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ATTORNEYS FOR PLAINTIFFS
GLAXO GROUP LIMITED and
SMITHKLINE BEECHAM CORPORATION

GLAXO GROUP LIMITED and SMITHKLINE BEECHAM CORPORATION,

Plaintiffs,

v.

DR. REDDY'S LABORATORIES, LTD. and REDDY-CHEMINOR, INC.

Defendants.

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

CIVIL ACTION NO. 01-4066 (WHW)
Honorable William H. Walls, U.S.D.J.
Honorable Susan D. Wigenton, U.S.M.J.

AMENDED COMPLAINT

Plaintiffs Glaxo Group Limited and SmithKline Beecham Corporation, for their Complaint against defendants Dr. Reddy's Laboratories, Ltd. and Reddy-Cheminor, Inc., aver and allege as follows:

JURISDICTION AND PARTIES

1. This is a civil action for patent infringement arising under the patent laws of the United States, 35 U.S.C. §§ 271 et seq. and 21 U.S.C. § 355, and the Federal Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

2. Plaintiff Glaxo Group Limited is an English corporation having a registered office at Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex, UB6 ONN, Middlesex, England.

3. Plaintiff SmithKline Beecham Corporation is a Pennsylvania corporation having a principal place of business at One Franklin Plaza, Philadelphia, Pennsylvania 19102. Plaintiffs Glaxo Group Limited and SmithKline Beecham Corporation are collectively referred to herein as "GlaxoSmithKline".

4. Defendant Dr. Reddy's Laboratories, Ltd. is a corporation organized under the laws of India, having a principal place of business in Hyderabad, India.

5. Defendant Reddy-Cheminor, Inc. is a New Jersey corporation and is a wholly-owned subsidiary of Dr. Reddy's Laboratories, Ltd., with a principal place of business at 66 South Maple Avenue, Ridgewood, New Jersey 07450. Defendants Dr. Reddy's Laboratories, Ltd. and Reddy-Cheminor, Inc. are collectively referred to herein as "Reddy".

6. This Court has jurisdiction pursuant to the patent laws of the United States, Title 35 U.S.C. and 28 U.S.C. §§ 1331 and 1338(a). Venue is proper in this district pursuant to 28 U.S.C. §§1391 and 1400(b).

FIRST CAUSE OF ACTION
INFRINGEMENT OF UNITED STATES PATENT NO. 4,695,578

7. On September 22, 1987 United States Letters Patent No. 4,695,578 ("the '578 patent"), entitled "1,2,3,9-TETRAHYDRO-3-IMIDAZOL-1-YLMETHYL-4H-CARBAZOL-4-ONES, COMPOSITION CONTAINING THEM, AND METHOD OF USING THEM TO TREAT NEURONAL 5HT FUNCTION DISTURBANCES" was duly and legally issued to Ian H. Coates et al. for an invention encompassing ondansetron, pharmaceutical compositions containing ondansetron, and methods of using it. Since its issuance, Glaxo Group Limited has been the assignee and owner of the '578 patent. SmithKline Beecham Corporation is the exclusive licensee of the '578 patent. A true and correct copy of the '578 patent is attached to this Complaint as Exhibit A.

8. GlaxoSmithKline is the holder of approved NDAs under Section 505(a) of the Act, 21 U.S.C. § 355(a), for ondansetron hydrochloride tablets and their use covered by the '578 patent.

9. On or about July 17, 2001, GlaxoSmithKline received a written Notice of Patent Certification from Reddy stating that Dr. Reddy has filed ANDA No. 76-183 seeking approval from the Food and Drug Administration ("FDA") to market ondansetron hydrochloride tablets pursuant to Section 505(j) of the Act, 21 U.S.C. § 355(j), prior to expiration of the '578 patent, and alleging that the '578 patent is not infringed and is invalid.

10. Defendant Reddy's infringement of the '578 patent has been and continues to be willful and deliberate with full knowledge of GlaxoSmithKline's rights in the '578 patent, rendering this case exceptional under 35 U.S.C.§ 285.

11. Defendant Reddy has infringed the '578 patent and such infringement will continue unless enjoined by this Court.

SECOND CAUSE OF ACTION
INFRINGEMENT OF UNITED STATES PATENT NO. 4,753,789

12. GlaxoSmithKline realleges and incorporates herein by reference the allegations in paragraphs 1-6 above.

13. On June 28, 1988, United States Patent No. 4,753,789 ("the '789 patent") entitled "METHOD FOR TREATING NAUSEA AND VOMITING" was duly and legally issued to Michael B. Tyers, et al. Since its issuance, Glaxo Group Limited has been the assignee and owner of the '789 patent. SmithKline Beecham Corporation is the exclusive licensee of the '789 patent. A true and correct copy of the '789 patent is attached to this Complaint as Exhibit B.

14. GlaxoSmithKline is the holder of approved NDAs under Section 505(a) of the Act, 21 U.S.C. § 355(a), for ondansetron hydrochloride tablets and their use covered by the '789 patent.

15. On or about July 17, 2001, GlaxoSmithKline received a written Notice of Patent Certification from Reddy stating that Reddy has filed ANDA No. 76-183 seeking approval from the FDA to market ondansetron hydrochloride tablets pursuant to Section 505(j) of the Act, 21 U.S.C. § 355(j), prior to expiration of the '789 patent, and alleging that the '789 is not infringed, is invalid and/or unenforceable.

16. Defendant Reddy's infringement of the '789 patent has been and continues to be willful and deliberate with full knowledge of GlaxoSmithKline's rights in the '789 patent, rendering this case exceptional under 35 U.S.C.§ 285.

17. Defendant Reddy has infringed the '789 patent and such infringement will continue unless enjoined by this Court.

THIRD CAUSE OF ACTION
INFRINGEMENT OF UNITED STATES PATENT NO. 5,578,628

18. GlaxoSmithKline realleges and incorporates herein by reference the allegations in paragraphs 1-6 above.

19. On November 26, 1996, United States Patent No. 5,578,628 ("the '628 patent") entitled "MEDICAMENTS FOR THE TREATMENT OF NAUSEA AND VOMITING" was duly and legally issued to Michael B. Tyers, et al. Since its issuance, Glaxo Group Limited has been the assignee and owner of the '628 patent. SmithKline Beecham Corporation is the exclusive licensee of the '628 patent. A true and correct copy of the '628 patent is attached to this Complaint as Exhibit C.

20. GlaxoSmithKline is the holder of approved NDAs under Section 505(a) of the Act, 21 U.S.C. § 355(a), for ondansetron hydrochloride tablets and their use covered by the '628 patent.

21. On or about July 17, 2001, GlaxoSmithKline received a written Notice of Patent Certification from Reddy stating that Reddy has filed ANDA No. 76-183 seeking approval from the FDA to market ondansetron hydrochloride tablets pursuant to Section 505(j) of the Act, 21 U.S.C. § 355(j), prior to expiration of the '628 patent, and alleging that the '628 patent is not infringed and is invalid.

22. Defendant Reddy's infringement of the '628 patent has been and continues to be willful and deliberate with full knowledge of GlaxoSmithKline's rights in the '628 patent, rendering this case exceptional under 35 U.S.C.§ 285.

23. Defendant Reddy has infringed the '628 patent and such infringement will continue unless enjoined by this Court.

FOURTH CAUSE OF ACTION FOR DECLARATORY JUDGMENT AND FOR AN INJUNCTION PURSUANT TO 35 U.S.C. § 283

24. On April 22, 1997, United States Patent No. 5,622,720 ("the '720 patent") entitled "PROCESS FOR REDUCING THE CRYSTAL SIZE OF ONDANSETRON HYDROCHLORIDE DIHYDRATE" was duly and legally issued to David T. Collin, et al. Since its issuance, Glaxo Group Limited has been the assignee and owner of the '720 patent. SmithKline Beecham Corporation is the exclusive licensee of the '720 patent. A true and correct copy of the '720 patent is attached as Exhibit D.

25. GlaxoSmithKline is the holder of approved new drug applications ("NDAs") under section 505(a) of the Federal Food, Drug and Cosmetic Act ("The Act"), 21 U.S.C. § 355(a), for ondansetron hydrochloride tablets and their use.

26. On or about July 17, 2001, Reddy filed or caused to be filed an Abbreviated New Drug Application ("ANDA") seeking to market, prior to the expiration of the '720 patent, an ondansetron hydrochloride product which is manufactured by the process covered by the '720 patent.

27. Reddy had actual notice of the '720 patent and other GlaxoSmithKline patents covering ondansetron hydrochloride.

28. The manufacture and sale by Reddy of ondansetron hydrochloride tablets during the term of the '720 patent will constitute patent infringement under 35 U.S.C. § 271 (g).

29. There is a substantial and continuing justifiable controversy between plaintiffs and defendant Reddy as to the infringement of the '720 patent. Defendants' actions have created

a reasonable apprehension in plaintiffs of imminent harm and loss resulting from the threatened actions of defendant in the importation and sale in the United States of the its ANDA product. Defendants' violation of plaintiffs' rights under the '720 patent prior to the expiration of this patent will cause plaintiffs irreparable injury.

30. Defendant Reddy's infringement of the '720 patent is willful and deliberate with full knowledge of GlaxoSmithKline's rights in the '720 patent, rendering this case exceptional under 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, plaintiffs pray for Judgment:

1. Finding that defendants have infringed United States Patent No. 4,695,578, and such infringement is willful and deliberate;

2. Finding that defendants have infringed United States Patent No. 4,753,789, and such infringement is willful and deliberate;

3. Finding that defendants have infringed United States Patent No. 5,578,628, and such infringement is willful and deliberate;

4. Declaring and adjudging that defendants infringe United States Patent No. 5,622,720 by its threatened acts of manufacture, importation and sale of products covered by said patent prior to the expiration of said patent,

5. Ordering that the effective date of any approval of defendants' application under Section 505(j) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C.§ 355(j), for ondansetron hydrochloride tablets and their use be not earlier than the expiration dates of United States Patents Nos. 5,622,720; 4,695,578; 4,753,789 and 5,578,628;

6. Awarding plaintiffs preliminary and final injunctions enjoining defendants and its officers, agents, servants, employees and privies from continued infringement of United States Patents Nos. 4,721,720; 4,695,578; 4,753,789 and 5,578,628;

7. Awarding plaintiffs their reasonable attorneys' fees, interest and costs of this action, pursuant to 35 U.S.C. § 285 and such other and further relief as this Court may deem just and proper.

Dated: March 1, 2002

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United States Patent [19]

Coates et al.

[11] **Patent Number: 4,695,578**

[45] **Date of Patent: Sep. 22, 1987**

[54] **1,2,3,9-TETRAHYDRO-3-IMIDAZOL-1-YLMETHYL-4H-CARBAZOL-4-ONES, COMPOSITION CONTAINING THEM, AND METHOD OF USING THEM TO TREAT NEURONAL 5HT FUNCTION DISTURBANCES**

[75] Inventors: **Ian H. Coates**, Hertfordshire; **James A. Bell**, Royston; **David C. Humber**, Ealing; **George B. Ewan**, Gerrard's Cross, all of England

[73] Assignee: **Glaxo Group Limited**, London, England

[21] Appl. No.: **931,032**

[22] Filed: **Nov. 17, 1986**

Related U.S. Application Data

[63] Continuation of Ser. No. 820,743, Jan. 22, 1986, abandoned, and a continuation-in-part of Ser. No. 694,790, Jan. 25, 1985, abandoned.

[30] **Foreign Application Priority Data**

Jan. 25, 1984	[GB]	United Kingdom	8401888
Oct. 15, 1984	[GB]	United Kingdom	8425959
Jan. 23, 1985	[GB]	United Kingdom	8501727
Jan. 23, 1985	[GB]	United Kingdom	8501728

[51] **Int. Cl.**[4] **A61K 31/415**; C07D 403/06
[52] **U.S. Cl.** **514/397**; 548/336
[58] **Field of Search** 548/336; 514/397

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,634,420	1/1972	Littell et al.	546/200
3,740,404	6/1973	Littell et al.	546/200
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115607	8/1984	European Pat. Off.	546/200
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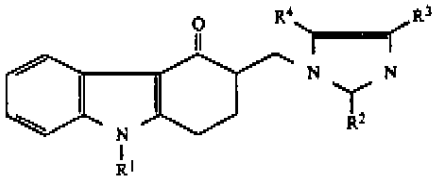
Evans, Aust. J. Chem., 26(11), pp. 2555–2558 (1973).
Littell et al., J. Med. Chem., 15(8), pp. 875–876 (1972).

Primary Examiner—Alan L. Rotman
Assistant Examiner—Kurt G. Briscoe
Attorney, Agent, or Firm—Bacon & Thomas

[57] **ABSTRACT**

The invention relates to compounds of formula (I).



(I)

wherein R_1 represents a hydrogen atom or a C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-6} alkenyl, C_{3-7} cycloalkyl-(C_{1-4}) alkyl, C_{3-10} alkynyl, phenyl or phenyl-C_{1-3} alkyl group, and one of the groups represented by R^2, R^3 and R^4 is a hydrogen atom or a C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl or phenyl-(C_{1-3}) alkyl group and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C_{1-6} alkyl group; and physiologically acceptable salts and solvates, e.g. hydrates thereof.

The compounds are potent selective antagonists at "neuronal" 5-hydroxytryptamine receptors and are useful in the treatment of migraine and psychotic disorders such as schizophrenia.

20 Claims, No Drawings

1,2,3,9-TETRAHYDRO-3-IMIDAZOL-1-YLMETHYL-4H-CARBAZOL-4-ONES, COMPOSITION CONTAINING THEM, AND METHOD OF USING THEM TO TREAT NEURONAL 5HT FUNCTION DISTURBANCES

This application is a continuation of application Ser. No. 820,743, filed Jan. 22,1986, and a continuation in-part of Ser. No. 694,790, filed Jan. 25, 1985, both abandoned.

This invention relates to heterocyclic compounds, to processes for their preparation, to pharmaceutical compositions containing them and to their medical use. In particular the invention relates to compounds which act upon certain 5-hydroxytryptamine (5HT) receptors.

5HT, which occurs endogenously in abundance in peripheral nerves and in blood platelets, is known to cause pain in man through a specific action on 5Ht receptors situated on terminals of primary afferent nerves. Compounds which antagonise the neuronal effects of 5HT have been shown to possess analgesic activity, for example, to relieve the pain of migraine. 5HT also causes depolarisation of the rat isolated vagus nerve preparation through the same 5HT-receptor mechanism, and inhibition of this effect correlates with an analgesic effect in vivo.

5HT also occurs widely in neuronal pathways in the central nervous system and disturbance of these 5HT containing pathways is known to alter behavioural syndromes, such as mood, psychomotor activity, appetite and memory. Since 'neuronal' 5HT- receptors of the same type as those present on primary afferent terminals are also present in the central nervous system, it is believed that compounds which antagonise the neuronal effects of 5HT will be useful in the treatment of conditions such as schizophrenia, anxiety, obesity and mania.

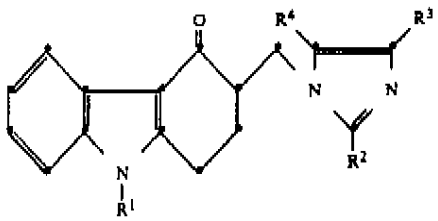
Existing treatments for such conditions suffer from a number of disadvantages. Thus, for example, known treatments for migraine include the administration of a vasoconstrictor such as ergotamine, which is non-selective and constricts blood vessels throughout the body. Ergotamine, therefore, possesses undesirable, and potentially dangerous, side effects. Migraine may also be treated by administering an analgesic such as aspirin or paracetamol, usually in combination with an antiemetic such as metaclopramide, but these treatments are of only limited value.

Similarly, existing treatments ffor psychotic disorders such as schizophrenia exhibit a number of serious side effects such as extrapyramidal side effects.

There is thus need for a safe and effective drug for the treatment of conditions where disturbance of 5HT containing pathways is involved, sych as migraine or psychotic disorders such as schizophrenia. It is believed a compound which is a potent and selective antagonist at 'neuronal' 5HT receptors will fulfil such a role.

We have now found a group of 3-imidazolylmethyltetrahydrocarbazolones which are potent and selective antagonists at 'neuronal' 5HT receptors.

The present invention provides a tetrahydrocarbazolone of the general formula (I):



(I)

wherein R^1 represents a hydrogen atom or a C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-6} alkenyl, C_{3-7} cycloalkyl-(C_{1-4}) alkyl, C_{3-10} alkynyl, phenyl or phenyl-C_{1-3} alkyl group, and one of the groups represented by R^2, R^3 and R^4 is a hydrogen atom or a C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl or phenyl-C_{1-3}alkyl group and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C_{1-6} alkyl group; and physiologically acceptable salts and solvates, e.g. hydrates, thereof.

A preferred class of compounds within the scope of general formula (I) is that wherein R^1 represents a hydrogen atom or a C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-6} alkenyl, phenyl or phenyl-C_{1-3}alkyl group, and one of the groups represented by R^2, R^3 and R^4 is a hydrogen atom or a C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl or phenyl-C_{1-3}alkyl group and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C_{1-6} alkyl group; and physiologically acceptable salts and solvates, e.g. hydrates, thereof.

It will be understood that when R^1 represents a C_{3-6} alkenyl group or a C_{3-10} alkynyl group, the double or triple bond may not be adjacent to the nitrogen atom.

Referring to the general formula (I), the alkyl groups represented by R^1, R^2, R^3 and R^4 may be straight chain or branched chain alkyl groups, for example, methyl, ethyl, propyl, prop-2-yl, butyl, but-2-yl, 2-methlprop-2-yl, pentyl, pent-3-yl or hexyl.

An alkenyl group may be, for example, a propenyl group.

A phenyl-C_{1-3} alkyl group may be, for example, a benzyl, phenethyl or 3-phenylpropyl group.

A cycloalkyl group may be, for example, a cyclopentyl, cyclohexyl or cycloheptyl group.

A C_{3-7} cycloalkyl-(C_{1-4}) alkyl group may be for example a cyclopropylmethyl, cyclopentenylpropyl or a cycloheptylmethyl group. When the cycloalkyl moiety contains 5,6, or 7 carbon atoms it may optionally contain one or two double bonds, and may be for example a cyclohexenyl or cyclohexadienyl group.

A C_{3-10} alkynyl group may be, for example, a 2-propynyl or 2-octynyl group.

It will be appreciated that the carbon atom at the 3-position of the tetrahydrocarbazolone ring is asymmetric and may exist in the R- or S- configuration. The present invention encompasses both the individual isomeric forms of the compounds of formula (I) and all mixtures, including racemic mixtures, thereof.

Suitable physiologically acceptable salts of the indoles of general formula (I) include acid addition salts formed with organic or inorganic acids for example, hydrochlorides, hydrobromides, sulphates, phosphates, citrates, fumarates and maleates. The solvates may, for example, be hydrates.

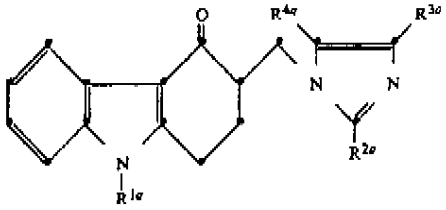
A preferred class of compounds represented by the general formula (I) is that wherein R^1 represents a hy-

drogen atom or a C_{1-6} alkyl, C_{3-6} cycloalkyl or C_{3-6} alkenyl group.

Another preferred class of compounds represented by the general formula (I) is that wherein one of the groups represented by R^2, R^3 and R^4 represents a C_{1-3} alkyl, C_{3-6} cycloalkyl or C_{3-6} alkenyl group and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C_{1-3} alkyl group.

A further preferred class of compounds represented by the general formula (I) is that wherein R^1 represents a hydrogen atom or a C_{1-6} alkyl, C_{5-6} cycloalkyl or C_{3-4} alkenyl group, and either R^2 represents a hydrogen atom and R^3 and/or R^4 represents a C_{1-3} alkyl group or R^2 represents a C_{1-3} alkyl group and both R^3 and R^4 represent hydrogen atoms.

A particularly preferred class of compounds according to the invention is that represented by the formula (Ia):



(Ia)

(wherein R^{1a} represents a hydrogen atom or a methyl, ethyl, propyl, prop-2yl, prop-2-enyl or cyclopentyl group; R^{3a} represents a hydrogen atom; and either R^{2a} represents a methyl, ethyl, propyl or prop-2yl group and R^{4a} represents a hydrogen atom or R^{2a} represents a hydrogen atom and R^{4a} represents a methyl or ethyl group) and physiologically acceptable salts and solvates (e.g. hydrates) thereof.

Preferred compounds are:

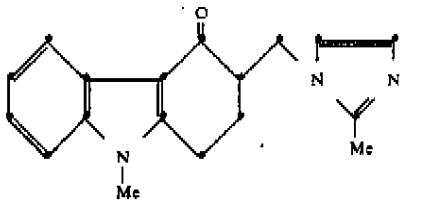
1,2,3,9-tetrahydro-3-[(2-methyl-1H-imidazol-1-yl)methyl]-9-(prop-2-enyl)-4H-carbazol-4-one;

9-cyclopentyl-1,2,3,9-tetrahydro-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one; and

1,2,3,9-tetrahydro-3-[2-methyl-1H-imidazol-1-yl)methyl]-9-(prop-2-yl)-4H-carbazol-4-one

and their physiologically acceptable salts and solvates.

A particularly preferred compound is 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one which may be represented by the formula (Ib):



(Ib)

and the physiologically acceptable salts and solvates (e.g. hydrates) thereof. A preferred form of this compound is the hydrochloride dihydrate.

It will be appreciated that the invention extends to other physiologically acceptable equivalents of the compounds according to the invention, i.e. physiologically acceptable compounds which are converted in vivo into the parent compound of formula (I).

Compounds of the invention are potent and selective antagonists of 5HT-induced responses of the rat isolated vagus nerve preparation and thus act as potent and selective antagonists of the 'neuronal' 5HT receptor type located on primary afferent nerves.

Compounds of the invention are of use as analgesics, for example in the alleviation of pain associated with migraine, headache and many other forms of pain for which 5HT is the endogenous mediator.

Experiments in animals have shown that compounds of the invention are also of use in the treatment of schizophrenia and other psychotic disorders. As indicated herein above 5HT occurs widely in the neuronal pathways in the central nervous system and disturbance of these 5HT containing pathways is known to alter may other behavioural syndromes such as mood, appetite and memory. Since 'neuronal' 5HT receptors of the same type as those present on primary afferent terminals are also present in the central nervous system the compounds of the invention may also be useful in the treatment of conditions such as anxiety, obesity and mania.

In particular, compounds of formula (Ia) as previously defined have been found to be highly selective and extremely potent in their action. They are well absorbed from the gastro-intestinal tract and are suitable for oral or rectal administration. The compounds of formula (Ia) do not prolong sleeping time in the pentobarbitone anaesthetised mouse indicating that there is no undesireable interaction with drug metabolising enzymes. Indeed they exhibit no effects on normal behaviour, are non-toxic and exhibit no undesirable effects in mice at doses up to·1 mg/kg intravenously.

As well as exhibiting the outstanding properties of the compounds of formula (Ia), the compound of formula (Ib) when administered to humans showed no untoward effects.

According to another aspect, the invention provides a method of treatment of a human or animal subject suffering from a condition caused by a disturbance of 'neuronal' 5HT function. Thus, for example, the invention provides a method of treatment of a human subject suffering from migraine pain or a psychotic disorder such as schizophrenia.

Accordingly, the invention also provides a pharmaceutical composition which comprises a least one compound selected from 3-imidazolylmethyltetrahydrocarbazolone derivatives of the general formula (I), their physiologically acceptable salts and solvates, e.g. hydrates, adapted for use in human or veterinary medicine, and formulated for administration by any convenient route.

Such compositions may be formulated in conventional manner using one or more physiologically acceptable carriers or excipients.

Thus the compounds of the invention may be formulated for oral, buccal, parenteral or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or the nose).

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcelluslose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sul-

phate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as supending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ehtyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds of the invention may be formulated for parenteral administration by injection. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds of the invention may also be formulated as a depot preparation. Such long acting formulations may be adminsitered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurised packs or a nebuliser, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluroethane, carbon dioxide or other suitable gas. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

A proposed dose of the compounds of the invention for administration in man (of approximately 70 kg body wight) is 0.5 to 20 mg, preferably 0.1 to 10 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day. The dose will depend on the route of administration and the body weight of the patient. It will be appreciated that it may be necessary to make routine variations to the dosage depending on the age and weight of the patient as well as the severity of the condition to be treated.

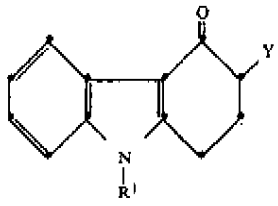
For oral administration a unit dose will preferably contain from 0.5 to 10 mg of the active ingredient. A unit dose for parenteral administration will preferably contain 0.1 to 10 mg of the active ingredient.

Aerosol formulations are preferably arranged so that each metered dose or 'puff' delivered from a pressurised aerosol contains 0.2 mg, of a compound of the invention, and, each dose administered via capsules and cartridges in an insufflator or an inhaler contains 0.2 to 20 mg of a compound of the invention. The overall daily dose by inhalation will be within the range 0.4 to 80 mg. Administration may be several times daily, for example from 2 to 8 times, giving for example 1, 2 or 3 doses each time.

The compunds of the invention may, if desired, be administered in combination with one or more other therapeutic agents, such as anti-nauseants.

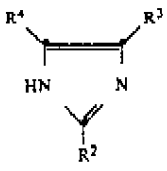
According to another aspect of the invention, compounds of general formula (I) and physiologically acceptable salts or solvates or physiologically acceptable equivalents thereof may be prepared by the general methods outlined hereinafter.

According to a first general process (A), a compound of general formula (I) or a physiologically acceptable salt or solvate or a physiologically acceptable equivalent thereof may be prepared by reacting a compound of general formula (II):



(II)

(wherein R^1 is as defined previously and Y represents a reactive substituent) or a protected derivative thereof with an imidazole of general formula (III):



(III)

(wherein R^2, R^3 and R^4 are as defined previously) or a salt thereof.

Examples of compounds of formula (II) employed as starting materials in the process (A) include compounds wherein Y represents a group selected from an alkenyl group $=CH_2$ or a group of formula CH_2Z where Z represents a readily displaceable atom or group such as a halogen atom, e.g. chlorine or bromine; an acyloxy group such as acetoxy, trifluoromethanesulphonyloxy, p-toluene sulphonyloxy or methanesulphonyloxy; a group $-N^+R^5R^6R^7X^-$, where R^5, R^6 and R^7, which may be the same or different each represents lower alkyl e.g. methyl, aryl e.g. phenyl or aralkyl e.g. benzyl, or R^5 and R^6 together with the nitrogen atom to which they are attached may form a 5- to 6-membered ring e.g.

a pyrrolidine ring, and X represents an anion such as a halide ion e.g. chloride, bromide or iodide; or a group $-NR^5R^6$ where R^5 and R^6 are as defined above, for example $-N(CH_3)_2$.

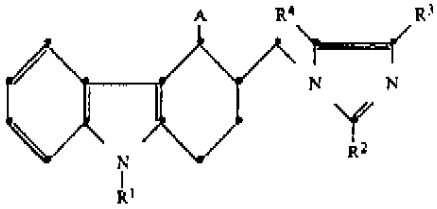
When Y represents the group $=CH_2$, the process may conveniently be carried out in a suitable solvent, examples of which include water; esters, e.g. ethyl acetate; ketones, e.g. acetone; or methylisobutylketone; amides, e.g. dimethylformamide; alcohols, e.g. ethanol; and ethers e.g. dioxan or tetrahydrofuran; or mixtures thereof. The process may be effected at a temperature of, for example, 20° to 100° C.

When Y represents the group CH_2Z, where Z is a halogen atom or an acyloxy group, the process may conveniently be carried out in a suitable solvent such as an amide, e.g. dimethylformamide; and alcohol, e.g. methanol or industrial methylated spirit; or a haloalkane, e.g. dichloromethane, and at a temperature of from −10° to 150° C., e.g. +20° to +100 ° C.

The reaction of a compound of formula (II) where Y represents the group CH_2Z where Z is the group $-N^+R^5R^6R^7X^-$, may conveniently be carried out in a suitable solvent such as water, an amide, e.g. dimethylformamide; a ketone, e.g. acetone; or an ether, e.g. dioxan, and at a temperature of from 20° to 150° C.

The reaction including a compound of formula (II) where Y represents the group $-CH_2Z$, where Z is the group $-NR^5R^6$, may conveniently be carried out in a suitable solvent such as water or an alcohol, e.g. methanol, or mixtures thereof, and at a temperature of from 20° to 150° C.

According to another general process (B) a compound of formula (I) may be prepared by oxidising a compound of formula (IV):



(IV)

(wherein A represents a hydrogen atom or a hydroxyl group and R^1, R^2, R^3 and R^4 are as previously defined) or a salt or a protected derivative thereof.

The oxidation process may be effected using conventional methods and the reagents and reaction conditions should be chosen such that they do not cause oxidation of the indole group. Thus, the oxidation process is preferably effected using a mild oxidising agent.

When oxidising a compound of formula (IV) in which A represents a hydrogen atom, suitable oxidising agents include quinones in the presence of water, e.g. 2,3-dichloro-5,6-dicyano-,1,4-benzoquinone or 2,3,5,6-tetrachloro-1,4-benzoquinone; selenium dioxide; a cerium (IV) oxidising reagent such as ceric ammonium nitrate or a chromium (VI) oxidising agent, e.g. a solution of chromic acid in acetone (for example Jones' reagent) or chromium trioxide in pyridine.

When oxidising a compound of formula (IV) in which A represents a hydroxyl group, suitable oxidising agents include quinones in the presence of water, e.g. 2,3-dichloro-5,6-dicyano-1,4-benzoquinone or 2,3,5,6-tetrachloro-1,4-benzoquinone; ketones, e.g. acetone, methylethylketone or cyclohexanone, in the presence of a base e.g. aluminium t-butoxide; a chromium (VI) oxidising agent, e.g. a solution of chromic acid in acetone (for example Jones reagent) or chromium trioxide in pyridine; an N-halosuccinimide, e.g. N-chlorosuccinimide or N-bromosuccinimide; a dialkylsulphoxide e.g. dimethylsulphoxide, in the presence of an activating agent such as N,N'-dicylohexylcarbodiimide or an acyl halide, e.g. oxalyl chloride or tosyl chloride; pyridine-sulphur trioxide complex; or a dehydrogenation catalyst such as copper chromite, zinc oxide, copper or silver.

Suitable solvents may be selected from ketones, e.g. acetone or butanone; ethers e.g. tetrahydrofuran or dioxan; amides, e.g. dimethylformamide; alcohols, e.g. methanol; hydrocarbons, e.g. benzene or toluene; halogenated hydrocarbons, e.g. dichloromethane; and water or mixtures thereof.

The process is conveniently effected at a temperature of −70° to +50° C. It will be understood that the choice of oxidising agent will affect the preferred reaction temperature.

According to another general process (C), a compound of formula (I) according to the invention or a salt or protected derivative thereof may be converted into another compound of formula (I) using conventional techniques. Such conventional techniques include alkylation, which may be effected at any position in a compound of formula (I) where one or more of R^1 and R^2 represents a hydrogen atom, and hydrogenation, which may, for example, be used to convert an alkenyl substituent into an alkyl substituent or a cycloalkenylalkyl group into a cycloalkylalkyl substitutent. The term "alkylation" includes the introduction of other groups such as cycloalkyl or alkenyl groups. Thus, for example, a compound of formula (I) in which R^1 represents a hydrogen atom may be converted into the corresponding compound in which R^1 represents a C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-6} alkenyl, C_{3-7} cycloalkyl-(C_{1-4}) alkyl, C_{3-10} alkynyl or phenyl-C_{1-3} alkyl group.

The above alkylation reactions may be effected using the appropriate alkylating agent selected from compounds of formula R^aX^a where R^a represents a C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-6} alkenyl, C_{3-7} cycloalkyl-(C_{1-4}) alkyl, C_{3-10} alkynyl or phenyl-C_{1-3} alkyl group, and X^a represents a leaving group such as a halide or an acyloxy group as previously defined for Y, or a sulphate of formula $(R^a)_2SO_4$.

The alkylation reaction is conveniently carried out in an inert organic solvent such as an amide, e.g. dimethylformamide; an ether, e.g. tetrahydrofuran; or an aromatic hydrocarbon, e.g. toluene, preferably in the presence of a base. Suitable bases include, for example, alkali metal hydrides such as sodium hydride, alkali metal amides such as sodium amide, alkali metal carbonates such as sodium carbonate or an alkali metal alkoxide such as sodium or potassium methoxide, ethoxide or t-butoxide. The reaction may conveniently be effected at a temperature in the range −20° to +100° C., preferably 0° to 50° C.

Hydrogenation according to general process (C) may be effected using conventional procedures, for example by using hydrogen in the presence of a noble metal catalyst e.g. palladium, Raney nickel, platinum, platinum oxide or rhodium. The catalyst may be supported on for example charcoal or a homogeneous catalyst such as tris(triphenylphosphine) rhodium chloride may be used. The hydrogenation will generally be effected in a solvent such as an alcohol, e.g. ethanol; an amide, e.g. dimethylformamide; an ether, e.g. dioxan; or an

ester, e.g. ethyl acetate, and at a temperature in the range −20° to 100° C., preferably 0° to 50° C.

It should be appreciated that in some of the above transformations it may be necessary or desirable to protect any sensitive groups in the compound to avoid undesirable side reactions. The protecting groups used in the preparation of compounds of formula (I) are desirably groups which may be readily split off at a suitable stage in the reaction sequence, conveniently at the last stage. For example, during any of the reaction sequences described above, it may be necessary to protect the keto group, for example, as ketal or a thioketal.

Compounds of general formula (I) may thus be prepared according to another general process (D), which comprises removal of any protecting groups from a protected form of a compound of formula (I). Deprotection may be effected using conventional techniques such as those described in 'Protective Groups in Organic Chemistry' Ed. J. F. W. McOmie (Plenum Press, 1973). Thus, a ketal such as an alkyleneketal group may be removed by treatment with a mineral acid such as hydrochloric acid. The thioketal group may be cleaved by treatment with a mercuric salt, e.g. mercuric chloride, in a suitable solvent, such as ethanol.

The compounds of formula (I) may be converted into their physiologically acceptable salts according to conventional methods. Thus, for example, the free base of general formula (I) may be treated with an appropriate acid, preferably with an equivalent amount in a suitable solvent (e.g. aqueous ethanol).

Physiologically acceptable equivalents of a compound of formula (I) may be prepared according to conventional methods.

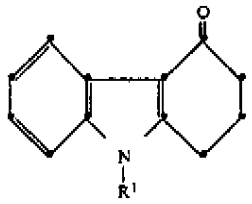
Individual enantiomers of the compounds of the invention may be obtained by resolution of a mixture of enantiomers (e.g. a racemic mixture) using conventional means, such as an optically active resolving acid; see for example 'Stereochemistry of Carbon Compounds' by E. L. Eliel (McGraw Hill 1962) and 'Tables of Resolving Agents' by S. H. Wilen.

Examples of optically active resolving acids that may be used to form salts with the racemic compounds include the (R) and (S) forms of organic carboxylic and sulphonic acids such as tartaric acid, di-p-toluoyltartartic acid, camphorsulphonic acid and lactic acid. The resulting mixture of isomeric salts may be separated, for example, by fractional crystallisation, into the diastereoisomers and if desired, the required optically active isomer may be converted into the free base.

The methods indicated above for preparing the compounds of the invention can be used as the last main step in the preparative sequence. The same general methods can be used for the introduction of the desired groups at an intermediate stage in the stepwise formation of the required compound, and it will be appreciated that these general methods can be combined in different ways in such multi-stage processes. The sequence of the reactions in multi-stage processes should of course be chosen so that the reaction conditions used do not affect groups in the molecule which are desired in the final product.

The starting materials of formula (II) wherein Y represents the group $=CH_2$ may be prepared from compounds of formula (II) where Y represents the group $CH_2N^+R^5R^6R^7X^-$ by reaction with a base in a suitable solvent. Examples of bases include alkali metal hydroxides, e.g. potassium hydroxide or alkali metal carbonates or hydrogen carbonates e.g. sodium hydrogen carbonate.

The quaternary salts may be formed from the corresponding tertiary amine by reaction with an alkylating agent such as methyl iodide or dimethyl sulphate, if preferred in a suitable solvent, e.g. dimethylformamide. The tertiary amine may be prepared by reaction of a tetrahydrocarbazolone of general formula (V):

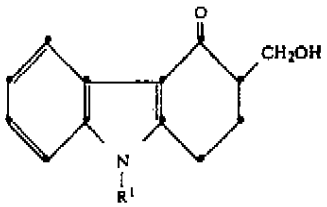


(V)

with formaldehyde and the corresponding secondary amine, if desired in a suitable solvent such as an alcohol, e.g. ethanol.

Compounds of general formula (V) may be prepared for example, by the method described by H. Iida et al. in J. Org. Chem. (1980) Vol 45, No. 15, pages 2938–2942.

The starting materials of general formula (II) where Y represents $-CH_2Z$ where Z is a halogen atom or an acyloxy group may be prepared from the corresponding hydroxymethyl derivative of general formula (VI):



(VI)

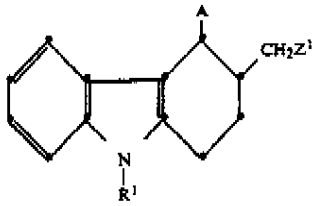
which may be obtained by reacting the tetrahydrocarbazolone of general formula (V) with formaldehyde, preferably in a suitable solvent such as an alcohol, e.g. ethanol, and preferably in the presence of a base.

Thus, the compounds where Z is a halogen atom may be obtained by reacting a compound of formula (VI) with a halogenating agent such as a phosphorus trihalide, e.g. phosphorus trichloride.

The compounds where Z is an acyloxy group may be prepared by reacting a compound of formula (VI) with an appropriate acylating agent such as an anhydride or a sulphonyl halide such as sulphonyl chloride.

Compounds of formula (II) where Y represents $-CH_2Z$ where Z is a halogen atom may also be prepared by reacting a compound of formula (II) where Y represents the group $=CH_2$ with the appropriate hydrogen halide, e.g. hydrogen chloride, conveniently in a suitable solvent such as an ether, e.g. diethyl ether.

Compounds of general formula (IV) may be prepared by reacting a compound of formula (VII):



(VII)

(wherein R^1 and A are as defined previously and Z^1 is a readily displaceable atom or group such as a halogen atom, an acyloxy group or the group $—N^+R^5R^6R^7X^-$ as previously defined for Z^1) with an imidazole of formula (III) according to the method of process (A) described herein.

Compounds of formula (VII) may be prepared by reducing compounds of formula (II) using for example lithium aluminium hydride or sodium borohydride.

Compounds of formula (VII) wherein A represents a hydrogen atom may also be prepared by reacting a compound of formula (VII) wherein A represents a hydroxyl group with a tosyl halide (e.g. tosyl chloride) and then reducing the resulting tosylate with lithium aluminium hydride.

Compounds of formula (IV) are novel compounds, and as such provide a further feature of the invention.

The following examples illustrate the invention. Temperatures are in °C. where indicated, solutions were dried over Na_2SO_4 and solids were dried in vacuo over P_2O_5 at 50° overnight. Chromatography was carried out using the technique described by W. C. Still et al (J. Org. Chem., 1978, 43, 2923–2925), on kieselgel 9385.

The following abbreviations define the eluent used for column chromatography and t.l.c.

(A) Methylene chloride-ethanol-0.88 ammonia 100:10:1
(B) Methylene chloride-ethanol-0.88 ammonia 100:9:1
(C) Methylene chloride-ethanol-0.88 ammonia 200:10:1
(D) Methylene chloride-ethanol-0.88 ammonia 400:10:1

PREPARATION 1

2,3,4,9-Tetrahydro-N,N,N-trimethyl-4-oxo-1H-carbazole-3-methanaminium iodide

A solution of 3-[(dimethylamino)methyl]-1,2,3,9-tetrahydro-4H-carbazol-4-one (0.53 g) in iodomethane (15 ml) was heated under reflux for 5 h and evaporated to dryness, giving the title compound as a white solid (0.84 g) m.p. 202°–205°.

PREPARATION 2

2,3,4,9-Tetrahydro-N,N,N,9-tetramethyl-4-oxo-1H-carbazole-3-methanaminium iodide

A suspension of 3-[(dimethylamino)methyl]-1,2,3,9-tetrahydro-9-methyl-4H-carbazol-4-one (3.80 g) in iodomethane (100 ml) was stirred at reflux for 57 h. The resulting suspension was concentrated in vacuo to give the title methanaminium iodide as a solid (5.72 g) m.p. 192°–195°.

PREPARATION 3

1,2,3,9-Tetrahydro-9-methyl-3-methylene-4H-carbazol-4-one

A solution of the product from Preparation 2 (5.0 g) in water (20 ml) was treated with 2N sodium carbonate (6.55 ml) and warmed at 35° for 45 mins. The resulting slurry was cooled to 0° and the solid was filtered off, washed with water and dried to give the title compound (2.8 g) m.p. 127°–129°.

PREPARATION 4

2,3,4,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-1H-carbazole maleate

Sodium borohyrdide (90 mg) was added under nitrogen to a stirred solution of the product from Example 7 (500 mg) in a mixture of methanol (3 ml) and chloroform (3 ml). Stirring was continuted for 48 h (further sodium borohydride (250 mg) was added after 17.75 h and 42 h), and then the suspension was partitioned between 2N hydrochloric acid (15 ml) and chloroform (3×10 ml). The aqueous layer was basified with solid sodium carbonate, extracted with chloroform (3×10 ml), and the combined extracts washed with water (2×10 ml) and brine (10 ml), dried and concentrated in vacuo. Column chromatography of the residual foam (557 mg) eluting with a mixture of dichloromethane, ethanol and 0.88 aqueous ammonia (300:10:1) afforded a solid (200 mg). This material was dissolved in refluxing absolute ethanol (3 ml) and a solution of maleic acid (80 mg) in refluxing absolute ethanol (1 ml) was added. The hot solution was filtered, stirred, and diluted with dry ether (40 ml) to give the title compound (240 mg) m.p. 138.5°–140°

PREPARATION 5

2,3,4,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-1H-carbazol-4-ol

The product from Example 7 (30.0 g) was added, under nitrogen, to a stirred suspension of lithium aluminium hydride (7.75 g) in dry tetrahydrofuran (750 ml). The mixture was stirred under reflux for 1 h and then cooled in ice. The suspension was cautiously diluted with aqueous tetrahydrofuran (15% H_2O; 100 ml) and water (100 ml), concentrated in vacuo and the residual solid extracted with dichloromethane (2×500 ml). The organic extracts were concentrated in vacuo and the residual solid (16.4 g) purified by short path column chromatography on silica (Kieselgel 60; Merck 7747; 500 g) eluted with a mixture of dichloromethane, ethanol and 0.88 aqueous ammonia (150:10:1) to give the title compound as a foam (13.4 g).

T.l.c. Silica, dichloromethane/ethanol/0.88 ammonia (150:10:1) Rf 0.34 and 0.36 (two pairs of diastereoisomers), detection u.v. and iodoplatinic acid.

N.m.r. δ[$CDCl_3$+CD_3OD (1 drop)] 1.6–2.3 and 2.6–3.0(5H,m), 2.32 and 2.40 (3H, s+s, Me in two different isomers), 3.32 (3H,s,NMe), 3.65–4.3(2H,m,$CHCH_2N$), 4.75–4.85(1H,m,CH—OH, 6.8–7.8 (CH,m,aromatic).

PREPARATION 6

1,2,3,9-Tetrahydro-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one

A suspension of the product from Preparation 1 (6.6 g) and 2-methyl imidazole (17.0 g) in dry dimethylform-

amide (75 ml) was stirred at 100° under nitrogen for 17.25 h then cooled in ice to deposit a solid. This material was purified by washing successively with dimethylformamide (2×7 ml) and dry ether (3×15 ml) followed by column chromatography (A) to give the title compound (1.6 g) m.p. 235°–238° dec.

which was filtered whilst warm. The filtrate was then diluted with dry ether to deposit a solid (0.6 g) which was recrystallised from absolute ethanol to give the title compound as a solid (0.27 g) m.p. 186°–187°.

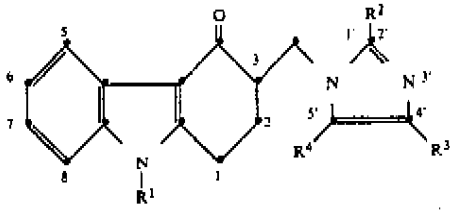
Analysis—Found: C,61.9;H,6.4;N,11.8. $C_{18}H_{19}N_3O.HCl.H_2O$ requires C,62.3;H,6.1;N,12.1%.

The following compounds were prepared by a similar procedure as detailed in Table I:

TABLE I

Ex. No.	Formula I R¹	R²	R³	R⁴	Wt S.M. (g)	Wt of appropriate Imidazole (g)	Vol. Solvent (ml)	Salt Formed	Wt. Product (g)	m.p.	Molecular Formula	Analysis (%) Found C	H	N	Requires C	H	N
1b	CH_3	H	H	H	2.00	4.10	30	HCl	0.78	199.5–200.5°	$C_{17}H_{17}N_3O.HCl.0.8H_2O$	62.05	5.5	12.7	61.8	5.9	12.7
1c	CH_3	H	CH_3	CH_3	0.8	0.6	5	Maleate	0.50	151–152	$C_{19}H_{21}N_3O.C_4H_4O_4.0.2H_2O$	64.6	6.0	9.8	64.7	6.0	9.8
1d	CH_3	^iPr	H	H	3.2	2.9	40	HCl	1.0	178–182°	$C_{20}H_{23}N_3O.HCl.0.5H_2O$	64.9	6.9	11.2	65.5	6.9	11.45
1e*	Me	H	CH_2Ph	H	0.8	1.2	5	HCl	0.25	130–135°	$C_{24}H_{23}N_3O.HCl.0.5H_2O$	69.1	6.1	9.9	69.5	6.1	10.1
1f*	Me	H	H	CH_2Ph				—	0.05	170–174°	$C_{24}H_{23}N_3O.1.5\ H_2O$	72.8	6.2	10.5	72.7	6.6	10.6
1g*	Me	ζ	H	H	1.0	1.6	30	HCl	0.3	150–155°	$C_{23}H_{27}N_3O.HCl.0.3H_2O$	68.5	7.55	10.4	68.4	7.15	10.4

*2,3,4,9-Tetrahydro-9,N,N,N—tetramethyl-4-oxo-1H—carbazol-3-methanaminium methosulphate used as starting material.
In the Table, ζ represents cyclohexyl.
Note 1
Compounds 1e and 1f were prepared in the same experiment and the isomers separated by short path chromatography (D. F. Taber, J. Org. Chem., 1982, 47, 1351) eluting with dichloromethane/ethanol/ 0.88 ammonia (300:10:1). The following ^1H n.m.r. data was obtained.



^1H NMR SPECTRA (obtained at 250 MHz)
Selected Proton Chemical Shifts (δ ppm) and multiplicities

	Solvent	Carbazolone Protons: Aromatic H-5,6,7,8	Aliphatic CH_2-1 and CH_2-2 H-3		Imidazolyl Methylene Protons	Imidazole Protons: H-2'	H-4' and/or H-5'
1e	d_6-DMSO	7.2–8.05	2.91–3.25	1.75–2.3	4.47(dd) and 4.64(dd)	9.20s	7.55s
1f	$CDCl_3$ + DMSO	7.15–8.05	2.6–3.05	1.75–2.1	4.02(dd) and 4.63(dd)	8.17s	6.93s
1g	d_6-DMSO	7.2–8.05	inter alia		4.42(dd) and 4.73(dd)	—	7.61d and 7.70
			2.9–3.3	1.6–2.2			

d = doublet
dd = doublet of doublets
s = singlet

EXAMPLE 1a

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one hydrochloride

A solution of the product of Preparation 2 (2.0 g) and 2-methylimidazole (5.0 g) in dry dimethylformamide (30 ml) was stirred, under nitrogen, at 95° for 16.75 h and then allowed to cool. The solid that crystallised was filtered off, washed with ice-cold, dry dimethylformamide (3×2 ml) and dry ether (2×10 ml) and then dried. The resulting solid (0.60 g) was suspended in a mixture of absolute ethanol (30 ml) and ethanolic hydrogen chloride (1 ml), and warmed gently to obtain a solution,

EXAMPLE 2

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one maleate

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methylimidazol-1-yl)methyl-4H-carbazol-4-one (300 mg) was suspended in hot ethanol (5 ml) and treated with maleic acid (116 mg). The solution was cooled and the white crystalline solid was filtered off and dried to give the title compound (300 mg) m.p. 132.3°.

EXAMPLE 3a

1,2,3,9-Tetrahydro-3-(1H-imidazol-1-ylmethyl)-4H-carbazol-4-one

A solution of the product of Preparation 1 (0.84 g) and imidazole (0.90 g) in dimethylformamide (25 ml) was heated at 105° for 6 h, cooled, added to water (200 ml) and extracted six times with ethyl acetate. The combined extract was washed, dried and evaporated to give a solid which was purified on a silica column (Merck 7734) eluting with ethyl acetate/methanol (4:1). Recrystallisation twice from ethyl acetate/methanol gave the title compound (0.095 g) as a crystalline solid m.p. 220°-222°.

T.l.c. Silica, dichloromethane/ethanol/0.88 ammonia (100:8:1) Rf 0.33, detection u.v. and iodoplatinic acid.

The following compounds were prepared by a similar procedure as detailed in Table II. Salt formation was carried out as described in Example 2.

EXAMPLE 4

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one

A solution of 1,2,3,9-tetrahydro-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one (1.0 g) in dry dimethylformamide (10 ml) was added dropwise under nitrogen to a stirred, ice-cooled suspension of sodium hydride (80% in oil; 0.11 g) in dry dimethylformamide (5 ml). After 0.5 h dimethylsulphate (0.34 ml) was added, and the solution stirred at room temperature for 4 h. The resultant solid was filtered off, washed with ice-cold dry dimethylformamide (2×5 ml) and dry ether (3×15 ml) and dried to give the title compound as a solid (0.25 g) m.p. 223°-224° (dec).

T.l.c. Silica, chloroform/methanol (93:7) Rf 0.27 detection u.v. and iodoplatinic acid, identical to the product from Example 1a.

The following compounds were prepared by a similar procedure using the appropriate alkylating agent as detailed in Table III.

TABLE II

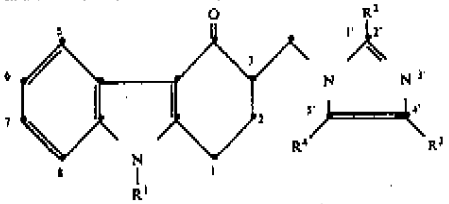
Ex. No.	Formula (I) R¹	R²	R³	R⁴	Wt S.M. (g)	Wt of appropriate Imidazole (g)	Vol Solvent (ml)	Rection Time/Temp. (h/°C.)	Salt Formed	Wt. Product (g)	m.p.
3b	H	CH_3	H	H	6.60	17.00	75	17.25/100	Maleate	0.40	155–156°
3c	H	CH_2CH_3	H	H	7.00	10.50	75	18/85	Maleate	0.48	154.5–156°
3d	H	CH_2Ph	H	H	3.00	3.10	25	24/100	Maleate	0.61	100.5–102°
3e	H	H	CH_3	H	1.00	2.2	5	18/95	Maleate	0.16	144–145.5°
3f	H	H	H	CH_3					Maleate	0.09	143–144°
3g	H	γ	H	H	1.80	1.0	20	20/100	HCl	0.11	142–146°

Ex. No.	^{1}H NMR SPECTRA (obtained at 250 MHz in d_6-DMSO) Selected Proton Chemical Shifts (δ ppm) and multiplicities: Carbazolone Aromatic H-5,6,7,8	Carbazolone Aliphatic CH_2-1 and CH_2-2 H-3	Imidazolyl Methylene	Imidazole H-2'	Imidazole H-4' and/or H-5'
3b	7.1–8.05	3.0–3.25 1.9–2.2	4.29(dd) and 4.69(dd)	—	7.57d and 7.67d
3c	7.15–8.05	3.0–3.25 1.9–2.2	4.32(dd) and 4.72(dd)	—	7.61d and 7.69d
3d	7.15–8.05	2.85–3.1 1.8–2.05	4.28(dd) and 4.71(dd)	—	7.59d and 7.71d
3e	7.15–8.05	3.0–3.20 1.75–2.25	4.48(dd) and 4.62(dd)	8.97s	7.46s
3f	7.15–8.05	3.0–3.20 1.90–2.20	4.29(dd) and 4.74(dd)	8.93s	7.41s
3g	7.1–8.0	2.9–3.2 1.75–2.1	6.32(dd) and 6.70(dd)	—	7.75d and 7.83d

NOTE 1

Compounds 3e and 3f were prepared in the same experiment and the isomers separated by preparative h.p.l.c. on Zorbax-Sil eluting with hexane/ethyl acetate/ethanol/0.88 ammonia (400:100:100:0.6).

In the Table, the positions of the protons are numbered with reference to the formula below.



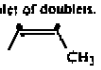
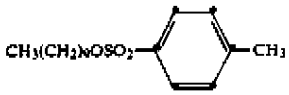
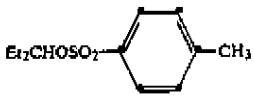
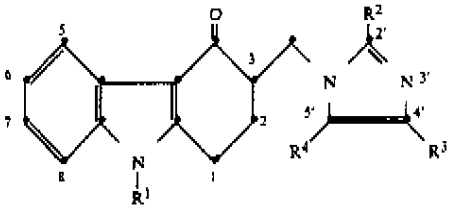
The symbols in Table II have the following meanings
d = doublet, dd = doublet of doublets, s = singlet
γ represents the group 

TABLE III

Example No.	Alkylating Agent	R^2	R^3	R^4	Reaction Time (h) at RT	Salt Formed	Wt. Product (g)	m.p.
4b	Me_2SO_4	CH_2CH_3	H	H	0.5	HCl	0.13	211–212°
4c	Me_2SO_4	CH_2Ph	H	H	4	Maleate	0.32	143–145°
4d	Et_2SO_4	CH_3	H	H	6.5	Maleate	0.67	159–160°
4e	$PhCH_2Br$	CH_3	H	H	5.75	Maleate	1.00	150–151.5°
4f	$CH_3(CH_2)_5I$	CH_3	H	H	7.25	Maleate	1.16	118–119°
4g	$Ph(CH_2)_3Br$	CH_3	H	H	5.75	Maleate	0.84	95–96.5°
4h		CH_3	H	H	4 (at 50°)	Oxalate	0.14	50–51°
4i		CH_3	H	H	14h (at 40° C.)	HCl	0.12	131–133°

Example No.	Molecular Formula	Analysis (%) Found C	Found H	Found N	Requires C	Requires H	Requires N
4b	$C_{19}H_{21}N_3O.HCl.0.5H_2O$	64.7	6.5	11.0	64.7	6.6	11.9
4c	$C_{24}H_{23}N_3O.C_4H_4O_4$	69.35	5.5	8.3	69.3	5.6	8.65
4d	$C_{19}H_{21}N_3O.C_4H_4O_4$	65.15	6.1	9.85	65.25	5.95	9.9
4e	$C_{24}H_{23}N_3O.C_4H_4O_4$	69.1	5.65	8.55	69.3	5.6	8.65
4f	$C_{23}H_{29}N_3O.C_4H_4O_4$	67.4	6.9	8.7	67.6	6.9	8.8
4g	$C_{26}H_{27}N_3O.C_4H_4O_4.0.2H_2O$	69.5	5.9	8.0	69.7	6.1	8.1
4h	$C_{27}H_{37}N_3O.C_2H_2O_4.0.3H_2O$	66.7	7.8	7.8	66.6	7.8	8.0
4i	$C_{22}H_{27}N_3O.HCl.1.1H_2O$	65.8	7.9	10.3	65.4	7.5	10.4

Note 1
The following ^1H n.m.r. data was obtained.



^1H NMR SPECTRA (obtained at 250 MHz)
Selected Proton Chemical Shifts (δ ppm) and multiplicities

	Solvent	Carvazolone Protons: Aromatic H-5,6,7,8	Carvazolone Protons: Aliphatic CH_2-1 and CH_2-2	Carvazolone Protons: Aliphatic H-3	Imidazolyl Methylene Protons	Imidazole Protons H-2'	Imidazole Protons H-4' and/or H-5'
4g	d_6-DMSO	7.15–8.1	2.9–3.2	1.9–2.2	6.29(dd) and 6.68(dd)	—	7.55d and 7.65d
4h	d_6-DMSO	7.2–8.1	2.9–3.3	1.8–2.2	6.26(dd) and 6.65(dd)	—	7.42d and 7.57d

d = doublet
dd = doublet of doublets

EXAMPLE 5

9-Cyclopentyl-1,2,3,9-tetrahydro-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one maleate

A solution of 1,2,3,9-tetrahydro-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one (1.20 g) in dry dimethylformamide (9 ml) was added to a stirred, ice-cooled, suspension of sodium hydride (80% in oil; 0.14 g) in dry dimethylformamide (2 ml) under nitrogen, and stirring continued for 0.25 h. Bromocyclopentane (0.51 ml) was added and the stirred solution heated at 100° for 18.5 h. The solution was allowed to cool and then partitioned between water (100 ml) and ethyl acetate (3×70 ml). The combined organic extracts were washed with 2N sodium carbonate (2×50 ml), water (2×50 ml) and brine (50 ml), dried, evaporated to dryness and purified by chromatography eluting with a mixture of dichloromethane, ethanol, 0.88 ammonia (150:10:1) to give an oil

(0.27 g). This oil was dissolved in refluxing absolute ethanol (7 ml) and a solution of maleic acid (0.10 g) in refluxing absolute ethanol (0.5 ml) was added. The hot solution was filtered, stirred and diluted with dry ether (20 ml). The resultant yellow gum was washed with dry ether (7×25 ml), and the combined mother-liquors and washings left to stand. The solid that crystallised from the solution was filtered off, washed with dry ether (3×5 ml) and dried to give the title salt as a white crystalline solid (0.058 g), m.p. 104.5°–106°

Analysis—Found: C,65.95;H,6.4;N,8.6. $C_{22}H_{25}N_3O.C_4H_4O_4O..6H_2O$ requires C,65.8;H,6.4;N,8.9%.

EXAMPLE 6

1,2,3,9-Tetrahydro-3-[(2-methyl-1H-imidazol-1-yl)methyl]-9-(2-propenyl)-4H-carbazol-4-one maleate

A solution of 1,2,3,9-tetrahydro-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one (1.0 g) in dry dimethylformamide (6 ml) was added to a stirred, ice-cooled suspension of sodium hydride (80% in oil; 0.12 g) in dry dimethylformamide (2 ml). After 0.25 h allyl bromide was added, the solution stirred at 0° for 0.25 h, and at room temperature for 20 h before partitioning between water (75 ml) and ethyl acetate (3×50 ml). The combined organic extracts were washed with water (2×50 ml), brine (50 ml), dried, and concentrated in vacuo and purified by chromatography eluting with a mixture of dichloromethane, ethanol, and 0.88 aqueous ammonia (200:10:1) to afford a solid (0.43 g). This solid was dissolved in refluxing absolute ethanol (2 ml) and a solution of maleic acid (0.18 g) in refluxing absolute ethanol (1 ml) was added. The hot solution was filtered, diluted with dry ether (4 ml) and the crystallised solid was filtered off, washed with dry ether (3×5 ml) and dried to give the title compound as a white solid (0.48 g), m.p. 150.5°–151°

Analysis—Found: C,66.3;H,5.75;N,9.6. $C_{20}H_{21}N_3O.C_4H_4O_4$ requires C,66.2;H,5.8;N,9.65%.

EXAMPLE 7

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one

A solution of 3-[(dimethylamino)methyl]-1,2,3,9-tetrahydro-9-methyl-4H-carbazol-4-one hydrochloride (1.7 g) in water (17 ml) was treated with 2-methylimidazole (1.4 g) and then heated under reflux for 20 h. The cooled mixture was filtered and the residue washed with water (3×15 ml) to give crude product (1.7 g) m.p. 221°–221.5°. This material was recrystallised from methanol to give the title compound (1.4 g) m.p. 231°–232°, identical by t.l.c. with product from Example 4.

EXAMPLE 8

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one

A suspension of the product from Preparation 3 (0.5 g) and 2-methylimidazole (0.4 g) in water (5 ml) was heated under reflux for 20 h. The cooled reaction mixture was filtered and the residue washed with water (3×10 ml), dried and recrystallized from methanol (18 ml) to give the title compound (0.3 g) m.p. 232°–234° (dec), identical by t.l.c. with the product from Example 4.

EXAMPLE 9

1,2,3,9-Tetrahydro-9-(1-methylethyl)-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one hydrochloride

Sodium hydride (80% dispersion in oil 0.208 g) was added to a stirred solution of 1,2,3,9-tetrahydro-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one (1.93 g) at 0° C. in DMF (35 ml) and the resultant suspension stirred at 0° C. for 0.25 h. 2-Bromopropane (0.78 ml) was then added and stirring continued at room temperature overnight, followed by 4 h at 40° C.

The reaction mixture was partitioned between sodium carbonate (2N; 200 ml) and ethyl acetate (2×150 ml). The combined organic extracts were washed with water (3×75 ml), dried, and evaporated in vacuo and the product purified by chromatography eluting with dichloromethane:ethanol:ammonia (100:8:1) to give an oil. This oil was dissolved in ethanol (3 ml), acidified with ethereal hydrogen chloride and diluted with dry ether to deposit the title compound as a white solid (0.13 g) m.p. 230°–232°,

Analysis—Found: C,65.3;H,6.6;N,11.1%. $C_{20}H_{23}N_3O.HCl.O.5H_2O$ requires C,65.4;H,6.9;N,11.45%.

EXAMPLE 10

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one hydrochloride dihydrate

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one (18.3 g) in a hot mixture of isopropanol (98 ml) and water (18.3 ml) was treated with concentrated hydrochloric acid (6.25 ml). The hot mixture was filtered and the filtrate diluted with isopropanol (90 ml) and stirred at room temperature for 17 h, cooled to 2° and the solid filtered off (21.6 g). A sample (6 g) was recrystallized from a mixture of water (6 ml) and isopropanol (10 ml) to give the title compound as a white crystalline solid (6 g) m.p. 178.5°–179.5°.

Analysis—Found: C,59.45;H,6.45;N,11.5. $C_{18}H_{19}N_3O.HCl.2H_2O$ requires C,59.1; H, 6.6; N,11.5%. Water assay—Found: 10.23%. $C_{18}H_{19}N_3O.HCl.2H_2O$ requires 9.85%.

EXAMPLE 11

1,2,3,9-Tetrahydro-3-[(2-methyl-1H-imidazol-1-yl)methyl]-9-phenyl-4H-carbazol-4-one maleate

(i)

3-[(Dimethylamino)methyl]-1,2,3,9-tetrahydro-9-phenyl-4H-carbazol-4-one hydrochloride

A solution of 1,2,3,9-tetrahydro-9-phenyl-4H-carbazol-4-one (3.90 g) dimethylamine hydrochloride (1.50 g) and paraformaldehyde (0.60 g) in glacial acetic acid was stirred at reflux under nitrogen for 42 h, allowed to cool and concentrated in vacuo. The residual brown gum was stirred with water (50 ml), ethyl acetate (50 ml) and brine (20 ml) for 0.25 h, and the resultant solid filtered off, washed with dry ether (4×30 ml) and dried to give the title compound (4.2 g). A portion of this solid (1.0 g) was recrystallised twice from absolute ethanol (10 ml) to give the title compound as a fawn powder (0.39 g) m.p. 193°–194° (dec).

(ii)

1,2,3,9-Tetrahydro-3-[(2-methyl-1H-imidazol-1-yl)methyl]-9-phenyl-4H-carbazol-4-one maleate

2-Methyl-1H-imidazole (1.4 g) was added, under nitrogen, to a stirred suspension of 3-[(dimethylamino)methyl]-1,2,3,9-tetrahydro-9-phenyl-4H-carbazol-4-one hydrochloride (2.0 g) in water (20 ml). The mixture was heated at 90° for 43 h and the solvent decanted from the fawn solid. Chloroform was added to the solid, the suspension was filtered through hyflo, the filtrate dried and concentrated in vacuo.

Chromatography of the residual fawn foam (2.04 g) eluting with a mixture of dichloromethane, ethanol and 0.88 aqueous ammonia (200:10:1) afforded a white foam (1.1 g). A solution of this foam in ethanol (3 ml) was treated with maleic acid (0.4 g) in ethanol (1 ml) followed by dry ether (40 ml) and the resultant gum triturated with dry ether (2×40 ml) to afford the title compound as a cream solid (1.37 g), m.p. 165°–166° (dec).

Analysis—Found: C,68.65;N,5.5;N,8.7. $C_{23}H_{21}N_3O.C_4H_4O_4$ requires C,68.8; N,5.3; N,8.9%.

EXAMPLE 12

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one phosphate (1:1)

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one (0.61 g) was dissolved in a hot mixture of phosphoric acid (90%, 0.13 ml) and water (10 ml), filtered through Hyflo and allowed to crystallize to give the title compound (0.5 g) m.p. 225°

Analysis—Found: C,55.1;H,5.6;N,10.55. $C_{18}H_{19}N_3O.H_3PO_4$ requires C,55.2;H,5.7;N,10.7%.

EXAMPLE 13

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one citrate (2:1)

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1yl)methyl]-4H-carbazol-4-one (0.89 g) was dissolved in ahot solution of citric acid (0.58 g) in ethanol (20 ml) and allowed to crystallize. The resulting crystalline solid was recrystallized by dissolving in acetone/water (2:1, 2 ml) and diluting with acetone (20 ml) to give the title compound (0.6 g) m.p. 162°.

EXAMPLE 14

1,2,3,9-Tetrahydro-3-[(2-propyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one hydrochloride

Iodomethane (0.75 ml) was added to a stirred solution of 3-[(dimethyl amino)methyl]-1,2,3,9-tetrahydro-4H-carbazol-4-one (2.9 g) in dry DMF (30 ml) and the solution stirred at room temperature for 30 min. A solution of 2-propyl-1H-imidazole (2 g) in DMF (5 ml) was added, and the solution stirred at 100° C. for 2 days, cooled and partitioned between sodium carbonate (2N, 150 ml) and ethyl acetate (2×100 ml). The combined extracts were washed with water (100 ml), dried and evaporated in vacuo. The residue was purified by column chromatography eluting with dichloromethane:ethanol:ammonia (400:30:3) to give the free base as a solid (1.2 g). A sample (0.2 g) was dissolved in absolute ethanol (5 ml), acidified with ethereal hydrogen chloride and diluted with dry ether (ca 200 ml) to give an oil. On scratching, the oil crystallised to give a solid (0.15 g). The salt was crystallised from a mixture of methanol and isopropyl acetate to give the title compound (0.08 g) m.p. 206°208° C.

Analysis—Found: C,65.6;H,6.8;N,12.0. $C_{19}H_{21}N_3O.HCl$ $0.2H_2O$ requires C,65.7;H,6.5;N,12.1%.

N.m.r. δ(CD_3SOCD_3) 0.94(3H,t,CH_3), 1.77(2H, sextet, $CH_2CH_2CH_3$), 1.9–2.15 and 2.95–3.2 (7H,m) 4.32 and 4.71 (2H, ABX, $CHCH_2N$), 7.1–8.0(6H, aromatic).

EXAMPLE 15

1,2,3,9-Tetrahydro-3-[(2-propyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one hydrochloride

A solution of the product from Example 3g (0.03 g) in methanol (15 ml) was hydrogenated at room temperature and pressure over 10% palladium oxide on charcoal (50% aq. paste, 0.03 g) for 4h (H_2 uptake, 5 ml). The catalyst was filtered off, and the filtrate evaporated in vacuo to given an oil. Trituration with ether gave the title compound as a white solid (0.03 g) m.p. 199°–203° C.

this material was identified by t.l.c. and n.m.r. to the product from Example 14.

EXAMPLE 16

1,2,3,9-Tetrahydro-3-[(2-propyl-1H-imidazol-1yl)methyl]-4H-carbazol-4-one hydrochloride

Sodium hydride (80% disp. in oil) was added, under nitrogen, to a stirred solution of the product from Example 14 (1.0 g) in dry DMF (20 ml) and the suspension stirred at room temperature for 30 min. 1-Bromopropane (0.35 ml) was added, and the solution stirred at 40° C. for 20 h. The solution was partitioned between sodium carbonate (2N, 150 ml) and ethyl acetate (2×100 ml). The combined extracts were washed with water (100 ml), dried and evaporated in vacuo to give an oil. The oil was purified by column chromatography eluting with dichloromethane:ethanol:ammonia (100:8:1) to give pure free base as an oil. The oil was dissolved in absolute ethanol (5 ml), acidified with ethereal hydrogen chloride, and diluted with dry ether (200 ml). The ether was decanted off the resulting oil and replaced with more dry ether (200 ml). On storage at 0° C. overnight the oil crystallised to give the title compound (0.53 g) m.p. 144°–147° C.

N.m.r. δ(CD_3SOCD_3) 0.90 and 0.93(6H,t+t, 2×Me), 1.65–2.2 and 2.9–3.25 (10H,m), 4.19(2H,t,CH_2CH_2N), 4.32 and 4.71(2H,c,uns/AB/ X,CH_2CH_2N), 7.15–8.1(6H,m,aromatic)

Analysis Found: C,66.6;H,7.7;N,10.0. $C_{22}H_{27}N_3O.HCl.07H_2O$ requires C,66.3;H,7.4;N,10.5%.

EXAMPLE 17

1,2,3,9-Tetrahydro-3-[(2-methyl-1H-imidazol-1-yl)methyl]-9-propyl-4H-carbazol-4-one maleate

A solution of the product from Example 6 (0.86 g) in a mixture of absolute ethanol (20 ml) and dry dimethylformamide (5 ml) was hydrogenated at room temperature and pressure over 5% platinum on carbon [(0.1 g, pre-reduced in absolute ethanol (10 ml)] for 1 h. (H_2 uptake=70 ml). The catalyst was filtered off, washed with ethanol, and the filtrate concentrated in vacuo to ca 15 ml. The residual solution was stirred, diluted with water (50 ml) and the precipitated solid filtered off, washed with water (3×15 ml) and dried to give a powder (0.73 g).

This material was dissolved in refluxing absolute ethanol (7 ml), filtered, and a solution of maleic acid (0.25 g) in refluxing absolute ethanol (1 ml) was added. The stirred solution was diluted with dry ether (50 ml) to give the title compound (0.84 g), m.p. 150°–151°

Analysis—Found: C,65.8;H,6.1;N,9.3; $C_{20}H_{23}N_3O.C_4H_4O_4$ requires C,65.9;H,6.2;N,9.6%.

EXAMPLE 18

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one

(i)3-(Chloromethyl)-1,2,3,9-tetrahydro-9-methyl-4H-carbazol-4-one

Ethereal hydrogen chloride (3.0 ml) was added to a stirred, ice-cooled solution of the product from Preparation 3 (1.90 g) in chloroform (15 ml), and the resultant suspension was stirred in a sealed vessel at room temperature for 16.5 h, concentrated in vacuo and the residual solid (2.27 g) purified by column chromatography eluting with chloroform to give the title compound (1.75 g) m.p. 109°–110.5°. An attempt to crystallise a portion of this material from ethyl acetate resulted in partial decomposition.

(ii)

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one

A solution of 3-(chloromethyl)-1,2,3,9-tetrahydro-9-methyl-4H-carbazol-4-one (0.50 g) and 2-methyl-1H-imidazole (1.60 g) in dry DMF was stirred under nitrogen at 90° for 3.75 h, and then poured onto water (25 ml). The suspension was stirred for 1 h, and the solid filtered off, washed with water (3×20 ml) and dried in vacuo at 50°, Column chromatography of this solid (0.53 g) eluting with a mixture of dichloromethane, ethanol and 0.88 aqueous ammonia (150:10:1) afforded the title compound (0.45 g) m.p. 228°–229°. This material was identical to the product from Example 7 by t.l.c. and n.m.r.

EXAMPLE 19

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one

A solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (170 mg) in dry tetrahydrofuran (1.5 ml) was added dropwise under nitrogen to a stirred, ice-cooled suspension of the product from Preparation 4 (100 mg) in a mixture of tetrahydrofuran (3.5 ml) and water (0.4 ml). The resultant blue solution was stirred for 1.5 h, and then concentrated in vacuo. Column chromatography of the residual solid eluting with a mixture of dichloromethane, ethanol and 0.88 ammonia (150:10:1) afforded the title compound (45 mg) m.p. 227°–228.5°. This material was identical to the product from Example 7 by t.l.c. and n.m.r.

EXAMPLE 20

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-4-carbazol-4-one

A solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (80 mg) in dry tetrahydrofuran (1.5 ml) was added dropwise under nitrogen to a stirred, ice-cooled suspension of the product from Preparation 5 (100 mg) in a mixture of tetrahydrofuran (3.5 ml) and water (0.4 ml). The resultant blue solution was stirred for 1.5 h, and then the red suspension was concentrated in vacuo. Column chromatography of the residual solid eluting with a mixture of dichloromethane, ethanol and 0.88 ammonia (150:10:1) afforded the title compound as a white solid (0.47 g) m.p. 227.5°–229°. This material was identical to the product from Example 7 by t.l.c. and n.m.r.

EXAMPLE 21

3S-1,2,3,9-Tetrahydro-3-[(2-methylimidazol-1-yl)methyl]-9-methyl-4H-carbazol-4-one maleate

A solution of the product from Example 7 (0.5 g) was dissolved in hot methanol (30 ml) and treated with a hot solution of (+)-di-p-toluoyl-D-tartaric acid monohydrate (0.7 g) in methanol (10 ml) and the resulting solution allowed to crystallise overnight to give the desired salt (0.68 g). This salt was dissolved in hot dimethylformamide (DMF, 20 ml), diluted with hot water (10 ml) and allowed to crystallise overnight. The product was filtered off, and dried in vacuo to give ca 90% enantiomerically pure (as shown by n.m.r.) (+)-di-p-toluoyl-D-tartaric acid salt (0.23 g) m.p. 231°–233°. A sample of the salt (0.15 g) was partitioned between 8% sodium bicarbonate (25 ml) and chloroform (2×25 ml). The combined extracts were dried and evaporated in vacuo to give pure free base (0.07 g). The base was dissolved in methanol (5 ml) acidified with maleic acid (0.03 g) and the salt precipitated by adding excess dry ether (80 ml) to give the title compound (0.062 g) m.p. 142°–145°.

T.l.c. Silica, dichloromethane/ethanol/0.88 ammonia (100:8:1) Rf 0.3 detection u.v. and iodoplatinic acid, identical to the product from Example 7. The enantiomer ratio, determined by ^1H n.m.r. was 93:7 (S:R). A sample of the maleate salt showed no significant optical rotation in methanol. The free base, regenerated from the maleate salt gave $[\alpha]_D^{25} - 14°$ (c 0.19, MeOH).

EXAMPLE 22

3R-1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1yl)methyl]-4H-carbazol-4-one maleate

A solution of the product from Example 7 (0.5 g) was dissolved in hot methanol (30 ml) was treated with a hot solution of (−)-di-p-toluoyl-L-tartaric acid monohydrate (0.7 g) in methanol (10 ml) and the resulting solution allowed to crystallise overnight to give the desired salt (0.8 g). This salt was dissolved in hot dimethylformamide (DMF, 20 ml), diluted with hot water (10 ml) and allowed to crystallise for 3 days. The product was filtered off, and dried in vacuo to give ca 95% enantiomerically pure (as shown by n.m.r.) (−)-di-p-toluoyl-L-tartaric salt (0.26 g) m.p. 170°–172°. A sample of the salt (0.2 g) was partitioned between 8% sodium bicarbonate (25 ml) and chloroform (2×25 ml). The combined extracts were dried and evaporated in vacuo to give pure free base (0.12 g). The base was dissolved in methanol (5 ml) acidified with maleic acid (0.045 g) and the salt precipitated by adding excess dry ether (80 ml) to give the title compound (0.08 g) m.p. 142°–145°.

T.l.c. Silica, dichloromethane/ethanol/0.88 ammonia (100:8:1) Rf 0.3 detection u.v. and iodoplatinic acid, identical to the product from Example 7. The enantiomer ratio, determined by ^1H n.m.r. was >95:5. A sample of the maleate salt showed no significant optical rotation in methanol. The free base, regenerated from the maleate salt, gave $[\alpha]_D^{24} + 16°$ (c 0.34, MeOH).

EXAMPLE 23

9-[(Cyclopropyl)methyl]-1,2,3,9-tetrahydro-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one,hydrochloride

Sodium hydride (80% disp. in oil 0.075 g) was added to a solution of the product from Preparation 6 (0.7 g) in dimethylformamide (20 ml) and stirred for 15 min. (Bromomethyl)cyclopropane (0.33 g) was added and the solution maintained at 40° for 4 h. before partitioning between aqueous sodium carbonate (2N, 100 ml) and ethyl acetate (2×50 ml). The combined organic extracts were washed with water (50 ml), dried and evaporated in vacuo to give an oil which was purified by column chromatography (B) to give pure free base. A solution of the free base in ethanol (15 ml) was acidified with ethereal hydrogen chloride and diluted with dry ether to precipitate the title compound (0.4 g) m.p. 120°–130°;

N.m.r. δ(CD_3SOCD_3) 0.4–0.6 (4H,m,cyclopropyl-CH_2CH_2—), 1.2–1.3 (1H,m,cyclopropyl-CH—) 2.7 (3H,s,—CH_3), 4.29 and 4.69 (2H, ABX,$CHCH_2N$) and 7.2–8.1 (6H,m,aromatic).

Analysis—Found: C,63.6;H,6.55;N,10.5. $C_{21}H_{23}N_3O.HCl.1.5H_2O$ requires C,63.5;H,6.8;N,10.6%.

EXAMPLE 24

1,2,3,9-Tetrahydro-3-[(2-methyl-1H-imidazol-1-yl)methyl]-9-(2-propynyl-4H-carbazol-4-one, oxalate

Sodium hydride (80% disp. in oil, 0.075 g) was added to a solution of the product from Preparation 6 (0.7 g) in dimethylformamide (10 ml) and stirred for 15 min. Propargyl bromide (0.44 g) was added and the solution maintained at 40° for 5 h before partitioning between aqueous sodium carbonate (2N, 100 ml) and ethyl acetate (2×50 ml). The combined organic layers were washed with water (2×50 ml), dried and evaporated in vacuo to give an oil which was purified by chromatography (B) to give a solid. This solid was dissolved in ethanol (10 ml) and a solution of oxalic acid (0.14 g) in methanol (5 ml) added. Addition of dry ether precipitated the title compound (0.35 g) m.p. 237°–238°.

N.m.r. δ(CD_3SOCD_3), 2.60 (3H,s,CH_3), 3.47 (1H,t,C≡C—H), 4.25 and 4.65 (2H, ABX $CHCH_2N$), 5.19 (2H,d,NCH_2C≡C), and 7.2–8.1 (6H,m,aromatic).

Analysis—Found: C,64.0; H, 5.0; N, 10.0. $C_{20}H_{19}N_3O.C_2H_2O_4.0.3H_2O$ requires C, 63.9; H, 5.1; N, 10.2%.

EXAMPLE 25

9-(Cyclobutylmethyl)-1,2,3,9-tetrahydro-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one maleate

A solution of 1,2,3,9-tetrahydro-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one (1.00 g) in dry dimethylformamide (10 ml) was added dropwise under nitrogen to a stirred suspension of sodium hydride (78% in oil; 0.12 g) in dry dimethylformamide (5 ml). The mixture was stirred for 1.5 h and a solution of cyclobutanemethanol (4-methylbenzenesulphonate) (2.35 g) in dry dimethylformamide (5 ml) was added. The solution was heated to 50°, stirred for 3.25 h, allowed to cool and concentrated in vacuo to ca 10 ml. The residual solution was poured onto water (100 ml) and extracted with ethyl acetate (3×100 ml). The combined extracts were washed with water (5×70 ml) and brine (70 ml), dried (Na_2SO_4) and concentrated in vacuo.

Flash chromatography (C) of the residual gum afforded a foam (0.67 g). A portion of this material (0.47 g) was dissolved in boiling absolute ethanol (2 ml) and a solution of maleic acid (0.15 g) in refluxing absolute ethanol (1 ml) was added. The stirred solution was diluted with dry ether (50 ml) and the resultant solid filtered off, washed with dry ether (3×15 ml) and dried in vacuo at 60° for 21 h to give the title compound as a solid (0.54 g) m.p. 125°–127°.

Analysis—Found: C, 66.3; H, 6.3; N, 8.8. $C_{22}H_{25}N_3O.C_4H_4O_4.0.58H_2O$ requires C, 65.9; H, 6.4; N, 8.9%.

N.m.r. δ(DMSO) includes 1.7–2.2 (8H,m,cyclobutane and H-2 ax); 2.65 (3H,s,Ar—CH_3); and 4.2–4.75 (4H,m,indole N—CH_2 and imidazole N—CH_2).

The following compounds were prepared according to the method of Example 3, using the reaction conditions given in Table IV hereinafter.

EXAMPLE 26

9-(Cyclopentylmethyl)-1,2,3,9-tetrahydro-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one maleate

m.p. 107°–108°.

Analysis—Found: C, 65.2; H, 6.55; N, 8.2. $C_{23}H_{27}N_3O.C_4H_4O_4.H_2O$ requires C, 65.4; H, 6.7; N, 8.5%.

N.m.r. δ(DMSO) includes 1.2–2.45 (11H,m,cyclopentane and H-2); 2.65 (3H,s,Ar—CH_3); 4.17 (2H,d,N—CH_2-cyclopentane); and 4.27, 4.66 (2H,ABX, imidazole NCH_2).

EXAMPLE 27

1,2,3,9-Tetrahydro-3-[(2-methyl-1H-imidazol-1-yl)methyl]-9-(2-octynyl)-4H-carbazol-4-one, maleate

m.p. 115°–116°.

Analysis—Found: C, 69.2; H, 6.6; N, 8.3. $C_{25}H_{29}N_3O.C_4H_4O_4$ requires C, 69.2; H, 6.6; N, 8.3%.

N.m.r. δ($CDCl_3$) includes 0.85 (3H,t,=C$(CH_2)_4CH_3$); 1.2–1.52 (6H,m,=C—$CH_2CH_2CH_2CH_2CH_3$); 2.8 (3H,s,Ar—CH_3); 4.53 (2H,ABX,$CHCH_2N$); and 4.80 (2H,t,NCH_2C=).

EXAMPLE 28

-(3-Cyclopentylpropyl)-1,2,3,9-tetrahydro-3-[(2-methyl-1H-imidazol-1-yl) methyl]-4H-carbazol-4-one, maleate

m.p. 119°–120.5°.

Analysis—Found: C, 69.1; H, 7.2; N, 8.3. $C_{25}H_{31}N_3O_4.C_4H_4O_4$ requires C, 68.9; H, 7.0; N, 8.3%.

N.m.r. δ($CDCl_3$) includes 0.95–1.85 (13 H, cyclopentane and CH_2CH_2CH); 2.80 (3H,s,Ar—CH_3); 4.08 (2H,t,NCH_2CH_2); and 4.55 (2H,ABx, NCH_2CH).

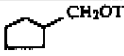
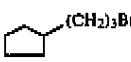
EXAMPLE 29

9-(Cycloheptylmethyl)-1,2,3,9-tetrahydro-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one, maleate

Analysis—Found: C, 66.6; H, 7.0; N, 7.7. $C_{25}H_{31}N_3O.1.5C_4H_4O_4$ requires C, 66.1; H, 6.6; N, 7.5%.

N.m.r. δ($CDCl_3$) includes 1.15–1.75 (12H,m,cycloheptane CH_2); 2.80 (3H,s,Ar—CH_3); 3.92 (2H,d,NCH_2-cycloheptane); and 4.56 (2H, ABX,NCH_2CH).

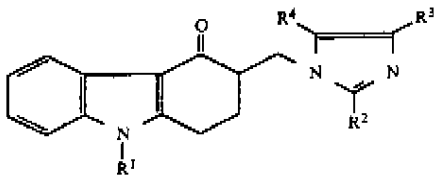
TABLE IV

Ex. No.	Starting material (g)	NaH (g)	Alkylating agent Structure	Weight (g)	Reaction time (h)	Reaction temp. (°C.)	Eluent	Yield of base (g)	SALT FORMATION (MALEATE) Wt. of base (g)	Wt. of acid (g)	Yield (g)
26	1.0	0.12		2.0	0.75 + 4.0	55	C	1.0	0.4	0.32	1.08
27	0.5	0.062	$BrCH_2C{\equiv}CC_5H_{11}$	0.378	0.25 + 6 60	RT 4–5	D	0.590	0.590	0.194	0.648
28	0.5	0.062		0.378	0.25 + 24	RT	C	0.615	0.615	0.203	0.507
29	0.2	0.024		0.151	0.25 + 20	RT	C	0.136	0.136	0.045	0.095

Tos = p-toluenesulphonyl
RT = room temperature

We claim:

1. A compound of formula (I)

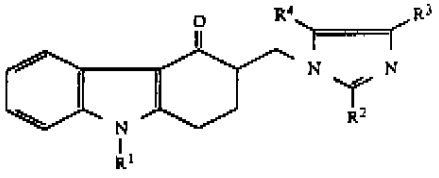

(I)

wherein R^1 represents a hydrogen atom or a C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-6} alkenyl, C_{3-7} cycloalkyl-(C_{1-4})alkyl, C_{3-10} alkynyl, phenyl or phenyl-C_{1-3} alkyl group, and one of the groups represented by R^2, R^3 and R^4 is a hydrogen atom or a C_{1-6}alkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl or phenyl-(C_{1-3}) alkyl group and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C_{1-6} alkyl group; or a physiologically acceptable salt or solvate thereof.

2. A compound according to claim 1 in which one of the groups represented by R^2, R^3 and R^4 represents a C_{1-3} alkyl, C_{3-6} cycloalkyl or C_{3-6} alkenyl group and each of the other two groups, which may be the same or different represents a hydrogen atom or a C_{1-3} alkyl group.

3. A compound according to claim 1 in which R^1 represents a hydrogen atom or a C_{1-6} alkyl, C_{5-6} cycloalkyl or C_{3-4} alkenyl group and either R^2 represents a hydrogen atom and R^3 and/or R^4 represents a C_{1-3} alkyl group or R^2 represents a C_{1-3} alkyl group and both R^3 and R^4 represent hydrogen atoms.

4. A compound of formula (I)


(I)

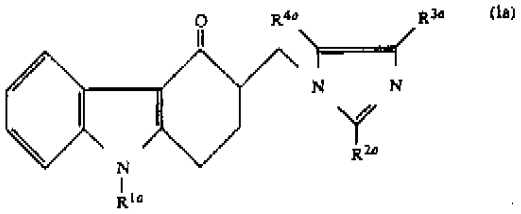
wherein R^1 represents a hydrogen atom or a C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-6} alkenyl, phenyl or phenyl-C_{1-3} alkyl group; and one of the groups represented by R^2, R^3 and R^4 is a hydrogen atom or a C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl or phenyl(C_{1-3}) alkyl group and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C_{1-6} alkyl group; or a physiologically acceptable salt or solvate thereof.

5. A compound according to claim 4 in which R^1 represents a hydrogen atom or a C_{1-6} alkyl, C_{3-6} cycloalkyl or C_{3-6} alkenyl group.

6. A compound according to claim 4 in which one of the groups represented R^2, R^3 and R^4 represents a C_{1-3} alkyl, C_{3-6} cycloalkyl or C_{3-6} alkenyl group and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C_{1-3} alkyl group.

7. A compound according to claim 4 in which R^1 represents a hydrogen atom or a C_{1-6} alkyl, C_{5-6} cycloalkyl or C_{3-4} alkenyl group and either R^2 represents a hydrogen atom and R^3 and/or R^4 represents a C_{1-3} alkyl group or R^2 represents a $C_{1-4\ 3}$ alkyl group and R^3 and R^4 both represent hydrogen atoms.

8. A compound of formula (Ia)


(Ia)

wherein R^{1a} represents a hydrogen atom or a methyl, ethyl, propyl, prop-2-yl, prop-2-enyl or cyclopentyl group; R^{3a} represents a hydrogen atom; and either R^{2a} represents a methyl, ethyl, propyl or prop-2-yl group and R^{4a} represents a hydrogen atom or R^{2a} represents a hydrogen atom and R^{4a} represents a methyl or ethyl group; or a physiologically acceptable salt or solvate thereof.

9. 1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one or a physiologically acceptable salt or solvate thereof.

10. 1,2,3,9-Tetrahydro-3-[(2-methyl-1H-imidazol-1-yl)-methyl]-9-(prop-2-enyl)-4H-carbazol-4-one; 9-Cyclopentyl-1,2,3,9-tetrahydro-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one; 1,2,3,9-Tetrahydro-3-[2-methyl-1H-imidazol-1-yl)methyl]-9-(prop-2-yl)-4H-carbazol-4-one; or a physiologically acceptable salt or solvate thereof.

11. A pharmaceutical composition for the treatment of a condition caused by disturbance of "neuronal" 5HT function comprising at least one compound of formula (I) as defined in claim 1 or a physiologically acceptable salt or solvate thereof in an amount effective to relieve said condition together with at least one physiologically acceptable carrier or exipient.

12. A method of treating a condition caused by disturbance of "neuronal" 5HT function which comprises administering to a patient an effective amount of a compound of formula (I) as defined in claim 1 or a physiologically acceptable salt or solvate thereof to relieve said condition.

13. The compound of claim 9 in the form of a hydrochloride salt.

14. The compound of claim 9 in the form of the hydrochloride dihydrate.

15. A pharmaceutical composition according to claim 11 in which said compound of formula (I) is 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4-H-carbazol-4-one or a physiologically acceptable salt or solvate thereof.

16. A pharmaceutical composition according to claim 15 in which said compound is present as a hydrochloride salt.

17. A pharmaceutical composition according to claim 15 in which said compound is present as the hydrochloride dihydrate.

18. A method according to claim 12 in which said compound of formula (I) is 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1yl)methyl]-4H-carbazol-4-one or a physiologically acceptable salt or solvate thereof.

19. A method according to claim 18 in which said compound is used as a hydrochloride salt.

20. A method according to claim 18 in which said compound is used as the hydrochloride dihydrate.

* * * * *

United States Patent [19]

Tyers et al.

[11] **Patent Number: 4,753,789**

[45] **Date of Patent: Jun. 28, 1988**

[54] **METHOD FOR TREATING NAUSEA AND VOMITING**

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[73] Assignee: **Glaxo Group Limited**, England

[21] Appl. No.: **877,805**

[22] Filed: **Jun. 24, 1986**

[30] **Foreign Application Priority Data**

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[51] **Int. Cl.**[4] **A61K 31/415**

[52] **U.S. Cl.** **424/10**; 514/397; 514/872; 514/917

[58] **Field of Search** 424/10; 514/397, 105, 514/872, 892, 917; 548/336

[56] **References Cited**

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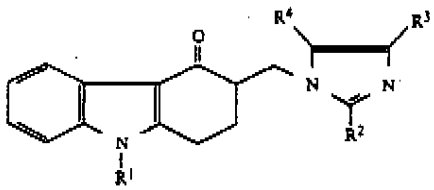
Primary Examiner—Jerome D. Goldberg
Assistant Examiner—Richard Kearse
Attorney, Agent, or Firm—Bacon & Thomas

[57] **ABSTRACT**

The invention relates to the use of compounds of the general formula (I)



(I)

wherein

R^1 represents a hydrogen atom or a C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycoalkyl-(C_{1-4}) alkyl, C_{3-6} alkenyl, C_{3-10} alkynyl, phenyl or phenyl-C_{1-3} alkyl group, and one of the groups represented by

R^2,R^3 and R^4 is a hydrogen atom or a C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl or phenyl - C_{1-3} alkyl group and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C_{1-6} alkyl group;

and physiologically acceptable salts and solvates thereof, for the relief of nausea and vomiting and/or the promotion of gastric emptying and for the manufacture of a medicament for this purpose. Promotion of gastric emptying may be for the relief of gastro-intestinal disorders associated with gastric stasis or may be of advantage of radiological examination procedures.

The invention also relates to a product containing a therapeutic agent liable to induce nausea and vomiting, e.g. a cytostatic agent such as a cyclophosphamide, an alkylating agent or a platinum complex, and a compound of the general formula (I) as a combined preparation for simultaneous separate or sequential use in therapy.

17 Claims, No Drawings

METHOD FOR TREATING NAUSEA AND VOMITING

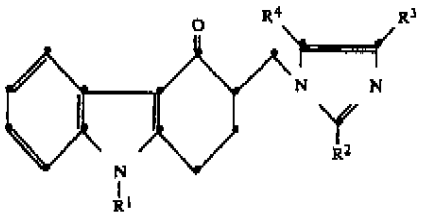
This invention relates to a new medical use for a group of heterocyclic compounds and pharmaceutical compositions containing them. In particular it relates to certain tetrahydrocarbazolone derivatives which may be used to promote gastric emptying and as anti-emetic agents.

A particularly important application for anti-emetic agents is in the prevention and treatment of nausea and vomiting associated with cancer chemotherapy. Emesis is a well-known and frequent side-effect of cancer chemotherapeutic agents, such as cisplatin. It causes serious problems in cancer chemotherapy, and in some patients emesis is so severe that therapy must be discontinued. Anti-emetic agents are therefore often administered in order to alleviate this side-effect of the cancer chemotherapeutic agent. The anti-emetic agents employed are usually benzamide derivatives, such as metoclopramide, which have dopamine antagonist activity.

Metoclopramide is also a gastric motility stimulant, i.e. it promotes gastric emptying. The promotion of gastric emptying is important in the treatment of gastro-intestinal disorders related to gastric stasis; and in radiological examinations.

In view of their dopamine antagonist activity benzamide derivatives such as metoclopramide themselves exhibit serious and undesirable side-effects, such as extra-pyramidal effect, i.e. tardive dyskinesia, acute dystonia, akathisia and tremor. There is thus a need for a safe and effective anti-emetic agent and gastric motility stimulant.

In our British patent application No. 2153821A and our European patent application No. 86300423 we disclose 3-imidazolylmethyltetrahydrocarbazolones which may be represented by the general formula (I)



(I)

wherein

R^1 represents a hydrogen atom or a C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkyl-(C_{1-4})alkyl, C_{3-6} alkenyl, C_{3-10}alkynyl, phenyl or phenyl-C_{1-3}alkyl group, and one of the groups represented by R^2, R^3 and R^4 is a hydrogen atom or a C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl or phenyl-C_{1-3}alkyl group and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C_{1-6} alkyl group; and physiologically acceptable salts and solvates, e.g. hydrates, thereof.

Suitable physiologically acceptable salts of the carbazolones of general formula (I) include acid addition salts formed with organic or inorganic acids for example, hydrochlorides, hydrobromides, sulphates, phosphates, citrates, fumarates and maleates. The solvates may, for example, be hydrates.

The aforementioned specifications also disclose physiologically acceptable equivalents of the compounds of

formula (I), i.e. physiologically acceptable compounds which are converted in vivo into the parent compound of formula (I).

The compounds of formula (I) are described in the aforementioned specifications as potent and selective antagonists of 5-hydroxytryptamine (5-HT) at 'neuronal' 5-HT receptors of the type located on terminals of primary afferent nerves, and which are also believed to be present in the central nervous system. The compounds are described as being of use in the treatment of a human or animal subject suffering from a condition caused by a disturbance of neuronal 5HT function, for example in the treatment of a human subject suffering from migraine pain or a psychotic disorder such as schizophrenia. It is also stated that the compounds may be useful in the treatment of conditions such as anxiety, obesity and mania.

We have now surprisingly found that compounds of formula (I) promote gastric emptying and also that they are anti-emetic.

Accordingly, the invention provides a method of treatment for the relief of nausea and vomiting, and/or the promotion of gastric emptying e.g. for the relief of gastro-intestinal disorders associated with gastric stasis, which comprises administering to a human or animal subject an effective amount of a compound of formula (I), or a physiologically acceptable salt or solvate thereof.

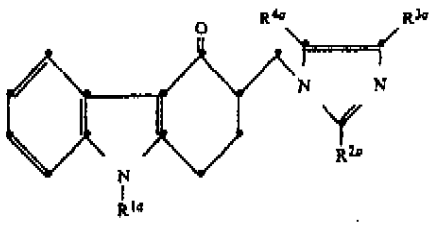
Tests in animals have shown that compounds of formula (I) enhance gastric emptying. The compounds are therefore of use in the treatment and/or prevention of conditions which may be relieved by the promotion of gastric emptying e.g. gastric stasis which may occur, for example, post-operatively, and symptoms of gastro-intestinal dysfunction such as occur with dyspepsia, peptic ulcer, reflux oseophagitis and flatulence. The compounds may also be used to promote gastric emptying in diagnostic radiological procedures, such as radiological examinations.

Tests in animals have also shown that compounds of formula (I) inhibit emesis. The compounds are therefore also of use as anti-emetic agents, i.e. in the prevention and treatment of nausea and vomiting. The compounds are especially valuable for the prevention of emesis induced by cancer chemotherapeutic agents such as cisplatin. Particular mention may also be made of the treatment of radiation-induced emesis. Thus, the compounds of formula (I) may be used in the prevention of emesis induced by radiation therapy, e.g. irradiation of the thorax or abdomen, such as in the treatment of cancer; or in the treatment of radiation sickness.

The compounds of formula (I) do not possess dopamine antagonist activity and thus will not produce the undesirable side effects found with known anti-emetic agents such as metoclopramide.

It will be appreciated that the compounds of formula (I) may be used prophylactically and references in this specification to treatment include prophylactic treatment as well as the alleviation of acute symptoms.

A preferred class of compounds for use according to the invention is that represented by the formula (Ia):



(Ia)

(wherein R^{1a} represents a hydrogen atom or a methyl, ethyl, propyl, prop-2-yl, prop-2-enyl or cyclopentyl group; R^{3a} represents a hydrogen atom; and either R^{2a} represents a methyl, ethyl, propyl or prop-2-yl group and R^{4a} represents a hydrogen atom or R^{2a} represents a hydrogen atom and R^{4a} represents a methyl or ethyl group) and physiologically acceptable salts and solvates (e.g. hydrates) thereof.

Preferred compounds for use according to the present invention are:

1,2,3,9-tetrahydro-3-[(2-methyl-1H-imidazol-1-yl)methyl]-9-(prop-2-enyl)-4H-carbazol-4-one;

9-cyclopentyl-1,2,3,9-tetrahydro-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one; and

1,2,3,9-tetrahydro-3-[(2-methyl-1H-imidazol-1-yl)methyl]-9-(prop-2-yl)-4H-carbazol-4-one and their physiologically acceptable salts and solvates.

A particularly preferred compound is 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one, and the physiologically acceptable salts and solvates (e.g. hydrates) thereof. A preferred form of this compound is the hydrochloride dihydrate.

The compounds of formula (Ia) are well absorbed from the gastro-intestinal tract. They do not prolong sleeping time in the pentobarbitone anaesthetised mouse indicating that there is no undesirable interaction with drug metabolising enzymes. Indeed they exhibit no effects on normal behaviour, are non-toxic and exhibit no undesirable effects in mice at doses up to 1 mg/kg intravenously.

Accordingly, the invention also provides a pharmaceutical composition which comprises at least one compound selected from 3-imidazolylmethyltetrahydrocarbazolone derivatives of the general formula (I), their physiologically acceptable salts and solvates, e.g. hydrates, for use in human or veterinary medicine, for the relief of nausea and vomiting and/or the promotion of gastric emptying e.g. for the relief of gastro-intestinal disorders associated with gastric stasis.

In a yet further aspect, the invention provides the use of a compound of formula (I) or a physiologically acceptable salt or solvate thereof, for the manufacture of a medicament for the relief of nausea and vomiting, and/or the promotion of gastric emptying e.g. for the relief of gastro-intestinal disorders associated with gastric stasis.

Pharmaceutical compositions for use in accordance with the present invention may be formulated in conventional manner using one or more physiologically acceptable carriers or excipients.

Thus the compounds of formula (I) and their physiologically acceptable salts and solvates may be formulated for oral, buccal, parenteral or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or the nose).

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administrations may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds of formula (I) may be formulated for parenteral administration by injection e.g. by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds of formula (I) may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of formula (I) may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For administration by inhalation the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurised packs or a nebuliser, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder

mix of a compound of formula (I) and a suitable powder base such as lactose or starch.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration.

A proposed dose of the compounds of the invention for administration in man (of approximately 70 kg body weight) is 0.05 to 20 mg, preferably 0.1 to 10 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day. The dose will depend on the route of administration and the body weight of the patient. It will be appreciated that it may be necessary to make routine variations to the dosage depending on the age and weight of the patient as well as the severity of the condition to be treated.

For oral administration a unit dose will preferaby contain from 0.5 to 8 mg of the active ingredient. A unit dose for parenteral administration will preferably contain 0.1 to 8 mg of the active ingredient.

Aerosol formulations are preferably arranged so that each metered dose or 'puff' delivered from a pressurised aerosol contains 0.2 mg to 4 mg of a compound of the invention, and each dose administered via capsules and cartridges in an insufflator or an inhaler contains 0.2 to 20 mg of a compound of the invention. The overall daily dose by inhalation will be within the range 0.4 to 80 mg. Administration may be several times daily, for example from 2 to 8 times, giving for example 1, 2 or 3 doses each time.

The compounds of formula (I) may be administered in combination with other therapeutic agents, for example to aid absorption of the therapeutic agent where this is hindered by the patient's condition, such as by gastric stasis associated with migraine. Thus, for example, the compounds may be administered in combination with antimigraine agents such as ergotamine, or antisecretory agents such as ranitidine. They may also be administered in combination with anticancer (e.g. cytostatic) drugs, for example to prevent nausea and vomiting associated with these agents. Cytostatic agents with which compounds of formula (I) may be administered include cyclophosphamide; alkylating agents; and platinum complexes such as cisplatin. Thus, a compound of formula (I) may be presented together with another therapeutic agent as a combined preparation for simultaneous, separate or sequential use, for the relief of nausea and vomiting, or gastrointestinal disorders associated with gastric stasis. Such a combined preparation may be, for example, a twin-pack. A preferred combination comprises a compound of formula (I) with a cytostatic agent, especially cisplatin.

In general, the presently available dosage forms of the known therapeutic agents will be suitable for use in such combined preparations. Thus, cisplatin may be provided in vials containing 10, 25 or 50 mg of the active ingredient.

The compounds of general formula (I) may be prepared by the process described in British patent application No. 2153821A. Analogous processes are also described in European patent application No. 86300423.

The efficacy of compounds of formula (I) in the promotion of gastric emptying and their anti-emetic activity have been demonstrated in standard animal models as described below.

(A) GASTRIC EMPTYING

Test compound:
1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one hydrochloride dihydrate

The effect of the test compound on gastric emptying was determined in guinea-pigs by following the progress of polystyrene-coated barium sulphate spheres (1 mm diameter) through the gut. The experimental method was based on that described by B. Costall et. al., Eur. J. Pharmacol 91, 197–205, 1983 and B. Cox et. al., Br. J. Pharmacol. 70, 104, 1980.

The spheres (approximately 30 in number) were administered orally in 0.2 ml carboxymethylcellulose with 0.05 ml glycerine. At the same time, the test compound was administered intraperitoneally at doses of 0.001, 0.01 and 0.1 mg/kg. The control animals received saline, administered intraperitoneally, in place of the test compound. Passage of the spheres through the gut was monitored at 30–60 minute intervals over a period of 2 hours by X-ray location. The number of spheres leaving the stomach was recorded and expressed as a percentage of the total.

The results are given in Table 1 below:

TABLE 1

Effect on test compound on gastric emptying in the guinea pig

Dose of test compound (mg/kg, i.p)*	n	Mean % Increase in gastric emptying (± s.e.) 1 hour	2 hours
0.001	4	21 ± 8.7	57 ± 10.5
0.01	4	33 ± 3.6	76.5 ± 11.2
0.1	4	47 ± 7.6	68 ± 5.0
Saline	5	10 ± 3.7	30 ± 8.5

*Dose expressed as corresponding weight of free base
n = number of animals
s.e. = standard error

(B) ANTI-EMESIS

Test compound:
1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]4H-carbazol-4-one hydrochloride dihydrate

The effect of the test compound on emesis was demonstrated in ferrets according to the general method described by Florezyk, Schurig and Bradner (Cancer Treatment Report, 1982 66(1) 187–9) and summarised below. Both the test compound and cisplatin were prepared and administered in normal saline. The dose of test compound was calculated as the free base.

(a) Control—without test compound: Emesis was induced in groups of 6 male ferrets weighing between 1.5–2 kg, by intravenous administration of cisplatin at a dose of 10 mg/kg. The onset of emesis occurred between 38 and 75 minutes after injection and over a period of 2 hours the number of vomits/retches (episodes) was in the range 30–62 (average 42±5 vomits/-retches per 2 h). Behavioural changes characteristic of emesis were also noted.

(b) With test compound: The test compound was administered to groups of 6 male ferrets (1.5–2 kg) by intravenous administration at doses of 0.01, 0.1 and 1 mg/kg, immediately prior to administration of cisplatin as described above. The animals were observed for 3 hours.

The results obtained are given in Table 2 below.

TABLE 2

	Onset of emesis (minutes)	Intensity of emesis (episodes 2 h)	Duration of emesis (hours)	Other observations
Compound				
Cisplatin (10 mg/kg i.v.) (control)	38–75	42 ± 5	2	Behavioural changes characteristic of emesis (e.g. increased or irregular respiration, backward locomotion, agitation)
Cisplatin (10 mg/kg i.v.) + Test Compound				
0.01 mg/kg i.v.	89–109	17 ± 2.9	1	Marked reduction in behavioural effects of cisplatin. In second and third hours after onset of emesis, the animals rested quietly and some slept
0.1 mg/kg i.v. 1 mg/kg i.v.	Emesis and behavioural changes were completely eliminated. After 30–40 minutes the animals rested quietly, and some slept.			

The effect of the test compound on emesis was also demonstrated following intraperitoneal administration, using a similar procedure to that described above.

Thus cisplatin was administered intraperitoneally to a group of 4 male ferrets at a dose of 9 mg/kg, and the time to onset of emesis and the number of emetic episodes were recorded. In a second group of four male ferrets the test compound was administered at a dose of 1 mg/kg i.p. 30 minutes before and 1 hour after intraperitoneal administration of cisplatin. The results are given in Table 3:

TABLE 3

Compound	Onset of emesis (minutes)	Mean no. of emetic episodes	Mean no. of retches
Cisplatin (9 mg/kg i.p.)	99.2 (± 8.8)	6 (± 2)	43 (± 10)
Cisplatin (9 mg/kg i.p.) + test compound (1 mg/kg i.p.)	emetic response completely abolished		

The following example illustrates the preparation of a compound of formula (I). Temperatures are in °C. Where indicated, solutions were dried over Na_2SO_4 and solids were dried in vacuo over P_2O_5 at 50° overnight. Chromatography was carried out using the technique described by W. C. Still et al (J. Org. Chem., 1978, 43, 2923–2925), on kieselgel 9385.

EXAMPLES

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]4H-carbazol-4-one hydrochloride

A solution of 2,3,4,9-tetrahydro-N,N,N,9-tetramethyl-4-oxo-1H-carbazole-3-methanaminium iodide (2.0 g) and 2-methylimidazole (5.0 g) in dry dimethylformamide (30 ml) was stirred, under nitrogen, at 95° for 16.75 h and then allowed to cool. The solid that crystallised was filtered off, washed with ice-cold, dry dimethylformamide (3×2 ml) and dry ether (2×10 ml) and then dried. The resulting solid (0.60 g) was suspended in a mixture of absolute ethanol (30 ml) and ethanolic hydrogen chloride (1 ml), and warmed gently to obtain a solution, which was filtered whilst warm. The filtrate was then diluted with dry ether to deposit a solid (0.6 g) which was recrystallised from absolute ethanol to give the *title compound* as a solid (0.27 g) m.p. 186°–187°.

Analysis Found: C, 61.9; H, 6.4; N, 11.8. $C_{18}H_{19}N_3O.HCl.H_2O$ requires C, 62.3; H, 6.1; N, 12.1%.

The following examples illustrate pharmaceutical formulations for use according to the invention, containing 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one hydrochloride dihydrate as the active ingredient (1.25 g of the hydrochloride dihydrate contains 1.00 g of the free base). Other compounds of formula (I) may be formulated in a similar manner.

EXAMPLE 2

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one

A solution of 3-[(dimethylamino)methyl]-1,2,3,9-tetrahydro-9-methyl-4H-carbazol-4-one hydrochloride (1.7 g) in water (17 ml) was treated with 2-methylimidazole (1.4 g) and then heated under reflux for 20 h. The cooled mixture was filtered and the residue washed with water (3×15 ml) to give crude product (1.7 g) m.p. 221°–221.5°. This material was recrystallized from methanol to give the *title compound* (1.4 g) m.p. 231°–232°.

EXAMPLE 3

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one hydrochloride dihydrate

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one (18.3 g) in a hot mixture of isopropanol (90 ml) and water (18.3 ml) was treated with concentrated hydrochloric acid (6.25 ml). The hot mixture was filtered and the filtrate diluted with isopropanol (90 ml) and stirred at room temperature for 17 h, cooled to 2° and the solid filtered off (21.6 g). A sample (6 g) was recrystallized from a mixture of water (6 ml) and isopropanol (10 ml) to give the *title compound* as a white crystalline solid (6 g) m.p. 178.5°–179.5°.

Analysis Found: C, 59.45; H, 6.45; N, 11.5. $C_{18}H_{19}N_3O.HCl.2H_2O$ requires C, 59.1; H, 6.6; N, 11.5%.

Water assay Found: 10.23%. $C_{18}H_{19}N_3O.HCl.2H_2O$ requires 9.85%.

TABLETS FOR ORAL ADMINISTRATION

Tablets may be prepared by the normal methods such as direct compression or wet granulation.

The tablets may be film coated with suitable film forming materials, such as hydroxypropyl methylcellulose, using standard techniques. Alternatively the tablets may be sugar coated.

Direct Compression

Tablet	mg/tablet	
Active Ingredient	4.688	28.125
Calcium Hydrogen Phosphate BP*	83.06	87.75
Croscarmellose Sodium NF	1.8	1.8
Magnesium Stearate BP	0.45	0.45
Compression weight	90.0	118.0

*of a grade suitable for direct compression.

The active ingredient was passed through a 60 mesh sieve, blended with the calcium hydrogen phosphate, croscarmellose sodium and magnesium stearate. The resultant mix was compressed into tablets using a Manesty F3 tablet machine fitted with 5.5 mm, flat bevelled edge punches.

Sub-Lingual Tablet	mg/tablet
Active Ingredient	2.5
Compressible Sugar NF	62.5
Magnesium Stearate BP	0.5
Compression Weight	65.0

The active ingredient is sieved through a suitable sieve, blended with the excipients and compressed using suitable punches. Tablets of other strengths may be prepared by altering either the ratio of active ingredient to excipients or the compression weight and using punches to suit.

Wet Granulation

Conventional Tablet	mg/tablet
Active Ingredient	2.5
Lactose BP	151.5
Starch BP	30.0
Pregelatinised Maize Starch BP	15.0
Magnesium Stearate BP	1.5
Compression Weight	200.0

The active ingredient is sieved through a suitable sieve and blended with lactose, starch and pregelatinised maize starch. Suitable volumes of purified water are added and the powders are granulated. After drying, the granules are screened and blended with the magnesium stearate. The granules are then compressed into tablets using 7 mm diameter punches.

Tablets of other strengths may be prepared by altering the ratio of active ingredient to lactose or the compression weight and using punches to suit.

Sub-Lingual Tablet	mg/tablet
Active Ingredient	2.5
Mannitol BP	56.5
Hydroxypropylmethylcellulose	5.0
Magnesium Stearate BP	1.5
Compression Weight	65.5

The active ingredient is sieved through a suitable sieve and blended with the mannitol and hydroxypropylmethylcellulose. Suitable volumes of purified water are added and the powders are granulated. After drying, the granules are screened and blended into tablets using suitable powders.

Tablets of other strengths may be prepared by altering the ratio of active ingredient to mannitol or the compression weight and punches to suit.

CAPSULES

CAPSULES	mg/tablet
Active Ingredient	2.5
*Starch 1500	97.0
Magnesium Stearate BP	1.0
Fill Weight	100.0

*a form of directly compressible starch.

The active ingredient is sieved and blended with the excipients. The mix is filled into size No. 2 hard gelatin capsules using suitable machinery. Other doses may be prepared by altering the fill weight and if necessary changing the capsule size to suit.

SYRUP

This may be either a sucrose or sucrose free presentation.

A. Sucrose Syrup		mg/5 ml dose
Active Ingredient		2.5
Sucrose BP		2750.0
Glycerine BP		500.0
Buffer, Flavour, Colour, Preservative		as required
Purified Water BP	to	5.0 ml

The active ingredient, buffer, flavour, colour and preservative are dissolved in some of the water and the glycerine is added. The remainder of the water is heated to dissolve the sucrose and is then cooled. The two solutions are combined, adjusted to volume and mixed. The syrup is clarified by filtration.

B. Sucrose-Free		mg/5 ml dose
Active Ingredient		2.5
Hydroxypropylmethylcellulose USP (viscosity type 4000)		22.5
Buffer, Flavour, Colour, Preservative, Sweetener		as required
Purified Water BP	to	5.0 ml

The hydroxypropylmethylcellulose is dispersed in hot water, cooled and then mixed with an aqueous solu-

tion containing the active ingredient and the other components of the formulation. The resultant solution is adjusted to volume and mixed. The syrup is clarified by filtration.

INJECTION

The injection may be administered by the intravenous or subcutaneous route.

Injection	µg/ml	
Active Ingredient	50	800
Dilute Hydrochloric Acid BP	to pH 3.5	to pH 3.5
Sodium Chloride Injection BP	to 1 ml	to 1 ml

The active ingredient was dissolved in a suitable volume of Sodium Chloride Injection BP, the pH of the resultant solution was adjusted to pH 3.5 with dilute hydrochloric acid BP then the solution was made to volume with sodium chloride injection BP and thoroughly mixed. The solution was filled into Type 1 clear glass 5 ml ampoules which were sealed under a headspace of air, by fusion of the glass then sterilised by autoclaving at 120° for not less than 15 minutes.

METERED DOSE PRESSURISED AEROSOL

Suspension Aerosol	mg/metered dose	Per can
Active Ingredient micronised	0.250	66 mg
Oleic Acid BP	0.020	5.28 mg
Trichlorofluoromethane BP	23.64	5.67 g
Dichlorodifluoromethane BP	61.25	14.70 g

The active ingredient is micronised in a fluid energy mill to a fine particle size range. The Oleic Acid is mixed with the Trichlorofluoromethane at a temperature of 10°–15° C. and the micronised drug is mixed into the solution with a high shear mixer. The suspension is metered into aluminium aerosol cans and suitable metering valves, delivering 85 mg of suspension are crimped onto the cans and the Dichlorodifluoromethane is pressure filled into the cans through the valves.

Solution Aerosol

	mg/metered dose	Per can
Active Ingredient	0.25	30.0 mg
Ethanol BP	7.500	1.80 g
Trichlorofluoromethane BP	18.875	4.35 g
Dichlorodifluoromethane BP	48.525	11.65 g

Oleic Acid BP, or a suitable surfactant e.g. Span 85 (sorbitan trioleate) may also be included).

The active ingredient is dissolved in the ethanol together with the Oleic Acid or surfactant if used. The alcoholic solution is metered into suitable aerosol containers followed by the trichlorofluoromethane. Suitable metering valves are crimped onto the containers and dichlorodifluoromethane is pressure filled into them through the valves.

Inhalation Cartridges

	mg/cartridge
Active Ingredient (micronised)	0.5
Lactose BP	to 25.00

The active ingredient is micronised in a fluid energy mill to a fine particle size range prior to blending with normal tabletting grade lactose in a high energy mixer. The powder blend is filled into No. 3 hard gelatin capsules on a suitable encapsulating machine. The contents of the cartridges are administered using a powder inhaler.

We claim:

1. A method of treatment for the relief of nausea and vomiting which comprises administering to a human or animal subject in need thereof an effective amount for treatment for the relief of nausea and vomiting of 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one or a physiologically acceptable salt or solvate thereof.

2. A method according to claim 1 wherein the 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one is in the form of its hydrochloride.

3. A method according to claim 1 wherein the 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one is in the form of its hydrochloride dihydrate.

4. A method according to claim 1 wherein said nausea and vomiting is induced by an anticancer drug.

5. A method according to claim 4 wherein the 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one is in the form of its hydrochloride dihydrate.

6. A method according to claim 4 wherein said anticancer drug is a cytostatic agent.

7. A method according to claim 6 wherein the 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one is in the form of its hydrochloride dihydrate.

8. A method according to claim 4 wherein said nausea and vomiting is induced by a platinum complex.

9. A method according to claim 8 wherein the 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one is in the form of its hydrochloride dihydrate.

10. A method according to claim 4 wherein said nausea and vomiting is induced by cisplatin.

11. A method according to claim 10 wherein the 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1)methyl]-4H-carbazol-4-one is in the form of its hydrochloride dihydrate.

12. A method according to claim 1 wherein said nausea and vomiting is induced by an alkylating agent.

13. A method according to claim 1 wherein said nausea and vomiting is induced by cyclophosphamide.

14. A method according to claim 12 wherein the 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one is in the form of its hydrochloride dihydrate.

15. A method according to claim 13 wherein the 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one is in the form of its hydrochloride dihydrate.

16. A method according to claim 1 wherein said nausea and vomiting is induced by radiation.

17. A method according to claim 16 wherein the 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one is in the form of its hydrochloride dihydrate.

* * * * *

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United States Patent [19]

Tyers et al.

[11] Patent Number: 5,578,628

[45] Date of Patent: *Nov. 26, 1996

[54] **MEDICAMENTS FOR THE TREATMENT OF NAUSEA AND VOMITING**

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[*] Notice: The portion of the term of this patent subsequent to Feb. 16, 2005, has been disclaimed.

[21] Appl. No.: **501,974**

[22] Filed: **Mar. 30, 1990**

Related U.S. Application Data

[60] Continuation of Ser. No. 315,314, Feb. 24, 1989, abandoned, which is a division of Ser. No. 177,042, Apr. 4, 1988, Pat. No. 4,929,632, which is a division of Ser. No. 877,805, Jun. 24, 1986, Pat. No. 4,753,789.

[30] **Foreign Application Priority Data**

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[51] **Int. Cl.**[6] **A61K 31/415**

[52] **U.S. Cl.** **514/397**

[58] **Field of Search** 514/397; 548/336, 548/439

[56] **References Cited**

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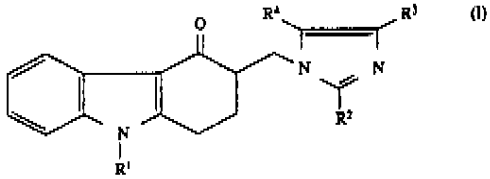
Primary Examiner—Raymond Henley, III
Attorney, Agent, or Firm—Bacon & Thomas

[57] **ABSTRACT**

The invention relates to the use of compounds of the general formula (I)



(I)

wherein

R^1 represents a hydrogen atom or a C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{-7} cycloalkyl-(C_{1-4}) alkyl, C_{3-6} alkenyl, C_{3-10} alkynyl, phenyl or phenyl-C_{1-3} alkyl group; and one of the groups represented by

R^2, R^3 and R^4 is a hydrogen atom or a C_{1-6} alkyl, C_{3-7}cycloalkynyl, C_{2-6} alkenyl or phenyl-C_{1-3} alkyl group and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C_{1-6} alkyl group; and physiologically acceptable salts and solvates thereof, for the relief of nausea and vomiting.

2 Claims, No Drawings

MEDICAMENTS FOR THE TREATMENT OF NAUSEA AND VOMITING

This application is a CONTINUATION of application Ser. No. 07/315,314, filed Feb. 24, 1989, now abandoned, which is a DIVISION of application Ser. No. 07/177,042, filed Apr. 4, 1988, now U.S. Pat. No. 4,929,632, which is a DIVISION of application Ser. No. 06/877,805, filed Jun. 24, 1986, now U.S. Pat. No. 4,753,789.

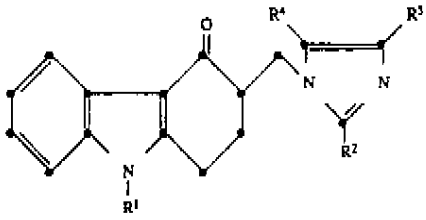
This invention relates to a new medical use for a group of heterocyclic compounds and pharmaceutical compositions containing them. In particular it relates to certain tetrahydocarbazolone derivatives which may be used to promote gastric emptying and as anti-emetic agents.

A particularly important application for anti-emetic agents is in the prevention and treatment of nausea and vomiting associated with cancer chemotherapy. Emesis is a well-known and frequent side-effect of cancer chemotherapeutic agents, such as cisplatin. It causes serious problems in cancer chemotherapy, and in some patients emesis is so severe that therapy must be discontinued. Anti-emetic agents are therefore often administered in order to alleviate this side-effect of the cancer chemotherapeutic agent. The anti-emetic agents employed are usually benzamide derivatives, such as metoclopramide, which have dopamine antagonist activity.

Metoclopramide is also a gastric mobility stimulant, i.e. it promotes gastric emptying. The promotion of gastric emptying is important in the treatment of gastro-intesinal disorders related to gastric stasis; and in radiological examinations.

In view of their dopamine antagonist activity benzamide derivatives such as metoclopramide themselves exhibit serious and undesirable side-effects, such as extra-pyramidal effects, i.e. tardive dyskinesia, acute distonia, akathisia and tremor. There is thus a need for a safe and effective anti-emetic agent and gastric mobility stimulant.

In our British patent application No. 2153821A and our European patent application No. 86300423 we disclose 3-imidazolylmehyltetrahydrocazbazolones which may be represented by the general formula (I)



(I)

wherein

R^1 represents a hydrogen atom or a C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkyl-(C_{1-4})alkyl, C_{3-6} alkenyl, C_{3-10}alkynyl, phenyl or phenyl-C_{1-3}alkyl group, and one of the groups represented by R^2, R^3 and R^4 is a hydrogen atom or a C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl or phenyl-C_{1-3}alkyl group and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C_{1-6} alkyl group;

and physiologically acceptable salts and solvates, e.g. hydrates, thereof.

Suitable physiologically acceptable salts of the carbazolones of general formula (I) include acid addition salts formed with organic or inorganic acids for example, hydrochlorides, hydrobromides, sulphates, phosphates, citrates, fumarates and maleates. The solvates may, for example, be hydrates.

The aforementioned specifications also disclose physiologically acceptable equivalents of the compounds of formula (I), i.e. physiologically acceptable compounds which are converted in vivo into the parent compound of formula (I).

The compounds of formula (I) are described in the aforementioned specifications as potent and selective antagonists of 5-hydroxytryptamine (5-HT) at 'neuronal' 5-HT receptors of the type located on terminals of primary afferent nerves, and which are also believed to be present in the central nervous system. The compounds are described as being of use in the treatment of a human or animal subject suffering from a condition caused by a disturbance of neuronal 5HT function, for example in the treatment of a human subject suffering from migraine pain or a psychotic disorder such as schizophrenia. It is also stated that the compounds may be useful in the treatment of conditions such as anxiety, obesity and mania.

We have now surprisingly found that compounds of formula (I) promote gastric emptying and also that they are anti-emetic.

Accordingly, the invention provides a method of treatment for the relief of nausea and vomiting, and/or the promotion of gastric emptying e.g. for the relief of gastro-intestinal disorders associated with gastric stasis, which comprises administering to a human or animal subject an effective amount of a compound of formula (I), or a physiologically acceptable salt or solvate thereof.

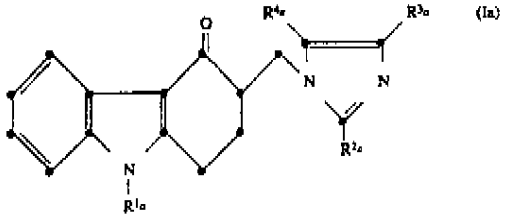
Tests in animals have shown that compounds of formula (I) enhance gastric emptying. The compounds are therefore of use in the treatment and/or prevention of conditions which may be relieved by the promotion of gastric emptying e.g. gastric stasis which may occur, for example, post-operatively, and symptoms of gastro-intestinal dysfunction such as occur with dyspepsia, peptic ulcer, reflux oesophagitis and flatulence. The compounds may also be used to promote gastric emptying in diagnostic radiological procedures, such as radiological examinations.

Tests in animals have also shown that compounds of formula (I) inhibit emesis. The compounds are therefore also of use as anti-emetic agents, i.e. in the prevention and treatment of nausea and vomiting. The compounds are especially valuable for the prevention of emesis induced by cancer chemotherapeutic agents such as cisplatin. Particular mention may also be made of the treatment of radiation-induced emesis. Thus, the compounds of formula (I) may be used in the prevention of emesis induced by radiation therapy, e.g. irradiation of the thorax or abdomen, such as in the treatment of cancer; or in the treatment of radiation sickness.

The compounds of formula (I) do not possess dopamine antagonist activity and thus will not produce the undesirable side effects found with known anti-emetic agents such as metoclopramide.

It will be appreciated that the compounds of formula (I) may be used prophylactically and references in this specification to treatment include prophylactic treatment as well as the alleviation of acute symptoms.

A preferred class of compounds for use according to the invention is that represented by the formula (Ia):



(Ia)

(wherein R^{1a} represents a hydrogen atom or a methyl, ethyl, propyl, prop-2-yl, prop-2-enyl or cyclopentyl group; R^{3a} represents a hydrogen atom; and either R^{2a} represents a methyl, ethyl, propyl or prop-2-yl group and R^{4a} represents a hydrogen atom or R^{2a} represents a hydrogen atom and R^{4a} represents a methyl or ethyl group) and physiologically acceptable salts and solvates (e.g. hydrates) thereof.

Preferred compounds for use according to the present invention are:

1,2,3,9-tetrahydro-3[(2-methyl-1H-imidazol-1-yl)methyl]-9-(prop-2-enyl)-4H-carbazol-4-one;

9-cyclopentyl-1,2,3,9-tetrahydro-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one; and

1,2,3,9-tetrahydro-3-[(2-methyl-1H-imidazol-1-yl)methyl]-9-(prop-2-yl)-4H-carbazol-4-one and their physiologically acceptable salts and solvates.

A particularly preferred compound is 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one, and the physiologically acceptable salts and solvates (e.g. hydrates) thereof. A preferred form of his compound is the hydrochloride dihydrate.

The compounds of formula (Ia) are well absorbed from the gastro-intestinal tract. They do not prolong sleeping time in the pentobarbiton anaesthetised mouse indicating that there is no undesirable interaction with drug metabolising enzymes. Indeed they exhibit no effects on normal behaviour, are non-toxic and exhibit no undesirable effects in mice at doses up to 1 mg/kg intravenously.

Accordingly, the invention also provides a pharmaceutical composition which comprises at least one compound selected from 3-imidazolylmethyltetrahydrocarbazolone derivatives of the general formula (I), their physiologically acceptable salts and solvates, e.g. hydrates, for use in human or veterinary medicine, for the relief of nausea and vomiting and/or the promotion of gastric emptying e.g. for the relief of gastro-intestinal disorders associated with gastric stasis.

In a yet further aspect, the invention provides the use of a compound of formula (I) or a physiologically acceptable salt or solvate thereof, for the manufacture of a medicament for the relief of nausea and vomiting, and/or the promotion of gastric emptying e.g. for the relief of gastro-intestinal disorders associated with gastric stasis.

Pharmaceutical compositions for use in accordance with the present invention may be formulated in conventional manner using one or more physiologically acceptable carriers or excipients.

Thus the compounds of formula (I) and their physiologically acceptable salts and solvates may be formulated for oral, buccal, parenteral or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or the nose).

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds of formula (I) may be formulated or parenteral administration by injection e.g. by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds of formula (I) may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of formula (I) may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For administration by inhalation the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurised packs or a nebuliser, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of formula (I) and a suitable powder base such as lactose or starch.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration.

A proposed dose of the compounds of the invention for administration in man (of approximately 70 kg body weight) is 0.05 to 20 mg, preferably 0.1 to 10 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day. The dose will depend on the route of administration and the body weight of the patient. It will be appreciated that it may be necessary to make routine variations to the dosage depending on the age and weight of the patient as well as the severity of the condition to be treated.

For oral administration a unit dose will preferably contain from 0.5 to 8 mg of the active ingredient. A unit dose for parenteral administration will preferably contain 0.1 to 8 mg of the active ingredient.

Aerosol formulations are preferably arranged so that each metered dose or 'puff' delivered from a pressurised aerosol contains 0.2 mg to 4 mg of a compound of the invention, and each dose administered via capsules and cartridges in an insufflator or an inhaler contains 0.2 to 20 mg of a compound of the invention. The overall daily dose by inhalation will be within the range 0.4 to 80 mg. Administration may be several times daily, for example from 2 to 8 times, giving for example 1, 2 or 3 doses each time.

The compounds of formula (I) may be administered in combination with other therapeutic agents, for example to aid absorption of the therapeutic agent where this is hindered by the patient's condition, such as by gastric stasis associated with migraine. Thus, for example, the compounds may be administered in combination with antimigraine agents such as ergotamine, or antisecretory agents such as ranitidine. They may also be administered in combination with anticancer (e.g. cytostatic) drugs, for example to prevent nausea and vomiting associated with these agents. Cytostatic agents with which compounds of formula (I) may be administered include cyclophosphamide; alkylating agents; and platinum complexes such as cisplatin. Thus, a compound of formula (I) may be presented together with another therapeutic agent as a combined preparation for simultaneous, separate or sequential use, for the relief of nausea and vomiting, or gastrointestinal disorders associated with gastric stasis. Such a combined preparation may be, for example, a twin-pack. A preferred combination comprises a compound of formula (I) with a cytostatic agent, especially cisplatin. In general, the presently available dosage forms of the known therapeutic agents will be suitable for use in such combined preparations. Thus, cisplatin may be provided in vials containing 10, 25 or 50 mg of the active ingredient.

The compounds of general formula (I) may be prepared by the process described in British patent application No. 2153821A. Analogous processes are also described in European patents application No. 86300423.

The efficacy of compounds of formula (I) in the promotion of gastric emptying and their anti-emetic activity have been demonstrated in standard animal models as described below.

(A) GASTRIC EMPTYING

Test compound:
1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one hydrochloride dihydrate

The effect of the test compound on gastric emptying was determined in guinea-pigs by following the progress of polystyrene-coated barium sulphate spheres (1 mm diameter) through the gut. The experimental method was based on that described by B. Costall et. al., Eur. J. Pharmacol 91, 197–205, 1983 and B. Cox et. al., Br. J Pharmacol. 70, 104, 1980.

The spheres (approximatley 30 in number) were administered orally in 0.2 ml carboxymethylcellulose with 0.05 ml glycerine. At the same time, the test compound was administered intraperitoneally at doses of 0.001, 0.01 and 0.1 mg/kg. The control animals received saline, administered intraperitoneally, in place of the test compound. Passage of the spheres through the gut was monitored at 30–60 minute intervals over a period of 2 hours by X-ray location. The number of spheres leaving the stomach was recorded and expressed as a percentage of the total.

The results are given in Table 1 below:

TABLE 1

Effect on test compound on gastric emptying in the guinea pig

Dose of test compound (mg/kg, i.p.)*	n	Mean % increase in gastric emptying (± s.e.) 1 hour	2 hours
0.001	4	21 ± 8.7	57 ± 10.5
0.01	4	33 ± 3.6	76.5 ± 11.2
0.1	4	47 ± 7.6	68 ± 5.0
Saline	5	10 ± 3.7	30 ± 8.5

*Dose expressed as corresponding weight of free base
n = number of animals
s.e. = standard error

(B) ANTI-EMESIS

Test compound:
1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one hydrochloride dihydrate

The effect of the test compound on emesis was demonstrated in ferrets according to the general method described by Florczyk, Schurig and Bradnet (Cancer Treatment Report, 1982 66(1) 187–9) and summarised below. Both the test compound and cisplatin were prepared and administered in normal saline. The dose of test compound was calculated as the free base.

a) Control—Without Test Compound

Emesis was induced in groups of 6 male ferrets weighing between 1.5–2 kg, by intravenous administration of cisplatin at a dose of 10 mg/kg. The onset of emesis occurred between 38 and 75 minutes after injection and over a period of 2 hours the number of vomits/retches (episodes) was in the range 30–62 (average 42±5 vomits/retches per 2 h). Behavioural changes characteristic of emesis were also noted.

b) With Test Compound

The test compound was administered to groups of 6 male ferrets (1.5-2 kg) by intravenous administration at doses of 0.01, 0.1 and 1 mg/kg, immediately prior to administration of cisplatin as described above. The animals were observed for 3 hours.

The results obtained are given in Table 2 below.

TABLE 2

Compound	Onset of emesis (minutes)	Intensity of emesis (episodes 2 h)	Duration of emesis (hours)	Other observations
Cisplatin (10 mg/kg i.v.) (control)	38–75	42 ± 5	2	Behavioural changes characteristic of emesis (e.g. increased or irregular respiration, backward locomotion, agitation)
Cisplatin (10 mg/kg i.v.) + Test Compound 0.01 mg/kg i.v.	89–109	17 ± 2.9	1	Marked reduction in behavioural effects of cisplatin. In second onset of emesis, the animals rested quietly and some slept
0.1 mg/kg i.v.	} Emesis and behavioural changes were completely eliminated. After 30–40 minutes the animals rested quietly, and some slept.			
1 mg/kg i.v.				

The effect of the test compound on emesis was also demonstrated following intraperitoneal administration, using a similar procedure to that described above.

Thus cisplatin was administered intraperitoneally to a group of 4 male ferrets at a dose of 9 mg/kg, and the time to onset of emesis and the number of emetic episodes were recorded. In a second group of four male ferrets the test compound was administered at a dose of 1 mg/kg i.p. 30 minutes before and 1 hour after intraperitoneal administration of cisplatin. The results are given in Table 3:

TABLE 3

Compound	Onset of emesis (minutes)	Mean no. of emetic episodes	Mean no. of retches
Cisplatin (9 mg/kg i.p.)	99.2 (± 8.8)	6 (± 2)	43 (± 10)
Cisplatin (9 mg/kg i.p.) + test compound (1 mg/kg i.p.)	emetic response completely abolished		

The following example illustrates the preparation of a compound of formula (I). Temperatures are in °C. Where indicated, solutions were dried over Na_2SO_4 and solids were dried in vacuo over P_2O_5 at 50° overnight. Chromatography was carried out using the technique described by W. C. Still et al (J. Org. Chem., 1978, 43, 2923–2925), on kieselgel 9385.

EXAMPLE

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl) methyl]-4H-carbazol-4-one hydrochloride

A solution of 2,3,4,9-tetrahydro-N,N,N,9-tetramethyl-4-oxo-1H-carbazole-3-methanaminium iodide (2.0 g) and 2-methylthiazole (5.0 g) in dry dimethylformamide (30 ml) was stirred, under nitrogen, at 95° for 16.75 h and then allowed to cool. The solid that crystallised was filtered off, washed with ice-cold, dry dimethylformamide (3×2 ml) and dry ether (2×10 ml) and then dried. The resulting solid (0.60 g) was suspended in a mixture of absolute ethanol (30 ml) and ethanolic hydrogen chloride (1 ml), and warmed gently to obtain a solution, which was filtered whilst warm. The

filtrate was then diluted with dry ether to deposit a solid (0.6 g) which was recrystallized from absolute ethanol to give the title compound as a solid (0.27 g) m.p. 186–187°.

Analysis Found: C,61.9;H,6.4;N,11.8.

$C_{18}H_{19}N_3O.HCl.H_2O$ requires C,62.3;H,6.1;N,12.1%.

The following examples illustrate pharmaceutical formulations for use according to the invention, containing 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one hydrochloride dihydrate as the active ingredient (1.25 g of the hydrochloride dihydrate contains 1.00 g of the free base). Other compounds of formula (I) may be formulated in a similar manner.

TABLETS FOR ORAL ADMINISTRATION

Tablets may be prepared by the normal methods such as direct compression or wet granulation.

The tablets may be film coated with suitable film forming materials, such as hydroxypropyl methylcellulose, using standard techniques. Alternatively the tablets may be sugar coated.

Direct Compression

Tablet	mg/tablet	
Active Ingredient	4.688	28.125
Calcium Hydrogen Phosphate BP*	83.06	87.75
Croscarmellose Sodium NF	1.8	1.8
Magnesium Stearate BP	0.45	0.45
Compression weight	90.0	118.0

*of a grade suitable for direct compression.

The active ingredient was passed through a 60 mesh sieve, blended with the calcium hydrogen phosphate, croscarmellose sodium and magnesium stearate. The resultant mix was compressed into tablets using a Manesty F3 tablet machine fitted with 5.5 mm. flat bevelled edge punches.

Sub-Lingual Tablet	mg/tablet
Active Ingredient	2.5
Compressible Sugar NF	62.5
Magnesium Stearate BP	0.5
Compression Weight	65.0

The active ingredient is sieved through a suitable sieve, blended with the excipients and compressed using suitable punches. Tablets of other strengths may be prepared by altering either the ratio of active ingredient to excipients or the compression weight and using punches to suit.

Wet Granulation

Conventional Tablet	mg/tablet
Active Ingredient	2.5
Lactose BP	151.5
Starch BP	30.0
Pregelatinised Maize Starch BP	15.0
Magnesium Stearate BP	1.5
Compression Weight	200.0

The active ingredient is sieved through a suitable sieve and blended with lactose, starch and pregelatinised maize starch. Suitable volumes of purified water are added and the powders are granulated. After drying, the granules are screened and blended with the magnesium stearate. The

granules are then compressed into tablets using 7 mm diameter punches.

Tablets of other strengths may be prepared by altering the ratio of active ingredient to lactose of the compression weight and using punches to suit.

Sub-Lingual Tablet	mg/tablet
Active Ingredient	2.5
Mannitol BP	56.5
Hydroxypropylmethylcellulose	5.0
Magnesium Stearate BP	1.5
Compression Weight	65.5

The active ingredient is sieved through a suitable sieve and blended with the mannitol and hydroxypropylmethylcellulose. Suitable volumes of purified water are added and the powders are granulated. After drying, the granules are screened and blended into tablets using suitable punches.

Tablets of other strengths may be prepared by altering the ratio of active ingredient to mannitol or the compression weight and punches to suit.

CAPSULES	mg/tablet
Active Ingredient	2.5
*Starch 1500	97.0
Magnesium Stearate BP	1.0
Fill Weight	100.0

*a form of directly compressible starch.

The active ingredient is sieved and blended with the excipients. The mix is filled into size No. 2 hard gelatin capsules using suitable machinery. Other doses may be prepared by altering the fill weight and if necessary changing the capsule size to suit.

SYRUP

This may be either a sucrose or sucrose free presentation.

A. Sucrose Syrup	mg/5 ml dose
Active Ingredient	2.5
Sucrose BP	2750.0
Glycerine BP	500.0
Buffer, Flavour, Colour, Preservative	as required
Purified Water BP to	5.0 ml

The active ingredient, buffer, flavour, colour and preservative are dissolved in some of the water and the glycerine is added. The remainder of the water is heated to dissolve the sucrose and is then cooled. The two solutions are combined, adjusted to volume and mixed. The syrup is clarified by filtration.

B. Sucrose-Free	mg/5 ml dose
Active Ingredient	2.5
Hydroxypropylmethylcellulose USP (viscosity type 4000)	22.5
Buffer, Flavour, Colour	as required
Preservative, Sweetener	
Purified Water BP to	5.0 ml

The hydroxypropylmethylcellulose is dispersed in hot water, cooled and then mixed with an aqueous solution containing the active ingredient and the other components of the formulation. The resultant solution is adjusted to volume and mixed. The syrup is clarified by filtration.

INJECTION

The injection may be administered by the intravenous or subcutaneous route.

Injection	µg/ml
Active Ingredient	50 800
Dilute Hydrochloric Acid BP to	pH 3.5 to pH 3.5
Sodium Chloride Injection BP to	1 ml to 1 ml

The active ingredient was dissolved in a suitable volume of Sodium Chloride Injection BP, the pH of the resultant solution was adjusted to pH 3.5 with dilute hydrochloric acid BP then the solution was made to volume with sodium chloride injection BP and thoroughly mixed. The solution was filled into Type 1 clear glass 5 ml ampoules which were sealed under a headspace of air, by fusion of the glass then sterilised by autoclaving at 120° for not less than 15 minutes.

METERED DOSE PRESSURISED AEROSOL

Suspension Aerosol	mg/metered dose	Per can
Active Ingredient micronised	0.250	66 mg
Oleic Acid BP	0.020	5.28 mg
Trichlorofluoromethane BP	23.64	5.67 g
Dichlorodifluoromethane BP	61.25	14.70 g

The active ingredient is micronised in a fluid energy mill to a fine particle size range. The Oleic Acid is mixed with the Trichlorofluoromethane at a temperature of 10°–15° C. and the micronised drug is mixed into the solution with a high shear mixer. The suspension is metered into aluminium aerosol cans and suitable metering valves, delivering 85 mg of suspension are crimped onto the cans and the Dichlorodifluoromethane is pressure filled into the cans through the valves.

Solution Aerosol	mg/metered dose	Per can
Active Ingredient	0.25	30.0 mg
Ethanol BP	7.500	1.80 g
Trichlorofluoromethane BP	18.875	4.35 g
Dichlorodifluoromethane BP	48.525	11.65 g
Oleic Acid BP, or a suitable surfactant e.g. Span 85 (sorbitan trioleate) may also be included).		

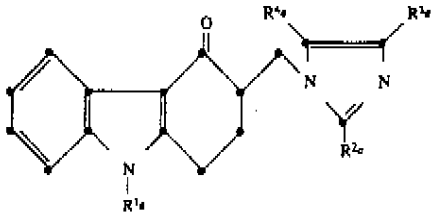
The active ingredient is dissolved in the ethanol together with the Oleic Acid or surfactant if used. The alcoholic solution is metered into suitable aerosol containers followed by the trichlorofluoromethane. Suitable metering valves are crimped onto the containers and dichlorodifluoromethane is pressure filled into them through the valves.

Inhalation Cartridges	mg/cartridge
Active Ingredient (micronised)	0.5
Lactose BP to	25.00

The active ingredient is micronised in a fluid energy mill to a fine particle size range prior to blending with normal tabletting grade lactose in a high energy mixer. The powder blend is filled into No. 3 hard gelatin capsules on a suitable encapsulating machine. The contents of the cartridges are administered using a powder inhaler.

We claim:

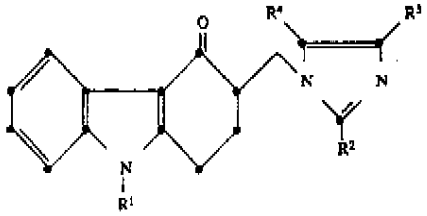
1. A method of treatment of nausea and vomiting which comprises administering to a human or animal subject in need thereof an effective amount for the treatment of nausea and vomiting of a compound of formula (Ia)



(Ia)

wherein R^{1a} represents a hydrogen atom or a methyl, ethyl, propyl, prop-2-yl, prop-2-enyl or cyclopentyl group; R^{3a} represents a hydrogen atom; and either R^{2a} represents a methyl, ethyl, propyl or prop-2-yl group and R^{4a} represents a hydrogen atom or R^{2a} represents a hydrogen atom and R^{4a} represents a methyl or ethyl group or a physiologically acceptable salt or solvate thereof.

2. A method of treatment of nausea and vomiting induced by an anti-cancer drug which is cisplatin, which comprises administering to a human or animal subject in need thereof an effective amount for the treatment of nausea and vomiting of a compound of formula (Ia)



(Ia)

wherein R^{1a} represents a hydrogen atom or a methyl, ethyl, propyl, prop-2-yl, prop-2-enyl or cyclopentyl group; R^{3a} represents a hydrogen atom; and either R^{2a} represents a methyl, ethyl, propyl or prop-2-yl group and R^{4a} represents a hydrogen atom or R^{2a} represents a hydrogen atom and R^{4a} represents a methyl or ethyl group or a physiologically acceptable salt or solvate thereof.

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United States Patent [19]

Collin

[11] Patent Number: 5,622,720

[45] Date of Patent: *Apr. 22, 1997

[54] **PROCESS FOR REDUCING THE CRYSTAL SIZE OF ONDANSETRON HYDROCHLORIDE DIHYDRATE**

[75] Inventor: **David T. Collin**, Ware, England

[73] Assignee: **Glaxo Group Limited**, London, England

[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,344,658.

[21] Appl. No.: **472,881**

[22] Filed: **Jun. 7, 1995**

Related U.S. Application Data

[63] Continuation of Ser. No. 239,237, May 6, 1994, abandoned, which is a continuation of Ser. No. 5,736, Jan. 19, 1993, Pat. No. 5,344,658, which is a continuation of Ser. No. 755,736, Sep. 6, 1991, abandoned, which is a continuation of Ser. No. 544,644, Jun. 27, 1990, abandoned.

[30] **Foreign Application Priority Data**

Jun. 28, 1989 [GB] United Kingdom 89/14804

[51] **Int. Cl.**[6] **A61K 9/14**

[52] **U.S. Cl.** **424/489**; 424/464; 424/465

[58] **Field of Search** 424/464, 465, 424/484, 489; 514/951, 960

[56] **References Cited**

U.S. PATENT DOCUMENTS

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Primary Examiner—Thurman K. Page
Assistant Examiner—James M. Spear
Attorney, Agent, or Firm—Bacon & Thomas

[57] **ABSTRACT**

The invention relates to a process for reducing the crystal size of ondansetron hydrochloride dihydrate produced by crystallization from solvent to a size which is suitable for effective distribution in a tablet blend, in particular 100% less that 250 μm. The ondansetron hydrochloride dihydrate is desolvated by drying at elevated temperature and reduced or atmospheric pressure and is then rehydrated.

14 Claims, No Drawings

PROCESS FOR REDUCING THE CRYSTAL SIZE OF ONDANSETRON HYDROCHLORIDE DIHYDRATE

This application is a Continuation of application Ser. No. 08/239,237, filed May 6, 1994, now abandoned, which is a Continuation of application Ser. No. 08/005,736, filed Jan. 19, 1993, now U.S. Pat. No. 5,344,658, which is a Continuation of application Ser. No. 07/755,736, filed Sep. 6, 1991, now abandoned, which is a Continuation of application Ser. No. 07/544,644, filed Jun. 27, 1990, now abandoned.

This invention relates to a process for reducing the crystal size of ondansetron hydrochloride dihydrate. More particularly the process involves desolvation and resolvation.

Reduction of crystal size through solvation and desolvation has been described previously, for instance for the compound griseofulvin (K. Sekiguchi et al., Chem. Pharm. Bull., 1968, 16, 2495–2502). Various techniques may be employed to effect desolvation such as drying at an elevated temperature and under vacuum, drying at an elevated temperature and at atmospheric pressure, drying at ambient temperature under a high vacuum, freeze-drying, or drying over a desiccant. However, the precise conditions of desolvation considerably affect the efficiency of the reduction in crystal size.

Ondansetron, the approved name for 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one, is a highly selective and potent antagonist of 5-hydroxytryptamine (5-HT) at 5-HT_3 receptors. Ondansetron, together with its physiologically acceptable salts and solvates, is described and claimed in British Patent No. 2153821B, and may be used in the treatment of a variety of conditions, including the nausea and vomiting induced by cancer chemotherapy and radiotherapy (as described, for example, in European Patent Specification No. 226226A).

The preferred form of ondansetron for pharmaceutical formulation is the hydrochloride dihydrate. Ondansetron hydrochloride dihydrate may be presented in a variety of formulations, one of which is as tablets for oral administration, when particularly suitable unit doses of the drug substance for the treatment of emesis are 5 mg and 10 mg.

In the tablet manufacturing process, ondansetron hydrochloride dihydrate is blended with suitable excipients, and the blend is then compressed into tablets.

Since a low dose of drug substance per tablet is required, for example, 5 mg of ondansetron hydrochloride dihydrate in a tablet of 125 mg compression weight, the distribution of the drug substance in the blend is critical in obtaining individual tablets with the correct drug content. Uniform drug distribution in the tablet blend may be achieved using drug substance of appropriate particle size. However, the ondansetron hydrochloride dihydrate obtained by methods described in the art, i.e. that obtained by simple crystallization from an aqueous solvent mixture with subsequent drying at ambient temperature and pressure contains particles which are too large (i.e. >250 μm) to give an homogeneous distribution of the drug substance in the tablet blend. Indeed if crystalline ondansetron hydrochloride dihydrate produced by such conventional methods were used in tablet manufacture, the tablets so produced would not possess an acceptable drug content which, for a 5 mg tablet, is 5 mg±0.25 mg of ondansetron hydrochloride dihydrate.

Attempts to mill crystals of ondansetron hydrochloride dihydrate to reduce their particle size have proved unsuccessful, for example, comminution milling of ondansetron hydrochloride dihydrate caused screen blockage of coarse and fine screens. Furthermore, although ondansetron hydrochloride dihydrate of particle size <250 μm can be obtained by passing the substance through a 60 mesh sieve (as described, for example, in UK Patent No. 2153821B), this method is not commercially viable.

We have now found a process which reduces the crystal size of ondansetron hydrochloride dihydrate produced by simple crystallization from solvent (more particularly aqueous solvent mixtures) to a size which is suitable for effective distribution of the drug substance in the tablet blend.

Thus the invention provides a process for reducing the crystal size of ondansetron hydrochloride dihydrate obtained by simple crystallization from solvent, more particularly an aqueous solvent mixture, to a size which is suitable for effective distribution in a tablet blend, which comprises desolvating the said drug substance by drying at an elevated temperature and reduced or atmospheric pressure, and then rehydrating the ondansetron hydrochloride so formed.

It is possible by means of the process according to the invention to reduce the crystal size of ondansetron hydrochloride dihydrate to the extent that the entire drug substance consists of particles of a sufficiently small size (i.e. less than 250 μm, of which typically about 80% by weight are less than 63 μm) to give an homogeneous distribution of the drug substance in the tablet blend.

Preferably, the ondansetron hydrochloride dihydrate obtained by crystallization is desolvated by heating at a temperature greater than 40° C. (e.g. 50° C.) and at reduced pressure (e.g. 200 torr or less) for more than 8 hours. Alternatively, the ondansetron hydrochloride dihydrate obtained by crystallization may be desolvated at ambient pressure by heating at a temperature of 50° C. or above (more preferably 100° C.).

Most preferably, ondansetron hydrochloride dihydrate obtained by crystallization is desolvated by heating at 50° C. at a pressure of 100 torr for 2 hours.

The desolvation process may be carried out with or without mechanical agitation.

The resultant ondansetron hydrochloride of reduced crystal size is then rehydrated, for example, by placing it in a humidified atmosphere of, for example, air or nitrogen, at ambient temperature. Rehydration will generally be continued until there is no further gain in weight.

According to another aspect, the invention provides crystalline ondansetron hydrochloride dihydrate characterized in that 100% of the crystals have a size of less than 250 μm and at least 80% by weight of the crystals have a crystal size of less than 63 μm (as measured by air-jet sieve analysis).

According to a yet further aspect, the invention provides a pharmaceutical composition in the form of tablets containing crystalline ondansetron hydrochloride dihydrate as active ingredient characterized in that 100% of the ondansetron hydrochloride dihydrate crystals have a size less than 250 μm and at least 80% by weight of the crystals have a crystal size of less that 63 μm (as measured by air-jet sieve analysis). Generally the composition will contain at least one physiologically acceptable carrier or excipient.

The invention is illustrated by the following examples. Temperatures are in °C. Crystal size was measured by air-jet sieve analysis.

EXAMPLE 1

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one hydrochloride dihydrate wherein the crystals are less than 250 μm

A solution of 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one (147 g) in a

mixture of isopropanol (670 ml), water (250 ml) and glacial acetic acid (76 ml) at ca. 60° was clarified by filtration and diluted with more water (61 ml) and isopropanol (650 ml). The solution was treated at 70° with 36% w/w hydrochloric acid (46 ml) and cooled to ca. 5°. The resulting suspension was filtered and the filtered solid was washed by displacement with isopropanol (600 ml) to give a solvent wet solid (269 g). A portion of this solid (91 g) was dried at ca. 50° and 200 torr for ca. 16h to give a solid (55 g).

A portion of the dried solid (26 g) was placed in a current of humidified air at ambient temperature until there was no further gain in weight and the title compound (29 g) was obtained.

Particle Size Distribution of Title Compound

Size (μm)	Cumulative % Undersize (by weight)
45	43.4
63	83.7
90	97.6
125	98.4
180	99.6
250	100.0

EXAMPLE 2

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one hydrochloride dihydrate wherein the crystals are less than 250 μm

The previous preparation was repeated except that after collection by filtration the solid was dried at ambient temperature and pressure to give large crystals (>45% by weight of crystals larger than 250 μm) of 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one hydrochloride dihydrate.

Particle Size Distribution of "Large Crystals"

Size (μm)	Cumulative % Undersize (by weight)
45	5.8
63	9.8
90	20.8
125	26.7
180	37.8
250	50.6
355	71.5
500	90.9
710	98.4
1000	98.6

A sample of this solid (26.9 g) was dried at ambient pressure and 100° for ca. 17h during which period the weight of the sample was reduced to 24.3 g. The sample was then exposed to ambient temperatures and humidities until it had regained its original weight to afford the title compound.

Particle Size Distribution of Title Compound

Size (μm)	Cumulative % Undersize (by weight)
45	47.6
63	94.8
90	100.0

EXAMPLE 3

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one hydrochloride dihydrate wherein the crystals are less than 250 μm.

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one hydrochloride dihydrate obtained by crystallization from a solvent was dried at 52° and 100 torr for 24h and then rehydrated to give the title compound.

Particle Size Distribution of Title Compound

Size (μm)	Cumulative % Undersize (by weight)
45	44.3
63	83.2
90	97.0
125	98.8
180	99.8
250	100.0

EXAMPLE 4

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one hydrochloride dihydrate wherein the crystals are less than 90 μm

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one hydrochloride dihydrate obtained by crystallization from a solvent was dried at 48° and 100 torr for 24h and then rehydrated to give the title compound.

Particle Size Distribution of Title Compound

Size (μm)	Cumulative % Undersize
45	49.0
63	92.4
90	100.0

1 claim:

1. A process for reducing the crystal size of ondansetron hydrochloride dihydrate produced by crystallization from solvent, in which said ondansetron hydrochloride dihydrate is desolvated by drying at elevated temperature and reduced or atmospheric pressure and is then rehydrated, wherein the resulting crystals are suitable for homogeneous distribution in a tablet blend, said tablet providing a pharmaceutically acceptable formulation in effective amounts for treatment of ondansetron responsive conditions.

2. A process according to claim 1, in which said ondansetron hydrochloride dihydrate is prepared by crystallization from an aqueous solvent mixture.

3. A process according to claim 1, in which said ondansetron hydrochloride dihydrate is desolvated by heating at a temperature greater than 40° C. and at reduced pressure for more than 8 hours.

4. A process according to claim 3, in which said ondansetron hydrochloride dihydrate is desolvated by heating at a temperature of about 50° C. at a pressure of about 100 torr for about 24 hours.

5. A process according to claim 1, in which said ondansetron hydrochloride dihydrate is desolvated by heating at a temperature of 50° C. or above at ambient pressure.

6. A process according to claim 5, in which said temperature is about 100° C.

7. A process according to claim 1, in which said ondansetron hydrochloride dihydrate is rehydrated in a humidified atmosphere at ambient temperature.

8. A process for reducing the crystal size of ondansetron hydrochloride dihydrate produced by crystallisation from solvent, in which said ondansetron hydrochloride dihydrate is desolvated by drying at elevated temperature and reduced or atmospheric pressure and is then rehydrated, wherein the resulting crystals are suitable for effective distribution in a tablet blend, said tablet providing a pharmaceutically acceptable formulation in effective amounts for treatment of ondansetron responsive conditions.

9. A process according to claim 8, in which said ondansetron hydrochloride dihydrate is prepared by crystallisation from an aqueous solvent mixture.

10. A process according to claim 8, in which said ondansetron hydrochloride dihydrate is desolvated by heating at a temperature greater than 40° C. and at reduced pressure for more than 8 hours.

11. A process according to claim 10, in which said ondansetron hydrochloride dihydrate is desolvated by heating at a temperature of about 50° C. at a pressure of about 100 torr for about 24 hours.

12. A process according to claim 8, in which said ondansetron hydrochloride dihydrate is desolvated by heating at a temperature of 50° C. or above at ambient pressure.

13. A process according to claim 12, in which said temperature is about 100° C.

14. A process according to claim 8, in which said ondansetron hydrochloride dihydrate is rehydrated in a humidified atmosphere at ambient temperature.

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