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(54) **ALKOXY SUBSTITUTED BENZIMIDAZOLE COMPOUNDS, PHARMACEUTICAL PREPARATIONS CONTAINING THE SAME, AND METHODS OF USING THE SAME**

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(52) **U.S. Cl.** **514/338**
(58) **Field of Search** 514/338

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(57) **ABSTRACT**

Compounds of the formula (Ia) are disclosed by the invention, along with compositions thereof optionally in combination with compounds of formulae (Ib). Methods of making and using the same are also disclosed.

12 Claims, No Drawings

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ALKOXY SUBSTITUTED BENZIMIDAZOLE COMPOUNDS, PHARMACEUTICAL PREPARATIONS CONTAINING THE SAME, AND METHODS OF USING THE SAME

CROSS-REFERENCE TO RELATED APPLICATIONS

The instant application claims priority to U.S. Provisional Application Serial No. 60/150,878 filed Aug. 26, 1999, the disclosure of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The invention generally relates to novel pharmaceutically active compounds, compositions comprising the same, pharmaceutical formulations of the same, methods of making the same, and methods of using the same.

BACKGROUND OF THE INVENTION

Various compounds used in inhibiting gastric acid secretion are known in the art and include a class of benzimidazole-substituted compounds, one of which is omeprazole. Omeprazole is currently commercially available in the formulation PRILOSEC®. In particular, U.S. Pat. No. 4,255,431 proposes such benzimidazole-substituted compounds generally described by the formula (III) in the '431 patent that allegedly encompasses omeprazole. Various methods of making these compounds are also proposed in the '431 patent.

European Pat. No. 0 124 495 B1 proposes various salts of omeprazole, namely alkaline salts of the formula (I) in the '495 reference which includes lithium, sodium, potassium, magnesium, and calcium salts, along with methods of making the salts. The methods of forming these salts may involve employing a hydroxide, alkoxide, or amine base, or cation exchange using a metal salt.

Erlandsson, P., et al. *J. Chromatography*, 532 (1990) pp. 305–319 propose separating the (−) and (+) enantiomers of omeprazole utilizing chromatographic techniques. In this publication, the separation is proposed to take place on a preparative scale using a cellulose-based chiral phase, e.g., trisphenyl-carbamoyl cellulose coated on 3-aminopropyl silica. It is appreciated that other schemes and processes are available for this separation.

PCT Publication No. WO 94/27988 proposes salts of the single enantiomers of omeprazole and methods of making the same. The process involves separating the two stereoisomers of a diastereomer mixture of an acyloxymethyl-substituted benzimidazole compound described by the formula (IV) set forth in this published application, followed by solvolysis of each separated diastereomer in an alkaline solution. Salts of the single enantiomers are formed and isolated by neutralizing aqueous solutions of the salts of the single enantiomers of omeprazole with a neutralizing agent.

PCT Publication No. WO 96/02535 proposes a process for the enantioselective synthesis of single enantiomers of omeprazole or its alkaline salts. The process employs an oxidizing agent and a chiral titanium complex which may include a titanium(IV) compound.

PCT Publication No. WO 98/54171 proposes the magnesium salt of the (−) enantiomer of omeprazole. The '171 publication also proposes a method of synthesizing the above magnesium salt as well as the potassium salt of (−) omeprazole that may be used as a suitable intermediate for preparing the magnesium salt. The potassium salt is taught to be useful in treating gastrointestinal diseases.

U.S. Pat. No. 5,386,032 to Brändström proposes an improved method for synthesizing omeprazole which involves reacting 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl-thio]-1H benzimidazole with m-chloroperoxybenzoic acid in a methylene chloride solution.

The teachings regarding the methods of making omeprazole as referred to in these references, salts thereof, enantiomers thereof, and salts of the enantiomers, as well as formulations which may include these compounds, all rely on the chemical structure of omeprazole being accurately determined and the referenced compound or compounds being consistently prepared using the referenced techniques. More specifically, a methoxy group on the benzimidazole ring has been explicitly stated in the literature to be present at the 5-position, in omeprazole, a racemic mixture, and an optically pure isomer of omeprazole designated as esomeprazole or s-omeprazole. Applicants have now unexpectedly discovered that the complexity of omeprazole and the intricacies of the bioactivity of each of its previously undiscovered attributes has never been disclosed. More specifically, Applicants have confirmed that the methods of the prior art do not yield a single compound having the methoxy group in the 5-position on the benzimidazole ring as previously taught, nor do all of the methods of the prior art yield consistent results. In fact, omeprazole as conventionally referred to as a bulk drug substance (in its solid state) is confirmed to be present in the form of two pharmaceutically active compounds having the methoxy group on the benzimidazole ring at the 6- and 5-positions. Additionally, Applicants have discovered the presence of a second chiral location at the pyridine ring plane in each of the two compounds such that each compound has two positional isomers and four diastereomers. Therefore, the present invention provides these individual compounds, along with any salts, hydrates, solvates, combinations thereof, and polymorphs thereof, compositions of the above, and methods of making the same which are not taught or suggested by the prior art.

SUMMARY OF THE INVENTION

The present invention generally provides compounds represented by formula (Ia), co-crystallized compositions of compounds represented by formulae (Ia) and (Ib), each described in detail herein, one or more pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof, and complexes thereof. Diastereomers of the above are also provided. The invention also provides compositions and pharmaceutical formulations of the above. Methods of making the above are also provided by the invention.

More specifically, the present discovery pertains to novel compounds, particularly a compound having a methoxy moiety at the 6-position on the benzimidazole ring, and compositions comprising compounds having methoxy groups at the 5- and 6-positions respectively. It is unexpected and highly uncommon that these individual compounds are present in co-crystalline form which comprise a single composition. Ratios of the above isomers can be manipulated, and novel compounds encompassing a myriad of ratios of diastereomers of such compounds are also provided. Each of these is described in greater detail hereinafter.

The invention also provides methods of administering the above compounds represented by formula (Ia) and the compositions of compounds represented by formulae (Ia) and (Ib) described in detail herein, along with one or more

optional pharmaceutically acceptable salts, solvates, hydrates, complexes, or combinations of these compounds, diastereomers thereof, compositions thereof, and pharmaceutically acceptable formulations of the above, to a mammal in need of treatment.

These and other aspects of the invention are set forth in greater detail herein.

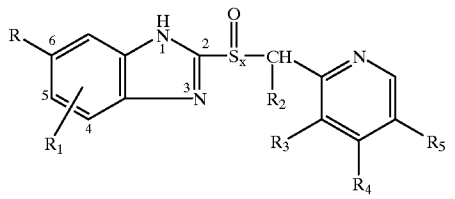
DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The invention is described hereinbelow in greater detail with reference to its preferred embodiments. These embodiments, however, are set forth to illustrate the invention and are not to be construed as a limitation thereof, the invention being defined by the claims.

In one aspect, the invention relates to a compound represented by the formula (Ia) as set forth below. Applicants have unexpectedly discovered that this compound, in solid state, has not been taught or suggested by the prior art. Additionally, it has been unexpectedly discovered that this newly-discovered compound has two distinct chiral locations: (1) a chiral center at the sulfoxide group and (2) a chiral plane located at the pyridinal moiety of such compound. More specifically, it has been furthered discovered that when R_4 is alkoxy, or other appropriate substituents, such group is locked into a fixed configuration generally perpendicular to the pyridine plane by the steric hindrance of the two substituents located in the R_3 and R_5 positions providing R_3 and R_5 are not hydrogen. The locked orientation of this substituent, preferably methoxy, gives rise to a chiral plane in which part or all of such substituent, preferably the methyl substituent of such preferred methoxy group, is located either above or below the unsymmetrical pyridine chiral plane.

The compound represented by formula (Ia) is as follows:

(Ia)



wherein:

S_x represents a chiral sulfur atom comprising at least one of the diastereomers represented by S_{xa} and S_{xb}, wherein S_{xa} is the (−) enantiomer and S_{xb} is the (+) enantiomer;

R is alkoxy;

R_1 is selected from the group consisting of hydrogen, alkyl, halogen, carboalkoxy, alkoxy, and alkanoyl;

R_2 is hydrogen or alkyl; and

R_3, R_4, and R_5 may be the same or different and are each selected from the group consisting of hydrogen, alkyl, alkoxy, and alkoxyalkoxy,

wherein when R_4 is alkoxy and neither R_3 nor R_5 are not hydrogen, the alkyl substituent of such alkoxy group is selected from the group consisting of at least one of the enantiomers represented by R_{4q} and R_{4z}; wherein R_{4q} is the (−) enantiomer and lies above the chiral plane; and R_{4z} is the (+) enantiomer and lies below the chiral plane;

or one or more pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof of said compound represented by formula (Ia).

In one embodiment, all of R_3, R_4, and R_5 are not hydrogen. In another embodiment, when two of R_3, R_4, and R_5 are hydrogen, the third is not methyl. The compound represented by formula (Ia) is preferably present in solid state.

The term "alkoxy" preferably refers to alkoxy groups having up to 5 carbon atoms, preferably up to 3 carbon atoms such as, for example, methoxy, ethoxy, n-propoxy, or isopropoxy.

The term "carboalkoxy" preferably refers to groups having up to 5 carbon atoms such as, for example, carbomethoxy, carboethoxy, carbopropoxy, and carbobutoxy.

The term "alkoxyalkoxy" preferably refers to groups having up to 5 carbon atoms such as, for example, methoxymethoxy, ethoxyethoxy, and the like. Methoxyethoxy is also encompassed under this definition.

The term "alkyl" preferably refers to alkyl groups having up to 7 carbon atoms, more preferably up to 4 carbon atoms, and is thus preferably selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, or isobutyl.

The term "halogen" refers to chloro, bromo, fluoro, or iodo.

The term "alkanoyl" preferably refers to groups having up to 4 carbon atoms. Examples include formyl, acetyl, and propionyl.

In a preferred embodiment, R is methoxy; R_1 is hydrogen; R_2 is hydrogen; R_3 is methyl; R_4 is methoxy; and R_5 is methyl.

Applicants note that throughout the provisional application upon which priority is claimed, the R_1 substituent was referred to as being in the 4-position in the compound represented by formula (Ia). For the purposes of the present application, the benzimidazole ring is numbered such that the R_1 substituent of the compound of formula (Ia) is present in the 6-position.

In various embodiments of the present invention, the compound represented by formula (Ia) may be present in the form of various individual diastereomers including, for example:

(a) S_{xa}—R_{4q};
(b) S_{xa}—R_{4z};
(c) S_{xb}—R_{4q}; and
(d) S_{xb}—R_{4z},

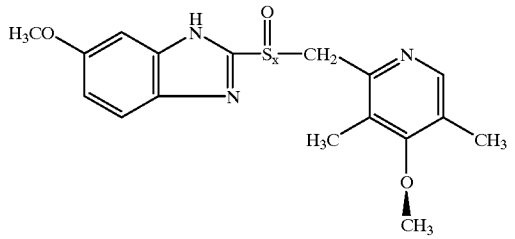
or one or more pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof. These descriptions are provided to permit differentiation of the various stereoisomers (diastereomers) throughout this document, and represent the following in standard chemical nomenclature:

(a) S_{xa}—R_{4q}, (S)—(S), or (−)—(−);
(b) S_{xa}—R_{4z}, (S)—(R), or (−)—(+);
(c) S_{xb}—R_{4q}, (R)—(S), or (+)—(−); and
(d) S_{xb}—R_{4z}, (R)—(R), or (+)—(+).

For the purposes of the invention, the term "enantiomer" as referred to herein, refers to diastereomer pairs that are non-superimposable mirror images of each other. The term "enantiomeric pair" as referenced herein refers to pairs of enantiomers that generate a racemic mixture. Examples of enantiomeric pairs include: (1) S—S and R—R and (2) S—R and R—S of the compounds of formulae (Ia) and/or (Ib). The term "(−) enantiomer" may encompass any of the diastereomers S—S or S—R and pair thereof. The term "(+) enantiomer" may encompass any of the diastereomers R—R and R—S and pair thereof.

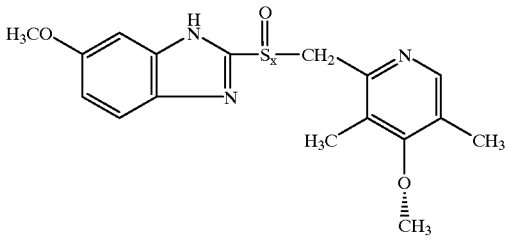
Preferred embodiments of various species of the compound represented by formula (Ia) are represented by the formulae (Iai), (Iaii), (Iaiii), and (Iaiv):

(Iai)



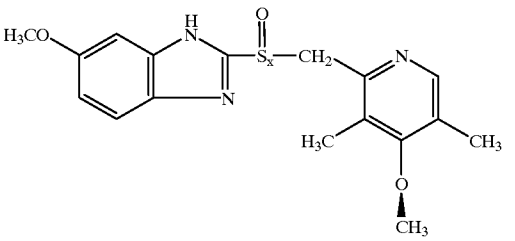
wherein S_x is S_{xa}, or one or more pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof of said compound represented by formula (Iai);

(Iaii)



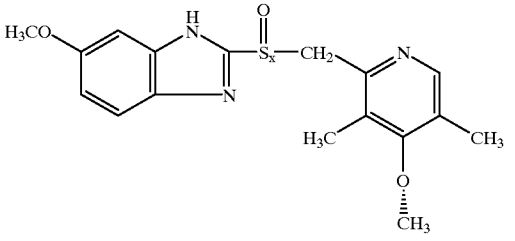
wherein S_x is S_{xa}, or one or more pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof of said compound represented by formula (Iaii);

(Iaiii)



wherein S_x is S_{xb}, or one or more pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof of said compound represented by formula (Iaiii); and

(Iaiv)

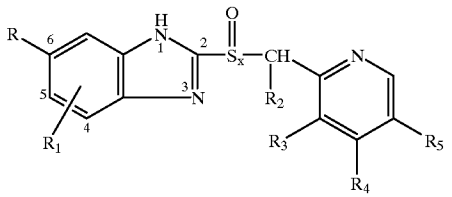


wherein S_x is S_{xb}, or one or more pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof of said compound represented by formula (Iaiv).

The above compounds may be made by various methods including those set forth in greater detail herein. Other methods may be also be employed.

In another aspect, the invention relates to a composition comprising two or more compounds represented by the formula (Ia) set forth below. In particular, and as discussed in greater detail herein, Applicants provide any combination of any of the four diastereomers in varying ratio amounts.

(Ia)



wherein:

S_x represents a chiral sulfur atom comprising at least one of the enantiomer represented by S_{xa} and S_{xb}, wherein S_{xa} is the (−) enantiomer and S_{xb} is the (+) enantiomer;

R is alkoxy;

R_1 is selected from the group consisting of hydrogen, alkyl, halogen, carboalkoxy, alkoxy, and alkanoyl;

R_2 is hydrogen or alkyl; and

R_3, R_4, and R_5 may be the same or different and are each selected from the group consisting of hydrogen, alkyl, alkoxy, and alkoxyalkoxy,

wherein when R_4 is alkoxy and neither R_3 nor R_5 are not hydrogen, the alkyl substituent of such alkoxy group is selected from the group consisting of at least one of the enantiomers represented by R_{4q} and R_{4z}, wherein R_{4q} is the (−) enantiomer and lies above the chiral plane; and R_{4z} is the (+) enantiomer and lies below the chiral plane;

or one or more pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof of said compounds represented by formula (Ia).

The composition of two or more compounds may contain various amounts of the enantiomers S_{xa}, S_{xb}, R_{4q}, and R_{4z}. Methods for making the various enantiomers and diastereomers are set forth herein. In one embodiment, for example, each of the diastereomers represented by S_{xa} and S_{xb} in the compounds represented by formula (Ia) is present in a range from about 0 percent (w/w) to about 100 percent (w/w) such that the total percentage of the sum of S_{xa} and S_{xb} equals about 100 percent (w/w). In another embodiment, each of the enantiomers represented by R_{4q} and R_{4z} is present in a range from about 0 percent (w/w) to about 100 percent (w/w) such that when the total percentage of the sum of R_{4q} and R_{4z} equals about 100 percent (w/w).

In the above composition, each of the at least two compounds, may be the same or different. Any number of combinations of individual diastereomers or combinations thereof of the compound represented by formula (Ia) may be present in the composition. Examples of such diastereomers are as follows: S_{xa}—R_{4q}; S_{xa}—R_{4z}; S_{xb}—R_{4q}; and S_{xb}—R_{4z}, or one or more pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof of the compound represented by formula (Ia).

In various embodiments, the above diastereomers or combinations thereof may be present in such a manner wherein the composition forms a racemic mixture. In other embodiments, the diastereomers may be present in such a manner wherein the composition does not form a racemic mixture.

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