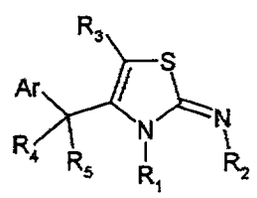
SUBSTITUTED IMIDAZOTHIAZOLES AS ANTIDEPRESSANT AGENTS

The present invention relates to novel 3-(benzo[*b*]thiophen-3-yl)imidazo[2,1-*b*]thiazoles which have affinity for 5-HT_{1A} receptors and which inhibit neuronal reuptake of 5-hydroxytryptamine and/or noradrenaline, to processes for their preparation, to pharmaceutical compositions containing them and to their use in the treatment of depression, anxiety, psychoses (for example schizophrenia), tardive dyskinesia, obesity, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, cerebral ischaemia, obsessive-compulsive behaviour, panic attacks, social phobias, eating disorders such as bulimia, anorexia, snacking and binge eating, non-insulin dependent diabetes mellitus, hyperglycaemia, hyperlipidaemia, stress, as an aid to smoking cessation and in the treatment and/or prophylaxis of seizures, neurological disorders such as epilepsy and/or conditions in which there is neurological damage such as stroke, brain trauma, cerebral ischaemia, head injuries and haemorrhage.

WO 98/41528 discloses that compounds of Formula A



A

including pharmaceutically acceptable salts thereof in the form of individual enantiomers, racemates, or other mixtures of enantiomers,

in which:

Ar is phenyl, naphthyl or benzo[*b*]thiophenyl, each of which may be optionally substituted by one or more substituents selected from a) halo, b) an alkyl group containing 1 to 3 carbon atoms optionally substituted by one or more halo, c) an alkoxy group containing 1 to 3 carbon atoms optionally substituted by one or more halo, d) an alkylthio group containing 1 to 3 carbon atoms optionally substituted by one or more halo, e) a phenoxy group optionally substituted by one or more halo or f) phenyl optionally substituted by one or more halo;

R_1 and R_2 , which may be the same or different, independently are a) H, b) an alkyl group containing 1 to 6 carbon atoms, c) an alkenyl group containing 3 to 6 carbon atoms, d) a cycloalkyl group containing 3 to 7 carbon atoms, e) a cycloalkylmethyl group in which the ring contains 3 to 7 carbon atoms, f) an aryl or heteroaryl group optionally substituted by one or more substituents selected from i) halo, ii) an alkyl group containing 1 to 3 carbon atoms optionally substituted by one or more halo, iii) an alkoxy group containing 1 to 3 carbon atoms optionally substituted by one or more halo, iv) an alkylthio group containing 1 to 3 carbon atoms optionally substituted by one or more halo, g) an arylalkyl or heteroarylalkyl group in which the alkyl chain contains 1 to 3 carbon atoms and in which the aryl or heteroaryl group may optionally be substituted by one or more substituents selected from i) halo, ii) an alkyl group containing 1 to 3 carbon atoms optionally substituted by one or more halo, iii) an alkoxy group containing 1 to 3 carbon atoms optionally substituted by one or more halo, iv) an alkylthio group containing 1 to 3 carbon atoms optionally substituted by one or more halo; or R_1 and R_2 form an alkylene chain optionally substituted by one or more alkyl groups each containing 1 to 3 carbon atoms, such that, together with the atoms to which they are attached, they form a 5 or 6 membered ring,

R_3 is a) H, b) an aryl or heteroaryl group optionally substituted by one or more substituents selected from i) halo, ii) an alkyl group containing 1 to 3 carbon atoms optionally substituted by one or more halo, iii) an alkoxy group containing 1 to 3 carbon atoms optionally substituted by one or more halo, iv) an alkylthio group containing 1 to 3 carbon atoms optionally substituted by one or more halo, c) an arylmethyl group in which the aryl is optionally substituted by one or more substituents selected from i) halo, ii) an alkyl group containing 1 to 3 carbon atoms optionally substituted by one or more halo, iii) an alkoxy group containing 1 to 3 carbon atoms optionally substituted by one or more halo, iv) an alkylthio group containing 1 to 3 carbon atoms optionally substituted by one or more halo; or d) an alkoxyalkyl group containing 3 to 6 carbon atoms; and

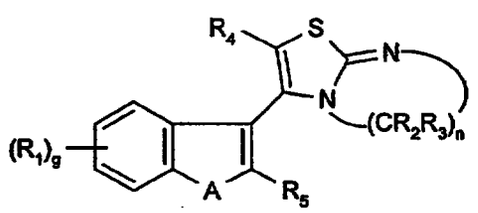
R_4 and R_5 , which may be the same or different, independently are an alkyl group containing 1 to 3 carbon atoms, or R_4 and R_5 together with the atom to which they are attached form a cycloalkyl ring containing 3 to 6 carbon atoms;

are useful in the treatment of depression, anxiety, Parkinson's disease, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy, and as

neuroprotective agents to protect against conditions such as stroke. The compounds of the present invention are not disclosed or suggested in this document.

Sharpe C.J and Shadbolt R.S. (Journal of Medicinal Chemistry, 1971, Vol 14 No.10, p977-982) disclose certain dihydroimidazo[2,1-*b*]thiazole compounds having antidepressant activity. However, the document also states that these compounds were generally less active and more toxic than the imidazolines also disclosed in the document. The compounds of the present invention are not disclosed or suggested in this document.

WO 97/02269 discloses that compounds of formula B



B

including pharmaceutically acceptable salts thereof

in which

A is $S(O)_p$ or O;

p is 0, 1 or 2;

g is 0, 1, 2, 3, or 4;

n is 2 or 3;

R_1 is a) halo, b) an alkyl group containing 1 to 3 carbon atoms optionally substituted by one or more halo, c) an alkoxy group containing 1 to 3 carbon atoms optionally substituted by one or more halo, d) an alkylthio group, an alkylsulphinyl group or an alkylsulphonyl group each containing 1 to 3 carbon atoms optionally substituted by one or more halo, e) hydroxy, f) an acyloxy group containing 1 to 3 carbon atoms, g) a hydroxyalkyl group containing 1 to 3 carbon atoms, h) cyano, i) an alkanoyl group containing 1 to 6 carbon atoms, j) an alkoxycarbonyl group containing 2 to 6 carbon atoms, k) a carbamoyl group or a carbamoylmethyl group each optionally *N*-substituted by one or two alkyl groups each containing 1 to 3 carbon atoms, l) a sulphamoyl or sulphamoylmethyl group each optionally *N*-substituted by one or two alkyl groups each containing 1 to 3 carbon atoms, or m) an amino group optionally

substituted by one or two alkyl groups each containing 1 to 3 carbon atoms; R_1 being the same or different when g is 2, 3 or 4;

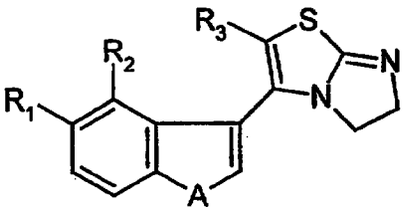
R_2, R_3 and R_4 independently are H or an alkyl group containing 1 to 3 carbon atoms optionally substituted by one or more halo; and

R_5 is a) halo, b) an alkyl group containing 1 to 3 carbon atoms optionally substituted by one or more halo, c) an alkoxy group containing 1 to 3 carbon atoms optionally substituted by one or more halo, d) an alkylthio group, an alkylsulphinyl group or an alkylsulphonyl group each containing 1 to 3 carbon atoms optionally substituted by one or more halo, e) hydroxy, f) an acyloxy group containing 1 to 3 carbon atoms, g) a hydroxyalkyl group containing 1 to 3 carbon atoms, h) cyano, i) an alkanoyl group containing 1 to 6 carbon atoms, j) an alkoxycarbonyl group containing 2 to 6 carbon atoms, k) a carbamoyl group or a carbamoylmethyl group each optionally *N*-substituted by one or two alkyl groups each containing 1 to 3 carbon atoms, l) a sulphamoyl or sulphamoylmethyl group each optionally *N*-substituted by one or two alkyl groups each containing 1 to 3 carbon atoms, m) an amino group optionally substituted by one or two alkyl groups each containing 1 to 3 carbon atoms, or n) H ;

have affinity for 5-HT_{1A} receptors and inhibit neuronal reuptake of 5-hydroxytryptamine and/or noradrenaline. These compounds are stated to be useful in the treatment of CNS disorders. However, these compounds exhibit activity as monoamine oxidase inhibitors and/or have affinity for other receptors, for example muscarinic receptors, and are therefore likely to cause undesired side effects. Surprisingly the present invention provides compounds with unexpectedly superior selectivity and efficacy. The compounds of the present invention are not specifically disclosed or suggested in WO 97/02269.

US4,160,768 discloses that 3-(2-benzofuranyl)-5,6-dihydroimidazo[2,1-*b*]-thiazole is useful as an anti-inflammatory agent. This document does not disclose or suggest the compounds of the present invention.

The present invention provides novel compounds of Formula I



I

including pharmaceutically acceptable salts thereof,

in which

A is S or O;

R_1 is H, halo, a C_{1-3} alkyl group or a C_{1-3} alkylthio group;

R_2 is H or fluoro; and

R_3 is methyl, ethyl or isopropyl.

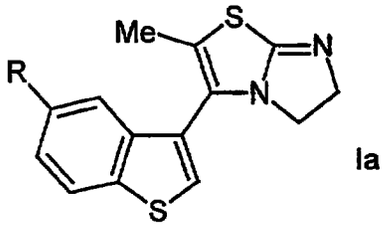
Preferred substituents R_1 are H, fluoro, chloro, bromo, methyl and methylthio.

Preferably A is S.

Preferably A is O.

More preferably R_3 is methyl.

A preferred group of compounds of Formula I is represented by Formula Ia



Ia

including pharmaceutically acceptable salts thereof in which R is H or chloro.

In preferred compounds of the present invention A is S ; R_1 is H, fluoro, or chloro; R_2 is H or fluoro; and R_3 is methyl.

In more preferred compounds of the present invention A is S; R_1 is H or fluoro: R_2 is H or fluoro; and R_3 is methyl.

In most preferred compounds of the present invention A is S; R_1 is H; R_2 is H; and R_3 is methyl.

Compounds of Formula I may exist as salts with pharmaceutically acceptable acids. The present invention includes all such salts. Examples of such salts include hydrochlorides, hydrobromides, sulphates, methanesulphonates, nitrates, maleates, formates, acetates, citrates, fumarates, tartrates [eg (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures], succinates, benzoates, oxalates and salts with amino acids such as glutamic acid. Such salts may be prepared by methods known to those skilled in the art.

Certain compounds of Formula I may exist in different tautomeric forms or as different geometric isomers, and the present invention includes each tautomer and/or geometric isomer of compounds of Formula I and mixtures thereof.

Certain compounds of Formula I may exist in different stable conformational forms which may be separable. For example, if a bulky group is present there may be restricted rotation about one or more single bond or bonds due to steric hindrance. Torsional asymmetry due to restricted rotation about an asymmetric single bond, for example because of steric hindrance or ring strain, may permit separation of different conformers. The present invention includes each conformational isomer of compounds of Formula I and mixtures thereof.

Certain compounds of Formula I and their salts may exist in more than one crystal form and the present invention includes each crystal form and mixtures thereof. Certain compounds of Formula I and their salts may also exist in the form of solvates, for example hydrates, and the present invention includes each solvate and mixtures thereof.

Certain compounds of Formula I contain one or more chiral centres, and exist in different optically active forms. When compounds of Formula I contain one chiral centre, the compounds exist in two enantiomeric forms and the present invention includes both enantiomers and mixtures of enantiomers. The enantiomers may be resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric salts which may be separated, for example, by crystallisation; formation of diastereoisomeric derivatives or complexes which may be separated, for example, by crystallisation, gas-liquid or liquid chromatography; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support for example silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired enantiomeric form. Alternatively, specific enantiomers may be synthesised by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

When a compound of Formula I contains more than one chiral centre it may exist in diastereoisomeric forms. The diastereoisomeric pairs may be separated by methods known to those skilled in the art, for example chromatography or crystallisation and the individual enantiomers within each pair may be separated as described above. The present invention includes each diastereoisomer of compounds of Formula I and mixtures thereof.

Specific compounds of Formula I are:-

3-(benzo[*b*]thiophen-3-yl)-2-methyl-5,6-dihydroimidazo[2,1-*b*]thiazole;
3-(5-chlorobenzo[*b*]thiophen-3-yl)-2-methyl-5,6-dihydroimidazo[2,1-*b*]thiazole;
3-(4-fluorobenzo[*b*]thiophen-3-yl)-2-methyl-5,6-dihydroimidazo[2,1-*b*]thiazole;
3-(benzo[*b*]thiophen-3-yl)-2-ethyl-5,6-dihydroimidazo[2,1-*b*]thiazole;
2-methyl-3-(5-methylbenzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole;

3-(benzo[*b*]thiophen-3-yl)-2-isopropyl-5,6-dihydroimidazo[2,1-*b*]thiazole;
2-methyl-3-[5-(methylthio)benzo[*b*]thiophen-3-yl]-5,6-dihydroimidazo[2,1-*b*]thiazole;
3-(5-fluorobenzo[*b*]thiophen-3-yl)-2-methyl-5,6-dihydroimidazo[2,1-*b*]thiazole;
3-(5-chlorobenzo[*b*]thiophen-3-yl)-2-ethyl-5,6-dihydroimidazo[2,1-*b*]thiazole;
3-(5-bromobenzo[*b*]thiophen-3-yl)-2-methyl-5,6-dihydroimidazo[2,1-*b*]thiazole; and
3-(benzo[*b*]furan-3-yl)-2-methyl-5,6-dihydroimidazo[2,1-*b*]thiazole

including pharmaceutically acceptable salts thereof.

The present invention also includes pharmaceutical compositions comprising a therapeutically effective amount of a compound of Formula I or a salt thereof together with a pharmaceutically acceptable diluent or carrier.

As used hereinafter, the term "active compound" denotes a compound of Formula I or a salt thereof. In therapeutic use, the active compound may be administered orally, rectally, parenterally or topically, preferably orally. Thus the therapeutic compositions of the present invention may take the form of any of the known pharmaceutical compositions for oral, rectal, parenteral or topical administration. Pharmaceutically acceptable carriers suitable for use in such compositions are well known in the art of pharmacy. The compositions of the invention may contain 0.1-99% by weight of active compound. The compositions of the invention are generally prepared in unit dosage form. Preferably the unit dosage of active ingredient is 1-500 mg. The excipients used in the preparation of these compositions are the excipients known in the pharmacist's art.

Compositions for oral administration are the preferred compositions of the invention and these are the known pharmaceutical forms for such administration, for example tablets, capsules, syrups and aqueous or oil suspensions. The excipients used in the preparation of these compositions are the excipients known in the pharmacist's art. Tablets may be prepared by mixing the active compound with an inert diluent such as calcium phosphate in the presence of disintegrating agents, for example maize starch, and lubricating agents, for example magnesium stearate, and tableting the mixture by known methods. The tablets may be formulated in a manner known to those skilled in the art so as to give a sustained release of the compounds of the present invention. Such tablets may, if desired, be provided with enteric

coatings by known methods, for example by the use of cellulose acetate phthalate. Similarly, capsules, for example hard or soft gelatin capsules, containing the active compound with or without added excipients, may be prepared by conventional means and, if desired, provided with enteric coatings in a known manner. The tablets and capsules may conveniently each contain 1 to 500 mg of the active compound. Other compositions for oral administration include, for example, aqueous suspensions containing the active compound in an aqueous medium in the presence of a non-toxic suspending agent such as sodium carboxymethylcellulose, and oily suspensions containing a compound of the present invention in a suitable vegetable oil, for example arachis oil.

Solid oral dosage forms may be formulated in a manner known to those skilled in the art so as to give a sustained release of the active compound. Enteric coated, solid oral dosage forms comprising compositions of the present invention may be advantageous, depending on the nature of the active compound. Various materials, for example shellac and/or sugar, may be present as coatings, or to otherwise modify the physical form of the oral dosage form. For example tablets or pills may, if desired, be provided with enteric coatings by known methods, for example by the use of cellulose acetate phthalate and/or hydroxy propyl methylcellulose phthalate.

Capsules and/or caplets (for example hard or soft gelatin capsules) comprising the active compound (with or without added excipients such as a fatty oil), may be prepared by conventional means and, if desired, provided with enteric coatings in a known manner. The contents of the capsule and/or caplet may be formulated using known methods to give sustained release of the active compound.

Liquid oral dosage forms comprising compositions of the present invention may be an elixir, suspension and/or syrup (for example, aqueous suspensions containing the active compound in an aqueous medium in the presence of a non-toxic suspending agent [such as sodium carboxymethylcellulose] and/or oily suspensions containing the active compound in a suitable vegetable oil [such as arachis oil and/or sunflower oil]). Liquid oral dosage forms may also comprise one or more sweetening agent, flavouring agent, preservatives and/or mixtures thereof.

The active compound may be formulated into granules with or without additional excipients. The granules may be ingested directly by the patient or they may be added to a suitable liquid carrier (for example water) before ingestion. The granules may contain disintegrants (for example a pharmaceutically acceptable effervescent couple formed from an acid and a carbonate or bicarbonate salt) to facilitate dispersion in the liquid medium.

Preferably each of the above oral dosage forms may contain from about 1 mg to about 1000 mg, more preferably from about 5 mg to about 500 mg (for example 10 mg, 50 mg, 100 mg, 200 mg or 400 mg) of the active compound.

Compositions of the invention suitable for rectal administration are the known pharmaceutical forms for such administration, for example, suppositories with hard fat, semi-synthetic glyceride, cocoa butter and/or polyethylene glycol bases.

Pharmaceutical compositions may also be administered parenterally (for example subcutaneously, intramuscularly, intradermally and/or intravenously [such as by injection and/or infusion] in the known pharmaceutical dosage forms for parenteral administration (for example sterile suspensions in aqueous and/or oily media and/or sterile solutions in suitable solvents, preferably isotonic with the blood of the intended patient). Parenteral dosage forms may be sterilised (for example by micro-filtration and/or using suitable sterilising agents [such as ethylene oxide]). Optionally one or more of the following pharmaceutically acceptable adjuvants suitable for parenteral administration may be added to parenteral dosage forms: local anaesthethetics, preservatives, buffering agents and/or mixtures thereof. Parenteral dosage forms may be stored in suitable sterile sealed containers (for example ampoules and/or vials) until use. To enhance stability during storage the parenteral dosage form may be frozen after filling the container and fluid (for example water) may be removed under reduced pressure.

Pharmaceutical compositions may be administered nasally in known pharmaceutical forms for such administration (for example sprays, aerosols,

nebulised solutions and/or powders). Metered dose systems known to those skilled in the art (for example aerosols and/or inhalers) may be used.

Pharmaceutical compositions may be administered to the buccal cavity (for example sub-lingually) in known pharmaceutical forms for such administration (for example slow dissolving tablets, chewing gums, troches, lozenges, pastilles, gels, pastes, mouthwashes, rinses and/or powders).

Compositions for topical administration may comprise a matrix in which the pharmacologically active compounds of the present invention are dispersed so that the compounds are held in contact with the skin in order to administer the compounds transdermally. A suitable transdermal composition may be prepared by mixing the pharmaceutically active compound with a topical vehicle, such as a mineral oil, petrolatum and/or a wax, for example paraffin wax or beeswax, together with a potential transdermal accelerant such as dimethyl sulphoxide or propylene glycol. Alternatively the active compounds may be dispersed in a pharmaceutically acceptable cream or ointment base. The amount of active compound contained in a topical formulation should be such that a therapeutically effective amount of the compound is delivered during the period of time for which the topical formulation is intended to be on the skin.

The compounds of the present invention may also be administered by continuous infusion either from an external source, for example by intravenous infusion or from a source of the compound placed within the body. Internal sources include implanted reservoirs containing the compound to be infused which is continuously released for example by osmosis and implants which may be (a) liquid such as a suspension or solution in a pharmaceutically acceptable oil of the compound to be infused for example in the form of a very sparingly water-soluble derivative such as a dodecanoate salt or (b) solid in the form of an implanted support, for example of a synthetic resin or waxy material, for the compound to be infused. The support may be a single body containing all the compound or a series of several bodies each containing part of the compound to be delivered. The amount of active compound present in an internal source should be such that a

therapeutically effective amount of the compound is delivered over a long period of time.

In some formulations it may be beneficial to use the compounds of the present invention in the form of particles of very small size, for example as obtained by fluid energy milling.

In the compositions of the present invention the active compound may, if desired, be associated with other compatible pharmacologically active ingredients.

The present invention also comprises a compound of Formula I for use as a medicament.

The pharmaceutical compositions containing a therapeutically effective amount of a compound of Formula I may be used to treat depression, anxiety, psychoses (for example schizophrenia), tardive dyskinesia, obesity, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, cerebral ischaemia, obsessive-compulsive behaviour, panic attacks, social phobias, eating disorders such as bulimia, anorexia, snacking and binge eating, non-insulin dependent diabetes mellitus, hyperglycaemia, hyperlipidaemia, and stress, in mammals particularly humans, and as an aid to smoking cessation in human beings. The compositions may also be used in the treatment and/or prophylaxis of seizures, neurological disorders such as epilepsy and/or conditions in which there is neurological damage such as stroke, brain trauma, cerebral ischaemia, head injuries and haemorrhage. Whilst the precise amount of active compound administered in such treatment will depend on a number of factors, for example the age of the patient, the severity of the condition and the past medical history, and always lies within the sound discretion of the administering physician, the amount of active compound administered per day is in the range 1 to 1000 mg preferably 5 to 500 mg given in single or divided doses at one or more times during the day.

In yet another aspect, the present invention provides the use of a compound of Formula I in the manufacture of a medicament for use in the treatment of depression, anxiety, psychoses (for example schizophrenia), tardive dyskinesia,

obesity, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, cerebral ischaemia, obsessive-compulsive behaviour, panic attacks, social phobias, eating disorders such as bulimia, anorexia, snacking and binge eating, non-insulin dependent diabetes mellitus, hyperglycaemia, hyperlipidaemia, stress, as an aid to smoking cessation, seizures, neurological disorders such as epilepsy and/or conditions in which there is neurological damage such as stroke, brain trauma, cerebral ischaemia, head injuries and haemorrhage.

The present invention also provides a method of treating depression, anxiety, psychoses (for example schizophrenia), tardive dyskinesia, obesity, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, cerebral ischaemia, obsessive-compulsive behaviour, panic attacks, social phobias, eating disorders such as bulimia, anorexia, snacking and binge eating, non-insulin dependent diabetes mellitus, hyperglycaemia, hyperlipidaemia, stress, seizures, neurological disorders such as epilepsy and/or conditions in which there is neurological damage such as stroke, brain trauma, cerebral ischaemia, head injuries and haemorrhage which comprises the administration of a therapeutically effective amount of a compound of Formula I to a patient in need thereof. The present invention also provides a method of aiding smoking cessation in human beings which comprises the administration of a therapeutically effective amount of a compound of Formula I to a patient in need thereof.

The present invention also provides a method of reducing the craving to smoke in human beings which comprises the administration of a therapeutically effective amount of a compound of Formula I to a patient in need thereof. The present invention also provides a method of reducing weight gain after smoking cessation in human beings which comprises the administration of a therapeutically effective amount of a compound of Formula I to a patient in need thereof.

In addition the compounds of the present invention may be useful in the treatment or prevention of metabolic diseases and conditions arising therefrom, for example non exercise activity thermogenesis and increased metabolic rate, sexual dysfunction, sleep apnoea, premenstrual syndrome, urinary incontinence, hyperactivity disorders, hiatial hernia and reflux esophagitis, pain, especially

neuropathic pain, weight gain associated with drug treatment, chronic fatigue syndrome, osteoarthritis and gout, cancers associated with weight gain, menstrual dysfunction, gallstones, orthostatic hypotension and pulmonary hypertension.

The compounds of the present invention may be useful in preventing cardiovascular disease, and in reducing platelet adhesiveness, in aiding weight loss after pregnancy and in aiding weight loss after smoking cessation.

The compounds of the present invention are particularly useful in treating obesity and related co-morbid conditions, for example, diabetes, hyperglycaemia and hyperlipidaemia. It is known that monoamine reuptake inhibitors which are used to treat obesity are often associated with cardiovascular side effects, for example, increased heart rate and increased blood pressure. The compounds of the present invention reduce the cardiovascular side effects which might be expected to occur from the administration of a monoamine reuptake inhibitor particularly a noradrenaline reuptake inhibitor. Whilst not wishing to be bound by theory it is likely that the combination of 5-HT_{1A} agonism in the compounds of the present invention reduces the cardiovascular side effects which might have arisen from their monoamine reuptake inhibition particularly their noradrenaline reuptake inhibition.

In another aspect the present invention provides a method of reducing the cardiovascular side effects of an anti-obesity drug comprising incorporating into the compound 5-HT_{1A} agonism.

In another aspect the present invention provides the use of a compound which is a 5-HT_{1A} agonist and which is a monoamine reuptake inhibitor particularly a noradrenaline reuptake inhibitor in the treatment of obesity and related co-morbid conditions without causing cardiovascular side effects.

The beneficial properties of especially preferred compounds of the present invention in reducing cardiovascular side-effects may be demonstrated in rat telemetry studies in which heart rate, blood pressure, body temperature and locomotor activity are recorded continuously over time. Suitable methods are described in: Brockway, BP, Mills, PA & Azar, SH (1991) A new method for

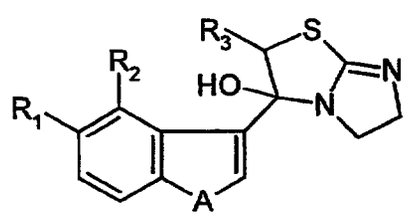
continuous chronic measurement of blood pressure, heart rate and activity in the rat via radio-telemetry. Clinical and Experimental Hypertension - Theory and Practice A13(5), 885-895 and Guiol, C, Ledoussal, C & Surgé, J-M (1992) A radiotelemetry system for chronic measurement of blood pressure and heart rate in the unrestrained rat. Validation of method. Journal of Pharmacological and Toxicological Methods 28, 99-105.

The 5-HT_{1A} agonism of especially preferred compounds of the present invention may be determined by electrophysiology by methods known to those skilled in the art.

Processes for the preparation of compounds of Formula I will now be described. The processes may be performed on an individual basis, or by multiple parallel synthesis, also known as High Speed Analoguing. The processes are preferably carried out at atmospheric pressure.

Compounds of Formula I may be prepared by methods disclosed in WO 97/02269. Additionally compounds of Formula I may be prepared by methods described below.

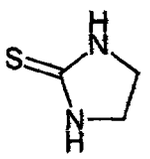
Compounds of Formula I may be prepared by dehydrating a compound of Formula II



II

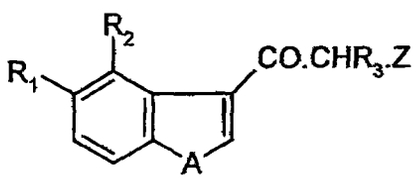
in which A, R_1, R_2, R_3, and g are as hereinbefore defined, optionally in the presence of an acid, for example acetic or sulphuric acid, at a temperature in the range 0-200°C; preferably in the range 20-150°C.

Compounds of Formula II may be prepared by reacting a compound of Formula III



III

with a compound of Formula IV

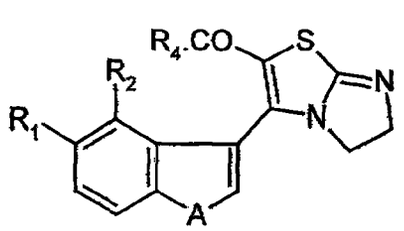


IV

in which Z is a leaving group, for example a halo such as bromo, and A, R_1, R_2, and R_3 are as hereinbefore defined, at a temperature in the range 0-200°C, in the presence of a solvent, for example ethanol and optionally in the presence of an acid, for example acetic acid; preferably by heating at a temperature in the range 20°C to the boiling point of the solvent used.

Compounds of Formula I may also be prepared directly by reacting a compound of Formula III with a compound of Formula IV at a temperature in the range of 0-200°C, optionally in the presence of an acid, for example acetic acid, and optionally in the presence of a solvent, for example ethanol, without isolation of the intermediate of Formula II; preferably by heating at a temperature in the range 20-150°C.

Compounds of Formula I in which R_3 is methyl or ethyl, may be prepared by reacting a compound of Formula V

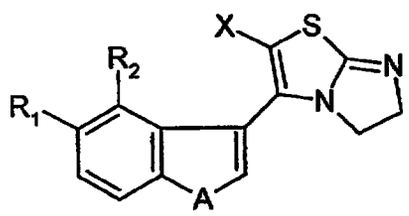


V

in which R_1, R_2 and A are as previously defined and R_4 is H or methyl with a reducing agent, for example borane/t-butylamine complex, optionally in the presence of a

catalyst, for example a Lewis acid catalyst such as aluminium chloride, in a solvent, for example dichloromethane, at a temperature in the range of –20 °C to the boiling point of the solvent used.

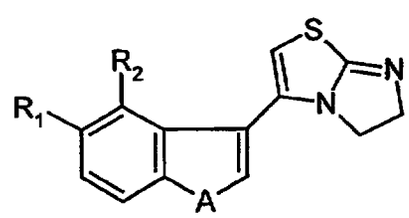
Compounds of Formula V may be prepared by reacting a compound of Formula VI



VI

in which X is a leaving group, for example bromo, with a metallating agent, for example ethylmagnesium chloride, followed by a formylating or acylating agent, for example dimethylformamide or *N*-methoxy-*N*-methylacetamide, in the presence of a solvent, for example tetrahydrofuran, at a temperature in the range of –50 °C to the boiling point of the solvent used.

Compounds of Formula VI in which X is bromo may be prepared by reacting a compound of Formula VII



VII

with a brominating agent, for example bromine or phenyltrimethylammonium tribromide, in the presence of a solvent, for example dichloromethane or tetrahydrofuran, at a temperature in the range of –50 °C to the boiling point of the solvent used.

Compounds of Formula VII may be prepared by methods disclosed in WO97/02269.

The ability of compounds of Formula I to interact with 5-hydroxytryptamine (5-HT) receptors has been demonstrated for the products of Examples 1 to 17 by the following test which determines the ability of the compounds to inhibittritiated ligand binding to 5-HT receptors *in vitro* and in particular to 5-HT_{1A} receptors.

Hippocampal tissue from the brains of male Sprague-Dawley rats (Charles River; weight range 150-250 g) was homogenised in ice-cold 50 mM Tris-HCl buffer (pH 7.7 when measured at 25°C, 1:40 w/v) and centrifuged at 40,000 g at 4°C for 10 minutes. The pellet was rehomogenised in the same buffer, incubated at 37°C for 10 minutes and centrifuged at 40,000 g at 4°C for 10 minutes. The final pellet was resuspended in 50 mM Tris-HCl buffer (pH 7.7) containing 4 mM $CaCl_2$, 0.1% L-ascorbic acid and 10 μM pargyline hydrochloride (equivalent to 6.25 mg wet weight of tissue/ml) and used immediately in the binding assay.

Membranes (400 μl; equivalent to 2.5 mg wet weight of tissue/tube) were incubated with 50 μl of [^{3}H]8-hydroxy-2-(dipropylamino)tetralin ([^{3}H]8-OH-DPAT) at a single concentration of 1 nM and 50 μl of distilled water (total binding) or 50 μl of test compound (at a single concentration of 10^{-6} M or at 10 concentrations ranging from 10^{-11}-10^{-3} M) or 50 μl of 5-HT (10 μM, non-specific binding) at 25°C for 30 minutes. The incubation was terminated by rapid filtration under vacuum through Skatron 11734 filters using a Skatron Cell Harvester. Filters were washed with ice-cold 50 mM Tris-HCl buffer, pH 7.7 (at 25°C, wash setting 9,9,0). The scored filter paper discs were punched out into vials, scintillation fluid added and radioactivity determined by liquid scintillation counting.

The ability of compounds of Formula I to interact with 5-hydroxytryptamine (5-HT) reuptake sites has been demonstrated for the products of Examples 1 to 17 by the following test which determines the ability of compounds to displace the standard ligand, [^{3}H]citalopram, from 5-HT reuptake sites *in vitro.*

Frontal cortical tissue from the brains of male Charles River rats weighing 150-250 g was homogenised in ice-cold 50 mM Tris-HCl, pH 7.4 (when measured at 25°C) containing 120 mM sodium chloride and 5 mM potassium chloride (Tris buffer; 1:30 w/v) and centrifuged at 40,000 g for 10 minutes. The supernatant was discarded and the pellet rehomogenised in Tris buffer, 1:60 w/v, and centrifuged at 40,000 g for 10 minutes. This step was repeated a further time. The final pellet was resuspended in 50 mM Tris-HCl, pH 7.4 containing 120 mM sodium chloride and 5 mM potassium chloride (equivalent to 3.125 mg wet weight of tissue/ml) and used immediately in the binding assay. All centrifugations were performed at 4°C.

Membranes (400 µl; equivalent to 1.25 mg wet weight of tissue/tube) were incubated with 50 µl [^{3}H]citalopram at a single concentration of 1.3 nM and 50 µl of distilled water (total binding) or 50 µl of test compound (at a single concentration of 10^{-6} M or at 10 concentrations ranging from 10^{-11}-10^{-3} M) or 50 µl of paroxetine (0.5 µM; non-specific binding) for 1 h at 27°C. Membrane bound radioactivity was recovered by filtration under vacuum through Skatron 11734 filters presoaked in 0.5% PEI using a Skatron Cell Harvester. Filters were then washed in ice-cold 50 mM Tris-HCl buffer, pH 7.4 (at 25°C, wash setting 9,9,0). The scored filter paper discs were punched out into vials, scintillation fluid added and radioactivity determined by liquid scintillation counting.

The ability of compounds of Formula I to interact with noradrenaline (NA) reuptake sites has been demonstrated for the products of Examples 1 to 17 by the following test which determines the ability of compounds to displace the standard ligand, [^{3}H]nisoxetine, from noradrenaline reuptake sites *in vitro*.

Frontal cortical tissue from the brains of male Charles River rats weighing 150-250 g was homogenised in ice-cold 50 mM Tris-HCl, pH 7.4 (at 25°C) containing 120 mM sodium chloride and 5 mM potassium chloride (Tris buffer; 1:60 w/v) using a Kinematic polytron (speed setting 6 for 10 seconds) and centrifuged at 40,000 g for 10 minutes. The supernatant was discarded and the pellet rehomogenised in Tris buffer, 1:60 w/v, and centrifuged at 40,000 g for 10 minutes. This step was repeated twice more so that, in total, the brain tissue was homogenised and centrifuged four times. The final pellet was resuspended in 50 mM Tris-HCl, pH 7.4 containing

300 mM sodium chloride and 5 mM potassium chloride (equivalent to 18.75 mg wet weight of tissue/ml) and used immediately in the binding assay. All centrifugations were performed at 4°C.

Membranes (400 µl; equivalent to 7.5 mg wet weight of tissue/tube) were incubated with 50 µl [^{3}H]nisoxetine at a single concentration of 0.6 nM and 50 µl of distilled water (total binding) or 50 µl of test compound (at a single concentration 10^{-6} M or at 10 concentrations ranging from 10^{-11}-10^{-3} M) or 50 µl of mazindol (1 µM; non-specific binding) for 4 h at 4°C. Membrane bound radioactivity was recovered by filtration under vacuum through Skatron 11734 filters using a Skatron cell harvester. Filters were rapidly washed with ice-cold 50 mM Tris-HCl, pH 7.4 containing 120 mM sodium chloride and 5 mM potassium chloride (wash setting 9,9,0). The scored filter paper discs were punched out into vials, scintillation fluid added and radioactivity determined by liquid scintillation counting.

The ability of compounds of Formula I to interact with muscarinic receptors has been demonstrated for the products of Examples 1-17 by the following test which determines the ability of compounds to displace the standard ligand, [^{3}H] *N*-methylscopolamine, from muscarinic receptors *in vitro*.

Frontal cortical tissue from the brains of male Charles River rats weighing 150-250 g was homogenised in ice-cold 20 mM HEPES buffer, pH 7.5 (measured at 25°C) containing 100 mM sodium chloride and 10 mM magnesium chloride (1:10 w/v) using a Polytron PT3100 (speed setting 21,700rpm, 3 x 5 seconds) and centrifuged at 49,500 g for 30 minutes at 4°C. The supernatant was discarded and the pellet rehomogenised in 20 mM HEPES buffer, pH 7.5 containing 100 mM sodium chloride and 10 mM magnesium chloride (equivalent to 12.5 mg wet weight of tissue/ml). Membranes were stored at -80°C until required.

Membranes were thawed, diluted 1:10 in ice-cold 20 mM HEPES buffer, pH 7.5 containing 100 mM sodium chloride and 10 mM magnesium chloride and homogenised using a Polytron PT3100 as above. Diluted membranes (200 µl; equivalent to 0.25 mg wet weight of tissue/tube) were incubated with 200 µl of 20 mM HEPES buffer, pH 7.5 containing 100 mM sodium chloride and 10 mM magnesium

chloride and 50 µl of [^{3}H]N-methylscopolamine at a single concentration of 0.15 nM and 50 µl of distilled water (total binding) or 50 µl of test compound (at a single concentration of 10^{-6} M or at 10 concentrations ranging from 10^{-11}- 10^{-3} M) or 50 µl of atropine sulphate (1 µM; non-specific binding) for 30 min at 30°C. Membrane bound radioactivity was recovered by filtration under vacuum through Skatron 11734 filters using a Skatron cell harvester. Filters were rapidly washed with ice-cold 20 mM HEPES buffer, pH 7.5 (wash 1,2 at setting 5,5). The scored filter paper discs were punched out into vials, scintillation fluid added and radioactivity determined by liquid scintillation counting.

For each of these tests measuring the ability of compounds of Formula I to displace standard ligands from 5-HT_{1A} receptors and 5-hydroxytryptamine (5-HT) and noradrenaline (NA) reuptake sites and muscarinic receptors *in vitro*, the percentage displacement of specific binding of tritiated ligand by 10^{-6} M test compound was calculated in the following way.

Firstly, specific binding of tritiated ligand in the absence (A) and presence (B) of test compound was determined:

In the absence of compound:

A (dpm) = Total binding (dpm) - Non-specific binding (dpm)

In the presence of compound (10^{-6} M):

B (dpm) = Binding at 10^{-6}M (dpm) - Non-specific binding (dpm)

The specific binding of tritiated ligand in the presence (B) of compound was then converted to a percentage of specific binding of tritiated ligand in the absence (A) of compound:

% Specific binding at 10^{-6} M = B (dpm) / A (dpm) x 100

The percentage displacement of specific binding of tritiated ligand by the test compound (10^{-6} M) was then obtained by subtraction of the percentage specific binding in the presence of compound from the percentage specific binding in the absence of compound, which is taken as the maximum binding and so equals 100%:

% Displacement at 10^{-6}M = 100 - % Specific binding at 10^{-6}M.

In some cases, displacement curves were then produced for compounds which displaced ≥50% of specific binding of the tritiated ligand at 10^{-6} M using a range of concentrations of the compound. The K_i was then calculated by fitting the following simultaneous equations (which are derived from the Feldman equations) by robust non-linear regression to data from three experiments simultaneously:

$$F_1 = [L]_{Tot} - B$$

$$K_i' = K_i\left(1 + \frac{F_1}{K_d}\right)$$

$$ab = \frac{C_k r_1 - L + K_i'}{2}$$

$$F_2 = -ab + \sqrt{ab^2 + K_i' L}$$

$$B = \begin{cases} N_K F_1 & \text{Non-specific data} \\ \dfrac{C_K r_1 F_1}{K_d + F_1 + \dfrac{K_d F_2}{K_i}} + N_k F_1 & \text{Otherwise} \end{cases}$$

where B is the concentration of bound ligand-receptor complex. This is calculated for each observation as:

$$B = \frac{DPM}{\text{Specific activity} \times \text{Volume of incubation}}$$

L is the concentration of compound

$[L]_{tot}$ is the concentration of the tritiated ligand used, calculated as:

$$[L]_{Tot} = \frac{\text{Mean DPM for Total DPM added samples} \times \text{Dilution}}{\text{Specific activity} \times \text{Volume of incubation}}$$

K_d is the equilibrium dissociation constant for the ligand.

F_1 and F_2 are the concentrations of free ligand and free compound respectively.

r_1 is the total concentration of the receptor in the first experiment. This must be multiplied by C_K for subsequent experiments (C_1=1).

N_K is the non-specific binding constant.

The results obtained in the above tests for 5-HT_{1A} binding and 5-HT and NA uptake, and muscarinic binding for the final products of Examples 1 – 17 hereinafter are given in Table 1 below. K_is are in nM and are means of three independent determinations. % Figures are for % displacement at 10^{-6} M for a single determination.

TABLE 1

Example No.	5-HT_{1A}	5-HT uptake	NA uptake	Muscarinic
1	5.6	266	3.1	352
2	2.3	292	13.2	268
3	98%	48%	102%	62%
4	3.4	212	2.8	274
5	3.6	217	1.4	342
6	2.8	113	1.1	530
7	13.6	194	1.4	49
8	0.6	183	89	157
9	39	0.28	3.03	179
10	1.4	177	16.6	147
11	11.5	238	7.3	342

Example No.	5-HT_{1A}	5-HT uptake	NA uptake	Muscarinic
12	NT	NT	NT	67%
13	1.0	123	7.5	194
14	2.0	47	3.3	8.7
15	1.8	86	2.8	230
16	8.8	33%	4.6	39%
17	9.0	12%	15.1	231

K_i values are n=1, mean of n=2 or mean of n=3.
NT = Not tested.

The ability of compounds of the invention to inhibit monoamine oxidase A activity is demonstrable by the following test.

The assay was performed using the following general procedure in which the tissue source was human placenta:

Enzyme	Substrate	Incubation	Reaction product	Method of detection
MAO-A(h)	Kynuramine (0.15mM)	30min/30°C	4-OHquinoline	Spectrophotometry

The compounds were tested at 1 and 10micromolar in duplicate.

Ref: Weyler, W. and Salach, J.I. (1985) Purification and properties of mitochondrial monoamine oxidase type A from human placenta. J. Biol. Chem., 260: 13199-13207.

Acute feeding studies

Animals and environment

Experiments were performed on male Sprague-Dawley rats (300-450 g at the start of the experiment) which were obtained from Charles River (Margate). Animals were individually-housed in polypropylene cages with metal grid floors at a temperature of 21±1 °C and 55% humidity. Polypropylene trays were placed below each cage. Animals were maintained on a reverse phase light-dark cycle. Lights were off from 09.30 h to 17.30 h during which time the room was illuminated by red light. Animals had free access to a powdered rat diet and tap water at all times. The diet was contained in glass feeding jars (10 cm diameter; 8 cm deep) with aluminium lids. Each lid had a hole (3 cm diameter) cut in it to allow access to the food. Animals were accustomed to these conditions for at least two weeks before experimentation.

Test procedure

On the day prior to testing, the animals were randomly allocated to treatment groups containing 6-8 rats, weighed and their food intakes over a 6 h period were measured. These baseline readings were taken to ensure that the body weights and food intakes of the different groups of rats were not significantly different before drug treatment. On the test day, animals were given vehicle or one of three doses of the test drug. All drugs were dosed orally at the onset of the dark phase since rats consume most of their food during this period. Feeding jars were weighed (to the nearest 0.1g) at the time of drug administration and 1, 2, 4, 6 and 24 h after dosing. At each reading, the trays below the cages were examined for spilt food which was then returned to the feeding jar. However, spillage of food from the feeding jars was generally negligible.

All drug doses are expressed as the free base. Drugs were dissolved in deionised water or suspended in 0.4% cellosize using a sonic bath.

Data analysis

Variations in body weight were accounted for by expressing the results as g/kg rat weight (treatment group means ± s.e.mean). ED_{50} values (the dose of a drug required to reduce food intake to 50% of the control values) were calculated from a logistic sigmoid curve using a dedicated computer program. Statistical comparisons between mean group intakes were made using analysis of variance and Dunnett's test (two-tailed).

The compounds of the present invention have surprisingly higher affinity for $5HT_{1A}$ receptors compared to compounds exemplified in WO97/02269.

Preferred compounds of the present invention additionally have surprisingly lower affinity for muscarinic receptors compared to the Examples of WO97/02269. For example, Example 1 of WO97/02269 has a K_i of 130 nM. Muscarinic affinity may cause undesired side-effects, for example dry mouth, blurred vision, sweating, palpitations, constipation and aggravation of narrow angle glaucoma (Blackwell, B. Adverse effects of antidepressant drugs. Part 1 Monoamine oxidase inhibitors and tricyclics. Drugs 21, 202-219, 1981). Obviously it is desirable for compounds to have minimal affinity for muscarinic receptors.

More preferred compounds of the present invention additionally have significantly reduced MAO_A inhibitory activity compared to compounds exemplified in WO97/02269.

In the above test the product of Example 1 of the present invention exhibits an IC_{50} of 1600 nM whereas Example 1 of WO97/02269 exhibits an IC_{50} of 33 nM. These results demonstrate the surprising improvement in selectivity of the compound of the present invention compared to compounds previously disclosed. The combination of inhibition of monoamine oxidase activity and 5-HT reuptake inhibition may cause serotonin syndrome (Sternbach, H. Serotonin syndrome. Am. J. Psychiatry 148, 705-713, 1991) which is highly undesirable.

Most preferred compounds of the present invention additionally have improved activity in acute feeding studies compared to compounds exemplified in

WO97/02269. In the above acute feeding studies the product of Example 1 of the present invention has ED_{50} at 2 h of 1.1 mg/kg whereas Example 1 of WO97/02269 has ED_{50} at 2 h of 4.5 mg/kg.

These results demonstrate the surprising improvement in efficacy of the compounds of the present invention compared to compounds disclosed in the prior art.

The invention is illustrated by the following Examples which are given by way of example only. The final products of each of these Examples were characterised by one or more of the following procedures: high performance liquid chromatography, elemental analysis, nuclear magnetic resonance spectroscopy, mass spectroscopy and infrared spectroscopy.

Examples

Example 1

a) Lithium *bis*(trimethylsilyl)amide (1M solution in tetrahydrofuran; 60 ml) was added dropwise at -70 °C under nitrogen to a stirred solution of 3-acetyl-benzo[*b*]thiophene (10 g) in tetrahydrofuran (250 ml), then the mixture was stirred at -70°C for 1 hour. A solution of iodomethane (3.54 ml) in tetrahydrofuran (20 ml) was added dropwise at -70°C over 15 minutes, the stirred mixture was allowed to warm to ambient temperature over 18 hours, then it was added to saturated aqueous ammonium chloride solution (300ml). The product was extracted into ethyl acetate (3 x 100 ml) then the combined extracts were washed with water (2 x 50 ml) and saturated aqueous sodium chloride solution (50 ml), dried (Na_2SO_4), and the solvent was removed *in vacuo*. The residue was purified by flash chromatography over silica in Biotage Flash 40i ® equipment using a 99:1 mixture of petroleum ether (b.p. 40 - 60 °C) and ethyl acetate as eluant. Appropriate fractions were combined and the solvents removed *in vacuo* to leave 3-propionylbenzo[*b*]thiophene as a colourless solid (2.7 g) which was used without further purification.

b) Phenyltrimethylammonium tribromide (13.35 g) was added in portions at 0-5°C under nitrogen over 30 minutes to a stirred solution of 3-propionyl-benzo[*b*]thiophene (6.75 g; prepared in a manner similar to that described above) in tetrahydrofuran (100 ml), then the mixture was stirred at 0°C for 20 minutes and at ambient temperature for 4 hours. The resulting solid was removed by filtration and washed with tetrahydrofuran (30 ml), then the filtrate and washings were combined and the solvent was removed *in vacuo*. The residue was dissolved in dichloromethane (200 ml), then the solution was washed with water (3 x 30 ml) and saturated aqueous sodium chloride solution (30 ml), dried (Na_2SO_4), and the solvent was removed to leave 1-(benzo[*b*]thiophen-3-yl)-2-bromopropan-1-one as a brown oil (9.2 g) which solidified slowly at ambient temperature and was used without further purification.

c) A mixture of the crude 1-(benzo[*b*]thiophen-3-yl)-2-bromopropan-1-one (9.2 g), 2-imidazolidinethione (3.5 g), ethanol (200 ml) and acetic acid (100 ml) was heated under reflux under nitrogen for 17 hours, then the solvents were removed *in vacuo*. The residue was triturated with ether (100 ml), then the resulting solid was collected by filtration and crystallised from ethanol to give 3-(benzo[*b*]thiophen-3-yl)-2-methyl-5,6-dihydroimidazo[2,1-*b*]thiazole hydrobromide as a white solid (4.9 g), m.p. 277 - 278°C.

Alternative preparation A

a) A solution of bromine (20 ml) in dichloromethane (100 ml) was added dropwise at approximately 5 °C to a stirred mixture of benzo[*b*]thiophene (50 g) and anhydrous sodium acetate (46 g) in dichloromethane (500 ml), the mixture was stirred at ambient temperature for 72 hours, then it was filtered and the solvent was removed *in vacuo*. The residue was distilled to give 3-bromobenzo[*b*]thiophene as a pale yellow oil (51.3 g), b.p. 93 – 104 °C at 53 Pa.

b) A stirred solution of *N,O*-dimethylhydroxylamine hydrochloride (50 g) in water (500 ml) was cooled in ice, and potassium carbonate (125 g) was added in portions over 10 minutes. Toluene (500 ml) was added, the stirred mixture was cooled to 0 °C, then propionyl chloride (43 ml) was added dropwise at 0 – 5 °C. When the

addition was complete, the mixture was stirred at 0°C for 5 minutes, the cooling bath was removed, and stirring was continued for a further 1 hour. The aqueous phase was separated and washed with toluene (2 x 100 ml), then the combined toluene solutions were washed with water (200 ml) and saturated aqueous sodium chloride solution (200 ml), dried (Na_2SO_4), and the solvent was removed *in vacuo* to leave *N*-methoxy-*N*-methylpropionamide as a colourless oil (19.9 g) which was used without further purification. Further product was isolated from the combined aqueous phases by extraction with ether (2 x 100 ml) followed by dichloromethane (2 x 100 ml). The combined extracts were dried (Na_2SO_4) and the solvents removed *in vacuo* to leave *N*-methoxy-*N*-methylpropionamide as a colourless oil (14.2 g) which was used without further purification.

c) A few crystals of iodine were added to a mixture of magnesium turnings (5.05 g) and tetrahydrofuran (25 ml), then 10 ml of a solution of 3-bromobenzo[*b*]thiophene (42.1 g) in tetrahydrofuran (200 ml) was added. The mixture was heated under nitrogen to initiate formation of the Grignard reagent, then the heat source was removed and the remainder of the 3-bromobenzo[*b*]thiophene solution was added, with stirring, at such a rate that gentle reflux was maintained. When the addition was complete (approximately 35 minutes), the mixture was stirred without heating for a further 35 minutes, then it was heated under reflux for 10 minutes and allowed to cool to ambient temperature. A solution of *N*-methoxy-*N*-methylpropionamide (23.1 g) in tetrahydrofuran (100 ml) was added over 2 minutes, the mixture was stirred at ambient temperature for 20 minutes and at reflux temperature for 5 hours, then it was cooled in ice and 2M hydrochloric acid (125 ml) was added dropwise. The mixture was stirred for 30 minutes, filtered (Celite), and the filtrate was concentrated *in vacuo* to remove the tetrahydrofuran. The product was extracted into ethyl acetate (2 x 300 ml), then the combined extracts were washed with water (2 x 200 ml) and saturated aqueous sodium chloride solution (2 x 200 ml), dried (Na_2SO_4), and the solvent was removed *in vacuo*. The residue was triturated with petroleum ether (b.p. 60 – 80 °C)(100 ml), and the resulting solid was collected by filtration and dried *in vacuo* at 45 °C for 6 hours to give 3-propionylbenzo[*b*]thiophene as a buff solid (23.3 g), m.p. 73 – 75 °C.

d) Phenyltrimethylammonium tribromide (8.6 g) was added in portions at 0-5°C under nitrogen over 10 minutes to a stirred solution of 3-propionylbenzo[*b*]thiophene (4.34 g) in tetrahydrofuran (80 ml), then the mixture was stirred at ambient temperature for 4 hours. The resulting solid was removed by filtration and washed with tetrahydrofuran (30 ml), then the filtrate and washings were combined and the solvent was removed *in vacuo* to leave 1-(benzo[*b*]thiophen-3-yl)-2-bromopropan-1-one as a brown oil which was used without further purification.

e) A mixture of the crude 1-(benzo[*b*]thiophen-3-yl)-2-bromopropan-1-one, 2-imidazolidinethione (2.33 g), and ethanol (120 ml) was heated under reflux under nitrogen for 15 minutes, then acetic acid (60 ml) was added, the mixture was heated under reflux for 24 hours, then the solvents were removed *in vacuo*. The residue was crystallised from ethanol (125 ml) to give 3-(benzo[*b*]thiophen-3-yl)-2-methyl-5,6-dihydroimidazo[2,1-*b*]thiazole hydrobromide as a white solid (4.4 g), m.p. 272 - 274°C.

Alternative preparation B

a) A mixture of 3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole hydrobromide (200 g; prepared in a manner similar to that described in WO 97/02269), saturated aqueous sodium carbonate solution (1000 ml) and dichloromethane (2000 ml) was stirred vigorously at ambient temperature for 1.5 hours, then the organic layer was separated, washed with water (500 ml), dried ($MgSO_4$) and the solvent was removed *in vacuo*. The process was repeated on the same scale, and the two products were combined to give 3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole as a pale yellow solid (264.3 g), which was used without further purification.

b) Bromine (55.5 ml) was added dropwise at 0-5 °C over 1.75 hours to a stirred solution of 3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole (264.3 g) in dichloromethane, then the mixture was stirred at 0°C for 30 minutes and at ambient temperature for 1 hour. The resulting solid was collected by filtration, washed with dichloromethane (300 ml) and dried *in vacuo* at 70°C to give 3-(benzo[*b*]thiophen-3-

yl)-2-bromo-5,6-dihydroimidazo[2,1-*b*]thiazole hydrobromide as a pale yellow solid (431 g) which was used without further purification.

c) 3-(Benzo[*b*]thiophen-3-yl)-2-bromo-5,6-dihydroimidazo[2,1-*b*]thiazole hydrobromide (170 g) was added in portions under nitrogen at 0-8°C over 1 hour to a stirred solution of ethylmagnesium chloride [2.0 M solution in ether (620 ml)] in tetrahydrofuran (1700 ml), then the mixture was stirred at 3°C for 1.5 hours. Dimethylformamide (136 ml) was added at 3-8 °C over 30 minutes, then the mixture was stirred at ambient temperature for 2 hours, cooled to 8°C and quenched by the cautious addition of saturated aqueous ammonium chloride solution (600 ml) and water (350 ml). Ethyl acetate (1500 ml) was added, the mixture was stirred at ambient temperature for 18 hours, and the resulting solid (Fraction 1) was collected by filtration. The organic layer of the filtrate was separated, washed with saturated aqueous sodium chloride solution (500 ml), dried ($MgSO_4$), and the solvents were removed *in vacuo*. The residue was dissolved in hot propan-2-ol (1000 ml) and the solution was filtered while hot then allowed to stand at ambient temperature for 20 hours. The resulting solid was collected by filtration, washed with propan-2-ol (100 ml) and dried *in vacuo* at 70°C to give 3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde as a yellow solid (19.4 g), m.p. 206°C. A mixture of the solid Fraction 1, dichloromethane (2100 ml), 2 M hydrochloric acid (250 ml) and water (1000 ml) was stirred at ambient temperature for 15 minutes, then triethylamine (80 ml) was added. The dichloromethane layer was separated, and further product was isolated from the aqueous layer by extraction into dichloromethane (500 ml). The combined dichloromethane solutions were dried ($MgSO_4$), and the solvent was removed *in vacuo* to give further 3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde as a yellow solid (63.0 g), m.p. 208°C

d) Borane/t-butylamine complex (18.3 g) was added in portions to an ice-cold, stirred suspension of finely-powdered aluminium chloride (14 g) in dichloromethane (330 ml), then the mixture was stirred at 0 °C for 55 minutes. A solution of 3-(benzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde (10g) in dichloromethane (70 ml) was added dropwise at 0 °C, then the mixture was stirred at 0 °C for 15 minutes and at ambient temperature for 21 hours. The mixture was

quenched by cautious addition of water (1000 ml) followed by 2.5 M hydrochloric acid (175 ml), then it was basified to pH 10 by the addition of 5M aqueous sodium hydroxide solution. The aqueous phase was separated and washed with dichloromethane (300 ml), then the combined dichloromethane solutions were dried ($MgSO_4$), and the solvent was removed *in vacuo*. Half (5g) of the residue was dissolved in ethanol (12 ml) and 48% hydrobromic acid (3.5 ml) was added. The mixture was diluted with ether (100 ml) and the resulting solid was collected by filtration, then it was suspended in ethanol (46 ml). The mixture was heated under reflux for 15 minutes, cooled in ice, and the resulting solid was collected by filtration, washed with ether (40 ml) and dried *in vacuo* to give 3-(benzo[*b*]thiophen-3-yl)-2-methyl-5,6-dihydroimidazo[2,1-*b*]thiazole hydrobromide as a white solid (3.54 g), m.p. 273 – 276°C.

Example 2

a) A solution of 3-bromo-5-chlorobenzo[*b*]thiophene (2g) in ether (20 ml) was added dropwise at –70 °C under nitrogen to a stirred solution of *n*-butyllithium (2.5 M solution in hexanes; 4.14 ml) in ether (46 ml), then the mixture was stirred at –70°C for 30 minutes. 2-Bromopropionyl chloride (1.67 g) was added in one portion, the mixture was stirred at –70 °C for 4 hours, then it was allowed to warm to 0 °C. The mixture was stirred at 0 °C for a further 30 minutes, then it was quenched by the addition of saturated aqueous ammonium chloride solution (50 ml). The aqueous layer was separated and washed with ether (2 x 30 ml), then the combined ethereal solutions were washed with saturated aqueous sodium chloride solution (2 x 30 ml) and dried (Na_2SO_4). The solvent was removed *in vacuo*, and the residue was purified by flash chromatography over silica using a 9:1 mixture of petroleum ether (b.p. 60 – 80 °C) and ethyl acetate as eluant. Appropriate fractions were combined and the solvents were removed *in vacuo* to leave 1-(5-chlorobenzo[*b*]thiophen-3-yl)-2-bromopropan-1-one (0.32 g) as a white solid which was used without further purification.

b) A mixture of 1-(5-chlorobenzo[*b*]thiophen-3-yl)-2-bromopropan-1-one (0.3 g), 2-imidazolidinethione (0.12 g), and ethanol (10 ml) was heated under reflux under nitrogen for 15 minutes, then acetic acid (4 ml) was added, the mixture was heated

under reflux for 24 hours, then the solvents were removed *in vacuo*. The residue was dissolved in the minimum volume of water, the solution was basified to pH12 by the addition of 5M aqueous sodium hydroxide solution, and the product was extracted into dichloromethane (3 x 30 ml). The extracts were dried (Na_2SO_4) and the solvent was removed *in vacuo*. The residue was purified by flash chromatography over silica in Biotage Flash 40i ® equipment using dichloromethane followed by a 20:1 mixture of dichloromethane and methanol as eluants. Appropriate fractions were combined and the solvents were removed *in vacuo* to leave 3-(5-chlorobenzo[*b*]thiophen-3-yl)-2-methyl-5,6-dihydroimidazo[2,1-*b*]thiazole as a yellow solid (0.1 g), m.p. 264 – 267°C.

Example 3

a) Methyl thioglycolate (62.87 ml) was added dropwise at 110°C under nitrogen to a stirred solution of triethylamine (244.85 ml) in dimethylformamide (400 ml), then the mixture was stirred at 110°C for 30 minutes. A solution of 2,6-difluorobenzaldehyde (100 g) in dimethylformamide (100 ml) was added rapidly, then the mixture was heated under reflux for 4 hours. The mixture was allowed to cool to ambient temperature, then it was added to a mixture of ice and water (4000 ml). The product was collected by filtration and dried *in vacuo* to give methyl 4-fluorobenzo[*b*]-thiophene-2-carboxylate as a white solid (110 g) which was used without further purification.

b) 2M Aqueous sodium hydroxide solution (1000 ml) was added to a stirred suspension of methyl 4-fluorobenzo[*b*]thiophene-2-carboxylate (110 g) in methanol (1500 ml) at ambient temperature under nitrogen. The mixture was stirred at ambient temperature for 4 hours, then the solution phase was separated from unreacted methyl 4-fluorobenzo[*b*]thiophene-2-carboxylate by decanting into 2M hydrochloric acid (3000 ml). The resulting solid was collected by filtration from the acidic mixture and dried *in vacuo* at 60°C to give 4-fluorobenzo[*b*]thiophene-2-carboxylic acid as a white solid (77 g) which was used without further purification. The remaining unreacted methyl 4-fluorobenzo[*b*]thiophene-2-carboxylate was dissolved in hot methanol (500 ml), then 2M aqueous sodium hydroxide solution

(250 ml) was added at ambient temperature. The mixture was stirred at ambient temperature for 8 hours, then it was added to 2M hydrochloric acid (1000 ml). The resulting solid was collected by filtration and dried *in vacuo* to give 4-fluorobenzo[*b*]-thiophene-2-carboxylic acid as a white solid (33 g).

c) Copper powder (40 g) was added to a stirred solution of 4-fluorobenzo[*b*]-thiophene-2-carboxylic acid (77 g) in quinoline (500 ml), then the mixture was stirred and heated at 180 - 200°C for 2 hours. The mixture was allowed to cool to ambient temperature, then it was added to 2M hydrochloric acid (1500 ml). Ethyl acetate (1000 ml) was added, the mixture was filtered through Celite ® which was subsequently washed with ethyl acetate (500 ml), then the combined organic layers were dried ($MgSO_4$), and the solvent removed *in vacuo*. The residue was purified by flash chromatography over silica using petroleum ether (b.p. 40 - 60°C) followed by a 25 : 1 mixture of petroleum ether (b.p. 40 - 60°C) and ethyl acetate as eluants. Appropriate fractions were combined and the solvents removed *in vacuo* to leave 4-fluorobenzo[*b*]thiophene as a colourless oil (50.46 g).

d) A solution of bromine (18.7 ml) in dichloromethane (200 ml) was added dropwise at -25°C to a stirred mixture of 4-fluorobenzo[*b*]thiophene (50.46 g) and anhydrous sodium acetate (40 g) in dichloromethane (400 ml) under nitrogen, the mixture was stirred at ambient temperature for 18 hours, then it was filtered and the solvent was removed *in vacuo*. The residue was dissolved in dichloromethane (approximately 50 ml) then water (300 ml) and zinc powder (approximately 40 g) were added under nitrogen. The mixture was heated under reflux for 4 hours, then allowed to stand at ambient temperature for 20 hours. Ethyl acetate (300 ml) was added, heating at reflux continued for 15 minutes, then the mixture was allowed to cool to ambient temperature. The mixture was filtered (Celite ®) and the filter cake washed with ethyl acetate (3 x 100 ml). The aqueous phase was separated and washed with ethyl acetate (200 ml), then the combined organic solutions were dried ($MgSO_4$), and the solvents were removed *in vacuo* to leave 3-bromo-4-fluorobenzo[*b*]thiophene as a light brown solid (59.4 g) which was used without further purification.

e) A solution of 3-bromo-4-fluorobenzo[*b*]thiophene (59.4 g) in tetrahydrofuran (250 ml) was added to a stirred solution of ethylmagnesium bromide [2.0 M solution in ether (190 ml)] in tetrahydrofuran (800 ml) at 0°C under nitrogen, then the mixture was heated under reflux for 1.5 hours and allowed to cool to ambient temperature. *N*-Methoxy-*N*-methylpropionamide (33.5 g) was added and the mixture heated under reflux for 2 hours. The mixture was allowed to cool to ambient temperature, then it was added to saturated aqueous ammonium chloride solution (1000 ml). The product was extracted into ethyl acetate (2 x 500 ml), then the combined extracts were dried ($MgSO_4$), and the solvent was removed *in vacuo*. The residue was purified by flash chromatography over silica using petroleum ether (b.p. 40 - 60°C) followed by dichloromethane as eluants. Appropriate fractions were combined and the solvents were removed *in vacuo* to leave 4-fluoro-3-propionylbenzo[*b*]thiophene as a red-brown solid (22 g).

f) Phenyltrimethylammonium tribromide (39.5 g) was added at 0°C under nitrogen to a stirred solution of 4-fluoro-3-propionylbenzo[*b*]thiophene (22 g) in tetrahydrofuran (300 ml), then the mixture was stirred at ambient temperature for 3 hours. The resulting solid was removed by filtration through silica and washed with dichloromethane, then the filtrate and washings were combined and the solvents were removed *in vacuo* to leave 2-bromo-1-(4-fluorobenzo[*b*]thiophen-3-yl)propan-1-one as a brown oil (approximately 40 g) which was used without further purification.

g) A mixture of the crude 2-bromo-1-(4-fluorobenzo[*b*]thiophen-3-yl)propan-1-one (approximately 40 g), 2-imidazolidinethione (10.71 g), ethanol (150 ml) and acetic acid (75 ml) was heated under reflux under nitrogen for 2 hours, then further 2-imidazolidinethione (2.2 g) was added and heating under reflux was continued for 2 hours. The mixture was cooled to 0°C, the resulting solid was collected by filtration and washed with ethanol (2 x 100 ml), then it was basified by stirring in a mixture of saturated aqueous sodium hydrogencarbonate solution (500 ml) and dichloromethane (500 ml) for 30 minutes. The organic layer was separated, the aqueous layer was shaken with dichloromethane (2 x 250 ml), then the combined dichloromethane solutions were dried ($MgSO_4$), and the solvent was removed *in vacuo*. The residue was dissolved in ethanol (200 ml), then concentrated hydrochloric acid (6 ml) was added at 0°C. The solvents were removed *in vacuo*,

then the residue was crystallised from ethanol (approximately 100 ml) to give 3-(4-fluorobenzo[*b*]thiophen-3-yl)-2-methyl-5,6-dihydroimidazo[2,1-*b*]thiazole hydrochloride as a white solid (17.5 g), m.p. 259 - 262°C.

Example 4

A solution of fumaric acid (2.13 g) in ethanol (40 ml) was added to a stirred solution of 3-(benzo[*b*]thiophen-3-yl)-2-methyl-5,6-dihydroimidazo[2,1-*b*]thiazole (5 g prepared in a manner similar to that described in Example 1 : Alternative preparation B) in ethanol (10 ml) at 0°C. The mixture was stirred at 0°C for 15 minutes then the resulting solid was collected by filtration and dried *in vacuo* to give 3-(benzo[*b*]-thiophen-3-yl)-2-methyl-5,6-dihydroimidazo[2,1-*b*]thiazole fumarate as a white solid (4.71 g), m.p. 179 - 181°C.

Example 5

Concentrated hydrochloric acid (4 ml) was added to a solution of 3-(benzo[*b*]thiophen-3-yl)-2-methyl-5,6-dihydroimidazo[2,1-*b*]thiazole (4.27 g; prepared in a manner similar to that described in Example 1 : Alternative preparation B) in ethanol (45 ml), then the mixture was added to ether (250 ml) and stirred for 15 minutes. The resulting solid was collected by filtration, washed with ether (50 ml) and dried *in vacuo* at 70°C to give 3-(benzo[*b*]thiophen-3-yl)-2-methyl-5,6-dihydroimidazo[2,1-*b*]thiazole hydrochloride as a white solid (3.50 g), m.p. 254 – 256°C.

Example 6

A solution of D,L-tartaric acid (1.43 g) in ethanol (30 ml) was added to a stirred solution of 3-(benzo[*b*]thiophen-3-yl)-2-methyl-5,6-dihydroimidazo[2,1-*b*]thiazole (2.66 g; prepared in a manner similar to that described in Example 1 : Alternative preparation B) in ethanol (28 ml). The resulting suspension was stirred for 5 minutes, then ether (80 ml) was added. The solid was collected by filtration, washed with ether (50 ml) and dried *in vacuo* at 70°C to give 3-(benzo[*b*]thiophen-3-yl)-2-methyl-5,6-dihydroimidazo[2,1-*b*]thiazole D,L-tartrate as a white solid (4.00 g), m.p. 204 – 205°C.

Example 7

In a manner similar to that described in Example 1 : Alternative preparation A, and starting with bromination of benzo[*b*]thiophene followed by reaction with magnesium then *N*-methoxy-*N*-methylbutyramide, 3-(benzo[*b*]thiophen-3-yl)-2-ethyl-5,6-dihydroimidazo[2,1-*b*]thiazole hydrobromide was prepared as a colourless solid, m.p. 219 - 221°C.

Example 8

a) A solution of 3-bromo-5-methylbenzo[*b*]thiophene (2.5 g; prepared by bromination of 5-methylbenzo[*b*]thiophene in a manner similar to that described in Example 1 : Alternative preparation A) in ether (5 ml) was added dropwise at –70°C under nitrogen to a stirred solution of *n*-butyllithium (1.6M solution in hexanes; 7 ml) in ether (20 ml), then the mixture was stirred at –70°C for 30 minutes. A solution of *N*-methoxy-*N*-methylpropionamide (1.3 g) in ether (5 ml) was added dropwise over 20 minutes, the mixture was stirred at –70°C for 3 hours and allowed to warm to ambient temperature over 20 hours, then it was quenched by the addition of 2M hydrochloric acid (25 ml). The ethereal layer was separated, washed with water (25 ml) and saturated aqueous sodium chloride solution (25 ml), dried ($MgSO_4$), and the solvents were removed *in vacuo*. The residue was purified by flash chromatography over silica using a 40:1 mixture of petroleum ether (b.p. 60 - 80°C) and ethyl acetate as eluant. Appropriate fractions were combined and the solvents removed *in vacuo* to leave a 20:1 mixture of 5-methyl-3-propionylbenzo[*b*]thiophene and 5-methyl-2-propionylbenzo[*b*]thiophene (1.2 g) as an off white solid which was used without further purification.

b) Phenyltrimethylammonium tribromide (2.25 g) was added in portions at 0°C to a stirred solution of 5-methyl-3-propionylbenzo[*b*]thiophene (1.2 g; prepared as described above) in tetrahydrofuran (20 ml), then the mixture was stirred at 0°C for 1 hour and at ambient temperature for 20 hours. The mixture was filtered and the solvent removed *in vacuo*. The residue was dissolved in dichloromethane (50 ml), then the solution was washed with water (2 x 50 ml), dried ($MgSO_4$), and the solvent

was removed *in vacuo* to leave a dark brown solid which was triturated with petroleum ether (b.p. 60 - 80°C) (50 ml). The solvent was removed *in vacuo* to leave 2-bromo-1-(5-methylbenzo[*b*]thiophen-3-yl)propan-1-one (0.75 g), which was heated under reflux under nitrogen with a mixture of 2-imidazolidinethione (0.27 g), ethanol (30 ml), and acetic acid (15 ml) for 24 hours. The solvents were removed *in vacuo*, the residue was triturated with ether (20 ml) and the resulting solid was collected by filtration and dried *in vacuo* to give 2-methyl-3-(5-methylbenzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole hydrobromide as a white solid (0.52 g), m.p. 266 - 269°C.

Example 9

In a similar to that described in Example 1 : Alternative preparation A, and starting with bromination of benzo[*b*]thiophene followed by reaction with magnesium then *N*-methoxy-3,*N*-dimethylbutyramide, 3-(benzo[*b*]thiophen-3-yl)-2-isopropyl-5,6-dihydroimidazo[2,1-*b*]thiazole hydrobromide was prepared as a light brown solid, m.p. 208 - 210°C.

Example 10

a) *sec*-Butyllithium (1.25M solution in a 92:8 cyclohexane:hexane mixture; 100 ml) was added dropwise at –70°C under nitrogen to a stirred solution of 4-fluorophenyl methyl sulphide (22.0 g) in tetrahydrofuran, then the mixture was stirred at –70 °C for 65 minutes. Dimethylformamide (13.2 ml) was added dropwise at -68°C to -70°C, the stirred mixture was allowed to warm to ambient temperature slowly over 20 hours, then it was added to a solution of acetic acid (10 ml) in water (500 ml). The product was extracted into ether (3 x 150 ml), then the combined extracts were washed with 2M hydrochloric acid (200 ml) and saturated aqueous sodium chloride solution (200 ml), dried (Na_2SO_4), and the solvents were removed *in vacuo*. The residue (25 g), which was used without further purification, was estimated to consist predominantly of a 2:3 mixture of 4-fluorophenyl methyl sulphide and 2-fluoro-5-(methylthio)benzaldehyde respectively by nuclear magnetic resonance spectroscopy.

b) A stirred mixture of methyl thioglycolate (8.9 ml), crude 2-fluoro-5-(methylthio)benzaldehyde (25 g; prepared as above), dimethyl acetamide (250 ml) and ethyl diisopropylamine (42 ml) was heated at 140 - 150°C under nitrogen for 3.5 hours, then the solvent was removed *in vacuo*. Water (650 ml) was added to the residue, then the product was extracted into dichloromethane (3 x 150 ml). The combined extracts were washed with water (3 x 150 ml), dried (Na_2SO_4), and the solvent removed *in vacuo*. The residue was purified by trituration with ether (250 ml), then the resulting solid was collected by filtration, washed with ether (2 x 50 ml), and dried *in vacuo* to give methyl 5-(methylthio)benzo[*b*]thiophene-2-carboxylate (13.3 g) as a pale yellow solid, m.p. 89.7 – 90.4°C.

c) Sodium hydroxide (8 g) was dissolved in water (100 ml) then the solution was added to a stirred solution of methyl 5-(methylthio)benzo[*b*]thiophene-2-carboxylate (23.8 g; prepared in a manner similar to that described above) in methanol (300 ml). The mixture was heated under reflux for 10 minutes then allowed to stand at ambient temperature for 3 days. The suspension was concentrated to a total volume of approximately 250 ml by heating, then water (100 ml) was added and the mixture hot filtered to remove insoluble material. A solution of concentrated hydrochloric acid (40 ml) in water (20 ml) was added to the filtrate, the resulting solid was collected by filtration and washed with water, then dried *in vacuo* at 80°C to give 5-(methylthio)-benzo[*b*]thiophene-2-carboxylic acid as a pale yellow solid (21 g), m.p 186 - 186.5°C.

d) A mixture of copper powder (5.3 g), 5-(methylthio)benzo[*b*]thiophene-2-carboxylic acid (20 g) and quinoline (100 ml) was stirred and heated under reflux under nitrogen for 30 minutes, then hot filtered. The filtrate was added to a mixture of concentrated hydrochloric acid (100 ml), ice (500 g) and ether (200 ml), then the resulting solid was collected by filtration and washed with ether. The aqueous phase was separated and further product was extracted from it into ether (2 x 150 ml). The combined ethereal layers were washed with 2M hydrochloric acid (200 ml) and water (200 ml), dried (Na_2SO_4), and the solvent removed *in vacuo* to give 5-(methylthio)-benzo[*b*]thiophene as a light brown solid (14.7 g) which was used without further purification.

e) A solution of 5-(methylthio)benzo[*b*]thiophene (14.7 g) in dichloromethane (180 ml) was added to a stirred mixture of aluminium bromide (26.2 g), bromoacetyl bromide (7.12 ml) and dichloromethane (120 ml) at <0°C under nitrogen, then the resulting dark red-brown solution was stirred at <0°C for 30 minutes and at ambient temperature for 20 hours. The solution was added to a mixture of ice (600 g) and concentrated hydrochloric acid (50 ml), then dichloromethane (300 ml) was added and insoluble materials removed by filtration (Celite ®). The aqueous phase was separated and further product was extracted from it into dichloromethane (300 ml), then the combined dichloromethane solutions were dried ($MgSO_4$), and the solvent was removed *in vacuo*. Acetic acid (200 ml) and dichloromethane (200 ml) were added to the residue, followed by a solution of 2-imidazolidinethione (5.29 g) in acetic acid (200 ml), then the dichloromethane was removed by distillation. The remaining mixture was heated under reflux for two hours, then the total volume was reduced to approximately 200 ml by heating *in vacuo*. The hot solution was separated by decantation from insoluble material, then it was allowed to cool. Further insoluble material was removed as before, then the solvents were removed *in vacuo* at 50°C. The residue was mixed with water (300 ml) and 5M aqueous sodium hydroxide solution (300 ml) then the product was extracted into dichloromethane (300 ml). The extract was dried (Na_2SO_4), and the solvent was removed *in vacuo*. The residue was partially purified by flash chromatography over silica using ethyl acetate then an 8:1:1 mixture of ethyl acetate, methanol and triethylamine as eluants. Appropriate fractions were combined and the solvents removed *in vacuo* to leave 3-[5-(methylthio)benzo[*b*]thiophen-3-yl]-5,6-dihydroimidazo[2,1-*b*]thiazole as a yellow-brown gum (3.6 g), which was used without further purification.

f) A solution of bromine (1.87 g) in dichloromethane (10 ml) was added to a stirred solution of 3-[5-(methylthio)benzo[*b*]thiophen-3-yl]-5,6-dihydroimidazo[2,1-*b*]thiazole (3.55 g; prepared as above) in dichloromethane (80 ml) whilst keeping the internal temperature below 20°C, then the dichloromethane phase was separated by decantation from insoluble materials and concentrated *in vacuo*. The residue was triturated with dichloromethane (10 ml), then the resulting solid was collected by filtration to give 2-bromo-3-[5-(methylthio)benzo[*b*]thiophen-3-yl]-5,6-dihydroimidazo-[2,1-*b*]thiazole hydrobromide as a yellow-brown solid (2.97 g), m.p. 260-265°C.

g) A solution of ethylmagnesium chloride [2.8M solution in tetrahydrofuran (8.76 ml)] was added at –10°C under nitrogen to a stirred suspension of 2-bromo-3-[5-(methylthio)benzo[*b*]thiophen-3-yl]-5,6-dihydroimidazo[2,1-*b*]thiazole hydrobromide (2.90 g) in tetrahydrofuran (40 ml), then the mixture was stirred at ambient temperature for 90 minutes and cooled to –5°C. Dimethylformamide (5 ml) was added, the resulting suspension was stirred for 2 hours at ambient temperature then ethyl acetate (200 ml) and saturated aqueous ammonium chloride solution (200 ml) were added. The ethyl acetate layer was separated, dried (Na_2SO_4), and the solvents removed *in vacuo* to give 3-[5-(methylthio)benzo[*b*]thiophen-3-yl]-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde as a solid (1.4 g), m.p. 157-158.5°C, which was used without further purification.

h) Borane/*t*-butylamine complex (1.04 g) was added at 0°C under nitrogen to a stirred suspension of powdered aluminium chloride (0.80 g) in dichloromethane (20 ml), then the mixture was stirred at 0°C for 1 hour. 3-[5-(Methylthio)benzo[*b*]-thiophen-3-yl]-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde (0.66 g: prepared as above) was added, then the mixture was stirred for 15 minutes at 0°C, and allowed to stand at ambient temperature for 20 hours. The mixture was quenched by cautious addition of water (25 ml) followed by 2M hydrochloric acid (25 ml), then warmed to decompose any borane complexes. The suspension was filtered, then the filtrate was made basic (pH 14) by the addition of 5M aqueous sodium hydroxide solution. The product was extracted into dichloromethane (2 x 50 ml), then the combined extracts were dried (Na_2SO_4), and the solvent was removed *in vacuo*. A solution of anhydrous oxalic acid (0.12 g) in ethyl acetate (10 ml) was added to a solution of the orange-yellow residue (0.39 g) in a mixture of dichloromethane (25 ml) and ethyl acetate (50 ml), then the dichloromethane was removed by distillation. The resulting solid was collected by filtration, washed with ethyl acetate (2 x 10 ml), then dried *in vacuo* to give 2-methyl-3-[5-(methylthio)benzo[*b*]thiophen-3-yl]-5,6-dihydroimidazo[2,1-*b*]thiazole oxalate as a white solid (0.36 g), m.p. 197°C.

Example 11

a) A solution of 5-fluorobenzo[*b*]thiophene (2.8 g: prepared from 2,5-difluorobenzaldehyde in a manner similar to that described in Examples 3 and 10) in

dichloromethane (27 ml) was added dropwise under nitrogen to a stirred mixture of aluminium chloride (7.34 g) and 2-bromopropionyl chloride (4.73 g) in dichloromethane (70 ml), the mixture was stirred at ambient temperature for 2.5 hours, then it was added to ice-cold water (250 ml) and stirred for 1 hour. The aqueous phase was separated and further product was extracted from it into dichloromethane (100 ml), then the combined dichloromethane solutions were washed with water (2 x 100 ml) and saturated aqueous sodium chloride solution (2 x 100 ml), dried (Na_2SO_4), and the solvent removed *in vacuo*. The residue was purified twice by flash chromatography over silica in Biotage Flash 40i ® equipment using a 9:1 mixture of petroleum ether (b.p. 60-80°C) and ether as eluant. Appropriate fractions were combined and the solvents removed *in vacuo* to leave a 9:1 mixture of 2-bromo-1-(5-fluorobenzo[*b*]thiophen-3-yl)propan-1-one and 2-bromo-1-(5-fluorobenzo[*b*]thiophen-2-yl)propan-1-one (2.1 g) which was used without further purification.

b) A mixture of crude 2-bromo-1-(5-fluorobenzo[*b*]thiophen-3-yl)propan-1-one (2.1 g; prepared as above), 2-imidazolidinethione (0.75 g) and ethanol (60 ml) was heated under reflux for 10 minutes, then acetic acid (30 ml) was added. The mixture was heated under reflux for 20 hours, allowed to stand at ambient temperature for 60 hours, then the solvents were removed *in vacuo*. The residue was triturated with ethanol (100 ml) and the resulting solid dissolved in hot ethanol (100 ml). The total volume was reduced to approximately 60 ml by distillation, then the mixture was allowed to cool to ambient temperature. The resulting solid was collected by filtration, dried *in vacuo* and recrystallised from ethanol (75 ml) to give 3-(5-fluorobenzo[*b*]thiophen-3-yl)-2-methyl-5,6-dihydroimidazo[2,1-*b*]thiazole hydrobromide as a white solid (0.45 g), m.p. 268-271°C.

Example 12

a) 3-(5-Fluorobenzo[*b*]thiophen-3-yl)-2-methyl-5,6-dihydroimidazo[2,1-*b*]thiazole was prepared by basification of a 58:42 mixture of 3-(5-fluorobenzo[*b*]thiophen-3-yl)-2-methyl-5,6-dihydroimidazo[2,1-*b*]thiazole hydrobromide and 3-(5-fluorobenzo[*b*]thiophen-2-yl)-2-methyl-5,6-dihydroimidazo[2,1-*b*]thiazole hydrobromide (prepared in a manner similar to that described in Example 11). The pure free base was obtained after purification by flash chromatography over silica in Biotage Flash 40i ® equipment using either a 9:1 followed by a 1:1 mixture of

dichloromethane and methanol, or a 97:3 followed by a 9:1 mixture of dichloromethane and methanol as eluants.

b) 5.5M Hydrochloric acid (4.3 ml) was added to a solution of 3-(5-fluorobenzo[*b*]thiophen-3-yl)-2-methyl-5,6-dihydroimidazo[2,1-*b*]thiazole (4.6 g) in ethanol (250 ml), the mixture was added dropwise whilst stirring to ether (400 ml), then ether (2000 ml) was added. The suspension was allowed to stand at ambient temperature for 3 days, then the resulting solid was collected by filtration, washed with ether (200 ml) and dried *in vacuo* at 40°C to give 3-(5-fluorobenzo[*b*]thiophen-3-yl)-2-methyl-5,6-dihydroimidazo[2,1-*b*]thiazole hydrochloride as a white solid (3.6 g), m.p. 243-244°C.

Example 13

Phenyltrimethylammonium tribromide (9.7 g) was added in portions at 0-5°C under nitrogen over 2 minutes to a solution of 5-chloro-3-propionylbenzo[*b*]thiophene (5.8 g; prepared from 3-bromo-5-chlorobenzo[*b*]thiophene by reaction with *n*-buyllithium followed by *N*-methoxy-*N*-methylpropionamide in a manner similar to that described in Example 2) in tetrahydrofuran (100 ml), then the mixture was stirred at ambient temperature for 2.5 hours. The resulting solid was removed by filtration, then the solvent was removed from the filtrate *in vacuo*. A mixture of the residue, 2-imidazolidinethione (2.65 g) and ethanol (120 ml) was heated under reflux for 15 minutes, then acetic acid (60 ml) was added. The mixture was heated under reflux for 24 hours, then the solvents were removed *in vacuo*. Ethanol (50 ml) was added to the residue, then the solvent was removed *in vacuo* to obtain a solid that was recrystallised from hot ethanol (250 ml), then dried *in vacuo* at 50°C to give 3-(5-chlorobenzo[*b*]thiophen-3-yl)-2-methyl-5,6-dihydroimidazo[2,1-*b*]thiazole hydrobromide as a pink solid (6.25 g), m.p. 283-286°C.

Example 14

In a manner similar to that described in Example 11, and starting with 5-chlorobenzo[*b*]thiophene [prepared in a manner similar to J Heterocycl Chem (1988), 25(4), 1271] and 2-bromobutyryl chloride, 3-(5-chlorobenzo[*b*]thiophen-3-yl)-2-ethyl-

5,6-dihydroimidazo[2,1-*b*]thiazole hydrobromide was prepared as an off-white solid, m.p. 285 - 289°C (shrinks 240°C).

Example 15

In a manner similar to that described in Example 11, and starting with 5-bromobenzo[*b*]thiophene (prepared from 5-bromo-2-fluorobenzaldehyde in a manner similar to that described in Example 3) and 2-bromopropionyl chloride, 3-(5-bromobenzo[*b*]thiophen-3-yl)-2-methyl-5,6-dihydroimidazo[2,1-*b*]thiazole hydrobromide was prepared as a brown solid, m.p. 272-275°C.

Example 16

A mixture of crude 2-bromo-1-(4-fluorobenzo[*b*]thiophen-3-yl)propan-1-one (54 g; prepared in a manner similar to that described in Example 3), 2-imidazolidinethione (19.4 g), ethanol (200 ml) and acetic acid (100 ml) was heated under reflux under nitrogen for 2 hours, then further 2-imidazolidinethione (2 g) was added and heating under reflux was continued for 30 minutes. The mixture was cooled to 0°C, and the resulting solid was collected by filtration then dried *in vacuo* to give 3-(4-fluorobenzo[*b*]thiophen-3-yl)-2-methyl-5,6-dihydroimidazo[2,1-*b*]thiazole hydrobromide as a pale yellow solid (52.1 g), m.p. 264-266°C.

Example 17

n-Butyllithium (2.5M solution in hexane; 14 ml) was added dropwise over 20 minutes at –70°C under nitrogen to a suspension of 3-(benzo[*b*]furan-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole (6.7 g; prepared using the procedure in Example 3 of WO 97/02269) in tetrahydrofuran (80 ml), then the mixture was stirred at –70°C for 30 minutes. Dimethylformamide (2.7 ml) was added, the mixture was allowed to warm to ambient temperature, then it was quenched by the addition of saturated aqueous ammonium chloride solution (200 ml). The product was extracted into dichloromethane (3 x 200 ml), then the extracts were washed with saturated aqueous sodium chloride solution (100 ml), dried (Na_2SO_4), and the solvents removed *in vacuo*. The residue was purified by flash chromatography over silica using a 9:1

mixture of dichloromethane and methanol as eluant. Appropriate fractions were combined and the solvents were removed *in vacuo* to leave a residue (4.3 g) which was purified by flash chromatography over silica in Biotage Flash 40i ® equipment using a 20:1 mixture of dichloromethane and methanol as eluant. Appropriate fractions were combined and the solvents were removed *in vacuo* to leave 3-(benzo[*b*]furan-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde as a brown solid (3.3 g), which was used without further purification.

A crude sample of 3-(benzo[*b*]furan-3-yl)-2-methyl-5,6-dihydroimidazo[2,1-*b*]thiazole (1.6 g) was prepared from 3-(benzo[*b*]furan-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole-2-carboxaldehyde (3.0 g; prepared in a manner similar to that described above) and borane/*t*-butylamine complex in a manner similar to that described in Example 1 : Alternative preparation B. The crude product was dissolved in dichloromethane (50 ml), then ether (50 ml) was added. The resulting solid was removed by filtration then the solvents were removed from the filtrate *in vacuo*. The residue was purified by flash chromatography over silica in Jones Flashmaster II ® equipment using dichloromethane, then a 9:1 mixture of dichloromethane and methanol as eluants. Appropriate fractions were combined and the solvents were removed *in vacuo* to leave a residue (4.3 g) which was purified by flash chromatography over silica in Biotage Flash 40i ® equipment using a 19:1 mixture of dichloromethane and methanol as eluant. Appropriate fractions were combined and the solvents were removed *in vacuo* to leave a residue (0.28 g), which was dissolved in methanol (5 ml). Water (5 ml) was added and the mixture was acidified to pH 1 by the addition of 2M hydrochloric acid. The methanol was removed from the cloudy solution *in vacuo*, then insoluble material was removed by filtration. The filtrate was basified to pH 12 by the addition of 2M aqueous sodium hydroxide solution, then the resulting solid was collected by filtration, washed with water (10 ml), and dried *in vacuo* to give 3-(benzo[*b*]furan-3-yl)-2-methyl-5,6-dihydroimidazo[2,1-*b*]thiazole as a white solid (0.18 g), m.p. 119 - 122°C.

Example A

The use of compounds of the present invention in the manufacture of pharmaceutical compositions is illustrated by the following description. In this description the term "active compound" denotes any compound of the invention but particularly any compound which is the final product of the preceding Examples.

a) Capsules

In the preparation of capsules, 10 parts by weight of active compound and 240 parts by weight of lactose are de-aggregated and blended. The mixture is filled into hard gelatin capsules, each capsule containing a unit dose or part of a unit dose of active compound.

b) Tablets

Tablets are prepared from the following ingredients.

	Parts by weight
Active compound	10
Lactose	190
Maize starch	22
Polyvinylpyrrolidone	10
Magnesium stearate	3

The active compound, the lactose and some of the starch are de-aggregated, blended and the resulting mixture is granulated with a solution of the polyvinyl-pyrrolidone in ethanol. The dry granulate is blended with the magnesium stearate and the rest of the starch. The mixture is then compressed in atabletting machine to give tablets each containing a unit dose or a part of a unit dose of active compound.

c) Enteric coated tablets

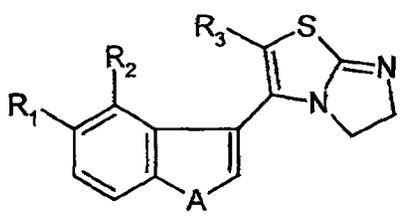
Tablets are prepared by the method described in (b) above. The tablets are enteric coated in a conventional manner using a solution of 20% cellulose acetate phthalate and 3% diethyl phthalate in ethanol:dichloromethane (1:1).

d) Suppositories

In the preparation of suppositories, 100 parts by weight of active compound is incorporated in 1300 parts by weight of triglyceride suppository base and the mixture formed into suppositories each containing a therapeutically effective amount of active ingredient.

Claims

1) Compounds of Formula I



I

including pharmaceutically acceptable salts thereof,

in which

A is S or O;

R_1 is H, halo, a C_{1-3} alkyl group or a C_{1-3} alkylthio group;

R_2 is H or fluoro; and

R_3 is methyl, ethyl or isopropyl.

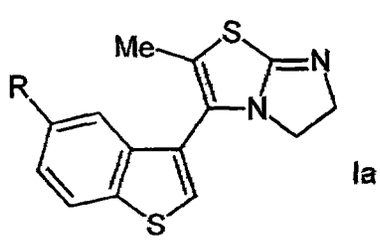
2) Compounds according to claim 1 in which A is S.

3) Compounds according to claim 1 in which A is O.

4) Compounds according to any previous claim in which R_1 is H, fluoro, chloro, bromo, methyl and methylthio.

5) Compounds according to any previous claim in which R_3 is methyl.

6) Compounds of Formula I according to claim 1 represented by Formula Ia



Ia

including pharmaceutically acceptable salts thereof,

in which R is H or chloro.

7) Compounds according to claim 1 in which A is S ; R_1 is H, fluoro, or chloro; R_2 is H or fluoro; and R_3 is methyl.

8) Compounds according to claim 1 in which A is S; R_1 is H or fluoro: R_2 is H or fluoro; and R_3 is methyl.

9) Compounds according to claim 1 in which A is S; R_1 is H; R_2 is H; and R_3 is methyl.

10) A compound according to claim 1 selected from:

3-(benzo[*b*]thiophen-3-yl)-2-methyl-5,6-dihydroimidazo[2,1-*b*]thiazole;
3-(5-chlorobenzo[*b*]thiophen-3-yl)-2-methyl-5,6-dihydroimidazo[2,1-*b*]thiazole;
3-(4-fluorobenzo[*b*]thiophen-3-yl)-2-methyl-5,6-dihydroimidazo[2,1-*b*]thiazole;
3-(benzo[*b*]thiophen-3-yl)-2-ethyl-5,6-dihydroimidazo[2,1-*b*]thiazole;
2-methyl-3-(5-methylbenzo[*b*]thiophen-3-yl)-5,6-dihydroimidazo[2,1-*b*]thiazole;
3-(benzo[*b*]thiophen-3-yl)-2-isopropyl-5,6-dihydroimidazo[2,1-*b*]thiazole;
2-methyl-3-[5-(methylthio)benzo[*b*]thiophen-3-yl]-5,6-dihydroimidazo[2,1-*b*]thiazole;
3-(5-fluorobenzo[*b*]thiophen-3-yl)-2-methyl-5,6-dihydroimidazo[2,1-*b*]thiazole;
3-(5-chlorobenzo[*b*]thiophen-3-yl)-2-ethyl-5,6-dihydroimidazo[2,1-*b*]thiazole;
3-(5-bromobenzo[*b*]thiophen-3-yl)-2-methyl-5,6-dihydroimidazo[2,1-*b*]thiazole; and
3-(benzo[*b*]furan-3-yl)-2-methyl-5,6-dihydroimidazo[2,1-*b*]thiazole

including pharmaceutically acceptable salts thereof.

11) A pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I as claimed in any one of claims 1 to 10 together with a pharmaceutically acceptable diluent or carrier.

12) A compound of Formula I for use as a medicament.

13) A compound of Formula I for use in the treatment of depression, anxiety, psychoses (for example schizophrenia), tardive dyskinesia, obesity, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, cerebral ischaemia, obsessive-compulsive behaviour, panic attacks, social phobias, eating disorders such as

bulimia, anorexia, snacking and binge eating, non-insulin dependent diabetes mellitus, hyperglycaemia, hyperlipidaemia, and stress, seizures, neurological disorders such as epilepsy and/or conditions in which there is neurological damage such as stroke, brain trauma, cerebral ischaemia, head injuries and haemorrhage. and as an aid to smoking cessation.

14) Use of a compound of Formula I in the manufacture of a medicament for use in the treatment of depression, anxiety, psychoses (for example schizophrenia), tardive dyskinesia, obesity, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, cerebral ischaemia, obsessive-compulsive behaviour, panic attacks, social phobias, eating disorders such as bulimia, anorexia, snacking and binge eating, non-insulin dependent diabetes mellitus, hyperglycaemia, hyperlipidaemia, stress seizures, neurological disorders such as epilepsy and/or conditions in which there is neurological damage such as stroke, brain trauma, cerebral ischaemia, head injuries and haemorrhage and as an aid to smoking cessation.

15) A method of treating, depression, anxiety, psychoses (for example schizophrenia), tardive dyskinesia, obesity, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, cerebral ischaemia, obsessive-compulsive behaviour, panic attacks, social phobias, eating disorders such as bulimia, anorexia, snacking and binge eating, non-insulin dependent diabetes mellitus, hyperglycaemia, hyperlipidaemia, and stress comprising the administration of a therapeutically effective amount of a compound of Formula I to a patient in need thereof.

16) A method of reducing the craving to smoke in human beings which comprises the administration of a therapeutically effective amount of a compound of Formula I, as claimed in any of claims 1 to 10, to a patient in need thereof.

17) A method of reducing weight gain after smoking cessation in human beings which comprises the administration of a therapeutically effective amount of a compound of Formula I, as claimed in any of claims 1 to 10, to a patient in need thereof.

14) A compound of Formula I, as claimed in any of claims 1 to 10, for use in the treatment or prevention of metabolic diseases and conditions arising therefrom, in particular non exercise activity thermogenesis and increased metabolic rate, sexual dysfunction, sleep apnoea, premenstrual syndrome, urinary incontinence, hyperactivity disorders, hiatial hernia and reflux esophagitis, pain, especially neuropathic pain, weight gain associated with drug treatment, chronic fatigue syndrome, osteoarthritis and gout, cancers associated with weight gain, menstrual dysfunction, gallstones, orthostatic hypotension and pulmonary hypertension.

15) A compound of Formula I, as claimed in any of claims 1 to 10, for use in the prevention of cardiovascular disease, in reducing platelet adhesiveness, in aiding weight loss after pregnancy or in aiding weight loss after smoking cessation.

16) Processes for the preparation of compounds of Formula I, as described herein.