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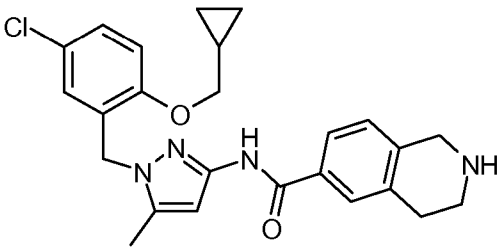
(54) **Title:** PYRAZOLE DERIVATIVES AND USE THEREOF AS INHIBITORS OF STEAROYL-COA DESATURASE



(I)

(57) **Abstract:** The present invention relates to compounds of formula (I) and salts thereof, to pharmaceutical compositions containing them and their use in medicine. In particular, the invention relates to compounds of formula (I) for inhibiting stearoyl-CoA desaturase (SCD) activity.

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PYRAZOLE DERIVATIVES AND USE THEREOF AS INHIBITORS OF STEAROYL-COA DESATURASE

FIELD OF THE INVENTION

The present invention relates to novel 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).

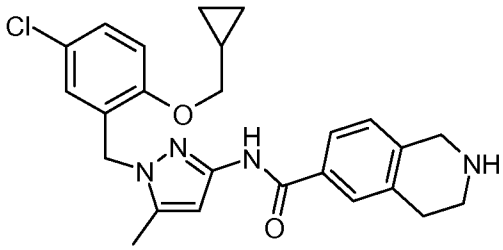
It has been shown that overexpression of Steroyl-CoA desaturase (SCD) in human cells in culture leads to a specific increase in the production of the amyloid plaque-forming Aβ42 peptide, and conversely, that reductions in SCD activity in human cells in culture leads to a specific decrease in the production 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.

WO2006/114313 describes certain pyrazole derivatives useful for modulating EP_1 receptor activity. The EP_1 receptor is a 7-transmembrane receptor and its natural ligand is the prostaglandin PGE_2. PGE_2 also has affinity for the other EP receptors (types EP_2, EP_3 and EP_4).

Based on the foregoing, there exists a need to identify compounds with improved potency for the treatment of SCD mediated disease.

The present invention provides a compound of formula (I):



(I)

or a 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 steatohepatitis (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.

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

In a further aspect of the invention, there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof. 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.

It will be appreciated that for use in medicine the salts of formula (I) should be physiologically (i.e. pharmaceutically) acceptable. Suitable physiologically 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-physiologically 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, which is incorporated herein by reference. Also included within the scope of the invention are solvates and hydrates of the compounds of formula (I).

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 water, methanol, ethanol and acetic acid. 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 and solvates.

Prodrugs of the compounds of formula (I) are included within 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 hydroxy 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).

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: 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 are 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.

In one aspect of the invention, the compounds of the invention may be useful in the treatment of 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, peripheral

vascular disease, reperfusion injury, angioplastic restenosis, hypertension, vascular complications of diabetes, thrombosis, hepatic steatosis, non-alcoholic steatohepatitis (NASH), other cardiovascular diseases and other diseases related to accumulation of lipids in the liver.

In another aspect of the invention, the compounds of the invention may be useful in the treatment of acne, dyslipidemia, hypertriglyceridemia, atherosclerosis, obesity, Type II diabetes, insulin resistance, hyperinsulinaemia, hepatic steatosis and/or non-alcoholic steatohepatitis (NASH).

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.

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

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 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 another 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 another 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.

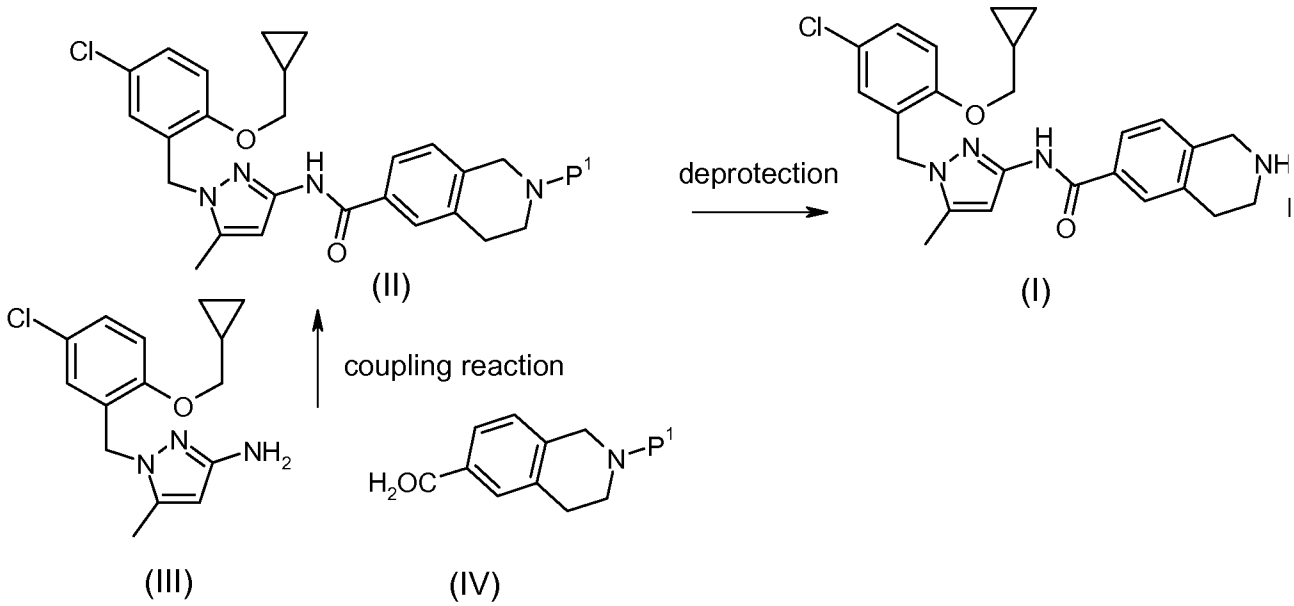
Since the compounds of the invention are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% 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 compounds of formula (I) form further aspects of the invention. Throughout the specification, general formulae are designated by Roman numerals (I), (II), (III), (IV) etc.

In a general process, compounds of formula (I) 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 group 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 to 80°C), and is followed by deprotection of compound of formula (II) under acidic conditions such as hydrochloric acid or trifluoracetic acid.

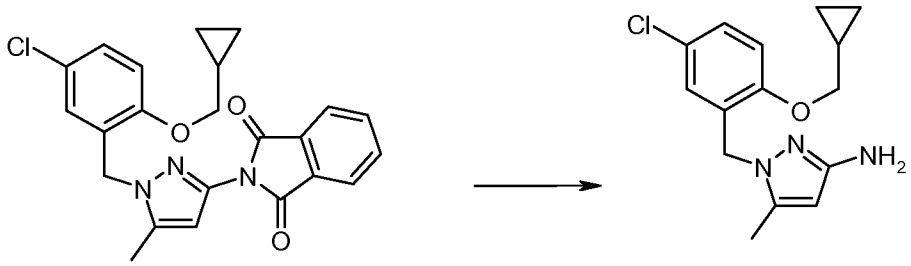
Scheme 1



Compounds of formula (III) may be prepared according to reaction scheme 2 by reacting compounds of formula (V) in the presence of hydrazine hydrate or NaOH (conc.) in a suitable solvent such as ethanol or methanol.

In a further aspect of the invention, there is provided a process for preparing compound for formula (I) or pharmaceutically acceptable salt thereof according to claim 1 which comprises reacting a compound of formula (III) with a compound of formula (IV) wherein P^1 represents a suitable nitrogen protecting group followed by deprotection of a compound of formula (II).

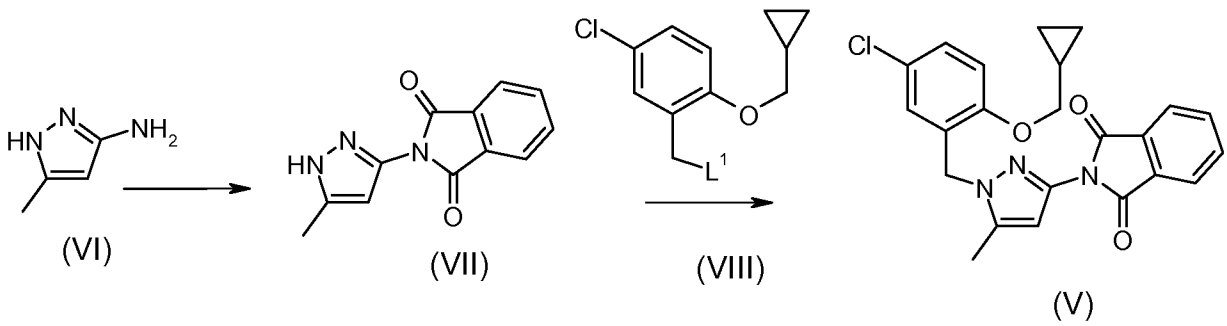
Scheme 2



(V) (III)

Compounds of formula (V) may be prepared according to reaction scheme 3 by reacting compound of formula (VI) with phthalic anhydride in a suitable solvent such as dioxane, followed by alkylation of compounds of formula (VII) with a compound of formula (VIII) where L^1 represents a leaving group such as halogen or tosylate in the presence of a base such as potassium carbonate in a suitable solvent such as acetonitrile suitably at reflux temperature.

Scheme 3



(VI) (VII) (VIII) (V)

Compounds of formula (VI), (IV) and (VIII) are commercially available 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.

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) and (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 a 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, ointments, creams or lotions, eye ointments and eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams.

The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about 1% up to about 98% of the formulation. More usually they will form up to about 80% of the formulation.

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 agent 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.

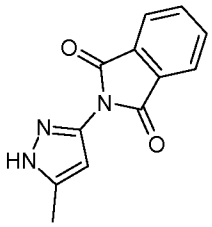
It will be recognised by one of skill in the art that the optimal quantity and spacing of individual dosages of a compound of the invention will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular mammal being treated, 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.

All publications, including, but not limited to, patents and patent applications cited in this specification, are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

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

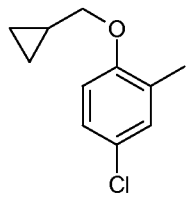
The following non-limiting examples illustrate the present invention.

Intermediate 1 : 2-(5-Methyl-1*H*-pyrazol-3-yl)-1*H*-isoindole-1,3(2*H*)-dione



To a solution of 5-methyl-1*H*-pyrazol-3-amine (50 g, 515 mmol) in dioxane (800 mL) was added phthalic anhydride (76.2 g, 515 mmol) and the reaction mixture was stirred at reflux for 24 hours. The resulting precipitate was filtered and the filtrate was concentrated to 150 mL leading to the crystallization of a second crop. The combined solids were then triturated in a mixture of EtOH/diisopropyl ether and filtered to give the title compound as a pale yellow solid (100 g, 86%).
LC/MS: m/z 228 $(M+H)^+$, Rt: 2.19 min.

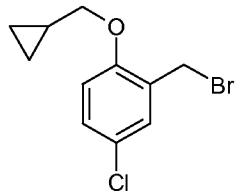
Intermediate 2: 4-chloro-2-methylphenyl cyclopropylmethyl ether



To a solution of 4-chloro-2-methylphenol (5.33 g, 37.4 mmol) in acetonitrile (125 mL) was added Cesiumcarbonate (24.4 g, 74.8 mmol) then 15 minutes later (bromomethyl)cyclopropane (7.57 g, 56.1 mmol). The reaction mixture was stirred at reflux for 17 hours. The resulting precipitate was filtered and the filtrate was evaporated under reduced pressure. The residue was put in ethyl acetate and the organic phase was washed with 10% potassium carbonate aqueous solution then with brine to give after evaporation the title compound as a yellow oil (6.89 g, 94%).

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.0 (brs, 1H), 6.96 (brd, 1H), 6.58 (d, 1H), 3.68 (d, 2H), 2.13 (s, 3H), 1.17 (m, 1H), 0.53 (m, 2H), 0.26 (m,2H).

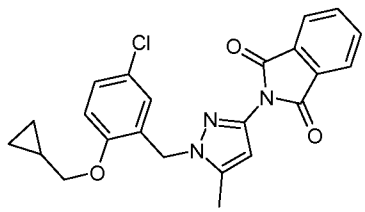
Intermediate 3: 2-(bromomethyl)-4-chlorophenyl cyclopropylmethyl ether



To a solution of 4-chloro-2-methylphenyl cyclopropylmethyl ether (see intermediate 2) (6.89 g, 35.0mmol) in CCl_4 (100 mL) was added AIBN (0.58 g, 3.5 mmol) and NBS (3.11 g, 17.5 mmol) and the reaction mixture was refluxed for 30 minutes, then a second portion of NBS (3.44 g, 19.3 mmol) was added and the reaction mixture was refluxed for 17h. After cooling the salts were removed by filtration and the filtrate was evaporated under reduced pressure. The residue was purified by flash column chromatography eluting with cyclohexane/DCM: 95/5 to 9/1 to give the title compound as a colorless oil (4.9 g, 51%).

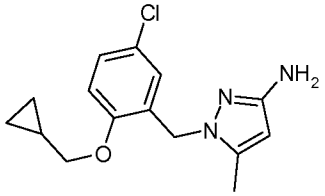
^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.18 (brs, 1H), 7.08 (brd, 1H), 6.63 (d, 1H), 4.40 (s, 2H), 3.75 (d, 2H), 1.18 (m, 1H), 0.53 (m, 2H), 0.28 (m,2H).

Intermediate 4: 2-[1-({5-chloro-2-[(cyclopropylmethyl)oxy]phenyl}methyl)-5-methyl-1*H*-pyrazol-3-yl]-1*H*-isoindole-1,3(2*H*)-dione



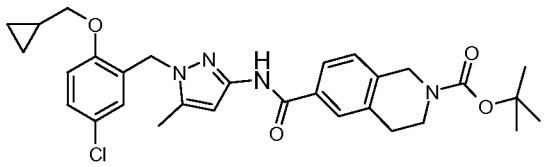
To a solution of 2-(5-Methyl-1*H*-pyrazol-3-yl)-1*H*-isoindole-1,3(2*H*)-dione (see intermediate 1) (1.58 g, 6.96 mmol) in CH_3CN (100 mL) were added potassium carbonate (1.154 g, 8.35 mmol) followed by intermediate 3 (2.3 g, 8.35 mmol) and the reaction mixture was stirred at 70°C for 2 days. After cooling the salts were removed by filtration and the filtrate was evaporated under reduced pressure. The oily residue was put in pentane and the resulting solid material was filtered and dried to give the title compound as a part of a mixture of regioisomer (1.0 g).
LC/MS: m/z 422 $(M+H)^+$, Rt: 3.58 and 3.70 min.

Intermediate 5: 1-({5-chloro-2-[(cyclopropylmethyl)oxy]phenyl}methyl)-5-methyl-1H-pyrazol-3-amine



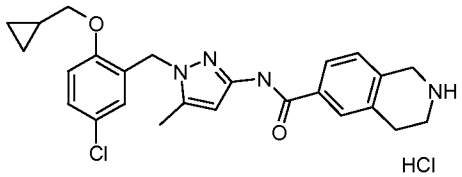
To a suspension of 2-[1-({5-chloro-2-[(cyclopropylmethyl)oxy]phenyl}methyl)-5-methyl-1H-pyrazol-3-yl]-1H-isoindole-1,3(2H)-dione (see intermediate 4) (1 g, mixture of regioisomer, 2.37 mmol) in EtOH (120 mL) was added hydrazine hydrate (574 µL, 11.85 mmol) and the reaction mixture was stirred at reflux for 1.5 hours. After cooling the precipitate was removed by filtration and the filtrate was evaporated under reduced pressure. The residue was purified by flash column chromatography eluting with DCM/MeOH: 98/2 to 95/5 to give the title compound as a white solid (200 mg, 29%).
LCMS: m/z 292 $(M+H)^+$, Rt : 3.10 min.

Intermediate 6: 1,1-Dimethylethyl 6-({[1-({5-chloro-2-[(cyclopropylmethyl)oxy] phenyl}methyl)-5-methyl-1*H*-pyrazol-3-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate



To a solution of 2-{[(1,1-dimethylethyl)oxy]carbonyl}-1,2,3,4-tetrahydro-6-isoquinolinecarboxylic acid (200 mg, 0.72 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (158 mg, 0.82 mmol), 1-hydroxybenzotriazole hydrate (111 mg, 0.82 mmol) and diisopropylethylamine (115 mg, 0.89 mmol) in DCM (15 mL) was added Intermediate 4 (200 mg, 0.69 mmol) and the mixture was stirred at room temperature for 4 days. The organic phase was then washed with HCl (1N), NaOH (1N) and brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by flash column chromatography eluting with DCM/EtOAc: 90/10 to give the title compound as yellow oil (316 mg, 84%).
LC/MS: m/z 551 $(M+H)^+$, Rt: 4.15 min.

Example 1 : N-[1-({5-chloro-2-[(cyclopropylmethyl)oxy]phenyl}methyl)-5-methyl-1H-pyrazol-3-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride



To a solution of 1,1-Dimethylethyl 6-({[1-({5-chloro-2-[(cyclopropylmethyl)oxy] phenyl}methyl)-5-methyl-1*H*-pyrazol-3-yl]amino}carbonyl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate (see intermediate 6) (0.3 g, 0.54 mmol) in EtOAc (15 mL) was

bubbled HCl(g) at room temperature. After 16 hours at room temperature, the resulting precipitate was filtered, washed with diisopropyl ether and recrystallized from EtOH to give the title compound as a pale yellow solid (103 mg, 39%).
HRMS calculated for $C_{25}H_{27}ClN_4O_2$ $(M+H)^+$ 451.1901, found: 451.1934, Rt: 2.98 min.

DEFINITIONS

AIBN	2,2'-Azobis(2-methylpropionitrile)
Boc	tertbutyloxy carbonyl
CCl_4	carbon tetrachloride
DCM	dichloromethane
DMF	dimethyl formamide
EtOAc	ethyl acetate
EtOH	ethanol
Fmoc	9-Fluorenylmethoxycarbonyl
HATU	O-(7-Azobenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HCl	hydrochloric acid
HOBt	1-hydroxybenzotriazole
MeOH	methanol
NaOH	sodium hydroxide
NBS	N-bromo succinimide

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.

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.

BIOLOGICAL ASSAYS

***In vitro* SCD 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.

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

HepG2 Assay:

Human HepG2 cells were grown on 24-well plates in BME media (Gibco cat# 41010-026) supplemented with 10% heat-inactivated fetal bovine serum, 1% Penicillin – Streptomycin – Glutamine (PSG) (Gibco cat# 10378-016), 1% MEM Non-Essential Amino Acids (NEAA) (Gibco cat# 11140-035), 1% MEM Sodium Pyruvate (Gibco cat# 11360-039) at 37°C under 5% CO_2 in a humidified incubator.

Test compounds were dissolved in RPMI 1640 (Gibco cat# 31870-025) supplemented with 1% PSG + 0.5 albumine fatty acid free (Sigma cat# A9205) and then incubated on subconfluent cells. [1-^{14}C]-stearate was added to each well at a final concentration of 0.4 µCi/mL to detect SCD-catalyzed [1-^{14}C]-oleate formation. After 4h 30min of incubation, culture medium was removed and cells were washed with PBS (2 * 1 mL) at room temperature. Labeled intracellular lipids were extracted for 30 min at room temperature with 500 µL of KOH 2.5M prepared in methanol/H_2O (4/1 v/v). Solubilized lipids were taken of and transfered to a glass tube and then incubated at 80°C for 1 h. After saponification, 700 µL of formic acid was added and vortexed vigourously and then 1 mL of cyclohexane was added and vortexed vigourously. 400 µl of the superior phase were transfered in a vial and evaporated overnight. Fatty acid were resuspended in 75 µL of chloroform and 30 µL were spoted with the Camag Atomatic TLC sampler 4 on a HPTLC plate previously impregnated with silver nitrate solution ($AgNO_3$) 1N. Fatty acid were separated using a freshly prepared solvent system consisting of 94% Chloroform/4% methanol/ 1% acetic acid/1% H_2O (v/v) using a Camag Automatic Developing Chamber. At the end of the migration, TLC plates were exposed for 4 days for autoradiography using Phosphor screen (Molecular dynamics). Spots corresponding to each labelled fatty acids were quantify using ImageQuant. The delta 9 desaturase activity was calculated by the ratio of 14C-oleate/(14C-oleate + 14C-stearate).

Results

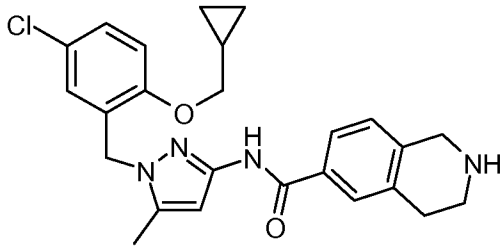
	Hep G2 IC_{50} Activity
Example 1	≥7.00 to <7.25
Compound A	≥6.50 to <6.75

A = *N*-[1-({5-chloro-2-[(2-methylpropyl)oxy]phenyl}methyl)-5-methyl-1*H*-pyrazol-3-yl]-1,2,3,4-tetrahydro-6-isoquinolinecarboxamide hydrochloride (WO2006/14313)

The compound of the present invention which has been tested demonstrates a surprisingly superior potency compared to compound A. Accordingly, the compound of the present invention is of potential therapeutic benefit in the treatment of SCD mediated disease.

Claims

1. A compound of formula (I):



(I)

or a salt thereof.

2. A compound of formula (I) or a salt thereof as claimed in claim 1 wherein the salt is a pharmaceutically acceptable salt.

3. A pharmaceutical composition comprising a compound for formula (I) or pharmaceutically acceptable salt thereof according to claim 1 together with at least one pharmaceutical carrier and/or excipient.

4. A compound for formula (I) or pharmaceutically acceptable salt thereof according to claim 1 for use in therapy.

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

6. Use of a compound for formula (I) or pharmaceutically acceptable salt thereof according to claim 1 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.

7. Use of a compound of formula (I) or pharmaceutically acceptable salt thereof according to claim 1 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).

8. Use of a compound of formula (I) or pharmaceutically acceptable salt thereof according to claim 1 for the manufacture of a medicament for treating and/or preventing acne.

9. A compound for formula (I) or pharmaceutically acceptable salt thereof according to claim 1 for use in treating and/or preventing a disease or a condition susceptible to amelioration by an SCD inhibitor.

10. A compound for formula (I) or pharmaceutically acceptable salt thereof according to claim 1 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.

11. A compound of formula (I) or pharmaceutically acceptable salt thereof according to claim 1 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).

12. A compound of formula (I) or pharmaceutically acceptable salt thereof according to claim 1 for use in treating and/or preventing acne.

13. 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 for formula (I) or pharmaceutically acceptable salt thereof according to claim 1.

14. 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 compound for formula (I) or pharmaceutically acceptable salt thereof according to claim 1.

15. 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 compound of formula (I) or pharmaceutically acceptable salt thereof according to claim 1.

16. A method of treating and/or preventing acne comprising administering to a subject a therapeutically effective amount of compound of formula (I) or pharmaceutically acceptable salt thereof according to claim 1.

17. 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/EP2008/059387

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/12 A61K31/435 A61P3/04 A61P25/28

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2008/074834 A (SMITHKLINE BEECHAM CORP [US]; BOUILLOT ANNE MARIE JEANNE [FR]) 26 June 2008 (2008-06-26) abstract; claim 1	1-17
P,X	WO 2008/074833 A (SMITHKLINE BEECHAM CORP [US]; DAUGAN ALAIN CLAUDE-MARIE [FR]) 26 June 2008 (2008-06-26) abstract; claim 1	1-17
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[X] Further documents are listed in the continuation of Box C.

[X] 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

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 October 2008	06/11/2008

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, Fax: (+31-70) 340-3016	Bérillon, Laurent

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INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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