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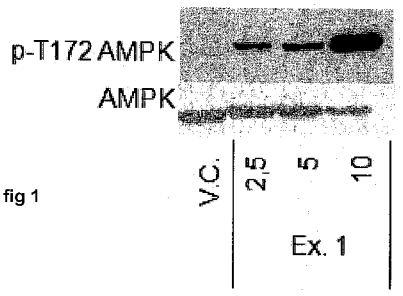
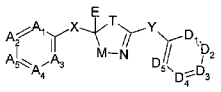


fig 1



(I)

(57) Abstract: According to the invention there is provided a compound of formula (I), wherein, X, T, Y1 E, M, A_1 to A_5 and D_1 to D_5 have meanings given in the description, which compounds are useful in the treatment of cancer.

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COMPOUNDS USEFUL AS INHIBITORS AS AMPK

Field of the Invention

This invention relates to pharmaceutically-useful compounds. The invention also relates to the use of such compounds in the treatment of cancer.

Background

AMPK represents a new target for the treatment of several diseases, including cancer.

Excess adiposity is associated to different degrees with an increased risk of developing cancers, such as colorectal adenomas, breast cancer (postmenopausal), endometrial cancer, kidney cancer, oesophageal adenocarcinoma, ovarian cancer, prostate cancer, pancreatic cancer, gallbladder cancer, liver cancer and cervical cancer (Calle and Kaaks (2004), *Nature Reviews Cancer,* **4**, 579-591).

Investigations have demonstrated that cancer cells require high rates of fatty acid and protein synthesis for their invasive growth and survival. Studies have shown that inhibition of cancer cell proliferation is possible using AMPK activators. The effects are associated with down-regulation of mTOR and eEF2. AMPK activators also suppress lipid synthesis in tumour cells. It has also been shown that it is a link between AMPK and other anti-cancer targets such as LKB1 and caspase-3 activation.

Recent studies suggest that hyperinsulinemia is correlated among other things to the incidence of colon and lethal breast and prostate cancer.

Elevated plasma free fatty acids (FFAs) stimulate pancreatic β-cells and is one cause of hyperinsulinemia.

In prostate cancer, hyperinsulinemia has been shown to be prospective risk factor for death and data support that the insulin level could be used as a marker of prostate cancer prognosis (Hammarsten and Högstedt (2005) *European Journal of Cancer*, **41**, 2887).

Several mechanisms may link hyperinsulinemia to the incidence and outcome of breast cancer. Firstly, chronic hyperinsulinemia results in increased production of ovarian testosterone and oestrogen and inhibition of hepatic production of sex hormone binding globulin, a sex-hormonal profile that is associated with breast cancer. Secondly, hyperinsulinemia suppresses hepatic production of insulin-like growth factor binding protein-1 (IGFBP-1), and thus increases circulating levels of IGF-1, which has potent mitogenic effect on breast tissue. Thirdly, insulin itself may have a direct mitogenic effect on breast cancer cells.

The study by Hardy *et al* ((2005), *J. Biol. Chem.* **280**, 13285) shows that FFAs directly stimulate the growth of breast cancer cells in a GPR40 dependent manner. Moreover, expression studies performed on tumor tissue isolated from 120 breast cancer patient shows a frequent expression of GPR40 emphasizing the clinical relevance of the findings of Hardy (see, for example, Ma *et al*, *Cancer Cell* (2004) **6**, 445).

Another expression study on clinical material from colon cancer patients suggests that similar mechanisms could be relevant also in these malignancies (see http://www.ncbi.nlm.nih.gov/projects/geo/gds/gds_browse.cgi?gds=1263).

Cancer cells in general exhibit an aberrant metabolism compared to non-transformed cells. Neoplastic cells synthesise lipids to a much larger extent than their normal counterparts and metabolise glucose differently. It has been suggested that this aberrant metabolism constitutes a therapeutic target. By interfering with one or, preferably, several of the pathways controlling cellular metabolism, cancer cells would be more sensitive than non-transformed cells, thus creating a therapeutic window. Examples of pathways/targets include glycolysis interfering agents, lipid synthesis pathway, AMPK activating agents and agents affecting mitochondrial function.

AMP-activated protein kinase (AMPK) is a protein kinase enzyme that consists of three protein sub-units and is activated by hormones, cytokines, exercise, and stresses that diminish cellular energy state (e.g. glucose deprivation). Activation of AMPK increases processes that generate adenosine 5'-triphosphate (ATP) (e.g., fatty-acid oxidation) and restrains others such as fatty acid-, glycerolipid- and protein-synthesis that consume ATP, but are not acutely necessary for survival. Conversely, when cells are presented with a sustained excess of glucose, AMPK activity diminishes and fatty acid-, glycerolipid- and protein-synthesis are enhanced. AMPK thus is a protein kinase

enzyme that plays an important role in cellular energy homeostasis. Therefore, the activation of AMPK is coupled to glucose lowering effects and triggers several other biological effects, including the inhibition of cholesterol synthesis, lipogenesis, triglyceride synthesis, and the reduction of hyperinsulinemia.

Given the above, AMPK is a preferred target for the treatment of the metabolic syndrome and especially type 2 diabetes. AMPK is also involved in a number of pathways that are important for many different diseases (e.g. AMPK is also involved in a number of pathways that are important in CNS disorders, fibrosis, osteoporosis, heart failure and sexual dysfunction).

AMPK is also involved in a number of pathways that are important in cancer. Several tumour suppressors are part of the AMP pathway. AMPK acts as a negative regulator of the mammalian TOR (mTOR) and EF2 pathway, which are key regulators of cell growth and proliferation. The deregulation may therefore be linked to diseases such as cancer (as well as diabetes). AMPK activators may therefore be of utility as anti-cancer drugs.

Current anti-diabetic drugs (e.g. metformin, glitazones) are known to not be significantly potent AMPK activators, but only activate AMPK indirectly and with low efficacy. However, due to the biological effects of AMPK activation at the cell level, compounds that are AMPK activators, and preferably direct activators of AMPK, may find utility as anti-cancer drugs, as well as for the treatment of many other diseases.

The listing or discussion of an apparently prior-published document in this specification should not necessarily be taken as an acknowledgement that the document is part of the state of the art or is common general knowledge.

Throughout this disclosure, various publications, patents and published patent specifications are referenced by an identifying citation. The disclosures of these publications, patents and published patent specifications are hereby incorporated by reference into the present disclosure to more fully describe the state of the art to which this invention pertains.

US 4,103,018 and US 4,665,083 disclose *inter alia* thiazolidinones. However, there is no mention or suggestion of the compounds disclosed in those documents in the treatment of cancer, nor (at all) of thiazolidinones that are substituted in the 5-position.

WO 2005/051890 discloses *inter alia* thiazolidinones (which are ultimately substituted with a cyclopropyl group) that may be useful in the treatment of diabetes. However, there is no mention or suggestion in this document of the use of the compounds in the treatment of cancer, nor of thiazolidinones that are substituted in the 5-position with a benzyl group.

EP 1 535 915 discloses various furan and thiophene-based compounds. Cancer is mentioned as one of numerous indications.

EP 1 559 422 discloses a huge range of compounds for use in the treatment of *inter alia* cancer. However, this document does not appear to relate to thiazolidinones.

US patent application US 2006/0089351 discloses various benzothiazole derivatives as neuropeptide Y receptor antagonists, and therefore of use in the treatment of eating disorders. International patent application WO 2006/020680 discloses a vast range of heterocyclic compounds as modulators of nuclear receptors.

International patent applications WO 2005/075471 and WO 2005/116002 disclose *inter alia* thiazolidinones and oxazolidinones as 11-β-hydroxysteroid dehydrogenase type 1 inhibitors. There is no mention or suggestion of the use of the disclosed compounds for the treatment of cancer, nor a teaching towards such thiazolidinones or oxazolidinones that are each substituted at the 5-position with a benzyl group.

International patent application WO 2006/040050 discloses certain quinazolinylmethylene thiazolinones as CDK1 inhibitors. Similarly, US patent application US 2006/0004045 discloses quinolinylmethylene thiazolinones.

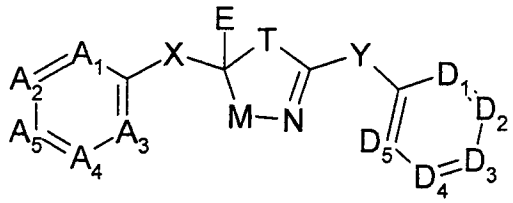
International patent applications WO 2007/010273 and WO 2007/010281 both disclose e.g. thiazolidin-4-one compounds that are able to antagonize the stimulatory effect of FFAs on cell proliferation when tested in an assay using a human breast cancer cell line (MDA-MB-231). Such compounds are thus indicated in the treatment of cancer.

International patent application PCT/GB2008/002620 (unpublished) discloses e.g. [1,4,2]Dithiazole 1,1-dioxide compounds that are able to antagonize the stimulatory effect of FFAs on cell proliferation when tested in an assay using a human breast cancer cell

line (MDA-MB-231). Such compounds are thus indicated in the treatment of cancer.

Disclosure of the Invention

According to the invention, there is provided a compound of formula I,



I

wherein:

X represents Q-[CR^xR^y]$_n$-Z;

Q and Z independently represent a bond, S or O;

R^x and R^y are independently selected from H, halo, C_{1-6} alkyl (optionally substituted by one or more halo atoms), or R^x and R^y are linked to form, along with the carbon atom to which they are attached, a non-aromatic 3- to 8-membered ring, optionally containing 1 to 3 heteroatoms selected from O, S and N, which ring is itself optionally substituted by one or more substituents selected from halo or C_{1-6} alkyl (optionally substituted by one or more halo atoms);

T represents S or O;

M represents -C(O)- or -$S(O)_2$-;

Y represents -NR^a-[CR^xR^y]$_m$- or -NR^aC(O)-[CR^xR^y]$_m$-;

R^a represents H or C_{1-6} alkyl (optionally substituted by one or more halo atoms);

E represents halo or C_{1-6} alkyl (optionally substituted by one or more groups selected from, -OR^b, aryl or heteroaryl (which latter two groups may be optionally substituted by one or more -R^c groups), or, preferably, halo);

A_1 to A_5 respectively represent C(R^1), C(R^2), C(R^3), C(R^4) and C(R^5), or, alternatively, up to two of A_1 to A_5 may independently represent N;

D_1 to D_5 each independently represent C(R^6), or, alternatively, up to two of D_1 to D_5 may independently represent N;

R^1 to R^5 independently represent H, halo, -R^7, -CF_3, -CN, -NO_2, -C(O)R^7, -C(O)OR^7, -$N(R^{7a})R^{7b}$, -$N(R^7)_3^+$, -SR^7, -OR^7, -NH(O)R^7 or -SO_3R^7, or any two of R^1 to R^5 which are adjacent to each other are optionally linked to form, along with two atoms of the essential benzene ring in the compound of formula I, an aromatic or non-aromatic 3- to

8-membered ring, optionally containing 1 to 3 heteroatoms selected from O, S and N, which ring is itself optionally substituted by one or more substituents selected from halo, $-R^7$, $-OR^7$ and =O;

R^c, on each occasion when used herein, independently represents H, halo, $-R^7$, $-CF_3$, -CN, $-NO_2$, $-C(O)R^7$, $-C(O)OR^7$, $-N(R^{7a})R^{7b}$, $-N(R^7)_3^+$, $-SR^7$, $-OR^7$, $-NH(O)R^7$ or $-SO_3R^7$, or any two R^c groups which are adjacent to each other are optionally linked to form, along with two atoms of the essential benzene ring in the compound of formula I, an aromatic or non-aromatic 3- to 8-membered ring, optionally containing 1 to 3 heteroatoms selected from O, S and N, which ring is itself optionally substituted by one or more substituents selected from halo, $-R^7$, $-OR^7$ and =O;

R^6 independently represents, on each occasion when used herein, H, cyano, $-NO_2$, halo, $-R^8$, $-OR^8$, $-N(R^8)C(O)R^8$, $-NR^9R^{10}$, $-SR^{11}$, $-Si(R^{12})_3$, $-OC(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)R^{14}$, $-C(O)NR^{15a}R^{15b}$, $-S(O)_2NR^{15c}R^{15d}$, aryl or heteroaryl (which aryl and heteroaryl groups are themselves optionally and independently substituted by one or more groups selected from halo and R^{16}), or any two R^6 groups which are adjacent to each other are optionally linked to form, along with two atoms of the essential benzene ring in the compound of formula I, an aromatic or non-aromatic 3- to 8-membered ring, optionally containing 1 to 3 heteroatoms selected from O, S and N, which ring is itself optionally substituted by one or more substituents selected from halo, $-R^7$, $-OR^7$ and =O;

R^7 is selected from H or C_1-C_6 alkyl, C_1-C_6 cycloalkyl, aryl and heteroaryl;

R^{7a} and R^{7b} are independently selected from H, or C_1-C_6 alkyl, C_1-C_6 cycloalkyl, aryl and heteroaryl, or R^{7a} and R^{7b} are optionally linked to form, along with the nitrogen atom to which they are attached, an aromatic or non-aromatic 3- to 8-membered ring, optionally containing 1 to 3 heteroatoms selected from O, S and N, which ring is itself optionally substituted by one or more substituents selected from halo, $-R^7$, $-OR^7$ and =O;

R^b and, more preferably, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15a}, R^{15b}, R^{15c} and R^{15d} independently represent H or R^{16};

R^{16} represents, on each occasion when used herein, C_{1-6} alkyl optionally substituted by one or more halo atoms;

n represents 3, or preferably, 1 or 2;

m represents 1, 2, or preferably 0;

or a pharmaceutically-acceptable salt or solvate, or a pharmaceutically functional derivative thereof.

N takes it normal designation (nitrogen) in compounds of formula I.

Pharmaceutically-acceptable salts that may be mentioned include acid addition salts and base addition salts. Such salts may be formed by conventional means, for example by reaction of a free acid or a free base form of a compound of formula I with one or more equivalents of an appropriate acid or base, optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using standard techniques (e.g. *in vacuo*, by freeze-drying or by filtration). Salts may also be prepared by exchanging a counter-ion of a compound of formula I in the form of a salt with another counter-ion, for example using a suitable ion exchange resin.

Examples of pharmaceutically acceptable addition salts include those derived from mineral acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric and sulphuric acids; from organic acids, such as tartaric, acetic, citric, malic, lactic, fumaric, benzoic, glycolic, gluconic, succinic, arylsulphonic acids; and from metals such as sodium, magnesium, or preferably, potassium and calcium.

"Pharmaceutically functional derivatives" of compounds of formula I as defined herein includes ester derivatives and/or derivatives that have, or provide for, the same biological function and/or activity as any relevant compound. Thus, for the purposes of this invention, the term also includes prodrugs of compounds of formula I.

The term "prodrug" of a relevant compound of formula I includes any compound that, following oral or parenteral administration, is metabolised *in vivo* to form that compound in an experimentally-detectable amount, and within a predetermined time (e.g. within a dosing interval of between 6 and 24 hours (i.e. once to four times daily)). For the avoidance of doubt, the term "parenteral" administration includes all forms of administration other than oral administration.

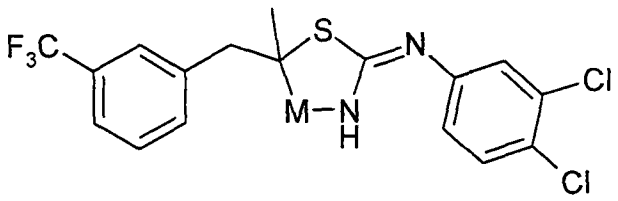
Prodrugs of compounds of formula I may be prepared by modifying functional groups present on the compound in such a way that the modifications are cleaved, *in vivo* when such prodrug is administered to a mammalian subject. The modifications typically are achieved by synthesizing the parent compound with a prodrug substituent. Prodrugs include compounds of formula I wherein a hydroxyl, amino, sulfhydryl, carboxy or carbonyl group in a compound of formula I is bonded to any group that may be cleaved *in vivo* to regenerate the free hydroxyl, amino, sulfhydryl, carboxy or carbonyl group, respectively.

Examples of prodrugs include, but are not limited to, esters and carbamates of hydroxy functional groups, esters groups of carboxyl functional groups, N-acyl derivatives and N-Mannich bases. General information on prodrugs may be found e.g. in Bundegaard, H. "Design of Prodrugs" p. I-92, Elesevier, New York-Oxford (1985).

Compounds of formula I, as well as pharmaceutically-acceptable salts, solvates and pharmaceutically functional derivatives of such compounds are, for the sake of brevity, hereinafter referred to together as the "compounds of formula I".

Compounds of formula I may contain double bonds and may thus exist as *E* (*entgegen*) and *Z* (*zusammen*) geometric isomers about each individual double bond. All such isomers and mixtures thereof are included within the scope of the invention.

Compounds of formula I may exist as regioisomers and may also exhibit tautomerism. All tautomeric forms and mixtures thereof are included within the scope of the invention. For example, the following tautomers are included within the scope of the invention:



wherein M is as hereinbefore defined. In such compounds, the relevant proton may be attached to either of the two different nitrogen atoms, and the 'proton shift' may be accompanied by one or more double bond shift.

Compounds of formula I contain one or more asymmetric carbon atoms and may therefore exhibit optical and/or diastereoisomerism. Diastereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. fractional crystallisation or HPLC, techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation (i.e. a 'chiral pool' method), by reaction of the appropriate starting material with a 'chiral auxiliary' which can subsequently be removed at a suitable stage, by derivatisation (i.e. a resolution, including a dynamic resolution), for example with a

homochiral acid followed by separation of the diastereomeric derivatives by conventional means such as chromatography, or by reaction with an appropriate chiral reagent or chiral catalyst all under conditions known to the skilled person. All stereoisomers and mixtures thereof are included within the scope of the invention.

Unless otherwise stated, the term "alkyl" refers to an unbranched or branched, cyclic, saturated or unsaturated (so forming, for example, an alkenyl or alkynyl) hydrocarbyl radical, which may be substituted or unsubstituted (with, for example, one or more halo atoms). Where the term "alkyl" refers to an acyclic group, it is preferably C_{1-10} alkyl and, more preferably, C_{1-6} alkyl (such as ethyl, propyl, (e.g. *n*-propyl or isopropyl), butyl (e.g. branched or unbranched butyl), pentyl or, more preferably, methyl). Where the term "alkyl" is a cyclic group (which may be where the group "cycloalkyl" is specified), it is preferably C_{3-12} cycloalkyl and, more preferably, C_{5-10} (e.g. C_{5-7}) cycloalkyl.

When used herein, alkylene refers to C_{1-10} (e.g. C_{1-6}) alkylene and, preferably C_{1-3} alkylene, such as pentylene, butylene (branched or unbranched), preferably, propylene (*n*-propylene or isopropylene), ethylene or, more preferably, methylene (i.e. $-CH_2-$).

The term "halogen", when used herein, includes fluorine, chlorine, bromine and iodine.

The term "aryl" when used herein includes C_{6-14} (such as C_{6-13} (e.g. C_{6-10})) aryl groups. Such groups may be monocyclic, bicyclic or tricyclic and have between 6 and 14 ring carbon atoms, in which at least one ring is aromatic. The point of attachment of aryl groups may be *via* any atom of the ring system. However, when aryl groups are bicyclic or tricyclic, they are linked to the rest of the molecule *via* an aromatic ring. C_{6-14} aryl groups include phenyl, naphthyl and the like, such as 1,2,3,4-tetrahydronaphthyl, indanyl, indenyl and fluorenyl. Most preferred aryl groups include phenyl.

The term "heteroaryl" when used herein refers to an aromatic group containing one or more heteroatom(s) (e.g. one to four heteroatoms) preferably selected from N, O and S (so forming, for example, a mono-, bi-, or tricyclic heteroaromatic group). Heteroaryl groups include those which have between 5 and 14 (e.g. 10) members and may be monocyclic, bicyclic or tricyclic, provided that at least one of the rings is aromatic. However, when heteroaryl groups are bicyclic or tricyclic, they are linked to the rest of the molecule *via* an aromatic ring. Heterocyclic groups that may be mentioned include benzothiadiazolyl (including 2,1,3-benzothiadiazolyl), isothiochromanyl and, more

preferably, acridinyl, benzimidazolyl, benzodioxanyl, benzodioxepinyl, benzodioxolyl (including 1,3-benzodioxolyl), benzofuranyl, benzofurazanyl, benzothiazolyl, benzoxadiazolyl (including 2,1,3-benzoxadiazolyl), benzoxazinyl (including 3,4-dihydro-2*H*-1,4-benzoxazinyl), benzoxazolyl, benzomorpholinyl, benzoselenadiazolyl (including 2,1,3-benzoselenadiazolyl), benzothienyl, carbazolyl, chromanyl, cinnolinyl, furanyl, imidazolyl, imidazo[1,2-*a*]pyridyl, indazolyl, indolinyl, indolyl, isobenzofuranyl, isochromanyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiaziolyl, isoxazolyl, naphthyridinyl (including 1,6-naphthyridinyl or, preferably, 1,5-naphthyridinyl and 1,8-naphthyridinyl), oxadiazolyl (including 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl and 1,3,4-oxadiazolyl), oxazolyl, phenazinyl, phenothiazinyl, phthalazinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinolizinyl, quinoxalinyl, tetrahydroisoquinolinyl (including 1,2,3,4-tetrahydroisoquinolinyl and 5,6,7,8-tetrahydroisoquinolinyl), tetrahydroquinolinyl (including 1,2,3,4-tetrahydroquinolinyl and 5,6,7,8-tetrahydroquinolinyl), tetrazolyl, thiadiazolyl (including 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl and 1,3,4-thiadiazolyl), thiazolyl, thiochromanyl, thiophenetyl, thienyl, triazolyl (including 1,2,3-triazolyl, 1,2,4-triazolyl and 1,3,4-triazolyl) and the like. Substituents on heteroaryl groups may, where appropriate, be located on any atom in the ring system including a heteroatom. The point of attachment of heteroaryl groups may be *via* any atom in the ring system including (where appropriate) a heteroatom (such as a nitrogen atom), or an atom on any fused carbocyclic ring that may be present as part of the ring system. Heteroaryl groups may also be in the *N*- or *S*-oxidised form. Particularly preferred heteroaryl groups include pyridyl, pyrrolyl, quinolinyl, furanyl, thienyl, oxadiazolyl, thiadiazolyl, thiazolyl, oxazolyl, pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrimidinyl, indolyl, pyrazinyl, indazolyl, pyrimidinyl, thiophenetyl, pyranyl, carbazolyl, acridinyl, quinolinyl, benzoimidazolyl, benzthiazolyl, purinyl, cinnolinyl and pterdinyl. Particularly preferred heteroaryl groups include monocylic heteroaryl groups.

For the avoidance of doubt, in cases in which the identity of two or more substituents in a compound of formula I may be the same, the actual identities of the respective substituents are not in any way interdependent. For example, given that D_1 to D_5 independently represent $C(R^6)$ then those R^6 groups may be the same or different. Similarly, in the situation in which R^6 and R^7 are both aryl groups substituted by one or more C_{1-6} alkyl groups, the alkyl groups in question may be the same or different. Additionally, in the situation in which R^b, or, more preferably, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15a}, R^{15b}, R^{15c} and R^{15d} independently represent R^{16} then those R^{16} groups may be

the same or different.

For the avoidance of doubt, when a term such as "*A_1 to A_5*" is employed herein, this will be understood by the skilled person to mean any of (i.e. some or all, as applicable) A^1, A^2, A^3, A^4 and A^5 inclusively.

Compounds of formula I that may be mentioned include those in which:
T represents S.

Compounds of formula I that may be mentioned include those in which:
T represents O.

Compounds of formula I that may be mentioned include those in which:
E represents halo or C_{1-3} alkyl (optionally substituted by one or more groups selected from, $-OR^b$, phenyl or pyridyl (which latter two groups may be optionally substituted by one or more $-R^c$ groups), or, preferably, halo).

Compounds of formula I that may be mentioned include those in which:
E represents halo or C_{1-3} alkyl (optionally substituted by one or more groups selected from, $-OR^b$, phenyl (which latter group may be optionally substituted by one or more $-R^c$ groups), or, preferably, halo).

Compounds of formula I that may be mentioned include those in which:
E represents halo or C_{1-6} alkyl optionally substituted by one or more halo atoms.

Compounds of formula I that may be mentioned include those in which:
E represents $-CH_2CH_3$, -F or particularly $-CH_3$.

Compounds of formula I that may be mentioned include those in which:
at least one of R^1 to R^5 is not H.

Further compounds of formula I that may be mentioned include those in which:
at least one of R^1 to R^5, when present, represents halo, $-R^7$, $-CF_3$, -CN, $-NO_2$, $-C(O)R^7$, $-C(O)OR^7$, $-N(R^{7a})R^{7b}$, $-N(R^7)_3^+$, $-SR^7$, $-OR^7$, $-NH(O)R^7$ or $-SO_3R^7$.

Yet further compounds of formula I that may be mentioned include those in which:

at least one of R^1 to R^5, when present, represents $-C(O)R^7$, $-N(R^7)_3^+$, or, more preferably, halo, $-R^7$, $-CF_3$, -CN, $-NO_2$, $-SR^7$, $-OR^7$ (e.g. $-OCH_3$, or more preferably, $-OCHF_2$ or $-OCF_3$), $-C(O)OR^7$, $-N(R^{7a})R^{7b}$ or a triazolyl group.

Yet further compounds of formula I that may be mentioned include those in which:
at least one of R^1 to R^5, when present, represents halo, $-R^7$, $-CF_3$, -CN, $-C(O)OR^7$, $-N(R^{7a})R^{7b}$, $-OR^7$ or a triazolyl group.

Yet further compounds of formula I that may be mentioned include those in which:
at least one of R^1 to R^5 represents $-CH_3$, $-OCH_3$, -CN, -Cl, -Br, -F, $-C(O)OCH_3$, $-C(O)OCH_3$, $-CF_3$, -OH, $-OCF_3$, $-OCF_2$ or a triazolyl group.

Yet further compounds of formula I that may be mentioned include those in which:
at least one of R^1 to R^5 represents $-CH_3$, $-OCH_3$, -Cl, -Br, -F, $-CF_3$, -OH, $-OCF_3$, $-OCF_2$ or a triazolyl group.

Yet further compounds of formula I that may be mentioned include those in which:
at least one R^c group, when present, represents halo, $-R^7$, $-CF_3$, -CN, $-C(O)OR^7$, $-N(R^{7a})R^{7b}$, $-OR^7$ or a triazolyl group.

Yet further compounds of formula I that may be mentioned include those in which:
at least one R^c group is present and represents $-CH_3$, $-OCH_3$, -CN, -Cl, -Br, -F, $-C(O)OCH_3$, $-C(O)OCH_3$, $-CF_3$, -OH, $-OCF_3$, $-OCF_2$ or a triazolyl group.

Yet further compounds of formula I that may be mentioned include those in which:
at least one R^c group is present and represents $-CH_3$, $-OCH_3$, -Cl, -Br, -F, $-CF_3$, -OH, $-OCF_3$, $-OCF_2$ or a triazolyl group.

Further compounds of formula I that may be mentioned include those in which:
R^6 independently represents $-NO_2$, or more preferably, H, -CN, -Br, -Cl, -F, $-R^8$, $-OR^8$, $-NR^9R^{10}$, $-SR^{11}$, $-C(O)OR^{13}$, $-C(O)R^{14}$, $-C(O)NR^{15a}R^{15b}$, $-S(O)_2NR^{15c}R^{15d}$, aryl or heteroaryl (which aryl and heteroaryl groups are themselves optionally and independently substituted by one or more groups selected from halo and R^{16}).

Yet further compounds of formula I that may be mentioned include those in which:
R^6 independently represents $-NO_2$, or more preferably, H, -CN, -Br, -Cl, -F, $-R^8$, $-OR^8$,

$-NR^9R^{10}$, $-C(O)R^{14}$, $-C(O)NR^{15a}R^{15b}$ or $-SR^{11}$.

Yet further compounds of formula I that may be mentioned include those in which:
R^6 independently represents, -CN, -Br, $-R^8$, $-C(O)R^{14}$, $-C(O)NR^{15a}R^{15b}$ or, most preferably, H, -F or -Cl.

Yet further compounds of formula I that may be mentioned include those in which:
at least one R^6 group is not H.

Compounds of formula I that may be mentioned include those in which:
R^a represents H or C_{1-3} alkyl (optionally substituted by one or more halo atoms);

Further compounds of formula I that may be mentioned include those in which:
R^a represents $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CF_2H$, or particularly H;

Further compounds of formula I that may be mentioned include those in which:
each $-[CR^xR^y]-$ unit may be independently selected from:

(a) a unit wherein R^x and R^y are independently selected from H, halo, C_{1-6} alkyl (optionally substituted by one or more halo atoms); and

(b) a unit wherein R^x and R^y are linked to form, along with the carbon atom to which they are attached, a non-aromatic 3- to 8-membered ring, optionally containing 1 to 3 heteroatoms selected from O, S and N, which ring is itself optionally substituted by one or more substituents selected from halo or C_{1-6} alkyl (optionally substituted by one or more halo atoms),

provided that no more than one unit is selected from (b)

(e.g. each $-[CR^xR^y]-$ unit may be independently selected from:

(a) a unit wherein R^x and R^y are independently selected from H, halo, C_{1-3} alkyl (optionally substituted by one or more halo atoms); and

(b) a unit wherein R^x and R^y are linked to form, along with the carbon atom to which they are attached, a non-aromatic ring selected from cyclobutyl, cyclopentyl, cyclohexyl or, more particularly, cyclopropyl, which ring is itself optionally substituted by one or more substituents selected from halo or C_{1-6} alkyl (optionally substituted by one or more halo atoms),

provided that no more than one unit (e.g. no units) is selected from (b).

Compounds of formula I that may be mentioned include those in which:

Y represents $-NR^a-[CR^xR^y]_m-$, or preferably -NH-.

Compounds of formula I that may be mentioned include those in which:
Y represents $-NR^aC(O)-[CR^xR^y]_m-$, or preferably $-NHR^aC(O)-$.

Compounds of formula I that may be mentioned include those in which:
X represents $Q-[CR^xR^y]_n-Z$, or more preferably $-[CH]_2-$.

Compounds of formula I that may be mentioned include those in which:
when either one of R^x and R^y is C_{1-6} alkyl, then it is unsubstituted, or more preferably substituted by one or more halo atoms.

Compounds of formula I that may be mentioned include those in which:
R^x and R^y are independently selected from H, halo, C_{1-6} alkyl (optionally substituted by one or more halo atoms).

Compounds of formula I that may be mentioned include those in which:
at least one of R^x and R^y is unsubstituted C_{1-6} alkyl.

Further compounds of formula I that may be mentioned include those in which:
n represents 2 or, more preferably, 1.

Yet further compounds of formula I that may be mentioned include those in which:
m represents 1 or, more preferably, 0.

More preferred compounds of formula I include those of the examples described hereinafter.

Preferred compounds of formula I include:

i) 2-(3,4-dichlorophenylamino)-5-methyl-5-(3-trifluoromethylbenzyl)-thiazol-4-one;
ii) 2-(3,4-dichlorophenylamino)-5-methyl-5-(3-bromobenzyl)-thiazol-4-one;
iii) 2-(3,4-dichlorophenylamino)-5-methyl-5-(3-fluorobenzyl)-thiazol-4-one;
iv) 2-(3,4-dichlorophenylamino)-5-methyl-5-(3-methoxybenzyl)-thiazol-4-one;
v) 2-(3,4-dichlorophenylamino)-5-methyl-5-(benzyl)-thiazol-4-one;
vi) 2-(3,4-dichlorophenylamino)-5-methyl-5-(3-chlorobenzyl)-thiazol-4-one;
vii) 2-(3,4-dichlorophenylamino)-5-methyl-5-(3-chloro-4-fluorobenzyl)-thiazol-4-one;

viii) 2-(3,4-dichlorophenylamino)-5-methyl-5-(4-trifluoromethylbenzyl)-thiazol-4-one;

ix) 3-[2-(3,4-dichlorophenylamino)-5-methyl-4-oxo-4,5-dihydrothiazol-5-ylmethyl]-benzonitrile;

x) 2-(4-fluorophenylamino)-5-methyl-5-(3-trifluoromethylbenzyl)-thiazol-4-one;

xi) 2-(4-fluorophenylamino)-5-methyl-5-(3-bromobenzyl)-thiazol-4-one;

xii) 2-(4-fluorophenylamino)-5-methyl-5-(3-fluorobenzyl)-thiazol-4-one;

xiii) 2-(4-fluorophenylamino)-5-methyl-5-(3-methoxybenzyl)-thiazol-4-one;

xiv) 2-(4-fluorophenylamino)-5-methyl-5-(benzyl)-thiazol-4-one;

xv) 2-(4-fluorophenylamino)-5-methyl-5-(3-chlorobenzyl)-thiazol-4-one;

xvi) 2-(4-fluorophenylamino)-5-methyl-5-(3-chloro-4-fluorobenzyl)-thiazol-4-one;

xvii) 2-(4-fluorophenylamino)-5-methyl-5-(4-trifluoromethylbenzyl)-thiazol-4-one;

xviii) 3-[2-4-fluorophenylamino)-5-methyl-4-oxo-4,5-dihydrothiazol-5-ylmethyl]-benzonitrile;

xix) 2-(3,4-dichlorophenylamino)-5-methyl-5-(4-fluorobenzyl)-thiazol-4-one;

xx) 2-(4-fluorophenylamino)-5-methyl-5-(4-fluorobenzyl)-thiazol-4-one;

xxi) 2-(3,4-dichlorophenylamino)-5-methyl-5-(4-methoxybenzyl)-thiazol-4-one;

xxii) 2-(4-fluorophenylamino)-5-methyl-5-(4-methoxybenzyl)-thiazol-4-one;

xxiii) 2-(4-fluorophenylamino)-5-methyl-5-(4- chlorobenzyl)-thiazol-4-one;

xxiv) 2-(3,4-dichlorophenylamino)-5-methyl-5-(2-methylbenzyl)-thiazol-4-one;

xxv) 2-(4-fluorophenylamino)-5-methyl-5-(2-methylbenzyl)-thiazol-4-one;

xxvi) 4-[2-(3,4-dichlorophenylamino)-5-methyl-4-oxo-4,5-dihydrothiazol-5-ylmethyl]-benzoic acid methyl ester;

xxvii) 4-[2-(4-fluorophenylamino)-5-methyl-4-oxo-4,5-dihydrothiazol-5-ylmethyl]-benzoic acid methyl ester;

xxviii) 4-[2-(3,4-dichlorophenylamino)-5-methyl-4-oxo-4,5-dihydrothiazol-5-ylmethyl]-benzoic acid;

xxix) 4-[2-(4-fluorophenylamino)-5-methyl-4-oxo-4,5-dihydrothiazol-5-ylmethyl]-benzoic acid;

xxx) 2-(3,4-dichlorophenylamino)-5-methyl-5-(2-phenoxyethyl)-thiazol-4-one;

xxxi) 2-(4-fluorophenylamino)-5-methyl-5-(2-phenoxyethyl)-thiazol-4-one;

xxxii) 2-(3,4-dichlorophenylamino)-5-methyl-5-(3-triazolobenzyl)-thiazol-4-one;

xxxiii) 2-(4-fluorophenylamino)-5-methyl-5-(3-triazolobenzyl)-thiazol-4-one;

xxxiv) 2-(3,4-dichlorophenylamino)-5-ethyl-5-(3-trifluoromethylbenzyl)-thiazol-4-one;

xxxv) 2-(3,4-dichlorophenylamino)-5-fluoro-5-(3-trifluoromethylbenzyl)-thiazol-4-one;

and

xxxvi) (3,4-dichlorophenyl)-[5-methyl-1,1-dioxo-5-(3-trifluoromethylbenzyl)-1,5-dihydro-

1-λ^6-[1,4,2]dithiazol-3-yl]-amine;

xxxvii) 5,5-dibenzyl-2-[(3,4-dichlorophenyl)amino]thiazol-4-one;

xxxviii) 2-[(3,4-dichlorophenyl)amino]-5,5-bis[[3-(trifluoromethyl)phenyl]methyl]thiazol-4-one;

xxxix) 2-[(3,4-dichlorophenyl)amino]-5,5-bis[(4-fluorophenyl)methyl]thiazol-4-one;

lx) 2-[(3,4-dichlorophenyl)amino]-5,5-bis[(4-methoxyphenyl)methyl]thiazol-4-one;

lxi) 6(2-(3,4-dichlorophenyl)imino-5-(methoxymethyl)-5-[[3-(trifluoromethyl)cyclohexa-2,4-dien-1-yl]methyl]thiazolidin-4-one; and

lxii) 4-[[5,5-bis[(4-chlorophenyl)methyl]-1,1-dioxo-1,4,2-dithiazol-3-yl]amino]benzoic acid.

More preferred compounds of formula I are compounds (i) to (xxxvi) above.

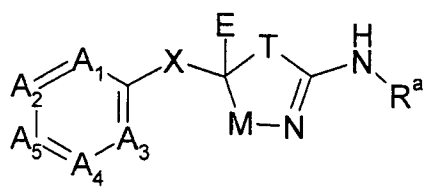
Compound names were derived using the commercially available software package Autonom (brand of nomenclature software provided as an add-on for use in the ISIS/Draw (TM) office suite marketed by MDL Information Systems).

Throughout this specification, structures may or may not be presented with chemical names. Where any question arises as to nomenclature, the structure prevails.

Compounds of formula I may be prepared in accordance with techniques that are well known to those skilled in the art, for example as described hereinafter.

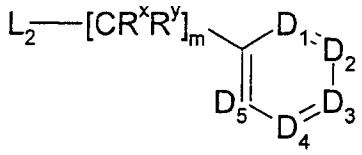
According to a further aspect of the invention there is provided a process for the preparation of a compound of formula I, which process comprises:

(i) for compounds of formula I wherein Y represents $-NR^a-[CR^xR^y]_m-$, reaction of a compound of formula II,



II

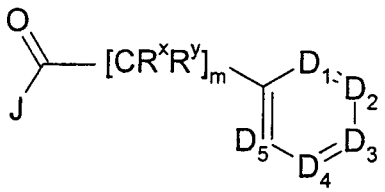
wherein A_1 to A_5, X, E, M, R^a and T are as hereinbefore defined, with a compound of formula III,



III

wherein L_2 represents a suitable leaving group such as iodo, bromo, chloro or a sulfonate group (e.g. $-OS(O)_2CF_3$, $-OS(O)_2CH_3$ or $-OS(O)_2PhMe$) and m, R^x, R^y and D_1 to D_5 are as hereinbefore defined, for example optionally in the presence of an appropriate metal catalyst (or a salt or complex thereof) such as Cu, $Cu(OAc)_2$, CuI (or CuI/diamine complex), copper tris(triphenylphosphine)bromide, $Pd(OAc)_2$, $Pd_2(dba)_3$ or $NiCl_2$ and an optional additive such as Ph_3P, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, xantphos, NaI or an appropriate crown ether such as 18-crown-6-benzene, in the presence of an appropriate base such as NaH, Et_3N, pyridine, *N,N'*-dimethylethylenediamine, Na_2CO_3, K_2CO_3, K_3PO_4, Cs_2CO_3, *t*-BuONa or *t*-BuOK (or a mixture of bases, optionally in the presence of 4Å molecular sieves), in a suitable solvent (e.g. dichloromethane, dioxane, toluene, ethanol, isopropanol, dimethylformamide, ethylene glycol, ethylene glycol dimethyl ether, water, dimethylsulfoxide, acetonitrile, dimethylacetamide, *N*-methylpyrrolidinone, tetrahydrofuran or a mixture thereof). This reaction may be carried out at room temperature or above (e.g. at a high temperature, such as the reflux temperature of the solvent system that is employed);

(ii) for compounds of formula I wherein Y represents $-NR^aC(O)-[CR^xR^y]_m-$, reaction of a compound of formula II as defined above, with a compound of formula IV,

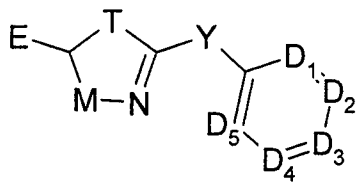


IV

wherein J is -OH, -Br or -Cl and m, R^x, R^y and D_1 to D_5 are as hereinbefore defined, for example under standard coupling reaction conditions. For example, when J is –Br or -Cl, in the presence of a suitable solvent (e.g. tetrahydrofuran, pyridine, toluene, dichloromethane, chloroform, acetonitrile or dimethylformamide), in the presence of a suitable base (e.g. triethylamine, Hunig's base, pyridine) and at an appropriate temperature (e.g. -20°C to 100°C). For example, when J is -OH, in the presence of a suitable coupling reagent (e.g. 1,1'-carbonyldiimidazole, *N,N'*-dicyclohexylcarbodiimide,

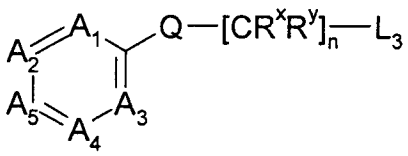
1-(3-dimethylamino-propyl)-3-ethylcarbodiimide (or hydrochloride thereof), *N,N'*-disuccinimidyl carbonate, benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate, 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluoro-phosphate, benzotriazol-1-yloxytris-pyrrolidinophosphonium hexafluorophosphate, bromo-tris-pyrrolidinophosponium hexafluoro-phosphate, 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetra-fluorocarbonate) or 1-cyclohexylcarbodiimide-3-propyloxymethyl polystyrene, a suitable base (e.g. sodium hydride, sodium bicarbonate, potassium carbonate, pyrrolidinopyridine, pyridine, triethylamine, tributylamine, trimethylamine, dimethylaminopyridine, diisopropylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene, sodium hydroxide, *N*-ethyldiisopropylamine, *N*-(methylpolystyrene)-4-(methylamino)pyridine, potassium bis(trimethylsilyl)-amide, sodium bis(trimethylsilyl)amide, potassium *tert*-butoxide, lithium diisopropylamide, lithium 2,2,6,6-tetramethylpiperidine or mixtures thereof) and an appropriate solvent (e.g. tetrahydrofuran, pyridine, toluene, dichloromethane, chloroform, acetonitrile or dimethylformamide);

(iii) for compounds of formula I wherein Z is a bond, reaction of a compound of formula V,



V

wherein E, M, T, Y and D_1 to D_5 are as hereinbefore defined, with a compound of formula VI,

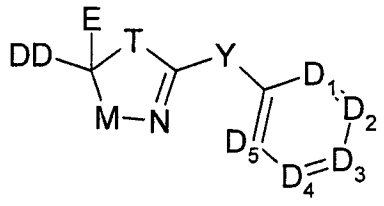


VI

wherein A_1 to A_5, Q, R^x, R^y and n are as hereinbefore defined and L_3 represents a suitable leaving group such as halo (e.g. chloro, bromo), under reaction conditions known to those skilled in the art, for example in the presence of a suitable base (e.g. NaH, NaOAc, nBuLi), in the presence of a suitable solvent (e.g. THF, diethyl ether,

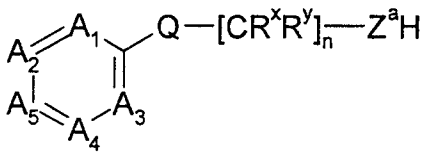
hexanes, toluene) and from reduced to elevated temperature (e.g. from -70°C to 150°C);

(iv) for compounds of formula I wherein X is Q-[CR^xR^y]$_n$-Z and Z represents O or S, reaction of a compound of formula VII,



VII

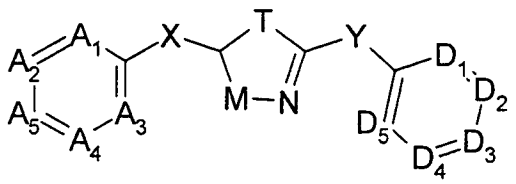
wherein E, M, T, Y and D_1 to D_5 are as hereinbefore defined and DD represents halo (e.g. chloro, bromo, iodo), with a compound of formula VIII,



VIII

wherein A_1 to A_5, Q, R^x, R^y and n are as hereinbefore defined and Z^a represents O or S, under reaction conditions known to those skilled in the art, for example in the presence of a suitable base (e.g. NaH, NaOAc, NaOH, NaOMe, NaOEt), in a suitable solvent (e.g. THF, diethylether, methanol, ethanol) and from reduced to elevated temperature (e.g. from -70°C to 150°C);

(v) for compounds of formula I wherein E is C_{1-6} alkyl optionally substituted by one or more halo atoms, reaction of a compound of formula IX,



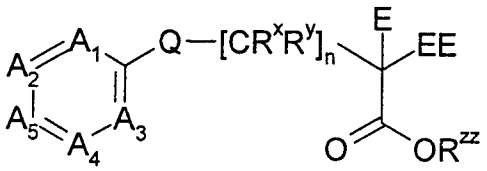
IX

wherein A_1 to A_5, M, X, T, Y and D_1 to D_5 are as hereinbefore defined, with a compound of formula X,

E^a-L_4 X

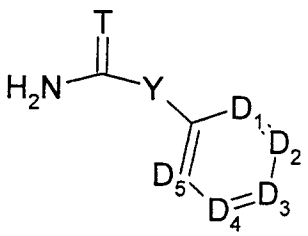
wherein E^a represents C_{1-6} alkyl optionally substituted by one or more halo atoms and L_4 represents a suitable leaving group such as halo (e.g. iodo), under reaction conditions known to those skilled in the art, e.g. such as those described in process (iv) above;

(vi) for compounds of formula I wherein Z is a bond and M is -C(O)-, reaction of a compound of formula XI,



XI

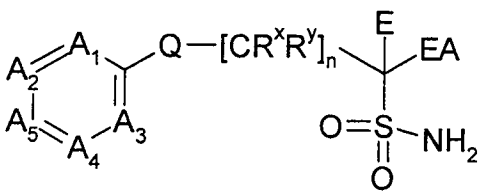
wherein A_1 to A_5, Q, R^x, R^y, n, and E are as hereinbefore defined, EE represents halo (e.g. chloro, bromo, iodo) and R^{zz} represents C_{1-4} alkyl, with a compound of formula XII,



XII

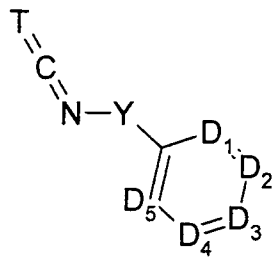
wherein T, Y and D_1 to D_5 are as hereinbefore defined, under reaction conditions known to those skilled in the art, e.g. in an appropriate solvent (e.g. toluene, xylenes, DCM, chloroform), optionally in the presence of an base (e.g. pyridine, Hunig's base, triethylamine) and at reduced to elevated temperatures (e.g. from 0°C to 140°C);

(vii) for compounds of formula I wherein Z is a bond and M is $-S(O)_2-$, reaction of a compound of formula XIII,



XIII

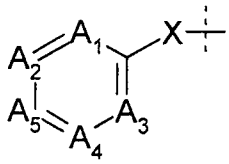
wherein A_1 to A_5, Q, n, R^x, R^y, and E are as hereinbefore defined and EA represents halo (e.g. chloro, bromo, iodo), with a compound of formula XIV,



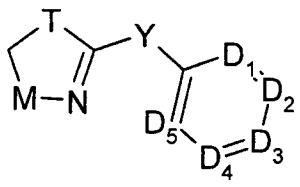
XIV

wherein T, Y and D_1 to D_5 are as hereinbefore defined, under reaction conditions known to those skilled in the art, e.g. in an appropriate solvent (e.g. toluene, xylenes, DCM, chloroform, acetonitrile), optionally in the presence of a base (e.g. pyridine, Hunig's base, triethylamine, potassium carbonate) and at reduced to elevated temperatures (e.g. from 0°C to 140°C); or

(viii) for compounds of formula I wherein Q and Z are both bonds, R^x and R^y both represent H on each occasion when used herein, and E is the same as the group:

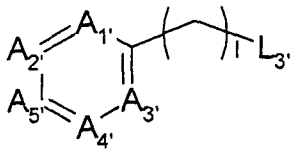


(i.e. E represents a C_{1-3} alkyl group substituted by an aryl or a six-membered heteroaryl group (containing one or two nitrogen atoms), which two groups may be optionally substituted by one or more -R^c groups that correspond to R^1 to R^5), reaction of a compound of formula XIVa,



XIVa

wherein M, T, Y and D_1 to D_5 are as hereinbefore defined, with a compound of formula XIVb,

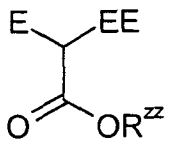


XIVb

wherein I represents 1 to 3, $L_{3'}$ represents a suitable leaving group such as halo (e.g. chloro, bromo) and $A_{1'}$ to $A_{5'}$ respectively represent $C(R^{1'})$, $C(R^{2'})$, $C(R^{3'})$, $C(R^{4'})$ and $C(R^{5'})$, or, alternatively, up to two of A_1 to A_5 may independently represent N, wherein $R^{1'}$ to $R^{5'}$ independently represent H, halo, $-R^7$, $-CF_3$, -CN, $-NO_2$, $-C(O)R^7$, $-C(O)OR^7$, $-N(R^{7a})R^{7b}$, $-N(R^7)_3^+$, $-SR^7$, $-OR^7$, $-NH(O)R^7$ or $-SO_3R^7$, or any two of $R^{1'}$ to $R^{5'}$ which are adjacent to each other are optionally linked to form, along with two atoms of the essential benzene ring in the compound of formula I, an aromatic or non-aromatic 3- to 8-membered ring, optionally containing 1 to 3 heteroatoms selected from O, S and N, which ring is itself optionally substituted by one or more substituents selected from halo, $-R^7$, $-OR^7$ and =O, and R^7, R^{7a} and R^{7b} are as defined hereinbefore, under reaction conditions known to those skilled in the art, for example as described in process (iii) above.

Compounds of formula XI may be prepared by:

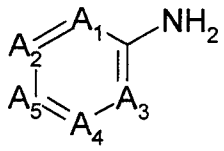
(a) reaction of a compound of formula XV,



XV

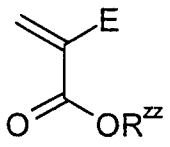
wherein E, EE and R^{zz} are as hereinbefore defined, with a compound of formula VI as hereinbefore defined, under reaction conditions known to those skilled in the art, for example in the presence of a suitable base (e.g. lithium diisopropylamide, sodium methoxide, sodium exthoxide), in a suitable solvent (e.g. methanol, ethanol, THF) and from reduced to elevated temperature (e.g. from -70°C to 100°C); and

(b) for compounds of formula XI wherein $Q\text{-}[CR^xR^y]_n$ is $-CH_2-$, reaction of a compound of formula XVI,



XVI

wherein A_1 to A_5 are as hereinbefore defined, with sodium nitrite, under reaction conditions known to those skilled in the art, for example, in the presence of a suitable acid (e.g. hydrochloric acid, hydrobromic acid, hydroiodic acid), a suitable solvent (e.g. acetone) and from reduced to elevated temperature (e.g. from -20°C to 50°C), followed by reaction of the resulting diazonium salt intermediate with a compound of formula XVII,

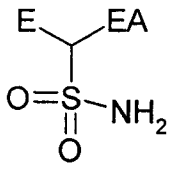


XVII

wherein E and R^{zz} are as hereinbefore defined, under reaction conditions known to those skilled in the art, for example in a suitable solvent (e.g. acetone) and in the presence of a suitable metal salt (e.g. CuCl, CuBr, CuI) and from reduced to elevated temperature (e.g. from -70°C to 50°C).

Compounds of formula XIII may be prepared by:

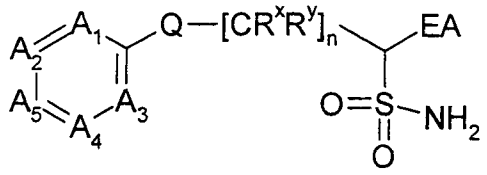
(aa) reaction of a compound of formula XVIII,



XVIII

wherein E and EA are as hereinbefore defined, with a compound of formula VI as hereinbefore defined, under reaction conditions known to those skilled in the art, e.g. such as those described in process (a) above;

(bb) reaction of a compound of formula XIX,



XIX

wherein A_1 to A_5, Q, R^x, R^y, n, and EA are as hereinbefore defined, with a compound of formula X as hereinbefore defined, under reaction conditions known to those skilled in the art, e.g. such as those described in process (a) above.

Compounds of formula XIVa or, more preferably, II, V, VII, IX, XIX may be prepared by synthetic methods analogous to those described hereinbefore.

Compounds of formulae XIVb or, more preferably, III, IV, VI, VIII, X, XII, XIV, XV, XVI, XVII and XVIII are either commercially available, are known in the literature, or may be obtained either by analogy with the processes described herein (or processes described in references contained herein), or by conventional synthetic procedures, in accordance with standard techniques, from available starting materials using appropriate reagents and reaction conditions.

Substituents, such as R_1, R_2, R_3 and R_4 in final compounds of formula I (or precursors thereto and other relevant intermediates) may be modified one or more times, after or during the processes described above by way of methods that are well known to those skilled in the art. Examples of such methods include substitutions, reductions (e.g. carbonyl bond reductions in the presence of suitable and, if necessary, chemoselective, reducing agents such as $LiBH_4$ or $NaBH_4$), oxidations, alkylations, acylations, hydrolyses, esterifications, and etherifications. The precursor groups can be changed to a different such group, or to the groups defined in formula I, at any time during the reaction sequence.

Compounds of formula I may be isolated from their reaction mixtures using conventional techniques.

It will be appreciated by those skilled in the art that, in the processes described above and hereinafter, the functional groups of intermediate compounds may need to be protected by protecting groups.

The protection and deprotection of functional groups may take place before or after a reaction in the above-mentioned schemes.

Protecting groups may be removed in accordance with techniques that are well known to those skilled in the art and as described hereinafter. For example, protected compounds/intermediates described herein may be converted chemically to unprotected compounds using standard deprotection techniques.

The type of chemistry involved will dictate the need, and type, of protecting groups as well as the sequence for accomplishing the synthesis.

The use of protecting groups is fully described in "*Protective Groups in Organic Chemistry*", edited by J W F McOmie, Plenum Press (1973), and "*Protective Groups in Organic Synthesis*", 3rd edition, T.W. Greene & P.G.M. Wutz, Wiley-Interscience (1999).

As used herein, the term "functional groups" means, in the case of unprotected functional groups, hydroxy-, thiolo-, aminofunction, carboxylic acid and, in the case of protected functional groups, lower alkoxy, N-, O-, S- acetyl, carboxylic acid ester.

Medical and Pharmaceutical Uses

Compounds of formula I are indicated as pharmaceuticals. According to a further aspect of the invention there is provided a compound of formula I, or a pharmaceutically-acceptable salt or solvate, or a pharmaceutically functional derivative thereof, for use as a pharmaceutical.

Advantageously, compounds of formula I may be AMPK agonists, i.e. they may activate AMPK. By 'activate AMPK', we mean that the steady state level of phosphorylation of the Thr-172 moiety of the AMPK-α subunit is increased compared to the steady state level of phosphorylation in the absence of the agonist. Alternatively, or in addition, we mean that there is a higher steady state level of phosphorylation of any other proteins downstream of AMPK, such as acetyl-CoA carboxylase (ACC).

As the compounds of formula I may be AMPK activators, they may therefore be useful in the treatment of diseases such as those described herein, especially cancer.

Compounds of formula I may reduce the rate of cell proliferation when tested in an assay using a human breast cancer cell line (e.g. MDA-MB-231). The compounds may thus possess a beneficial inhibitory effect on the ability of tumors of this type, and of cancers generally, to survive. Compounds of formula I may also reduce the rate of cell proliferation when tested in other cancer cells lines such as MCF-7, PC-3, Jurkat, Skov-3, HL60, MV4-11, HT-29, K562, MDA-MB231, HCT116wt, HCT116P53-/-, A-549, DU-145, LOVO, HCT-116 and PANC-1.

Compounds of formula I are therefore indicated for use in the treatment of cancer.

According to a further aspect of the invention, there is provided the use of a compound of formula I, or a pharmaceutically-acceptable salt or solvate, or a pharmaceutically functional derivative thereof, for the manufacture of a medicament for the treatment of cancer.

The compounds of formula I may be useful in the treatment of both primary and metastatic cancers.

The term "cancer" will be understood by those skilled in the art to include one or more diseases in the class of disorders that is characterized by uncontrolled division of cells and the ability of these cells to invade other tissues, either by direct growth into adjacent tissue through invasion, proliferation or by implantation into distant sites by metastasis.

In a preferred embodiment, compounds of formula I are capable of inhibiting the proliferation of cancer cells. By "proliferation" we include an increase in the number and/or size of cancer cells.

Alternatively, or preferably in addition, compounds of formula I are capable of inhibiting metastasis of cancer cells.

By "metastasis" we mean the movement or migration (*e.g.* invasiveness) of cancer cells from a primary tumor site in the body of a subject to one or more other areas within the subject's body (where the cells can then form secondary tumors). Thus, in one embodiment the invention provides compounds and methods for inhibiting, in whole or in part, the formation of secondary tumors in a subject with cancer. It will be appreciated by skilled persons that the effect of a compound of formula I on "metastasis" is distinct from

any effect such a compound may or may not have on cancer cell proliferation.

Advantageously, compounds of formula I may be capable of inhibiting the proliferation and/or metastasis of cancer cells selectively.

By "selectively" we mean that the combination product inhibits the proliferation and/or metastasis of cancer cells to a greater extent than it modulates the function (e.g. proliferation) of non-cancer cells. Preferably, the compound inhibits the proliferation and/or metastasis of cancer cells only.

Compounds of formula I may be suitable for use in the treatment of any cancer type, including all tumors (non-solid and, preferably, solid tumors). For example, the cancer cells may be selected from the group consisting of cancer cells of the breast, bile duct, brain, colon, stomach, reproductive organs, thyroid, hematopoietic system, lung and airways, skin, gallbladder, liver, nasopharynx, nerve cells, kidney, prostate, lymph glands and gastrointestinal tract. Preferably, the cancer is selected from the group of colon cancer (including colorectal adenomas), breast cancer (e.g. postmenopausal breast cancer), endometrial cancer, cancers of the hematopoietic system (e.g. leukemia, lymphoma, etc), thyroid cancer, kidney cancer, oesophageal adenocarcinoma, ovarian cancer, prostate cancer, pancreatic cancer, gallbladder cancer, liver cancer and cervical cancer. More preferably, the cancer is selected from the group of colon, prostate and, particularly, breast cancer. Where the cancer is a non-solid tumor, it is preferably a hematopoietic tumor such as a leukemia (e.g. Acute Myelogenous Leukemia (AML), Chronic Myelogenous Leukemia (CML), Acute Lymphocytic Leukemia (ALL), Chronic Lymphocytic Leukemia (CLL).

Preferably, the cancer cells are breast cancer cells.

According to a further aspect of the invention there is provided a method of treatment of cancer, which method comprises the administration of an effective amount of a compound of formula I, or a pharmaceutically-acceptable salt or solvate, or a pharmaceutically functional derivative thereof, to a patient in need of such treatment.

Compounds of formula I may also be of use in the treatment of a disorder or condition ameliorated by the activation of AMPK.

According to a further aspect of the invention, there is provided the use of a compound of formula I, or a pharmaceutically-acceptable salt or solvate, or a pharmaceutically functional derivative thereof, for the manufacture of a medicament for the treatment of a disorder or condition ameliorated by the activation of AMPK.

The terms "disorder or condition ameliorated by the activation of AMPK" will be understood by those skilled in the art to include, in addition to cancer, diabetes, hyperinsulinemia and associated conditions, a condition/disorder where fibrosis plays a role, sexual dysfunction, osteoporosis and neurodegenerative diseases.

Compounds of formula I may thus also be indicated for use in the treatment of a disorder or a condition caused by, linked to, or contributed to by, hyperinsulinemia.

The terms "disorder or condition caused by, linked to, or contributed to by, hyperinsulinemia" or "treatment of hyperinsulinemia or an associated condition" will be understood by those skilled in the art to include hyperinsulinemia and associated conditions, such as type 2 diabetes, glucose intolerance, insulin resistance, metabolic syndrome, dyslipidemia, hyperinsulinism in childhood, hypercholesterolemia, high blood pressure, obesity, fatty liver conditions, diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, cardiovascular disease, atherosclerosis, cerebrovascular conditions such as stroke, systemic lupus erythematosus, neurodegenerative diseases such as Alzheimer's disease, and polycystic ovary syndrome. Other disease states include progressive renal disease such as chronic renal failure. Preferred disorders include hyperinsulinemia and, particularly, type 2 diabetes.

Certain compounds of formula I may also have the additional advantage that they exhibit partial agonist activity and may therefore be useful in conditions, such as late type 2 diabetes, in which stimulation of the production of insulin is required. By "agonist activity", we include direct and indirect-acting agonists.

According to a further aspect of the invention there is provided a method of treatment of a disorder or condition ameliorated by the activation of AMPK, which method comprises the administration of an effective amount of a compound of formula I, or a pharmaceutically-acceptable salt or solvate, or a pharmaceutically functional derivative thereof, to a patient in need of such treatment.

Compounds of formula I may thus also be of use in the treatment of a condition/disorder where fibrosis plays a role. Compounds of formula I may also be useful in the treatment of sexual dysfunction (e.g. the treatment of erectile dysfunction).

A condition/disorder where fibrosis plays a role includes (but is not limited to) scar healing, keloids, scleroderma, pulmonary fibrosis (including idiopathic pulmonary fibrosis), nephrogenic systemic fibrosis, and cardiovascular fibrosis (including endomyocardial fibrosis), systemic sclerosis, liver cirrhosis, eye macular degeneration, retinal and vitreal retinopathy, Crohn's/inflammatory bowel disease, post surgical scar tissue formation, radiation and chemotherapeutic-drug induced fibrosis, and cardiovascular fibrosis.

Compounds of formula I may thus also be of use in the treatment of osteoporosis.

Compounds of formula I may thus also be of use in the treatment of inflammation.

Compounds of formula I may thus also be of use in the treatment of sexual dysfunction.

Compounds of formula I may thus also be of use in the treatment of heart failure.

Compounds of formula I may also be of use in the treatment of lung disease.

Compounds of formula I may also be of use in the treatment of obesity.

Compounds of formula I may also be of use in the treatment of dry-type age-related macular degeneration.

Compounds of formula I may also be of use as an agent for cardioprotection.

Compounds of formula I may thus also be of use in the treatment of neurodegenerative diseases (e.g. Alzheimer´s disease, Parkinson´s disease and Huntington´s disease, amyotrophic lateral sclerosis, polyglutamine disorders, such as spinal and bulbar muscular atrophy (SBMA), dentatorubral and pallidoluysian atrophy (DRPLA), and a number of spinocerebellar ataxias (SCA)).

For the avoidance of doubt, in the context of the present invention, the terms "treatment",

"therapy" and "therapy method" include the therapeutic, or palliative, treatment of patients in need of, as well as the prophylactic treatment and/or diagnosis of patients which are susceptible to, the relevant disease states.

"Patients" include mammalian (including human) patients.

The term "effective amount" refers to an amount of a compound, which confers a therapeutic effect on the treated patient (e.g. sufficient to treat or prevent the disease). The effect may be objective (i.e. measurable by some test or marker) or subjective (i.e. the subject gives an indication of or feels an effect).

In accordance with the invention, compounds of formula I may be administered alone, but are preferably administered orally, intravenously, intramuscularly, cutaneously, subcutaneously, transmucosally (e.g. sublingually or buccally), rectally, transdermally, nasally, pulmonarily (e.g. tracheally or bronchially), topically, by any other parenteral route, in the form of a pharmaceutical preparation comprising the compound in a pharmaceutically acceptable dosage form. Preferred modes of delivery include oral, intravenous, cutaneous or subcutaneous, nasal, intramuscular, or intraperitoneal delivery.

Compounds of formula I will generally be administered as a pharmaceutical formulation in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier, which may be selected with due regard to the intended route of administration and standard pharmaceutical practice. Such pharmaceutically acceptable carriers may be chemically inert to the active compounds and may have no detrimental side effects or toxicity under the conditions of use. Suitable pharmaceutical formulations may be found in, for example, Remington *The Science and Practice of Pharmacy*, 19th ed., Mack Printing Company, Easton, Pennsylvania (1995). For parenteral administration, a parenterally acceptable aqueous solution may be employed, which is pyrogen free and has requisite pH, isotonicity, and stability. Suitable solutions will be well known to the skilled person, with numerous methods being described in the literature. A brief review of methods of drug delivery may also be found in e.g. Langer, *Science* **249**, 1527 (1990).

Otherwise, the preparation of suitable formulations may be achieved non-inventively by the skilled person using routine techniques and/or in accordance with standard and/or accepted pharmaceutical practice.

Another aspect of the present invention includes a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I, or a pharmaceutically-acceptable salt or solvate, or a pharmaceutically functional derivative thereof, in combination with a pharmaceutically acceptable excipient, such as an adjuvant, diluent or carrier.

The amount of compound of formula I in the formulation will depend on the severity of the condition, and on the patient, to be treated, as well as the compound(s) which is/are employed, but may be determined non-inventively by the skilled person.

Depending on the disorder, and the patient, to be treated, as well as the route of administration, compounds of formula I may be administered at varying therapeutically effective doses to a patient in need thereof.

However, the dose administered to a mammal, particularly a human, in the context of the present invention should be sufficient to effect a therapeutic response in the mammal over a reasonable timeframe. One skilled in the art will recognize that the selection of the exact dose and composition and the most appropriate delivery regimen will also be influenced by *inter alia* the pharmacological properties of the formulation, the nature and severity of the condition being treated, and the physical condition and mental acuity of the recipient, as well as the potency of the specific compound, the age, condition, body weight, sex and response of the patient to be treated, and the stage/severity of the disease.

Administration may be continuous or intermittent (e.g. by bolus injection). The dosage may also be determined by the timing and frequency of administration. In the case of oral or parenteral administration the dosage can vary from about 0.01 mg to about 1000 mg per day of a compound of formula I (or, if employed, a corresponding amount of a pharmaceutically acceptable salt or prodrug thereof).

In any event, the medical practitioner, or other skilled person, will be able to determine routinely the actual dosage, which will be most suitable for an individual patient. The above-mentioned dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

The compounds of formula I may be used or administered in combination with one or more additional drugs useful in the treatment of cancer, in combination therapy.

According to a further aspect of the invention, there is provided a combination product comprising:

(A) a compound of formula I; and

(B) another therapeutic agent useful in the treatment of cancer,

wherein each of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

Other therapeutic agents useful in the treatment of cancer include standard cancer therapies, such as cytostatica, irradiation and photodynamic therapy, among others known to the physician.

It is preferred that the other therapeutic agent is a cytostatic (such as a taxane (e.g. docetaxel and, particularly, paclitaxel) or preferably, a platin (e.g. cisplatin and carboplatin) or an anthracycline (e.g. doxorubicin)) or an angiogenesis inhibitor, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative of either of these. However, the other therapeutic agent may also be selected from:

(i) tamoxifen, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(ii) an aromatase inhibitor (i.e. a compound that blocks the production of estrogen from adrenal androgens *via* the aromatase pathway in peripheral tissues), or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof. Preferred AIs include anastrozole, letrozole and exemastane;

(iii) trastuzumab (Herceptin), or another antibody that is useful in the treatment of cancer, such as bevacizumab, cetuximab or panitumumab;

(iv) a tyrosine kinase inhibitor (i.e. a compound that blocks (or is capable of blocking), to a measurable degree, the autophosphorylation of tyrosine residues, thereby preventing activation of the intracellular signalling pathways in tumor cells), or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof. Preferred TKIs include inhibitors of the vascular endothelial growth factor (VEGF) family, and/or the HER-family of TKs, such as HER-1/Human Epidermal Growth Factor (EGFR; erbB1), HER3 (erbB3), HER4 (erbB4) and, more particularly, HER2 (erbB2). Preferred TKIs thus include imatinib,

gefitinib, erlotinib, canertinib, sunitinib, zactima, vatalanib, sorafenib, leflunomide and, particularly, lapatinib;

(v) a glitazone, such as troglitazone, pioglitazone and rosiglitazone, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(vi) a biguanide such as phenformin, buformin, or, most preferably, metformin, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(vii) a statin, such as fluvastatin, simvastatin, rosuvastatin, pravastatin, atorvastatin and, particularly, lovastatin, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(viii) an inhibitor of activity of the mammalian target of rapamycin (mTOR), such as rapamycin, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(ix) an oligomycin, such as oligomycin A, oligomycin B, oligomycin C, oligomycin D (rutamycin A), oligomycin E, oligomycin F, rutamycin B, 44-homooligomycin A and 44-homooligomycin B, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(x) AICAR (aminoimidazole carboxamide ribonucleotide), or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(xi) a peroxisome proliferator-activated receptor (PPAR) agonist (which also include thiazolidinediones), or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(xii) A-769662, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(xiii) D942 (5-(3-(4-(2-(4-Fluorophenyl)ethoxy)-phenyl)propyl)furan-2-carboxylic acid), or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(xiv) AM251 (a CB_1 receptor antagonist), or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(xv) a SIRT1 activator, such as resveratrol and SRT-1720 (N-[2-[3-(piperazin-1-ylmethyl)imidazo[2,1-b][1,3]thiazol-6-yl]phenyl]quinoxal-ine-2-carboxamide), or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof; and/or

(xvi) salidroside, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof.

By "agonist" we include direct and indirect-acting agonists.

It has recently been suggested in the literature (see, for example, *Mol. Cancer Ther.*, **5**, 430 (2006), *Cancer Res.*, **66**, 10269 (2006) and *Int. J. Cancer*, **118**, 773 (2006)) that the above mentioned compound classes (v) to (vii) may be used in the treatment of cancer, as described herein.

When the other therapeutic agent is (particularly) in category (i) or (ii) above, combination products according to the invention are particularly useful in the treatment of ER-positive cancers and/or early-stage breast cancers, for example in adjuvant therapy (i.e. reducing the risk of the cancer coming back after surgery), in neo-adjuvant therapy (before surgery, to shrink a large breast cancer so that a lumpectomy is possible), in the control of breast cancers that have come back after initial treatment, or in the control of breast cancers that cannot be removed when first diagnosed. Such combination products according to the invention are also particularly useful in the treatment of patients at a high risk of breast cancer.

When the other therapeutic agent is (particularly) in category (iii) or (iv) above, combination products according to the invention are particularly useful in the treatment of HER2-positive cancers.

Pharmaceutically-acceptable salts, solvates or pharmaceutically functional derivatives of any of the compounds listed in categories (i), (ii) and (iv) to (xvi) above are as described hereinbefore. In particular, when the other therapeutic agent is tamoxifen, preferred pharmaceutically-acceptable salts include those of citric acid, when the other therapeutic agent is imatinib, preferred pharmaceutically-acceptable salts include mesylate salts and when the other therapeutic agent is sunitinib, preferred pharmaceutically-acceptable salts include maleate salts.

Combination products as described herein provide for the administration of compound of formula I in conjunction with the other therapeutic agent, and may thus be presented either as separate formulations, wherein at least one of those formulations comprises compound of formula I, and at least one comprises the other therapeutic agent, or may be presented (i.e. formulated) as a combined preparation (i.e. presented as a single formulation including compound of formula I and the other therapeutic agent).

Thus, there is further provided:

(1) pharmaceutical formulations including a compound of formula I; another therapeutic agent useful in the treatment of cancer; and a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(2) kits of parts comprising components:

(a) a pharmaceutical formulation including a compound of formula I in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(b) a pharmaceutical formulation including another therapeutic agent useful in the treatment of cancer, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier,

which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

Components (a) and (b) of the kits of parts described herein may be administered simultaneously or sequentially.

According to a further aspect of the invention, there is provided a method of making a kit of parts as defined above, which method comprises bringing component (a), as defined above, into association with a component (b), as defined above, thus rendering the two components suitable for administration in conjunction with each other.

By bringing the two components "into association with" each other, we include that components (a) and (b) of the kit of parts may be:

(i) provided as separate formulations (i.e. independently of one another), which are subsequently brought together for use in conjunction with each other in combination therapy; or

(ii) packaged and presented together as separate components of a "combination pack" for use in conjunction with each other in combination therapy.

Thus, there is further provided a kit of parts comprising:

(I) one of components (a) and (b) as defined herein; together with

(II) instructions to use that component in conjunction with the other of the two

components.

The kits of parts described herein may comprise more than one formulation including an appropriate quantity/dose of compound of formula I, and/or more than one formulation including an appropriate quantity/dose of the other therapeutic agent, in order to provide for repeat dosing. If more than one formulation (comprising either active compound) is present, such formulations may be the same, or may be different in terms of the dose of either compound, chemical composition(s) and/or physical form(s).

With respect to the kits of parts as described herein, by "administration in conjunction with", we include that respective formulations comprising compound of formula I and the other therapeutic agent are administered, sequentially, separately and/or simultaneously, over the course of treatment of the relevant condition.

Thus, in respect of the combination product according to the invention, the term "administration in conjunction with" includes that the two components of the combination product (compound of formula I and the other therapeutic agent) are administered (optionally repeatedly), either together, or sufficiently closely in time, to enable a beneficial effect for the patient, that is greater, over the course of the treatment of the relevant condition, than if either a formulation comprising compound of formula I, or a formulation comprising the other therapeutic agent, are administered (optionally repeatedly) alone, in the absence of the other component, over the same course of treatment. Determination of whether a combination provides a greater beneficial effect in respect of, and over the course of treatment of, a particular condition will depend upon the condition to be treated or prevented, but may be achieved routinely by the skilled person.

Further, in the context of a kit of parts according to the invention, the term "in conjunction with" includes that one or other of the two formulations may be administered (optionally repeatedly) prior to, after, and/or at the same time as, administration with the other component. When used in this context, the terms "administered simultaneously" and "administered at the same time as" include that individual doses of compound of formula I and the other therapeutic agent are administered within 48 hours (e.g. 24 hours) of each other.

The compounds/combinations/methods/uses described herein may have the advantage

that, in the treatment of the conditions described herein, they may be more convenient for the physician and/or patient than, be more efficacious than, be less toxic than, have better selectivity, have a broader range of activity than, be more potent than, produce fewer side effects than, or may have other useful pharmacological properties over, similar compounds, combinations, methods (treatments) or uses known in the prior art for use in the treatment of those conditions or otherwise, for example over the compounds disclosed in international patent applications WO 2007/010273 and WO 2007/010281.

Further, such advantages may stem from the compounds of formula I being AMPK activators (e.g. especially where it is stated that the compounds described herein may have better selectivity, and may produce fewer side effects, e.g. gastrointestinal side effects).

Preferred, non-limiting examples which embody certain aspects of the invention will now be described, with reference to the following figures:

Figure 1, which shows the effect of the compound of Example 1 on AMPK phosphorylation. After starvation of PC3 cells in serum-free medium for 5 h, and 2.5, 5 and 10 μM of the compound of Example 1 was added and incubated for an additional 24 h. The Figure provides representative immunoblots of AMPK phosphorylation by the compound of Example 1. The compound of Example 1 stimulates AMPK phosphorylation in PC3 cells. (V.C. = vehicle control.)

Figure 2, which shows the effect of the compound of Example 1 on eEF2 phosphorylation. After starvation of PC3 cells in serum-free medium for 5 h, 10 μM of the compound of Example 1 was added and incubated for an additional 24 h. The Figure provides representative immunoblots of eEF2 phosphorylation by the compound of Example 1. The compound of Example 1 stimulates eEF2 phosphorylation in PC3 cells

Examples

The invention is illustrated by the following examples, in which the following abbreviations may be employed:

BrdU 5-bromo-2-deoxyuridine
nBuLi N-butyl lithium
DCM dichloromethane
DMF dimethylformamide
DMSO dimethylsulfoxide
ES electro spray
Et_2O diethyl ether
EtOAc ethyl acetate
EtOH ethanol
LC liquid chromatography
MeOH methanol
MS mass spectrometry
MTBE methyl *tert*-butyl ether
NMR nuclear magnetic resonance
THF tetrahydrofuran

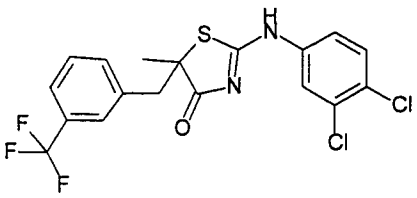
Where no preparative routes are included, the relevant intermediate is commercially available (e.g. from Chemical Diversity, San Diego, CA, USA or other available commercial sources).

General Procedures

LC-MS was performed on a Sciex API 150 LC/ES-MS equipped with an ACE 3 C8 column (30 x 3.0 mm) using a flow of 1 mL/min. Two gradient systems of acetonitrile in water (with 0.1% TFA) are used for elution: **A)** 5-100% under 10 min, then 2 min 100% isocratic or **B)** 90-100% under 2 min, then 2 min 100% isocratic. Direct inlet ES-MS was also performed on a Bruker Esquire LC/ES-MS. ^1H nuclear magnetic resonance was recorded on a Bruker Avance DRX 400 spectrometer at 400.01 MHz using residual solvent as internal standard.

Example 1

2-(3,4-Dichlorophenylamino)-5-methyl-5-(3-trifluoromethylbenzyl)-thiazol-4-one



Route A

(a)(i) 1-(3,4-Dichlorophenyl)-3-(4-methoxybenzyl)-thiourea

A solution of 4-methoxybenzyl amine (40 mmol) in THF (80 mL) was slowly added over about 5 min to a solution of 3,4-dichlorophenylisocyanate (40 mmol) in dry THF (170 mL). The mixture was stirred at room temperature for 10 min, then at reflux for about 2.5 h. The solvent was evaporated to give a white solid residue. The solid was dried on a high-vacuum pump for 2 days and 14.3 g (quantitative yield) of the product was obtained, which was used in step (b) without further purification.

(a)(ii) 2-Bromopropionic acid ethyl ester

1 M HCl in Et_2O (5 mL) was added to a solution of 2-bromopropionic acid (25 g) in EtOH (200 mL). The mixture was refluxed over night and the solvents were then evaporated to give a yellow oil, 20.4 g (approximately 75% yield).

1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 4.36 (q, *J*=7.00 Hz, 1 H) 4.24 (qd, *J*=7.16, 2.69 Hz, 2 H) 1.83 (d, *J*=7.08 Hz, 3 H) 1.31 (t, *J*=7.20 Hz, 3 H).

(b) 2-[(*E*)-3,4-Dichlorophenylimino]-3-(4-methoxy-benzyl)-5-methylthiazolidin-4-one

A solution of 2-bromopropionic acid ethyl ester (2 eqivalents; from step (a)(ii) above) in EtOH (50 mL) was added to a slurry of NaOAc (2.4 g) and 1-(3,4-dichloro-phenyl)-3-(4-methoxybenzyl)-thiourea (5 g; from step (a)(i) above) in EtOH (150 mL). The mixture was heated at 60 °C and stirred for one week. The solvent was then removed under reduced pressure and the solid was triturated twice with Et_2O to give 2-[(E)-3,4-dichloro-phenylimino]-3-(4-methoxy-benzyl)-5-methylthiazolidin-4-one as a yellow solid with >90% purity. The product was further purified flash column chromatography on silica gel using a gradient of 90:10 to 80:20 hexane/EtOAc to give the product as a yellow oil (2.17 g) after evaporation.

1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 7.41 – 7.45 (m, 2 H) 7.40 (d, *J*=8.30 Hz, 1

H) 7.07 (d, *J*=2.44 Hz, 1 H) 6.85 – 6.89 (m, 2 H) 6.81 (dd, *J*=8.30, 2.44 Hz, 1 H) 4.96 (d, *J*=13.92 Hz, 1 H) 4.90 (d, *J*=13.92 Hz, 1 H) 4.09 (q, *J*=7.32 Hz, 1 H) 3.81 (s, 3 H) 1.63 (d, *J*=7.32 Hz, 3 H)

(c) 2-[(*E*)-3,4-Dichlorophenylimino]-3-(4-methoxybenzyl)-5-methyl-5-(4-trifluoromethylbenzyl)-thiazolidin-4-one

A solution of 2-[(E)-3,4-Dichlorophenylimino]-3-(4-methoxybenzyl)-5-methylthiazolidin-4-one (1.15 g, from step (b) above) in dry THF (40 mL) was added to a slurry of NaH (150 mg) in dry THF (10 mL) under nitrogen giving a solution with a bright yellow color. After stirring at room temperature for 1 h, 1-bromomethyl-3-trifluoromethylbenzene (1 equivalent) was added and the reaction was stirred until LC-MS analysis indicated that the reaction was complete. The reaction was quenched by slow addition of few drops of H_2O. Another 50 mL H_2O was added, followed by about 100mL EtOAc. The phases were separated and the aq. phase was extracted using 3x EtOAc (100 mL). The combined organic phases were washed using 1x H_2O followed by 1x Brine (300 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure to afford the crude product as a yellow oil (1.9 g). The crude product was purified by flash column chromatography on silica using a gradient of 90:10 to 80:20 petrolium ether/EtOAc.

1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 7.48 (d, *J*=7.32 Hz, 1 H) 7.44 (s, 1 H) 7.35 (d, *J*=8.55 Hz, 1 H) 7.17 – 7.25 (m, 4 H) 6.87 (d, *J*=2.44 Hz, 1 H) 6.77 – 6.82 (m, 2 H) 6.58 (dd, *J*=8.42, 2.32 Hz, 1 H) 4.77 (d, *J*=14.16 Hz, 1 H) 4.66 (d, *J*=13.92 Hz, 1 H) 3.81 (s, 3 H) 3.35 (d, *J*=13.92 Hz, 1 H) 2.97 (d, *J*=13.67 Hz, 1 H) 1.73 (s, 3 H)

(d) 2-(3,4-Dichlorophenylamino)-5-methyl-5-(3-trifluoromethylbenzyl)-thiazol-4-one

2-[(E)-3,4-Dichlorophenylimino]-3-(4-methoxybenzyl)-5-methyl-5-(3-trifluoromethylbenzyl)-thiazolidin-4-one (from step (c) above) (180 mg) was heated in neat trifluoroacetic acid (approximately 5 mL) for about 3 h. Diethyl ether was added to the reaction mixture until good solubility was observed (25 mL). The organic phase was washed with 1M NaOH (3x 15 mL) and the combined alkaline washings were back-extracted once with diethyl ether (20 mL). The combined organic extracts were washed with 1x H_2O (20 mL) and 1x Brine (20 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 20-25% EtOAc in n-hexane) to yield 215 mg of product. HPLC shows approximately 95% purity.

1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 1.76 (s, 3 H) 3.03 (d, *J*=13.67 Hz, 1 H) 3.38 (d, *J*=13.67 Hz, 1 H) 6.70 (dd, *J*=8.55, 1.95 Hz, 1 H) 6.98 (d, *J*=1.71 Hz, 1 H) 7.39

(d,*J*=8.55 Hz, 1 H) 7.40 – 7.47 (m, 2 H) 7.51 (s, 1 H) 7.59 (d, *J*=7.57 Hz, 1 H) 8.77 (br. s., 1H (NH)).

Route B

(a) 2-Chloro-2-methyl-3-(3-trifluoromethylphenyl)-propionic acid methyl ester

3-Trifluoromethylphenylamine (30 mmol) was added to a mixture of HCl (15 mL) and HOAc (5 mL) which immediately produced a precipitate. The mixture was cooled to approximately -10°C (EtOH + dry ice) and $NaNO_2$ (33 mmol) dissolved in water (5.25 mL) was added dropwise while the temperature was maintained between -15°C and -5°C. The mixture was then stirred at a temperature between -10°C and -5°C for 45 min.

$CuCl_2$ and water (12 mL, green solution) were added to a solution of methyl methacrylate in acetone (100 mL). The (cold) diazonium salt solution (produced above) was added dropwise to the resulting solution. After addition of the diazonium salt solution was complete the reaction was stirred for 5 h at room temperature. HPLC-MS showed several peaks, one of the which corresponded to the expected product (m/z=281, MS pattern shows chlorine present). The reaction was put into the freezer overnight (16 h). The reaction was the following day by adding water (250 mL), which formed a two phase system. The mixture was extracted with $CHCl_3$ (3x50 mL) and the combined organic phases were washed with water (2x30 mL) and brine (30 mL), dried over $MgSO_4$ and the solvent removed under reduced pressure to give 4.636 g of a light brown liquid. Purification by flash chromatography (silica gel, 0-10% EtOAc in n-hexane) gave 2.798 g (33%) of a clear oil.

1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 7.53 - 7.58 (m, 1 H) 7.49 (s, 1 H) 7.44 (d, *J*=5.13 Hz, 2 H) 3.79 (s, 3 H) 3.39 (s, 2 H) 1.73 (s, 3 H).

(b) 2-(3,4-Dichlorophenylamino)-5-methyl-5-(3-trifluoromethylbenzyl)-thiazol-4-one

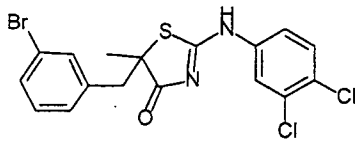
(3,4-Dichlorophenyl)-thiourea (160 mg) and 1,5-diazabicyclonon-5-ene (88 mg) were mixed in dioxane (5 mL) and stirred for 1 hour. 2-Chloro-2-methyl-3-(3-trifluoromethyl-phenyl)-propionic acid methyl ester (200 mg, from step (a) above) was added and the temperature raised to 80°C. The reaction was stirred for 72 hours at room temperature. The reaction mixture was then added to diethyl ether (100 mL) and water (50 mL) added to the resultant mixture. The organic phase was washed with 1 M Na_2CO_3 (2x50 mL), 1M phosphoric acid (2x50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give 274 mg of a crude oil. A precipitate formed upon addition of

heptane/EtOAc which was removed by filtration (thiourea, ~80 mg). The residue was purified by flash column chromatography (silica gel, 20% EtOAc in petroleum ether). The pure fractions were pooled and concentrated to yield 20 mg (46 mmol, 7%) of a light yellow oil. Purity: >90%, NMR in accordance with the product (see step (c) of Route A).

Example 2

The following compounds were prepared in a parallel synthesis approach in a small scale in accordance with Route A of Example 1. HPLC purity and/or NMR data is provided.

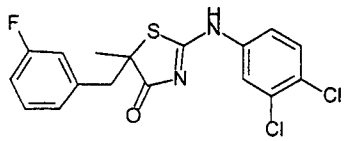
A) 2-(3,4-dichlorophenylamino)-5-methyl-5-(3-bromobenzyl)-thiazol-4-one



purity 96%,

1H NMR (500 MHz, Chloroform-*d*) δ ppm 7.46 (d, *J*=7.81 Hz, 1 H) 7.42 (s, 1 H) 7.40 - 7.42 (m, 1 H) 7.20 (t, *J*=7.81 Hz, 1 H) 7.14 - 7.17 (m, 1 H) 7.02 (d, *J*=1.71 Hz, 1 H) 6.75 (dd, *J*=8.30, 1.71 Hz, 1 H) 3.28 (d, *J*=13.67 Hz, 1 H) 2.95 (d, *J*=13.67 Hz, 1 H) 1.75 (s, 3 H);

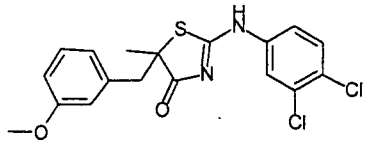
B) 2-(3,4-dichlorophenylamino)-5-methyl-5-(3-fluorobenzyl)-thiazol-4-one



purity 95%,

1H NMR (500 MHz, Chloroform-*d*) δ ppm 7.42 (d, *J*=8.55 Hz, 1 H) 7.29 (dt, *J*=8.06, 6.10 Hz, 1 H) 6.98 - 7.08 (m, 3 H) 6.96 (dd, *J*=9.64, 1.83 Hz, 1 H) 6.79 (dd, *J*=8.55, 1.95 Hz, 1 H) 3.30 (d, *J*=13.92 Hz, 1 H) 3.01 (d, *J*=13.92 Hz, 1 H) 1.73 (s, 3 H);

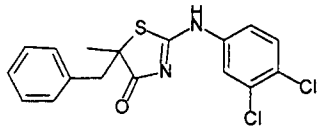
C) 2-(3,4-dichlorophenylamino)-5-methyl-5-(3-methoxybenzyl)-thiazol-4-one



purity 90%

1H NMR (500 MHz, Chloroform-*d*) δ ppm 7.41 (d, *J*=8.55 Hz, 1 H) 7.24 (t, *J*=7.93 Hz, 1 H) 7.07 (br. s., 1 H) 6.76 - 6.88 (m, 4 H) 3.79 (s, 3 H) 3.29 (d, *J*=13.67 Hz, 1 H) 3.00 (d, *J*=13.67 Hz, 1 H) 1.73 (s, 3 H);

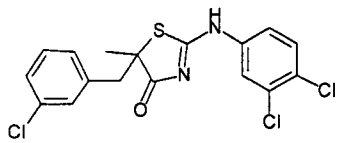
D) 2-(3,4-dichlorophenylamino)-5-methyl-5-(benzyl)-thiazol-4-one



purity 95%

1H NMR (500 MHz, Chloroform-*d*) δ ppm 7.42 (d, *J*=8.55 Hz, 1 H) 7.32 (d, *J*=2.20 Hz, 3 H) 7.19 - 7.25 (m, 2 H) 7.08 (s, 1 H) 6.83 (dd, *J*=8.55, 1.46 Hz, 1 H) 3.32 (d, *J*=13.92 Hz, 1 H) 3.03 (d, *J*=13.67 Hz, 1 H) 1.73 (s, 3 H)

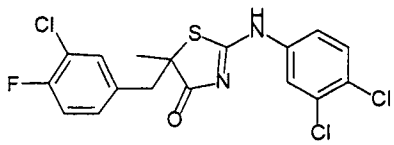
E) 2-(3,4-dichlorophenylamino)-5-methyl-5-(3-chlorobenzyl)-thiazol-4-one



purity 95%,

1H NMR (500 MHz, Chloroform-*d*) δ ppm 7.41 (d, *J*=8.55 Hz, 1 H) 7.28 - 7.32 (m, 1 H) 7.23 - 7.27 (m, 2 H) 7.11 (d, *J*=7.57 Hz, 1 H) 7.04 (s, 1 H) 6.78 (d, *J*=8.30 Hz, 1 H) 3.28 (d, *J*=13.92 Hz, 1 H) 2.97 (d, *J*=13.67 Hz, 1 H) 1.74 (s, 3 H);

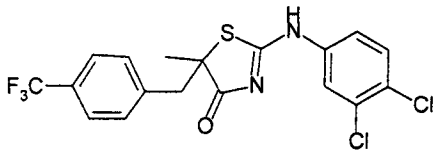
F) 2-(3,4-dichlorophenylamino)-5-methyl-5-(3-chloro-4-fluorobenzyl)-thiazol-4-one



purity 98%

1H NMR (500 MHz, Chloroform-*d*) δ ppm 7.40 (d, *J*=8.30 Hz, 1 H) 7.29 (d, *J*=7.08 Hz, 1 H) 7.08 (d, *J*=7.81 Hz, 2 H) 7.00 (d, *J*=1.95 Hz, 1 H) 6.73 (dd, *J*=8.55, 1.71 Hz, 1 H) 3.26 (d, 1 H) 2.92 (d, *J*=13.92 Hz, 1 H) 1.74 (s, 3 H);

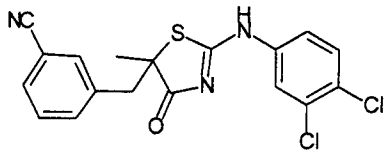
G) 2-(3,4-dichlorophenylamino)-5-methyl-5-(4-trifluoromethylbenzyl)-thiazol-4-one



purity 100%

1H NMR (500 MHz, Chloroform-*d*) δ ppm 7.57 (d, *J*=8.06 Hz, 2 H) 7.39 (d, *J*=8.55 Hz, 1 H) 7.34 (d, *J*=8.06 Hz, 2 H) 6.98 (d, *J*=1.95 Hz, 1 H) 6.72 (dd, *J*=8.67, 1.83 Hz, 1 H) 3.36 (d, *J*=13.67 Hz, 1 H) 3.06 (d, *J*=13.67 Hz, 1 H) 1.74 (s, 3 H);

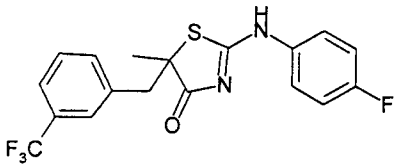
H) 3-[2-(3,4-dichlorophenylamino)-5-methyl-4-oxo-4,5-dihydrothiazol-5-ylmethyl]-benzonitrile



purity 98%,

1H NMR (500 MHz, Chloroform-*d*) δ ppm 8.04 (br. s., 1 H) 7.62 (d, *J*=7.08 Hz, 1 H) 7.53 (s, 1 H) 7.42 - 7.48 (m, 2 H) 7.41 (d, *J*=8.55 Hz, 1 H) 6.95 (d, *J*=1.95 Hz, 1 H) 6.70 (dd, *J*=8.67, 1.34 Hz, 1 H) 3.35 (d, *J*=13.92 Hz, 1 H) 3.01 (d, *J*=13.67 Hz, 1 H) 1.76 (s, 3H);

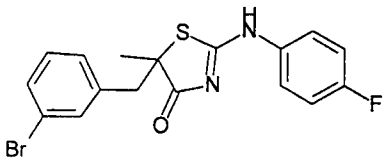
I) 2-(4-fluorophenylamino)-5-methyl-5-(3-trifluoromethylbenzyl)-thiazol-4-one



purity 95%,

1H NMR (500 MHz, Chloroform-*d*) δ ppm 7.52 - 7.58 (m, 1 H) 7.48 (br. s., 1 H) 7.37 - 7.43 (m, 2 H) 7.02 - 7.09 (m, 2 H) 6.94 - 7.00 (m, 2 H) 3.36 (d, *J*=13.92 Hz, 1 H) 3.03 (d, *J*=13.92 Hz, 1 H) 1.73 (s, 3H);

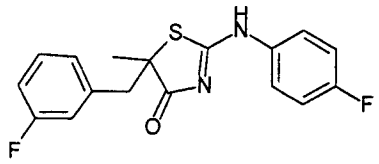
J) 2-(4-fluorophenylamino)-5-methyl-5-(3-bromobenzyl)-thiazol-4-one



purity 97%

1H NMR (500 MHz, Chloroform-*d*) δ ppm 7.43 (dt, *J*=7.05, 1.91 Hz, 1 H) 7.38 (t, *J*=1.46 Hz, 1 H) 7.15 (t, *J*=7.57 Hz, 1 H) 7.10 - 7.15 (m, 1 H) 7.05 - 7.12 (m, 4 H) 3.25 (d, 1 H) 2.96 (d, *J*=13.79 Hz, 1 H) 1.70 (s, 3 H);

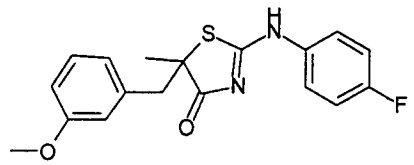
K) 2-(4-fluorophenylamino)-5-methyl-5-(3-fluorobenzyl)-thiazol-4-one



purity 100%,

1H NMR (500 MHz, Chloroform-*d*) δ ppm 7.23 - 7.28 (m, 2 H) 7.02 - 7.09 (m, 2 H) 6.92 - 7.02 (m, 4 H) 3.28 (d, *J*=13.67 Hz, 1 H) 3.00 (d, *J*=13.92 Hz, 1 H) 1.70 (s, 3 H);

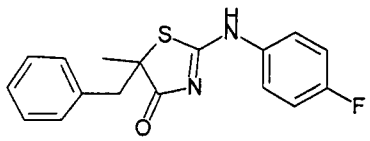
L) 2-(4-fluorophenylamino)-5-methyl-5-(3-methoxybenzyl)-thiazol-4-one



purity 98%,

1H NMR (500 MHz, Chloroform-*d*) δ ppm 7.22 (t, *J*=7.93 Hz, 1 H) 7.05 - 7.15 (m, 4 H) 6.84 (ddd, *J*=8.30, 2.56, 0.85 Hz, 1 H) 6.79 (d, *J*=7.57 Hz, 1 H) 6.73 - 6.76 (m, 1 H) 3.76 (s, 3 H) 3.27 (d, *J*=13.79 Hz, 1 H) 3.02 (d, *J*=13.79 Hz, 1 H) 1.71 (s, 3 H);

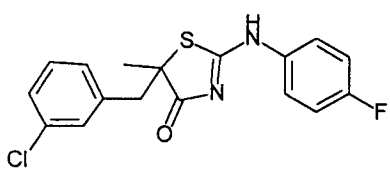
M) 2-(4-fluorophenylamino)-5-methyl-5-(benzyl)-thiazol-4-one



purity 99%,

1H NMR (500 MHz, Chloroform-*d*) δ ppm 7.29 - 7.35 (m, 3 H) 7.17 - 7.22 (m, 2 H) 7.09 - 7.15 (m, 4 H) 3.33 (d, *J*=13.92 Hz, 1 H) 3.06 (d, *J*=13.92 Hz, 1 H) 1.74 (s, 3 H);

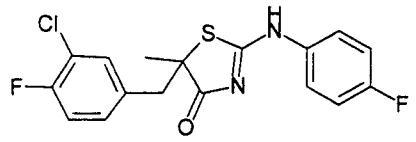
N) 2-(4-fluorophenylamino)-5-methyl-5-(3-chlorobenzyl)-thiazol-4-one



purity 99%,

1H NMR (500 MHz, Chloroform-*d*) δ ppm 7.28 (ddd, *J*=8.18, 1.83, 1.10 Hz, 1 H) 7.22 (t, *J*=1.59 Hz, 1 H) 7.22 (t, *J*=7.73 Hz, 1 H) 7.06 - 7.13 (m, 5 H) 3.26 (d, *J*=13.79 Hz, 1 H) 2.99 (d, *J*=13.79 Hz, 1 H) 1.71 (s, 3 H);

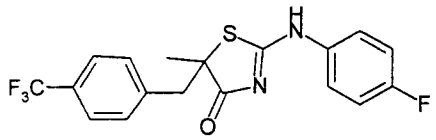
O) 2-(4-fluorophenylamino)-5-methyl-5-(3-chloro-4-fluorobenzyl)-thiazol-4-one



purity 100%,

1H NMR (500 MHz, Chloroform-*d*) δ ppm 7.27 (dd, *J*=6.84, 1.83 Hz, 1 H) 7.04 - 7.11 (m, 5 H) 7.04 (t, *J*=8.42 Hz, 1 H) 3.22 (d, *J*=14.04 Hz, 1 H) 2.94 (d, *J*=14.04 Hz, 1 H) 1.70 (s, 3 H);

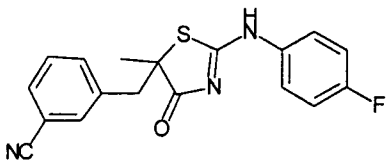
P) 2-(4-fluorophenylamino)-5-methyl-5-(4-trifluoromethylbenzyl)-thiazol-4-one



purity 99%,

1H NMR (500 MHz, Chloroform-*d*) δ ppm 7.54 (d, *J*=8.30 Hz, 2 H) 7.33 (d, *J*=8.06 Hz, 2 H) 7.02 - 7.10 (m, 2 H) 6.92 - 7.00 (m, 2 H) 3.33 (d, *J*=13.92 Hz, 1 H) 3.07 (d, *J*=13.67 Hz, 1 H) 1.70 (s, 3 H);

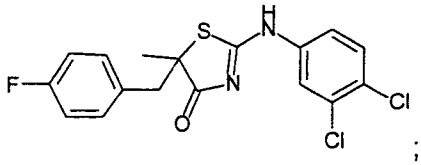
Q) 3-[2-4-fluorophenylamino]-5-methyl-4-oxo-4,5-dihydrothiazol-5-ylmethyl]-benzonitrile



purity 95%,

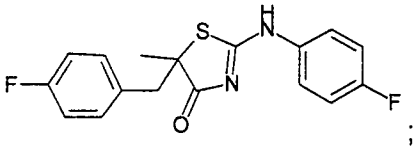
1H NMR (500 MHz, Chloroform-*d*) δ ppm 7.60 - 7.66 (m, 1 H) 7.50 (br. s., 1 H) 7.42 - 7.49 (m, 2 H) 7.07 - 7.19 (m, 4 H) 3.37 (d, *J*=14.16 Hz, 1 H) 3.08 (d, *J*=14.16 Hz, 1 H) 1.77 (s, 3 H);

R) 2-(3,4-dichlorophenylamino)-5-methyl-5-(4-fluorobenzyl)-thiazol-4-one



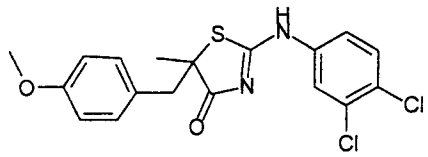
;

S) 2-(4-fluorophenylamino)-5-methyl-5-(4-fluorobenzyl)-thiazol-4-one



;

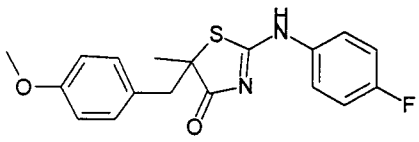
T) 2-(3,4-dichlorophenylamino)-5-methyl-5-(4-methoxybenzyl)-thiazol-4-one



purity 97%,

1H NMR (500 MHz, Chloroform-*d*) δ ppm 7.41 (d, *J*=8.55 Hz, 1 H) 7.10 - 7.16 (m, 2 H) 7.06 (d, *J*=1.95 Hz, 1 H) 6.76 - 6.87 (m, 3 H) 3.80 (s, 3 H) 3.25 (d, *J*=13.92 Hz, 1 H) 2.95 (d, *J*=13.92 Hz, 1 H) 1.71 (s, 3 H);

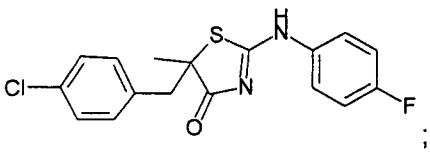
U) 2-(4-fluorophenylamino)-5-methyl-5-(4-methoxybenzyl)-thiazol-4-one



purity 99%,

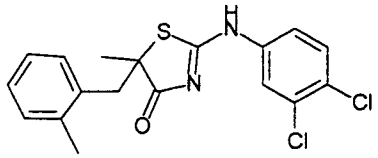
1H NMR (500 MHz, Chloroform-*d*) δ ppm 7.10 - 7.16 (m, 2 H) 7.05 - 7.10 (m, 4 H) 6.79 - 6.85 (m, 2 H) 3.79 (s, 3 H) 3.23 (d, *J*=13.92 Hz, 1 H) 2.98 (d, *J*=14.04 Hz, 1 H) 1.69 (s, 3 H);

V) 2-(4-fluorophenylamino)-5-methyl-5-(4-chlorobenzyl)-thiazol-4-one,



;

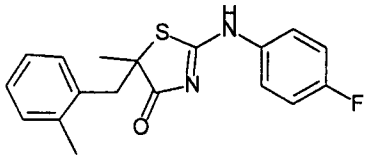
W) 2-(3,4-dichlorophenylamino)-5-methyl-5-(2-methylbenzyl)-thiazol-4-one



purity 98%,

1H NMR (500 MHz, Chloroform-*d*) δ ppm 7.37 (d, *J*=8.55 Hz, 1 H) 7.16 - 7.24 (m, 3 H) 7.10 - 7.17 (m, 1 H) 6.92 (br. s., 1 H) 6.71 (d, *J*=7.32 Hz, 1 H) 3.31 (d, *J*=14.16 Hz, 1 H) 3.17 (d, *J*=14.16 Hz, 1 H) 2.34 (s, 3 H) 1.75 (s, 3 H);

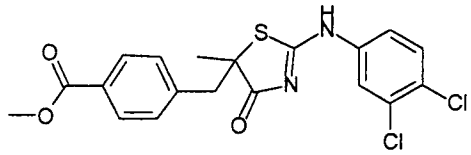
X) 2-(4-fluorophenylamino)-5-methyl-5-(2-methylbenzyl)-thiazol-4-one



purity 97%,

1H NMR (500 MHz, Chloroform-*d*) δ ppm 7.15 - 7.22 (m, 3 H) 7.11 - 7.15 (m, 1 H) 7.00 - 7.10 (m, 4 H) 3.29 (d, *J*=14.28 Hz, 1 H) 3.21 (d, *J*=14.40 Hz, 1 H) 2.32 (s, 3 H) 1.73 (s, 3 H);

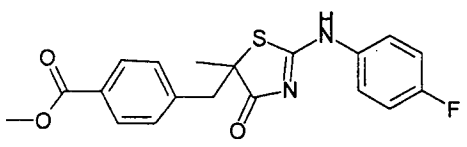
Y) 4-[2-(3,4-dichlorophenylamino)-5-methyl-4-oxo-4,5-dihydrothiazol-5-ylmethyl]-benzoic acid methyl ester



purity 98%,

1H NMR (500 MHz, Chloroform-*d*) δ ppm 7.98 (dd, *J*=7.08, 1.71 Hz, 1 H) 7.93 (br, s., 1 H) 7.35 - 7.44 (m, 3 H) 6.97 (d, *J*=1.71 Hz, 1 H) 6.73 (dd, *J*=8.42, 1.83 Hz, 1 H) 3.92 (s, 3 H) 3.35 (d, *J*=13.67 Hz, 1 H) 3.04 (d, *J*=13.92 Hz, 1 H) 1.74 (s, 3 H);

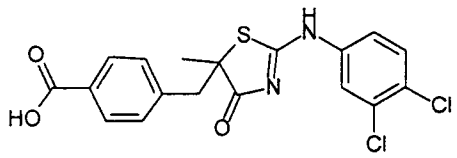
Z) 4-[2-(4-fluorophenylamino)-5-methyl-4-oxo-4,5-dihydrothiazol-5-ylmethyl]-benzoic acid methyl ester



purity 95%,

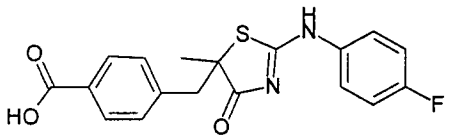
1H NMR (500 MHz, Chloroform-*d*) δ ppm 7.96 - 8.03 (m, 1 H) 7.92 (br. s., 1 H) 7.36 - 7.44 (m, 2 H) 6.99 - 7.15 (m, 4 H) 3.93 (s, 3 H) 3.37 (d, *J*=13.92 Hz, 1 H) 3.10 (d, *J*=13.92 Hz, 1 H) 1.76 (s, 3 H);

AA) 4-[2-(3,4-dichlorophenylamino)-5-methyl-4-oxo-4,5-dihydrothiazol-5-ylmethyl]-benzoic acid



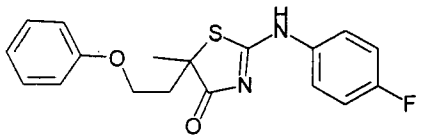
purity 90%;

BB) 4-[2-(4-fluorophenylamino)-5-methyl-4-oxo-4,5-dihydrothiazol-5-ylmethyl]-benzoic acid



purity 98%;

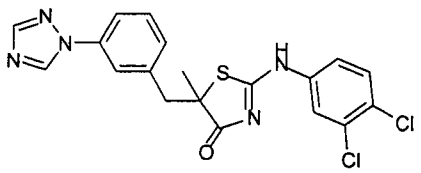
CC) 2-(4-fluorophenylamino)-5-methyl-5-(2-phenoxyethyl)-thiazol-4-one



purity 95%

1H NMR (500 MHz, Chloroform-*d*) δ ppm 7.23 - 7.30 (m, 2 H) 6.99 - 7.06 (m, 2 H) 6.90 - 6.99 (m, 3 H) 6.86 (d, *J*=7.81 Hz, 2 H) 4.06 - 4.22 (m, 2 H) 2.63 (ddd, *J*=14.83, 8.48, 6.47 Hz, 1 H) 2.20 (dd, *J*=14.65, 4.39 Hz, 1 H) 1.73 (s, 3 H);

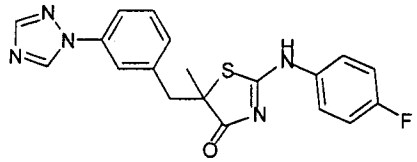
DD) 2-(3,4-dichlorophenylamino)-5-methyl-5-(3-triazolobenzyl)-thiazol-4-one,



purity 95%,

1H NMR (500 MHz, Chloroform-*d*) δ ppm 8.57 (s, 1 H) 8.11 (s, 1 H) 7.60 - 7.67 (m, 2 H) 7.40 (d, *J*=8.55 Hz, 1 H) 7.34 - 7.39 (m, 2 H) 7.05 (d, *J*=2.20 Hz, 1 H) 6.80 (dd, *J*=8.55, 2.20 Hz, 1 H) 3.36 (d, *J*=13.67 Hz, 1 H) 3.06 (d, *J*=13.92 Hz, 1 H) 1.75 (s, 3 H);

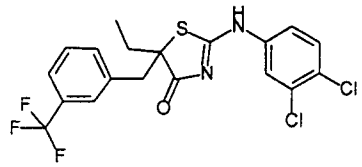
EE) 2-(4-fluorophenylamino)-5-methyl-5-(3-triazolobenzyl)-thiazol-4-one



purity 95%,

1H NMR (500 MHz, Chloroform-*d*) δ ppm 8.55 (s, 1 H) 8.11 (s, 1 H) 7.62 (d, *J*=8.55 Hz, 2 H) 7.38 (d, *J*=8.30 Hz, 2 H) 6.99 - 7.09 (m, 2 H) 6.85 - 6.96 (m, 2 H) 3.36 (d, *J*=13.92 Hz, 1 H) 3.05 (d, *J*=13.92 Hz, 1 H) 1.74 (s, 3 H); and

FF) 2-(3,4-dichlorophenylamino)-5-ethyl-5-(3-trifluoromethylbenzyl)-thiazol-4-one



purity 100%,

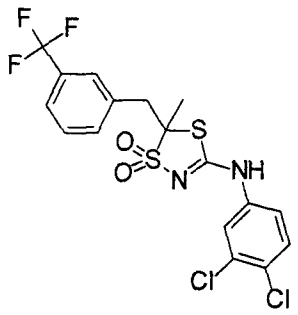
1H NMR (500 MHz, Chloroform-*d*) δ ppm 9.04 (br. s., 1 H) 7.58 (d, *J*=6.84 Hz, 1 H) 7.51 (s, 1 H) 7.36 - 7.46 (m, 3 H) 6.98 (d, *J*=2.20 Hz, 1 H) 6.70 (dd, *J*=8.55, 2.20 Hz, 1 H) 3.37 (d, *J*=13.67 Hz, 1 H) 3.05 (d, *J*=13.92 Hz, 1 H) 2.20 (dq, *J*=14.34, 7.26 Hz, 1 H) 1.87 (dq, *J*=14.37, 7.45, 7.28 Hz, 1 H) 1.08 (t, *J*=7.20 Hz, 3 H),

using the appropriate reagents. For example, for compound (j) above, 4-fluorophenylisocyanate was used in place of 3,4-dichlorophenylisocyanate in step (a) and 3-bromobenzylbromide was used in place of 3-trifluoromethylbenzylbromide in step (c) of Route A.

For compound (FF), 2-bromobutyric acid methyl ester was used instead of 2-bromopropionic acid ethyl ester in step (b) of Route A above.

Example 3

(3,4-Dichlorophenyl)-[5-methyl-1,1-dioxo-5-(3-trifluoromethylbenzyl)-1,5-dihydro-1-λ⁶-[1,4,2]dithiazol-3-yl]-amine



(a) C-Chloro-N-(4-methoxybenzyl)-methanesulfonamide

Potassium carbonate and 4-methoxybenzylamine were mixed in acetonitrile (400 mL) and chloromethansulfonyl chloride in acetonitrile (100 mL) was added dropwise over 1.5 hours. The mixture was stirred at room temperature for 3.5 h and then the suspension was filtered and concentrated *in vacua* to yield 27.4 g of crude material as a light yellow solid. The residue was digested with methanol and the resulting white solid was collected by filtration to yield 8.177 g (33%) of the desired compound. The residue after the first crystallization was evaporated to dryness and recrystallized from MeOH/water to yield another 7.458 g (30%) of the desired compound. Total yield: 15.635 g (63%).

ES-MS: 267 [M+NH4]+; 272 [M+Na]+, 1H NMR (500 MHz, CDCl3) δ ppm 3.82 (s, 3 H) 4.32 (s, 2 H) 4.36 (s, 2 H) 4.91 (br. s., 1 H) 6.91 (d, J=8.79 Hz, 2 H) 7.29 (d, J=8.55 Hz, 2 H).

(b) (3,4-Dichlorophenyl)-[2-(4-methoxybenzyl)-1,1-dioxo-1λ⁶-[1,4,2]dithiazolid-in-(3E)-ylidene]-amine

3,4-Dichlorophenyl isothiocyanate in CH_3CN (100 mL) was added dropwise over 2 h to a slurry consisting of K_2CO_3 and C-Chloro-N-(4-methoxy-benzyl)-methanesulfonamide (from step (a) above) in CH_3CN (150 mL) at room temperature. After 5 h, an additional 500 mg of 3,4-dichlorophenyl isothiocyanate was added and the reaction was quenched when LC-MS analysis indicated that the reaction had reached completion. The reaction was quenched by the addition of triethylenetetramine (4.368 g, 4.49 mL, 1 eq), the resultant mixture was filtered and then the solvent was evaporated. The residue was dissolved in Et_2O:EtOAc (1:1, 500 mL) and a suspension formed, which was washed with 1M Na_3PO_4 (3x50 mL). To the organic phase was then washed with 2M NaOH (4x50 mL), water (50 mL) and brine (50 mL). The combined organic phase were dried over

$MgSO_4$ and evaporation of the solvents gave 8.62 g of a yellow oil. The material was purified by flash column chromatography (silica gel, 10-20% EtOAc in n-hexane) to give 4,012 g (32%) of an off-white solid (Purity: 98%).

1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 3.82 (s, 3 H) 4.36 (s, 2 H) 4.89 (s, 2 H) 6.76 (dd, *J*=8.30, 2.44 Hz, 1 H) 6.89 (d, *J*=8.79 Hz, 2 H) 7.02 (d, *J*=2.44 Hz, 1 H) 7.40 (d,*J*=8.55 Hz, 1 H) 7.45 (d, *J*=8.55 Hz, 2 H).

(c) (3,4-Dichlorophenyl)-[2-(4-methoxybenzyl)-1,1-dioxo-5-(3-trifluoromethyl-benzyl)-1-λ^6-[1,4,2]dithiazolidin-(3E)-ylidene]-amine

(3,4-Dichloro-phenyl)-[2-(4-methoxy-benzyl)-1,1-dioxo-1-λ^6-[1,4,2]dithiazolidin-(3E)-ylidene]-amine (3.6 g, from step (b) above) was dissolved in DMF (50 mL) and K_2CO_3 (6 g), KI (2.1 g) and 3-trifluoromethylbenzylbromide (3.1 g) were added. The reaction mixture was stirred at room temperature for 24h and then EtOAc (300 mL) was added. The resulting organic phase was washed with water (4x30 mL) and brine (30 mL), dried over $MgSO_4$ and evaporated to yield 7,408 g of crude product as a yellow oil, which was purified by flash column chromatography: (silica gel, 10-20% EtOAc in n-hexane) to yield 2.512 g (50%) of pure product.

1H NMR (500 MHz, Chloroform-d) δ ppm 3.16 (dd, J=14.53, 8.91 Hz, 1 H) 3.64 (dd, J=14.40, 5.13 Hz, 1 H) 3.82 (s, 3 H) 4.74 (dd, J=8.91, 5.25 Hz, 1 H) 4.84 (s, 2 H) 6.68 (dd, J=8.30, 2.44 Hz, 1 H) 6.86 – 6.91 (m, 2 H) 6.94 (d, J= 2.44 Hz, 1 H) 7.37 (d, J=8.55 Hz, 1 H) 7.39 (d, J=8.06 Hz, 1 H) 7.41 – 7.49 (m, 4 H) 7.58 (d, J=7.81 Hz, 1 H).

(d) (3,4-Dichlorophenyl)-[5-methyl-1,1-dioxo-5-(3-trifluoromethylbenzyl)-1,5-dihydro-1-λ^6-[1,4,2]dithiazol-3-yl]-amine

To a 1.0 M solution in THF of LiHMDS (8.1 mL) was added (3,4-Dichloro-phenyl)-[2-(4-methoxybenzyl)-1,1-dioxo-5-(3-trifluoromethylbenzyl)-1λ^6-[1,4,2]dithiazolidin-(3E)-ylidene]-amine (2.331 g, from step (c) above) in dry THF (25 mL) at room temperature. After 20 min, MeI (378 µL) was added. After 3 h additional LiHMDS (1 mL, 1 mmol) and MeI (190 µL, 3 mmol) were added. After 1 h the residue was worked up, by the addition of Toluene (100 mL) and the organic phase was washed with water (4x10 mL) and brine (10 mL), dried over $MgSO_4$ and the solvent removed under reduced pressure to yield a yellow oil which was dissolved in CH_2Cl_2 (20 mL). Trifluoroacetic acid (624 µL) was added and the resulting mixture stirred at room temperature for 30 min. The solvent was removed under reduced pressure to yield a brownish oil which was purified by flash column chromatography (silica gel, 20-30% EtOAc in n-hexane) to give 1.181 g (59%) of the title compound that is 98% pure according to HPLC. The yellow amorphous product

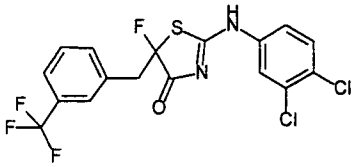
was triturated with n-hexane:Et2O (approximately 10:1) to yield 969 mg (51%) of a pale yellow powder.

HPLC purity: 99%

1H NMR (500 MHz, DMSO-*d*6) δ ppm 1.70 (s, 3 H) 3.50 (s, 2 H) 7.45 (d, *J*=8.06 Hz, 1 H) 7.58 (t, *J*=7.69 Hz, 1 H) 7.66 (d, *J*=8.79 Hz, 2 H) 7.74 (d, *J*=7.57 Hz, 1 H) 7.81 (s, 2 H).

Example 4

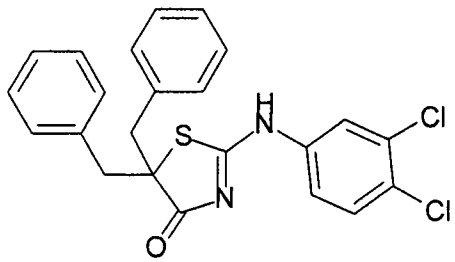
2-(3,4-dichlorophenylamino)-5-fluoro-5-(3-trifluoromethylbenzyl)-thiazol-4-one



The title compound may be prepared using procedures described in the specification above (e.g. by using bromofluoro acetic acid methyl ester instead of 2-bromopropionic acid ethyl ester in step (b) of Route A above).

Example 5

5,5-dibenzyl-2-[(3,4-dichlorophenyl)amino]thiazol-4-one



2-(3,4-Dichlorophenyl)imino-3-[(2,4-dimethoxyphenyl)methyl]thiazolidin-4-one was formed from 1-(3,4-dichlorophenyl)-3-[(2,4 dimethoxyphenyl)methyl]-thiourea and methyl 2-bromoacetate following the procedure set out in Example 1, step (b) above. A solution of 20 mg 2-(3,4-dichlorophenyl)imino-3-[(2,4-dimethoxyphenyl)methyl]thiazolidin-4-one in 300 µL dry 2-MeTHF was added to 5 mg solid NaH in a vial. Immediately, a solution of benzyl bromide (20 mg, 2.4 equivalents) in 100 µL dry 2-MeTHF was added, followed by 100 µL dry THF. The vial was stirred at room temperature for about 2 hours until LCMS analysis indicated >95% conversion to product. The reaction was quenched by the addition of a few drops of H_2O. Another 300 µL H_2O was added and the organic phase was separated. The remaining aqueous phase was extracted once using EtOAc, the organic phases were then combined and the solvent evaporated under reduced

pressure. Conversion of the resulting intermediate to the title compounds was effected using the procedure described above for Example 1, step(d).

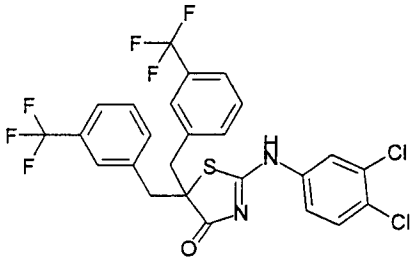
The product was purified by RP-HPLC to give 4.1 mg of the product with 98% purity.

1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 3.07 (d, *J*=13.92 Hz, 2 H) 3.45 (d, *J*=13.92 Hz, 2 H) 6.58 (d, *J*=8.79 Hz, 1 H) 6.80 (br. s., 1 H) 7.23 (dd, *J*=6.59, 2.93 Hz, 4 H) 7.28 - 7.33 (m, 6 H) 7.36 (d, *J*=8.55 Hz, 1 H).

Example 6

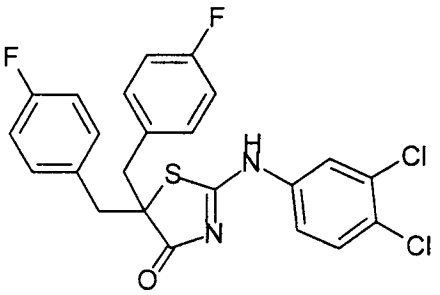
The following compounds were prepared in accordance with the methods used in Example 5. HPLC purity and/or NMR data is provided.

A) 2-[(3,4-dichlorophenyl)amino]-5,5-bis[[3-(trifluoromethyl)phenyl]methyl]thiazol-4-one



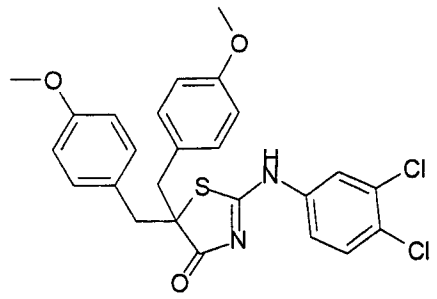
1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 3.11 (d, *J*=13.67 Hz, 2 H) 3.54 (d, *J*=13.92 Hz, 2 H) 6.51 (d, *J*=8.55 Hz, 1 H) 6.80 (s, 1 H) 7.37 (d, *J*=8.55 Hz, 1 H) 7.40 - 7.48 (m, 4 H) 7.50 (s, 2 H) 7.59 (d, *J*=6.84 Hz, 2 H);

B) 2-[(3,4-dichlorophenyl)amino]-5,5-bis[(4-fluorophenyl)methyl]thiazol-4-one



1H NMR (500 MHz, METHANOL-*d*4) δ ppm 3.01 (d, *J*=13.43 Hz, 1.4 H) 3.12 (d, *J*=13.67 Hz, 0.6 H) 3.38 (d, *J*=13.67 Hz, 2 H) 6.58 (d, *J*=7.81 Hz, 1 H) 6.73 (br. s., 1 H) 6.99 (t, *J*=8.42 Hz, 4 H) 7.22 - 7.33 (m, 4 H) 7.36 (d, *J*=8.55 Hz, 1 H); and

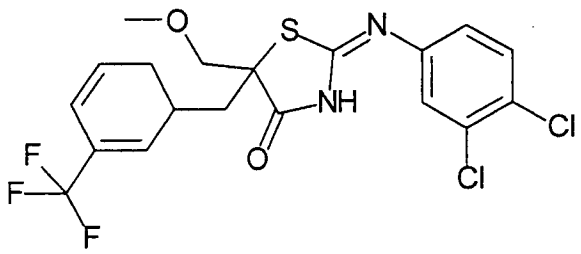
C) 2-[(3,4-dichlorophenyl)amino]-5,5-bis[(4-methoxyphenyl)methyl]thiazol-4-one



1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 3.01 (d, *J*=13.92 Hz, 2 H) 3.37 (d, *J*=13.92 Hz, 2 H) 3.80 (s, 6 H) 6.64 (d, *J*=7.81 Hz, 1 H) 6.81 - 6.85 (m, 4 H) 6.86 (br. s., 1 H) 7.11 -7.17 (m, 4 H) 7.37 (d, *J*=8.30 Hz, 1 H).

Example 7

6(2-(3,4-dichlorophenyl)imino-5-(methoxymethyl)-5-[[3-(trifluoromethyl)cyclohexa-2,4-dien-1-yl]methyl]thiazolidin-4-one



2-(3,4-Dichlorophenyl)imino-3-[(2,4-dimethoxyphenyl)methyl]-5-[3(trifluoromethyl)phenyl]-methyl]thiazolidin-4-one was formed from 1-(3,4-dichlorophenyl)-3-[(2,4 dimethoxyphenyl)methyl]-thiourea and methyl 2-bromo-3-[3-(trifluoromethyl)phenyl]propanoate following the procedure set out in Example 1, step (b) above.

A solution of 27 mg 2-(3,4-dichlorophenyl)imino-3-[(2,4-dimethoxyphenyl)methyl]-5 [[3-(trifluoromethyl)phenyl]methyl]thiazolidin-4-one in 300 µL dry 2-Me-THF was added to 4 mg solid NaH in a vial. The atmosphere was changed to N_2 and immediately afterwards 13 mg bromo(methoxy)methane was added in a solution of 100 µL dry 2-MeTHF. Finally, 100 µL dry THF was added and the reaction mixture was stirred at -20°C for 24 hours, where LCMS indicated >90% conversion. The reaction was quenched by addition of a few drops of H_2O, followed by a further 300 µL H_2O. Approximately 300 µL EtOAc was then added and the phases were separated. The aqueous phase was extracted

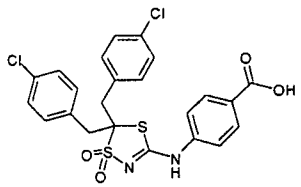
once more using EtOAc and the combined organic extracts were dried ($MgSO_4$) and the solvents evaporated under reduced pressure.

Conversion of the resulting intermediate to the title compounds was effected using the procedure described above for Example 1, step(d). The product was purified using RP-HPLC to give 1.6 mg of the product with 98% purity.

1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 3.18 (d, *J*=13.67 Hz, 1 H) 3.36 (d, *J*=13.92 Hz, 1 H) 3.44 (s, 3 H) 3.67 (d, *J*=9.77 Hz, 1 H) 3.84 (d, *J*=9.52 Hz, 1 H) 6.69 (d, *J*=7.57 Hz, 1 H) 6.97 (br. s., 1 H) 7.38 (d, *J*=8.55 Hz, 1 H) 7.40 - 7.43 (m, 1 H) 7.45 (t, *J*=7.57 Hz, 1 H) 7.51 (s, 1 H) 7.59 (d, *J*=7.32 Hz, 1 H).

Example 8

4-[[5,5-bis[(4-chlorophenyl)methyl]-1,1-dioxo-1,4,2-dithiazol-3-yl]amino]benzoic acid



224 mg of (3,4-Dichlorophenyl)-[2-(4-methoxybenzyl)-1,1-dioxo-1λ^6-[1,4,2]dithiazolidin-ylidene]-amine (see Example 3, steps (a) and (b)) and 103 mg 3-chlorobenzyl bromide were mixed in 5 ml of dry THF under nitrogen. The solution was cooled to -72°C using a dry ice/ethanol bath. LiHMDS was diluted to 0.2 M (0.2 mmol/ml) with dry THF and added with a syringe pump at 0.5 ml/h. The reaction was checked every half hour after 2 hours. Both the monobenzylated and dibenzylated products are formed. The reaction mixture was stirred for 5 h and then the reaction was quenched with 4 mL of saturated aqueous NaHCO3 solution, followed by 4 ml of EtOAc. The aqueous phase was washed with 3 times of 3 ml of ethyl acetate and concentrated. The residue was crudely purified with flash chromatography (silica, 20% EtOAc in petroleum ether). Some separation of the mono and dibenzylated products was achieved. The purest fractions of the two compounds were pooled separately and concentrated. The residues were dissolved in 200 µL of DCM and treated with 50 µL of Me_2S and 200 µL of TFA. After 1 day the deprotection was complete and the reactions were concentrated. The dibenzylated product was purified by HPLC (40-70% acetonitrile/water+0.1% TFA, ACE, C-8) to give

the product as a white solid, 12 mg, 23 µmol, 5% yield.

1H NMR (500 MHz, DMSO-*d*6) δ ppm 3.40 - 3.56 (m, 4 H) 7.27 - 7.38 (m, 8 H) 7.45 (s, 2 H) 7.88 (d, *J*=8.55 Hz, 2 H) 11.10 (br. s., 1 H) 12.90 (br. s., 1 H), MS: [M+H]+, HPLC purity: 100%.

Biological Tests

Descriptions of the cancer cell lines including source, tumor type, and morphology may be obtained from the American Type Culture Collection (ATCC) or its website (www.atcc.org). The cell lines are both from primary tumors and metastatic sites (for example, MCF-7, MDA-MB231, HT-29, SKOV-3 and PC-3 among others tested).

Test A

Cell Proliferation Assay

Reagents

Dulbecco's modified Eagle's medium (D-MEM) +1000mg/L Glucose +GlutaMAX™1 + Pyruvate (Gibco #21885-025)

V/V Foetal Bovine Serum (Gibco 10500-064)

5-bromo-2-deoxyuridine (BrdU)

Dimethyl sulfoxide (DMSO)

PC-3 and MCF-7 cancer cell lines were propagated in D-MEM (Gibco 21885) supplemented with 10% Foetal calf serum. 15000 cells per well were seeded in 96 well plates and incubated overnight. The culture media was changed to serum-free D-MEM for 24 h. The culture media was then changed to serum free D-MEM containing either 0.2 % DMSO as vehicle control or 10, 5, or 2.5 µM (as indicated below) of the compound of Example 1, Example 2(a), Examples 2(c) to 2(h), Example 2(ii) or Example 3 in 0.2% DMSO in quadruplicate. After 18 h incubation, BrdU was added according to manufacturer's recommendations. After 6 h incubation in the presence of BrdU, the culture media was removed and BrdU incorporation was measured using "Cell Proliferation ELISA, BrdU colorimetric" Roche (11647229001) according to manufacturer's recommendations.

Results

Proliferation rate of PC-3 and MCF-7 cells are reduced by relevant concentrations of the test compounds as measured by BrdU incorporation.

For example, in the above assay, the compounds of Example 1, Example 2(A), Examples 2(C) to 2(H), Example 2(FF) and Example 3 relative to the vehicle control (which displayed a BrdU incorporation of 1 unit) displayed the following (approximate) units of BrdU incorporations at the indicated concentrations in Table 1 below.

Table 1

Example No.	PC3 Units of BrdU incorporation/μM	MCF-7 Units of BrdU incorporation/μM
1	0.05/5	0.0/5
2(A)	0.05/5	0.2/5
2(C)	0.05/10	0.0/10
2(D)	0.05/10	0.0/10
2(E)	0.05/5	0.0/5
2(F)	0.1/5	0.25/5
2(G)	0.0/5	0.1/5
2(H)	0.35/10	0.35/10
2(FF)	0.2/2.5	0.15/2.5
3	0.1/2.5	0.1/5
5	0.07	5
6a	0.31	1.25
6b	0.26	2.5

Other Cell Proliferation Assays

The preparation of the above assay is repeated using different cancer cell lines. The cell lines MDA-MB-231, Jurkat and Skov-3 may be used.

Test B

***In vivo* Mouse Model – Test 1**

5 week old Athymic BALB/cA nude mice are delivered from Taconic (Denmark) and kept under barrier conditions for 1 week acclimatisation. At 6 weeks, 17 mice are injected subcutaneously on the flank with 1.8×10^6 MDA-MB-231 human breast cancer cells (LGC Promochem-ATCC) in a 50/50 v/v solution of phosphate buffered saline (PBS) (Gibco 10010-015, Invitrogen) Matrigel HC (BD Biosciences).

After 11 days, palpable tumors are observed in 16 mice. 2 mice are sacrificed and the tumors dissected and examined. 2 groups of 7 mice each are treated once daily by intraperitoneal injections of 1-10 mg/kg bodyweight of test compound in 79% PBS/20% Solutol HS 15(BASF)/1% DMSO or vehicle control respectively for 5-30 days. The mice are sacrificed by cervical dislocation and tumors are dissected.

Histology

The tumor tissue are fixated overnight in PBS (containing 4% w/v paraformaldehyde (Scharlau PA0095, Sharlau Chemie SA, Spain) at +4°C. The tumor tissue is cryopreserved by 24 hour incubation in PBS containing 30% w/v sucrose (BDH #102745C (www.vwr.com) at +4°C and is embedded in Tissue-Tek embedding media (Sakura Finetek Europa BV, Netherlands). 10 µm cryosections are generated and stained with Mayers Hematoxylin (Dako) for 5 minutes and destained for 3 x 10 minutes in tap water. Slides are mounted using Dako faramount aqueous mounting medium and are examined using a Nikon Eclipse TS 100 microscope documented using a Nikon coolpix 4500.

The tumors from mice treated with test compound and vehicle are analyzed for morphology by microscopic examination of hematoxylin stained cryosections.

***In vivo* Mouse Model – Test 2**

The above test procedure is followed, but 16 (rather than 17) mice are injected subcutaneously.

After 6 days, palpable tumors were observed in the 16 mice. 2 groups of 8 mice each were treated once daily by intraperitoneal injections of 7.5 mg/kg bodyweight of test compound in 79% PBS/20% Solutol HS 15(BASF)/1% DMSO or vehicle control respectively for 27 days. Tumor size is measured by calliper every third day.

The results of the tumor area in the first group of mice (treated with test compound) were compared against the second ('untreated') group of mice after a certain number of days.

Test C

Activation of AMPK and eEF2

Test compound

The compound of Example 1 was synthesized by iNovacia AB, Stockholm. A stock solution of 10 μM was prepared by dissolving the compound in 100% DMSO.

Cell line and cell culture

Human PC3 cells were purchased from LGC Promochem-ATCC (ATCC catalog no CRL-1435). PC3 cells were maintained in Dulbecco's modified Eagle's medium (Gibco 21885) containing 5% fetal bovine serum (Gibco 10500-064), 25μg/ml Gentamicin (Gibco 15750) and 1x non essential amino acids (Gibco 11140). The cells were incubated in a humidified atmosphere of 5% CO2 at 37°C and passaged every 3 days by trypsinization. For experiments, PC3 cells were cultured in complete medium with 10% fetal bovine serum in 60-mm-diameter dishes, grown to 70-80% confluence and cultured in serum-free Dulbecco's modified Eagle's medium for 5 h. Cells were then treated with 2.5, 5 or 10 μM of the compound of Example 1 for 24 h. The final concentration of DMSO did not exceed 0.1%, which did not affect AMPK or eEF2 phosphorylation. 0.1% DMSO was used as control.

Western Blot analysis

PC3 cells were lysed in buffer (100mM TRIS pH 6,8, 2%w/v Sodium dodecylsulfate (SDS), 10mM NaF, 10mM β-glycerophosphate, 1mM Na Vanadate). Cell debris is removed by centrifugation at 14,000 X g for 15 min at 4°C and the resulting supernatant is used for Western blotting. Protein concentrations of the lysates were measured using a BCA protein assay kit (Pierce #23225). For Western blotting, 15 μg protein was loaded in each well of a 4-12% bis/tris gel for AMPK or eEF2 detection (Criterion precast gel

Bio-Rad #345-0117) and run according to manufacturers recommendation. Gels were blotted onto a nitrocellulose filters (Hybond-C extra Amersham #RPN203E). Filters were blocked in 20mM TRIS pH 7,5, 137mM NaCl, 25%v/v Tween20 and 5%w/v fat free powdered milk for 30 min. Filters were incubated overnight in blocking solution with phospho-AMPK (Thr172) or phospho-eEF2 (Thr56) (Cell signalling #2531 and #2331). Filters were washed in 20mM TRIS pH 7.5, 137mM NaCl, 25%v/v Tween20 for 3x5min. Filters were incubated in blocking solution with secondary antibody, peroxidase conjugated Goat anti-rabbit IgG (Jackson immunoResearch #111-035-003) at room temperature for 1h. Filters were washed as above for 3x10 min. Signal was developed with SuperSignal West Dura ECL kit (Pierce #1859024) and exposed to Hyperfilm ECL (Amersham #28906837).

Results

Compound Example 1 stimulates AMPK phosphorylation

To investigate whether AMPK is activated by the compound Example 1 in PC3 cells, the phosphorylation of AMPK and its downstream target, eEF2 were used as indicators of AMPK activation. The Western blot result showed that the compound of Example 1 stimulated the phosphorylation of Thr-172 of the AMPK α-subunit. Moreover, AMPK activation by the compound of Example 1 in PC3 cells was further confirmed by enhanced phosphorylation of eEF2. These results indicate that the compound of Example 1 stimulates AMPK phosphorylation and downstream activity (see Figures 1 and 2).

Test D

***In vitro* cytotoxicity data with several cell lines in a 96 well plate**

SRB Cytotoxicity Study

Cells are seeded and grown in the presence of varying concentrations of test compound(s) for a period of 3 days (72 hours). The cells are then fixed to the plate and exposed to the dye sulphorhodamine B (SRB). The varying amounts of inhibition of proliferation produces a standard curve from which the IC_{50} value is determined.

Section A: Seeding the cells into the plate

96 well plates in this assay are seeded at seeding density determined for each cell line accordingly.

Adherent cells:

1. Harvest cells and count. All procedures associated with harvesting and preparing cell suspensions will be carried out in a Class II hood.
2. Assay uses a sterile 96 well plate cell culture plate (Microtest flat bottom tissue culture plate, Falcon 3072).
3. Dilute cells to appropriate seeding density.
4. Add 100µL of the cell suspension to wells B1 to G12.
5. Add 100µL of media to all Blank wells (A1 to A12, H1 to H12).
6. Incubate plate(s) overnight at 37 °C in a 5% CO_2 incubator.

Suspension cells:

1. Harvest cells and count. All procedures associated with harvesting and preparing cell suspensions will be carried out in a Class II hood.
2. Assay uses a sterile 96 well plate cell culture plate (Microtest flat bottom tissue culture plate, Falcon 3072).
3. Dilute cells to appropriate seeding density.
4. Add 100µL of the cell suspension to wells B1 to G12.
5. Add 100µL of media to all Blank wells (A1 to A12, H1-H12).
6. Add drugs to cells immediately after plating.

Section B: Adding Test Compound(s) to cells

7. Prepare compound plate for test compound(s) and transfer diluted compound to prepared assay plate in section A.
8. On compound plate add 100µL of cell culture medium to well B3-G3 to B10-G10.
9. Dilute the test articles to 250µM in the cell culture medium in a separate tube, which will make start concentration of 50µM. Stock concentration of test compound(s) is 10mM, therefore dilute 1:40 to obtain 250 µM concentration.
10. Add 200µL of the diluted batch of drug to empty wells B2 to G2 and mix by pipetting up and down 3 times.
11. Transfer 100µL from each of these wells (using a multichannel pipette) to wells B2-G2 etc and continue to dilute 1:2 across the plate to column 10. Discard the excess 100µL from each row in column 10. Column 11 contains DMSO control. Row 12 contains 100µL blank medium.

12. DMSO control same as drug: dilute 100% DMSO 1:40 in medium. Pipette 100µL to empty row 11 on compound plate. From this 25µL will be added to assay plate containing cells, which will give end concentration of 0.5%.

Blank control: Pipette 100µL blank medium to row 1 and 12, 25µL form this will be added to assay plate containing cells.

13. Using a new set of tips, transfer the drug dilutions from the compound plate onto the assay plate containing the cells (25µL of diluted drug transferred to the 100µL of cells in the assay plate. The end volume will be 125µL). Start with lowest drug concentrations.

14. Incubate the assay plate at 37°C in a 5% CO_2 incubator for 3 days.

Section C: Fixing and staining the cells

At the end of the incubation period the cells will need to be fixed and the SRB assay performed as described below:

1. Transfer the plate from the incubator in the cell culture suite to 4°C, leave cells for an hour.

2. Adherent cell lines: Fix cells to the plate by carefully adding 30µL of cold 50% v/v Trichloroacetic acid (TCA BDH 102863H) to the cell culture medium already in the wells so the final concentration of TCA is 10% v/v.

Suspension cell lines: Fix cells to the plate by carefully adding 30µL of cold 80% v/v Trichloroacetic acid (TCA BDH 102863H) to the cell culture medium already in the wells so the final concentration of TCA is 16% v/v.

1. Incubate at 4 °C for 1 hour.

2. Submerge plate in a plastic container containing distilled water such that each well fills with water. Leave to soak for 1 minute. Flick off wash solution into the sink and repeat this washing step a further four times. Finally, flick off wash solution and leave to air dry.

3. When wells are completely dry add 100µl of 0.4% w/v Sulforhodamine B (SRB Sigma S1402) in 1% v/v acetic acid to each well and incubate at room temperature for 30 minutes.

4. Flick off SRB and wash four times by submerging the plates for 1 minute in 1% v/v acetic acid. Flick off wash solution and leave to air dry.

5. When wells are completely dry add 100µl of 10mM Tris base pH 10.5 (pH adjusted to 10.5 using sodium hydroxide solution). Place on a plate shaker and mix for 5 min. Read the plate at 564nm using the SPECTRAmax microplate spectrophotometer acquiring

data.

Test E

Clonogenic Assay Results

Section A: Seeding the assay plates

24 well plates (Falcon Cat no: 353047) in this assay are seeded at seeding density determined for each cell line accordingly.

Base Agar:

1. Melt 1.6% Agar (invitrogen Select Agar) in microwave, and cool to 40-42°C in a waterbath.
2. Warm cell culture Media + 20% FBS + 2X of any other cell culture supplements required to 40-42°C in waterbath. Allow at least 30 minutes for temperature to equilibrate.
3. Mix equal volumes of the two solutions to give 0.8% Agar + Media +10% FBS + 1X cell culture supplements.
4. Add 0.2 ml/well, allow setting. The plates can be stored at 4°C for up to 1 week.

Top Agar:

1. Melt 0.8% Agar (invitrogen Select Agar) in microwave, and cool to 40°C in a waterbath.
2. Warm Media + 20% FBS + 2X of any other cell culture supplements required to the same temperature.
3. Harvest cells and count. All procedures associated with harvesting and preparing cell suspensions will be carried out in a Class II hood.
4. Dilute cells in Media to appropriate seeding density.
5. Label the 24 well plates with base agar appropriately (if the plate is stored in the refrigerator, remove the plate from 4°C about 30 minutes prior to plating to allow them to warm up to room temperature).
6. For plating mix equal volumes of Media + 20% FBS + 2X cell culture supplements + cells and soft Agar 0.8% solution to a 15ml capped centrifuge tube, mix gently and add 0.2ml to each replicate well (usually plate out in quadruplicate).
7. Incubate plate(s) overnight at 37°C in a 5% CO_2 incubator

Section B: Adding test compound to cells

1. Prepare compound plate for test compound(s) and then transfer diluted compound to prepared assay plate in section A.

2. Dilute the test compound(s) to 120μM in the cell culture medium in a separate tube, which will make start concentration of 40μM.

Stock concentration of test compound(s) is 10mM, therefore dilute 1:83.3 to obtain 120 μM concentration.

3. Make dilutions of the drug test solution by 1:2, 3 times from the start concentration of 120μM to prepare the test drug concentrations at 20, 10 and 5 μM.

4. Transfer 200μL from each test concentration to each well by quadruplicate. Column 6 contains 40μM test compound(s). Column 5 contains 20μM test compound(s), Column 4 contains 10 μM test compound(s), and Column 3 contains 5μM test compound(s).

5. DMSO controls same as drug: dilute 100% DMSO 1:83.3 in medium. Pipette 200μL to Column 2 on compound plate by quadruplicate., which will give end concentration of 0.4%.

6. Blank control: Pipette 200μL blank medium per well to Column 1 by quadruplicate.

7. Incubate the assay plate at 37°C in a 5% CO_2 incubator for 2-3 weeks.

Section C: Staining and counting the cell colonies

At the end of the incubation period the cell colonies will need to be stained and count as described below:

1. Mark the bottom of each well dividing each well at least in four sections.
2. Stain plates with 0.2ml of 0.005% Crystal Violet for 1 hour at 37°C 5%

CO_2 in a humidified incubator.

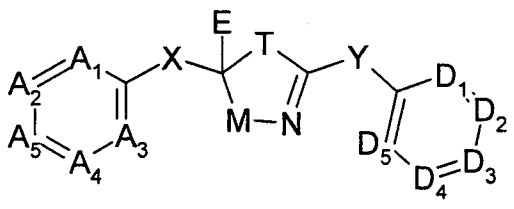
3. Count the colonies per well for each test group using a dissecting microscope.

4. To consider a group of cells as a colony at least each colony must have 50 cells.

5. Calculate the average of number of colonies of each well per group and calculate the % of inhibition of cell colonies formation produced by test compound using the formula %T/C, in which T is the test group and C is the controls.

Claims

1. A compound of formula I,



I

wherein:

X represents Q-[CR^xR^y]$_n$-Z;

Q and Z independently represent a bond, S or O;

R^x and R^y are independently selected from H, halo, C_{1-6} alkyl (optionally substituted by one or more halo atoms), or R^x and R^y are linked to form, along with the carbon atom to which they are attached, a non-aromatic 3- to 8-membered ring, optionally containing 1 to 3 heteroatoms selected from O, S and N, which ring is itself optionally substituted by one or more substituents selected from halo or C_{1-6} alkyl (optionally substituted by one or more halo atoms);

T represents S or O;

M represents -C(O)- or -$S(O)_2$-;

Y represents -NR^a-[CR^xR^y]$_m$- or -NR^aC(O)-[CR^xR^y]$_m$-;

R^a represents H or C_{1-6} alkyl (optionally substituted by one or more halo atoms);

E represents halo or C_{1-6} alkyl (optionally substituted by one or more groups selected from, -OR^b, aryl or heteroaryl (which latter two groups may be optionally substituted by one or more -R^c groups), or halo);

A_1 to A_5 respectively represent C(R^1), C(R^2), C(R^3), C(R^4) and C(R^5), or, alternatively, up to two of A_1 to A_5 may independently represent N;

D_1 to D_5 each independently represent C(R^6), or, alternatively, up to two of D_1 to D_5 may independently represent N;

R^1 to R^5 independently represent H, halo, -R^7, -CF_3, -CN, -NO_2, -C(O)R^7, -C(O)OR^7, -$N(R^{7a})R^{7b}$, -$N(R^7)_3^+$, -SR^7, -OR^7, -NH(O)R^7 or -SO_3R^7, or any two of R^1 to R^5 which are adjacent to each other are optionally linked to form, along with two atoms of the essential benzene ring in the compound of formula I, an aromatic or non-aromatic 3- to 8-membered ring, optionally containing 1 to 3 heteroatoms selected from O, S and N,

which ring is itself optionally substituted by one or more substituents selected from halo, $-R^7$, $-OR^7$ and =O;

R^c, on each occasion when used herein, independently represents H, halo, $-R^7$, $-CF_3$, $-CN$, $-NO_2$, $-C(O)R^7$, $-C(O)OR^7$, $-N(R^{7a})R^{7b}$, $-N(R^7)_3^+$, $-SR^7$, $-OR^7$, $-NH(O)R^7$ or $-SO_3R^7$, or any two R^c groups which are adjacent to each other are optionally linked to form, along with two atoms of the essential benzene ring in the compound of formula I, an aromatic or non-aromatic 3- to 8-membered ring, optionally containing 1 to 3 heteroatoms selected from O, S and N, which ring is itself optionally substituted by one or more substituents selected from halo, $-R^7$, $-OR^7$ and =O;

R^6 independently represents H, cyano, $-NO_2$, halo, $-R^8$, $-OR^8$, $-N(R^8)C(O)R^8$, $-NR^9R^{10}$, $-SR^{11}$, $-Si(R^{12})_3$, $-OC(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)R^{14}$, $-C(O)NR^{15a}R^{15b}$, $-S(O)_2NR^{15c}R^{15d}$, aryl or heteroaryl (which aryl and heteroaryl groups are themselves optionally and independently substituted by one or more groups selected from halo and R^{16}), or any two R^6 groups which are adjacent to each other are optionally linked to form, along with two atoms of the essential benzene ring in the compound of formula I, an aromatic or non-aromatic 3- to 8-membered ring, optionally containing 1 to 3 heteroatoms selected from O, S and N, which ring is itself optionally substituted by one or more substituents selected from halo, $-R^7$, $-OR^7$ and =O;

R^7 is selected from H or C_1-C_6 alkyl, C_1-C_6 cycloalkyl, aryl and heteroaryl;

R^{7a} and R^{7b} are independently selected from H, or C_1-C_6 alkyl, C_1-C_6 cycloalkyl, aryl and heteroaryl, or R^{7a} and R^{7b} are optionally linked to form, along with the nitrogen atom to which they are attached, an aromatic or non-aromatic 3- to 8-membered ring, optionally containing 1 to 3 heteroatoms selected from O, S and N, which ring is itself optionally substituted by one or more substituents selected from halo, $-R^7$, $-OR^7$ and =O;

R^b, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15a}, R^{15b}, R^{15c} and R^{15d} independently represent H or R^{16};

R^{16} represents C_{1-6} alkyl optionally substituted by one or more halo atoms;

n represents 1, 2 or 3;

m represents 0, 1 or 2;

or a pharmaceutically-acceptable salt or solvate, or a pharmaceutically functional derivative thereof.

2. A compound of formula I as claimed in Claim 1, wherein T represents S.

3. A compound of formula I as claimed in Claim 1 or Claim 2, wherein E represents halo or C_{1-6} alkyl optionally substituted by one or more halo atoms.

4. A compound of formula I as claimed in any one of Claims 1 to 3, wherein E represents $-CH_2CH_3$, -F or $-CH_3$.

5. A compound of formula I as claimed in any one of Claims 1 to 4, wherein at least one of R^1 to R^5, when present, represents $-C(O)R^7$, $-N(R^7)_3^+$, halo, $-R^7$, $-CF_3$, -CN, $-NO_2$, $-SR^7$, $-OR^7$, $-C(O)OR^7$ or $-N(R^{7a})R^{7b}$.

6. A compound of formula I as claimed in any one of Claims 1 to 5, wherein at least one of R^1 to R^5, when present, represents halo, $-R^7$, $-CF_3$, -CN, $-C(O)OR^7$, $-N(R^{7a})R^{7b}$, $-OR^7$ or a triazolyl group.

7. A compound of formula I as claimed in any one of Claims 1 to 6, wherein at least one of R^1 to R^5, when present, represents $-CH_3$, $-OCH_3$, -Cl, -Br, -F, $-CF_3$, -OH, $-OCF_3$, $-OCF_2$ or a triazolyl group.

8. A compound of formula I as claimed in any one of Claims 1 to 7, wherein R^6 independently represents H, -CN, -Br, -Cl, -F, $-R^8$, $-OR^8$, $-NR^9R^{10}$, $-SR^{11}$, $-C(O)OR^{13}$, $-C(O)R^{14}$, $-C(O)NR^{15a}R^{15b}$, $-S(O)_2NR^{15c}R^{15d}$, aryl or heteroaryl (which aryl and heteroaryl groups are themselves optionally and independently substituted by one or more groups selected from halo and R^{16}).

9. A compound of formula I as claimed in any one of Claims 1 to 8, wherein R^6 independently represents H, -CN, -Br, -Cl, -F, $-R^8$, $-OR^8$, $-NR^9R^{10}$, $-C(O)R^{14}$, $-C(O)NR^{15a}R^{15b}$ or $-SR^{11}$.

10. A compound of formula I as claimed in any one of Claims 1 to 9, wherein R^6 independently represents, -CN, -Br, $-R^8$, $-C(O)R^{14}$, $-C(O)NR^{15a}R^{15b}$, H, -F or -Cl.

11. A compound of formula I as claimed in any one of Claims 1 to 10, wherein Y represents -NH- or -NHC(O)-.

12. A compound of formula I as claimed in any one of Claims 1 to 11, wherein n represents 2 or 1 and/or m represents 1 or 0.

13. A compound as claimed in Claim 1, which is selected from the group:

i) 2-(3,4-dichlorophenylamino)-5-methyl-5-(3-trifluoromethylbenzyl)-thiazol-4-one;

ii) 2-(3,4-dichlorophenylamino)-5-methyl-5-(3-bromobenzyl)-thiazol-4-one;

iii) 2-(3,4-dichlorophenylamino)-5-methyl-5-(3-fluorobenzyl)-thiazol-4-one;

iv) 2-(3,4-dichlorophenylamino)-5-methyl-5-(3-methoxybenzyl)-thiazol-4-one;

v) 2-(3,4-dichlorophenylamino)-5-methyl-5-(benzyl)-thiazol-4-one;

vi) 2-(3,4-dichlorophenylamino)-5-methyl-5-(3-chlorobenzyl)-thiazol-4-one;

vii) 2-(3,4-dichlorophenylamino)-5-methyl-5-(3-chloro-4-fluorobenzyl)-thiazol-4-one;

viii) 2-(3,4-dichlorophenylamino)-5-methyl-5-(4-trifluoromethylbenzyl)-thiazol-4-one;

ix) 3-[2-(3,4-dichlorophenylamino)-5-methyl-4-oxo-4,5-dihydrothiazol-5-ylmethyl]-benzonitrile;

x) 2-(4-fluorophenylamino)-5-methyl-5-(3-trifluoromethylbenzyl)-thiazol-4-one;

xi) 2-(4-fluorophenylamino)-5-methyl-5-(3-bromobenzyl)-thiazol-4-one;

xii) 2-(4-fluorophenylamino)-5-methyl-5-(3-fluorobenzyl)-thiazol-4-one;

xiii) 2-(4-fluorophenylamino)-5-methyl-5-(3-methoxybenzyl)-thiazol-4-one;

xiv) 2-(4-fluorophenylamino)-5-methyl-5-(benzyl)-thiazol-4-one;

xv) 2-(4-fluorophenylamino)-5-methyl-5-(3-chlorobenzyl)-thiazol-4-one;

xvi) 2-(4-fluorophenylamino)-5-methyl-5-(3-chloro-4-fluorobenzyl)-thiazol-4-one;

xvii) 2-(4-fluorophenylamino)-5-methyl-5-(4-trifluoromethylbenzyl)-thiazol-4-one;

xviii) 3-[2-4-fluorophenylamino)-5-methyl-4-oxo-4,5-dihydrothiazol-5-ylmethyl]-benzonitrile;

xix) 2-(3,4-dichlorophenylamino)-5-methyl-5-(4-fluorobenzyl)-thiazol-4-one;

xx) 2-(4-fluorophenylamino)-5-methyl-5-(4-fluorobenzyl)-thiazol-4-one;

xxi) 2-(3,4-dichlorophenylamino)-5-methyl-5-(4-methoxybenzyl)-thiazol-4-one;

xxii) 2-(4-fluorophenylamino)-5-methyl-5-(4-methoxybenzyl)-thiazol-4-one;

xxiii) 2-(4-fluorophenylamino)-5-methyl-5-(4- chlorobenzyl)-thiazol-4-one;

xxiv) 2-(3,4-dichlorophenylamino)-5-methyl-5-(2-methylbenzyl)-thiazol-4-one;

xxv) 2-(4-fluorophenylamino)-5-methyl-5-(2-methylbenzyl)-thiazol-4-one;

xxvi) 4-[2-(3,4-dichlorophenylamino)-5-methyl-4-oxo-4,5-dihydrothiazol-5-ylmethyl]-benzoic acid methyl ester;

xxvii) 4-[2-(4-fluorophenylamino)-5-methyl-4-oxo-4,5-dihydrothiazol-5-ylmethyl]-benzoic acid methyl ester;

xxviii) 4-[2-(3,4-dichlorophenylamino)-5-methyl-4-oxo-4,5-dihydrothiazol-5-ylmethyl]-benzoic acid;

xxix) 4-[2-(4-fluorophenylamino)-5-methyl-4-oxo-4,5-dihydrothiazol-5-ylmethyl]-benzoic acid;

xxx) 2-(3,4-dichlorophenylamino)-5-methyl-5-(2-phenoxyethyl)-thiazol-4-one;

xxxi) 2-(4-fluorophenylamino)-5-methyl-5-(2-phenoxyethyl)-thiazol-4-one;

xxxii) 2-(3,4-dichlorophenylamino)-5-methyl-5-(3-triazolobenzyl)-thiazol-4-one;

xxxiii) 2-(4-fluorophenylamino)-5-methyl-5-(3-triazolobenzyl)-thiazol-4-one;

xxxiv) 2-(3,4-dichlorophenylamino)-5-ethyl-5-(3-trifluoromethylbenzyl)-thiazol-4-one;

xxxv) 2-(3,4-dichlorophenylamino)-5-fluoro-5-(3-trifluoromethylbenzyl)-thiazol-4-one; and

xxxvi) (3,4-dichlorophenyl)-[5-methyl-1,1-dioxo-5-(3-trifluoromethylbenzyl)-1,5-dihydro-1-λ^6-[1,4,2]dithiazol-3-yl]-amine;

xxxvii) 5,5-dibenzyl-2-[(3,4-dichlorophenyl)amino]thiazol-4-one;

xxxviii) 2-[(3,4-dichlorophenyl)amino]-5,5-bis[[3-(trifluoromethyl)phenyl]methyl]thiazol-4-one;

xxxix) 2-[(3,4-dichlorophenyl)amino]-5,5-bis[(4-fluorophenyl)methyl]thiazol-4-one;

lx) 2-[(3,4-dichlorophenyl)amino]-5,5-bis[(4-methoxyphenyl)methyl]thiazol-4-one;

lxi) 6(2-(3,4-dichlorophenyl)imino-5-(methoxymethyl)-5-[[3-(trifluoromethyl)cyclohexa-2,4-dien-1-yl]methyl]thiazolidin-4-one; and

lxii) 4-[[5,5-bis[(4-chlorophenyl)methyl]-1,1-dioxo-1,4,2-dithiazol-3-yl]amino]benzoic acid.

14. A compound as defined in any one of Claims 1 to 13, or a pharmaceutically-acceptable salt or solvate, or a pharmaceutically functional derivative thereof, for use as a pharmaceutical.

15. A pharmaceutical formulation including a compound as defined in any one of Claims 1 to 13, or a pharmaceutically-acceptable salt or solvate, or a pharmaceutically functional derivative thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

16. A combination product comprising:

(A) a compound of formula I as defined in any one of Claims 1 to 13, or a pharmaceutically-acceptable salt or solvate, or a pharmaceutically functional derivative thereof; and

(B) another therapeutic agent useful in the treatment of cancer,

wherein each of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

17. A combination product as claimed in Claim 16 which comprises a pharmaceutical

formulation including a compound of formula I as defined in any one of Claims 1 to 13, or a pharmaceutically-acceptable salt or solvate, or a pharmaceutically functional derivative thereof; another therapeutic agent useful in the treatment of cancer; and a pharmaceutically-acceptable adjuvant, diluent or carrier.

18. A combination product as claimed in Claim 16, which comprises a kit of parts comprising components:

(a) a pharmaceutical formulation including a compound of formula I as defined in any one of Claims 1 to 13, or a pharmaceutically-acceptable salt or solvate, or a pharmaceutically functional derivative thereof, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(b) a pharmaceutical formulation including another therapeutic agent useful in the treatment of cancer in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier,

which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

19. A kit of parts as claimed in Claim 18, wherein components (A) and (B) are suitable for sequential, separate and/or simultaneous use in the treatment of cancer.

20. A combination product as claimed in any one of Claims 16 to 19, wherein the other therapeutic agent is selected from:

(i) a cytostatic, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(ii) an angiogenesis inhibitor, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(iii) tamoxifen, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(iv) an aromatase inhibitor, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(v) trastuzumab (Herceptin), or another antibody that is useful in the treatment of cancer;

(vi) a tyrosine kinase inhibitor, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(vii) a glitazone, or a pharmaceutically-acceptable salt, solvate or pharmaceutically

functional derivative thereof;

(viii) biguanides, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(ix) a statin, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(x) an inhibitor of activity of the mammalian target of rapamycin (mTOR), or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(xi) an oligomycin, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(xii) AICAR (aminoimidazole carboxamide ribonucleotide), or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(xiii) a peroxisome proliferator-activated receptor (PPAR) agonist, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(xiv) A-769662, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(xv) D942 (5-(3-(4-(2-(4-Fluorophenyl)ethoxy)-phenyl)propyl)furan-2-carboxylic acid), or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(xvi) AM251, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof;

(xvii) a SIRT1 activator, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof; and/or

(xviii) salidroside, or a pharmaceutically-acceptable salt, solvate or pharmaceutically functional derivative thereof.

21. A combination product as claimed in Claim 20, wherein the other therapeutic agent is selected from cisplatin, doxorubicin, tamoxifen, anastrozole, letrozole, exemastane, herceptin, imatinib, gefitinib, erlotinib, canertinib, sunitinib, zactima, vatalanib, sorafenib, leflunomide, lapatinib, rosiglitazone, metformin, fluvastatin, simvastatin, rosuvastatin, pravastatin, atorvastatin, lovastatin and rapamycin.

22. A combination product as claimed in Claim 21, wherein the other therapeutic agent is selected from cisplatin, doxorubicin, tamoxifen and herceptin.

23. The use of a compound of formula I as defined in any one of Claims 1 to 13, or a pharmaceutically-acceptable salt or solvate, or a pharmaceutically functional derivative thereof, or a combination product as defined in any one of Claims 16 to 22, for the manufacture of a medicament for the treatment of cancer.

24. A compound as defined in any one of Claims 1 to 13, or a pharmaceutically acceptable salt or solvate, or a pharmaceutically functional derivative thereof, or a combination product as defined in any one of Claims 16 to 22, for use in the treatment of cancer.

25. A method of treatment of cancer, which method comprises the administration of an effective amount of a compound of formula I as defined in any one of Claims 1 to 13, or a pharmaceutically-acceptable salt or solvate, or a pharmaceutically functional derivative thereof, or a combination product as defined in any one of Claims 16 to 22, to a patient in need of such treatment.

26. A kit of parts as claimed in Claim 19, a use as claimed in Claim 23, a compound or combination product as claimed in Claim 24, or a method as claimed in Claim 25, wherein the cancer is a solid tumor or a hematopoietic tumor.

27. A kit of parts, use, compound, combination or method as claimed in Claim 26, where the cancer is a solid tumor of the colon, the breast or the prostate.

28. A kit of parts, use, compound, combination or method as claimed in Claim 27, wherein the cancer is of the breast.

29. A kit of parts, use, compound, combination or method as claimed in Claim 27, where the cancer is a hematopoietic tumor that is a leukemia.

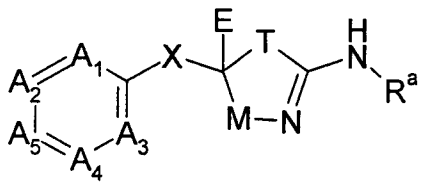
30. A kit of parts comprising:
(I) one of components (a) and (b) as defined in Claim 18, any one of Claims 19 to 22 or 26 to 29 (as dependent on Claim 18); together with
(II) instructions to use that component in conjunction with the other of the two components.

31. A method of making a kit of parts as defined in Claim 18, any one of Claims 19 to 22

or 26 to 29 (as dependent on Claim 18), which method comprises bringing a component (a) into association with a component (b), thus rendering the two components suitable for administration in conjunction with each other.

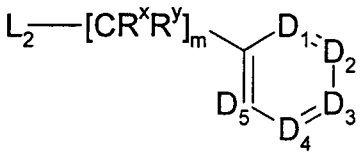
32. A process for the preparation of a compound of formula I as defined in any one of Claims 1 to 13, which process comprises:

(i) for compounds of formula I wherein Y represents $-NR^a-[CR^xR^y]_m-$, reaction of a compound of formula II,



II

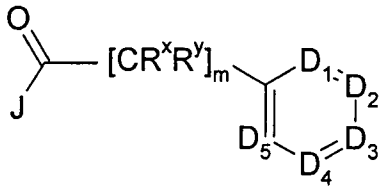
wherein A_1 to A_5, X, E, M, R^a and T are as defined in Claim 1, with a compound of formula III,



III

wherein L_2 represents a suitable leaving group and m, R^x, R^y and D_1 to D_5 are as defined in Claim 1;

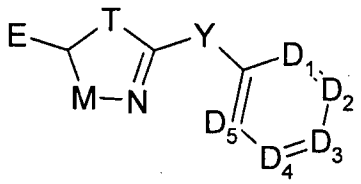
(ii) for compounds of formula I wherein Y represents $-NR^aC(O)-[CR^xR^y]_m-$, reaction of a compound of formula II as defined above, with a compound of formula IV,



IV

wherein J is -OH, -Br or -Cl and m, R^x, R^y and D_1 to D_5 are as defined in Claim 1;

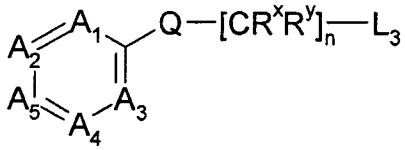
(iii) for compounds of formula I wherein Z is a bond, reaction of a compound of formula V,



V

wherein E, M, T, Y and D_1 to D_5 are as defined in Claim 1, with a compound of formula

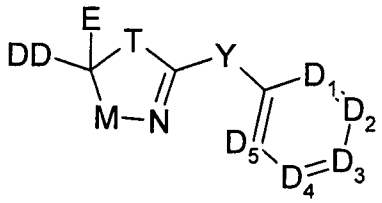
VI,



VI

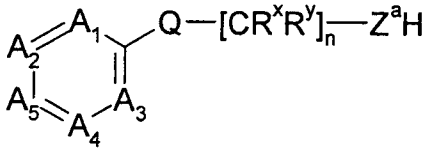
wherein A_1 to A_5, Q, R^x, R^y and n are as defined in Claim 1 and L_3 represents a suitable leaving group;

(iv) for compounds of formula I wherein X is Q-$[CR^xR^y]_n$-Z and Z represents O or S, reaction of a compound of formula VII,



VII

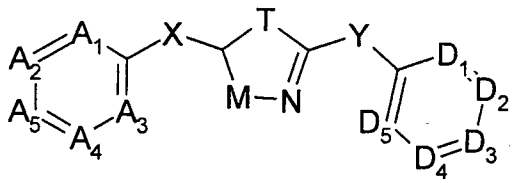
wherein E, M, T, Y and D_1 to D_5 are as defined in Claim 1 and DD represents halo with a compound of formula VIII,



VIII

wherein A_1 to A_5, Q, R^x, R^y and n are as defined in Claim 1 and Z^a represents O or S;

(v) for compounds of formula I wherein E is C_{1-6} alkyl optionally substituted by one or more halo atoms, reaction of a compound of formula IX,



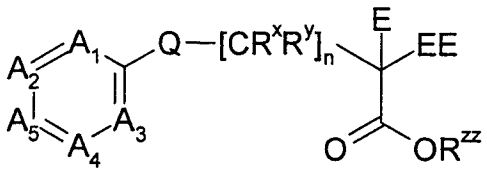
IX

wherein A_1 to A_5, M, X, T, Y and D_1 to D_5 are as defined in Claim 1, with a compound of formula X,

E^a-L_4 X

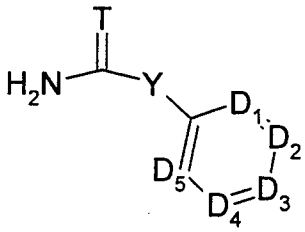
wherein E^a represents C_{1-6} alkyl optionally substituted by one or more halo atoms and L_4 represents a suitable leaving group;

(vi) for compounds of formula I wherein Z is a bond, reaction of a compound of formula XI,



XI

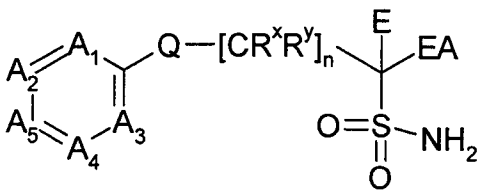
wherein A_1 to A_5, Q, R^x, R^y, n, and E are as defined in Claim 1, EE represents halo and R^{zz} represents C_{1-4} alkyl, with a compound of formula XII,



XII

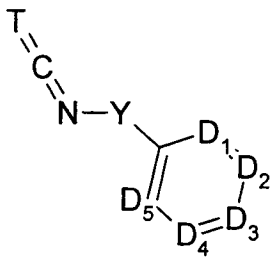
wherein T, Y and D_1 to D_5 are as defined in Claim 1;

(vii) for compounds of formula I wherein Z is a bond and M is $-S(O)_2-$, reaction of a compound of formula XIII,



XIII

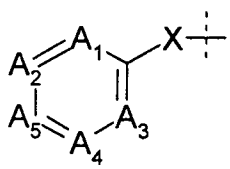
wherein A_1 to A_5, Q, R^x, R^y, n and E are as defined in Claim 1 and EA represents halo, with a compound of formula XIV,



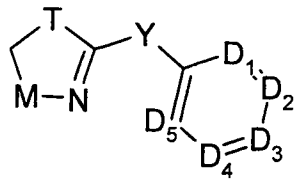
XIV

wherein T, Y and D_1 to D_5 are as defined in Claim 1; or

(viii) for compounds of formula I wherein Q and Z are both bonds, R^x and R^y both represent H, and E is the same as the group:

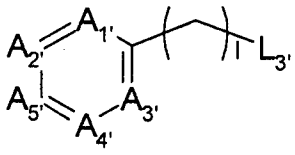


reaction of a compound of formula XIVa,



XIVa

wherein M, T, Y and D_1 to D_5 are as hereinbefore defined, with a compound of formula XIVb,



XIVb

wherein I represents 1 to 3, $L_{3'}$ represents a suitable leaving group and $A_{1'}$ to $A_{5'}$ respectively represent $C(R^{1'})$, $C(R^{2'})$, $C(R^{3'})$, $C(R^{4'})$ and $C(R^{5'})$, or, alternatively, up to two of A_1 to A_5 may independently represent N, wherein $R^{1'}$ to $R^{5'}$ independently represent H, halo, $-R^7$, $-CF_3$, $-CN$, $-NO_2$, $-C(O)R^7$, $-C(O)OR^7$, $-N(R^{7a})R^{7b}$, $-N(R^7)_3^+$, $-SR^7$, $-OR^7$, $-NH(O)R^7$ or $-SO_3R^7$, or any two of $R^{1'}$ to $R^{5'}$ which are adjacent to each other are optionally linked to form, along with two atoms of the essential benzene ring in the compound of formula I, an aromatic or non-aromatic 3- to 8-membered ring, optionally containing 1 to 3 heteroatoms selected from O, S and N, which ring is itself optionally substituted by one or more substituents selected from halo, $-R^7$, $-OR^7$ and =O, wherein R^7, R^{7a} and R^{7b} are as defined in Claim 1.

Fig 1

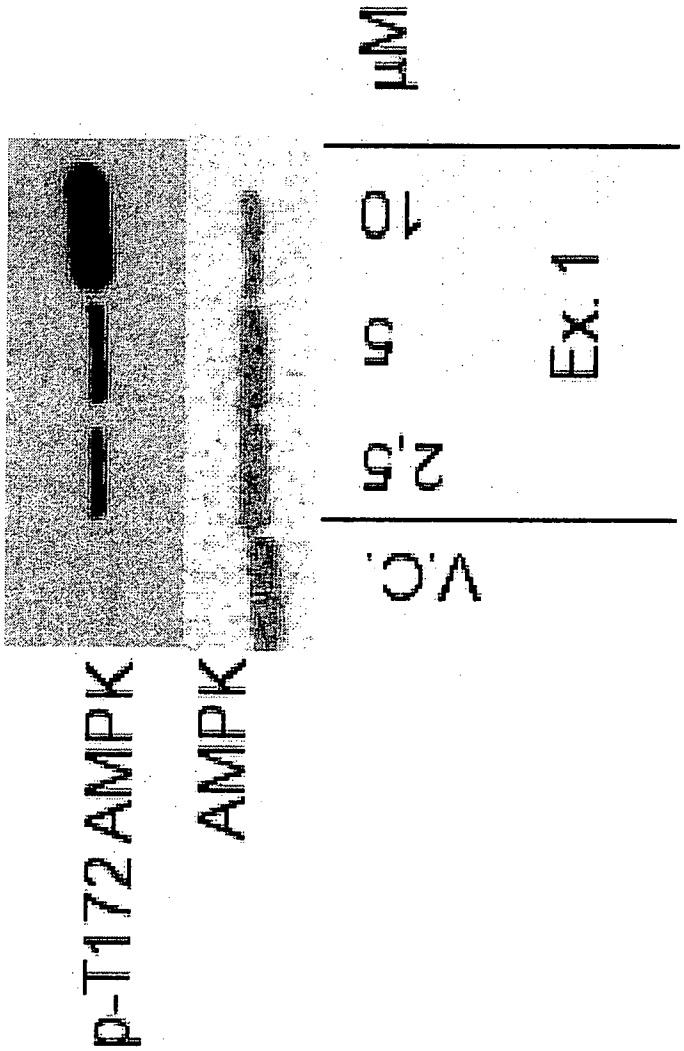
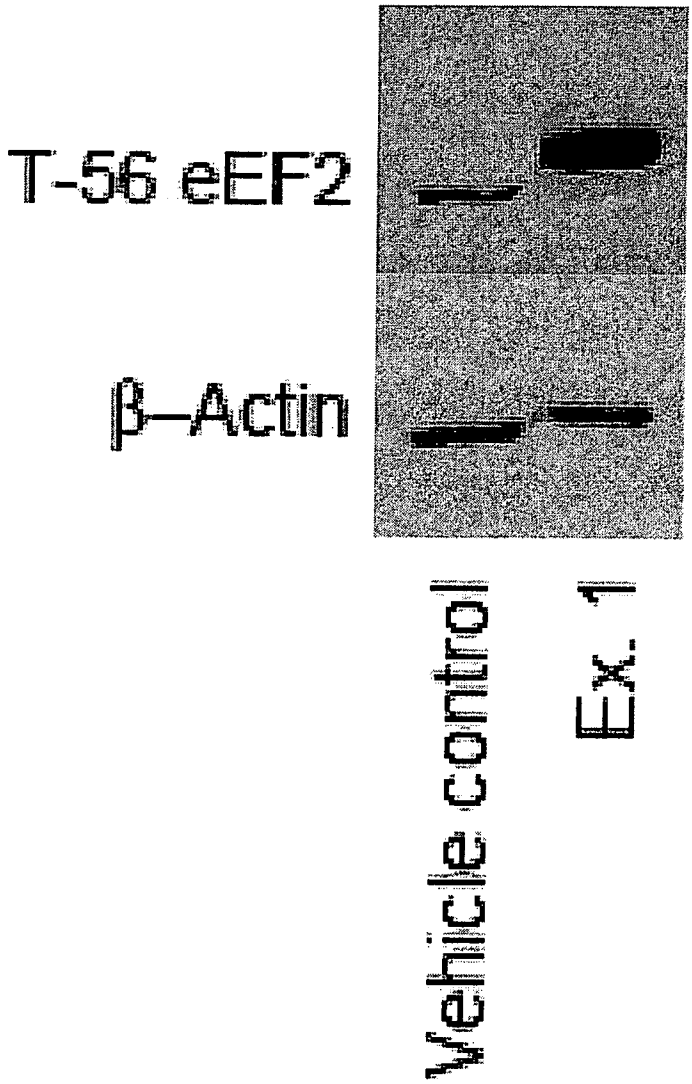


Fig 2



INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2010/000144

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D277/42 C07D417/10 C07D285/01 A61K31/426 A61P35/00
ADD.

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, BIOSIS, CHEM ABS Data, WPI 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.
X	FOTSCH CHRISTOPHER ET AL: "Further Studies with the 2-Amino-1,3-thiazol-4(5H)-one Class of 11 beta-Hydroxysteroid Dehydrogenase Type 1 Inhibitors: Reducing Pregnane X Receptor Activity and Exploring Activity in a Monkey Pharmacodynamic Model" JOURNAL OF MEDICINAL CHEMISTRY, vol. 51, no. 24, December 2008 (2008-12), pages 7953-7967, XP002582999 ISSN: 0022-2623 scheme 4, product of step b; page 7957 ----- -/--	1-12,32

[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

"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

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Date of the actual completion of the international search	Date of mailing of the international search report
1 June 2010	24/06/2010

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	Gutke, Hans-Jürgen

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International application No
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