COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952-1973

APPLICATION FOR A PATENT

We, THE WELLCOME FOUNDATION LIMITED

of Unicorn House, 160 Euston Road, LONDON NW1 2BP, ENGLAND

hereby apply for the grant of a Patent for an invention entitled:

HALOGEN SUBSTITUTED DIPHENYL SULFIDES

which is described in the accompanying complete specification. This Application is a Convention Application and is based on the Application numbered: 8912971-2 for a Patent or similar protection made in United Kingdom on 6 June 1989.

Our address for service is:

GRIFFITH HACK & CO
71 YORK STREET
SYDNEY NSW 2000

DATED this 5th day of June 1990

THE WELLCOME FOUNDATION LIMITED
By their Patent Attorney

GRIFFITH HACK & CO

TO: THE COMMISSIONER OF PATENTS
COMMONWEALTH OF AUSTRALIA
ASSIGNEE - APPLICANT

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952 (AS AMENDED)

DECLARATION IN SUPPORT OF AN APPLICATION FOR A PATENT

In support of an Application made by:
THE WELLCOME FOUNDATION LIMITED

for a patent for an invention entitled:
HALOGEN SUBSTITUTED DIPHENYLSULFIDES

Michael Peter Jackson
Of LANGLEY COURT, BECKENHAM, KENT BR3 3BS, ENGLAND.

Do solemnly and sincerely declare as follows:

1. I am authorised by the above mentioned applicant for the patent to make this declaration on its behalf.

2. The name and address of each actual inventor of the invention is as follows:

   NARIMAN BOMANSHAW MEHTA
   4207 UNION STREET,
   RALEIGH,
   NORTH CAROLINA 27609,
   USA.

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   NORTH CAROLINA 27707,
   USA.

3. The basic application(s) as defined by Section 141 of the Act was(ware) made as follows:

   Country: UNITED KINGDOM
   on 6th June 1989
   in the name(s) THE WELLCOME FOUNDATION LIMITED
   and in the name(s) THE WELLCOME FOUNDATION LIMITED
   and in the name(s) THE WELLCOME FOUNDATION LIMITED
   and in the name(s) THE WELLCOME FOUNDATION LIMITED

4. The basic application(s) referred to in the preceding paragraph of this Declaration was(ware) the first application(s) made in a Convention country in respect of the invention the subject of this application.

Declared at BECKENHAM, this 15th day of May 1990

Signed: Griffith Hassel & Frazer
Position: HEAD GROUP PATENTS & AGREEMENTS

GRIFFITH HASSEL & FRAZER, P.O. BOX 2133, G.P.O., SYDNEY, N.S.W. 2001
AUSTRALIA
Title
HALOGEN SUBSTITUTED DIPHENYLSULFIDES

International Patent Classification(s)
C07C 323/32  C07C 319/20  C07C 323/62  A61K 031/135

Application No.: 56841/90
Application Date: 05.06.90

Priority Data
Number: 8912971
Date: 06.06.89
Country: GB UNITED KINGDOM

Publication Date: 13.12.90

Applicant(s)
THE WELLCOME FOUNDATION LIMITED

Inventor(s)
NARIMAN BOMANSHAW MEHTA; LAWRENCE EDWARD BRIEADDY; CLAUDIA ELIZABETH BAXTER HOLLINGSWORTH; BARRETT RANDOLPH COOPER

Attorney or Agent
GRIFFITH HACK & CO. SYDNEY

Claim

1. A compound of the formula (I)

\[ \text{CH}_2\text{OH} \quad \text{CH}_2\text{NRR'} \]

\[ \text{Z} \quad \text{S} \quad \text{S} \quad \text{Z} \]

\[ (\text{I}) \]

wherein R and R' are the same or different and are each hydrogen or straight or branched alkyl of 1 to 6 carbon atoms and Z is halo, or a pharmaceutically acceptable ester or salt thereof.

9. A compound of formula (IV)

\[ \text{CHO} \quad \text{CONRR'} \]

\[ \text{Z} \quad \text{S} \quad \text{S} \quad \text{Z} \]

\[ (\text{IV}) \]

wherein Z is halo and R and R' are the same or different and
are each hydrogen or straight or branched alkyl of 1 to 6 carbon atoms.

10. A compound of formula (VA) and/or (VB)

\[
\begin{align*}
\text{(VA)} & \quad \begin{array}{c}
\text{CH}_3\text{OH} \\
\text{Z}
\end{array} \\
\text{CONR}^1
\end{align*}
\]

\[
\begin{align*}
\text{(VB)} & \quad \begin{array}{c}
\text{CHO} \\
\text{Z}
\end{array} \\
\text{CH}_2\text{NR}^1
\end{align*}
\]

wherein Z is halo and R and R\(^1\) are the same or different and are each hydrogen or straight or branched alkyl of 1 to 6 carbon atoms.

11. A compound of formula (VIII)

\[
\begin{align*}
\text{(VIII)} & \quad \begin{array}{c}
\text{CO}_2\text{H} \\
\text{Z}
\end{array} \\
\text{CN}
\end{align*}
\]

wherein Z is halo.

12. A compound of formula (IXA) and/or (IXB)
13. A pharmaceutical formulation which comprises a compound of formula (I) or pharmaceutically acceptable ester or salt thereof according to any one of claims 1 to 7 in association with a pharmaceutically acceptable carrier.
COMMONWEALTH OF AUSTRALIA
PATENTS ACT 1952
COMPLETE SPECIFICATION
FOR OFFICE USE

Short Title: 
Int. Cl: 

Application Number: 
Lodged: 

Complete Specification-Lodged: 
Accepted: 
Lapsed: 
Published: 

Priority: 

Related Art: 

TO BE COMPLETED BY APPLICANT

Name of Applicant: THE WELLCOME FOUNDATION LIMITED
Address of Applicant: Unicorn House, 160 Euston Road, LONDON NW1 2BF, ENGLAND
Actual Inventor: Nariman Bomanshaw Mehta; Lawrence Edward Brileaddy; Claudia Elizabeth Baxter Hollingsworth and Barrett Randolph Cooper
Address for Service: GRIFFITH HASSEL & CO
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Complete Specification for the invention entitled:
HALOGEN SUBSTITUTED DIPHENYLSULFIDES

The following statement is a full description of this invention, including the best method of performing it known to us:-

15431-V:AMP:RK
HALOGEN SUBSTITUTED DIPHENYSULFIDES

The present invention relates to halogen-substituted diphenylsulfides, processes for their preparation, pharmaceutical formulations containing them, and their use in medicine, in particular, for the treatment of depression.


The compounds of the present invention selectively inhibit serotonin uptake in brain to a degree which is surprisingly better than the compounds disclosed in UK Patent Specification 1,561,072. The compounds of the present invention are therefore useful in the treatment of depression in mammals.

In particular, the present invention is directed to compounds represented by formula (I)

\[
\begin{align*}
\text{CH}_2\text{OH} & \quad \text{CH}_2\text{NRR}^1 \\
\text{Z} & \quad \text{S} \\
\text{R} & \quad \text{R}^1
\end{align*}
\]

where Z is halo, e.g., fluoro, bromo, iodo, or, preferably, chloro, R and R^1 are the same or different and are each hydrogen or straight or

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branched alkyl of 1 to 6 carbon atoms, most preferably methyl; pharmaceutically acceptable esters; and salts thereof.

Compounds of formula (I) having particularly good antidepressant properties are those wherein $R$ and $R^1$ are selected from $H$ and $\text{CH}_3$ and $Z$ is chloro, and pharmaceutically acceptable esters and salts thereof.

Pharmaceutically acceptable esters of formula (I) include carboxylic acid esters in which the non-carbonyl moiety of the ester grouping is selected from straight or branched chain alkyl (e.g., methyl, n-propyl, t-butyl), alkoxyalkyl (e.g., methoxymethyl), aralkyl (e.g., benzyl), aryloxyalkyl (e.g., phenoxymethyl), aryl (e.g., phenyl) optionally substituted by halogen, $C_{1-4}$ alkyl or $C_{1-4}$ alkoxy, nitro or amino; sulfonate esters such as alkylsulfonyl; or alkylarylsulfonyl (e.g., methanesulfonyl or tosylsulfonyl); and amino acid esters such as the aliphatic and aromatic amino acid esters (e.g., Gly, Ala, Val, Leu, Ile, Phe, Tyr and Trp) and other naturally occurring amino acid esters as well as the ester of $\beta$-alanine. Pharmaceutically acceptable acid addition salts of the esters are within the scope of this invention and, where the ester moiety itself contains an amino group, diacid addition salts. In the above ester groups, the alkyl groups (including those in alkoxy groupings) contain 1 to 12 carbon atoms, preferably 1 to 4 carbons, and the aryl groups are preferably phenyl or naphthyl.

Acid addition salts of the compounds of formula (I) are within the scope of the present invention. Such salts include those which may be used in intermediate process operations as well as those which are acceptable as final pharmaceutical products. Examples of pharmaceutically acceptable salts of formula (I) are those prepared from e.g., hydrochloric, sulfuric, phosphoric, toluenesulfonic, maleic, fumaric, tartaric, citric, pamoic, succinic, and nitric acids.

The compounds of formula (I) are serotonin uptake inhibitors as demonstrated by their ability to block the uptake of biogenic amines.
in rat synaptosomal preparations. The compounds of formula (I) and pharmaceutically acceptable salts and esters thereof are useful in the treatment of depression in mammals, including humans.

The present invention provides a compound of formula (I) or a pharmaceutically acceptable salt or ester thereof for use in medicine. There is further provided the use of a compound of formula (I) or a pharmaceutically acceptable salt or ester thereof in the manufacture of a medicament for treating depression. Additionally, there is provided a method of treating depression in humans which comprises administering to a patient an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or ester thereof.

Preferred compounds of formula (I) are:

5-chloro-2-(((dimethylamino)methyl)phenyl)thio)benzyl alcohol
5-chloro-2-(((methylamino)methyl)phenyl)thio)benzyl alcohol
and pharmaceutically acceptable salts and esters thereof, particularly
5-chloro-2-(((dimethylamino)methyl)phenyl)thio)benzyl acetate

The compounds of formula (I) may be synthesized by any method known in the art for making compounds of an analogous structure.
The compounds of formula (I) may be prepared as indicated in the following reaction scheme:

\[
\text{(II)} + \text{(III)} \rightarrow \text{(IV)}
\]

\[
\text{(II)} \quad \text{(III)} \quad \text{(IV)}
\]

and/or

\[
\text{(VA)} \rightarrow \text{(I)}
\]

\[
\text{and/or} \quad \text{(VB)} \rightarrow \text{(I)}
\]
where L is a leaving group eg. chloro, and Z, R and R₁ are as hereinbefore defined; and optionally forming a pharmaceutically acceptable ester or salt thereof.

The preparation of a compound of formula (IV) may be carried out in a suitable polar solvent for example, in dimethylformamide, dimethylacetamide or dimethylsulfoxide, in the presence of a base, eg., potassium carbonate, at a temperature in the range of 20°C to 200°C.

The reduction of a compound of formula (IV) to the compound of formula (I) may be carried out with a hydride reducing agent, for example, diborane or lithium aluminum hydride at a temperature from 20 - 70°C. The reduction proceeds through the intermediate of formula (VA) and/or (VB) which may optionally be isolated. Preferably however, the reduction of a compound of formula (IV) to a compound of formula (I) is carried out in a single operation.

Compounds of formula (II) may be prepared by oxidation of the corresponding alcohol which may itself be prepared by the reduction of the corresponding carboxylic acid. Compounds of formula (III) may be prepared by amidation of the corresponding carboxylic acid which itself may be obtained by the oxidation of the corresponding aldehyde. Compounds of formula (II) and (III) may be prepared by the methods described in Bondinell et al., J.Med.Chem., 23(5), 506, (1980) and Schindlbauer, Monatsh Chem., 99(5), 1799 (1968).

Compounds of formulae (IV), (VA) and (VB) are novel and represent useful intermediates and are also within the scope of the present invention.

Esters of formula (I) may be prepared by methods well known in the art of organic chemistry, for example, treatment of the alcohol with an acid halide in the presence of an appropriate acid acceptor such as triethylamine.

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Acid addition salts may be prepared by reaction with a suitable solvent and the appropriate acid.

Alternatively, compounds of formula (I) may be prepared as indicated in the following reaction scheme:

\[
\begin{align*}
\text{(VI)} & \quad \text{(VII)} & \quad \text{(VIII)} \\
\text{and/or} & \\
\text{(IXA)} & \\
\text{(IXB)}
\end{align*}
\]

where Z is as defined hereinbefore; and optionally converting the resulting compound of formula (I), wherein R and R₁ are both hydrogen, into another compound of formula (I), as defined hereinbefore; and

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optionally forming a pharmaceutically acceptable ester or salt thereof.

The reaction leading to the compound of formula (VIII) may be carried out in a suitable polar, aprotic solvent such as dimethylformamide or dimethylacetamide, in the presence of an alkali metal lower alkoxide, for example, sodium methoxide or potassium carbonate.

The compound of formula (VIII) may be reduced to a compound of formula (I) using, for example, diborane or lithium aluminium hydride at a temperature from 20 to 100°C. This reduction proceeds through the intermediate compounds of formula (IXA) and/or (IXB) which may optionally be isolated. Preferably, however, the preparation of a compound of formula (I), wherein R and R' are H, is obtained from a compound of formula (VIII) in a single operation.

The optional conversion of the resulting compound into another compound of formula (I) may be carried out by methods well known in the art of organic chemistry, for example in the case where R and/or R' is methyl, by reaction with an aldehyde such as formaldehyde in the presence of acid, such as formic acid.

Compounds of formulae (VIII), (IXA) and (IXB) are novel and represent useful intermediates and are also within the scope of the present invention.

Pharmaceutically acceptable esters and salts of the compounds of formula (I) may be prepared as described previously.

The compounds of formula (I) and pharmaceutically acceptable esters and salts thereof may be used in treating depression of three main types: neurotic or reactive depression with anxiety, somatic concern and tension; psychotic or endogenous depression with emotional withdrawal, motor retardation, blunted affect, guilt feelings and conceptual disorganisation; and a group showing features of both

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neurotic and psychotic depression with hostility and suspiciousness. Compounds of formula (I) and pharmaceutically acceptable esters and salts thereof may also be used for the treatment of anxiety, obsessive compulsive disorders, and alcoholism. Compounds of formula (I) and pharmaceutically acceptable esters and salts thereof may also be used to potentiate the analgesic effect of morphine. (See Diagnostics and Statistical Manual of Mental Disorders, third edition, Revised 1987, for descriptions of the above mentioned disorders).

The compounds of this invention or pharmaceutically acceptable esters or salts thereof may be administered orally, parenterally or rectally. The preferred antidepressant dosage for parenteral administration of a compound of formula (I) (calculated as the base) is 0.5 mg/kg to 40 mg/kg of mammal body weight per day, and the most preferred dosage is 1 mg/kg to 10 mg/kg of mammal body weight per day.

For the oral and rectal mode of administration, the preferred antidepressant dosage of a compound of formula (I) (calculated as the base) is about 1 mg/kg to 50 mg/kg of mammal body weight per day, while the most preferred dosage (estimated as the base) is 1 mg/kg to 20 mg/kg of mammal body weight per day. A compound of formula (I), or a pharmaceutically acceptable ester or salt thereof, is preferably administered four times daily although the number of daily administrations of the medication and the total dose will vary according to the mammal being treated, and according to the exercise of the physician's discretion.

For example, for the treatment of depression in humans, the preferred unit dosage of a compound of formula (I) or a pharmaceutically acceptable ester or salt thereof (calculated as the base) for oral administration, or administration as a suppository, is about 1 mg to 200 mg, with the more preferred unit dosage being about 5 mg to
100 mg, and the most preferred unit dosage being about 10 mg to 50 mg. All the above doses are given in terms of the weight of a compound of formula (I) in the form of its base, but as will be appreciated from the foregoing information, doses are preferably administered in the form of a pharmaceutically acceptable ester or salt of a compound of formula (I). The preferred dosage for the treatment of anxiety, obsessive compulsive disorders and alcoholism are the same as dosages described above for the treatment of depression. For decreasing the amount of morphine required for analgesia the preferred dosage of compounds of formula (I) and pharmaceutically acceptable esters and salts thereof (calculated as the base) are three or four times greater than the dosages required for depression, anxiety or obsessive compulsive disorders.
According to the present invention, in yet another aspect, there is provided a pharmaceutical composition, preferably in unit dosage form, comprising a compound of formula (I), or a pharmaceutically acceptable ester or salt thereof, together with a pharmaceutically acceptable carrier.

A pharmaceutical composition containing a compound of formula (I), or a pharmaceutically acceptable ester or salt thereof, may be presented in discrete units such as tablets, capsules, ampoules (i.e., for injection), suppositories or liposomes each containing an effective antidepressant non-toxic amount of the compound and one or more pharmaceutically acceptable carriers.

Conveniently the compound of formula (I) or a pharmaceutically acceptable ester or salt thereof comprises from 5 to 95% by weight of the composition.

The pharmaceutical compositions may be in the form of an oral unit dose preparation for example a cachet, tablet or capsule. Suitable pharmaceutically acceptable carriers for such compositions include solid diluents such as lactose, cornstarch, micronized silica gel, or merely the capsule shell as well as other excipients well known in the art for this purpose.

The pharmaceutical compositions may further take the form of those suitable for rectal use as a suppository with the usual pharmaceutically acceptable carriers such as cocoa butter. Those for parenteral use include an ampoule of a sterile solution or suspension with water or other pharmaceutically acceptable liquid as the carrier therefor, or an ampoule of a sterile powder for dilution with a pharmaceutically acceptable liquid.

It should be understood that in addition to the aforementioned ingredients, the pharmaceutical compositions of this invention may include one or more of additional ingredients such as diluents,
buffers, flavoring agents, binders, surface active agents, thickeners, lubricants, preservatives, and the like. The compositions may be prepared by admixture of the ingredients, and, if necessary, shaping the resulting mass, and filling into suitable containers.

The following examples are provided by way of an illustration of the present invention and should in no way constitute a limitation thereof.
EXAMPLE 1

Preparation of 2-((4-Chloro-2-formylphenyl)thio)-N,N-dimethylbenzamide

Potassium carbonate (27.6 g) was added to a solution of 2,5-dichlorobenzaldehyde (30.2 g) (Bondinelli et al., J. Med. Chem., 23(5), 506 (1980)) and 2-thio-N,N-dimethylbenzamide (Schindlbauer, Monatsh. Chem., 99(5), 1799 (1968)) (36.3 g) in 500 mL of dimethylformamide. The reaction mixture was stirred at 160°C for four hours, added to 2.5 liters of chilled water and extracted with EtOAc to give 50.2 g of a tan solid. Recrystallisation from acetone/hexane mixtures gave 43.5 g (80% yield) of 2-((4-chloro-2-formylphenyl)thio)-N,N-dimethylbenzamide, m.p. 87°-88°C.

Anal.Cald. for C_{16}H_{14}ClNO_2S; C 60.09; H 4.41; N 4.38; S 10.03
Found: C 60.16; H 4.42; N 4.36; S 9.97.

EXAMPLE 2

Preparation of 5-Chloro-2-((2-dimethylamino)methyl)phenyl)thio)-benzyl Alcohol

2-((4-Chloro-2-formylphenyl)thio)-N,N-dimethylbenzamide (10.0 g) was dissolved in 80 mL of anhydrous tetrahydrofuran and, under nitrogen, added to 80 mL of 1.0 M diborane at room temperature. The reaction mixture was refluxed for 2 hr and then stirred at room temperature for 17 hr. The reaction mixture was treated with 100 mL of 50% HCl, warmed on a steam bath for 1 hr and concentrated in vacuo. Treatment with solid NaOH and extraction with EtOAc gave the free base as a yellow oil. This base was dissolved in ether. To the resulting clear solution was added an excess of etherial HCl. The resulting
Hydrochloride salt was recrystallized from MeOH/EtOAc mixtures to give 7.4 g (70% yield) of 5-chloro-2-((2-((dimethylamino)methyl)phenyl)thio)benzyl alcohol hydrochloride, m.p. 176°-177°C.

Anal. Calc'd for C_{16}H_{11}Cl NOS.HCl: C, 55.81; H 5.56; N 4.07; S 9.31;
Found C, 55.73; H 5.59; N 4.06; S 9.25;

\( \delta \)NMR(MeSO-d$_6$): 6.98 (s, 1, NH), 6.96-7.93 (m, 7H, aromatic), 5.60 (s, 1, OH), 4.54 (s, 2H, OCH$_2$), 4.42 (s, 2H, NOCH$_2$), 2.73 (s, 6H, NMe$_2$).

**EXAMPLE 3**

**Preparation of 2-Carboxy-4-chloro-2'-cyano-diphenylsulfide**

2-Bromobenzonitrile (81.2 g) was dissolved in 125 mL of dimethylacetamide and added to a warm solution (80°C) of 2-thio-5-chlorobenzoic acid (78.3 g) and sodium methoxide (44.8 g) in 700 mL of dimethylacetamide and stirred for 17 hr at 100°C. The reaction mixture was added to 2 liters of chilled water, acidified with concentration HCl, filtered, triturated with 5% NaHCO$_3$, filtered and dried to give 108.7 g (90%) of 2-carboxy-4-chloro-2'-cyano-diphenylsulfide, m.p. 197°-200°C.

**EXAMPLE 4**

**Preparation of 2-Aminomethyl-2'-hydroxymethyl-4'-chlorodiphenylsulfide**

2-Carboxy-4-chloro-2'-cyano-diphenylsulfide (40.0 g) was dissolved in 100 mL of tetrahydrofuran and added, under nitrogen, to an ice chilled solution of 156 mL of 1.0 M diborane. After complete addition, the reaction was refluxed for 2 hr and then stirred at room temperature for 17 hr. The reaction mixture was treated with 100 mL of 50% HCl, warmed on a steam bath for 1 hr and concentrated in vacuo. After treatment with solid NaOH and extraction with EtOAc, 30.0 g of the free base was obtained as an orange oil. This base was dissolved in
ether. To the resulting clear solution was added an excess of etherial HCl. The hydrochloride salt was recrystallized from MeOH/EtOAc mixtures to afford 35.9 g (82% yield) of 2-aminomethyl-2'-aminomethyl-2'-hydroxymethyl-4'-chlorodiphenyl-sulfide, m.p. 192°-194°C.

Anal. Calcd for C_{14}H_{14}ClNO_2S.HCl: C 53.17; H 4.78; N 4.46; S 9.14
Found C 53.15; H 4.86; N 4.54.

EXAMPLE 5

Preparation of 5-Chloro-2-((2-((methylamino)methyl)phenyl)thio)-benzyl Alcohol

Formic acid (1.5 g, 96%) and acetic anhydride (3.4 g) were mixed and warmed at 60°C for 2 hr. 2-Aminomethyl-2'-hydroxymethyl-4'-chlorodiphenyl sulfide (7.9 g) in 25 mL of tetrahydrofuran was added and stirred at room temperature for 3 hr. The reaction mixture was diluted with water, basified with 50% NaOH and extracted with EtOAc. After concentration in vacuo, the residue was dissolved in 50 mL of tetrahydrofuran and added to LiAlH_4 (1.1 g) in 100mL of tetrahydrofuran. The reaction was refluxed for 4 hr, cooled, and 120 mL of a saturated aqueous solution of Na_2SO_4 was added. The organic layer was separated, concentrated and chromatographed on silica gel with MeOH to give the free base (4.0 g). This base was dissolved in ether. To the resulting solution was added an excess of etherial HCl. Recrystallization of the hydrochloride salt from MeOH/EtOAc mixtures gave 3.1 g (34% yield) of 5-chloro-2-((2-((methylamino)-methyl)phenyl)thio)benzyl alcohol, m.p. 163°-164°C.

Anal. Calcd for C_{15}H_{14}ClNO_2S.HCl: C 52.33; H 4.39; N 0.40; S 9.31
Found C 52.18; H 4.49; N 3.98; S 9.21.
EXAMPLE 6

Preparation of 5-Chloro-2-((2-((dimethylamino)methyl)phenyl)thio)benzyl Acetate

A solution of acetyl chloride (2.5 g) in 50 mL of acetonitrile was added dropwise to a solution of 9.8 g of 5-chloro-2-((2-dimethylamino)methyl)phenylthio)benzyl alcohol in 25 mL of triethylamine and 200 mL of acetonitrile. The reaction mixture was stirred for 3 hr at room temperature, filtered and concentrated in vacuo to give a yellow oil. This oil was chromatographed on silica gel with EtOAc as the eluent. Concentration of solvents afforded 3.8 g (34% yield) of 5-chloro-2-((2-((dimethylamino)methyl)phenyl)thio)benzyl acetate as a light yellow oil. Upon standing, oil crystallized to a beige solid, m.p. 41-44°C.

Anal. Calcd. for C_{18}H_{20}ClNO_{2}S: C 61.79; H 5.76; N 4.00; S 9.17; Found C 61.75; H 5.79; N 3.95; S 9.11.

EXAMPLE 7

Preparation of 2-((4-Fluoro-2-formylphenyl)thio)-N,N-dimethylbenzamide

Potassium carbonate (21.3 g) was added to a solution of 2,5-difluorobenzaldehyde (19.8 g) and 2-thio-N,N-dimethylbenzamide (27.9 g) in 500 mL of dimethylformamide. The reaction mixture was stirred at 100°C for three hours, added to 1.4 liters of chilled water and extracted with EtOAc to get 31.8 g of a red oil. The oil was chromatographed on silica gel with 60% toluene/40% EtOAc to get 21.09 g of a red oil.
The compounds of formula (I) are serotonin uptake inhibitors as demonstrated by their ability to block the uptake of biogenic amines.

EXAMPLE 8

Preparation of 5-Fluoro-2-((2-dimethylamino)methyl)phenyl)thio)benzyl Alcohol

2-((4-fluoro-2-formylphenyl)thio)N,N-dimethylbenzamide (21.0 g) was dissolved in 100 ml of anhydrous tetrahydrofuran and, under nitrogen, 120 ml of 1.0M diborane were added at room temperature. The reaction mixture was refluxed for ninety minutes, cooled to room temperature, treated with 200 ml of 50% HCl, warmed on a steam bath for 1 hr and concentrated in vacuo. Treatment with aqueous sodium hydroxide and extraction with EtOAc gave the free base as a yellow oil. The base was dissolved in diethyl ether and acidified with ethereal HCl to give a beige solid. The hydrochloride salt was triturated with warm acetone to give 10.9 g (48%) of 5-fluoro-2-((2-dimethylamino)methyl)phenyl)thio)benzyl alcohol, m.p. 148-150°C.

Anal. Calcd. C, H, FNOS HCl; C, 58.62; H, 5.84; N, 4.27; S, 9.78. Found: C, 58.67; H, 5.86; N, 4.31; S, 9.70.

EXAMPLE 9

Activity Studies

Uptake of 3H-Biogenic Amines in Crude Synaptosomal Preparations of Rat Hypothalamus and Striatum.

A 0.5 ml aliquot of a crude synaptosomal preparation prepared according to the technique of Ferris et al., J. Pharm. Exp. Ther., 181, 407 (1972) and Patrick et al., J. Pharm. Exp. Ther., 241, 152 (1987) was incubated in a standard incubation medium containing 10 μM iproniazid, 1 M ascorbate and 0.1μM of either 3H-dopamine, 3H-1-norepinephrine or 3H-serotonin. Final volumes were 3 ml.

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All incubations were conducted for 3 minutes under an atmosphere of 95% O₂-5% CO₂. The uptake at 0°C and 37°C was determined in each experiment and the difference between the two determinations represented the accumulation of ³H-amine by the temperature-dependent uptake process. Test compounds were dissolved in the standard incubation medium and preincubated with the crude synaptosomal preparation for 5 minutes, before the addition of the labeled substrate.

Reactions were stopped by the addition of 2 mL of ice-cold 0.32 M sucrose containing 25 mM Tris buffer, pH 7.4, and rapid cooling in an ice-bath. Samples were centrifuged at 49,600 x g for 10 minutes.

The resulting pellet was washed with 5 mL of 0.9% saline and again centrifuged. The washed pellet was resuspended in 2 mL of 0.4 N perchloric acid and centrifuged to remove the precipitated protein. A 1 mL aliquot of the supernatant was taken for determination of radioactivity.

Table II

<table>
<thead>
<tr>
<th>Compound</th>
<th>Norepinephrine</th>
<th>Dopamine*</th>
<th>Serotonin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example 2</td>
<td>5.5 ± 1.0 x 10⁻⁸</td>
<td>15% at 10⁻⁵</td>
<td>2.1 ± 0.4 x 10⁻⁹</td>
</tr>
<tr>
<td>Example 5</td>
<td>1.1 ± 3.9 x 10⁻⁷</td>
<td>38% at 10⁻⁵</td>
<td>2.1 ± 1.0 x 10⁻⁸</td>
</tr>
</tbody>
</table>

*Percent inhibition is mean of triplicate assay with S.E.M. < ± 5%.

RTS/JH/17.5.90.
EXAMPLE 10

Formulations

A. Tablet

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount per Tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>A compound of formula (I)</td>
<td>150 mg</td>
</tr>
<tr>
<td>(as the base)</td>
<td></td>
</tr>
<tr>
<td>Lactose</td>
<td>85 mg</td>
</tr>
<tr>
<td>Cornstarch</td>
<td>50 mg</td>
</tr>
<tr>
<td>Micronized silica gel</td>
<td>10 mg</td>
</tr>
<tr>
<td>Polyvinylpyrrolidone</td>
<td>5 mg</td>
</tr>
</tbody>
</table>

The lactose, cornstarch and compound of formula (I) are mixed together and granulated with a binder (polyvinylpyrrolidone in an alcoholic solution) to form granules. The granules are passed through a 16-20 mesh screen, then air dried, lubricated with micronized silica gel and compressed into tablets. A film coat may then be applied if desired.
B. Capsule

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount per Tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>A compound of formula (I) (as the base)</td>
<td>150 mg</td>
</tr>
<tr>
<td>Lactose</td>
<td>125 mg</td>
</tr>
<tr>
<td>Cornstarch</td>
<td>125 mg</td>
</tr>
</tbody>
</table>

The above ingredients are mixed and filled into a two piece hard gelatin capsule.

C. Parenteral Solution

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount per Tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>A compound of formula (I) (as a pharmaceutically acceptable salt)</td>
<td>125 mg (calculated as free base)</td>
</tr>
<tr>
<td>Sterile water for injections, q.s. to</td>
<td>1.0 mL</td>
</tr>
</tbody>
</table>

A pharmaceutically acceptable salt of a compound of formula (I) is dissolved in sterile water under sterile conditions to make 1.0 mL. Such a solution may be packaged in a sealed sterile ampoule to provide a unit dose or in a sterile vial for multiple doses. If the formulation is to be packed in a multi-dose container, the addition of a bacteriostat such as 0.2 to 0.5% w/v of phenol is desirable.

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D. Suppository

150 mg of the hydrochloride salt of a compound of formula (I) is mixed with 250 mg of softened or salted cocoa butter, and a suppository is formed by chilling and shaping in a mold.

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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of the formula (I)

   \[ \text{CH}_2\text{OH} \quad \text{CH}_2\text{NRR}^1 \]

   \[ \text{Z} \quad \text{S} \]

   \[ \text{(I)} \]

   wherein \( R \) and \( R^1 \) are the same or different and are each hydrogen or straight or branched alkyl of 1 to 6 carbon atoms and \( Z \) is halo, or a pharmaceutically acceptable ester or salt thereof.

2. A compound as claimed in claim 1, wherein \( R \) and \( R^1 \) are the same or different and are each hydrogen or methyl.

3. A compound as claimed in either of the preceding claims, wherein \( Z \) is chloro.

4. 5-chloro-2-((2-((dimethylamino)methyl)phenyl)thio)benzyl alcohol or a pharmaceutically acceptable ester or salt thereof.

5. 5-chloro-2-((2-((methylamino)methyl)phenyl)thio)benzyl alcohol or a pharmaceutically acceptable ester or salt thereof.

6. 5-chloro-2-((2-dimethylamino)methyl)phenyl)thio)benzyl acetate or a pharmaceutically acceptable salt thereof.

7. The hydrochloride salt of 5-chloro-2-((2-((dimethylamino)methyl)phenyl)thio)benzyl alcohol.
8. A process for the preparation of a compound as defined in any one of claims 1 to 7 or a pharmaceutically acceptable ester or salt thereof, which comprises

(a) reducing a compound of formula (VA) and/or (VB)

\[
\begin{align*}
\text{(VA)} & \quad \text{CH}_2\text{OH} & \text{CONRR'}^1 \\
\text{(VB)} & \quad \text{CHO} & \text{CH}_2\text{NRR'}^1
\end{align*}
\]

wherein \( Z \) is halo and \( R \) and \( R^1 \) are the same or different and are each hydrogen or straight or branched alkyl of 1 to 6 carbon atoms; or

(b) reducing a compound of formula (IXA) and/or (IXB)

\[
\begin{align*}
\text{(IXA)} & \quad \text{CH}_2\text{OH} & \text{CO}_2\text{H} & \text{CN} \\
\text{(IXB)} & \quad \text{Z} & \text{CH}_2\text{NH}_2 & \text{CO}_2\text{H}
\end{align*}
\]
wherein Z is halo; and optionally converting the resulting compound of formula (I), wherein R and R¹ are both hydrogen, into another compound of formula (I);

and optionally converting the compound of formula (I) so obtained to a pharmaceutically acceptable ester or salt thereof.

9 A compound of formula (IV)

\[
\begin{align*}
\text{CHO} & \quad \text{CONRR'} \\
\text{Z} & \quad \text{S} \\
\end{align*}
\]

(IV)

wherein Z is halo and R and R¹ are the same or different and are each hydrogen or straight or branched alkyl of 1 to 6 carbon atoms.

10. A compound of formula (VA) and/or (VB)

\[
\begin{align*}
\text{CH}_2\text{OH} & \quad \text{CONRR'} \\
\text{Z} & \quad \text{S} \\
\end{align*}
\]

(VA)

\[
\begin{align*}
\text{CHO} & \quad \text{CH}_2\text{NRR'} \\
\text{Z} & \quad \text{S} \\
\end{align*}
\]

(VB)

wherein Z is halo and R and R¹ are the same or different and

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are each hydrogen or straight or branched alkyl of 1 to 6 carbon atoms.

11. A compound of formula (VIII)

\[
\begin{array}{c}
\text{CO}_2\text{H} \\
\text{CN} \\
\text{Z} \\
\end{array}
\]

(VIII)

wherein Z is halo.

12. A compound of formula (IXA) and/or (IXB)

\[
\begin{array}{c}
\text{CH}_2\text{OH} \\
\text{CN} \\
\text{Z} \\
\end{array}
\quad
\begin{array}{c}
\text{CO}_2\text{H} \\
\text{CH}_2\text{NH}_2 \\
\text{Z} \\
\end{array}
\]

(IXA)

(IXB)

wherein Z is halo.

13. A pharmaceutical formulation which comprises a compound of formula (I) or pharmaceutically acceptable ester or salt thereof according to any one of claims 1 to 7 in association with a pharmaceutically acceptable carrier.

14. A compound as claimed in any of claims 1 to 7 for use in therapy.
15. Use of a compound or a pharmaceutically acceptable ester or salt thereof as claimed in any of claims 1 to 7 in the manufacture of a medicament for the prophylaxis or treatment of depression.

16. Use of a compound or a pharmaceutically acceptable ester or salt thereof as claimed in any of claims 1 to 7 in the manufacture of a medicament for the prophylaxis or treatment of anxiety.

17. Use of a compound or a pharmaceutically acceptable ester or salt thereof as claimed in any of claims 1 to 7 in the manufacture of a medicament for the prophylaxis or treatment of obsessive compulsive disorders.

18. Use of a compound or a pharmaceutically acceptable ester or salt thereof as claimed in any of claims 1 to 7 in the manufacture of a medicament for the prophylaxis or treatment of alcoholism.

19. Use of a compound or a pharmaceutically acceptable ester or salt thereof as claimed in any of claims 1 to 7 in the manufacture of a medicament for the potentiation of the analgesic effect of morphine.
free base was obtained as an orange oil. This base was dissolved in

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20. A compound of formula (I) substantially as described with reference to any one of examples 2, 4, 5, 6 and 8.

21. A compound of formula (IV) substantially as described with reference to example 1 or 7.

22. A compound of formula VIII substantially as described with reference to example 3.

23. A formulation comprising a compound of formula (I) substantially as described with reference to any one of examples 10A - 10D.

Dated this 5th day of June 1990

THE WELLCOME FOUNDATION LIMITED
By their Patent Attorney
GRIFFITH HACK AND CO.