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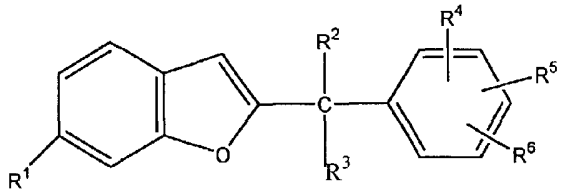
(54) Title: BENZOFURAN DERIVATIVES, FORMULATIONS AND USES THEREOF



(I)

(57) Abstract: The present invention is concerned with benzofuran derivatives, pharmaceutical formulations and products containing the same, and uses thereof. More particularly, there is disclosed a compound of formula (I), or a pharmaceutically acceptable salt, or prodrug thereof formula (I) where R^1 is hydroxy, C_{1-6} alkoxy or halogen; R^2 is a 5- or 6- membered heterocyclic ring containing one or more nitrogen heteroatoms; R^3 is hydrogen or hydroxy; and R^4, R^5, and R^6, which may be the same or different, are selected from the group consisting of hydrogen, halo, cyano, CF_3, C_{1-6} alkyl, hydroxy and C_{1-6} alkoxy. The compound is a potent non-steroidal inhibitors of $P450_{AROM}$ capable of substantially inhibiting the conversion of androstenedione to oestrone. Inhibitors according to the present invention are, therefore, useful in the treatment of oestrogen dependent or mediated diseases.

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Benzofuran derivatives, formulations and uses thereof

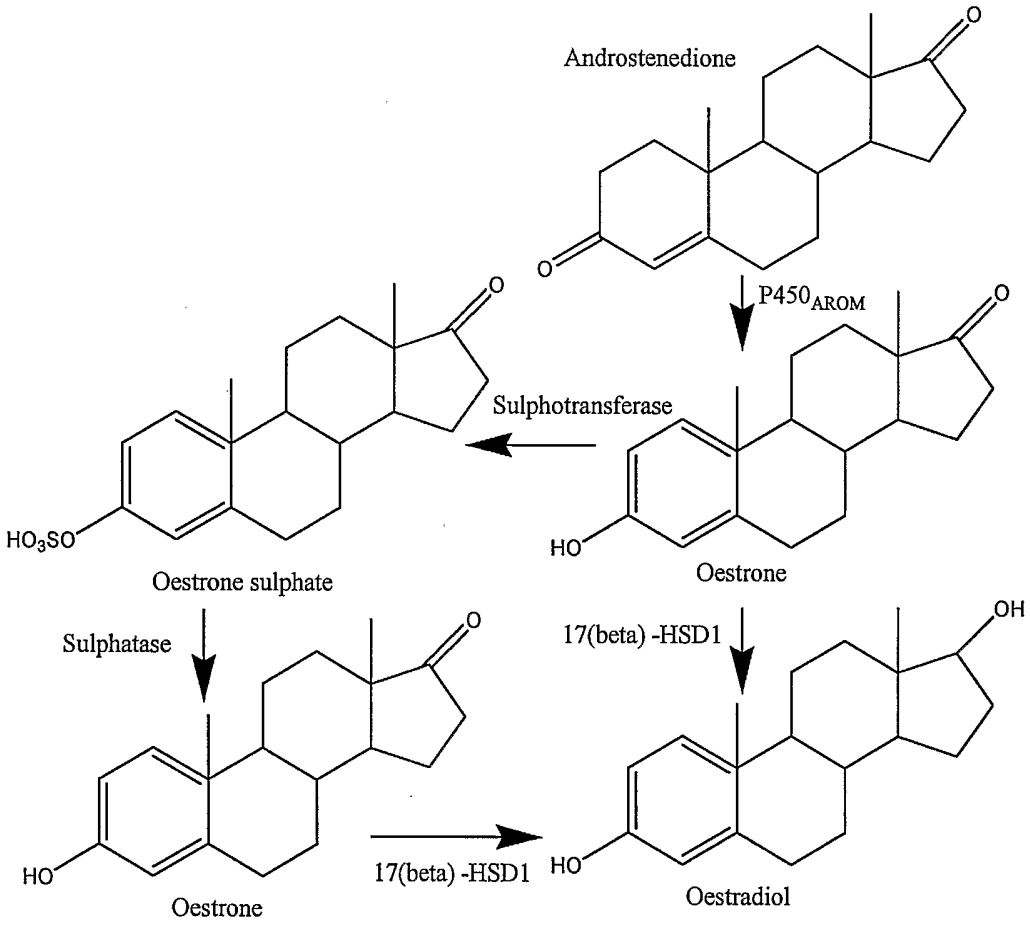
The present invention is concerned with benzofuran derivatives, pharmaceutical formulations and products containing the same, and uses thereof.

Breast cancer is the most common cause of death in women aged 40-50 years in Western countries, affecting about 1 million women world-wide per year. Oestrogens stimulate growth in hormone-dependent breast cancer, therefore modern treatment strategies aim to remove the influence of oestrogens on tumour growth generally by administration of an oestrogen-receptor antagonist, such as tamoxifen or the like. Alternative or additional (typically sequential) treatment can involve inhibition of a specific target enzyme operable in the steroidogenic pathway for oestrogen synthesis, for example inhibition of P450 aromatase ($P450_{AROM}$), 17β-hydroxysteroid dehydrogenase (17β-HSD) type 1 isoenzyme or the metabolic enzyme oestrogen sulphatase.

Despite the marked fall of oestrogen plasma levels in postmenopausal women, the breast tissue concentration of oestrogens is similar to that of pre-menopausal women and much greater (5- to 45- fold greater) than in plasma. $P450_{AROM}$ activity has been reported in non-malignant and malignant breast tissue and 17β-HSD type 1 is also present. Oestrone sulphate, as a potential source of oestrone, does not appear to be taken up in breast tissue. Local activity in the conversion of androstenedione to oestrone by $P450_{AROM}$ and interconversion of oestrone and oestradiol by 17β-HSD type 1 could therefore account, at least partially, for the high oestrogen concentration in breast tissue.

P450 aromatase ($P450_{AROM}$) is a NADPH, oxygen-dependent mono-

oxygenase consisting of a cytochrome P450 haem-protein and a flavoprotein. The role of $P450_{AROM}$ in the steroidogenic pathway for the synthesis of oestrogens is as follows.

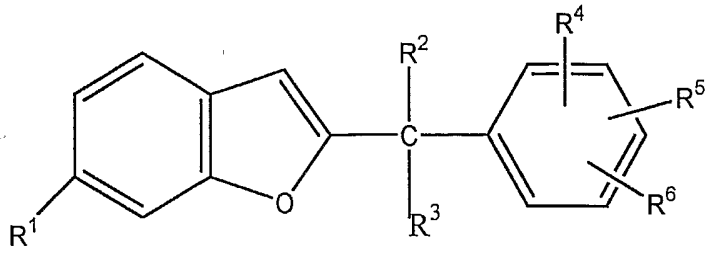


$P450_{AROM}$ catalyses the conversion of androstenedione to oestrone. Oestradiol, the major oestrogen, is produced from oestrone. Inhibitors of human $P450_{AROM}$ are, therefore, generally expected to be useful in the treatment of oestrogen dependent or mediated diseases substantially as hereinafter described in more detail.

Inhibitors of $P450_{AROM}$ fall into two main categories, steroidal and non-steroidal inhibitors. Non steroidal inhibitors have been used clinically for therapeutic treatment of hormone-dependent breast cancer, for example non-steroidal inhibitors such as fadrozole, anastrazole, letrozole and the like. Non-steroidal inhibitors typically act via a competitive mechanism involving interaction of a co-ordinating group of the inhibitor compound with the Fe^{3+} of the haem group in the active site of $P450_{AROM}$. The inhibitors' co-ordinating group is often a nitrogen atom contained within an imidazole or triazole component of the inhibitor compound.

We have now developed potent non-steroidal inhibitors of $P450_{AROM}$ capable of substantially inhibiting the conversion of androstenedione to oestrone. Inhibitors according to the present invention are, therefore, useful in the treatment of oestrogen dependent or mediated diseases.

According to the present invention, therefore, there is provided a compound of formula (I), or a pharmaceutically acceptable salt, or prodrug thereof



(I)

where

R^1 is hydroxy, C_{1-6} alkoxy or halogen;

R^2 is a 5- or 6- membered heterocyclic ring containing one or more nitrogen heteroatoms;

R^3 is hydrogen or hydroxy; and

R^4, R^5, and R^6, which may be the same or different, are selected from the group consisting of hydrogen, halo, cyano, CF_3, C_{1-6} alkyl, hydroxy and C_{1-6} alkoxy.

As used herein, 'alkyl' may be a straight or branched chain group, for example methyl, ethyl, n-propyl, isopropyl, t-butyl or the like.

As used herein, "halo" can be bromo, chloro, fluoro or iodo.

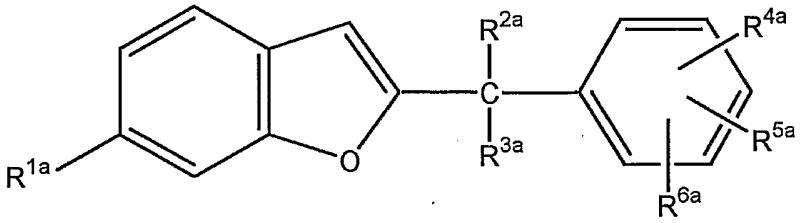
Preferably R^1 in Formula (I) is C_{1-6} alkoxy, more preferably C_{1-3} alkoxy and most preferably methoxy.

Typically, R^2 in formula (I) is a 5- or 6- membered heterocyclic ring selected from the group consisting of imidazole, triazole (in particular 1, 2, 4- triazole) and pyridine.

Typically, R^4, R^5, and R^6 in formula (I) are selected so as

to represent mono-, di- or tri- substitution of the phenyl ring to which they are attached, such as 2-, 3-, 4-, 2, 3-, 2, 4- substitution or the like and preferably, therefore, at least one of R^4, R^5 and R^6 is selected from the group consisting of halo, cyano, CF_3, C_{1-6} alkyl, hydroxy and c_{1-6} alkoxy. In the preferred case of mono- substitution of the above described phenyl ring, R^4 can be selected from the group consisting of halo, cyano, CF_3, C_{1-6} alkyl, hydroxy and c_{1-6} alkoxy and R^5 and R^6 both represent hydrogen. More preferably, R^4 can be selected from the group consisting of halo, cyano, C_{1-3} alkyl, hydroxy and C_{1-3} alkoxy and R^5 and R^6 both represent hydrogen. Even more preferably, R^4 is halo (typically fluoro or chloro) or C_{1-3} alkoxy (typically methoxy) substituted in the 4- position of the phenyl ring to which R^4 is attached, and R^5 and R^4 both represent hydrogen. In the case of di-substitution of the above described phenyl ring, R^4 and R^5 can be selected from the group consisting of halo, cyano, CF_3, C_{1-6} alkyl, hydroxy and c_{1-6} alkoxy and R^6 represents hydrogen. More preferably, R^4 and R^5 can be selected from the group consisting of halo, cyano, C_{1-3} alkyl, hydroxy and C_{1-3} alkoxy and R^6 represents hydrogen.

A preferred sub-group of compounds according to the present invention can be represented by formula (IA), whereby there is provided a compound of formula (IA), or a pharmaceutically acceptable salt or prodrug thereof



(IA)

where:

R^{1a} is hydroxy or C_{1-3} alkoxy;

R^{2a} is a 5- or 6-membered heterocyclic ring containing one or more nitrogen heteroatoms;

R^{3a} is hydrogen or hydroxy;

R^{4a} is halo or C_{1-3}alkoxy; and R^{5a} and R^{6a} are both hydrogen.

Preferably R^{1a} in formula (IA) is C_{1-3} alkoxy, and more preferably methoxy.

Typically, R^{2a} in formula (IA) is a 5- or 6-membered heterocyclic ring selected from the group consisting of imidazole, triazole (in particular 1, 2, 4- triazole) and pyridine.

Typically, R^{4a} in formula (IA) is halo (typically fluoro or chloro) or C_{1-3} alkoxy (typically methoxy) substituted in the 4- position of the phenyl ring to which R^{4a} is attached.

Preferred compounds according to the present invention include:

1-[(6-Methoxy-benzo[*b*]furan-2-yl)4-fluoro(phenyl)methyl]-1*H*-1,2,4-triazole;

1-[(6-Methoxy-benzo[*b*]furan-2-yl)4-chloro(phenyl)methyl]-1*H*-1,2,4-triazole;

1-[(6-Methoxy-benzo[*b*]furan-2-yl)4-methoxy(phenyl)methyl]-1*H*-1,2,4-triazole;

1-[(6-Methoxy-benzo[*b*]furan-2-yl)4-methoxy(phenyl)methyl]-1*H*-imidazole;

1-[(6-Methoxy-benzo[*b*]furan-2-yl)4-fluoro(phenyl)methyl)]-3-pyridylmethanol;

1-[(6-Methoxy-benzo[*b*]furan-2-yl)4-chloro(phenyl)methyl)]-3-

pyridylmethanol;

4-[6-Methoxy-benzofuran-2-yl)-1*H*-1,2,4-triazol-1-yl-methyl]-benzonitrile;

1-[(6-Methoxy-benzofuran-2-yl)-(4-nitro-phenyl)-methyl]-1*H*-1,2,4-triazole;

1-[(6-Methoxy-benzofuran-2-yl)-*p*-tolyl-methyl]-1*H*-1,2,4-triazole;

1-[(6-Methoxy-benzofuran-2-yl)-(4-trifluoromethyl-phenyl)-methyl]-1*H*-1,2,4-triazole;

1-[(6-Methoxy-benzofuran-2-yl)-(4-ethyl-phenyl)-methyl]-1*H*-1,2,4-triazole;

4-[(6-Hydroxy-benzofuran-2-yl)-[1,2,4]triazol-1-yl-methyl]-benzonitrile;

2-[(4-Nitro-phenyl)-[1,2,4]triazol-1-yl-methyl]-benzofuran-6-ol; and

2-[(4-Chloro-phenyl)-[1,2,4]triazol-1-yl-methyl]-benzofuran-6-ol.

Even more preferred compounds according to the present invention include:

1-[(6-Methoxy-benzo[*b*]furan-2-yl)4-fluoro(phenyl)methyl]-1*H*-1,2,4-triazole;

1-[(6-Methoxy-benzo[*b*]furan-2-yl)4-chloro(phenyl)methyl]-1*H*-1,2,4-triazole;

1-[(6-Methoxy-benzo[*b*]furan-2-yl)4-methoxy(phenyl)methyl]-1*H*-1,2,4-triazole;

1-[(6-Methoxy-benzo[*b*]furan-2-yl)4-methoxy(phenyl)methyl]-1*H*-imidazole;

1-[(6-Methoxy-benzo[*b*]furan-2-yl)4-fluoro(phenyl)methyl)]-3-pyridylmethanol; and

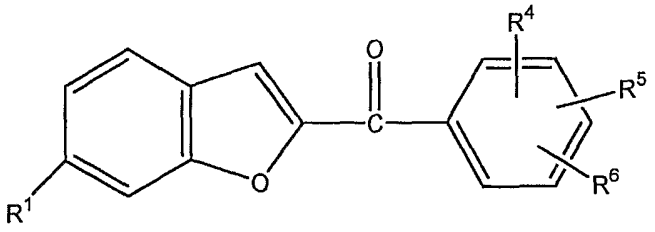
1-[(6-Methoxy-benzo[*b*]furan-2-yl)4-chloro(phenyl)methyl)]-3-pyridylmethanol.

Suitable pharmaceutically acceptable salts of a compound

according to the present invention substantially as hereinbefore described can include acid addition salts derived from inorganic and organic acids, such as hydrochlorides, hydrobromides, sulphates, phosphates, citrates, tartrates, maleates, fumarates, succinates, p-toluenesulphonates, methanesulphonates and the like. Other suitable salts will be readily apparent to one skilled in the art. Salts which are not pharmaceutically acceptable may be useful in the preparation of compounds of the present invention substantially as hereinbefore described and these may form a further part of the invention.

The present invention further includes within its scope prodrugs of a compound according to the present invention substantially as hereinbefore described and in general such prodrugs will be functional derivatives of a compound according to the present invention which are readily convertible *in vivo* into the required compound. Conventional procedures for selection and preparation of suitable prodrug derivatives are well known in the art.

There is also provided by the present invention a process of preparing a compound substantially as hereinbefore described, which process comprises preparing a compound of formula (I) substantially as hereinbefore described from an intermediate ketone compound of formula (II)

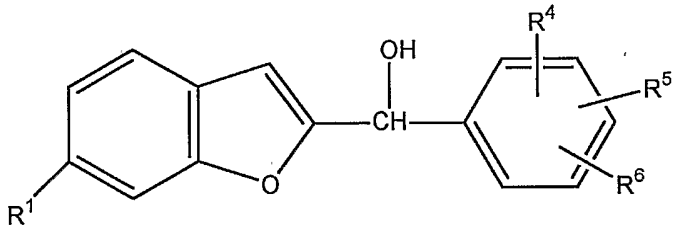


(II)

where

R^1, R^4, R^5 and R^6 are substantially as hereinbefore described.

For compounds of formula (I) substantially as hereinbefore described where R^2 is a 5-membered heterocycle, and R^3 is hydrogen, such a compound of formula (I) is typically prepared from a compound of formula (II) via an intermediate carbinol compound of formula (III)



(III)

where

R^1, R^4, R^5 and R^6 are substantially as hereinbefore described, essentially by reaction of a compound of formula (III) with $(Het_a)_2S=O$, where Het_a represents a 5-membered heterocycle as represented by R^2 substantially as hereinbefore described.

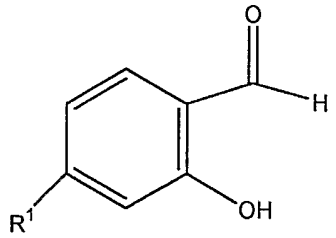
Suitably, such a 5-membered heterocycle, Het_a, is provided in an organic suspension, typically in acetronitrile or the like, to which is added a solution of a thionyl halide, typically thionylchloride in acetonitrile or the like, and the reaction mixture stirred for about one hour. An activated alkali metal carbonate, such as potassium carbonate, can be added to the reaction mixture, followed by the addition of a solution of an intermediate carbinol

compound of formula (III). The resulting mixture is then maintained under an inert atmosphere, such as nitrogen, and stirred for three to four days, to yield a compound of formula (I).

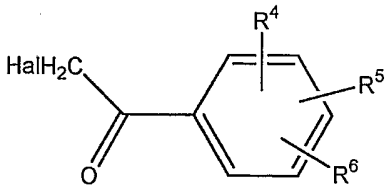
An intermediate carbinol compound of formula (III) is typically prepared from an intermediate ketone compound of formula (II), by employing suitable reducing techniques, such as the reducing agent sodium borohydride or the like, with stirring in an inert atmosphere, such as nitrogen, for about 2 hours.

For compounds of formula (I) substantially as hereinbefore described, where R^2 is a 6-membered heterocycle and R^3 is hydroxy, such a compound of formula (I) is suitably prepared directly from an intermediate ketone compound of formula (II) substantially as hereinbefore described, essentially by reaction of a compound of formula (II) with Het_b-Mg-Hal, where Het_b represents a 6-membered heterocycle as represented by R^2 substantially as hereinbefore described and Hal represents halo selected from bromo, chloro, fluoro and iodo. Typically, halo-substituted Het_b, such as 3-bromo-pyridine, is added to magnesium turnings, the reaction mixture heated to 60 to 80°C for about 2 hours and then an intermediate ketone compound of formula (II) is added to the reaction mixture, followed by further heating at 60 to 80°C for about 1 hour so as to yield a compound of formula (I) where R^2 is a 6-membered heterocycle and R^3 is hydroxy.

An intermediate ketone compound of formula (II) is typically prepared from the following intermediate compounds (IV) and (V)



(IV)



(V)

where

R^1, R^4, R^5 and R^6 are substantially as hereinbefore described and Hal represents a halo substituent selected from bromo, chloro, fluoro and iodo, typically bromo.

Typically an alkali metal salt, suitably the sodium salt, of a compound of formula (IV) is initially prepared by the addition of an alkali metal hydride to a compound of formula (IV). A solution of a compound of formula (V) is then added, the reaction mixture heated to about 70 to 90°C for about 1½ hours under an inert atmosphere, such as nitrogen, followed by the addition of an alkali metal alkoxide, such as sodium methoxide and further heating as above for about 1 hour.

A compound of formula (V) can suitably be prepared from the corresponding acetophenone, employing synthetic techniques known in the art.

Compounds according to the present invention are inhibitors of $P450_{AROM}$ and are, therefore, useful as therapeutic agents for treating oestrogen dependent or mediated diseases. For example, compounds according to the present invention are

useful as therapeutic agents for treating malignant and benign diseases of the breast, endometrium and ovary. These diseases include breast cancer, endometrial cancer, fibrocystic breast disease, endometriosis, polycystic ovarian diseases and the like. A compound according to the present invention substantially as hereinbefore described may also be useful in the treatment of Cushing's syndrome, gynecomastia, premature labour, precocious puberty, feminising adrenal tumours, and may also be of use in female fertility control, by inhibiting ovulation and egg nidation.

In particular, compounds according to the present invention are useful as therapeutic agents where inhibition of $P450_{Arom}$ is required. Compounds according to the present invention substantially as hereinbefore described are particularly useful in the treatment of hormone-dependent breast cancer. The term "treatment" as used herein includes both the amelioration of the symptoms of established oestrogen dependent or mediated diseases and the prophylaxis of such diseases.

According to a further aspect of the present invention, there is provided, for use in therapy, a compound, according to the present invention, substantially as hereinbefore described, in particular for the treatment of conditions where a lowering of the levels of oestrone and/or oestradiol in animals (especially humans) would be beneficial.

In a particular aspect of the present invention, there is provided a compound according to the present invention substantially as hereinbefore described for use in the treatment of hormone-dependent breast cancer.

There is further provided by the present invention a compound according to the present invention substantially as hereinbefore described, for use in the manufacture of a medicament for inhibition of $P450_{AROM}$. More particularly, there is provided a compound according to the present invention substantially as hereinbefore described, for use in the manufacture of a medicament for the treatment of oestrogen dependent or mediated diseases, substantially as herein before described, particularly for the treatment of hormone-dependent breast cancer.

While it is possible for a compound according to the present invention to be administered as a substantially pure chemical, it is preferable that such a compound is included in a pharmaceutical formulation. There is, therefore, still further provided by the present invention a pharmaceutical formulation comprising a compound according to the present invention substantially as herein before described, together with at least one pharmaceutically acceptable carrier, diluent or excipient therefor, and optionally other therapeutically acceptable ingredients. The carriers must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to a recipient thereof.

Other therapeutically acceptable ingredients suitable for inclusion in formulations according to the present invention include at least one further inhibitor of the steroidogenic pathway. Preferably, such a further inhibitor can be selected from the group consisting of inhibitors of any of the following steroidogenesis pathway enzymes- 17β-HSD isoforms, $P450_{AROM}$ and oestrogen sulphatase.

In a further aspect of the present invention for use in the

treatment of hormone-dependent breast cancer, a compound according to the present invention substantially as hereinbefore described is preferably used together with at least one inhibitor of 17β-HSD isoforms and/or oestrogen sulphatase. There is, therefore, further provided by the present invention a pharmaceutical composition comprising a compound according to the present invention substantially as hereinbefore described and at least one inhibitor of 17β-HSD isoforms and/or oestrogen sulphatase, together with one or more pharmaceutically acceptable carriers, excipients or diluents therefor.

The present invention also provides, a product comprising a compound according to the present invention substantially as hereinbefore described and at least one further inhibitor of the steroidogenic pathway substantially as hereinbefore described, for simultaneous, separate or sequential administration to a mammal for treating oestrogen dependent or mediated diseases, such as hormone-dependent breast cancer substantially as hereinbefore described.

Formulations according to the present invention include those suitable for oral, rectal, nasal, implant, parenteral and topical administration, although the most suitable route will generally depend upon the condition of a patient and the specific oestrogen dependent or mediated disease being treated. The precise amount of a compound according to the present invention substantially as hereinbefore described to be administered to a patient will be the responsibility of an attendant physician, although the dose employed will depend upon a number of factors, including the age and sex of the patient, the specific oestrogen dependent or mediated disease being treated and the route

of administration substantially as described above.

There is further provided by the present invention a method of treating a mammal (especially a human) suffering from or susceptible to an oestrogen dependent or mediated disease, such as hormone-dependent breast cancer substantially as hereinbefore described, which method comprises administering to said mammal a therapeutically effective amount of a compound according to the present invention substantially as hereinbefore described or a pharmaceutically acceptable salt or prodrug thereof.

The present invention will now be further illustrated by the following intermediates and examples, which do not limit the scope of the invention in any way.

Intermediates

Preparation of Intermediates 1 and 2

To solution of sodium hydride (60 %, 11 mmol) in dry *N,N*-dimethylformamide (10 mL) was added a solution of 2-hydroxy-4-methoxybenzaldehyde (10 mmol) in dry *N,N*-dimethylformamide (6 mL) dropwise. Hydrogen gas was liberated to give a yellow solution of the sodium salt. A solution of a phenacyl bromide (10 mmol, 4-fluorophenylacyl bromide for Intermediate 1, 4-chlorophenylacyl bromide for Intermediate 2 and 4-methoxyphenylacyl bromide for Intermediate 3) in dry *N,N*-dimethylformamide (10 mL) was then added dropwise and the reaction heated under nitrogen at 80 °C for 1.5 h. Sodium methoxide (2.5 mmol) was added to the mixture and heating continued for another hour (t.l.c. system : petroleum ether-ethyl acetate 4:1 v/v). After cooling, the reaction was evaporated to about a third of

its volume, diluted with dichloromethane (100 mL), washed with water (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure.

Intermediate 1

2- [1-Oxo-1-(4'-fluorophenyl)methyl]-6-methoxybenzofuran

Yield : 75 %, mp (EtOAc) 155-156 °C. ^1H NMR: δ 8.12 (dd, *J* = 5.5, 8.6 Hz, 2H, Ar), 7.63 (d, *J* = 8.7 Hz, 1H, Ar), 7.53 (s, 1H, H-3, furan), 7.26 (t, *J* = 8.6 Hz, 2H, Ar), 7.15 (d, *J* = 1.7 Hz, 1H, Ar), 7.02 (dd, *J* = 2.1, 8.6 Hz, 1H, Ar), 3.90 (s, 3, CH_3). ^{13}C NMR: δ 182.7 (C=O, C-1), 167.6 and 164.2 (C, C-4'), 161.7 (C, C-6), 158.1 (C, C-7a), 152.2 (C, C-2), 134.1 (C, C-1'), 132.4 and 132.3 (CH, C-2' and C-6'), 124.1 (CH, C-4), 120.7 (C, C-4a), 117.5 (CH, C-3), 116.2 and 116.0 (CH, C-3' and C-5'), 115.1 (CH, C-5), 96.0 (CH, C-7), 56.2 (CH_3). Microanalysis calcd for $C_{16}H_{11}FO_3$, C 71.11%, H 4.10%, found C 70.94%, H 4.10%.

Intermediate 2

2- [1-Oxo-1-(4'-chlorophenyl)methyl]-6-methoxybenzofuran

Yield : 80 %, mp (CH_2Cl_2) 173-174 °C. ^1H NMR: δ 8.03 (d, *J* = 8.5 Hz, 2H, Ar), 7.65 (d, *J* = 8.7 Hz, 1H, Ar), 7.57 (s, 1H, H-3, furan), 7.54 (d, *J* = 3.9 Hz, 2H, Ar), 7.15 (d, *J* = 1.6 Hz, 1H, Ar), 7.02 (dd, *J* = 2.2, 8.7 Hz, 1H, Ar), 3.95 (s, 3, CH_3). ^{13}C NMR: δ 182.9 (C=O, C-1), 161.8 (C, C-6), 158.1 (C, C-7a), 152.1 (C, C-2), 139.5 (C, C-1'), 136.2 (C, C-4'), 131.2 (CH, C-2' and C-6'), 129.3 (CH, C-3' and C-5'), 124.1 (CH, C-4), 120.7 (C, C-4a), 117.7 (CH, C-3), 115.2 (CH, C-5), 96.0 (CH, C-7), 56.2 (CH_3). Microanalysis calcd for $C_{16}H_{11}ClO_3$, C 67.03%, H 3.87%, found C 66.69%, H 3.92%.

Intermediate 3

2- [1-Oxo-1-(4'-methoxyphenyl)methyl]-6-methoxybenzofuran

Yield : 65 %, mp 136-140 °C. ^{1}H NMR: δ 8.12 (dd, *J* = 2.0, 6.9 Hz, 2H, H-3′ and H-5′), 7.62 (d, *J* = 8.7 Hz, 1H, H-4), 7.50 (d, *J* = 0.8 Hz, 1H, H-3), 7.15 (d, *J* = 1.8 Hz, 1H, H-7), 7.06 (dd, *J* = 2.0, 6.9 Hz, 2H, H-2′ and H-6′), 7.01 (dd, *J* = 2.2, 8.7 Hz, 1H, H-5), 3.95 (s, 3, CH_3), 3.94 (s, 3, CH_3). ^{13}C NMR: δ 182.9 (C=O, C-1), 163.8 (C, C-4'), 161.4 (C, C-2), 157.8 (C, C-6), 152.6 (C, C-7a), 132.2 (CH, C-2' and C-6'), 130.5 (C, C-1'), 123.9 (CH, C-5), 120.8 (C, C-3a), 116.7 (CH, C-4), 114.7 (CH, C-7), 114.2 (CH, C-3' and C-5'), 96.1 (CH, C-3), 56.2 (CH_3), 56.0 (CH_3).

Preparation of Intermediates 4, 5 and 6

To a suspension of each of Intermediates 1, 2 and 3 (3 mmol) in dry dioxane (7 mL) was added sodium borohydride (3 mmol) and the reaction stirred at room temperature under nitrogen for 2 hours. The reaction was concentrated under reduced pressure and 2M aqueous hydrochloric acid (approx. 10 mL) added to the resulting syrup. This solution was extracted into diethyl ether (100 mL), washed with water (2 x 25 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the respective carbinol in quantitative yield which was used in the next reaction without any further purification. T.l.c. system: petroleum ether-ethyl acetate 3:1 v/v. Intermediate 4 was derived from Intermediate 1, Intermediate 5 was derived from Intermediate 2 and Intermediate 6 was derived from Intermediate 3.

Examples

Preparation of Examples 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12

To a cooled (10 °C) suspension of 1,2,4-triazole (6 mmol) in dry acetonitrile (4 mL) was added a solution of thionyl chloride (1.5 mmol) in dry acetonitrile (2 mL) and the reaction stirred at 10 °C for one hour. Activated potassium carbonate (1.5 mmol) was then added, followed by a solution of Intermediate 4 (1.5 mmol) in dry acetonitrile (4 mL). The reaction was stirred under nitrogen at room temperature for 3-4 days then the reaction mixture was filtered to remove solid residues. The filtrate was concentrated under reduced pressure then redissolved in dichloromethane (100 mL) and this solution washed with water (2 x 50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash column chromatography (petroleum ether-ethyl acetate 80:20 v/v increasing to 60:40 v/v). T.l.c. system : petroleum ether-ethyl acetate 1:1 v/v to yield the title compound of Example 1. The above preparation was repeated for Intermediate 5 to yield the title compound of Example 2 and for Intermediate 6 to yield the title compounds of Example 3 and 4 (for Example 4, an initial suspension of imidazole (6mmol) in dry acetonitrile is added to thionyl chloride as above).

Example 1

1-[(6-Methoxy-benzo[*b*]furan-2-yl)4-fluoro(phenyl)methyl]-1*H*-1, 2,4-triazole

Yield : 83 % (syrup). ^1H NMR: δ 8.18 (s, 1H, triazole), 8.08 (s, 1H, triazole), 7.59 (d, J = 8.6 Hz, 1H, Ar), 7.33 (m, 2H, Ar), 7.16 (dt, J = 3.0, 5.1, 8.6 Hz, 2H, Ar), 7.04 (d, J = 7.1 Hz, 1H, Ar), 6.94 (dd, J = 2.3, 8.6 Hz, 1H, Ar), 6.85 (s, 1H, H-3), 6.55 (s, 1, H-1), 3.89 (s, 3, CH_3). ^{13}C NMR: δ 165.0 (C, C-4'), 159.2 (C, C-7a), 156.9 (C, C-6), 152.7 (CH, triazole), 151.5 (C, C-2), 143.6 (CH, triazole), 132.1 (C, C-1'), 130.0 and 129.8 (CH, C-2' and C-6'), 122.1 (CH, C-4), 120.9 (C, C-3a), 116.7 and 116.4 (CH, C-3' and

C-5'), 113.1 (CH, C-5), 108.4 (CH, C-3), 96.3 (CH, C-7), 62.0 (CH, C-1), 56.1 (CH_3).

Example 2

1-[(6-methoxy-benzo[*b*]furan-2-yl)4-chloro(phenyl)methyl)]-1*H*-1, 2, 4-triazole

Yield : 80 % (syrup). ^1H NMR: δ 8.18 (s, 1H, triazole), 8.06 (s, 1H, triazole), 7.59 (d, *J* = 8.6 Hz, 1H, Ar), 7.32 (m, 2H, Ar), 7.13 (dt, *J* = 2.9, 5.0, 8.6 Hz, 2H, Ar), 7.02 (d, *J* = 1.9 Hz, 1H, Ar), 6.92 (dd, *J* = 2.2, 8.6 Hz, 1H, Ar), 6.85 (s, 1H, H-3), 6.53 (s, 1, H-1), 3.85 (s, 3, CH_3). ^{13}C NMR: δ 161.7 (C, C-7a), 159.1 (C, C-6), 156.9 (C, C-4'), 152.7 (CH, triazole), 151.5 (C, C-2), 143.6 (CH, triazole), 132.1 (C, C-1'), 130.0 and 129.9 (CH, C-2' and C-6'), 122.1 (CH, C-4), 120.9 (C, C-4a), 116.6 and 116.4 (CH, C-3' and C-5'), 113.1 (CH, C-5), 108.3 (CH, C-3), 96.3 (CH, C-7), 61.9 (CH, C-1), 56.1 (CH_3).

Example 3

1-[(6-Methoxy-benzo[*b*]furan-2-yl)4-methoxy(phenyl)methyl)]-1*H*-1,2,4-triazole

Yield : 85 %. ^1H NMR: δ 8.09 (s, 1H, triazole), 8.01 (s, 1H, triazole), 7.38 (d, *J* = 8.6 Hz, 1H, H-4), 7.24 (dd, *J* = 2.1, 8.8 Hz, 2H, H-3′ and H-5′), 6.97 (d, *J* = 1.9 Hz, 1H, H-7), 6.92 (dd, *J* = 2.0, 6.8 Hz, 2H, H-2′ and H-6′), 6.87 (dd, *J* = 2.2, 8.6 Hz, 1H, H-5), 6.75 (s, 1H, H-3), 6.47 (s, 1H, H-1), 3.82 (s, 3, CH_3), 3.63 (s, 3, CH_3). ^{13}C NMR: δ 160.5 (C, C-7a), 159.0 (C, C-6), 156.8 (C, C-4'), 152.6 (CH, triazole), 152.3 (C, C-2), 143.5 (CH, triazole), 129.5 (CH, C-3' and C-5'), 128.1 (C, C-1′), 122.0 (CH, C-4), 121.1 (C, C-4a), 114.9 (CH, C-2' and C-6'), 112.9 (CH, C-5), 107.9 (CH, C-3), 96.3 (CH, C-7), 62.2 (CH, C-1), 56.1 (CH_3), 55.8 (CH_3). Microanalysis calcd for $C_{19}H_{17}N_3O_3$

(335.3559) C 68.05%, H 5.11%, N 12.52%, found C 68.19%, H 5.14%, N 12.54%.

Example 4

1-[(6-Methoxy-benzo[*b*]furan-2-yl)4-methoxy(phenyl)methyl)]-1*H*-imidazole

Yield : 80 % (syrup). ^{1}H NMR: δ 7.66 (s, 1H, H-2″), 7.49 (d, *J* = 8.6 Hz, 1H, H-4), 7.26 (m, 3H, , H-3′, H-5′ and H-5), 7.09 (d, *J* = 2.0 Hz, 1H, H-7), 7.01 (m, 4H, H-2′, H-6′, H-4″, H-5″), 6.63 (s, 1H, H-3), 6.53 (s, 1H, H-1), 3.95 (s, 3, CH_3), 3.93 (s, 3, CH_3). Microanalysis calcd for $C_{20}H_{18}N_2O_3.0.5\ H_2O$ (345.18292) C 70.35%, H 5.43%, N 7.77%, found C 69.96%, H 5.58%, N 8.16%.

Example 5

4-[6-Methoxy-benzofuran-2-yl)-1*H*-1,2,4-triazol-1-yl-methyl]-benzonitrile

Yield : 73 % (yellow solid). m.p. : 57-59 °C. ^{1}H NMR: δ 8.24 (s, 1, triazole), 8.11 (s, 1, triazole), 7.77 (d, J = 8.3 Hz, 2, Ar), 7.42 (m, 3, Ar), 7.01 (d, J = 1.9 Hz, 1, Ar), 6.96 (m, 2, Ar), 6.63 (s, 1, H-1), 3.90 (s, 3, OCH_3). ^{13}C NMR: δ 159.43 (CH, triazole), 157.00 (C, C-4′), 153.04 (C, C-7a), 149.42 (C, C-2), 143.87 (CH, C-3′′), 141.42 (C, C-3a), 133.26 (overlap CH, C-2′, C-6′), 128.64 (overlap CH, C-3′, C-5′), 122.29 (CH, C-4′′), 120.65 (C, C-1′), 118.53 (CH, C-6), 113.51 (CH, C-5), 113.46 (CH, C-4), 96.30 (CH, C-7), 61.99 (CN), 56.17 (OCH_3). Microanalysis calcd for $C_{19}H_{14}N_4O_2\bullet 0.2H_2O$ (333.948) C 68.33 %, H 4.35 %, N 16.78 %, found C 68.34 %, H 4.27 %, N 16.78 %.

Example 6

1-[(6-Methoxy-benzofuran-2-yl)-(4-nitro-phenyl)-methyl]-1*H*-1,2,4-triazole

Yield : 30 % (yellow solid). ^{1}H NMR: δ 8.33 (s, 1, triazole), 8.31 (s, 1, triazole), 8.25 (s, , 1, Ar), 8.12 (s, 1, Ar), 7.49 (m, 3, Ar), 7.05 (d, J = 1.8 Hz, 1, Ar), 7.00 (m, 2, Ar), 6.65 (s, 1, H-1), 3.90 (s, 3, OCH_3). ^{13}C NMR: δ 159.47 (CH, triazole), 157.02 (C, C-4'), 153.10 (C, C-7a), 149.84 (C, C-2), 148.59 (C, C-3a), 143.86 (CH, C-3''), 143.22 (CH, C-4''), 128.90 (overlap CH, C-2', C-6'), 124.65 (overlap CH, C-3', C-5'), 122.31 (C, C-1'), 120.63 (CH, C-6), 113.50 (CH, C-5), 109.15 (CH, C-4), 96.30 (CH, C-7), 19.04 (OCH_3). Microanalysis calcd for $C_{18}H_{14}N_4O_4$ (350.33) C 61.71 %, H 4.03 %, N 15.98 %, found C 61.44 %, H 4.08 %, N 15.65 %.

Example 7
1-[(6-Methoxy-benzofuran-2-yl)-*p*-tolyl-methyl]-1*H*-1,2,4-triazole

Yield : 7 % (yellow syrup). ^{1}H NMR: δ 8.17 (s, 1, triazole), 8.07 (s, 1, triazole), 7.44 (d, J=8.6Hz, 1, Ar), 7.27 (m, 4, Ar), 7.03 (d, J=2Hz, 1, Ar), 6.93 (dd, J = 2.2 Hz, 1, Ar), 6.83 (s,1, Ar), 6.54 (s, 1, Ar), 3.88 (s, 3, OCH_3), 2.42 (s, 3, CH_3). ^{13}C NMR: δ 159.00 (CH, triazole), 156.85 (CH, triazole), 152.12 (C, C-4'), 143.58 (CH, C-3''), 139.54 (C, C-7a), 133.19 (C, C-2), 130.17 (overlap CH, C-2', C-6'), 129.92 (C, C-3a), 127.98 (overlap CH, C-3', C-5'), 122.01 (CH, C-4''), 121.09 (CH, C-6), 112.597 (CH, C-5), 108.07 (CH, C-4), 96.36 (CH, C-7), 19.04 (OCH_3), 21.61 (CH_3).

Example 8
1-[(6-Methoxy-benzofuran-2-yl)-(4-trifluoromethyl-phenyl)-methyl]-1*H*-1,2,4-triazole

Yield : 28 % (yellow syrup). ^{1}H NMR: δ 8.28 (d, J=23.6Hz, 1, triazole), 8.11 (s, 1, triazole), 7.75 (m , 3, Ar), 7.46 (m, 3, Ar), 7.34 (d, J=9.8Hz, 1, Ar), 7.05 (s, 1, Ar), 6.96

(m, 1, Ar), 6.60 (s, 1, H-1), 3.90 (s, 3, OCH_3). ^{13}C NMR: δ 159.34 (CH, triazole), 156.98 (CH, triazole), 153.44 (C, C-4'), 152.92 (C, C-7a), 150.62 (C, C-2), 143.75 (CH, C-3''), 128.32 (overlap CH, C-2', C-6'), 128.24 (overlap CH, C-3', C-5'), 126.58 (CH, C-4''), 126.51 (CH, C-6), 126.46 (CH, C-5), 122.21 (CH, C-4), 120.79 (C, C-1'), 113.332 (CH,), 108.86 (CH, C-7), 56.15 (CH_3), 19.04 (OCH_3).

Example 9

1-[(6-Methoxy-benzofuran-2-yl)-(4-ethyl-phenyl)-methyl]-1*H*-1,2,4-triazole

Yield : 77 % (yellow amorphous solid). ^1H NMR: δ 8.33 (s, 1, triazole), 8.18 (s, 1, triazole), 7.43 (d, J=8.6Hz, 1, Ar), 7.28 (m, 4, Ar), 7.03 (d, J = 1.9 Hz, 1, Ar), 6.93 (dd, J=2.2 Hz, 1, Ar), 6.84 (s, 1, Ar), 6.65 (s, 1, H-1), 3.87 (s, 3, OCH_3), 2.72 (dd, J=7.6Hz, 2, CH_2), 1.30 (m, 3, CH_3). ^{13}C NMR δ 159.00 (CH, triazole), 156.85 (CH, triazole), 152.58 (C, C-4'), 152.20 (C, C-7a), 145.76 (C, C-2), 143.63 (CH, C-3''), 133.45 (C, C-3a), 128.99 (overlap CH, C-2', C-6'), 128.05 (overlap CH, C-3', C-5'), 122.02 (CH, C-4''), 121.12 (C, C-1'), 112.97 (CH, C-6), 108.05 (CH, C-5), 96.36 (CH, C-7), 62.51 (CH, C-4), 56.10 (OCH_3), 28.97 (CH_2), 15.82 (CH_3). Microanalysis calcd for $C_{20}H_{19}N_3O_2$ (333.389) C 72.05 %, H 5.74 %, N 12.60 %, found C 71.78 %, H 5.74 %, N 12.41 %.

Example 10

4-[(6-Hydroxy-benzofuran-2-yl)-[1,2,4]triazol-1-yl-methyl]-benzonitrile

Yield : 85 % (yellow solid), m.p. : 57-59 °C. ^1H NMR: δ 8.29 (s, 1, OH), 8.22 (s, 1, triazole), 8.17 (s, 1, triazole), 7.76 (d, J = 8.3 Hz, 2, Ar), 7.43 (dd, J = 3.2 Hz, 3, Ar), 6.93 (m, 3, Ar), 6.61 (s, 1, H-1). ^{13}C NMR: δ 156.95 (CH,

triazole), 156.40 (CH, triazole), 152.38 (C, C-4'), 149.25 (C, C-7a), 143.69 (C, C-2), 141.12 (C, C-3a), 133.28 (overlap CH, C-2', C-6'), 128.62 (overlap CH, C-3', C-5'), 122.58 (CH, C-3''), 120.27 (C, C-1'), 118.43 (CH, C-4''), 114.05 (CH, C-6), 113.63 (CH, C-5), 109.50 (CH, C-4), 98.62 (CH, C-7).

Example 11

2-[(4-Nitro-phenyl)-[1,2,4]triazol-1-yl-methyl]-benzofuran-6-ol

Yield : 86 % (yellow solid), m.p. : 57-59 °C. ^{1}H NMR: δ 8.43 (s, 1, OH), 8.32 (m, 3, 2 x triazole, Ar), 8.20 (s, 1, Ar), 7.43 (m, 3, Ar), 6.95 (m, 3, Ar), 6.65 (s, 1, Ar). ^{13}C NMR: δ 156.98 (CH, triazole), 156.47 (CH, triazole), 152.42 (C, C-4'), 149.08 (C, C-7a), 148.67 (C, C-2), 143.73 (C, C-3a), 142.85 (C, C-1'), 128.89 (overlap CH, C-2', C-6'), 124.68 (overlap CH, C-3', C-5'), 122.60 (CH, C-3''), 129.43 (CH, C-4''), 123.33 (CH, C-6), 121.47 (CH, C-5), 114.09 (CH, C-4), 109.59 (CH, C-7), 98.63 (CH, C-3), 62.50 (CH, C-1).

Example 12

2-[(4-Chloro-phenyl)-[1,2,4]triazol-1-yl-methyl]-benzofuran-6-ol

Yield : 76 % (yellow solid), m.p. : 57-59 °C. ^{1}H NMR: δ 9.08 (s, 1, OH), 8.32 (s, 1, triazole), 8.20 (s, 1, triazole), 7.47 (m, 3, Ar), 7.37 (s, 1, Ar), 7.31 (dd, J = 1.7 Hz, 2, Ar), 6.95 (m, 3, Ar), 6.61 (s, 1, H-1). ^{13}C NMR: δ 156.91 (CH, triazole), 156.42 (CH, triazole), 151.99 (C, C-4'), 150.15 (C, C-7a), 143.47 (C, C-2), 135.72 (C, C-3a), 134.48 (C, C-1'), 129.77 (overlap CH, C-2', C-6'), 129.30 (overlap CH, C-3', C-5'), 122.41 (CH, C-3''), 120.29 (CH, C-4''), 113.91 (CH, C-6), 109.09 (CH, C-5), 98.62 (CH, C-4). Microanalysis calcd for $C_{17}H_{12}ClN_3O_3$ (325.753) C 61.80 %, H 3.88 %, N 12.47 %, found C 61.99 %, H 3.67 %, N 12.75 %.

Preparation of Examples 13 and 14

To a mixture of dry magnesium turnings (25 mmol) and iodine (3 crystals) in anhydrous THF (30 mL) was added 3-bromopyridine (25 mmol) and the reaction heated at 70 °C for 2 h. Intermediate 1 (5 mmol) in dry THF (7 mL) was then added to the reaction mixture, which was heated at 70 °C for a further 1 h. The reaction mixture was filtered and the filtrate concentrated under reduced pressure. The resulting residue was dissolved in dichloromethane (40 mL) and this solution washed with water (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash column chromatography (petroleum ether-ethyl acetate 60:40 - 40:60 v/v). T.l.c. system : petroleum ether-ethyl acetate 3:1 v/v to yield the title compound of Example 5. The above preparation was repeated for Intermediate 2 to yield the title compound of Example 6.

Example 13

1-[(6-Methoxy-benzo[*b*]furan-2-yl)4-fluoro(phenyl)methyl)]-3-pyridylmethanol

Yield : 80 %, mp 65-67 °C. ^{1}H NMR: δ 8.64 (d, *J*= 2.3 Hz, 1, Ar), 8.60 (dd, *J* = 1.6, 4.8 Hz, 1, Ar), 7.78 (dt, *J* = 2.0, 8.1 Hz, 1, Ar), 7.38 (m, 4, Ar), 7.10 (m, 2, Ar), 7.02 (d, *J* = 1.9 Hz, 1, Ar), 6.93 (dd, *J* = 2.2, 8.6 Hz, 1, Ar), 6.28 (d, *J* = 0.7 Hz, 1, H-3), 3.89 (s, 3, CH_3), 3.74 (s, 1, OH). Microanalysis calcd for $C_{21}H_{16}FNO_3.0.1\ H_2O$ (351.16222) C 71.83%, H 4.65%, N 3.99%, found C 71.67%, H 4.58%, N 3.98%.

Example 14

1-[(6-Methoxy-benzo[*b*]furan-2-yl)4-

chloro(phenyl)methyl)]-3-pyridylmethanol

Yield : 80 %, mp 67-69 °C. ^{1}H NMR: δ 8.58 (d, J = 10.9 Hz, 2, Ar), 7.76 (dt, J = 2.0, 8.0 Hz, 1, Ar), 7.37 (m, 7, Ar), 7.00 (s, 1, Ar), 6.93 (dd, J = 2.2, 8.5 Hz, 1, Ar), 6.29 (d, J = 0.7 Hz, 1, H-3), 4.19 (s, 1, OH), 3.88 (s, 3, CH_3). Microanalysis calcd for $C_{21}H_{16}ClNO_3.0.1\ H_2O$ (367.61682) C 68.61%, H 4.44%, N 3.81%, found C 68.47%, H 4.38%, N 3.80%.

Example 15

Enzyme Assay

Preparation of Human Placental Microsomes

Freshly delivered full-term placenta was removed of connective tissue and then cut into small pieces and stored in ice. The placenta was washed with Tris pH 7.4 buffer, containing 25 mM KCl, 5 mM MgCl and 0.25 mM sucrose, and initially blended to a fine consistency using a commercial food blender. The blended placenta was then homogenised using a Potter-Elvejhem homogeniser. The homogenate was centrifuged at 12,000 rpm for 15 min at 4 °C using a Sorvall OTD ultracentrifuge, then the supernatant ultracentrifuged at 38,000 rpm for 60 min at 4 °C. The supernatant was decanted, the remaining pellets, the microsomal fraction, were dispersed in Tris buffer using a homogeniser then stored in vials at -80 °C. Protein concentration of both the microsomal and cytosolic fractions was determined using the Pierce BCA protein assay.

Aromatase Enzyme Assays

A solution of [1,2,6,7-^{3}H]androstenedione and androstenedione (0.5 μM final concentration) was

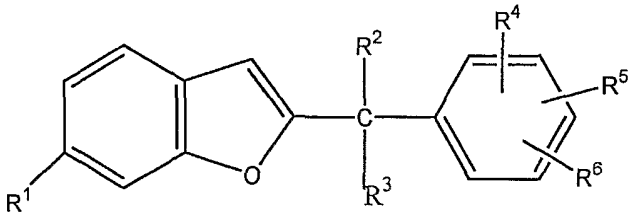
incubated in test tubes at 37 °C for 15 min with the human placental microsomal preparation (8.24 mg/mL, 30 µL), phosphate buffer (400 µL, 50 mM, pH 7.4) and NADPH (50 µL, 16 mM) in the presence of a compound according to the present invention (10 µL, 1 mmol or 5 mmol - 20 or 100 µM final concentrations respectively) in EtOH. Control experiments were run with EtOH (10 µL) in place a compound according to the present invention . The reaction was quenched by the addition of aqueous $HgCl_2$ (30 µL, 1 mM) followed by an aqueous suspension of charcoal (1 mL, 1% by weight). The test tubes were centrifuged (15 min, 3000 rpm), then the supernatant liquid placed in scintillation vial to which 2 mL of scintillation fluid was added. The ^3H_2O contained in each vial was then determined using a LKB Wallac, 1217, Rack-beta scintillation counter.

IC_{50} values calculated for compounds according to the present invention were as follows:

Example Number	IC_{50}(nM)
1	49
2	44
3	160
4	130
5	12
6	600
7	100
8	130
9	1230
10	20
11	60
12	1460
13	170
14	100

Claims:

1. A compound of formula (I), or a pharmaceutically acceptable salt, or prodrug thereof



(I)

where

R^1 is hydroxy, C_{1-6} alkoxy or halogen;
R^2 is a 5- or 6- membered heterocyclic ring containing one or more nitrogen heteroatoms;
R^3 is hydrogen or hydroxy; and
R^4, R^5, and R^6, which may be the same or different, are selected from the group consisting of hydrogen, halo, cyano, CF_3, C_{1-6} alkyl, hydroxy and C_{1-6} alkoxy.

2. A compound according to claim 1, wherein R^1 is C_{1-6}alkoxy.

3. A compound according to claim 2, wherein R^1 is methoxy.

4. A compound according to any of claims 1 to 3, wherein R^2 is imidazole, triazole or pyridine.

5. A compound according to any of claims 1 to 4, wherein at least one of R^4, R^5 and R^6 is selected

from the group consisting of halo, cyano, CF_3, C_{1-6} alkyl, hydroxy and c_{1-6} alkoxy.

6. A compound according to claim 5, wherein R^4 is selected from the group consisting of halo, cyano, CF_3, C_{1-6} alkyl, hydroxy and c_{1-6} alkoxy and R^5 and R^6 both represent hydrogen.

7. A compound according to claim 6, wherein R^4 can be selected from the group consisting of halo, cyano, C_{1-3} alkyl, hydroxy and C_{1-3} alkoxy and R^5 and R^6 both represent hydrogen.

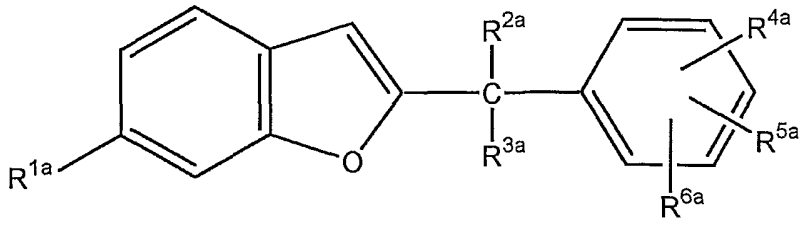
8. A compound according to claim 7, wherein R^4 is halo or C_{1-3} alkoxy substituted in the 4-position of the phenyl ring to which R^4 is attached, and R^5 and R^4 both represent hydrogen.

9. A compound according to claim 8, wherein R^4 is fluoro, chloro or methoxy.

10. A compound according to claim 5, wherein R^4 and R^5 are independently selected from the group consisting of halo, cyano, CF_3, C_{1-6} alkyl, hydroxy and c_{1-6} alkoxy and R^6 represents hydrogen.

11. A compound according to claim 10, wherein R^4 and R^5 are independently selected from the group consisting of halo, cyano, C_{1-3} alkyl, hydroxy and C_{1-3} alkoxy and R^6 represents hydrogen.

12. A compound of formula (IA), or a pharmaceutically acceptable salt or prodrug thereof



(IA)

where:

R^{1a} is hydroxy or C_{1-3} alkoxy;

R^{2a} is a 5- or 6-membered heterocyclic ring containing one or more nitrogen heteroatoms;

R^{3a} is hydrogen or hydroxy;

R^{4a} is halo or C_{1-3}alkoxy; and R^{5a} and R^{6a} are both hydrogen.

13. A compound according to claim 12, wherein R^{1a} is C_{1-3} alkoxy.

14. A compound according to claim 13, wherein R^{1a} is methoxy.

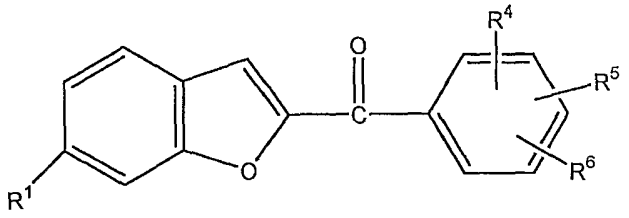
15. A compound according to any of claims 12 to 14, wherein R^{2a} is imidazole, triazole or pyridine.

16. A compound according to any of claims 12 to 15, wherein R^{4a} is halo or C_{1-3} alkoxy substituted in the 4- position of the phenyl ring to which R^{4a} is attached.

17. A compound according to claim 16, wherein R^{4a} is fluoro, chloro or methoxy.

18. 1-[(6-Methoxy-benzo[*b*]furan-2-yl)4-fluoro(phenyl)methyl]-1*H*-1,2,4-triazole;
1-[(6-Methoxy-benzo[*b*]furan-2-yl)4-chloro(phenyl)methyl]-1*H*-1,2,4-triazole;
1-[(6-Methoxy-benzo[*b*]furan-2-yl)4-methoxy(phenyl)methyl]-1*H*-1,2,4-triazole;
1-[(6-Methoxy-benzo[*b*]furan-2-yl)4-methoxy(phenyl)methyl]-1*H*-imidazole;
1-[(6-Methoxy-benzo[*b*]furan-2-yl)4-fluoro(phenyl)methyl)]-3-pyridylmethanol; and/or
1-[(6-Methoxy-benzo[*b*]furan-2-yl)4-chloro(phenyl)methyl)]-3-pyridylmethanol.

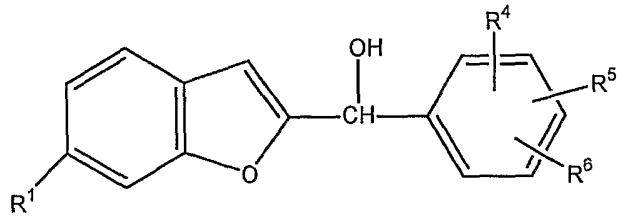
19. A process of preparing a compound of formula (I) according to claim 1, from an intermediate ketone compound of formula (II)



(II)

where R^1, R^4, R^5 and R^6 are as defined in claim 1.

20. A process according to claim 19, wherein a compound of formula (I) where R^2 is a 5-membered heterocycle as defined in claim 1, and R^3 is hydrogen as defined in claim 1, is prepared from an intermediate ketone compound of formula (II) via an intermediate carbinol compound of formula (III)



(III)

where
R^1, R^4, R^5 and R^6 are as defined in claim 1, by reaction of a compound of formula (III) with $(Het_a)_2S=O$, where Het_a represents a 5-membered heterocycle as represented by R^2 and as defined in claim 1.

21. A process according to claim 19, wherein a compound of formula (I) where R^2 is a 6-membered heterocycle as defined in claim 1, and R^3 is hydroxy as defined in claim 1, is prepared from an intermediate ketone compound of formula (II) by reaction with Het_b-Mg-Hal, where Het_b represents a 6-membered heterocycle as represented by R^2 and as defined in claim 1 and Hal represents halo selected from bromo, chloro, fluoro and iodo.

22. A pharmaceutical formulation comprising a compound according to any of claims 1 to 18, together with a pharmaceutically acceptable carrier, diluent or excipient therefor.

23. A pharmaceutical formulation according to claim 22, which further comprises at least one further inhibitor of the steroidogenic pathway.

24. A product comprising a compound according to any of claims 1 to 18, and at least one further inhibitor of the steroidogenic pathway, for simultaneous, separate or sequential administration to a mammal for treating oestrogen dependent or mediated diseases.

25. A product according to claim 24, wherein said further inhibitor comprises at least one inhibitor of 17β-HSD isoforms and/or oestrogen sulphatase.

26. For use in therapy, a compound according to any of claims 1 to 18.

27. A compound according to any of claims 1 to 18, for use in the manufacture of a medicament for inhibition of $P450_{AROM}$.

28. A compound according to any of claims 1 to 18, for use in the manufacture of a medicament for the treatment of oestrogen dependent or mediated diseases.

29. A compound according to any of claims 1 to 18, for use in the manufacture of a medicament for the treatment of hormone-dependent breast cancer.

30. A method of treating a mammal suffering from or susceptible to an oestrogen dependent or mediated disease, which method comprises administering to said mammal a therapeutically effective amount of a compound according to any of claims 1 to 18.

31. 1-[(6-Methoxy-benzo[*b*]furan-2-yl)4-fluoro(phenyl)methyl]-1*H*-1,2,4-triazole;
1-[(6-Methoxy-benzo[*b*]furan-2-yl)4-chloro(phenyl)methyl]-1*H*-1,2,4-triazole;
1-[(6-Methoxy-benzo[*b*]furan-2-yl)4-methoxy(phenyl)methyl]-1*H*-1,2,4-triazole;
1-[(6-Methoxy-benzo[*b*]furan-2-yl)4-methoxy(phenyl)methyl]-1*H*-imidazole;
1-[(6-Methoxy-benzo[*b*]furan-2-yl)4-fluoro(phenyl)methyl)]-3-pyridylmethanol;
1-[(6-Methoxy-benzo[*b*]furan-2-yl)4-chloro(phenyl)methyl)]-3-pyridylmethanol;
4-[6-Methoxy-benzofuran-2-yl)-1*H*-1,2,4-triazol-1-yl-methyl]-benzonitrile;

1-[(6-Methoxy-benzofuran-2-yl)-(4-nitro-phenyl)-methyl]-1*H*-1,2,4-triazole;

1-[(6-Methoxy-benzofuran-2-yl)-*p*-tolyl-methyl]-1*H*-1,2,4-triazole;

1-[(6-Methoxy-benzofuran-2-yl)-(4-trifluoromethyl-phenyl)-methyl]-1*H*-1,2,4-triazole;

1-[(6-Methoxy-benzofuran-2-yl)-(4-ethyl-phenyl)-methyl]-1*H*-1,2,4-triazole;

4-[(6-Hydroxy-benzofuran-2-yl)-[1,2,4]triazol-1-yl-methyl]-benzonitrile;

2-[(4-Nitro-phenyl)-[1,2,4]triazol-1-yl-methyl]-benzofuran-6-ol; and/or

2-[(4-Chloro-phenyl)-[1,2,4]triazol-1-yl-methyl]-benzofuran-6-ol.

INTERNATIONAL SEARCH REPORT

Interna I Application No
PCT/GB 03/04454

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D405/06 A61P35/00 A61K31/343 A61K31/415

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61P A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 18791 A (LOMBARDI PAOLO ;MENARINI FARMA IND (IT); PIETRO GIOVANNA DI (IT)) 7 May 1998 (1998-05-07) claims 1,4,11; examples; table 1 ---	1-31
Y	VINH T K ET AL: "1'(Benzofuran-2-yl)phenylmethyl!-Triazoles and -Tetrazoles - Potent Competitive Inhibitors of Aromatase" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 9, no. 14, 19 July 1999 (1999-07-19), pages 2105-2108, XP004171646 ISSN: 0960-894X Scheme 1 figures 1,2 --- -/--	1-31

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 January 2004	16/02/2004

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

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WHOMSLEY R ET AL: "SUBSTITUTED 1-((BENZOFURANO-2YL)-(PHENYLMETHYL)-IMIDAZOLES AS POTENT INHIBITORS OF AROMATASE IN VITRO AND IN FEMALE RATS IN VIVO" JOURNAL OF STEROID BIOCHEMISTRY AND MOLECULAR BIOLOGY, ELSEVIER SCIENCE LTD., OXFORD, GB, vol. 44, no. 4-6, 1993, pages 675-676, XP002266745 ISSN: 0960-0760 table 1 ---	1-31
Y	EP 0 257 171 A (MENARINI SAS) 2 March 1988 (1988-03-02) page 3 -----	19-21

INTERNATIONAL SEARCH REPORT

Inte ional application No.
PCT/GB 03/04454

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 30 is directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compounds.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

Internat Application No
PCT/GB 03/04454

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