(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 January 2010 (21.01.2010)

PCT

(10) International Publication Number
WO 2010/007482 A2

(51) International Patent Classification:
C07D 277/56 (2006.01) *A61K 31/426* (2006.01)

(21) International Application Number:
PCT/IB2009/006146

(22) International Filing Date:
3 July 2009 (03.07.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

1496/MUM/2008	16 July 2008 (16.07.2008)	IN
61/087,833	11 August 2008 (11.08.2008)	US
1881/MUM/2008	5 September 2008 (05.09.2008)	IN
61/097,268	16 September 2008 (16.09.2008)	US
2381/MUM/2008	10 November 2008 (10.11.2008)	IN
61/119,436	3 December 2008 (03.12.2008)	US

(71) Applicant *(for all designated States except US)*: **GLENMARK PHARMACEUTICALS S.A.** [CH/CH]; Chemin De La Combeta 5, CH-2300 La Chaux-de-fonds (CH).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **GHARAT, Laxmikant, Atmaram** [IN/IN]; Flat No-203, Tirupati Apartments, Pokhran Road No-2, Majiwada,, Maharashtra, 400 601 Thane (IN). **NARAYANA, Lakshminarayana** [IN/IN]; No. 302, Emerald, Aradhanadeep CHS, Plot No. 85, Sector 6, Koparkhairane, Maharashtra, Navi Mumbai 400 709 (IN). **THOMAS, Abraham** [IN/IN]; Flat No. 5, 11th Floor, Building No. A-6, Millennium Towers, Sector 9, Sanpada, Maharashtra, Navi Mumbai 400 705 (IN). **KHAIRATKAR-JOSHI, Neelima** [IN/IN]; C-101, Devprayag CHS, Bhakti Mandir Rd., Hari Niwas, Pachpakhadi, Maharashtra, Thane -400 602 (IN). **SHAH, Daisy, Manish** [IN/IN]; Padmashree Building, 1st Floor, Flat no.4, Anant Patil Marg,, Gokhale Road, Dadar, Maharashtra, Mumbai 400 028 (IN).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

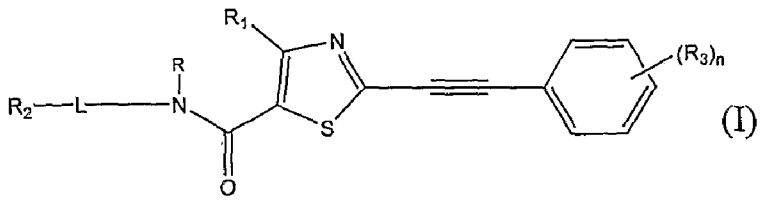
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

(54) Title: THIAZOLE DERIVATIVES AS STEAROYL COA DESATURASE INHIBITORS



(I)

(57) Abstract: The present invention provides thiazole derivatives as Stearoyl CoA Desaturase (SCD) inhibitors. In particular, the compounds described herein are useful for treating or preventing diseases, conditions and/or disorders modulated by Stearoyl CoA Desaturase 1 (SCD 1) inhibitors. 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) inhibitors.

WO 2010/007482 A2

THIAZOLE DERIVATIVES AS STEAROYL CoA DESATURASE INHIBITORS

Related Applications

This application claims the benefit of Indian provisional application numbers 1496/MUM/2008, filed on July 16, 2008; 1881/MUM/2008, filed on Sep 05, 2008; and 2381/MUM/2008, filed on Nov 10, 2008; and U.S. provisional application numbers 61/087,833, filed on Aug 11, 2008; 61/097,268, filed on Sep 16, 2008; and 61/119,436 filed on Dec 03, 2008, all of which are hereby incorporated by reference in their entirety.

Technical Field

The present patent application relates to Thiazole derivatives with SCD1 activity.

Background

Metabolic energy balance is important for well-being which 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.*, (2002), 288, 1723-1727). 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*, (2005), 6, 169-174). 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.,* (2005), 56, 45-62). 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,* (2005), 6, 169-174).

Stearoyl CoA desaturase 1 (SCD1) is shown to be a key enzyme that plays crucial role in lipid metabolism and body weight control (*Science,* (2002), 297, 240-243; *Obesity Reviews,* (2005), 6, 169-174; *J. Clinical Investigation,* (2005), 1-9). 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 (*Proc. Natl. Acad. Sci.,* (1974), 71, 4565-4569; *J. Biol Chem.,* (1976), 251, 5095-5103). SCD1 has two preferred substrates palmitoyl 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.,* (1976), 431, 469-480; *J. Biol. Chem.,* (1993), 268, 6823-6826; *Diabetes,* (1991), 40, 280-289; *Neurochem Res.,* (1994), 26, 771-782; *Arthritis Rheum.,* (2000), 43, 894-900; *Cancer Lett.*, (2001), 173, 139-144).

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,* (2002), 297, 240-243), fat chickens (*Am. Soc Nutri Scie.,* 249-256 (1997)) and obese human subjects (*Cell Metab.,* (2005), 2, 251-61) 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 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.,* (1997), 249-256). 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.*, (2000), 275, 30132-30138; *Science*, (2002), 297, 240-243). 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.*, (2001), 131, 2260-2268; *PNAS*, (2002), 99, 11482-11486). SCD1 is documented as a key enzyme in regulating hepatic lipogenesis and 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.*, (2003), 3, 271-280). 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.*, (2000), 1486 (2-3), 285-292; *Biochem Biophys Res Commun.*, (2001), 284 689-693). Conjugated linoleic acid (CLA) administration through feed reduces body fat and increases lean body mass in several animal species (*Lipids*, (1997), 32, 853-858; *FASEB*, 12, A836 (1998); *Lipids*, (1999), 34, 243- 248). 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.*, (2005) F 1-9).

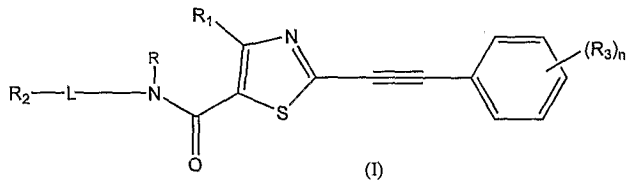
US 2006/009459 and WO 2005/011653, WO 2005/01164, WO 2005/011655, WO 2005/011656 and WO 2005/011657 disclose certain pyridazine derivatives, pyridyl derivatives, and piperazine derivatives and their use for inhibiting human stearoyl-CoA desaturase (hSCD) activity. US 2004/072877 is directed to a method 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 SCD1. In particular, there is a need for novel compounds that are used for treating obesity, diabetes, cardiovascular disease and complications thereof.

Summary

The present invention provides Thiazole compounds as SCD1 inhibitors, which are used in the treatment of diseases, conditions or disorders modulated by SCD1, and processes for the synthesis of these compounds.

In one aspect, the compound of the present invention is



(I)

wherein,

R is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted cycloalkyl;

R_1 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted haloalkyl, fully or partially substituted haloalkyl, substituted or unsubstituted haloalkyloxy, fully or partially substituted haloalkyloxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, or substituted or unsubstituted heteroaryl;

R_2 is substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclyl; wherein substituents are independently selected from halogen, nitro, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkoxy, substituted or unsubstituted haloalkyl, fully or partially substituted haloalkyl, substituted or unsubstituted haloalkyloxy, fully or partially substituted haloalkyloxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, or substituted or unsubstituted heteroaryl;

at each occurrence R_3 is independently selected from hydrogen, hydroxyl, cyano, nitro, halogen, acetyl, acetoxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted haloalkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cyclcoalkylalkyl, substituted or unsubstituted cyclcoalkyloxy, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted alkoxyaryl, substituted or unsubstituted arylalkyl, –O-C(O)-R', -$C(O)NR^aR^b$, -$SONR^aR^b$, -$SO_2NR^aR^b$, -OR^a, -$COOR^a$, -$C(O)R^a$, -$C(S)R^a$, -$C(O)ONR^aR^b$, -$NR^aC(O)OR^b$, -NR^aR^b, -$NR^aC(O)R^b$, or –$NR^aCONR^aR^b$;

at each occurrence R^a and R^b are same or different and are independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heterocyclylalkyl;

R' is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocyclyl;

'n' is an integer selected from 1 to 5, both inclusive;

L is (C_1-C_6) alkylene linker which may be further substituted with halogen or alkyl.

It should be understood that the formula (I) structurally encompasses all prodrugs, stereoisomers, including enantiomers and diastereomers, and pharmaceutically acceptable salts that may be contemplated from the chemical structure of the genus described herein.

According to one embodiment, specifically provided are compounds of the formula (I) in which L is –CH_2-, –CH_2–CH_2-, –CH_2–CH_2–CH_2-, –CH(-CH_3)-, or alkoxy (-O-CH_2–CH_2-).

According to another embodiment, specifically provided are compounds of the formula (I) in which R is hydrogen.

According to another embodiment, specifically provided are compounds of the formula (I) in which R_1 is substituted or unsubstituted alkyl, preferably methyl.

According to another embodiment, specifically provided are compounds of the formula (I) in which R_1 is substituted or unsubstituted cycloalkyl (eg., cyclopropyl), fully or partially substituted haloalkyl (eg., trifluoroalkyl).

According to another embodiment, specifically provided are compounds of the formula (I) in which R_2 is substituted or unsubstituted aryl; wherein aryl is preferably unsubstituted phenyl.

According to another embodiment, specifically provided are compounds of the formula (I) in which R_2 is substituted or unsubstituted aryl; wherein aryl is preferably mono substituted phenyl. In this embodiment, substituent is halogen (eg., fluorine, chlorine), alkoxy (eg., methoxy) or haloalkyl (eg., trifluoroalkyl).

According to another embodiment, specifically provided are compounds of the formula (I) in which R_2 is substituted or unsubstituted aryl; wherein aryl is preferably di or tri substituted phenyl. In this embodiment, substituents are independently selected from halogen (eg., fluorine, chlorine or bromine).

According to another embodiment, specifically provided are compounds of the formula (I) in which R_2 is substituted or unsubstituted heteroaryl, preferably pyridine.

According to another embodiment, specifically provided are compounds of the formula (I) in which R_3 is independently selected from fluoro, hydroxy, methyl, ethyl, trifluoromethyl, or triflouoromethoxy; preferably hydroxy. In this embodiment, 'n' is 1 or 2.

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-5-Benzyl-2-[2-(3-hydroxyphenyl)-1-ethynyl]-4-methyl-1,3-thiazole-5-carboxamide;

N-5-Benzyl-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-methyl-1,3-thiazole-5-carboxamide;

N-5-(3-Pyridylmethyl)-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-methyl-1,3-thiazole-5-carboxamide;

N-5-(3-Pyridylmethyl)-2-[2-(3-hydroxyphenyl)-1-ethynyl]-4-methyl-1,3-thiazole-5-carboxamide;

N-5-(2-Pyridylmethyl)-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-methyl-1,3-thiazole-5-carboxamide;

2-[(4-Hydroxy phenyl) ethynyl]- 4 -methyl- *N* - (2-phenyl ethyl)-1,3thiazole-5-carboxamide;

N-(4-Fluorobenzyl)-2-[(4-hydroxyphenyl)ethynyl]-4-methyl 1,3-thiazole-5-carboxamide;

2-[(4-Hydroxyphenyl)ethynyl]-4-methyl-*N*-(3-phenylpropyl)-1,3-thiazole-5-carboxamide;

N-5-[(*1R*)-1-Phenylethyl]-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-methyl-1,3-thiazole-5-carboxamide;

N-5-[(*1S*)-1-Phenylethyl]-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-methyl-1,3-thiazole-5-carboxamide;

N-(4-Chlorobenzyl)-2-[(4-hydroxyphenyl)ethynyl]-4-methyl-1,3-thiazole-5-carboxamide;

N-[1-(4-Fluorophenyl)ethyl]-2-[(4-hydroxyphenyl)ethynyl]-4-methyl-1,3-thiazole-5-carboxamide;

N-(2,4-Difluorobenzyl)-2-[(4-hydroxyphenyl)ethynyl]-4-methyl-1,3-thiazole-5-carboxamide;

N-[2-(4-Fluorophenyl)ethyl]-2-[(4-hydroxyphenyl)ethynyl]-4-methyl-1,3-thiazole-5-carboxamide;

N-(3-Chlorobenzyl)-2-[(4-hydroxyphenyl)ethynyl]-4-methyl-1,3-thiazole-5-carboxamide;

2-[(4-Hydroxyphenyl)ethynyl]-*N*-(4-methoxybenzyl)-4-methyl-1,3-thiazole-5-carboxamide;

2-[(4-Hydroxyphenyl)ethynyl]-4-methyl-*N*-[4-(trifluoromethyl)benzyl]-1,3-thiazole-5-carboxamide;

N-(2,6-Difluorobenzyl)-2-[(4-hydroxyphenyl)ethynyl]-4-methyl-1,3-thiazole-5-carboxamide;

N-(2-Chlorobenzyl)-2-[(4-hydroxyphenyl)ethynyl]-4-methyl-1,3-thiazole-5-carboxamide;

N-5-(3-Phenylpropyl)-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-trifluoromethyl-1,3-thiazole-5-carboxamide;

N-5-Phenethyl-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-trifluoromethyl-1,3-thiazole-5-carboxamide;

N-5-(4-Fluorobenzyl)-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-trifluoromethyl-1,3-thiazole-5-carboxamide;

N-5-(4-Trifluoromethylbenzyl)-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-trifluoromethyl-1,3-thiazole-5-carboxamide;

N-5-(4-Methoxybenzyl)-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-trifluoromethyl-1,3-thiazole-5-carboxamide;

N-5-Benzyl-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-trifluoromethyl-1,3-thiazole-5-carboxamide;

4-Cyclopropyl-2-[(4-hydroxyphenyl) ethynyl]-*N*-phenyl propyl-1,3-thiazole-5-carboxamide;

4-Cyclopropyl-*N*-(4-fluorobenzyl)-2-[(4-hydroxyphenyl)ethynyl]-1,3-thiazole-5-carboxamide;

N-[2-(4-Fluorophenoxy)ethyl]-2-[(4-hydroxyphenyl)ethynyl]-4-methyl-1,3-thiazole-5-carboxamide;

2-[(4-Hydroxyphenyl)ethynyl]-4-methyl-*N*-(2-phenoxyethyl)-1,3-thiazole-5-carboxamide; and

N-(2,4-Dichlorobenzyl)-2-[(4-hydroxyphenyl)ethynyl]-4-methyl-1,3-thiazole-5-carboxamide or prodrugs, such as those with linkages –OCO- (oxycarbonyl), -OCOO- etc. at the phenolic hydroxyl group, pharmaceutically acceptable salts thereof, stereoisomers thereof, of compounds 1 to 30 are also contemplated.

In another aspect, provided herein is a pharmaceutical composition comprising a therapeutically effective amount of one or more compounds of Formula (I) 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 SCD1 in a subject comprising administering to the subject in need thereof a therapeutically effective amount of one or more compounds of Formula (I), or a pharmaceutical composition as described herein.

In another aspect, there is provided a method of inhibiting lipid metabolism that proceeds via a Stearoyl-CoA Desaturase-1 (SCD1) mediated pathway in a subject, the method including administering to the subject in need thereof a therapeutically effective amount of one or more compounds of Formula I, that exhibits increased SCD1 inhibitory activity in a target tissue in comparison with SCD1 activity in a reference tissue.

Preferably, in the method according to the above aspect, the target and reference tissues are selected from liver and skin. In one preferred variant, the target tissue is liver and

the reference tissue is skin. While the invention is not limited by any specific theory, the selective SCD1 inhibitor is believed to decrease conversion of saturated fatty acids to unsaturated fatty acids in liver cells to a greater extent than in skin cells. The preferred fatty acids are selected from palmitoyl CoA and stearoyl CoA.

In one variant in accordance with the above aspects, the subject is a cell. In another variant, the subject is a mammal, preferably, a human.

For SCD-1 inhibitors selective for liver, the preferred ratio of EC35 for the SCD-1 inhibitor in skin cells to that in liver cells is greater than 1.

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

Detailed Description

The following definitions apply to terms as used herein:

The terms "halogen" or "halo" includes fluorine, chlorine, bromine, or iodine.

The term "alkyl" refers to hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to eight carbon atoms, and 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 (*tert*-butyl). The term "C_{1-6} alkyl" refers to an alkyl chain having 1 to 6 carbon atoms. Unless set forth or recited to the contrary, all alkyl groups described or claimed herein may be straight chain or branched, substituted or unsubstituted.

The term "alkenyl" refers to an hydrocarbon chain containing from 2 to 10 carbon atoms and including at least one carbon-carbon double bond. Non-limiting examples of alkenyl groups include ethenyl, 1-propenyl, 2-propenyl (allyl), iso-propenyl, 2-methyl-1-propenyl, 1-butenyl, and 2-butenyl. Unless set forth or recited to the contrary, all alkenyl groups described or claimed herein may be straight chain or branched, substituted or unsubstituted.

The term "alkynyl" refers to a hydrocarbyl radical having at least one carbon-carbon triple bond, and having 2 to about 12 carbon atoms (with radicals having 2 to about 10 carbon atoms being preferred). Non-limiting examples of alkynyl groups include ethynyl, propynyl, and butynyl. Unless set forth or recited to the contrary, all alkynyl groups described or claimed herein may be straight chain or branched, substituted or unsubstituted.

The term "alkylene" refers to divalent of alkyl group, wherein alkyl is as defined above.

The term "haloalkyl" is used to denote a group comprised of an alkyl group substituted with halogen atom, where alkyl group is as defined above and halogen is used to denote fluorine, chlorine, bromine or iodine, an example of such group is trifluoromethyl, difluoromethyl.

The term "alkoxy" denotes an alkyl group attached via an oxygen linkage to the rest of the molecule. Representative examples of such groups are $-OCH_3$ and $-OC_2H_5$. Unless set forth or recited to the contrary, all alkoxy groups described or claimed herein may be straight chain or branched, substituted or unsubstituted.

The term "haloalkoxy" unless otherwise specified refers to an haloalkyl group attached via an oxygen linkage to the rest of the molecule. Representative examples of such groups are $-OCF_3$ and $-OC_2F_5$.

The term "cycloalkyl" denotes a non-aromatic mono or multicyclic ring system of 3 to about 12 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Examples of multicyclic cycloalkyl groups include, but are not limited to, perhydronaphthyl, adamantyl and norbornyl groups, bridged cyclic groups or sprirobicyclic groups, e.g., sprio(4,4)non-2-yl. Unless set forth or recited to the contrary, all cycloalkyl groups described or claimed herein may be substituted or unsubstituted.

The term "cycloalkylalkyl" refers to a cyclic ring-containing radical having 3 to about 8 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. Unless set forth or recited to the contrary, all cycloalkylalkyl groups described or claimed herein may be substituted or unsubstituted.

The term "cycloalkenyl" refers to a cyclic ring-containing radical having 3 to about 8 carbon atoms with at least one carbon-carbon double bond, such as cyclopropenyl, cyclobutenyl, and cyclopentenyl. Unless set forth or recited to the contrary, all cycloalkenyl groups described or claimed herein may be substituted or unsubstituted.

The term "aryl" refers to an aromatic radical having 6 to 14 carbon atoms, including monocyclic, bicyclic and tricyclic aromatic systems, such as phenyl, naphthyl,

tetrahydronapthyl, indanyl, and biphenyl. Unless set forth or recited to the contrary, all aryl groups described or claimed herein may be substituted or unsubstituted.

The term "arylalkyl" refers to an 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 "heterocyclyl" and "heterocyclic ring" "heterocyclic group" refers to a stable 3- to 15-membered ring radical which consists of carbon atoms and from one to five heteroatoms selected from nitrogen, phosphorus, oxygen and sulfur. For purposes of this invention, the heterocyclic ring radical may be a monocyclic, bicyclic 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; and the ring radical may be partially or fully saturated (i.e., heterocyclic or heteroaryl). Examples of such heterocyclic ring radicals include, but are not limited to, azetidinyl, acridinyl, benzodioxolyl, benzodioxanyl, benzofuranyl, carbazolyl, cinnolinyl, dioxolanyl, indolizinyl, naphthyridinyl, perhydroazepinyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pyridyl, pteridinyl, purinyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrazolyl, imidazolyl, tetrahydroisoquinolinyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolinyl, oxazolidinyl, triazolyl, indanyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolinyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyl, decahydroisoquinolyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzooxazolyl, furyl, tetrahydrofuranyl, tetrahydropyranyl, thienyl, 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. Unless set forth or recited to the contrary, all heterocyclyl groups described or claimed herein may be substituted or unsubstituted, including those included in more complex substructures.

The term "heteroaryl" refers to an aromatic heterocyclic ring radical. 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. Unless set forth or recited to the contrary, all

heteroaryl groups described or claimed herein may be substituted or unsubstituted, including those included in more complex substructures.

The term "heterocyclylalkyl" refers to a 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.

The term "heteroarylalkyl" refers to a 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.

Unless otherwise specified, the term "substituted" as used herein refers to a group or moiety having one or more of the substituents attached to the structural skeleton of the group or moiety, including, but not limited to such substituents as 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 cycloalkenylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclylalkyl ring, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring, substituted or unsubstiuted 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 cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted heterocyclylalkyl ring, substituted or unsubstituted heteroarylalkyl, or substituted or unsubstituted heterocyclic ring. 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 "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 "inhibiting lipid metabolism that proceeds via an SCD-1-mediated pathway" denotes alteration in normal functioning of lipid metabolic pathway that involves SCD-1 enzyme, including, particularly, a decrease in lipid formation via a pathway facilitated by the SCD-1 enzyme.

The term "selective SCD-1 inhibitor" denotes a substance that affects activity of SCD-1 enzyme in a differential manner, particularly, a substance that selectively affects SCD activity in one tissue type as compared to SCD-1 activity of the same substance in another tissue type. For instance, a substance is a selective SCD-1 inhibitor if the SCD-1 inhibitory activity of the substance in target tissue is greater than SCD-1 inhibitory activity of the substance in reference tissue. An agent may be a selective inhibitor for liver SCD-1 by having a lower EC_{35} in liver cells than in skin cells.

The term "target tissue" with respect to SCD-1 activity denotes a tissue type in which SCD-1 inhibition is intended to be exerted via administration of a substance having SCD-1 inhibitory activity. Non-limiting examples of "target tissue" include liver, skin and cornea.

The term "reference tissue" with respect to SCD-1 activity denotes a tissue type in which SCD-1 inhibition is not intended to be exerted via administration of a substance having SCD-1 inhibitory activity. Non-limiting example of a "reference tissue" include liver, skin and cornea.

The term EC_{35} refers to the concentration of the compound which inhibits the activity of the enzyme half way between the baseline and maximum response of approximately 70%.

The term IC_{50} refers to the concentration of inhibitor that reduces enzyme activity by 50%.

The term "treating" or "treatment" of a state, disorder or condition includes: (a) preventing or delaying the appearance of clinical symptoms of the state, disorder or condition

developing in a subject that may be afflicted with or predisposed to the state, disorder or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder or condition; (b) inhibiting the state, disorder or condition, i.e., arresting or reducing the development of the disease or at least one clinical or subclinical symptom thereof; or (c) relieving the disease, i.e., causing regression of the state, disorder or condition or at least one of its clinical or subclinical symptoms.

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 cause the effect in the subject which is the purpose of the administration. 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), tartrates, 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).

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 regiomers 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 mixture 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, flavouring agents, colorants, or any combination of the foregoing. 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 ampoule, 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.

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

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 ceratin 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.

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 hepatic 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; tumors (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 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; 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 cholesterol.

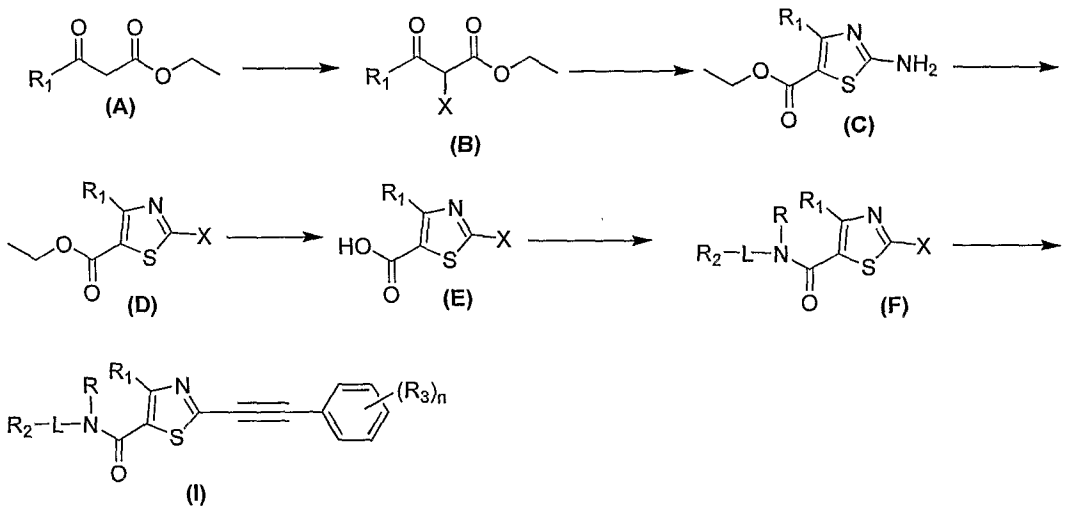
In another embodiment, there is provided a method for preventing, ameliorating or treating a disease or condition selected from obesity or related diseases, conditions; Type II diabetes; atherosclerosis, hypertension; lipidemia, dyslipidemia, microalbuminemia, hyperuricaemia, hypercholesterolemia, hyperlipidemias,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

General Methods of Preparation

The compounds described herein, including compounds of general formula (I), 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 to 3. All possible stereoisomers are also envisioned within the scope of this invention.

The starting materials for the below reaction schemes 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 through the reaction schemes as follows, wherein all symbols are as defined above.

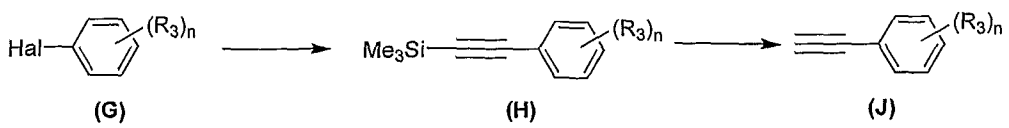
Scheme 1



Scheme 1 depicts a method for preparing the compounds described by general formula (I) wherein all symbols are as defined above. In this scheme, compound of formula (A) is converted to a compound of formula (B) wherein X is halogen, for example, by reacting with molecular halogen or with a halo substituted succinimide in a halogenated solvent or acetonitrile, THF, diethyl ether, acetic acid or the like known in the art of organic synthesis. Compound of formula (B) is converted to a compound of formula (C) by reacting with thiourea (*J. Chem. Soc., Perkin Trans 1,* (1982), 159-164) known in the art of organic synthesis. Compound of formula (C) is converted to a compound of formula (D) by reacting under Sandmeyer reaction conditions with an alkali nitrite in an aqueous acid in the presence of an alkali halide known in the art of organic synthesis. Compound of formula (D) is converted to a compound of formula (E) by reacting with an aqueous alkali under standard ester hydrolysis conditions known in the art of organic synthesis. Compound of formula (E) is converted to a compound of formula (F) by reacting with an appropriately substituted amine under standard amidation conditions employing a coupling reagent such as EDCI.HCl (1-ethyl-3-(3-dimethylaminopropyl) carbodiimide) hydrochloride) or BOP (benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate) in the presence of a base such as triethylamine or diisopropylethylamine with or without a catalyst such as DMAP (Dimethylaminopyridine) as known in the art of organic synthesis. Compound of formula (F) is converted to a compound of formula (I) by reacting with an appropriately substituted acetylene under Sonogashira reaction conditions using a base such as triethylamine, diisopropylethylamine or the like or tetra-*n*-butylammonium fluoride with or without a solvent like DMSO (Dimethyl sulfoxide) in the presence of a copper catalyst such as copper iodide and a palladium catalyst such as (tetrakistriphenylphosphine)palladium(0), in the temperature range of room temperature to 100 °C. Compound of formula (I) (when R_3 is O-C(O)-R') can be hydrolyzed to get hydroxyl compound of formula (I) under general ester hydrolysis conditions known in the art.

Substituted acetylene compounds can be prepared as per Scheme 2:

Scheme 2

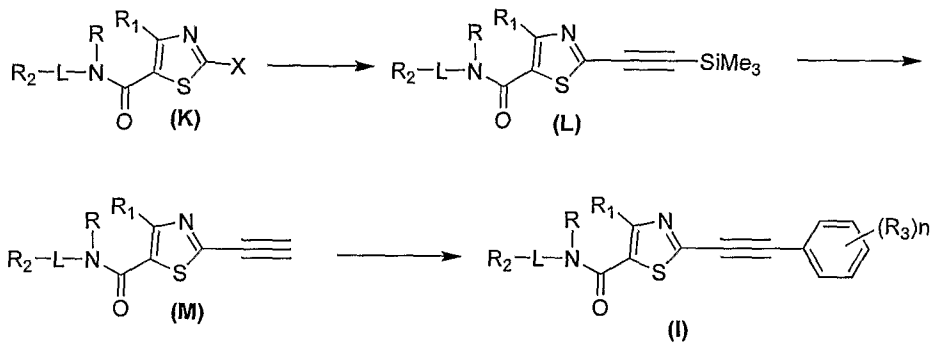


Compound of formula (G) is converted to a compound of formula (H) by reacting with a silyl acetylene under Sonogashira reaction conditions using a base such as

triethylamine, diisopropylethylamine etc., in a solvent such as DMSO in the presence of copper iodide and a palladium catalyst such as (tetrakistriphenylphosphine)palladium(0), in the temperature range of room temperature to 100 °C. Compound of formula (H) is further converted to a compound of formula (J) by reacting with tetra-*n*-butylammonium fluoride in the presence of a solvent such as dichloromethane in the temperature range of 0 to 80 °C.

Alternately, the compounds of formula (I) can also be prepared as per the following general scheme 3.

Scheme 3

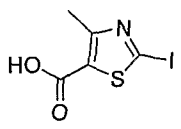


Compound of formula (K) is converted to compound of formula (L) by reacting with the silyl acetylene under Sonogashira reaction conditions using a base such as triethylamine, diisopropylethylamine or the like with a solvent such as DMSO in the presence of a copper catalyst (eg., copper iodide) and a palladium catalyst (eg.,(tetrakistriphenylphosphine) palladium(0)), in the temperature range of room temperature to 100 °C. Compound of formula (L) is converted to a compound of formula (M) by reacting with tetra-*n*-butylammonium fluoride in the presence of a solvent such as dichloromethane in the temperature range of 0 to 80 °C. Compound of formula (M) is converted to formula (I) by reacting with an appropriately substituted aryl halide under Sonogashira reaction conditions. Compound of formula (I) (when R_3 is O-C(O)-R') can be converted to a hydroxyl compound of formula (I) under general ester hydrolysis conditions known in the art.

EXPERIMENTAL

Intermediates

Intermediate 1: 2-Iodo-4-methyl-1,3-thiazole-5-carboxylic acid:



Prepared as per the procedure described in *J. Chem. Soc. Perkin Trans.-1*, (1982), 159-164.

Step1: Ethyl 2-amino-4-methyl-1,3-thiazole-5-carboxylate:

To a solution of ethyl 2-chloro acetoacetate (10 g, 60.75 mmoles) in ethanol (50 mL) was added thiourea (1 eq) and refluxed the reaction mixture for 4 h. The reaction mixture was cooled, and then added crushed ice, neutralized with ammonia. The precipitate was then filtered and dried under vacuum to give 11.5 g of the desired product. ^{1}H NMR (DMSO-d_6) δ 7.69 (s, 2H), 4.16-4.09 (q, J = 6.6 Hz, 2H), 2.36 (s, 3H), 1.22 (t, J = 6.9 Hz, 3H). MS (*m/z*): 185.40 $(M-H)^+$.

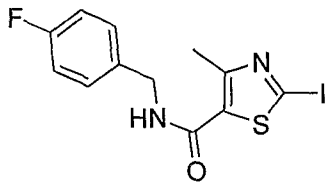
Step 2: Ethyl 2-iodo-4-methyl-1,3-thiazole-5-carboxylate:

A slurry of ethyl 2-amino-4-methyl-1,3-thiazole-5-carboxylate (11.4 g, 61.21 mmoles) and a solution of NaI (2 eq) in water (80 mL) was added to a stirred solution at -8 °C of $CuSO_4$ (1.5 eq) and H_2SO_4 (175 mL) in water (425 mL). A solution of $NaNO_2$ (1.9 eq) in water (25 mL) was added beneath the surface of the mixture for 30 min and the mixture was allowed to warm to 8 °C for 1 h. The reaction mixture was then extracted with diethyl ether and the organic layer was then dried over Na_2SO_4 and concentrated to get 6.5 g of the desired product. ^{1}H NMR ($CDCl_3$) δ 4.28-4.21 (q, J = 6.9 Hz, 2H), 2.63 (s, 3H), 1.27 (t, J = 6.9 Hz, 3H).

Step 3: 2-Iodo-4-methyl-1,3-thiazole-5-carboxylic acid:

A mixture of ethyl 2-iodo-4-methyl-1,3-thiazole-5-carboxylate (6.5 g, 21.87 mmoles) and KOH (2.4 eq) in 15 % aqueous ethanol (60 mL) was refluxed for 2 h. Ethanol was evaporated from the reaction mixture and washed with diethyl ether. The aqueous layer was then acidified with 2 N HCl. The precipitated product was then filtered and dried under vacuum to get 5.7 g of desired product. ^{1}H NMR (DMSO-d_6) δ 13.17 (br s, 1H), 2.60 (s, 3H). MS (*m/z*): 267.83 $(M-H)^+$.

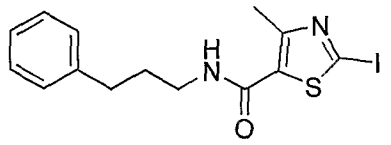
Intermediate 2: *N*-(4-Fluorobenzyl)-2-iodo-4-methyl-1,3-thiazole-5-carboxamide:



To a solution of intermediate 1 (0.5g, 1.86 mmoles) in CH_2Cl_2 (10 mL) at room temperature was added EDCI. HCl (1.5 eq) followed by *N, N'*-diisopropylethylamine (3 eq), HOBT

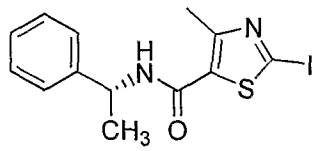
(hydroxybenzotriazole) (1 eq) and 4-fluoro benzylamine (1 eq) and stirred the reaction mixture at room temperature for 16 h. The reaction mixture was then diluted with dichloromethane (30 mL) and washed with water (20 mL) followed by brine, dried over Na_2SO_4 and concentrated. The crude was then purified by column chromatography to get 0.4 g of the desired product. ^{1}H NMR (DMSO-d_6) δ 8.78 (br, s, 1H), 7.35-7.30 (m, 2H), 7.14 (t, J = 8.7 Hz, 2H), 4.36 (d, J = 5.7 Hz, 2H), 2.54 (s, 3H).

Intermediate-3: 2-Iodo-4-methyl-*N*-(3-phenylpropyl)-1,3-thiazole- 5-carboxamide:



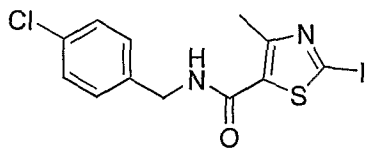
The title compound was prepared by following the similar procedure as described in intermediate 2 by using intermediate 1 (0.4 g, 1.49 mmoles) and 3-phenylpropan-1-amine (1 eq) to get 0.28 g of the required product. ^{1}H NMR (DMSO-d_6) δ 7.30-7.10 (m, 5H); 5.61 (br s, 1H); 3.46-3.40 (q, J = 6.0 Hz, 2H); 2.70 (t, J = 7.5 Hz, 2H); 2.62(s, 3H); 1.94 (p, J = 7.5 Hz, 2H).

Intermediate- 4: 2-Iodo-4-methyl-*N*-[(*S*)-(-)(1-phenylethyl)]-1,3-thiazole-5- carboxamide:



The title compound was prepared by following the similar procedure as described in intermediate 2 by using intermediate 1 (0.4 g, 1.49 mmoles) and (*S*)-(-)1-phenylethanamine (1 eq) to get 0.26 g of the required product. ^{1}H NMR ($CDCl_3$) δ 7.40-7.25(m, 5H); 5.85 (br d, 1H); 5.21(p, J = 7.2 Hz, 1H); 2.66 (s, 3H); 1.57 (br d, 3H).

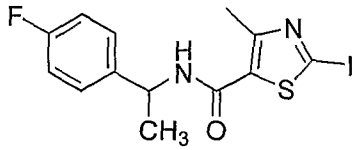
Intermediate- 5: *N*-(4-Chlorobenzyl)-2-iodo-4-methyl-1,3-thiazole-5- carboxamide:



The title compound was prepared by following the similar procedure as described in intermediate 2 by using intermediate 1 (0.4 g, 1.49 mmoles) and 1-(4-chlorophenyl)methanamine (1 eq) to get 0.32 g of the required product. ^{1}H NMR (DMSO-d_6)

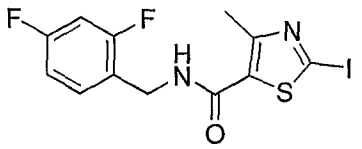
δ 8.80 (t, 3H); 7.38 (d, *J* = 8.4Hz, 2H); 7.30(d, *J* = 8.4 Hz, 2H); 4.37(d, 2H, *J* = 5.7 Hz); 2.55 (s, 3H).

Intermediate-6: *N*-[1-(4-Fluorophenyl)ethyl]-2-iodo-4-methyl-1,3-thiazole-5 carboxamide:



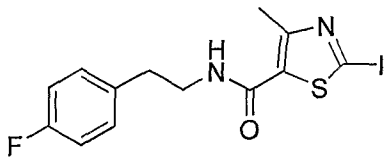
The title compound was prepared by following the similar procedure as described in intermediate 2 by using intermediate 1 (0.4 g, 1.49 mmoles) and 1-(4-fluorophenyl)ethanamine (1 eq) to get 0.25 g of the required product. ^{1}H NMR (DMSO-d_6) δ 8.67 (d, 1H, *J* = 8.1 Hz); 7.39-7.36 (m, 2H); 7.13 (t, 2H, *J* = 17.4 Hz); 5.06-5.01(m, 1H); 2.50 (s, 3H); 1.42(s, 3H).

Intermediate- 7: *N*-(2,4-Difluorobenzyl)-2-iodo-4-methyl-1,3-thiazole-5- carboxamide:



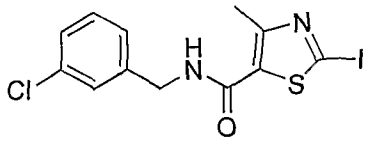
The title compound was prepared by following the similar procedure as described in intermediate 2 by using intermediate 1 (0.4 g, 1.49 mmoles) and 1-(2,4-difluorophenyl)methanamine (1 eq) to get 0.31 g of the required product. ^{1}H NMR (DMSO-d_6) δ 8.77 (t, 1H); 7.37 (q, 1H, *J* = 7.2 Hz); 7.26 (t, 1H); 7.04 (t, 1H); 4.38 (d, 2H, *J* = 5.4 Hz); 2.53 (s, 3H).

Intermediate- 8: *N*-[2-(4-Fluorophenyl)ethyl]-2-iodo-4-methyl-1,3-thiazole-5- carboxamide:



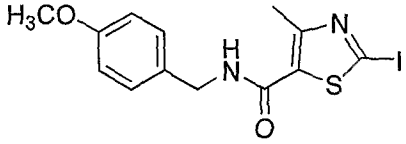
The title compound was prepared by following the similar procedure as described in intermediate 2 by using intermediate 1 (0.4 g, 1.49 mmoles) and 2-(4-fluorophenyl)ethanamine (1 eq) to get 0.30 g of the required product. ^{1}H NMR (DMSO-d_6) δ 8.27 (br s, 1H); 7.06-7.11 (m, 2H); 7.24-7.20 (m, 2H); 3.39(m, 2H); 2.78 (t, 2H, *J* = 13.5 Hz); 2.45 (s,3H).

Intermediate- 9: *N*-(3-Chlorobenzyl)-2-iodo-4-methyl-1,3-thiazole-5-carboxamide:



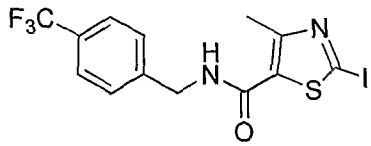
The title compound was prepared by following the similar procedure as described in intermediate 2 by using intermediate 1 (0.4 g, 1.49 mmoles) and 1-(3-chlorophenyl) methanamine(1 eq) to get 0.28 g of the required product. ^{1}H NMR (DMSO-d_6) δ 8.08 (m, 1H); 7.35-7.25 (m, 4H); 4.36 (d, 2H, *J* = 6.0 Hz); 2.55 (s, 3H).

Intermediate- 10: 2-Iodo-*N*-(4-methoxybenzyl)-4-methyl-1,3-thiazole-5-carboxamide:



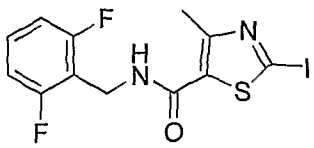
The title compound was prepared by following the similar procedure as described in intermediate 2 by using intermediate 1 (0.4 g, 1.49 mmoles) and 1-(4-methoxyphenyl) methanamine (1 eq) to get 0.32 g of the required product. ^{1}H NMR (DMSO-d_6) δ 8.71 (m, 1H); 7.19 (d, 2H, *J* = 8.1 Hz); 6.86 (d, 2H, *J* = 9.0 Hz); 4.30 (d, 2H, *J* = 5.7 Hz); 3.71 (s, 3H); 2.53(s, 3H).

Intermediate- 11: 2-Iodo-4-methyl-*N*-[4-(trifluoromethyl)benzyl]-1,3-thiazole-5-carboxamide:



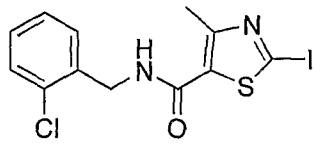
The title compound was prepared by following the similar procedure as described in intermediate 2 by using intermediate 1 (0.4 g, 1.49 mmoles) and 1-[4-(trifluoromethyl) phenyl]methanamine (1 eq) to get 0.27 g of the required product.^{1}H NMR (DMSO-d_6) δ 7.60 (d, 2H, *J* = 7.8 Hz); 7.42 (d, 2H, *J* = 7.8 Hz); 6.10 (br s, 1H); 4.63 (d, 2H, *J* = 5.7 Hz); 2.70 (s, 3H).

Intermediate- 12: *N*-(2,6-Difluorobenzyl)-2-iodo-4-methyl-1,3-thiazole-5-carboxamide:



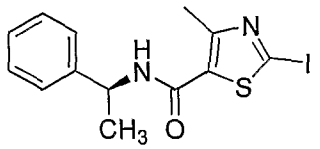
The title compound was prepared by following the similar procedure as described in intermediate 2 by using intermediate 1 (0.4 g, 1.49 mmoles) and 1-(2,6-difluorophenyl) methanamine (1 eq) to get 0.29 g of the required product. ^{1}H NMR (DMSO-d_6) δ 8.73 (m, 1H); 7.40-7.33 (m, 1H); 7.07 (t, 2H, J = 15.6 Hz); 4.43 (d, 2H, J = 5.4 Hz); 2.49 (s, 3H).

Intermediate- 13: *N*-(2-Chlorobenzyl)-2-iodo-4-methyl-1,3-thiazole-5-carboxamide:



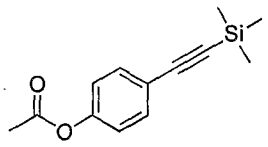
The title compound was prepared by following the similar procedure as described in intermediate 2, using intermediate 1 (0.4 g, 1.49 mmoles) and 2-Chlorobenzylamine (1 eq) to get 0.30 g of the required product. ^{1}H NMR (DMSO-d_6) δ 8.80 (br, s, 1H), 7.44 (d, J = 7.8 Hz, 1H), 7.35-7.20 (m, 3H), 4.45 (d, J = 5.1 Hz, 2H), 2.56 (s, 3H).

Intermediate- 14: 2-Iodo-4-methyl-*N*-[(*R*)-(+)-(1-phenylethyl)]-1,3-thiazole-5- carboxamide:



The title compound was prepared by following the similar procedure as described in intermediate 2 by using intermediate 1 (0.4 g, 1.49 mmoles) and (*R*)-(+)1-phenylethanamine (1 eq) to get 0.30 g of the required product. ^{1}H NMR ($CDCl_3$) δ 7.38-7.25(m, 5H); 5.90-5.82 (m, 1H); 5.21 (p, J = 7.2 Hz, 1H); 2.66 (s, 3H); 1.59 (d, J = 3.3 Hz, 3H); MS (*m/z*): 373.04 $(M)^+$.

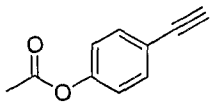
Intermediate- 15: 4-(Trimethylsilanylethynyl)-phenylacetate:



To a solution of 4-acetoxy iodobenzene (6.0 g, 22.89 mmoles) in DMSO (25 mL) was added trimethylsilyl acetylene (1.1 eq) followed by triethylamine (3 eq), CuI (0.05 eq) and tetrakis (triphenylphosphine)palladium(0) (0.03 eq) and the reaction mixture was stirred at room temperature for 6 h. The reaction mixture was then diluted with water and extracted with ethyl acetate. The organic layer was then dried over Na_2SO_4, concentrated and purified by

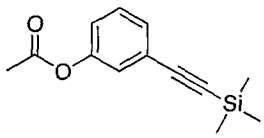
column chromatography to get 4.5 g of the desired product. ^{1}H NMR (DMSO-d_6) δ 7.48 (d, J = 8.7 Hz, 2H), 7.12 (d, J = 8.4 Hz, 2H), 2.26 (s, 3H), 0.23 (s, 9H).

Intermediate- 16: 4-(1-Ethynyl)phenylacetate:



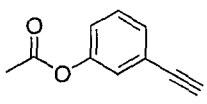
To a solution of 4-(trimethylsilanylethynyl)-phenylacetate (4.4 g, 18.93 mmoles) in dichloromethane (50 mL) at 0 °C was added tetra-*n*-butylammonium fluoride (0.5 eq) and stirred the reaction mixture at room temperature for 1 h. The reaction mixture was then diluted with dichloromethane, washed with water, dried over Na_2SO_4, concentrated and purified by column chromatography to get 1.9 g of the desired product. ^{1}H NMR ($CDCl_3$) δ 7.47 (d, J = 7.8 Hz, 2H), 7.03 (d, J = 8.1 Hz, 2H), 3.05 (s, 1H), 2.29 (s, 3H).

Intermediate- 17: 3-(Trimethylsilanylethynyl)-phenylacetate:



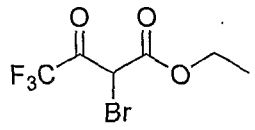
To a solution of 3-acetoxy iodobenzene (6.0 g, 22.89 mmoles) in DMSO (25 mL) was added trimethylsilyl acetylene (1.1 eq) followed by triethylamine (3 eq), CuI (0.05 eq) and tetrakis (triphenylphosphine) palladium(0) (0.03 eq) and the reaction mixture was stirred at room temperature for 6 h. The reaction mixture was then diluted with water and extracted with ethyl acetate. The organic layer was then dried over Na_2SO_4, concentrated and purified by column chromatography to get 4.3 g of the desired product. ^{1}H NMR ($CDCl_3$) δ 7.30-7.25 (m, 2H), 7.18 (s, 1H), 7.05-6.95 (m, 1H), 2.28 (s, 3H), 0.24 (s, 9H).

Intermediate- 18: 3-(1-Ethynyl)phenylacetate:



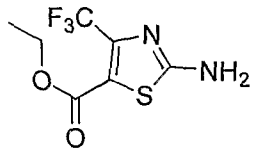
To a solution of 3-(trimethylsilanylethynyl)-phenylacetate (4.0 g, 17.21 mmoles) in dichloromethane (50 mL) at 0 °C was added tetra-*n*-butylammonium fluoride (0.5 eq) and stirred the reaction mixture at room temperature for 1 h. The reaction mixture was then diluted dichloromethane, washed with water, dried over Na_2SO_4, concentrated and purified by column chromatography to get 1.5 g of the desired product. ^{1}H NMR ($CDCl_3$) δ 7.35-7.25 (m, 2H), 7.19 (s, 1H), 7.10-7.00 (m, 1H), 3.08 (s, 1H), 2.29 (s, 3H).

Intermediate 19: Ethyl 2-bromo-4,4,4-trifluoro-3-oxobutanoate:



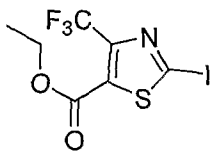
Solution of ethyl 4,4,4-trifluoro-3-oxobutanoate (5g, 27.16 mmoles) in CCl_4 (50ml) was chilled at 10-15 °C and added bromine solution (0.97 eq). Stir at room temperature for 1 h. Added chloroform and reaction mass washed with DM water (100ml) followed by sodium bisulphite solution (50ml). Collect organic layer dried over sodium sulphate and excess of solvent distilled out and concentrated to get 4.48 g of desired product. ^{1}H NMR ($CDCl_3$) δ 4.33 (m, 1H); 1.30 (m,3H).

Intermediate 20: Ethyl 2-amino-4-(trifluoromethyl)-1,3-thiazole-5-carboxylate:



To a solution of ethyl 2-bromo-4,4,4-trifluoro-3-oxobutanoate (4.48 g, 17.03 mmoles) in ethanol (50 ml) added thiourea (2 eq) and refluxed at 85 °C for 24 h. Then ethanol was distilled out, added chilled water, adjusted pH 10-14 with Ammonia solution. The obtained precipitate was then filtered and dried in oven at 40-45 °C to give 1.7 g of desired product. ^{1}H NMR ($CDCl_3$) δ 8.22 (s, 2H); 4.21 (q, 2H, J = 13.8Hz); 1.23 (t, 3H, J =13.8 Hz). MS (*m/z*): 239.19 $(M-H)^-$.

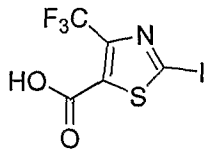
Intermediate 21: Ethyl 2-iodo-4-(trifluoromethyl)-1,3-thiazole-5-carboxylate:



To solution of Para toluene sulphonic acid (2.3 g, 13.35 mmoles) in acetonitrile (20 ml) was slowly added powdered ethyl 2-amino-4-(trifluoromethyl)-1,3-thiazole-5-carboxylate(1 g, 4.16 mmoles). Heat the reaction mixture at 40-50 °C for 30mins. The reaction mixture was then cooled to 10-15 °C. Then solution of $NaNO_2$ (2 eq) added and KI (2.5 eq) was added to above reaction mixture and maintained at room temperature for 1 h. Then reaction mass was quenched in ice cold water (30ml). The reaction mixture was extracted with dichloromethane (100ml) and further extracted with dichloromethane. Washed the total organic layers with 5%

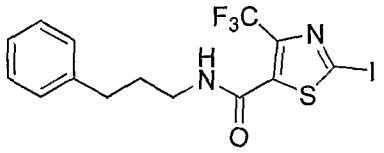
sodium bisulphate solution (100ml), dried over Na_2SO_4 and concentrated. The crude was then purified by column chromatography to get 0.755 g of the desired product. ^{1}H NMR ($CDCl_3$) δ 4.30 (q, 2H, *J* = 14.7 Hz); 1.28 (t, 3H, *J* =13.5 Hz); MS (*m/z*): 351.91 $(M+H)^+$

Intermediate 22: 2-Iodo-4-(trifluoromethyl)-1,3-thiazole-5-carboxylic acid:



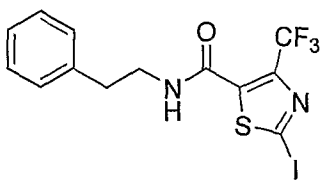
To a solution of 2-iodo-4-(trifluoromethyl)-1,3-thiazole-5-carboxylate (3.4 g, 9.68 mmoles) in THF at was added solution NaOH (2 eq) and stir at room temperature. Distilled out the solvent completely and DM water (2 ml) was added and adjusted pH to 1 with 1N HCl. The obtained precipitate was filtered, washed with DM water to get 2.4 g of desired product.

Intermediate 23: 2-Iodo-*N*-(3-phenylpropyl)-4-(trifluoromethyl)-1,3-thiazole-5-carboxamide:



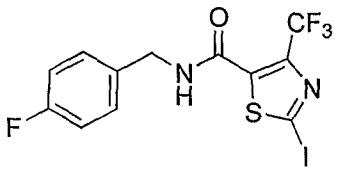
To a solution of 2-Iodo-4-(trifluoromethyl)-1,3-thiazole-5-carboxylic acid (0.211 g, 0.65 mmoles) in dichloro ethane was added EDCI.HCl (1 eq), HOBT (1 eq) and DIPEA (*N,N*-diisopropylethylamine) (0.230 g) followed by phenylpropylamine (0.108 g) and stirred at room temperature for 3 h. To above reaction mixture was added ethyl acetate and DM water (5 ml) and extracted into organic layer. Further aqueous layer was extracted with ethyl acetate (2 x 10ml). Total organic layers dried over Na_2SO_4 and concentrated. The obtained crude product was purified through column chromatography to get 0.191g of desired product. ^{1}H NMR (DMSO-d_6) δ 8.95 (br, s, 1H), 7..27 (t, *J* = 14.7 Hz, 3H), 7.18 (d, *J* = 7.8 Hz, 2H), 3.19-3.21 (q, *J* = 6.0 Hz, 2H), 2.36 (t, *J* = 15.3 Hz, 2H); 1.75 (t, *J* = 14.1 Hz, 2H). MS (*m/z*); 440.92 $(M+H)^+$.

Intermediate 24: 2-iodo-*N*-(2-Phenylethyl)-4-(trifluoromethyl)-1,3-thiazole-5-carboxamide:



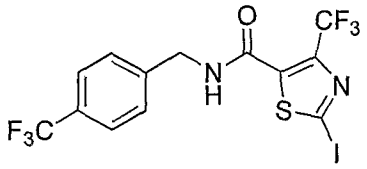
The title compound was prepared by following the similar procedure as described in intermediate 23 by using intermediate 22 (0.35 g, 1.08 mmoles) and phenylethylamine (1 eq) instead of phenylpropylamine to get 0.171g of the desired product. ^{1}H NMR (DMSO-d_6) δ 8.98 (br, s, 1H), 7..27 (t, J = 6.6 Hz, 3H), 7.20 (d, J = 7.2 Hz, 2H), 3.43(d, J = 6.6 Hz, 2H), 2.76 (t, J = 7.2 Hz, 2H).

Intermediate 25: 2-Iodo-*N*-(4-fluorobenzyl)-4-(trifluoromethyl)-1,3-thiazole-5-carboxamide:



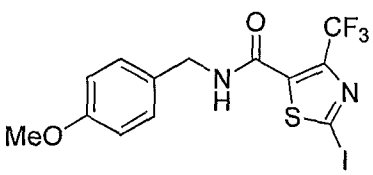
The title compound was prepared by following the similar procedure as described in intermediate 23 by using intermediate 22 (0.35 g, 1.08 mmoles) and 4-fluorobenzylamine (1 eq) instead of phenylpropylamine to get 0.21 g of the desired product. ^{1}H NMR (DMSO-d_6) δ 9.42 (br, s, 1H), 7.40-7.30 (m, 2H), 7.20-7.10 (m, 2H), 4.39 (d, J = 6.0 Hz, 2H).

Intermediate 26: 2-Iodo-*N*-(4-trifluoromethyl benzyl)-4-(trifluoromethyl)-1,3-thiazole-5-carboxamide:



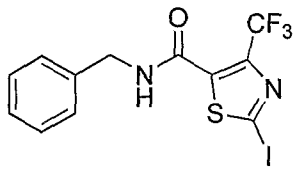
The title compound was prepared by following the similar procedure as described in intermediate 23 by using intermediate 22 (0.35 g, 1.08 mmoles) and 4-trifluoromethylbenzyl amine (1 eq) instead of phenylpropylamine to get 0.14 g of the desired product. ^{1}H NMR (DMSO-d_6) δ 9.51 (br, s, 1H), 7.70 (d, J = 8.1 Hz, 2H), 7.48 (d, J = 7.8 Hz, 2H), 4.50 (d, J = 5.7 Hz, 2H). MS (*m/z*): 478.86 $(M-H)^-$.

Intermediate 27: 2-Iodo-*N*-(4-methoxy benzyl)-4-(trifluoromethyl)-1,3-thiazole-5- carbox amide:



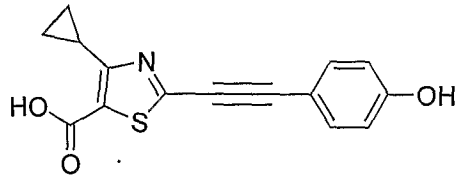
The title compound was prepared by following the similar procedure as described in intermediate 23 by using intermediate 22 (0.35 g, 1.08 mmoles) and 4-methoxybenzylamine (1 eq) instead of phenylpropylamine to get 0.18 g of the desired product. ^{1}H NMR (DMSO-d_6) δ 9.34 (br, s, 1H), 7.19 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 4.33 (d, J = 6.0 Hz, 2H), 3.72 (s, 3H).

Intermediate 28: 2-Iodo-*N*-benzyl-4-(trifluoromethyl)-1,3-thiazole-5-carboxamide:



The title compound was prepared by following the similar procedure as described in intermediate 23 by using intermediate 22 (0.35 g, 1.08 mmoles) and benzylamine (1 eq) instead of phenylpropylamine to get 0.19 g of the desired product. ^{1}H NMR (DMSO-d_6) δ 9.42 (br, s, 1H), 7.35-7.25 (m, 5H), 4.41 (d, J = 6.0 Hz, 2H).

Intermediate 29: 4-Cyclopropyl-2-[(4-hydroxyphenyl)ethynyl]-1,3-thiazole-5-carboxylic acid



Step 1: Ethyl 2-bromo-3-cyclopropyl-3-oxopropanoate:

To a solution of ethyl 3-cyclopropyl-3-oxopropanoate (400 mg, 2.56 mmoles) in CCl_4 (10 ml) was added aq. Br_2 (0.99 eq) and the reaction mixture was stirred at room temperature for 1 h. Then the reaction mixture was quenched in water and the organic layer was washed with sodium bisulphate and then washed with water and concentrated to give 500 mg of desired product. ^{1}H NMR ($CDCl_3$) δ 5.61 (m, 1H); 4.21 (q, 2H, J = 28.2 Hz), 2.51 (m, 1H); 1.41(t, 3H, J = 16.5 Hz); 1.31(m, 2H); 0.95 (m, 2H).

Step 2: Ethyl 2-amino-4-cyclopropyl-1,3-thiazole-5-carboxyl ate:

To a solution of thiourea (500 mg, 6.57 mmoles) in ethanol (10 ml) was added 2-bromoethyl cyclopropyl acetate (1.16 eq) and heated to 80 °C. Evaporate the ethanol then water was added and extracted with ethyl acetate, and purified through column to get 500 mg of desired product. ^{1}H NMR ($CDCl_3$) δ 7.69 (s br, 2H); 4.15 (q, 2H, J = 21.6 Hz), 2.87 (m, 1H); 1.22 (t, 3H, J = 14.1 Hz); 0.88 (m, 4H).

Step 3: Ethyl -4-cyclopropyl-2-iodo 1,3-thiazole-5-carboxylate:

To a solution of ethyl 2-amino-4-cyclopropyl-1,3-thiazole-5-carboxylate (0.5 g, 2.35 mmoles) in acetonitrile (10 ml) was added PTSA (*p*-toluenesulfonicacid) (4.0 eq) and stirred for 30 min. Allow the reaction mixture at 0 °C and was added KI (2.5 eq) and $NaNO_2$ (2.0 eq) and stirred for 30 min at 0 °C. Then raise the temperature to 90 °C for 15 min and quenched in water and then extracted with ethyl acetate. Organic layer was concentrated and purified through column to get 400 mg of desired product. ^{1}H NMR (DMSO-d_6) δ 4.27 (q, 2H, J = 13.8 Hz); 2.91 (m, 1H); 1.26 (t, 3H, J = 13.8 Hz); 1.09 (m, 2H); 0.97 (m,2H).

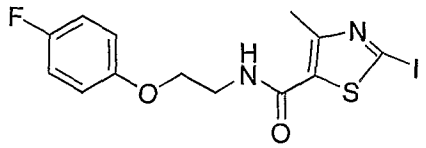
Step 4: Ethyl 2-{[4-(acetyloxy) phenyl] ethynyl}-4-cyclopropyl-1, 3-thiazole-5-carboxylate:

To a solution of ethyl-4-cyclopropyl-2-iodo 1,3-thiazole-5-carboxylate (0.45 g, 1.39 mmoles) in DMSO (5 ml) and triethylamine (2ml) was added 4-acetoxy phenyl acetylene (1 eq) and $Pd(PPh_3)Cl_2$ (0.03 eq) and stirred for 2 h at room temperature. Then quenched in water and extracted in ethyl acetate and concentrated to get 450mg of desired product. ^{1}H NMR (DMSO-d_6) δ 7.73 (d, 2H, J = 8.1 Hz); 7.25(d, 2H, J = 8.1 Hz); 4.32 (q, 2H, J = 21.0 Hz); 2.98 (m, 1H); 2.87(s, 3H); 1.30(t, 3H, J = 13.8 Hz); 1.29 (m,2H); 1.04 (m,2H).

Step 5: 4-Cyclopropyl-2-[(4-hydroxyphenyl)ethynyl]-1,3-thiazole-5-carboxylic acid:

To a solution of ethyl 2-{[4-(acetyloxy) phenyl]ethynyl}-4-cyclopropyl-1,3-thiazole-5-carboxylate (400 mg, 1.12 mmoles) in ethanol was added sodium hydroxide (3.3 eq) and stirred at room temperature. Then quenched in water and acidified with acetic acid to get 270 mg of desired product. ^{1}H NMR (DMSO-d_6) δ 13.52 (s br, 1H); 10.23 (s,1H); 7.48 (d, 2H, J = 8.4 Hz); 6.82 (d, 2H, J = 8.1 Hz); 2.98 (m, 1H); 1.08 (m, 2H); 0.99 (m,2H).

Intermediate 30: *N*-[2-(4-Fluorophenoxy)ethyl]-2-iodo-4-methyl-1,3-thiazole-5-carboxamide:



Step 1- *tert*-Butyl (2-hydroxyethyl)carbamate:

To a solution of 2-aminoethanol (1 g, 16.32 mmoles) in dichloromethane (10 ml) was added triethylamine (3 eq) and stirred for 10 mins. Then BOC anhydride (1.2 eq) was added to the reaction mixture and stirred for 2 h at room temperature. Then the reaction mixture was quenched in ice cold water and extracted with dichloromethane. The organic layer was

washed with water and concentrated to get desired product. ^{1}H NMR ($CDCl_3$) δ 7.25 (s, 1H), 3.69 (t, 2H, J = 12.6 Hz), 3.48 (s,1H); 3.28 (m, 2H).

Step 2: *tert*-Butyl [2-(4-fluorophenoxy)ethyl]carbamate :

Under nitrogen atmosphere to a solution of 4-fluoro phenol (0.5g, 4.46 mmoles) and *tert*-butyl (2-hydroxyethyl) carbamate (1 eq) in tetrahydrofuran (2.5 ml) was added triphenyl phosphine (1.5 eq) and diethylazodicarboxylate (1.2 eq) drop wise and refluxed the reaction mixture for 3 h. Then the reaction mixture was quenched in ice cold water and extracted with ethyl acetate. The organic layer was washed with water and concentrated to get desired product. The crude product was further purified by column chromatography to get 275 mg of pure desired product. ^{1}H NMR ($CDCl_3$) δ 7.24 (s, 1H), 6.92 (m, 2H); 6.49 (m, 2H); 3.96 (t, 2H, J = 9.6 Hz), 3.50 (m,2H); 1.45 (s, 9H)

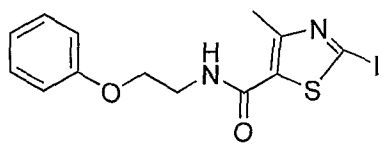
Step 3: Hydrochloride salt of 2-(4-fluorophenoxy)ethanamine:

To *tert*-butyl [2-(4-fluorophenoxy)ethyl]carbamate added ethyl acetate HCl and stirred at room temperature for 15 mins. Then ethyl acetate was evaporated and the product was dried and used for next step.

Step 4: *N*-[2-(4-Fluorophenoxy)ethyl]-2-iodo-4-methyl-1,3-thiazole-5-carboxamide:

To the solution of intermediate 1 (300 mg, 1.11 mmoles) in dichloromethane was added DIPEA (2 eq.), HOBT (1 eq), and EDCI (1.5 eq) followed by the addition of product of step 1 dissolved in dichloromethane and DIPEA (1 eq). The reaction mixture was then stirred at room temperature for 6 h. Then quenched the reaction mixture with ice cold water and extracted with dichloromethane. Then the organic layer was washed with brine and water and dried over Na_2SO_4 and concentrated to get crude product. The crude material was purified through column chromatography to get 200 mg of the desired product. ^{1}H NMR ($CDCl_3$) δ 8.45 (m, 1H); 7.09 (m, 2H); 6.95 (m, 2H); 4.04 (t, 2H); 3.53 (d, 2H, J =5.1 Hz); 2.52 (s, 3H).

Intermediate 31: 2-Iodo-4-methyl-*N*-(2-phenoxyethyl)-1,3-thiazole-5-carboxamide:



Step 1: *tert*-butyl (2-phenoxyethyl)carbamate:

By following the similar procedure as described in step-2 of intermediate-30 by using phenol (0.5 g, 5.31 mmoles) and *tert*-butyl (2-hydroxyethyl) carbamate (step 1, intermediate 30, 1

eq) to get 300 mg of the desired product. ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 3H); 6.97 (m, 1H); 6.87 (m, 2H); 4.02 (t, 2H, J = 9.3 Hz); 3.52 (m, 2H); 1.45 (s, 3H)

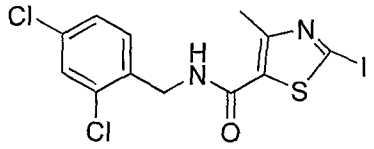
Step 2: Hydrochloride salt of 2-phenoxyethanamine:

To *tert*-butyl (2-phenoxyethyl)carbamate added ethyl acetate HCl and stirred at room temperature for 15 mins. Then ethyl acetate was evaporated and the product was dried and used for next step. ^{1}H NMR ($CDCl_3$) δ 8.16 (m, 2H); 7.30 (t, 2H, J = 15.3 Hz); 6.96 (d, 3H, J = 8.4 Hz); 4.16 (t, 2H, J = 9.3 Hz); 3.19 (m, 2H)

Step 3: 2-Iodo-4-methyl-*N*-(2-phenoxyethyl)-1,3-thiazole-5-carboxamide:

To the solution of intermediate 1 (300 mg, 1.11 mmoles) in dichloromethane was added DIPEA (3 eq) and BOP reagent (1 eq). Then the solution of hydrochloride salt of 2-phenoxyethanamine (1 eq) in dichloromethane and DIPEA (1 eq) was added to the above reaction mixture and maintained at room temperature for 3 h. The reaction mixture was quenched with ice cold water and extracted with dichloromethane. Then the organic layer was washed with brine and water and dried over anhydrous sodium sulphate and concentrated to get crude product. The crude material was purified by column chromatography to get 175 mg of the desired product. ^{1}H NMR ($CDCl_3$): δ 8.45 (br s, 1H); 7.26 (t, 2H, J = 15.6 Hz); 6.90 (m, 3H); 4.06 (t, 2H, J = 11.1 Hz); 3.56 (m, 2H); 2.53 (s, 3H).

Intermediate 32: *N*-(2,4-Dichlorobenzyl)-2-iodo-4-methyl-1,3-thiazole-5-carboxamide:

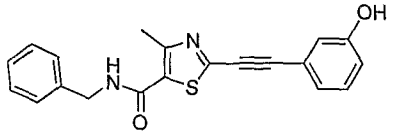


By following the similar procedure as described in intermediate 2 by using intermediate 1 (0.4 g, 1.48 mmoles) and 1-(2,4-dichlorophenyl) methanamine (1 eq) to get 0.3 g of the required product. ^{1}H NMR ($CDCl_3$) δ 8.80 (t, 1H); 7.60 (s, 1H); 7.40 (d, 1H, J = 8.4 Hz); 7.34 (d, 1H, J = 8.1 Hz); 4.42 (d, 2H, J = 5.4 Hz); 2.55(s, 3H).

Examples

Example 1

N-5-Benzyl-2-[2-(3-hydroxyphenyl)-1-ethynyl]-4-methyl-1,3-thiazole-5-carboxamide:



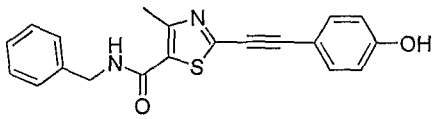
Step 1: *N*-5-Benzyl-2-bromo-4-methyl-1,3-thiazole-5-carboxamide:

To a solution of 2-iodo-4-methyl-1,3-thiazole-5-carboxylic acid (intermediate 1, 0.5g, 1.85 mmoles) in DMF (3 mL) at room temperature was added BOP reagent (1 eq) and stirred the reaction mixture at room temperature for 30 min. To the above reaction mixture added *N, N'*-diisopropylethylamine (2 eq) followed by benzylamine (1 eq) and maintained at room temperature for 3 h. The reaction mixture was then diluted with water (10 mL) and extracted with ethyl acetate (2 x 25 mL). The organic layer was then washed with water (3 x 20 mL) followed by brine, dried over Na_2SO_4 and concentrated. The crude was then purified by column chromatography to get 350 mg of the desired product. ^{1}H NMR (DMSO-d_6) δ 8.83 (br, t, 1H), 7.35-7.25 (m, 5H), 4.39 (d, J = 6.0 Hz, 2H), 2.54 (s, 3H).

Step 2: To *N*-5-Benzyl-2-iodo-4-methyl-1,3-thiazole-5-carboxamide (100 mg, 0.28 mmoles) (step 1) was added tetra-*n*-butyl-ammonium fluoride (3 eq) followed by 3-(1-ethynyl)phenylacetate (1 eq) and stirred the reaction mixture at 80 °C for 3 h. The reaction mixture was then diluted with ethyl acetate and washed with water. The organic layer was then dried over Na_2SO_4, concentrated and purified by column chromatography to get 45 mg of the desired product. ^{1}H NMR (DMSO-d_6) δ 9.88 (s, 1H), 8.91 (br t, 1H), 7.35-7.20 (m, 6H), 7.06 (d, J = 7.5 Hz, 1H), 6.97 (s, 1H), 6.91 (d, J = 6.0 Hz, 1H), 4.43 (d, J = 6.0 Hz, 2H), 2.58 (s, 3H). MS (*m/z*): 347.30 $(M-H)^+$.

Example 2

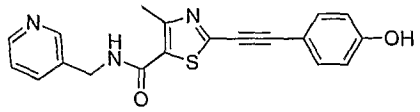
N-5-Benzyl-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-methyl-1,3-thiazole-5-carboxamide:



The title compound was prepared by following the similar procedure as described in step 2 of example 1, using the product of step 1 of example 1 (100 mg, 0.28 mmoles) and 4-(1-ethynyl) phenylacetate (1 eq) instead of 3-(1-ethynyl) phenylacetate to get 38 mg of the desired product. ^{1}H NMR ($CDCl_3$) δ 10.21 (s, 1H), 8.85 (br t, 1H), 7.47 (d, J = 8.4 Hz, 2H), 7.40-7.20 (m, 5H), 6.82 (d, J = 8.1 Hz, 2H), 4.42 (d, J = 5.4 Hz, 2H), 2.57 (s, 3H); MS (*m/z*): 347.33 $(M-H)^+$.

Example 3

N-5-(3-Pyridylmethyl)-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-methyl-1,3-thiazole-5-carboxamide:



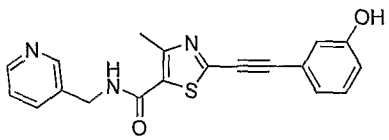
Step 1: *N*-5-(3-Pyridylmethyl)-2-bromo-4-methyl-1,3-thiazole-5-carboxamide:

By following the similar procedure as described in Step 1 of example 1, using intermediate 1 (0.5 g, 1.86 mmoles) and 3-(aminomethyl) pyridine (1 eq) instead of benzylamine to get 350 mg of the desired product. ^{1}H NMR (DMSO-d_6) δ 8.87 (br, t, 1H), 8.51 (s, 1H), 8.44 (d, J = 3.6 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.39-7.32 (m, 1H), 4.42 (d, J = 6.0 Hz, 2H), 2.54 (s, 3H).

Step 2: By following the similar procedure as described in step 2 of example 1 using *N*-5-(3-pyridylmethyl)-2-iodo-4-methyl-1,3-thiazole-5-carboxamide (100 mg, 0.28 mmoles) and 4-(1-ethynyl)phenylacetate (1 eq) to get 41 mg of the desired product. ^{1}H NMR (DMSO-d_6) δ 10.22 (s, 1H), 8.90 (br t, 1H), 8.53 (s, 1H), 8.45 (br s, 1H), 7.73 (d, J = 6.3 Hz, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.37 (br s, 1H), 6.82 (d, J = 8.1 Hz, 2H), 4.44 (d, J = 4.8 Hz, 2H), 2.57 (s, 3H). MS (*m/z*): 350.29 $(M+H)^+$.

Example 4

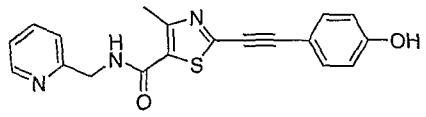
N-5-(3-Pyridylmethyl)-2-[2-(3-hydroxyphenyl)-1-ethynyl]-4-methyl-1,3-thiazole-5-carboxamide



The title compound was prepared by following the similar procedure as described in step 2 of example 1, using *N*5-(3-pyridylmethyl)-2-iodo-4-methyl-1,3-thiazole-5-carboxamide (100 mg, 0.28 mmoles) and 3-(1-ethynyl) phenylacetate to get 32 mg of the desired product. ^{1}H NMR (DMSO-d_6) δ 10.22 (s, 1H), 8.90 (br t, 1H), 8.53 (s, 1H), 8.45 (br s, 1H), 7.73 (d, J = 6.3 Hz, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.37 (br s, 1H), 6.82 (d, J = 8.1 Hz, 2H), 4.44 (d, J = 4.8 Hz, 2H), 2.57 (s, 3H). MS (*m/z*): 350.39 $(M+H)^+$.

Example 5

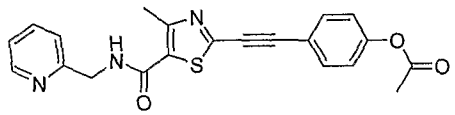
N-5-(2-Pyridylmethyl)-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-methyl-1,3-thiazole-5-carboxamide:



Step 1: *N*-5-(2-Pyridylmethyl)-2-iodo-4-methyl-1,3-thiazole-5-carboxamide:

To a solution of 2-iodo-4-methyl-1,3-thiazole-5-carboxylic acid (intermediate 1, 0.5g, 1.86 mmoles) in dichloromethane (10 mL) at room temperature was added EDCI. HCl (1.5 eq) followed by *N, N'*-diisopropylethylamine (3 eq), HOBT (1 eq) and 2-(aminomethyl) pyridine (1 eq) and stirred the reaction mixture at room temperature for 16 h. The reaction mixture was then diluted with CH_2Cl_2 (30 mL) and washed with water (20 mL) followed by brine, dried over Na_2SO_4 and concentrated. The crude was then purified by column chromatography to get 400 mg of the desired product. ^{1}H NMR (DMSO-d_6) δ 8.82 (br, t, 1H), 8.48 (d, J = 3.9 Hz, 1H), 7.74 (t, J = 6.0 Hz, 1H), 7.30-7.20 (m, 2H), 4.48 (d, J = 6.0 Hz, 2H), 2.57 (s, 3H).

Step 2: 4-{2-[4-Methyl-5-(2-pyridylmethylcarbamoyl)-1,3-thiazol-2-yl]-1-ethynyl}-phenyl acetate:



To a solution of *N*-5-(2-pyridylmethyl)-2-iodo-4-methyl-1,3-thiazole-5-carboxamide (100 mg, 0.28 mmoles) in DMSO (6 mL) was added 4-(1-ethynyl)phenylacetate (1 eq) followed by triethylamine (3 eq), CuI (0.05 eq) and tetrakis (triphenylphosphine) palladium(0) (0.03 eq) and the reaction mixture was stirred at room temperature for 6 h. The reaction mixture was then diluted with water and extracted with ethyl acetate. The organic layer was then dried over Na_2SO_4, concentrated and purified by column chromatography to get 70 mg of the desired product. ^{1}H NMR (DMSO-d_6) δ 8.94 (br t, 1H), 8.49 (d, J = 5.4 Hz, 1H), 7.80-7.65 (m, 3H), 7.65-7.55 (m, 1H), 7.32 (d, J = 7.5 Hz, 1H), 7.25 (d, J = 8.4 Hz, 2H), 4.52 (d, J = 6.0 Hz, 2H), 2.61 (s, 3H), 2.29 (s, 3H). MS (*m/z*): 392.24 $(M+H)^+$.

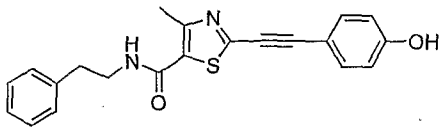
Step 3: *N*-5-(2-Pyridylmethyl)-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-methyl-1,3-thiazole-5-carboxamide:

To a solution of 4-{2-[4-methyl-5-(2-pyridylmethylcarbamoyl)-1,3-thiazol-2-yl]-1-ethynyl}-phenylacetate (60 mg, 0.15 mmoles) in a mixture of THF, methanol and water (3:2:1, 6 mL respectively) was added lithium hydroxide hydrate (2 eq) and stirred the reaction mixture at room temperature for 4 h. Solvent was then evaporated from the reaction mixture on rotavapor, residue was neutralized with 1N HCl and extracted with ethyl acetate. The organic

layer was then dried over Na_2SO_4, concentrated and purified through column chromatography to get 35 mg of the desired product. ^{1}H NMR (DMSO-d_6) δ 10.2 (br s, 1H), 8.90 (br t, 1H), 8.50 (d, *J* = 3.9 Hz, 1H), 7.76 (br t, 1H), 7.48 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.30-7.25 (m, 1H), 6.83 (d, *J* = 8.1 Hz, 2H), 4.52 (d, *J* = 5.4 Hz, 2H), 2.59 (s, 3H).

Example 6

2-[(4-Hydroxy phenyl) ethynyl]- 4 -methyl- *N*-(2-phenyl ethyl)-1,3-thiazole-5-carboxamide:



Step 1: *N*-5-phenethyl-2-iodo-4-methyl-1,3-thiazole-5-carboxamide:

By following the similar procedure as described in step 1 of example 5 using intermediate 1 (0.5 g, 1.85 mmoles) and phenethylamine (1 eq) instead of 2-(aminomethyl) pyridine to get 400 mg of the desired product. ^{1}H NMR (DMSO-d_6) δ 8.29 (br, s, 1H), 7.35-7.15 (m, 5H), 3.48-3.38 (q, *J* = 6.9 Hz, 2H), 2.79 (t, *J* = 6.9 Hz, 2H), 2.46 (s, 3H).

Step 2: 4 [(4- Methyl -5-{[(2-phenyl ethyl)amino] -1,3-thiazol-2-yl)-1-ethynyl]-phenyl acetate

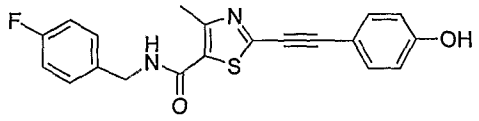
By following the similar procedure as described in step 2 of example 5, using 2-Iodo-4-methyl-*N*-(2-phenylethyl)-1,3-thiazole-5-carboxamide (300 mg, 0.80 mmoles) instead of *N*5-(2-pyridylmethyl)-2-iodo-4-methyl-1,3-thiazole-5-carboxamide to get 120 mg of the desired product.^{1}H NMR (DMSO-d_6) δ 10.21 (br s, 1H); 8.37 (br t, 1H);7.70(d, *J* = 8.4 Hz, 2H); 7.46 (d, *J* = 8.4 Hz, 2H); 7.30m, 5H); 6.82 (d, *J* = 8.7 Hz, 2H), 3.50-3.40 (m, 2H), 2.90-2.80 (m, 2H); 2.48 (s, 3H); 2.29(s, 3H).

Step 3: 2-[(4-Hydroxy phenyl)ethynyl]-4-methyl-*N*-(2-phenylethyl)-1,3-thiazole-5-carbox amide:

By following the similar deacetylation procedure as described in step 3, example 5 using 4 [(4-methyl-5-{[(2-phenyl ethyl)amino]-1,3-thiazol-2-yl)-1-ethynyl]-phenyl acetate (60 mg, 0.15 mmoles) to get 29 mg of the desired product. ^{1}H NMR (DMSO-d6) δ 10.21 (br s, 1H); 8.37 (br t, 1H); 7.46 (d, *J* = 8.4 Hz, 2H); 7.35-7.15 (m, 5H); 6.82 (d, *J* = 8.4 Hz, 2H), 3.50-3.40 (m, 2H), 2.82 (t, *J* = 6.9 Hz, 2H); 2.47 (s,3H). MS (*m/z*):- 363.25 $(M+H)^+$.

Example 7

N-(4-Fluorobenzyl)-2-[(4-hydroxyphenyl) ethynyl] – 4- methyl 1,3-thiazole- 5-carboxamide:



Step 1: 4-[(5-{[(4-Fluorobenzyl)amino]carbonyl}-4-methyl-1,3-thiazol-2-yl)ethynyl]phenyl acetate:

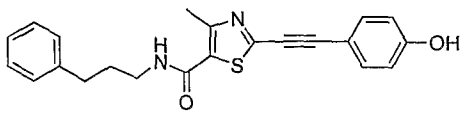
By following the similar procedure as described in step 2 of example 5 by using *N*-(4-fluorobenzyl)-2-iodo-4-methyl-1,3-thiazole-5-carboxamide (intermediate 2, 200 mg, 0.53 mmoles) instead of *N*5-(2-pyridylmethyl)-2-iodo-4-methyl-1,3-thiazole-5-carboxamide to get 120 mg of the desired product.^{1}H NMR ($CDCl_3$) δ 7.57 (d, J = 8.4 Hz, 2H) ; 7.35-7.30 (m, 2H); 7.11 (d, J = 8.7 Hz, 2H); 7.03 (t, J = 8.7 Hz, 2H), 6.03 (br s, 1H); 4.57 (d, J = 5.4 Hz, 2H); 2.71 (s, 3H); 2.31 (s, 3H); MS: 409.45 $[M+H]^+$.

Step 2: *N*-(4-Fluorobenzyl)-2-[(4-hydroxyphenyl)ethynyl]-4-methyl-1,3-thiazole-5-carboxamide:

By following the similar procedure as described in step 3 of example 5 using 4-[(5-{[(4-fluorobenzyl)amino]carbonyl}-4-methyl-1,3-thiazol-2-yl) ethynyl]phenylacetate (80 mg, 0.19 mmoles) to get 34 mg of the desired product. ^{1}H NMR ($CDCl_3$) 7.44 (d, J = 9.0 Hz, 2H); 7.38-7.28 (m, 2H); 7.03 (t, J = 8.1 Hz, 2H); 6.82 (d, J = 8.7 Hz, 2H); 6.05-5.98 (m, 1H); 5.65-6.55 (m, 1H); 4.57(d, J = 6.0 Hz, 2H); 2.70 (s, 3H). MS (*m/z*): 367.30 $(M+H)^+$.

Example 8

2-[(4-Hydroxyphenyl)ethynyl]-4-methyl-*N*-(3-phenylpropyl)-1,3-thiazole-5-carboxamide:



Step 1: 4-[4- Methyl -5{[(3-phenylpropyl)amino]carbonyl}-1,3-thiazol-2-yl)-ethynyl phenyl acetate:

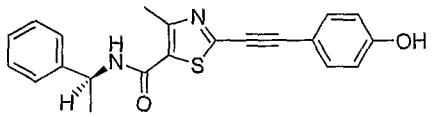
By following the similar procedure as described in step 2 of example 5 using 2-iodo-4-methyl-*N*-(3-phenylpropyl)-1,3-thiazole-5-carboxamide (intermediate 3, 200 mg, 0.51 mmoles) instead of *N*5-(2-pyridylmethyl)-2-iodo-4-methyl-1,3-thiazole-5-carboxamide to get 148 mg of the desired product. ^{1}H NMR (DMSO-d_6) δ 8.38 (m, 1H); 7.70 (d, J = 8.4 Hz, 2H); 7.26-7.15 (m, 7H); 3.23 (q, J = 5.7 Hz, 2H); 2.62 (m, 5H); 2.28 (s, 3H); 1.81 (p, J = 7.2 Hz, 2H).

Step 2: 2-[(4-Hydroxyphenyl)ethynyl]-4-methyl-*N*-(3-phenylpropyl)-1,3-thiazole-5-carboxamide:

By following the similar procedure as described in step 3 of example 5 using 4-[4-Methyl -5{[(3-phenylpropyl)amino]carbonyl}-1,3-thiazol-2-yl)-ethynyl phenyl acetate (80 mg, 0.19 mmoles) to get 27 mg of the desired product. ^{1}H NMR ($CDCl_3$) δ 7.42 (d, J = 8.7 Hz, 2H) ; 7.30-7.15 (m, 5H); 6.83 (d, J = 8.4 Hz, 2H); 6.07 (s, 1H); 5.71 (br s,1H); 3.49-3.42 (q, J = 6.3 Hz, 2H); 2.71(t, J =7.5 Hz, 2H); 2.65 (s, 3H); 1.96 (p, J = 6.9 Hz, 2H); MS (*m/z*): 377.33 $(M+H)^+$.

Example 9

N-5-[(*1R*)-1-Phenylethyl]-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-methyl-1,3-thiazole-5-carboxamide:



Step 1: 4-[2-{4-Methyl-5-[(*1R*)-1-phenylethylcarbamoyl]-1,3-thiazol-2-yl}-1-ethynyl)phenyl acetate:

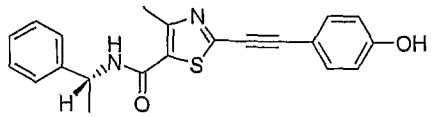
By following the similar procedure as described in step 2 of example 5 using 2-iodo-4-methyl-*N*-[(*R*)-(+)(1-phenylethyl)]-1,3-thiazole-5- carboxamide (intermediate 14, 240 mg, 0.64 mmoles) instead of *N*-5-(2-pyridylmethyl)-2-iodo-4-methyl-1,3-thiazole-5-carboxamide to get 130 mg of the desired product. ^{1}H NMR ($CDCl_3$) δ 7.57 (d, J = 8.4 Hz, 2H); 7.37-7.25 (m, 5H); 7.10 (d, J = 8.4 Hz, 2H); 5.94 (d, J = 6.9 Hz, 1H); 5.25 (p, J = 6.9 Hz, 1H); 2.69 (s, 3H); 2.31 (s, 3H); 1.60 (d, J = 6.9 Hz, 3H).

Step 2: *N*-5-[(*1R*)-1-Phenylethyl]-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-methyl-1,3-thiazole-5-carboxamide:

By following the similar procedure as described in step 3 of example 5 using 4-[2-{4-methyl-5-[(*1R*)-1-phenylethylcarbamoyl]-1,3-thiazol-2-yl}-1-ethynyl)phenyl acetate (100 mg, 0.25 mmoles) to get 80 mg of the desired product. ^{1}H NMR ($CDCl_3$) δ 7.42 (d, J = 8.7 Hz, 2H) ; 7.38-7.25 (m, 5H); 6.82 (d, J = 8.7 Hz, 2H); 6.05-5.90 (m, 2H); 5.30-5.20 (m, 1H) ; 2.68 (s, 3H); 1.63-1.60 (br d, 3H); MS (*m/z*): 361.42$(M-H)^+$.

Example 10

N-5-[(*1S*)-1-Phenylethyl]-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-methyl-1,3-thiazole-5-carbox amide:



Step 1: 4-[2-{4-Methyl-5-[(1*S*)-1-phenylethylcarbamoyl]-1,3-thiazol-2-yl}-1-ethynyl)phenyl acetate:

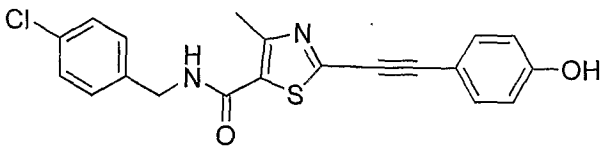
By following the similar procedure as described in step 2 of example 5 using *N*-5-[(*1S*)-1-phenylethyl]-2-iodo-4-methyl-1,3-thiazole-5-carboxamide (intermediate 4, 250 mg, 0.67 mmoles) instead of *N*-5-(2-pyridylmethyl)-2-iodo-4-methyl-1,3-thiazole-5-carboxamide to get 330 mg of the desired product. ^{1}H NMR ($CDCl_3$) δ 7.57 (d, J = 8.4 Hz, 2H); 7.40-7.25 (m, 5H); 7.10 (d, J = 8.7 Hz, 2H); 5.95 (d, J = 7.2 Hz, 1H); 5.25 (p, J = 7.2 Hz, 1H); 2.69 (s, 3H); 2.31 (s, 3H), 1.61 (d, J = 6.9 Hz, 3H).

Step 2: *N*-5-[(*1S*)-1-phenylethyl]-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-methyl-1,3-thiazole-5-carboxamide:

By following the similar procedure as described in step 3 example 5 using 4-[2-{4-Methyl-5-[(1*S*)-1-phenylethylcarbamoyl]-1,3-thiazol-2-yl}-1-ethynyl)phenyl acetate (80 mg, 0.2 mmoles) to get 45 mg of the desired product. ^{1}H NMR ($CDCl_3$) δ 7.40 (d, J = 8.1 Hz, 2H); 7.39-7.28 (m, 5H); 6.82 (d, J = 8.1 Hz, 2H); 6.16 (s, 1H); 5.98 (d, J = 8.1 Hz, 1H), 5.25 (p, J = 6.9 Hz,1H); 2.68 (s, 3H); 1.60 (d, J = 6.3Hz, 3H); MS (*m/z*): 363.33$(M+H)^+$.

Example 11

N-(4-Chlorobenzyl)-2-[(4-hydroxyphenyl)ethynyl]-4-methyl-1,3-thiazole-5-carboxamide:



Step 1: 4-[(5-{[(4-Chlorobenzyl)amino]carbonyl}-4-methyl-1,3-thiazol-2-yl)ethynyl]phenyl acetate:

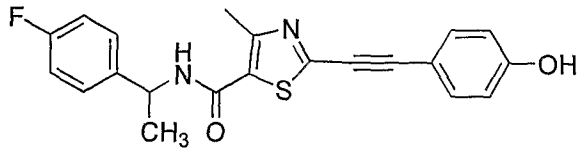
By following the similar procedure as described in step 2 of example 5 using intermediate 5 (200 mg, 0.51 mmoles), to get 70 mg of the desired product. ^{1}H NMR ($CDCl_3$) δ 8.92 (m,1H); 7.71 (d, 1H, J = 8.1Hz); 7.39 (d, 1H, J = 8.1Hz); 7.32(d, 2H, J = 8.4 Hz); 7.25 (d, 2H, J = 9.0 Hz); 4.41 (d, 1H, J = 5.7 Hz) 2.58 (s, 3H); 2.29(s, 2H).

Step 2: *N*-(4-Chlorobenzyl)-2-[(4-hydroxyphenyl)ethynyl]-4-methyl-1,3-thiazole-5-carboxamide:

By following the similar procedure as described in step 3 of example 5 using 4-[(5-{[(4-Chlorobenzyl)amino]carbonyl}-4-methyl-1,3-thiazol-2-yl)ethynyl]phenyl acetate (50 mg, 0.118 mmoles) to get 14 mg of the desired product. ^{1}H NMR ($CDCl_3$) δ 10.20 (s, 1H); 8.87 (m,1H); 7.47 (d, 2H, J = 8.4 Hz); 7.38 (d, 2H, J =8.4 Hz); 7.31(d, 2H, J = 7.8 Hz); 6.82 (d, 2H, J = 9.0 Hz); 4.40 (d, 2H, J = 5.4 Hz); 2.56 (s, 3H); MS (*m/z*): 383.54 $(M+H)^+$.

Example 12

N-[1-(4-Fluorophenyl)ethyl]-2-[(4-hydroxyphenyl)ethynyl]-4-methyl-1,3-thiazole-5-carboxamide:



Step 1: 4-{[5-({[1-(4-Fluorophenyl)ethyl]amino}carbonyl)-4-methyl-1,3-thiazol-2-yl] ethynyl}phenylacetate:

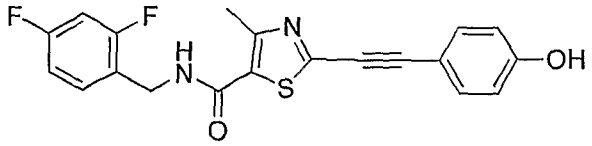
By following the similar procedure as described in step 2 of example 5, using intermediate 6 (200 mg, 0.51 mmoles) to get 165 mg of the desired product. ^{1}H NMR ($CDCl_3$) δ 8.79 (d, 1H, J=7.2 Hz); 7.70 (d, 2H, J=7.2 Hz); 7.37-7.42 (m, 2H); 7.24 (d, 2H, J=8.1 Hz); 7.14 (t, 2H, J =17.7 Hz); 5.07 (m, 1H); 2.54 (s, 3H); 2.29 (s, 3H); 1.44(d, 3H, J=7.5 Hz)

Step 2: *N*-[1-(4-Fluorophenyl)ethyl]-2-[(4-hydroxyphenyl)ethynyl]-4-methyl-1,3-thiazole-5-carboxamide:

By following the similar procedure as described in step 3 of example 5 using 4-{[5-({[1-(4-fluorophenyl)ethyl]amino}carbonyl)-4-methyl-1,3-thiazol-2-yl]ethynyl}phenylacetate (50 mg, 0.12 mmoles) to get 14 mg of the desired product. ^{1}H NMR ($CDCl_3$) δ 10.20 (s, 1H); 8.74 (d, 1H, J=7.8 Hz); 7.47-7.41 (m, 4H); 7.14 (t, 2H, J=17.4 Hz); 6.81(d, 2H, J = 8.4 Hz); 5.09 – 5.05 (m, 1H); 2.52 (s, 3H); 1.44(d, 3H, J=6.6 Hz); MS (*m/z*):382.45$(M+H)^+$.

Example 13

N-(2,4-Difluorobenzyl)-2-[(4-hydroxyphenyl)ethynyl]-4-methyl-1,3-thiazole-5-carboxamide:



Step 1: 4-[(5-{[(2,4-Difluorobenzyl)amino]carbonyl}-4-methyl-1,3-thiazol-2-yl)ethynyl] phenylacetate:

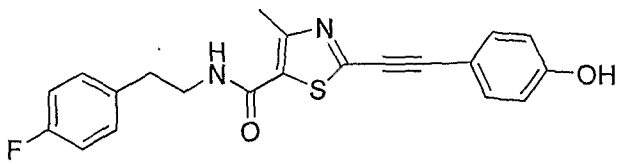
By following the similar procedure as described in step 2 of example 5, using intermediate 7 (100 mg, 0.25 mmoles) to get 28 mg of the desired product. ^{1}H NMR ($CDCl_3$) δ 8.90 (t, 1H); 7.71 (d, 2H, J = 8.4 Hz); 7.42-7.40 (m,1H); 7.24 (d, 3H, J = 8.4 Hz); 7.06 (t, 1H); 4.42 (d, 2H); 2.57(s, 1H); 2.29 (s, 1H)

Step 2: *N*-(2,4-difluorobenzyl)-2-[(4-hydroxyphenyl)ethynyl]-4-methyl-1,3-thiazole-5-carboxamide:

By following the similar procedure as described in step 3 of example 5 using 4-[(5-{[(2,4-difluorobenzyl)amino]carbonyl}-4-methyl-1,3-thiazol-2-yl)ethynyl]phenylacetate (23 mg, 0.054 mmoles) to get 9 mg of the desired product. ^{1}H NMR ($CDCl_3$) δ 10.21 (s,1H); 8.84 (t, 1H); 7.47-7.39 (m, 3H); 7.21 (t, 1H, J = 20.1Hz); 7.07(t, 1H, J = 7.5Hz); 6.82 (d, 2H, J = 8.4 Hz); 4.41 (d, 2H, J = 4.8 Hz); 2.55(s, 3H).

Example 14

N-[2-(4-Fluorophenyl)ethyl]-2-[(4-hydroxyphenyl)ethynyl]-4-methyl-1,3-thiazole-5-carboxamide:



Step 1: 4-{[5-({[2-(4-Fluorophenyl)ethyl]amino}carbonyl)-4-methyl-1,3-thiazol-2-yl] ethynyl}phenylacetate:

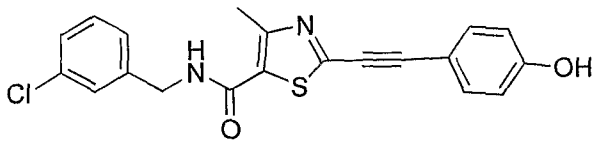
By following the similar procedure as described in step 2 of example 5 using intermediate 8 (150 mg, 0.38 mmoles) to get 85 mg of the desired product. ^{1}H NMR ($CDCl_3$)δ 8.41(t, 1H); 7.70 (d, 2H, J = 8.4 Hz); 7.25 (m, 4H); 7.10(t, 1H, J = 17.7 Hz); 3.43 (m, 2H); 2.81 (t, 2H, J = 14.1 Hz); 2.29 (s, 3H).

Step 2: *N*-[2-(4-Fluorophenyl)ethyl]-2-[(4-hydroxyphenyl)ethynyl]-4-methyl-1,3-thiazole-5-carboxamide:

By following the similar procedure as described in step 3 of example 5 using 4-{[5-({[2-(4-fluorophenyl)ethyl]amino}carbonyl)-4-methyl-1,3-thiazol-2-yl]ethynyl}phenylacetate (80 mg, 0.19 mmoles) to get 21 mg of the desired product. ^{1}H NMR ($CDCl_3$) δ 10.21 (s, 1H); 8.35 (t, 1H); 7.46 (d, J = 8.4 Hz, 2H), 7.27-7.22 (m, 2H); 7.07(t, 2H, J = 7.5 Hz); 6.82 (d, 2H, J = 8.7 Hz); 3.44-3.42 (m, 2H); 2.81 (t, 2H, J = 13 Hz), 2.62 (s, 3H); MS (*m/z*): 382.82 $(M+H)^{+.}$

Example 15

N-(3-Chlorobenzyl)-2-[(4-hydroxyphenyl)ethynyl]-4-methyl-1,3-thiazole-5-carboxamide:



Step 1: 4-[(5-{[(3-Chlorobenzyl)amino]carbonyl}-4-methyl-1,3-thiazol-2-yl)ethynyl]phenyl acetate:

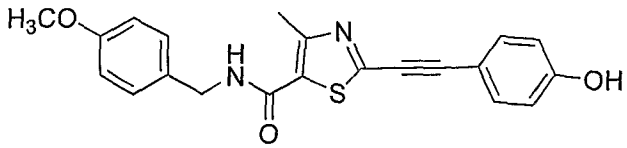
By following the similar procedure as described in step 2 example 5 using intermediate 9 (150 mg, 0.38 mmoles) to get 90 mg of the desired product. ^{1}H NMR ($CDCl_3$) δ 8.94 (t, 1H, J = 12.0 Hz); 7.71 (d, 2H, J = 9.0 Hz); 739-7.24 (m, 6H); 4.43(d, 2H, J = 5.4 Hz); 2.60 (s, 3H); 2.29 (s, 3H).

Step 2: *N*-(3-Chlorobenzyl)-2-[(4-hydroxyphenyl)ethynyl]-4-methyl-1,3-thiazole-5-carboxamide:

By following the similar procedure as described in step 3 of example 5 using 4-[(5-{[(3-chlorobenzyl)amino]carbonyl}-4-methyl-1,3-thiazol-2-yl)ethynyl]phenyl acetate (50 mg, 0.118 mmoles) to get 21 mg of the desired product. ^{1}H NMR ($CDCl_3$) δ 10.22 (s,1H); 8.88 (t, 1H, J = 11.7 Hz); 7.47 (d, 2H, J = 8.7 Hz); 7.39-7.25 (m, 4H); 6.83 (d, 2H, J = 8.7 Hz); 4.42 (d, 2H, J = 5.1 Hz); 2.57 (s, 3H); MS (*m/z*): 383.66 $(M+H)^+$.

Example 16

2-[(4-Hydroxyphenyl)ethynyl]-*N*-(4-methoxybenzyl)-4-methyl-1,3-thiazole-5-carboxamide:



Step 1: 4-[(5-{[(3-Chlorobenzyl)amino]carbonyl}-4-methyl-1,3-thiazol-2-yl)ethynyl]phenyl acetate:

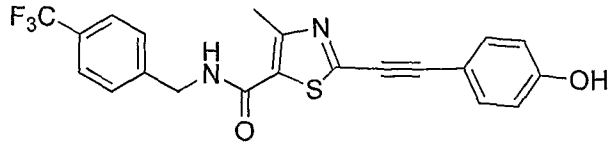
By following the similar procedure as described in step 2 of example 5 using intermediate 10 (150 mg, 0.386 mmoles) to get 55 mg of the desired product. ^{1}H NMR ($CDCl_3$) δ 8.85 (t, 1H); 7.70 (d, 2H, J = 8.7 Hz); 7.24 (t, 2H, J = 14.1 Hz); 6.88 (d, 2H, J = 8.7 Hz); 4.35(d, 2H, J = 6.0 Hz); 3.72 (s, 3H); 2.57 (s, 3H); 2.29 (s,3H)

Step 2: 2-[(4-Hydroxyphenyl)ethynyl]-*N*-(4-methoxybenzyl)-4-methyl-1,3-thiazole-5-carboxamide:

By following the similar procedure as described in step 3 of example 5 using 4-[(5-{[(4-methoxybenzyl)amino]carbonyl}-4-methyl-1,3-thiazol-2-yl)ethynyl]phenyl acetate (50 mg, 0.119 mmoles) to get 24 mg of the desired product. ^{1}H NMR ($CDCl_3$) δ 10.22 (s,1H); 8.80-8.78 (m, 1H); 7.47(d, 2H, J = 8.1 Hz); 7.22 (d, 2H, J = 8.4 Hz); 6.88-6.81 (m, 4H); 4.34 (d, 2H, J = 5.4 Hz); 3.72 (s, 3H); 2.55 (s,3H).

Example 17

2-[(4-Hydroxyphenyl)ethynyl]-4-methyl-*N*-[4-(trifluoromethyl)benzyl]-1,3-thiazole-5-carbox amide:



Step 1: 4-{[4-Methyl-5-({[4-(trifluoromethyl)benzyl]amino}carbonyl)-1,3-thiazol-2-yl] ethynyl}phenylacetate:

By following the similar procedure as described in step 2 of example 5 using intermediate 11 (100 mg, 0.23 mmoles) to get 55 mg of the desired product. ^{1}H NMR ($CDCl_3$) δ 8.99 (t, 1H); 7.72-7.68 (m,4H); 7.52 (d, 2H, J = 8.4 Hz); 7.25 (d, 2H, J = 8.4 Hz); 4.51(d, 2H, J = 5.1 Hz); 2.60 (s, 3H); 2.29 (s,3H); MS (*m/z*): 459.34 $(M+H)^+$.

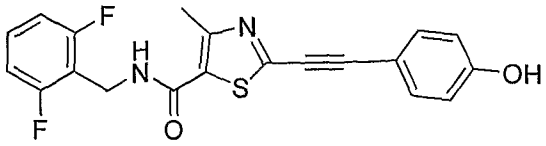
Step 2: 2-[(4-Hydroxyphenyl)ethynyl]-4-methyl-*N*-[4-(trifluoromethyl) benzyl]-1,3-thiazole-5-carboxamide:

By following the similar procedure as described in step 3 of example 5, using 4-{[4-Methyl-5-({[4-(trifluoromethyl)benzyl]amino}carbonyl)-1,3-thiazol-2-yl] ethynyl}phenylacetate (50 mg, 0.11 mmoles) to get 14 mg of the desired product. ^{1}H NMR ($CDCl_3$) δ 10.23 (s,1H);

8.93 (t, 1H, J = 6.0 Hz); 7.69 (d, 2H, J = 8.1 Hz); 7.53-7.46 (m,4H); 6.83 (d, 2H, J = 8.7 Hz); 4.50 (d, 2H, J = 5.1Hz); 2.58 (s, 3H).

Example 18

N-(2,6-Difluorobenzyl)-2-[(4-hydroxyphenyl)ethynyl]-4-methyl-1,3-thiazole-5-carboxamide:



Step 1: 4-[(5-{[(2,6-Difluorobenzyl)amino]carbonyl}-4-methyl-1,3-thiazol-2-yl)ethynyl] phenylacetate:

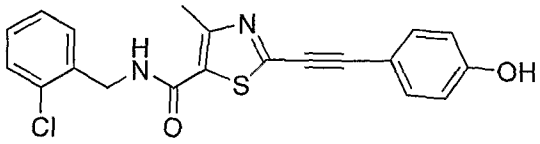
By following the similar procedure as described in step 2 example 5 using intermediate 12 (150 mg, 0.38 mmoles) to get 60 mg of the desired product. ^{1}H NMR ($CDCl_3$) δ 8.87 (t, 1H, J = 6.0 Hz); 7.70 (d, 2H, J = 8.4 Hz); 7.37-7.41 (m, 1H); 7.24(d, 2H, J = 9.0 Hz); 7.09 (t, 2H, J = 15.6 Hz); 4.48 (d, 2H, J = 5.1 Hz); 2.53 (s, 3H); 2.29 (s, 3H).

Step 2: *N*-(2,6-Difluorobenzyl)-2-[(4-hydroxyphenyl)ethynyl]-4-methyl-1,3-thiazole-5-carboxamide:

By following the similar procedure as described in step 3 of example 5 using 4-[(5-{[(2,6-difluorobenzyl)amino]carbonyl}-4-methyl-1,3-thiazol-2-yl)ethynyl]phenylacetate (50mg, 0.18 mmoles) to get 30 mg of the desired product. ^{1}H NMR ($CDCl_3$) δ 10.22 (s,1H); 8.79-8.81 (m, 1H); 7.46 (d, 2H, J = 8.1 Hz); 7.41-7.36 (m, 1H); 7.08 (t, 2H, J = 15.6 Hz); 6.82 (d, 2H, J = 8.4 Hz); 4.47 (d, 2H, J = 4.8 Hz); 2.50 (s, 3H).

Example 19

N-(2-Chlorobenzyl)-2-[(4-hydroxyphenyl)ethynyl]-4-methyl-1,3-thiazole-5-carboxamide:



Step1: 4-[(5-{[(2-Chlorobenzyl)amino]carbonyl}-4-methyl-1,3-thiazol-2-yl)ethynyl]phenyl acetate:

By following the similar procedure as described in step 2 of example 5 using intermediate 13 (200 mg, 0.51 mmoles) to get 80 mg of the desired product. ^{1}H NMR ($CDCl_3$) δ 8.92 (br s,

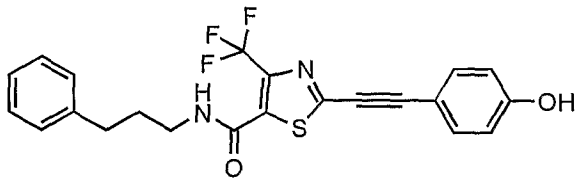
1H); 7.71 (d, J = 8.4 Hz, 2H); 7. 45 (d, J = 6.9 Hz, 1H); 7.40-7.30 (m, 3H); 7.25 (d, J = 8.7 Hz, 2H); 4.49 (d, J = 5.4 Hz, 2H); 2.60 (s, 3H); 2.29 (s, 3H).

Step 2: *N*-(2-Chlorobenzyl)-2-[(4-hydroxyphenyl)ethynyl]-4-methyl-1,3-thiazole-5-carboxamide:

By following the similar procedure as described in step 3 of example 5 using 4-[(5-{[(2-Chlorobenzyl)amino]carbonyl}-4-methyl-1,3-thiazol-2-yl)ethynyl]phenyl acetate (60 mg, 0.14 mmoles) to get 27 mg of the desired product. ^{1}H NMR (DMSO-d_6) δ 10.23 (s,1H); 8. 85 (br s,1H); 7.55-7.45 (m, 3H); 7.35-7.25 (m, 3H); 6.83 (d, J = 8.4 Hz, 2H); 4.49 (d, J = 5.4 Hz, 2H); 2.58 (s, 3H); MS (*m/z*); 383.56$(M+H)^+$.

Example 20

N-5-(3-Phenylpropyl)-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-trifluoromethyl-1,3-thiazole-5-carboxamide:



Step 1: 4-{2-[5-(3-Phenylpropylcarbamoyl)-4-trifluoromethyl-1,3-thiazol-2-yl]-1-ethynyl}-phenylacetate:

To a solution of 2-iodo-*N*-(3-phenylpropyl)-4-(trifluoromethyl)-1,3-thiazole-5- carboxamide (intermediate 23, 100 mg, 0.227 mmoles) in dry DMSO (4 mL) was added 4-(1-ethynyl)phenylacetate (intermediate 16, 1 eq) followed by copper iodide (0.04 eq), tetrakis tripheylphosphine palladium(0) (0.03 eq) and triethylamine (3 eq) and the reaction mixture was stirred at room temperature for overnight. The reaction mixture was then diluted with ethyl acetate (30 mL), washed with water (2 x 20 mL), dried over Na_2SO_4 and concentrated. The crude was then purified by column chromatography to get 85 mg of the title product. ^{1}H NMR (DMSO-d_6) δ 9.06 (br s, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.30-7.15 (m, 7H), 3.30-3.20 (m, 2H), 2.61 (t, J = 6.9 Hz, 2H), 2.29 (s, 3H), 1.78 (m, 2H). MS (*m/z*); 473.57 $(M+H)^+$.

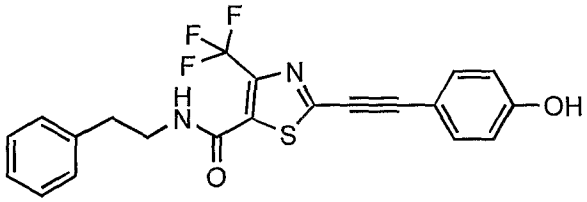
Step 2: *N*-5-(3-Phenylpropyl)-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-trifluoromethyl-1,3-thiazole-5-carboxamide:

To a solution of 4-{2-[5-(3-Phenylpropylcarbamoyl)-4-trifluoromethyl-1,3-thiazol-2-yl]-1-ethynyl}phenylacetate (70 mg, 0.15 mmoles) in a mixture of THF, methanol and water

(3:2:1, 6 mL respectively) was added lithium hydroxide hydrate (2 eq) and stirred the reaction mixture at room temperature for 4 h. Evaporated the solvent and the obtained residue was neutralized with 1N HCl and extracted with ethyl acetate. The organic layer was then dried over Na_2SO_4, concentrated and purified through column chromatography to get 40 mg of the desired product. ^{1}H NMR (DMSO-d_6) δ 10.31 (s, 1H), 9.03 (br s, 1H), 7.53 (d, J = 8.4 Hz, 2H), 7.30-7.15 (m, 5H), 6.84 (d, J = 8.1 Hz, 2H), 3.30-3.20 (m, 2H), 2.60 (t, J = 8.4 Hz 2H), 1.85-1.75 (m, 2H).

Example 21

N-5-Phenethyl-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-trifluoromethyl-1,3-thiazole-5-carboxamide:



Step 1: 4-[2-(5-Phenethylcarbamoyl-4-trifluoromethyl-1,3-thiazol-2-yl)-1-ethynyl]-phenyl acetate:

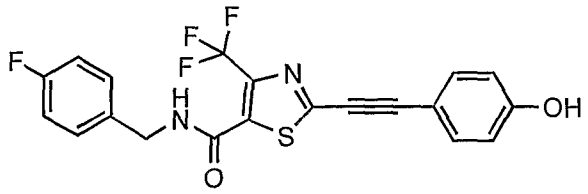
By following the similar procedure as described in step 1 of example 20, using 2-iodo-*N*-(2-phenylethyl)-4-(trifluoromethyl)-1,3-thiazole-5-carboxamide (intermediate 24, 160 mg, 0.37 mmoles) instead of 2-iodo-*N*-(3-phenylpropyl)-4-(trifluoromethyl)-1,3-thiazole-5-carboxamide to get 0.16 g of the desired product. ^{1}H NMR (DMSO-d_6) δ 9.08 (t, J = 5.4 Hz, 1H), 7.77 (d, J = 8.7 Hz, 2H), 7.35-7.17 (m, 7H), 3.50-3.44 (q, J = 6.9 Hz, 2H), 2.81 (t, J = 7.2 Hz 2H), 2.29 (s, 3H); MS (*m/z*); 459.27 $(M+H)^+$.

Step 2: *N*-5-Phenethyl-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-trifluoromethyl-1,3-thiazole-5-carboxamide:

By following the similar procedure as described in step 2 of example 20, using 4-[2-(5-phenethylcarbamoyl-4-trifluoromethyl-1,3-thiazol-2-yl)-1-ethynyl]-phenylacetate (60 mg, 0.131 mmoles) instead of 4-{2-[5-(3-phenylpropylcarbamoyl)-4-trifluoromethyl-1,3-thiazol-2-yl]-1-ethynyl}-phenyl acetate to get 35 mg of the title compound. ^{1}H NMR (DMSO-d_6) δ 10.32 (s, 1H), 9.06 (br s, 1H), 7.53 (d, J = 8.1 Hz, 2H), 7.35-7.20 (m, 5H), 6.85 (d, J = 8.4 Hz, 2H), 3.50-3.42 (q, J = 6.9 Hz, 2H), 2.80 (t, J = 7.2 Hz, 2H); MS (*m/z*): 417.17 $(M+H)^+$.

Example 22

N-5-(4-Fluorobenzyl)-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-trifluoromethyl-1,3-thiazole-5-carboxamide:



Step 1: 4-{2-[5-(4-Fluorobenzylcarbamoyl)-4-trifluoromethyl-1,3-thiazol-2-yl]-1-ethynyl}-phenylacetate:

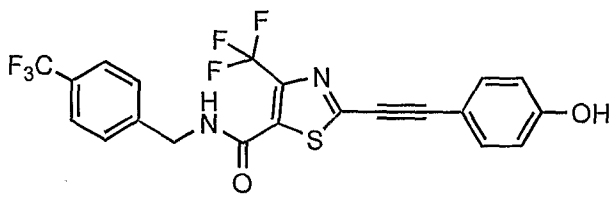
By following the similar procedure as described in step 1 of example 20 using 2-iodo-*N*-(4-fluorobenzyl)-4-(trifluoromethyl)-1,3-thiazole-5-carboxamide (intermediate 25, 100 mg, 0.23 mmoles) instead of 2-iodo-*N*-(3-phenylpropyl)-4-(trifluoromethyl)-1,3-thiazole-5-carboxamide to get 0.14 g of the desired product. ^{1}H NMR (DMSO-d_6) δ 9.52 (br s, 1H), 7.77 (d, J = 8.7 Hz, 2H), 7.40-7.30 (m, 2H), 7.28 (d, J = 9.0 Hz, 2H), 7.20-7.10 (m, 2H), 4.43 (d, J = 5.4 Hz, 2H), 2.29 (s, 3H); MS (*m/z*): 462.94 $(M)^+$.

Step 2: *N*5-(4-Fluorobenzyl)-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-trifluoromethyl-1,3-thiazole-5-carboxamide:

By following the similar procedure as described in step 2 of example 20 using 4-{2-[5-(4-fluorobenzylcarbamoyl)-4-trifluoromethyl-1,3-thiazol-2-yl]-1-ethynyl}-phenylacetate (60 mg, 0.13 mmoles) instead of 4-{2-[5-(3-phenylpropylcarbamoyl)-4-trifluoromethyl-1,3-thiazol-2-yl]-1-ethynyl}-phenyl acetate to get 35 mg of the title compound. ^{1}H NMR (DMSO-d_6) δ 10.30 (s, 1H), 9.50 (br s, 1H), 7.53 (d, J = 8.1 Hz, 2H), 7.40-7.30 (m, 2H), 7.20-7.10 (m, 2H), 6.84 (d, J = 8.7 Hz, 2H), 4.43 (d, J = 5.7 Hz, 2H); MS (*m/z*): 421.15 $(M+H)^+$.

Example 23

N-5-(4-Trifluoromethylbenzyl)-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-trifluoromethyl-1,3-thiazole-5-carboxamide:



Step 1: 4-{2-[4-Trifluoromethyl-5-(4-trifluoromethylbenzylcarbamoyl)-1,3-thiazol-2-yl]-1-ethynyl}-phenylacetate:

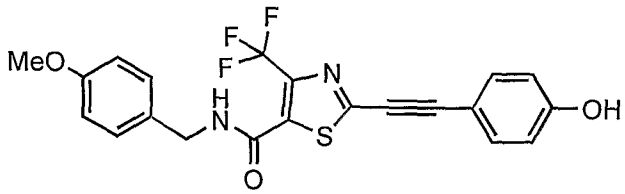
By following the similar procedure as described in step 1 of example 20 using 2-iodo-*N*-(4-trifluoromethylbenzyl)-4-(trifluoromethyl)-1,3-thiazole-5-carboxamide (intermediate 26, 150 mg, 0.31 mmoles) instead of 2-iodo-*N*-(3-phenylpropyl)-4-(trifluoromethyl)-1,3-thiazole-5-carboxamide to get 0.20 g of the desired product. ^{1}H NMR (DMSO-d_6) δ 9.61 (s, 1H), 7.76 (d, J = 8.7 Hz, 2H), 7.72 (d, J = 7.8 Hz, 2H), 7.51 (d, J = 7.8 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 4.54 (d, J = 6.0 Hz, 2H), 2.29 (s, 3H); MS (*m/z*): 513.14 $(M+H)^+$.

Step 2: *N*-5-(4-Trifluoromethylbenzyl)-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-trifluoromethyl-1,3-thiazole-5-carboxamide:

By following the similar procedure as described in step 2 of example 20, using 4-{2-[4-trifluoromethyl-5-(4-trifluoromethylbenzylcarbamoyl)-1,3-thiazol-2-yl]-1-ethynyl}-phenyl acetate (50 mg, 0.098 mmoles) instead of 4-{2-[5-(3-phenylpropylcarbamoyl)-4-trifluoromethyl-1,3-thiazol-2-yl]-1-ethynyl}-phenyl acetate to get 35 mg of the title compound. ^{1}H NMR (DMSO-d_6) δ 10.30 (s, 1H), 9.58 (br s, 1H), 7.71 (d, J = 7.2 Hz, 2H), 7.60-7.50 (m, 4H), 6.84 (d, J = 8.4 Hz, 2H), 4.53 (d, J = 6.9 Hz, 2H). MS (*m/z*): 471.19 $(M+H)^+$.

Example 24

N-5-(4-Methoxybenzyl)-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-trifluoromethyl-1,3-thiazole-5-carboxamide:



Step 1: 4-{2-[5-(4-Methoxybenzylcarbamoyl)-4-trifluoromethyl-1,3-thiazol-2-yl]-1-ethynyl}-phenylacetate:

By following the similar procedure as described in step 1 of example 20 using 2-iodo-*N*-(4-methoxybenzyl)-4-(trifluoromethyl)-1,3-thiazole-5-carboxamide (intermediate 27, 130 mg, 0.29 mmoles) instead of 2-iodo-*N*-(3-phenylpropyl)-4-(trifluoromethyl)-1,3-thiazole-5-carboxamide to get 0.17 g of the desired product. ^{1}H NMR (DMSO-d_6) δ 9.44 (br s, 1H), 7.76

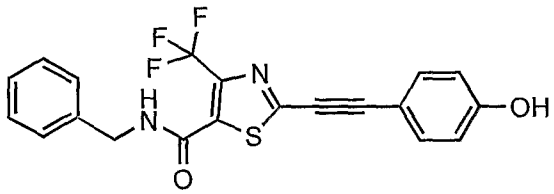
(d, J = 8.4 Hz, 2H), 7.27 (d, J = 9.0 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.1 Hz, 2H), 4.37 (d, J = 4.5 Hz, 2H), 3.73 (s, 3H), 2.29 (s, 3H). MS (*m/z*): 475.28 $(M+H)^+$.

Step 2: *N*-5-(4-methoxybenzyl)-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-trifluoromethyl-1,3-thiazole-5-carboxamide:

By following the similar procedure as described in step 2 of example 20, using 4-{2-[5-(4-methoxybenzylcarbamoyl)-4-trifluoromethyl-1,3-thiazol-2-yl]-1-ethynyl}-phenylacetate (60 mg, 0.126 mmoles) instead of 4-{2-[5-(3-Phenylpropylcarbamoyl)-4-trifluoromethyl-1,3-thiazol-2-yl]-1-ethynyl}-phenylacetate to get 30 mg of the title compound. ^{1}H NMR (DMSO-d_6) δ 10.30 (s, 1H), 9.41 (br s, 1H), 7.52 (d, J = 8.1 Hz, 2H), 7.21 (d, J = 8.1 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 4.36 (d, J = 6.0 Hz, 2H), 3.73 (s, 3H). MS (*m/z*): 433.42 $(M+H)^+$.

Example 25

N-5-Benzyl-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-trifluoromethyl-1,3-thiazole-5-carboxamide:



Step 1: 4-{2-[5-(Benzylcarbamoyl)-4-trifluoromethyl-1,3-thiazol-2-yl]-1-ethynyl}-phenyl acetate:

By following the similar procedure as described in step 1 of example 20 using 2-iodo-*N*-benzyl-4-(trifluoromethyl)-1,3-thiazole-5-carboxamide (intermediate 28, 150 mg, 0.36 mmoles) instead of 2-iodo-*N*-(3-phenylpropyl)-4-(trifluoromethyl)-1,3-thiazole-5-carboxamide to get 0.17 g of the desired product. ^{1}H NMR (DMSO-d_6) δ 9.52 (br s, 1H), 7.76 (d, J = 8.7 Hz, 2H), 7.35-7.20 (m, 7H), 4.45 (d, J = 6.0 Hz, 2H), 2.29 (s, 3H).

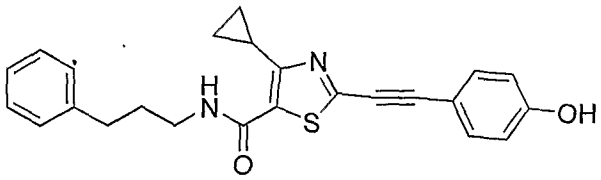
Step 2: *N*-5-Benzyl-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-trifluoromethyl-1,3-thiazole-5-carboxamide:

By following the similar procedure as described in step 2 of example 20 using 4-{2-[5-(benzylcarbamoyl)-4-trifluoromethyl-1,3-thiazol-2-yl]-1-ethynyl}-phenylacetate (60 mg, 0.135 mmoles) instead of 4-{2-[5-(3-Phenylpropylcarbamoyl)-4-trifluoromethyl-1,3-thiazol-2-yl]-1-ethynyl}-phenyl acetate to get 30 mg of the title compound. ^{1}H NMR (DMSO-d_6) δ

10.32 (s, 1H), 9.50 (t, J = 5.4 Hz, 1H), 7.53 (d, J = 8.1 Hz, 2H), 7.35-7.20 (m, 5H), 6.84 (d, J = 8.1 Hz, 2H), 4.44 (d, J = 6.0 Hz, 2H).

Example 26

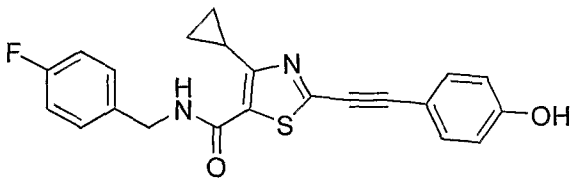
4-Cyclopropyl-2-[(4-hydroxyphenyl) ethynyl]-*N*-phenyl propyl-1,3-thiazole-5-carboxamide:



To a solution of intermediate 29 (100 mg, 0.35 mmoles) in THF, was added DIPEA (3 eq), DMAP (0.1 eq), HOBT (1 eq) and EDCI (1.5 eq). Then 3-phenyl propylamine (1 eq) was added and stirred the reaction mixture for 12 h at room temperature. The reaction mixture was then quenched in water, extracted with ethyl acetate and concentrated to get 22 mg of desired product. ^{1}H NMR (DMSO-d_6) δ 10.19 (s,1H); 8.36 (s,1H); 7.44 (d, 2H, J = 7.8 Hz); 7.15-7.26 (m, 5H); 6.82 (d, 2H, J = 7.8 Hz); 3.23 (m, 2H); 2.73 (m, 1H); 2.60 (t, 2H); 1.81 (m, 2H); 1.00 (m, 2H); 0.94 (m, 2H).

Example 27

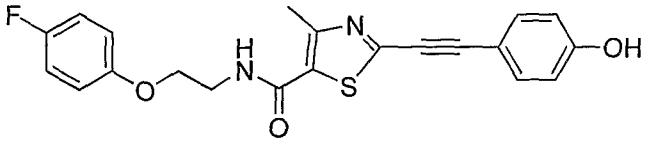
4-Cyclopropyl-*N*-(4-fluorobenzyl)-2-[(4-hydroxyphenyl)ethynyl]-1,3-thiazole-5-carboxamide:



The title compound was prepared by following the similar procedure as described in example 26 by using intermediate-29 (100 mg, 0.35 mmoles) and 4-fluoro benzylamine (1 eq) to get 20 mg of the desired product. ^{1}H NMR (DMSO-d_6) δ 10.21(s, 1H); 8.89 (t, 1H); 7.45 (d, 2H, J = 8.7 Hz); 7.31 (t, 2H, J = 6.0 Hz); 7.14 (t, 2H, J = 17.7 Hz); 6.82 (d, 2H, J = 8.7 Hz); 4.38 (d, 2H, J = 5.7 Hz); 2.80 (m,1H); 1.01 (m, 2H); 0.95 (m, 2H)

Example 28

N-[2-(4-Fluorophenoxy)ethyl]-2-[(4-hydroxyphenyl)ethynyl]-4-methyl-1,3-thiazole-5-carboxamide:



a) 4-{[5-({[2-(4-fluorophenoxy)ethyl]amino}carbonyl)-4-methyl-1,3-thiazol-2-yl]ethynyl} phenylacetate:

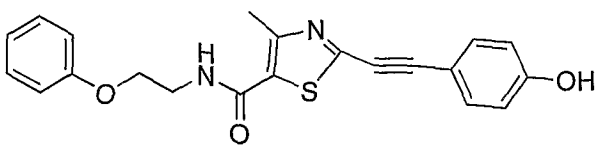
To the solution of intermediate 30 (150 mg, 0.37 mmoles) in DMSO was added CuI and $Pd(pph_3)_4$ and TEA followed by addition of 4-ethynylphenylacetate and stirred the reaction mixture at room temperature for 6 h. Then quenched the reaction mixture in ice cold water and extracted with ethyl acetate then the organic layer was dried over anhydrous sodium sulphate and concentrated to get crude product which was further purified by column chromatography to get 100 mg of the desired product. ^{1}H NMR ($CDCl_3$) δ 8.57 (t, 1H); 7.70 (d, 2H, J = 8.4 Hz); 7.24 (d, 2H, J = 8.1Hz); 7.13 (m, 2H); 6.94 (m, 2H); 4.07 (t, 2H, J = 10.8 Hz); 3.57 (d, 2H, J = 5.1Hz); 2.56 (s, 3H); 2.29 (s, 3H).

b) *N*-[2-(4-Fluorophenoxy)ethyl]-2-[(4-hydroxyphenyl)ethynyl]-4-methyl-1,3-thiazole-5-carboxamide:

To the solution of 4-{[5-({[2-(4-fluorophenoxy)ethyl]amino}carbonyl)-4-methyl-1,3-thiazol-2-yl]ethynyl}phenylacetate (80 mg, 0.18 mmoles) in THF, water and methanol was added $LiOH.H_2O$. Stirred the reaction mixture for 2 h at room temperature. Then solvent was distilled out and acidified with dilute HCl and extracted with ethyl acetate. Then the organic layer was dried over Na_2SO_4 and concentrated to get crude product which was purified by column chromatography to get 50 mg of the desired compound. ^{1}H NMR ($CDCl_3$) δ 10.23 (br s, 1H); 8.53 (t, 1H); 7.46 (d, 2H, J = 8.4 Hz); 7.09 (m, 2H); 6.96 (m, 2H); 6.82 (m, 2H); 4.07 (s, 2H); 3.58 (m, 2H); 2.55 (s, 3H); MS (*m/z*):397.21$(M+H)^+$.

Example 29

2-[(4-Hydroxyphenyl)ethynyl]-4-methyl-*N*-(2-phenoxyethyl)-1,3-thiazole-5-carboxamide:



a) 4-[(4-Methyl-5-{[(2-phenoxyethyl)amino]carbonyl}-1,3-thiazol-2-yl)ethynyl]phenyl acetate:

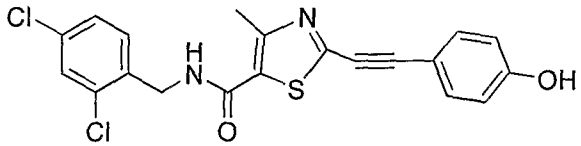
The title compound was prepared by following the similar procedure as described in step 'a' of example 28 using intermediate 31 (160 mg, 0.41 mmoles) to get 100 mg of the desired compound. ^{1}H NMR ($CDCl_3$) δ 8.58 (t, 1H); 7.70 (d, 2H, J=8.4 Hz); 7.26 (m, 4H); 6.92 (m, 3H); 4.09 (t, 2H, J= 9.0 Hz); 3.59 (m, 2H); 2.57 (s, 3H); 2.29 (s, 3H).

b) 2-[(4-Hydroxyphenyl)ethynyl]-4-methyl-*N*-(2-phenoxyethyl)-1,3-thiazole-5-carboxamide:

This compound was prepared by following the similar procedure as described in step 'b' of example 28, using 4-[(4-methyl-5-{[(2-phenoxyethyl)amino]carbonyl}-1,3-thiazol-2-yl)ethynyl]-phenyl acetate (150 mg, 0.36 mmoles) to get 80 mg of the target compound. ^{1}H NMR ($CDCl_3$) δ 10.23 (br s, 1H); 8.54 (m, 1H); 7.47 (d, 2H, J = 8.4 Hz); 7.27 (m, 2H); 6.82 (m, 5H); 4.07-4.08 (s, 2H); 3.58 (s, 2H); 2.55 (s, 3H); MS (*m/z*):379.33 $(M+H)^+$.

Example 30

N-(2,4-Dichlorobenzyl)-2-[(4-hydroxyphenyl)ethynyl]-4-methyl-1,3-thiazole-5-carboxamide:



a) 4-[(5-{[(2,4-Dichlorobenzyl)amino]carbonyl}-4-methyl-1,3-thiazol-2-yl)ethynyl]phenyl acetate:

The title compound was prepared by following the similar procedure as described in step 2 of example 5 using intermediate 32 (200 mg, 0.47 mmoles) to get 150 mg of the desired product. ^{1}H NMR ($CDCl_3$) δ 8.93 (t, 1H); 7.69 (d, 2H, J = 8.4 Hz); 7.62 (s, 1H); 7.36-7.43 (m, 2H); 7.23 (d, 2H, J = 8.4 Hz); 7.46 (d, 2H, J = 5.4 Hz); 2.59 (s, 3H); 2.29 (s, 3H).

b) *N*-(2,4-Dichlorobenzyl)-2-[(4-hydroxyphenyl)ethynyl]-4-methyl-1,3-thiazole-5carboxamide

The title compound was prepared by following the similar procedure as described in step 3 of example 5 using 4-[(5-{[(2,4-dichlorobenzyl)amino]carbonyl}-4-methyl-1,3-thiazol-2-yl)ethynyl]phenylacetate (100 mg, 0.218 mmoles) to get 70 mg of the desired compound. ^{1}H NMR ($CDCl_3$) δ 10.23 (s, 1H); 8.78 (t, 1H); 7.61 (s, 1H); 7.46 (d, 2H, J = 8.4 Hz); 7.40-7.35 (m, 2H); 6.82 (d, 2H, J =8.1 Hz); 4.45 (d, 2H, J = 5.4 Hz); 2.57 (s, 3H); MS (*m/z*): 415.68 $(M+H)^+$.

Pharmacological activity

The general values of the compounds in treating diseases or conditions may be established in industry standard animal models for demonstrating the efficacy of compounds described herein in treating the diseases and/or conditions described herein. The compounds of the present invention may be tested for their inhibitory activity for SCD, preferable SCD1, following the procedures known to a person ordinary skill in the art. Therefore, any process for measuring the activity of SCD enzymes including, for example, mouse or human SCD enzymes, may be utilized to assay the activity of the compounds useful in the methods of the present invention in inhibiting said SCD enzymes. As example, the following protocol was employed for testing compounds of the present invention. This protocol is illustrative and is not meant to limit to the scope of the present invention.

The identification of compounds as SCD1 inhibitors was carried out using microsomal SCD1 enzyme by the method of Barbara R Talamo *et.al Analytical Biochemistry.*, (1969), 29, 300-304. In this assay the microsomal SCD1 enzyme desaturates its substrate (American Radiochemicals) Stearoyl CoA 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 preincubated in reaction buffer with the enzyme for 10 minutes at 30 °C with shaking. Reaction buffer was essentially as described by Mark G Obukowicz, *et al., JPET*, (1998), 287, 157-166, except that the $MgCl_2$, ATP (Sigma) and CoA (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. The values are as given in table 1.

The IC_{50} (nM) values of the compounds are set forth in Table 1 wherein "A" refers to an IC_{50} value of less than 100 nM, "B" refers to IC_{50} value in range of 100.01 - 250 nM, "C" refers to an IC_{50} value in range of 250.01 - 500 nM and "D" refers to an IC_{50} value of more than 500 nM.

Table 1: Compounds IC_{50} (nM) values in ranges:

Example No	% Inhibition (10 μM)	IC_{50} (nM) (In ranges)
1	82.36	D
2	99	B
3	94	D
4	77	D
5	52.8	-nd-
6	79	C
7	96.06	A
8	100	A
9	91.44	B
10	90.3	C
11	95.00	A
12	91.00	A
13	92.00	C
14	97.00	A
15	89.30	B
16	95.00	C
17	88.60	D
18	96.00	B
19	96.00	A
20	61.06	-nd-
21	43.90	-nd-
22	38.70	-nd-
23	41.00	-nd-

24	--	-nd-
25	27.60	-nd-
26	94.00	A
27	80.00	D
28	97.4	B
29	92.8	D
30	85.2	B

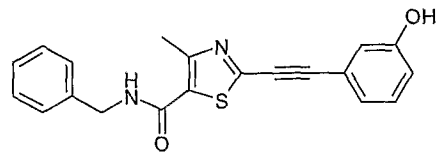
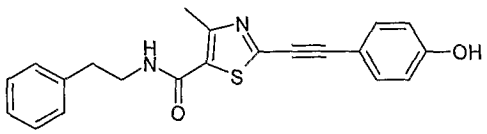
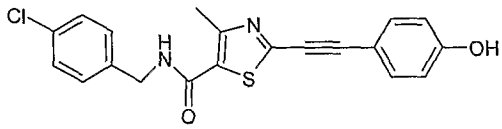
nd - not determined

Whole cell based assay to screen for agents that differentially modulate SCD-1 activity present in different tissues.

The whole cell based assay was adapted to screen for agents that differentially modulate SCD-1 activity present in different tissues. Two cell lines namely human liver cell line (hepatocellular carcinoma HepG2) and human skin cell line (epidermal carcinoma A431) were used. HepG2 cells were seeded in a 24 well plate in complete MEM medium. A431 cells were seeded in a 12 well plate in complete DMEM medium. HepG2 cells were induced with LXR agonist T0901317 in medium containing 4.5 gm/litre glucose and 0.1% fatty acid free BSA for 3 days with media change every day (Wang *et al.*, *Journal of Lipid Research.*, (2004), *45*, 972-980). A431 cells were not induced. The cells were preincubated in plain medium containing 0.1 nM to 10 μM concentrations of potential SCD-1 modulatory compounds for 15 – 30 minutes at 37 °C and further challenged with 0.25 to 7.5 μCi tritiated Stearoyl CoA. The cells were incubated for last 6 hours in 5% CO_2 incubator at 37 °C or in specific embodiments for 4 h to 30 h. At the end of the incubation, the incubation medium was collected into tubes. Dowex AG 1-X8 resin pre-equilibrated with distilled ethanol:water was added to the tubes to separate the unconsumed substrate from the labeled water. The tubes were then vortexed for 5 minutes and centrifuged at 14000 rpm for 20 minutes at room temperature. The supernatant from the tubes was mixed with the scintillation fluid and radioactivity counted in the Packard topcount scintillation counter. Counts obtained were normalized per million cells. Inhibition of enzyme activity was calculated as the percent of maximum reaction control that contained no test compound. For active compounds, EC_{35} was calculated from dose response curve by non linear regression analysis using GraphPadPRISM

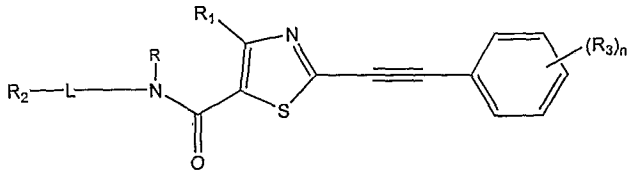
software. The ratio of EC_{35} for skin cells to EC_{35} for liver cells was calculated. The EC_{35} values for liver and skin cells along with their ratios are given in Tables 2.

Table 2: Compounds Selective For Liver Over Skin

SN	Structure	IC_{50} (nM)	hLiver EC_{35} (nM)	hSkin EC_{35} (nM)	Fold Skin: liver
1		<1000	3441	6905	2.00
2		<500	490	982	2.00
3		<100	698	> 10,000	> 15

WE CLAIM:

1. The compound of the formula (I):



or pharmaceutically acceptable salts thereof;

wherein R is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted cycloalkyl;

R_1 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted haloalkyl, fully or partially substituted haloalkyl, substituted or unsubstituted haloalkyloxy, fully or partially substituted haloalkyloxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, or substituted or unsubstituted heteroaryl;

R_2 is substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocyclyl; wherein substituents are independently selected from halogen, nitro, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkoxy, substituted or unsubstituted haloalkyl, fully or partially substituted haloalkyl, substituted or unsubstituted haloalkyloxy, fully or partially substituted haloalkyloxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, or substituted or unsubstituted heteroaryl;

at each occurrence R_3 is independently selected from hydrogen, hydroxyl, cyano, nitro, halogen, acetyl, acetoxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted haloalkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cyclcoalkylalkyl, substituted or unsubstituted cyclcoalkyloxy, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted alkoxyaryl, substituted or unsubstituted arylalkyl, –O-C(O)-R', -C(O)NR^aR^b,

$-SONR^aR^b$, $-SO_2NR^aR^b$, $-OR^a$, $-COOR^a$, $-C(O)R^a$, $-C(S)R^a$, $-C(O)ONR^aR^b$, $-NR^aC(O)OR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, or $-NR^aCONR^aR^b$;

at each occurrence R^a and R^b may be same or different and are independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heterocyclylalkyl;

R' is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocyclyl;

'n' is an integer selected from 1 to 5, both inclusive and

L is (C_1-C_6) alkylene linker which may be further substituted with halogen or alkyl.

2. The compounds according to claim 1, wherein R_1 is substituted or unsubstituted alkyl or cycloalkyl.

3. The compounds according to claim 1, wherein R_3 is hydroxyl.

4. The compounds according to claim 1, wherein R_2 is substituted or unsubstituted aryl.

5. The compounds according to claim 1, wherein L is (C_1-C_6) alkylene linker which is optionally substituted with alkyl.

6. The compound selected from:

N-5-Benzyl-2-[2-(3-hydroxyphenyl)-1-ethynyl]-4-methyl-1,3-thiazole-5-carboxamide;

N-5-Benzyl-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-methyl-1,3-thiazole-5-carboxamide;

N-5-(3-Pyridylmethyl)-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-methyl-1,3-thiazole-5-carboxamide;

N-5-(3-Pyridylmethyl)-2-[2-(3-hydroxyphenyl)-1-ethynyl]-4-methyl-1,3-thiazole-5-carboxamide;

N-5-(2-Pyridylmethyl)-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-methyl-1,3-thiazole-5-carboxamide;

2-[(4-Hydroxy phenyl) ethynyl]- 4 -methyl- *N* - (2-phenyl ethyl)-1,3thiazole-5-carboxamide;

N-(4-Fluorobenzyl)-2-[(4-hydroxyphenyl)ethynyl]-4-methyl 1,3-thiazole-5-carboxamide;

2-[(4-Hydroxyphenyl)ethynyl]-4-methyl-*N*-(3-phenylpropyl)-1,3-thiazole-5-carboxamide;

N-5-[(*1R*)-1-Phenylethyl]-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-methyl-1,3-thiazole-5-carboxamide;

N-5-[(*1S*)-1-Phenylethyl]-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-methyl-1,3-thiazole-5-carboxamide;

N-(4-Chlorobenzyl)-2-[(4-hydroxyphenyl)ethynyl]-4-methyl-1,3-thiazole-5-carboxamide;

N-[1-(4-Fluorophenyl)ethyl]-2-[(4-hydroxyphenyl)ethynyl]-4-methyl-1,3-thiazole-5-carboxamide;

N-(2,4-Difluorobenzyl)-2-[(4-hydroxyphenyl)ethynyl]-4-methyl-1,3-thiazole-5-carboxamide;

N-[2-(4-fluorophenyl)ethyl]-2-[(4-hydroxyphenyl)ethynyl]-4-methyl-1,3-thiazole-5-carboxamide;

N-(3-Chlorobenzyl)-2-[(4-hydroxyphenyl)ethynyl]-4-methyl-1,3-thiazole-5-carboxamide;

2-[(4-Hydroxyphenyl)ethynyl]-*N*-(4-methoxybenzyl)-4-methyl-1,3-thiazole-5-carboxamide;

2-[(4-Hydroxyphenyl)ethynyl]-4-methyl-*N*-[4-(trifluoromethyl)benzyl]-1,3-thiazole-5-carboxamide;

N-(2,6-Difluorobenzyl)-2-[(4-hydroxyphenyl)ethynyl]-4-methyl-1,3-thiazole-5-carboxamide;

N-(2-Chlorobenzyl)-2-[(4-hydroxyphenyl)ethynyl]-4-methyl-1,3-thiazole-5-carboxamide;

N-5-(3-Phenylpropyl)-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-trifluoromethyl-1,3-thiazole-5-carboxamide;

N-5-Phenethyl-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-trifluoromethyl-1,3-thiazole-5-carboxamide;

N-5-(4-Fluorobenzyl)-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-trifluoromethyl-1,3-thiazole-5-carboxamide;

N-5-(4-Trifluoromethylbenzyl)-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-trifluoromethyl-1,3-thiazole-5-carboxamide;

N-5-(4-Methoxybenzyl)-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-trifluoromethyl-1,3-thiazole-5-carboxamide;

N-5-Benzyl-2-[2-(4-hydroxyphenyl)-1-ethynyl]-4-trifluoromethyl-1,3-thiazole-5-carboxamide;

4-Cyclopropyl-2-[(4-hydroxyphenyl) ethynyl]-*N*-phenyl propyl-1,3-thiazole-5-carboxamide;

4-Cyclopropyl-*N*-(4-fluorobenzyl)-2-[(4-hydroxyphenyl)ethynyl]-1,3-thiazole-5-carboxamide;

N-[2-(4-Fluorophenoxy)ethyl]-2-[(4-hydroxyphenyl)ethynyl]-4-methyl-1,3-thiazole-5-carboxamide;

2-[(4-Hydroxyphenyl)ethynyl]-4-methyl-*N*-(2-phenoxyethyl)-1,3-thiazole-5-carboxamide and

N-(2,4-Dichlorobenzyl)-2-[(4-hydroxyphenyl)ethynyl]-4-methyl-1,3-thiazole-5-carboxamide or pharmaceutically acceptable salt thereof.

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

8. A method of 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 claim 1 to 7.

9. The method of claim 8, 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.

10. The method of claim 9, wherein the disorder is obesity.