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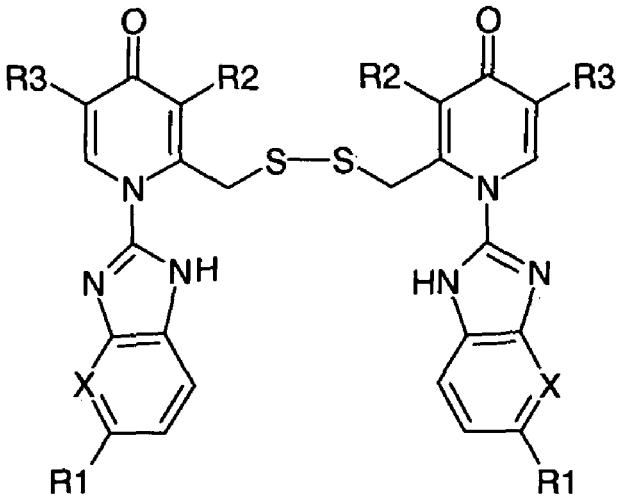
(54) Title: PYRIDONE DERIVATIVES AS ACID SECRETION INHIBITORS AND PROCESS FOR PREPARATION THEREOF



Pyridone disulphide derivatives (I)

(57) Abstract: Provided are pyridine disulphide derivatives of Formula (I) and their preparation, pharmaceutical composition. The pyridine disulphide derivatives are useful in the treatment of gastrointestinal disorders. wherein, R^1, R^2 and R^3 are independently alkyl, alkoxy, halogen, halogenated alkoxy, halogenated alkyl, hydrogen and could be same or different and X is CH or N. R^1 is methyl, methoxy, fluorine, trifluoromefhyl, difluoromethoxy and hydrogen, R^2 is methyl, methoxy and hydrogen, and R^3 is methyl and hydrogen.

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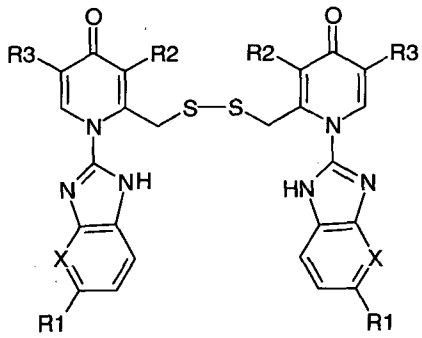
PYRIDONE DERIVATIVES AS ACID SECRETION INHIBITORS AND PROCESS FOR PREPARATION THEREOF

FIELD OF THE INVENTION

The present invention relates to stable pyridone disulphide derivatives of general formula (I), their preparation and utilization for the treatment of ailments related to the stomach and intestine.



Pyridone disulphide derivatives (I)

Wherein, R_1, R_2 and R_3 are alkyl, alkoxy, halogen, halogenated alkoxy, halogenated alkyl, hydrogen and could be same or different and X is CH or N.

R_1 is methyl, methoxy, fluorine, trifluoromethyl, difluoromethoxy and hydrogen,

R_2 is methyl, methoxy and hydrogen, R_3 is methyl and hydrogen.

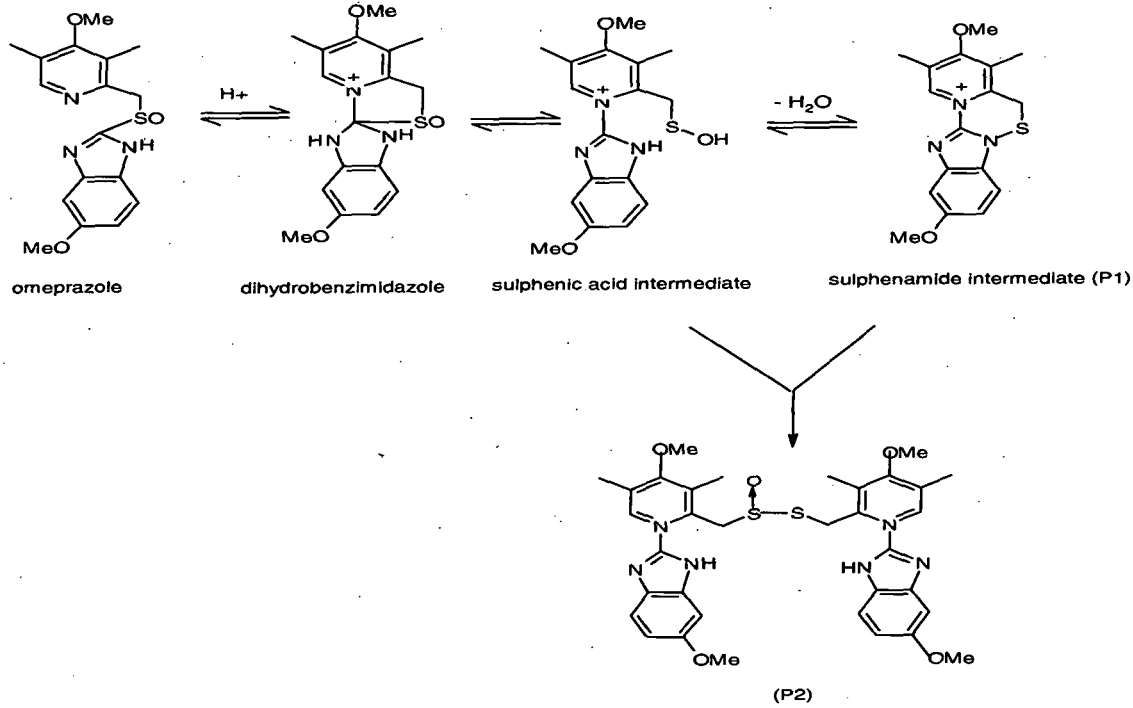
BACKGROUND OF THE INVENTION

Gastrointestinal disorders such as peptic ulcers, gastroesophageal reflux and heartburns arising out of excessive secretion of acidic gastric fluids are amongst the widely encountered diseases in modern age. These diseases, if not controlled, have a tendency to aggravate and ultimately result in gastric cancer. The initial treatment for this indication involved use of histamine-H_2-receptor antagonists such as cimetidine as acid secretion inhibitors, which was later followed by introduction of the proton-pump inhibitors (PPIs), collectively known as the prazoles.

The vast majority of the proton-pump inhibitors belonging to prazole group of compounds are benzimidazole derivatives comprising of two heterocyclic moieties, imidazole and pyridine which are linked through a methylene sulfinyl [$-CH_2S(O)-$] group. The mode of action involves inhibition of gastric acid secretion in the lumen of the stomach by blockage of (H^+/K^+)ATPase enzyme of the parietal cell, which is

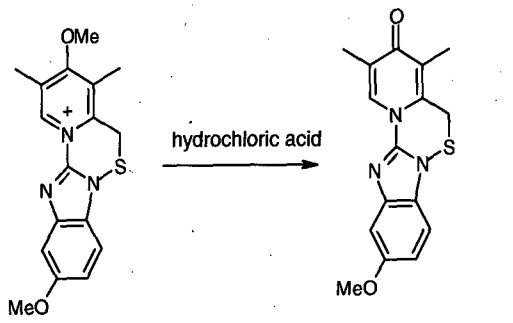
responsible for gastric acid production and is located in the secretory membranes of the parietal cells. Incidentally, the prazole group of compounds are by themselves, not active inhibitors of this enzyme but are transformed within the acid compartments of the parietal cells into the active inhibitors.

Portugaliae Electrochimica Acta (2008), 433-448 discloses that in case of omeprazole, the inactive drug is converted to its active form by a probable mechanism which involves protonation and removal of a water molecule to form a sulfenamide intermediate of formula (P1). This intermediate reversibly reacts with the sulfenic acid from which it has been generated and leads to the molecule (P2), which possesses a disulfide linkage between the benzimidazo pyridine fragments. (Scheme-1)



Scheme-1: Mechanism for formation of sulfenamide intermediate and the disulfide

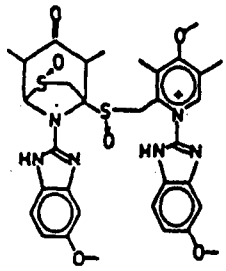
The intermediate (P1), as discussed in Acta Chemica Scandinavica (1989), 43, 536-548, also undergoes aryl oxygen cleavage on treatment with hydrochloric acid to provide a pyridone derivative (P3) **(Scheme-2).**



sulphenamide intermediate (P1) pyridone derivative (P3)

Scheme-2: Reaction of sulfenamide (P1) to pyridone derivative (P3)

The pyridone derivative (P3) gets further converted to compound (P4), similar to the disulfide compound (P2). Herein, it is pertinent to note that the pyridone derivative (P3) is known to be an unstable intermediate in the reactions of prazoles occurring in the acidic environment and readily converts to the disulfoxide derivative (P4).



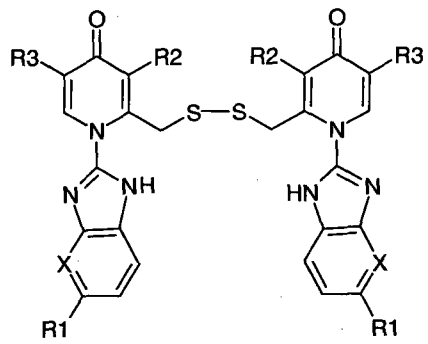
Disulfoxide derivative (P4)

It has also been reported that sulfenamides characterized by structures similar to compound (P1) are difficult to isolate and are usually isolated as acid addition salts. US 4,636,499 discloses methods for the preparation of the sulfenamides which can be employed for providing gastrointestinal cytoprotective effects during the treatment of gastrointestinal inflammatory diseases in mammals. The process comprises treatment of the respective prazole having a sulfoxide functional group with prohibitively expensive acids like HPF_6, HBF_4 or $HAuCl_4$. Hence, the resulting sulfenamide is in the form of an acid addition salt with the said acids, which unfortunately cannot be administered as such and needs to be converted to its free base followed by optional treatment with pharmaceutically acceptable acids.

US 4,769,456, US 5,162,317 also disclose methods for preparing sulphenamides, which apparently due to difficulty in isolation of the product are isolated as their salts with

costly acids like fluoroboric acid, tetrafluoroboric acid or hexafluorophosphoric acid and not suitable for therapeutic use.

The present inventors, while carrying out research for identifying compounds that are themselves active inhibitors of gastric acid secretion in the stomach, through serendipity were successful in isolating compounds of formula (I) in a stable form. These compounds were found to exhibit instant therapeutic action against gastrointestinal disorders, without being converted further into any other active form.



Pyridone disulphide derivatives (I)

wherein, R_1, R_2 and R_3 are independently alkyl, alkoxy, halogen, halogenated alkoxy, halogenated alkyl, hydrogen and could be the same or different and X is CH or N,
R_1 is methyl, methoxy, fluorine, trifluoromethyl, difluoromethoxy and hydrogen,
R_2 is methyl, methoxy and hydrogen, R_3 is methyl and hydrogen.

After an extensive study of the literature reports relating to the active compounds for gastrointestinal secretion inhibitory activity of prazoles, it was found that compounds of the invention having formula (I) were novel. Earlier, it was not possible to synthesize or isolate these compounds due to their unstable nature. Further, it was also found that the invented compounds having the pyridone moiety and the disulfide linkage were different from similar disulfide compounds (compound P2) disclosed in International Journal of Pharmaceutics (2006), 323, p.110-116. Another noteworthy finding about compounds of formula (I) was that they were found to be at least six times more potent than the prazole compounds. This would significantly lower the dosage of the active ingredient and also minimize any untoward side effects that are associated with higher dosage as compared to prior art compounds having similar therapeutic action. The compounds of the embodied invention were prepared and isolated as stable, crystalline

or amorphous solids, depending upon the structure of the compound and the method employed for their isolation.

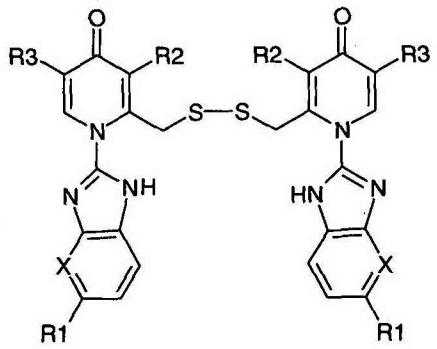
OBJECT OF THE INVENTION

An object of present invention is to provide stable, crystalline or amorphous pyridone disulfide compounds of formula (I) and its stereoisomers useful as proton pump inhibitors for exhibiting gastric acid secretion inhibitory activity.

A further object of the invention is to obtain pyridone disulfide derivatives of formula (I) having desired purity and with associated impurities conforming to regulatory limits.

SUMMARY OF THE INVENTION

An aspect of the present invention is to provide stable pyridone disulfide compounds of formula (I).



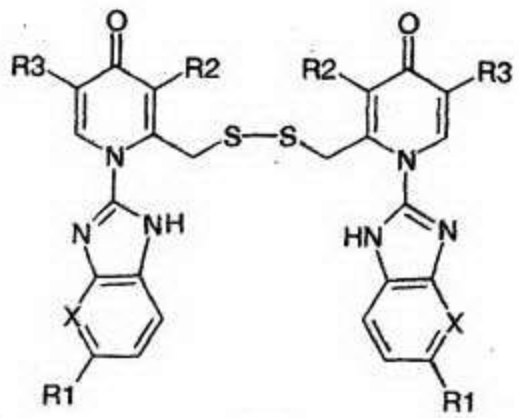
Pyridone disulphide derivatives (I)

wherein, R_1, R_2 and R_3 are independently alkyl, alkoxy, halogen, halogenated alkoxy, halogenated alkyl, hydrogen and could either be the same or different and X is CH or N

R_1 is methyl, methoxy, fluorine, trifluoromethyl, difluoromethoxy and hydrogen,

R_2 is methyl, methoxy and hydrogen, R_3 is methyl and hydrogen.

In particular the invention provides pyridone disulfide derivatives and its stereoisomers of formula (I)



(I)

wherein, R_1, R_2 and R_3 are independently alkyl, alkoxy, halogen, halogenated alkoxy, halogenated alkyl, hydrogen and could be same or different and X is CH or N.

The invention also provides a process for preparation of pyridone disulfide derivatives and its stereoisomers of formula (I) comprising treatment of compound (IV) with a dealkylating agent to give compound of formula (V), which was then oxidized to give compound of formula (VI), and further treatment with an acid in presence of a solvent, in a pH range of 4.5 to 8.5, provided compound of formula (I) conforming to regulatory specifications.

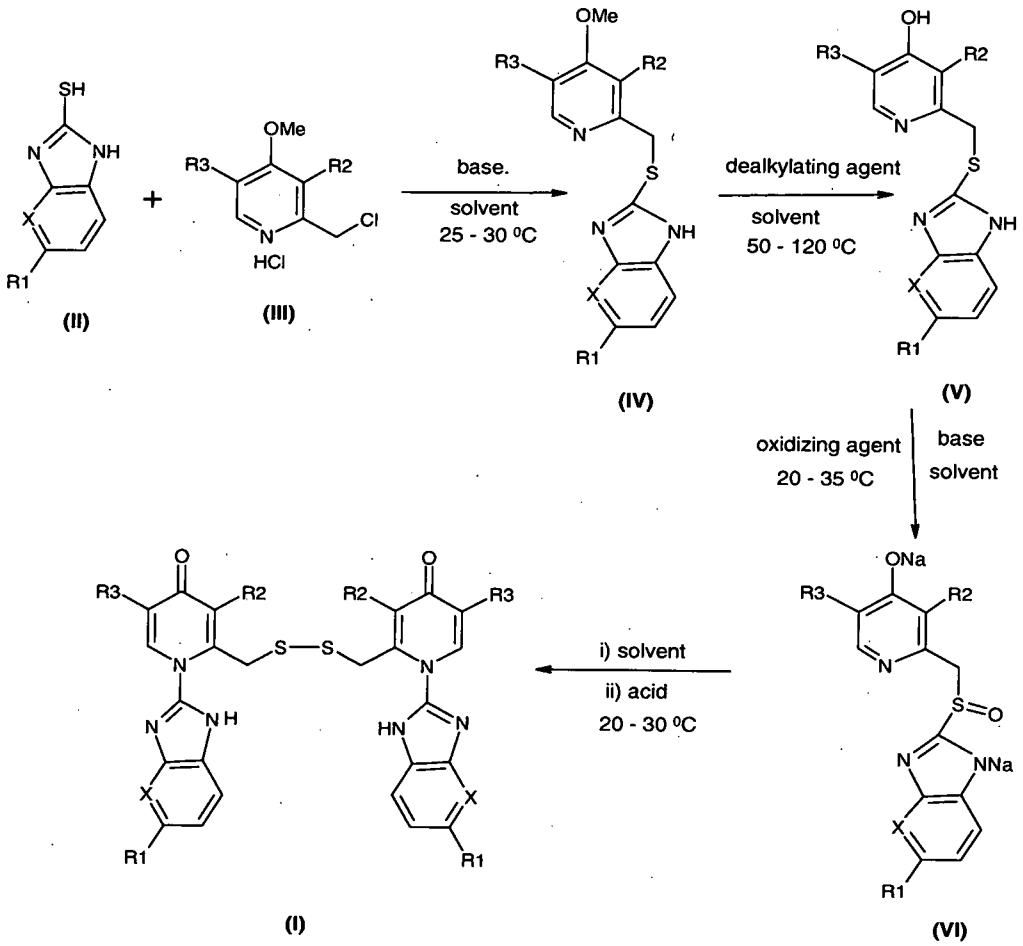
The invention also provides a pharmaceutical composition comprising an active pharmaceutical ingredient as provided by this specification along with an acceptable pharmaceutical excipient and its use for treating gastrointestinal disorders.

Yet another aspect of the present invention is to provide a process for the preparation of stable pyridone disulfide derivatives of formula (I) comprising treatment of compound (IV) with a dealkylating agent to give compound of formula (V) followed by oxidation to give compound of formula (VI) and further treatment with an acid in presence of a solvent in the pH range of 4.5 to 8.5 to provide a compound of formula (I) conforming to regulatory specifications.

(followed by page 6)

DETAILED DESCRIPTION OF THE INVENTION

In an embodiment, the present invention provides novel pyridone disulfide derivatives of formula (I), process for their preparation and isolation of stable compounds of formula (I) in the pH range of 4.5 to 8.5. The invention also includes the preparation of stereoisomeric isomers of stable pyridone disulfide derivatives.



Scheme-3: Method embodied in the present invention for preparation of pyridine disulphide derivatives of formula (I)

The meaning of term 'stable' used herein indicates that the compound of formula (I) is obtained in a stable form, crystalline or amorphous, not easily prone to degradation during storage.

In yet another embodiment, the present invention provides a process for preparation and isolation of novel pyridone disulfide derivatives of formula (I), comprising of the following steps.

Step 1 involved reaction of substituted benzimidazo-2-thiol or substituted imidazo-pyridine-2-thiol (compound II) with substituted-2-chloromethyl-4-methoxy-pyridine derivative (compound III) in presence of a base and solvent to give substituted

methoxy-2-pyridinyl-methylsulfidyl benzimidazole or the corresponding imidazo-pyridine derivative (compound IV).

The base was selected from the group comprising of sodium hydroxide, potassium hydroxide, calcium hydroxide, barium hydroxide etc. The solvent was selected from the group comprising of water, methanol, ethanol, isopropanol, butanol etc. and mixtures thereof. The reaction was carried out at 20–40^{0}C. After completion of the reaction as monitored by TLC, the mixture was filtered to give the respective substituted methoxy-2-pyridinyl-methylsulfidyl benzimidazole derivative or imidazo-pyridine derivative (compound IV) having desired purity.

Step 2 involved regioselective dealkylation of substituted methoxy-2-pyridinyl methyl-sulfidyl benzimidazole or imidazo-pyridine derivative (compound IV) in presence of a dealkylating agent and a solvent to give compound of formula (V).

Various dealkylating agents such as sodium sulfide, hydrobromic acid, aluminium chloride etc. were used. In case of sodium sulfide, the reaction was carried out in the temperature range of 80 to 110^{0}C, in presence of a solvent. The solvent was selected from the group comprising of nitriles, alcohols, polar aprotic solvents such as N-methyl pyrrolidone, dimethyl formamide, dimethyl acetamide water or mixtures thereof.

After completion of the reaction based on TLC, the reaction mass was cooled and neutralized with an acid such as acetic acid. Filtration of the obtained solid and drying gave the respective substituted hydroxy-2-pyridinyl-methylsulfidyl-benzimidazole or imidazo-pyridine derivative (compound V) having desired purity.

Alternatively, the dealkylation was also carried out by employing aqueous hydrobromic acid or using Lewis acid halides such as aluminium chloride, zinc chloride, optionally in presence of decanethiol. The reaction was carried out at a temperature ranging from 50-110°C, depending upon the type of the dealkylating reagent used.

After completion of the reaction as monitored by TLC, the product was isolated by concentrating the mixture and adding water followed by addition of an organic solvent like methanol to the aqueous layer at around neutral pH to obtain the desired product of formula (V).

Step 3 comprised treatment of substituted hydroxy-2-pyridinyl-methyl-sulfidyl-benzimidazole or imidazo-pyridine derivative (compound V) with an oxidizing agent to give compound of formula (VI). This step involved treatment of compound of formula

(V) with an oxidizing agent such as (10)-camphorsulfonyl oxaziridine (CSO) and its stereoisomers or an alkali metal hypochlorite to provide the sulfoxide derivative of formula (VI). The sulfide derivative (V) was treated with the oxidizing agent at 20-35^{0}C in presence of a base and organic solvent like isopropanol. The base was selected from inorganic or organic bases. The inorganic base was selected from the group comprising of alkali metal hydroxides, carbonate and bicarbonates etc while the organic base was selected from DBU, triethyl amine, diisopropyl ethyl amine etc. The solvent was selected from the group comprising of alcohols such as methyl alcohol, ethyl alcohol, isopropyl alcohol etc. or mixtures thereof.

After completion of reaction, as monitored by TLC, the reaction mass was filtered and the filtrate concentrated to get the desired compound (VI) which was optionally treated with organic solvents such as methanol, methyl tertiary butyl ether, toluene etc. or used as such for further reaction.

When oxidation was carried out using hypochlorite, compound (V) was added to a mixture of sodium hydroxide, water and methanol, followed by addition of sodium hypochlorite solution and the reaction was carried out at 20-35^{0}C. The reaction was monitored by TLC and after completion, the reaction mass was extracted with an organic solvent and the organic layer was then concentrated to give the desired compound (VI).

Alternatively, after reaction completion, the mass was carried forward for the next reaction. The pH of the reaction mass was adjusted in range of 4.5 to 8.5 using acid and the mass was stirred at 20-35^{0}C. Optionally an organic solvent such as methanol or ethyl acetate or solvent mixture was added during stirring and resulting solid was filtered after completion of the reaction as monitored by TLC, to give compound of formula (I).

Step 4 comprised treatment of compound (VI) with an acid in a solvent to obtain pH between 4.5 and 8.5, preferably 6.5 to 8, which was then stirred and filtered to obtain the desired compound (I).

The solvent was selected from the group comprising of water and organic solvents or mixtures thereof. The organic solvent was selected from the group comprising of ethers, esters, alcohols, ketones, hydrocarbons and halogenated hydrocarbons. The ethers were selected from the group comprising of dimethyl ether, dimethoxyethane, methyl-tertiary butyl ether etc. The solvents were selected from the group comprising of

ethyl acetate, acetone, methanol, toluene, xylene, dichloromethane etc. The acid employed was selected from an organic or mineral acid or a mixture thereof. The mineral acid was selected from the group comprising of hydrochloric acid, sulfuric acid and nitric acid. The organic acid was selected from the group comprising of acetic acid, citric acid, propionic acid, lactic acid etc., but preferably acetic acid.

In this step, the acid was slowly added with stirring to the mixture of compound (VI) and solvent(s) at 20-35^{0}C, till the desired pH was obtained. The desired pH range varied for different substrates in the class of compound (VI) and ranged from 4.5 to 8.5 but preferably between 6.5 and 8.0. After completion of the reaction, the desired compound of formula (I) separated out from the reaction mixture, filtered and dried. Optionally, the compound of formula (I) was subjected to purification procedures such as crystallization, solvent treatment, treatment with acid, column chromatography etc. to obtain the desired purity. The desired compounds were obtained as stable, crystalline or amorphous solids and were characterized by ^{1}H NMR, ^{13}C NMR and MS.

The different compounds obtained by varying the substituent in the general formula (I) are provided in **Tables 1A and 1B**.

Table 1A: Pyridone Disulphide Derivatives of formula (I-A), X=CH

Name of the Compound	Substituents		
	R_1	R_2	R_3
I-A-1	H	H	H
I-A-2	H	CH_3	CH_3
I-A-3	H	OCH3	H
I-A-4	CH_3	CH_3	CH_3
I-A-5	CH_3	OCH_3	H
I-A-6	OCH_3	CH_3	CH_3
I-A-7	OCH3	OCH3	H
I-A-8	F	CH_3	CH_3
I-A-9	CF_3	OCH_3	H
I-A-10	$OCHF_2$	CH_3	CH_3
I-A-11	$OCHF_2$	OCH_3	H
I-A-12	H or CH_3	CH_3	CH_3
I-A-13	CH_3 or $OCHF_2$	CH_3	CH_3
I-A-14	H or $OCHF_2$	CH_3	CH_3

Table 1B: Pyridone Disulphide Derivatives of formula (I-B), X=N

Name of the Compound	Substituents		
	R_1	R_2	R_3
I-B-1	H	CH_3	CH_3
I-B-2	OCH_3	OCH_3	H
I-B-3	OCH_3	CH_3	CH_3

For clinical use, the compounds of the invention were utilized for pharmaceutical formulations for oral, rectal, parenteral or other modes of administration. The pharmaceutical formulation contains a compound of the invention in combination with a pharmaceutically acceptable carrier, which could be in the form of a solid, semisolid or liquid diluent, or a capsule. Usually the amount of active compound is between 0.1 and 95.0% by weight of the preparation. When the compound of the present invention is to be administered as a therapeutic or preventive agent for peptic ulcer, it may be administered orally (powder, granule, capsule, syrup etc.), parenterally (suppositories, injections), as external preparations or as intravenous drips. It may be administered in a dose of approximately 0.01 to 200 mg/kg/day, preferably 0.05 to 50 mg/kg/day and still preferably 0.1 to 10 mg/kg/day in one to several portions. For a solid preparation for oral administration, the active component is mixed with filler and a binder, a disintegrating agent, a lubricant, a colorant and/or a corrigent, etc. The obtained mixture is then formulated into tablets, coated tablets, granules, powders or capsules. Examples of fillers include lactose, corn starch etc while binders include polyvinyl alcohol, polyvinyl ether, methylcellulose etc. Disintegrating agents include starch, agar, gelatin powder, crystalline cellulose, etc. Lubricants include magnesium stearate, talc, polyethylene glycol, silica and hardened vegetable oils. Examples of the corrigent include cocoa powder, mentha herb, aromatic powder, mentha oil, borneol and cinnamon powder. In case of injections, the active component is mixed with various additives such as a pH modifier, a buffer, a stabilizer or a solubilizing agent, if required. Thus a subcutaneous, intramuscular or intravenous injection is obtained.

The principles, preferred embodiments and modes of operation of the present invention have been described in the foregoing examples. The invention which is intended to be

protected herein, however, is not to be construed limited to the particular forms disclosed, since these are to be regarded as illustrative rather than restrictive. Variations and changes may be made by those skilled in the art, without departing from the spirit of the invention.

EXAMPLES

EXAMPLE 1 Preparation of (I-A-11) 1-(5-(difluoromethoxy)-1H-benzo[d]imidazol-2-yl)-2-((2-((1-(5-(difluoromethoxy)-1H-benzo[d]imidazol-2-yl)-1,4-dihydro-3-methoxy-4-oxopyridin-2-yl)methyl)disulfinyl)methyl)-3-methoxypyridin-4(1H)-one)

1(i) Preparation of IV-A-11: Methanol (270 ml) was added to a solution of NaOH (41.5gms) in water (180 ml), followed by addition of 5-difluoromethoxy-2-mercapto-1H-benzimidazole (105.2gms). A solution of 2-chloromethyl-3,4-dimethoxy-pyridine.hydrochloride (100.3gms in water (150 ml) was gradually added to the reaction mixture and stirred at 25-30^{0}C till completion of the reaction.. After completion, as monitored by TLC, the reaction mixture was filtered and the obtained solid was dried to give compound IV-A-11, Yield: 140.6 gm (83%).

1H NMR (400 MHz, CDCl3): δ 8.27 (d, J = 5.6 Hz, 1H), 7.48 (d, J = 8.8 Hz, 1H), 7.32 (d, J = 2 Hz, 1H), 6.99 (dd, J = 2.4, 8.8 Hz, 1H), 6.87 (d, J = 5.6 Hz, 1H), 6.50 (t, J = 74.8 Hz, 1H), 4.39 (s, 2H), 3.95 (s, 3H), 3.93 (s, 3H), ESI-MS: 368.9 (M+1).

1(ii) Preparation of V-A-11: The solution of compound IV-A-11(50.7gms) and sodium sulfide (38.6 gm, assay 55%) in N-methyl pyrrolidone (700ml) were heated to 90 to 100°C and stirred at the same temperature. After completion of the reaction, as monitored by TLC, the reaction mass was quenched with water and pH was adjusted to 6.7 using aqueous acetic acid (50%). The obtained suspension was filtered and solid was dried to get compound V-A-11, Yield: 29.5 gm.

^{1}H NMR (400 MHz, DMSO d_6): δ 7.66 (br.s, 1H), 7.48 (br.s, 1H), 7.30 (br.s, 1H), 7.16 (t, J = 74.4 Hz, 1H), 6.98 (dd, J = 2.0, 8.0 Hz, 1H), 6.25 (br.s, 1H), 4.54 (s, 2H), 3.76 (s, 3H), ESI-MS: 353.7 (M+1).

1(iii) Preparation of VI-A-11: (1R)-(-)-(10-camphorsulfonyl) oxaziridine (33.7gm) was gradually added to a solution of V-A-11 (50.1 gm), and sodium hydroxide (12.4 gm) in isopropyl alcohol (350 ml) at 25 to 30°C. The reaction mixture was stirred at 25 to 30°C. The reaction mass was filtered and the filtrate was concentrated under vacuum to obtain VI-A-11(60.1gm), and carried forward for next reaction.

1(iv) Preparation of I-A-11: Aqueous acetic acid (50%) was gradually added to a solution of VI-A-11 (190.5 gm) in ethyl acetate (1900 ml) and water (1140 ml) at 25 to 30°C till the reaction mass attained pH 7.3. The mass was stirred till completion of the

reaction as monitored by TLC. The suspension thus obtained was filtered and solid was dried to give compound I-A-11, Yield: 14.1 gm

^{1}H NMR (400 MHz, DMSO d_6): δ 13.0 (s, 1H, D_2O exchangable), 7.88 (s, 1H), 7.47 (br.s, 1H), 7.03 (br.s, 1H), 6.88 (dd, J = 2.0, 8.8 Hz 1H), 4.09 (s, 2H), 3.79 (s, 3H), 1.90 (s, 3H), 1.88 (s, 3H). ^{13}C NMR (100 MHz, DMSO d_6): δ 177.2, 156.3, 145.2, 141.7, 137.5, 124.0, 122.2, 112.6, 56.5, 36.8, 13.3, 11.4. ESI-MS: 627 in negative ion mode.

General procedures for preparation of compound IV, compound V and compound VI are given below.

A. Preparation of compound IV (Scheme-3): The reaction of substituted benzimidazothiol derivatives or substituted imidazopyridine-thiol derivatives (compound II) with substituted methoxypyridinium hydrochloride derivatives (compound III) was carried out at 25-30^{0}C, in presence of an aqueous solution of sodium hydroxide and methanol. After completion of the reaction, based on TLC monitoring, the mixture was filtered and the solid dried to give the respective substituted methoxy-pyridinyl-methylsulfidyl-imidazole or imidazopyridine derivatives (compound IV).

B. Preparation of compound V

B.1- (using sodium sulfide): The solution of compound IV in N-methyl pyrrolidone was treated with sodium sulfide at 80–110^{0}C till completion of the reaction. The mixture was cooled and the pH was adjusted between 6 and 7 with acetic acid. Filtration of the obtained solid and drying gave compound V.

B.2 - (using HBr/acetic acid): A stirred mixture of compound IV, acetic acid and aqueous HBr were heated to 100-110^{0}C till the reaction completion. The reaction mass was cooled, concentrated under reduced pressure and the residue diluted with water and washed with dichloromethane. The aqueous layer was neutralized by addition of sodium carbonate solution and diluted with methanol. The solid thus obtained was washed with a aqueous methanol and dried to give compound V.

B.3 - (using $AlCl_3$): Compound IV and aluminium chloride were stirred in chloroform and heated to 50-70°C till the reaction was complete. The reaction mass was cooled, quenched with water and concentrated. Hydrochloric acid was added to the residue and the aqueous layer was neutralized with aqueous sodium carbonate solution. The precipitated solid was filtered, dried to give compound V.

C. Preparation of compound VI

C.1 - (using camphorsulfonyl oxaziridine): (10)-camphorsulfonyl oxaziridine or its stereoisomers was gradually added to a solution of compound V and sodium hydroxide in isopropyl alcohol at 25-30°C and stirred till completion of the reaction. The reaction mass was filtered and the filtrate concentrated under vacuum to obtain compound VI, which was directly used for further reaction. Alternatively, the residue obtained after concentration was dissolved in methanol, concentrated and further recrystallized from toluene to give compound VI.

C.2 (using sodium hypochlorite): Compound V was added to a stirred mixture of aqueous sodium hydroxide and methanol. Sodium hypochlorite solution was added at 25-30^{0}C and stirred at same temperature till completion of the reaction. The mixture was extracted with an organic solvent and the organic layer after separation was concentrated to give compound (VI). Alternatively, the reaction mass containing compound VI was carried forward for the next reaction, without isolating the product.

D - Preparation of compound I: Compound VI dissolved in water or an organic solvent or mixtures thereof was treated with acid, which was gradually added to it at 25-30^{0}C, till the pH of the reaction mixture was in the range of 4.5 to 8.5. The mass was stirred till completion of the reaction as monitored by TLC. The suspension thus obtained was filtered and solid was dried to get compound I, which was optionally purified using suitable methods.

EXAMPLE 2: Solid oral formulation (tablets) containing the active ingredient.

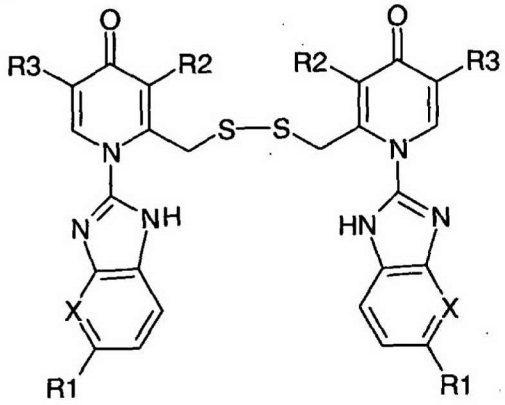
A tablet containing compound (I) was prepared from the following ingredients:

Ingredients	% w/w
1. Active compound	20
2. lactose	73
3. Methyl cellulose	0.5
4. Polyvinylpyrrolidone	5.0
5. Magnesium stearate	1.5

The active ingredient was mixed with lactose, and granulated with a water solution of methyl cellulose. The wet mass was forced through a sieve and the granulate was dried in an oven. The granulate after drying, was mixed with polyvinylpyrrolidone and magnesium stearate. The dry mixture was pressed into tablet cores (10 000 tablets), each tablet containing 20 % by weight of the active substance; in a tableting machine using 6 mm diameter punches.

Claims:

1. Pyridone disulfide derivatives and its stereoisomers of formula (I)



(I)

wherein, R_1, R_2 and R_3 are independently alkyl, alkoxy, halogen, halogenated alkoxy, halogenated alkyl, hydrogen and could be same or different and X is CH or N.

2. Pyridone disulfide derivatives of formula (I) according to claim 1, wherein R_1 is selected from the group comprising of methyl, methoxy, fluorine, trifluoromethyl, difluoromethoxy and hydrogen.
3. Pyridone disulfide derivatives of formula (I) according to claim 1, wherein R_2 is selected from the group comprising of methyl, methoxy and hydrogen.
4. Pyridone disulfide derivatives of formula (I) according to claim 1, wherein R_3 is selected from the group comprising of methyl and hydrogen.
5. The process for preparation of pyridone disulfide derivatives and stereoisomers thereof of formula (I) comprising treatment of compound (IV) with a dealkylating agent to give a compound of formula (V), oxidization to give a compound of formula (VI), and further treatment with an acid in the presence of a solvent, in the pH range of 4.5 to 8.5, to provide a compound of formula (I).
6. The process according to claim 5, wherein the dealkylating agent is selected from the group comprising of sodium sulfide, hydrobromic acid and aluminium chloride.
7. The process according to claim 5, wherein the oxidizing agents is selected from 10-camphorsulfonyl oxaziridine or its stereoisomers and sodium hypochlorite.

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8. The process according to claim 5 wherein compound of formula (I) is obtained by treating compound (VI) with an acid selected from the group comprising of an organic acid like acetic acid, citric acid, propionic acid and lactic acid or a mineral acid such as hydrochloric acid, sulfuric acid and nitric acid and the solvent is selected from the group comprising of esters, alcohols, ketones, hydrocarbons, halogenated hydrocarbons, water and mixtures thereof.

9. A pharmaceutical composition comprising an active pharmaceutical ingredient as claimed in claim 1 along with acceptable pharmaceutical excipients and its use for treatment of gastrointestinal disorders.

10. Pyridone disulfide derivative of formula (I) according to claim 1 wherein the pyridone disulfide derivative is a compound selected from the group consisting of:
1-(5-(difluoromethoxy)-1H-benzo[d]imidazol-2-yl)-2-((2-((1-(5-(difluoromethoxy)-1H-benzo[d]imidazol-2-yl)-1,4-dihydro-3-methoxy-4-oxopyridin-2-yl)methyl)disulfinyl) methyl)-3-methoxypyridin-4(1H)-one (compound I-A-11);
2-((2-((1-(1H-benzo[d]imidazol-2-yl)-1,4-dihydro-4-oxopyridin-2-yl)methyl)disulfinyl) methyl)-1-(1H-benzo[d]imidazol-2-yl)pyridin-4(1H)-one (compound I-A-1);
2-((2-((1-(1H-benzo[d]imidazol-2-yl)-1,4-dihydro-3,5-dimethyl-4-oxopyridin-2-yl)methyl) disulfinyl)methyl)-1-(1H-benzo[d]imidazol-2-yl)-3,5-dimethylpyridin-4(1H)-one (compound I-A-2);
2-((2-((1-(1H-benzo[d]imidazol-2-yl)-1,4-dihydro-3-methoxy-4-oxopyridin-2-yl)methyl) disulfinyl)methyl)-1-(1H-benzo[d]imidazol-2-yl)-3-methoxypyridin-4(1H)-one (compound I-A-3);
2-((2-((1,4-dihydro-3,5-dimethyl-1-(5-methyl-1H-benzo[d]imidazol-2-yl)-4-oxopyridin-2-yl) methyl)disulfinyl)methyl)-3,5-dimethyl-1-(5-methyl-1H-benzo[d]imidazol-2-yl)pyridin-4 (1H)-one (compound I-A-4);
2-((2-((1,4-dihydro-3-methoxy-1-(5-methyl-1H-benzo[d]imidazol-2-yl)-4-oxopyridin-2-yl) methyl)disulfinyl)methyl)-3-methoxy-1-(5-methyl-1H-benzo[d]imidazol-2-yl)pyridin-4(1H) -one (compound I-A-5);
2-((2-((1,4-dihydro-1-(5-methoxy-1H-benzo[d]imidazol-2-yl)-3,5-dimethyl-4-oxopyridin-2-yl) methyl)disulfinyl)methyl)-1-(5-methoxy-1H-benzo[d]imidazol-2-yl)-3,5-dimethylpyridin-4 (1H)-one (compound I-A-6);
2-((2-((1,4-dihydro-3-methoxy-1-(5-methoxy-1H-benzo[d]imidazol-2-yl)-4-oxopyridin-2-yl) methyl)disulfinyl)methyl)-3-methoxy-1-(5-methoxy-1H-benzo[d]imidazol-2-yl)pyridin-4 (1H)-one (compound I-A-7);
1-(5-fluoro-1H-benzo[d]imidazol-2-yl)-2-((2-((1-(5-fluoro-1H-benzo[d] imidazol-2-yl)-1,4-dihydro-3,5-dimethyl-4-oxopyridin-2-yl)methyl)disulfinyl) methyl)-3,5-dimethylpyridin-4(1H)-one (compound I-A-8);
1-(5-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-2-((2-((1-(5-(trifluoromethyl)-1H-benzo[d] imidazol-2-yl)-1,4-dihydro-3-methoxy-4-oxopyridin-2-yl)methyl)disulfinyl methyl)-3-methoxypyridin-4(1H)-one (compound I-A-9);
1-(5-(difluoromethoxy)-1H-benzo[d]imidazol-2-yl)-2-((2-((1-(5-(difluoromethoxy)-1H-benzo [d]imidazol-2-yl)-1,4-dihydro-3,5-dimethyl-4-oxopyridin-2-yl)methyl) disulfinyl) methyl)-3,5-dimethylpyridin-4(1H)-one (compound I-A-10);

and pharmaceutically acceptable salts thereof.