1 540 023

PATENT SPECIFICATION (11) 1 540 023

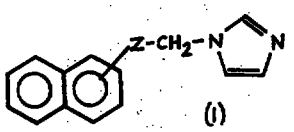
(21) Application No. 50470/77 (22) Filed 5 Dec. 1977
(44) Complete Specification published 7 Feb. 1979
(51) INT CL² C07D 233/60 A61K 31/415
(52) Index at acceptance
C2C 1410 215 222 226 22Y 246 250 252 25Y 29X 29Y 30Y 351 355 360 362 36Y 386 43X 509 50Y 623 625 652 665 770 778 802 80Y UL WK
(72) Inventor KEITH A. M. WALKER

(19)

(54) 1-(NAPHTHYLETHYL)IMIDAZOLE DERIVATIVES

(71) We, SYNTEX (U.S.A.) INC., a Corporation organised under the laws of the State of Delaware, United States of America, of 3401 Hillview Avenue, Palo Alto, California 94304, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to certain 1-(naphthyl-ethyl)imidazole derivatives. More particularly, the present invention relates to compounds of formula (I), namely:



(I)

wherein Z is hydroxymethylene or carbonyl and the pharmaceutically acceptable acid addition salts thereof. The term "pharmaceutically acceptable acid addition salts" refers to salts of the free bases of formula (I), which salts possess the desired pharmacological activity and which are neither biologically nor otherwise undesirable. Such salts may be formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid or phosphoric acid; or with organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, and the like.

Compounds of formula (I) wherein Z is hydroxymethylene possess a chiral center. Accordingly, these compounds may be prepared in either optically active form, or as a racemic mixture. Unless otherwise specified, the compounds described herein are all in the racemic form. However, the scope of the subject invention is not to be limited to the racemic form but is to encompass the individual optical isomers of the subject compounds.

If desired, compounds of formula (I) wherein Z is hydroxymethylene may be prepared in optically active form by conventional resolution means known per se, for example, by the separation (e.g., fractional crystallization) of the disastereomeric salts formed by reaction of, e.g. racemic compounds of formula (I) wherein Z is hydroxymethylene with an optically active acid, or by separation of the diastereomeric esters formed by reaction of such a racemic alcohol wherein Z is hydroxymethylene with an optically active acid. Exemplary of such optically active acids are the optically active forms of camphor-10-sulfonic acid, α-bromocamphor-π-sulfonic acid, camphoric acid, menthoxyacetic acid, tartaric acid, malic acid, diacetyltartaric acid, pyrrolidone-5-carboxylic acid, and the like. The separate pure diasteromeric salts or esters may be then be cleaved by standard means to afford the respective optical isomers of the desired compound.

Compounds of formula (I) exhibit a broad spectrum of CNS related activity such as anticonvulsant activity (as demonstrated by the maximal electroshock seizure test), anorexigenic, antidepressant and muscle relaxing activity; as well as activity of other types such as inhibition of gastric secretion and antihypertensive activities.

The compounds of the present invention can be used for treating and/or

SEE ERRATA SLIP ATTACHED

preventing convulsions in a mammalian subject by administering a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable acid addition salt thereof. Another aspect of the present invention relates to pharmaceutical compositions useful for the treatment and/or prevention of convulsions in a mammalian subject comprising a compound of formula (I), or a pharmaceutically acceptable acid addition salt thereof, in admixture with a pharmaceutically acceptable non-toxic carrier. For this utility compounds of formula (I) wherein Z is carbonyl are particularly preferred.

The compounds of the present invention can also be used for inhibiting gastric secretion in a mammalian subject by administering a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable acid addition salt thereof. Still another aspect of the present invention relates to pharmaceutical compositions useful for the inhibition of gastric secretion in a mammalian subject comprising a compound of formula (I), or a pharmaceutically acceptable acid addition salt thereof, in admixture with a pharmaceutically acceptable non-toxic carrier.

In the practice of the above described methods a therapeutically effective amount of the compound of formula (I) or a pharmaceutical composition containing same is administered via any of the usual and acceptable methods known in the art, either singly or in combination with another compound or compounds of the present invention or other pharmaceutical agents. These compounds or compositions can thus be administered orally or parenterally (i.e. intramuscularly, subcutaneously and intraveneously), and can be administered either in the form of solid or liquid dosages including tablets, solutions, suspensions, and the like, as discussed in more detail hereinbelow. Oral administration is preferred.

The administration can be conducted in a single unit dosage form with continuous therapy or in single dosage therapy ad libitum. The method may be practiced when relief of symptoms is specifically required, i.e. therapeutically, or as continuous or prophylactic treatment.

In view of the foregoing as well as in consideration of the degree of severity of the condition being treated, age of subject and so forth, all of which factors are determinable by routine experimentation by one skilled in the art, the effective dosage in accordance herewith can vary over a wide range. Generally, a therapeutically effective amount for anticonvulsant use ranges from about 0.1 to about 300 mg./kg. body weight per day and preferably about from 1 to about 100 mg./kg. body weight per day. In alternate terms, for an average adult human subject, a therapeutically effective amount in accordance herewith would be, in preferred embodiments, from about 70 mg. to about 7 g. per day per subject. A therapeutically effective amount for inhibition of gastric secretion ranges from about 0.1 to about 300 mg./kg. body weight per day and preferably from about 0.25 to about 100 mg./kg. body weight per day. In alternative terms, for an average adult human subject, a therapeutically effective amount in accordance herewith would be, in preferred embodiments from about 18 mg. to about 7 g. per day per subject.

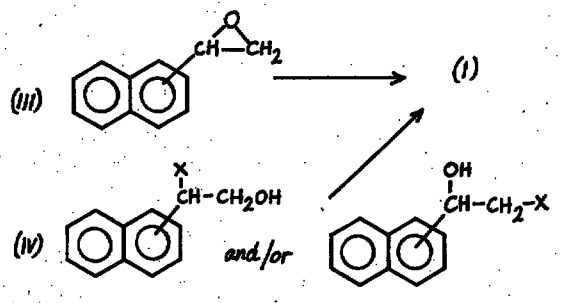
Useful pharmaceutical carriers for the preparation of the pharmaceutical compositions hereof can be solids or liquids. Thus, the compositions can take the form of tablets, pills, capsules, powders, sustained release formulations, solutions, suspensions, elixirs, and the like. Carriers can be selected from the various oils, including those of petroleum, animal, vegetable or synthetic origin, for example, peanut oil, soybean oil, mineral oil, sesame oil, and the like. Water, saline, aqueous dextrose, and glycols are preferred liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk, glycerol, propylene glycol, water, ethanol, and the like. Suitable pharmaceutical carriers and their formulations are described in "Remington's Pharmaceutical Sciences" by E. W. Martin. Such compositions will, in any event, contain a therapeutically effective amount of the active compound together with a suitable amount of carrier so as to prepare the proper dosage form for proper administration to the subject.

The compounds of the present invention may be prepared according to methods well known in the art. For example, compounds of formula (I) wherein Z is carbonyl may be prepared in a manner analogous to that described in U.S. Patent 3,717,655 to Godefroi et al. This method comprises reacting a halomethyl

naphthyl ketone with imidazole in an inert organic solvent. The starting halomethyl naphthyl ketones are known or may be prepared by halogenation of the corresponding methyl naphthyl ketone by known means, for example, utilizing cupric bromide. The preparation of ketones of formula (I) by the above described method may be carried out in an inert organic solvent, for example, dimethylformamide at a temperature between about −10 and +40°C.

Preparation of compounds of formula (I) wherein Z is hydroxymethylene may be accomplished by the reduction of the corresponding ketone or acid addition salt thereof under standard conditions, for example, by the use of sodium tetrahydroborate in a protic solvent, for example, methanol, at a temperature between −20 and +20°C.

Compounds of formula (I) wherein Z is hydroxymethylene may also be prepared according to the following reaction sequence:

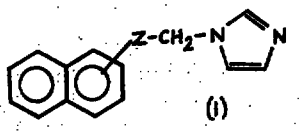


wherein the epoxide (III) or the halohydrin (IV) is treated with imidazole and/or an alkali salt (preferably the sodium salt) thereof in a polar aprotic solvent such as dimethylformamide, dimethylsulfoxide or tetrahydrofuran at a temperature between about 0 and 100°C. Treatment of the epoxide requires one mole of imidazole in the presence of 0.05—1 mole of imidazole salt.

Treatment of the halohydrin requires slightly over one mole of imidazole salt, since the halohydrin is first converted in situ to the epoxide.

The subject compounds of formula (I) can be isolated as free bases; however, since many of the compounds in base form are oils and gums and/or not water soluble it is often more convenient to isolate and further characterize such compounds as acid addition salts. These salts are prepared in the usual manner, i.e., by reaction of the free base with a suitable inorganic or organic acid, for example one of the pharmaceutically acceptable acids described above. If desired, the salt can be readily converted to the free base by treatment with a base such as potassium or sodium carbonate or potassium or sodium hydroxide.

In summary, another aspect of the present invention concerns a process for the preparation of a free base compound of the formula

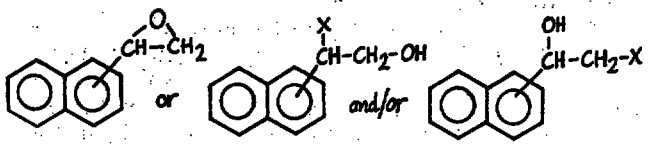


wherein Z is hydroxymethylene or carbonyl, or a pharmaceutically acceptable non-toxic acid addition salt thereof, which process comprises:

(a) the preparation of a compound of formula (I) wherein Z is carbonyl by reaction of a halomethyl naphthyl ketone with imidazole, or

(b) the preparation of a compound of formula (I) wherein Z is hydroxymethylene by reduction of a compound of formula (I) wherein Z is carbonyl, or

(c) the preparation of a compound of formula (I) wherein Z is hydroxymethylene by reaction of a compound of the formula



wherein X is halo with imidazole and/or an alkali metal salt thereof, and

(d) optionally converting a free base to the corresponding acid addition salt, or

(e) optionally converting an acid addition salt to the corresponding free base.

The following specific description is given to enable those skilled in the art to more clearly understand and practice the present invention. It should not be considered as a limitation upon the scope of the invention but merely as illustrative and representative thereof.

Example 1

To a stirred, ice-cooled slurry of 35 g. of imidazole in 25 ml. of dimethylformamide is added 24.9 g. of bromomethyl 2-naphthyl ketone. The mixture is stirred for 2 hours at 0°C., and then allowed to come to room temperature and stirred overnight. The solution is poured into water and the resulting sticky solid filtered off, washed with water and dissolved in benzene. Thereafter the resultant benzene solution is dried (azeotroped) to afford 1-(2-naphthoylmethyl)imidazole which is converted to its hydrochloride acid addition salt by addition of ethereal hydrogen chloride until precipitation is complete. The salt is crystallized by the addition of ethyl acetate and the resulting solid recrystallized from methanol/acetone to yield colorless needles of 1-(2-naphthoylmethyl)imidazole hydrochloride, m.p. 226—228.5°C. (decomp.).

Example 2

To 9.4 g. of the above obtained 1-(2-naphthoylmethyl)imidazole hydrochloride in 200 ml. of methanol at 0—5°C. is added, with stirring, excess sodium tetrahydroborate. After stirring for 30 minutes at 0°C., the reaction mixture is evaporated to dryness. The resultant residue is treated with 200 ml. of water and the product which crystallizes is filtered off, washed with water and recrystallized from ethyl acetate to yield 1-[2-hydroxy-2-(2-naphthyl)ethyl]-imidazole as off-white blades, m.p. 156—160.5°C. (slight decomp.).

Example 3

Methyl 1-naphthyl ketone (10.1 g.), in 50 ml of a 1:1 mixture of chloroform and ethyl acetate is treated with 26.5 g. of copper (ii) bromide. The resulting reaction mixture is heated under reflux with vigorous stirring until the evolution of hydrogen bromide ceases. When the reaction is complete the solvent is removed, ether is added and the copper (I) bromide is removed by filtration. Evaporation of the filtrate under reduced pressure yields crude bromomethyl 1-naphthyl ketone.

The above mentioned bromomethyl 1-naphthyl ketone is then treated according to the procedure previously recited in Example 1 to afford 1-(1-naphthoylmethyl)imidazole which after 2 recrystallizations from benzene gave colorless flakes, m.p. 113.5—117°C.

Example 4

To 7.0 g. of the above 1-(1-naphtholymethyl)imidazole in 50 ml. methanol at 0—5°C is added with stirring excess sodium tetrahydroborate. After stirring for thirty minutes the solvent was removed and the residue treated with water. The product was filtered off, washed with water and recrystallized from ethyl acetate as snow-white microcrystals of 1-[2-hydroxy-2-(1-naphthyl)ethyl]imidazole (5.60 g.) m.p. 112.5—115°C. (slight decomp.).

Example 5

Ethereal hydrogen chloride is added dropwise to a solution of 1.0 g. 1-(2-naphthoylmethyl)imidazole in 100 ml. anhydrous benzene until precipitation is complete. The product is filtered, washed with ether, air dried and recrystallized from methanol/acetone to yield 1-(2-naphthoylmethyl)imidazole hydrochloride, m.p. 226—228.5°C. (decomp.).

In a similar manner, all compounds of formula (I) in free base form may be converted to the acid addition salts by treatment with the appropriate acid, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, and the like.

(14)

Example 6

1-(2-Naphthoylmethyl)imidazole hydrochloride (1.0 g.) suspended in 50 ml. of ether is stirred with excess dilute aqueous potassium carbonate solution until the salt is completely dissolved. The organic layer is then separated, washed twice with water, dried over magnesium sulfate and evaporated to yield 1-(2-naphthoylmethyl)imidazole.

In a similar manner the acid addition salts of all compounds of formula (I) may be converted to the corresponding compounds in free base form.

Example 7

Maximal Electroshock Test in Mice

This test was performed in the standard manner, essentially as described by Swinyard et al., J. Pharm. Exp. Ther., Vol. 106, pp. 319—330 (1952).

Groups of 10 male Hilltop ICR-derived mice weighing 20—30 grams were dosed intraperitoneally with a solution or suspension of drug in saline 15 minutes prior to a transcorneal maximum electroshock (50 milliamps, 0.2 seconds). The mice were observed for the occurrence of tonic extension, tonic flexion, clonic seizures and death. An active compound was capable of antagonizing the occurrence of the tonic extension which occurred immediately after the electroshock.

ED_{50} values (and 95% confidence limits) are as follows:

Compound	ED_{50} mg/kg (95% confidence limits)
1-(2-naphthoylmethyl)imidazole	23 (20—25)
1-[2-hydroxy-2-(2-naphthyl) ethyl]imidazole	74 (55—110)
1-(1-naphthoylmethyl)imidazole	approx. 60
1-[2-hydroxy-2-(1-naphthyl)-ethyl]imidazole	37 (32—53)

Example 8

Groups of 3 male ICR derived mice weighing 18—24 grams were given a single dose of compound intraperitoneally. The following doses were employed: 1, 3, 10, 30, 100, 300 or 1,000 mg/kg. After five days lethalities were determined. The LD_{50} values are as follows:

Compound	LD_{50} (mg/kg)
1-(2-naphthoylmethyl)imidazole	100—300
1-[2-hydroxy-2-(2-naphthyl)ethyl]-imidazole	300—1000
1-[2-hydroxy-3-(1-naphthyl)ethyl]-imidazole	300—1000
1-(1-naphthoylmethyl)imidazole	100—300

Example 9

The following illustrates a pharmaceutical composition for oral administration which may be prepared for the compounds of the present invention, e.g.

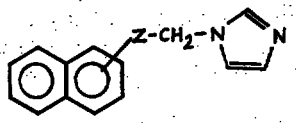
1-(2-naphthoylmethyl)imidazole or

	parts by weight
Active compound	200
Magnesium stearate	3
Starch	30
Lactose	116
Polyvinylpolypyrrolidone	3

The above ingredients are combined and granulated using methanol as the solvent. The formulation is then dried and formed into tablets (containing 200 mg. of active compound each) with an appropriate tabletting machine.

WHAT WE CLAIM IS:—

1. A compound of the formula



wherein Z is hydroxymethylene or carbonyl and the pharmaceutically acceptable acid addition salts thereof.

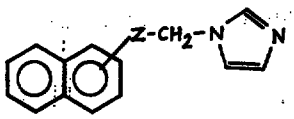
2. The compound of Claim 1, wherein Z is carbonyl.

3. The compound of Claim 2 which is 1-(2-naphthoylmethyl)imidazole and the pharmaceutically acceptable acid addition salts thereof.

4. The compound of Claim 1, wherein Z is hydroxymethylene.

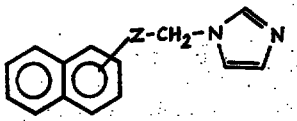
5. The compound of Claim 4 which is 1-[2-hydroxy-2-(1-naphthyl)ethyl]imidazole and the pharmaceutically acceptable acid addition salts thereof.

6. A method for treating and preventing convulsions in a non-human mammalian subject comprising administering to said subject a therapeutically effective amount of a compound of the formula



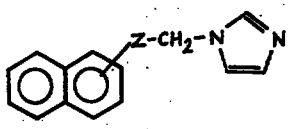
wherein Z is hydroxymethylene or carbonyl, or a pharmaceutically acceptable acid addition salt thereof.

7. A pharmaceutical composition comprising a therapeutically effective amount of a compound of the formula



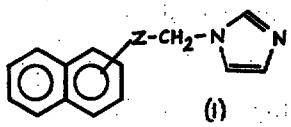
wherein Z is hydroxymethylene or carbonyl, or a pharmaceutically acceptable acid addition salt thereof; in admixture with a pharmaceutically acceptable, non-toxic carrier.

8. A method for inhibiting gastric secretion in a non-human mammalian subject comprising administering to said subject a therapeutically effective amount of a compound of the formula



wherein Z is hydroxymethylene or carbonyl, or a pharmaceutically acceptable acid addition salt thereof.

9. A process for the preparation of a free base compound of the formula



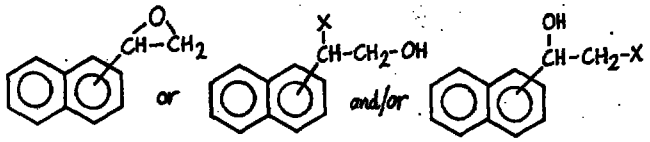
(I)

wherein Z is hydroxymethylene or carbonyl, or a pharmaceutically acceptable acid addition salt thereof, which process comprises:

(a) the preparation of a compound of formula (I) wherein Z is carbonyl by reaction of a halomethyl naphthyl ketone with imidazole, or

(b) the preparation of a compound of formula (I) wherein Z is hydroxymethylene by reduction of a compound of formula (I) wherein Z is carbonyl, or

(c) the preparation of a compound of formula (I) wherein Z is hydroxymethylene by reaction of a compound of the formula



wherein X is halo with imidazole and/or an alkali metal salt thereof, and

(d) optionally converting a free base to the corresponding acid addition salt, or

(e) optionally converting an acid addition salt to the corresponding free base.

10. A compound of Claim 1 as exemplified herein.

11. A process for preparing a compound of Claim 1, substantially as described herein.

12. A compound of Claim 1 whenever prepared by a process according to Claim 10 or Claim 11.

13. A pharmaceutical composition comprising a compound of any one of Claims 2 to 5, 10 and 12, in admixture with a pharmaceutically acceptable non-toxic carrier.

14. A pharmaceutical composition substantially as described herein comprising a compound of Claim 1 in admixture with a pharmaceutically acceptable non-toxic carrier.

MEWBURN ELLIS & CO.,
Chartered Patent Agents,
70/72 Chancery Lane,
London, WC2A 1AD,
Agents for the Applicants.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1979
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.



(8)

ERRATA

SPECIFICATION No. 1,540,023

Page 1, line 37, *for* separate *read* separated
Page 2, line 42, *for* alternative *read* alternate
Page 3, line 16, *after* alkali *insert* metal
Page 4, line 30, *for* (ii) *read* (II)
Page 4, line 35, *after* above *delete* mentioned
insert obtained
Page 5, line 15, *for* maximum *read* maximal

THE PATENT OFFICE
11th September, 1979