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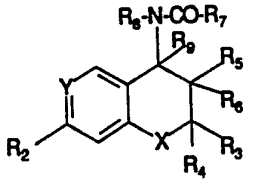
(54) Title: BENZO- AND PYRIDOPYRAN DERIVATIVES HAVING ANXIOLYTIC AND ANTI-CONVULSANT ACTIVITY



(I)

(57) Abstract

A method of treatment and/or prophylaxis of anxiety and/or mania, and/or depression and/or the effects associated with withdrawal from substances of abuse, and/or disorders treatable and/or preventable with anticonvulsive agents, comprising administering to the sufferer in need thereof an effective or prophylactic amount of a compound of formula (I) or pharmaceutically acceptable salt thereof, wherein either Y is N and R_2 is hydrogen, or Y is C-R_1, where either one of R_1 and R_2 is hydrogen and the other is selected from the class of hydrogen, C_{3-8} cycloalkyl, C_{1-6} alkyl optionally interrupted by oxygen or substituted by hydroxy, C_{1-6} alkoxy or substituted aminocarbonyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonyloxy, C_{1-6} alkoxy, nitro, cyano, halo, trifluoromethyl, CF_3S, or a group CF_3-A-, where A is -CF_2-, -CO-, -CH_2- or CH(OH), trifluoromethoxy, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, C_{1-6} alkoxysulphinyl, C_{1-6} alkoxysulphonyl, aryl, heteroaryl, arylcarbonyl, heteroarylcarbonyl, arylsulphinyl, heteroarylsulphinyl, arylsulphonyl, heteroarylsulphonyl in which any aromatic moiety is optionally substituted, C_{1-6} alkylcarbonylamino, C_{1-6} alkoxycarbonylamino, C_{1-6} alkyl-thiocarbonyl, C_{1-6} alkoxy-thiocarbonyl, C_{1-6} alkyl-thiocarbonyloxy, 1-mercapto C_{2-7} alkyl, formyl, or aminosulphinyl, aminosulphonyl or aminocarbonyl, any amino moiety being optionally substituted by one or two C_{1-6} alkyl groups, or C_{1-6} alkylsulphinylamino, C_{1-6} alkylsulphonylamino, C_{1-6} alkoxysulphinylamino or C_{1-6} alkoxysulphonylamino, or ethylenyl terminally substituted by C_{1-6} alkylcarbonyl, nitro or cyano, or -C(C_{1-6} alkyl)NOH or -C(C_{1-6} alkyl)NNH_2, or one of R_1 and R_2 is nitro, cyano or C_{1-3} alkylcarbonyl and the other is methoxy or amino optionally substituted by one or two C_{1-6} alkyl or by C_{2-7} alkanoyl; one or R_3 and R_4 is hydrogen or C_{1-4} alkyl and the other is C_{1-4} alkyl or R_3 and R_4 together are C_{2-5} polymethylene; R_5 is C_{1-6} alkylcarbonyloxy, benzoyloxy, ONO_2, benzyloxy, phenyloxy or C_{1-6} alkoxy and R_6 and R_9 are hydrogen or R_5 is hydroxy and R_6 is hydrogen or C_{1-2} alkyl and R_9 is hydrogen; R_7 is fluorophenyl; R_8 is hydrogen or C_{1-6} alkyl; the R_8-N-CO-R_7 group being trans to the R_5 group; and X is oxygen or NR_{10} where R_{10} is hydrogen or C_{1-6} alkyl.

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BENZO-AND PYRIDOPYRAN DERIVATIVES HAVING ANXIOLYTIC AND ANTI-CONVULSANT ACTIVITY

This invention relates to a novel method of treatment and to novel compounds for use in such a method.

European Published Patent Application No. 0126311 discloses substituted benzopyran compounds having blood pressure lowering activity, including 6-acetyl-trans-4-(4-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol.

Also EP-A-0 376 524, EP-A-0 205 292, EP-A-0 250 077, EP-A-0 093 535, EP-A-0 150 202, EP-A-0 076 075 and WO/89/05808 (Beecham Group plc) describe certain benzopyran derivatives which possess anti-hypertensive activity.

EP-A-0 350 805 (Biersdorf), EP-A-0 277 611, EP-A-0 277612, EP-A-0 337 179 and EP-A-0 355 565 (Hoechst Aktiengesellschaft); and EP-A-0 466 131 (Nissan Chemical Industries Ltd) also describe certain benzopyran derivatives which are believed to possess anti-hypertensive activity.

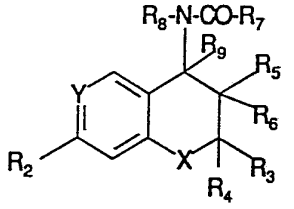
EP-A-0 430 621 and EP-A-0 385 584 (Beecham Group plc) describe the resolution of certain intermediates useful in the preparation of the compounds described in the above mentioned patent applications.

EP-A-0 194 885 (E. Lilly) describes certain amino substituted benzopyran derivatives possessing anti-convulsant activity.

It has now been surprisingly found that certain compounds of formula (I) possess anxiolytic and anti-convulsant activity, and are also believed to have utility in the treatment or prevention of mania, depression and the effects associated with withdrawal from substances of abuse.

Accordingly, the present invention provides a method of treatment and/or prophylaxis of anxiety and/or mania, and/or depression and/or the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, and/or disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy, comprising

administering to the sufferer in need thereof an effective or prophylactic amount of a compound of formula (I) or pharmaceutically acceptable salt thereof:



(I)

wherein:

either Y is N and R_2 is hydrogen, or Y is C-R_1

where:

either one of R_1 and R_2 is hydrogen and the other is selected from the class of hydrogen, C_{3-8} cycloalkyl, C_{1-6} alkyl optionally interupted by oxygen or substituted by hydroxy, C_{1-6} alkoxy or substituted aminocarbonyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonyloxy, C_{1-6} alkoxy, nitro, cyano, halo, trifluoromethyl, CF_3S, or a group CF_3-A-, where A is -CF_2-, -CO-, -CH_2- or CH(OH), trifluoromethoxy, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, C_{1-6} alkoxysulphinyl, C_{1-6} alkoxysulphonyl, aryl, heteroaryl, arylcarbonyl, heteroarylcarbonyl, arylsulphinyl, heteroarylsulphinyl, arylsulphonyl, heteroarylsulphonyl in which any aromatic moiety is optionally substituted, C_{1-6} alkylcarbonylamino, C_{1-6} alkoxycarbonylamino, C_{1-6} alkyl-thiocarbonyl, C_{1-6} alkoxy-thiocarbonyl, C_{1-6} alkyl-thiocarbonyloxy, 1-mercapto C_{2-7} alkyl, formyl, or aminosulphinyl, aminosulphonyl or aminocarbonyl, any amino moiety being optionally substituted by one or two C_{1-6} alkyl groups, or C_{1-6} alkylsulphinylamino, C_{1-6} alkylsulphonylamino,C_{1-6} alkoxysulphinylamino or C_{1-6} alkoxysulphonylamino, or ethylenyl terminally substituted by C_{1-6} alkylcarbonyl, nitro or cyano, or -C(C_{1-6} alkyl)NOH or -C(C_{1-6} alkyl)NNH_2, or one of R_1 and R_2 is nitro, cyano or C_{1-3} alkylcarbonyl and the other is methoxy or amino optionally substituted by one or two C_{1-6} alkyl or by C_{2-7} alkanoyl;

one of R_3 and R_4 is hydrogen or C_{1-4} alkyl and the other is C_{1-4} alkyl or R_3 and R_4 together are C_{2-5} polymethylene;

R_5 is C_{1-6} alkylcarbonyloxy, benzoyloxy, ONO_2, benzyloxy, phenyloxy or C_{1-6} alkoxy and R_6 and R_9 are hydrogen or R_5 is hydroxy and R_6 is hydrogen or C_{1-2} alkyl and R_9 is hydrogen;

R_7 is fluorophenyl;

R_8 is hydrogen or C_{1-6} alkyl;

the R_8-N-CO-R_7 group being trans to the R_5 group;

and X is oxygen or NR_{10} where R_{10} is hydrogen or C_{1-6} alkyl.

Compounds of formula (I) include those in which Y is C-R_1, where;

either one of R_1 and R_2 is hydrogen and the other is selected from the class of hydrogen, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonyloxy, C_{1-6} alkylhydroxymethyl, nitro, cyano, chloro, trifluoromethyl, trifluoromethoxy, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, C_{1-6} alkoxysulphinyl, C_{1-6} alkoxysulphonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkoxycarbonylamino, C_{1-6} alkyl-thiocarbonyl, C_{1-6} alkoxy-thiocarbonyl, C_{1-6} alkyl-thiocarbonyloxy, 1-mercapto C_{2-7} alkyl, formyl, or aminosulphinyl, aminosulphonyl or aminocarbonyl, the amino moiety being optionally substituted by one or two C_{1-6} alkyl groups, or C_{1-6} alkylsulphinylamino, C_{1-6} alkylsulphonylamino,C_{1-6} alkoxysulphinylamino or C_{1-6} alkoxysulphonylamino, or ethylenyl terminally substituted by C_{1-6} alkylcarbonyl, nitro or cyano, or -C(C_{1-6} alkyl)NOH or -C(C_{1-6} alkyl)NNH_2, or one of R_1 and R_2 is nitro, cyano or C_{1-3} alkylcarbonyl and the other is methoxy or amino optionally substituted by one or two C_{1-6} alkyl or by C_{2-7} alkanoyl;

one of R_3 and R_4 is hydrogen or C_{1-4} alkyl and the other is C_{1-4} alkyl or R_3 and R_4 together are C_{2-5} polymethylene;

R_5 is hydroxy and R_6 is hydrogen;

R_7 is fluorophenyl;

R_8 is hydrogen or C_{1-6} alkyl; and

R_9 is hydrogen;

the R_8-N-CO-R_7 group being trans to the R_5 group.

All C_{1-6} alkyl or alkyl containing groups in formula (I) are preferably selected from methyl, ethyl, n- and iso-propyl, n-, iso-, sec- and tert-butyl.

Suitable C_{3-8} cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

Aryl includes but is not limited to phenyl and naphthyl.

Heteroaryl includes a 5- or 6- membered monocyclic or 9- or 10- membered bicyclic of which 5- or 6- membered monocyclic heteroaryl is preferred. In addition, 5- or 6-membered monocyclic or 9- or 10-membered bicyclic heteroaryl preferably contains one, two or three heteroatoms which are selected from the class of oxygen, nitrogen and sulphur and which, in the case of there being more than one heteroatom, are the same or different. Examples of 5- or 6-membered monocyclic heteroaryl containing one, two or three heteroatoms which are selected from the class of oxygen, nitrogen and sulphur include furyl, thienyl, pyrryl, oxazolyl, thiazolyl, imidazolyl and thiadiazolyl, and pyridyl, pyridazyl, pyrimidyl, pyrazolyl and triazolyl. Preferred examples of such groups include furanyl, thienyl, pyrryl and pyridyl, in particular 2- and 3-furyl, 2- and 3-pyrryl, 2- and 3-thienyl, and 2-, 3- and 4-pyridyl. Examples of 9- or 10-membered bicyclic heteroaryl containing one, two or three heteroatoms which are selected from the class of oxygen, nitrogen and sulphur include benzofuranyl, benzothienyl, indolyl and indazolyl, quinolyl and isoquinolyl, and quinazolyl. Preferred examples of such groups include 2- and 3-benzofuryl, 2- and 3-benzothienyl, and 2- and 3-indolyl, and 2- and 3-quinolyl.

Suitable examples of groups or atoms for optional substitution of aryl and heteroaryl include one, two or three substituents independently selected

from C_{1-4} alkyl, C_{1-4} alkoxy, halo (such as fluoro, chloro, bromo), hydroxy, nitro,cyano and SO_nH, where n=0 to 2.

Preferably R_2 is hydrogen.

Examples of suitable R_1 substituents include cyano, methoxy, trifluoromethoxy, chloro, trifluoromethyl, ethylcarbonyl, acetyl, hydrogen, methyl, ethyl, iso-propyl,tertiary-butyl, nitro, C_2F_5, methoxycarbonyl, phenylsulphonyl, phenyl, fluoro, iodo, cyclopentyl, aminocarbonylmethyl and 1-hydroxyethyl. Preferably R_1 is cyano, acetyl or ethyl.

Preferably R_3 and R_4 are both methyl.

Preferably R_5 is hydroxy and R_6 and R_9 are hydrogen or R_5 is hydroxy, R_6 is C_{1-2} alkyl and R_9 is hydrogen, more preferably R_5 is hydroxy and R_6 and R_9 are hydrogen.

It should be appreciated that the term fluorophenyl relating to R_7 encompasses phenyl which has 1,2,3,4 or 5 fluoro groups attached to the phenyl ring. Preferably there are 1 or 2 fluoro groups attached to the phenyl ring and most preferably there is 1 fluoro group attached to the ring.

The fluoro group or groups may be in any position around the phenyl ring, preferably in the case of mono fluorophenyl the fluoro is in the 3 or 4 position.

In the case of difluorophenyl, preferably the fluoro substituents are at positions 2,4 or 3,4.

Preferably R_8 is hydrogen or C_{1-4} alkyl, more preferably R_8 is hydrogen, methyl or ethyl.

Preferably X is oxygen.

It should be appreciated that the compounds of formula (I) may have chiral carbon atoms at positions 2, 3 and 4 and therefore may exist as enantiomers. The present invention extends to each enantiomer and to

mixtures thereof including racemates. Preferably the compounds of formula (I) exist as 4S, 3R enantiomers.

It should also be appreciated that certain R_1 substituents also have chiral centres and therefore may exist as enantiomers. The present invention extends to each enantiomer and to mixtures thereof including racemates

An example of a compound of formula (I) is trans-6-acetyl-4-(4-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-o1 (compound X).

The following novel compounds of formula (I) also form an aspect of the present invention, (herein referred to as compounds of formula (I')):

trans-6-Cyano-3,4-dihydro-2,2-dimethyl-4-(4-fluoro-benzoylamino)2H-1-benzopyran-3-ol, (Example 5),

trans-6-Chloro-3,4-dihydro-2,2-dimethyl-4-(4-fluoro-benzoylamino)2H-1-benzopyran-3-ol, (Example 6),

trans-6-Trifluoromethyl-4-(4-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol, (Example 7),

trans-6-Cyano-4-(4-fluorobenzoylmethylamino)-3,4-dihydro- 2,2-dimethyl-2H-1-benzopyran-3-ol, (Example 8),

trans-6-Ethylcarbonyl-3,4-dihydro-2,2-dimethyl-4-(4-fluorobenzoylamino)2H-1-benzopyran-3-ol, (Example 9),

trans-6-Ethylcarbonyl-3,4-dihydro-2,2-dimethyl-4-(4-fluorobenzoylmethylamino)2H-1-benzopyran-3-ol, (Example 10),

trans-6-Acetyl-4-(4-fluorobenzoylmethylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol, (Example 11),

trans-6-Cyano-3,4-dihydro-4-(4-fluorobenzoylethylamino)-2,2-dimethyl-2H-1-benzopyran-3-ol (Example 12),

trans-4-(4-Fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-7-nitro-2H-1-benzopyran-3-ol (Example 13),

trans-6-Acetyl-4-(4-Fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol (Example 18),

trans-6-Acetyl-4R-(4-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3S-ol (Example 19),

trans-6-Acetyl-4S-(4-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3R-ol (Example 20),

trans-6-Cyano-4S-(4-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3R-ol (Example 25),

trans-6-Cyano-4-(4-fluorobenzoylamino)-3,4-dihydro-2,2,3-trimethyl-2H-1-benzopyran-3-ol (Example 26),

trans-4-(4-Fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-6-nitro-2H-1-benzopyran-3-ol (Example 27),

trans-4-(4-Fluorobenzoylamino)-3,4-dihydro-6-methoxycarbonyl-2,2-dimethyl-2H-1-benzopyran-3-ol (Example 30),

trans-6-Fluoro-4-(4-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol (Example 34),

trans-4-(4-fluorobenzoyl-methylamino)-6-trifluoromethyl-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol (Example 42),

trans-4-(4-Fluorobenzoylamino)-3,4-dihydro-6-iodo-2,2-dimethyl-2H-1-benzopyran-3-ol (Example 47) and

trans- 6-Aminocarbonylmethyl-4-(4-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol (Example 49).

The administration to the mammal may be by way of oral or parenteral administration.

An amount effective to treat the disorders hereinbefore described depends on the usual factors such as the nature and severity of the disorders being treated and the weight of the mammal. However, a unit dose will normally contain 1 to 1000 mg, suitably 1 to 500 mg, for example an amount in the range of from 2 to 100 mg such as 2, 5, 10, 20, 30, 40, 50 and 100 mg of the active compound. Unit doses will normally be administered once or more than once per day, for example 2, 3, 4, 5 or 6 times a day, more usually 2 to 4 times a day, such that the total daily dose is normally in the range, for a 70 kg adult of 1 to 1000 mg, for example 50 to 500 mg, that is in the range of approximately 0.01 to 50 mg/kg/day, more usually 0.1 to 50 mg/kg/day, for example 1 to 50 mg/kg/day.

It is greatly preferred that the compound of formula (I) is administered in the form of a unit-dose composition, such as a unit dose oral, rectal, topical or parenteral (especially intravenous) composition.

Such compositions are prepared by admixture and are suitably adapted for oral or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable and infusable solutions or suspensions or suppositories. Orally administrable compositions are preferred, in particular shaped oral compositions, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate. Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate.

These solid oral compositions may be prepared by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral formulations also include conventional sustained release formulations, such as tablets or granules having an enteric coating.

For parenteral administration, fluid unit dose forms are prepared containing the compound and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also 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 sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is

included in the composition to facilitate uniform distribution of the compound of the invention.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

The present invention further provides a pharmaceutical composition for use in the treatment and/or prophylaxis of anxiety and/or mania and/or depression and/or the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzadiazepines and/or disorders treatable or preventable with anti-convulsive agents, such as epilepsy, which comprises a compound of formula (I), or a pharmaceutically acceptable salt thereof, in particular, compounds of examples 1 to 50, and a pharmaceutically acceptable carrier.

In a further aspect the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in particular compounds of examples 1 to 50 inclusive, for the manufacture of a medicament for the treatment and/or prophylaxis of anxiety and/or mania and/or depression and/or the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzadiazepines and/or disorders treatable or preventable with anti-convulsive agents, such as epilepsy.

Such compositions may be prepared in the manner as hereinbefore described.

The invention also provides novel compounds of formula (I) and pharmaceutically acceptable salts thereof wherein R_7 is 2- or 3-fluorophenyl, 2, 4- or 3,4- difluorophenyl. Such compounds will hereinafter be referred to as compounds of formula (Ia).

Examples of compounds of formula (Ia) include:

trans-6-Cyano-3,4-dihydro-2,2-dimethyl-4-(3-fluoro-benzoylamino)2H-1-benzopyran-3-ol (Example 1),

trans-6-Cyano-3,4-dihydro-2,2-dimethyl-4-(2-fluoro-

benzoylamino)2H-1-benzopyran-3-ol (Example 2),

trans-6-Trifluoromethoxy-3,4-dihydro-2,2-dimethyl-4-(3-fluorobenzoylamino)2H-1-benzopyran-3-ol (Example 3),

trans-6-Cyano-4S-(3-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3R-ol (Example 21),

trans-6-Cyano-4R-(3-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3S-ol (Example 22),

trans-6-Cyano-4S-(2-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3R-ol (Example 24),

trans-6-Cyano-4S-(2,4-difluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3R-ol (Example 28),

trans-6-Acetyl-4-(3-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol (Example 31),

trans-4-(2-Fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-pyrano[3,2-c]pyridin-3-ol (Example 38),

trans-4-(3-Fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-pyrano[3,2-c]pyridin-3-ol (Example 39),

trans-6-Cyano-4-(3,4-difluorbenzoyl-methylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol (Example 41) and

trans-6-cyano-4S-(3,4-difluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3R-ol (Example 44).

The invention further provides novel compounds of formula (I) and pharmaceutically acceptable salts thereof wherein Y is CR_1 where R_1 and R_2 are both hydrogen or one of R_1 and R_2 is trifluoromethoxy, C_{1-6} alkyl optionally interrupted with oxygen or substituted with hydroxy, C_{1-6} alkoxy or substituted amino-carbonyl, CF_3A-(where A is $-CF_2-$, -CO-, $-CH_2$) or CH(OH)), aryl sulphonyl, aryl C_{3-8} cycloalkyl, C_{1-6} alkoxy,

heteroaryl, arylcarbonyl, heteroarylcarbonyl, arylsulphinyl, heteroarylsulphinyl, heteroarylsulphonyl, in which any aromatic moiety is optionally substituted and the other is hydrogen. Such compounds will hereinafter be referred to as compounds of formula (Ib).

`Examples of compounds of formula (Ib) include:

trans-6-Trifluoromethoxy-3,4-dihydro-2,2-dimethyl-4-(3-fluorobenzoylamino)2H-1-benzopyran-3-ol (Example 3),

trans-3,4-Dihydro-2,2-dimethyl-4-(4-fluorobenzoylamino)-2H-1-benzopyran-3-ol (Example 4),

trans-4-(4-Fluorobenzoylamino)-3,4-dihydro-2,2,6-trimethyl-2H-1-benzopyran-3-ol (Example 14),

trans-6-Ethyl-4-(4-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol (Example 15),

trans-6-Ethyl-4-(4-fluorobenzoylethylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol (Example 16),

trans-4-(4-Fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-6-isopropyl-2H-1-benzopyran-3-ol (Example 17),

trans-6-Ethyl-4-(4-fluorobenzoylmethylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol (Example 23),

trans-4-(4-Fluorobenzoylamino)-6-pentafluoroethyl-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol (Example 29),

trans-4-(4-Fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-6-phenylsulphonyl-2H-1-benzopyran-3-ol (Example 32),

trans-4-(4-Fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-6-phenyl-2H-1-benzopyran-3-ol (Example 33),

trans-6-Ethyl-4S-(4-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3R-ol (Example 35),

trans-4R-(4-Fluorobenzoylamino)-3,4-dihydro-6-(1-hydroxyethyl)-2,2-dimethyl-2H-1-benzopyran-3S-ol (Example 36),

trans-4S-(4-Fluorobenzoylamino)-3,4-dihydro-6-(1-hydroxyethyl)-2,2-dimethyl-2H-1-benzopyran-3R-ol (Example 37),

trans-4-(4-fluorobenzoyl-methylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol (Example 43),

trans-6-t-Butyl-4-(4-Fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol (Example 46),

trans-4-(4-Fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-6-cyclopentyl-2H-1-benzopyran-3-ol (Example 48) and

trans- 4-(4-Fluorobenzoylamino)-3,4-dihydro-6-methoxy-2,2-dimethyl-2H-1-benzopyran-3-ol (Example 50).

The present invention also provides novel compounds of formula (I) and pharmaceutically acceptable salts thereof, where Y is N and R_2 is hydrogen. Such compounds will hereinafter be referred to as compounds of formula (Ic).

Examples of compounds of formula (Ic) include:

trans-4-(2-Fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-pyrano[3,2-c]pyridin-3-ol (Example 38),

trans-4-(3-Fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-pyrano[3,2-c]pyridin-3-ol (Example 39) and

trans-4-(4-Fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-pyrano[3,2-c]pyridin-3-ol (Example 40).

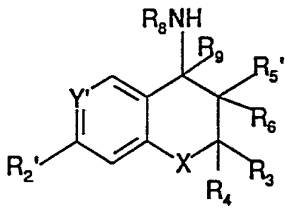
The present invention also provides novel compounds of formula (I) and pharmaceutically acceptable salts thereof, where X is NR_{10} where R_{10} is hydrogen or C_{1-6} alkyl. Such compounds will hereinafter be referred to as compounds of formula (Id).

An example of a compound of formula (Id) is:

trans-6-Cyano-4-(4-fluorobenzoylamino)-2,2-dimethyl-1,2,3,4-tetrahydroquinolin-3-ol (Example 45).

Generally, compounds of formula (I) may be prepared by procedures generally described or analogous to those described in EP-0126311, EP-0376524, EP-205292, EP-0250077, EP-0093535, EP-0150202, EP-0076075, WO/89/05808, EP-0350805, EP-0277611, EP-0277612, EP-0337179, EP-0355565 and EP-0466131.

The invention also provides a process for the preparation of novel compounds of formula (I')or pharmaceutically acceptable salts thereof, which comprises acylating a compound of formula (II'):



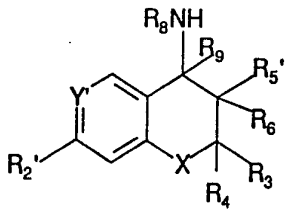
(II')

wherein Y', R_2' and R_5' are the required variables Y, R_2 or R_5 as defined in formula (I) or a group convertible thereto and R_3, R_4, R_6, R_8, R_9 and X are the required variables as defined in formula (I), the R_8NH group being trans to the R_5 group, with and acylating agent of formula (IIIb):

$$R_7COL,$$

where R_7 is as required and as defined in formula (I) and L_1 is a leaving group; thereafter optionally or as necessary and in any appropriate order converting any R_1', R_2' and R_5' groups to R_1, R_2 and R_5 respectively, interconverting R_8 when hydrogen to C_{1-6} alkyl, separating any enantiomers and forming a pharmaceutically acceptable salt or solvate.

In particular, the present invention also provides a process for the preparation of compounds of formula (Ia), or a pharmaceutically acceptable salt thereof, which comprises acylating a compound of formula (IIa):



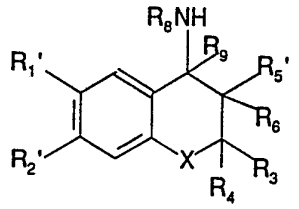
(IIa)

wherein Y', R_2' and R_5' are Y, R_2 or R_5 as defined in formula (I) or a group convertible thereto and R_3, R_4, R_6, R_8, R_9 and X are as defined in formula (I), the R_8NH group being trans to the R_5' group, with an acylating agent of formula (IIIa):

$$R_7{}^aCOL_1 \qquad \text{(IIIa)}$$

where $R_7{}^a$ is 2- or 3-fluorophenyl or 2,4- or 3,4- difluorophenyl and L_1 is a leaving group; thereafter optionally or as necessary and in any appropriate order converting any Y', R_2' or R_5' group to Y, R_2 or R_5 respectively, interconverting R_8 when hydrogen to C_{1-6} alkyl, separating any entantioners and forming a pharmaceutically acceptable salt or solvate.

The present invention also provides a process for the preparation of compounds of formula (Ib), or a pharmaceutically acceptable salt thereof, which comprises acylating a compound of formula (IIb):



(IIb)

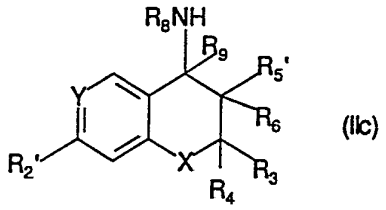
where R_1' and R_2' are both hydrogen or one of R_1 and R_2 is trifluoromethoxy, C_{1-6} alkyl optionally interrupted with oxygen or substituted with hydroxy, C_{1-6} alkoxy or substituted aminocarbonyl, CF_3A- (where A is CF_2,-CO-,-CH_2- or CH(OH)), aryl, aryl sulphonyl, aryl

C_{3-8} cycloalkyl, C_{1-6} alkoxy, heteroaryl, arylcarbonyl, heteroarylcarbonyl, arylsulphinyl, heteroarylsulphinyl, heteroarylsulphonyl, in which any aromatic moiety is optionally substituted and the other is hydrogen, or groups convertible to any of these; R_5' is R_5 as defined in formula (I) or a group convertible thereto and R_3, R_4, R_6, R_8, R_9 and X are as defined in formula (I) the R_8NH group being trans to the R_5' group, with a compound of formula (IIIb):

$$R_7COL_1 \qquad \text{(IIIb)}$$

where R_7 is as defined in formula (I) and L_1 is a leaving group; thereafter optionally or as necessary and in any appropriate order converting any R_1', R_2' and R_5' groups to R_1, R_2 and R_5 respectively, interconverting R_8 when hydrogen to C_{1-6} alkyl, separating any enantiomers and forming a pharmaceutically acceptable salt or solvate.

The present invention also provides a process for the preparation of compounds of formula (Ic), or a pharmaceutically acceptable salt thereof, which comprises acylating a compound of formula (IIc):



(IIc)

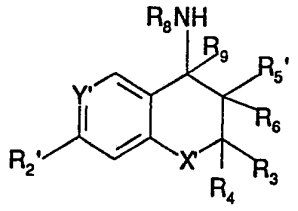
in which Y is N, R_5' is R_5, as defined in relation to formula (I) or a group convertible to R_5 and R_2' is hydrogen or a group convertible thereto, R_6, R_3, R_4, R_8, R_9 and X are as defined in formula (I), the R_8NH group being trans to the R_5' group, with an acylating agent of formula (IIIb):

$$R_7COL_1 \qquad \text{(IIIb)}$$

where R_7 is as defined in formula (I) and L_1 is a leaving group; thereafter optionally or as necessary and in any appropriate order converting any R_2' or R_5' group to hydrogen or R_5 respectively, interconverting R_8 when

hydrogen to C_{1-6} alkyl, separating any enantiomers and forming a pharmaceutically acceptable salt or solvate.

The present invention also provides a process for the preparation of compounds of formula (Id), or a pharmaceutically acceptable salt thereof, which comprises acylating a compound of formula (IId):



(IId)

in which X' is NR_{10}' where R_{10}' is hydrogen or C_{1-6} alkyl or a group convertible thereto, Y', R_2' and R_5 are Y, R_2 and R_5 respectively as defined in formula (I) or groups convertible thereto and R_3, R_4, R_6, R_8 and R_9 are as defined in formula (I), the R_8NH group being trans to the R_5' group, with an acylating agent of formula (IIIb):

$$R_7COL_1 \qquad \text{(IIIb)}$$

where R_7 is as defined in formula (I) and L_1 is a leaving group, thereafter optionally or as necessary and in any appropriate order converting any Y', R_{10}', R_2' or R_5' group to Y, R_{10}, R_2 or R_5 respectively, interconverting R_8 when hydrogen to C_{1-6} alkyl, separating any enantiomers and forming a pharmaceutically acceptable salt or solvate.

Examples of suitable leaving groups L_1 include those mentioned in the above-mentioned patents, in particular EP-A-0 126 311 or are conventional in the art.

The reaction conditions which may be used to carry out the above reactions are as outlined or analogous to those described in the above-mentioned patents, in particular EP-A-0 126 311.

In particular, the leaving group (L_1) is a group that is displaceable by a primary or secondary amino nucleophile. Examples of such a group include C_{1-4} alkylcarbonyloxy and halogen, such as chloro and bromo. When the leaving group (L_1) is any of these examples, the acylating agent

of formula (IIIa) or (IIIb) is either an acid anhydride or an acid halide. When it is an acid anhydride, it is, preferably, a mixed anhydride, which may be prepared in situ from an aromatic or heteroaromatic carboxylic acid and an alkyl chlorocarbonate, such as ethyl chloroformate.

When the acylating agent of formula (IIIa) or (IIIb) is an acid anhydride, the acylation of the compound formula (IIa), (IIb), (IIc) or (IId) is, preferably carried out using the anhydride as the solvent in the presence of an acid acceptor, such as sodium acetate.

When the acylating agent of formula (IIIa) or (IIIb) is an acid halide, the acylation of the compound of formula (IIa), (IIb), (IIc) or (IId), is, preferably, carried out in a non-aqueous medium, such as methylene chloride, in the presence of an acid acceptor, such as triethylamine, trimethylamine or pyridine.

Examples of suitable groups convertible to Y (or R_1), R_2 and R_5 include those described in the above-mentioned patents or are conventional in the art.

Interconversions of R_8 when hydrogen to C_{1-6} alkyl may be carried out using conventional alkylation procedures for example using an alkylhalide in the presence of a base.

It should be appreciated that racemates for formula (I) may be resolved or enantiomerically purified compounds of formula (I) may be prepared using procedures conventional in the art and in particular using the procedures outlined in EP-0430631 and EP-0355584.

Suitably, the procedures outlined in or analogous to those described in Example 35 of the present specification may be used to prepare specific enantiomers of any compounds of formulae (I), (I'), (Ia), (Ib), (Ic) or (Id).

Compounds of formulae (I'), (IIa), (IIb), (IIc) and (IId) may be prepared from readily available starting materials using the procedures outlined or analogous to those described in the above-mentioned patents.

Compounds of formulae (IIIa) and (IIIb) are either commercially available or may be prepared according to conventional procedures known in the art of organic chemistry.

Novel compounds of formulae (I'), (IIa), (IIb), (IIc) and (IId) form an aspect of the present invention.

Compounds of formula (I) in which R_5 is hydroxy, R_6 is C_{1-2} alkyl and R_9 is hydrogen may be prepared according to the procedures outlined in R. Gericke *et al.* J. Med. Chem. Vol.34, p3074(1991).

The invention also provides a pharmaceutical composition comprising a compound of formula (I'), (Ia), (Ib), (Ic) or (d), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The invention also provides the use of a compound of formula (I'), (Ia), (Ib), (Ic) or (Id), or a pharmaceutically acceptable salt thereof, in the treatment and/or prophylaxis of anxiety and/or mania and/or depression and/or the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzadiazepines and/or disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy.

The following examples and pharmacological test results illustrate the present invention:

The following compounds were prepared by methods analgous to those described in the abovementioned patents publications.

Example 1

trans-6-Cyano-3,4-dihydro-2,2-dimethyl-4-(3-fluoro-benzoylamino)2H-1-benzopyran-3-ol.

Mpt. 193-194°C.

Example 2

trans-6-Cyano-3,4-dihydro-2,2-dimethyl-4-(2-fluoro-benzoylamino)2H-1-benzopyran-3-ol

Mpt.163-5°

Example 3

trans-6-Trifluoromethoxy-3,4-dihydro-2,2-dimethyl-4-(3-fluorobenzoylamino)2H-1-benzopyran-3-ol
Mpt. 127-30°C

Example 4

trans-3,4-Dihydro-2,2-dimethyl-4-(4-fluorobenzoylamino)-2H-1-benzopyran-3-ol

Mpt. 174-5°C

Example 5

trans-6-Cyano-3,4-dihydro-2,2-dimethyl-4-(4-fluoro-benzoylamino)2H-1-benzopyran-3-ol,

Mpt. 229-230°C.
3R, 4S isomer (compound B) Mpt. 224-5°C

Example 6

trans-6-Chloro-3,4-dihydro-2,2-dimethyl-4-(4-fluoro-benzoylamino)2H-1-benzopyran-3-ol,

Mpt. 177-9°C

Example 7

trans-6-Trifluoromethyl-4-(4-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol,

Mpt. 185-7°C

Example 8

trans-6-Cyano-4-(4-fluorobenzoylmethylamino)-3,4-dihydro- 2,2-dimethyl-2H-1-benzopyran-3-ol,

Mpt. 230-4°C

Example 9

trans-6-Ethylcarbonyl-3,4-dihydro-2,2-dimethyl-4-(4-fluorobenzoylamino)2H-1-benzopyran-3-ol,

Mpt. 205-207°C.

Example 10

trans-6-Ethylcarbonyl-3,4-dihydro-2,2-dimethyl-4-(4-fluorobenzoylmethylamino)2H-1-benzopyran-3-ol,

Mpt. 210-212°C.

Example 11

trans-6-Acetyl-4-(4-fluorobenzoylmethylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol,

Mpt. 207-8°C

Example 12

trans-6-Cyano-3,4-dihydro-4-(4-fluorobenzoylethylamino)-2,2-dimethyl-2H-1-benzopyran-3-ol
mp 172-175 °C

Example 13

trans-4-(4-Fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-7-nitro-2H-1-benzopyran-3-ol
mp 231-233 °C

Example 14

trans-4-(4-Fluorobenzoylamino)-3,4-dihydro-2,2,6-trimethyl-2H-1-benzopyran-3-ol
mp 185-186 °C

Example 15

trans-6-Ethyl-4-(4-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol
mp 235-237 °C

Example 16

trans-6-Ethyl-4-(4-fluorobenzoylethylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol
mp 175 °C

Example 17

trans-4-(4-Fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-6-isopropyl-2H-1-benzopyran-3-ol
mp 235-236 °C

Example 18

trans-6-Acetyl-4-(4-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol
mp 203 °C

Example 19

trans-6-Acetyl-4R-(4-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3S-ol
mp 162-163 °C

Example 20

trans-6-Cyano-4S-(3-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3R-ol
mp 164 °C

Example 21

trans-6-Cyano-4S-(3-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3R-ol
mp 221 °C

Example 22

trans-6-Cyano-4R-(3-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3S-ol
mp 221 °C

Example 23

trans-6-Ethyl-4-(4-fluorobenzoylmethylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol
mp 162-164 °C

Example 24

trans-6-Cyano-4S-(2-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3R-ol
mp 163-165 °C

Example 25

trans-6-Cyano-4S-(4-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3R-ol
mp 224-225 °C

Example 26

trans-6-Cyano-4-(4-fluorobenzoylamino)-3,4-dihydro-2,2,3-trimethyl-2H-1-benzopyran-3-ol
mp 218-220 °C

Example 27

trans-4-(4-Fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-6-nitro-2H-1-benzopyran-3-ol
mp 197-198 °C

Example 28

trans-6-Cyano-4S-(2,4-difluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3R-ol
mp 175-176 °C

Example 29

trans-4-(4-Fluorobenzoylamino)-6-pentafluoroethyl-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol
mp 181 °C

Example 30

trans-4-(4-Fluorobenzoylamino)-3,4-dihydro-6-methoxycarbonyl-2,2-dimethyl-2H-1-benzopyran-3-ol
mp 198 °C

Example 31

trans-6-Acetyl-4-(3-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol
mp 212 °C

Example 32

trans-4-(4-Fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-6-phenylsulphonyl-2H-1-benzopyran-3-ol
mp 239-240 °C

Example 33

trans-4-(4-Fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-6-phenyl-2H-1-benzopyran-3-ol
mp 164-165 °C

Example 34

trans-6-Fluoro-4-(4-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol
mp 164-165 °C

Example 35

trans-6-Ethyl-4S-(4-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3R-ol

(-)-Mandelic acid was used to resolve the residue from resolution of trans-4-amino-6-ethyl-2,2-dimethyl-chroman-3-ol (to give the 3S, 4R enantiomer - as described in EPA 412 760) under standard resolving conditions using acetone as recrystallisation solvent. This furnished trans-4S-amino-6-ethyl-2,2-dimethylchroman-3R-ol D-mandelate.

The 4S, 3R-aminoalcohol mandelate (4.0 g) was dissolved in dichloromethane (250 ml) and triethylamine (3.34 ml) and cooled in an ice bath. To this stirred solution was added 4-fluorobenzoyl chloride (1.7 g) dropwise. On completion of addition the reaction mixture was allowed to attain room temperature and was stirred overnight. The solvent was evaporated and the residue was taken up in ethyl acetate (150 ml). This solution was washed with 5% sodium bicarbonate solution, and brine, and dried over anhydrous magnesium sulphate. Filtration and evaporation and recrystallisation of the residue from Ethyl acetate-hexane gave the title compound of example 35. mp 132-136°C. $\alpha D/20$ + 69.1° (methanol, c=1.0).

NMR(CDCL3)δ	1.21 (3H, t, J = 8 Hz)
	1.28 (3H, s)
	1.49 (3H, s)
	2.88 (2H, q, J = 8 Hz)
	3.76 (1H, d, J = 9 Hz)
	4.46 (1H, broad s)
	5.21 (1H, t, J = 9,8 Hz)
	6.41 (1H, d, J = 8 Hz)
	6.80 (1H, d, J = 9 Hz)
	7.07 (2H, irregular m)
	7.17 (2H, t, J = 9 Hz)
	7.74 (2H, m)

Example 36

trans-4R-(4-Fluorobenzoylamino)-3,4-dihydro-6-(1-hydroxyethyl)-2,2-dimethyl-2H-1-benzopyran-3S-ol
mp 132-133 °C

Example 37

trans-4S-(4-Fluorobenzoylamino)-3,4-dihydro-6-(1-hydroxyethyl)-2,2-dimethyl-2H-1-benzopyran-3R-ol
mp 133-134 °C

Example 38

trans-4-(2-Fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-pyrano[3,2-c]pyridin-3-ol
mp 254 °C

Example 39

trans-4-(3-Fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-pyrano[3,2-c]pyridin-3-ol
mp 259-261 °C

Example 40

trans-4-(4-Fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-pyrano[3,2-c]pyridin-3-ol
mp 254-255 °C

Example 41

trans-6-Cyano-4-(3,4-difluorbenzoyl-methylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol
mp 199-200°C

Example 42

trans-4-(4-fluorobenzoyl-methylamino)-6-trifluoromethyl-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol
mp 196-197°C

Example 43

trans-4-(4-fluorobenzoyl-methylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol
mp 160-161°C

Example 44

trans-6-cyano-4S-(3,4-difluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3R-ol
mp 227°C

Example 45

trans-6-Cyano-4-(4-fluorobenzoylamino)-2,2-dimethyl-1,2,3,4-tetrahydroquinolin-3-ol
mp 244-248 °C

Example 46

trans-6-t-Butyl-4-(4-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol
mp 163-166 °C

Example 47

trans-4-(4-Fluorobenzoylamino)-3,4-dihydro-6-iodo-2,2-dimethyl-2H-1-benzopyran-3-ol
mp 204-205 °C

Example 48

trans-4-(4-Fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-6-cyclopentyl-2H-1-benzopyran-3-ol
mp 173-174 °C

Example 49

trans- 6-Aminocarbonylmethyl-4-(4-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol
mp 190 °C

Example 50

trans- 4-(4-Fluorobenzoylamino)-3,4-dihydro-6-methoxy-2,2-dimethyl-2H-1-benzopyran-3-ol
mp 155-156 °C

PHARMACOLOGICAL DATA

1. Geller-Seifter Procedure

Potential anxiolytic properties are evaluated using the Geller-Seifter procedure based on that originally described by Geller and Seifter, (1960) Psychopharmacologia, 1, 482-492. This procedure has been shown to be selective for drugs with anxiolytic properties (Cook and Sepinwall, (1975) "Mechanism of Action of Benzodiazepines" ed. Costa, E. and Greengard, P., Raven Press, New York, pp. 1-28).

Rats are trained on a variable interval 30 sec schedule (VI30) to press a lever in order to obtain food reward. The 5 min sessions of the VI30 schedule alternate with 2-5 min of a schedule (FR5) in which every 5th lever press is followed by presentation of a food pellet paired with a 0.5 sec mild footshock. The total study lasts approximately 30 mins. Rats typically respond with high rates of lever pressing under the VI30 schedule and low response rates under the FR5 'conflict' session. Anxiolytic drugs increase the suppressed response rates of rats in a 'conflict' session.

Drugs are administered intraperitoneally or orally to groups of 3-8 rats 30 to 60 mins before testing.

The results are expressed as the percentage increase in the square root of the total number of lever presses in the FR5 'conflict' session. Square root transformation is necessary to normalise the data for statistical analysis using parametric methods.

The compound of Example 4 showed a significant increase in responding in the 'conflict' session at a dose of 10mg/kg p.o.

2. MES TEST

The maximal electroshock seizure (MES) test in rodents is one of the most widely used models of human grand mal epilepsy[1]. In this model,

anticonvulsant agents elevate the threshold to electrically-induced seizures whilst proconvulsants lower the seizure threshold.

Method

Mice (male, Charles River, U.K. CD-1 strain, 25-30g) are randomly assigned to groups of 10-20 and dosed orally or intraperitoneally at a dose volume of 10ml/kg with various doses of compound (1-100 mg/kg) or vehicle. Mice are then subjected at 30 or 60 min post dose to a variable voltage electroshock (0.1 sec., 50 Hz, sine wave form) via a buccal and a subcutaneous electrode. The mean voltage and standard error required to induce a tonic seizure in 50% (CV_{50}) of the mice in the group is determined by the 'up and down' method of Dixon and Mood (1948)[2]. Statistical comparisons between vehicle- and drug-treated groups are made using the method of Litchfield and Wilcoxon (1949)[3].

In control animals the CV_{50} is usually 40 - 50V. Hence the first animal in the control group is subjected to a voltage of 45V. If a tonic seizure does not ensue, the voltage is increased for a subsequent mouse. If a tonic convulsion does occur, then the voltage is decreased, and so on until all the animals in the group have been tested.

The percentage increase or decrease in CV_{50} for each group compared to the control is calculated.

Studies are carried out using a Heathkit shock generator with totally variable control of shock level from 0 to 200V and voltage steps of 5V are used.

Drugs are suspended in 1% methyl cellulose.

Reference

1. Swinyard, E.A. (1972). Electrically-induced convulsions. In: Experimental Models of Epilepsy ed. Purpura, D.P. et al., 433-458, Raven Press, New York.

2. Dixon, W.J. and Mood, A.M. (1948). J. Amer. Stat. Assn., 43, 109-126.

3. Litchfield, J.T. and Wilcoxon, F. (1949). J. Pharmacol. Exp. Ther. 96, 99-113.

Results

Compounds of Examples 1-3, 5, 7, 8, 18, 20, 21, 25, 30, 31, 35 and 37 and compound X showed a significant increase in CV_{50} at a dose of 10 mg/kg p.o.

3. X-Maze

Introduction

The X-maze test of anxiety (Handley and Mithani, 1984) examines the exploratory response of naive rats in an environment which offers both anxiogenic (open arms) and relatively non-anxiogenic (closed arms) areas. A selective increase in exploration of the open arms following drug pretreatment is therefore postulated to indicate anxiolytic effects.

Method

The X-maze was raised 70cm above the floor and consisted of two enclosed arms 45cm (long) x 15cm (wide) x 10cm (high) and two open arms 45 x 10 x 1cm arranged such that the two arms of each type were opposite each other. Both arm types were marked into two equal sections. Rats were placed onto the centre of the X-maze and observed for a period of 10 minutes during which time the following parameters were recorded: 1) the number of entries onto, and the time spent on, (a) open arms, (b) closed arms, (c) end of open arms and (d) end of closed arms. 2) the number of sections crossed. The fear-drive evoked in the open arms exceeds that in the enclosed arms and rats typically show a clear preference for the enclosed arms. Anxiolytic drugs increase the number of entries made onto, and the time spent on, the outer half of the open arms, and also the percentage of entries made onto, and the time spent on, the whole of the open arms. These four measures of anxiety, and also the

total number of sections traversed, were calculated for each animal. Drugs are administered intraperitoneally or orally to groups of 6 to 12 rats 30 to 60 mins before testing. Statistical comparisons between vehicle- and drug-treated groups were made using a Mann-Whitney 'U' test (two tailed).

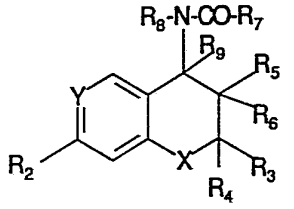
S.L. Handley and S. Mithani, Arch. Pharmacol., 1984 327 1-5

RESULTS

The compound of Example 21, caused a significant increase in open arm entries at a dose of 30 mg/kg p.o.

Claims

1. A method of treatment and/or prophylaxis of anxiety and/or mania, and/or depression and/or the effects associated with withdrawal from substances of abuse, and/or disorders treatable and/or preventable with anti-convulsive agents, comprising administering to the sufferer in need thereof an effective or prophylactic amount of a compound of formula (I) or pharmaceutically acceptable salt thereof:



(I)

wherein:

either Y is N and R_2 is hydrogen, or Y is C-R_1

where:

either one of R_1 and R_2 is hydrogen and the other is selected from the class of hydrogen, C_{3-8} cycloalkyl, C_{1-6} alkyl optionally interupted by oxygen or substituted by hydroxy, C_{1-6} alkoxy or substituted aminocarbonyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonyloxy, C_{1-6} alkoxy, nitro, cyano, halo, trifluoromethyl, CF_3S, or a group CF_3-A-, where A is -CF_2-, -CO-, -CH_2- or CH(OH), trifluoromethoxy, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, C_{1-6} alkoxysulphinyl, C_{1-6} alkoxysulphonyl, aryl, heteroaryl, arylcarbonyl, heteroarylcarbonyl, arylsulphinyl, heteroarylsulphinyl, arylsulphonyl, heteroarylsulphonyl in which any aromatic moiety is optionally substituted, C_{1-6} alkylcarbonylamino, C_{1-6} alkoxycarbonylamino, C_{1-6} alkyl-thiocarbonyl, C_{1-6} alkoxy-thiocarbonyl, C_{1-6} alkyl-thiocarbonyloxy, 1-mercapto C_{2-7} alkyl, formyl, or aminosulphinyl, aminosulphonyl or aminocarbonyl, any amino moiety being optionally substituted by one or two C_{1-6} alkyl groups, or C_{1-6} alkylsulphinylamino, C_{1-6} alkylsulphonylamino,C_{1-6} alkoxysulphinylamino or C_{1-6} alkoxysulphonylamino, or ethylenyl

terminally substituted by C_{1-6} alkylcarbonyl, nitro or cyano, or -C(C_{1-6} alkyl)NOH or -C(C_{1-6} alkyl)NNH_2, or one of R_1 and R_2 is nitro, cyano or C_{1-3} alkylcarbonyl and the other is methoxy or amino optionally substituted by one or two C_{1-6} alkyl or by C_{2-7} alkanoyl;

one of R_3 and R_4 is hydrogen or C_{1-4} alkyl and the other is C_{1-4} alkyl or R_3 and R_4 together are C_{2-5} polymethylene;

R_5 is C_{1-6} alkylcarbonyloxy, benzoyloxy, ONO_2, benzyloxy, phenyloxy or C_{1-6} alkoxy and R_6 and R_9 are hydrogen or R_5 is hydroxy and R_6 is hydrogen or C_{1-2} alkyl and R_9 is hydrogen;

R_7 is fluorophenyl;

R_8 is hydrogen or C_{1-6} alkyl;

the R_8-N-CO-R_7 group being trans to the R_5 group;

and X is oxygen or NR_{10} where R_{10} is hydrogen or C_{1-6} alkyl.

2. A pharmaceutical composition for use in the treatment and/or prophylaxis of anxiety and/or mania and/or depression and/or the effects associated with withdrawal from substances of abuse and/or disorders treatable or preventable with anti-convulsive agents, which comprises an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined in claim 1, and a pharmaceutically acceptable carrier.

3. The use of a compound of formula (I), as defined in claim 1, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of anxiety and/or mania and/or depression and/or the effects associated with withdrawal from substances of abuse and/or disorders treatable or preventable with anti-convulsive agents.

4. A method according to claim 1 in which the compound of formula (I) has the following variables wherein;

Y is C-R_1, where:

either one of R_1 and R_2 is hydrogen and the other is selected from the class of hydrogen, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonyloxy, C_{1-6} alkylhydroxymethyl, nitro, cyano, chloro, trifluoromethyl, trifluoromethoxy, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, C_{1-6} alkoxysulphinyl, C_{1-6} alkoxysulphonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkoxycarbonylamino, C_{1-6} alkyl-thiocarbonyl, C_{1-6} alkoxy-thiocarbonyl, C_{1-6} alkyl-thiocarbonyloxy, 1-mercapto C_{2-7} alkyl, formyl, or aminosulphinyl, aminosulphonyl or aminocarbonyl, the amino moiety being optionally substituted by one or two C_{1-6} alkyl groups, or C_{1-6} alkylsulphinylamino, C_{1-6} alkylsulphonylamino,C_{1-6} alkoxysulphinylamino or C_{1-6} alkoxysulphonylamino, or ethylenyl terminally substituted by C_{1-6} alkylcarbonyl, nitro or cyano, or -C(C_{1-6} alkyl)NOH or -C(C_{1-6} alkyl)NNH_2, or one of R_1 and R_2 is nitro, cyano or C_{1-3} alkylcarbonyl and the other is methoxy or amino optionally substituted by one or two C_{1-6} alkyl or by C_{2-7} alkanoyl;

one of R_3 and R_4 is hydrogen or C_{1-4} alkyl and the other is C_{1-4} alkyl or R_3 and R_4 together are C_{2-5} polymethylene;

R_5 is hydroxy and R_6 is hydrogen;

R_7 is fluorophenyl;

R_8 is hydrogen or C_{1-6} alkyl; and

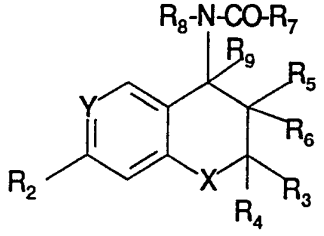
R_9 is hydrogen;

the R_8-N-CO-R_7 group being trans to the R_5 group.

5. A pharmaceutical composition according to claim 2 wherein the compound of formula (I) is as defined in claim 4.

6. A use according to claim 3 wherein the compound of formula (I) is as defined in claim 4.

7. A compound of formula (Ia) or a pharmaceutically acceptable salt thereof



(Ia)

wherein variables Y, R_2, R_3, R_4, R_5, R_6, R_8, R_9 and X are as defined in relation to formula (I) in claim 1 and R_7 is 2- or 3-fluorophenyl or where R_7 is 2, 4- or 3,4- difluorophenyl.

8. A compound of formula (Ia) as defined in claim 7 selected from the group consisting of;

trans-6-Cyano-3,4-dihydro-2,2-dimethyl-4-(3-fluoro-benzoylamino)2H-1-benzopyran-3-ol (Example 1),

trans-6-Cyano-3,4-dihydro-2,2-dimethyl-4-(2-fluoro-benzoylamino)2H-1-benzopyran-3-ol (Example 2),

trans-6-Trifluoromethoxy-3,4-dihydro-2,2-dimethyl-4-(3-fluorobenzoylamino)2H-1-benzopyran-3-ol (Example 3),

trans-6-Cyano-4S-(3-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3R-ol (Example 21),

trans-6-Cyano-4R-(3-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3S-ol (Example 22),

trans-6-Cyano-4S-(2-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3R-ol (Example 24),

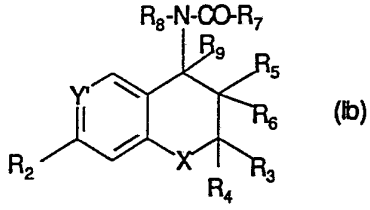
trans-6-Cyano-4S-(2,4-difluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3R-ol (Example 28),

trans-6-Acetyl-4-(3-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol (Example 31),

trans-6-Cyano-4-(3,4-difluorbenzoyl-methylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol (Example 41) and

trans-6-cyano-4S-(3,4-difluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3R-ol (Example 44) or a pharmaceutically acceptable salt thereof.

9. A compound of formula (Ib) or pharmaceutically acceptable salts thereof:



(Ib)

wherein variables R_3, R_4, R_5, R_6, R_7, R_8, R_9 and X are as defined in relation to formula (I) in claim 1 and Y is CR_1 where R_1 and R_2 are both hydrogen or one of R_1 and R_2 is trifluoromethoxy, C_{1-6} alkyl optionally interrupted with oxygen or substituted with hydroxy, C_{1-6} alkoxy or substituted amino-carbonyl, CF_3A-(where A is $-CF_2-$, -CO-, $-CH_2$) or CH(OH), aryl sulphonyl, aryl C_{3-8} cycloalkyl, C_{1-6} alkoxy, heteroaryl, arylcarbonyl, heteroarylcarbonyl, arylsulphinyl, heteroarylsulphinyl, heteroarylsulphonyl, in which any aromatic moiety is optionally substituted and the other is hydrogen.

10. A compound of formula (Ib) as defined in claim 9 selected from the group consisting of:

trans-3,4-Dihydro-2,2-dimethyl-4-(4-fluorobenzoylamino)-2H-1-benzopyran-3-ol (Example 4),

trans-4-(4-Fluorobenzoylamino)-3,4-dihydro-2,2,6-trimethyl-2H-1-benzopyran-3-ol (Example 14),

trans-6-Ethyl-4-(4-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol (Example 15),

trans-6-Ethyl-4-(4-fluorobenzoylethylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol (Example 16),

trans-4-(4-Fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-6-isopropyl-2H-1-benzopyran-3-ol (Example 17),

trans-6-Ethyl-4-(4-fluorobenzoylmethylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol (Example 23),

trans-4-(4-Fluorobenzoylamino)-6-pentafluoroethyl-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol (Example 29),

trans-4-(4-Fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-6-phenylsulphonyl-2H-1-benzopyran-3-ol (Example 32),

trans-4-(4-Fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-6-phenyl-2H-1-benzopyran-3-ol (Example 33),

trans-6-Ethyl-4S-(4-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3R-ol (Example 35),

trans-4R-(4-Fluorobenzoylamino)-3,4-dihydro-6-(1-hydroxyethyl)-2,2-dimethyl-2H-1-benzopyran-3S-ol (Example 36),

trans-4S-(4-Fluorobenzoylamino)-3,4-dihydro-6-(1-hydroxyethyl)-2,2-dimethyl-2H-1-benzopyran-3R-ol (Example 37),

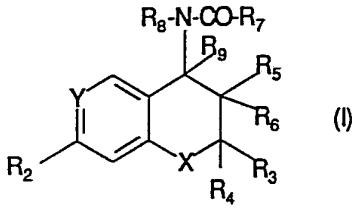
trans-4-(4-fluorobenzoyl-methylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol (Example 43),

trans-6-t-Butyl-4-(4-Fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol (Example 46),

trans-4-(4-Fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-6-cyclopentyl-2H-1-benzopyran-3-ol (Example 48) and

trans- 4-(4-Fluorobenzoylamino)-3,4-dihydro-6-methoxy-2,2-dimethyl-2H-1-benzopyran-3-ol (Example 50), or a pharmaceutically acceptable salt thereof.

11. A compound of formula (Ic), or a pharmaceutically acceptable salt thereof:



where R_3, R_4, R_5, R_6, R_7, R_8, R_9 and X are as defined in relation to formula (I) in claim 1 and Y is N and R_2 is hydrogen.

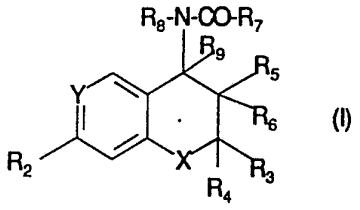
12. A compound of formula (Ic) as defined in claim 11, selected from the group consisting of:

trans-4-(2-Fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-pyrano[3,2-c]pyridin-3-ol (Example 38),

trans-4-(3-Fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-pyrano[3,2-c]pyridin-3-ol (Example 39) and

trans-4-(4-Fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-pyrano[3,2-c]pyridin-3-ol (Example 40), or a pharmaceutically acceptable salt thereof.

13. A compound of formula (Id), or a pharmaceutically acceptable salt thereof:



(I)

where X is NR_{10} where R_{10} is hydrogen or C_{1-6} alkyl and Y, R_2, R_3, R_4, R_5, R_6, R_7, R_8, and R_9 are as defined in relation to formula (I) in claim 1,.

14. A compound of formula (Id) as defined in claim 13, selected from the group consisting of:

trans-6-Cyano-4-(4-fluorobenzoylamino)-2,2-dimethyl-1,2,3,4-tetrahydroquinolin-3-ol (Example 45), or a pharmaceutically acceptable salt thereof.

15. A compound of formula (I') selected from the group consisting of:

trans-6-Cyano-3,4-dihydro-2,2-dimethyl-4-(4-fluoro-benzoylamino)2H-1-benzopyran-3-ol, (Example 5),

trans-6-Chloro-3,4-dihydro-2,2-dimethyl-4-(4-fluoro-benzoylamino)2H-1-benzopyran-3-ol, (Example 6),

trans-6-Trifluoromethyl-4-(4-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol, (Example 7),

trans-6-Cyano-4-(4-fluorobenzoylmethylamino)-3,4-dihydro- 2,2-dimethyl-2H-1-benzopyran-3-ol, (Example 8),

trans-6-Ethylcarbonyl-3,4-dihydro-2,2-dimethyl-4-(4-fluorobenzoylamino)2H-1-benzopyran-3-ol, (Example 9),

trans-6-Ethylcarbonyl-3,4-dihydro-2,2-dimethyl-4-(4-fluorobenzoylmethylamino)2H-1-benzopyran-3-ol, (Example 10),

trans-6-Acetyl-4-(4-fluorobenzoylmethylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol, (Example 11),

trans-6-Cyano-3,4-dihydro-4-(4-fluorobenzoylethylamino)-2,2-dimethyl-2H-1-benzopyran-3-ol (Example 12),

trans-4-(4-Fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-7-nitro-2H-1-benzopyran-3-ol (Example 13),

trans-6-Acetyl-4-(4-Fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol (Example 18),

trans-6-Acetyl-4R-(4-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3S-ol (Example 19),

trans-6-Acetyl-4S-(4-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3R-ol (Example 20),

trans-6-Cyano-4S-(4-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3R-ol (Example 25),

trans-6-Cyano-4-(4-fluorobenzoylamino)-3,4-dihydro-2,2,3-trimethyl-2H-1-benzopyran-3-ol (Example 26),

trans-4-(4-Fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-6-nitro-2H-1-benzopyran-3-ol (Example 27),

trans-4-(4-Fluorobenzoylamino)-3,4-dihydro-6-methoxycarbonyl-2,2-dimethyl-2H-1-benzopyran-3-ol (Example 30),

trans-6-Fluoro-4-(4-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol (Example 34),

trans-4-(4-fluorobenzoyl-methylamino)-6-trifluoromethyl-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol (Example 42),

trans-4-(4-Fluorobenzoylamino)-3,4-dihydro-6-iodo-2,2-dimethyl-2H-1-benzopyran-3-ol (Example 47) and

trans- 6-Aminocarbonylmethyl-4-(4-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3-ol (Example 49) or a pharmaceutically acceptable salt thereof.

16. A compound of formula (Ia), (Ib), (Ic) or (Id), according to any one of claims 7, 9, 11 and 13, or a pharmaceutically acceptable salt thereof wherein R_3 and R_4 are both methyl.

17. A compound of formula (Ia), (Ib), (Ic) or (Id), according to any one of claims 7, 9, 11, 13 and 16, or a pharmaceutically acceptable salt thereof wherein R_5 is hydroxy and R_6 and R_9 are hydrogen.

18. A compound of formula (Ia), (Ib) or (Ic) according to any one of claims 7, 9, 11, 16 and 17, or a pharmceutically acceptable salt thereof wherein X is oxygen.

19. A compound of formula (Ia), (Ib) or (Id) according to any one of claims 7, 9, 13 and 16 to 19, or a pharmceutically acceptable salt thereof wherein Y is R_1 and R_1 is cyano, methoxy, trifluoromethoxy, chloro, trifluoromethyl, ethylcarbonyl, acetyl, hydrogen, methyl, ethyl, iso-propyl,tertiary-butyl, nitro, C_2F_5, methoxycarbonyl, phenylsulphonyl, phenyl, fluoro, iodo, cyclopentyl, aminocarbonylmethyl and 1-hydroxyethyl and R_2 is hydrogen

20. A compound according to claim 19 wherein R_1 is cyano, ethyl or acetyl and R_2 is hydrogen.

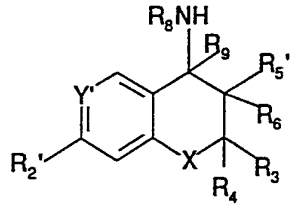
21. A compound of formula (Ib), (Ic) or (Id) according to any one of claims 9, 11, 13 and 16 to 20, or a pharmaceutically acceptable salt thereof wherein R_7 is 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl or 3,4-difluorophenyl.

22. A compound of formula (Ia), (Ib), (Ic) or (Id), according to any one of claims 7, 9, 11, 13 and 16 to 21, or a pharmaceutically acceptable salt thereof wherein R_8 is hydrogen, methyl or ethyl.

23. A compound of formula (Ia), (Ib), (Ic) or (Id), according to any one of claims 7, 9, 11, 13and 16 to 22, or a pharmaceutically acceptable salt thereof wherein the compound has the 4S,3R configuration.

24. A process for the preparation of compounds of formula (I') as listed in claim 15, or pharmaceutically acceptable salts thereof:

which comprises acylating a compound of formula (II'):



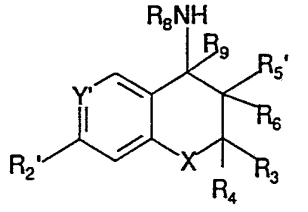
(II')

wherein Y', R_2' and R_5' are the required variables Y, R_2 or R_5 as defined in formula (I) or a group convertible thereto and R_3, R_4, R_6, R_8, R_9 and X are the required variables as defined in formula (I), the R_8NH group being trans to the R_5 group, with and acylating agent of formula (IIIb):

$$R_7COL_1 \qquad \text{(IIIb)}$$

where R_7 is as required and as defined in formula (I) and L_1 is a leaving group; thereafter optionally or as necessary and in any appropriate order converting any R_1', R_2' and R_5' groups to R_1, R_2 and R_5 respectively, interconverting R_8 when hydrogen to C_{1-6} alkyl, separating any enantiomers and forming a pharmaceutically acceptable salt or solvate.

25. A process for the preparation of compounds of formula (Ia) as defined in claim 7, or a pharmaceutically acceptable salt thereof, which comprises acylating a compound of formula (IIa):



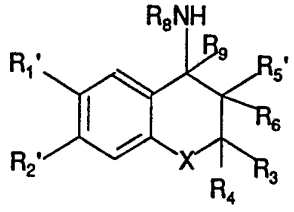
(IIa)

wherein Y', R_2' and R_5' are Y, R_2 or R_5 as defined in formula (I) or a group convertible thereto and R_3, R_4, R_6, R_8, R_9 and X are as defined in formula (I), the R_8NH group being trans to the R_5' group, with an acylating agent of formula (IIIa):

$$R_7{}^aCOL_1 \qquad \text{(IIIa)}$$

where $R_7{}^a$ is 2- or 3-fluorophenyl or 2,4- or 3,4- difluorophenyl and L_1 is a leaving group; thereafter optionally or as necessary and in any appropriate order converting any Y', R_2' or R_5' group to Y, R_2 or R_5 respectively, interconverting R_8 when hydrogen to C_{1-6} alkyl, separating any entantioners and forming a pharmaceutically acceptable salt or solvate.

26. A process for the preparation of compounds of formula (Ib) as defined in claim 9, or a pharmaceutically acceptable salt thereof, which comprises acylating a compound of formula (IIb):



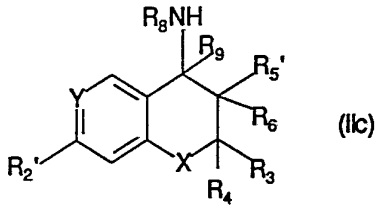
(IIb)

where R_1' and R_2' are both hydrogen or one of R_1 and R_2 is trifluoromethoxy, C_{1-6} alkyl optionally interrupted with oxygen or substituted with hydroxy, C_{1-6} alkoxy or substituted aminocarbonyl, CF_3A- (where A is CF_2,-CO-,-CH_2- or CH(OH)), aryl, aryl sulphonyl, aryl C_{3-8} cycloalkyl, C_{1-6} alkoxy, heteroaryl, arylcarbonyl, heteroarylcarbonyl, arylsulphinyl, heteroarylsulphinyl, heteroarylsulphonyl, in which any aromatic moiety is optionally substituted and the other is hydrogen, or groups convertible to any of these; R_5' is R_5 as defined in formula (I) or a group convertible thereto and R_3, R_4, R_6, R_8, R_9 and X are as defined in formula (I) the R_8NH group being trans to the R_5' group, with a compound of formula (IIIb):

R_7COL_1 (IIIb)

where R_7 is as defined in formula (I) and L_1 is a leaving group; thereafter optionally or as necessary and in any appropriate order converting any R_1', R_2' and R_5' groups to R_1, R_2 and R_5 respectively, interconverting R_8 when hydrogen to C_{1-6} alkyl, separating any enantiomers and forming a pharmaceutically acceptable salt or solvate.

27. A process for the preparation of compounds of formula (Ic)as defined in claim 11, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt thereof, which comprises acylating a compound of formula (IIc):



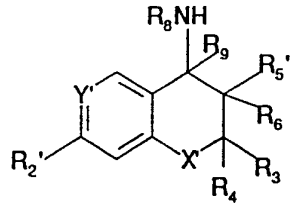
(IIc)

in which Y is N, R_5' is R_5, as defined in relation to formula (I) or a group convertible to R_5 and R_2' is hydrogen or a group convertible thereto, R_6, R_3, R_4, R_8, R_9 and X are as defined in formula (I), the R_8NH group being trans to the R_5' group, with an acylating agent of formula (IIIb):

R_7COL_1 (IIIb)

where R_7 is as defined in formula (I) and L_1 is a leaving group; thereafter optionally or as necessary and in any appropriate order converting any R_2' or R_5' group to hydrogen or R_5 respectively, interconverting R_8 when hydrogen to C_{1-6} alkyl, separating any enantiomers and forming a pharmaceutically acceptable salt or solvate.

28. A process for the preparation of compounds of formula (I) as defined in claim 11, or a pharmaceutically acceptable salt thereof, which comprises acylating a compound of formula (IId):



(IId)

in which X' is NR_{10}' where R_{10}' is hydrogen or C_{1-6} alkyl or a group convertible thereto, Y', R_2' and R_5 are Y, R_2 and R_5 respectively as defined in formula (I) or groups convertible thereto and R_3, R_4, R_6, R_8 and R_9 are as defined in formula (I), the R_8NH group being trans to the R_5' group, with an acylating agent of formula (IIIb):

$$R_7COL_1 \qquad \text{(IIIb)}$$

where R_7 is as defined in formula (I) and L_1 is a leaving group, thereafter optionally or as necessary and in any appropriate order converting any Y', R_{10}', R_2' or R_5' group to Y, R_{10}, R_2 or R_5 respectively, interconverting R_8 when hydrogen to C_{1-6} alkyl, separating any enantiomers and forming a pharmaceutically acceptable salt or solvate.

29. A pharmaceutical composition comprising a compound of formula (I'), (Ia), (Ib), (Ic) or (Id), as defined in claims 15, 7, 9, 11 and 13 respectively, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

30. The use of a compound of formula (I'), (Ia), (Ib), (Ic) or (Id), as defined in claims 15, 7, 9, 11 and 13 respectively, or a pharmaceutically acceptable salt thereof, in the treatment and/or prophylaxis of anxiety and/or mania and/or depression and/or the effects associated with withdrawal from substances of abuse and/or disorders treatable and/or preventable with anti-convulsive agents.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 92/01045

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 31/35 C 07 D 311/68 C 07 D 311/72
C 07 D 491/04 C 07 D 311/70 C 07 D 215/48 //(C 07 D 491/04 311/70, 215/48, //(C 07 D 491/04, 311:00, 213:00)

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K C 07 D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	EP,A,0126311 (BEECHAM GROUP) 28 November 1984, see pages 2-3; claims 1,24,25,27; example 13 (cited in the application) ---	14,24, 29
X	EP,A,0205292 (BEECHAM GROUP) 17 December 1986, see column 2, line 15 - column 3, line 7; claims 1,6,8,11; examples 5,8-11 (cited in the application) ---	7,9,11, 12,16-19,21-23,25, 27,29
X	EP,A,0250077 (BEECHAM GROUP) 23 December 1987, see page 2 - page 4, line 4; claims 1,8,9,11; example 8 (cited in the application) ---	9,10,16 -19,21, 22,26, 29
A	EP,A,0370901 (SANOFI) 30 May 1990, see page 3, line 26 - page 4, line 5 --- -/-	1-3

° Special categories of cited documents :[10]

"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

"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

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
16-07-1992	25. 09. 92
International Searching Authority: EUROPEAN PATENT OFFICE	Signature of Authorized Officer: Natalie Weinberg

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	US,A,4334067 (S. OHNO et al.) 8 June 1982, see column 1	1-3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB92/01045

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:

Remark: Although claims 1,4,30 are directed to methods of treatment of the human or animal body (Rule 39.1(iv)PCT), 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 searches 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.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9201045 SA 60477

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 03/08/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		AU-A- 2808184	22-11-84
		CA-A- 1236458	10-05-88
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		JP-A- 56063981	30-05-81
		JP-B- 60023115	05-06-85
		JP-C- 1302292	14-02-86
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		DE-A- 3040727	27-08-81
		FR-A,B 2468601	08-05-81
		GB-A,B 2064514	17-06-81