R_a and R_b are hydrogen or halogen; and 'p' is 0.

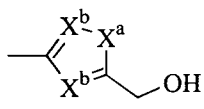
Another preferred embodiment is a compound of formula (II), wherein X_1 is oxygen; X_2 is $-CR_aR_b$. In this embodiment R_a and R_b are hydrogen; and 'p' is 1.

Another preferred embodiment is a compound of formula (II), wherein R is substituted or unsubstituted 5 or 6 membered heteroaryl or heterocyclyl.

Another preferred embodiment is a compound of formula (II), wherein R is R'.

Another preferred embodiment is a compound of formula (II), wherein R' is substituted or unsubstituted 5 membered heterocycle selected from



or

wherein X^a is O; X^b is N; and R_2 is substituted or unsubstituted alkyl, (for example substituent is halogen) or heterocyclyl.

Another preferred embodiment is a compound of formula (II), wherein R' is

substituted or unsubstituted 5 or 6 membered heteroaryl or heterocycle, preferably selected from substituted or unsubstituted pyridine, tetrazole or imidazole.

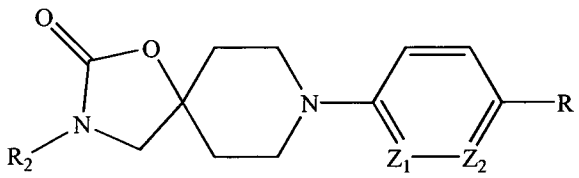
Another preferred embodiment is a compound of formula (II), wherein R' is $C(O)NR^xR^y$. In this embodiment R^x and R^y are hydrogen or substituted or unsubstituted alkyl, wherein substituent is straight or branched chain alkyl.

Another preferred embodiment is a compound of formula (II), wherein R is -L-R_d, where R_d substituted or unsubstituted alkynyl.

Another preferred embodiment is a compound of formula (II), wherein R is R', wherein R' substituted or unsubstituted alkynyl.

Another preferred embodiment is a compound of formula (II), wherein R is -L-R_d or R'. In this embodiment L is -C≡C-; and R_d is substituted or unsubstituted aryl, wherein substituent is -OH or -OC(O)CH3.

Another preferred embodiment of the present invention is a compound of Formula (III),



Formula (III)

R_2, Z_1, Z_2, and R are as defined in formula (I) & formula (II),

or a pharmaceutically acceptable salt thereof, solvate thereof, an ester thereof, a stereoisomer thereof, a polymorph thereof, a prodrug thereof, a metabolite thereof or an N-oxide thereof,

Another preferred embodiment is a compound of formula (III), wherein Z_1 is N; and Z_2 is CR_2. In this embodiment R_2 is hydrogen.

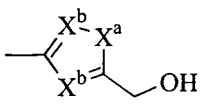
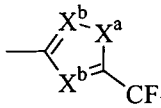
Another preferred embodiment is a compound of formula (III), wherein Z_1 and Z_2 are N.

Another preferred embodiment is a compound of formula (III), wherein R_2 is substituted or unsubstituted aryl, where substituent is halogen, preferably fluoro.

Another preferred embodiment is a compound of formula (III), wherein R is substituted or unsubstituted 5 or 6 membered heteroaryl or heterocyclyl.

Another preferred embodiment is a compound of formula (III), wherein R is R'.

Another preferred embodiment is a compound of formula (III), wherein R is R'; R' is substituted or unsubstituted 5 membered heterocycle selected from

 and  ; wherein X^a is O; X^b is N; and R_2 is substituted or unsubstituted alkyl, or heterocyclyl.

Another preferred embodiment is a compound of formula (III), wherein R is -L-R_d, where R_d substituted or unsubstituted alkynyl.

Another preferred embodiment is a compound of formula (III), wherein R is R', wherein R' substituted or unsubstituted alkynyl.

Another preferred embodiment is a compound of formula (III), wherein R is -L-R_d. In this embodiment L is -C≡C-; and R_d is substituted or unsubstituted aryl, wherein substituent is -OH or -OC(O)CH_3.

Representative examples of compounds of the present invention are provided below. These compounds are illustrative in nature only and do not limit the scope of the invention.

N-(3-Methylbutyl)-6-(4-oxo-3,4-dihydro-1'H-spiro[chromene-2,4'-piperidin]-1'-yl)nicotinamide (compound No.1),

6-(7-Fluoro-4-oxo-3,4-dihydro-1'H-spiro[chromene-2,4'-piperidin]-1'-yl)-N-(3-methylbutyl) nicotinamide (compound No.2),

6-(6-Chloro-4-oxo-3,4-dihydro-1'H-spiro[chromene-2,4'-piperidin]-1'-yl)-N-(3-methyl-butyl)nicotinamide (compound No.3),

6-(6,8-Dichloro-4-oxo-3,4-dihydro-1'H-spiro[chromene-2,4'-piperidin]-1'-yl)-N-(3-methylbutyl)nicotinamide (compound No.4),

6-(4,4-Difluoro-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidin]-1'-yl)-*N*-(3-methylbutyl) Nicotinamide (compound No.5),

6-(5,8-Dichloro-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidin]-1'-yl)-*N*-(3-methylbutyl) Nicotinamide (compound No.6),

(5*S*)-3-[8-Fluoro-(3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidin]-1'-yl]pyridine-3-yl-5-(hydroxymethyl)-1,3-oxazolidin-2-one: (compound No.7),

(5*S*)-5-(Hydroxymethyl)-3-[6-(1'*H*-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)pyridin-3-yl]-1,3-oxazolidin-2-one (compound No.8),

(5*S*)-3-[6-(4-Fluoro-1'*H*-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)pyridin-3-yl]-5-(hydroxymethyl)-1,3-oxazolidin-2-one (compound No.9),

{3-[6-(4-Fluoro-1'*H*-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)pyridin-3-yl]-1,2,4-oxadiazol-5-yl}methanol (compound No.10),

8-Fluoro-1'-{5-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2-yl}-3,4-dihydrospiro[chromene-2,4'-piperidine] (compound No.11),
{3-[6-(8-Fluoro-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidin]-1'-yl)pyridin-3-yl]-1,2,4-oxadiazol-5-yl}methanol (compound No.12),
{3-[6-(8-Fluoro-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidin]-1'-yl)pyridin-3-yl]-1,2,4-oxadiazol-5-yl}pyridin-2-ol (compound No.13),
3-(2-Fluorophenyl)-8-{5-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2-yl}-1-oxa-3,8-diazaspiro[4.5]decan-2-one (compound No.14),
3-(2-Fluorophenyl)-8-{5-[5-(hydroxymethyl)-1,2,4-oxadiazol-3-yl]pyridin-2-yl}-1-oxa-3,8-diazaspiro[4.5]decan-2-one (compound No.15),
8-Chloro-1'-[5-(1*H*-tetrazol-5-yl)pyridin-2-yl]-3,4-dihydrospiro[chromene-2,4'-piperidine]: (compound No.16),
8-Chloro-1'-[5-(5-methyl-1,3,4-oxadiazol-2-yl)pyridin-2-yl]-3,4-dihydrospiro[chromene-2,4'-piperidine]: (compound No.17),
5,8-Dichloro-1'-[5-(5-methyl-1,3,4-oxadiazol-2-yl)pyridin-2-yl]-3,4-dihydrospiro[chromene-2,4'-piperidine]: (compound No.18),
8-Fluoro-1'-[6-(1*H*-imidazol-1-yl)pyridazin-3-yl]-3,4-dihydrospiro[chromene-2,4'-piperidine] (compound No.19),
8-Chloro-1'-[6-(1*H*-imidazol-1-yl)pyridazin-3-yl]-3,4-dihydrospiro[chromene-2,4'-piperidine]: (compound No.20),
8-Chloro-1'-(6-pyridin-3-ylpyridazin-3-yl)-3,4-dihydrospiro[chromene-2,4'-piperidine]: (compound No.21),
3-{[6-(4-Fluoro-1'*H*-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)pyridazin-3-yl]ethynyl}phenyl acetate (compound No.22),
3-{[6-(4-Fluoro-1'*H*-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)pyridazin-3-yl]ethynyl}phenol (compound No.23),
3-{[8-Fluoro-(3,4-dihydrospiro[chromene-2,4'-piperidin]-1'-yl)pyridazin-3-yl]ethynyl}phenyl acetate (compound No.24),
3-{[8-Fluoro-3,4-dihydrospiro[chromene-2,4'-piperidin]-1'-yl)pyridazin-3-yl]ethynyl}phenol (compound No.25),
3-{2-Fluorophenyl)-8-[6-(2-oxo-1-oxa-3,8-diazaspiro[4.5]dec-8-yl)pyridazin-3-yl] ethynyl}phenyl acetate: (compound No.26),
3-{2-Fluorophenyl)-8-{6-[(3-hydroxyphenyl)ethynyl]pyridazin-3-yl}-1-oxa-3,8-diazaspiro[4.5]decan-2-one: (compound No.27),

and a pharmaceutically acceptable salt thereof, solvate thereof, an ester thereof, a stereoisomer thereof, a polymorph thereof, a prodrug thereof, a metabolite thereof or an N-oxide thereof.

In another aspect, provided herein is a pharmaceutical composition comprising a therapeutically effective amount of one or more compounds of Formula (I), Formula (II) or Formula (III) and optionally one or more pharmaceutically acceptable excipients, carriers, diluents or mixture thereof.

In another aspect, provided herein is a method for preventing, ameliorating or treating a disease, disorder or syndrome modulated by SCD in a subject comprising administering to the subject in need thereof a therapeutically effective amount of one or more compounds of Formula (I), Formula (II) or Formula (III) or a pharmaceutical composition as described herein.

In another aspect, provided herein is a method for preventing, ameliorating or treating a disease, disorder or syndrome modulated by SCD1 in a subject comprising administering to the subject in need thereof a therapeutically effective amount of one or more compounds of Formula (I) Formula (II) or Formula (III) or a pharmaceutical composition as described herein.

The diseases, disorders, and syndromes are selected, but are not limited to, obesity, for example, obesity resulting from genetics, diet, food intake volume, a metabolic disorder, a hypothalamic disorder, age, abnormal adipose mass distribution, abnormal adipose compartment distribution, compulsive eating disorders, motivational disorders, which include the desire to consume sugars, carbohydrates, alcohols or drugs or any ingredient with hedonic value, reduced activity or combination thereof; overweight conditions; anorexia; bulimia; cachexia; dysregulated appetite; or obesity related diseases, disorders, and symptoms; diabetes (including Type I and Type II diabetes); diabetic complications; glucose tolerance; hyperinsulinemia; insulin sensitivity or resistance; hepatic steatosis; increased abdominal girth; metabolic syndrome; cardiovascular diseases including, for example, atherosclerosis, dyslipidemia, elevated blood pressure, microalbuminemia, hyperuricaemia, hypercholesterolemia, hyperlipidemias, atherosclerosis, hypertriglyceridemias, arteriosclerosis or combination thereof; osteoarthritis; dermatological diseases; sleep disorders including, for example, disturbances of circadian rhythm, dysomnia, insomnia, sleep apnea, narcolepsy or combination thereof; cholelithiasis; hepatomegaly; steatosis; syndrome X; abnormal alanine aminotransferase levels; polycystic ovarian disease; inflammation; non-alcoholic fatty liver disease; skin disorder; respiratory diseases or

disorders including, for example, sinusitis, asthma, bronchitis or combination thereof; pancreatitis; rheumatoid arthritis; cystic fibrosis; pre-menstrual syndrome; cancer; neoplasia; malignancy; metastases; tumours (benign or malignant); hepatomas; neurological diseases; psychiatric disorders; multiple sclerosis; viral diseases/infections or any combination thereof; the disease or condition related to serum levels of triglyceride, LDL, HDL, VLDL, total cholesterol.

Methods described herein can include one or more of the following embodiments. For example, In one embodiment, there is provided a method for preventing, ameliorating or treating a disease or condition selected from obesity or related disease conditions; diabetes (including Type I and Type II diabetes); diabetic complications; glucose tolerance; hyperinsulinemia; insulin sensitivity or resistance; metabolic syndromes; cardiovascular diseases including, for example, atherosclerosis, hypertension, lipidemia, dyslipidemia, elevated blood pressure, microalbuminemia, hyperuricaemia, hypercholesterolemia, hyperlipidemias, hypertriglyceridemias, arteriosclerosis or combination thereof; respiratory diseases or disorders including, for example, sinusitis, asthma, bronchitis or combination thereof; or any combination thereof; the disease or condition related to serum levels of triglyceride, LDL, HDL, VLDL or total cholesterol.

In another embodiment, there is provided a method for preventing, ameliorating or treating a disease or condition selected from obesity or related diseases, conditions; Type II diabetes; atherosclerosis, hypertension; lipidemia, dyslipidemia, microalbuminemia, hyperuricaemia, hypercholesterolemia, hyperlipidemias, hypertriglyceridemias, or a combination thereof;

In another embodiment, provided herein is a method for preventing, ameliorating or treating a disease or condition related to serum levels of triglyceride, LDL, HDL, VLDL, total cholesterol or a combination thereof.

In yet another embodiment, there is provided a method for preventing, ameliorating or treating a disease or condition selected from obesity or complication thereof, type II diabetes or complication thereof; cardiovascular diseases or complication thereof, or a combination of these.

In another aspect, provided herein is a method for treating a disease or disorder described herein comprising administering concurrently or sequentially one or more compounds described herein with one or more active ingredients known to those skilled in the art.

The combination therapy can include one or more of the following embodiments. For example, the one or more active ingredients are selected from antidiabetic agents including, for example, PPARα, PPARγ and/or PPARδ agonists or antagonists, sulfonylurea drugs, non-sulfonylurea secretagogues, α-glucosidase inhibitors, insulin sensitizers, hepatic glucose output lowering compounds, insulin and insulin derivatives or a combination thereof.

In another embodiment, the one or more active ingredients are selected from anti obesity drugs including, for example, β-3 agonists, CB (CB1 and/or CB2) receptor modulators, neuropeptide Y5 inhibitors, ciliary neurotropic factor and derivatives, appetite suppressants or a combination thereof.

In another embodiment, the one or more active ingredients are selected from HMG COA reductase inhibitors, CETP inhibitors, lipid lowering drugs, fatty acid lowering compounds, ACAT inhibitors, bile acid sequestrants, bile acid reuptake inhibitors, microsomal triglycerides transport inhibitors, fibric acid derivatives, guggle lipids or a combination thereof.

In yet another embodiment, the one or more active ingredients are selected from antihypertensive drugs including, for example, β-blockers, ACE inhibitors, calcium channel blockers, diuretics, renine inhibitors, AT-1 receptor antagonists, Endothelin receptor antagonists or a combination thereof.

In yet another aspect, provided herein are processes for preparing compounds of the present invention.

Detailed Description of the Invention

Definitions:

The following definitions apply to terms as used herein

The term "alkyl" unless otherwise specified refers to substituted or unsubstituted straight or branched saturated hydrocarbon chain having 1 to 20 carbon atoms, which is attached to the rest of the molecule by a single bond, e.g., methyl, ethyl, n-propyl, 1-methylethyl (isopropyl), n-butyl, n-pentyl, and 1,1-dimethylethyl (t-butyl). Alkyl groups are optionally interrupted by atom(s) or group(s) independently selected from oxygen, sulfur, $S(O)_m$, NR^t (wherein R^t is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or aryl).

The term "alkenyl" unless otherwise specified refers to substituted or unsubstituted aliphatic hydrocarbon group containing at least one double bond and which may be a straight or branched chain having 2 to about 20 carbon atoms, with *cis* or *trans*; *E* or *Z* stereochemistry e.g., ethenyl, 1-propenyl, 2-propenyl (allyl), iso-propenyl, 2-methyl-1-

propenyl, 1-butenyl, and 2-butenyl. Alkenyl groups are optionally interrupted by atom(s) or group(s) independently selected from oxygen, sulfur, $S(O)_m$, NR^t (wherein R^t is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or aryl).

The term "alkynyl" unless otherwise specified refers to substituted or unsubstituted straight or branched chain hydrocarbyl radical having at least one carbon-carbon triple bond, and having 2 to about 20 carbon atoms, e.g., ethynyl, propynyl, and butynyl. It is optionally interrupted by atom(s) or group(s) independently selected from oxygen, sulfur, $S(O)_m$, NR^t (wherein R^t is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or aryl).

The term "alkoxy" unless otherwise specified refers to an alkyl group attached via an oxygen linkage to the rest of the molecule. Representative examples of such groups are $-OCH_3$ and $-OC_2H_5$.

The term "cycloalkyl" unless otherwise specified refers to substituted or unsubstituted non-aromatic mono or multicyclic ring system of 3 to about 20 carbon atoms, which may optionally contain one or more olefinic bonds unless constrained by the definition, such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. It also includes the cyclic ring system fused with an aryl ring, spiro systems. Examples of multicyclic cycloalkyl groups include, but are not limited to, perhydronapththyl, adamantyl and norbornyl groups, bridged cyclic groups and spirobicyclic groups, e.g., spiro (4,4) non-2-yl.

The term "cycloalkylalkyl" unless otherwise specified refers to substituted or unsubstituted cyclic ring-containing radical having 3 to about 20 carbon atoms directly attached to an alkyl group. The cycloalkylalkyl group may be attached to the main structure at any carbon atom in the alkyl group that results in the creation of a stable structure. Non-limiting examples of such groups include cyclopropylmethyl, cyclobutylethyl, and cyclopentylethyl.

The term "cycloalkylaryl" unless otherwise specified refers to substituted or unsubstituted cyclic ring-containing radical having 3 to about 20 carbon atoms directly attached to an aryl group. Non-limiting examples of such groups include phenylcyclopropyl, phenylcyclobutyl, and phenylcyclopentyl.

The term "cycloalkenyl" refers to substituted or unsubstituted cyclic ring-containing radical having 3 to about 20 carbon atoms with at least one carbon-carbon double bond, such as cyclopropenyl, cyclobutenyl, and cyclopentenyl.

The term "cycloalkenylalkyl" unless otherwise specified refers to substituted or unsubstituted cycloalkenyl ring directly attached to an alkyl group.

The term "aryl" unless otherwise specified refers to substituted or unsubstituted carbocyclic aromatic radical having 6 to 14 carbon atoms, wherein the ring is mono-, bi-, or tricyclic, such as, but not limited to, phenyl, naphthyl, tetrahydronapthyl, indanyl, and biphenyl.

The term "arylalkyl" unless otherwise specified refers to substituted or unsubstituted aryl group as defined above directly bonded to an alkyl group as defined above, e.g., $-CH_2C_6H_5$ and $-C_2H_5C_6H_5$.

The term "carbocyclic ring" or "carbocyclyl" unless otherwise specified refers to a saturated, partially saturated or unsaturated carbocyclic hydrocarbon ring; carbocyclic rings are aromatic, partially aromatic or nonaromatic; carbocyclic rings are monocyclic or polycyclic. Polycyclic carbocyclic groups can be fused, spiro, or bridged ring systems. Monocyclic carbocyclic groups may contain 4 to 10 carbon atoms, typically 4 to 7 carbon atoms, and more typically 5 to 6 carbon atoms in the ring. Bicyclic carbocyclic groups may contain 8 to 12 carbon atoms, typically 9 to 10 carbon atoms in the rings. Carbocyclic rings may be substituted or unsubstituted.

The term "heterocyclic ring" or "heterocyclyl" unless otherwise specified refers to substituted or unsubstituted non-aromatic 3 to 15 membered ring radical which consists of carbon atoms and from one to five heteroatoms selected from nitrogen, phosphorus, oxygen and sulfur. The heterocyclic ring radical may be a mono-, bi- or tricyclic ring system, which may include fused, bridged or spiro ring systems, and the nitrogen, phosphorus, carbon, oxygen or sulfur atoms in the heterocyclic ring radical may be optionally oxidized to various oxidation states. In addition, the nitrogen atom may be optionally quaternized; also, unless otherwise constrained by the definition the heterocyclic ring or heterocyclyl may optionally contain one or more olefinic bond(s). Examples of such heterocyclic ring radicals include, but are not limited to, azepinyl, azetidinyl, acridinyl, benzodioxolyl, benzodioxanyl, benzofuranyl, carbazolyl, cinnolinyl, dioxolanyl, indolizinyl, thienyl, naphthyridinyl, perhydroazepinyl, phenazinyl, phenothiazinyl, phenoxazinyl, indolyl, phthalazinyl, pyridyl, pteridinyl, purinyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrazoyl, imidazolyl, tetrahydroisquinolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolinyl, oxazolidinyl, triazolyl, indanyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolinyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, isoindolyl, indolinyl, isoindolinyl, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyl, decahydroisoquinolyl, benzimidazolyl, thiadiazolyl, benzopyranyl,

benzothiazolyl, benzooxazolyl, furyl, tetrahydrofuryl, tetrahydropyranyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, dioxaphospholanyl, oxadiazolyl, chromanyl, and isochromanyl. The heterocyclic ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The term "heteroaryl" unless otherwise specified refers to substituted or unsubstituted 5 to 14 membered aromatic heterocyclic ring radical with one or more heteroatom(s) independently selected from N, O or S. The heteroaryl may be a mono-, bi- or tricyclic ring system. The heteroaryl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure. Examples of such heteroaryl ring radicals include, but are not limited to, oxazolyl, imidazolyl, pyrrolyl, furanyl, triazinyl, pyridinyl, pyrimidinyl, pyrazinyl, benzofuranyl, indolyl, benzothiazolyl, benzoxazolyl, carbazolyl, quinazonyl and the like.

The term "heteroarylalkyl" unless otherwise specified refers to substituted or unsubstituted heteroaryl ring radical directly bonded to an alkyl group. The heteroarylalkyl radical may be attached to the main structure at any carbon atom in the alkyl group that results in the creation of a stable structure, wherein the heteroaryl and alkyl are the same as defined earlier.

The term "heterocyclylalkyl" unless otherwise specified refers to substituted or unsubstituted heterocyclic ring radical directly bonded to an alkyl group. The heterocyclylalkyl radical may be attached to the main structure at any carbon atom in the alkyl group that results in the creation of a stable structure wherein the heterocyclyl and alkyl are the same as defined earlier.

Unless otherwise specified, the term "substituted" as used herein refers to substitution with any one or any combination of the following substituents: hydroxy, halogen, carboxyl, cyano, nitro, oxo (=O), thio (=S), substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted amino, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclylalkyl ring, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted guanidine, $-COOR^x$, $-C(O)R^x$, $-C(S)R^x$, $-C(O)NR^xR^y$, $-C(O)ONR^xR^y$, $-NR^xCONR^yR^z$, $-N(R^x)SOR^y$, $-N(R^x)SO_2R^y$, -(=N-

$N(R^x)R^y$), $-NR^xC(O)OR^y$, $-NR^xR^y$, $-NR^xC(O)R^y$, $-NR^xC(S)R^y$, $-NR^xC(S)NR^yR^z$, $-SONR^xR^y$, $-SO_2NR^xR^y$, $-OR^x$, $-OR^xC(O)NR^yR^z$, $-OR^xC(O)OR^y$, $-OC(O)R^x$, $-OC(O)NR^xR^y$, $-R^xNR^yC(O)R^z$, $-R^xOR^y$, $-R^xC(O)OR^y$, $-R^xC(O)NR^yR^z$, $-R^xC(O)R^y$, $-R^xOC(O)R^y$, $-SR^x$, $-SOR^x$, $-SO_2R^x$, and $-ONO_2$, wherein R^x, R^y and R^z are independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclylalkyl, or substituted or unsubstituted amino. According to one embodiment, the substituents in the aforementioned "substituted" groups cannot be further substituted. For example, when the substituent on "substituted alkyl" is "substituted aryl", the substituent on "substituted aryl" cannot be "substituted alkenyl".

The term "protecting group" or "P" refers to a substituent that is employed to block or protect a particular functionality while other functional groups on the compound may remain reactive. For example, an "amino-protecting group" is a substituent attached to an amino group that blocks or protects the amino functionality in the compound. Suitable amino-protecting groups include, but are not limited to, acetyl, trifluoroacetyl, t-butoxycarbonyl (BOC), benzyloxycarbonyl (CBz) and 9-fluorenylmethylenoxycarbonyl (Fmoc). Similarly, a "hydroxy-protecting group" refers to a substituent of a hydroxy group that blocks or protects the hydroxy functionality. Suitable hydroxy-protecting groups include, but are not limited to, acetyl, benzyl, tetrahydropyranyl and silyl. A "carboxy-protecting group" refers to a substituent of the carboxy group that blocks or protects the carboxy functionality. Suitable carboxy-protecting groups include, but are not limited to, $-CH_2CH_2SO_2Ph$, cyanoethyl, 2-(trimethylsilyl)ethyl, 2-(trimethyl silyl) ethoxymethyl, 2-(p-toluenesulfonyl)ethyl, 2-(p-nitrophenylsulfenyl)ethyl, 2-(diphenyl phosphino)-ethyl, and nitroethyl. For a general description of protecting groups and their use, see, T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991.

The term "analog" refers to a compound that is a structural derivative of a parent compound that differs from it by a single element.

The term "prodrug" refers to a compound that is transformed *in vivo* to yield a compound of formula (I) or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms, such as through

hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, *ed.* Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

The term "polymorph" refers to a compound that has the ability to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice.

The term "treating" or "treatment" of a state, disorder or condition includes:

The term "subject" includes mammals (especially humans) and other animals, such as domestic animals (e.g., household pets including cats and dogs) and non-domestic animals (such as wildlife).

A "therapeutically effective amount" means the amount of a compound that, when administered to a subject for treating a state, disorder or condition, is sufficient to effect such treatment. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, physical condition and responsiveness of the subject to be treated.

Pharmaceutically acceptable salts forming part of this invention include salts derived from inorganic bases (such as Li, Na, K, Ca, Mg, Fe, Cu, Zn, and Mn), salts of organic bases (such as N,N'-diacetylethylenediamine, glucamine, triethylamine, choline, hydroxide, dicyclohexylamine, metformin, benzylamine, trialkylamine, and thiamine), salts of chiral bases (such as alkylphenylamine, glycinol, and phenyl glycinol), salts of natural amino acids (such as glycine, alanine, valine, leucine, isoleucine, norleucine, tyrosine, cystine, cysteine, methionine, proline, hydroxy proline, histidine, ornithine, lysine, arginine, and serine), salts of non-natural amino acids (such as D-isomers or substituted amino acids), salts of guanidine, salts of substituted guanidine (wherein the substituents are selected from nitro, amino, alkyl, alkenyl, or alkynyl), ammonium salts, substituted ammonium salts, and aluminum salts. Other pharmaceutically acceptable salts include acid addition salts (where appropriate) such as sulphates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates (such as trifluoroacetate), tartarates, maleates, citrates, fumarates, succinates, palmoates, methanesulphonates, benzoates, salicylates, benzenesulfonates, ascorbates, glycerophosphates, and ketoglutarates. Yet other pharmaceutically acceptable salts include, but are not limited to, quaternary ammonium salts of the compounds of invention with alkyl halides or alkyl sulphates (such as MeI or Me_2SO_4).

Pharmaceutically acceptable solvates includes hydrates and other solvents of crystallization (such as alcohols). The compounds of the present invention may form solvates with low molecular weight solvents by methods known in the art.

Compounds described herein can comprise one or more asymmetric carbon atoms and thus can occur as racemic mixtures, enantiomers and diastereomers. These compounds can also exist as conformers/rotamers. All such isomeric forms and/or regioisomers of these compounds are expressly included in the present invention. Although the specific compounds exemplified in this application may be depicted in a particular stereochemical configuration, compounds having either the opposite stereochemistry at any given chiral centre are envisioned as a part thereof.

Pharmaceutical Compositions

The pharmaceutical composition of the present invention comprises one or more compounds described herein and one or more pharmaceutically acceptable excipients, carriers, diluents or mixture thereof. The compounds described herein may be associated with one or more pharmaceutically acceptable excipients, carriers, diluents or mixtures thereof in the form of capsule, sachet, paper or other container.

Examples of suitable carriers include, but are not limited to, water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatin, lactose, terra alba, sucrose, dextrin, magnesium carbonate, sugar, cyclodextrin, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethyl cellulose and polyvinylpyrrolidone.

The carrier or diluent may include a sustained release material, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax.

The pharmaceutical composition may also include one or more pharmaceutically acceptable auxiliary agents, wetting agents, emulsifying agents, suspending agents, preserving agents, salts for influencing oxmetic pressure, buffers, sweetening agents, flavoring agents, colorants, or any combination of the aforegoing. The pharmaceutical composition of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the subject by employing methods known in the art.

The pharmaceutical compositions of the present invention may be prepared by conventional techniques, e.g., as described in Remington: The Science and Practice of

Pharmacy, 20th Ed., 2003 (Lippincott Williams & Wilkins). For example, the active compound is mixed with a carrier, or diluted by a carrier, or enclosed within a carrier, which may be in the form of an ampule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be a solid, semi-solid, or liquid material that acts as a vehicle, excipient, or medium for the active compound. The active compound is adsorbed on a granular solid container, for example, in a sachet.

The pharmaceutical compositions may be in conventional forms, for example, capsules, tablets, aerosols, solutions, suspensions or products for topical application.

The route of administration may be any route which effectively transports the active compound of the invention to the appropriate or desired site of action. Suitable routes of administration include, but are not limited to, oral, nasal, pulmonary, buccal, subdermal, intradermal, transdermal, parenteral, rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic (such as with an ophthalmic solution) or topical (such as with a topical ointment). The oral route is preferred.

Solid oral formulations include, but are not limited to, tablets, capsules (soft or hard gelatin), dragees (containing the active ingredient in powder or pellet form), troches and lozenges. Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, cornstarch, and/or potato starch. A syrup or elixir is used in cases where a sweetened vehicle is employed.

A typical tablet that may be prepared by conventional tabletting techniques may contain: (1) Core: Active compound (as free compound or salt thereof), 250 mg colloidal silicon dioxide (Aerosil®), 1.5 mg microcrystalline cellulose (Avicel®), 70 mg modified cellulose gum (Ac-Di-Sol®), and 7.5 mg magnesium stearate; (2) Coating: HPMC, approx. 9 mg Mywacett 9-40 T and approx. 0.9 mg acylated monoglyceride

Liquid formulations include, but are not limited to, syrups, emulsions, soft gelatin and sterile injectable liquids, such as aqueous or non-aqueous liquid suspensions or solutions.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Suitable doses of the compounds for use in treating the diseases and disorders described herein can be determined by those skilled in the relevant art. Therapeutic doses are generally identified through a dose ranging study in humans based on preliminary evidence derived from the animal studies. Doses must be sufficient to result in a desired therapeutic

benefit without causing unwanted side effects. Mode of administration, dosage forms, suitable pharmaceutical excipients, diluents or carriers can also be well used and adjusted by those skilled in the art. All changes and modifications are envisioned within the scope of the present invention.

Methods of Treatments and Combination Therapy

The present invention further provides a method of treating a disease, condition or disorder modulated by a stearoyl CoA desaturase, especially those modulated by SCD1, in a subject by administering to the subject in need thereof a therapeutically effective amount of a compound or a pharmaceutical composition described herein.

Diseases, conditions, and disorders that are modulated by a stearoyl CoA desaturase, include, but are not limited to, diabetes, diabetes related syndromes, disorders or diseases obesity, obesity related diseases, conditions, and disorders, cardiovascular diseases (such as atherosclerosis), hepatic steatosis and other metabolic syndromes, metabolism related syndromes, disorders and diseases, and non-alcoholic fatty liver disease.

SCD, particularly human SCD, can be regulated to treat obesity. Obesity and overweight are defined as an excess of body fat relative to lean body mass. An increase in caloric intake or a decrease in energy expenditure or both can bring about this imbalance leading to surplus energy being stored as fat. In contrast, anorexia and cachexia are characterized by an imbalance in energy intake versus energy expenditure leading to a negative energy balance and weight loss. Agents that either increase energy expenditure and/or decrease energy intake, absorption or storage would be useful for treating obesity, overweight, and associated comorbidities. Agents that increase energy intake and/or decrease energy expenditure or increase the amount of lean tissue would be useful for treating cachexia, anorexia, and wasting disorders. An SCD gene, translated proteins and agents which modulate the gene or portions of the gene or its products are useful for treating obesity, overweight, anorexia, cachexia, wasting disorders, appetite suppression, appetite enhancement, increases or decreases in satiety, modulation of body weight, and/or other eating disorders such as bulimia. Accordingly, diseases, conditions, and disorders that are modulated by a stearoyl CoA desaturase, include, but are not limited to, obesity, overweight, anorexia, cachexia, wasting disorders, appetite suppression, appetite enhancement, and other eating disorders such as bulimia. Furthermore, the compounds of the present invention increase or decrease in satiety and modulate body weight.

Obesity related syndromes, disorders and diseases include, but are not limited to, obesity as a result of (i) genetics, (ii) diet, (iii) food intake volume, (iv) a metabolic disorder,

(v) a hypothalmic disorder, (vi) age, (vii) abnormal adipose mass distribution, (viii) abnormal adipose compartment distribution, (ix) compulsive eating disorders, and (x) motivational disorders which include the desire to consume sugars, carbohydrates, alcohols or drugs or any ingredient with hedonic value. Symptoms associated with obesity related syndromes, disorders, and diseases include, but are not limited to, reduced activity. Obesity also increases the likelihood of sleep apnea, gallstones, osteoporosis and certain cancers.

Diabetes related syndromes, disorders and diseases include, but are not limited to, glucose dysregulation, insulin resistance, glucose intolerance, hyperinsulinemia, dyslipidemia, hypertension, obesity, and hyperglycemia.

Cardiovascular diseases include, but are not limited to, (i) coronary artery disease, (ii) atherosclerosis, (iii) heart disease, (iv) hypercholesterolemia, (v) hypertriglyceridemia, (vi) hypertriglyceridemia secondary to another disorder or disease (such as hyperlipoproteinemias), (vii) hyperlipidemia, (viii) disorders of serum levels of triglycerides, VLDL, HDL, and LDL, (ix) cholesterol disorders, (x) cerebrovascular disease (including but not limited to, stroke, ischemic stroke and transient ischemic attack (TIA)), (xi) peripheral vascular disease, and (xii) ischemic retinopathy.

Metabolism related syndromes, disorders or diseases include, but are not limited to, (i) metabolic syndrome, (ii) dyslipidemia, (iii) elevated blood pressure, (iv) insulin sensitivity or resistance, (v) Type II diabetes, (vi) Type I diabetes, (vii) diabetic complications, (viii) increased abdominal girth, (ix) glucose tolerance, (x) microalbuminemia, (xi) hyperuricaemia, (xii) hyperinsulinemia, (xiii) hypercholesterolemia, (xiv) hyperlipidemias, (xv) atherosclerosis, (xvi) hypertriglyceridemias, (xvii) arteriosclerosis and other cardiovascular diseases, (xviii) osteoarthritis, (xix) dermatological diseases, (xx) sleep disorders (e.g., disturbances of circadian rhythm, dysomnia, insomnia, sleep apnea and narcolepsy), (xxi) cholelithiasis, (xxii) hepatomegaly, (xxiiii) steatosis, (xxiv) syndrome X, (xxv) abnormal alanine aminotransferase levels, (xxvi) polycystic ovarian disease, and (xxvii) inflammation.

Non-alcoholic fatty liver disease can manifest as hepatic steatosis (or fatty liver) and can progress to hepatitis, drug-induced hepatitis, hepatoma, fibrosis, hepatic cirrhosis, liver failure, non-alcoholic steatohepatitis, non-alcoholic hepatitis, acute fatty liver, and fatty liver of pregnancy.

Other disorders or diseases mediated by SCD include, but are not limited to, skin disorder, inflammation, respiratory diseases or disorders (e.g., sinusitis, asthma, and bronchitis), pancreatitis, osteoarthritis, rheumatoid arthritis, cystic fibrosis, pre-menstrual

syndrome., cancer, neoplasia, malignancy, metastases, tumours (benign or malignant), carcinogenesis, hepatomas, neurological diseases, psychiatric disorders, multiple sclerosis, and viral diseases and infections.

In a preferred embodiment, compounds of the invention will, in a subject, increase HDL levels and/or decrease triglyceride levels and/or decrease LDL or non-HDL-cholesterol levels. In another embodiment, compounds of the invention will, in a subject, increase body lean mass and decrease obesity. In another embodiment, compounds of the invention will, in a subject, decrease hepatitic steatosis.

Methods described herein can also include one or more of the following embodiments. For example, in one embodiment, the diseases, disorders, and syndromes are selected, but are not limited to, obesity, for example, obesity resulting from genetics, diet, food intake volume, a metabolic disorder, a hypothalmic disorder, age, abnormal adipose mass distribution, abnormal adipose compartment distribution, compulsive eating disorders, motivational disorders, which include the desire to consume sugars, carbohydrates, alcohols or drugs or any ingredient with hedonic value, reduced activity or combination thereof; overweight conditions; anorexia; bulimia; cachexia; dysregulated appetite; or obesity related diseases, disorders, and symptoms; diabetes (including Type I and Type II diabetes); diabetic complications; glucose tolerance; hyperinsulinemia; insulin sensitivity or resistance; hepatic steatosis; increased abdominal girth; metabolic syndrome; cardiovascular diseases including, for example, atherosclerosis, dyslipidemia, elevated blood pressure, microalbuminemia, hyperuricaemia, hypercholesterolemia, hyperlipidemias, atherosclerosis, hypertriglyceridemias, arteriosclerosis or combination thereof; osteoarthritis; dermatological diseases; sleep disorders including, for example, disturbances of circadian rhythm, dysomnia, insomnia, sleep apnea, narcolepsy or combination thereof; cholelithiasis; hepatomegaly; steatosis; syndrome X; abnormal alanine aminotransferase levels; polycystic ovarian disease; inflammation; non-alcoholic fatty liver disease; skin disorder; respiratory diseases or disorders including, for example, sinusitis, asthma, bronchitis or combination thereof; pancreatitis; rheumatoid arthritis; cystic fibrosis; pre-menstrual syndrome; cancer; neoplasia; malignancy; metastases; tumours (benign or malignant); hepatomas; neurological diseases; psychiatric disorders; multiple sclerosis; viral diseases/infections or any combination these diseases, disorders, conditions and/or syndromes thereof; the disease or condition related to serum levels of triglyceride, LDL, HDL, VLDL, total chlolesterol.

In another embodiment, there is provided a method for preventing, ameliorating or treating a disease or condition selected from obesity or related diseases, conditions; diabetes

(including Type I and Type II diabetes); diabetic complications; glucose tolerance; hyperinsulinemia; insulin sensitivity or resistance; metabolic syndromes; cardiovascular diseases including, for example, atherosclerosis, lipidemia, dyslipidemia, elevated blood pressure, microalbuminemia, hyperuricaemia, hypercholesterolemia, hyperlipidemias, hypertriglyceridemias, arteriosclerosis or combination thereof; respiratory diseases or disorders including, for example, sinusitis, asthma, bronchitis or combination thereof; or any combination these diseases, disorders, conditions and/or syndromes thereof; the disease or condition related to serum levels of triglyceride, LDL, HDL, VLDL, total chlolesterol.

In another embodiment, there is provided a method for preventing, ameliorating or treating a disease or condition selected from obesity or related diseases, conditions; Type II diabetes; atherosclerosis, hypertension; lipidemia, dyslipidemia, microalbuminemia, hyperuricaemia, hypercholesterolemia, hyperlipidemias, hypertriglyceridemias, or combination thereof. In another embodiment, there is provided a method for preventing, ameliorating or treating a disease or condition related to serum levels of triglyceride, LDL, HDL, VLDL, total chlolesterol. In yet another embodiment there is provided a method for preventing, ameliorating or treating a disease or condition selected from obesity or complication thereof, type II diabetes or complication thereof; cardiovascular diseases or complication thereof, or a combination of these.

The compounds of this invention may also be used in conjunction with other active ingredients for the treatment of the diseases, conditions and/or disorders described herein.

Therefore, provided herein is a method for treating a disease or disorder described herein comprising administering concurrently or sequentially one or more compounds described herein with one or more active ingredients known to those skilled in the art. Suitable active ingredients that may be used in combination with the compounds of the present invention include, but are not limited to, anti-obesity agents such as apolipoprotein-B secretion/microsomal triglyceride transfer protein (apo-B/MTP) inhibitors, 11β-hydroxy steroid dehydrogenase-1 (11β-HSD type 1) inhibitors, peptide YY_{3-36} or analogs thereof, MCR-4 agonists, cholecystokinin-A (CCK-A) agonists, monoamine reuptake inhibitors (such as sibutramine), sympathomimetic agents, β_3 adrenergic receptor agonists, dopamine receptor agonists (such as bromocriptine), melanocyte-stimulating hormone receptor analogs, $5HT_{2c}$ receptor agonists, melanin concentrating hormone antagonists, leptin (the OB protein), leptin analogs, leptin receptor agonists, galanin antagonists, lipase inhibitors (such as tetrahydrolipstatin, i.e. orlistat), anorectic agents (such as a bombesin agonist), neuropeptide-Y receptor antagonists, thyromimetic agents, dehydroepiandrosterone or an analog thereof,

glucocorticoid receptor agonists or antagonists, orexin receptor antagonists, glucagon-like peptide-1 (GLP-1) receptor agonists, Protein Tyrosine Phosphatase (PTP-1B) inhibitors, dipeptidyl peptidase IV (DPP-IV) inhibitors, ciliary neurotrophic factors (such as Axokine™ available from Regeneron Pharmaceuticals, Inc., Tarrytown, N.Y. and Procter & Gamble Company, Cincinnati, Ohio), human agouti-related protein (AGRP) inhibitors, ghrelin receptor antagonists, histamine 3 receptor antagonists or inverse agonists, and neuromedin U receptor agonists. Other anti-obesity agents, including the preferred agents set forth herein below, are well known, or will be readily apparent in light of the instant disclosure, to one of ordinary skill in the art.

Antiobesity agents can be selected, for example, from U.S Patent. Nos. 4,929,629; 3,752,814; 5,274,143; 5,420,305; 5,540,917; 5,643,874; U.S Publication No. 2002/0141985 and PCT Publication No. WO 03/027637. All of the above recited references are incorporated herein by reference. Especially preferred are anti-obesity agents such as orlistat, sibutramine, bromocriptine, ephedrine, leptin, peptide YY_{3-36} or an analog thereof (including the complete peptide YY), and pseudoephedrine. Preferably, compounds of the present invention and combination therapies are administered in conjunction with exercise and a sensible diet.

The compounds of the present invention may be used alone or in combination with active ingredients in the manufacture of a medicament for the therapeutic applications described herein.

The combination therapy can include one or more of the following embodiments. For example, the one or more active ingredients are selected from antidiabetic agents including, for example, PPARα, PPARγ and/or PPARδ agonists or antagonists (*e.g.*, rosiglitazone, troglitazone or pioglitazone), sulfonylurea drugs (*e.g.*, glyburide, glimepiride, chlorpropamide, tolbutamide or glipizide), non-sulfonylurea secretagogues, α-glucosidase inhibitors (*e.g.*, acrabose, miglitol or voglibose), insulin sensitizers (*e.g.*, PPARγ agonists such as troglitazone, pioglitazone, englitazone, MCC-555, rosiglitazone or other thiazolidinones or no-thiazolidinones; biguanides such as metformin or phenformin; PTP-IB inhibitors; dipeptidyl peptidase IV (DPP-IV) inhibitors), hepatic glucose output lowering compounds (*e.g.*, glucagone antagonists such as glucophage or glucophage XR), insulin and insulin derivatives or a combination thereof.

In another embodiment, the one or more active ingredients are selected from anti obesity drugs including, for example, β-3 agonists, CB receptor modulators (CB1 and/or CB2 such as rimonabant, GRC-10801 and its analogs, GRC-10693 and its analogs), neuropeptide

Y5 inhibitors, ciliary neurotropic factor and derivatives (*e.g.,* axikine) , appetite suppressants (*e.g.,* sibutramine), lipase inhibitors (*e.g.,* orlistat) or a combination thereof.

In another embodiment, the one or more active ingredients are selected from HMG COA reductase inhibitors (*e.g.,* lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin, itavastatin, cerivastatin or ZD-4522), CETP inhibitors (*e.g.,* torcetrapib), lipid lowering drugs, fatty acid lowering compounds, ACAT inhibitors, bile acid sequestrants (*e.g.,* cholestyramine, cholestipol or dextran) , bile acid reuptake inhibitors, microsomal triglycerides transport inhibitors, fibric acid derivatives (*e.g.,* clofibrate, fenofibrate, bezafibrate, ciprofibrate, beclofibrate, etofibrate or gemfibrozil), guggle lipids, or a combination thereof.

In yet another embodiment, the one or more active ingredients are selected from antihypertensive drugs including, for example, β-blockers, ACE inhibitors, calcium channel blockers, diuretics, renine inhibitors, AT-1 receptor antagonists, Endotheline receptor antagonists or a combination thereof.

List of abbreviations:

BOP - (Benzotriazole-1yloxy) tris (dimethylamino) phosphonium hexafluorophosphate

DAST - (Diethylamino) sulfur trifluoride

DBU – 1,8 – diazabicyclo [5.4.0]undec-7-ene

PTC – Phase Transfer Catalyst

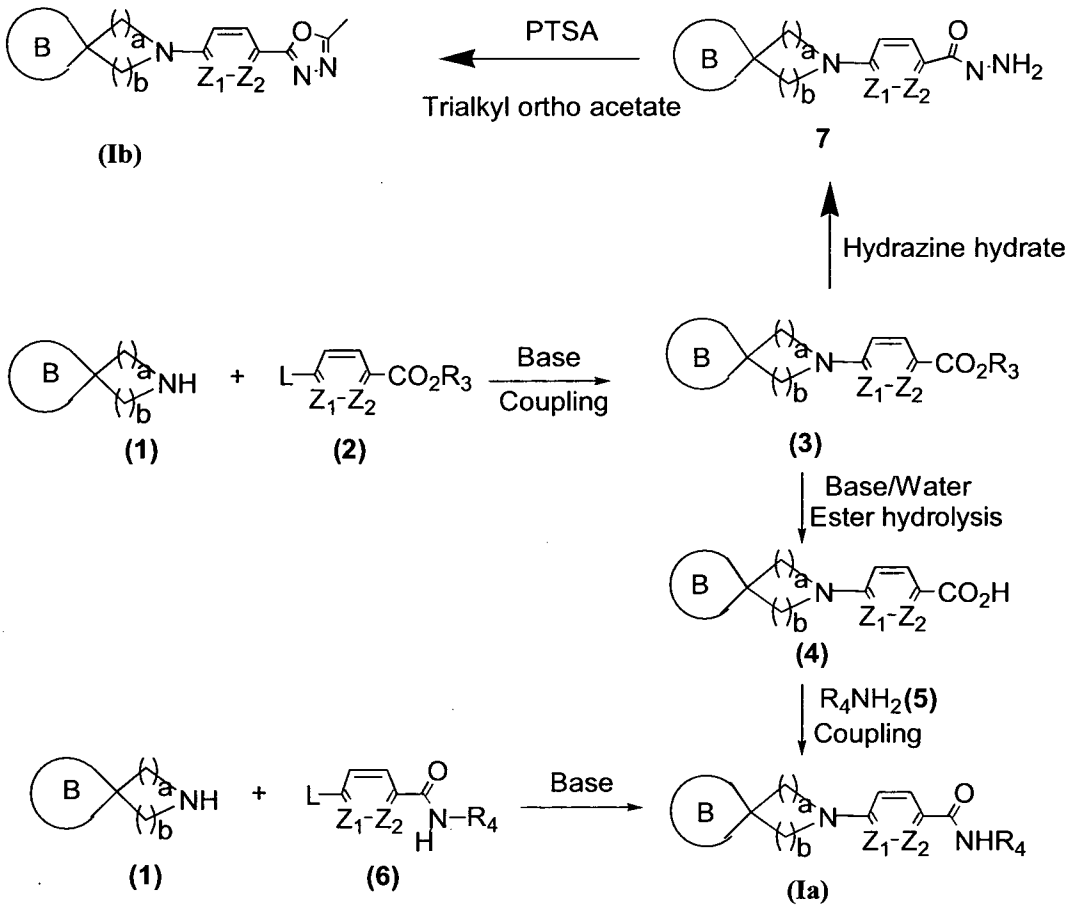
AC_2O – Acetic anhydride

PTSA – Para-toluene sulfonic acid

General Methods of Preparation

The compounds described herein, including compounds of general formulae (I), (II) and (III) and specific examples, are prepared using techniques known to one of ordinary skill in the art. The compounds described herein are prepared through the reaction sequences as depicted in Schemes 1-5. Further, in the following schemes, where specific bases, acids, reagents, solvents, cyclizing agents, coupling agents, etc., are mentioned, it is understood that other bases, acids, reagents, solvents, cyclizing agents, coupling agents, etc., known to one of ordinary skill in the art may also be used and are included within the scope of the present invention. Modifications to reaction conditions, for example, temperature, duration of the reaction or combination thereof, are envisioned as part of the present invention. All possible stereoisomers are also envisioned within the scope of this invention.

Scheme 1:



R_3 is H or alkyl; R_4 is substituted or unsubstituted alkyl;

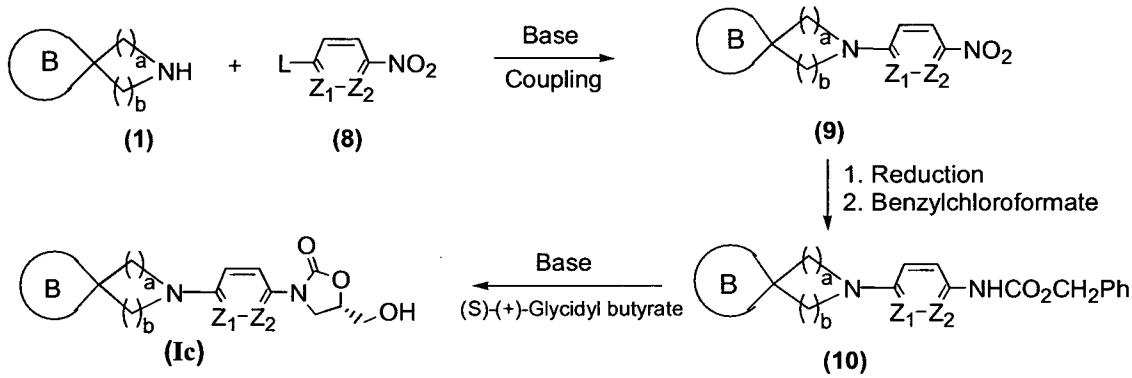
The starting materials for the above reaction scheme are commercially available or can be prepared according to methods known to one skilled in the art or by methods disclosed herein. In general, the compounds according to the present invention may be prepared in the above reaction scheme as follows, wherein all symbols are as defined above.

A general approach for the synthesis of compound of formula (Ia) is described in synthetic scheme 1. The symbols mentioned here are as described above. Spirocyclic compound of formula (1) is prepared by methods known in the art of organic synthesis. The compound of formula (1) is converted to compound of formula (Ia), for example, by one of the following two approaches. According to one approach, the compound of formula (1) is coupled with a halo-heteroaryl ester of formula (2) (where L is leaving group such as halogen) in presence of base such as alkali metal carbonate, alkali metal bicarbonate alkali metal hydroxide, alkali metal hydride; and potassium iodide to afford a compound of formula (3). Hydrolysis of the ester of a formula (3) results into carboxylic acid of formula (4) in presence of base, such as

alkali metal carbonate, alkali metal hydroxide or alkali metal hydride, which is then coupled with an amine of formula (5) in presence of organic base (e.g., triethylamine and/or isoamylamine); and BOP to afford a compound of general formula (I) of the invention. Alternatively, in another approach the compounds of formula (I) may also be prepared by the direct coupling between the free amine of formula (1) with an amide of formula (6) (where L is leaving group such as halogen) in the presence of PTC for example tetra-n-butylammonium bromide and a suitable base for example DBU.

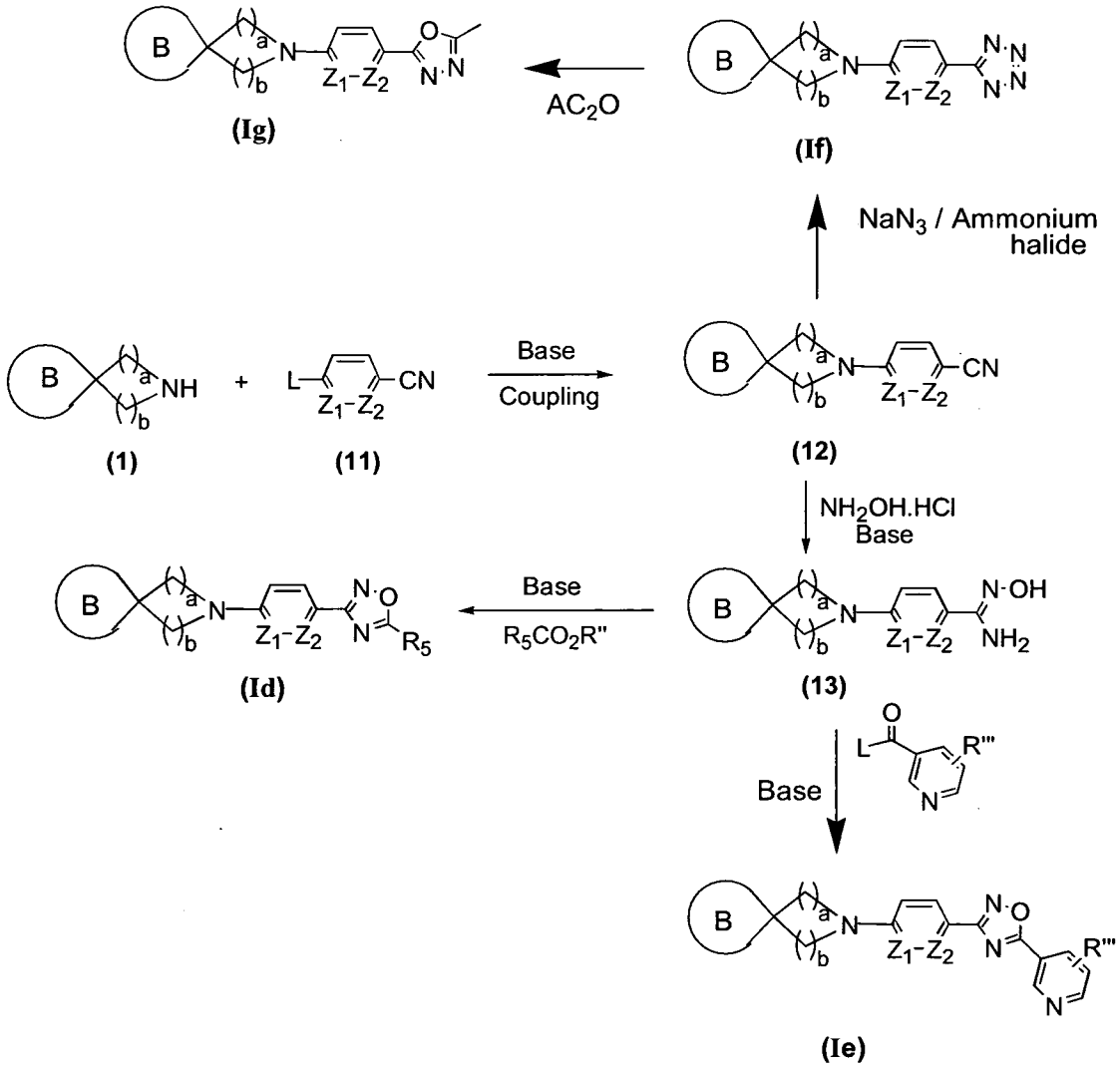
Compound of formula (3) is reacted with hydrazine hydrate in suitable solvent to afford compound of formula (7) which is then elaborated to compound of formula (Ib) by reacting with trialkyl ortho acetate in presence of PTSA through the procedure known in the art.

Scheme 2:



Compound of formula **(1)** is coupled with a nitro compound of formula **(8)** (where L is leaving group such as halogen) in presence of a base such as alkali metal carbonate, alkali metal hydroxide or alkali metal hydride; and potassium iodide to afford the nitro compound of formula **(9)** which upon reduction using suitable reducing agent for example, Pd/C in appropriate solvent ratio for example toluene and ethanol, and followed by reaction with benzylchloroformate in suitable base such as alkali metal carbonate, alkali metal bicarbonate, alkali metal hydroxide or alkali metal hydride, affords carbamate of a general formula **(10)**. Carbamate of a general formula **(10)** is then reacted with (S)-(+)-glycidyl butyrate in the presence of suitable base for example n- butyl lithium, to afford oxazolidinone of a general formula **(Ic)**.

Scheme 3:

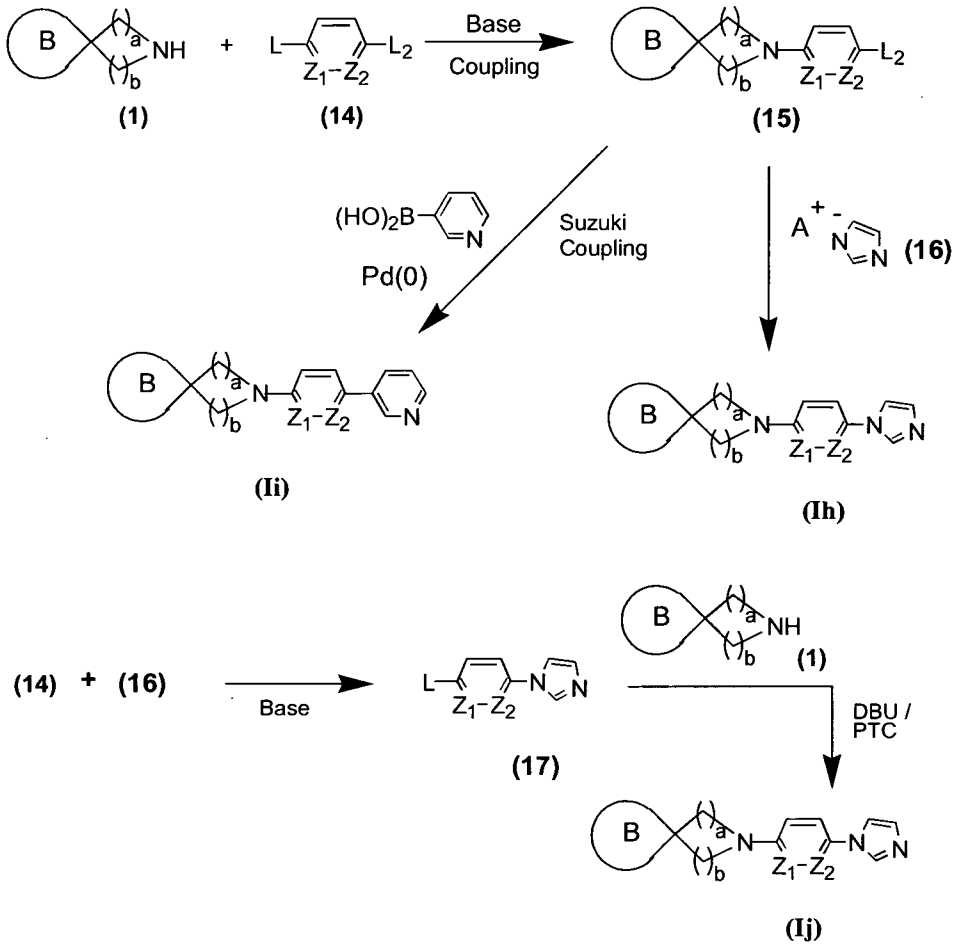


R" is alkyl or $C(O)CF_3$; R_5 IS CH_2OH, CF_3 or $C(O)CF_3$; R''' is H, halogen or OH; L is halogen;

Compound of formula **(1)** is coupled with a cyano compound of formula **(11)** (where L is leaving group such as halogen) in presence of a base for example diisopropylethylamine to afford the cyano compound of formula **(12)** which upon further reaction with hydroxylamine hydrochloride in suitable base as such as alkali metal carbonate, alkali metal bicarbonate, alkali metal hydroxide, alkali metal hydride, affords amidoxime of formula **(13)**. Amidoxime of a general formula **(13)** is then reacted with ester of a formula R_5CO_2 R" in the presence of suitable base such as alkali metal carbonate, alkali metal bicarbonate, alkali metal hydroxide or alkali metal hydride, to afford 1,2,4-oxadiazole of a general formula **(Id)**.

Compound of formula **(13)** is reacted with substituted or unsubstituted nicotinoyl halide in presence of base such as pyridine to afford compound of formula **(Ie).** Compound of formula is **(12)** reacted with sodium azide and ammonium halide to afford compound of formula **(If)** which is then reacted with AC_2O to afford compound of formula **(Ig)**

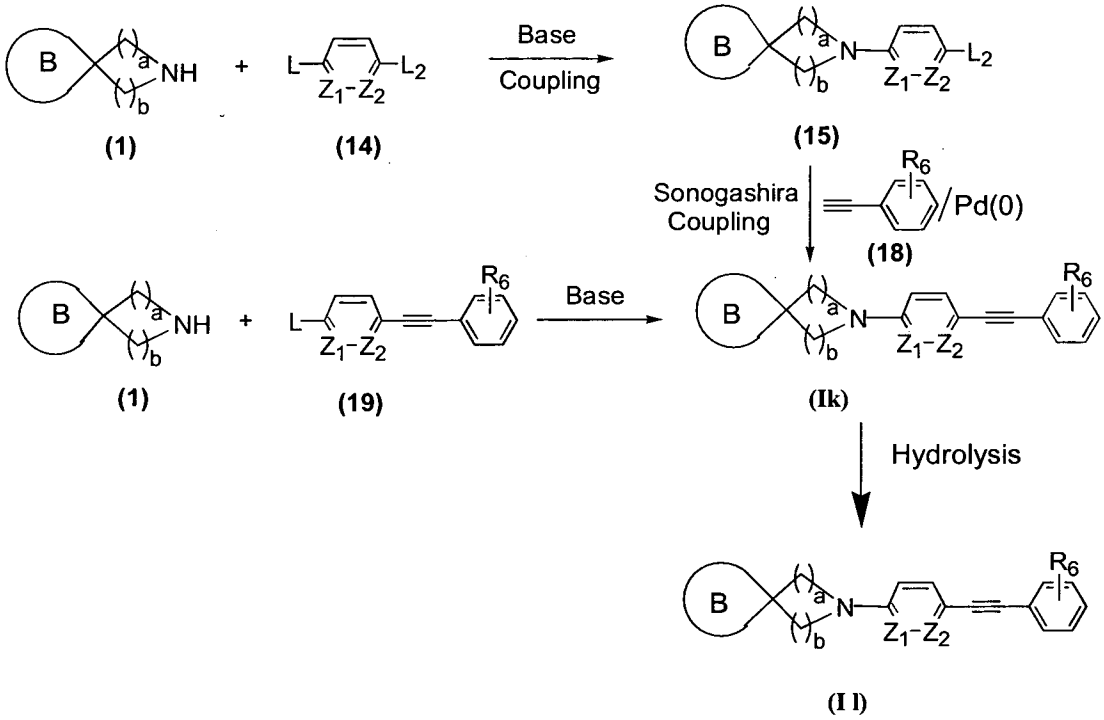
Scheme 4:



The free amine of formula **(1)** is coupled with a halo compound of formula **(14)** (where L and L_2 is leaving group, such as halogen) in the presence of a suitable base such as alkali metal carbonate, alkali metal bicarbonate, alkali metal hydroxide, alkali metal hydride to gives a compound of formula **(15)** (L_2 is leaving group, such as halogen) which upon reaction with compound of a formula **(16)** (where A is alkali metal salt for example sodium or lithium) gives compound of a general formula **(Ih)**. Compound of a general formula **(15)** Suzuki coupling, for example with suitable substituted or unsubstituted aryl or heteroaryl boronic acid (for example pyridine boronic acid) in the presence of Pd(0) catalyst (for example pelladium acetate) and triphenyl phosphine to affords compound of a general formula **(Ii)**.

Compound of formula **(14)** is reacted with compound of formula **(16)** (where A is alkali metal salt for example sodium or lithium) to give a compound of formula **(17)** which is then combined with compound of formula **(1)** in presence of DBU/PTC to afford compound of formula **(Ij)**.

Scheme 5:



R_6 is as defined in description for R_1;

The free amine of formula **(1)** is coupled with a halo compound of formula **(14)** (where L and L_2 is leaving group, such as halogen) in the presence of a base such as alkali metal carbonate, alkali metal bicarbonate, alkali metal hydroxide, alkali metal hydride to gives a compound of formula **(15)** (where L_2 is leaving group, such as halogen) which upon Sonogashira coupling with acetylene compound of a general formula **(18)** in presence of Pd(0) for example $PdCl_2$ and triphenyl phosphine and CuI to gives compound of a general formula **(Ik)**. Alternatively, the compounds of formula **(Ik)** of this invention may also be prepared by the direct coupling between the free amine of formula **(1)** with acetylene compound of a general formula **(19)** (where L is leaving group, such as halogen) in the presence of a suitable base as given above.

Hydrolysis of the compounds of formula **(Ik)** to offord compound of formula **(Il)** in presence of base, such as alkali metal carbonate, alkali metal bicarbonate, alkali metal hydroxide, and alkali metal hydride.

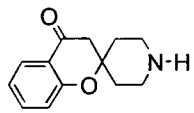
The following spirocyclic amine intermediates were prepared by following literature references cited above and specific synthetic procedures are given below to illustrate the scope of the invention.

The spiro(chromene-2,4'-piperidin)-4(3*H*)-one and its derivatives required for the present invention were prepared by following a literature procedures: (1). Fletcher S. R. *et al.; J. Med. Chem.* **2002**, *45*, 492-503; (2). Yang L. *et al.; Bioorg. Med. Chem. Lett.* **1998**, *8*, 107-112 and references cited therein; (3). Chandrasekhar S. *Tetrahedron Lett.* **2005**, *46*, 6991-6993; (4). Lau C. K. *et al.; J. Org. Chem.* **1989**, *54*, 491-494. The spiro-1,3-benzodiaxole-2,4'-piperidine derivatives were prepared by the following a literature procedure (Moltzen E. K. *et al.; J. Med. Chem.* **1995**, *38*, 2009-2017). The 1-oxa-3,8-diazaspiro[4,5]decan-2-one derivatives were prepared by using a similar approach described in the following literature references: (1). Caroon J. M. *et al.; J. Med. Chem.* **1981**, *24*, 1320-1328; (2). Smith P. W. *et al.; J. Med. Chem.* **1995**, *38*, 3772-3779; (3). Mullen G. *et al.; J. Med. Chem.* **2000**, *43*, 4045-4050.

Experimental

Intermediates

Intermediate 1: Spiro[chromene-2,4'-piperidin]-4(3*H*)-one



Step 1: *tert*-Butyl 4-oxo-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidine]-1'-carboxylate:

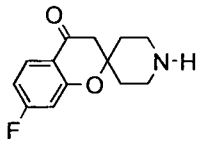
To a stirred solution of 2-hydroxyacetophenone (2.35 ml, 19.521 mmol) in anhydrous dimethylformamide (DMF) (30 ml) was added *N*-BOC piperidone (3.89 g, 19.523 mmol) followed by *L*-proline (674 mg, 5.861 mmol). The reaction mixture was stirred at 80 °C for 24 h. The reaction mixture was allowed to cool to room temperature and diluted with water (100 ml) and ethyl acetate (100 ml). The layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 100 ml) and the combined organic layers were washed with water (100 ml), brine (50 ml) and dried (Na_2SO_4). The solvent was evaporated to get a crude residue which was purified by silica gel column chromatography using 5 % ethyl acetate in petroleum ether to get 2.2 g of the product as an off-white solid; IR (KBr) 2925, 1694, 1463, 1157 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 9H), 1.55-1.70 (m, 2H), 2.02 (d, J = 13.5 Hz, 2H), 2.72 (s, 2H), 3.22 (t, J = 11.4 Hz, 2H), 3.87 (d, J = 12.3 Hz, 2H), 6.96-7.06 (m, 2H), 7.49 (t, J = 8.7 Hz, 1H), 7.86 (d, J = 7.8 Hz, 1H); ESI-MS (*m/z*) 316.31 $(M-H)^-$.

Step 2: Spiro[chromene-2,4'-piperidin]-4(3*H*)-one:

To a stirred solution of Step 1 intermediate (1.0 g, 3.151 mmol) was added 1:1 trifluoroacetic acid and dichloromethane (25 ml) at 0 °C and stirred at the same temperature for 2 h. The residue obtained after the evaporation of the solvent was dissolved in chloroform

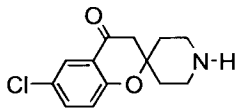
(50 ml), basified with 1 *N* NaOH, extracted with ethyl acetate (3 x 50 ml). The combined organic layers were washed with water, brine (50 ml) and dried (Na_2SO_4). The solvent was evaporated to get 624 mg of the product as an off-white solid; IR (KBr) 2925, 1688, 1462, 1231, 764 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.58-1.72 (m, 2H), 1.89 (s, 1H), 2.02 (d, J = 12.9 Hz, 2H), 2.73 (s, 2H), 2.82-2.95 (m, 2H), 3.05 (t, J = 11.1 Hz, 2H), 6.94-7.04 (m, 2H), 7.49 (t, J = 6.9 Hz, 1H), 7.85 (d, J = 7.8 Hz, 1H); ESI-MS (*m/z*) 218.25 $(M+H)^+$.

Intermediate 2: 7-Fluorospiro[chromene-2,4'-piperidin]-4(3*H*)-one



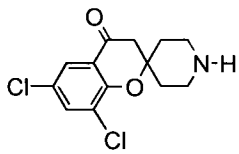
This intermediate was prepared in two steps from 4-fluoro-2-hydroxyacetophenone and *N*-BOC-piperidone as described in the preparation of intermediate 1 to give the product as an off-white solid; IR (KBr) 2929, 1678, 1471, 1249, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.65-1.75 (m, 3H), 2.00 (d, J = 12.9 Hz, 2H), 2.71 (s, 2H), 2.82-2.92 (m, 2H), 2.96-3.10 (m, 2H), 6.64-6.78 (m, 2H), 7.82-7.92 (m, 1H); ESI-MS (*m/z*) 236.29 $(M+H)^+$.

Intermediate 3: 6-Chlorospiro[chromene-2,4'-piperidin]-4(3*H*)-one



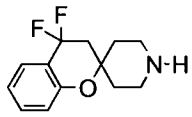
This intermediate was prepared in two steps from 5-chloro-2-hydroxyacetophenone and *N*-BOC-piperidone as described in the preparation of intermediate 1 to give the product as an off-white solid, IR (KBr) 2923, 1698, 1459, 1243, 834 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60 (br s, 3H), 1.99 (d, J = 13.2 Hz, 2H), 2.72 (s, 2H), 2.82-2.92 (m, 2H), 2.95-3.08 (m, 2H), 6.95 (d, J = 8.7 Hz, 1H), 7.42 (dd, J = 6.3, 2.7 Hz, 1H), 7.81 (s, 1H); ESI-MS (*m/z*) 252.28 $(M+H)^+$.

Intermediate 4: 6,8-Dichlorospiro[chromene-2,4'-piperidin]-4(3*H*)-one



This intermediate was prepared in two steps from 3,5-dichloro-2-hydroxyacetophenone and *N*-BOC-piperidone as described in the preparation of intermediate 1 to give the product as an off-white solid, IR (KBr) 2923, 2875, 1591, 1482, 1327, 1193, 752 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.50-1.65 (m, 2H), 1.82 (d, J = 12.6 Hz, 2H), 2.55-2.90 (m, 7H), 7.63 (s, 1H), 7.93 (s, 1H); ESI-MS (*m/z*) 285.15 $(M+H)^+$.

Intermediate 5: 4,4-Difluoro-3,4-dihydrospiro[chromene-2,4'-piperidine]



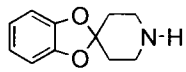
Step 1: *tert*-Butyl 4,4-difluoro-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidine]-1'-carboxylate:

To a stirred solution of Intermediate 1, Step 1 (500 mg, 1.583 mmol) was added (diethylamino) sulfur trifluoride (DAST) (1.5 ml, 11.406 mmol) at room temperature. The reaction mixture was stirred at 85 °C for 4 h. The reaction mixture was allowed to cool to room temperature and poured onto ice. The product was extracted with ethyl acetate (3 x 100 ml) and the combined organic layers were washed with water (100 ml), brine (50 ml) and dried (Na_2SO_4). The solvent was evaporated to get a crude residue which was purified by silica gel column chromatography using 5% ethyl acetate in petroleum ether to get 193 mg of the product as pale yellow oil; IR (KBr) 2974, 1695, 1462, 1159, 752 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 1.75-1.85 (m, 2H), 2.00-2.10 (m, 2H), 2.82-2.90 (m, 2H), 3.12-3.25 (m, 2H), 3.85-3.96 (br m, 1H), 4.05-4.15 (br m, 1H), 6.95-7.12 (m, 2H), 7.54 (t, J = 7.5 Hz, 1H), 7.90 (d, J = 7.5 Hz, 1H); ESI-MS (*m/z*) 340.52 $(M+H)^+$.

Step 2: 4,4-Difluoro-3,4-dihydrospiro[chromene-2,4'-piperidine]:

Step 1 intermediate (1 g, 3.151 mmol) was deprotected using 1:1 trifluoroacetic acid and dichloromethane (25 ml) as described in Step 2, Intermediate 1 to give 624 mg of the product as an oil; IR (KBr) 2930, 1699, 1609, 1462, 1217, 1193, 759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.12-1.32 (m, 4H), 2.84 (br s, 1H), 3.00-3.18 (m, 6H), 7.00-7.10 (m, 2H), 7.54 (t, J = 6.9 Hz, 1H), 7.90 (d, J = 8.1 Hz, 1H); ESI-MS (*m/z*) 240.26 $(M+H)^+$.

Intermediate 6: Spiro[1,3-benzodioxole-2,4'-piperidine]



Step 1: Ethyl 1'*H*-spiro[1,3-benzodioxole-2,4'-piperidine]-1'-carboxylate:

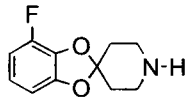
To a stirred solution of 1-(ethoxycarbonyl)-4-piperidone (2 g, 11.703 mmol) in toluene (30 ml) was added catechol (1.55 g, 14.046 mmol) followed by *p*-toluenesulphonic acid monohydrate (0.33 g, 1.734 mmol) at room temperature. The reaction mixture was heated to reflux for 18 h. The reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate (3 x 50 ml), washed with 2 *N* NaOH. The combined organic layers were concentrated under reduced pressure to get a crude residue which was purified by silica gel column chromatography using 15% ethyl acetate in petroleum ether to get 1.8 g of the

product as a white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, J = 7.5 Hz, 3H), 1.97 (br s, 4H), 3.67 (br s, 4H), 4.14 (q, J = 7.5 Hz, 2H), 6.73-6.80 (m, 4H); ESI-MS (*m/z*) 264.52 $(M+H)^+$.

Step 2: Spiro[1,3-benzodioxole-2,4'-piperidine]:

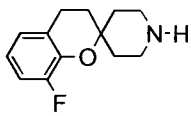
To a stirred solution of Step 1 intermediate (1.8 g, 6.847 mmol) in ethanol (25 ml) was added sodium hydroxide (0.82 g, 20.516 mmol) in water (2 ml) at room temperature. The reaction mixture was heated to reflux for 24 h. The reaction mixture was allowed to cool to room temperature, washed with brine, extracted with dichloromethane (3 x 50 ml) and dried (Na_2SO_4). The solvent was evaporated to get a crude residue which was purified by silica gel column chromatography using 5% methanol in chloroform to get 1.01 g of the product as a white solid; IR (Neat) 3064, 2928, 1485, 1236, 1061, 738 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.96 (br s, 4H), 3.03 (br s, 4H), 6.72-6.75 (m, 4H); ESI-MS (*m/z*) 192.70 $(M+H)^+$.

Intermediate 7: 4-Fluorospiro[1,3-benzodioxole-2,4'-piperidine]



This compound was prepared in two steps according to the procedure described in Intermediate 6, Steps 1 and 2 using 3-fluorocatechol (2.78 g, 21.733 mmol), 1-(ethoxycarbonyl)-4-pieridone (3.1 g, 18.116 mmol) and *p*-toluenesulphonic acid monohydrate (0.689 g, 3.622 mmol) followed by deprotection with sodium hydroxide to afford the required compound as an off-white solid: IR (KBr) 3050, 2930, 1497, 1247, 1083, 758 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84 (br s, 1H), 1.98-2.02 (m, 4H), 3.05-3.09 (m, 4H), 6.54-6.63 (m, 2H), 6.67-6.74 (m, 1H); ESI-MS (*m/z*) 210.68 $(M+H)^+$.

Intermediate 8: 8-Fluoro-3,4-dihydrospiro[chromene-2,4'-piperidine]



Step 1: *tert*-Butyl 8-fluoro-4-oxo-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidine]-1'-carboxylate:

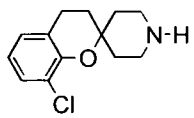
To a stirred solution of 3-fluoro-2-hydroxyacetophenone (1.6 g, 10.387 mmol) and pyrrolidine (0.86 ml, 10.406 mmol) in methanol (50 ml) was added *N-tert*-butoxycarbonyl-4-piperidone (2.07 g, 10.394 mmol) at room temperature over 20 min. The reaction mixture was stirred at the same temperature for 24 h. The reaction mixture was concentrated and partitioned between ethyl acetate (50 ml) and 2*N* hydrochloric acid (50 ml). The organic layer was washed with brine, dried (Na_2SO_4) and the crude product obtained after concentrating

under reduced pressure was purified by silica gel column chromatography using 30% ethyl acetate in petroleum ether to afford 2.86 g of the product as a yellow solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.40 (s, 9H), 1.50-1.80 (m, 2H), 1.90-2.00 (m, 2H), 2.92 (s, 2H), 3.00-3.20 (m, 2H), 3.60-3.80 (m, 2H), 6.90-7.10 (m, 1H), 7.50-7.60 (m, 2H).

Step 2: 8-Fluoro-3,4-dihydrospiro[chromene-2,4'-piperidine]:

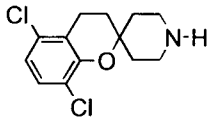
To a stirred solution of Step 1 intermediate (5 g, 14.918 mmol) in ethanol (50 ml) was added sodium borohydride ($NaBH_4$) (0.564 g, 14.91 mmol) at room temperature over 30 min. The reaction mixture was stirred at the same temperature for 1 h. The reaction mixture was treated with water and the residue obtained after the evaporation of the solvent was diluted with ethyl acetate (50 ml) and water (50 ml). The organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to afford *tert*-butyl 8-fluoro-4-hydroxy-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidine]-1'-carboxylate as a white solid. This solid was used as such for the next deoxygenation step. Trimethylsilane (6.58 g, 56.606 mmol) was added to a solution of *tert*-butyl 8-fluoro-4-hydroxy-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidine]-1'-carboxylate (5 g, 14.827 mmol) in trifluoroacetic acid (50 ml) and the resulting mixture was heated to reflux for 18 h. The reaction mixture was allowed to cool to room temperature, concentrated under reduced pressure to get a crude residue. Diethyl ether (200 ml) was added to this residue and the mixture was stirred, filtered and air dried to afford trifluoroacetate salt of 8-fluoro-3,4-dihydrospiro[chromene-2,4'-piperidine] which was neutralized by sodium bicarbonate solution to get 2.6 g of the product as a white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.40-170 (m, 4H), 1.78 (t, J = 6.3 Hz, 2H), 2.70-2.90 (m, 6H), 6.70-6.80 (m, 1H), 6.85 (d, J = 7.5 Hz, 1H), 6.96 (t, J = 8.7 Hz, 1H); ESI-MS (*m/z*) 222.82 $(M+H)^+$.

Intermediate 9: 8-Chloro-3,4-dihydrospiro[chromene-2,4'-piperidine]



This compound was prepared in two steps according to the procedure described in Intermediate 8, Steps 1 and 2 using 3-chloro-2-hydroxyacetophenone (9 g, 52.776 mmol), *N*-BOC piperidone (10.5 g, 52.703 mmol), pyrrolidine (4.4 ml, 52.731 mmol) followed by $NaBH_4$ reduction and deprotection with triethylsilane and trifluoroacetic acid to afford the product as a pale yellow solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.44-1.60 (m, 2H), 1.66 (d, J = 13.2 Hz, 2H), 1.78 (t, J = 6.9 Hz, 2H), 2.70-2.96 (m, 6H), 6.78 (d, J = 7.8 Hz, 1H), 7.02 (d, J = 7.8 Hz, 1H), 7.18 (d, J = 7.8 Hz, 1H); ESI-MS (*m/z*) 238.41 $(M+H)^+$.

Intermediate 10: 5,8-Dichloro-3,4-dihydrospiro[chromene-2,4'-piperidine]



Step 1: *tert*-Butyl 5,8-dichloro-4-oxo-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidine]-1'-carboxylate:

To a stirred solution of 3,6-dichloro-2-hydroxy acetophenone (10 g, 48.776 mmol) in methanol (50 ml) was added pyrrolidine (4.1 ml, 48.776 mmol) and stirred at room temperature for 30 min. Then *N*-BOC piperidone (4.86 g, 24.398 mmol) was added to the reaction mixture over 15 min and stirred at the same temperature for 24 h. The residue obtained after the evaporation of the solvent was treated with ethyl acetate and 2 *N* HCl. The aqueous layer was extracted with ethyl acetate (3 x 100 ml). The combined organic layers were washed with water (100 ml), brine (100 ml), dried (Na_2SO_4) and the crude product obtained after the evaporation of the solvent was purified on silica gel column chromatography using 10% ethyl acetate in petroleum ether to give 8.5 g of the product as an off-white solid; IR (KBr) 2929, 1696, 1412, 1249, 1169, 757 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20-1.36 (m, 2H), 1.46 (s, 9H), 2.01 (d, J = 13.5 Hz, 2H), 2.78 (s, 2H), 3.12-3.30 (m, 2H), 3.95 (br s, 2H), 6.96 (d, J = 8.4 Hz, 1H), 7.41 (d, J = 8.7 Hz, 1H); ESI-MS (*m/z*) 385.39 $(M-H)^-$.

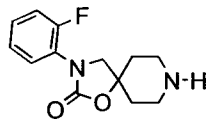
Step 2: 5,8-Dichlorospiro[chromene-2,4'-piperidine]:

To a stirred solution of step 1 intermediate (3.64 g, 9.428 mmol) in tetrahydrofuran (15 ml) was added 1 *M* borane tetrahydrofuran solution (56.6 ml, 56.542 mmol) at 0 °C over 30 min. The reaction mixture was allowed to warm to room temperature and heated to reflux for 18 h. 5 *N* HCl was added to this reaction mixture and stirred at the same temperature for 18 h. The reaction mixture was allowed to cool to room temperature, concentrated to get a residue which was basified with 2 *N* NaOH and extracted with chloroform. The combined organic layers were washed with water (100 ml), brine (100 ml), dried (Na_2SO_4) and the crude product obtained after the evaporation of the solvent was purified on silica gel column chromatography using 5% ethyl acetate in petroleum ether to give 2.2 g of the product as an off-white solid; IR (KBr) 2925, 1456, 1421 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.62-1.78 (m, 2H), 2.00 (d, J = 13.2 Hz, 2H), 2.52 (s, 1H), 2.92 (d, J = 12.3 Hz, 2H), 3.19 (t, J = 11.7 Hz, 2H), 5.72 (d, J = 9.9 Hz, 1H), 6.68 (d, J = 9.9 Hz, 1H), 6.82 (d, J = 8.7 Hz, 1H), 7.07 (d, J = 8.7 Hz, 1H); ESI-MS (*m/z*) 270.40 $(M+H)^+$.

Step 3: 5,8-Dichloro-3,4-dihydrospiro[chromene-2,4'-piperidine]:

To a stirred solution of Step 2 intermediate (1.2 g, 4.442 mmol) was added 1 *N* HCl (8.5 ml) followed by palladium on carbon (300 mg) and stirred at room temperature for 3.5 days. The reaction mixture was filtered under suction and concentrated to get a residue. The residue was basified with 1 *N* NaOH, extracted with chloroform (3 x 50 ml). The combined organic layers were washed with water (100 ml), brine (100 ml), dried (Na_2SO_4) to afford 820 mg of the crude product as an off-white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50-1.60 (m, 2H), 1.75-1.90 (m, 5H), 2.76 (t, *J* = 6.3 Hz, 2H), 2.87 (d, *J* = 11.7 Hz, 2H), 3.08 (t, *J* = 11.7 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 1H); ESI-MS (*m/z*) 272.40 $(M+H)^+$.

Intermediate 11: 3-(2-Fluorophenyl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one



Step 1: 6-Benzyl-1-oxa-6-azaspiro[2.5]octane:

To a stirred solution of *N*-benzyl-4-piperidone (12 g, 6.383 mmol) in toluene (120 ml) was added trimethylsulfoxonium iodide (15.3 g, 6.974 mmol) followed by tetra-*n*-butyl ammonium bromide (3 g, 9.511 mmol) and NaOH (3.8 g, 9.511 mmol) in water (40 ml) at room temperature. The reaction mixture was stirred at 80 °C for 5 h. The reaction mixture was allowed to cool to room temperature, the layers were separated and the aqueous layer was extracted with toluene (4 x 100 ml). The combined organic layers were washed with water (150 ml), brine (100 ml) and dried (Na_2SO_4). The crude product obtained after the evaporation of the solvent gave 12.8 g of the product as a colorless liquid; IR (KBr) 2939, 1952, 1601, 1454, 1052, 749 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50-1.60 (m, 2H), 1.78-1.90 (m, 2H), 2.55-2.60 (m, 4H), 2.64 (s, 2H), 3.55 (s, 2H), 7.31 (s, 5H); ESI-MS (*m/z*) 204.55 $(M+H)^+$.

Step 2: 1-Benzyl-4-{[(2-fluorophenyl)amino]methyl}piperidin-4-ol:

To a stirred solution of Step 1 intermediate (2 g, 9.836 mmol) was added 2-fluoroaniline (1.2 g, 10.822 mmol) at room temperature. The reaction mixture was stirred at 160 °C for 15 h. The reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate and extracted with 1 *N* aqueous HCl. The layers were separated and the aqueous layer was basified with NaOH solution and extracted with ethyl acetate (3 x 100 ml). The combined organic layers were washed with brine, dried (Na_2SO_4) and the crude product which was obtained after the evaporation of the solvent was purified on silica gel column chromatography using 2% methanol in chloroform to give 820 mg of the product as a liquid;

IR (KBr) 3408, 2939, 1620, 1523, 1253, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.68 (d, *J* = 12.0 Hz, 4H), 2.30-2.42 (m, 2H), 2.60-2.70 (m, 2H), 3.13 (d, *J* = 6.0 Hz, 2H), 3.53 (s, 3H), 4.18 (br s, 1H, *exchangeable with D_2O*), 6.58-6.65 (m, 1H), 6.74 (t, *J* = 8.7 Hz, 1H), 6.94 (q, *J* = 5.4 Hz, 2H), 7.30 (s, 5H); ESI-MS (*m/z*) 315.65 $(M+H)^+$.

Step 3: 8-Benzyl-3-(2-fluorophenyl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one:

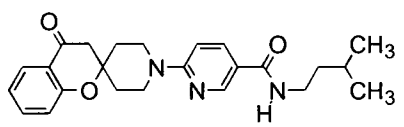
To a stirred solution of Step 2 intermediate (800 mg, 2.544 mmol) in dry tetrahydrofuran (10 ml) was added triphosgene (377 mg, 1.272 mmol) followed by diisopropylethylamine (1.5 ml, 1.15 g, 8.905 mmol) at -10 °C. The reaction mixture was stirred at the same temperature for 1 h, allowed to warm to room temperature and stirred at the same temperature for 48 h. The reaction mixture was diluted with ethyl acetate (3 x 50 ml), washed with water (50 ml), brine and dried (Na_2SO_4). The solvent was evaporated to get a crude product which was purified on silica gel column chromatography using 30% ethyl acetate in chloroform to give 315 mg of the product as an off-white solid; IR (KBr) 2951, 1745, 1508, 1240, 765 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.82-1.92 (m, 2H), 2.07 (d, *J* = 13.2 Hz, 2H), 2.60 (br s, 4H), 3.54 (s, 2H), 3.76 (s, 2H), 7.05-7.18 (m, 2H), 7.30-7.38 (m, 6H), 7.51 (t, *J* = 8.1 Hz, 1H); ESI-MS (*m/z*) 341.90 $(M+H)^+$.

Step 4: 3-(2-Fluorophenyl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one:

To a stirred solution of Step 3 intermediate (300 mg, 0.881 mmol) in ethanol (50 ml) was added 10% palladium on carbon at room temperature under 60 psi H_2 pressure and the reaction mixture was stirred at the same temperature and pressure for 6 h. The reaction mixture was filtered, washed with ethanol and evaporated under reduced pressure to get 226 mg of the product as a semisolid; IR (KBr) 3409, 2926, 1651, 1163, 1016 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.80-1.92 (m, 2H), 2.00-2.20 (m, 4H), 2.58-2.70 (m, 1H), 2.92-3.00 (m, 1H), 3.12 (t, *J* = 10.8 Hz, 1H), 3.77 (s, 2H), 7.05-7.15 (m, 1H), 7.17-7.30 (m, 2H), 7.51 (t, *J* = 8.1 Hz, 1H), 7.42-7.54 (m, 1H); ESI-MS (*m/z*) 341.90 $(M+H)^+$.

The invention is described in detail by the examples, given below, which are provided by way of illustration only and therefore should not be construed to limit the scope of the present invention.

Example 1: Preparation of *N*-(3-Methylbutyl)-6-(4-oxo-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidin]-1'-yl)nicotinamide



Step 1: Methyl 6-(4-oxo-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidin]-1'-yl)nicotinate:

To a stirred solution of Intermediate 1 (175 mg, 0.813 mmol) in acetonitrile (10 ml) was added methyl 6-chloronicotinate (152 mg, 0.892 mmol) followed by K_2CO_3 (223 mg, 1.624 mmol) and potassium iodide (134 mg, 0.813 mmol). The reaction mixture was heated to reflux and stirred for 18 h. The reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (50 ml). The combined organic layers were washed with water (100 ml), saturated sodium bicarbonate (100 ml), brine (50 ml) and dried (Na_2SO_4). The solvent was evaporated to get a crude residue which was purified by silica gel column chromatography using 30% ethyl acetate in petroleum ether to get 101 mg of the product as an off-white solid; IR (KBr) 2947, 1698, 1548, 1473, 762 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.65-1.78 (m, 2H), 1.97 (d, J = 13.2 Hz, 2H), 2.87 (s, 2H), 3.37-3.45 (m, 2H), 3.78 (s, 3H), 4.21 (d, J = 12.3 Hz, 2H), 6.92 (d, J = 8.7 Hz, 1H), 7.09 (t, J = 9.3 Hz, 2H), 7.54-7.64 (m, 1H), 7.70-7.78 (m, 1H), 7.94 (d, J = 8.7 Hz, 1H), 8.64 (s, 1H); ESI-MS (*m/z*) 353.43 $(M+H)^+$.

Step 2: 6-(4-Oxo-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidin]-1'-yl)nicotinic acid:

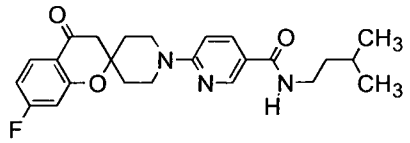
To a stirred solution of Step 1 intermediate (96 mg, 0.272 mmol) in tetrahydrofuran (8 ml) was added lithium hydroxide (36 mg, 0.871 mmol) in water (3 ml) and heated to reflux for 5 h. The reaction mixture was diluted with ethyl acetate (50 ml) and the layers were separated. The aqueous layer was extracted with ethyl acetate, washed with brine (50 ml), dried (Na_2SO_4) and evaporated to get 80 mg of the product as a white solid; IR (KBr) 2923, 1721, 1698, 1482, 1193, 771 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.62-1.80 (m, 2H), 1.97 (d, J = 12.9 Hz, 2H), 2.87 (s, 2H), 3.38-3.45 (m, 2H), 4.20 (d, J = 12.3 Hz, 2H), 6.82-6.90 (m, 1H), 7.00-7.18 (m, 2H), 7.50-7.65 (m, 1H), 7.74 (d, J = 6.3 Hz, 1H), 7.92 (d, J = 6.9 Hz, 1H), 8.62 (s, 1H), 12.50 (br s, 1H); ESI-MS (*m/z*) 337.33 $(M-H)^-$.

Step 3: *N*-(3-Methylbutyl)-6-(4-oxo-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidin]-1'-yl)nicotinamide:

To a stirred solution of Step 2 intermediate (80 mg, 0.241 mmol) in tetrahydrofuran (5 ml) was added triethylamine (170 µl, 1.203 mmol) followed by (Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP) (0.117 g, 0.262 mmol) over 10 min. 3-methylbutan-1-amine (31 µl, 0.262 mmol) was then added and the reaction mixture stirred at room temperature for 15 h. The reaction mixture was diluted with ethyl acetate (50 ml), washed with brine and dried (Na_2SO_4). The solvent was evaporated to get a crude residue which was purified by silica gel column chromatography using 45% ethyl acetate in petroleum ether to get 21 mg of the product as an off-white solid; IR (Neat) 2926,

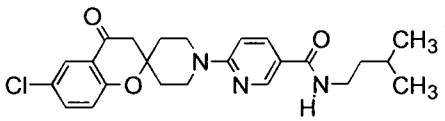
1634, 1462, 1223, 722 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (d, *J* = 6.3 Hz, 6H), 1.49 (d, *J* = 7.2 Hz, 2H), 1.65-1.78 (m, 3H), 2.14 (d, *J* = 13.5 Hz, 2H), 2.74 (s, 2H), 3.38-3.45 (m, 4H), 4.16 (d, *J* = 13.5 Hz, 2H), 5.87 (br s, 1H), 6.65 (d, *J* = 8.4 Hz, 1H), 7.01 (d, *J* = 7.8 Hz, 2H), 7.45-7.55 (m, 1H), 7.85-7.95 (m, 2H), 8.52 (s, 1H); ESI-MS (*m/z*) 408.46 $(M+H)^+$.

Example 2: Preparation of 6-(7-Fluoro-4-oxo-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidin]-1'-yl)-*N*-(3-methylbutyl)nicotinamide



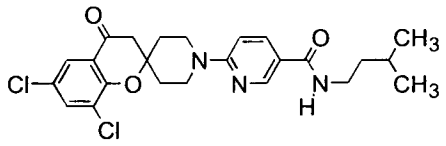
The title compound was synthesized in three steps by following the procedure of Example 1 using methyl 6-chloronicotinate (321 mg, 1.871 mmol), Intermediate 2 (400 mg, 1.701 mmol) and 3-methylbutan-1-amine (62 µl, 0.535 mmol) to yield 28 mg of the product as a white solid; IR (KBr) 2923, 2875, 1591, 1482, 1193, 752 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, *J* = 6.6 Hz, 6H), 1.23 (s, 2H), 1.35-1.45 (m, 2H), 1.58-1.78 (m, 3H), 1.96 (d, *J* = 13.2 Hz, 2H), 2.88 (s, 2H), 3.20-3.30 (m, 2H), 4.15 (d, *J* = 12.3 Hz, 2H), 6.88-6.98 (m, 2H), 7.02 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.78-7.88 (m, 1H), 7.94 (dd, *J* = 7.5, 1.8 Hz, 1H), 8.20 (s, 1H), 8.58 (d, *J* = 2.1 Hz, 1H); ESI-MS (*m/z*) 426.39 $(M+H)^+$.

Example 3: Preparation of 6-(6-Chloro-4-oxo-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidin]-1'-yl)-*N*-(3-methyl-butyl)nicotinamide



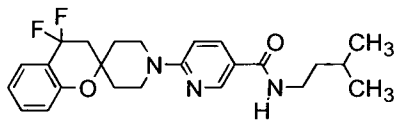
The title compound was synthesized in three steps by following the procedure of Example 1 using methyl 6-chloronicotinate (525 mg, 3.102 mmol), Intermediate 3 (700 mg, 2.786 mmol) and 3-methylbutan-1-amine (49 µl, 0.424 mmol) to yield 29 mg of the product as a pale yellow solid; IR (KBr) 2932, 1696, 1610, 1466, 1213, 822 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, *J* = 6.6 Hz, 6H), 1.39 (d, *J* = 6.6 Hz, 2H), 1.55-1.80 (m, 3H), 1.96 (d, *J* = 13.5 Hz, 2H), 2.90 (s, 2H), 3.20-3.30 (m, 4H), 4.14 (d, *J* = 13.2 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 1H), 7.60-7.65 (m, 2H), 7.93 (d, *J* = 8.1 Hz, 1H), 8.18 (br s, 1H), 8.58 (s, 1H); ESI-MS (*m/z*) 442.47 $(M+H)^+$.

Example 4: Preparation of 6-(6,8-Dichloro-4-oxo-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidin]-1'-yl)-*N*-(3-methylbutyl)nicotinamide



The title compound was synthesized in three steps by following the procedure of Example 1 using methyl 6-chloronicotinate (660 mg, 3.848 mmol), Intermediate 4 (1 g, 3.501 mmol) and 3-methylbutan-1-amine (49 µl, 0.424 mmol) to yield 11 mg of the product as a pale yellow solid; IR (KBr) 2949, 2875, 1621, 1562, 1482, 1203, 792 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, J = 6.6 Hz, 6H), 1.25-1.45 (m, 4H), 1.55-1.65 (m, 1H), 1.74 (t, J = 12.3 Hz, 2H), 2.00 (d, J = 12.9 Hz, 2H), 2.98 (s, 2H), 3.20-3.30 (m, 2H), 4.25 (d, J = 12.6 Hz, 2H), 6.90 (d, J = 8.7 Hz, 1H), 7.67 (s, 1H), 7.55-8.02 (m, 2H), 8.19 (s, 1H), 8.58 (s, 1H); ESI-MS (*m/z*) 476.46 $(M+H)^+$.

Example 5: Preparation of 6-(4,4-Difluoro-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidin]-1'-yl)-*N*-(3-methylbutyl)nicotinamide



Method A:

Step 1: Methyl 6-(4,4-difluoro-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidin]-1'-yl)nicotinate:

A solution of step1 intermediate, Example 1 (200 mg, 0.567 mmol) in DAST (1ml, 7.568 mmol) was heated to 75 °C for 18 h. The reaction mixture was poured onto crushed ice and extracted with ethyl acetate (3 x 50 ml). The combined organic layers were washed with brine and dried (Na_2SO_4). The solvent was evaporated to get a crude residue which was purified by silica gel column chromatography using 15% ethyl acetate in chloroform to get 80 mg of the product as a yellow solid; IR (KBr) 2930, 1712, 1603, 1462, 1223, 964 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.70-1.80 (m, 2H), 1.90-2.00 (m, 2H), 2.80-2.90 (m, 2H), 3.00-3.10 (m, 2H), 3.79 (s, 3H), 4.31 (d, J = 14.1 Hz, 1H), 4.49 (d, J = 14.7 Hz, 1H), 6.80-7.00 (m, 1H), 7.16-7.24 (m, 2H), 7.64-7.74 (m, 2H), 7.84 (d, J = 7.5 Hz, 1H), 7.97 (d, J = 8.4, 2.7 Hz, 1H), 8.66 (s, 1H); ESI-MS (*m/z*) 375.51 $(M+H)^+$.

Step 2: 6-(4,4-Difluoro-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidin]-1'-yl)nicotinic acid:

Hydrolysis of Step 1 Intermediate (70 mg, 0.187 mmol) using lithium hydroxide (39 mg, 0.928 mmol) in tetrahydrofuran (2 ml) and water (1 ml) according to the procedure described in Step 2, Example 1 afforded 76 mg of the product as a white solid; IR (KBr) 2959, 1737, 1624, 1483, 1236, 1095 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.80-2.00 (m,

4H), 2.90-3.10 (m, 4H), 4.30 (d, J = 12.9 Hz, 1H), 4.48 (d, J = 11.7 Hz, 1H), 6.90 (d, J = 9.0 Hz, 2H), 7.18-7.25 (m, 2H), 7.70 (t, J = 8.7 Hz, 1H), 7.84-7.96 (m, 1H), 8.64 (s, 1H), 12.50 (br s, 1H); ESI-MS (*m/z*) 360.32 $(M)^+$.

Step 3: 6-(4,4-Difluoro-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidin]-1'-yl)-*N*-(3-methylbutyl)nicotinamide:

Coupling reaction of Step 2 Intermediate (70 mg, 0.194 mmol) using BOP reagent (95 mg, 0.213 mmol), triethylamine (0.14 ml, 0.971 mmol) and isoamylamine (25 µl, 0.213 mmol) in tetrahydrofuran (3 ml) according to the procedure described in Step 3, Example 1 afforded 17 mg of the product as a yellow solid; IR (KBr) 2960, 1727, 1615, 1455, 1095 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, J = 6.6 Hz, 6H), 1.00-1.15 (m, 3H), 1.41 (q, J = 6.9 Hz, 2H), 1.55-1.65 (m, 1H), 1.70-1.82 (m, 2H), 1.90-2.15 (m, 2H), 2.90-3.18 (m, 2H), 4.26 (d, J = 12.0 Hz, 1H), 4.44 (d, J = 12.3 Hz, 1H), 6.89 (d, J = 9.3 Hz, 1H), 7.30-7.50 (m, 2H), 7.70 (t, J = 7.8 Hz, 1H), 7.84 (d, J = 8.1 Hz, 1H), 7.95 (d, J = 9.0 Hz, 1H), 8.21 (s, 1H), 8.58 (s, 1H); ESI-MS (*m/z*) 430.52 $(M+H)^+$.

Method B:

Step 1: *tert*-Butyl 4,4-difluoro-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidine]-1'-carboxylate:

To the BOC protected Intermediate 1 (500 mg, 1.586 mmol) was added DAST (1.5 ml, 11.406 mmol) at room temperature and the reaction mixture was stirred at 85 °C for 4 h. The reaction mixture was allowed to cool to room temperature, poured onto ice and extracted with ethyl acetate (3 x 50 ml). The combined organic layers were washed with water (100 ml), saturated sodium bicarbonate (100 ml), brine (50 ml) and dried (Na_2SO_4). The solvent was evaporated to get a crude residue which was purified by silica gel column chromatography using 5% ethyl acetate in petroleum ether to get 193 mg of the product as pale yellow oil; IR (Neat) 2974, 1695, 1462, 1226, 757 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 1.75-1.84 (br s, 2H), 2.01-2.09 (br s, 2H), 2.82-2.90 (m, 2H), 3.12-3.23 (m, 2H), 3.85-3.92 (m, 1H), 4.00-4.10 (m, 1H), 6.99-7.10 (m, 2H), 7.54 (t, J = 7.5 Hz, 1H), 7.90 (d, J = 7.5 Hz, 1H); ESI-MS (*m/z*) 340.16 $(M+H)^+$.

Step 2: 4,4-Difluoro-3,4-dihydrospiro[chromene-2,4'-piperidine]:

Step 1 intermediate (180 mg, 0.531 mmol) was deprotected using 1:1 trifluoroacetic acid and dichloromethane (6 ml) as described in Step 2, Intermediate 1 to get 114 mg of the product as an off-white solid which was used as such for the next step.

Step 3: Methyl 6-(4,4-difluoro-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidin]-1'-yl)nicotinate:

Coupling reaction of Step 2 Intermediate (100 mg, 0.418 mmol) with methyl 6-chloronicotinate (79 mg, 0.461 mmol) in acetonitrile (15 ml) using potassium iodide (70 mg, 0.418 mmol) and K_2CO_3 (120 mg, 0.836 mmol) according to the procedure described in Step 1, Example 1 afforded 532 mg of the product as a semisolid; IR (KBr) 2963, 2869, 1672, 1591, 1208, 1023, 752 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, J = 6.6 Hz, 6H), 1.00-1.15 (m, 3H), 1.41 (q, J = 6.9 Hz, 2H), 1.55-1.65 (m, 1H), 1.70-1.82 (m, 2H), 1.90-2.15 (m, 2H), 2.90-3.18 (m, 2H), 4.26 (d, J = 12.0 Hz, 1H), 4.44 (d, J = 12.3 Hz, 1H), 6.89 (d, J = 9.3 Hz, 1H), 7.30-7.50 (m, 2H), 7.70 (t, J = 7.8 Hz, 1H), 7.84 (d, J = 8.1 Hz, 1H), 7.95 (d, J = 9.0 Hz, 1H), 8.21 (s, 1H), 8.58 (s, 1H); ESI-MS (*m/z*) 375.51 $(M+H)^+$.

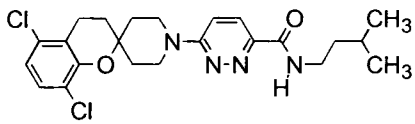
Step 4: 6-(4,4-Difluoro-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidin]-1'-yl)nicotinic acid:

This intermediate was prepared using Step 3 intermediate (70 mg, 0.187 mmol) and lithium hydroxide (39 mg, 0.928 mmol) according to the procedure described in Step 2, Method A to give 80 mg of the product as a white solid which showed identical IR and ^1H NMR spectra to the product obtained by Step 2, Method A.

Step 5: 6-(4,4-Difluoro-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidin]-1'-yl)-*N*-(3-methylbutyl)nicotinamide:

The title compound was prepared as described in Step 3, Method A, using Step 4 intermediate (70 mg, 0.194 mmol), BOP (95 mg, 0.213 mmol) and isoamylamine (25 µl, 0.213 mmol) in presence of triethylamine (0.14 ml, 0.971 mmol) to give 19 mg of the product as a yellow solid which showed identical IR and ^1H NMR spectra to the product obtained by Step 3, Method A.

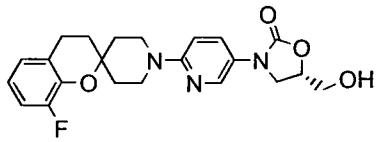
Example 6: Preparation of 6-(5,8-Dichloro-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidin]-1'-yl)-*N*-(3-methylbutyl)nicotinamide



To a stirred solution of Intermediate 10 (100 mg, 0.373 mmol) in dioxane (10 ml) was added 6-chloro-*N*-(3-methylbutyl)pyridazine-3-carboxamide (84 mg, 0.373 mmol) followed by tetra-*n*-butylammonium bromide (20 mg, 0.062 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.11 ml, 0.742 mmol). The reaction mixture was heated to reflux for 18 h. The reaction mixture was allowed to cool to room temperature and the residue obtained after the evaporation of the solvent was purified by silica gel column chromatography using 5% ethyl

acetate in chloroform to get 58 mg of the compound as a white solid; IR (KBr) 3382, 2946, 1660, 1585, 1454, 1245 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (s, 7H), 1.44-1.58 (m, 2H), 1.68-1.80 (m, 2H), 1.85-2.00 (m, 4H), 2.81 (br s, 2H), 3.42-3.60 (m, 4H), 4.30-4.45 (m, 2H), 6.93 (d, *J* = 19.2 Hz, 2H), 7.10-7.22 (m, 1H), 7.80-7.90 (m, 1H), 7.92-8.02 (m, 1H); ESI-MS (*m/z*) 463.43 $(M+H)^+$.

Example 7: Preparation of (5*S*)-3-[8-Fluoro-(3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidin]-1'-yl]pyridine-3-yl-5-(hydroxymethyl)-1,3-oxazolidin-2-one:



Step 1: 8-Fluoro-1'-(5-nitropyridin-2-yl)-3,4-dihydrospiro[chromene-2,4'-piperidine]:

Coupling reaction of Intermediate 8 (200 mg, 0.904 mmol) in acetonitrile (2 ml) with 2-chloro-5-nitropyridine (157 mg, 0.990 mmol) in the presence of K_2CO_3 (250 mg, 1.809 mmol) and KI (150 mg, 0.903 mmol) as described in Step 1, Example 1 afforded 203 mg of the product as a yellow solid; IR (KBr) 2933, 1606, 1476, 1349, 1223 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.60-1.80 (m, 2H), 1.84-2.00 (m, 4H), 2.70-2.90 (m, 2H), 3.40-3.60 (m, 2H), 4.20-4.40 (m, 2H), 6.70-6.90 (m, 1H), 6.90-7.10 (m, 3H), 8.20 (dd, *J* = 9.3, 2.7 Hz, 1H), 7.68 (d, *J* = 9.3 Hz, 1H); ESI-MS (*m/z*) 344.60 $(M+H)^+$.

Step 2: 6-(8-Fluoro-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidin]-1'-yl)pyridin-3-amine:

Step 1 above intermediate (200 mg, 0.582 mmol) in 1:1 toluene and ethanol (40 ml) was reduced by 10% palladium on carbon (40 mg) as described in Step 2, Example 6 to give 133 mg of the product as a grey solid; IR (KBr) 3453, 2847, 1571, 1477, 1249, 917 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.60-1.80 (m, 2H), 1.84-2.00 (m, 4H), 2.70-2.90 (m, 2H), 3.40-3.60 (m, 2H), 4.20-4.40 (m, 2H), 6.70-6.90 (m, 1H), 6.90-7.10 (m, 3H), 8.20 (dd, *J* = 9.3, 2.7 Hz, 1H), 7.68 (d, *J* = 9.3 Hz, 1H); ESI-MS (*m/z*) 344.60 $(M+H)^+$.

Step 3: Benzyl [6-(8-fluoro-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidin]-1'-yl)pyridin-3-yl]carbamate:

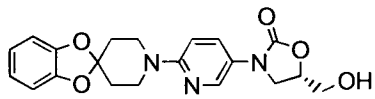
This intermediate was prepared by coupling Step 2 intermediate (125 mg, 0.399 mmol) in 2:1 mixture of acetone (2 ml) and water (1 ml) with benzyl chloroformate (985 mg, 0.598 mmol) in presence of $NaHCO_3$ (100 mg, 1.198 mmol) as described in Step 3, Example 6 to give 155 mg of the product as a grey solid; IR (KBr) 2924, 1713, 1537, 1221, 918 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.60-1.90 (m, 6H), 2.77 (t, *J* = 6.3 Hz, 2H), 3.20-3.40 (m,

2H), 3.80-4.00 (m, 2H), 5.11 (s, 2H), 6.70-6.90 (m, 3H), 6.90-7.10 (m, 1H), 7.20-7.40 (m, 5H), 7.50-7.70 (m, 1H), 8.15 (s, 1H), 9.50 (s, 1H); ESI-MS (*m/z*) 448.64 $(M+H)^+$.

Step 4: (5*S*)-3-[8-Fluoro-(3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidin]-1'-yl]pyridine-3-yl-5-(hydroxymethyl)-1,3-oxazolidin-2-one:

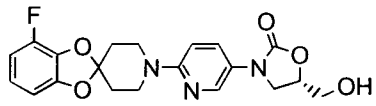
To a stirred solution of Step 3 intermediate (145 mg, 0.324 mmol) in dry THF (3 ml) was added 1.6 *M* n-butyl lithium in hexane (62 mg, 0.968 mmol) and the mixture was stirred at -78 °C for 1 h and (*S*)-(+)-glycidyl butyrate (70 mg, 0.485 mmol) was added over 5 min. The reaction mixture was stirred at the same temperature for 1 h. The reaction mixture was allowed to warm to room temperature and stirred at the same temperature overnight. The reaction mixture was treated with saturated ammonium chloride solution and extracted with ethyl acetate (3 x 50 ml), washed with water (100 ml). The combined organic layers were washed with brine (50 ml) and dried (Na_2SO_4) and evaporated under reduced pressure to get a residue which was purified by silica gel column chromatography using 2% methanol in chloroform to get 40 mg of the compound as a white solid; IR (KBr) 3485, 2924, 1733, 1498, 1225, 1140 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.60-1.90 (m, 6H), 2.77 (t, J = 6.3 Hz, 2H), 3.20-3.40 (m, 1H), 3.50-3.70 (m, 3H), 3.70-3.90 (m, 1H), 3.90-4.10 (m, 3H), 5.19 (m, 1H), 6.70-6.90 (m, 1H), 6.90-7.10 (m, 3H), 7.70-7.80 (m, 1H), 8.18 (d, J = 2.1 Hz, 1H); ESI-MS (*m/z*) 414.86 $(M+H)^+$.

Example 8: Preparation of (5*S*)-5-(Hydroxymethyl)-3-[6-(1'*H*-spiro[1,3-benzodiaxole-2,4'-piperidin]-1'-yl)pyridin-3-yl]-1,3-oxazolidin-2-one



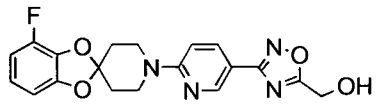
This compound was prepared in 4 steps according to the procedure described in example 7, Steps 1 to 4 using Intermediate 6 (500 mg, 2.615 mmol) and 2-chloro-5-nitropyridine (456 mg, 2.876 mmol) to afford 96 mg of the product as an off-white solid; IR (KBr) 3377, 2849, 1711, 1498, 1239, 1072, 754 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.92-1.98 (br m, 4H), 3.45-3.56 (m, 1H), 3.63-3.80 (m, 6H), 4.00-4.10 (m, 1H), 4.66 (br s , 1H), 5.20-5.30 (m, 1H), 6.78-6.81 (m, 2H), 6.86-6.89 (m, 2H), 6.99 (d, J = 9.3 Hz, 1H), 6.84 (dd, J = 9.3, 2.4 Hz, 11H), 8.20 (s, 1H); ESI-MS (*m/z*) 384.39 $(M+H)^+$.

Example 9: (5*S*)-3-[6-(4-Fluoro-1'*H*-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)pyridin-3-yl]-5-(hydroxymethyl)-1,3-oxazolidin-2-one



The title compound was synthesized in four steps by following the procedure described in Example 7 using 2-chloro-5-nitropyridine (250 mg, 1.578 mmol), Intermediate 7 (300 mg, 1.434 mmol), 1.6 *M* n-butyl lithium in hexane (1.29 ml, 2.067 mmol) and *S*-(+)-glycidyl butyrate (151 µl, 1.034 mmol) to yield 110 mg of the compound as a white solid; IR (KBr) 3407, 2847, 1720, 1497, 1097, 776 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.02-2.12 (br m, 4H), 3.55-3.57 (m, 1H), 3.64-3.80 (m, 6H), 4.03 (t, J = 9.0 Hz, 1H), 4.67 (br s , 1H), 5.21 (t, J = 5.7 Hz, 1H), 6.78-6.81 (m, 3H), 7.00 (d, J = 9.3 Hz, 1H), 7.84 (d, J = 6.9 Hz, 1H), 8.21 (s, 1H); ESI-MS (*m/z*) 402.76 $(M+H)^+$.

Example 10: Preparation of {3-[6-(4-Fluoro-1'*H*-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)pyridin-3-yl]-1,2,4-oxadiazol-5-yl}methanol



Step 1: 6-(4-Fluoro-1'*H*-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)nicotinonitrile:

To a stirred solution of Intermediate 7 (209 mg, 0.998 mmol) in anhydrous dimethylsulfoxide (DMSO) (2 ml) was added diisopropylethylamine (0.44 ml, 2.501 mmol) followed by 2-chloro-5-cyanopyridine (152 mg, 1.101 mmol) and heated the reaction mixture was heated to 80 °C for 18 h. The reaction mixture was poured into water (50 ml) and extracted with ethyl acetate (3 x 50 ml). The combined organic layers were washed with water (100 ml), brine (50 ml) and dried (Na_2SO_4). The solvent was evaporated to get a crude residue which was purified by silica gel column chromatography using 5% ethyl acetate in chloroform to get 213 mg of the product as an off-white solid; IR (KBr) 3421, 2963, 2214, 1598, 1428, 1347, 1126, 1011, 763 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.10 (t, J = 5.4 Hz, 4H), 3.93 (t, J = 5.4 Hz, 4H), 6.57-6.75 (m, 4H), 7.62 (d, J = 9.3 Hz, 1H), 8.40 (s, 1H); ESI-MS (*m/z*) 312.31 $(M+H)^+$.

Step 2: 6-(4-Fluoro-1'*H*-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)-*N*'-hydroxypyridine-3-carboximidamide:

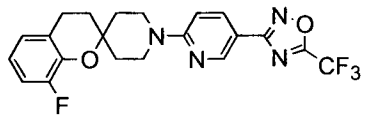
To a stirred solution of Step 1 intermediate (200 mg, 0.642 mmol) in methanol (10 ml) was added $NaHCO_3$ (540 mg, 6.424 mmol) followed by 97% hydroxylamine hydrochloride (460 mg, 6.424 mmol) at room temperature and heated to reflux for 15 h. The residue obtained after the evaporation of the solvent was treated with water (50 ml), extracted with ethyl acetate (3 x 50 ml). The combined organic layers were washed with brine (50 ml)

and dried (Na_2SO_4) and concentrated to get a crude residue which was purified by silica gel column chromatography using 60% ethyl acetate in petroleum ether to get 165 mg of the product as a white solid; IR (KBr) 3461, 2927, 1636, 1508, 1422, 1244, 1122, 1084, 931 cm^{-1}; ^1H NMR (300 MHz, DMO-d_6) δ 2.00-2.30 (br m, 4H), 3.78-3.80 (br m, 4H), 5.75 (br s, 2H), 6.79-6.82 (m, 3H), 6.94 (d, J = 8.7 Hz, 1H), 7.78 (d, J = 9.3 Hz, 1H), 8.39 (s, 1H), 9.44 (br s, 1H); ESI-MS (*m/z*) 345.74 $(M+H)^+$.

Step 3: {3-[6-(4-Fluoro-1'*H*-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)pyridin-3-yl]-1,2,4-oxadiazol-5-yl}methanol:

To a cold stirring solution of Step 2 intermediate (70 mg, 0.203 mmol) in anhydrous dimethylformamide (5 ml) was added 60% sodium hydride in mineral oil (10 mg, 0.254 mmol). Then Ethyl glycolate (27 mg, 0.264 mmol) was then added over 15 min and the mixture was stirred at 0 °C for 1 h. The reaction mixture was allowed to warm to room temperature and stirred at the same temperature overnight. The mixture was poured into water (50 ml), extracted with ethyl acetate (3 x 50 ml). The combined organic layers were washed with brine (50 ml), dried (Na_2SO_4) and evaporated under reduced pressure to get a residue which was purified by silica gel column chromatography using 3% methanol in chloroform to get 30 mg of the compound as a white solid; IR (KBr) 3200, 2932, 1615, 1408, 1089, 768 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 2.00-2.15 (br m, 4H), 3.80-3.95 (br m, 4H), 4.76 (d, J = 6.3 Hz, 2H), 6.04 (t, J = 6.3 Hz, 1H), 6.80-6.83 (m, 3H), 7.10 (d, J = 8.7 Hz, 1H), 8.05 (d, J = 9.6 Hz, 1H), 8.70 (s, 1H); ESI-MS (*m/z*): 385.64 $(M+H)^+$.

Example 11: Preparation of 8-Fluoro-1'-{5-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2-yl}-3,4-dihydrospiro[chromene-2,4'-piperidine]



Step 1: 6-(8-Fluoro-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidin]-1'-yl)nicotinonitrile:

Coupling reaction of Intermediate 8 (200 mg, 0.904 mmol) and using 2-chloro-5-cyanopyridine (138 mg, 0.996 mmol) in presence of diisopropylethylamine (0.39 ml, 2.259 mmol) in anhydrous DMSO (2 ml) according to the procedure described in Step 1, Example 10 afforded 17 mg of the product as an off-white solid; IR (KBr) 2925, 2210, 1608, 1474, 1226, 1096, 958, 809 cm-1; 1H NMR (300 MHz, DMSO-d6) δ 1.60-1.90 (m, 6H), 2.78 (t, J = 6.3 Hz, 2H), 3.20-3.40 (m, 2H), 4.10-4.30 (m, 2H), 6.70-6.90 (m, 1H), 6.90-7.00 (m, 3H), 7.82 (d, J = 9.0 Hz, 1H), 8.45 (s, 1H); ESI-MS (*m/z*) 324.70 $(M+H)^+$.

Step 2: 6-(8-Fluoro-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidin]-1'-yl)-*N*'-hydroxypyridine-3-carboximidamide:

This intermediate was prepared by treating Step 1 Intermediate (250 mg, 0.773 mmol) with 97% hydroxylamine hydrochloride (540 mg, 7.769 mmol) in presence of $NaHCO_3$ (650 mg, 7.738 mmol) in methanol (5 ml) according to the procedure described in Step 2, Example 10 to afford 221 mg of the product as an off-white solid; IR (KBr) 3436, 2851, 1638, 1616, 1518, 1478, 1263, 1077, 940, 776 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.60-1.90 (m, 6H), 2.78 (t, J = 6.3 Hz, 2H), 3.20-3.40 (m, 2H), 4.10-4.30 (m, 2H), 5.73 (s, 2H), 6.70-7.00 (m, 4H), 7.70-7.80 (m, 1H), 8.37 (s, 1H), 9.41 (s, 1H); ESI-MS (*m/z*) 357.74 $(M+H)^+$.

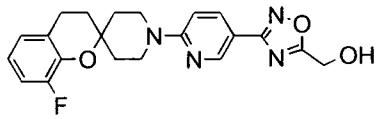
Step 3: 6-(8-Fluoro-*N*'-[(trifluoroacetyl)oxy]-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidine]-1'-yl)pyridine-3-carboximidamide:

To a stirred solution of Step 2 intermediate (75 mg, 0.212 mmol) in 1,4-dioxane (2 ml) was added K_2CO_3 (60 mg, 0.435 mmol) followed by trifluoroacetic anhydride (33 µl, 0.233 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 18 h. The reaction mixture was diluted with ethyl acetate (50 ml) and water (50 ml) and the layers were separated. The organic layer was washed with water, brine and dried (Na_2SO_4). The solvent was evaporated to get 80 mg of the crude residue which was used as such for the next step.

Step 4: 8-Fluoro-1'-{5-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2-yl}-3,4-dihydrospiro[chromene-2,4'-piperidine]:

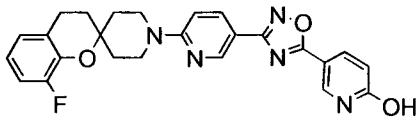
A stirred solution of Step 3 intermediate (80 mg, 0.176 mmol) in toluene (3 ml) was heated to reflux for 18 h. The reaction mixture was allowed to cool to room temperature, evaporated under vacuum to get a crude residue which was purified by silica gel column chromatography using 5% ethyl acetate in chloroform to get 45 mg of the compound as an off-white solid; IR (KBr) 3434, 2924, 1617, 1482, 1222, 991, 770 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.64-1.76 (m, 2H), 1.80-1.90 (m, 4H), 2.78 (br s, 2H), 4.21 (d, J = 13.8 Hz, 2H), 6.70-6.80 (m, 1H), 6.85-7.05 (m, 3H),8.00-8.10 (m, 1H), 8.71 (s, 1H); ESI-MS (*m/z*) 435.22 $(M+H)^+$.

Example 12: Preparation of {3-[6-(8-Fluoro-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidin]-1'-yl)pyridin-3-yl]-1,2,4-oxadiazol-5-yl}methanol



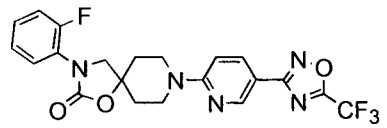
To a stirred solution of Step 2 intermediate, Example 11 (105 mg, 0.295 mmol) in DMF (2 ml) was added 60% sodium hydride in mineral oil (15 mg, 0.625 mmol) at 0 °C. The resulting yellow colored clear solution was stirred at the same temperature for 30 min. Then to this, ethyl glycolate (0.036 ml, 0.384 mmol) was added over 15 min at 0 °C. The reaction mixture was allowed to stir at room temperature for 18 h. The reaction mixture was diluted with ethyl acetate, washed with water, brine, dried (Na_2SO_4) and evaporated under reduced pressure to give 61 mg of the product as an off-white solid; IR (KBr) 2926, 1622, 1478, 1221, 1099 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.60-1.90 (m, 6H), 2.78 (t, J = 6.3 Hz, 2H), 3.20-3.40 (m, 2H), 4.10-4.30 (m, 2H), 4.75 (d, J = 6.3 Hz, 2H), 6.04 (t, J = 6.3 Hz, 1H), 6.70-6.80 (m, 1H), 6.90-7.00 (m, 3H), 8.00 (dd, J = 9.3, 2.4 Hz, 1H), 8.68 (s, 1H) ESI-MS (*m/z*) 397.31 $(M+H)^+$.

Example 13:Preparation of {3-[6-(8-Fluoro-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidin]-1'-yl)pyridin-3-yl]-1,2,4-oxadiazol-5-yl}pyridin-2-ol



To a stirred solution of Step 2 intermediate, Example 11 (50 mg, 0.146 mmol) in pyridine (2 ml) was added 6-hydroxynicotinoyl chloride (33 mg, 0.214 mmol) at room temperature. The reaction mixture was heated to reflux for 15 min. The reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate (50 ml) and washed with 1 *N* HCl. The organic layer was washed with brine and dried (Na_2SO_4). The solvent was evaporated to get a crude residue which was purified by silica gel column chromatography using 3% methanol in chloroform to get 28 mg of the compound as an off-white solid; IR (KBr) 3332, 2921, 1606, 1418, 1224, 1098 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.60-1.75 (m, 2H), 1.78-1.90 (m, 4H), 2.78 (br s, 2H), 3.15 (d, J = 4.8 Hz, 2H), 4.10-4.20 (m, 2H), 6.35 (d, J = 9.6 Hz, 2H), 6.75-7.05 (m, 5H), 7.80 (d, J = 9.3 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 8.41 (d, J = 17.1 Hz, 2H); ESI-MS (*m/z*) 460.19 $(M+H)^+$.

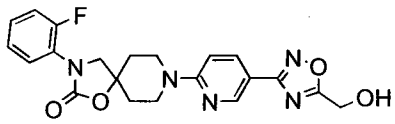
Example 14: Preparation of 3-(2-Fluorophenyl)-8-{5-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2-yl}-1-oxa-3,8-diazaspiro[4.5]decan-2-one



This compound was prepared in 4 steps according to the procedure described in Example 11, Steps 1 to 4 using Intermediate 11 (400 mg, 1.591 mmol), 2-chloro-5-

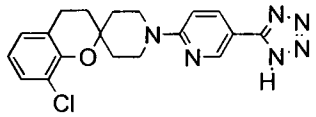
cyanopyridine (244 mg, 1.753 mmol) and diisopropylethylamine (696 µl, 3.991 mmol) in anhydrous DMF at room temperature to afford 9 mg of the compound as a white solid; IR (KBr) 2922, 1754, 1614, 1163, 759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.88 (t, J = 10.2 Hz, 2H), 2.18 (d, J = 12.9 Hz, 2H), 3.60 (t, J = 10.8 Hz, 2H), 3.80 (s, 2H), 4.27 (d, J = 13.8 Hz, 2H), 6.74 (d, J = 9.6 Hz, 1H), 7.10-7.20 (m, 3H), 7.53 (t, J = 7.8 Hz, 1H), 8.08 (d, J = 9.3 Hz, 1H), 8.85 (s, 1H); ESI-MS (*m/z*) 464.06 $(M+H)^+$.

Example 15: Preparation of3-(2-Fluorophenyl)-8-{5-[5-(hydroxymethyl)-1,2,4-oxadiazol-3-yl]pyridin-2-yl}-1-oxa-3,8-diazaspiro[4.5]decan-2-one



This compound was prepared from Step 2, Intermediate 14 (140 mg, 0.365 mmol), according to the procedure described in Example 12 using 60% sodium hydride (11 mg, 1.253 mmol) and ethyl glycolate (49 mg, 1.301 mmol) to get 64 mg of the compound as a white solid; IR (KBr) 3210, 2923, 1756, 1611, 1408, 1223, 770 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.97 (br s, 4H), 3.59 (br s, 2H), 3.85 (s, 2H), 4.02 (d, J = 13.8 Hz, 2H), 4.75 (d, J = 6.3 Hz, 2H), 6.02 (t, J = 6.9 Hz, 1H), 7.05 (d, J = 9.3 Hz, 1H), 7.20-7.38 (m, 3H), 7.55 (t, J = 8.4 Hz, 1H), 8.01 (d, J = 9.0 Hz, 1H), 8.68 (s, 1H); ESI-MS (*m/z*) 426.22 $(M+H)^+$

Example 16: Preparation of 8-Chloro-1'-[5-(1*H*-tetrazol-5-yl)pyridin-2-yl]-3,4-dihydrospiro[chromene-2,4'-piperidine]



Step 1: 6-(8-Chloro-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidin]-1'-yl)nicotinonitrile:

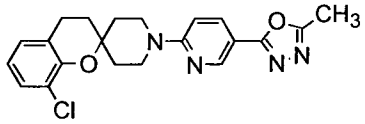
To a stirred solution of Intermediate 9 (500 mg, 2.102 mmol) in dimethylsulfoxide (5 ml) was added 2-chloro-5-cyanopyridine (320 mg, 2.309 mmol) followed by *N,N*-diisopropyl ethylamine (0.9 ml, 5.261 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 18 h. The reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate (50 ml), washed with water, brine, dried (Na_2SO_4) and evaporated under reduced pressure to give a crude product which was purified by silica gel column chromatography using 20% ethyl acetate in petroleum ether to give 580 mg of the product as an off-white solid; IR (KBr) 2942, 2262, 1591, 1479, 1246, 1086, 950, 791 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.60-1.90 (m, 6H), 2.78 (t, J = 6.3 Hz, 2H), 3.20-3.40 (m, 2H), 4.29 (d, J = 14.1

Hz, 2H), 6.82 (t, J = 7.8, 1H), 6.96 (d, J = 9.3 Hz, 1H), 7.06 (d, J = 6.9 Hz, 1H), 7.82 (dd, 6.9, 2.4 Hz, 1H), 8.46 (s, 1H); ESI-MS (*m/z*) 340.63 $(M+H)^+$.

Step 2: 8-Chloro-1'-[5-(1*H*-tetrazol-5-yl)pyridin-2-yl]-3,4-dihydrospiro[chromene-2,4'-piperidine]:

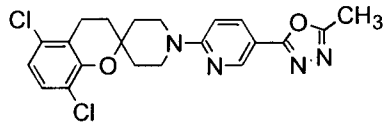
To a stirred solution of Step 1 intermediate (80 mg, 0.235 mmol) in anhydrous dimethylformamide (1 ml) was added ammonium chloride (16 mg, 0.299 mmol) followed by sodium azide (18 mg, 0.277 mmol) at room temperature. The reaction mixture was stirred at 90 °C for 18 h. The reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate (50 ml), washed with water (50 ml), brine (50 ml), dried (Na_2SO_4) and evaporated under reduced pressure to get a crude product which was purified by silica gel column chromatography using 2% methanol in chloroform to give 30 mg of the compound as an off-white solid; IR (KBr) 2918, 1605, 1491, 1239, 1028 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.60-1.90 (m, 6H), 2.79 (br s, 2H), 3.15 (s, 2H), 4.27 (d, J = 12.6 Hz, 2H), 6.82 (t, J = 7.8 Hz, 1H), 7.06 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 9.3 Hz, 1H), 8.72 (s, 1H); ESI-MS (*m/z*) 383.21 $(M+H)^+$.

Example 17: Preparation of 8-Chloro-1'-[5-(5-methyl-1,3,4-oxadiazol-2-yl)pyridin-2-yl]-3,4-dihydrospiro[chromene-2,4'-piperidine]



To a stirred solution of Step 2 intermediate, Example 16 (100 mg, 0.261 mmol) was added acetic anhydride (2 ml) at room temperature. The reaction mixture was heated to reflux for 2 h. The reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate (50 ml) and water (50 ml). The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water (50 ml), brine (50 ml), dried (Na_2SO_4) and evaporated under reduced pressure to get a crude product which was purified by silica gel column chromatography using 15% ethyl acetate in chloroform to give 42 mg of the compound as an off-white solid; IR (KBr) 2952, 1608, 1459, 1240, 916 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.60-1.90 (m, 6H), 2.53 (s, 3H), 2.70-2.85 (m, 2H), 3.25-3.42 (m, 2H), 4.28 (d, J = 13.2 Hz, 2H), 6.82 (t, J = 7.8 Hz, 1H), 7.04 (t, J = 9.6 Hz, 2H), 7.21 (d, J = 7.8 Hz, 1H), 7.97 (d, J = 6.6 Hz, 1H), 8.62 (s, 1H); ESI-MS (*m/z*) 397.48 $(M+H)^+$.

Example 18: Preparation of 5,8-Dichloro-1'-[5-(5-methyl-1,3,4-oxadiazol-2-yl)pyridin-2-yl]-3,4-dihydrospiro[chromene-2,4'-piperidine]



Step 1: Methyl 6-(5,8-dichloro-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidin]-1'-yl)nicotinate:

This intermediate was prepared by coupling Intermediate 10 (300 mg, 1.102 mmol) in acetonitrile (20 ml) with methyl-6-chloronicotinate (208 mg, 1.212 mmol) in presence of K_2CO_3 (305 mg, 2.204 mmol) and KI (183 mg, 1.102 mmol) as described in Step 1, Example 1 to get 160 mg of the product as a white solid; IR (Neat) 2945, 1658, 1416, 1218, 1031 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.58-1.70 (m, 2H), 1.82-1.98 (m, 4H), 2.80 (t, *J* = 6.6 Hz, 2H), 3.45 (t, *J* = 12.3 Hz, 2H), 3.85 (s, 3H), 4.30 (d, *J* = 14.4 Hz, 2H), 6.61 (d, *J* = 9.0 Hz, 1H), 6.88 (d, *J* = 8.7 Hz, 1H), 7.14 (d, *J* = 8.7 Hz, 1H), 7.98 (d, *J* = 9.0 Hz, 1H), 8.76 (s, 1H); ESI-MS (*m/z*) 407.24 $(M+H)^+$.

Step 2: 6-(5,8-dichloro-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidin]-1'-yl)nicotinohydrazide:

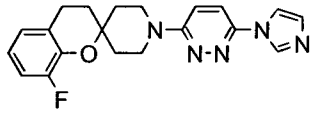
To a stirred solution of Step 1 intermediate (160 mg, 0.393 mmol) in methanol (5 ml) was added hydrazine hydrate (3 ml) in chloroform (4 ml) and the reaction mixture was heated to reflux for 18 h. The solvent was evaporated to give the product as a white solid; IR (KBr) 2927, 1603, 1415, 1091, 756 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.60-1.75 (m, 2H), 1.82-1.98 (m, 4H), 2.58 (s, 3H), 2.81 (t, *J* = 6.6 Hz, 2H), 3.46 (t, *J* = 12.6 Hz, 2H), 4.29 (d, *J* = 12.6 Hz, 2H), 6.71 (d, *J* = 9.0 Hz, 1H), 6.88 (d, *J* = 9.0 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 8.02 (d, *J* = 8.7 Hz, 1H), 8.72 (s, 1H); ESI-MS (*m/z*) 409.22 $(M+H)^+$.

Step 3: 5,8-Dichloro-1'-[5-(5-methyl-1,3,4-oxadiazol-2-yl)pyridin-2-yl]-3,4-dihydrospiro[chromene-2,4'-piperidine]:

To a stirred solution of 6-(5,8-dichloro-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidin]-1'-yl)nicotinohydrazide was added trimethyl orthoacetate (2 ml) and *p*-toluenesulfonic acid monohydrate (7 mg, 0.039 mmol) at room temperature. The reaction mixture was heated to reflux for 18 h. The residue obtained after the evaporation of the solvent was purified by silica gel column chromatography using 20% ethyl acetate in chloroform to get 27 mg of the compound as a white solid; IR (KBr) 2945, 1615, 1591, 1497, 1238, 1091 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60-1.75 (m, 2H), 1.82-1.98 (m, 4H), 2.58 (s, 3H), 2.81 (t, *J* = 6.6 Hz, 2H), 3.46 (t, *J* = 12.6 Hz, 2H), 4.29 (d, *J* = 12.6 Hz, 2H), 6.71 (d,

J = 9.0 Hz, 1H), 6.88 (d, J = 9.0 Hz, 1H), 7.14 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 8.7 Hz, 1H), 8.72 (s, 1H); ESI-MS (*m/z*) 431.26 $(M+H)^+$.

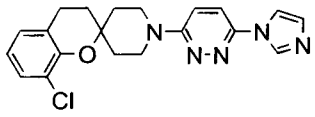
Example 19: Preparation of 8-Fluoro-1'-[6-(1*H*-imidazol-1-yl)pyridazin-3-yl]-3,4-dihydrospiro[chromene-2,4'-piperidine]



Step 1: 3-Chloro-6-(1*H*-imidazol-1-yl)pyridazine: To a stirred solution of imidazole (4.56 g, 67.123 mmol) in anhydrous dimethylformamide (25 ml) was added 60% sodium hydride in mineral oil (2.6 g, 67.123 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 1 h. This sodium salt solution of imidazole was added to 3,6-dichloropyridazine (10 g, 67.123 mmol) in anhydrous DMF (25 ml) at 0 °C. The resulting solution was allowed to warm to room temperature and stirred for 18 h. The reaction mixture was diluted with ethyl acetate (50 ml), washed with water, brine and dried (Na_2SO_4). The solvent was evaporated to get a crude residue which was purified by silica gel column chromatography using 10% methanol in chloroform to get 5.8 g of the product as an off-white solid; IR (KBr) 3121, 3045, 1474, 1433, 1170, 1032, 839 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.22 (s, 1H), 8.08 (s, 1H), 8.19 (d, J = 9.0 Hz, 1H), 8.33 (d, J = 9.3 Hz, 1H), 8.66 (s, 1H); ESI-MS (*m/z*) 181.26 $(M+H)^+$.

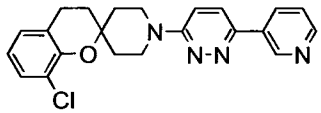
Step 2: 8-Fluoro-1'-[6-(1*H*-imidazol-1-yl)pyridazin-3-yl]-3,4-dihydrospiro[chromene-2,4'-piperidine]: To a stirred solution of Intermediate 8 (100 mg, 0.296 mmol) in 1,4-dioxane (2 ml) was added was added Step 1 intermediate (60 mg, 0.332 mmol) followed by tetra-*n*-butylammonium bromide (2 mg, 0.006 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.09 ml, 0.624 mmol). The reaction mixture was heated to reflux and stirred for 18 h. The reaction mixture was allowed to cool to room temperature and the residue obtained after the evaporation of the solvent was purified by silica gel column chromatography using 1% methanol in chloroform to get 60 mg of the compound as an off-white solid; IR (KBr) 2948, 1589, 1473, 1210, 1082, 757 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.70-1.90 (m, 6H), 2.79 (t, J = 6.3 Hz, 2H), 4.42 (d, J = 10.8 Hz, 2H), 4.14 (d, J = 13.5 Hz, 2H), 6.73-6.83 (m, 1H), 6.90-7.05 (m, 2H), 7.11 (s, 1H), 7.59 (d, J = 10.2 Hz, 1H), 7.83-7.90 (m, 2H), 8.43 (s, 1H); ESI-MS (*m/z*) 366.41 $(M+H)^+$.

Example 20: Preparation of 8-Chloro-1'-[6-(1*H*-imidazol-1-yl)pyridazin-3-yl]-3,4-dihydrospiro[chromene-2,4'-piperidine]



This compound was prepared in 2 steps according to the procedure described in Example 19, Steps 1 and 2 to get 11 mg of the compound as an off-white solid; IR (KBr) 2976, 1498, 1261, 1046, 791 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.70-1.90 (m, 6H), 2.80 (t, J = 6.0 Hz, 2H), 3.30-3.42 (m, 2H), 4.22 (d, J = 12.6 Hz, 2H), 6.82 (t, J = 7.8 Hz, 1H), 7.02-7.15 (m, 2H), 7.22 (d, J = 8.7 Hz, 1H), 7.59 (d, J = 9.9 Hz, 1H), 7.89 (d, J = 8.7 Hz, 1H), 8.43 (s, 1H); ESI-MS (*m/z*) 382.50 $(M+H)^+$.

Example 21: Preparation of 8-Chloro-1'-(6-pyridin-3-ylpyridazin-3-yl)-3,4-dihydrospiro[chromene-2,4'-piperidine]



Step 1: 8-Chloro-1'-(6-iodopyridazin-3-yl)-3,4-dihydrospiro[chromene-2,4'-piperidine]:

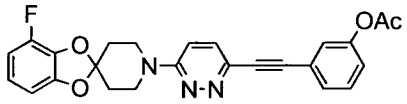
To a magnetically stirred solution of Intermediate 9 (500 mg, 2.102 mmol) in anhydrous DMF (5 ml) was added sodium carbonate (49 mg, 4.623 mmol) and 3,6-diiodopyridazine (77 mg, 2.321 mmol) at room temperature. The reaction mixture was heated to 80 °C for 2 days. The reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate (50), washed with water, brine, dried (Na_2SO_4) and evaporated under reduced pressure to get the crude product which was purified by silica gel column chromatography using 20% ethyl acetate in petroleum ether to give 550 mg of the product as an off-white solid; IR (KBr) 2987, 1491, 1462, 1266, 950, 791 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.60-1.90 (m, 6H), 2.78 (t, J = 6.9 Hz, 2H), 3.25-3.35 (m, 2H), 4.14 (d, J = 13.8 Hz, 2H), 6.81 (t, J = 7.8 Hz, 1H), 7.00-7.18 (m, 2H), 7.21 (d, J = 6.9 Hz, 1H), 7.66 (d, J = 9.3 Hz, 1H); ESI-MS (*m/z*) 442.29 $(M+H)^+$.

Step 2: 8-Chloro-1'-(6-pyridin-3-ylpyridazin-3-yl)-3,4-dihydrospiro[chromene-2,4'-piperidine]:

To a stirred solution of Step 1 intermediate (100 mg, 0.226 mmol) in isopropanol (2 ml) was added 3-pyridine boronic acid (29 mg, 0.236 mmol) at room temperature under nitrogen. The reaction mixture was stirred at the same temperature for 30 min. The resulting solution was treated with palladium acetate (150 mg, 0.668 mmol), triphenylphosphine (530 mg, 2.022 mmol), 2 *M* aqueous Na_2CO_3 (0.14 ml, 0.274 mmol) and water (1 ml) and heated to reflux for 18 h. The hot reaction mixture was treated with water, allowed to cool to room temperature and extracted with ethyl acetate (3 x 50 ml). The combined organic layers were

washed with water, brine, dried (Na_2SO_4) and evaporated under reduced pressure to get the crude product which was purified by silica gel column chromatography using 20% ethyl acetate in chloroform to give 35 mg of the compound as an off-white solid; IR (KBr) 2969, 1522, 1479, 1260, 950, 791 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.65-1.90 (m, 6H), 2.80 (t, J = 6.3 Hz, 2H), 3.35-3.60 (m, 2H), 4.30 (d, J = 13.5 Hz, 2H), 6.82 (t, J = 7.8 Hz, 1H), 7.07 (d, J = 6.9 Hz, 1H), 7.22 (d, J = 7.2 Hz, 1H), 7.40-7.55 (m, 2H), 8.01 (d, J = 9.3 Hz, 1H), 8.36 (d, J = 7.8 Hz, 1H), 8.57 (dd, J = 5.1, 1.5 Hz, 1H), 9.18 (s, 1H); ESI-MS (*m/z*) 393.30 $(M+H)^+$.

Example 22: Preparation of 3-{[6-(4-Fluoro-1'*H*-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)pyridazin-3-yl]ethynyl}phenyl acetate



Step 1: 4-Fluoro-1'-(6-iodopyridazin-3-yl)spiro[1,3-benzodioxole-2,4'-piperidine]:

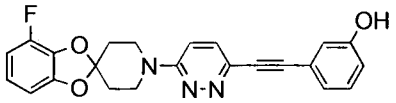
To a stirred solution of Intermediate 7 (165 mg, 0.791 mmol) in anhydrous DMF (5 ml) was added 3,6-diidopyridazine (288 mg, 0.871 mmol) followed by Na_2CO_3 (184 mg, 1.738 mmol) and stirred the reaction mixture at 80 °C for 5 days. The reaction mixture was poured into water (50 ml) and extracted with ethyl acetate (3 x 50 ml). The combined organic layers were washed with water (100 ml), brine (50 ml) and dried (Na_2SO_4). The solvent was evaporated to get a crude residue which was purified by silica gel column chromatography using 15% ethyl acetate in petroleum ether to get 221 mg of the product as a white solid; IR (KBr) 3020, 2927, 1642, 1575, 1434, 1213, 1037, 758 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.11 (t, J = 6.3 Hz, 4H), 3.89 (t, J = 5.4 Hz, 4H), 6.57-6.74 (m, 4H), 7.49 (d, J = 9.3 Hz, 1H); ESI-MS (*m/z*) 414.73 $(M+H)^+$.

Step 2: 3-{[6-(4-Fluoro-1'*H*-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)pyridazin-3-yl]ethynyl}phenyl acetate:

To a solution of Step 1 intermediate (200 mg, 0.484 mmol) in anhydrous DMSO (6 ml) was added 3-(1-ethynyl)phenyl acetate (85 mg, 0.532 mmol) followed by triethylamine (0.201 ml, 1.452 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 0.009 mmol) and CuI (5 mg, 0.026 mmol) and the reaction mixture was stirred at room temperature for 15 h. The reaction mixture was poured into water (50 ml) and extracted with ethyl acetate (3 x 50 ml). The combined organic layers were washed with water (100 ml), brine (50 ml) and dried (Na_2SO_4). The solvent was evaporated to get a crude residue which was purified by silica gel column chromatography using 20% ethyl acetate in petroleum ether to get 80 mg of the compound as a buff colored

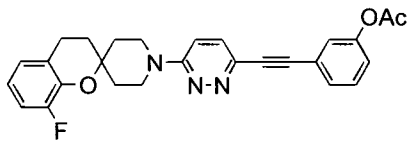
solid; IR (KBr) 3446, 2929, 1769, 1589, 1473, 1210, 1082, 757 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.10-2.20 (br m, 4H), 2.28 (s, 3H), 3.80-4.00 (br m, 4H), 6.82 (d, J = 9.3 Hz, 3H), 7.22 (s, 1H), 7.38-7.47 (m, 4H), 7.62 (d, J = 8.7 Hz, 1H); ESI-MS (m/z) 446.76 $(M+H)^+$.

Example 23: Preparation of 3-{[6-(4-Fluoro-1'*H*-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)pyridazin-3-yl]ethynyl}phenol



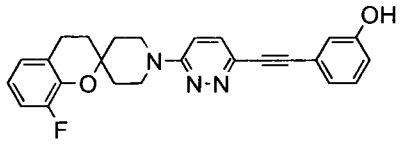
To a solution of Example 22 (60 mg, 0.135 mmol) in methanol (1 ml) was added lithium hydroxide monohydrate (11 mg, 0.271 mmol) and the reaction mixture was stirred at room temperature for 15 h. The residue obtained after evaporation of the solvent was treated with water (10 ml), acidified with glacial acetic acid to pH 4 and extracted with ethyl acetate (3 x 50 ml). The combined organic layers were washed with water (100 ml), brine (50 ml) and dried (Na_2SO_4). The solvent was evaporated to get a crude residue which was purified by silica gel column chromatography using 5% methanol in chloroform to get 35 mg of the compound as a white solid; IR (KBr) 3446, 2929, 1769, 1589, 1473, 1210, 1082, 757 cm^{-1}; ^1H NMR (300 MHz, DMSO-*d6*) δ 2.10-2.20 (br m, 4H), 3.80-4.00 (br m, 4H), 6.80-6.83 (m, 4H), 6.93 (s, 1H), 7.00 (d, J = 7.8 Hz, 1H), 7.20-7.23 (m, 1H), 7.40 (d, J = 9.3 Hz, 1H), 7.60 (d, J = 9.3 Hz, 1H), 9.76 (br s, 1H); ESI-MS (m/z) 404.76 $(M+H)^+$.

Example 24: Preparation of 3-{[8-Fluoro-(3,4-dihydrospiro[chromene-2,4'-piperidin]-1'-yl)pyridazin-3-yl]ethynyl}phenyl acetate



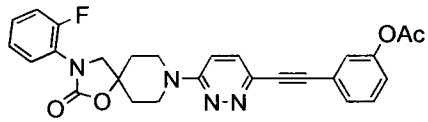
This compound was prepared in two steps from Intermediate 8 according to the procedure described in Example 22, Steps 1 and 2 to afford 96 mg of the compound as a pale yellow solid; IR (KBr) 3445, 1770, 1577, 1477, 1424, 1204, 1158, 955, 779 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.60-1.90 (m, 6H), 2.28 (s,3H), 2.79 (t, J = 6.3 Hz, 2H), 3.20-3.40 (m, 2H), 4.10-4.30 (m, 2H), 6.70-6.90 (m, 1H), 6.90-7.10 (m, 2H), 7.10-7.30 (m, 1H), 7.30-7.40 (m, 2H), 7.40-7.50 (m, 2H), 7.57 (d, J = 9.3 Hz, 1H); ESI-MS (m/z) 458.54 $(M+H)^+$.

Example 25: Preparation of 3-{[8-Fluoro-3,4-dihydrospiro[chromene-2,4'-piperidin]-1'-yl)pyridazin-3-yl]ethynyl}phenol



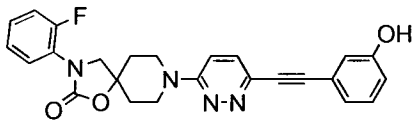
The title compound was obtained by the hydrolysis of Example 23 (175 mg, 0.382 mmol) using lithium hydroxide (32 mg, 0.762 mmol) according the procedure described in Example 23 to afford 103 mg of the compound as an off-white solid; IR (KBr) 3445, 2929, 1588, 1481, 1260, 1086, 950, 791 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.60-1.90 (m, 6H), 2.79 (t, J = 6.3 Hz, 2H), 3.20-3.40 (m, 2H), 4.10-4.30 (m, 2H), 6.70-6.90 (m, 2H), 6.90-7.10 (m, 4H), 7.20-7.30 (m, 1H), 7.31 (d, J = 9.3 Hz, 1H), 7.54 (d, J = 9.3 Hz, 1H); ESI-MS (*m/z*) 416.46 $(M+H)^+$.

Example 26: Preparation of 3-{2-Fluorophenyl)-8-[6-(2-oxo-1-oxa-3,8-diazaspiro[4.5]dec-8-yl)pyridazin-3-yl]ethynyl}phenyl acetate



This compound was prepared from Intermediate 11 (900 mg, 3.596 mmol) using Na_2CO_3 (838 mg, 7.914 mmol) and 2,6-diiodopyridazine (1.3 g, 3.955 mmol) in anhydrous DMF (10 ml) according to the procedure described in Example 22, Steps 1 and 2 to afford 70 mg of the compound as an off-white solid; IR (KBr) 2922, 2344, 1759, 1584, 1223, 755 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.99 (br s, 4H), 2.28 (s, 3H), 3.63 (br s, 2H), 3.86 (s, 2H), 4.07 (d, J = 12.0 Hz, 1H), 7.16-7.30 (m, 1H), 7.35-7.42 (m, 5H), 7.46 (s, 2H), 7.57 (s, 2H); ESI-MS (*m/z*) 487.28 $(M+H)^+$.

Example 27: Preparation of 3-{2-Fluorophenyl)-8-{6-[(3-hydroxyphenyl)ethynyl]pyridazin-3-yl}-1-oxa-3,8-diazaspiro[4.5]decan-2-one



The title compound was synthesized by the hydrolysis of Example 26 (30 mg, 0.061 mmol) using lithium hydroxide (5 mg, 0.123 mmol) at room temperature for 18 h to give 22 mg of the compound as a buff colored solid; IR (KBr) 3050, 2924, 2212, 1753, 1592, 1451, 1229, 1104 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.99 (br s, 4H), 3.63 (br s, 2H), 3.87 (s, 2H), 4.04 (br s, 2H), 6.70-6.90 (m, 3H), 7.10-7.38 (m, 5H), 7.50-7.62 (m, 2H), 9.75 (br s, 1H); ESI-MS (*m/z*) 443.76 $(M-H)^-$.

In-vitro assay of compounds of the present invention:

The in-vitro activity of the compounds of the present invention against stearoyl coenzyme desaturase was determined by following conversion of radiolabeled stearoyl-CoA to oleoyl-CoA using human SCD1 enzyme by using a previously published assay procedure with some modifications (Talamo, B. R. and Bloch, K. *Analytical Biochemistry,* **1969**, *29*, 300-304). This assay protocol is only illustrative and is not meant to limit the scope of the present invention.

In this assay the microsomal SCD1 enzyme desaturates its substrate, Stearoyl CoA (purchased from American Radiochemicals Ltd.) which is tritiated at C9 and C10 positions. Test compounds were dissolved in dimethylsulfoxide and tested at 10 μM final concentration. Before substrate addition, the test compound or standard reference compound (conjugated linoleic acid at 100 μM final concentration) were pre-incubated in reaction buffer with the enzyme for 10 minutes at 30 °C with shaking. Reaction buffer was prepared as described in literature (Obukowicz M. G. *et al. JPET*, 1998, 287, 157-166) except that the $MgCl_2$, ATP (purchased from Sigma) and CoA (purchased from Sigma) concentrations were changed to 4.9 mM, 7.2 mM and 0.54 mM respectively. The desaturation reaction was initiated by addition of 0.5 μCi of ^3H stearoyl CoA and incubated at 37 °C for 30 minutes with shaking. A control reaction was set without any test compound / reference inhibitor to capture maximum enzymatic activity in the assay. Inhibition of enzyme activity was calculated as a percent of this control reaction giving maximum catalysis and the results are given in Table 1.

The following table provides data that exemplifies respresentative compounds or examples and their percentage (%) inhibition data.

Table 1: Tritiated water release assay at 10 μM concentration of test compounds

S. No.	Example	% Inhibition
1	Compond No 1	33
2	Compond No 2	0
3	Compond No 3	13
4	Compond No 4	-
5	Compond No 5	32
6	Compond No 6	94
7	Compond No 7	94
8	Compond No 8	58.7
9	Compond No 9	74.8
10	Compond No 10	71.8

11	Compond No11	25
12	Compond No 12	93
13	Compond No 13	33
14	Compond No 14	47
15	Compond No 15	92
16	Compond No 16	66
17	Compond No 17	59
18	Compond No 18	72
19	Compond No 19	93
20	Compond No 20	93
21	Compond No 21	89.5
22	Compond No 22	88
23	Compond No 23	65
24	Compond No 24	94
25	Compond No 25	92
26	Compond No 26	91
27	Compond No 27	97
28	Conjugated Linoleic Acid	86

* Conjugated Linoleic acid was used as a reference standard

It is to be understood that any ranges, ratios and ranges or ratios that can be formed by or derived from any of the data disclosed herein represent further embodiments of the present disclosure and are included as part of the disclosure as if they were explicitly set forth.

Although the invention herein has been described with reference to particular embodiments, it is to be understood that these embodiments are merely illustrative of the principles and applications of the present invention. It is therefore to be understood that numerous modifications may be made to the illustrative embodiments and that other arrangements may be devised without departing from the spirit and scope of the present invention as described above. All publications and patent applications cited in this application are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated herein by reference.

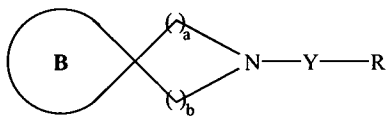
References:

1. Barbara R Talamo and Konrad Bloch 'A New Assay for fatty Acid Desaturation' *Analytical Biochemistry,* 29, 300-304 (1969).

2. Mark G Obukowicz, Dean J Welsch, William J Salsgiver, Cynthia L Marin-Berger, Kevin S Chinn, Kevin L Duffin, Amiram Raz and Phillip Needleman 'Novel, Selective Δ6 or Δ5 Fatty Acid Desaturase Inhibitors as Antiinflammatory Agents in mice' *JPET*, 287, 157-166 (1998) .

Claims:

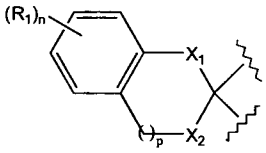
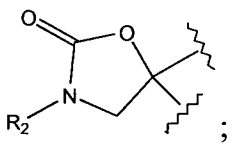
1. The compound has the formula (I)



Formula (I)

wherein:

ring B is selected from

 and  ;

X_1 and X_2 are independently selected from $-CR_aR_b$, $-CR_aR_b-CR_aR_b$, $-CR_aR_bC(O)-$, $-C(O)CR_aR_b-$, $-NR_c-$, -S- or -O;

Y is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,or substituted or unsubstituted heterocyclyl;

R is $-L-R_d$ or R';

R' is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocyclyl;

L is $-(CR_aR_b)_n-$, $-C(R_a)=C(R_a)-$, or $-C\equiv C-$;

R_d is selected from H, halogen, nitro, cyano, $-COOR^x$, $-C(O)R^x$, $-C(S)R^x$, $-C(O)NR^xR^y$, $-C(O)ONR^xR^y$, $-NR^xCONR^yR^z$, $-N(R^x)SOR^y$, $-N(R^x)SO_2R^y$, $-NR^xC(O)OR^y$, $-NR^xR^y$, $-NR^xC(O)R^y$, $-NR^xC(S)R^y$, $-NR^xC(S)NR^yR^z$, $-SONR^xR^y$, $-SO_2NR^xR^y$, $-OR^x$, $-OC(O)R^x$, $-OC(O)NR^xR^y$, $-SR^x$, $-SOR^x$, $-SO_2R^x$, $-ONO_2$, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocycle, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each occurrence of R_1 is selected from H, halogen, nitro, cyano, $-COOR^x$, $-C(O)R^x$, $-C(S)R^x$, $-C(O)NR^xR^y$, $-C(O)ONR^xR^y$, $-NR^xCONR^yR^z$, $-N(R^x)SOR^y$, $-N(R^x)SO_2R^y$, -

$NR^xC(O)OR^y$, $-NR^xR^y$, $-NR^xC(O)R^y$, $-NR^xC(S)R^y$, $-NR^xC(S)NR^yR^z$, $-SONR^xR^y$, $-SO_2NR^xR^y$, $-OR^x$, $-OC(O)R^x$, $-OC(O)NR^xR^y$, $-SR^x$, $-SOR^x$, $-SO_2R^x$, $-ONO_2$, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocycle, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R_2 is selected from H, $-COOR^x$, $-C(O)R^x$, $-C(S)R^x$, $-C(O)NR^xR^y$, $-C(O)ONR^xR^y$, $-NR^xCONR^yR^z$, $-N(R^x)SOR^y$, $-N(R^x)SO_2R^y$, $-NR^xC(O)OR^y$, $-NR^xR^y$, $-NR^xC(O)R^y$, $-NR^xC(S)R^y$, $-NR^xC(S)NR^yR^z$, $-SONR^xR^y$, $-SO_2NR^xR^y$, substituted or unsubstituted alkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocyclyl;

R^x, R^y and R^z are independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclylalkyl, or substituted or unsubstituted amino;

R_a,R_b, and R_c are independently selected from hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclylalkyl, or substituted or unsubstituted amino;

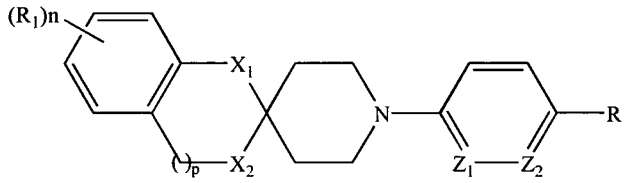
'a' and 'b' are independently an integer selected from1, 2 or 3;

'n' is an integer selected from 0, 1, 2, 3 or 4;

'p' is an integer selected from 0 or 1.

or a pharmaceutically acceptable salt thereof, solvate thereof, an ester thereof, a stereoisomer thereof, a polymorph thereof, a prodrug thereof, a metabolite thereof or an N-oxide thereof,

2. The compound according to claim 1, as represented by Formula (II):



Formula (II)

Wherein,

X_1 and X_2 are independently selected from $-CR_aR_b$, $-CR_aR_b-CR_aR_b$, $-CR_aR_bC(O)-$, $-C(O)\ CR_aR_b-$, or -O;

Z_1, and Z_2 are selected from N or CR_1;

R is -L-R_d or R';

L is $-(CR_aR_b)_n-$, $-C(R_a)=C(R_a)-$, or $-C\equiv C-$;

R' is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocyclyl;

R_d is selected from H, halogen, nitro, cyano, $-COOR^x$, $-C(O)R^x$, $-C(S)R^x$, $-C(O)NR^xR^y$, $-C(O)ONR^xR^y$, $-NR^xCONR^yR^z$, $-N(R^x)SOR^y$, $-N(R^x)SO_2R^y$, $-NR^xC(O)OR^y$, $-NR^xR^y$, $-NR^xC(O)R^y$, $-NR^xC(S)R^y$, $-NR^xC(S)NR^yR^z$, $-SONR^xR^y$, $-SO_2NR^xR^y$, $-OR^x$, $-OC(O)R^x$, $-OC(O)NR^xR^y$, $-SR^x$, $-SOR^x$, $-SO_2R^x$, $-ONO_2$, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocycle, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each occurrence of R_1 is selected from H, halogen, nitro, cyano, $-COOR^x$, $-C(O)R^x$, $-C(S)R^x$, $-C(O)NR^xR^y$, $-C(O)ONR^xR^y$, $-NR^xCONR^yR^z$, $-N(R^x)SOR^y$, $-N(R^x)SO_2R^y$, $-NR^xC(O)OR^y$, $-NR^xR^y$, $-NR^xC(O)R^y$, $-NR^xC(S)R^y$, $-NR^xC(S)NR^yR^z$, $-SONR^xR^y$, $-SO_2NR^xR^y$, $-OR^x$, $-OC(O)R^x$, $-OC(O)NR^xR^y$, $-SR^x$, $-SOR^x$, $-SO_2R^x$, $-ONO_2$, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted

cycloalkenyl, substituted or unsubstituted heterocycle, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^x, R^y and R^z are independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclylalkyl, or substituted or unsubstituted amino;

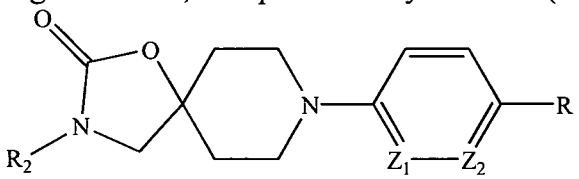
R_a,R_b, and R_c are independently selected from hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclylalkyl, or substituted or unsubstituted amino;

n is an integer selected from 0, 1, 2, 3 or 4;

p is an integer selected from 0 or 1.

or a pharmaceutically acceptable salt thereof, solvate thereof, an ester thereof, a stereoisomer thereof, a polymorph thereof, a prodrug thereof, a metabolite thereof or an N-oxide thereof,

3. The compound according to claim 1, as represented by Formula (III):



Formula (III)

Wherein,

Z_1, and Z_2 are selected from N or CR_1;

R is -L-R_d or R';

R' is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or

unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocyclyl;

L is $-(CR_aR_b)_n-$, $-C(R_a)=C(R_a)-$, or $-C\equiv C-$;

R_d is selected from H, halogen, nitro, cyano, $-COOR^x$, $-C(O)R^x$, $-C(S)R^x$, $-C(O)NR^xR^y$, $-C(O)ONR^xR^y$, $-NR^xCONR^yR^z$, $-N(R^x)SOR^y$, $-N(R^x)SO_2R^y$, $-NR^xC(O)OR^y$, $-NR^xR^y$, $-NR^xC(O)R^y$, $-NR^xC(S)R^y$, $-NR^xC(S)NR^yR^z$, $-SONR^xR^y$, $-SO_2NR^xR^y$, $-OR^x$, $-OC(O)R^x$, $-OC(O)NR^xR^y$, $-SR^x$, $-SOR^x$, $-SO_2R^x$, $-ONO_2$, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocycle, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each occurrence of R_1 is selected from H, halogen, nitro, cyano, $-COOR^x$, $-C(O)R^x$, $-C(S)R^x$, $-C(O)NR^xR^y$, $-C(O)ONR^xR^y$, $-NR^xCONR^yR^z$, $-N(R^x)SOR^y$, $-N(R^x)SO_2R^y$, $-NR^xC(O)OR^y$, $-NR^xR^y$, $-NR^xC(O)R^y$, $-NR^xC(S)R^y$, $-NR^xC(S)NR^yR^z$, $-SONR^xR^y$, $-SO_2NR^xR^y$, $-OR^x$, $-OC(O)R^x$, $-OC(O)NR^xR^y$, $-SR^x$, $-SOR^x$, $-SO_2R^x$, $-ONO_2$, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocycle, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R_2 is selected from H, $-COOR^x$, $-C(O)R^x$, $-C(S)R^x$, $-C(O)NR^xR^y$, $-C(O)ONR^xR^y$, $-NR^xCONR^yR^z$, $-N(R^x)SOR^y$, $-N(R^x)SO_2R^y$, $-NR^xC(O)OR^y$, $-NR^xR^y$, $-NR^xC(O)R^y$, $-NR^xC(S)R^y$, $-NR^xC(S)NR^yR^z$, $-SONR^xR^y$, $-SO_2NR^xR^y$, substituted or unsubstituted alkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocyclyl;

R^x, R^y and R^z are independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclylalkyl, or substituted or unsubstituted amino;

R_a,R_b, and R_c are independently selected from hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclylalkyl, or substituted or unsubstituted amino;

'n' is an integer selected from 0, 1, 2, 3 or 4.

or a pharmaceutically acceptable salt thereof, solvate thereof, an ester thereof, a stereoisomer thereof, a polymorph thereof, a prodrug thereof, a metabolite thereof or an N-oxide thereof,

4. The compound according to claim 1 or 2, wherein X_1 and X_2 are independently selected from $-CR_aR_b$, $-CR_aR_bC(O)-$, or $-O$.

5. The compound according to claim 2 or 3, wherein Z_1, and Z_2 are N or CR_1.

6. The compound according to claim 2 or 3, wherein R is $-L-R_d$; where L is $-C\equiv C-$; R_d is H, substituted or unsubstituted heterocycle, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

7. The compound according to claim 2 or 3, wherein R is R'; where R' is substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted alkyl or substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl.

8. The compound according to claim 3, wherein: R_2 is H, substituted or unsubstituted heterocycle, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

9. The compound according to claim 8, wherein R_2 is substituted or unsubstituted aryl; wherein substituents are halogen, OH, substituted or unsubstituted alkyl.

10. The compound according to claim 9, wherein substituent is halogen.

11. The compound according to claim 10, wherein halogen is fluoro.

12. The compound according to claim 3, wherein: R is -L-Rd; L is $-C\equiv C-$; R_d is selected from H, substituted or unsubstituted heterocycle, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

13. The compound according to claim 3, wherein: R is R'; where R' is substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl, substituted or

unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted alkyl or substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl.

14. The compound according to claim 1, 2 or 3, selected from the group consisting of following:

(5S)-3-[8-Fluoro-(3,4-dihydro-1'H-spiro[chromene-2,4'-piperidin]-1'-yl]pyridine-3-yl-5-(hydroxymethyl)-1,3-oxazolidin-2-one: (compound No.7),

(5S)-5-(Hydroxymethyl)-3-[6-(1'H-spiro[1,3-benzodiaxole-2,4'-piperidin]-1'-yl)pyridin-3-yl]-1,3-oxazolidin-2-one (compound No.8),

(5S)-3-[6-(4-Fluoro-1'H-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)pyridin-3-yl]-5-(hydroxymethyl)-1,3-oxazolidin-2-one (compound No.9),

{3-[6-(4-Fluoro-1'H-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)pyridin-3-yl]-1,2,4-oxadiazol-5-yl}methanol (compound No.10),

8-Fluoro-1'-{5-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2-yl}-3,4-dihydrospiro[chromene-2,4'-piperidine] (compound No.11),

{3-[6-(8-Fluoro-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidin]-1'-yl)pyridin-3-yl]-1,2,4-oxadiazol-5-yl}methanol (compound No.12),

{3-[6-(8-Fluoro-3,4-dihydro-1'*H*-spiro[chromene-2,4'-piperidin]-1'-yl)pyridin-3-yl]-1,2,4-oxadiazol-5-yl}pyridin-2-ol (compound No.13),

3-(2-Fluorophenyl)-8-{5-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]pyridin-2-yl}-1-oxa-3,8-diazaspiro[4.5]decan-2-one (compound No.14),

3-(2-Fluorophenyl)-8-{5-[5-(hydroxymethyl)-1,2,4-oxadiazol-3-yl]pyridin-2-yl}-1-oxa-3,8-diazaspiro[4.5]decan-2-one (compound No.15),

8-Chloro-1'-[5-(1*H*-tetrazol-5-yl)pyridin-2-yl]-3,4-dihydrospiro[chromene-2,4'-piperidine]: (compound No.16),

8-Chloro-1'-[5-(5-methyl-1,3,4-oxadiazol-2-yl)pyridin-2-yl]-3,4-dihydrospiro[chromene-2,4'-piperidine]: (compound No.17),

5,8-Dichloro-1'-[5-(5-methyl-1,3,4-oxadiazol-2-yl)pyridin-2-yl]-3,4-dihydrospiro[chromene-2,4'-piperidine]: (compound No.18),

8-Fluoro-1'-[6-(1*H*-imidazol-1-yl)pyridazin-3-yl]-3,4-dihydrospiro[chromene-2,4'-piperidine] (compound No.19),

8-Chloro-1'-[6-(1*H*-imidazol-1-yl)pyridazin-3-yl]-3,4-dihydrospiro[chromene-2,4'-piperidine]: (compound No.20),

8-Chloro-1'-(6-pyridin-3-ylpyridazin-3-yl)-3,4-dihydrospiro[chromene-2,4'-piperidine]: (compound No.21),

3-{[6-(4-Fluoro-1'*H*-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)pyridazin-3-yl]ethynyl}phenyl acetate (compound No.22),

3-{[6-(4-Fluoro-1'*H*-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)pyridazin-3-yl]ethynyl}phenol (compound No.23),

3-{[8-Fluoro-(3,4-dihydrospiro[chromene-2,4'-piperidin]-1'-yl)pyridazin-3-yl]ethynyl}phenyl acetate (compound No.24),

3-{[8-Fluoro-3,4-dihydrospiro[chromene-2,4'-piperidin]-1'-yl)pyridazin-3-yl]ethynyl}phenol (compound No.25),

3-{2-Fluorophenyl)-8-[6-(2-oxo-1-oxa-3,8-diazaspiro[4.5]dec-8-yl)pyridazin-3-yl]ethynyl}phenyl acetate (compound No.26),

3-{2-Fluorophenyl)-8-{6-[(3-hydroxyphenyl)ethynyl]pyridazin-3-yl}-1-oxa-3,8-diazaspiro[4.5]decan-2-one (compound No.27)

and pharmacuetically acceptable salts thereof.

15. A pharmaceutical composition comprising a compound of of claim 1 and a pharmaceutically acceptable excipient.

16. The pharmaceutical composition of claim 15, further comprising one or more therapeutic agents selected from anti-obesity agents, dipeptidyl peptidase IV (DPP-IV) inhibitors, Protein Tyrosine Phosphatase (PTP-1B) inhibitors and anorectic agents.

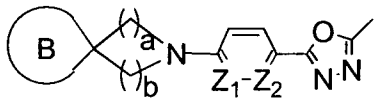
17. A method for treating a disease, disorder or syndrome mediated by stearoyl CoA desaturase 1 in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-16.

18. The method of claim 17, wherein the disease, condition or disorder is selected from obesity, appetite disorder, diabetes, impaired glucose tolerance, insulin resistance, a lipid disorder, metabolic syndrome and fatty liver disease.

19. The method of claim 17 or 18, further comprising administering one or more therapeutic agents selected from antiobesity agents, insulin or insulin mimetics, insulin secretagogues, α-glucosidase inhibitors, glucagon receptor antagonists, cholesterol lowering agents, PPARδ agonists, DPP IV inhibitors, dyslipidemic agents, CETP inhibitors, HMG-COA reductase inhibitors, fibrates, guggle lipids and SCD1 inhibitors.

20. The method of claim 17, wherein the disorder is obesity.

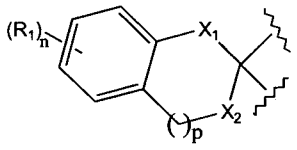
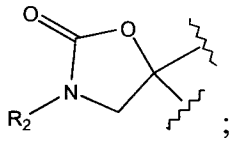
21. The process for the preparation of compounds of formula (Ib):



(Ib)

Wherein

ring B is


and

;

Z_1 and Z_2 are selected from N or CR_1;

X_1 and X_2 are independently selected from $-CR_aR_b$, $-CR_aR_bC(O)-$, $-C(O)CR_aR_b-$ or -O;

'p' is an integer selected from 0 or 1;

'n' is an integer selected from 0, 1, 2, 3 or 4;

R_5 CH_2OH, CF_3 or $C(O)CF_3$;

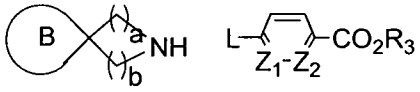
each occurrence of R_1 is selected from H, halogen, nitro, cyano, $-COOR^x$, $-C(O)R^x$, $-C(S)R^x$, $-C(O)NR^xR^y$, $-C(O)ONR^xR^y$, $-NR^xCONR^yR^z$, $-N(R^x)SOR^y$, $-N(R^x)SO_2R^y$, $-NR^xC(O)OR^y$, $-NR^xR^y$, $-NR^xC(O)R^y$, $-NR^xC(S)R^y$, $-NR^xC(S)NR^yR^z$, $-SONR^xR^y$, $-SO_2NR^xR^y$, $-OR^x$, $-OC(O)R^x$, $-OC(O)NR^xR^y$, $-R^xNR^yC(O)R^z$, $-R^xOR^y$, $-R^xC(O)OR^y$, $-R^xC(O)NR^yR^z$, $-R^xC(O)R^y$, $-R^xOC(O)R^y$, $-SR^x$, $-SOR^x$, $-SO_2R^x$, $-ONO_2$, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocycle, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R_2 is selected from H, $-COOR^x$, $-C(O)R^x$, $-C(S)R^x$, $-C(O)NR^xR^y$, $-C(O)ONR^xR^y$, $-NR^xCONR^yR^z$, $-N(R^x)SOR^y$, $-N(R^x)SO_2R^y$, $-NR^xC(O)OR^y$, $-NR^xR^y$, $-NR^xC(O)R^y$, $-NR^xC(S)R^y$, $-NR^xC(S)NR^yR^z$, $-SONR^xR^y$, $-SO_2NR^xR^y$, substituted or unsubstituted alkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocyclyl; and

'a' and 'b' are independently an integer selected from1, 2 or 3;

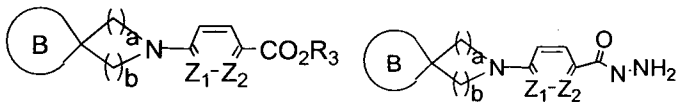
the method comprising the steps of:

(i) the compound of formula (1) coupled with formula (2) to afford formula (3) in presence of base



(1) (2) wherein R_3 is H or alkyl; and L is halogen;

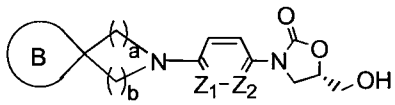
(ii) the compound of formula (3) reacts with hydrazine hydrate to give formula (7)



(3) 7 ;

(iii) the compound of formula (7) reacts with trialkyl ortho acetate (trimethyl ortho acetate) and PTSA to give Formula (Ib).

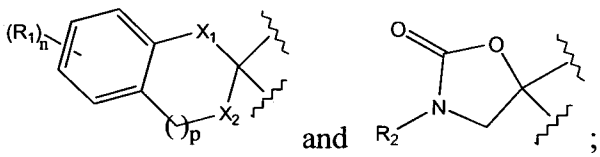
22. The process for the preparation of compounds of formula (Ic):



(Ic)

Wherein

ring B is



;

Z_1 and Z_2 are selected from N or CR_1;

X_1 and X_2 are independently selected from $-CR_aR_b$, $-CR_aR_bC(O)-$, $-C(O)CR_aR_b-$ or -O;

'p' is an integer selected from 0 or 1;

'n' is an integer selected from 0, 1, 2, 3 or 4;

each occurrence of R_1 is selected from H, halogen, nitro, cyano, $-COOR^x$, $-C(O)R^x$, $-C(S)R^x$, $-C(O)NR^xR^y$, $-C(O)ONR^xR^y$, $-NR^xCONR^yR^z$, $-N(R^x)SOR^y$, $-N(R^x)SO_2R^y$, $-NR^xC(O)OR^y$, $-NR^xR^y$, $-NR^xC(O)R^y$, $-NR^xC(S)R^y$, $-NR^xC(S)NR^yR^z$, $-SONR^xR^y$, $-SO_2NR^xR^y$, $-OR^x$, $-OC(O)R^x$, $-OC(O)NR^xR^y$, $-R^xNR^yC(O)R^z$, $-R^xOR^y$, $-R^xC(O)OR^y$, $-R^xC(O)NR^yR^z$, $-R^xC(O)R^y$, $-R^xOC(O)R^y$, $-SR^x$, $-SOR^x$, $-SO_2R^x$, $-ONO_2$, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocycle, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

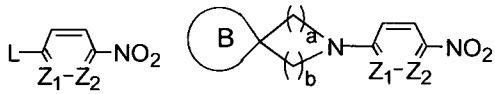
R_2 is selected from H, $-COOR^x$, $-C(O)R^x$, $-C(S)R^x$, $-C(O)NR^xR^y$, $-C(O)ONR^xR^y$, $-NR^xCONR^yR^z$, $-N(R^x)SOR^y$, $-N(R^x)SO_2R^y$, $-NR^xC(O)OR^y$, $-NR^xR^y$, $-NR^xC(O)R^y$, $-NR^xC(S)R^y$, $-NR^xC(S)NR^yR^z$, $-SONR^xR^y$, $-SO_2NR^xR^y$, substituted or unsubstituted alkyl,

substituted or unsubstituted haloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocyclyl; and

'a' and 'b' are independently an integer selected from1, 2 or 3;

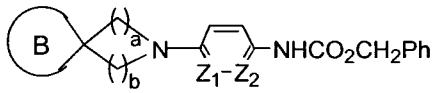
the method comprising the steps of:

(i) the compound of formula (1) coupled with formula (8) to afford formula (9) in presence of base



(8) (9) wherein L is halogen;

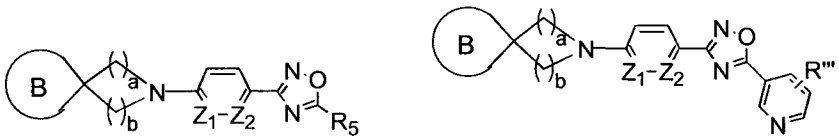
(ii) the nitro group in formula (9) reduced and followed by condensation with benzyl chloro formate to give formula (10)



(10) ;

(iii) formula (10) combined with glycidyl butyrate and base to give formula (Ic).

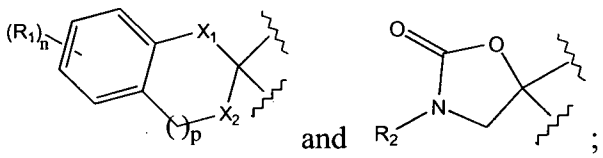
23. The process for the preparation of compounds of formula (Id) and formula (Ie):



(Id) and (Ie)

Wherein

ring B is



and ;

Z_1 and Z_2 are selected from N or CR_1;

X_1 and X_2 are independently selected from $-CR_aR_b$, $-CR_aR_bC(O)-$, $-C(O)CR_aR_b-$ or -O;

'p' is an integer selected from 0 or 1;

'n' is an integer selected from 0, 1, 2, 3 or 4;

each occurrence of R_1 is selected from H, halogen, nitro, cyano, $-COOR^x$, $-C(O)R^x$, $-C(S)R^x$, $-C(O)NR^xR^y$, $-C(O)ONR^xR^y$, $-NR^xCONR^yR^z$, $-N(R^x)SOR^y$, $-N(R^x)SO_2R^y$, -

$NR^xC(O)OR^y$, $-NR^xR^y$, $-NR^xC(O)R^y$, $-NR^xC(S)R^y$, $-NR^xC(S)NR^yR^z$, $-SONR^xR^y$, $-SO_2NR^xR^y$, $-OR^x$, $-OC(O)R^x$, $-OC(O)NR^xR^y$, $-R^xNR^yC(O)R^z$, $-R^xOR^y$, $-R^xC(O)OR^y$, $-R^xC(O)NR^yR^z$, $-R^xC(O)R^y$, $-R^xOC(O)R^y$, $-SR^x$, $-SOR^x$, $-SO_2R^x$, $-ONO_2$, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocycle, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R_5 is CH_2OH, CF_3 or $C(O)CF_3$;

R''' is H, halogen or OH;

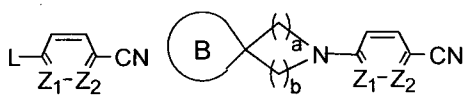
R_2 is selected from H, $-COOR^x$, $-C(O)R^x$, $-C(S)R^x$, $-C(O)NR^xR^y$, $-C(O)ONR^xR^y$, $-NR^xCONR^yR^z$, $-N(R^x)SOR^y$, $-N(R^x)SO_2R^y$, $-NR^xC(O)OR^y$, $-NR^xR^y$, $-NR^xC(O)R^y$, $-NR^xC(S)R^y$, $-NR^xC(S)NR^yR^z$, $-SONR^xR^y$, $-SO_2NR^xR^y$, substituted or unsubstituted alkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocyclyl; and

'a' and 'b' are independently an integer selected from1, 2 or 3;

the method comprising the steps of:

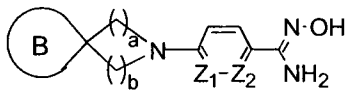
(I)

(i) The compound of formula (1) coupled with formula (11) to afford formula (12) in presence of base



(11) (12) wherein L is halogen;

(ii) formula (12) reacts with hydroxyl amine hydrochloride in presence of base to afford formula(13)

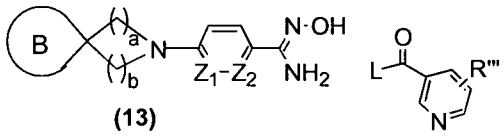


(13) ;

(iii) formula(13) cyclised by reacting with R_5COOR'' where R'' is alkyl or $C(O)CF_3$; in presence of base to afford formula (Id).

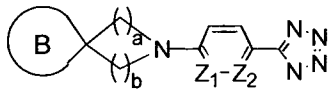
(II)

(i) The compound of formula (13) coupled with substituted or unsubstituted nicotinoyl halide in presence of base to afford formula (Ie)



(13) wherein L is halogen.

24. The process according to claim 23, for the preparation of compounds of formula (If):

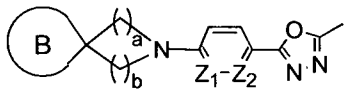


(If)

the method comprising the steps of:

(i) formula (12) reacts with sodium azide and ammonium halide to produce formula (If).

25. The process according to claim 23 and 24, for the preparation of compounds of formula (Ig):

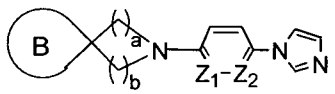


(Ig)

the method comprising the steps of:

(i) the compound of formula (If) reacts with AC_2O to afford formula (Ig).

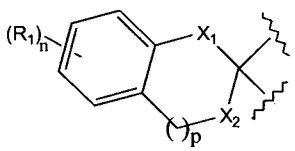
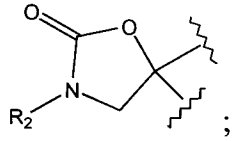
26. The process for the preparation of compounds of formula (Ih):



(Ih)

wherein

ring B is

 and  ;

Z_1 and Z_2 are selected from N or CR_1;

X_1 and X_2 are independently selected from $-CR_aR_b$, $-CR_aR_bC(O)-$, $-C(O)CR_aR_b-$ or -O;

'p' is an integer selected from 0 or 1;

'n' is an integer selected from 0, 1, 2, 3 or 4;

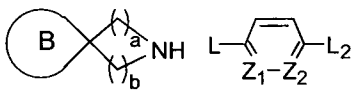
each occurrence of R_1 is selected from H, halogen, nitro, cyano, -$COOR^x$, -$C(O)R^x$, -$C(S)R^x$, -$C(O)NR^xR^y$, -$C(O)ONR^xR^y$, -$NR^xCONR^yR^z$, -$N(R^x)SOR^y$, -$N(R^x)SO_2R^y$, -$NR^xC(O)OR^y$, -NR^xR^y, -$NR^xC(O)R^y$, -$NR^xC(S)R^y$, -$NR^xC(S)NR^yR^z$, -$SONR^xR^y$, -$SO_2NR^xR^y$, -OR^x, -$OC(O)R^x$, -$OC(O)NR^xR^y$, -$R^xNR^yC(O)R^z$, -R^xOR^y, -$R^xC(O)OR^y$, -$R^xC(O)NR^yR^z$, -$R^xC(O)R^y$, -$R^xOC(O)R^y$, -SR^x, -SOR^x, -SO_2R^x, -ONO_2, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocycle, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R_2 is selected from H, -$COOR^x$, -$C(O)R^x$, -$C(S)R^x$, -$C(O)NR^xR^y$, -$C(O)ONR^xR^y$, -$NR^xCONR^yR^z$, -$N(R^x)SOR^y$, -$N(R^x)SO_2R^y$, -$NR^xC(O)OR^y$, -NR^xR^y, -$NR^xC(O)R^y$, -$NR^xC(S)R^y$, -$NR^xC(S)NR^yR^z$, -$SONR^xR^y$, -$SO_2NR^xR^y$, substituted or unsubstituted alkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocyclyl; and

'a' and 'b' are independently an integer selected from1, 2 or 3;

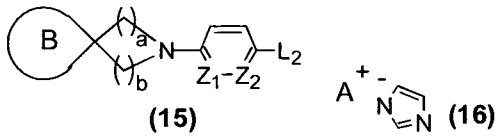
the method comprising the steps of:

(i) the compound of formula (1) coupled with formula (14) to afford formula (15) in presence of base



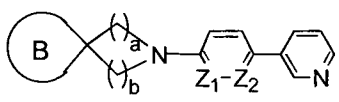
(1) (14) wherein L and L_2 are halogen;

(ii) formula (15) coupled with formula (16) where A is alkali metal, to afford formula (Ih)



(15) (16)

27. The process according to claim 26, for the preparation of compounds of formula (Ii):

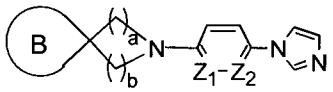


(Ii)

the method comprising the steps of:

(i) formula (15) reacts with pyridine boronic acid in presence of palladium acetate and triphenyl phosphine to afford formula (Ii).

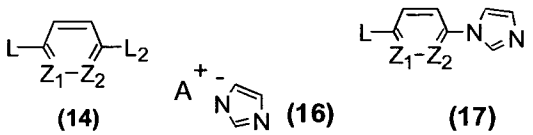
28. The process according to claim 26, for the preparation of compounds of formula (Ij):



(Ij)

the method comprising the steps of:

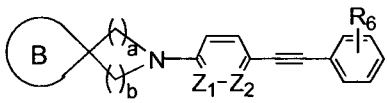
(i) the compound of formula (14) coupled with formula (16) to afford formula (17) in presence of base



(14) (16) (17)

(ii) formula (17) reacts with formula (1) in presence of DBU and PTC to afford formula (Ij).

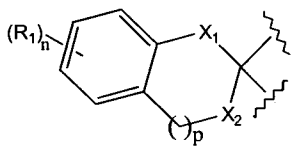
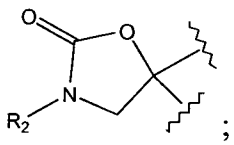
29. The process for the preparation of compounds of formula (Ik):



(Ik)

Wherein

ring B is

 and  ;

Z_1 and Z_2 are selected from N or CR_1;

R_6 is H, -$COOR^x$, -$C(O)R^x$, -$C(S)R^x$, -$C(O)NR^xR^y$, -$C(O)ONR^xR^y$, -$NR^xCONR^yR^z$, -$N(R^x)SOR^y$, -$N(R^x)SO_2R^y$, -$NR^xC(O)OR^y$, -NR^xR^y, -$NR^xC(O)R^y$, -$NR^xC(S)R^y$, -$NR^xC(S)NR^yR^z$, -$SONR^xR^y$, -$SO_2NR^xR^y$, substituted or unsubstituted alkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocyclyl;

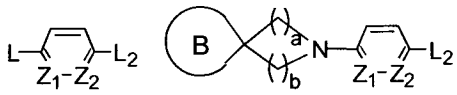
R_2 is selected from H, -$COOR^x$, -$C(O)R^x$, -$C(S)R^x$, -$C(O)NR^xR^y$, -$C(O)ONR^xR^y$, -$NR^xCONR^yR^z$, -$N(R^x)SOR^y$, -$N(R^x)SO_2R^y$, -$NR^xC(O)OR^y$, -NR^xR^y, -$NR^xC(O)R^y$, -$NR^xC(S)R^y$, -$NR^xC(S)NR^yR^z$, -$SONR^xR^y$, -$SO_2NR^xR^y$, substituted or unsubstituted alkyl,

substituted or unsubstituted haloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocyclyl; and

'a' and 'b' are independently an integer selected from1, 2 or 3;

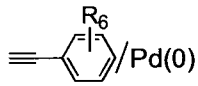
the method comprising the steps for the preparation of Formula (Ik) and formula (Il):

(a) (i) the compound of formula (1) coupled with formula (14) to afford formula (15) in presence of base



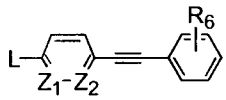
(14) (15) wherein L and L_2 are halogen;

(ii) formula (15) coupled with (Sonogashria coupling) formula (18) in presence of $PdCl_2$, triphenyl phosphine and CuI to afford formula (Ik)



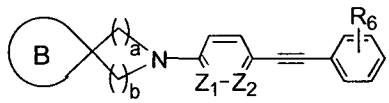
(18) or

(b) (i) the compound of formula (1) coupled with formula (19) to afford formula (Ik) in presence of base



(19)

30. The process according claim 29, for the preparation of compounds of formula (Il):



(I l)

the method comprising the steps of:

(i) base hydrolysis of formula (Ik) to give formula (Il).