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U1S S2417**

(56) Documents Cited

**None**

(58) Field of Search

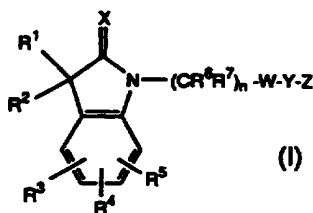
**UK CL (Edition O ) C2C CQZ CTT**

**INT CL<sup>6</sup> C07D**

**ONLINE: CAS**

(54) **Pharmaceutical indole derivatives**

(57) A pharmaceutical compound of the formula



in which

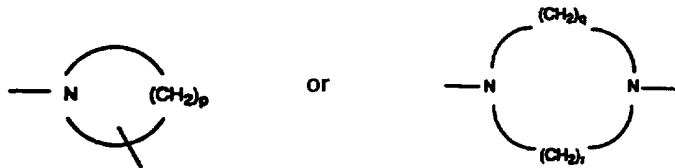
$R^1$  and  $R^2$  are each hydrogen,  $C_{1-4}$  alkyl,  $C_{1-4}$  alkoxy,  $HO-C_{1-4}$  alkyl,  $C_{1-4}$  alkoxy- $C_{1-4}$  alkyl,  $C_{1-4}$  alkylthio, halo, Ph or  $PhCR'R''$ - where Ph is optionally substituted phenyl and  $R'$  and  $R''$  are each hydrogen or  $C_{1-4}$  alkyl, or  $R^1$  and  $R^2$  together with the carbon atom to which they are attached form a  $C_{3-6}$  cycloalkyl group,  $>C=O$ ,  $>C=NOR'$  where R is hydrogen or  $C_{1-4}$  alkyl

$R^3$ ,  $R^4$  and  $R^5$  are each hydrogen, halo, nitro,  $C_{1-4}$  alkyl,  $C_{1-4}$  alkoxy,  $C_{1-4}$  alkylthio,  $C_{1-4}$  alkyl-CO-,  $C_{1-4}$  alkyl-S(O)<sub>m</sub>-where m is 0, 1 or 2,  $R'R''N-SO_2$ -,  $COOR'$ ,  $CONR'R''$ -,  $-NR'R''$ -,  $-N(OR')COOR''$ -,  $-COR'$ -,  $-NHSO_2R'$ -, where  $R'$  and  $R''$  are each hydrogen or  $C_{1-4}$  alkyl,

$R^6$  and  $R^7$  are each hydrogen or  $C_{1-4}$  alkyl, and n is 1 to 6,

X is oxygen or sulphur,

W is



where p is 4 to 7, and q and r are each 1 to 3,

Y is  $>CO$  or  $-CH(OH)-$ ,

and

Z is optionally substituted phenyl or optionally substituted heteroaryl;

and salts and esters thereof.

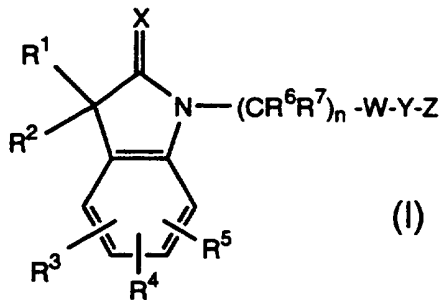
GB 2 308 362 A

PHARMACEUTICAL COMPOUNDS

This invention relates to pharmaceutical compounds, their preparation and use.

5

The compounds of the invention are of the formula:



10 in which

R<sup>1</sup> and R<sup>2</sup> are each hydrogen, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, HO-C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy-C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkylthio, halo, Ph, PhCR'R''- where Ph is optionally substituted phenyl and R' and R'' are each hydrogen or C<sub>1-4</sub> alkyl, or R<sup>1</sup> and R<sup>2</sup> together with the carbon atom to which they are attached form a C<sub>3-6</sub> cycloalkyl group, >C=O, >C=NOR' where R' is hydrogen or C<sub>1-4</sub> alkyl,

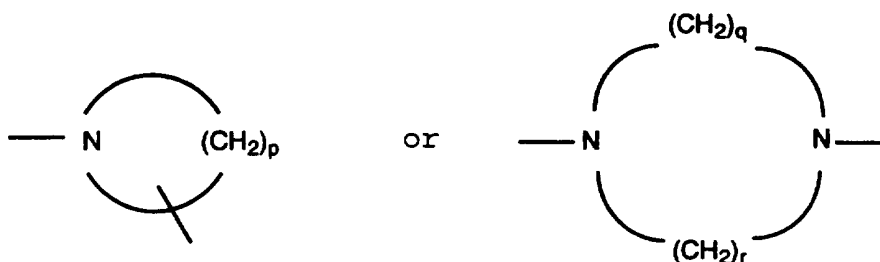
20 R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are each hydrogen, halo, nitro, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkylthio, C<sub>1-4</sub> alkyl-CO-, C<sub>1-4</sub> alkyl-S(O)<sub>m</sub>- where m is 0, 1 or 2, R'R''N-SO<sub>2</sub>-, -COOR', -CONR'R'', -NR'R'', -N(OR')COOR'', -COR', -NHSO<sub>2</sub>R', where R' and R'' are each hydrogen or C<sub>1-4</sub> alkyl,

R<sup>6</sup> and R<sup>7</sup> are each hydrogen or C<sub>1-4</sub> alkyl, and n is 1 to 6,

X is oxygen or sulphur,

5

W is



10 where p is 4 to 7, and q and r are each 1 to 3,

Y is  $\text{>CO}$  or  $\text{-CH(OH)-}$ ,

and

15

Z is optionally substituted phenyl or optionally substituted heteroaryl;

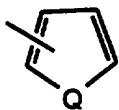
and salts and esters thereof.

20

The compounds of the invention are indicated for use in the treatment of diseases of the central nervous system. They are active in tests that indicate serotonergic modulation.

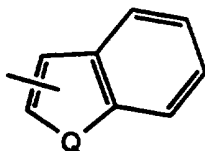
In the above formula (I), a C<sub>1-4</sub> alkyl group includes methyl, ethyl, propyl, isopropyl, butyl and tert. butyl, and is preferably methyl or ethyl. A C<sub>1-4</sub> alkoxy group is one such alkyl group linked to a ring via an oxygen atom, and a halo atom is preferably chlorine, bromine or fluorine, and especially chlorine or fluorine. A substituted phenyl group is phenyl substituted with one or more, for example one to three, substituents selected from, for example C<sub>1-4</sub> alkyl, especially methyl, C<sub>1-4</sub> alkoxy, especially methoxy and ethoxy, hydroxy, nitro, cyano, halo, especially chloro or fluoro, trihalomethyl, especially trifluoromethyl, carboxy and C<sub>1-4</sub> alkoxy-carbonyl.

A heteroaryl group can have one or more hetero atoms selected from, for example, oxygen, nitrogen and sulphur and preferably contains from 5 to 10 carbon atoms. Preferably a heteroaryl group is of the formula:



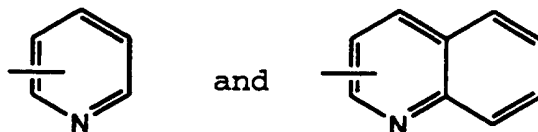
20

where Q is -O-, -S- or -NR-, and R is hydrogen or C<sub>1-6</sub> alkyl. Alternatively, a heteroaryl group can comprise a benzene fused ring as, for example:



25

Further heteroaryl groups include those of the formula:

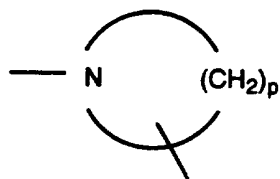


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When  $n$  is greater than 1, the values of  $R^6$  and  $R^7$  need not be identical in each repeating methylene unit.

Preferred compounds are those having one or more of the following features:

- (i) X is oxygen
- (ii)  $R^1$  and  $R^2$  are each hydrogen,  $C_{1-4}$  alkyl,  $C_{1-4}$  alkylthio or benzyl
- (iii)  $R^1$  and  $R^2$  are both methyl
- (iv)  $R^1$  is hydrogen and  $R^2$  is methyl
- (v)  $R^3$ ,  $R^4$  and  $R^5$  are each hydrogen, halo or  $C_{1-4}$  alkyl
- (vi)  $R^6$  and  $R^7$  are both hydrogen
- (vii)  $n$  is 2
- (viii) W is



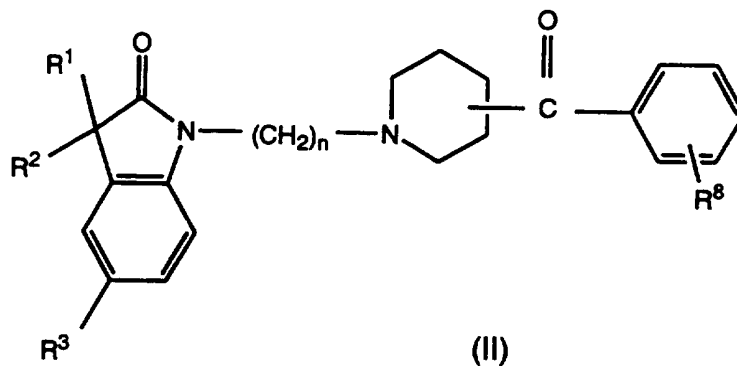
(ix) p is 5

5 (x)

Y is  $>CO$

(xi) Z is optionally substituted phenyl

10 A preferred group of compounds is of the formula:



15 in which  $R^1$  and  $R^2$  are each hydrogen or  $C_{1-4}$  alkyl,  $R^3$  and  $R^4$  are each hydrogen,  $C_{1-4}$  alkyl or halo,  $n$  is 2, and  $R^8$  is hydrogen or halo. A particularly preferred group is one in which  $R^1$  and  $R^2$  are both hydrogen and  $R^3$  is hydrogen or fluoro,  $n$  is 2 and  $R^8$  is halo, preferably fluoro; and salts thereof.

20

It will be appreciated that the compounds of the invention can contain one or more asymmetric carbon atoms which gives rise to isomers. The compounds are normally prepared as racemic mixtures and can conveniently be used as such, but  
5 individual isomers can be isolated by conventional techniques if so desired. Such racemic mixtures and individual optical isomers form part of the present invention. It is preferred to use an enantiomerically pure form.

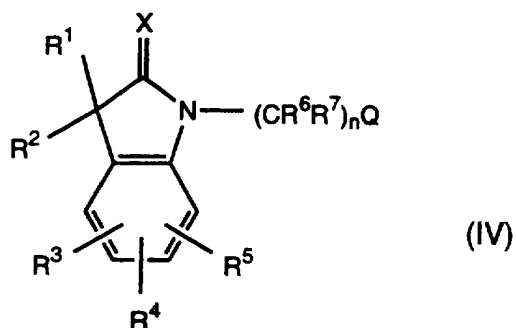
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It is, of course, possible to prepare salts of the compounds of the invention and such salts are included in the invention. Acid addition salts are preferably the pharmaceutically acceptable, non-toxic addition salts with  
15 suitable acids, such as those with inorganic acids, for example hydrochloric, hydrobromic, nitric, sulphuric or phosphoric acids, or with organic acids, such as organic carboxylic acids, for example, glycollic, maleic, hydroxymaleic, fumaric, malic, tartaric, citric, salicylic,  
20 *o*-acetoxybenzoic, or organic sulphonic, 2-hydroxyethane sulphonic, toluene-*p*-sulphonic, or naphthalene-2-sulphonic acid.

In addition to pharmaceutically-acceptable salts, other  
25 salts are included in the invention. They may serve as intermediates in the purification of compounds or in the preparation of other, for example pharmaceutically-

acceptable, acid addition salts, or are useful for identification, characterisation or purification.

The invention also includes a process for producing a  
5 compound of formula (I) above, which comprises reacting a compound of the formula H-W-Y-Z (III) with a compound of the formula:



10

where the substituents have the values given above, and Q is a leaving group, for example, halo or a mesylate or tosylate.

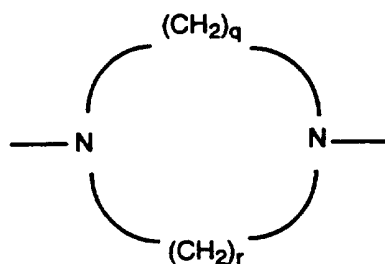
15 The reaction is preferably carried out in an inert organic solvent such as, for example, methyl isobutyl ketone or acetonitrile, and at a temperature of from 80° C. to 110° C. The reaction takes place in alkaline conditions by the use of, for example, sodium carbonate or potassium carbonate.

20

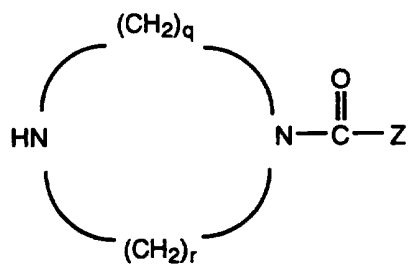
Compounds of formula (III) are either known or can be prepared by methods well known in the art.

In the case of compounds in which W is





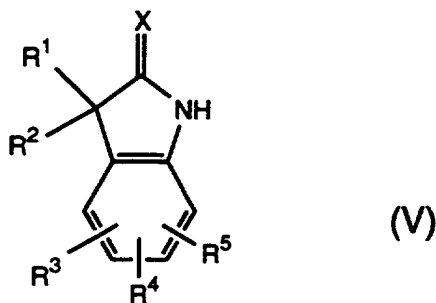
compounds can be prepared reacting the partially protected  
5 nitrogen containing cyclic amine with a phenyl or heteroaryl  
carbonyl halide, followed by deprotection, to give compounds  
of the formula:



10

optionally followed by reduction to give the compound of  
formula (III) in which Y is -CH(OH)-.

Compounds of formula (IV) are either known or can be  
15 prepared by methods well known in the art as, for example,  
by reacting a compound of the formula:

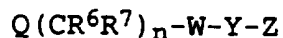


with a compound of the formula  $Q'(CR^6R^7)_nQ$ , where  $Q'$  is also a leaving group.

5

An alternative route to the compounds of the invention consists of an analogous, reverse, condensation of the principal components of the molecule as, for example, by reacting a compound of the formula (V) above, with a

10 compound of the formula



Such reagents can be made as described above or by analogous  
15 methods.

As mentioned above, the compounds of the invention have useful central nervous system activity. The compounds are active at the serotonin, 5-HT<sub>1Dα</sub>, receptor. Their binding  
20 activity has been demonstrated in a test described by Zgombick, J. M. et al., Molecular Pharmacology Vol. 40 1992, pages 1036-1042, and compounds of the invention as described in the following Examples have a  $K_i$  of from 2 nM to 5,000 nM. Some of the compounds, for example those of

formula III, also possess binding activity at the 5-HT<sub>1Dβ</sub> receptor. Furthermore, compounds have activity at the 5-HT<sub>2A</sub> receptors as shown in the test described by Leysen, J. E. et al., Molecular Pharmacology Vol. 21 1981, 5 pages 301-314.

Because of their selective affinity for the 5-HT receptors, the compounds of the present invention are indicated for use in treating a variety of conditions such as obesity, 10 bulimia, alcoholism, pain, depression, hypertension, ageing, memory loss, sexual dysfunction, anxiety, schizophrenia, gastrointestinal disorders, headache, cardiovascular disorders, smoking cessation, drug addiction, emesis, Alzheimer's and sleep disorders.

15

The compounds of the invention are effective over a wide dosage range, the actual dose administered being dependent on such factors as the particular compound being used, the condition being treated and the type and size of mammal 20 being treated. However, the dosage required will normally fall within the range of 0.01 to 20 mg/kg per day, for example in the treatment of adult humans, dosages of from 0.5 to 100 mg per day may be used.

25 The compounds of the invention will normally be administered orally or by injection and, for this purpose, the compounds will usually be utilised in the form of a pharmaceutical composition. Such compositions are prepared in a manner

well known in the pharmaceutical art and comprise at least one active compound.

Accordingly the invention includes a pharmaceutical  
5 composition comprising as active ingredient a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, associated with a pharmaceutically acceptable excipient. In making the compositions of the invention, the active ingredient will usually be mixed with a carrier, or  
10 diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. The excipient may be a solid, semi-solid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Some examples of suitable  
15 excipients are lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, syrup, methyl cellulose, methyl- and propyl-hydroxybenzoate, talc, magnesium stearate or oil. The compositions of the invention may, if desired,  
20 be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient.

Depending on the route of administration, the foregoing  
25 compositions may be formulated as tablets, capsules or suspensions for oral use and injection solutions or suspensions for parenteral use or as suppositories. Preferably the compositions are formulated in a dosage unit form, each dosage

containing from 0.5 to 100 mg, more usually 1 to 100 mg, of the active ingredient.

The following Examples illustrate the invention:

EXAMPLE 1

2(3,3-Dimethyloxindolyl)ethanol : 3,3-Dimethyloxindole  
(prepared by the method of Endler and Becker; Organic  
5 Syntheses Coll. vol. 4 page 657) was dissolved in dry  
dimethylformamide under nitrogen at room temperature.  
Sodium hydride (60% dispersion in mineral oil) (1.05  
equivalents) was added and the mixture was stirred until gas  
evolution ceased. 2-(2-Chloroethoxy)tetrahydro-2H-pyran  
10 (1.05 equivalents) and Sodium iodide (0.1 equivalents) was  
added and the mixture was warmed to 75° C. for 15 hours.  
Water was added and the mixture was concentrated under  
reduced pressure. The residue was taken up in ethyl acetate,  
washed (x 3) with water, dried (MgSO<sub>4</sub>), filtered and  
15 concentrated under reduced pressure. The resulting oil was  
taken up in methanol, paratoluenesulphonic acid (0.1  
equivalents) was added and the mixture was stirred at room  
temperature for 12 hours. The mixture was concentrated under  
reduced pressure, taken up in ethyl acetate, washed (x 3)  
20 with aqueous sodium hydrogen carbonate solution dried  
(MgSO<sub>4</sub>), filtered and concentrated under reduced pressure.  
The resulting oil was purified by chromatography on silica  
gel, eluent hexane/ethyl acetate, to give 2(3,3-  
dimethyloxindolyl)ethanol which was characterised by <sup>1</sup>H nmr  
25 and MS.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.4(6H s), 3.05 (1H broad), 3.95(4H s),  
6.96(1H d), 7.04(1H t), 7.12(2H m).

MS shows 206 (MH<sup>+</sup>) base peak.

1-{2-[4-(4-Fluorobenzoyl)-1-piperidinyl]-1-ethyl}-3,3-

5 dimethyl-indol-2(3H)-one monohydrochloride : 2(3,3-

Dimethyloxindolyl)ethanol and triethylamine (1.1

equivalents) was dissolved in dichloromethane under nitrogen and cooled to less than 5° C. in an ice/water bath.

Methanesulfonyl chloride (1.05 equivalents) was added and

10 the mixture was stirred for one hour with cooling. The

mixture was washed with cold dilute hydrochloric acid, dried (MgSO<sub>4</sub>), filtered and concentrated under reduced pressure.

The resulting oil was dissolved in dry acetonitrile,

4-fluorobenzoylpiperidine (1 equivalent as its

15 paratoluenesulfonate salt), potassium carbonate (3

equivalents) and potassium iodide (0.1 equivalents) were

added. The mixture was stirred vigorously and heated under gentle reflux for two days. The mixture was poured into

chloroform, washed with water, dried (MgSO<sub>4</sub>), filtered and

20 concentrated under reduced pressure. The resulting oil was

taken up in 5N hydrochloric acid whereupon a white solid

separated. This solid was recrystallised from ethanol to

give 1-{2-[4-(4-fluorobenzoyl)-1-piperidinyl]-1-ethyl}-3,3-

dimethyl-indol-2(3H)-one monohydrochloride. Melting point

25 236-8° C.

EXAMPLE 2

3-Methyl-3-methylthiooxindole : Oxindole and

5 tetramethylethylenediamine (2.2 equivalents) was dissolved in freshly distilled tetrahydrofuran under nitrogen and cooled to  $-75^{\circ}$  C. in an acetone/dry ice bath.

n-Butyllithium (2.2 equivalents) was added and the mixture was stirred at  $-75^{\circ}$  C. for 30 minutes. Iodomethane (1

10 equivalent) was added and the mixture was allowed to warm to  $-20^{\circ}$  C., the mixture was recooled to  $-75^{\circ}$  C. then dimethyl disulfide (1 equivalent) was added and the mixture was allowed to warm to room temperature. Water (5 ml) was added and the mixture was concentrated under reduced pressure to a  
15 yellow oil. Column chromatography on silica gel (eluent ethyl acetate/hexane) gave 3-methyl-3-methylthiooxindole as a yellow oil which solidified on standing.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ) d 1.61(3H s), 1.91(3H s), 6.96(1H d), 7.04(1H  
20 t), 7.12(2H m), 8.05 (1h broad).

2-(3-Methyl-3-methylthiooxindolyl)ethanol : Prepared from  
3-methyl-3-methylthiooxindole and 2-(2-  
chloroethoxy)tetrahydro-2H-pyran as described in Example 1.

25

MS shows 238 ( $\text{MH}^+$ ) base peak.



1-(2-[4-(4-Fluorobenzoyl)-1-piperidinyl]-1-ethyl)-3-methyl-3-methylthio-indol-2(3H)-one monohydrochloride : Prepared from 2-(3-methyl-3-methylthio oxindolyl)ethanol, via the methanesulfonate, and 4-fluorobenzoylpiperidine tosylate as described in Example 1.

Melting point 198-201° C.

10 EXAMPLE 3

1-(2-[4-(4-Fluorobenzoyl)-1-piperidinyl]-1-ethyl)-3-methyl-indol-2(3H)-one monohydrochloride : 1-(2-[4-(4-Fluorobenzoyl)-1-piperidinyl]-1-ethyl)-3-methyl-3-methylthio-indol-2(3H)-one was dissolved in ethanol, Raney Nickel was added and the mixture was stirred at room temperature until TLC indicated reaction was complete. The mixture was filtered and concentrated under reduced pressure to give the crude product which was purified by column chromatography on silica gel (eluent ethyl acetate/hexane). The resulting clear oil was dissolved in ethanol, ethanolic HCl was added and the mixture was concentrated under reduced pressure to give a white solid which recrystallised from 2 propanol to give 1 {2-[4-(4-Fluorobenzoyl)-1-piperidinyl]-1-ethyl}-3-methyl-indol-2(3H)-one monohydrochloride. Melting point 209-211° C.

EXAMPLE 4

3-Benzyl-3-methylthiooxindole : 3-Benzylloxindole (prepared from oxindole and benzaldehyde by the method of Daisley and Walker J. Chem. Soc. (C) (1971) page 1373) and tetramethylethylenediamine (2.2 equivalents) was dissolved in freshly distilled tetrahydrofuran under nitrogen and cooled to  $-75^{\circ}$  C. in an acetone/dry ice bath.

n-Butyllithium (2.2 equivalents) was added and the mixture was stirred at  $-75^{\circ}$  C. for 30 minutes. Dimethyl disulfide (1 equivalent) was added and the mixture was allowed to warm to room temperature. Water (5 ml) was added and the mixture was concentrated under reduced pressure to a yellow oil.

Column chromatography on silica gel (eluent ethyl acetate/hexane) gave 3-benzyl-3-methylthiooxindole as a yellow oil which solidified on standing.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.91(3H s), 3.25(1H d), 3.42(1H d), 6.76(1H d), 6.94(1H t), 7.12(5H m), 7.20(1H t), 7.28(1H t), 8.08(1H broad).

2-(3-Benzyl-3-methylthiooxindolyl)ethanol : Prepared from 3-benzyl-3-methylthiooxindole and 2-(2-chloroethoxy)tetrahydro-2H-pyran as described in Example 1.

MS shows 314 ( $\text{MH}^+$ ) base peak.

1-(2-[4-(4-Fluorobenzoyl)-1-piperidinyl]-1-ethyl)-3-benzyl-3-methylthio-indol-2(3H)-one monohydrochloride : Prepared from 2-(3-benzyl-3-methylthio oxindolyl)ethanol, via the methanesulfonate, and 4-fluorobenzoylpiperidine tosylate as  
5 described in Example 1.

Melting point 182-184° C.

10 EXAMPLE 5

1-(2-[4-(4-Fluorobenzoyl)-1-piperidinyl]-1-ethyl)-3-benzyl-indol-2(3H)-one monohydrochloride : Prepared by Raney Nickel reduction of 1-(2-[4-(4-Fluorobenzoyl)-1-piperidinyl]-1-ethyl)-3-benzyl-3-methylthio-indol-2(3H)-one as described in  
15 Example 1.

Melting point 213-216° C.

20

EXAMPLE 6

3-Benzyl-3-methyloxindole : 3-Benzylloxindole (prepared from oxindole and benzaldehyde by the method of Daisley and  
25 Walker J. Chem. Soc. (C) (1971) page 1373) and tetramethylethylenediamine (2.2 equivalents) was dissolved in freshly distilled tetrahydrofuran under nitrogen and cooled to -75° C. in an acetone/dry ice bath.

n-Butyllithium (2.2 equivalents) was added and the mixture was stirred at  $-75^{\circ}$  C. for 30 minutes. Iodomethane (1.1 equivalent) was added and the mixture was allowed to warm to room temperature. Water (5 ml) was added and the mixture  
5 was concentrated under reduced pressure to a yellow oil. Column chromatography on silica gel (eluent ethyl acetate/hexane) gave 3-benzyl-3-methyloxindole as a yellow oil which solidified on standing.

10 MS shows 238 ( $MH^{+}$ ) base peak and 255 ( $M+NH_4^{+}$ ).

2-(3-Benzyl-3-methyloxindolyl)ethanol : Prepared from 3-benzyl-3-methyloxindole and 2-(2-chloroethoxy)tetrahydro-2H-pyran.

15

MS shows 282 ( $MH^{+}$ ) base peak.

1-(2-[4-(4-Fluorobenzoyl)-1-piperidinyl]-1-ethyl)-3-benzyl-3-methyl-indol-2(3H)-one monohydrochloride : Prepared from

20 2-(3-benzyl-3-methyl oxindolyl) ethanol, via the methanesulfonate, and 4-fluorobenzoylpiperidine tosylate.

Melting point  $204-207^{\circ}$  C.

EXAMPLE 7

2-(3-Methyl-3-ethyloxindolyl)ethanol : Prepared from  
5 3-methyl-3-ethyloxindole (prepared by the method of Endler  
and Becker; Organic Syntheses Coll. vol. 4 page 657) and  
2-(2-chloroethoxy)tetrahydro-2H-pyran.

MS shows 220 (MH<sup>+</sup>) base peak.

10

1-{2-[4-(4-Fluorobenzoyl)-1-piperidinyl]-1-ethyl}-3-methyl-  
3-ethyl-indol-2(3H)-one monohydrochloride : Prepared from  
2-(3-methyl-3-ethyloxindolyl)ethanol, via the  
methanesulfonate, and 4-fluorobenzoylpiperidine tosylate as  
15 described above.

Melting point 210-212° C.

20 EXAMPLE 8

3-Isopropyl-3-methylthiooxindole : Prepared from  
3-isopropylloxindole (prepared from oxindole and acetone by  
the method of Daisley and Walker, J. Chem. Soc. (C) (1971)  
25 page 1373) by the method described above for 3 benzyl-3-  
methylthiooxindole.

MS shows 222 (M<sup>+</sup>) base peak.

2-(Isopropyl-3-methylthioxindolyl)ethanol : Prepared from 3-methyl-3-methylthioxindole and 2-(2-chloroethoxy)tetrahydro-2H-pyran.

5

MS shows 266 (MH<sup>+</sup>) base peak.

1-{2-[4-(4-Fluorobenzoyl)-1-piperidinyl]-1-ethyl}-3-isopropyl-3-methylthio-indol-2(3H)-one monohydrochloride :

10 Prepared from 2-(3-isopropyl-3-methylthio oxindolyl)ethanol, via the methanesulfonate, and 4-fluorobenzoylpiperidine tosylate.

Melting point 150-152° C.

15

EXAMPLE 9

1-{2-[4-(4-Fluorobenzoyl)-1-piperidinyl]-1-ethyl}-3-

20 isopropyl-indol-2(3H)-one monohydrochloride : Prepared by Raney Nickel reduction of 1-{2-[4-(4-fluorobenzoyl)-1-piperidinyl]-1-ethyl}-3-isopropyl-3-methylthioindol-2(3H)-one as described above.

25 Melting point 207-209° C.

EXAMPLE 10

5-Bromo-3,3-dimethyloxindole : 3,3-Dimethyloxindole was  
5 dissolved in chloroform and stirred at room temperature  
under nitrogen. Bromine (1 equivalent) was added and the  
mixture was heated under reflux until HBr evolution ceased  
and the bromine colour was discharged from the solution.  
The solution was washed with sodium metabisulphite solution  
10 and sodium hydrogen carbonate solution, dried (MgSO<sub>4</sub>),  
filtered and concentrated to dry under reduced pressure to  
give 5-bromo-3,3-dimethyloxindole as a yellow solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.39 (6H s), 6.8 (1H d), 7.3 (2H m), 7.9 (1H  
15 broad)

2-(5-Bromo-3,3-dimethyloxindolyl)ethanol : Prepared from  
5-bromo-3,3-dimethyloxindole and 2-(2-  
chloroethoxy)tetrahydro-2H-pyran.

20

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.39 (6H s), 3.05 (1H broad), 3.95 (4H s),  
6.8 (1H d), 7.3 (2H m),

1-(2-[4-(4-Fluorobenzoyl)-1-piperidinyl]-1-ethyl)-5-bromo-  
25 3,3-dimethyl-indol-2(3H)-one monohydrochloride : Prepared  
from 2-(5-bromo-3,3-dimethyl oxindolyl)ethanol, via the  
methanesulfonate, and 4-fluorobenzoylpiperidine tosylate.

Melting point 208-211° C.

EXAMPLE 11

5

5-Methanesulfonyl-3,3-dimethyloxindole: 5-Bromo-3,3-dimethyloxindole was dissolved in freshly distilled tetrahydrofuran with tetramethylethylenediamine (2 equivalents) and was cooled to -75° C. under nitrogen.

10

nButyllithium (2.4 equivalents) was added and the mixture was stirred at -75° C. for 40 minutes. Dimethyl disulfide (1.2 equivalents) was added and the mixture was allowed to warm to room temperature. Water (5 ml) was added and the mixture was concentrated under reduced pressure, the

15

resulting oil was taken up in dichloromethane, washed with dilute hydrochloric acid, dried (MgSO<sub>4</sub>), filtered and concentrated to dry under reduced pressure. The resulting oil was taken up in acetic acid, sodium perborate (5 equivalents) was added and the mixture was stirred at 50° C.

20

overnight. The mixture was poured into water and extracted with ethyl acetate. The combined organic phases were washed with 2N sodium hydroxide solution, dried (MgSO<sub>4</sub>), filtered and concentrated under reduced pressure. Column

25

chromatography on silica gel (eluent ethyl acetate/hexane) gave 5-methane sulfonyl -3,3-dimethyloxindole as a pale yellow solid.

MS shows 240 (MH<sup>+</sup>) base peak and 257 (M+NH<sub>4</sub>).



2-(5-Methane sulfonyl-3,3-dimethyloxindolyl)ethanol:

Prepared from 5-methanesulfonyl-3,3-dimethyloxindole and 2-(2-chloroethoxy)tetrahydro-2H-pyran.

5

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.41 (6H s), 2.5 (1H broad), 3.05 (3H s), 3.95 (4H s), 7.18 (1H d), 7.76 (1H s), 7.84 (1H d)

1-{2-[4-(4-Fluorobenzoyl)-1-piperidinyl]-1-ethyl}-5-

10 methanesulfonyl-3,3-dimethyl-indol-2(3H)-one

monohydrochloride : Prepared from 2-(5-methanesulfonyl-3,3-dimethyl oxindolyl)ethanol, via the methanesulfonate, and 4-fluorobenzoyl piperidine tosylate.

15 Melting point 223-226° C.

EXAMPLE 12

20 2-(5-Fluoro-3,3-dimethyloxindolyl)ethanol: 5-Fluorooxindole (prepared according to the method of Clark et al., Synthesis (1991) 871) was dissolved in freshly distilled tetrahydrofuran with tetramethylethylenediamine (2 equivalents) and was cooled to -75° C. under nitrogen.

25 nButyllithium (2.4 equivalents) was added and the mixture was stirred at -75° C. for 40 minutes. Iodomethane (2.4 equivalents) was added and the mixture was allowed to warm to room temperature. After two hours' stirring at this

temperature, water (5 ml) was added and the mixture was concentrated under reduced pressure, the resulting oil was taken up in dichloromethane, washed with dilute hydrochloric acid, dried ( $\text{MgSO}_4$ ), filtered and concentrated to dry under reduced pressure to give a yellow oil. This oil was dissolved in N-methylpyrrolidone and stirred at room temperature under nitrogen. Sodium hydride (1.1 equivalents) was added and the mixture was stirred until gas evolution ceased. 2-(2-Chloroethoxy)tetrahydro-2H-pyran (1.05 equivalents) and Sodium Iodide (0.1 equivalents) was added and the mixture was warmed to  $75^\circ \text{C}$ . for 15 hours. Water was added and the mixture was concentrated under reduced pressure. The residue was taken up in ethyl acetate, washed (x 3) with water, dried ( $\text{MgSO}_4$ ), filtered and concentrated under reduced pressure. The resulting oil was taken up in methanol, paratoluenesulphonic acid (0.1 equivalents) was added and the mixture was stirred at room temperature for 12 hours. The mixture was concentrated under reduced pressure, taken up in ethyl acetate, washed (x 3) with aqueous sodium hydrogen carbonate solution dried ( $\text{MgSO}_4$ ), filtered and concentrated under reduced pressure. The resulting oil was purified by column chromatography on silica gel, (eluent hexane/ethyl acetate) to give 2(5-fluoro-3,3-dimethyloxindolyl)ethanol as a yellow oil.

MS shows 224 ( $\text{MH}^+$ ) base peak and 241 ( $\text{M}+\text{NH}_4$ )

1-(2-[4-(4-Fluorobenzoyl)-1-piperidinyl]-1-ethyl)-5-fluoro-3,3-dimethyl-indol-2(3H)-one monohydrochloride : Prepared from 2 (5-fluoro-3,3-dimethyl oxindolyl)ethanol, via the methanesulfonate, and 4-fluorobenzoyl piperidine tosylate as  
5 described above.

Melting point 221-223° C.

10 EXAMPLE 13

5,6-Difluorooxindole : 3,4-Difluoroacetonitrile was added dropwise to 90% fuming nitric acid stirred and cooled in an ice/water bath. After 15 hours' stirring the mixture was  
15 poured into water, neutralised with sodium bicarbonate and extracted into dichloromethane. The organic phase was dried (MgSO<sub>4</sub>), filtered and concentrated under reduced pressure. The resulting oil was dissolved in boron trifluoride acetic acid complex, water (1 ml) was added and the mixture was  
20 heated under reflux for three hours. The mixture was poured into water, the pH was adjusted to pH4 and the mixture was extracted with ethyl acetate. The organic phase was dried (MgSO<sub>4</sub>), filtered and concentrated under reduced pressure. The resulting oily solid was dissolved in acetic acid, iron  
25 powder was added and the mixture was heated under reflux for 1 hour. The mixture was filtered through Celite and concentrated under reduced pressure to a dark oil. Column

chromatography on silica gel (eluent chloroform/methanol) gave 5,6-difluorooxindole as an orange solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.48(2H s), 6.7(1H dd), 7.05(1H dd),  
5 8.65(1H broad)

2-(5,6-Difluoro-3,3-dimethyloxindolyl)ethanol: Prepared from 5,6-difluoro oxindole.

10 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.38(6H s), 3.20(1H broad), 3.84(4H m),  
6.7(1H dd), 7.03(1H dd)

1-(2-[4-(4-Fluorobenzoyl)-1-piperidinyl]-1-ethyl)-5-fluoro-3,3-dimethyl-indol-2(3H)-one monohydrochloride : Prepared  
15 from 2-(5-fluoro-3,3-dimethyl oxindolyl)ethanol, via the methanesulfonate, and 4-fluorobenzoyl piperidine tosylate as described above.

Melting point 223-225° C.

20

#### EXAMPLE 14

2-(4-Methoxy-3,3-dimethyloxindolyl)ethanol: Prepared from  
25 4-methoxyoxindole (prepared according to the method of Clark et al., Synthesis (1991) 871).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) d 1.42(6H s), 2.8(1H broad), 3.75(4H m),  
3.8(3H s), 6.57(2H t), 7.06(1H dd),

1-(2-[4-(4-Fluorobenzoyl)-1-piperidinyl]-1-ethyl)-4-methoxy-  
5 3,3-dimethyl-indol-2(3H)-one monohydrochloride : Prepared  
from 2-(4-methoxy-3,3-dimethyl oxindolyl)ethanol, via the  
methanesulfonate, and 4-fluorobenzoyl piperidine tosylate.

Melting point 224-227° C.

10

EXAMPLE 15

2-(3,3,5-Trimethyloxindolyl)ethanol : Prepared from  
15 3,3,5-trimethyloxindole (prepared by the method of Endler  
and Becker; Organic Syntheses Coll. vol. 4 page 657).

MS shows 220 (MH<sup>+</sup>) base peak and 237 (M+NH<sub>4</sub>)

20 1-(2-[4-(4-Fluorobenzoyl)-1-piperidinyl]-1-ethyl)-3,3,5-  
trimethyl-indol-2(3H)-one monohydrochloride : Prepared from  
2-(3,3,5-trimethyl oxindolyl)ethanol, via the  
methanesulfonate, and 4-fluorobenzoyl piperidine tosylate.

25 Melting point 228-230° C.

EXAMPLE 16

2-(5-Chloro-3,3-dimethyloxindolyl)ethanol : Prepared from  
5 5-chloro-3,3-dimethyloxindole (prepared by the method of  
Endler and Becker; Organic Syntheses Coll. vol. 4 page 657).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.39 (6H s), 3.05 (1H broad), 3.95 (4H s),  
6.8 (1H d), 7.3 (2H m),

10

1-{2-[4-(4-Fluorobenzoyl)-1-piperidinyl]-1-ethyl}-5-chloro-  
3,3-dimethyl-indol-2(3H)-one monohydrochloride : Prepared  
from 2-(5-chloro-3,3-dimethyl oxindolyl)ethanol, via the  
methanesulfonate, and 4-fluorobenzoyl piperidine tosylate.

15

Melting point 175-176° C.

EXAMPLE 17

20

2-(3,3,7-Trimethyloxindolyl)ethanol : Prepared from  
3,3,7-trimethyloxindole (prepared by the method of Endler  
and Becker; Organic Syntheses Coll. vol. 4 page 657).

25 MS shows 220 (MH<sup>+</sup>) base peak and 237 (M+NH<sub>4</sub>)

1-{2-[4-(4-Fluorobenzoyl)-1-piperidinyl]-1-ethyl}-3,3,7-  
trimethyl-indol-2(3H)-one monohydrochloride : Prepared from

2-(3,3,7-trimethyl oxindolyl)ethanol, via the  
methanesulfonate, and 4-fluorobenzoyl piperidine tosylate.

Melting point 150-152° C.

5

EXAMPLE 18

2-(5-Methoxy-3,3-dimethyloxindolyl)ethanol : Prepared from  
10 5-methoxy-3,3-dimethyloxindole (prepared by the method of  
Endler and Becker; Organic Syntheses Coll. vol. 4 page 657).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ1.39 (6H s), 3.05 (1H broad), 3.82 (3H s),  
3.95 (4H s), 6.8 (1H d), 7.3 (2H m),

15

1-(2-[4-(4-Fluorobenzoyl)-1-piperidinyl]-1-ethyl)-5-methoxy-  
3,3-dimethyl-indol-2(3H)-one monohydrochloride : Prepared  
from 2-(5-chloro-3,3-dimethyl oxindolyl)ethanol, via the  
methanesulfonate, and 4-fluorobenzoyl piperidine tosylate.

20

EXAMPLE 19

3,3,4-Trimethyloxindole and 3,3,6-Trimethyloxindole :  
25 Prepared from N-isobutyl-3-methylphenylhydrazide by the  
method of Endler and Becker; Organic Syntheses Coll. vol. 4  
page 657 and separated by preparative HPLC.

Melting point - 3,3,4-Trimethyloxindole -133° C.

Melting point - 3,3,6-Trimethyloxindole -178° C.

5 2-(3,3,4-Trimethyloxindolyl)ethanol : Prepared from 3,3,4-trimethyloxindole (prepared by the method of Endler and Becker; Organic Syntheses Coll. vol. 4 page 657) as described above.

10 MS shows 220 (MH<sup>+</sup>) base peak and 237 (M+NH<sub>4</sub>)

1-{2-[4-(4-Fluorobenzoyl)-1-piperidinyl]-1-ethyl}-3,3,4-trimethyl-indol-2(3H)-one monohydrochloride : Prepared from 2-(3,3,4-trimethyl oxindolyl)ethanol, via the methanesulfonate, and 4-fluorobenzoyl piperidine tosylate as described above.

Melting point 211-214° C.

20

EXAMPLE 20

2-(3,3,6-Trimethyloxindolyl)ethanol : Prepared from 3,3,6-trimethyloxindole (prepared by the method of Endler and Becker; Organic Syntheses Coll. vol. 4 page 657) as described above.

MS shows 220 (MH<sup>+</sup>) base peak and 237 (M+NH<sub>4</sub>)



1-(2-[4-(4-Fluorobenzoyl)-1-piperidinyl]-1-ethyl)-3,3,6-trimethyl-indol-2(3H)-one monohydrochloride : Prepared from 2-(3,3,6-trimethyl oxindolyl)ethanol, via the  
5 methanesulfonate, and 4-fluorobenzoyl piperidine tosylate as described above.

Melting point 198.5-200.5° C.

10

EXAMPLE 21

1-(2-Chloroethyl)-1,3-dihydro-2H-indol-2-one : 1-(2-Chloroethyl)-1H-indole-2,3-dione [C.A. Reg no. 77218-99-6]  
15 was suspended in acetic acid and hydrogenated at 60 p.s.i., at room temperature, in the presence of 70% perchloric acid and 5% palladium on charcoal for 24 hours. The clear solution was filtered and concentrated under reduced pressure. The residue was purified by chromatography on  
20 silica gel, eluent chloroform, to give 1-(2-Chloroethyl)-1,3-dihydro-2H-indol-2-one as a white solid.

Melting point 74° C.

25 1-(2-[4-(4-Fluorobenzoyl)-1-piperidinyl]-1-ethyl)-1,3-dihydro-2H-indol-2-one hydrochloride : 1-(2-Chloroethyl)-1,3-dihydro-2H-indol-2-one and 4-fluorobenzoyl piperidine (1 equivalent as its paratoluenesulphonate salt) were added to a

solution of sodium carbonate (8 equivalents) and water. The mixture was stirred mechanically at reflux for 9 hours. The hot solution was cooled (ice-water bath) and the hard solid was broken up, filtered, washed with water and dried. The solid was purified by chromatography on silica gel, eluent chloroform-1% methanol, to give an oil. The pure freebase was dissolved in a little chloroform, ethanolic HCl was added, the solution was evaporated to dryness and triturated with ether to give 1-(2-[4-(4-fluorobenzoyl)-1-piperidinyl]-1-ethyl)1,3-dihydro-2H-indol-2-one hydrochloride as a white solid.

Melting point 205° C.

15

EXAMPLE 22

1-(2-Chloroethyl)-5-fluoro-1H-indole-2,3-dione :

5-Fluoroisatin was dissolved in dimethylformamide. Sodium hydride (60% dispersion in mineral oil) (1.2 equivalents) was added in portions with stirring and cooling (ice-water bath) and the mixture was stirred until gas evolution ceased.

1-Bromo-2-chloroethane (1.2 equivalents) was added dropwise. The mixture was stirred at room temperature for 24 hours and then quenched into water and extracted into chloroform. The combined organic phases were washed with water, dried (MgSO<sub>4</sub>), filtered and concentrated under reduced pressure. The resulting oil was purified by chromatography on silica

gel, eluent chloroform, to give 1-(2-Chloroethyl)-5-fluoro-1H-indole-2,3-dione as a red solid.

Melting point 103° C.

5

1-(2-chloroethyl)-1,3-dihydro-5-fluoro-2-oxo-2H-indole-3-spiro-2'-1,3 dithiane

A solution of 1-(2-chloroethyl)-5-fluoro-1H-indole-2,3-dione, propanedithiol (1.2 equivalents) in chloroform was added dropwise to a stirred solution of boron trifluoride etherate in acetic acid and chloroform which was maintained at a gentle reflux throughout the addition. After 6 hours' reaction the mixture was cooled, washed with water and sodium hydrogen carbonate solution, dried (MgSO<sub>4</sub>) and filtered through a pad of flash silica using chloroform as eluent. The combined fractions were evaporated under reduced pressure to give 1-(2-chloroethyl)-1,3-dihydro-5-fluoro-2-oxo-2H-indole-3-spiro-2'-1,3 dithiane.

15  
20

Melting point 122° C.

EXAMPLE 23

25

1-(2-Chloroethyl)-5-fluoro-1,3-dihydro-2H-indole-2-one :  
1-(2-chloroethyl)-1,3-dihydro-5-fluoro-2-oxo-2H-indole-3-spiro-2'-1,3 dithiane was dissolved in a mixture of

ethanol/tetrahydrofuran (3:2). Raney nickel was added and the mixture was heated under reflux with vigorous stirring for 3 hours. The cooled solution was filtered, evaporated under reduced pressure and triturated with ether to give  
5 1-(2-Chloroethyl)-5-fluoro-1,3-dihydro-2H-indole-2-one as a white solid.

Melting point 127° C.

10 1-{2-[4-(4-Fluorobenzoyl)-1-piperidinyl]-1-ethyl}-5-fluoro-1,3-dihydro-2H-indol-2-one hydrochloride : Prepared from 1-(2-chloroethyl)-5-fluoro-1,3-dihydro-2H-indole-2-one and 4-fluorobenzoyl piperidine (1 equivalent as its paratoluenesulphonate salt) by the aqueous coupling procedure  
15 described above.

Melting point 221-223° C.

20 EXAMPLE 24

1-(2-Chloroethyl)-3,3-difluorooxindole : 1-(2-Chloroethyl)-1H-indole-2,3-dione [C.A. Reg no. 77218-99-6] was heated to 65° C. under nitrogen in diethylaminosulfur trifluoride.  
25 The reaction mixture was poured onto water and extracted with chloroform. The organic phase was washed with sodium hydrogen carbonate solution, dried (MgSO<sub>4</sub>) and filtered to give 1-(2-chloroethyl)-3,3-difluorooxindole as a dark oil.

MS shows 231 and 233 (MH<sup>+</sup>)

1-{2-[4-(4-Fluorobenzoyl)-1-piperidinyl]-1-ethyl}-3,3-

5 difluoro-indol-2(3H)-one monohydrochloride :

1-(2-Chloroethyl)-3,3-difluorooxindole, 4-fluorobenzoyl  
piperidine (1 equivalent as its paratoluenesulphonate salt),  
potassium carbonate (3 equivalents) and potassium iodide  
(0.1 equivalents) were dissolved in N-methyl pyrrolidone and  
10 heated with stirring to 85° C. for 6 hours. The reaction  
mixture was poured into water and extracted into ethyl  
acetate. dried (MgSO<sub>4</sub>), filtered and concentrated under  
reduced pressure. The resulting oil was purified by  
chromatography on silica gel, eluent hexane/ethyl acetate,  
15 to give a yellow oil. The oil was dissolved in ethanol,  
ethanolic HCl was added and the mixture was concentrated  
under reduced pressure to give a white solid. This was  
taken up in hot ethyl acetate and refrigerated whereupon a  
white solid precipitated, this was collected by filtration  
20 to give 1-{2-[4-(4-Fluorobenzoyl)-1-piperidinyl]-1-ethyl}-  
3,3-difluoro-indol-2(3H)-one monohydro chloride.

Melting point 202-205° C.

EXAMPLE 25

1-(2-Chloroethyl)-3,3,5-triifluorooxindole : Prepared from  
5 1-(2-chloroethyl)-5-fluoro-1H-indole-2,3-dione and  
diethylaminosulfur trifluoride.

MS shows 249 and 251 (MH<sup>+</sup>)

10 1-{2-[4-(4-Fluorobenzoyl)-1-piperidinyl]-1-ethyl}-3,3,5-  
trifluoro-indol-2(3H)-one monohydrochloride : Prepared from  
1-(2-chloroethyl)-3,3,5-trifluorooxindole and  
4-fluorobenzoyl piperidine.

15 Melting point 209-212° C.

EXAMPLE 26

20 3-Cyclopropyl oxindole: 60% Sodium hydride (2.4 g, 60 mmols)  
was suspended in dimethylformamide (15 mls) and cooled to  
0° C. N-acetyl oxindole (prepared by the method of  
Robertson et al., J. Med. Chem. 1986 page 1832) was added  
dropwise as a dimethylformamide(80 mls) solution over  
25 20 minutes. Mixture stirred at ambient temperature for  
20 minutes then 1,2-dibromoethane added dropwise at 10° C.  
Mixture stirred at ambient temperature for 48 hours. Water  
(20 mls) added and mixture concentrated *in vacuo*. 0.5 M

hydrochloric acid (80 mls) added and mixture extracted with chloroform (2 x 100 mls). Washed with 0.5 M hydrochloric acid (3 x 50 mls) and brine (50 mls). Dried over magnesium sulphate, filtered and concentrated *in vacuo* then columned  
5 on flash silica eluent chloroform-2% methanol.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ 1.54 (2H m), 1.78 (2H m), 6.82 (1H d), 7.02 (2H m), 7.22 (1H m), 9.0 (1H broad)

10

EXAMPLE 27

2-(3-cyclopropyl oxindolyl)ethanol : Prepared from  
3-cyclopropyloxindole and 2-(2-chloroethoxy)tetrahydro-2H-  
15 pyran.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ 1.54 (2H m), 1.78 (2H m), 3.85 (4H m), 6.82 (1H d), 7.02 (2H m), 7.22 (1H m)

20 1-(2-(4-(4-fluorobenzoyl)-1-piperidinyl)-1-ethyl)-1,3-dihydro-3-spiro-1-cyclopropyl-2H-indole-2-one monohydrochloride : Prepared from 2-(3-cyclopropyl oxindolyl)ethanol via the methanesulfonate, and 4-fluorobenzoylpiperidine tosylate.

25

Melting point 238-240° C.

EXAMPLE 28

2-(3-Phenyl-3-methyloxindolyl)ethanol : Prepared from  
3-phenyl-3-methyloxindole (prepared by the method of Endler  
5 and Becker; Organic Syntheses Coll. vol. 4 page 657) and  
2-(2-chloroethoxy)tetrahydro-2H-pyran.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ1.78 (3H s), 6.82 (1H d), 7.02 (2H m), 7.22  
(1H m), 7.3 (5H m), 9.25 (1H broad)

10

1-(2-(4-(4-fluorobenzoyl)-1-piperidinyl)-1-ethyl)-3-methyl-  
3-phenyl-1,3-dihydro-2H-indol-2-one monohydrochloride :

Prepared from 2-(3-phenyl-3-methyloxindolyl)ethanol via the  
methanesulfonate, and 4-fluorobenzoylpiperidine tosylate.

15

Melting point 215-216° C.

EXAMPLE 29

20

Tablets each containing 10 mg of active ingredient are made  
up as follows:



	Active ingredient	10 mg
	Starch	160 mg
	Microcrystalline cellulose	100 mg
5	Polyvinylpyrrolidone (as 10% solution in water)	13 mg
	Sodium carboxymethyl starch	14 mg
	Magnesium stearate	3 mg
		_____
	Total	300 mg

10

The active ingredient, starch and cellulose are mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders and passed through a sieve. The granules so produced are dried and re-passed through a

15 sieve. The sodium carboxymethyl starch and magnesium stearate are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 300 mg.

20

EXAMPLE 30

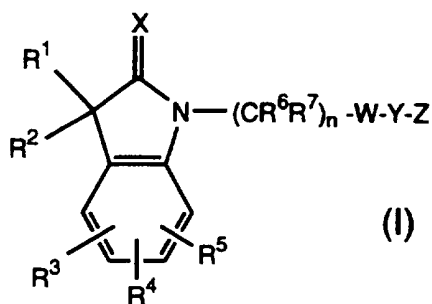
Capsules each containing 20 mg of medicament are made as follows:

	Active ingredient	20 mg
	Dried starch	178 mg
	Magnesium stearate	2 mg
5		_____
	Total	200 mg

The active ingredient, starch and magnesium stearate are  
passed through a sieve and filled into hard gelatine  
10 capsules in 200 mg quantities.

CLAIMS

1. A compound of the formula:



5

in which

R<sup>1</sup> and R<sup>2</sup> are each hydrogen, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy,  
10 HO-C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy-C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkylthio,  
halo, Ph, PhCR'R''- where Ph is optionally substituted  
phenyl and R' and R'' are each hydrogen or C<sub>1-4</sub> alkyl,  
or R<sup>1</sup> and R<sup>2</sup> together with the carbon atom to which  
they are attached form a C<sub>3-6</sub> cycloalkyl group, >C=O,  
15 >C=NOR' where R' is hydrogen or C<sub>1-4</sub> alkyl,

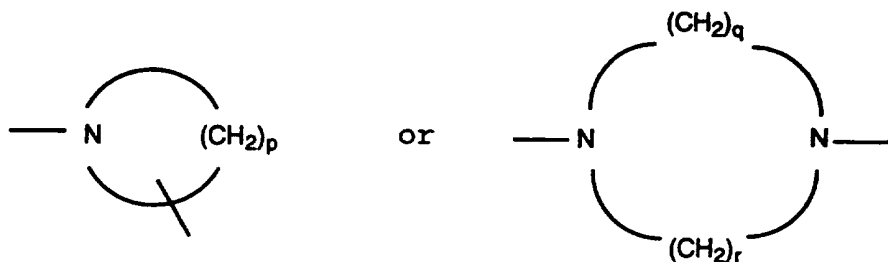
R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are each hydrogen, halo, nitro, C<sub>1-4</sub>  
alkyl, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkylthio, C<sub>1-4</sub> alkyl-CO-, C<sub>1-4</sub>  
alkyl-S(O)<sub>m</sub>- where m is 0, 1 or 2, R'R''N-SO<sub>2</sub>-, -COOR',  
20 -CONR'R'', -NR'R'', -N(OR')COOR'', -COR', -NHSO<sub>2</sub>R',  
where R' and R'' are each hydrogen or C<sub>1-4</sub> alkyl,

R<sup>6</sup> and R<sup>7</sup> are each hydrogen or C<sub>1-4</sub> alkyl, and n is 1 to  
6,

X is oxygen or sulphur,

W is

5



where p is 4 to 7, and q and r are each 1 to 3,

10

Y is  $\text{>CO}$  or  $\text{-CH(OH)-}$ ,

and

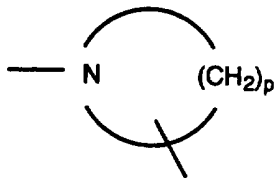
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Z is optionally substituted phenyl or optionally substituted heteroaryl;

and salts and esters thereof.

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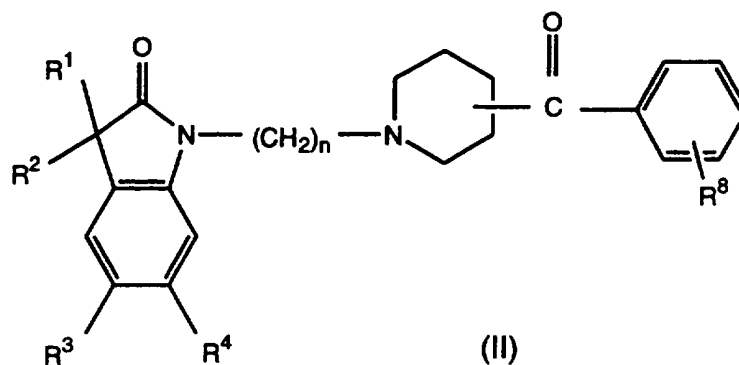
2. A compound according to claim 1 in which X is oxygen and W is:



3. A compound according to either of claims 1 and 2 in which Z is optionally substituted phenyl.

4. A compound of the formula:

5



10 in which  $R^1$  and  $R^2$  are each hydrogen or  $C_{1-4}$  alkyl,  $R^3$  and  $R^4$  are each hydrogen,  $C_{1-4}$  alkyl or halo,  $n$  is 2, and  $R^8$  is hydrogen or halo. A particularly preferred group is one in which  $R^1$  and  $R^2$  are both methyl, or  $R^1$  is hydrogen and  $R^2$  is methyl,  $R^3$  and  $R^4$  are both hydrogen,  $n$  is 2 and  $R^8$  is halo, preferably fluoro, and salts thereof.

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5. A compound according to claim 1 or a pharmaceutically-acceptable salt or ester thereof, for use as a pharmaceutical.

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6. A pharmaceutical formulation comprising a compound according to claim 1 or a pharmaceutically-acceptable salt or ester thereof together with a pharmaceutically-acceptable carrier or diluent therefor.



Application No: GB 9525963.6  
Claims searched: 1-6

Examiner: Roy Honeywood  
Date of search: 5 March 1996

**Patents Act 1977  
Search Report under Section 17**

**Databases searched:**

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:  
UK CI (Ed.O): C2C (CTT CQZ)  
Int CI (Ed.6): C07D  
Other: ONLINE: CAS

**Documents considered to be relevant:**

Category	Identity of document and relevant passage	Relevant to claims
	None	

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.