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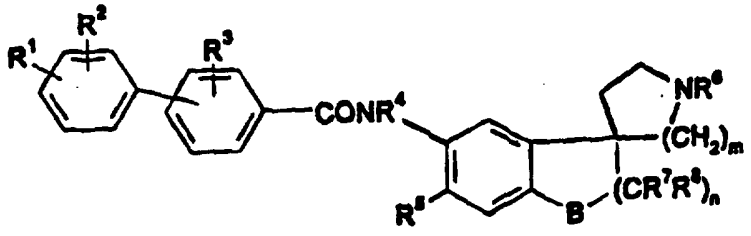

(I)

(57) Abstract

Compounds of formula (I) in which B is oxygen, $CR^{17}R^{18}$ or NR^{19} where R^{17}, R^{18} and R^{19} are independently hydrogen or C_{1-6}alkyl or B is a group $S(O)_b$ where b is 1, 2, or 3; and R^6 is a group $-(CH_2)_p-R^{15}$ where R^{15} is OR^{16} or SR^{16} is hydrogen or C_{1-6}alkyl or R^{15} is $NR^{10}R^{11}$ where R^{10} and R^{11} are as defined for R^1; have been found to exhibit $5TH_{1B}$ antagonist activity.

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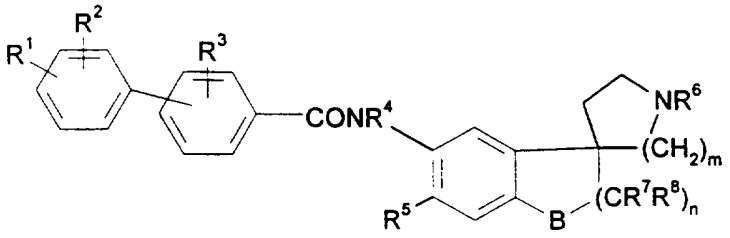
AZASPIRO DERIVATIVES WITH $5HT_{1B}$ ACTIVITY

The present invention relates to novel piperidine derivatives, processes for their preparation, and pharmaceutical compositions containing them.

EPA 0 533 266/7/8 disclose a series of benzanilide derivatives which are said to possess $5HT_{1D}$ receptor antagonist activity. These compounds are said to be of use in the treatment of various CNS disorders. The $5HT_{1D\beta}$ receptor has now been reclassified as the $5HT_{1B}$ receptor (P.R Hartig et al Trends in Pharmacological Science, 1996, **17**, 103 - 105.

A structurally distinct class of compounds have now been discovered and have been found to exhibit $5HT_{1B}$ antagonist activity. In a first aspect, the present invention therefore provides a compound of formula (I) or a salt or N-oxide thereof:



(I)

in which

R^1 is hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, COC_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, acyl, nitro, trifluoromethyl, cyano, SR^9, SOR^9, SO_2R^9, $NR^9CONR^{10}R^{11}$, $NR^{10}SO_2R^{11}$, $SO_2NR^{10}R^{11}$, CO_2R^{10}, $CONR^{10}R^{11}$, $CO_2NR^{10}R^{11}$, $CONR^{10}(CH_2)_aCO_2R^{11}$, $(CH_2)_aNR^{10}R^{11}$, $(CH_2)_aCONR^{10}R^{11}$, $(CH_2)_aNR^{10}COR^{11}$, $(CH_2)_aCO_2C_{1-6}$alkyl, $CO_2(CH_2)_aOR^{10}$, $NR^{10}R^{11}$, $N{=}CNR^9NR^{10}R^{11}$, $NR^{10}CO(CH_2)_aNR^{10}R^{11}$, $NR^{10}CO_2R^{11}$, $CONHNR^{10}R^{11}$, $CR^{10}{=}NOR^{11}$, $CNR^{10}{=}NOR^{11}$, where R^9, R^{10} and R^{11} are independently hydrogen or C_{1-6}alkyl and a is 1 to 4; or R^1 is an optionally substituted 5 to 7-membered heterocyclic ring containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;

R^2 and R^3 are independently hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, C_{1-6}alkylOC_{1-6}alkyl, acyl, aryl, acyloxy, hydroxy, nitro, trifluoromethyl, cyano, CO_2R^{10}, $CONR^{10}R^{11}$, $NR^{10}R^{11}$ where R^{10} and R^{11} are independently hydrogen or C_{1-6}alkyl;

R^4 is hydrogen or C_{1-6}alkyl;

R^5 is hydrogen or C_{1-6}alkyl or R^4 and R^5 together form a group -A- where A is $(CR^{13}R^{14})_q$ where q is 2, 3 or 4 and R^{13} and R^{14} are independently hydrogen or C_{1-6}alkyl or A is $(CR^{13}R^{14})_r$-D where r is 0, 1, 2 or 3 and D is oxygen, sulphur or $CR^{13}=CR^{14}$;

R^6 is a group $-(CH_2)_p-R^{15}$ where R^{15} is OR^{16} or SR^{16} where R^{16} is hydrogen or C_{1-6}alkyl or R^{15} is $NR^{10}R^{11}$ where R^{10} and R^{11} are as defined for R^1;

R^7 and R^8 are independently hydrogen or C_{1-6}alkyl;

B is oxygen, $CR^{17}R^{18}$ or NR^{19} where R^{17}, R^{18} and R^{19} are independently hydrogen or C_{1-6}alkyl or B is a group $S(O)_b$ where b is 1, 2 or 3;

m is 1, 2 or 3; and

n is 1, 2 or 3.

C_{1-6}alkyl groups, whether alone or as part of another group, may be straight chain or branched.

Suitably R^1 is hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, COC_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, acyl, nitro, trifluoromethyl, cyano, SR^9, SOR^9, SO_2R^9, $NR^9CONR^{10}R^{11}$, $NR^{10}SO_2R^{11}$, $SO_2NR^{10}R^{11}$, CO_2R^{10}, $CONR^{10}R^{11}$, $CO_2NR^{10}R^{11}$, $CONR^{10}(CH_2)_aCO_2R^{11}$, $(CH_2)_aNR^{10}R^{11}$, $(CH_2)_aCONR^{10}R^{11}$, $(CH_2)_aNR^{10}COR^{11}$, $(CH_2)_aCO_2C_{1-6}$alkyl, $CO_2(CH_2)_aOR^{10}$, $NR^{10}R^{11}$, $N=CNR^9NR^{10}R^{11}$, $NR^{10}CO(CH_2)_aNR^{10}R^{11}$, $NR^{10}CO_2R^{11}$, $CONHNR^{10}R^{11}$, $CR^{10}=NOR^{11}$, $CNR^{10}=NOR^{11}$, where R^9, R^{10} and R^{11} are independently hydrogen or C_{1-6}alkyl and a is 1 to 4; or R^1 is an optionally substituted 5 to 7-membered heterocyclic ring containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur.

When R^1 is a 5 to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur suitable heterocyclic rings include thienyl, furyl, pyrrolyl, triazolyl, diazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyridyl, pyrimidyl and pyrazinyl. The heterocyclic rings can be linked to the remainder of the molecule via a carbon atom or, when present, a nitrogen atom. Suitable substituents for these rings include R^2 and R^3 groups as defined above. Preferably R^1 is optionally substituted oxadiazolyl. Preferred substituents for such oxadiazolyl groups include C_{1-6}alkyl such as methyl or ethyl. Most preferably R^1 is

a 5-methyl-1,3,4-oxadiazol-2-yl group.

Suitably R^2 and R^3 are independently hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, C_{1-6}alkylOC_{1-6}alkyl, acyl, aryl, acyloxy, hydroxy, nitro, trifluoromethyl, cyano, CO_2R^{10},

$CONR^{10}R^{11}$, $NR^{10}R^{11}$ where R^{10} and R^{11} are independently hydrogen or C_{1-6}alkyl. Preferably R^2 is C_{1-6}alkyl, in particular methyl. Preferably R^3 is hydrogen.

Suitably R^4 is hydrogen or C_{1-6}alkyl and R^5 is hydrogen or C_{1-6}alkyl or R^4 and R^5 together form a group -A- where A is $(CR^{13}R^{14})_q$ where q is 2, 3 or 4 and R^{13} and R^{14} are independently hydrogen or C_{1-6}alkyl or A is $(CR^{13}R^{14})_r$-D where r is 0, 1, 2 or 3 and D is oxygen, sulphur or $CR^{13}=CR^{14}$. Preferably R^4 and R^5 form a group -A-. Preferably A is $(CH_2)_2$.

Suitably R^6 is a group $-(CH_2)_p-R^{15}$ where R^{15} is OR^{16} or SR^{16} where R^{16} is hydrogen or C_{1-6}alkyl or R^{15} is $NR^{10}R^{11}$ where R^{10} and R^{11} are as defined for R^1. Preferably R^6 is a group $-(CH_2)_p-R^{15}$ where p is 2 and R^{15} is hydroxy.

Suitably R^7 and R^8 are independently hydrogen or C_{1-6}alkyl, preferably R^7 and R^8 are both hydrogen.

Suitably m is 1, 2 or 3. Preferably m is 2 forming a spiropiperidine ring.

Suitably B is oxygen, $CR^{17}R^{18}$ or NR^{19} where R^{17}, R^{18} and R^{19} are independently hydrogen or C_{1-6}alkyl or B is a group $S(O)_b$ where b is 1, 2 or 3, preferably B is oxygen.

Suitably n is 1, 2 or 3, preferably n is 1.

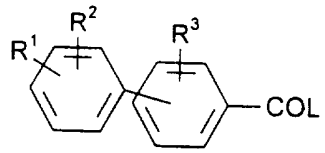
Particularly preferred compounds of the invention include:
1'-(2-Hydroxyethyl)-5-(2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-f]indole-3,4'-piperidine],
1'-(2-Hydroxyethyl)-5-(2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-f]indole-3,4'-piperidine],
1'-(2-Dimethylaminoethyl)-5-(2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-f]indole-3,4'-piperidine],
1'-(2-Methoxyethyl)-5-(2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-f]indole-3,4'-piperidine]
or pharmaceutically acceptable salts thereof.

Preferred salts of the compounds of formula (I) are pharmaceutically acceptable salts. These include acid addition salts such as hydrochlorides, hydrobromides, phosphates, acetates, fumarates, maleates, tartrates, citrates, oxalates, methanesulphonates and p-toluenesulphonates.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and the mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the invention.

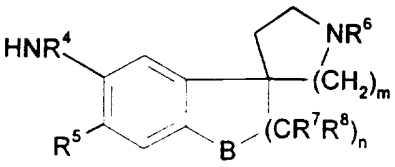
In a further aspect the present invention provides a process for the preparation of a compound of formula (I) which comprises.

(a) reaction of a compound of formula (II):



(II)

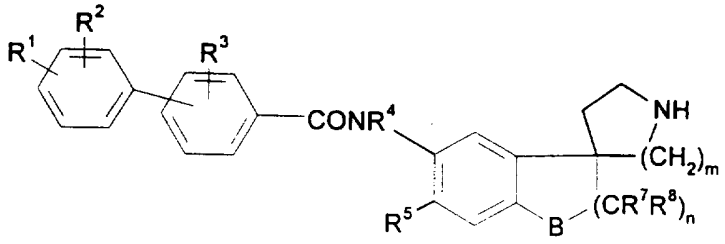
in which R^1, R^2 and R^3 are as defined in formula (I) and L is a leaving group. with a compound of formula (III):



(III)

wherein R^4, R^5, R^6, R^7, R^8, A, B, m and n are as defined in formula (I); or

(b) reacting a compound of formula (IV):



(IV)

wherein R^1, R^2, R^3, R^4, R^5, R^7, R^8, A, B, m and n are as defined in formula (I) with a compound of formula (V):

$$L'\text{-}R^6$$

(V)

where R^6 is as defined in formula (I) and L' is a leaving group;

and optionally thereafter (a) or (b) in any order:

- converting a compound of formula (I) into another compound of formula (I)
- forming a pharmaceutically acceptable salt.

Suitable activated carboxylic acid derivatives of formula (II) include acyl halides and acid anhydrides. Activated compounds of formula (II) can also be prepared by reaction of the corresponding carboxylic acid with a coupling reagent such as carbonyldiimidazole, dicyclohexylcarbodiimide or diphenylphosphorylazide. Preferably the group L is halo, particularly chloro.

Compounds of formulae (II) and (III) are typically reacted together in an inert organic solvent such as DMF, THF or dichloromethane at ambient or elevated temperature in the presence of a base such as an alkali metal hydroxide, triethylamine or pyridine.

Alternatively L is an ester forming group such that the resulting esters of formula (II) can be reacted with compounds of formula (III) in the presence of an organo-aluminium reagent such as trimethylaluminium. Such a reaction is typically carried out in the presence of an inert solvent such as toluene.

Intermediate compounds of formulae (II) can be prepared using standard procedures such as those outlined in EPA 533266/7/8. Intermediate compounds of formula (III) can be prepared using standard procedures. Certain intermediate compounds of formula (III) are novel and form a further aspect of the invention.

Reaction of compounds of formulae (IV) and (V) is suitably carried out in the presence of a base in an inert solvent. Preferably L' is a halo, in particular chloro. Preferably the reaction is carried out in an alcoholic solvent at elevated temperature using potassium carbonate as base.

Intermediate compounds of formulae (IV) can be prepared using an analogous coupling procedure to that outlined above for compounds of formulae (II) and (III) using suitable nitrogen protection. Compounds of formula (V) are commercially available or can be prepared using standard procedures.

It will be appreciated to those skilled in the art that it may be necessary to protect certain reactive substituents during some of the above procedures. Standard protection and deprotection techniques can be used. For example, primary amines can be protected as phthalimide, benzyl, benzyloxycarbonyl or trityl derivatives. These groups can be removed by conventional procedures well known in the art.

Carboxylic acid groups can be protected as esters. Aldehyde or ketone groups can be protected as acetals, ketals, thioacetals or thioketals. Deprotection is achieved using standard conditions.

Salts and N-oxides can be prepared using standard procedures. For example N-oxides can be prepared using meta-chloroperoxybenzoic acid or hydrogen peroxide.

$5HT_{1B}$ Antagonists, and in particular the compounds of the present invention, are expected to be of use in the treatment of CNS disorders such as mood disorders, including depression, seasonal effective disorder and dysthymia; anxiety disorders, including generalised anxiety, panic disorder, agoraphobia, social phobia, obsessive compulsive disorder and post-traumatic stress disorder; memory disorders, including dementia, amnestic disorders and age-associated memory impairment; and disorders of eating behaviours, including anorexia nervosa and bulimia nervosa. Other CNS disorders include Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced Parkinsonism and tardive dyskinesias, as well as other psychiatric disorders.

$5HT_{1B}$ Antagonists, and in particular compounds of the present invention, may also be of use in the treatment of endocrine disorders such as hyperprolactinaemia, in the treatment of vasospasm (particularly in the cerebral vasculature) and hypertension, as well as disorders in the gastrointestinal tract where changes in motility and secretion are involved. They may also be of use in the treatment of sexual dysfunction and hypothermia.

Therefore, the present invention, provides a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in therapy.

The present invention also provides a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment of the aforementioned disorders.

In another aspect the invention provides the use of a compound of general formula (I) or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of the aforementioned disorders.

In a further aspect the invention provides a method of treating the aforementioned disorders which comprises administering an effective amount to a patient in need of such treatment of a compound of general formula (I) or a pharmaceutically acceptable salt or solvate thereof.

In particular the invention provides a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment or prophylaxis of depression.

It will be appreciated by those skilled in the art that the compounds according to the invention may advantageously be used in conjunction with one or more other therapeutic agents, for instance, different antidepressant agents.

The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks or months.

The following Examples illustrate the preparation of compounds of the invention.

Example 1

1'-(2-Hydroxyethyl)-5-(2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-f]indole-3,4'-piperidine]

A stirred solution of 5-(2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-f]indole-3,4'-piperidine] (E3 in WO 96/19477, 0.44g, 0.87 mmole) in 2-butanone (30 ml) was treated with potassium carbonate (0.36g, 2.6 mmole) and 2-chloroethanol (0.18 ml, 2.6 mmole) and heated under reflux for 56 hours, then additional potassium carbonate (0.36 g, 2.6 mmole) and 2-chloroethanol (0.18 ml, 2.6 mmole) added. Reflux was continued for a further 30 hours, then the mixture was concentrated *in vacuo* and the residue treated with 10% Na_2CO_3 solution and extracted with ethyl acetate. The extract was dried, concentrated *in vacuo* and the residue chromatographed on silica gel eluting with 0-10% methanol/chloroform to afford the title compound as a pale yellow oil (0.18g, 38%). This was converted to its hydrochloride salt and crystallised from acetone mp. >230°C.

^{1}H NMR (free base) (250MHz, $CDCl_3$) δ (ppm): 8.15 (s, 1H - low integration), 8.02 (s, 1H), 7.97 (d, 1H), 7.63 (d, 2H), 7.43 (d, 2H), 7.35 (d, 1H), 6.68 (s, 1H), 4.40 (br s, 2H), 4.12 (br t, 2H), 3.65 (br t, 2H), 3.08 (t, 2H), 2.95 (br m, 2H), 2.69 (s, 3H), 2.65-2.50 (m, 3H), 2.36 (s, 3H), 2.30-1.95 (m, 4H), 1.90-1.70 (m, 2H)

Example 2

1'-(2-Hydroxyethyl)-5-(2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-f]indole-3,4'-piperidine]

A stirred solution of 5-(2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-f]indole-3,4'-piperidine] (E17 in WO 96/19477, 1.5g, 2.9 mmole) in ethanol (30 ml) was treated with sodium carbonate (1.2g, 11.6 mmole) and 2-bromoethanol (0.41 ml, 5.8 mmole) and heated under reflux for 20 hours. The reaction mixture was concentrated *in vacuo* and the residue treated with water (10 ml) and extracted with chloroform. The extract was dried (Na_2SO_4), concentrated *in vacuo* and the residue chromatographed on silica gel eluting with 0-6% methanol/chloroform to afford the title compound as a yellow solid (0.9g, 56%). This was converted to its hydrochloride salt and crystallised from acetone m.p. > 250°C.

^{1}H NMR (free base) (250 MHz, $CDCl_3$) δ (ppm): 8.15 (br s, 1H - low integration), 8.00 (d, 1H), 7.92 (dd, 1H), 7.65 (d, 2H), 7.42 (d, 2H), 7.38 (d, 1H), 6.68 (s, 1H), 4.42 (br s,

2H), 4.12 (br m, 2H), 3.65 (br t, 2H), 3.09 (t, 2H), 2.94 (br m, 2H), 2.66 (s, 3H), 2.58 (br t, 2H), 2.38 (s, 3H), 2.25-1.95 (m, 4H), 1.90-1.65 (m, 2H).

Example 3

1'-(2-Dimethylaminoethyl)-5-(2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-f]indole-3,4'-piperidine]

A stirred solution of 5-(2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-f]indole-3,4'-piperidine] (E17 in WO 96/19477, 500 mg, 0.99 mmole) in ethanol (40 ml) was treated with sodium carbonate (419 mg, 3.9 mmole) and 2-dimethylaminoethyl chloride hydrochloride (287mg, 1.98 mmole) and heated under reflux for 48 hours. The reaction mixture was concentrated *in vacuo* and the residue treated with 10% Na_2CO_3 solution and extracted with ethyl acetate. The extract was dried (Na_2SO_4), concentrated *in vacuo* and the residue chromatographed on silica gel eluting with 0-8% methanol/chloroform to afford the title compound as a yellow/beige solid (75 mg, 13%). This was converted to its hydrochloride salt and crystallised from acetone/ether m.p. 246-248°C.

^{1}H NMR (free base) (250 MHz, $CDCl_3$) δ (ppm): 8.15 (br s, 1H - low integration), 8.00 (d, 1H), 7.91 (dd, 1H), 7.63 (d, 2H), 7.42 (d, 2H), 7.38 (d, 1H), 6.68 (s, 1H), 4.40 (br s, 2H), 4.10 (br s, 2H), 3.08 (t, 2H), 2.96 (br m, 2H), 2.65 (s, 3H), 2.53 (br t, 2H), 2.38 (s, 3H), 2.31 (br s, 6H), 2.15-1.95 (m, 2H), 1.90-1.45 (m, 6H).

Example 4

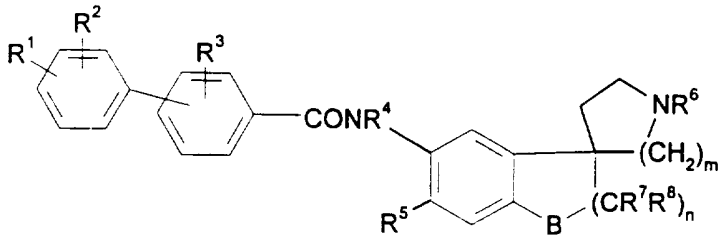
1'-(2-Methoxyethyl)-5-(2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-f]indole-3,4'-piperidine]

The title compound was prepared from 5-(2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-f]indole-3,4'-piperidine] (E17 in WO 96/19477) and 2-bromoethyl methyl ether using a similar procedure to Example 2, with a reaction time of 31 hours heating under reflux (33%). Hydrochloride salt m.p. 238-240°C.

^{1}H NMR (free base) (250 MHz, $CDCl_3$) δ (ppm): 8.15 (br s, 1H - low integration), 7.98 (d, 1H), 7.91 (dd, 1H), 7.63 (d, 2H), 7.42 (d, 2H), 7.37 (d, 1H), 6.67 (s, 1H), 4.40 (br s, 2H), 4.10 (br m, 2H), 3.54 (br t, 2H), 3.37 (s, 3H), 3.07 (t, 2H), 2.98 (br m, 2H), 2.64 (s, 3H), 2.60 (br t, 2H), 2.37 (s, 3H), 2.25-1.65 (m, 6H).

CLAIMS:

1. A compound of formula (I) or a salt or N-oxide thereof:



(I)

in which

R^1 is hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, COC_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, acyl, nitro, trifluoromethyl, cyano, SR^9, SOR^9, SO_2R^9, $NR^9CONR^{10}R^{11}$, $NR^{10}SO_2R^{11}$, $SO_2NR^{10}R^{11}$, CO_2R^{10}, $CONR^{10}R^{11}$, $CO_2NR^{10}R^{11}$, $CONR^{10}(CH_2)_aCO_2R^{11}$, $(CH_2)_aNR^{10}R^{11}$, $(CH_2)_aCONR^{10}R^{11}$, $(CH_2)_aNR^{10}COR^{11}$, $(CH_2)_aCO_2C_{1-6}$alkyl, $CO_2(CH_2)_aOR^{10}$, $NR^{10}R^{11}$, $N{=}CNR^9NR^{10}R^{11}$, $NR^{10}CO(CH_2)_aNR^{10}R^{11}$, $NR^{10}CO_2R^{11}$, $CONHNR^{10}R^{11}$, $CR^{10}{=}NOR^{11}$, $CNR^{10}{=}NOR^{11}$, where R^9, R^{10} and R^{11} are independently hydrogen or C_{1-6}alkyl and a is 1 to 4; or R^1 is an optionally substituted 5 to 7-membered heterocyclic ring containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;

R^2 and R^3 are independently hydrogen, halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, C_{1-6}alkylOC_{1-6}alkyl, acyl, aryl, acyloxy, hydroxy, nitro, trifluoromethyl, cyano, CO_2R^{10}, $CONR^{10}R^{11}$, $NR^{10}R^{11}$ where R^{10} and R^{11} are independently hydrogen or C_{1-6}alkyl;

R^4 is hydrogen or C_{1-6}alkyl;

R^5 is hydrogen or C_{1-6}alkyl or R^4 and R^5 together form a group -A- where A is $(CR^{13}R^{14})_q$ where q is 2, 3 or 4 and R^{13} and R^{14} are independently hydrogen or C_{1-6}alkyl or A is $(CR^{13}R^{14})_r$-D where r is 0, 1, 2 or 3 and D is oxygen, sulphur or $CR^{13}{=}CR^{14}$;

R^6 is a group $-(CH_2)_p$-R^{15} where R^{15} is OR^{16} or SR^{16} where R^{16} is hydrogen or C_{1-6}alkyl or R^{15} is $NR^{10}R^{11}$ where R^{10} and R^{11} are as defined for R^1;

R^7 and R^8 are independently hydrogen or C_{1-6}alkyl;

B is oxygen, $CR^{17}R^{18}$ or NR^{19} where R^{17}, R^{18} and R^{19} are independently hydrogen or C_{1-6}alkyl or B is a group $S(O)_b$ where b is 1, 2 or 3;
m is 1, 2 or 3; and
n is 1, 2 or 3.

2. A compound according to claim 1 in which R^1 is oxadiazole.

3. A compound according to claim 1 or 2 in which R^2 is C_{1-6}alkyl.

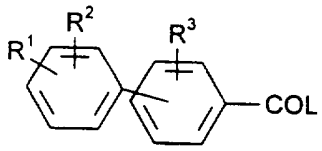
4. A compound according to any one of claims 1 to 3 in which m is 2 and n is 1.

5. A compound according to any one of claims 1 to 4 in which R^6 is a group $(CH_2)_2OH$.

6 A compound according to claim 1 which is:
1'-(2-Hydroxyethyl)-5-(2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-2-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-f]indole-3,4'-piperidine],
1'-(2-Hydroxyethyl)-5-(2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-f]indole-3,4'-piperidine],
1'-(2-Dimethylaminoethyl)-5-(2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-f]indole-3,4'-piperidine],
1'-(2-Methoxyethyl)-5-(2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-f]indole-3,4'-piperidine]
or pharmaceutically acceptable salts or N-oxides thereof.

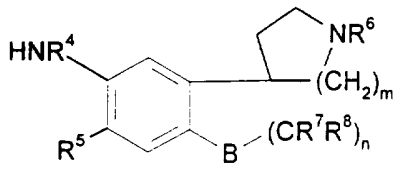
7. A process for the preparation of a compound of formula (I) which comprises:

(a) reaction of a compound of formula (II):



(II)

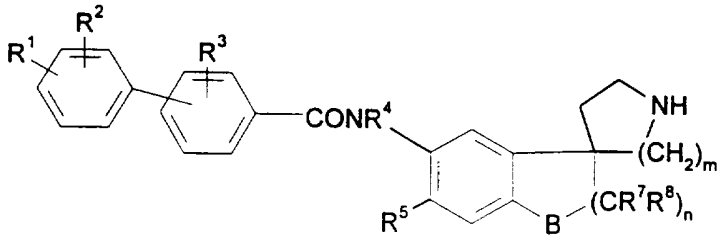
in which R^1, R^2 and R^3 are as defined in formula (I) and L is a leaving group.
with a compound of formula (III):



(III)

wherein R^4, R^5, R^6, R^7, R^8, A, B, m and n are as defined in formula (I); or

(b) reacting a compound of formula (IV):



(IV)

wherein R^1, R^2, R^3, R^4, R^5, R^7, R^8, A, B, m and n are as defined in formula (I) with a compound of formula (V):

$$L'\text{-}R^6$$

(V)

where R^6 is as defined in formula (I) and L' is a leaving group;

and optionally thereafter (a) or (b) in any order:

- converting a compound of formula (I) into another compound of formula (I)
- forming a pharmaceutically acceptable salt.

8. A compound of formula (III) as defined in claim 7.

9. A compound according to any one of claims 1 to 6 for use in therapy.

10. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 6 in association with a pharmaceutically acceptable carrier or excipient.

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/EP 96/04657

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D491/20 A61K31/435 C07D471/10 C07D487/10 C07D471/20
C07D487/20 C07D491/107 C07D495/10 C07D495/20
//(C07D491/20,307:00,221:00,209:00)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D 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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 533 266 A (GLAXO) 24 March 1993 cited in the application see page 4, line 47 - page 5, line 34; claim 1 ---	1,9
P,A	WO 96 11934 A (SMITHKLINE BEECHAM) 25 April 1996 see page 4, line 31 - line 38; claim 1 ---	1,9
P,A	WO 96 19477 A (SMITHKLINE BEECHAM) 27 June 1996 see page 85; claim 1 -----	1,9

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

☒ 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
4 February 1997	10.02.97

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	Alfaro Faus, I

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No
PCT/EP 96/04657

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-533266	24-03-93	AU-A- 2452992	- 25-03-93
		CA-A- 2078506	19-03-93
		HU-A- 66319	28-11-94
		JP-A- 6107649	19-04-94
		US-A- 5356893	18-10-94
		ZA-A- 9207107	08-09-93
WO-A-9611934	25-04-96	NONE	
WO-A-9619477	27-06-96	AU-A- 4343396	10-07-96