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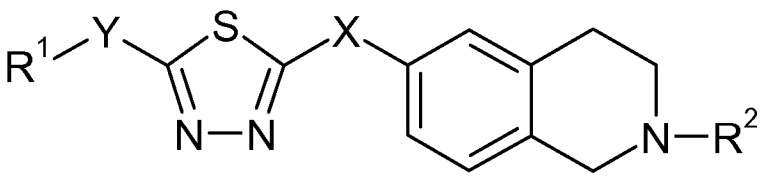

(I)

(57) Abstract: The present invention relates to substituted thiadiazole compounds of the formula (I) and pharmaceutically acceptable salts thereof, to pharmaceutical compositions containing them and their use in medicine. In particular, the invention relates to compounds for modulating SCD activity.

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THIADIAZOLE DERIVATIVES, INHIBITORS OF STEAROYL-COA DESATURASE

FIELD OF THE INVENTION

The present invention relates to a novel class of compounds believed to be inhibitors of stearoyl-CoA desaturase (SCD), compositions comprising said compounds, methods of synthesis and uses for such compounds in treating and/or preventing various diseases, including those mediated by SCD enzyme, such as diseases related to elevated lipid levels, cardiovascular disease, diabetes, obesity, metabolic syndrome, skin disorders such as acne, diseases or conditions related to cancer and the treatment of symptoms linked to the production of the amyloid plaque-forming Aβ42 peptide such as Alzheimer's disease and the like.

BACKGROUND OF THE INVENTION

Acyl desaturase enzymes catalyze the formation of double bonds in fatty acids derived from either dietary sources or *de novo* synthesis in the liver. Mammals synthesise at least three fatty acid desaturases of differing chain length that specifically catalyze the addition of double bonds at the delta-9, delta-6, and delta-5 positions. Stearoyl-CoA desaturases (SCDs) introduce a double bond in the C9-C10 position of saturated fatty acids. The preferred substrates for the enzymes are palmitoyl-CoA (16:0) and stearoyl-CoA (18:0), which are converted to palmitoleoyl-CoA (16:1) and oleoyl-CoA (18:1), respectively. The resulting mono-unsaturated fatty acids may then be employed in the preparation of phospholipids, triglycerides, and cholesteryl esters, *in vivo*.

A number of mammalian SCD genes have been cloned. For example, two genes have been cloned from rats (SCD1, SCD2) and four SCD genes have been isolated from mice (SCD1, 2, 3 and 4). While the basic biochemical roles of SCD has been known in rats and mice since the 1970's (Jeffcoat, R *et al., Elsevier Science* (1984), Vol 4, pp. 85-112; de Antueno, RJ, *Lipids* (1993), Vol. 28, No. 4, pp. 285-290), it has only recently been directly implicated in human diseases processes.

A single SCD gene, SCD1, has been characterized in humans. SCD1 is described in Brownlie *et al*, WO 01/62954. A second human SCD isoform has been identified, and because it bears little sequence homology to known mouse or rat isoforms it has been named human SCD5 or hSCD5 (WO 02/26944).

Whilst not wishing to be bound by theory, it is thought that inhibition of the activity of SCD *in vivo* can be used to ameliorate and/or treat one or more diseases such as dyslipidemia, hypoalphalipoproteinemia, hyperbetalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial hypercholesterolemia, angina,

ischemia, cardiac ischemia, stroke, myocardial infarction, atherosclerosis, obesity, Type I diabetes, Type II diabetes, insulin resistance, hyperinsulinaemia, metabolic syndrome; other cardiovascular diseases e.g. peripheral vascular disease, reperfusion injury, angioplastic restenosis, hypertension, vascular complications of diabetes, thrombosis; hepatic steatosis, non-alcoholic steatohepatitis (NASH) and other diseases related to accumulation of lipids in the liver.

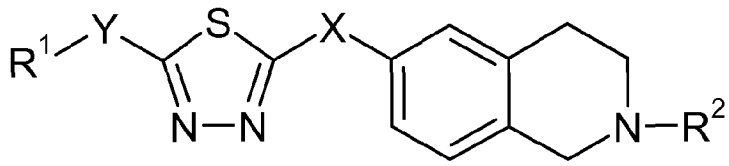
An SCD-mediated disease or condition also includes a disorder of polyunsaturated fatty acid (PUFA) disorder, or a skin disorder, including but not limited to eczema, acne, psoriasis, keloid scar formation or prevention, diseases related to production or secretions from mucous membranes, such as monounsaturated fatty acids, wax esters, and the like (US2006/0205713A1, WO2007/046868, WO2007/046867). SCD has been shown to play a physiological role in cholesterol homeostasis and the de novo biosynthesis of cholesterol esters, triglycerides and wax esters required for normal skin and eyelid function and therefore may be useful in the treatment of acne and other skin conditions (Makoto et al. J of Nutrition (2001), 131(9), 2260-2268, Harrison et al. J of Investigative Dermatology (2007) 127(6), 1309-1317).

An SCD-mediated disease or condition also includes but is not limited to a disease or condition which is, or is related to cancer, neoplasia, malignancy, metastases, tumours (benign or malignant), carcinogenesis, hepatomas and the like (US2006/0205713A1, WO2007/046868, WO2007/046867). Recently, SCD-1 has been identified as playing a role in human tumor cell survival and therefore has potential as an anticancer target (Morgan-Lappe et al. 2007 Cancer Res. 67(9) 4390-4398).

It has been shown that overexpression of Steroyl-CoA desaturase (SCD) in human cells in culture leads to a specific increase in the production of the amyloid plaque-forming Aβ42 peptide, and conversely, that reductions in SCD activity in human cells in culture leads to a specific decrease in the production of Aβ42. Therefore, SCD inhibitors may also be useful for treating, delaying the onset of symptoms, or slowing the progression of symptoms of mild cognitive impairment (MCI), Alzheimer's Disease (AD), cerebral amyloid angiopathy (CAA) or dementia associated with Down Syndrome (DS) and other neurodegenerative diseases characterized by the formation or accumulation of amyloid plaques comprising Aβ42 (US2007/0087363A1; Myriad Genetics).

WO2005/011657 describes certain piperazine derivatives useful for modulating SCD activity.

The present invention provides a compound of formula (I) for inhibiting SCD activity:



(I)

wherein:

X represents -CONH-, -NHCO- or -N(CH_3)CO-,

R^1 represents:

(i) a substituent selected from: H, -C_{1-6}alkyl or -C_{3-6}cycloalkyl,

(ii) -C_{6-10}aryl (such as phenyl or naphthyl) optionally substituted by one, two or three groups independently selected from:

(a) -C_{1-6}alkyl (such as -CH_3), -C_{1-6}haloalkyl (such as -CF_3), -C_{3-6}cycloalkyl, -C_{1-6}alkoxy (such as -OCH_3), -OR^3, -CN or halogen (such as chloro, bromo or fluoro),

(b) -C_{6-10}aryl (such as phenyl), -C_{5-10}heteroaryl or -C_{5-10}heterocyclyl, wherein the -C_{6-10}aryl, -C_{5-10}heteroaryl or -C_{5-10}heterocyclyl ring is optionally substituted by one, two or three groups independently selected from: -C_{1-6}alkyl (such as -CH_3), -C_{1-6}haloalkyl (such as -CF_3), -C_{1-6}alkoxy (such as -OCH_3), -OR^3, -CN or halogen (such as chloro, bromo or fluoro),

(iii) -C_{5-10}heteroaryl or -C_{5-10}heterocyclyl wherein the -C_{5-10}heteroaryl or -C_{5-10}heterocyclyl is optionally substituted by one, two or three groups independently selected from:

(a) -C_{1-6}alkyl (such as -CH_3), -C_{1-6}haloalkyl (such as -CF_3), -C_{3-6}cycloalkyl, -C_{1-6}alkoxy (such as -OCH_3), -OR^3, -CN or halogen (such as chloro, bromo or fluoro),

(b) -C_{6-10}aryl (such as phenyl), -C_{5-10}heteroaryl or -C_{5-10}heterocyclyl wherein the -C_{6-10}aryl, -C_{5-10}heteroaryl or -C_{5-10}heterocyclyl ring is optionally substituted by one, two or three groups independently selected from: -C_{1-6}alkyl (such as -CH_3), -C_{1-6}haloalkyl (such as -CF_3), -C_{1-6}alkoxy (such as -OCH_3), -OR^3, -CN or halogen (such as chloro, bromo or fluoro),

Y represents -$(CH_2)_m$-, -$O(CH_2)_m$- or -$NR^7(CH_2)_m$-,

R^2 represents H, -C_{1-6}alkyl, -C(=O)C_{1-6}alkyl, -C(=O)C_{3-6}cycloalkyl, -C(=O)C_{6-10}aryl, -C(=O)C_{1-6}alkylOH, -COC_{1-3}alkylNR^4R^5 or -C_5heteroarylR^6,

R^3 represents -C_{1-6}haloalkyl (such as -CF_3) or -C_{3-6}cycloalkyl,

R^4 represents H or -C_{1-3}alkyl (such as -CH_3),

R^5 represents H or -C_{1-3}alkyl (such as -CH_3),

R^6 represents -C_{1-3}alkylOH,

R^7 represents H or -C_{1-3}alkyl (such as -CH_3), and

m represents 1-4

or a pharmaceutically acceptable salt thereof.

The said compounds have been found to inhibit SCD activity and may therefore be useful in the treatment of SCD-mediated diseases such as diseases or conditions caused by or associated with an abnormal plasma lipid profile including dyslipidemia, hypoalphalipoproteinemia, hyperbetalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial hypercholesterolemia, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, atherosclerosis, obesity, Type I diabetes, Type II diabetes, insulin resistance, hyperinsulinaemia and metabolic syndrome; other cardiovascular diseases e.g. peripheral vascular disease, reperfusion injury, angioplastic restenosis, hypertension, vascular complications of diabetes, thrombosis, hepatic steatosis, non-alcoholic steatoheptatis (NASH) and other diseases related to accumulation of lipids in the liver; skin disorders e.g. eczema, acne, psoriasis, keloid scar formation or prevention, and diseases related to production or secretions from mucous membranes; cancer, neoplasia, malignancy, metastases, tumours (benign or malignant), carcinogenesis, hepatomas and the like; mild cognitive impairment (MCI), Alzheimer's Disease (AD), cerebral amyloid angiopathy (CAA) or dementia associated with Down Syndrome (DS) and other neurodegenerative diseases characterized by the formation or accumulation of amyloid plaques comprising Aβ42.

In one aspect of the invention,
X represents –CONH- or -NHCO-;
R^1 represents:
(i) a substituent selected from: H, -C_{1-6}alkyl or -C_{3-6}cycloalkyl,
(ii) -C_{6-10}aryl (such as phenyl) optionally substituted by one, two or three groups independently selected from:
  (a) -C_{1-6}alkyl, -C_{1-6}haloalkyl (such as -CF_3), -C_{3-6}cycloalkyl, -C_{1-6}alkoxy, -OC_{1-6}haloalkyl (such as -OCF_3), -OR^3, -CN or halogen (such as chloro, bromo or fluoro),
  (b) -C_{6-10}aryl (such as phenyl), -C_{5-10}heteroaryl or -C_{5-10}heterocyclyl, wherein the -C_{6-10}aryl, -C_{5-10}heteroaryl or -C_{5-10}heterocyclyl ring is optionally substituted by one, two or three groups independently selected from: -C_{1-6}alkyl, -OR^3, -C_{1-6}alkoxy, -C_{1-6}haloalkyl (such as -CF_3), -CN or halogen (such as chloro, bromo or fluoro),
(iii) -C_{5-10}heteroaryl or -C_{5-10}heterocyclyl wherein the -C_{5-10}heteroaryl or -C_{5-10}heterocyclyl is optionally substituted by one, two or three groups independently selected from:
  (a) -C_{1-6}alkyl, -C_{1-6}haloalkyl (such as -CF_3), -C_{3-6}cycloalkyl, -C_{1-6}alkoxy, -OC_{1-6}haloalkyl (such as -OCF_3), -OR^3, -CN or halogen (such as chloro, bromo or fluoro),
  (b) -C_{6-10}aryl (such as phenyl), -C_{5-10}heteroaryl or -C_{5-10}heterocyclyl wherein the -C_{6-10}aryl, -C_{5-10}heteroaryl or -C_{5-10}heterocyclyl ring is optionally substituted by one, two or three groups independently selected from: -C_{1-6}alkyl, -OR^3, -

C_{1-6}alkoxy -C_{1-6}haloalkyl (such as -CF_3), -CN or halogen (such as chloro, bromo or fluoro),

Y represents -$(CH_2)_m$-, -$O(CH_2)_m$- or -$NR^4(CH_2)_m$-,

R^2 represents H, -C_{1-6}alkyl, -$C(=O)C_{1-6}$alkyl, -$C(=O)C_{3-6}$cycloalkyl or -$C(=O)C_{6-10}$aryl,

R^3 represents -C_{1-6}haloalkyl (such as -CF_3) or -C_{3-6}cycloalkyl,

R^4 represents H or -CH_3, and

m represents 1-4

or a pharmaceutically acceptable salt thereof.

In one aspect of the invention, X represents -NHCO-. In another aspect of the invention, X represents -CONH-. In another aspect of the invention, X represents -$N(CH_3)CO$-.

In one aspect of the invention, R^1 represents:

(i) a substituent selected from: H or -C_{3-6}cycloalkyl,

(ii) -C_{6-10}aryl (such as phenyl or naphthyl) optionally substituted by one, two or three groups independently selected from:

(a) -C_{1-6}alkyl (such as -CH_3), -C_{1-6}haloalkyl (such as -CF_3), -C_{3-6}cycloalkyl, -C_{1-6}alkoxy (such as -OCH_3), -OR^3, -CN or halogen (such as chloro, bromo or fluoro),

(b) -C_{6-10}aryl (such as phenyl), -C_{5-10}heteroaryl or -C_{5-10}heterocyclyl, wherein the -C_{6-10}aryl, -C_{5-10}heteroaryl or -C_{5-10}heterocyclyl ring is optionally substituted by one, two or three groups independently selected from: -C_{1-6}alkyl (such as -CH_3), -C_{1-6}haloalkyl (such as -CF_3), -C_{1-6}alkoxy (such as -OCH_3), -OR^3, -CN or halogen (such as chloro, bromo or fluoro),

(iii) -C_{5-10}heteroaryl or -C_{5-10}heterocyclyl wherein the -C_{5-10}heteroaryl or -C_{5-10}heterocyclyl is optionally substituted by one, two or three groups independently selected from:

(a) -C_{1-6}alkyl (such as -CH_3), -C_{1-6}haloalkyl (such as -CF_3), -C_{3-6}cycloalkyl, -C_{1-6}alkoxy (such as -OCH_3), -OR^3 , -CN or halogen (such as chloro, bromo or fluoro),

(b) -C_{6-10}aryl (such as phenyl), -C_{5-10}heteroaryl or -C_{5-10}heterocyclyl wherein the -C_{6-10}aryl, -C_{5-10}heteroaryl or -C_{5-10}heterocyclyl ring is optionally substituted by one, two or three groups independently selected from: -C_{1-6}alkyl (such as -CH_3), -C_{1-6}haloalkyl (such as -CF_3), -C_{1-6}alkoxy (such as -OCH_3), -OR^3, -CN or halogen (such as chloro, bromo or fluoro).

In another aspect of the invention, R^1 represents -C_{3-6}cycloalkyl. In another aspect of the invention, R^1 represents cyclohexane.

In another aspect of the invention, R^1 represents -C_{6-10}aryl optionally substituted by: one, two or three groups independently selected from:

(a) -C_{1-6}alkyl (such as -CH_3), -C_{1-6}haloalkyl (such as -CF_3), -C_{3-6}cycloalkyl, -C_{1-6}alkoxy (such as -OCH_3), -OR^3, -CN or halogen (such as chloro, bromo or fluoro), or

(b) -C_{6-10}aryl (such as phenyl) optionally substituted by one, two or three groups independently selected from: -C_{1-6}alkyl (such as -CH_3), -C_{1-6}alkoxy (such as -OCH_3), -OR^3, -C_{1-6}haloalkyl (such as -CF_3), -CN or halogen (such as chloro, bromo or fluoro).

In another aspect of the invention, R^1 represents -C_{6-10}aryl optionally substituted by: one, two or three groups independently selected from:

(a) -C_{1-6}alkyl, -C_{1-6}haloalkyl (such as -CF_3), -C_{3-6}cycloalkyl, -C_{1-6}alkoxy, -OR^3, -CN, halogen or

(b) -C_{6-10}aryl (such as phenyl) optionally substituted by one, two or three groups independently selected from: -C_{1-6}alkyl, -OR^3, -C_{1-6}alkoxy, -C_{1-6}haloalkyl (such as -CF_3), -CN or halogen.

In another aspect of the invention, R^1 represents phenyl optionally substituted by: one, two or three groups independently selected from:

(a) -C_{1-6}alkyl (such as -CH_3), -C_{1-6}haloalkyl (such as -CF_3), -C_{3-6}cycloalkyl, -C_{1-6}alkoxy (such as -OCH_3), -OR^3, -CN or halogen (such as chloro, bromo or fluoro),

(b) or phenyl optionally substituted by one, two or three groups independently selected from: -C_{1-6}alkyl (such as -CH_3), -C_{1-6}alkoxy (such as -OCH_3), -OR^3 , -C_{1-6}haloalkyl (such as -CF_3), -CN or halogen (such as chloro, bromo or fluoro).

In another aspect of the invention, R^1 represents phenyl optionally substituted by: one, two or three groups independently selected from:

(a) -C_{1-6}alkyl, -C_{1-6}haloalkyl (such as -CF_3), -C_{3-6}cycloalkyl, -C_{1-6}alkoxy, -OR^3, -CN, halogen or

(b) phenyl optionally substituted by one, two or three groups independently selected from: -C_{1-6}alkyl, -OR^3, -C_{1-6}alkoxy -C_{1-6}haloalkyl (such as -CF_3), -CN or halogen.

In another aspect of the invention, R^1 represents phenyl optionally substituted by: one, two or three groups independently selected from:

(a) -C_{1-3}alkyl (such as -CH_3), -C_{1-3}haloalkyl (such as -CF_3), -C_{3-6}cycloalkyl, -C_{1-3}alkoxy (such as -OCH_3), -OR^3, -CN or halogen (such as chloro, bromo or fluoro),

(b) or phenyl optionally substituted by one, two or three groups independently selected from: -C_{1-3}alkyl (such as -CH_3), -OR^3, -C_{1-3}alkoxy (such as -OCH_3), , -C_{1-3}haloalkyl (such as -CF_3), -CN or halogen (such as chloro, bromo or fluoro).

In another aspect of the invention, R^1 represents phenyl optionally substituted by: one or two groups independently selected from:

(a) $-C_{1-3}$alkyl (such as $-CH_3$), $-C_{1-3}$haloalkyl (such as $-CF_3$), $-C_{3-6}$cycloalkyl, $-C_{1-3}$alkoxy (such as $-OCH_3$), $-OR^3$, -CN or halogen (such as chloro, bromo or fluoro),

(b) or phenyl optionally substituted by one, two or three groups independently selected from: $-C_{1-3}$alkyl (such as $-CH_3$), $-OR^3$, $-C_{1-3}$alkoxy (such as $-OCH_3$), $-C_{1-3}$haloalkyl (such as $-CF_3$), -CN or halogen (such as chloro, bromo or fluoro).

In another aspect of the invention, R^1 represents phenyl optionally substituted by one, two or three groups independently selected from:

(a) $-C_{1-6}$alkyl (such as $-CH_3$), $-C_{1-6}$haloalkyl (such as $-CF_3$), $-C_{1-6}$alkoxy (such as $-OCH_3$), $-OC_{1-6}$haloalkyl (such as $-OCF_3$), -CN or halogen (such as chloro, bromo or fluoro) or

(b) phenyl optionally substituted by one, two or three groups independently selected from: halogen (such as chloro), -CN or $-CF_3$.

In another aspect of the invention, R^1 represents phenyl optionally substituted by one, two or three groups independently selected from:

(a) $-C_{1-6}$alkyl, $-C_{1-6}$haloalkyl (such as $-CF_3$), $-C_{1-6}$alkoxy, -CN, halogen (such as chloro, bromo or fluoro) or

(b) phenyl optionally substituted by one, two or three groups independently selected from: halogen (such as chloro), -CN or CF_3.

In another aspect of the invention, R^1 represents phenyl optionally substituted by one, two or three groups independently selected from:

(a) $-C_{1-6}$alkyl (such as $-CH_3$), $-C_{1-6}$haloalkyl (such as $-CF_3$), $-C_{1-6}$alkoxy (such as $-OCH_3$), $-OC_{1-6}$haloalkyl (such as $-OCF_3$), halogen (such as chloro, bromo or fluoro) or

(b) phenyl optionally substituted by one, two or three groups independently selected from: halogen (such as chloro).

In another aspect of the invention, R^1 represents phenyl optionally substituted by one, two or three groups independently selected from:

(a) $-C_{1-3}$alkyl (such as $-CH_3$), $-C_{1-3}$haloalkyl (such as $-CF_3$), $-C_{1-3}$alkoxy (such as $-OCH_3$), $-OC_{1-3}$haloalkyl (such as $-OCF_3$), halogen (such as chloro, bromo or fluoro) or

(b) phenyl optionally substituted by one, two or three groups independently selected from: halogen (such as chloro).

In another aspect of the invention, R^1 represents phenyl optionally substituted by one, two or three groups independently selected from:

(a) $-C_{1-6}$haloalkyl (such as $-CF_3$), halogen (such as chloro, bromo or fluoro) or

(b) phenyl optionally substituted by one, two or three groups independently selected from: halogen (such as chloro).

In another aspect of the invention, R^1 represents phenyl optionally substituted by one, two or three groups independently selected from: $-CH_3$, $-OCH_3$, $-OCH_2CH(CH_3)_2$, $-CF_3$, $-OCF_3$ or halogen (such as chloro, bromo or fluoro).

In another aspect of the invention, R^1 represents phenyl optionally substituted by one or two groups independently selected from: $-CF_3$, $-CH_3$, $-OCH_3$, $-OCH_2CH(CH_3)_2$, $-CF_3$, $-OCF_3$ or halogen (such as chloro, bromo or fluoro).

In another aspect of the invention, R^1 represents phenyl optionally substituted by one, two or three groups independently selected from: $-CF_3$ or halogen (such as chloro, bromo or fluoro).

In another aspect of the invention, R^1 represents phenyl optionally substituted by one or two groups independently selected from: $-CF_3$ or halogen (such as chloro, bromo or fluoro).

In another aspect of the invention, R^1 represents phenyl optionally substituted by one group independently selected from: $-CF_3$, $-CH_3$, $-OCH_3$, $-OCH_2CH(CH_3)_2$, $-CF_3$, $-OCF_3$ or halogen (such as chloro, bromo or fluoro).

In another aspect of the invention, R^1 represents phenyl substituted by phenyl, such as 2-phenyl, the second phenyl ring being optionally substituted by halogen (for example chloro).

In another aspect of the invention, R^1 represents phenyl substituted by phenyl.

In another aspect of the invention, R^1 represents naphthyl optionally substituted by: one, two or three groups independently selected from:

(a) $-C_{1-6}$alkyl (such as $-CH_3$), $-C_{1-6}$haloalkyl (such as $-CF_3$), $-C_{3-6}$cycloalkyl, $-C_{1-6}$alkoxy (such as $-OCH_3$), $-OR^3$, -CN or halogen (such as chloro, bromo or fluoro) or

(b) phenyl optionally substituted by one, two or three groups selected from $-C_{1-6}$alkyl (such as $-CH_3$), $-OR^3$, $-C_{1-6}$alkoxy (such as $-OCH_3$), , $-C_{1-6}$haloalkyl (such as $-CF_3$), -CN or halogen (such as chloro, bromo or fluoro).

In another aspect of the invention, R^1 represents naphthyl optionally substituted by: one, two or three groups independently selected from:

(a) $-C_{1-6}$alkyl, $-C_{1-6}$haloalkyl (such as $-CF_3$), $-C_{3-6}$cycloalkyl, $-C_{1-6}$alkoxy, $-OR^3$, -CN, halogen or

(b) phenyl optionally substituted by one, two or three groups selected from: -C_{1-6}alkyl, -OR^3, -C_{1-6}alkoxy, -C_{1-6}haloalkyl (such as -CF_3), -CN or halogen.

In another aspect of the invention, R^1 represents naphthyl.

In another aspect of the invention, R^1 represents tetrahydronaphthalenyl optionally substituted by: one, two or three groups independently selected from:

(a) -C_{1-6}alkyl (such as -CH_3), -C_{1-6}haloalkyl (such as -CF_3), -C_{3-6}cycloalkyl, -C_{1-6}alkoxy (such as -OCH_3), -OR^3, -CN or halogen (such as chloro, bromo or fluoro), or

(b) phenyl optionally substituted by one, two or three groups selected from: -C_{1-6}alkyl (such as -CH_3), -C_{1-6}haloalkyl (such as -CF_3), -C_{1-6}alkoxy (such as -OCH_3), -OR^3, -CN or halogen (such as chloro, bromo or fluoro).

In another aspect of the invention, R^1 represents tetrahydronaphthalenyl.

In another aspect of the invention, R^1 represents -C_{5-10}heteroaryl or -C_{5-10}heterocyclyl wherein the -C_{5-10}heteroaryl or -C_{5-10}heterocyclyl is optionally substituted by one, two or three groups independently selected from:

(a) -C_{1-6}alkyl (such as -CH_3), -C_{1-6}haloalkyl (such as -CF_3), -C_{3-6}cycloalkyl, -C_{1-6}alkoxy (such as -OCH_3), -OR^3, -CN or halogen (such as chloro, bromo or fluoro),

(b) -C_{6-10}aryl (such as phenyl), -C_{5-10}heteroaryl or -C_{5-10}heterocyclyl wherein the -C_{6-10}aryl, -C_{5-10}heteroaryl or -C_{5-10}heterocyclyl ring is optionally substituted by one, two or three groups independently selected from: -C_{1-6}alkyl (such as -CH_3), -C_{1-6}haloalkyl (such as -CF_3), -C_{1-6}alkoxy (such as -OCH_3), -OR^3, -CN or halogen (such as chloro, bromo or fluoro).

In another aspect of the invention, R^1 represents -C_{5-10}heteroaryl or -C_{5-10}heterocyclyl wherein the -C_{5-10}heteroaryl or -C_{5-10}heterocyclyl is optionally substituted by one, two or three groups independently selected from:

(a) -C_{1-6}alkyl, -C_{1-6}haloalkyl (such as -CF_3), -C_{3-6}cycloalkyl, -C_{1-6}alkoxy, -OR^3, -CN or halogen (such as chloro, bromo or fluoro),

(b) -C_{6-10}aryl (such as phenyl), -C_{5-10}heteroaryl or -C_{5-10}heterocyclyl wherein the -C_{6-10}aryl, -C_{5-10}heteroaryl or -C_{5-10}heterocyclyl ring is optionally substituted by one, two or three groups independently selected from: -C_{1-6}alkyl, -OR^3, -C_{1-6}alkoxy, -C_{1-6}haloalkyl (such as -CF_3), -CN or halogen (such as chloro, bromo or fluoro).

In another aspect of the invention, R^1 represents a -C_{5-10}heteroaryl. In another aspect of the invention, R^1 represents a -C_6heteroaryl. In another aspect of the invention, R^1 represents pyridine. In another aspect of the invention, R^1 represents a -C_5heteroaryl. In another aspect of the invention, R^1 represents thiophene.

In another aspect of the invention, R^1 represents a -C_{5-10}heteroaryl. In another aspect of the invention, R^1 represents a -C_8heteroaryl. In another aspect of the invention, R^1 represents benzothiophene. In another aspect of the invention, R^1 represents indole. In another aspect of the invention, R^1 represents N-methyl indole.

In another aspect of the invention, R^1 represents dihydro-2H-chromene optionally substituted by: one, two or three groups independently selected from:

(a) -C_{1-6}alkyl (such as -CH_3), -C_{1-6}haloalkyl (such as -CF_3), -C_{3-6}cycloalkyl, -C_{1-6}alkoxy (such as -OCH_3), -OR^3 , -CN or halogen (such as chloro, bromo or fluoro) or

(b) phenyl optionally substituted by one, two or three groups selected from: -C_{1-6}alkyl (such as -CH_3), -C_{1-6}haloalkyl (such as -CF_3), -C_{1-6}alkoxy (such as -OCH_3), -OR^3, -CN or halogen (such as chloro, bromo or fluoro).

In another aspect of the invention, R^1 represents dihydro-2H-chromene.

In one aspect of the invention, Y represents -$(CH_2)_m$-, -$O(CH_2)_m$ or -$NR^7(CH_2)_m$-. In another aspect of the invention, Y represents -$(CH_2)_m$- or -$O(CH_2)_m$-. In another aspect of the invention, Y represents -$(CH_2)_m$-. In another aspect of the invention, Y represents -$O(CH_2)_m$-. In another aspect of the invention, Y represents -CH_2-, -OCH_2-, -OCH_2CH_2-, -C_2H_4- or -$N(CH_3)CH_2$-. In another aspect of the invention, Y represents -CH_2-, -OCH_2-, -OCH_2CH_2- or -C_2H_4-. In another aspect of the invention, Y represents -CH_2- (methylene). In another aspect of the invention, Y represents -C_2H_4- (ethylene). In another aspect of the invention, Y represents -OCH_2-. In another aspect of the invention, Y represents -OCH_2CH_2-. In another aspect of the invention, Y represents -$N(CH_3)CH_2$-.

In one aspect of the invention, R^2 represents hydrogen. In another aspect of the invention, R^2 represents -C_3H_7. In another aspect of the invention, R^2 represents -$C(=O)C_{1-6}$alkyl or -$C(=O)C_{6-10}$aryl. In another aspect of the invention, R^2 represents -C(=O)phenyl. In another aspect of the invention, R^2 represents -$C(=O)C_3H_7$. In another aspect of the invention, R^2 represents -$C(=O)C_6H_5$. In another aspect of the invention, R^2 represents -$C(=O)C_{1-6}$alkylOH. In another aspect of the invention, R^2 represents -$C(=O)CH_2OH$. In another aspect of the invention, R^2 represents -$C(=O)C(CH_3)_2OH$. In another aspect of the invention, R^2 represents -$COCH_2N(CH_3)_2$. In another aspect of the invention, R^2 represents thiazoleCH_2OH.

In one aspect of the invention, R^3 represents -OC_{1-6}haloalkyl (such as -OCF_3). In another aspect of the invention, R^3 represents -OC_{1-3}haloalkyl (such as -OCF_3). In another aspect of the invention, R^3 represents -OC_{3-6}cycloalkyl.

In one aspect of the invention, R^4 represents -C_{1-3}alkyl (such as -CH_3). In another aspect of the invention, R^4 represents -CH_3 (methyl). In another aspect of the invention, R^4 represents hydrogen.

In one aspect of the invention, R^5 represents -C_{1-3}alkyl (such as -CH_3). In another aspect of the invention, R^5 represents -CH_3 (methyl). In another aspect of the invention, R^5 represents hydrogen.

In one aspect of the invention, R^7 represents -C_{1-3}alkyl (such as -CH_3). In another aspect of the invention, R^7 represents -CH_3 (methyl). In another aspect of the invention, R^7 represents hydrogen.

In one aspect of the invention, m represents 0, 1, 2 or 3. In another aspect of the invention, m represents 1 or 2.

Each of the aspects of the invention are independent unless stated otherwise. Nevertheless the skilled person will understand that all the permutations of the aspects of described are within the scope of the invention. Thus it is to be understood that the present invention covers all combinations of suitable, convenient and exemplified groups described herein. For example, in one aspect the invention provides a compound of formula (I) wherein X represents –NHCO- and R^2 represents H.

Certain compounds of formula (I) may exist in stereoisomeric forms (e.g. they may contain one or more asymmetric carbon atoms). The individual stereoisomers (enantiomers and diastereomers) and mixtures of these are included within the scope of the present invention. The invention also extends to conformational isomers of compounds of formula (I) and any geometric (*cis* and/or *trans*) isomers of said compounds. Likewise, it is understood that compounds of formula (I) may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention.

It will be appreciated that racemic compounds of formula (I) may be optionally resolved into their individual enantiomers. Such resolutions may conveniently be accomplished by standard methods known in the art. For example, a racemic compound of formula (I) may be resolved by chiral preparative HPLC.

It will also be appreciated that compounds of the invention which exist as polymorphs, and mixtures thereof, are within the scope of the present invention.

As used herein, the term "alkyl" refers to straight or branched hydrocarbon chains containing the specified number of carbon atoms. For example, C_{1-6}alkyl means a straight or branched alkyl containing at least 1, and at most 6, carbon atoms. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-

propyl, n-butyl, n-pentyl, n-hexyl, isobutyl, isopropyl, t-butyl and 1,1-dimethylpropyl. However, when a moiety is defined such that alkyl bears a substituent it will be clear to the skilled person from the context that alkyl may include alkylene, for example methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$) and propylene ($-CH_2CH_2CH_2-$).

As used herein, the term "alkoxy" refers to a straight or branched alkoxy group containing the specified number of carbon atoms. For example, C_{1-6}alkoxy means a straight or branched alkoxy group containing at least 1, and at most 6, carbon atoms. Examples of "alkoxy" as used herein include, but are not limited to, methoxy, ethoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy, 2-methylprop-1-oxy, 2-methylprop-2-oxy, pentoxy and hexyloxy. The point of attachment may be on the oxygen or carbon atom.

As used herein, the term "halogen" or "halo" refers to a fluorine (fluoro), chlorine (chloro), bromine (bromo) or iodine (iodo) atom.

As used herein, the term "haloalkyl" refers to an alkyl group having one or more carbon atoms and wherein at least one hydrogen atom is replaced with a halogen atom, for example a trifluoromethyl group and the like.

As used herein, the term "cycloalkyl" refers to a saturated cyclic group containing 3 to 10 carbon ring-atoms, such as 3 to 6 carbon ring-atoms. Examples include cyclopropyl, cyclopentyl and cyclohexyl.

As used herein, the term "C_{5-10}heteroaryl" refers to an aromatic cyclic group containing 5 to 10 ring-atoms 1, 2, 3 or 4 of which are hetero-atoms independently selected from nitrogen, oxygen and sulphur and the remaining ring-atoms are carbon, e.g. benzothiophenyl, indolyl or thienyl. This definition includes both monocyclic and bicyclic ring systems and bicyclic structures at least a portion of which is aromatic and the other part is saturated, partially or fully unsaturated.

As used herein, the term 'aryl' means an aromatic carbocyclic moiety. The definition includes both monocyclic and bicyclic ring systems and bicyclic structures at least a portion of which is aromatic and the other part is saturated, partially or fully unsaturated. Examples of aromatic, aryl groups include naphthyl, anthryl, phenanthryl, indanyl, indenyl, azulenyl, azulanyl, fluorenyl, phenyl and napthyl, and more specifically phenyl.

As used herein, the term "C_{5-10}heterocyclyl" refers to a cyclic group containing 5 to 10 ring-atoms 1, 2, 3 or 4 of which are hetero-atoms independently selected from nitrogen, oxygen and sulphur and the remaining ring-atoms are carbon, wherein said cyclic group is saturated, partially or fully unsaturated but, which is not aromatic e.g. tetrahydrofuran, dihydrofuran, 1,4-dioxane, morpholine, 1,4-dithiane, piperazine, piperidine, 1,3-dioxolane, imidazolidine, imidazoline, pyrroline, pyrrolidine,

tetrahydropyran, dihydropyran, oxathiolane, 1,3-dioxane, 1,3-dithiane, oxathiane or thiomorpholine. This definition includes bicyclic structures provided the moiety is non-aromatic.

Examples of heterocyclyl and heteroaryl groups include: furyl, thienyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, dioxolanyl, oxazolyl, thiazolyl, imidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyranyl, pyridyl, piperidinyl, homopiperazinyl, dioxanyl, morpholino, dithianyl, thiomorpholino, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, sulfolanyl, tetrazolyl, triazinyl, azepinyl, oxazepinyl, thiazepinyl, diazepinyl and thiazolinyl, benzimidazolyl, benzoxazolyl, imidazopyridinyl, benzoxazinyl, benzothiazinyl, benzothiophenyl oxazolopyridinyl, benzofuranyl, quinolinyl, quinazolinyl, quinoxalinyl, dihydroquinazolinyl, benzothiazolyl, phthalimido, benzofuranyl, benzodiazepinyl, indolyl and isoindolyl.

As used herein, the term "substituted" refers to substitution with the named substituent or substituents, multiple degrees of substitution being allowed unless otherwise stated.

For the avoidance of doubt, the term "independently" means that where more than one substituent is selected from a number of possible substituents, those substituents may be the same or different.

As used herein, the term "pharmaceutically acceptable" means a compound which is suitable for pharmaceutical use.

Salts of compounds of formula (I) which are suitable for use in medicine are those wherein the counterion is pharmaceutically acceptable. However, salts having non-pharmaceutically acceptable counterions are within the scope of the present invention, for example, for use as intermediates in the preparation of other compounds of formula (I) and their pharmaceutically acceptable salts.

Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include for example acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, malic, mandelic, acetic, fumaric, glutamic, lactic, citric, tartaric, benzoic, benzenesulfonic, *p*-toluenesulfonic, methanesulfonic, ethanesulfonic or naphthalenesulfonic acid. Other non-pharmaceutically acceptable salts e.g. oxalates, may be used, for example in the isolation of compounds of formula (I) and are included within the scope of this invention. Reference is made to Berge et al. J. Pharm. Sci., 1977, 66, 1-19.

Certain of the compounds of formula (I) may form acid addition salts with one or more equivalents of the acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms thereof.

Solvates of the compounds of formula (I) and solvates of the salts of the compounds of formula (I) are included within the scope of the present invention.

As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula (I) or a salt thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include but are not limited to, water, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Most preferably the solvent used is water and the solvate may also be referred to as a hydrate.

Solvates of compounds of formula (I) which are suitable for use in medicine are those wherein the solvent is pharmaceutically acceptable. However, solvates having non-pharmaceutically acceptable solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of other compounds of formula (I) and their pharmaceutically acceptable salts.

Prodrugs of the compounds of formula (I) are included with the scope of the present invention.

As used herein, the term "prodrug" means a compound which is converted within the body, e.g. by hydrolysis in the blood, into its active form that has medical effects. Pharmaceutically acceptable prodrugs are described in T. Higuchi and V. Stella, Prodrugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987 and in D. Fleishner, S. Ramon and H. Barba "Improved oral drug delivery: solubility limitations overcome by the use of prodrugs", Advanced Drug Delivery Reviews (1996) 19(2) 115-130. Prodrugs are any covalently bonded carriers that release a compound of structure (I) in vivo when such prodrug is administered to a patient. Prodrugs are generally prepared by modifying functional groups in a way such that the modification is cleaved in vivo yielding the parent compound. Prodrugs may include, for example, compounds of this invention wherein hydroxyl or amine groups are bonded to any group that, when administered to a patient, cleaves to form the hydroxy or amine groups. Thus, representative examples of prodrugs include (but are not limited to) phosphonate, carbamate, acetate, formate and benzoate derivatives of hydroxy and amine functional groups of the compounds of formula (I).

Phosphonates and carbamates may be active in their own right and/or be hydrolysable under *in vivo* conditions in the human body. Suitable pharmaceutically acceptable *in vivo* hydrolysable ester groups include those which break down readily in the human body to leave the parent acid or its salt. A phosphonate is formed by reaction with phosphorous (phosphonic) acid, by methods well known in the art. For example, phosphonates may be derivatives such as $RP(O)(OR)_2$ and the like. A carbamate is an ester of carbamic acid.

In one aspect of the invention there is provided a compound, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

N-(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,

N-[5-(1-naphthalenylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,

N-(5-{[(3,4-dichlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,

N-(5-{[(4-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,

N-[5-(phenylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,

N-{5-[(4-chlorophenyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,

N-{5-[(3,4-dichlorophenyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,

N-[5-(2-thienylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,

N-[5-(2-naphthalenylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,

N-[5-(cyclohexylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,

N-[5-(2-phenylethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,

N-[5-(1H-indol-3-ylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,

N-(5-{[(2,5-dichlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,

N-{5-[(1-naphthalenyloxy)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,

N-(5-{[(2-chloro-4-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,

N-(5-{[(2-chloro-5-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,

N-[5-(1-benzothien-3-ylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-[5-(3-thienylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-{5-[2-(1-naphthalenyl)ethyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-{5-[2-(2-chlorophenyl)ethyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-{5-[(2-bromophenyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(3-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(4-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(3-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-[5-({[2-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-[5-({[3-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[3-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-{5-[(5,6,7,8-tetrahydro-1-naphthalenyloxy)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-{5-[(2-chlorophenyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[2-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-[5-({[4-(methyloxy)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-{5-[(2-biphenylyloxy)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[4-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-{5-[({5-chloro-2-[(2-methylpropyl)oxy]phenyl}oxy)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-{5-[(4-fluorophenyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-[5-({[2-(methyloxy)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,

N-{5-[(1-methyl-1H-indol-3-yl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-[5-(3-pyridinylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-[5-(5,6,7,8-tetrahydro-2-naphthalenylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-[5-(3,4-dihydro-2H-chromen-6-ylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{2-[(2-chlorophenyl)oxy]ethyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2,4-dichlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-{5-[(2'-chloro-2-biphenylyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-{5-[(2-fluorophenyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-{5-[(3-chlorophenyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2,6-dichlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2-methylphenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(3,4-dimethylphenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-{5-[(2,4-dichlorophenyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-[5-({2-[(trifluoromethyl)oxy]phenyl}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2-chloro-3,5-difluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2-chloro-6-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-[5-({[2-chloro-3-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2,4,5-trichlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-[5-({[2-chloro-5-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-{5-[(4-chloro-2-fluorophenyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[4-fluoro-2-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,

N-(5-{[5-chloro-2-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-[5-({[4-fluoro-2-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-[5-({[2-chloro-4-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(3-chloro-5-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-[5-({[5-fluoro-2-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2,4-difluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
5-{[(2-chlorophenyl)oxy]methyl}-N-(1,2,3,4-tetrahydro-6-isoquinolinyl)-1,3,4-thiadiazole-2-carboxamide,
N-(5-{[(2-chlorophenyl)(methyl)amino]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-N-methyl-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-2-(hydroxyacetyl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-2-(2-hydroxy-2-methylpropanoyl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-2-(N,N-dimethylglycyl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-2-(phenylcarbonyl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
2-butanoyl-N-(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-2-propyl-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-2-[5-(hydroxymethyl)-1,3-thiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide, or
5-[(3,4-dichlorophenyl)methyl]-*N*-(1,2,3,4-tetrahydro-6-isoquinolinyl)-1,3,4-thiadiazole-2-carboxamide.

In another aspect of the invention there is provided a compound, selected from the group consisting of:
N-(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-[5-(1-naphthalenylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-(5-{[(3,4-dichlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,

N-(5-{[(4-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-[5-(phenylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-{5-[(4-chlorophenyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-{5-[(3,4-dichlorophenyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-[5-(2-thienylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-[5-(2-naphthalenylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-[5-(cyclohexylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-[5-(2-phenylethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-[5-(1H-indol-3-ylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-(5-{[(2,5-dichlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-{5-[(1-naphthalenyloxy)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-(5-{[(2-chloro-4-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-(5-{[(2-chloro-5-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-[5-(1-benzothien-3-ylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-[5-(3-thienylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-{5-[2-(1-naphthalenyl)ethyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-{5-[2-(2-chlorophenyl)ethyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-{5-[(2-bromophenyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-(5-{[(2-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-(5-{[(3-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-(5-{[(4-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,

N-(5-{[(3-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-[5-({[2-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-[5-({[3-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-(5-{[3-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-{5-[(5,6,7,8-tetrahydro-1-naphthalenyloxy)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-{5-[(2-chlorophenyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-(5-{[2-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-[5-({[4-(methyloxy)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-{5-[(2-biphenylyloxy)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-(5-{[4-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-{5-[({5-chloro-2-[(2-methylpropyl)oxy]phenyl}oxy)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-{5-[(4-fluorophenyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-[5-({[2-(methyloxy)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-{5-[(1-methyl-1H-indol-3-yl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-[5-(3-pyridinylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-[5-(5,6,7,8-tetrahydro-2-naphthalenylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-[5-(3,4-dihydro-2H-chromen-6-ylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-(5-{2-[(2-chlorophenyl)oxy]ethyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-(5-{[(2,4-dichlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-{5-[(2'-chloro-2-biphenylyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-{5-[(2-fluorophenyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,

N-{5-[(3-chlorophenyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-(5-{[(2,6-dichlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-(5-{[(2-methylphenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-(5-{[(3,4-dimethylphenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-{5-[(2,4-dichlorophenyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-[5-({2-[(trifluoromethyl)oxy]phenyl}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-(5-{[(2-chloro-3,5-difluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-(5-{[(2-chloro-6-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-[5-({[2-chloro-3-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-(5-{[(2,4,5-trichlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-[5-({[2-chloro-5-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-{5-[(4-chloro-2-fluorophenyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-(5-{[4-fluoro-2-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-(5-{[5-chloro-2-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-[5-({[4-fluoro-2-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-[5-({[2-chloro-4-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-(5-{[(3-chloro-5-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-[5-({[5-fluoro-2-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-(5-{[(2,4-difluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
5-{[(2-chlorophenyl)oxy]methyl}-N-(1,2,3,4-tetrahydro-6-isoquinolinyl)-1,3,4-thiadiazole-2-carboxamide hydrochloride,
N-(5-{[(2-chlorophenyl)(methyl)amino]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,

N-(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-N-methyl-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride,
N-(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-2-(hydroxyacetyl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-2-(2-hydroxy-2-methylpropanoyl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-2-(N,N-dimethylglycyl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-2-(phenylcarbonyl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
2-butanoyl-N-(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-2-propyl-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-2-[5-(hydroxymethyl)-1,3-thiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide, or
5-[(3,4-dichlorophenyl)methyl]-*N*-(1,2,3,4-tetrahydro-6-isoquinolinyl)-1,3,4-thiadiazole-2-carboxamide hydrochloride.

The compounds of the invention have been found to inhibit SCD activity and may therefore be useful in regulating lipid levels, e.g. plasma lipid levels. Diseases or conditions caused by or associated with an abnormal plasma lipid profile and for the treatment of which the compounds of the invention may be useful include include dyslipidemia, hypoalphalipoproteinemia, hyperbetalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial hypercholesterolemia, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, atherosclerosis, obesity, Type I diabetes, Type II diabetes, insulin resistance, hyperinsulinaemia and metabolic syndrome. Other cardiovascular diseases for which the compounds of the present invention may be useful include peripheral vascular disease, reperfusion injury, angioplastic restenosis, hypertension, vascular complications of diabetes and thrombosis. Other diseases or conditions include hepatic steatosis, non-alcoholic steatohepatitis (NASH) and other diseases related to accumulation of lipids in the liver.

The compounds of the invention may also be useful in the treatment of skin disorders e.g. eczema, acne, psoriasis, keloid scar formation or prevention, and diseases related to production or secretions from mucous membranes.

The compounds of the invention may also be useful in the treatment of cancer, neoplasia, malignancy, metastases, tumours (benign or malignant), carcinogenesis, hepatomas and the like.

The compounds of the invention may also be useful in the treatment of mild cognitive impairment (MCI), Alzheimer's disease (AD), cerebral amyloid angiopathy (CAA) or

dementia associated with Down Syndrome (DS) and other neurodegenerative diseases characterized by the formation or accumulation of amyloid plaques comprising Aβ42.

Within the context of the present invention, the terms describing the indications used herein are classified in the Merck Manual of Diagnosis and Therapy, 17th Edition and/or the International Classification of Diseases 10th Edition (ICD-10). The various subtypes of the disorders mentioned herein are contemplated as part of the present invention.

In one aspect, the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in medical therapy.

In one aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating and/or preventing a disease or a condition susceptible to amelioration by an SCD inhibitor.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating and/or preventing acne, cancer, dyslipidemia, hypertriglyceridemia, atherosclerosis, obesity, Type II diabetes, insulin resistance, hyperinsulinaemia, hepatic steatosis and/or non-alcoholic steatohepatitis (NASH).

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating and/or preventing acne, cancer, dyslipidemia, atherosclerosis, insulin resistance, hyperinsulinaemia, Type II diabetes and/or hepatic steatosis.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating and/or preventing acne.

In one aspect, the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in treating and/or preventing a disease or a condition susceptible to amelioration by an SCD inhibitor in a mammal, including human.

In another aspect, the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in treating and/or preventing acne, cancer, dyslipidemia, hypertriglyceridemia, atherosclerosis, obesity, Type II diabetes, insulin resistance, hyperinsulinaemia, hepatic steatosis and/or non-alcoholic steatohepatitis (NASH).

In another aspect, the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in treating and/or preventing acne, cancer, dyslipidemia, atherosclerosis, insulin resistance, hyperinsulinaemia, Type II diabetes and/or hepatic steatosis.

In another aspect, the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in treating and/or preventing acne.

In one aspect, the invention provides a method for treating and/or preventing a disease or a condition susceptible to amelioration by an SCD inhibitor, which method comprises administering to a subject, for example a mammal, including human, a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides a method for treating and/or preventing a acne, cancer, dyslipidemia, hypertriglyceridemia, atherosclerosis, obesity, Type II diabetes, insulin resistance, hyperinsulinaemia, hepatic steatosis and/or non-alcoholic steatohepatitis (NASH), which method comprises administering to a subject, for example a mammal, including human, a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides a method for treating and/or preventing acne, cancer, dyslipidemia, atherosclerosis, insulin resistance, hyperinsulinaemia, Type II diabetes and/or hepatic steatosis, which method comprises administering to a subject, for example a mammal, including human, a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides a method for treating and/or preventing acne, which method comprises administering to a subject, for example a mammal, including human, a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

It will be appreciated that reference to "treatment" and "therapy" includes acute treatment or prophylaxis as well as the alleviation of established symptoms.

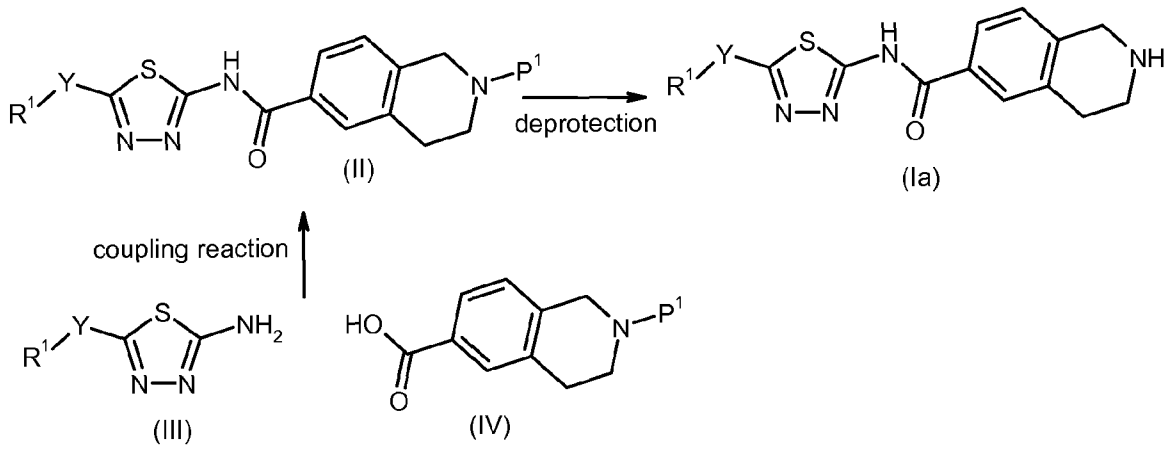
Since the compounds of the invention are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions; these less pure preparations of the compounds should contain at least 1%, more suitably at least 5% and preferably from 10 to 59% of a compound of the invention.

Processes for the preparation of the compounds of formula (I) form further aspects of the invention. R^1, R^2, R^3, R^4, R^5, R^6, R^7, X and Y are as defined above unless otherwise specified. Throughout the specification, general formulae are designated by Roman numerals (I), (II), (III), (IV) etc.

In certain instances final compounds of formula (I) can be converted into other compounds of formula (I) by techniques known to those in the art, for example, carboxylic acid substituents can be converted to esters or amides by routine techniques.

In a general process, compounds of formula (I), wherein X represents -NHCO-, Y represents $-OCH_2-$, $-CH_2-$, $-CH_2CH_2-$, $-OCH_2CH_2-$ or $-NR^7CH_2-$ (wherein R^7 represents H or $-CH_3$) and R^2 represents H (formula (Ia)) may be prepared according to reaction scheme 1 by reacting compounds of formula (III) and compounds of formula (IV), wherein P^1 represents a suitable nitrogen protecting groups such as Boc, to form a compound of formula (II). The reaction is suitably carried out in the presence of a coupling reagent such as HATU, EDCI and/or HOBt, in a suitable solvent such as DCM (suitably at room temperature to reflux) or DMF (suitably at room temperature), and is followed by deprotection of compound of formula (II) under acidic conditions such as hydrochloric acid in a suitable solvent such as ethyl acetate.

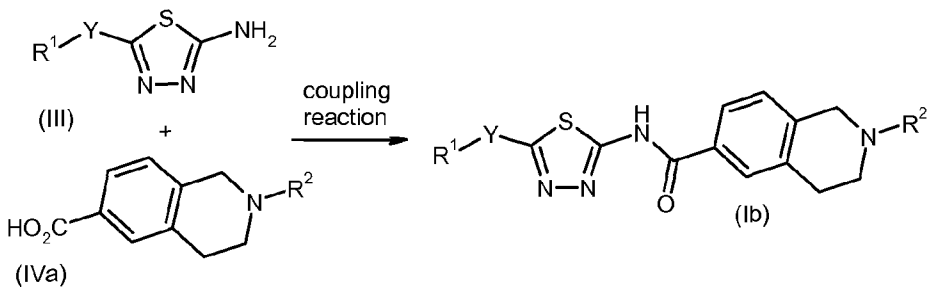
Scheme 1



Accordingly, in one aspect the invention provides a process for the preparation of compounds of the formula (Ia) by reacting compounds of formula (III), wherein R^1 and Y are defined above, with compounds of formula (IV), wherein P^1 is defined above, in the presence of a coupling agent, followed by deprotection of compounds of formula (II).

Compounds of formula (I), wherein X represents –NHCO-, Y represents -OCH_2-, -CH_2-, -CH_2CH_2- or -OCH_2CH_2- or -NR^7CH_2- (wherein R^7 represents H or -CH_3) and R^2 represents -C_{1-6}alkyl (formula (Ib)) may be prepared according to reaction scheme 2 by reacting compounds of formula (III) and compounds of formula (IVa) in the presence of a coupling reagent such as HATU, EDCI and/or HOBt, in a suitable solvent such as DCM (suitably at room temperature to reflux).

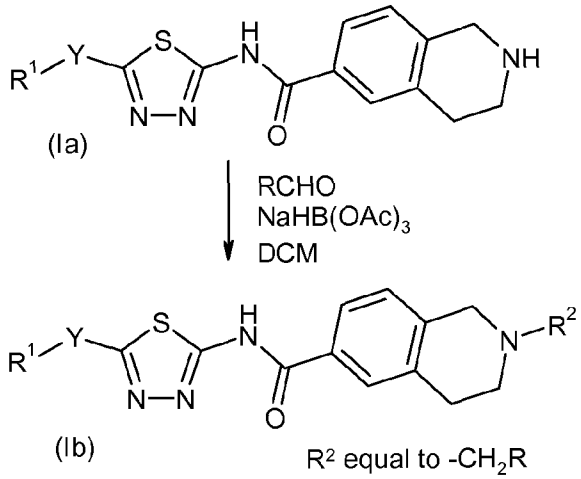
Scheme 2



Accordingly, in one aspect the invention provides a process for the preparation of compounds of the formula (Ib) by reacting compounds of formula (III), wherein R^1 and Y are defined above, with compounds of formula (IVa), wherein R^2 is defined above, in the presence of a coupling agent.

Compounds of formula (I), wherein X represents –NHCO-, Y represents -OCH_2-, -CH_2-, -CH_2CH_2- or -OCH_2CH_2- and R^2 represents -C_{1-6}alkyl (formula Ib) may also be prepared according to reaction scheme 3 by reacting compounds of formula (Ia) with a compound of formula R-CHO wherein R represents -C_{1-5}alkyl (in order to form an R^2 group which is –CH_2-R) in the presence of reductive agent such as Triacetoxy sodium borohydride, in a suitable solvent such as dichloromethane (suitably at room temperature).

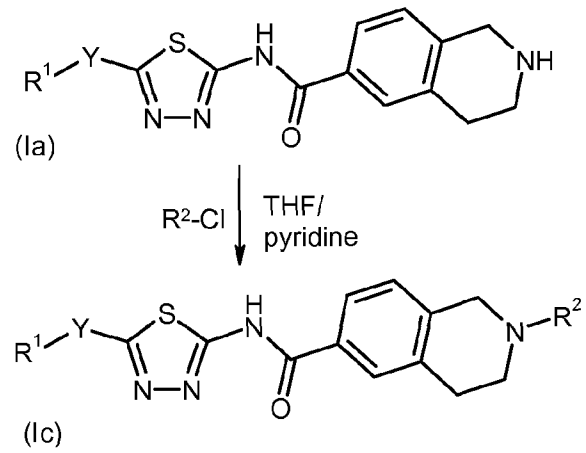
Scheme 3



Accordingly, in one aspect the invention provides a process for the preparation of compounds of the formula (Ib) by reacting a compound of formula (Ia), wherein R^1 and Y are defined above, with a compound of formula R-CHO, wherein R is defined above, in the presence of a reductive agent.

Compounds of formula (I), wherein X represents –NHCO-, Y represents $-OCH_2-$, $-CH_2-$, $-CH_2CH_2-$ or $-OCH_2CH_2-$ and R^2 represents $-C(=O)-C_{1-6}$alkyl, $-C(=O)-C_{3-6}$cycloalkyl or $-C(=O)-C_{6-10}$aryl (formula Ic) may be prepared according to reaction scheme 4 by reacting compounds of formula (Ia) with a compound of formula R^2-Cl in the presence of a base such as pyridine, in a suitable solvent such as THF (suitably at room temperature to reflux) or in the presence of a base such as triethylamine in dichloromethane as solvent at room temperature.

Scheme 4

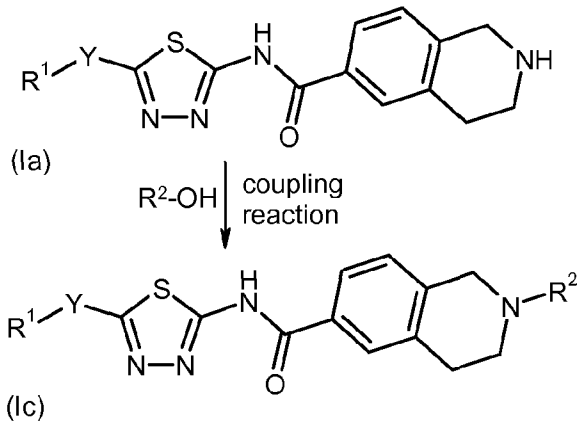


Accordingly, in one aspect the invention provides a process for the preparation of compounds of the formula (Ic) by reacting a compound of formula (Ia), wherein R^1 and

Y are defined above, with a compound of formula R^2-Cl, wherein R^2 is defined above, in the presence of a base.

Compounds of formula (I), wherein X represents –NHCO-, Y represents -OCH_2-, -CH_2-, -CH_2CH_2- or -OCH_2CH_2- and R^2 represents -C(=O)-C_{1-6}alkyl, -C(=O)-C_{3-6}cycloalkyl or -C(=O)-C_{6-10}aryl (formula Ic) may also be prepared according to reaction scheme 5 by reacting compounds of formula (Ia) with a compound of formula R^2-OH in the presence of a coupling reagent such as HATU, EDCI and/or HOBt, in a suitable solvent such as DMF (suitably at room temperature).

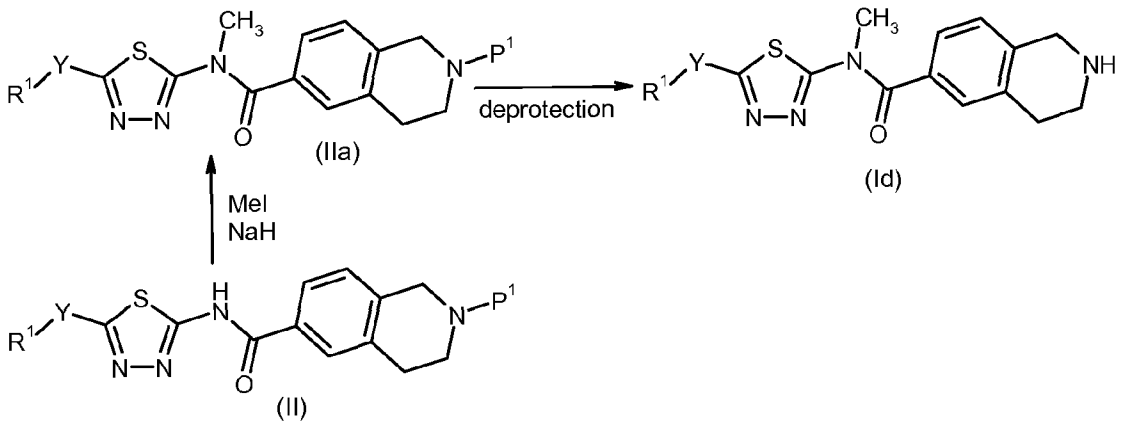
Scheme 5



Accordingly, in one aspect the invention provides a process for the preparation of compounds of the formula (Ic) by reacting a compound of formula (Ia), wherein R^1 and Y are defined above, with a compound of formula R^2-OH, wherein R^2 is defined above, in the presence of a coupling reagent.

Compounds of formula (I), wherein X represents –N(CH_3)CO-, Y represents -OCH_2-, -CH_2-, -CH_2CH_2- or -OCH_2CH_2- and R^2 represents H (formula (Id)) may be prepared according to reaction scheme 6 by reacting compounds of formula (II), wherein P^1 represents a suitable nitrogen protecting group such as Boc, with a halogenated methane compound (such as iodomethane) with a base such as sodium hydride in a suitable solvent such as THF (suitably at room temperature) and followed by deprotection of compound of formula (IIa) under acidic conditions such as hydrochloric acid in a suitable solvent such as ethyl acetate.

Scheme 6

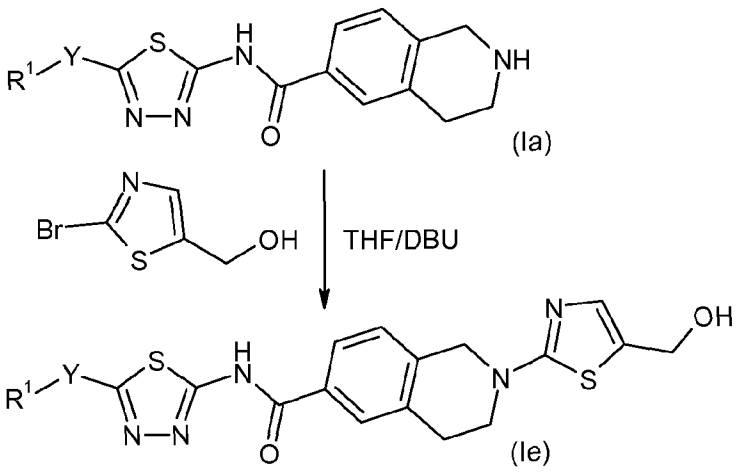


Accordingly, in one aspect the invention provides a process for the preparation of compounds of the formula (Id) by reacting compounds of formula (II), wherein R^1, Y and P^1 are defined above, with a halogenated methane compound, followed by deprotection of compounds of the formula (IIa).

Compounds of formula (I), wherein X represents $-N(CH_3)CO-$ and R^2 is other than H, may be synthesised by methods known to one skilled in the art using compounds of the formula (Id) and the processes described in schemes 3, 4, 5 and 7.

Compounds of formula (I), wherein X represents –NHCO-, Y represents $-OCH_2-$, $-CH_2-$, $-CH_2CH_2-$ or $-OCH_2CH_2-$ and R^2 represents -thiazoleCH_2OH (formula Ie) may be prepared according to reaction scheme 7 by reacting compounds of formula (Ia) with (2-bromo-1,3-thiazol-5-yl)methanol in the presence of a base such as DBU, in a suitable solvent such as THF (suitably at room temperature to 60°C).

Scheme 7

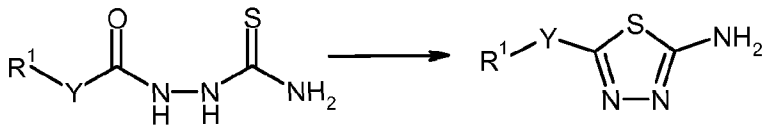


Accordingly, in one aspect the invention provides a process for the preparation of compounds of the formula (Ie) by reacting compounds of formula (Ia), wherein R^1 and

Y are defined above, with (2-bromo-1,3-thiazol-5-yl)methanol in the presence of a base.

Compounds of formula (III) wherein Y represents $-OCH_2-$, $-CH_2-$, $-CH_2CH_2-$, $-OCH_2CH_2-$ or $-NR^7CH_2-$ (wherein R^7 represents H or $-CH_3$) may be prepared according to reaction scheme 8 by reacting compounds of formula (VIII) in the presence of methane sulphonic acid in a suitable solvent such as toluene suitably at reflux or in presence of phosphorous tribromide (suitably at room temperature to 60°C).

Scheme 8

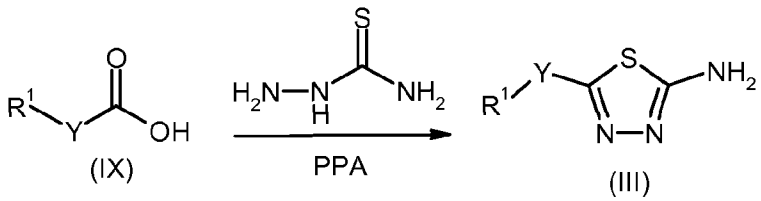


(VIII) (III)

Accordingly, in one aspect the invention provides a process for the preparation of compounds of the formula (III) by reacting compounds of formula (VIII), wherein R^1 and Y are defined above, in the presence of methane sulphonic acid in a suitable solvent.

Compounds of formula (III) wherein Y represents $-OCH_2-$, $-CH_2-$, $-CH_2CH_2-$ or $-OCH_2CH_2-$ may also be prepared according to reaction scheme 9 by reacting compounds of formula (IX) in the presence of hydrazinecarbothioamide in a suitable solvent such as polyphosphoric acid (suitably at room temperature to 110°C).

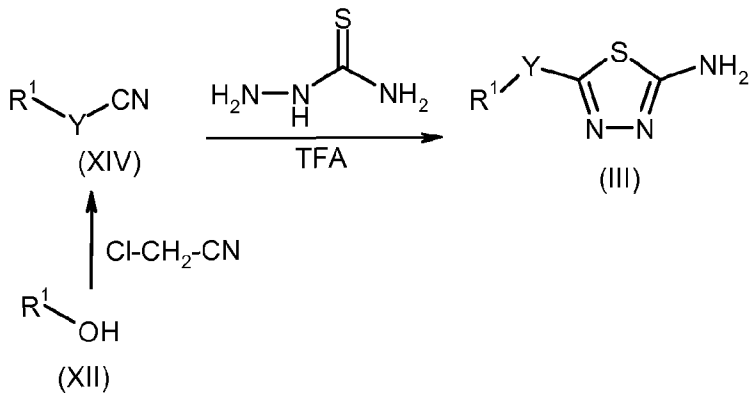
Scheme 9



(IX) PPA (III)

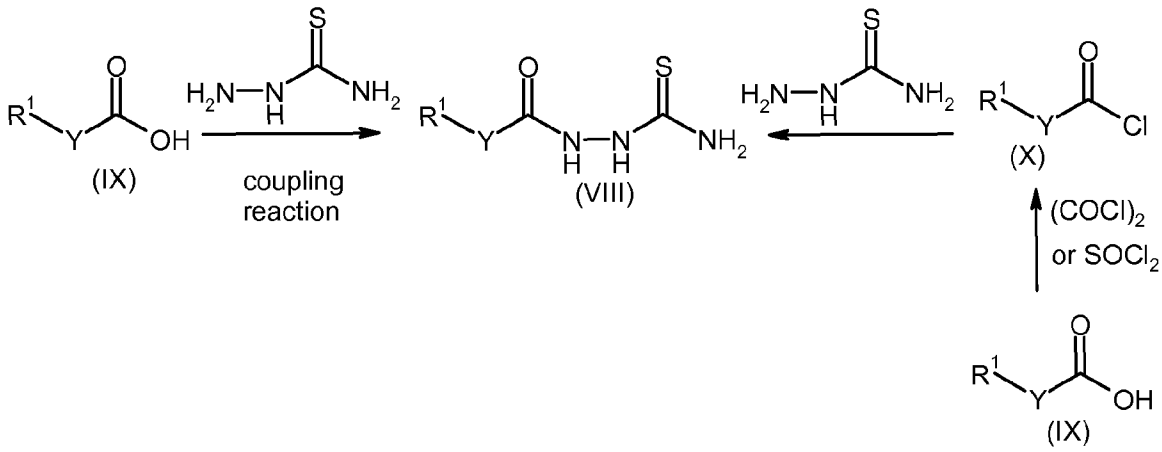
Compounds of formula (III) wherein Y represents $-OCH_2-$, $-CH_2-$, $-CH_2CH_2-$ or $-OCH_2CH_2-$ may also be prepared according to reaction scheme 10 by reacting compounds of formula (XIV) in the presence of hydrazinecarbothioamide in a suitable solvent such as trifluoroacetic acid (suitably at reflux). Compounds of formula (XIV) when Y is $-OCH_2-$ may be prepared according to reaction scheme 8 by reacting compound of formula (XII) with a reagent such as 2-chloroacetonitrile in the presence of a base such as potassium carbonate in a suitable solvent such as acetone

Scheme 10



Compounds of formula (VIII) wherein Y represents $-OCH_2-$, $-CH_2-$, $-CH_2CH_2-$, $-OCH_2CH_2-$ or $-NR^7CH_2-$ (wherein R^7 represents H or $-CH_3$) may be prepared according to reaction scheme 11 by reacting compounds of formula (IX) with hydrazinecarbothioamide in the presence of a coupling reagent such as HATU, EDCI and/or HOBt, in a suitable solvent such as DMF (suitably at room temperature to 80°C). Compounds of formula (VIII) may also be prepared according to reaction scheme 11 by reacting compounds of formula (X) with hydrazinecarbothioamide with a base such as pyridine in a suitable solvent such as DMF (suitably at room temperature to reflux). Compounds of formula (X) may be prepared by reacting compounds of formula (IX) with a chlorinating agent such as oxalyl chloride or thionyl chloride in a suitable solvent such as dichloromethane.

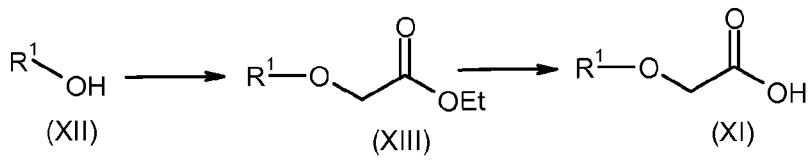
Scheme 11



Compounds of formula (XI), wherein Y represents $-OCH_2-$, may be prepared according to reaction scheme 12 by reacting compounds of formula (XII) with a reagent such as ethyl bromoacetate or ethyl chloroacetate in the presence of a base such as potassium carbonate in a suitable solvent such as acetone, followed by saponification of compound of formula (XIII) with a base such as sodium hydroxide or potassium

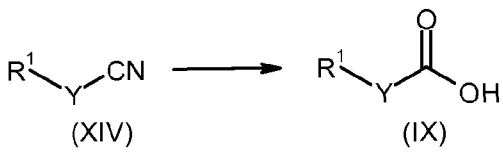
hydroxide in a suitable solvent such as ethanol or methanol (suitably at room temperature to reflux).

Scheme 12



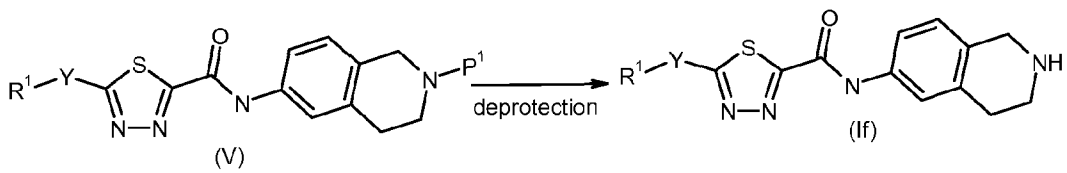
Compounds of formula (IX) wherein Y represents $-OCH_2-$, $-CH_2-$, $-CH_2CH_2-$ or $-OCH_2CH_2-$ may be prepared according to reaction scheme 13 by reacting compounds of formula (XIV) with a reagent such as sodium hydroxide in a suitable solvent such as water (suitably at room temperature to reflux).

Scheme 13



Compounds of formula (I), wherein X represents –CONH-, Y represents $-OCH_2-$, $-CH_2CH_2-$ or $-OCH_2CH_2-$ and R^2 represents hydrogen (formula (If)) may be prepared according to reaction scheme 14 by deprotection of compounds of formula (V), wherein P^1 represents a suitable nitrogen protecting group such as Boc, under acidic conditions such as hydrochloric acid or trifluoracetic acid.

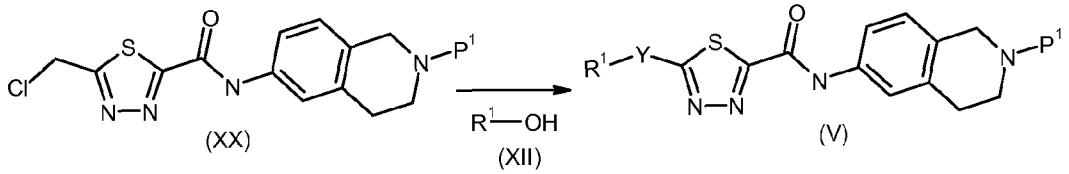
Scheme 14



Accordingly, in one aspect the invention provides a process for the preparation of compounds of the formula (If), wherein R^1 and Y are defined above, by deprotecting compounds of the formula V, wherein P^1 is defined above, under acidic conditions.

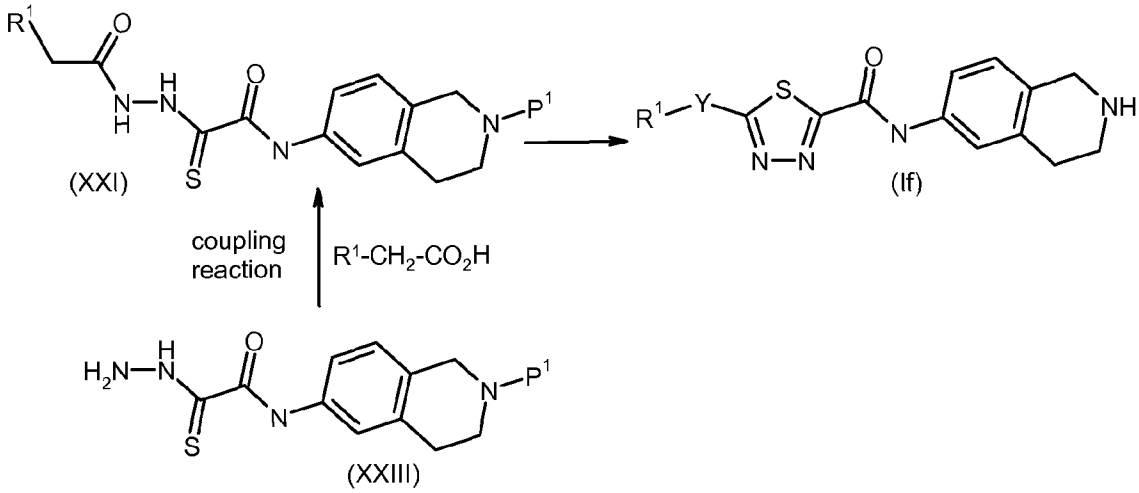
Compounds of formula (V), wherein X represents –CONH- and Y represents $-OCH_2-$, may be prepared according to reaction scheme 15 by reacting compounds of formula (XX), wherein P^1 represents a suitable nitrogen protecting groups such as Boc, with a compound of formula (XII) in the presence of a base such as potassium carbonate in a suitable solvent such as acetone (suitably at room temperature to reflux).

Scheme 15



Compounds of formula (I), wherein X represents –CONH-, Y represents -CH_2- and R^2 represents hydrogen (formula (If)), may be prepared according to reaction scheme 16 by reacting compounds of formula (XXII), wherein P^1 represents a suitable nitrogen protecting group such as Boc, and compounds of formula (XXIII) to form a compound of formula (XXI). The reaction is suitably carried out in the presence of a coupling reagent such as HATU, EDCI and/or HOBt, in a suitable solvent such as DCM (suitably at room temperature to reflux) or DMF (suitably at room temperature), and is followed by reaction of compound of formula (XXI) in presence of phosphorous tribromide in a suitable solvent such as dichloromethane (suitably at room temperature to reflux).

Scheme 16

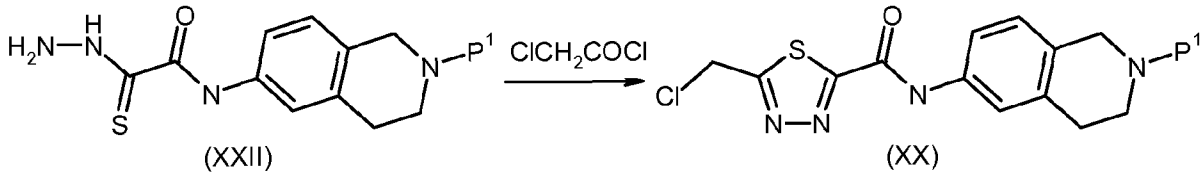


Accordingly, in one aspect the invention provides a process for the preparation of compounds of the formula (If), wherein R^1 and Y are defined above, by reacting compounds of formula (XXII) and compounds of formula (XXIII), followed by reaction of compound of formula (XXI) in presence of phosphorous tribromide.

Compounds of formula (I), wherein X represents -CONH- and R^2 is other than H, may be synthesised by methods known to one skilled in the art using compounds of the formula (If) and the processes as described in schemes 3, 4, 5 and 7.

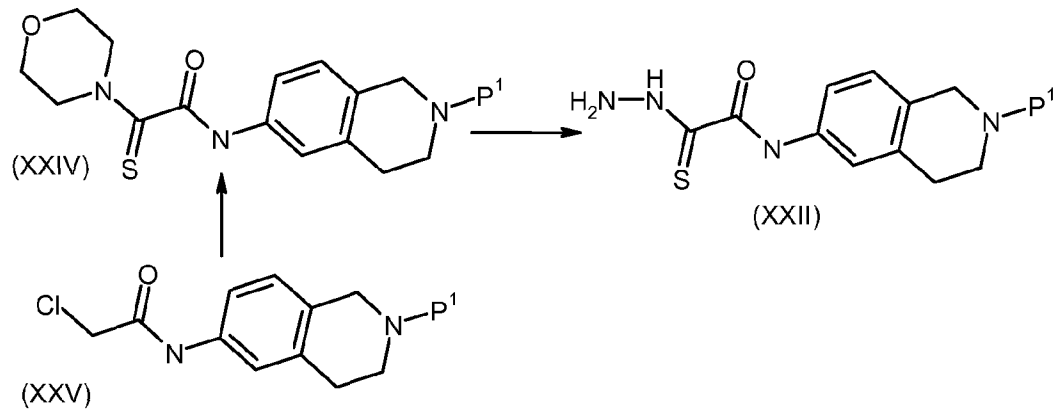
Compounds of formula (XX) may be prepared according to reaction scheme 17 by reacting compounds of formula (XXII) with a reagent such as chloroacetyl chloride in a suitable solvent such as DMF (suitably at room temperature).

Scheme 17



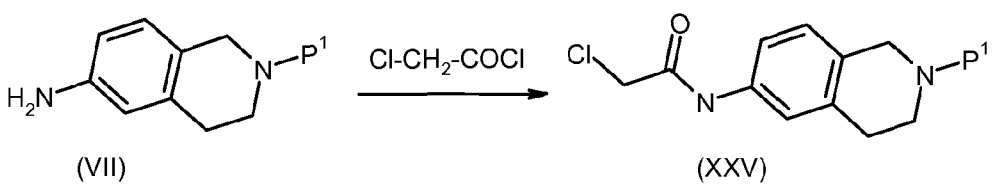
Compounds of formula (XXII) may be prepared according to reaction scheme 18 by reacting compounds of formula (XXV), wherein P^1 represents a suitable nitrogen protecting group such as Boc, with a reagent such as sulphur and morpholine in a suitable solvent such as DMF (suitably at room temperature). The reaction is followed by reaction of compounds of formula (XXIV) with a reagent such as hydrazine hydrate in a suitable solvent such as DMF (suitably at room temperature).

Scheme 18



Compounds of formula (XXV) may be prepared according to reaction scheme 19 by reacting compounds of formula (VII), wherein P^1 represents a suitable nitrogen protecting group such as Boc, with a reagent such as chloroacetyl chloride in a suitable solvent such as THF (suitably at room temperature).

Scheme 19



Compounds of the formula (IV), (VI) (VII), (XII), (XIV) and (XXIII) are commercially available compounds or may be prepared by methods known in the literature or processes known to those skilled in the art.

Further details for the preparation of compounds of formula (I) are found in the examples section hereinafter.

The compounds of the invention may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000 compounds, and more preferably 10 to 100 compounds. Libraries of compounds of the invention may be prepared by a combinatorial 'split and mix' approach or by multiple parallel syntheses using either solution phase or solid phase chemistry, by procedures known to those skilled in the art. Thus according to a further aspect there is provided a compound library comprising at least 2 compounds of the invention.
Those skilled in the art will appreciate that in the preparation of compounds of formula (I) and/or salts thereof it may be necessary and/or desirable to protect one or more sensitive groups in the molecule or the appropriate intermediate to prevent undesirable side reactions. Suitable protecting groups for use according to the present invention are well known to those skilled in the art and may be used in a conventional manner. See, for example, "Protective groups in organic synthesis" by T.W. Greene and P.G.M. Wuts (John Wiley & sons 1991) or "Protecting Groups" by P.J. Kocienski (Georg Thieme Verlag 1994). Examples of suitable amino protecting groups include acyl type protecting groups (e.g. formyl, trifluoroacetyl, acetyl), aromatic urethane type protecting groups (e.g. benzyloxycarbonyl (Cbz) and substituted Cbz), aliphatic urethane protecting groups (e.g. 9-fluorenylmethoxycarbonyl (Fmoc), t-butyloxycarbonyl (Boc), isopropyloxycarbonyl, cyclohexyloxycarbonyl) and alkyl or aralkyl type protecting groups (e.g. benzyl, trityl, chlorotrityl).

Various intermediate compounds used in the above-mentioned process, including but not limited to certain compounds of formulae (II), (V), constitute a further aspect of the present invention.

The compounds of formula (I) or pharmaceutically acceptable salt(s) thereof may also be used in combination with other therapeutic agents. The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or pharmaceutically acceptable salt thereof together with one or more further therapeutic agent(s).

Compounds of the invention may be administered in combination with other therapeutic agents. Preferred therapeutic agents are selected from the list: an inhibitor of cholesteryl ester transferase (CETP inhibitors), a HMG-CoA reductase inhibitor, a microsomal triglyceride transfer protein, a peroxisome proliferator-activated receptor

activator (PPAR), a bile acid reuptake inhibitor, a cholesterol absorption inhibitor, a cholesterol synthesis inhibitor, a fibrate, niacin, an ion-exchange resin, an antioxidant, an inhibitor of AcylCoA: cholesterol acyltransferase (ACAT inhibitor), a cannabinoid 1 antagonist a bile acid sequestrant a corticosteroid, a vitamin D3 derivative, a retinoid, an immunomodulator, an anti androgen, a keratolytic agent, an anti-microbial, a platinum chemotherapeutic, an antimetabolite, hydroxyurea, a taxane, a mitotic disrupter, an anthracycline, dactinomycin, an alkylating agent and a cholinesterase inhibitor.

When the compound of formula (I) or pharmaceutically acceptable salt thereof is used in combination with a second therapeutic agent the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art. It will be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with at least one pharmaceutically acceptable carrier and/or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations by any convenient route.

When administration is sequential, either the SCD inhibitor or the second therapeutic agent may be administered first. When administration is simultaneous, the combination may be administered either in the same or different pharmaceutical composition.

When combined in the same formulation it will be appreciated that the two compounds must be stable and compatible with each other and the other components of the formulation. When formulated separately they may be provided in any convenient formulation, conveniently in such manner as are known for such compounds in the art.

The invention also includes a pharmaceutical composition comprising one or more compounds of formula (I) or pharmaceutically acceptable salt(s) in combination with one or more excipients.

The compounds of the invention may be administered in conventional dosage forms prepared by combining a compound of the invention with standard pharmaceutical carriers or diluents according to conventional procedures well known in the art. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

The pharmaceutical compositions of the invention may be formulated for administration by any route, and include those in a form adapted for oral, topical or parenteral administration to mammals including humans.

The compositions may be in the form of tablets, capsules, powders, granules, lozenges, creams or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

The topical formulations of the present invention may be presented as, for instance, dispersions, lotions, creams, gels, pastes, powders, aerosol sprays, syrups or ointments on sponges or cotton applicators, and solutions or suspensions in an aqueous liquid, non-aqueous liquid, oil-in-water emulsion, or water-in-oil liquid emulsion.

Creams, lotions, or ointments, may be prepared as rinse-off or leave-on products, as well as two stage treatment products for use with other skin cleansing or managing compositions. The compositions can be administered as a rinse-off product in a higher concentration form, such as a gel, and then a leave-on product in a lower concentration to avoid irritation of the skin. Each of these forms is well understood by those of ordinary skill in the art, such that dosages may be easily prepared to incorporate the pharmaceutical composition of the invention.

Ointments are hydrocarbon-based semisolid formulations containing dissolved or suspended drugs. Creams and lotions are semi-solid emulsion systems and the term is applied both to water/oil or oil/water. Gel formulations are semi-solid systems in which a liquid phase is trapped in a polymeric matrix.

By way of non-limiting example, the ointments may contain one or more hydrophobic carriers selected from, for example, white soft paraffin or other mineral waxes, liquid paraffin, non-mineral waxes, long chain alcohols, long chain acids and silicones. The ointment may contain in addition to the hydrophobic carriers some hydrophillic carriers selected from, for example, propylene glycol and polyethylene glycol in combination with an appropriate surfactant/co-surfactant system. The carrier compositions of the creams or lotions are typically based on water, white soft paraffin and an appropriate surfactant/co-surfactant system, in combination with other carriers/components selected from, for example, propylene glycol, butylene glycol glycerinemonostearate, PEG-glycerinemonostearate, esters such as C_{12-15} alkyl benzoate, liquid paraffin, non-mineral waxes, long chain alcohols, long chain acids silicones, non-silicone polymers. The gels may by way of example be formulated using isopropyl alcohol or ethyl alcohol, propylene glycol and water with a gelling agent such as hydroxyethyl cellulose, suitably in combination with minor components, for example one or more of butylene glycol and a wetting agent such as a poloxamer.

An ointment, cream, lotion, gel, and the like, can further comprise a moisturizing agent. The moisturizing agent can be a hydrophobic moisturizing agent such as ceramide, borage oil, tocopherol, tocopherol linoleate, dimethicone or a mixture thereof or a hydrophilic moisturizing agent such as glycerine, hyaluronic acid, sodium peroxylinecarbolic acid, wheat protein, hair keratin amino acids, or a mixture thereof.

The compositions according to the invention may also comprise conventional additives and adjuvants for dermatological applications, such as preservatives, acids or bases used as pH buffer excipients and antioxidants.

The present invention encompasses administration via a transdermal patch or other forms of transdermal administration. Suitable formulations for transdermal administration are known in the art, and may be employed in the methods of the present invention. For example, suitable transdermal patch formulations for the administration of a pharmaceutical compound are described in, for example, U.S. Pat. No. 4, 460,372 to Campbell et al., U.S. Pat. No. 4,573,996 to Kwiatek et al., U. S. Pat. No. 4,624,665 to Nuwayser, U.S. Pat. No. 4,722,941 to Eckert et al., and U.S. Pat. No. 5, 223,261 to Nelson et al.

One suitable type of transdermal patch for use in the methods of the present invention encompasses a suitable transdermal patch includes a backing layer which is non-permeable, a permeable surface layer, an adhesive layer substantially continuously coating the permeable surface layer, and a reservoir located or sandwiched between the backing layer and the permeable surface layer such that the backing layer extends around the sides of the reservoir and is joined to the permeable surface layer at the edges of the permeable surface layer. The reservoir contains a compound of formula (I) or pharmaceutically acceptable salt thereof, alone or in combination, and is in fluid contact with the permeable surface layer. The transdermal patch is adhered to the skin by the adhesive layer on the permeable surface layer, such that the permeable surface layer is in substantially continuous contact with the skin when the transdermal patch is adhered to the skin. While the transdermal patch is adhered to the skin of the subject, the compound of formula (I) or pharmaceutically acceptable salt thereof contained in the reservoir of the transdermal patch is transferred via the permeable surface layer, from the reservoir, through the adhesive layer, and to the skin of the patient. The transdermal patch may optionally also include one or more penetration-enhancing agents in the reservoir that enhance the penetration of the compound of formula (I) or pharmaceutically acceptable salt thereof through the skin.

Examples of suitable materials which may comprise the backing layer are well known in the art of transdermal patch delivery, and any conventional backing layer material may be employed in the transdermal patch of the instant invention.

Suitable penetration-enhancing agents are well known in the art as well. Examples of conventional penetration-enhancing agents include alkanols such as ethanol, hexanol, cyclohexanol, and the like, hydrocarbons such as hexane, cyclohexaue, isopropylbenzene; aldebydes and ketones such as cyclohexanone, acetamide, N,N-di(lower alkyl)acetamides such as N,N-diethylacetamide, N,N-dimethyl acetamide, N-(2-hydroxyethyl) acetamide, esters such as N,N-di-lower alkyl sulfoxides; essential oils such as propylene glycol, glycerine, glycerol monolaurate, isopropyl myristate, and ethyl oleate, salicylates, and mixtures of any of the above.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring or colouring agents.

Preparations for oral administration may be suitably formulated to give controlled/extended release of the active compound.

Suppositories will contain conventional suppository bases, e.g. cocoa-butter or other glyceride.

For parenteral administration, fluid unit dosage forms are prepared utilising the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing.

Advantageously, agents such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry

lyophilised powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% by weight, preferably from 10-60% by weight, of the active ingredient, depending on the method of administration. Where the compositions comprise dosage units, each unit will preferably contain from 50-500 mg of the active ingredient. The dosage as employed for adult human treatment will preferably range from 100 to 3000 mg per day, for instance 1500 mg per day depending on the route and frequency of administration. Such a dosage corresponds to 1.5 to 50 mg/kg per day. Suitably the dosage is from 5 to 20 mg/kg per day.

It will be recognised by one of skill in the art that the optimal quantity and spacing of individual dosages of a compound of the invention will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular mammal being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of a compound of the invention given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

The invention also extends to novel intermediates disclosed herein, used in the preparation of compounds of formula (I)

DEFINITIONS

AcOEt	ethyl acetate
Boc	tertbutyloxy carbonyl
CCl_4	carbon tetrachloride
DIPEA	diisopropylethylamine
DCM	dichloromethane
DMF	dimethylformamide
Et_3N	triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
Fmoc	9-Fluorenylmethoxycarbonyl
HATU	O-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HCl	hydrochloric acid
HOBt	1-hydroxybenzotriazole

m-CPBA	meta chloroperbenzoic acid
MeCN	acetonitrile
Me	methyl
MeOH	methanol
$NaBH_3CN$	sodium cyanoborohydride
$NaHB(OAc)_3$	triacetoxy sodium borohydride
NaOH	sodium hydroxide
Net_3	triethylamine
NH_2NH_2	hydrazine
PPA	polyphosphoric acid
$Pd(PPh_3)_4$	Palladium tetrakis

Regardless of how the preparation of compounds are represented in the present specification no inference can be drawn that particular batches (or mixtures of two or more batches) of intermediates were used in the next stage of the preparation. The examples and intermediates are intended to illustrate the synthetic routes suitable for preparation of the same, to assist the skilled persons understanding of the present invention.

Where reference is made to the use of a "similar" procedure, as will be appreciated by those skilled in the art, such a procedure may involve minor variation, for example reaction temperature, reagent/solvent amount, reaction time, work-up conditions or chromatographic purification conditions.

Analytical methods LC-MS

Analytical HPLC was conducted on a X-terra MS C18 column (2.5 µm 3 x 30 mm id) eluting with 0.01M ammonium acetate in water (solvent A) and 100% acetonitrile using the following elution gradient: 0 to 4 minutes, 5 to 100%B; 4 to 5 minutes, 100%B at a flow-rate of 1.1 mL/min with a temperature of 40°C.

The mass spectra (MS) were recorded on a micromass ZQ-LC mass spectrometer using electrospray positive ionisation [ES+ve to give MH^+ molecular ion] or electrospray negative ionisation [ES-ve to give $(M-H)^-$ molecular ion] modes.

Analytical methods LC-HRMS

Analytical HPLC was conducted on an Uptisphere-hsc column (3 µm 30 x 3 mm id) eluting with 0,01M ammonium acetate in water (solvent A) and 100% acetonitrile (solvent B) using the following elution gradient: 0 to 0.5 minutes, 5%B; 0.5 to 3.5 minutes, 5 to 100%B; 3.5 to 4 minutes, 100%B; 4 to 4.5 minutes, 100 to 5%B; 4.5 to 5.5 minutes, 5%B at a flow-rate of 1.3 mL/min with a temperature of 40°C.

The mass spectra (MS) were recorded on a micromass LCT, mass spectrometer using electrospray positive ionisation [ES+ve to give MH^+ molecular ion] or electrospray negative ionisation [ES-ve to give $(M-H)^-$ molecular ion] modes.

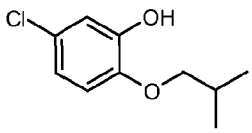
Analytical method GC-MS

Analytical GC was conducted on a DB-1ms column (Agilent Technologies), 0.1µm 10m x 0.1mm id) eluting with an Helium flow of 0.5ml/min and pressure at 3.4 bar and with a gradient temperature: 0 to 0.35 min, 100°C; 0.35min to 6min, 100°C to 250°C (ramp of 80°C/min).

The mass spectra (MS) were recorded on a Agilent Technologies G5973 mass spectrometer using electronic impact ionisation.

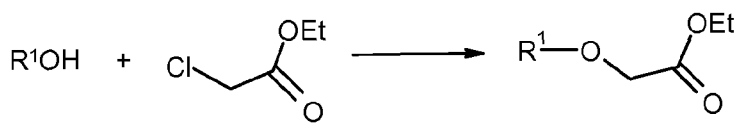
The following non-limiting examples illustrate the present invention.

Intermediate 1: 5-Chloro-2-[(2-methylpropyl)oxy]phenol

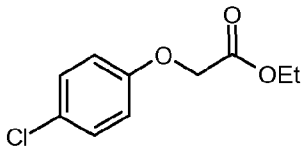


5-Chloro-2-[(2-methylpropyl)oxy]benzaldehyde (10 g, 47.17 mmol) was dissolved in dichloromethane (80 ml). The solution was cooled to 65°C. m-CPBA 85% (8.85 g, 51.45 mmol) was added slowly. The mixture was stirred at room temperature overnight. The solid was filtered and the filtrate was concentrated. The residue was diluted with methanol (80 ml). The solution was cooled below 20°C and a solution of NaOH 20% (43 ml, 0.215 mol) was added. The mixture was stirred for 30 min and was acidified with concentrated HCl. The mixture was cooled to 5°C. The solid was filtered, washed with cold water. The solid was dissolved with ethyl acetate, washed with brine, dried over Na_2SO_4 and the organic phase was concentrated. The residue was purified by flash column chromatography eluting with pentane/ethyl acetate 10:1 to give the title compound (9 g, 96%).
^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 6.9 (s, 1H), 6.8 (m, 2H), 3.80 (d, 2H), 2.10 (m, 1H), 1.00 (d, 6H).

The following Intermediates were prepared using the generic reaction scheme (Scheme 12)



Intermediate 2: Ethyl [(4-chlorophenyl)oxy]acetate



To a solution of 4-chlorophenol (25.6 g, 0.2 mol.) in DMF were added potassium carbonate (41.4 g, 0.2 mol.) and then drop-wise, ethyl chloroacetate (21.2 ml, 0.2 mol.). The solution was heated at 70°C overnight. After filtration, the filtrate was poured into water and extracted with ethyl acetate. The organic layer was washed with water then brine, dried on sodium sulphate and evaporated to dryness to give the title compound as a dark oil (30 g, 70%).

LC/MS: m/z 215 $(M+H)^+$, Rt: 4.66 min.

The following Intermediates were similarly prepared by a method analogous to that described for Intermediate 2.

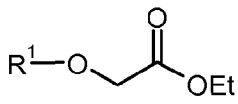
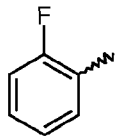
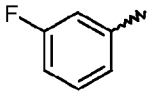
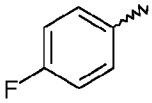
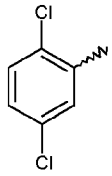
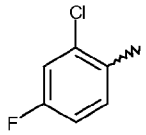
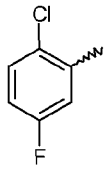
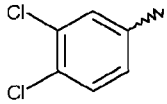
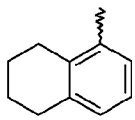
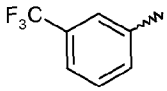
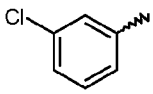
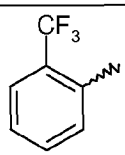
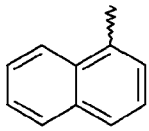
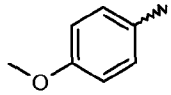
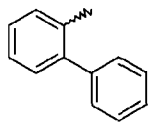
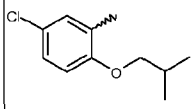
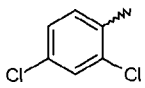
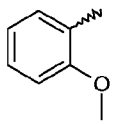


Table 1

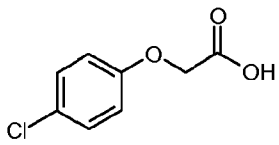
Intermediate No.	R^1	From:	Physical data
3 Ethyl [(2-fluorophenyl)oxy] acetate		Commercially available	LC/MS: m/z 199 (M+H)+ Rt: 3.34 min
4 Ethyl [(3-fluorophenyl)oxy] acetate		Commercially available	LC/MS: m/z 199 (M+H)+ Rt: 3.39 min
5 Ethyl [(4-fluorophenyl)oxy] acetate		Commercially available	LC/MS: m/z 199 (M+H)+ Rt: 3.26 min
6 Ethyl [(2,5-dichlorophenyl) oxy]acetate		Commercially available	^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.33 (d, 1H, J=8.54 Hz), 6.96 (dd, 1H, J=2.25 Hz, 8.41 Hz), 8.85 (d, 1H, J=2.08 Hz), 4.71 (s, 2H), 4.31 (q, 2H, J=7.15 Hz), 1.33 (t, 3H, J=7.15 Hz).

7 Ethyl [(2-chloro-4-fluorophenyl)oxy]acetate		Commercially available	^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.08 (dd, 1H, J=3.04 Hz, 7.95 Hz), 6.81 (m, 2H), 4.59 (s, 2H), 4.19 (q, 2H, J=7.29 Hz), 1.22 (t, 3H, J=7.29 Hz).
8 Ethyl [(2-chloro-5-fluorophenyl)oxy]acetate		Commercially available	^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.35 (dd, 1H, J=6.10 Hz, 8.71 Hz), 6.70 (td, 1H, J=2.67 Hz, 8.06 Hz), 6.60 (dd, 1H, J=2.61 Hz, 10.07 Hz), 4.70 (s, 2H), 4.30 (q, 2H, J=7.14 Hz), 1.32 (t, 3H, J=7.33 Hz).
9 Ethyl [(3,4-dichlorophenyl)oxy]acetate		Commercially available	^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.4 (d, 1H), 7.0 (s, 1H), 6.8 (d, 1H), 4.6 (s, 2H), 4.2 (q, 2H), 1.3 (t, 3H).
10 Ethyl (5,6,7,8-tetrahydro-1-naphthalenyloxy)acetate		Commercially available	^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.05 (t, 1H, J=8.07 Hz), 6.76 (d, 1H, 7.83 Hz), 6.54 (d, 1H, J=8.31 Hz), 4.64 (s, 2H), 4.29 (q, 2H, J=7.12 Hz), 2.78 (m, 4H), 1.81 (m, 4H), 1.33 (t, 3H, J=7.12 Hz).
11 Ethyl {[3-(trifluoromethyl)phenyl] oxy}acetate		Commercially available	^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.40 (t, 1H), 7.26 (dd, 1H), 7.14 (s, 1H), 7.1 (dd, 1H), 4.65 (s, 2H), 4.27 (q, 2H), 1.29 (t, 3H).
12 Ethyl [(3-chlorophenyl)oxy] acetate		Commercially available	LC/MS: m/z 215 (M+H)+ Rt: 3.49 min
13 Ethyl {[2-(trifluoromethyl)phenyl] oxy}acetate		Commercially available	^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.6 (dd, 1H), 7.5 (t, 1H), 7.06 (t, 1H), 6.87 (d, 1H),

			4.72 (s, 2H), 4.26 (q, 2H), 1.28 (t, 3H).
14 Ethyl (1-naphthalenyloxy) acetate		Commercially available	^{1}H NMR (300 MHz, DMSO, ppm) δ: 8.40 (m, 1H), 7.83 (m, 1H), 7.53 (m, 3H), 7.37 (t, 1H, J=7.78 Hz), 6.74 (d, 1H, J=7.56 Hz), 4.83 (s, 2H), 4.33 (q, 2H, J=7.30 Hz), 1.34 (t, 3H, J=7.30Hz).
15 Ethyl {[4-(methyloxy)phenyl] oxy}acetate		Commercially available	^{1}H NMR (300 MHz, DMSO, ppm) δ: 6.80 (s, 4H), 4.6 (s, 2H), 4.3 (q, 2H), 3.75 (s, 3H), 1.3 (t, 3H).
16 Ethyl (2-biphenylyloxy) acetate		Commercially available	^{1}H NMR (300 MHz, DMSO, ppm) δ: 7.49 (d, 2H), 7.35 (t, d, 5H), 7.1 (dd, 2H), 4.8 (s, 2H), 4.1 (q, 2H), 1.2 (t, 3H).
17 Ethyl ({5-chloro-2-[(2-methylpropyl)oxy]phenyl} oxy)acetate		5-Chloro-2-[(2-methylpropyl) oxy]phenol (Intermediate 1)	^{1}H NMR (300 MHz, DMSO, ppm) δ: 6.95-6.70 (m, 3H), 4.62 (s, 2H), 4.22 (q, 2H), 3.75 (d, 2H), 2.10 (m, 1H), 1.25 (t, 3H), 1.05 (d, 6H).
18 Ethyl [(2,4-dichlorophenyl) oxy]acetate		Commercially available	^{1}H NMR (300 MHz, DMSO, ppm) δ: 7.42 (d, 1H), 7.19 (dd, 1H), 6.49 (d, 1H), 4.70 (s, 2H), 4.27 (q, 2H), 1.31 (t, 3H).
19 Ethyl {[2-(methyloxy)phenyl] oxy}acetate		Commercially available	Not isolated

The following Intermediates were prepared using the generic reaction scheme (Scheme 12)

Intermediate 20: [(4-Chlorophenyl)oxy]acetic acid



To a solution of ethyl [(4-chlorophenyl)oxy]acetate (Intermediate 2) (60 g, 0.28 mol.) in methyl alcohol was added a solution of potassium hydroxide (28 g, 0.5 mol.) in water. The solution was heated at 70°C overnight. After concentration under reduced pressure, the mixture was cooled with iced water and concentrated HCl (20 ml, 10 M) was added. The resulting solid material was filtered and dried to give the title compound as a white solid (40 g, 77%).

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.3 (d, 2H), 6.9 (d, 2H), 4.6 (s, 2H).

The following compounds were similarly prepared by a method analogous to that described for Intermediate 20.

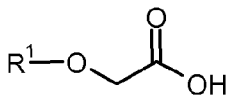
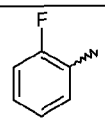
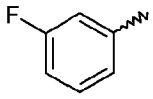
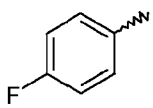
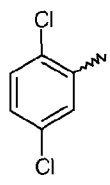
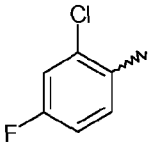
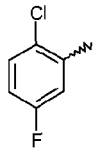
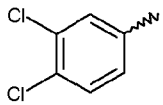
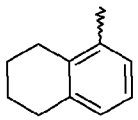
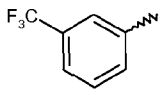
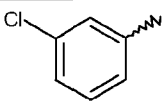
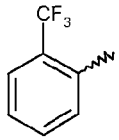
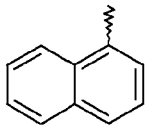
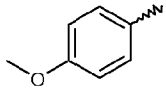
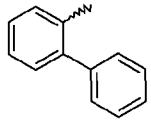
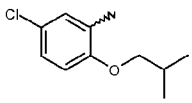
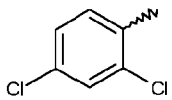
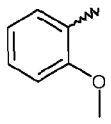


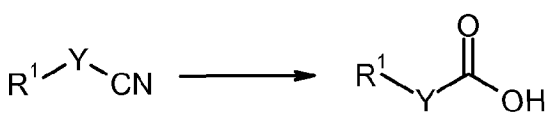
Table 2

Intermediate No	R^1	From Intermediate No.	Physical data
21 [(2-fluorophenyl)oxy] acetic acid		3 Ethyl [(2-fluorophenyl) oxy]acetate	LC/MS: m/z 171 $(M+H)^+$ Rt: 2.54 min
22 [(3-fluorophenyl)oxy] acetic acid		4 Ethyl [(3-fluorophenyl) oxy]acetate	LC/MS: m/z 171 $(M+H)^+$ Rt: 2.70 min
23 [(4-fluorophenyl)oxy] acetic acid		5 Ethyl [(4-fluorophenyl) oxy]acetate	^{1}H NMR (300 MHz, DMSO, ppm) δ: 7.1 (d, 2H), 6.94 (d, 2H), 4.65 (s, 2H).
24 [(2,5-dichlorophenyl) oxy]acetic acid		6 Ethyl [(2,5-dichlorophenyl)oxy] acetate	^{1}H NMR (300 MHz, CDCl3, ppm) δ: 7.46 (d, 1H, J=8.39 Hz), 7.16 (d, 1H, J=2.42 Hz), 7.04 (dd, 1H,

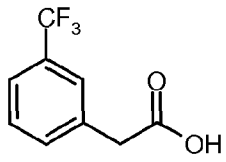
Intermediate No	R^1	From Intermediate No.	Physical data
			J=2.42 Hz, 8.57 Hz), 4.86 (s, 2H).
25 [(2-chloro-4-fluorophenyl)oxy] acetic acid		7 Ethyl [(2-chloro-4-fluorophenyl)oxy]acetate	^{1}H NMR (300 MHz, DMSO, ppm) δ: 7.45 (dd, 1H, J=2.99 Hz, 8.35 Hz), 7.16 (td, 1H, J=3.07 Hz, 9.12 Hz), 7.06 (dd, 1H, J=5.14Hz, 9.27 Hz), 4.80 (s, 2H).
26 [(2-chloro-5-fluorophenyl)oxy] acetic acid		8 Ethyl [(2-chloro-5-fluorophenyl)oxy]acetate	^{1}H NMR (300 MHz, DMSO, ppm) δ: 7.46 (dd, 1H, J=6.29 Hz, 8.76 Hz), 6.98 (dd, 1H, J=2.88 Hz, 10.90 Hz), 6.82 (td, 1H, J=2.81 Hz, 8.36 Hz), 4.78 (s, 2H).
27 [(3,4-dichlorophenyl)oxy] acetic acid		9 Ethyl [(3,4-dichlorophenyl) oxy]acetate	^{1}H NMR (300 MHz, CDCl3, ppm) δ: 7.4 (d, 1H), 7.05 (s, 1H), 6.8 (d, 1H), 4.6 (s, 2H).
28 (5,6,7,8-tetrahydro-1-naphthalenyloxy) acetic acid		10 Ethyl (5,6,7,8-tetrahydro-1-naphthalenyloxy) acetate	^{1}H NMR (300 MHz, DMSO, ppm) δ: 7.00 (t, 1H, J=8.14 Hz), 6.66 (d, 1H, J=7.74 Hz), 6.58 (d, 1H, J=8.14 Hz), 4.65 (s, 2H), 2.69 (m, 2H), 2.61 (m, 2H), 1.70 (m, 4H).
29 {[3-(trifluoromethyl) phenyl]oxy}acetic acid		11 Ethyl {[3-(trifluoromethyl) phenyl]oxy}acetate	^{1}H NMR (300 MHz, DMSO, ppm) δ: 7.5 (t, 1H), 7.3 (m, 3H), 4.8 (s, 2H).
30 [(3-chlorophenyl)oxy] acetic acid		12 Ethyl [(3-chlorophenyl) oxy]acetate	Not isolated

Intermediate No	R^1	From Intermediate No.	Physical data
31 {[2-(trifluoromethyl) phenyl]oxy}acetic acid		13 Ethyl {[2-(trifluoromethyl) phenyl]oxy}acetate	LC/MS: m/z 250 $(M+H)^+$ Rt: 3.30 min
32 (1-naphthalenyloxy) acetic acid		14 Ethyl (1-naphthalenyloxy) acetate	^{1}H NMR (300 MHz, DMSO, ppm) δ: 8.21 (m, 1H), 7.89 (m, 1H), 7.53 (m, 3H), 7.40 (t, 1H, J=7.80 Hz), 6.88 (d, 1H, J=7.54 Hz), 4.88 (s, 2H).
33 {[4-(methyloxy)phenyl] oxy}acetic acid		15 Ethyl {[4-(methyloxy)phenyl] oxy}acetate	^{1}H NMR (300 MHz, DMSO, ppm) δ: 6.9 (s, 4H), 4.5 (s, 2H), 3.6 (s, 3H).
34 (2-biphenylyloxy) acetic acid		16 Ethyl (2-biphenylyloxy) acetate	^{1}H NMR (300 MHz, DMSO, ppm) δ: 7.6-6.9 (m, 9H), 4.3 (s, 2H).
35 ({5-chloro-2-[(2-methylpropyl)oxy] phenyl}oxy)acetic acid		17 Ethyl ({5-chloro-2-[(2-methylpropyl)oxy] phenyl}oxy)acetate	^{1}H NMR (300 MHz, DMSO, ppm) δ: 7.00-6.80 (m, 3H), 4.6 (s, 2H), 3.75 (d, 2H), 2.00 (m, 1H), 1.00 (d, 6H).
36 [(2,4-dichlorophenyl) oxy]acetic acid		18 Ethyl [(2,4-dichlorophenyl) oxy]acetate	^{1}H NMR (300 MHz, DMSO, ppm) δ: 7.59 (d, 1H), 7.35 (dd, 1H), 7.607 (d, 1H), 4.84 (s, 2H).
37 {[2-(methyloxy)phenyl] oxy}acetic acid		19 Ethyl {[2-(methyloxy) phenyl] oxy}acetate	^{1}H NMR (300 MHz, DMSO, ppm) δ: 7.1 (m, 4H), 4.75 (s, 2H), 3.8 (s, 3H).

The following Intermediates were prepared using the generic reaction scheme (Scheme 13)



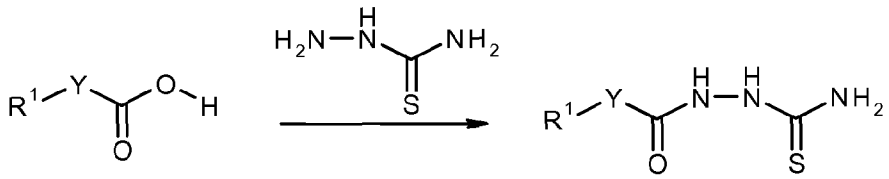
Intermediate 38: [3-(Trifluoromethyl)phenyl]acetic acid



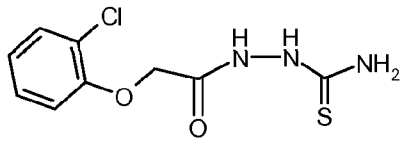
A solution of [3-(trifluoromethyl)phenyl]acetonitrile (5.4 g, 0.03 mmol) and NaOH (6g, 0.15 mmol) in water was refluxed overnight. After cooling, the pH was adjusted to 2 with dilute HCl. The precipitate was filtered, washed with water and dried to give the title compound as a solid (5.2 g, 87%).

^{1}H NMR (300 MHz, DMSO, ppm) δ: 7.6 (m, 4H), 3.7 (s, 2H).

The following Intermediates were prepared using the generic reaction scheme (Scheme 11)



Intermediate 39: 2-{[(2-Chlorophenyl)oxy]acetyl}hydrazinecarbothioamide



Three coupling reactions were carried out simultaneously on a 10 g scale.

A solution of 2-chlorophenoxyacetic acid (10 g, 54 mmol), HATU (22.4 g, 59 mmol) and NEt_3 (11.1 mL, 80 mmol) in DMF was stirred at room temperature for 1 hour. Hydrazinecarbothioamide (5.9 g, 64 mmol) was added, and the reaction mixture was stirred at room temperature for two days. After evaporation under reduced pressure of the solvent of the three combined mixtures, the residue was diluted with water and the formed precipitate was filtered and dried to give the title compound as a pale yellow powder.

Total yield: 36.6 g, 87%.

LC/MS: m/z 260 $(M+H)^+$, Rt: 2.09 min.

The following Intermediates were similarly prepared by a method analogous to that described for Intermediate 39.

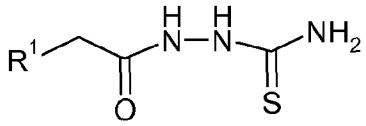
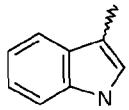
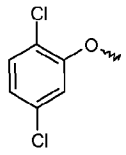
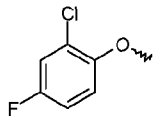
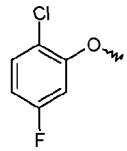
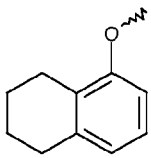
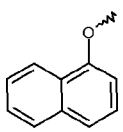
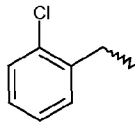
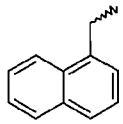
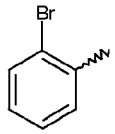
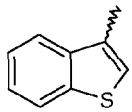
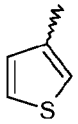
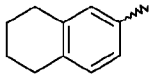
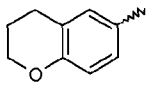
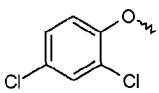
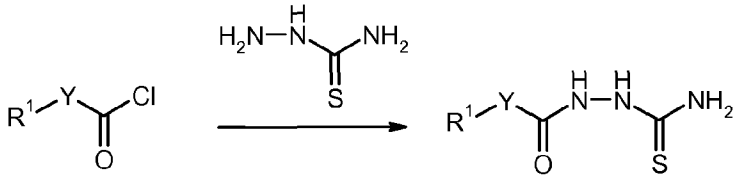


Table 3

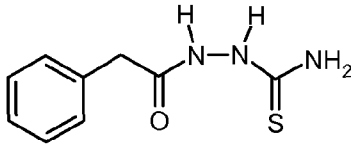
Intermediate No.	R^1	From Intermediate No.	Physical data
40 2-(1H-indol-3-ylacetyl) hydrazinecarbothioamide		Commercially available	LC/MS: m/z 249 $(M+H)^+$, Rt: 1.49 min.
41 2-{[(2,5-dichlorophenyl)oxy]acetyl} hydrazinecarbothioamide		24 [(2,5-dichlorophenyl) oxy]acetic acid	LC/MS: m/z 295 $(M+H)^+$ Rt: 2.29 min
42 2-{[(2-chloro-4-fluorophenyl)oxy]acetyl} hydrazinecarbothioamide		25 [(2-chloro-4-fluorophenyl) oxy]acetic acid	LC/MS: m/z 278 $(M+H)^+$ Rt: 2.10 min
43 2-{[(2-chloro-5-fluorophenyl)oxy]acetyl} hydrazinecarbothioamide		26 [(2-chloro-5-fluorophenyl) oxy]acetic acid	^1H NMR (300 MHz, DMSO, ppm) δ: 8.77 (dd, 1H, J=1.52 Hz, 4.37 Hz), 8.54 (dd, 1H, J=1.35 Hz, 8.56 Hz), 8.00 (bs, 1H), 7.67 (bs, 1H), 7.50 (s, 1H), 4.76 (s, 2H).
44 2-[(5,6,7,8-tetrahydro-1-naphthalenyloxy)acetyl] hydrazinecarbothioamide		28 (5,6,7,8-tetrahydro-1-naphthalenyloxy) acetic acid	1H NMR (300 MHz, DMSO, ppm) δ: 8.75 (dd, 1H, J=1.29 Hz, 4.58 Hz), 8.53 (dd, 1H, J=1.29 Hz, 8.56 Hz), 7.49 (s, 1H), 4.65 (s, 2H), 2.69 (m, 4H), 1.70 (m, 4H).
45 2-[(1-naphthalenyloxy)acetyl] hydrazinecarbothioamide		32 (1-naphthalenyloxy) acetic acid	LC/MS: m/z 276 $(M+H)^+$ Rt: 2.36 min

Intermediate No.	R^1	From Intermediate No.	Physical data
46 2-[3-(2-chlorophenyl)propanoyl] hydrazinecarbothioamide		Commercially available	LC/MS: m/z 258 $(M+H)^+$ Rt: 2.10 min
47 2-[3-(1-naphthalenyl)propanoyl] hydrazinecarbothioamide		Commercially available	LC/MS: m/z 274 $(M+H)^+$ Rt: 2.52 min
48 2-[(2-bromophenyl)acetyl] hydrazinecarbothioamide		Commercially available	LC/MS: m/z 290 $(M+H)^+$ Rt: 1.73 min
49 2-(1-benzothien-3-ylacetyl)hydrazine carbothioamide		Commercially available	Not isolated
50 2-(3-thienylacetyl) hydrazinecarbothioamide		Commercially available	Not isolated
51 2-(5,6,7,8-tetrahydro-2-naphthalenylacetyl) hydrazinecarbothioamide		Commercially available	LC/MS: m/z 264.14 $(M+H)^+$ Rt: 2.39 min
52 2-(3,4-dihydro-2*H*-chromen -6-ylacetyl) hydrazinecarbothioamide		Commercially available	LC/MS: m/z 266.2 $(M+H)^+$ Rt: 1.87 min
53 2-{[(2,4-dichlorophenyl)oxy]acetyl} hydrazinecarbothioamide		36 [(2,4-dichlorophenyl) oxy]acetic acid	LC/MS: m/z 294.1 $(M+H)^+$ Rt: 2.36 min

The following Intermediates were prepared using the generic reaction scheme (Scheme 11)



Intermediate 54: 2-(Phenylacetyl)hydrazinecarbothioamide



A solution of phenylacetyl chloride (5.27mL, 0.04 mol.) in DMF (100 mL) was added at room temperature to a solution of thiosemicarbazide (3.64g, 0.04 mol.) and pyridine (3.23 mL, 0.04 mol.) in DMF. After stirring for 8 hours, the mixture was poured into iced water and the pH was adjusted to 9 with ammonia. After extraction of the aqueous layer with ethyl acetate, the organic layer was washed with water, dried on Na_2SO_4 and after filtration was evaporated to dryness. Then the residue was recrystallized in ethyl acetate to give the title compound as a solid (1.878g, 22%).
LC/MS: m/z 210 $(M+H)^+$, Rt: 1.75 min.

The following Intermediates were similarly prepared by a method analogous to that described for Intermediate 54.

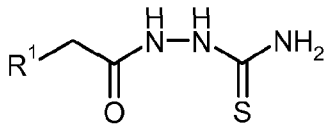
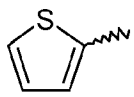
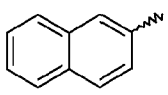
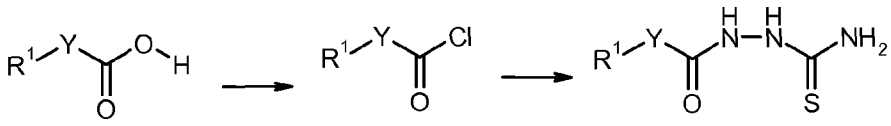


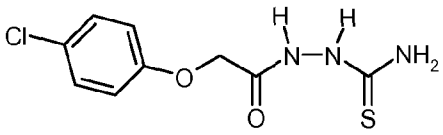
Table 4

Intermediate No.	R^1	From:	Physical data
55 2-(2-thienylacetyl) hydrazinecarbothioamide		Commercially available	LC/MS: m/z 214 $(M-H)^+$ Rt: 2.74 min
56 2-(2-naphthalenylacetyl) hydrazinecarbothioamide		Commercially available	^1H NMR (300 MHz, DMSO, ppm) δ: 7.85 (m, 3H), 7.78 (bs, 1H), 7.48 (m, 3H), 3.34 (s, 2H).

The following Intermediates were prepared using the generic reaction scheme (Scheme 11)



Intermediate 57: (Method A) 2-{[(4-Chlorophenyl)oxy]acetyl}hydrazinecarbothioamide



To a solution of [(4-chlorophenyl)oxy]acetic acid (Intermediate 20) (13.0g, 0.07 mol.) in chloroform was slowly added thionyl chloride (7.5 mL, 0.1 mol.). The solution was refluxed for 4 hours. Then the solvent was evaporated under vacuum. The residue was dissolved in DMF then added at room temperature to a solution of thiosemicarbazide (7.28g, 0.08 mol.) and pyridine (7.8g, 0.1 mol.) in DMF. After stirring for 2 hours, the mixture was poured in to ice-water and the solid material was filtered and dried to give the title compound as a white solid (16g, 88%).

LC/MS: m/z 260 $(M+H)^+$, Rt: 2.69 min.

The following Intermediates were similarly prepared by a method analogous to that described for Intermediate 57.

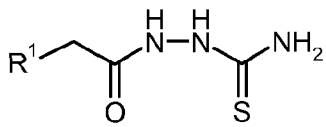
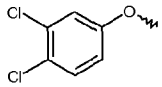
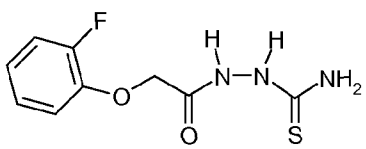


Table 5

Intermediate No.	R^1	From Intermediate No.	Physical data
58 2-{[(3,4-dichlorophenyl) oxy]acetyl} hydrazinecarbothioamide		27 [(3,4-dichlorophenyl) oxy]acetic acid	LC/MS: m/z 294 $(M-H)^+$ Rt: 2.72 min

Intermediate 59: (Method B) 2-{[(2-fluorophenyl)oxy]acetyl}hydrazinecarbothioamide



To a solution of [(2-fluorophenyl)oxy]acetic acid (Intermediate 21) (3g, 0.018 mol.) in dichloromethane cooled at 0°C, was slowly added oxalyl chloride (3.07 mL, 0.035 mol.). After stirring for 2 hours at room temperature, the solvent was evaporated under vacuum. The residue was dissolved in DMF then added to a solution of thiosemicarbazide (1.63g, 0.018 mol.) and pyridine (0.95 ml, 0.018 mol.) in DMF and cooled with an ice-water bath. After stirring for 4 hours, the mixture was poured into iced-water. The resulting solid material was filtered and dried to give the title compound (3g, 67%).
LC/MS: m/z 244 $(M+H)^+$, Rt: 2.13 min.

The following Intermediates were similarly prepared by a method analogous to that described for Intermediate 59.

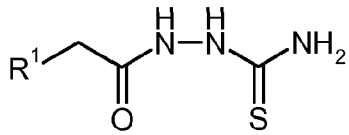
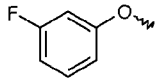
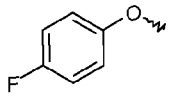
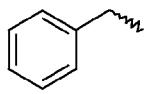
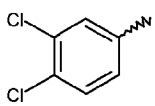
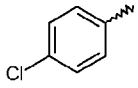
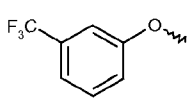
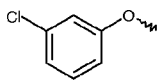
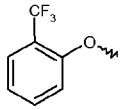
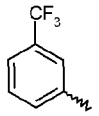
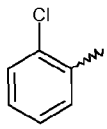
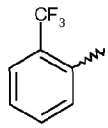
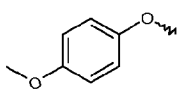
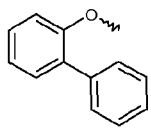
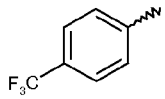
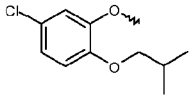
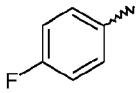
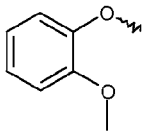


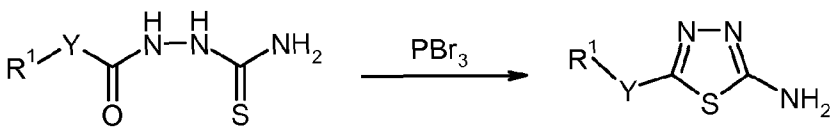
Table 6

Intermediate No.	R^1	From Intermediate No.	Physical data
60 2-{[(3-fluorophenyl)oxy]acetyl}hydrazinecarbothioamide		22 [(3-fluorophenyl)oxy]acetic acid	LC/MS: m/z 244 $(M+H)^+$ Rt: 2.25 min
61 2-{[(4-fluorophenyl)oxy]acetyl}hydrazinecarbothioamide		23 [(4-fluorophenyl)oxy]acetic acid	LC/MS: m/z 244 $(M+H)^+$ Rt: 2.16 min
62 2-(3-phenylpropanoyl)hydrazinecarbothioamide		Commercially available	^1H NMR (300 MHz, DMSO, ppm) δ: 7.23 (m, 5H), 2.83 (t, 2H, J=7.54 Hz), 2.42 (t, 2H, J=7.54 Hz).
63 2-[(3,4-dichlorophenyl)acetyl]hydrazinecarbothioamide		Commercially available	LC/MS: m/z 278 $(M+H)^+$ Rt: 2.53 min

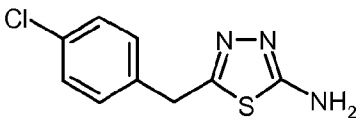
Intermediate No.	R^1	From Intermediate No.	Physical data
64 2-[(4-chlorophenyl)acetyl] hydrazinecarbothioamide		Commercially available	LC/MS: m/z 244 $(M+H)^+$ Rt: 2.23 min
65 2-({[3- (trifluoromethyl)phenyl] oxy}acetyl)hydrazine carbothioamide		29 {[3- (trifluoromethyl) phenyl] oxy}acetic acid	LC/MS: m/z 294 $(M+H)^+$ Rt: 2.76 min
66 2-{[(3- chlorophenyl)oxy]acetyl} hydrazinecarbothioamide		30 [(3-chlorophenyl) oxy]acetic acid	LC/MS: m/z 262 $(M+H)^+$ Rt: 2.06 min
67 2-({[2- (trifluoromethyl)phenyl] oxy}acetyl)hydrazine carbothioamide		31 {[2- (trifluoromethyl) phenyl]oxy} acetic acid	LC/MS: m/z 294 $(M+H)^+$ Rt: 2.72 min
68 2-{[3- (trifluoromethyl)phenyl] acetyl}hydrazine carbothioamide		38 [3- (Trifluoromethyl) phenyl]acetic acid	^1H NMR (300 MHz, DMSO, ppm) δ: 10.03 (bs, 1H), 9.24 (bs, 1H), 7.58 (m, 4H), 3.6 (s, 2H).
69 2-[(2-chlorophenyl)acetyl] hydrazinecarbothioamide		Commercially available	^1H NMR (300 MHz, DMSO, ppm) δ: 9.99 (bs, 1H), 9.26 (bs, 1H), 7.4 (m, 2H), 7.26 (m, 2H), 3.6 (s, 2H).
70 2-{[2- (trifluoromethyl)phenyl] acetyl}hydrazine carbothioamide		Commercially available	^1H NMR (300 MHz, DMSO, ppm) δ: 9.99 (s, 1H), 9.26 (s, 1H), 7.58-7.68 (m, 3H), 7.42-7.46 (m, 3H), 3.70 (s, 2H).
71 2-({[4- (methyloxy)phenyl]oxy} acetyl)hydrazine carbothioamide		33 {[4-(methyloxy) phenyl] oxy}acetic acid	LC/MS: m/z 256 $(M+H)^+$ Rt: 1.88 min

Intermediate No.	R^1	From Intermediate No.	Physical data
72 2-[(2-biphenylyloxy)acetyl] hydrazinecarbothioamide		34 (2-biphenylyloxy) acetic acid	^{1}H NMR (300 MHz, DMSO, ppm) δ: 7.6-6.9 (m, 9H), 4.6 (s, 2H).
73 2-{[4-(trifluoromethyl)phenyl] acetyl}hydrazine carbothioamide		Commercially available	^{1}H NMR (300 MHz, DMSO, ppm) δ: 10.02 (s, 1H), 9.24 (s, 1H), 7.91 (m, 4H), 7.51-7.65 (m, 2H), 3.59 (s, 2H).
74 2-[({5-chloro-2-[(2-methylpropyl)oxy]phenyl} oxy)acetyl]hydrazine carbothioamide		35 ({5-chloro-2-[(2-methylpropyl)oxy] phenyl}oxy)acetic acid	^{1}H NMR (300 MHz, DMSO, ppm) δ: 7.75 (m, 3H), 5.4 (s, 2H), 4.5 (d, 2H), 2.8 (m, 1H), 1.80 (d, 6H).
75 2-[(4-fluorophenyl)acetyl] hydrazinecarbothioamide		Commercially available	LC/MS: m/z 228 $(M+H)^+$ Rt: 3.19 min
76 2-({[2-(methyloxy)phenyl] oxy}acetyl) hydrazinecarbothioamide		37 [(2,4-dichlorophenyl) oxy]acetic acid	^{1}H NMR (300 MHz, DMSO, ppm) δ: 9.96 (s, 1H), 9.26 (s, 1H), 7.91 (s, 1H), 7.52 (s, 1H), 6.95 (m, 4H), 4.52 (s, 2H), 3.75 (s, 3H).

The following Intermediates were prepared using the generic reaction scheme (Scheme 8)



Intermediate 77: 5-[(4-Chlorophenyl)methyl]-1,3,4-thiadiazol-2-amine



A mixture of the 2-[(4-chlorophenyl)acetyl]hydrazinecarbothioamide (Intermediate 64) (5g, 0.020 mol.) and PBr_3 (30 mL, 0.146 mol.) was heated at 60°C for 16 hours. Then the reaction was poured into ice-water and the pH was adjusted to 9 with ammonia. After filtration of the suspension, the solid material was dried to give the title compound as a solid (3.6 g, 79%).
LC/MS: m/z 226 $(M+H)^+$, Rt: 3.55 min.

The following Intermediates were similarly prepared by a method analogous to that described for Intermediate 77.

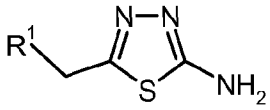
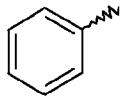
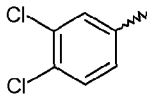
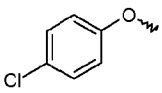
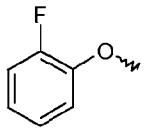
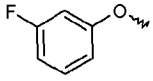
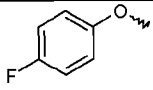
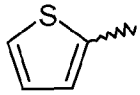
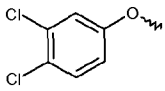
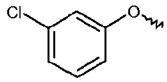
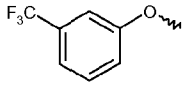
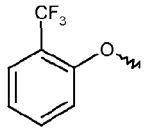
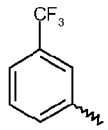
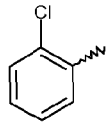
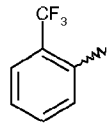
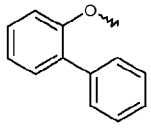
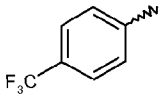
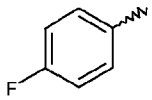


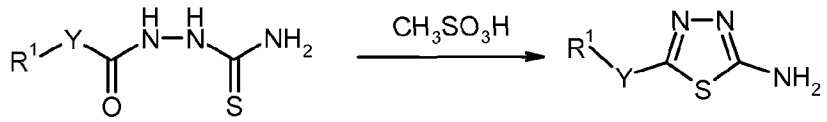
Table 7

Intermediate No.	R^1	From Intermediate No.	Physical data
78 5-(phenylmethyl)-1,3,4-thiadiazol-2-amine		54 2-(phenylacetyl) hydrazine carbothioamide	LC/MS: m/z 192 $(M+H)^+$ Rt: 2.07 min
79 5-[(3,4-dichlorophenyl)methyl]-1,3,4-thiadiazol-2-amine		63 2-[(3,4-dichlorophenyl)acetyl] hydrazinecarbothioamide	LC/MS: m/z 260 $(M+H)^+$ Rt: 3.89 min
80 5-{[(4-chlorophenyl)oxy] methyl}-1,3,4-thiadiazol-2-amine		57 2-{[(4-chlorophenyl)oxy]acetyl} hydrazinecarbothioamide	LC/MS: m/z 242 $(M+H)^+$ Rt: 3.79 min
81 5-{[(2-fluorophenyl)oxy] methyl}-1,3,4-thiadiazol-2-amine		59 2-{[(2-fluorophenyl)oxy]acetyl} hydrazinecarbothioamide	LC/MS: m/z 226 $(M+H)^+$ Rt: 3.39 min
82 5-{[(3-fluorophenyl)oxy] methyl}-1,3,4-thiadiazol-2-amine		60 2-{[(3-fluorophenyl)oxy]acetyl} hydrazinecarbothioamide	LC/MS: m/z 226 $(M+H)^+$ Rt: 3.47 min
83 5-{[(4-fluorophenyl)oxy]		61 2-{[(4-	LC/MS: m/z 226 $(M+H)^+$

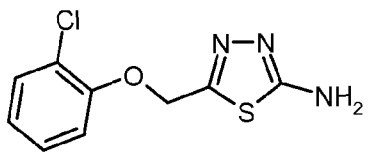
Intermediate No.	R^1	From Intermediate No.	Physical data
methyl}-1,3,4-thiadiazol-2-amine		fluorophenyl)oxy]acetyl} hydrazinecarbothioamide	Rt: 3.42 min
84 5-(2-thienylmethyl)-1,3,4-thiadiazol-2-amine		55 2-(2-thienylacetyl) hydrazinecarbothioamide	LC/MS: m/z 198 $(M+H)^+$ Rt: 2.05 min
85 5-{[(3,4-dichlorophenyl)oxy] methyl}-1,3,4-thiadiazol-2-amine		58 2-{[(3,4-dichlorophenyl) oxy]acetyl} hydrazinecarbothioamide	LC/MS: m/z 276 $(M+H)^+$ Rt: 4.07 min
86 5-{[(3-chlorophenyl)oxy] methyl}-1,3,4-thiadiazol-2-amine		66 2-{[(3-chlorophenyl)oxy]acetyl} hydrazinecarbothioamide	LC/MS: m/z 242 $(M+H)^+$ Rt: 3.70 min
87 5-({[3-(trifluoromethyl)phenyl] oxy}methyl)-1,3,4-thiadiazol-2-amine		65 2-({[3-(trifluoromethyl) phenyl]oxy}acetyl) hydrazinecarbothioamide	LC/MS: m/z 276 $(M+H)^+$ Rt: 3.98 min
88 5-({[2-(trifluoromethyl)phenyl] oxy}methyl)-1,3,4-thiadiazol-2-amine		67 2-({[2-(trifluoromethyl) phenyl]oxy}acetyl) hydrazinecarbothioamide	LC/MS: m/z 276 $(M+H)^+$ Rt: 3.88 min
89 5-{[3-(trifluoromethyl)phenyl] methyl}-1,3,4-thiadiazol-2-amine		68 2-{[3-(trifluoromethyl) phenyl]acetyl} hydrazinecarbothioamide	^1H NMR (300 MHz, DMSO, ppm) δ : 7.6 (m, 4H), 4.25 (s, 2H).
90 5-[(2-chlorophenyl)methyl]-1,3,4-thiadiazol-2-amine		69 2-[(2-chlorophenyl)acetyl] hydrazinecarbothioamide	1H NMR (300 MHz, DMSO, ppm) δ: 7.46-7.0 (m, 4H), 4.23 (s, 2H).

Intermediate No.	R^1	From Intermediate No.	Physical data
91 5-{[2-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-amine		70 2-{[2-(trifluoromethyl)phenyl]acetyl}hydrazinecarbothioamide	LC/MS: m/z 260 $(M+H)^+$ Rt: 2.21 min
92 5-[(2-biphenylyloxy)methyl]-1,3,4-thiadiazol-2-amine		72 2-[(2-biphenylyloxy)acetyl]hydrazinecarbothioamide	^{1}H NMR (300 MHz, DMSO, ppm) δ: 7.5-7.0 (m, 11H), 5.25 (s, 2H).
93 5-{[4-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-amine		73 2-{[4-(trifluoromethyl)phenyl]acetyl}hydrazinecarbothioamide	^{1}H NMR (300 MHz, DMSO, ppm) δ: 7.7 (d, 2H), 7.5 (d, 2H), 7.1 (m, 2H), 4.25 (s, 2H).
94 5-[(4-fluorophenyl)methyl]-1,3,4-thiadiazol-2-amine		75 2-[(4-fluorophenyl)acetyl]hydrazinecarbothioamide	^{1}H NMR (300 MHz, DMSO, ppm) δ: 7.2 (d, 2H), 7.1 (d, 2H), 7.00 (s, 2H), 4.1 (s, 2H).

The following Intermediates were prepared using the generic reaction scheme (Scheme 8)



Intermediate 95: 5-{[(2-Chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-amine



To a solution of 2-{[(2-Chlorophenyl)oxy]acetyl}hydrazinecarbothioamide (Intermediate 39) (36.6 g, 0.14 mol) in toluene (250 ml) was added drop by drop methane sulphonic acid (13.7 mL, 0.21 mol) and the reaction mixture was stirred at reflux for 2 hours. The solvent was evaporated. The residue was diluted with water and ammonia solution

was added until pH=9. The formed precipitated was filtered and dried to give the title compound as a pale yellow solid (20.3 g, 60%).
LC/MS: m/z 242 $(M+H)^+$, Rt: 2.57 min.

The following Intermediates were similarly prepared by a method analogous to that described for Intermediate 95.

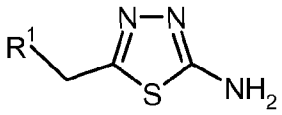
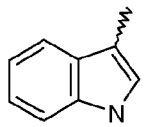
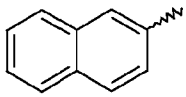
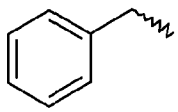
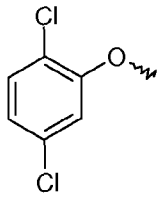
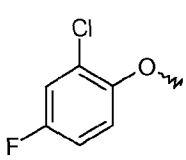
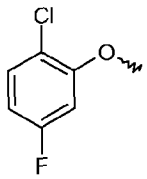
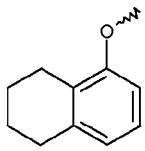
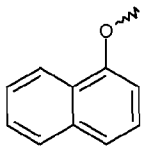
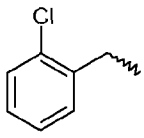
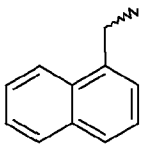
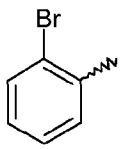
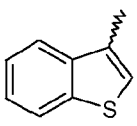
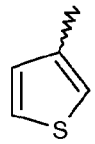
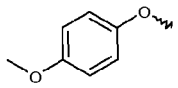
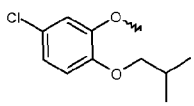
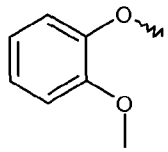
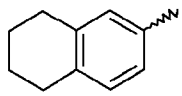
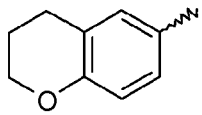
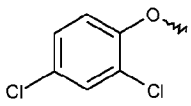


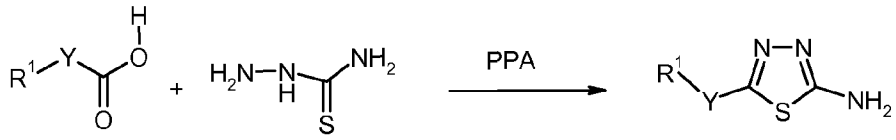
Table 8

Intermediate No.	R^1	From Intermediate No.	Physical data
96 5-(1H-indol-3-ylmethyl)-1,3,4-thiadiazol-2-amine		40 2-(1H-indol-3-ylacetyl)hydrazine carbothioamide	LC/MS: m/z 231 $(M+H)^+$, Rt: 2.07 min.
97 5-(2-naphthalenylmethyl)-1,3,4-thiadiazol-2-amine		56 2-(2-naphthalenylacetyl) hydrazine carbothioamide	^{1}H NMR (300 MHz, DMSO, ppm) δ: 7.90 (m, 3H), 7.83 (bs, 1H), 7.52 (m, 2H), 7.44 (dd, 1H, J=1.77 Hz, 8.32 Hz), 4.36 (s, 2H).
98 5-(2-phenylethyl)-1,3,4-thiadiazol-2-amine		62 2-(3-phenylpropanoyl) hydrazine carbothioamide	^{1}H NMR (300 MHz, DMSO, ppm) δ: 7.19 (m, 5H), 3.04 (t, 2H, J=7.27 Hz), 2.87 (t, 2H, J=8.16 Hz).
99 5-{[(2,5-dichlorophenyl)oxy] methyl}-1,3,4-thiadiazol-2-amine		41 2-{[(2,5-dichlorophenyl)oxy] acetyl}hydrazine carbothioamide	^{1}H NMR (300 MHz, DMSO, ppm) δ: 7.49 (d, 1H, J=8.56 Hz), 7.46 (d, 1H, J=2.27 Hz), 7.09 (dd, 1H, J=2.35 Hz, 8.47 Hz), 5.44 (s, 2H).
100 5-{[(2-chloro-4-fluorophenyl)oxy] methyl}-1,3,4-thiadiazol-2-amine		42 2-{[(2-chloro-4-fluorophenyl)oxy] acetyl}hydrazine carbothioamide	^{1}H NMR (300 MHz, DMSO, ppm) δ: 7.47 (dd, 1H, J=3.15 Hz, 8.41 Hz), 7.33 (m, 1H), 7.21 (td, 1H, J=3.15 Hz,

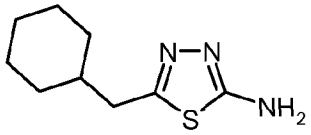
Intermediate No.	R^1	From Intermediate No.	Physical data
			8.10 Hz), 5.37 (s, 2H).
101 5-{[(2-chloro-5-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-amine		43 2-{[(2-chloro-5-fluorophenyl)oxy]acetyl}hydrazinecarbothioamide	^{1}H NMR (300 MHz, DMSO, ppm) δ: 7.50 (dd, 1H, 8.93 Hz, 6.09 Hz), 7.30 (dd, 1H, J=2.81 Hz, 10.48 Hz), 6.88 (dd, 1H, J=2.94 Hz, 8.31 Hz), 5.42 (s, 2H).
102 5-[(5,6,7,8-tetrahydro-1-naphthalenyloxy) methyl]-1,3,4-thiadiazol-2-amine		44 2-[(5,6,7,8-tetrahydro-1-naphthalenyloxy) acetyl]hydrazine carbothioamide	^{1}H NMR (300 MHz, DMSO, ppm) δ: 7.04 (t, 1H, J=7.96 Hz), 6.86 (d, 1H, J=7.96 Hz), 6.70 (d, 1H, J=7.62 Hz), 5.24 (s, 2H), 2.69 (m, 2H), 2.56 (m, 2H), 1.70 (m, 4H).
103 5-[(1-naphthalenyloxy) methyl]-1,3,4-thiadiazol-2-amine		45 2-[(1-naphthalenyloxy) acetyl]hydrazine carbothioamide	LC/MS: m/z 258 $(M+H)^+$ Rt: 2.69 min
104 5-[2-(2-chlorophenyl)ethyl]-1,3,4-thiadiazol-2-amine		46 2-[3-(2-chlorophenyl) propanoyl]hydrazinecarbothioamide	LC/MS: m/z 240 $(M+H)^+$ Rt: 2.49 min
105 5-[2-(1-naphthalenyl)ethyl]-1,3,4-thiadiazol-2-amine		47 2-[3-(1-naphthalenyl) propanoyl]hydrazinecarbothioamide	LC/MS: m/z 256 $(M+H)^+$ Rt: 2.88 min
106 5-[(2-bromophenyl)methyl]-1,3,4-thiadiazol-2-amine		48 2-[(2-bromophenyl)acetyl]hydrazinecarbothioamide	LC/MS: m/z 272 $(M+H)^+$ Rt: 2.36 min
107 5-(1-benzothien-3-ylmethyl)-1,3,4-thiadiazol-2-amine		49 2-(1-benzothien-3-ylacetyl) hydrazine	^{1}H NMR (300 MHz, DMSO, ppm) δ: 8.00 (m, 1H), 7.84 (m, 1H), 7.64 (s, 1H), 7.40 (m,

Intermediate No.	R^1	From Intermediate No.	Physical data
		carbothioamide	2H), 4.43 (s, 2H).
108 5-(3-thienylmethyl)-1,3,4-thiadiazol-2-amine		50 2-(3-thienylacetyl) hydrazine carbothioamide	LC/MS: m/z 198(M+H)$^+$ Rt: 1.93 min
109 5-({[4-(methyloxy)phenyl] oxy}methyl)-1,3,4-thiadiazol-2-amine		71 2-({[4-(methyloxy) phenyl]oxy}acetyl) hydrazine carbothioamide	^{1}H NMR (300 MHz, DMSO, ppm) δ: 6.95 (d, 2H), 6.85 (d, 2H), 5.2 (s, 2H), 3.7 (s, 3H).
110 5-[({5-chloro-2-[(2-methylpropyl)oxy]phenyl}oxy)methyl]-1,3,4-thiadiazol-2-amine		74 2-[({5-chloro-2-[(2-methylpropyl)oxy] phenyl}oxy)acetyl] hydrazine carbothioamide	^{1}H NMR (300 MHz, DMSO, ppm) δ: 7.3 (m, 2H), 7.2 (s, 1H), 7.00 (s, 2H), 5.3 (s, 2H), 3.75 (d, 2H), 2.00 (m, 1H), 1.00 (d, 6H).
111 5-({[2-(methyloxy)phenyl] oxy}methyl)-1,3,4-thiadiazol-2-amine		76 2-({[2-(methyloxy)phenyl] oxy}acetyl)hydrazine carbothioamide	^{1}H NMR (300 MHz, DMSO, ppm) δ: 7.25 (s, 2H), 7.00 (m, 4H), 5.25 (s, 2H), 3.75 (s, 3H).
112 5-(5,6,7,8-tetrahydro-2-naphthalenylmethyl)-1,3,4-thiadiazol-2-amine		51 2-(5,6,7,8-tetrahydro-2-naphthalenylacetyl) hydrazine carbothioamide	LC/MS: m/z 246 (M+H)$^+$ Rt: 2.53 min
113 5-(3,4-dihydro-2*H*-chromen-6-ylmethyl)-1,3,4-thiadiazol-2-amine		52 2-(3,4-dihydro-2*H*-chromen-6-ylacetyl)hydrazine carbothioamide	LC/MS: m/z 248 (M+H)$^+$ Rt: 2.12 min
114 5-{[(2,4-dichlorophenyl)oxy] methyl}-1,3,4-thiadiazol-2-amine		53 2-{[(2,4-dichlorophenyl)oxy] acetyl}hydrazine carbothioamide	LC/MS: m/z 276 (M+H)$^+$ Rt: 2.51 min

The following Intermediates were prepared using the generic reaction scheme (Scheme 9)

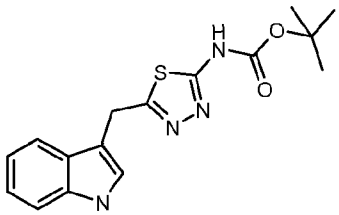


Intermediate 115: 5-(Cyclohexylmethyl)-1,3,4-thiadiazol-2-amine



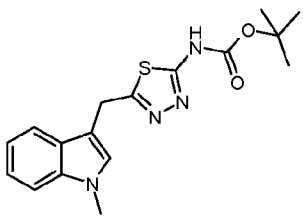
Hydrazinecarbothioamide (0.32 g, 3.5 mmol) in PPA (50 g) was heated at 110°C until dissolution. Cyclohexylacetic acid (0.5 g, 3.5 mmol.) was added and the reaction mixture was heated at 110°C for 2 hours. After cooling, the reaction was poured in ice and aqueous ammonia was added until pH=9. The formed precipitated was filtered and dried to give the title compound as a white solid (0.4 g, 69.4%).
LC/MS: m/z 198 (M+H)+, Rt: 2.49 min

Intermediate 116: 1,1,1-Dimethylethyl [5-(1*H*-indol-3-ylmethyl)-1,3,4-thiadiazol-2-yl]carbamate



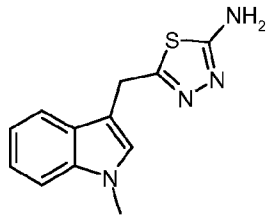
A solution of 5-(1*H*-indol-3-ylmethyl)-1,3,4-thiadiazol-2-amine, 5-(1H-indol-3-ylmethyl)-1,3,4-thiadiazol-2-amine (Intermediate 96) (500 mg, 2.2 mmol), anhydride boc (521 mg, 2.4 mmol) and triethylamine (300 µl, 2.2 mmol) in THF was stirred at 50°C overnight. The mixture was evaporated. The residue was diluted with dichloromethane, washed with water and the organic phase was dried over Na_2SO_4 to give after evaporation the title compound as brown crystals (550 mg, 76%).
LC/MS: m/z 331.2 (M+H)+, Rt: 2.92 min

Intermediate 117: 1,1-Dimethylethyl {5-[(1-methyl-1*H*-indol-3-yl)methyl]-1,3,4-thiadiazol-2-yl}carbamate



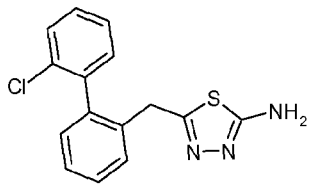
To a solution of 1,1-dimethylethyl [5-(1*H*-indol-3-ylmethyl)-1,3,4-thiadiazol-2-yl]carbamate, (Intermediate 116) (550 mg, 1.66 mmol) and NaH 60% (133 mg, 3.33 mmol) in THF stirred for 1 hour at room temperature, was added methyl iodide (125 µl, 2 mmol). The reaction mixture was stirred at room temperature for 4 hours. The mixture was then heated at 50°C overnight and NaH 60%(133 mg, 3.33 mmol) and methyl iodide (52 µl, 0.83 mmol) were added and the mixture was stirred at 50°C for a further night. The mixture was hydrolysed and evaporated under reduced pressure. The residue was purified by flash column chromatography eluting with a gradient DCM 100% to DCM/MeOH: 60/40 to give the title compound as yellow crystals (100 mg, 17%).
LC/MS: m/z 345.2 (M+H)+, Rt: 3.18 min

Intermediate 118: 5-[(1-Methyl-1*H*-indol-3-yl)methyl]-1,3,4-thiadiazol-2-amine



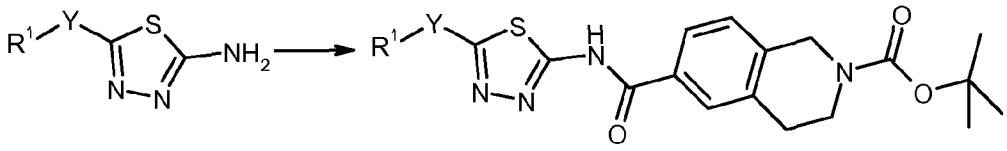
HCl(g) was bubbled at 0°C in EtOAc and 1,1-dimethylethyl {5-[(1-methyl-1*H*-indol-3-yl)methyl]-1,3,4-thiadiazol-2-yl}carbamate (Intermediate 117) (100 mg, 0.3 mmol) was added. The reaction mixture was stirred at room temperature overnight. The mixture was evaporated and the residue was recrystallised with acetonitrile to give the title compound as a solid (40 mg, 55%).
LC/MS: m/z 245.08 (M+H)+, Rt: 2.37 min

Intermediate 119: 5-[(2'-Chloro-2-biphenylyl)methyl]-1,3,4-thiadiazol-2-amine

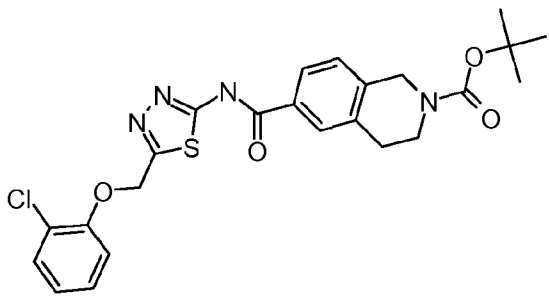


A solution of 5-[(2-bromophenyl)methyl]-1,3,4-thiadiazol-2-amine (Intermediate 106) (500 mg, 1.75 mmol), $Pd(PPh_3)_4$ (50 mg), Na_2CO_3 2M (3.5 ml, 7 mmol) and 2-chlorophenylboronic acid (354 mg, 2.3 mmol) in DME was stirred at reflux for 48 hours. The mixture was evaporated. The residue was diluted with dichloromethane, washed with water. The organic phase was dried over Na_2SO_4, filtered and evaporated. The obtained solid was recrystallised with acetonitrile to give the title compound as a solid (125 mg, 24%).
LC/MS: m/z 302.02 (M+H)+, Rt: 2.98 min.

The following Intermediates were prepared using the generic reaction scheme (Scheme 1):



Intermediate 120: 1,1-Dimethylethyl 6-{[(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate



A solution of 2-{[(1,1-dimethylethyl)oxy]carbonyl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxylic acid (14.3 g, 52 mmol), HATU (29.5 g, 77.6 mmol), DIPEA (14.6 mL, 62 mmol) in DMF was stirred at room temperature for 1 hour. 5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-amine, (Intermediate 95) (15 g, 62 mmol) was added and the mixture was stirred at room temperature overnight. The DMF was evaporated under reduced pressure and the residue was dissolved in EtOAc. The organic phase was then washed with water and filtered to eliminate an insoluble. The aqueous phase was re-extracted with EtOAc, and the organic phase was dried over sodium sulphate, filtered and evaporated under reduced pressure. The residue was then diluted with DCM and the insoluble was filtered. All the organic phases were combined, dried over sodium sulphate, filtered and evaporated under reduced pressure to give the title compound (14 g, 62%).

^{1}H NMR (300 MHz, DMSO, ppm) δ: 7.96 (s, 1H), 7.93 (d, 1H), 7.48 (d, 1H), 7.36 (m, 3H), 7.04 (m, 1H), 5.64 (s, 2H), 4.59 (s, 2H), 3.60 (t, 2H), 2.86 (t, 2H), 1.44 (s, 9H).

The following Intermediates were similarly prepared by a method analogous to that described for Intermediate 120.

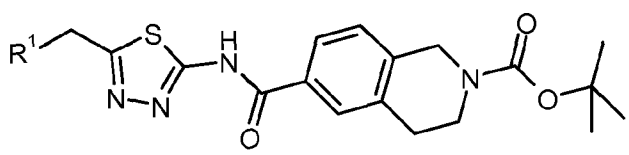
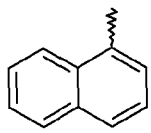
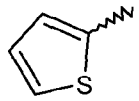
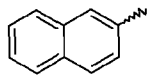
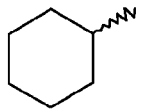
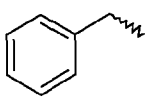
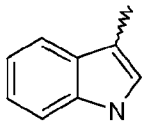
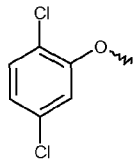
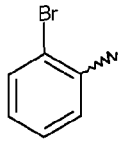
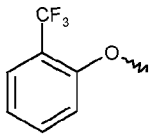
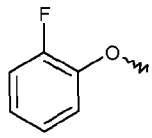
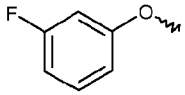
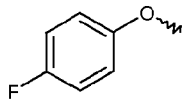
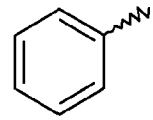
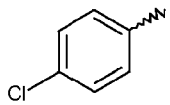
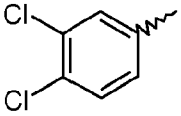
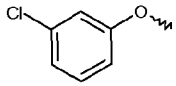
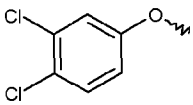
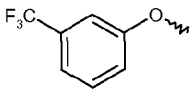
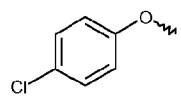
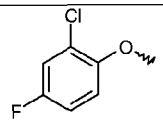
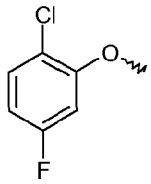
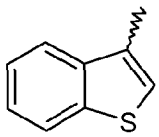
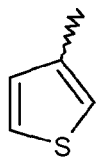
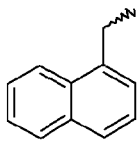
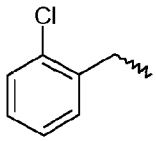


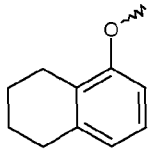
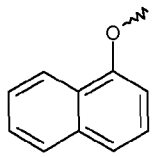
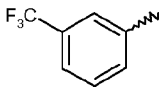
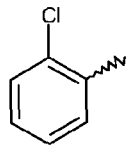
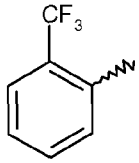
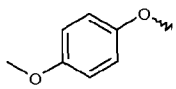
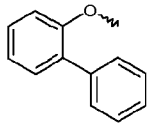
Table 9

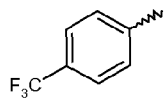
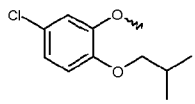
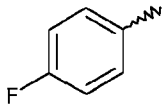
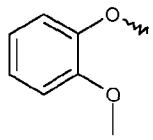
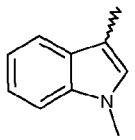
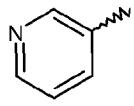
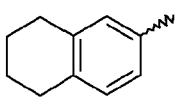
Intermediate No.	R^1	From Intermediate No.	Physical data
121 1,1-dimethylethyl 6-({[5-(1-naphthalenylmethyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1H)-isoquinolinecarboxylate		Commercially available	LC/MS: m/z 501 $(M+H)^+$ Rt: 3.69 min.
122 1,1-dimethylethyl 6-({[5-(2-thienylmethyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		84 5-(2-thienylmethyl)-1,3,4-thiadiazol-2-amine	LC/MS: m/z 457 $(M+H)^+$ Rt: 3.14 min
123 1,1-dimethylethyl 6-({[5-(2-naphthalenylmethyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		97 5-(2-naphthalenylmethyl)-1,3,4-thiadiazol-2-amine	LC/MS: m/z 501 $(M+H)^+$ Rt: 3.89 min
124 1,1-dimethylethyl 6-({[5-(cyclohexylmethyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		115 5-(Cyclohexylmethyl)-1,3,4-thiadiazol-2-amine	^{1}H NMR (300 MHz, DMSO, ppm) δ: 7.8 (m, 2H), 7.3 (d, 1H), 7.0 (s, 1H), 4.6 (brs, 2H), 3.6 (t, 2H), 2.85 (m, 4H), 1.55-1.8 (m, 11H), 1.45 (s,3H).
125 1,1-dimethylethyl 6-({[5-(2-phenylethyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		98 5-(2-phenylethyl)-1,3,4-thiadiazol-2-amine	LC/MS: m/z 465 $(M+H)^+$ Rt: 3.73 min
126 1,1-dimethylethyl 6-({[5-(1*H*-indol-3-ylmethyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		96 5-(1H-indol-3-ylmethyl)-1,3,4-thiadiazol-2-amine	LC/MS: m/z 278 $(M+H)^+$ Rt: 3.30 min

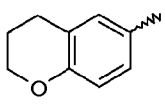
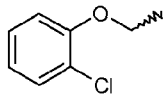
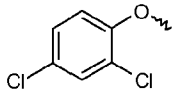
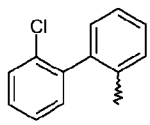
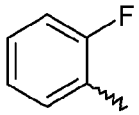
Intermediate No.	R^1	From Intermediate No.	Physical data
127 1,1-dimethylethyl 6-{[(5-{[(2,5-dichlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		99 5-{[(2,5-dichlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-amine	LC/MS: m/z 535 $(M+H)^+$ Rt: 4.02 min
128 1,1-dimethylethyl 6-[({5-[(2-bromophenyl)methyl]-1,3,4-thiadiazol-2-yl}amino)carbonyl]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		106 5-[(2-bromophenyl)methyl]-1,3,4-thiadiazol-2-amine	LC/MS: m/z 530 $(M+H)^+$ Rt: 3.83 min
129 1,1-dimethylethyl 6-({[5-({[2-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		88 5-({[2-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-amine	LC/MS: m/z 535 $(M+H)^+$ Rt: 3.70 min
130 1,1-dimethylethyl 6-{[(5-{[(2-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		81 -{[(2-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-amine	LC/MS: m/z 485.2 $(M+H)^+$ Rt: 3.71 min
131 1,1-dimethylethyl 6-{[(5-{[(3-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		82 5-{[(3-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-amine	LC/MS: m/z 485.3 $(M+H)^+$ Rt: 3.74 min
132 1,1-dimethylethyl 6-{[(5-{[(4-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		83 5-{[(4-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-amine	LC/MS: m/z 485 $(M+H)^+$ Rt: 3.49 min
133 1,1-dimethylethyl 6-({[5-(phenylmethyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-		78 5-(phenylmethyl)-1,3,4-thiadiazol-2-amine	LC/MS: m/z 451 $(M+H)^+$ Rt: 3.47 min

Intermediate No.	R^1	From Intermediate No.	Physical data
dihydro-2(1*H*)-isoquinolinecarboxylate			
134 1,1-dimethylethyl 6-[({5-[(4-chlorophenyl)methyl]-1,3,4-thiadiazol-2-yl}amino)carbonyl]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		77 5-[(4-chlorophenyl)methyl]-1,3,4-thiadiazol-2-amine	LC/MS: m/z 485 $(M+H)^+$ Rt: 3.65 min
135 1,1-dimethylethyl 6-[({5-[(3,4-dichlorophenyl)methyl]-1,3,4-thiadiazol-2-yl}amino)carbonyl]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		79 5-[(3,4-dichlorophenyl)methyl]-1,3,4-thiadiazol-2-amine	LC/MS: m/z 519 $(M+H)^+$ Rt: 3.81 min.
136 1,1-dimethylethyl 6-{[(5-{[(3-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		86 5-{[(3-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-amine	LC/MS: m/z 501 $(M+H)^+$ Rt: 3.95 min
137 1,1-dimethylethyl 6-{[(5-{[(3,4-dichlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		85 5-{[(3,4-dichlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-amine	LC/MS: m/z 535 $(M+H)^+$ Rt: 3.89 min
138 1,1-dimethylethyl 6-({[5-({[3-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		87 5-({[3-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-amine	LC/MS: m/z 535 $(M+H)^+$ Rt: 3.97 min
139 1,1-dimethylethyl 6-{[(5-{[(4-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		80 5-{[(4-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-amine	LC/MS: m/z 501 $(M+H)^+$ Rt: 3.73 min.
140 1,1-dimethylethyl 6-{[(5-{[(2-chloro-4-		100 5-{[(2-chloro-4-fluorophenyl)oxy]m	LC/MS: m/z 519 $(M+H)^+$ Rt: 3.89 min.

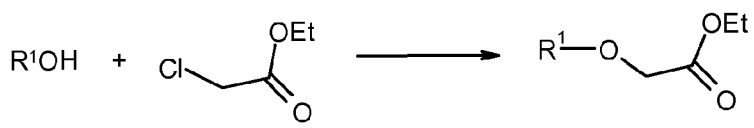
Intermediate No.	R^1	From Intermediate No.	Physical data
fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		ethyl}-1,3,4-thiadiazol-2-amine	
141 1,1-dimethylethyl 6-{[(5-{[(2-chloro-5-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		101 5-{[(2-chloro-5-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-amine	LC/MS: m/z 519 $(M+H)^+$ Rt: 3.90 min.
142 1,1-dimethylethyl 6-({[5-(1-benzothien-3-ylmethyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		107 5-(1-benzothien-3-ylmethyl)-1,3,4-thiadiazol-2-amine	LC/MS: m/z 507 $(M+H)^+$ Rt: 3.88 min.
143 1,1-dimethylethyl 6-({[5-(3-thienylmethyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		108 5-(3-thienylmethyl)-1,3,4-thiadiazol-2-amine	LC/MS: m/z 457 $(M+H)^+$ Rt: 3.61 min.
144 1,1-dimethylethyl 6-[({5-[2-(1-naphthalenyl)ethyl]-1,3,4-thiadiazol-2-yl}amino)carbonyl]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		105 5-[2-(1-naphthalenyl)ethyl]-1,3,4-thiadiazol-2-amine	LC/MS: m/z 515 $(M+H)^+$ Rt: 4.00 min.
145 1,1-dimethylethyl 6-[({5-[2-(2-chlorophenyl)ethyl]-1,3,4-thiadiazol-2-yl}amino)carbonyl]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		104 5-[2-(2-chlorophenyl)ethyl]-1,3,4-thiadiazol-2-amine	LC/MS: m/z 500 $(M+H)^+$ Rt: 3.91 min.
146 1,1-dimethylethyl 6-[({5-[(5,6,7,8-tetrahydro-1-naphthalenyloxy)methyl]-1,3,4-		102 5-[(5,6,7,8-tetrahydro-1-naphthalenyloxy)m	LC/MS: m/z 521 $(M+H)^+$ Rt: 4.01 min.

Intermediate No.	R^1	From Intermediate No.	Physical data
thiadiazol-2-yl}amino)carbonyl]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		ethyl]-1,3,4-thiadiazol-2-amine	
147 1,1-dimethylethyl 6-[({5-[(1-naphthalenyloxy)methyl]-1,3,4-thiadiazol-2-yl}amino)carbonyl]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		103 5-[(1-naphthalenyloxy)methyl]-1,3,4-thiadiazol-2-amine	LC/MS: m/z 517 $(M+H)^+$ Rt: 3.94 min.
148 1,1-dimethylethyl 6-{[(5-{[3-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		89 5-{[3-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-amine	LC/MS: m/z 519.2 $(M+H)^+$ Rt: 3.67 min.
149 1,1-dimethylethyl 6-[({5-[(2-chlorophenyl)methyl]-1,3,4-thiadiazol-2-yl}amino)carbonyl]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		90 5-[(2-chlorophenyl)methyl]-1,3,4-thiadiazol-2-amine	LC/MS: m/z 485.2 $(M+H)^+$ Rt: 3.61 min.
150 1,1-dimethylethyl 6-{[(5-{[2-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		91 5-{[2-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-amine	LC/MS: m/z 519.1 $(M+H)^+$ Rt: 3.65 min.
151 1,1-dimethylethyl 6-({[5-({[4-(methyloxy)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		109 5-({[4-(methyloxy)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-amine	LC/MS: m/z 497.15 $(M+H)^+$ Rt: 3.58 min.
152 1,1-dimethylethyl 6-[({5-[(2-biphenylyloxy)methyl]-1,3,4-thiadiazol-2-yl}amino)carbonyl]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		92 5-[(2-biphenylyloxy)methyl]-1,3,4-thiadiazol-2-amine	LC/MS: m/z 543.2 $(M+H)^+$ Rt: 3.83 min.

Intermediate No.	R^1	From Intermediate No.	Physical data
153 1,1-dimethylethyl 6-{[(5-{[4-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		93 5-{[4-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-amine	LC/MS: m/z 519.2 $(M+H)^+$ Rt: 3.68 min.
154 1,1-dimethylethyl 6-[({5-[({5-chloro-2-[(2-methylpropyl)oxy]phenyl}oxy)methyl]-1,3,4-thiadiazol-2-yl}amino)carbonyl]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		110 5-[({5-chloro-2-[(2-methylpropyl)oxy]phenyl}oxy)methyl]-1,3,4-thiadiazol-2-amine	LC/MS: m/z 573.2 $(M+H)^+$ Rt: 4.06 min.
155 1,1-dimethylethyl 6-[({5-[(4-fluorophenyl)methyl]-1,3,4-thiadiazol-2-yl}amino)carbonyl]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		94 5-[(4-fluorophenyl)methyl]-1,3,4-thiadiazol-2-amine	LC/MS: m/z 469.16 $(M+H)^+$ Rt: 3.49 min.
156 1,1-dimethylethyl 6-({[5-({[2-(methyloxy)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		111 5-({[2-(methyloxy)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-amine	LC/MS: m/z 497.1 $(M+H)^+$ Rt: 3.40 min.
157 1,1-dimethylethyl 6-[({5-[(1-methyl-1*H*-indol-3-yl)methyl]-1,3,4-thiadiazol-2-yl}amino)carbonyl]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		118 5-[(1-methyl-1*H*-indol-3-yl)methyl]-1,3,4-thiadiazol-2-amine	LC/MS: m/z 504.14 $(M+H)^+$ Rt: 3.60 min.
158 1,1-dimethylethyl 6-({[5-(3-pyridinylmethyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		Commercially available	LC/MS: m/z 452.09 (M+H) Rt: 2.96 min.
159 1,1-dimethylethyl 6-({[5-(5,6,7,8-tetrahydro-2-naphthalenylmethyl)-1,3,4-		112 5-(5,6,7,8-tetrahydro-2-naphthalenylmethy	LC/MS: m/z 505.13 $(M+H)^+$ Rt: 4.01 min.

Intermediate No.	R^1	From Intermediate No.	Physical data
thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		l)-1,3,4-thiadiazol-2-amine	
160 1,1-dimethylethyl 6-({[5-(3,4-dihydro-2*H*-chromen-6-ylmethyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		113 5-(3,4-dihydro-2*H*-chromen-6-ylmethyl)-1,3,4-thiadiazol-2-amine	LC/MS: m/z 507.1 $(M+H)^+$ Rt: 3.52 min.
161 1,1-dimethylethyl 6-{[(5-{2-[(2-chlorophenyl)oxy]ethyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		Commercially available	LC/MS: m/z 515.15 $(M+H)^+$ Rt: 3.67 min.
162 1,1-dimethylethyl 6-{[(5-{[(2,4-dichlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		114 5-{[(2,4-dichlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-amine	LC/MS: m/z 535.05 $(M+H)^+$ Rt: 3.85 min.
163 1,1-dimethylethyl 6-[({5-[(2'-chloro-2-biphenylyl)methyl]-1,3,4-thiadiazol-2-yl}amino)carbonyl]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		119 5-[(2'-chloro-2-biphenylyl)methyl]-1,3,4-thiadiazol-2-amine	LC/MS: m/z 561.3 $(M+H)^+$ Rt: 3.88 min.
164 1,1-dimethylethyl 6-[({5-[(2-fluorophenyl)methyl]-1,3,4-thiadiazol-2-yl}amino)carbonyl]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		Commercially available	LC/MS: m/z 469.08 $(M+H)^+$ Rt: 3.56 min.

The following Intermediates were prepared using the generic reaction scheme (Scheme 12)



The following Intermediates were similarly prepared by a method analogous to that described for Intermediate 2.

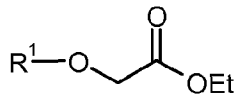
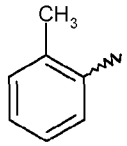
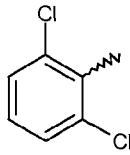
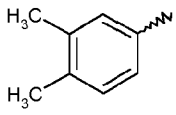
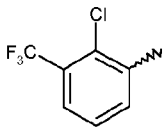
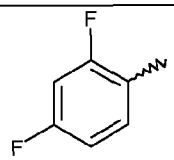
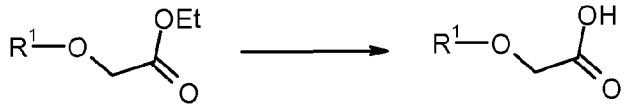


Table 10

Intermediate No.	R^1	From:	Physical data
165 Ethyl [(2-methylphenyl) oxy]acetate		Commercially available	^{1}H NMR (300 MHz, DMSO, ppm) δ: 7.12 (m, 2H), 6.82 (m, 2H), 4.76 (s, 2H), 4.14 (q, 2H), 2.18 (s, 3H), 1.19 (t, 3H).
166 Ethyl [(2,6-dichlorophenyl)oxy]acetate		Commercially available	^{1}H NMR (300 MHz, DMSO, ppm) δ: 7.48 (d, 2H), 7.19 (t, 1H), 4.64 (s, 2H), 4.17 (q, 2H), 1.21 (t, 3H).
167 Ethyl [(3,4-dimethylphenyl)oxy]acetate		Commercially available	^{1}H NMR (300 MHz, DMSO, ppm) δ: 7.03 (d, 2H), 6.74 (d, 1H), 6.65 (dd, 1H), 4.58 (s, 2H), 4.27 (q, 2H), 2.23 (s, 3H), 2.20 (s, 3H), 1.30 (t, 3H).
168 Ethyl {[2-chloro-3-(trifluoromethyl)phenyl] oxy}acetate		Commercially available	LC/MS: m/z 283 (M+H)+ Rt: 2.02 min
169 Ethyl [(2,4-difluorophenyl)oxy]acetate		Commercially available	LC/MS: m/z 217 (M+H)+ Rt: 1.85 min

The following Intermediates were prepared using the generic reaction scheme (Scheme 12)



The following compounds were similarly prepared by a method analogous to that described for Intermediate 20.

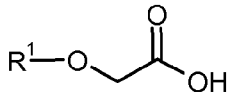
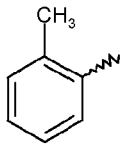
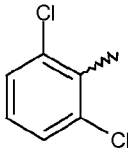
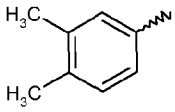
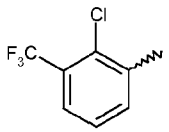
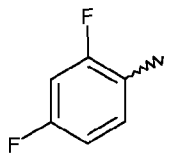
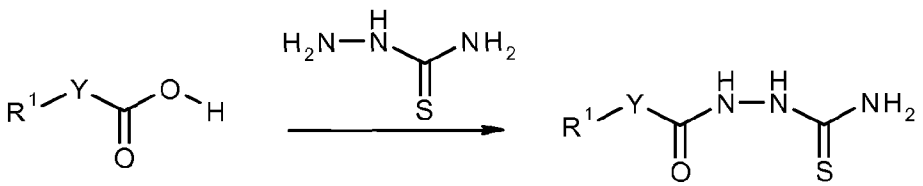


Table 11

Intermediate No.	R^1	From Intermediate No.	Physical data
170 [(2-methylphenyl)oxy] acetic acid		165 Ethyl [(2-methylphenyl) oxy]acetate	^{1}H NMR (300 MHz, DMSO, ppm) δ: 7.11 (m, 2H), 6.79 (m, 2H), 4.66 (s, 2H), 2.16 (s, 3H).
171 [(2,6-dichlorophenyl) oxy]acetic acid		166 Ethyl [(2,6-dichlorophenyl) oxy]acetate	^{1}H NMR (300 MHz, DMSO, ppm) δ: 7.49 (d, 2H), 7.19 (t, 1H), 4.55 (s, 2H).
172 [(3,4-dimethylphenyl) oxy]acetic acid		167 Ethyl [(3,4-dimethylphenyl)oxy] acetate	LC/MS: m/z 181.1 (M+H)+ Rt: 3.00 min
173 {[2-chloro-3-(trifluoromethyl) phenyl]oxy}acetic acid		168 Ethyl {[2-chloro-3-(trifluoromethyl) phenyl]oxy}acetate	LC/MS: m/z 255 (M+H)+ Rt: 2.17 min
174 [(2,4-difluorophenyl) oxy]acetic acid		169 Ethyl [(2,4-difluorophenyl) oxy]acetate	^{1}H NMR (300 MHz, DMSO, ppm) δ: 7.31 (m, 1H), 7.12 (m, 1H), 7.02 (m, 1H), 4.77 (s, 2H).

The following Intermediates were prepared using the generic reaction scheme (Scheme 11)



The following compounds Intermediates were similarly prepared by a method analogous method to that described for Intermediate 39.

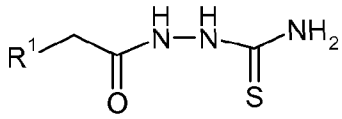
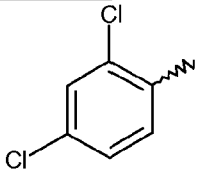
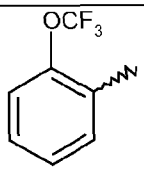
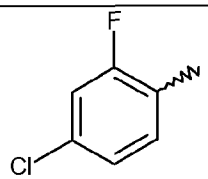
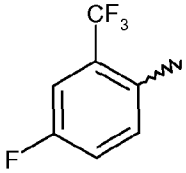
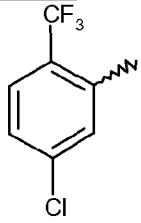
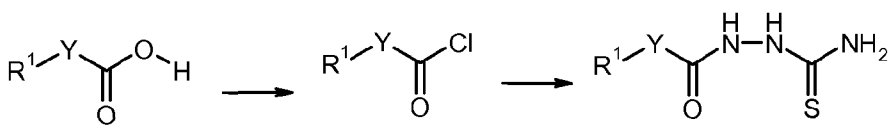


Table 12

Intermediate No.	R^1	From:	Physical data
175 2-[(2,4-dichlorophenyl)acetyl] hydrazinecarbothioamide		Commercially available	LC/MS: m/z 279 (M+H)+ Rt: 2.21 min
176 2-({2-[(trifluoromethyl)oxy] phenyl}acetyl) hydrazinecarbothioamide		Commercially available	LC/MS: m/z 294 (M+H)+ Rt: 2.17 min
177 2-[(4-chloro-2-fluorophenyl)acetyl] hydrazinecarbothioamide		Commercially available	LC/MS: m/z 262.0 (M+H)+ Rt: 2.02 min
178 2-{[4-fluoro-2-(trifluoromethyl)phenyl] acetyl}hydrazine carbothioamide		Commercially available	LC/MS: m/z 296 (M+H)+ Rt: 2.15 min
179 2-{[5-chloro-2-(trifluoromethyl)phenyl] acetyl}hydrazine carbothioamide		Commercially available	LC/MS: m/z 313 (M+H)+ Rt: 2.34 min

The following Intermediates were prepared using the generic reaction scheme (Scheme 11)



The following Intermediates were similarly prepared by a method analogous to that described for Intermediate 57.

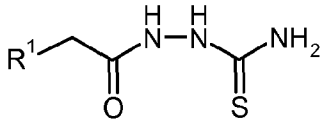
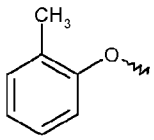
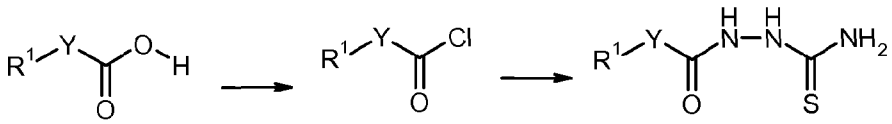


Table 13

Intermediate No.	R^1	From Intermediate No.	Physical data
180 2-{[(2-methylphenyl) oxy]acetyl} hydrazinecarbothioamide		[(2-methylphenyl) oxy]acetic acid 170	^{1}H NMR (300 MHz, DMSO, ppm) δ: 9.96 (bs, 1H), 9.26 (bs, 1H), 7.88 (bs, 1H), 7.50 (bs, 1H), 7.10 (m, 2H), 6.83 (m, 2H), 4.56 (s, 2H), 2.16 (s, 3H).

The following Intermediates were prepared using the generic reaction scheme (Scheme 11)



The following compounds were similarly prepared by a method analogous to that described for Intermediate 59.

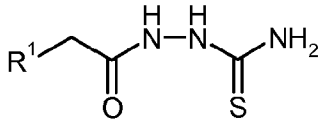
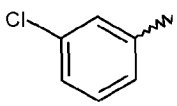
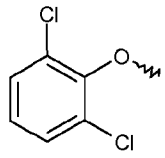
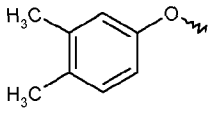
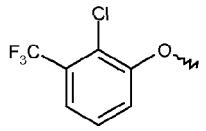
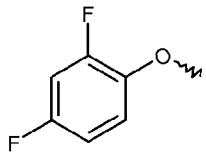
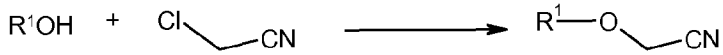


Table 14

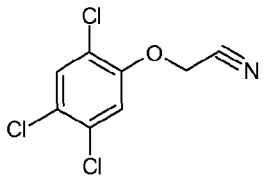
Intermediate No.	R^1	From Intermediate No.	Physical data
181 2-[(3-chlorophenyl)acetyl] hydrazinecarbothioamide		Commercially available	1H NMR (300 MHz, DMSO, ppm) δ: 10.1 (bs, 1H), 9.24 (bs, 1H), 7.90 (bs, 1H), 7.56 (bs, 1H), 7.32 (m, 4H), 3.52 (s, 2H).

182 2-{[(2,6-dichlorophenyl)oxy]acetyl}hydrazine carbothioamide		171 [(2,6-dichlorophenyl)oxy]acetic acid	LC/MS: m/z 295.1 (M+H)+ Rt: 1.50 min
183 2-{[(3,4-dimethylphenyl)oxy]acetyl}hydrazinecarbothioamide		172 [(3,4-dimethylphenyl)oxy]acetic acid	1H NMR (300 MHz, DMSO, ppm) δ: 10.02 (s, 1H), 9.25 (s, 1H), 7.87 (s, 1H), 7.48 (s, 1H), 6.99 (d, 1H), 6.66 (m, 2H), 4.47 (s, 1H), 2.13 (d, 6H).
184 2-({[2-chloro-3-(trifluoromethyl)phenyl]oxy}acetyl)hydrazinecarbothioamide		173 {[2-chloro-3-(trifluoromethyl)phenyl]oxy}acetic acid	LC/MS: m/z 328 (M+H)+ Rt: 1.57 min
185 2-{[(2,4-difluorophenyl)oxy]acetyl}hydrazine carbothioamide		174 [(2,4-difluorophenyl)oxy]acetic acid	LC/MS: m/z 262 (M+H)+ Rt: 1.31 min

The following Intermediates were prepared using the generic reaction scheme (Scheme 10)



Intermediate 186: [(2,4,5-Trichlorophenyl)oxy]acetonitrile



To a solution of 2,4,5-trichlorophenol (3 g, 15.2 mmol.) in acetone (50 mL) were added potassium carbonate (2.3 g, 16.7 mmol.) and then dropwise 2-chloroacetonitrile (1.26 g, 16.7 mmol.). The solution was refluxed overnight. After filtration, the filtrate was concentrated to dryness then poured into water (50 mL) and extracted with DCM (200 mL). The organic layer was washed with water then brine, dried on sodium sulphate and evaporated to dryness to give the title compound as dark solid (4.7 g, quantitative) which was used without further purification.

^{1}H NMR (300 MHz, DMSO, ppm) δ: 7.82 (s, 1H), 7.66 (s, 1H), 5.44 (s, 2H).

The following Intermediates were similarly prepared by a method analogous to that described for Intermediate 186

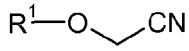
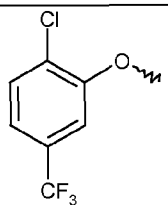
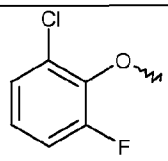
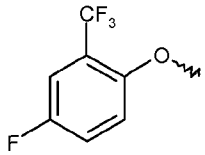
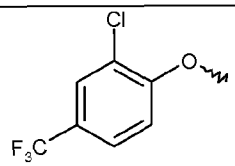
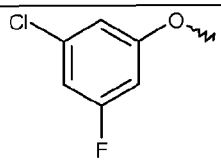
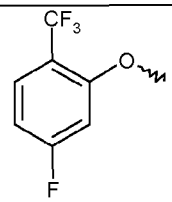
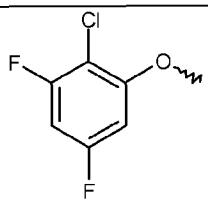
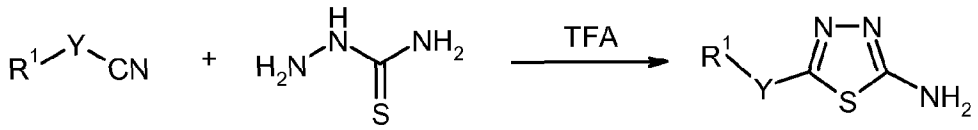


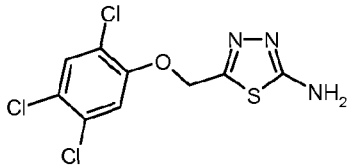
Table 15

Intermediate No.	R^1	From:	Physical data
187 {[2-chloro-5-(trifluoromethyl) phenyl]oxy}acetonitrile		Commercially available	^{1}H NMR (300 MHz, CDCl3, ppm) δ: 7.55 (d, 1H), 7.28 (d, 1H), 7.26 (d, 1H), 4.89 (s, 2H).
188 [(2-chloro-6-fluorophenyl) oxy]acetonitrile		Commercially available	^{1}H NMR (300 MHz, CDCl3, ppm) δ: 7.12 (m, 1H), 7.08 (m, 2H), 4.86 (s, 2H).
189 {[4-fluoro-2-(trifluoromethyl) phenyl]oxy}acetonitrile		Commercially available	^{1}H NMR (300 MHz, CDCl3, ppm) δ: 7.37 (dd, 1H), 7.30 (m, 1H), 7.15 (m, 1H), 4.84 (s, 2H).
190 {[2-chloro-4-(trifluoromethyl)phenyl]oxy}acetonitrile		Commercially available	^{1}H NMR (300 MHz, CDCl3, ppm) δ: 7.71 (d, 1H), 7.57 (dd, 1H), 7.14 (d, 1H), 4.90 (s, 2H).
191 [(3-chloro-5-fluorophenyl)oxy]acetonitrile		Commercially available	^{1}H NMR (300 MHz, CDCl3, ppm) δ: 6.85 (d, 1H), 6.79 (s, 1H), 6.63 (d, 1H), 4.75 (s, 2H).
192 {[5-fluoro-2-(trifluoromethyl)phenyl] oxy}acetonitrile		Commercially available	^{1}H NMR (300 MHz, CDCl3, ppm) δ: 7.65 (m, 1H), 6.87 (m, 2H), 4.86 (s, 2H).
193 [(2-chloro-3,5-difluorophenyl) oxy]acetonitrile		Commercially available	^{1}H NMR (300 MHz, DMSO, ppm) δ: 6.72 (td, 1H), 6.65 (dt, 1H), 4.85 (s, 2H).

The following Intermediates were prepared using the generic reaction scheme (Scheme 10)



Intermediate 194: 5-{[(2,4,5-Trichlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-amine



A mixture of [(2,4,5-trichlorophenyl)oxy]acetonitrile (Intermediate 186) (4.7 g, maximum 15.2 mmol.) and thiosemicarbazide (1.7 g, 18.6 mmol.) in trifluoroacetic acid (20 mL) was refluxed for 3 hours. Trifluoroacetic acid was removed under reduced pressure. To the residue was added 20 ml of cooled water and the mixture was adjusted to ph = 6 to 7 with concentrated ammonia. The resulting solid material was filtered to give crude product which was stirred in methyl alcohol (20 mL) for 1.5 hours. Then the solid material was filtered and dried to give the title compound as a white solid (4.45 g, 94%).
LC/MS: m/z 311.9 $(M+H)^+$, Rt: 2.53 min.

The following Intermediates were similarly prepared by a method analogous to that described for Intermediate 194.

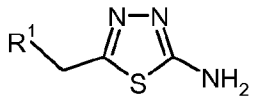
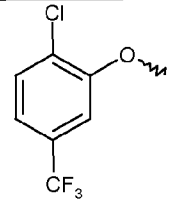
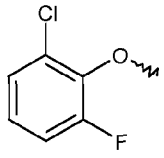
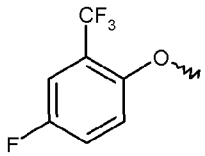
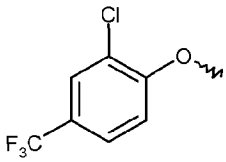
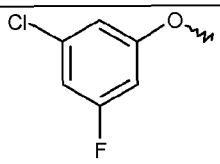
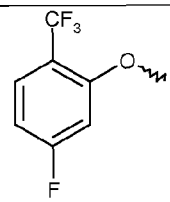
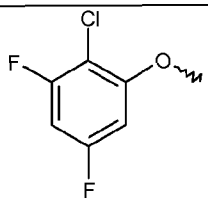
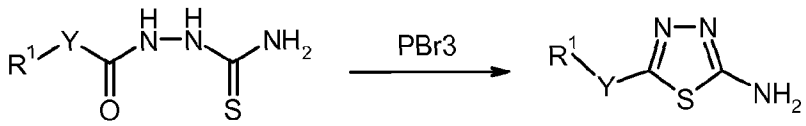


Table 16

Intermediate No.	R^1	From Intermediate No.	Physical data
195 5-({[2-chloro-5-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-amine		187 {[2-chloro-5-(trifluoromethyl)phenyl]oxy}acetonitrile	LC/MS: m/z 310.0 $(M+H)^+$, Rt: 2.44 min.

Intermediate No.	R^1	From Intermediate No.	Physical data
196 5-({[2-chloro-5-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-amine		188 [(2-chloro-6-fluorophenyl)oxy]acetonitrile	LC/MS: m/z 260.0 $(M+H)^+$, Rt: 2.12 min.
197 5-({[4-fluoro-2-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-amine		189 {[4-fluoro-2-(trifluoromethyl)phenyl]oxy}acetonitrile	LC/MS: m/z 294.0 $(M+H)^+$, Rt: 2.33 min.
198 5-({[2-chloro-4-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-amine		190 {[2-chloro-4-(trifluoromethyl)phenyl]oxy}acetonitrile	LC/MS: m/z 310.0 $(M+H)^+$, Rt: 2.46 min.
199 5-{[(3-chloro-5-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-amine		191 [(3-chloro-5-fluorophenyl)oxy]acetonitrile	LC/MS: m/z 260.0 $(M+H)^+$, Rt: 2.29 min.
200 5-{[(3-chloro-5-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-amine		192 {[5-fluoro-2-(trifluoromethyl)phenyl]oxy}acetonitrile	LC/MS: m/z 294.0 $(M+H)^+$, Rt: 2.31 min.
201 5-{[(2-chloro-3,5-difluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-amine		193 [(2-chloro-3,5-difluorophenyl)oxy]acetonitrile	LC/MS: m/z 278.0 $(M+H)^+$, Rt: 2.29 min.

The following Intermediates were prepared using the generic reaction scheme (Scheme 8)



The following Intermediates were similarly prepared by a method analogous to that described for Intermediate 77.

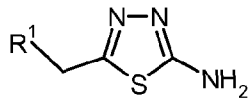
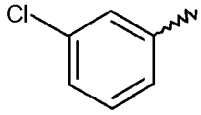
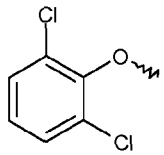
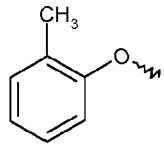
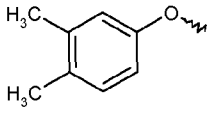
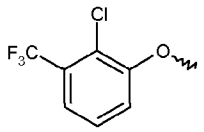
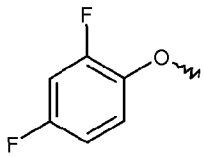
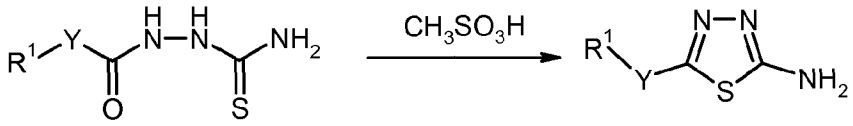


Table 17

Intermediate No.	R^1	From Intermediate No.	Physical data
202 5-[(2-chlorophenyl)methyl]-1,3,4-thiadiazol-2-amine		181 2-[(3-chlorophenyl)acetyl] hydrazinecarbothioamide	LC/MS: m/z 226.0 (M+H)+, Rt: 3.42 min.
203 5-{[(2,6-dichlorophenyl)oxy] methyl}-1,3,4-thiadiazol-2-amine		182 2-{[(2,6-dichlorophenyl)oxy] acetyl}hydrazine carbothioamide	LC/MS: m/z 277 (M+H)+, Rt: 2.33 min.
204 5-{[(2-methylphenyl)oxy] methyl}-1,3,4-thiadiazol-2-amine		180 2-{[(2-methylphenyl)oxy]acetyl} hydrazinecarbothioamide	LC/MS: m/z 222.0 (M+H)+, Rt: 3.71 min.
205 5-{[(3,4-dimethylphenyl)oxy] methyl}-1,3,4-thiadiazol-2-amine		183 2-{[(3,4-dimethylphenyl)oxy] acetyl}hydrazine carbothioamide	LC/MS: m/z 236.0 (M+H)+, Rt: 2.33 min.
206 5-({[2-chloro-3-(trifluoromethyl)phenyl] oxy}methyl)-1,3,4-thiadiazol-2-amine		184 2-({[2-chloro-3-(trifluoromethyl)phenyl] oxy}acetyl) hydrazinecarbothioamide	LC/MS: m/z 310 (M+H)+, Rt: 2.43 min.
207 5-{[(2,4-difluorophenyl)oxy] methyl}-1,3,4-thiadiazol-2-amine		185 2-{[(2,4-difluorophenyl)oxy] acetyl}hydrazine carbothioamide	LC/MS: m/z 244 (M+H)+, Rt: 2.06 min.

The following Intermediates were prepared using the generic reaction scheme (Scheme 8)



The following Intermediates were similarly prepared by analogous method to that described for Intermediate 95.

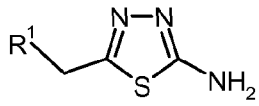
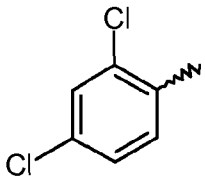
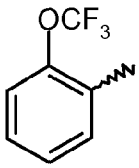
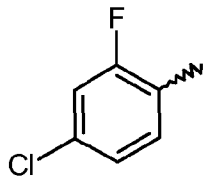
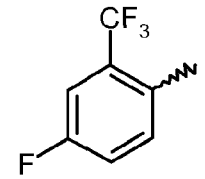
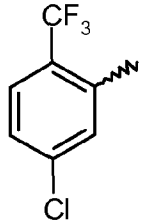
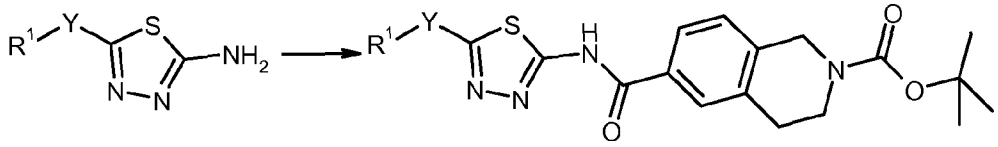


Table 18

Intermediate No.	R^1	From Intermediate No.	Physical data
208 5-[(2,4-dichlorophenyl)methyl]-1,3,4-thiadiazol-2-amine		175 2-[(2,4-dichlorophenyl)acetyl] hydrazinecarbothioamide	LC/MS: m/z 260 $(M+H)^+$ Rt: 2.61 min
209 5-({2-[(trifluoromethyl)oxy] phenyl}methyl)-1,3,4-thiadiazol-2-amine		176 2-({2-[(trifluoromethyl)oxy] phenyl}acetyl)hydrazinecarbothioamide	^{1}H NMR (300 MHz, DMSO, ppm) δ: 7.41 (m, 4H), 7.07 (bs, 2H), 4.20 (s, 2H).
210 5-[(4-chloro-2-fluorophenyl)methyl]-1,3,4-thiadiazol-2-amine		177 2-[(4-chloro-2-fluorophenyl)acetyl] hydrazinecarbothioamide	LC/MS: m/z 244.0 $(M+H)^+$ Rt: 2.47 min
211 5-{[4-fluoro-2-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-amine		178 2-{[4-fluoro-2-(trifluoromethyl)phenyl] acetyl}hydrazine carbothioamide	LC/MS: m/z 278 $(M+H)^+$, Rt: 2.58 min.
212 5-{[5-chloro-2-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-amine		179 2-{[5-chloro-2-(trifluoromethyl)phenyl] acetyl}hydrazine carbothioamide	LC/MS: m/z 294 $(M+H)^+$, Rt: 2.73 min.

The following Intermediates were prepared using the generic reaction scheme (Scheme 1):



The following Intermediates were similarly prepared by a method analogous to that described for Intermediate 120.

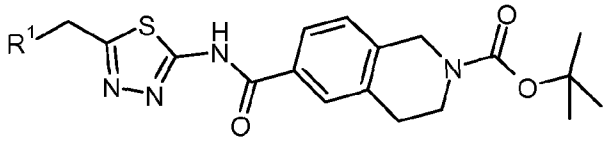
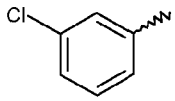
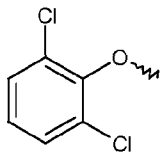
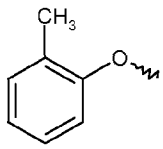
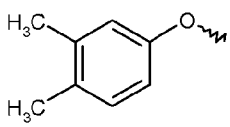
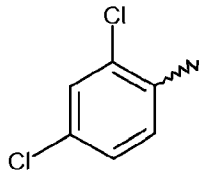
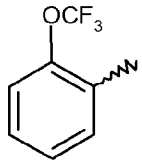
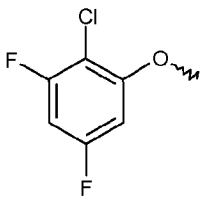
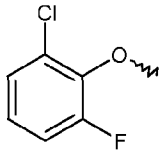
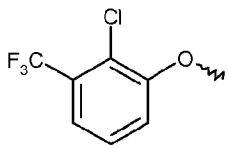
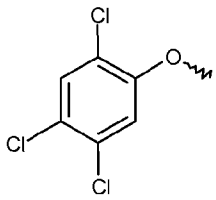
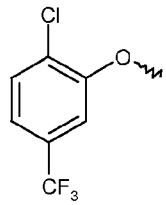
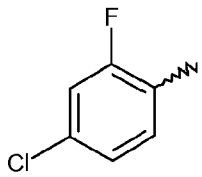
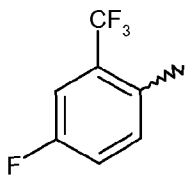
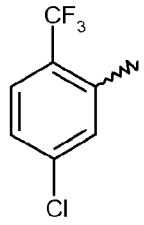
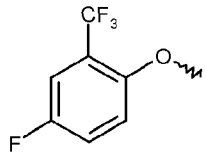
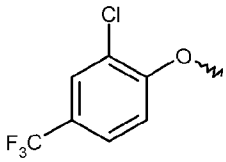
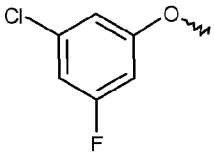
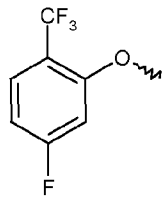


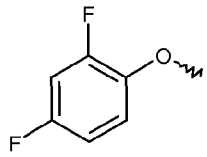
Table 19

Intermediate No.	R^1	From Intermediate No.	Physical data
213 1,1-dimethylethyl 6-[({5-[(3-chlorophenyl)methyl]-1,3,4-thiadiazol-2-yl}amino)carbonyl]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		202 5-[(2-chlorophenyl)methyl]-1,3,4-thiadiazol-2-amine	LC/MS: m/z 485.0 (M+H)+ Rt: 3.59 min.
214 1,1-dimethylethyl 6-{[(5-{[(2,6-dichlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		203 5-{[(2,6-dichlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-amine	LC/MS: m/z 535.06 (M+H)+ Rt: 3.88 min.
215 1,1-dimethylethyl 6-{[(5-{[(2-methylphenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		204 5-{[(2-methylphenyl)oxy]methyl}-1,3,4-thiadiazol-2-amine	^{1}H NMR (400 MHz, DMSO, ppm) δ: 13.06 (bs, 1H), 7.95 (m, 2H), 7.39 (d, 1H), 7.18 (m, 3H), 6.93 (m, 1H), 5.55 (s, 2H), 4.61 (bs, 2H), 3.61 (m, 2H), 2.88 (m, 2H), 2.23 (s, 3H), 1.45 (s, 9H).

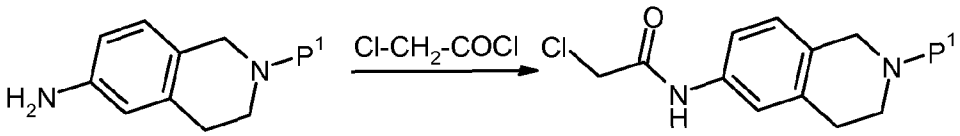
216 1,1-dimethylethyl 6-{[(5-{[(3,4-dimethylphenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		205 5-{[(3,4-dimethylphenyl)oxy]methyl}-1,3,4-thiadiazol-2-amine	LC/MS: m/z 494.8 (M+H)+ Rt: 3.82 min.
217 1,1-dimethylethyl 6-[({5-[(2,4-dichlorophenyl)methyl]-1,3,4-thiadiazol-2-yl}amino)carbonyl]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		208 5-[(2,4-dichlorophenyl)methyl]-1,3,4-thiadiazol-2-amine	LC/MS: m/z 519 (M+H)+ Rt: 4.30 min.
218 1,1-dimethylethyl 6-({[5-({2-[(trifluoromethyl)oxy]phenyl}methyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		209 5-({2-[(trifluoromethyl)oxy]phenyl}methyl)-1,3,4-thiadiazol-2-amine	LC/MS: m/z 535.1 (M+H)+ Rt: 3.74 min.
219 1,1-dimethylethyl 6-{[(5-{[(2-chloro-3,5-difluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		201 5-{[(2-chloro-3,5-difluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-amine	LC/MS: m/z 536.0 (M+H)+ Rt: 3.67 min
220 1,1-dimethylethyl 6-{[(5-{[(2-chloro-6-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		196 5-({[2-chloro-5-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-amine	^{1}H NMR (400 MHz, DMSO, ppm) δ: 13.06 (bs, 1H), 7.95 (m, 2H), 7.35 (m, 3H), 7.23 (m, 1H), 5.53 (s, 2H), 4.60 (bs, 2H), 3.60 (t, 2H), 2.88 (t, 2H), 1.45 (s, 9H).

221 1,1-dimethylethyl 6-({[5-({[2-chloro-3-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		206 5-({[2-chloro-3-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-amine	LC/MS: m/z 568.8 (M+H)+ Rt: 3.86 min.
222 1,1-dimethylethyl 6-{[(5-{[(2,4,5-trichlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		194 5-{[(2,4,5-trichlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-amine	LC/MS: m/z 568.7 (M+H)+ Rt: 4.03 min.
223 1,1-dimethylethyl 6-({[5-({[2-chloro-5-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		195 5-({[2-chloro-5-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-amine	LC/MS: m/z 569.0 (M+H)+ Rt: 3.91 min.
224 1,1-dimethylethyl 6-({[5-({[2-chloro-5-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		210 5-[(4-chloro-2-fluorophenyl)methyl]-1,3,4-thiadiazol-2-amine	LC/MS: m/z 503.08 (M+H)+ Rt: 3.78 min.
225 1,1-dimethylethyl 6-{[(5-{[4-fluoro-2-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		211 5-{[4-fluoro-2-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-amine	LC/MS: m/z 537.0 (M+H)+ Rt: 3.74 min.

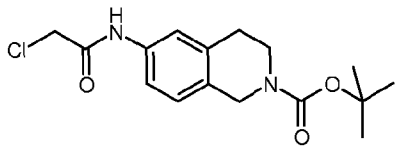
226 1,1-dimethylethyl 6-{[(5-{[5-chloro-2-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		212 5-{[5-chloro-2-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-amine	LC/MS: m/z 553.0 (M+H)+ Rt: 3.85 min.
227 1,1-dimethylethyl 6-({[5-({[4-fluoro-2-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		197 5-({[4-fluoro-2-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-amine	LC/MS: m/z 553.1 (M+H)+ Rt: 3.85 min.
228 1,1-dimethylethyl 6-({[5-({[2-chloro-4-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		198 5-({[2-chloro-4-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-amine	LC/MS: m/z 569.1 (M+H)+ Rt: 4.02 min.
229 1,1-dimethylethyl 6-{[(5-{[(3-chloro-5-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		199 5-{[(3-chloro-5-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-amine	LC/MS: m/z 518.7 (M+H)+ Rt: 3.81 min.
230 1,1-dimethylethyl 6-({[5-({[5-fluoro-2-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		200 5-{[(3-chloro-5-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-amine	LC/MS: m/z 552.8 (M+H)+ Rt: 3.74 min.

231 1,1-dimethylethyl 6-{[(5-{[(2,4-difluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate		207 5-{[(2,4-difluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-amine	1H NMR (400 MHz, DMSO, ppm) δ: 13.05 (bs, 1H), 7.95 (m, 2H), 7.38 (m, 3H), 7.07 (t, 1H), 5.59 (s, 2H), 4.59 (bs, 2H), 3.60 (t, 2H), 2.87 (t, 2H), 1.44 (s, 9H).

The following Intermediates were prepared using the generic reaction scheme (Scheme 19)



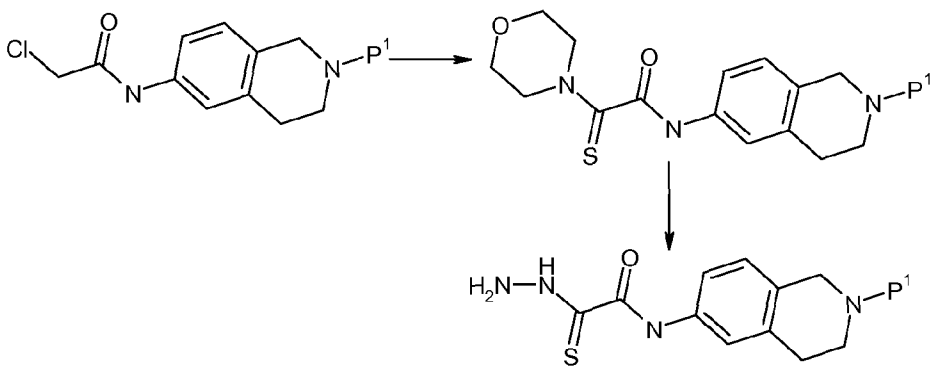
Intermediate 232: 1,1-Dimethylethyl 6-[(chloroacetyl)amino]-3,4-dihydro-2(1H)-isoquinolinecarboxylate



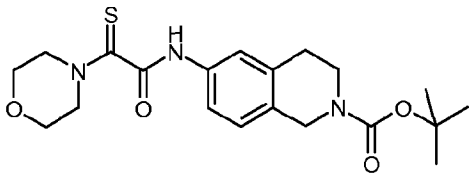
To a solution of 1,1-dimethylethyl 6-amino-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate (9.5 g, 38.3 mmol.) in THF (350 mL) under nitrogen and cooled to 0°C were added sodium hydrogenocarbonate (8 g, 95.6 mmol.) and after 2 to 3 minutes of stirring, drop-wise, a solution of chloroacetyl chloride (6.1 ml, 76.5 mmol.) in THF (10 mL). The mixture was stirred at 0°C for 10 minutes then heated up to room temperature and stirred for 2.5 hours. The mixture was poured into an aqueous saturated solution of sodium hydrogenocarbonate and ethyl acetate (500ml) was added. The organic layer was washed three times with aqueous saturated solution of sodium hydrogenocarbonate then dried on sodium sulphate, filtered and evaporated to dryness to give the title compound as yellow oil which crystallised slowly (14.09 g, quantitative yield).

^{1}H NMR (400 MHz, DMSO, ppm) δ: 10.2 (bs, 1H), 7.44 (bs, 1H), 7.36 (bd, 1H), 7.12 (d, 1H), 4.45 (m, 2H), 4.23 (s, 2H), 3.54 (t, 2H), 2.75 (t, 2H), 1.43 (s, 9H).

The following Intermediates were prepared using the generic reaction scheme (Scheme 18)



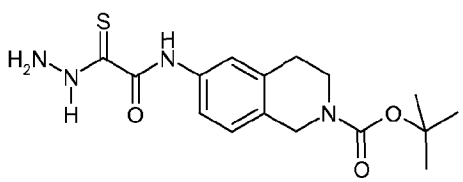
Intermediate 233: 1,1-Dimethylethyl 6-{[4-morpholinyl(thioxo)acetyl]amino}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate



To a solution of morpholine (4.6 mL, 52 mmol.) in DMF (30 mL) were added at room temperature sulphur S_8 (4.2 g, 130 mmol) and then a solution of 1,1-dimethylethyl 6-[(chloroacetyl)amino]-3,4-dihydro-2(1H)-isoquinolinecarboxylate (Intermediate 232) (12.43 g, maximum 38.3 mmol) in DMF (170mL). After stirring for 24 hours, water was added. The solid material was difficult to filter and the partially filtered material was poured in acetone. The remaining solid material was removed by filtration. The two filtrates were diluted with DCM then dried on sodium sulphate, filtered and evaporated to dryness. The residue was purified by flash column chromatography eluting with a gradient cyclohexane 100% to cyclohexane/EtOAc: 40/60 to give the title compound as a yellow oil (3.05 g, 19.6%).

^{1}H NMR (400 MHz, DMSO, ppm) δ: 10.56 (bs, 1H), 7.48 (bs, 1H), 7.38 (bd, 1H), 7.14 (d, 1H), 4.45 (m, 2H), 4.12 (t, 2H), 3.76 (t, 2H), 3.68 (bs, 4H), 3.53 (t, 2H), 2.76 (t, 2H), 1.43 (s, 9H).

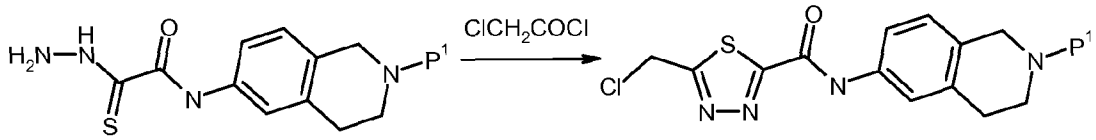
Intermediate 234: 1,1-Dimethylethyl 6-{[hydrazino(thioxo)acetyl]amino}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate



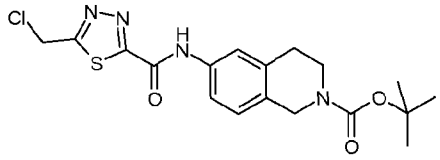
To a solution of 1,1-dimethylethyl 6-{[4-morpholinyl(thioxo)acetyl]amino}-3,4-dihydro-2(1H)-isoquinolinecarboxylate (Intermediate 233) (3.05 g, 7.5 mmol.) in DMF (25 mL)

was added hydrazine hydrate (5 mL, 103 mmol). After stirring overnight at room temperature, water was added and pH was adjusted to pH = 4 to 5 with concentrated hydrochloride solution. The solid material was filtered and washed twice with a minimal amount of water. The residue was refluxed in ethyl alcohol. After return to room temperature, the solid was filtered and washed with ethyl alcohol to give after drying the title compound as a beige solid (1.64 g, 63%).
^{1}H NMR (400 MHz, DMSO, ppm) δ: 10.14 (bs, 1H), 7.56 (m, 2H), 7.16 (d, 1H), 4.47 (bs, 2H), 3.55 (t, 2H), 2.77 (t, 2H), 1.43 (s, 9H).

The following Intermediates were prepared using the generic reaction scheme (Scheme 17)

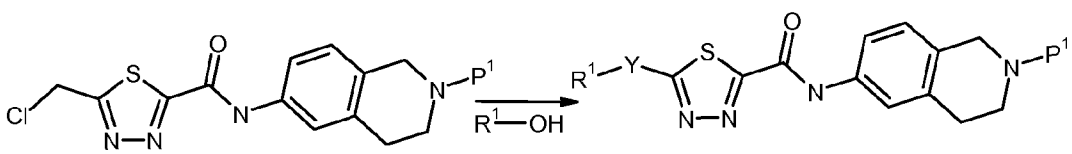


Intermediate 235: 1,1-Dimethylethyl 6-({[5-(chloromethyl)-1,3,4-thiadiazol-2-yl]carbonyl}amino)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate

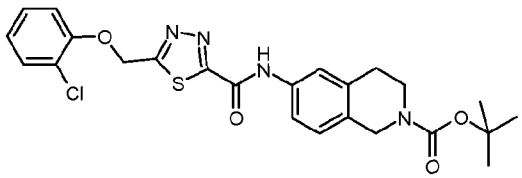


To a solution of 1,1-dimethylethyl 6-{[hydrazino(thioxo)acetyl]amino}-3,4-dihydro-2(1H)-isoquinolinecarboxylate (Intermediate 234) (1 g, 2.85 mmol.) in DMF (40 mL) was added under nitrogen and dropwise a solution of chloroacetyl chloride (2.3 ml, 28.5 mmol.) in a small volume of DMF. After stirring overnight at room temperature, water was added. The pasty solid was isolated from the liquid layer, dissolved in DCM and evaporated to dryness. The residue was purified by flash column chromatography eluting with a gradient DCM 100% to DCM/MeOH : 96/4 to give the title compound as light yellow oil which crystallized slowly (232 mg g, 20%).
^{1}H NMR (400 MHz, DMSO, ppm) δ: 11.15 (s, 1H), 7.69 (s, 1H), 7.62 (d, 1H), 7.18 (d, 1H), 5.34 (s, 2H), 4.48 (bs, 2H), 3.56 (t, 2H), 2.78 (t, 2H), 1.44 (s, 9H).

The following Intermediates were prepared using the generic reaction scheme (Scheme 15)



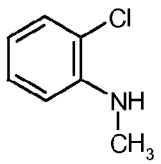
Intermediate 236: 1,1-Dimethylethyl 6-{[(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)carbonyl]amino}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate



To a solution of 2-chlorophenol (60 mg, 0.47 mmol.) in acetone (10 mL) was added potassium carbonate (102 mg, 0.74 mmol) then after 1 hour of stirring at room temperature 1,1-dimethylethyl 6-({[5-(chloromethyl)-1,3,4-thiadiazol-2-yl]carbonyl}amino)-3,4-dihydro-2(1H)-isoquinolinecarboxylate (Intermediate 235) (232 mg, 0.57 mmol). The mixture was refluxed for 5 hours then an addition amount of 2-chlorophenol (12 mg, 0.1 mmol) was added and the mixture was heated overnight at 45°C. After return to room temperature, the solid material was removed by filtration and the filtrate was evaporated to dryness. The crude material was poured in DCM and water was added. The aqueous layer was extracted with DCM and the combined organic layer was washed with brine then dried on sodium sulphate. After filtration and evaporation to dryness, the residue was purified by flash column chromatography eluting with a gradient DCM 100% to DCM/MeOH : 96/4. After evaporation of the right fractions, the material was crystallized with a small volume of diisopropyl ether to give after drying the title compound as an off white solid (140 mg, 49%).

^{1}H NMR (400 MHz, DMSO, ppm) δ: 11.14 (s, 1H), 7.69 (bs, 1H), 7.63 (d, 1H), 7.51 (d, 1H), 7.36 (d, 2H), 7.18 (d, 1H), 7.07 (m, 1H), 5.79 (s, 2H), 4.48 (bs, 2H), 3.56 (t, 2H), 2.78 (t, 2H), 1.44 (s, 9H).

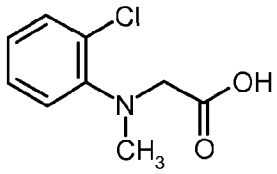
Intermediate 237: 2-Chloro-*N*-methylaniline



To a solution of 2-chloro aniline (26 g, 0.204 mol.) in THF (260 mL) was added butyl lithium (2.5 M, 80 mL, 0.2 mol) at -50°C. The reaction was stirred at -50°C for 0.5 hours then allowed to reach room temperature. After 0.5 hours at room temperature, the mixture was cooled to -50°C then iodomethane (12.4 mL, 0.2 mol.) was added. After stirring at -50°C for 0.5 hours, the mixture was warmed up to room temperature and stirred for 5 hours. The mixture was poured in saturated NH_4Cl solution then the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with water then dried on sodium sulphate. After filtration and evaporation to

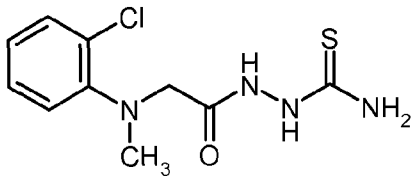
dryness, the residue was purified by flash column chromatography eluting with EtOAc/petroleum ether: 1/100 to give the title compound as a clear oil (12 g, 42%).
^{1}H NMR (300 MHz, DMSO, ppm) δ: 7.21 (d, 1H), 7.13 (t, 1H), 6.50 (m, 2H), 5.45 (bs, 1H), 2.72 (d, 3H).

Intermediate 238: *N*-(2-Chlorophenyl)-*N*-methylglycine



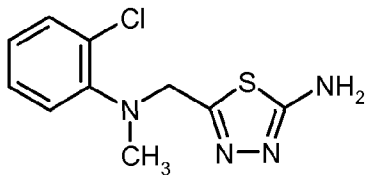
To a solution of the 2-chloro-N-methylaniline (Intermediate 237) (8g, 0.057 mol.) in acetonitrile (340 mL) was added oxoacetic acid (42.2 g, 0.57 mol.). After stirring for 0.5 hours at room temperature, $NaBH_3CN$ (17.7 g, 0.285 mol) was added in portions by keeping the temperature below 40°C. The mixture was stirred at room temperature for 2 hours then acetic acid (23 mL) was added drop-wise. After stirring for 1 hour, the solid material was removed by filtration and the filtrate was concentrated to dryness. The residue was poured in water and the pH was adjusted to 9 with aqueous NaOH. After extraction of the aqueous layer with EtOAc, the aqueous layer was acidified to pH: 4 with diluted HCl. The white solid was filtered, washed with water then dried to give the title compound as a white solid (7g, 62%).
LC/MS: m/z 200.1 $(M+H)^+$, Rt: 1.67 min.

Intermediate 239: 2-{[(2-Chlorophenyl)(methyl)amino]acetyl}hydrazinecarbothioamide



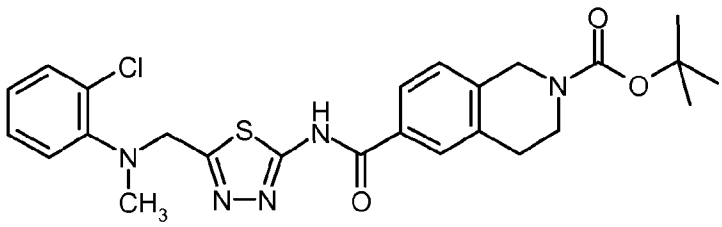
To a solution of N-(2-chlorophenyl)-N-methylglycine (Intermediate 238) (3g, 0.015 mol.) in dichloromethane containing 3 drops of DMF, was slowly added oxalyl chloride (2.3 g, 0.018 mol.). After stirring for 2 hours at room temperature, the solvent was evaporated under vacuum. The residue was dissolved in DMF (10 mL) then added to a solution of thiosemicarbazide (1.45g, 0.016 mol.) and pyridine (1.26 g, 0.016 mol.) in DMF (30 mL). After stirring for 2 hours at room temperature, the mixture was poured into water (500mL) and stirred for several hours. The resulting solid material was filtered, washed with EtOAc and dried to give the title compound as a white solid (3g, 69%).
LC/MS: m/z 273.0 $(M+H)^+$, Rt: 2.07 min.

Intermediate 240: 5-{[(2-Chlorophenyl)(methyl)amino]methyl}-1,3,4-thiadiazol-2-amine



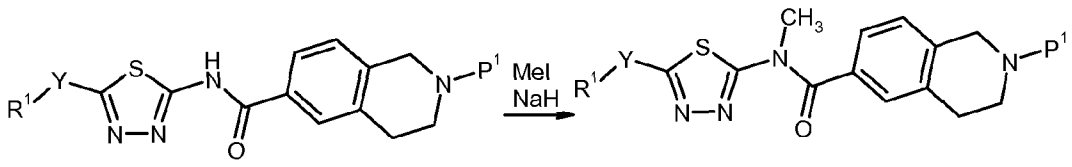
To a solution of 2-{[(2-chlorophenyl)(methyl)amino]acetyl}hydrazinecarbothioamide (Intermediate 239) (3g, 11 mmol) in toluene (20 ml) was added drop by drop methane sulphonic acid (9 mL, 138 mmol) and the reaction mixture was refluxed for 3 hours. The solvent was evaporated. The residue was diluted with water and ammonia solution was added until pH=8. The solid material was filtered, washed with water and EtOAc, and dried to give the title compound as a white solid (2 g, 71%).
LC/MS: m/z 255.1 $(M+H)^+$, Rt: 2.17 min.

Intermediate 241: 1,1-Dimethylethyl 6-{[(5-{[(2-chlorophenyl)(methyl)amino]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate

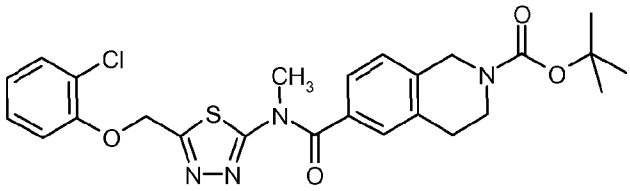


A solution of 2-{[(1,1-dimethylethyl)oxy]carbonyl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxylic acid (555 mg, 2 mmol), HATU (989 mg, 2.6 mmol), triethylamine (0.26 mL, 2.6mmol) in DMF (15 mL) and 5-{[(2-chlorophenyl)(methyl)amino]methyl}-1,3,4-thiadiazol-2-amine (Intermediate 240) (509 mg, 2 mmol) was stirred at room temperature overnight. The DMF was evaporated under reduced pressure and the residue was dissolved in DCM. The organic phase was dried over sodium sulphate, filtered and evaporated under reduced pressure. The residue was purified by flash column chromatography eluting with a gradient DCM 100% to DCM/MeOH: 98/2. After evaporation of the right fractions, the material was triturated in hot methyl alcohol, to give after filtration and drying the title compound as a white solid (300 mg, 29%).
HRMS calculated for $C_{25}H_{28}ClN_5O_3S$ $(M+H)^+$ 514.1680, found: 514.1651, Rt: 3.47 min.

The following Intermediates were prepared using the generic reaction scheme (Scheme 6)

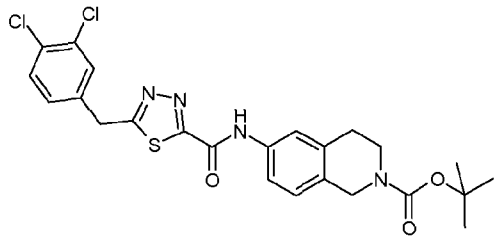


Intermediate 242: 1,1-Dimethylethyl 6-{[(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)(methyl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate



To a solution of 5-[(2'-chloro-2-biphenylyl)methyl]-1,3,4-thiadiazol-2-amine 1,1-dimethylethyl 6-{[(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1H)-isoquinolinecarboxylate (Intermediate 120) (180 mg, 0.36 mmol.) in THF (10 mL) was added NaH 60% in mineral oil (15 mg, 0.378 mmol) then after 1 hour of stirring at room temperature iodomethane (53 mg, 0.378 mmol). The mixture was stirred for 2 days at room temperature. After evaporation to dryness, the crude material was poured in DCM and washed with water. After filtration and evaporation to dryness, the residue was triturated with diisopropyl ether to give after drying the title compound as a light yellow solid (150 mg, 81%).
LC/MS: m/z 515 $(M+H)^+$, Rt: 4.18 min.

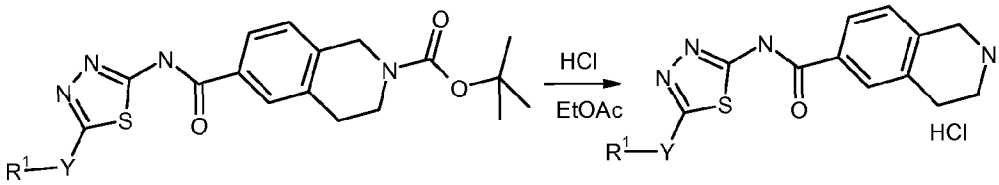
Intermediate 243: 1,1-Dimethylethyl 6-[({5-[(3,4-dichlorophenyl)methyl]-1,3,4-thiadiazol-2-yl}carbonyl)amino]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate



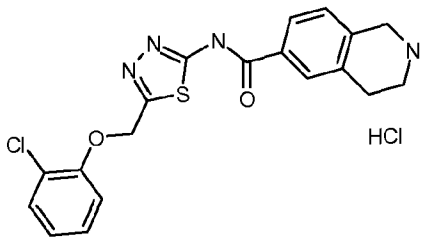
A solution of (3,4-dichlorophenyl)acetic acid (320 mg, 1.56 mmol), HATU (890 mg, 2.34 mmol), DIPEA (270 µL, 2.34 mmol) in DMF (15 mL) was stirred at room temperature for 1 hour. 1,1-dimethylethyl 6-{[hydrazino(thioxo)acetyl]amino}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate, (Intermediate 234) (600 mg, 1.71 mmol) was added and the mixture was stirred at room temperature for 10 days. The DMF was evaporated under reduced pressure and the residue was dissolved in dichloromethane. The organic phase was then washed with water. The aqueous phase was extracted with dichloromethane. Then the combined organic phase was treated

with brine, dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified by flash column chromatography eluting with a gradient DCM 100% to DCM/MeOH : 96/4 to give the title compound as yellow oil (200 mg, 24%).
LC/MS : m/z : 518.9 $(M+H)^+$, Rt : 3.96 min.

The following Examples were prepared using the generic reaction scheme (Scheme 1):



Example 1: *N*-(5-{[(2-Chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride



HCl(g) was bubbled at 0°C in EtOAc until the solvent was saturated and 1,1-dimethylethyl 6-{[(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate, (Intermediate 120) (14 g, 28 mmol) was added. The reaction mixture was stirred at room temperature for 2 hours. The resulting precipitate was filtered, washed with EtOAc and dried to give the title compound as a white solid after triturating with acetonitrile (11.8 g, 97%).
HRMS calculated for $C_{19}H_{17}ClN_4O_2S$ $(M+H)^+$ 401.0839, found: 401.0850, Rt: 2.34 min.
MP: 300.4°C

The following Examples were similarly prepared by a method analogous to that described for Example 1

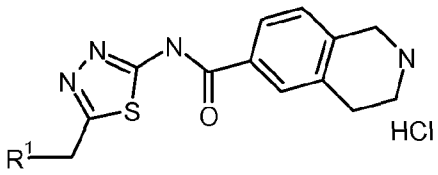
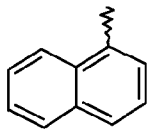
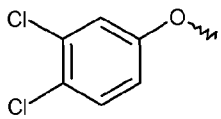
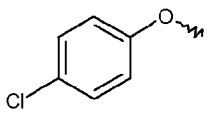
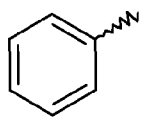
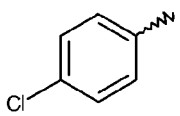
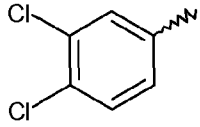
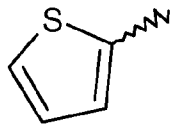
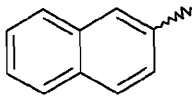
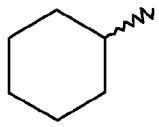
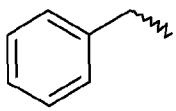
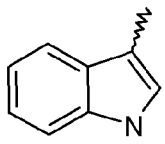
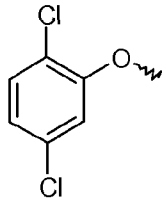
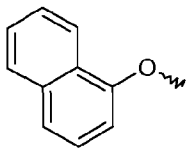
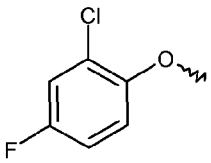
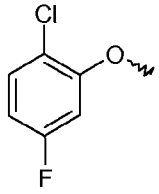
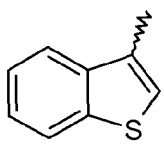
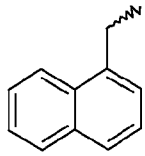
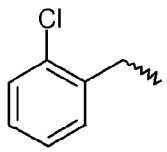
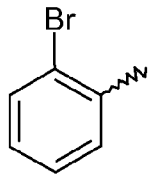
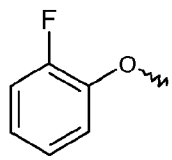


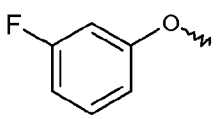
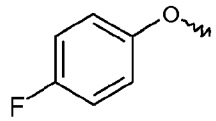
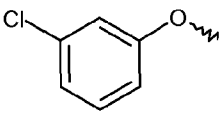
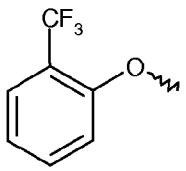
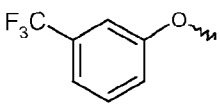
Table 20

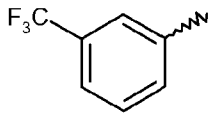
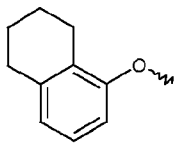
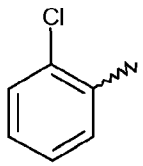
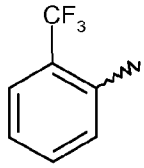
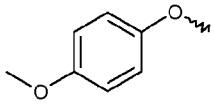
Example No.	R^1	From Intermediate No.	Physical data
2 N-[5-(1-naphthalenylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		121 1,1-dimethylethyl 6-({[5-(1-naphthalenylmethyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1H)-isoquinolinecarboxylate	HRMS $(M+H)^+$: calculated for $C_{23}H_{21}N_4OS$ Theo: 401.1436, Found: 401.1463, Rt: 2.53 min. MP: 335.6°C
3 N-(5-{[(3,4-dichlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		137 1,1-dimethylethyl 6-{[(5-{[(3,4-dichlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1H)-isoquinolinecarboxylate	HRMS $(M+H)^+$: calculated for $C_{19}H_{16}Cl_2N_4O_2S$ Theo: 435.0449 Found: 435.0486 Rt: 2.22 min MP: 276°C
4 N-(5-{[(4-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		139 1,1-dimethylethyl 6-{[(5-{[(4-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1H)-isoquinolinecarboxylate	HRMS $(M+H)^+$: calculated for $C_{19}H_{17}ClN_4O_2S$ Theo: 401.0839 Found: 401.0819 Rt: 2.06 min MP: 277°C
5 N-[5-(phenylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		133 1,1-dimethylethyl 6-({[5-(phenylmethyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS $(M+H)^+$: calculated for $C_{19}H_{18}N_4OS$. Theo: 351.1280 Found: 351.1311 Rt: 1.90 min MP: 291.0°C
6 N-{5-[(4-chlorophenyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide		134 1,1-dimethylethyl 6-[({5-[(4-chlorophenyl)methyl]-1,3,4-thiadiazol-2-yl}amino)carbonyl]-3,4-dihydro-2(1*H*)-	HRMS $(M+H)^+$: calculated for $C_{19}H_{17}ClN_4OS$ Theo: 385.0890 Found: 385.0896 Rt: 2.07 min

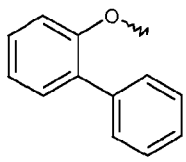
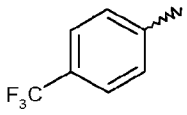
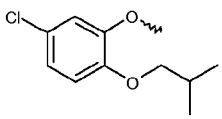
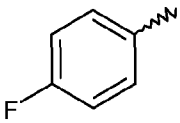
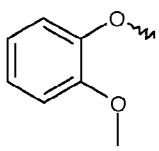
Example No.	R^1	From Intermediate No.	Physical data
hydrochloride		isoquinolinecarboxylate	MP: 285.6°C
7 -{5-[(3,4-dichlorophenyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		135 1,1-dimethylethyl 6-[({5-[(3,4-dichlorophenyl)methyl]-1,3,4-thiadiazol-2-yl}amino)carbonyl]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS $(M+H)^+$: calculated for $C_{19}H_{16}Cl_2N_4OS$ Theo: 419.0500 Found: 419.0507 Rt: 2.19 min MP: 287°C
8 N-[5-(2-thienylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		122 1,1-dimethylethyl 6-({[5-(2-thienylmethyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS $(M+H)^+$: calculated for $C_{17}H_{16}N_4OS_2$ Theo: 357.0844 Found: 357.0879 Rt: 2.1 min MP: 334°C
9 N-[5-(2-naphthalenylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		123 1,1-dimethylethyl 6-({[5-(2-naphthalenylmethyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS $(M+H)^+$: calculated for $C_{23}H_{20}N_4OS$ Theo: 401.1436 Found: 401.1438 Rt: 2.37 min MP: 308.7°C
10 N-[5-(cyclohexylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		124 1,1-dimethylethyl 6-({[5-(cyclohexylmethyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS $(M+H)^+$: calculated for $C_{19}H_{24}N_4OS$ Theo: 357.1749 Found: 357.1736 Rt: 2.37 min MP: 317.8°C
11 N-[5-(2-phenylethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		125 1,1-dimethylethyl 6-({[5-(2-phenylethyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS $(M+H)^+$: calculated for $C_{20}H_{20}N_4OS$ Theo: 365.1436 Found: 365.1436 Rt: 2.20 min MP: 312.1°C
12 N-[5-(1H-indol-3-ylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-		126 1,1-dimethylethyl 6-({[5-(1*H*-indol-3-ylmethyl)-1,3,4-thiadiazol-2-	HRMS $(M+H)^+$: calculated for $C_{21}H_{19}N_5OS$ Theo: 389.1310

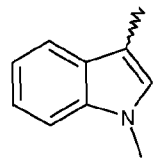
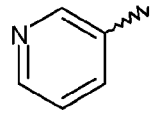
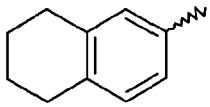
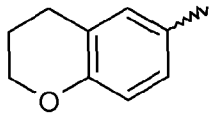
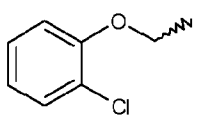
Example No.	R^1	From Intermediate No.	Physical data
isoquinolinecarboxamide hydrochloride		yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	Found: 389.1394 Rt: 2.12 min MP: 313.1°C
13 N-(5-{[(2,5-dichlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		127 1,1-dimethylethyl 6-{[(5-{[(2,5-dichlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1H)-isoquinolinecarboxylate	HRMS $(M+H)^+$: calculated for $C_{19}H_{16}Cl_2N_4O_2S$ Theo: 435.0449 Found: 435.0474 Rt: 2.62 min MP: 330.1°C:
14 N-{5-[(1-naphthalenyloxy)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		147 1,1-dimethylethyl 6-[({5-[(1-naphthalenyloxy)methyl]-1,3,4-thiadiazol-2-yl}amino)carbonyl]-3,4-dihydro-2(1H)-isoquinolinecarboxylate	HRMS $(M+H)^+$: calculated for $C_{23}H_{20}N_4O_2S$ Theo: 417.1385 Found: 417.1882 Rt: 2.62 min MP:295.1°C
15 N-(5-{[(2-chloro-4-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		140 1,1-dimethylethyl 6-{[(5-{[(2-chloro-4-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS $(M+H)^+$: calculated for $C_{19}H_{16}ClFN_4O_2S$ Theo: 419.0745 Found: 419.0780 Rt: 2.43 min MP: 298°C:
16 N-(5-{[(2-chloro-5-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		141 1,1-dimethylethyl 6-{[(5-{[(2-chloro-5-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS $(M+H)^+$: calculated for $C_{19}H_{16}ClFN_4O_2S$ Theo: 419.0745 Found: 419.0746 Rt: 2.47 min MP: 346.2°C:
17 N-[5-(1-benzothien-3-ylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-		142 1,1-dimethylethyl 6-({[5-(1-benzothien-3-ylmethyl)-1,3,4-	HRMS $(M+H)^+$: calculated for $C_{21}H_{18}FN_4O_2S$ Theo: 407.1000

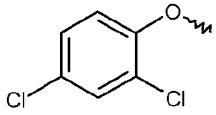
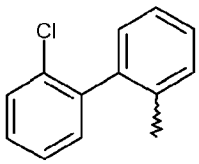
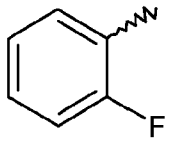
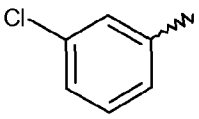
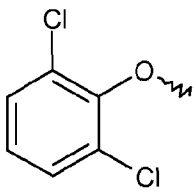
Example No.	R^1	From Intermediate No.	Physical data
isoquinolinecarboxamide hydrochloride		thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	Found: 407.1023 Rt: 2.47 min MP: 325.1°C:
18 N-[5-(3-thienylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		143 1,1-dimethylethyl 6-({[5-(3-thienylmethyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS $(M+H)^+$: calculated for $C_{17}H_{16}N_4OS_2$ Theo: 357.0844 Found: 357.0863 Rt: 2.12 min MP: 331.9°C:
19 N-{5-[2-(1-naphthalenyl)ethyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		144 1,1-dimethylethyl 6-[({5-[2-(1-naphthalenyl)ethyl]-1,3,4-thiadiazol-2-yl}amino)carbonyl]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS $(M+H)^+$: calculated for $C_{24}H_{22}N_4OS$ Theo: 415.1592 Found: 415.1593 Rt: 2.66 min MP: 333.2°C
20 N-{5-[2-(2-chlorophenyl)ethyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		145 1,1-dimethylethyl 6-[({5-[2-(2-chlorophenyl)ethyl]-1,3,4-thiadiazol-2-yl}amino)carbonyl]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS $(M+H)^+$: calculated for $C_{20}H_{19}ClN_4OS$ Theo: 399.1046 Found: 399.1072 Rt: 2.53 min MP:318.2 °C
21 N-{5-[(2-bromophenyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		128 1,1-dimethylethyl 6-[({5-[(2-bromophenyl)methyl]-1,3,4-thiadiazol-2-yl}amino)carbonyl]-3,4-dihydro-2(1H)-isoquinolinecarboxylate	HRMS $(M+H)^+$: calculated for $C_{19}H_{17}BrN_4OS$ Theo: 429.0385 Found: 429.0413 Rt: 2.40 min MP: 309.7°C
22 N-(5-{[(2-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		130 1,1-dimethylethyl 6-{[(5-{[(2-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS $(M+H)^+$: calculated for $C_{19}H_{17}FN_4O_2S$ Theo: 385.1134 Found: 385.1155 Rt: 2.27 min MP : 250-260°C

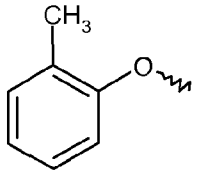
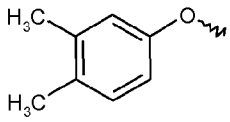
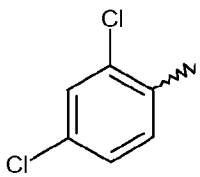
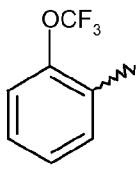
Example No.	R^1	From Intermediate No.	Physical data
23 N-(5-{[(3-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		131 1,1-dimethylethyl 6-{[(5-{[(3-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS $(M+H)^+$: calculated for $C_{19}H_{17}FN_4O_2S$ Theo: 385.1134 Found: 385.1168 Rt: 2.33 min MP : 250-260°C
24 N-(5-{[(4-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		132 1,1-dimethylethyl 6-{[(5-{[(4-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS $(M+H)^+$: calculated for $C_{19}H_{17}FN_4O_2Sl$ Theo: 385.1134 Found: 385.1168 Rt: 2.25 min MP : 240-250°C
25 N-(5-{[(3-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		136 1,1-dimethylethyl 6-{[(5-{[(3-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1H)-isoquinolinecarboxylate	HRMS $(M+H)^+$: calculated for $C_{19}H_{17}ClN_4O_2S$. Theo: 401.0839 Found: 401.0847 Rt: 2.55 min MP: 281.7°C
26 N-[5-({[2-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		129 1,1-dimethylethyl 6-({[5-({[2-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1H)-isoquinolinecarboxylate	HRMS $(M+H)^+$: calculated for $C_{20}H_{17}F_3N_4O_2S$ Theo: 435.1102 Found: 435.1144 Rt: 2.50 min MP: 300.2°C
27 N-[5-({[3-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		138 1,1-dimethylethyl 6-({[5-({[3-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-	HRMS $(M+H)^+$: calculated for $C_{20}H_{17}F_3N_4O_2S$ Theo: 435.1102 Found: 435.1101 Rt: 2.50 min MP: 298.9°C

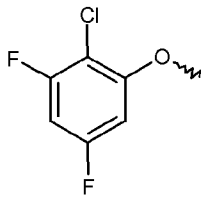
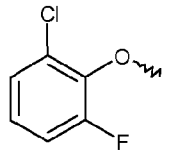
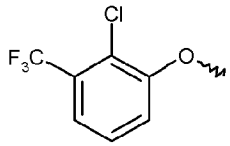
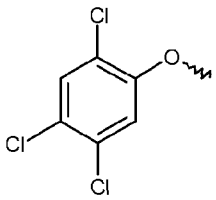
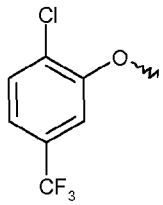
Example No.	R^1	From Intermediate No.	Physical data
		dihydro-2(1H)-isoquinolinecarboxylate	
28 N-(5-{[3-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		148 1,1-dimethylethyl 6-{[(5-{[3-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1H)-isoquinolinecarboxylate	HRMS $(M+H)^+$: calculated for $C_{20}H_{17}F_3N_4OS$ Theo: 419.1153 Found: 419.1161 Rt: 2.41 min MP: 290.7°C
29 N-{5-[(5,6,7,8-tetrahydro-1-naphthalenyloxy)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		146 1,1-dimethylethyl 6-[({5-[(5,6,7,8-tetrahydro-1-naphthalenyloxy)methyl]-1,3,4-thiadiazol-2-yl}amino)carbonyl]-3,4-dihydro-2(1H)-isoquinolinecarboxylate	HRMS $(M+H)^+$: calculated for $C_{23}H_{24}N_4O_2S$ Theo: 421.1698 Found: 421.1689 Rt: 2.81 min MP: 297.6°C
30 N-{5-[(2-chlorophenyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		149 1,1-dimethylethyl 6-[({5-[(2-chlorophenyl)methyl]-1,3,4-thiadiazol-2-yl}amino)carbonyl]-3,4-dihydro-2(1H)-isoquinolinecarboxylate	HRMS $(M+H)^+$: calculated for $C_{19}H_{17}ClN_4OS$ Theo: 385.0811 Found: 385.0920 Rt: 2.28 min MP: 287°C
31 N-(5-{[2-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		150 1,1-dimethylethyl 6-{[(5-{[2-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS $(M+H)^+$: calculated for $C_{20}H_{17}F_3N_4OS$ Theo: 419.1153 Found: 419.1185 Rt: 2.37 min MP: 292.7°C
32 N-[5-({[4-(methyloxy)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-		151 1,1-dimethylethyl 6-({[5-({[4-(methyloxy)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-	HRMS $(M+H)^+$: calculated for $C_{20}H_{20}N_4O_3S$ Theo: 397.1334 Found: 397.1318

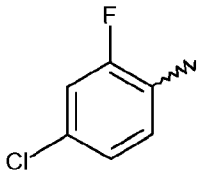
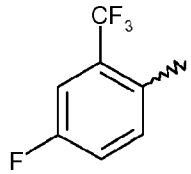
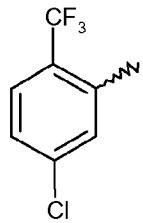
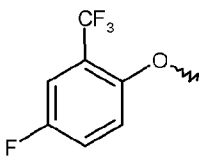
Example No.	R^1	From Intermediate No.	Physical data
isoquinolinecarboxamide hydrochloride		yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	Rt: 2.16 min MP: 271°C
33 N-{5-[(2-biphenylyloxy)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		152 1,1-dimethylethyl 6-[({5-[(2-biphenylyloxy)methyl]-1,3,4-thiadiazol-2-yl}amino)carbonyl]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS $(M+H)^+$: calculated for $C_{25}H_{22}N_4O_2S$ Theo: 443.1542 Found: 443.1524 Rt: 2.58 min MP: 278.2°C
34 N-(5-{[4-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		153 1,1-dimethylethyl 6-{[(5-{[4-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS $(M+H)^+$: calculated for $C_{20}H_{17}F_3N_4OS$ Theo: 419.1153 Found: 419.1183 Rt: 2.41 min MP: 284°C
35 N-{5-[({5-chloro-2-[(2-methylpropyl)oxy]phenyl}oxy)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		154 1,1-dimethylethyl 6-[({5-[({5-chloro-2-[(2-methylpropyl)oxy]phenyl}oxy)methyl]-1,3,4-thiadiazol-2-yl}amino)carbonyl]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS $(M+H)^+$: calculated for $C_{23}H_{25}ClN_4O_3S$ Theo: 473.1414 Found: 473.1448 Rt: 2.76 min MP: 276.1°C
36 N-{5-[(4-fluorophenyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		155 1,1-dimethylethyl 6-[({5-[(4-fluorophenyl)methyl]-1,3,4-thiadiazol-2-yl}amino)carbonyl]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS $(M+H)^+$: calculated for $C_{19}H_{17}FN_4OS$ Theo: 369.1185 Found: 369.1220 Rt: 2.19 min MP: 294.6°C
37 N-[5-({[2-(methyloxy)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide		156 1,1-dimethylethyl 6-({[5-({[2-(methyloxy)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-	HRMS $(M+H)^+$: calculated for $C_{20}H_{20}N_4O_3S$ Theo: 397.1334 Found: 397.1361 Rt: 2.07 min

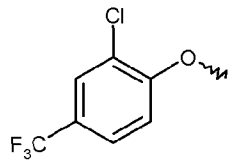
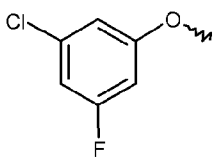
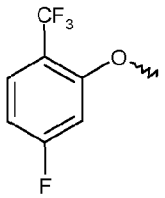
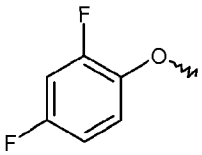
Example No.	R^1	From Intermediate No.	Physical data
hydrochloride		dihydro-2(1*H*)-isoquinolinecarboxylate	MP: 279.7°C
38 N-{5-[(1-methyl-1H-indol-3-yl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		157 1,1-dimethylethyl 6-[({5-[(1-methyl-1*H*-indol-3-yl)methyl]-1,3,4-thiadiazol-2-yl}amino)carbonyl]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS $(M+H)^+$: calculated for $C_{22}H_{21}N_5OS$ Theo: 404.1545 Found: 404.1576 Rt: 2.31 min MP: 311.5°C
39 N-[5-(3-pyridinylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		158 1,1-dimethylethyl 6-({[5-(3-pyridinylmethyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS $(M+H)^+$: calculated for $C_{18}H_{17}N_5OS$ Theo: 352.1232 Found: 352.1206 Rt: 1.70 min
40 N-[5-(5,6,7,8-tetrahydro-2-naphthalenylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		159 1,1-dimethylethyl 6-({[5-(5,6,7,8-tetrahydro-2-naphthalenylmethyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS $(M+H)^+$: calculated for $C_{23}H_{24}N_4OS$ Theo: 405.1744 Found: 405.1725 Rt: 2.60 min MP: 313.6°C
41 N-[5-(3,4-dihydro-2H-chromen-6-ylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		160 1,1-dimethylethyl 6-({[5-(3,4-dihydro-2*H*-chromen-6-ylmethyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS $(M+H)^+$: calculated for $C_{22}H_{22}N_4O_2S$ Theo: 407.1542 Found: 407.1560 Rt: 2.26 min MP: 323°C
42 N-(5-{2-[(2-chlorophenyl)oxy]ethyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide		161 1,1-dimethylethyl 6-{[(5-{2-[(2-chlorophenyl)oxy]ethyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-	HRMS $(M+H)^+$: calculated for $C_{20}H_{19}ClN_4O_2S$ Theo: 415.0995 Found: 415.1005 Rt: 2.32 min

Example No.	R^1	From Intermediate No.	Physical data
hydrochloride		dihydro-2(1*H*)-isoquinolinecarboxylate	
43 N-(5-{[(2,4-dichlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		162 1,1-dimethylethyl 6-{[(5-{[(2,4-dichlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS $(M+H)^+$: calculated for $C_{19}H_{16}Cl_2N_4O_2S$ Theo: 435.0449 Found: 435.0492 Rt: 2.44 min MP: 295.1°C
44 N-{5-[(2'-chloro-2-biphenylyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		163 1,1-dimethylethyl 6-[({5-[(2'-chloro-2-biphenylyl)methyl]-1,3,4-thiadiazol-2-yl}amino)carbonyl]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS $(M+H)^+$: calculated for $C_{25}H_{21}ClN_4OS$ Theo: 461.1203 Found: 461.1229 Rt: 2.78 min MP: 320.4°C
45 N-{5-[(2-fluorophenyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		164 1,1-dimethylethyl 6-[({5-[(2-fluorophenyl)methyl]-1,3,4-thiadiazol-2-yl}amino)carbonyl]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS $(M+H)^+$: calculated for $C_{19}H_{17}FN_4OS$ Theo: 369.1185 Found: 369.1164 Rt: 2.15 min MP: 319°C
46 N-{5-[(3-chlorophenyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		213 1,1-dimethylethyl 6-[({5-[(3-chlorophenyl)methyl]-1,3,4-thiadiazol-2-yl}amino)carbonyl]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS (M+H)+: calculated for $C_{19}H_{17}ClN_4OS$ Theo: 385.0890 Found: 385.0910 Rt: 2.34 min MP: 302.2°C
47 N-(5-{[(2,6-dichlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide		214 1,1-dimethylethyl 6-{[(5-{[(2,6-dichlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-	HRMS (M+H)+: calculated for $C_{19}H_{16}Cl_2N_4O_2S$ Theo: 435.0449 Found: 435.0453 Rt: 2.40 min

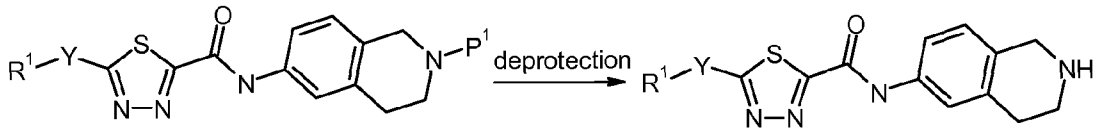
Example No.	R^1	From Intermediate No.	Physical data
hydrochloride		dihydro-2(1*H*)-isoquinolinecarboxylate	MP: 304.8°C
48 N-(5-{[(2-methylphenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		215 1,1-dimethylethyl 6-{[(5-{[(2-methylphenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS (M+H)+: calculated for $C_{20}H_{20}N_4O_2S$ Theo: 381.1385 Found: 381.1382 Rt: 2.29 min MP: 311.3°C
49 N-(5-{[(3,4-dimethylphenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		216 1,1-dimethylethyl 6-{[(5-{[(3,4-dimethylphenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS (M+H)+: calculated for $C_{21}H_{22}N_4O_2S$ Theo: 395.1542 Found: 395.1538 Rt: 2.37 min MP: 291°C
50 N-{5-[(2,4-dichlorophenyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		217 1,1-dimethylethyl 6-[({5-[(2,4-dichlorophenyl)methyl]-1,3,4-thiadiazol-2-yl}amino)carbonyl]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS (M+H)+: calculated for $C_{19}H_{16}Cl_2N_4OS$ Theo: 419.0500 Found: 419.0529 Rt: 2.51 min MP: 308.7°C
51 N-[5-({2-[(trifluoromethyl)oxy]phenyl}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide		218 1,1-dimethylethyl 6-({[5-({2-[(trifluoromethyl)oxy]phenyl}methyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS (M+H)+: calculated for $C_{20}H_{17}F_3N_4O_2S$ Theo: 435.1103 Found: 435.1113 Rt: 2.46 min MP: 293.9°C

Example No.	R^1	From Intermediate No.	Physical data
52 N-(5-{[(2-chloro-3,5-difluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		219 1,1-dimethylethyl 6-{[(5-{[(2-chloro-3,5-difluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS (M+H)+: calculated for $C_{19}H_{15}ClF_2N_4O_2S$ Theo: 437.0650 Found: 437.0656 Rt: 2.00 min MP > 260°C
53 N-(5-{[(2-chloro-6-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		220 1,1-dimethylethyl 6-{[(5-{[(2-chloro-6-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS (M+H)+: calculated for $C_{19}H_{16}ClFN_4O_2S$ Theo: 419.0745 Found: 419.0750 Rt: 2.31 min MP: 318.9°C
54 N-[5-({[2-chloro-3-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		221 1,1-dimethylethyl 6-({[5-({[2-chloro-3-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS (M+H)+: calculated for $C_{20}H_{16}ClF_3N_4O_2S$ Theo: 469.0713 Found: 469.0748 Rt: 2.16 min MP: 312.9°C
55 N-(5-{[(2,4,5-trichlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		222 1,1-dimethylethyl 6-{[(5-{[(2,4,5-trichlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS (M+H)+: calculated for $C_{19}H_{15}Cl_3N_4O_2S$ Theo: 469.0060 Found: 469.0037 Rt: 2.66 min MP: 291.8°C
56 N-[5-({[2-chloro-5-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		223 1,1-dimethylethyl 6-({[5-({[2-chloro-5-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-	HRMS (M+H)+: calculated for $C_{20}H_{16}ClF_3N_4O_2S$ Theo: 469.0713 Found: 469.0674 Rt: 2.57 min MP: 317.5°C

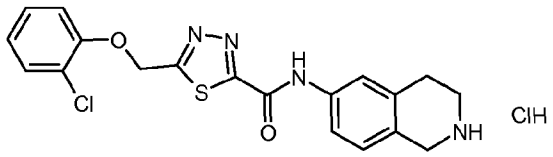
Example No.	R^1	From Intermediate No.	Physical data
		isoquinolinecarboxylate	
57 N-{5-[(4-chloro-2-fluorophenyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		224 1,1-dimethylethyl 6-({[5-({[2-chloro-5-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS (M+H)+: calculated for $C_{19}H_{16}ClFN_4OS$ Theo: 403.0796 Found: 403.0764 Rt: 2.31 min MP: 300.2°C
58 N-(5-{[4-fluoro-2-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		225 1,1-dimethylethyl 6-{[(5-{[4-fluoro-2-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS (M+H)+: calculated for $C_{20}H_{16}F_4N_4OS$ Theo: 437.1059 Found: 437.1079 Rt: 2.47 min MP: 306.2°C
59 N-(5-{[5-chloro-2-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		226 1,1-dimethylethyl 6-{[(5-{[5-chloro-2-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS (M+H)+: calculated for $C_{20}H_{16}ClF_3N_4OS$ Theo: 453.0764 Found: 453.0772 Rt: 2.57 min MP: 304.7°C
60 N-[5-({[4-fluoro-2-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		227 1,1-dimethylethyl 6-({[5-({[4-fluoro-2-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS (M+H)+: calculated for $C_{20}H_{16}F_4N_4O_2S$ Theo: 453.1008 Found: 453.1029 Rt: 2.43 min MP: 299.4°C

Example No.	R^1	From Intermediate No.	Physical data
61 N-[5-({[2-chloro-4-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		228 1,1-dimethylethyl 6-({[5-({[2-chloro-4-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS (M+H)+: calculated for $C_{20}H_{16}ClF_3N_4O_2S$ Theo: 469.0713 Found: 469.0720 Rt: 2.58 min MP: 326.3°C
62 N-(5-{[(3-chloro-5-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		229 1,1-dimethylethyl 6-{[(5-{[(3-chloro-5-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS (M+H)+: calculated for $C_{20}H_{16}ClFN_4O_2S$ Theo: 419.0782 Found: 419.0745 Rt: 2.47 min MP: 308.2°C
63 N-[5-({[5-fluoro-2-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		230 1,1-dimethylethyl 6-({[5-({[5-fluoro-2-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS (M+H)+: calculated for $C_{20}H_{16}F_4N_4O_2S$ Theo: 453.1008 Found: 453.0993 Rt: 2.48 min MP > 260°C
64 N-(5-{[(2,4-difluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride		213 1,1-dimethylethyl 6-{[(5-{[(2,4-difluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	HRMS (M+H)+: calculated for $C_{19}H_{16}F_2N_4O_2S$ Theo: 403.1040 Found: 403.1007 Rt: 2.25 min MP: 288.3°C

The following Examples were prepared using the generic reaction scheme (Scheme 14)

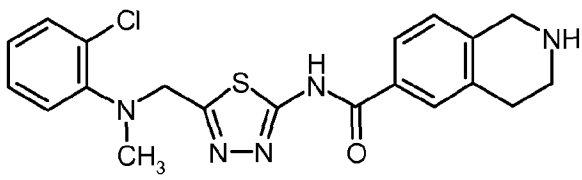


Example 65: 5-{[(2-Chlorophenyl)oxy]methyl}-*N*-(1,2,3,4-tetrahydro-6-isoquinolinyl)-1,3,4-thiadiazole-2-carboxamide hydrochloride



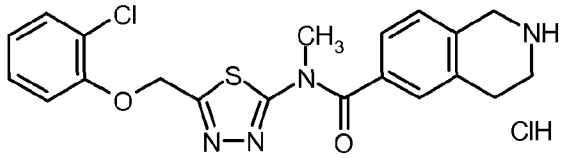
HCl(g) was bubbled at 0°C in EtOAc until the solvent was saturated and 1,1-dimethylethyl 6-{[(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)carbonyl]amino}-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate (Intermediate 236) (140 mg, 0.28 mmol) was added. The reaction mixture was stirred at room temperature for 3.5 hours. The resulting precipitate was filtered, washed with EtOAc and dried to give the title compound as an off white solid (115 mg, 94%).
HRMS calculated for $C_{19}H_{17}ClN_4O_2S$ $(M+H)^+$ 401.0839, found: 401.0853, Rt: 2.48 min.
MP: 285°C

Example 66: *N*-(5-{[(2-Chlorophenyl)(methyl)amino]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride



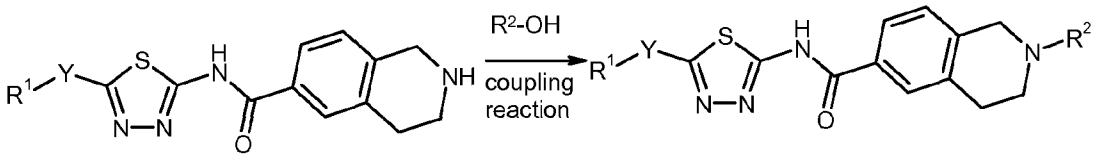
HCl(g) was bubbled at 0°C in EtOAc until the solvent was saturated and 1,1-dimethylethyl 6-{[(5-{[(2-chlorophenyl)(methyl)amino]methyl}-1,3,4-thiadiazol-2-yl)amino]carbonyl}-3,4-dihydro-2(1H)-isoquinolinecarboxylate (Intermediate 241) (270 mg, 0.52 mmol) was added. The reaction mixture was stirred at room temperature overnight. The resulting precipitate was filtered, washed with EtOAc and dried to give the title compound as an off white solid (214 mg, 91%).
HRMS calculated for $C_{20}H_{20}ClN_5OS$ $(M+H)^+$ 414.1155, found: 414.1133, Rt: 2.10 min.
MP: 169-171°C

Example 67: *N*-(5-{[(2-Chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-*N*-methyl-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride

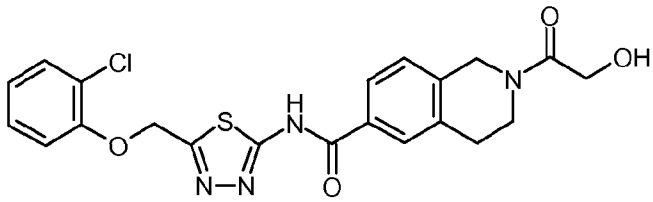


HCl(g) was bubbled at 0°C in EtOAc until the solvent was saturated and 1,1-dimethylethyl 6-{[(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)(methyl)amino]carbonyl}-3,4-dihydro-2(1H)-isoquinolinecarboxylate (Intermediate 242) (138 mg, 0.27 mmol) was added. The reaction mixture was stirred at room temperature overnight. The resulting precipitate was filtered, washed with EtOAc and hot methyl alcohol and dried to give the title compound as a white solid (81 mg, 72%).
HRMS calculated for $C_{20}H_{19}ClN_4O_2S$ $(M+H)^+$ 415.0995, found: 415.0979, Rt: 2.59 min.
MP > 260°C

The following Examples were prepared using the generic reaction scheme (Scheme 5)



Example 68: *N*-(5-{[(2-Chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-2-(hydroxyacetyl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide



A solution of N-(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide (Example 1) (218 mg, 0.5 mmol), hydroxyacetic acid (46 mg, 0.6 mmol), HATU (247 mg, 0.65 mmol), triethylamine (132 mg, 1.3 mmol) in DMF was stirred at room temperature for 4 days. The DMF was evaporated under reduced pressure and the residue was dissolved in dichloromethane. The organic phase was then washed with a solution of sodium hydrogenocarbonate then dried over sodium sulphate. After filtration and evaporation under reduced pressure, the residue was purified by flash column chromatography eluting with a gradient DCM 100% to DCM/MeOH: 98/2 to give the title compound as white solid (115 mg, 50%).
HRMS calculated for $C_{21}H_{19}ClN_4O_4S$ $(M+H)^+$ 459.0894, found: 459.0937, Rt: 2.56 min
MP: 133-135°C

The following compounds were similarly prepared by a method analogous to that described for Example 68.

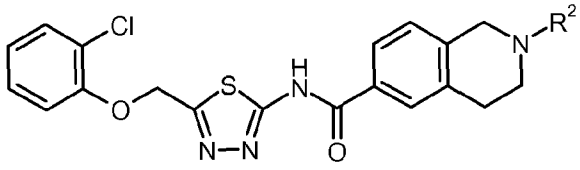
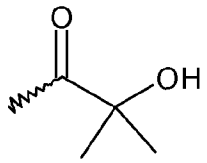
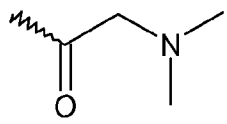
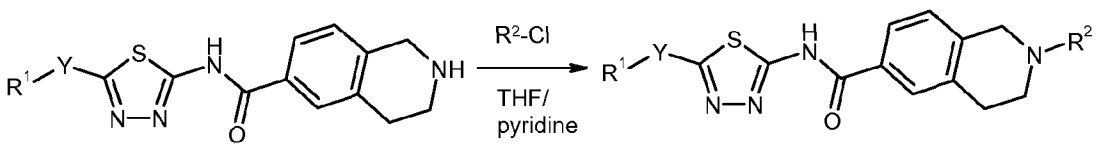


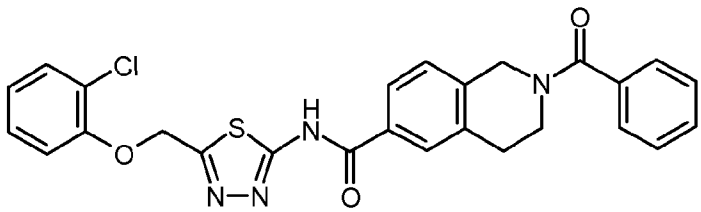
Table 21

Example No.	R^2	From Example No.	Physical data
69 *N*-(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-2-(2-hydroxy-2-methylpropanoyl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide		1 N-(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide	HRMS (M+H)+: calculated for $C_{23}H_{23}ClN_4O_4S$ Theo: 487.1207 Found: 487.1206 Rt: 2.69 min MP: 196-198°C
70 *N*-(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-2-(*N*,*N*-dimethylglycyl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide		1 N-(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide	HRMS (M+H)+: calculated for $C_{23}H_{24}ClN_5O_3S$ Theo: 486.1367 Found: 486.1364 Rt: 2.44 min MP: 109-111°C

The following Examples were prepared using the generic reaction scheme (Scheme 4)



Example 71: *N*-(5-{[(2-Chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-2-(phenylcarbonyl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide



To a solution of N-(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide (Example 1) (210 mg, 0.48 mmol) in THF (10 mL) were added pyridine (0.232 mL, 2.88 mmol) then benzoyl chloride (0.122 mL, 1.06 mmol). The reaction mixture was stirred at room temperature overnight. The THF was evaporated under reduced pressure and the residue was dissolved in EtOAc. The organic phase was washed with water then dried over sodium sulphate. After filtration and evaporation under reduced pressure, the residue was purified by flash column chromatography eluting with a gradient DCM 100% to DCM/MeOH: 98/2 to give the title compound as white solid (40 mg, 17%).
HRMS calculated for $C_{26}H_{21}ClN_4O_3S$ $(M+H)^+$ 505.1101, found: 505.1140, Rt: 2.99 min
MP: 186-188°C

The following compounds were similarly prepared by a method analogous to that described for Example 71.

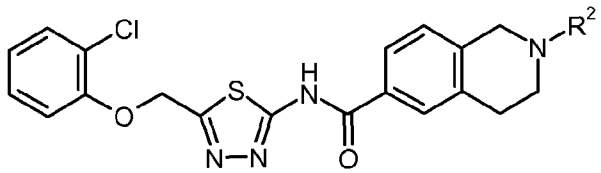
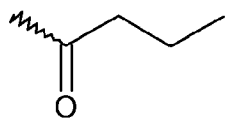
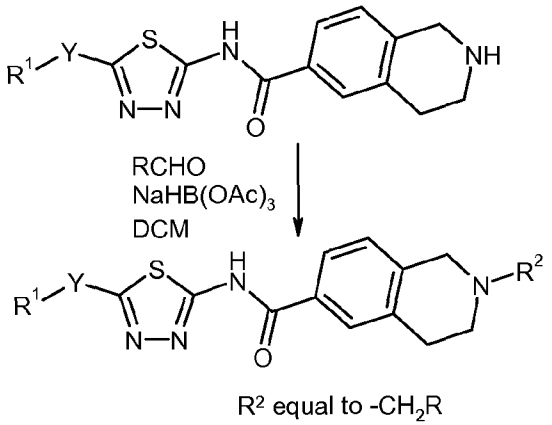


Table 22

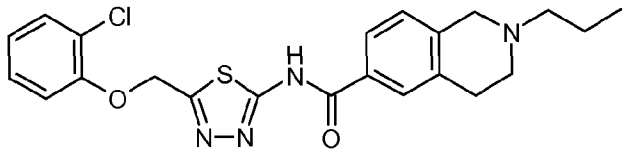
Example No.	R^2	From Example No.	Physical data
72 2-butanoyl-*N*-(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinoline carboxamide		1 N-(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide	HRMS (M+H)+: calculated for $C_{23}H_{23}ClN_4O_3S$ Theo: 471.1258 Found: 471.1242 Rt: 2.86 min MP: 187-189°C

The following Examples were prepared using the generic reaction scheme (Scheme 3)



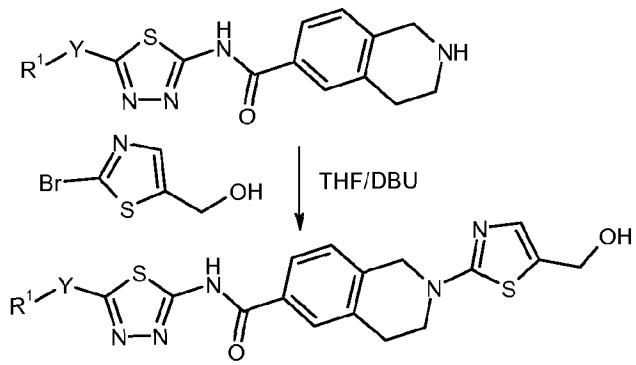
R^2 equal to $-CH_2R$

Example 73: *N*-(5-{[(2-Chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-2-propyl-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide

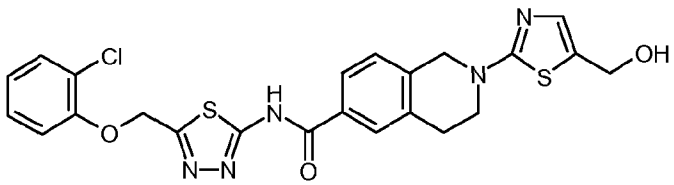


To a suspension of N-(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide (Example 1) (200 mg, 0.45 mmol) in DCM (10 mL) was added triethylamine (138 mg, 1.37 mmol). After stirring for 5 minutes, propanal (132 mg, 2.28 mmol) $NaHB(OAc)_3$ (483 mg, 2.28 mmol) and acetic acid (82 mg, 1.37 mmol) were added. The reaction mixture was stirred at room temperature for 2 days. The mixture was then washed with a solution of sodium hydrogenocarbonate and dried over sodium sulphate. After filtration and evaporation under reduced pressure, the residue was purified by flash column chromatography eluting with DCM to give the title compound as white solid (115 mg, 58%).
HRMS calculated for $C_{22}H_{23}ClN_4O_2S$ $(M+H)^+$ 443.1308, found: 443.1279, Rt: 2.97 min
MP: 186-188°C

The following Examples were prepared using the generic reaction scheme (Scheme 7)

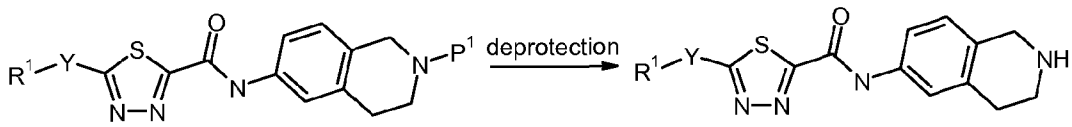


Example 74: *N*-(5-{[(2-Chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-2-[5-(hydroxymethyl)-1,3-thiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide



A mixture of N-(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide (Example 1) (218 mg, 0.5 mmol), DBU (0.224 mL, 1.5 mmol) and (2-bromo-1,3-thiazol-5-yl)methanol (97 mg, 0.5 mmol) in THF (10 mL) was stirred overnight at 80°C. Then extra amounts of DBU (0.075 mL, 0.5 mmol) and (2-bromo-1,3-thiazol-5-yl)methanol (97 mg, 0.5 mmol) were added and the mixture was stirred overnight at 60°C. The THF was evaporated under reduced pressure and the residue was dissolved in DCM. The organic phase was washed with water then dried over sodium sulphate. After filtration and evaporation under reduced pressure, the residue was purified by flash column chromatography eluting with a gradient DCM/MeOH: 99/1 to DCM/MeOH: 95/5 to give after trituration in cold DCM and drying the title compound as white solid (15 mg, 6%).
HRMS calculated for $C_{23}H_{20}ClN_5O_3S_2$ $(M+H)^+$ 514.0775, found: 514.0770, Rt: 2.70 min
MP: 237-239°C

The following Example was prepared using the generic reaction scheme (scheme 14)



The following compounds were similarly prepared by analogous method to that described for Example 65.

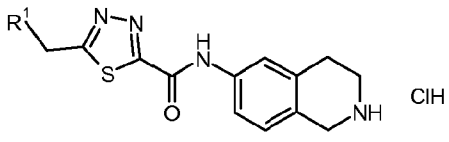
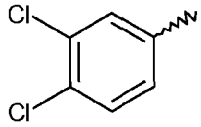


Table 23

Example No.	R^1	From Intermediate No:	Physical data
75 5-[(3,4-dichlorophenyl)methyl]-*N*-(1,2,3,4-tetrahydro-6-		243 1,1-Dimethylethyl 6-[({5-[(3,4-dichlorophenyl)methyl]-	HRMS (M+H)+: calculated for $C_{19}H_{16}Cl_2N_4OS$ Theo: 419.0500

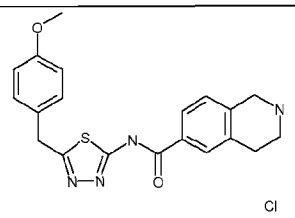
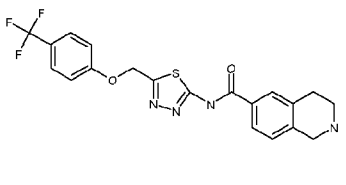
Example No.	R^1	From Intermediate No:	Physical data
isoquinolinyl)-1,3,4-thiadiazole-2-carboxamide hydrochloride		1,3,4-thiadiazol-2-yl}carbonyl)amino]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate	Found: 419.0492 Rt: 2.59 min MP: 282.4°C

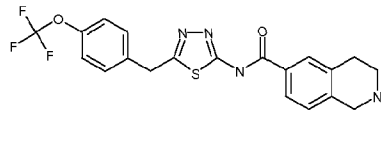
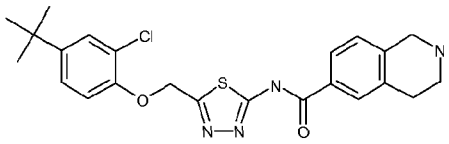
BIOLOGICAL ASSAY

The compounds of the present invention may be analysed *in vitro* for SCD activity using an assay based on the production of $[^3H]H_2O$, which is released during the enzyme-catalyzed generation of the monounsaturated fatty acyl CoA product. The assay is performed in a 96-well filtration plates. The titrated substrate used in the assay is the [9,10-^{3}H] stearoyl Coenzyme A. After incubation for 6 minutes of SCD-containing rat microsomes (2 µg protein) and substrate (1 µM), the labelled fatty acid acyl-CoA species and microsomes are absorbed with charcoal and separated from $[^3H]H_2O$ by centrifugation. The formation of $[^3H]H_2O$ is used as a measure of SCD activity. Compounds at concentrations starting at 10 µM to 0.1 nM or vehicle (DMSO) are preincubated for 5 minutes with the microsomes before addition of the substrate. The concentration-responses are fitted with sigmoidal curves to obtain IC_{50} values.

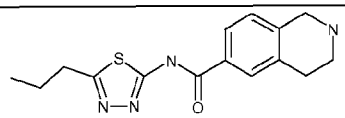
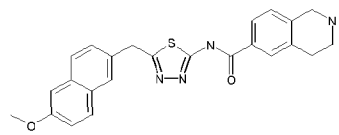
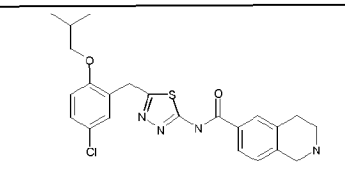
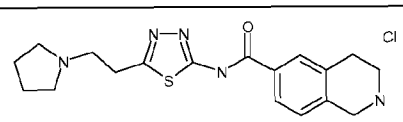
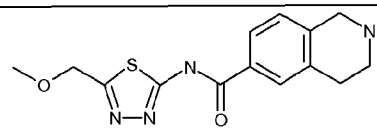
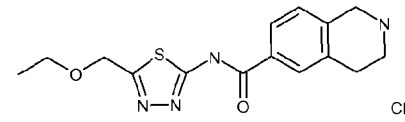
All of the synthetic Example compounds 1- 74 tested by the above described *in vitro* assay for SCD activity were found to exhibit an average pIC_{50} value of greater than 5.5.

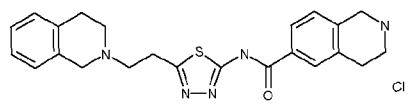
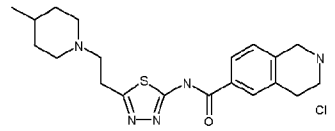
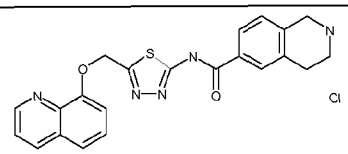
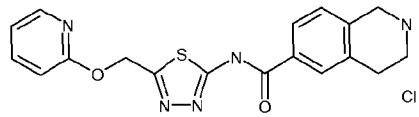
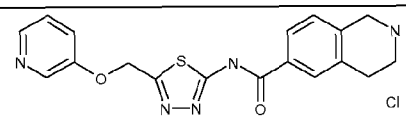
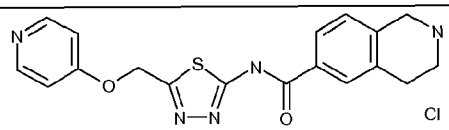
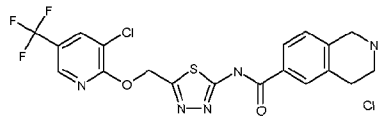
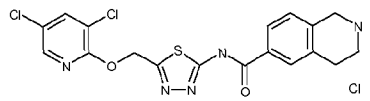
The following compounds were prepared according similar protocols to above described and when tested by the above described *in vitro* assay for SCD activity were found to exhibit an average pIC_{50} value in the range 5-5.5.

Structure	Name
	N-(5-{[4-(methyloxy)phenyl]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride
	N-[5-({[4-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride

	N-[5-({4-[(trifluoromethyl)oxy]phenyl}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride
	N-[5-({[2-chloro-4-(1,1-dimethylethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride

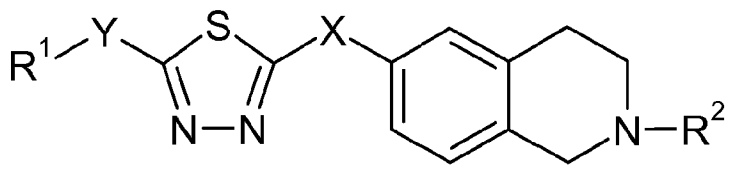
The following compounds were also prepared and when tested by the above described *in vitro* assay for SCD activity were found to exhibit an average pIC_{50} value of less than 5.

Structure	Name
	N-(5-propyl-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride
	N-(5-{[6-(methyloxy)-2-naphthalenyl]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride
	N-[5-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride
	N-{5-[2-(1-pyrrolidinyl)ethyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride
	N-{5-[(methyloxy)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride
	N-{5-[(ethyloxy)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride

	N-{5-[2-(3,4-dihydro-2(1H)-isoquinolinyl)ethyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride
	N-{5-[2-(4-methyl-1-piperidinyl)ethyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride
	N-{5-[(8-quinolinyloxy)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride
	N-{5-[(2-pyridinyloxy)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride
	N-{5-[(3-pyridinyloxy)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride
	N-{5-[(4-pyridinyloxy)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride
	N-[5-({[3-chloro-5-(trifluoromethyl)-2-pyridinyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride
	N-(5-{[(3,5-dichloro-2-pyridinyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride

Claims

1. A compound of formula (I):



(I)

wherein:

X represents -CONH-, -NHCO- or -N(CH_3)CO-,

R^1 represents:
(i) a substituent selected from: H, -C_{1-6}alkyl or -C_{3-6}cycloalkyl,
(ii) -C_{6-10}aryl optionally substituted by one, two or three groups independently selected from:
- (a) -C_{1-6}alkyl, -C_{1-6}haloalkyl, -C_{3-6}cycloalkyl, -C_{1-6}alkoxy, -OR^3, -CN, or halogen,
- (b) -C_{6-10}aryl, -C_{5-10}heteroaryl or -C_{5-10}heterocyclyl, wherein the -C_{6-10}aryl, -C_{5-10}heteroaryl or -C_{5-10}heterocyclyl ring is optionally substituted by one, two or three groups independently selected from: -C_{1-6}alkyl, -C_{1-6}haloalkyl, -C_{1-6}alkoxy, -OR^3, -CN, or halogen,

(iii) -C_{5-10}heteroaryl or -C_{5-10}heterocyclyl wherein the -C_{5-10}heteroaryl or -C_{5-10}heterocyclyl is optionally substituted by one, two or three groups independently selected from:
- (a) -C_{1-6}alkyl, -C_{1-6}haloalkyl, -C_{3-6}cycloalkyl, -C_{1-6}alkoxy, -OR^3, -CN or halogen,
- (b) -C_{6-10}aryl, -C_{5-10}heteroaryl or -C_{5-10}heterocyclyl wherein the -C_{6-10}aryl, -C_{5-10}heteroaryl or -C_{5-10}heterocyclyl ring is optionally substituted by one, two or three groups independently selected from: -C_{1-6}alkyl, -C_{1-6}haloalkyl, -C_{1-6}alkoxy, -OR^3, -CN, or halogen,

Y represents -$(CH_2)_m$-, -$O(CH_2)_m$-, or -$NR^7(CH_2)_m$-,
R^2 represents H, -C_{1-6}alkyl, -C(=O)C_{1-6}alkyl, -C(=O)C_{3-6}cycloalkyl -C(=O)C_{6-10}aryl, -C(=O)C_{1-6}alkylOH, -COC_{1-3}alkylNR^4R^5 or -C_5heteroarylR^6,
R^3 represents -C_{1-6}haloalkyl or -C_{3-6}cycloalkyl,
R^4 represents H or -C_{1-3}alkyl,
R^5 represents H or -C_{1-3}alkyl,
R^6 represents -C_{1-3}alkylOH,
R^7 represents H or -CH_3, and
m represents 1-4
or a pharmaceutically acceptable salt thereof.

2. A compound of formula (I) or pharmaceutically acceptable salt thereof according to claim 1 wherein X represents -NHCO-.

3. A compound of formula (I) or pharmaceutically acceptable salt thereof according to claim 1 or 2 wherein R^1 represents -C_{3-6}cycloalkyl.

4. A compound of formula (I) or pharmaceutically acceptable salt thereof according to any one of claims 1 to 3 wherein R^1 represents -C_{6-10}aryl optionally substituted by: one, two or three groups independently selected from:

(a) -C_{1-6}alkyl, -C_{1-6}haloalkyl, -C_{3-6}cycloalkyl, -C_{1-6}alkoxy, -OR^3, -CN or halogen or

(b) -C_{6-10}aryl optionally substituted by one, two or three groups independently selected from: -C_{1-6}alkyl , -C_{1-6}alkoxy, -OR^3, -C_{1-6}haloalkyl, -CN or halogen.

5. A compound of formula (I) or pharmaceutically acceptable salt thereof according to any one of claims 1 to 4 wherein Y represents -CH_2, -OCH_2-, -OCH_2CH_2-, -C_2H_4- or -$N(CH_3)CH_2$-.

6. A compound of formula (I) or pharmaceutically acceptable salt thereof according to any one of claims 1 to 5 wherein R^2 represents hydrogen.

7. A compound of formula (I) according to claim 1 selected from:
N-(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-[5-(1-naphthalenylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(3,4-dichlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(4-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-[5-(phenylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-{5-[(4-chlorophenyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-{5-[(3,4-dichlorophenyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-[5-(2-thienylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-[5-(2-naphthalenylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-[5-(cyclohexylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-[5-(2-phenylethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,

N-[5-(1H-indol-3-ylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2,5-dichlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-{5-[(1-naphthalenyloxy)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2-chloro-4-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2-chloro-5-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-[5-(1-benzothien-3-ylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-[5-(3-thienylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-{5-[2-(1-naphthalenyl)ethyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-{5-[2-(2-chlorophenyl)ethyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-{5-[(2-bromophenyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(3-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(4-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(3-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-[5-({[2-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-[5-({[3-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[3-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-{5-[(5,6,7,8-tetrahydro-1-naphthalenyloxy)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-{5-[(2-chlorophenyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[2-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-[5-({[4-(methyloxy)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,

N-{5-[(2-biphenylyloxy)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[4-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-{5-[({5-chloro-2-[(2-methylpropyl)oxy]phenyl}oxy)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-{5-[(4-fluorophenyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-[5-({[2-(methyloxy)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-{5-[(1-methyl-1H-indol-3-yl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-[5-(3-pyridinylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-[5-(5,6,7,8-tetrahydro-2-naphthalenylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-[5-(3,4-dihydro-2H-chromen-6-ylmethyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{2-[(2-chlorophenyl)oxy]ethyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2,4-dichlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-{5-[(2'-chloro-2-biphenylyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-{5-[(2-fluorophenyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-{5-[(3-chlorophenyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2,6-dichlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2-methylphenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(3,4-dimethylphenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-{5-[(2,4-dichlorophenyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-[5-({2-[(trifluoromethyl)oxy]phenyl}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2-chloro-3,5-difluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2-chloro-6-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,

N-[5-({[2-chloro-3-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2,4,5-trichlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-[5-({[2-chloro-5-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-{5-[(4-chloro-2-fluorophenyl)methyl]-1,3,4-thiadiazol-2-yl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[4-fluoro-2-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[5-chloro-2-(trifluoromethyl)phenyl]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-[5-({[4-fluoro-2-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-[5-({[2-chloro-4-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(3-chloro-5-fluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-[5-({[5-fluoro-2-(trifluoromethyl)phenyl]oxy}methyl)-1,3,4-thiadiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2,4-difluorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
5-{[(2-chlorophenyl)oxy]methyl}-N-(1,2,3,4-tetrahydro-6-isoquinolinyl)-1,3,4-thiadiazole-2-carboxamide,
N-(5-{[(2-chlorophenyl)(methyl)amino]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-N-methyl-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-2-(hydroxyacetyl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-2-(2-hydroxy-2-methylpropanoyl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-2-(N,N-dimethylglycyl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-2-(phenylcarbonyl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
2-butanoyl-N-(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-2-propyl-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide,
N-(5-{[(2-chlorophenyl)oxy]methyl}-1,3,4-thiadiazol-2-yl)-2-[5-(hydroxymethyl)-1,3-thiazol-2-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide, and

5-[(3,4-dichlorophenyl)methyl]-*N*-(1,2,3,4-tetrahydro-6-isoquinolinyl)-1,3,4-thiadiazole-2-carboxamide,
or a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition comprising a compound of formula (I) or pharmaceutically acceptable salt thereof according to any one of claims 1 to 7 together with at least one pharmaceutical carrier and/or excipient.

9. A compound of formula (I) or pharmaceutically acceptable salt thereof according to any one of claims 1 to 7 for use in therapy.

10. Use of a compound of formula (I) or pharmaceutically acceptable salt thereof according to any one of claims 1 to 7 for the manufacture of a medicament for treating and/or preventing a disease or a condition susceptible to amelioration by an SCD inhibitor.

11. Use of a compound of formula (I) or pharmaceutically acceptable salt thereof according to any one of claims 1 to 7 for the manufacture of a medicament for treating and/or preventing diseases or conditions caused by or associated with an abnormal plasma lipid profile including dyslipidemia, hypoalphalipoproteinemia, hyperbetalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial hypercholesterolemia, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, atherosclerosis, obesity, Type I diabetes, Type II diabetes, insulin resistance, hyperinsulinaemia and metabolic syndrome; peripheral vascular disease, reperfusion injury, angioplastic restenosis, hypertension, vascular complications of diabetes, thrombosis, hepatic steatosis, non-alcoholic steatohepatitis (NASH) and other diseases related to accumulation of lipids in the liver; eczema, acne, psoriasis, keloid scar formation or prevention, and diseases related to production or secretions from mucous membranes; cancer, neoplasia, malignancy, metastases, tumours (benign or malignant), carcinogenesis, hepatomas and the like; mild cognitive impairment (MCI), Alzheimer's Disease (AD), cerebral amyloid angiopathy (CAA) or dementia associated with Down Syndrome (DS) and other neurodegenerative diseases characterized by the formation or accumulation of amyloid plaques comprising Aβ42.

12. Use of a compound of formula (I) or pharmaceutically acceptable salt thereof according to any one of claims 1 to 7 for the manufacture of a medicament for treating and/or preventing acne, dyslipidemia, hypertriglyceridemia, atherosclerosis, obesity, Type II diabetes, insulin resistance, hyperinsulinaemia, hepatic steatosis and/or non-alcoholic steatohepatitis (NASH).

13. A compound of formula (I) or pharmaceutically acceptable salt thereof according to any one of claims 1 to 7 for use in treating and/or preventing a disease or a condition susceptible to amelioration by an SCD inhibitor.

14. A compound of formula (I) or pharmaceutically acceptable salt thereof according to any one of claims 1 to 7 for use in treating and/or preventing diseases or conditions caused by or associated with an abnormal plasma lipid profile including dyslipidemia, hypoalphalipoproteinemia, hyperbetalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial hypercholesterolemia, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, atherosclerosis, obesity, Type I diabetes, Type II diabetes, insulin resistance, hyperinsulinaemia and metabolic syndrome; peripheral vascular disease, reperfusion injury, angioplastic restenosis, hypertension, vascular complications of diabetes, thrombosis, hepatic steatosis, non-alcoholic steatohepatitis (NASH) and other diseases related to accumulation of lipids in the liver; eczema, acne, psoriasis, keloid scar formation or prevention, and diseases related to production or secretions from mucous membranes; cancer, neoplasia, malignancy, metastases, tumours (benign or malignant), carcinogenesis, hepatomas and the like; mild cognitive impairment (MCI), Alzheimer's Disease (AD), cerebral amyloid angiopathy (CAA) or dementia associated with Down Syndrome (DS) and other neurodegenerative diseases characterized by the formation or accumulation of amyloid plaques comprising Aβ42.

15. A compound of formula (I) or pharmaceutically acceptable salt thereof according to any one of claims 1 to 7 for use in treating and/or preventing acne, dyslipidemia, hypertriglyceridemia, atherosclerosis, obesity, Type II diabetes, insulin resistance, hyperinsulinaemia, hepatic steatosis and/or non-alcoholic steatohepatitis (NASH).

16. A method of treating and/or preventing a disease or a condition susceptible to amelioration by an SCD comprising administering to a subject a therapeutically effective amount of a compound of formula (I) or pharmaceutically acceptable salt thereof according to any one of claims 1 to 7.

17. A method of treating and/or preventing diseases or conditions caused by or associated with an abnormal plasma lipid profile including dyslipidemia, hypoalphalipoproteinemia, hyperbetalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial hypercholesterolemia, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, atherosclerosis, obesity, Type I diabetes, Type II diabetes, insulin resistance, hyperinsulinaemia and metabolic syndrome; peripheral vascular disease, reperfusion injury, angioplastic restenosis, hypertension, vascular complications of diabetes, thrombosis, hepatic steatosis, non-alcoholic steatohepatitis (NASH) and other diseases related to accumulation of lipids in the liver; eczema, acne, psoriasis, keloid scar formation or prevention, and diseases related to production or

secretions from mucous membranes; cancer, neoplasia, malignancy, metastases, tumours (benign or malignant), carcinogenesis, hepatomas and the like; mild cognitive impairment (MCI), Alzheimer's Disease (AD), cerebral amyloid angiopathy (CAA) or dementia associated with Down Syndrome (DS) and other neurodegenerative diseases characterized by the formation or accumulation of amyloid plaques comprising Aβ42 comprising administering to a subject a therapeutically effective amount of a compound of formula (I) or pharmaceutically acceptable salt thereof according to any one of claims 1 to 7.

18. A method of treating and/or preventing acne, dyslipidemia, hypertriglyceridemia, atherosclerosis, obesity, Type II diabetes, insulin resistance, hyperinsulinaemia, hepatic steatosis and/or non-alcoholic steatohepatitis (NASH) comprising administering to a subject a therapeutically effective amount of a compound of formula (I) or pharmaceutically acceptable salt thereof according to any one of claims 1 to 7.

19. A compound of formula (I) or a pharmaceutically acceptable salt thereof in combination with one or more active agent(s) selected from an inhibitor of cholesteryl ester transferase (CETP inhibitors), a HMG-CoA reductase inhibitor, a microsomal triglyceride transfer protein, a peroxisome proliferator-activated receptor activator (PPAR), a bile acid reuptake inhibitor, a cholesterol absorption inhibitor, a cholesterol synthesis inhibitor, a fibrate, niacin, an ion-exchange resin, an antioxidant, an inhibitor of AcylCoA: cholesterol acyltransferase (ACAT inhibitor), a cannabinoid 1 antagonist, a bile acid sequestrant, a corticosteroid, a vitamin D3 derivative, a retinoid, an immunomodulator, an anti androgen, a keratolytic agent, an anti-microbial, a platinum chemotherapeutic, an antimetabolite, hydroxyurea, a taxane, a mitotic disrupter, an anthracycline, dactinomycin, an alkylating agent and a cholinesterase inhibitor.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/052276

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D417/12 A61K31/404 A61P25/28 A61P35/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2006/122014 A2 (VERTEX PHARMACEUTICALS INCORPORATED, USA) 16 November 2006 (2006-11-16) claims 49,51,55; example 45	1-19
Y	WERMUTH C G: "MOLECULAR VARIATIONS BASED ON ISOSTERIC REPLACEMENTS" PRACTICE OF MEDICINAL CHEMISTRY, 1 January 1996 (1996-01-01), pages 203-237, XP002190259 pages 217-219, paragraphs II-E2,II-F	1-19
Y	WO 2005/011655 A (XENON PHARMACEUTICALS INC [CA]; ABREO MELWYN [US]; CHAFEEV MIKHAIL [CA) 10 February 2005 (2005-02-10) 7th cmp. of page 143, pages 37-43; claim 1	1-19

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 May 2008	21/05/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Bareyt, Sébastian

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2008/052276

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		NO 20076306 B	07-12-2007
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		JP 2007500717 T	18-01-2007
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		US 2005065143 A1	24-03-2005