(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 February 2007 (01.02.2007)

PCT

(10) International Publication Number
WO 2007/012650 A1

(51) International Patent Classification:
C07D 213/69 (2006.01) *A61K 31/4439* (2006.01)
C07D 401/12 (2006.01) *C07D 471/04* (2006.01)
A61P 1/04 (2006.01)

(21) International Application Number:
PCT/EP2006/064666

(22) International Filing Date: 26 July 2006 (26.07.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
05106868.2 26 July 2005 (26.07.2005) EP

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

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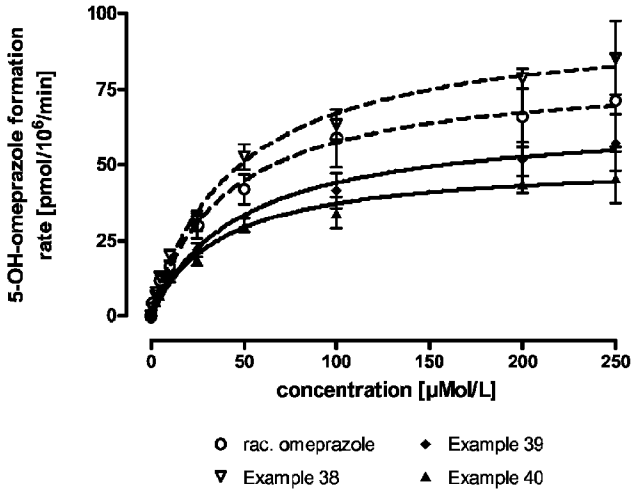
(54) Title: ISOTOPICALLY SUBSTITUTED PROTON PUMP INHIBITORS



Kinetics of 5-hydroxy-omeprazole formation from [1H]omeprazole and examples 38, 39, and 40.

(57) Abstract: The invention relates to benzimidazoles of Formula (1) and to pharmaceutical compositions comprising these compounds, further to intermediates of Formula (2 and 3).

WO 2007/012650 A1

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Isotopically Substituted Proton Pump Inhibitors

Subject matter of the invention

The present invention relates to isotopically substituted proton pump inhibitors and their (R)- and (S)-enantiomers. These compounds can be used in the pharmaceutical industry for preparing pharmaceutical compositions.

Background of the invention

Owing to their H^+/K^+-ATPase-inhibitory action, pyridin-2-ylmethylsulphinyl-1H-benzimidazoles, such as those known, for example, from EP-A-0005129, EP-A-0166287, EP-A-0174726, EP-A-0254588 and EP-A-0268956 are of considerable importance in the therapy of disorders associated with an increased secretion of gastric acid.

Examples of active compounds from this group which are commercially available or in clinical development are 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulphinyl]-1H-benzimidazole (INN: omeprazole), (S)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulphinyl]-1H-benzimidazole (INN: esomeprazole), 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole (INN: pantoprazole), 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methylsulphinyl]-1H-benzimidazole (INN: lansoprazole), 2-{[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methylsulphinyl}-1H-benzimidazole (INN: rabeprazole) and 5-methoxy-2-((4-methoxy-3,5-dimethyl-2-pyridylmethyl)sulphinyl)-1H-imidazo[4,5-b]pyridine (INN: tenatoprazole).

The above mentioned sulphinyl derivatives are, owing to their mechanism of action, also referred to as proton pump inhibitors or, abbreviated, as PPI.

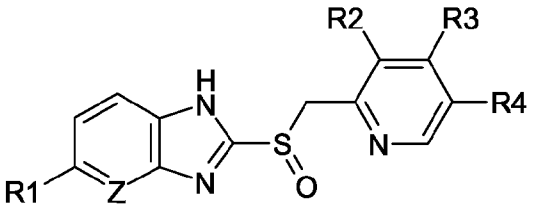
Description of the related art

US Patent 6,818,200 discloses dihydropyridine compounds and antibiotics wherein at least one hydrogen atom is replaced by a deuterium atom. The deuterated compounds are obtained by reacting the H-form with mixtures of deuterium oxide and a suitable catalyst in sealed vessels at drastic reaction conditions, i.e. at elevated temperatures (60-80°C) and for prolonged reaction times (up to 190 hours). It further discloses some influence on the pharmacological properties of these compounds due to the H/D exchange.

Disclosure of the invention

It has now surprisingly been found that isotopically substituted compounds as disclosed in detail below influences significantly the inhibition of acid secretion.

The invention relates to compounds of the general formula 1



in which
R1 is hydrogen or 1-4C-alkoxy
R2 is 1-4C-alkyl or 1-4C-alkoxy
R3 is 1-4C-alkyl, 1-4C-alkoxy or 2-8C-alkoxyalkoxy
R4 is hydrogen or 1-4C-alkyl
Z is C-H or N
and pharmaceutical acceptable salts, solvates, preferably hydrates, and solvates, preferably hydrates of the salts thereof, wherein at least one hydrogen atom of R1, R2, R3, R4 or any combination of R1, R2, R3 and R4 is replaced by a deuterium atom.

1-4C-Alkyl represents straight-chain or branched alkyl groups having 1 to 4 carbon atoms. Examples which may be mentioned are the butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl and, preferably, the methyl group.

1-4C-Alkoxy represents a group, which in addition to the oxygen atom contains one of the aforementioned 1-4C-alkyl groups or fluorinated 1–4C-alkyl groups. Examples for 1-4C-alkyl groups which may be mentioned are the butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy, ethoxy and, preferably, the methoxy group. Examples for fluorinated 1-4C-alkyl groups are 2,2,3,3,3-pentafluoropropyl, 2,2,3,3-tetrafluoropropyl, 1-(trifluoromethyl)-2,2,2-trifluoroethyl, 2,2,3,3,4,4,4-heptafluorobutyl and, preferably, 2,2,2-trifluoroethyl and difluoromethyl.

2-8C-Alkoxyalkoxy represents a group, which in addition to the oxygen atom contains an internal alkylene which contains 1-4C alkylene groups and a terminal alkyl group which contains 1-4C alkyl groups and being connected by an oxygen atom to the internal alkylene group. Examples are methoxymethoxy, methoxyethoxy, ethoxymethoxy, ethoxypropoxy, ethoxyisopropoxy, isopropoxymethoxy, propoxymethoxy, methoxybutoxy, methoxyisobutoxy, propoxyethoxy, isopropoxyethoxy, propoxypro-

poxy, isopropoxyisopropoxy, isopropoxypropoxy, propoxyisopropoxy, ethoxybutoxy, ethoxyisobutoxy, ethoxy-sec-butoxy, ethoxy-tert-butoxy and preferably methoxypropoxy.

According to the invention, within the meaning of salts all salts with inorganic and organic bases are included, in particular the salts with alkali metals, such as the lithium, sodium and potassium salts, or the salts with alkaline earth metals, such as the magnesium and calcium salts, but also other pharmacologically compatible salts, such as, for example, the aluminium or the zinc salts. Particularly preferred are the sodium and the magnesium salts.

Pharmacologically incompatible salts, which can initially be obtained, for example, as process products in the production of the compounds according to the invention on the industrial scale, which are also within the scope of the invention, are - for the production of pharmaceutical compositions - converted into the pharmacologically tolerable salts by processes known to the person skilled in the art.

It is known to the person skilled in the art that the compounds according to the invention and their salts, if, for example, they are isolated in crystalline form, can contain various amounts of solvents. The invention therefore also comprises all solvates and in particular all hydrates of the compounds of the formula 1, and also all solvates and in particular all hydrates of the salts of the compounds of the formula 1. Within the meaning of solvates all pharmaceutically acceptable solvents resulting in such solvates are included.

Concerning the nomenclature of the compounds according to the invention the terms “deutero” or “deuterio” should indicate a deuterium atom ([^{2}H]). Similarly, the pre-terms “bis“ or “di” and ”tri” or “tris”, respectively should indicate the occurrence of two or three, for example deuterio atoms in a specific group, i.e. 1,1-dideuterio-2,2,2-trifluoroethoxy or trideuteriomethoxy .

Preferred within the scope of the invention are compounds of formula 1 wherein at least one of the hydrogen atoms of R3 is replaced by a deuterium atom and R3 is a 1-2C alkoxy group or a 2-5C-alkoxyalkoxy group.

Preferred are compounds of formula 1 wherein R2 is a 1-4C alkyl group and R3 is a 2-8C-alkoxyalkoxy group, wherein at least one of the hydrogen atoms of R2, R3 or R2 and R3 is replaced by a deuterium atom.

Preferred are compounds of formula 1 wherein R1 is a 1-4C alkoxy group, R2 and R4 are a 1-4C alkyl group and R3 is a 1-4C-alkoxy group, wherein at least one of the hydrogen atoms of R1, R3, R4 or any combination of R1, R3 and R4 is replaced by a deuterium atom.

Preferred are also compounds of formula 1 wherein R1 is hydrogen, methoxy or difluoromethoxy, R2 is methyl or methoxy, R3 is methoxy, 2,2,2-trifluoroethoxy or methoxypropoxy, R4 is hydrogen or methyl and wherein at least one of the hydrogen atoms of R3 is replaced by a deuterium atom.

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