

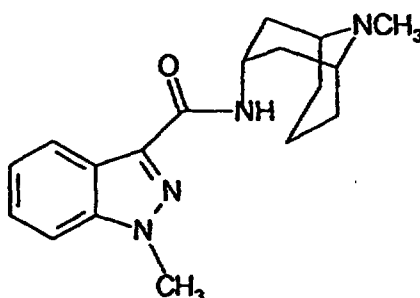
Description

This invention relates to a novel compound having useful pharmacological properties, to pharmaceutical compositions containing it, to a process for its preparation, and to its use as a pharmaceutical.

UK Patent Applications, GB 2100259A, 2125398A (corresponding to WO 84/00166) and GB 2145416A (corresponding to WO 85/01048), describe aryl esters and amides having an azabicyclic side chain and possessing 5-HT (5-Hydroxytryptamine) antagonist activity.

A novel, structurally distinct compound has now been discovered. This compound has 5-HT antagonist activity.

Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

The pharmaceutically acceptable salts of the compound of the formula (I) include acid addition salts with conventional acids such as hydrochloric, hydrobromic, boric, phosphoric, sulphuric acids and pharmaceutically acceptable organic acids such as acetic, tartaric, maleic, citric, succinic, benzoic, ascorbic, methanesulphonic, α -keto glutaric, α -glycerophosphoric, and glucose-1-phosphoric acids.

The pharmaceutically acceptable salts of the compound of the formula (I) are usually acid addition salts with acids such as hydrochloric, hydrobromic, phosphoric, sulphuric, citric, tartaric, lactic and acetic acid.

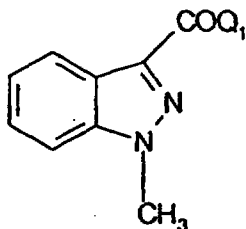
Preferably the acid addition salt is the hydrochloride salt.

Examples of pharmaceutically acceptable salts include quaternary derivatives of the compound of formula (I) such as the compounds quaternised by compounds R_{10} -T wherein R_{10} is C_{1-6} alkyl, phenyl- C_{1-6} alkyl or C_5-7 cycloalkyl, and T is a radical corresponding to an anion of an acid. Suitable examples of R_{10} include methyl, ethyl and n- and iso-propyl; and benzyl and phenethyl. Suitable examples of T include halide such as chloride, bromide and iodide.

Examples of pharmaceutically acceptable salts of the compound of formula (I) also form internal salts such as pharmaceutically acceptable N-oxides.

The compound of the formula (I) and its pharmaceutically acceptable salts, (including quaternary derivatives and N-oxides) may also form pharmaceutically acceptable solvates, such as hydrates, which are included whenever the compound and salts are herein referred to.

The invention also provides a process for the preparation of a compound of formula (I), or a pharmaceutically acceptable salt thereof, which process comprises reacting a compound of formula (II):



(II)



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Q₁ is a group displaceable by a nucleophile, and thereafter optionally forming a pharmaceutically acceptable salt of the resultant compound of formula (I).

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The compounds of formula (II) and (III) are known compounds.

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colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art, for example with an enteric coating.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycolate.

5 Suitable lubricants include, for example, magnesium stearate.

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

15 Oral liquid preparations are usually in the form of aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs or are presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and flavouring or colouring agents.

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

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be
25 either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

30 Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure of ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

35 The invention further provides a method of treatment or prophylaxis of migraine, cluster headache, trigeminal neuralgia and/or emesis in mammals, such as humans, which comprises the administration to the mammal of an effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof.

40 An amount effective to treat the disorders hereinbefore described depends on the nature and severity of the disorder being treated and the weight of the mammal. However, a unit dose for a 70kg adult will normally contain 0.5 to 1000mg for example 1 to 500mg, of the compound of the invention. Unit doses may be administered once or more than once a day, for example, 2,3 or 4 times a day, more usually 1 to 3 times a day, that is in the range of approximately 0.001 to 50 mg/kg/day, more usually 0.002 to 25 mg/kg/day.

No adverse toxicological effects are indicated at any of the aforementioned dosage ranges.

45 The invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance, in particular for use in the treatment of migraine, cluster headache, trigeminal neuralgia and/or emesis.

The following Example illustrates the preparation of the compound of formula (I).

50 N.B. Nomenclature is based on Chemical Abstracts Index Guide 1977 published by the American Chemical Society.

Example

N-(endo-9-Methyl-9-azabicyclo[3.3.1]non-3-yl)-1-methylindazole-3-carboxamide monohydrochloride

55 A stirred solution of 1-methylindazole-3-carboxylic acid chloride(0.77g) in dichloromethane (50ml) was treated with a solution of endo-9-methyl-9-azabicyclo[3.3.1]nonan-3-amine (0.7g) and triethylamine (0.7ml) in dichloromethane (30ml). After 2h, the reaction mixture was washed with saturated aqueous NaHCO₃ -

(100ml) and dried (K_2CO_3). The oil remaining after evaporation of the solvent was purified by column chromatography (TLC-alumina, $CHCl_3$) and treated with hydrogen chloride to give the title compound m.p. 290-2°C.

1H NMR (270 MHz, $CDCl_3$)

δ : 8.30 (d, 1H) 7.50-7.20 (m, 4H)
4.80-4.50 (m, 1H)
4.12 and 4.10 (2-s, 3H)
3.75-3.55 (m, 2H)
2.99 and 2.91 (2-s, 3H)
2.82-2.40 (m, 4H)
2.20-2.00 (m, 2H)
1.90-1.60 (m, 4H)

Pharmacology

Antagonism of the von Bezold-Jarisch reflex

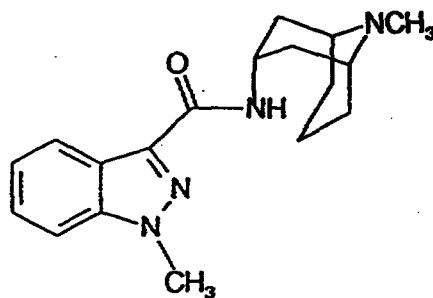
The compound of the Example was evaluated for antagonism of the von Bezold-Jarisch reflex evoked by 5-HT in the anaesthetised rat according to the following method:

Male rats 250-350g, were anaesthetised with urethane (1.25g/kg intraperitoneally) and blood pressure and heart rate recorded as described by Fozard J.R. et al., J. Cardiovasc. Pharmacol. 2, 229-245 (1980). A submaximal dose of 5-HT (usually 6 μ g/kg) was given repeatedly by the intravenous route and changes in heart rate quantified. The compound was given intravenously and the concentration required to reduce the 5-HT evoked response to 50% of the control response (ED_{50}) was then determined.

The compound gave an ED_{50} value of 0.7 μ g/kg.

Claims

1. A compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

2. N-(endo-9-Methyl-9-azabicyclo[3.3.1]non-3-yl)-1-methylindazole-3-carboxamide monohydrochloride.

3. A process for the preparation of a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt thereof, which process comprises reacting a compound of formula (II):



(100ml) and dried (K_2CO_3). The oil remaining after evaporation of the solvent was purified by column chromatography (TLC-alumina, $CHCl_3$) and treated with hydrogen chloride to give the title compound m.p. 290-2°C.

1H NMR (270 MHz, $CDCl_3$)

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4.80-4.50 (m, 1H)
4.12 and 4.10 (2-s, 3H)
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2.99 and 2.91 (2-s, 3H)
10 2.82-2.40 (m, 4H)
2.20-2.00 (m, 2H)
1.90-1.60 (m, 4H)

Pharmacology

Antagonism of the von Bezold-Jarisch reflex

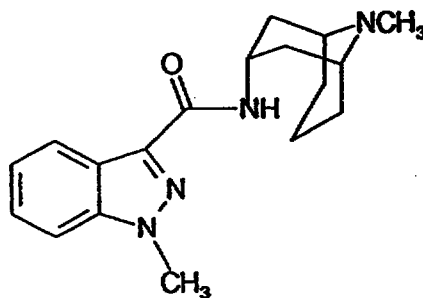
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- 25 The compound gave an ED_{50} value of 0.7 μ g/kg.

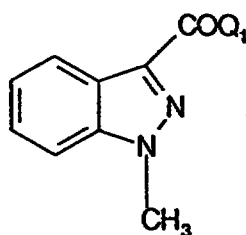
Claims

1. A compound of formula (I), or a pharmaceutically acceptable salt thereof:



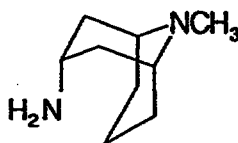
(I)

2. N-(endo-9-Methyl-9-azabicyclo[3.3.1]non-3-yl)-1-methylindazole-3-carboxamide monohydrochloride.
3. A process for the preparation of a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt thereof, which process comprises reacting a compound of formula (II):



(II)

with a compound of formula (III):



(III)

wherein

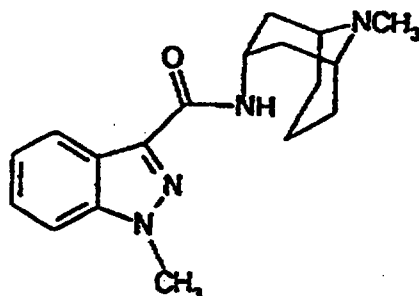
Q₁ is a group displaceable by a nucleophile, and thereafter optionally forming a pharmaceutically acceptable salt of the resultant compound of formula (I).

4. A pharmaceutical composition comprising a compound according to claim 1 or 2, and a pharmaceutically acceptable carrier.
5. A composition according to claim 4, adapted for parenteral administration.
6. A composition according to claim 4, adapted for oral administration.
7. A compound according to claim 1 or 2 for use as an active therapeutic substance.
8. A compound according to claim 1 or 2, for use in the treatment of emesis.
9. A compound according to claim 1 or 2, for use in the treatment of cytotoxic agent induced vomiting and nausea.
10. A compound according to claim 1 or 2 for use in the treatment of migraine, cluster headache or trigeminal neuralgia.
11. A compound according to claim 1 or 2 for use in the treatment of CNS disorders.
12. Use of a compound according to claim 1 or 2 in the manufacture of a medicament for use in the treatment of emesis.
13. Use of a compound according to claim 1 or 2 in the manufacture of a medicament for use in the treatment of cytotoxic agent induced vomiting and nausea.
14. Use of a compound according to claim 1 or 2 in the manufacture of a medicament for use in the treatment of migraine, cluster headache or trigeminal neuralgia.
15. Use of a compound according to claim 1 or 2 in the manufacture of a medicament for use in the treatment of CNS disorders.



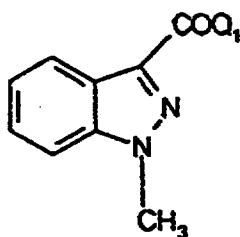
Patentansprüche

1. Verbindung der Formel (I) oder ein pharmazeutisch verträgliches Salz davon:



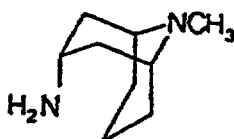
(I)

2. N-(endo-9-Methyl-9-azabicyclo[3.3.1]non-3-yl)-1-methylindazol-3-carboxamid-monohydrochlorid.
3. Verfahren zur Herstellung einer Verbindung der Formel (I) gemäß Anspruch 1 oder eines pharmazeutisch verträglichen Salzes davon, wobei das Verfahren die Umsetzung einer Verbindung mit der Formel (II):



(II)

mit einer Verbindung der Formel (III):



(III)

umfaßt, in der

Q₁ einen durch ein Nukleophil ersetzbaren Rest bedeutet, und anschließend gegebenenfalls Herstellen eines pharmazeutisch verträglichen Salzes aus der erhaltenen Verbindung der Formel (I).

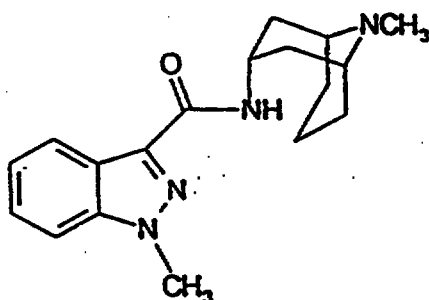
4. Arzneimittel, umfassend eine Verbindung gemäß Anspruch 1 oder 2 und einen pharmazeutisch verträglichen Träger.
5. Mittel nach Anspruch 4, formuliert zur parenteralen Verabreichung.
6. Mittel nach Anspruch 4, formuliert zur oralen Verabreichung.
7. Verbindung nach Anspruch 1 oder 2, zur Verwendung als therapeutischen Wirkstoff.
8. Verbindung nach Anspruch 1 oder 2 zur Verwendung bei der Behandlung von Übelkeit.



9. Verbindung nach Anspruch 1 oder 2 zur Verwendung bei der Behandlung von durch ein cytotoxisches Mittel induziertem Erbrechen und Brechreiz.
10. Verbindung nach Anspruch 1 oder 2 zur Verwendung bei der Behandlung von Migräne, clusterartigem Kopfschmerz oder trigeminaler Neuralgie.
11. Verbindung nach Anspruch 1 oder 2 zur Verwendung bei der Behandlung von ZNS-Erkrankungen.
12. Verwendung einer Verbindung nach Anspruch 1 oder 2 zur Herstellung eines Arzneimittels zur Verwendung bei der Behandlung von Übelkeit.
13. Verwendung einer Verbindung nach Anspruch 1 oder 2 zur Herstellung eines Arzneimittels zur Verwendung bei der Behandlung von durch ein cytotoxisches Mittel induziertem Erbrechen oder Brechreiz.
14. Verwendung einer Verbindung nach Anspruch 1 oder 2 zur Herstellung eines Arzneimittels zur Verwendung bei der Behandlung von Migräne, clusterartigem Kopfschmerz oder trigeminaler Neuralgie.
15. Verwendung einer Verbindung nach Anspruch 1 oder 2 zur Herstellung eines Arzneimittels zur Verwendung bei der Behandlung von ZNS-Erkrankungen.

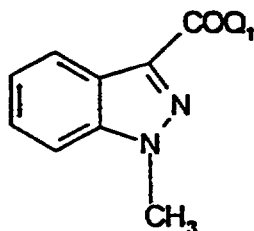
Revendications

1. Composé de formule (I) ou sel de celui-ci acceptable du point de vue pharmaceutique :



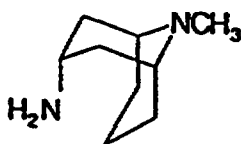
(I)

2. Monochlorhydrate de N-(endo-9-méthyl-9-azabicyclo[3,3,1]non-3-yl)-1-méthylindazole-3-carboxamide.
3. Procédé pour la préparation d'un composé de formule (I) suivant la revendication 1 ou d'un sel de celui-ci acceptable du point de vue pharmaceutique, lequel procédé comprend la réaction d'un composé de formule (II) :



(II)

avec un composé de formule (III) :



(III)

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Q₁ est un groupe pouvant être déplacé par un nucléophile, et ensuite la formation éventuelle d'un sel acceptable du point de vue pharmaceutique du composé résultant de formule (I).

4. Composition pharmaceutique comprenant un composé suivant la revendication 1 ou 2 et un support acceptable du point de vue pharmaceutique.
5. Composition suivant la revendication 4, adaptée pour l'administration parentérale.
6. Composition suivant la revendication 4, adaptée pour l'administration orale.
7. Composé suivant la revendication 1 ou 2, pour l'utilisation en tant que substance thérapeutique active.
8. Composé suivant la revendication 1 ou 2, pour l'utilisation dans le traitement de l'émèse.
9. Composé suivant la revendication 1 ou 2, pour l'utilisation dans le traitement de vomissements et de nausées induits par un agent cytotoxique.
10. Composé suivant la revendication 1 ou 2, pour l'utilisation dans le traitement de la migraine, des accès de maux de tête ou de la névralgie faciale.
11. Composé suivant la revendication 1 ou 2, pour l'utilisation dans le traitement de troubles du système nerveux central.
12. Utilisation d'un composé suivant la revendication 1 ou 2, dans la fabrication d'un médicament destiné à être utilisé dans le traitement de l'émèse.
13. Utilisation d'un composé suivant la revendication 1 ou 2, dans la fabrication d'un médicament destiné à être utilisé dans le traitement de vomissements et de nausées induits par un agent cytotoxique.
14. Utilisation d'un composé suivant la revendication 1 ou 2, dans la fabrication d'un médicament destiné à être utilisé dans le traitement de la migraine, des accès de maux de tête ou de la névralgie faciale.
15. Utilisation d'un composé suivant la revendication 1 ou 2, dans la fabrication d'un médicament destiné à être utilisé dans le traitement des troubles du système nerveux central.