PRODRUGS OF PROTON PUMP INHIBITORS

BACKGROUND OF THE INVENTION

3. Cross-reference to Related Application

The present application is a continuation-in-part of application serial number 09/131,481, filed on August 10, 1998.

2. Field of the Invention

The present invention is directed to prodrugs of proton pump inhibitors which are useful as anti-ulcer agents. More particularly, the present invention is directed to prodrugs that slowly hydrolyze to provide benzimidazole-type proton pump inhibitors which inhibit exogenously or endogenously gastric acid secretion and thus can be used in the prevention and treatment of gastrointestinal inflammatory diseases in mammals, including humans.

3. Brief Description of the Prior Art

Benzimidazole derivatives intended for inhibiting gastric acid secretion are disclosed in the United States Patent Nos. 4,045,563; 4,255,431; 4,628,098; 4,686,230; 4,758,579; 4,965,269; 5,021,433; 5,430,042 and 5,708,017. Generally speaking, the benzimidazole-type inhibitors of gastric acid secretion work by undergoing a rearrangement to form a thiophilic species which then covalently binds to gastric H,K-ATPase, the enzyme involved in the final step of proton production in the parietal cells, and thereby inhibits the enzyme. Compounds which inhibit the gastric H,K-ATPase enzyme are generally known in the field as "proton pump inhibitors" (PPI).

Some of the benzimidazole compounds capable of inhibiting the gastric H,K-ATPase enzyme have found substantial use as drugs in human medicine and are known under such names as LANSOPRAZOLE (United States Patent No. 4,628,098), OMEPRAZOLE (United States Patent Nos. 4,255,431 and 5,693,818), PANTOPRAZOLE (United States Patent No. 4,758,579), and RABEPRAZOLE (United States Patent No. 5,045,552). The diseases treated

by proton pump inhibitors and specifically by the four above-mentioned drugs include peptic ulcer, heart burn, reflux esophagitis errosive esophagitis, non-ulcer dispepsia, infection by Helicobacter pylori, alrynitis and asthma among others.

Whereas the proton pump inhibitor type drugs represent substantial advance in the field of human and veterinary medicine, they are not totally without shortcomings or disadvantages. The shortcomings of the presently used proton pump inhibitor (PPI) type drugs can be best explained by a more detailed description of the mode of their action, the diseases or condition against which they are employed and the circumstances of their application. Thus, acid related diseases include but are not limited to erosive esophagitis, esophageal reflux, gastric and duodenal ulcer, non-ulcer dyspepsia and infection by *Helicobacter pylori*. Current therapy of all but the infection by *H. pylori* bacteria involves treatment with drugs designed to suppress acid secretion, one type of which are the above-mentioned proton pump inhibitors.

The presently used proton pump inhibitors are pyridyl methyl sulfinyl benzimidazoles (or compounds of closely related structure) with a pK_a of 4.0 to 5.0. Their mechanism of action requires accumulation in the acidic space of the parietal cell (secretory canaliculus, pH ca. 1.0) and subsequently hydrogen ion catalyzed conversion to the reactive thiophilic species that is capable of inhibiting the gastric ATPase, enzyme resulting in effective inhibition of gastric secretion. Because of this mechanism the presently used PPI type drugs require specialized gastro protection to remain active for duodenal absorption. For this reason, and due to sensitivity to degradation in the acid milieu of the stomach, oral formulations of the PPI drugs are usually enteric coated. The need for enteric coating is a shortcoming because enteric coating is expensive and moisture sensitive.

Because of the requirement for accumulation in the acid space of the

parietal cell, acid secretion is necessary for the efficacy of the PPI type drugs. It was found that the plasma half life of these drugs is between 60 to 90 minutes. All acid pumps are not active at any one time, rather only about 75 % are active on the average during the time the drug is present in the blood following oral administration. It was also found in medical experience that on a currently used once-a-day oral administration therapy the maximal inhibition of stimulated acid output is approximately 66 %. This is due to a combination of the short plasma half life of the drug, to the limited number of acid pumps active during presentation of the drug and to the turn-over of acid pumps. In present practice it is not possible to control night time acid secretion by evening therapy of oral administration because the drug is dissipated from the plasma by the time acid secretion is established after midnight. The ideal target for healing in acid related diseases and for treatment of *H. pylori* infection (in conjunction with antibiotics), as well as for relief of symptoms of non-ulcer dyspepsia would be full inhibition of acid secretion. With the currently used PPI type drugs this is achieved only by intravenous infusion; in case of the drug OMEPRAZOLE this requires intravenous infusion of 8 mg per hour. Clearly, there is a need in the art for a drug or drugs acting through the mechanism of PPI -type drugs which can attain or approach full inhibition of acid secretion through oral therapy.

Because of the less than full inhibition of acid secretion and less than 24 hour inhibition through oral administration that is attained by the current dosage forms of currently used PPI-type drugs, therapy for healing of gastric and duodenal ulcerations is 4 to 8 weeks. This is in spite of the fact that the generation time of surface cells of the esophagus, stomach and duodenum is approximately 72 hours. Undoubtedly the presently observed prolonged healing times with these drugs is due to inadequate acid suppression and acid related damage. The foregoing underscores the need in the art for a drug or

drugs acting through the mechanism of PPI -type drugs which can attain or approach full inhibition of acid secretion through oral therapy.

As further pertinent background to the present invention, applicants note the concept of prodrugs which is well known in the art. Generally speaking, prodrugs are derivatives of *per se* drugs, which after administration undergo conversion to the physiologically active species. The conversion may be spontaneous, such as hydrolysis in the physiological environment, or may be enzyme catalyzed. From among the voluminous scientific literature devoted to prodrugs in general, the foregoing examples are cited: **Design of Prodrugs** (Bundgaard H. ed.) 1985 Elsevier Science Publishers B. V. (Biomedical Division), Chapter 1; Design of Prodrugs: Bioreversible derivatives for various functional groups and chemical entities (Hans Bundgaard); *Bundgaard et al.* **Int. J. of Pharmaceutics** *22* (1984) 45 - 56 (Elsevier); *Bundgaard et al.* **Int. J. of Pharmaceutics** *29* (1986) 19 - 28 (Elsevier); *Bundgaard et al.* **J. Med. Chem.** 32 *(1989) 2503 - 2507* **Chem. Abstracts 93**, 137935y (*Bundgaard et al.*); **Chem. Abstracts 95**, 138493f (*Bundgaard et al.*); **Chem. Abstracts 95**, 138592n (*Bundgaard et al.*); **Chem. Abstracts 110**, 57664p (*Alminger et al.*); **Chem. Abstracts 115**, 64029s (*Buur et al.*); **Chem. Abstracts 115**, 189582y (*Hansen et al.*); **Chem. Abstracts 117**, 14347q (*Bundgaard et al.*); **Chem. Abstracts 117**, 55790x (*Jensen et al.*); and **Chem. Abstracts 123**, 17593b (*Thomsen et al.*).

As far as the present inventors are aware, there are no prodrugs of the proton pump inhibitors presently in use. However, several United States patents describe compounds which can act as prodrugs of certain proton pump inhibitors. Specifically, United States Patent No. 4,686,230 (*Rainer et al.*) describes derivatives of pyridyl methyl sulfinyl benzimidazoles which include a group designated "R_5" on one of the benzimidazole nitrogens. The "R_5" group is expected to cleave under physiological condition, or under the

influence of an enzyme to provide the corresponding compound with a free N-H bond (see column 3 of United States Patent No. 4,686,230). United States Patent Nos. 5,021,433 (*Alminger et al.*), 4,045,563 (*Berntsson et al.*), 4,965,269 and (*Brändström et al.*) also describe pyridyl methyl sulfinyl benzimidazoles where one of the nitrogens of the benzimidazole moiety bears a substituent that cleaves under physiological or enzymatic conditions.

The present invention represents further advance in the art in that it provides prodrugs of improved structure of the proton pump inhibitor type drugs and provides proof of the suitability of the prodrugs of the invention for use as prodrug of proton pump inhibitors, with improved efficacy in therapy of acid related diseases due to prolongation of the presence of the proton pump inhibitors in the body.

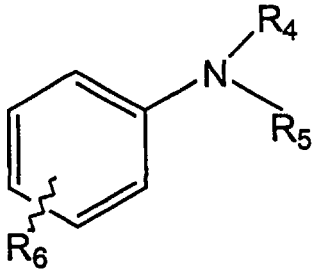
SUMMARY OF THE INVENTION

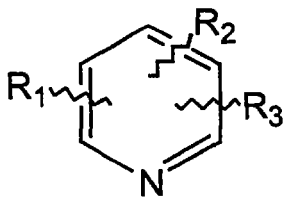
The present invention relates to compounds of **Formula 1**

$$Het_1 - X - S(O) - Het_2$$

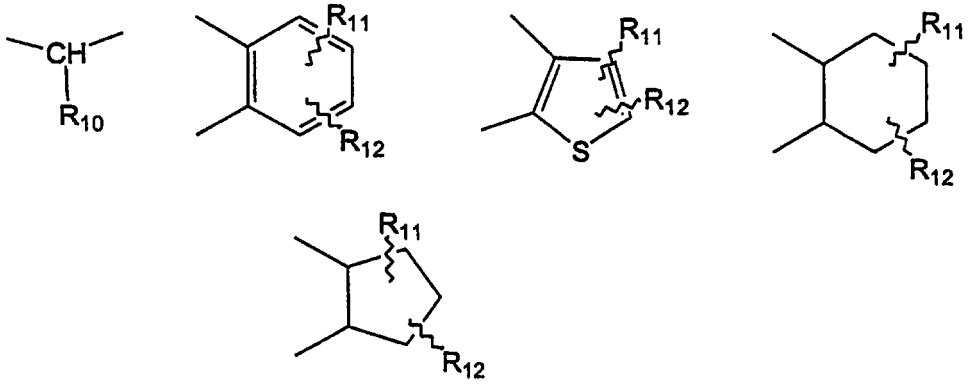
wherein

Het_1 is selected from the formulas shown below

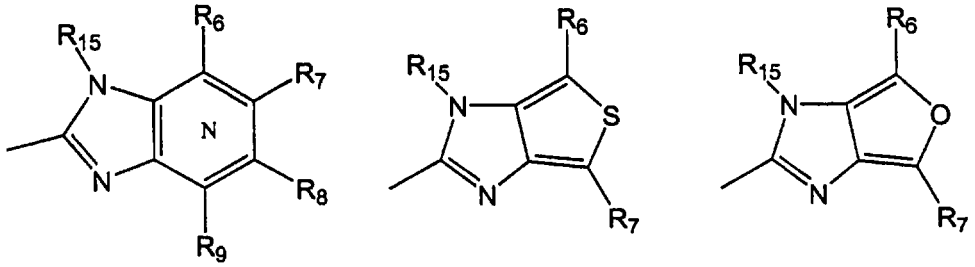




X is selected from the formulas



and Het_2 is selected from the formulas



where N in the benzimidazole moiety means that one of the ring carbons may be exchanged for an unsubstituted N atom;

R_1, R_2 and R_3 are independently selected from hydrogen, alkyl of 1 to 10 carbons, fluoro substituted alkyl of 1 to 10 carbons, alkoxy of 1 to 10 carbons, fluoro substituted alkoxy of 1 to 10 carbons, alkylthio of 1 to 10 carbons, fluoro substituted alkylthio of 1 to 10 carbons, alkoxyalkoxy of 2 to 10 carbons, amino, alkylamino and dialkylamino each of the alkyl groups in said alkylamino and dialkyl amino groups having 1 to 10 carbons, halogen, phenyl, alkyl substituted phenyl, alkoxy substituted phenyl, phenylalkoxy, each of the alkyl groups in said alkyl substituted phenyl, alkoxy substituted phenyl and phenylalkoxy having 1 to 10 carbons, piperidino, morpholino or two of the R_1, R_2 and R_3 groups jointly forming a 5 or 6 membered ring having 0 or 1 heteroatom selected from N, S and O;

R_4 and R_5 are independently selected from hydrogen, alkyl of 1 to 10 carbons, fluoro substituted alkyl of 1 to 10 carbons, phenylalkyl, naphthylalkyl and heteroarylalkyl, alkyl in said phenylalkyl, naphthylalkyl and heteroarylalkyl groups having 1 to 10 carbons;

$R_{6'}$ is hydrogen, halogen, alkyl of 1 to 10 carbons, fluoro substituted alkyl of 1 to 10 carbons, alkoxy having 1 to 10 carbons or fluoro substituted alkoxy having 1 to 10 carbons;

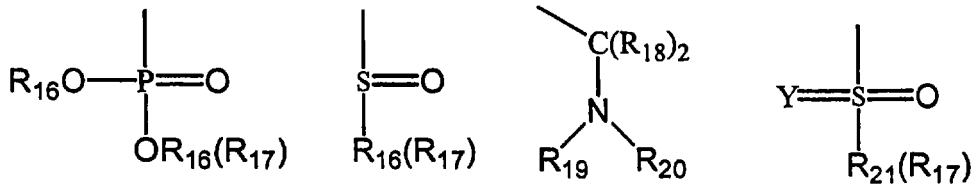
R_6 through R_9 are independently selected from hydrogen, halogen, alkyl of 1 to 10 carbons, halogen substituted alkyl of 1 to 10 carbons, alkoxy of 1 to 10 carbons, halogen substituted alkoxy of 1 to 10 carbons, alkylcarbonyl, alkoxycarbonyl the alkyl group in said alkylcarbonyl and alkoxycarbonyl having 1 to 10 carbons, oxazolyl, imidazolyl, thiazolyl, morpholinyl, piperazinyl, pyrazinyl, pyrazolyl, or any two adjacent ones of the R_6 through R_9 groups may form a ring that may optionally include a

heteroatom selected from N, O and S and said ring may be further substituted;

R_{10} is hydrogen, alkyl of 1 to 10 carbons, or R_{10} may form an alkylene chain together with R_3,

R_{11} and R_{12} are independently selected from hydrogen, halogen, alkyl of 1 to 10 carbons and halogen substituted alkyl of 1 to 10 carbons;

R_{15} is selected from the formulas below



where

R_{16} is alkyl of 1 to 10 carbons, morpholino, piperidino, phenyl, naphthyl or heteroaryl having 1 to 3 heteroatoms selected from N, O or S, said morpholino. piperidino phenyl, naphthyl or heteroaryl groups being unsubstituted, or substituted with 1 to 5 R_{17} groups;

R_{17} is alkyl of 1 to 10 carbons, halogen substituted alkyl of 1 to 10 carbons, alkoxy having 1 to 10 carbons, halogen substituted alkoxy of 1 to 10 carbons, alkylthio having 1 to 10 carbons, halogen substituted alkylthio of 1 to 10 carbons, alkoxy carbonyl having 1 to 10 carbons, halogen substituted alkoxy carbonyl having 1 to 10 carbons, F, Cl, Br, I, NO_2 , CN, OCOalkyl, NH_2 , alkylamino and dialkylamino where in said OCOalkyl, , alkylamino and

dialkylamino groups each of said alkyl group has 1 to 10 carbons, further R_{17} is ureidoyl (RNHCONH-), guanidinyl, carbamoyl, N-substituted carbamoyl, alkylcarbonyl having 1 to 10 carbons, (alkoxycarbonyl)alkoxy groups of each of said alkoxy group has 1 to 10 carbons, (alkoxycarbonyl)alkyl groups of each of said alkoxy or alkyl group has 1 to 10 carbons, (carbamoyl)alkoxy having 1 to 10 carbons, (N-alkylcarbamoyl)alkoxy having 1 to 10 carbons, (N,N-dialkylcarbamoyl)alkoxy having 1 to 10 carbons, (N-substituted or unsubstituted carbamoyl)poly(alkoxy) having 1 to 10 carbons, (N-substituted or unsubstituted carbamoyl)alkyl having 1 to 10 carbons, [N-(heteroaryl)carbamoyl]alkyl having 1 to 10 carbons, [N-(heteroaryl)carbamoyl]alkoxy having 1 to 10 carbons, [N-(substituted heteroaryl)carbamoyl]alkoxy having 1 to 10 carbons, [N-(substituted aryl)carbamoyl]alkoxy having 1 to 10 carbons, poly(alkoxy) group of each of said alkoxy group has 1 to 10 carbons, cyclic polyalkoxy (such as crown ether moiety), guanidinyl group, ureido group, dialkylamino-poly(alkoxy) group, [N-(carbamoylalkyl)carbamoyl]alkoxy, [N-(carbamoylalkyl)carbamoyl]alkyl, [N-[[N-(heteroaryl) carbamoyl]alkyl]carbamoyl]alkoxy, [N-[[N-(substituted heteroaryl) carbamoyl]alkyl]carbamoyl]alkoxy, [(tri-alkyl)ammonium]-alkoxy, (sulfonato)alkyl, (sulfonato)alkoxy, N-[sulfonato)alkyl]amido, (substituted)maleimido-, (substituted)succinimido;

R_{18} is independently selected from H, alkyl of 1 to 10 carbons and phenyl;

R_{19} and R_{20} are independently selected from H, alkyl of 1 to 10 carbons, halogen substituted alkyl of 1 to 10 carbons, or R_{19} and R_{20} together with the N atom may form a 4 to 10 membered ring that may include one more heteroatom selected from N, O or S, said N heteroatom being unsubstituted or substituted with an alkyl group of 1 to 10 carbons, or with an aryl or heteroaryl group, and

R_{21} is alkyl, (aryl)alkyl, (heteroaryl)alkyl, phenyl, naphthyl or heteroaryl having 1 to 3 heteroatoms indpendently selected from N, O and S, said phenyl, naphthyl or heteroaryl groups being unsubstituted or substituted with 1 to 5 R_{17} groups,

Y is O or $=NR_{16}$,

or to a pharmaceutically acceptable salt of said compounds.

The compounds of the invention are sulfoxides and have an asymmetric center in the sulfur atom. Both the pure enatiomers, racemic mixtures and unequal mixtures of the two are within the scope of the present invention. Some of the compounds of the invention may have one or more asymmetric carbon atoms (for example in a branch-chained alkyl group) and some other compounds may have a second sulfoxide providing still another asymmetric center in the sulfur atom. All optical isomers, racemates, diastereomers and their mixtures are within the scope of the invention.

The compounds of the invention act as prodrugs of proton pump inhibitor type drugs which are useful for inhibiting gastric acid secretion. The compounds of the invention have excellent stability in tablet or capsule form, are acid stable, have excellent bioavailability and plasma half life extending up to 5 - 6 hours which is significantly longer than the plasma half life of the presently used proton pump inhibitors.

DETAILED DESCRIPTION OF THE INVENTION

The chemical structure of the compounds of the invention is shown and described in broad terms in the Summary of the Invention in connection with **Formula 1**. As it can be seen in the formula, the compounds of the invention are pyridyl methyl sulfinyl benzimidazoles, or compounds of closely related structure, wherein one of the benzimidazole nitrogens is substituted with a group (designated $\mathbf{R_{15}}$ in **Formula 1**) that gradually cleaves under physiological conditions and thereby provides the pyridyl methyl sulfinyl

benzimidazole compound (or compound of closely related structure) which has a free N-H function in the benzimidazole (or related) moiety. The compound thus obtained by cleavage of the R_{15} group then undergoes the acid catalyzed rearrangement and provides the thiophilic species which inhibits the H,K-ATPase enzyme involved in gastric acid production. Thus, the novel compounds of the present invention bearing the R_{15} group are prodrugs of the proton pump inhibitor compounds which could also be depicted by **Formula 1**, where, however the R_{15} group would be designated hydrogen.

Generally speaking, among the prodrugs compounds of the present invention those are preferred wherein the structure of the pyridyl methyl sulfinyl benzimidazole or structurally related moiety is also preferred in the prior art. In other words, preferably prodrugs are provided in accordance with the present invention for those proton pump inhibitor drugs which are themselves preferred.

Referring now to the specific designation of symbols in connection with **Formula 1**, compounds are preferred in accordance with the present invention wherein the moiety designated Het_1 is pyridyl substituted with alkyl, O-alkyl and/or O-fluoroalkyl groups. Most preferred substituents for the pyridine moiety, designated R_1, R_2 and R_3 in **Formula 1**, are CH_3O-, CH_3-, CF_3CH_2O- and $CH_3O(CH_2)_3O$- .

The moiety designated **X** in **Formula 1** is preferably a methylene (-CH_2-) group, or a -CHR_{10} group and the methylene or -CHR_{10} group is preferably attached in α position to the nitrogen in the pyridine moiety. Compounds where the **X** is *ortho* phenylene or substituted *ortho* phenylene are also preferred; in the most preferred compounds **X** is methylene.

Referring now to the group designated Het_2 in **Formula 1**, this moiety is preferably a substituted benzimidazole. The R_6 through R_9 groups preferably are selected from hydrogen, chlorine and fluoro-substituted alkoxy

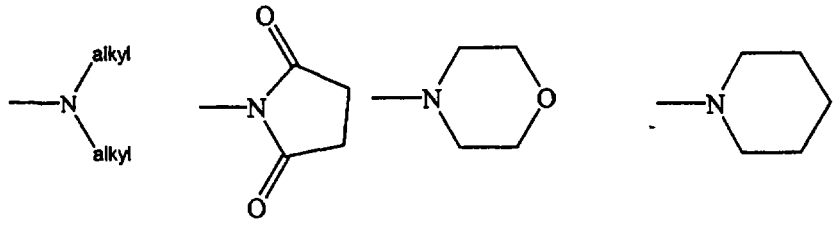
groups, with hydrogen, chlorine, CF_2HO- and CH_3O- being even more preferred.

Referring now to the group designated $\mathbf{R_{15}}$ in connection with **Formula 1** it will be apparent to those skilled in the art that this group represents the principal novel structural feature of the present invention. Among the $\mathbf{R_{15}}$ groups shown in connection with **Formula 1** the arylsulfonyl groups (designated $\mathbf{R_{21}(R_{17})}$SOY- where Y is O) are preferred. In the arylsulfonyl groups the aryl portion ($\mathbf{R_{21}}$) is preferably phenyl, substituted or unsubstituted with the $\mathbf{R_{17}}$ group. When the phenyl group ($\mathbf{R_{21}}$) is substituted, then the substituent ($\mathbf{R_{17}}$) is preferably selected from Cl, Br, F, lower alkyl, lower alkoxy, trifluoromethyl, trifluoromethoxy, di-(lower alkyl)amino, lower alkoxycarbonyl, ureidoyl (RNHCONH-), guanidinyl, carbamoyl, N-substituted carbamoyl, (N-substituted carbamoyl)alkyl, di-(lower alkylamino)alkoxy, (morpholin-4-yl)alkoxy, (morpholin-4-yl)polyalkoxy, di-(lower alkylamino)alkyl, poly(alkoxy)alkoxy, cyclic poly(alkoxy), (carbamoyl)alkoxy, [(N-(lower alkyl)carbamoyl]alkoxy, [N,N-(lower dialkyl)carbamoyl)alkoxy, (N,N-dialkylcarbamoyl)alkyl, [N-(heteroaryl)carbamoyl]alkyl, [N-(heteroaryl)carbamoyl]alkoxy, [N-(aryl)carbamoyl]alkoxy, [N-[(N-substituted carbamoyl)alkyl]carbamoyl]alkoxy, (sulfonato)alkyl, (sulfonato)alkoxy, N-[sulfonato)alkyl]amido, (substituted)maleimido-, (substituted)succinimido and [(tri-alkyl)ammonium]-alkoxy. Even more preferably the phenyl group is unsubstituted ($\mathbf{R_{17}}$ is H) or the substituent of the phenyl ($\mathbf{R_{21}}$) group is selected from Cl, Br, F, methyl, methoxy, trifluoromethyl, trifluoromethoxy, dimethylamino, ethoxycarbonyl, carbamoyl, guanidinyl, ureidoyl, (carbamoyl)methoxy, [N-(pyridyl)carbamoyl]methoxy, morpholinyl, (morpholin-4-yl)alkoxy, [(morpholin-4-yl)alkoxy]alkoxy, 2-(dimethylamino)ethoxy, [N-[(carbamoyl) methyl]carbamoyl]methoxy,

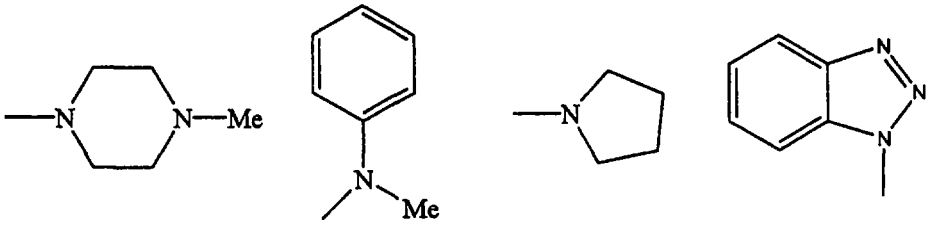
sodium(sulfonato)alkoxy, (trimethylammonium)alkoxy, poly(alkoxy), and cyclic tetra- or penta-ethyleneoxy groups. Preferably there is only one $\mathbf{R}_{17}$ substituent (other than hydrogen) in the phenyl ($\mathbf{R}_{21}$) moiety, and preferably the $\mathbf{R}_{17}$ substituent is in a position *para* (1,4) or *meta* (1,3) to the sulfonyl (SO_2) group.

In other embodiments of the compounds of the invention the physiologically labile substituent $\mathbf{R}_{15}$ is a sulfinyl group, designated $\mathbf{R}_{16}(\mathbf{R}_{17})$SO- in connection with **Formula 1**. Preferred groups for the $\mathbf{R}_{16}(\mathbf{R}_{17})$ combination are the same as for the $\mathbf{R}_{21}(\mathbf{R}_{17})$ combination, still more preferred are phenyl, 4-methylphenyl, 4-methoxyphenyl and 4-trifluoromethylphenyl. In this specification lower alkyl or lower alkoxy has 1 to 6 carbons.

In still other embodiments of the compounds of the invention the physiologically labile substituent $\mathbf{R}_{15}$ forms a *Mannich* base, designated $\mathbf{R}_{19}\mathbf{R}_{20}$N-C$(\mathbf{R}_{18})_2$ - in connection with **Formula 1**. In these *Mannich* base type compounds $\mathbf{R}_{18}$ is preferably H or lower alkyl, most preferably H or methyl. The $\mathbf{R}_{19}\mathbf{R}_{20}$N groups preferably are di-(lower alkyl)amino, *N*-succinimidyl, *N*-morpholinyl, *N*-piperidinyl, *N*-(*N*-4-methyl)hexahydropyrazinyl, *N,N*-phenyl,methyl-amino, *N*-tetrahydropyrrolyl, and N-(benzotriazol-1-yl), as depicted below and designated respectively by formulas 2 through 8 and 8a:



Formula 2 3 4 5

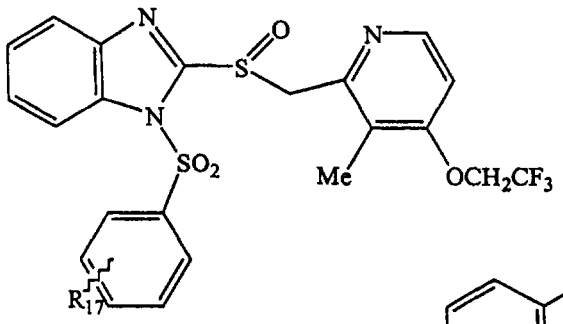


Formula 6 7 8 8a

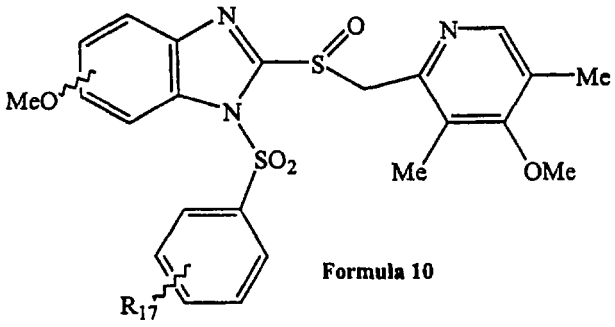
The most preferred groups for the $\mathbf{R_{19}R_{20}N}$- combination in accordance with the present invention are dimethylamino, *N*-morpholino, and *N*-piperidinyl.

The most preferred compounds of the invention are those wherein the proton pump inhibitor portion is the same as in the widely used proton pump inhibitor drugs known under the names LANSOPRAZOLE, OMEPRAZOLE, PANTOPRAZOLE and RABEPRAZOLE and wherein the $\mathbf{R_{15}}$ group is a benzenesulfonyl group mono-substituted either in the 4 (*para*) or in the 3 (*meta*) position with a Cl, Br, F, CH_3, CH_3O, CF_3, CF_3O-, $(CH_3)_2N$ NH_2CO, NH_2CONH, $NH_2C(=NH)NH$, 4-morpholino, 2-(4-morpholinyl)ethoxy, 2-[2-(4-morpholinyl)ethoxy]ethoxy, 3-(4-morpholinyl)propoxy, poly(alkoxy), $Na^+ {}^-O_3S\text{-}CH_2CH_2CH_2\text{-}O$, $X^- (CH_3)_3N^+CH_2CH_2O$- (X is an anion, such as a halogen ion), NH_2COCH_2O, (pyridyl)$NHCOCH_2O$, $NH_2COCH_2NH_2COCH_2O$, $(CH_3)_2NCH_2$ or EtOCO group. These compounds are shown by **Formulas 9, 10, 11 and 12**, respectively, where $\mathbf{R_{17}}$* represents said Cl, Br, F, CH_3, CH_3O, CF_3, CF_3O-, $(CH_3)_2N$, NH_2CO, NH_2CONH, $NH_2C(=NH)NH$, 4-morpholino, 2-(4-morpholinyl)ethoxy, 2-[2-

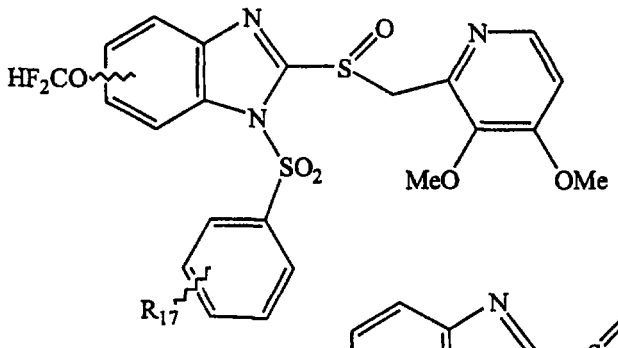
(4-morpholinyl)ethoxy]ethoxy, 3-(4-morpholinyl)propoxy, poly(alkoxy), NH_2COCH_2O, (pyridyl)$NHCOCH_2O$, $NH_2COCH_2NH_2COCH_2O$, $(CH_3)_2NCH_2$, $Na^+ {}^-O_3S\text{-}CH_2CH_2CH_2\text{-}O$, $(CH_3)_3N^+CH_2CH_2O$-, or EtOCO groups in the 4 (*para*) or in the 3 (*meta*) position of the phenyl ring, and where the numbering of the benzimidazole ring is shown in the formulas. In **Formula 10** the CH_3O- group can occupy the 5 or the 6 position of the benzimidazole moiety, and in **Formula 11** the CF_2HO- group can occupy the 5 or the 6 position of the benzimidazole moiety.



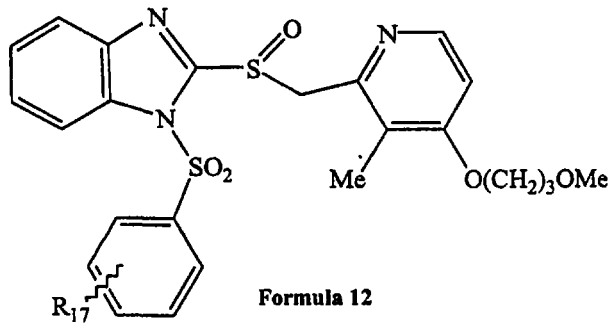
Formula 9



Formula 10



Formula 11



Formula 12

The compounds of the invention include 2-[[(3-chloro-4-morpholino-2-pyridyl)methyl]sulfinyl]-5-methoxy-(1H)-benzimidazole, 2-[[[4-(2,2,3,3,4,4,4-heptafluorobutyl)oxy]-2-pyridyl]methyl]sulfinyl]-1H-thieno[3,4-d]imidazole, 2-[[(4-ethythio-3-methyl-2-pyridyl)methyl]sulfinyl]-1h-benzimidazole 2-[(3-methoxyphenyl)methylsulfinyl]-1H-benzimidazole, 2-[(3-methoxyphenyl)methylsulfinyl]imidazolo[5,4-c]pyridine, 2-[(3-methoxyphenyl)methylsulfinyl]imidazolo[4,5-c]pyridine, and 2-[(3-methoxyphenyl)methylsulfinyl]-5-nitro-benzimidazole, of which 1-position have R_{15} group. R_{15} group of these compounds is a benzenesulfonyl group mono-substituted either in the 4 (para) or in the 2 (meta) position with a Cl, Br, F, CH_3, CH_3O, CF_3, CF_3O, $(CH_3)_2N$, NH_2CO, NH_2CONH, $NH_2C(=NH)NH$, 4-morpholino, 2-(4-morpholinyl)ethoxy, 2-[2-(4-

morpholinyl)ethoxy]ethoxy, 3-(4-morpholinyl)propoxy, NH_2COCH_2O, (pyridyl)$NHCOCH_2O$, $NH_2COCH_2NH_2COCH_2O$, $(CH_3)_2NCH_2$, $Na^+ {}^-O_3S$-$CH_2CH_2CH_2$-O, $(CH_3)_3N^+CH_2CH_2O$-, or EtOCO group.

Examples of the presently most preferred compounds of the invention are as follows:

1-benzenesulfonyl-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,

1-benzenesulfonyl-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,

1-benzenesulfonyl-5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,

1-benzenesulfonyl-6-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,

1-benzenesulfonyl-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole,

1-(p-chlorobenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,

1-(p-chlorobenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,

1-(p-chlorobenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,

1-(p-chlorobenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,

1-(p-chlorobenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole,

1-(p-bromobenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,

1-(p-bromobenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-

pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-bromobenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-bromobenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-bromobenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-fluorobenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-fluorobenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-fluorobenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-fluorobenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-fluorobenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-methylbenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-methylbenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-methylbenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-methylbenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-methylbenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-methoxybenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-

pyridyl)methylsulfinyl]-1H-benzimidazole,

1-(p-methoxybenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,

1-(p-methoxybenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,

1-(p-methoxybenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,

1-(p-methoxybenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole,

1-(3-trifluoromethylbenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,

1-(3-trifluoromethylbenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,

1-(3-trifluoromethylbenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,

1-(3-trifluoromethylbenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,

1-(3-trifluoromethylbenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole,

1-(p-trifluoromethoxybenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,

1-(p-trifluoromethoxybenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,

1-(p-trifluoromethoxybenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,

1-(p-trifluoromethoxybenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,

1-(p-trifluoromethoxybenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-

trifluoroethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-dimethylaminobenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-dimethylaminobenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-dimethylaminobenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-ethoxycarbonylbenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-ethoxycarbonylbenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(pyridine-3-sulfonyl)-5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-(pyridine-3-sulfonyl)-6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-(pyridine-3-sulfonyl)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole,
1-(pyridine-3-sulfonyl)-5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-(pyridine-3-sulfonyl)-6-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-[4-[(morpholin-4-yl)phenyl]sulfonyl]-5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-[4-[(morpholin-4-yl)phenyl]sulfonyl]-6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
N-[4-[[5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]benzimidazol-1-yl]sulfonyl]phenyl]urea,
N-[4-[[6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-

pyridyl)methyl]sulfinyl]benzimidazol-1-yl]sulfonyl]phenyl]urea,

N-(4-{[2-({[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}phenyl)urea,

N-(4-{[2-({[4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}phenyl)urea,

N-(4-{[2-{[(3,4-di(methoxy)-2-pyridyl)methyl]sulfinyl}-5-(difluoromethoxy)-benzimidazol-1-yl]sulfonyl}phenyl)urea,

N-(4-{[2-{[(3,4-di(methoxy)-2-pyridyl)methyl]sulfinyl}-6-(difluoromethoxy)-benzimidazol-1-yl]sulfonyl}phenyl)urea,

15-{[2-({[4-(3-methoxypropoxy-3-methyl-2-pyridyl]methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}-1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene,

15-{[2-({[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}-1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene,

15-[(5-methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]-1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene,

15-[(6-methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]-1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene,

15-[(5-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]-1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene,

15-[(6-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]-1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene,

2-{4-[(5-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-

pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}acetamide,
2-{4-[(5-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-
pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-
pyridyl)acetamide,
N-(carbamoylmethyl)-2-{4-[(5-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-
pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}acetamide,
2-{4-[(6-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-
pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}acetamide,
2-{4-[(6-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-
pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-
pyridyl)acetamide,
N-(carbamoylmethyl)-2-{4-[(6-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-
pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}acetamide,
2-(4-{[2-({[3-methyl-4-(2,2,2-trifluoroethoxy)-2-
pyridyl]methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}phenoxy)acetamide,
2-(4-{[2-({[3-methyl-4-(2,2,2-trifluoroethoxy)-2-
pyridyl]methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}phenoxy)-N-(2-
pyridyl)acetamide,
N-(carbamoylmethyl)-2-(4-{[2-({[3-methyl-4-(2,2,2-trifluoroethoxy)-2-
pyridyl]methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}phenoxy)acetamide,
2-{4-[(5-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-
pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}acetamide,
2-{4-[(5-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-
pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-
pyridyl)acetamide,
N-(carbamoylmethyl)-2-{4-[(5-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-
pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}acetamide,
2-{4-[(6-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-

pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}acetamide,
2-{4-[(6-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-
pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-
pyridyl)acetamide,
N-(carbamoylmethyl)-2-{4-[(6-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-
pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}acetamide,
2-(4-{[2-({[4-(3-methoxypropoxy)-3-methyl-2-
pyridyl]methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}phenoxy)acetamide,
2-(4-{[2-({[4-(3-methoxypropoxy)-3-methyl-2-
pyridyl]methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}phenoxy)-N-(2-
pyridyl)acetamide,
N-(carbamoylmethyl)-2-(4-{[2-({[4-(3-methoxypropoxy)-3-methyl-2-
pyridyl]methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}phenoxy)acetamide,
1-[[4-{3-(morpholin-4-yl) propoxy} phenyl]sulfonyl]-5-(difluoromethoxy)-2-
[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-[[4-{3-(morpholin-4-yl) propoxy} phenyl]sulfonyl]-6-(difluoromethoxy)-2-
[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-[[4-{3-(morpholin-4-yl) propoxy} phenyl]sulfonyl]-5-methoxy-2-[[(3,5-
dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-[[4-{3-(morpholin-4-yl) propoxy} phenyl]sulfonyl]-6-methoxy-2-[[(3,5-
dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-[[4-{3-(morpholin-4-yl) propoxy} phenyl]sulfonyl]-2-[(3-methyl-4-
methoxypropoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-[[4-{3-(morpholin-4-yl) propoxy} phenyl]sulfonyl]-2-[(3-methyl-4-(2,2,2-
trifluoroethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-2-[[[(4-(3-methoxypropoxy)-
3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole,
1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-5-(difluoromethoxy)-2-[[(3,4-

dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]]-1H-benzimidazole,
1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-6-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]]-1H-benzimidazole,
1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]- 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole,
1-[{(N,N-dimethylamino)methyl}benzene-4-sulfonyl]-5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-[2-acetamido-4-methyl-5-thiazolylsulfonyl]-5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-(thiophene-2-sulfonyl)-5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-[{(N,N-dimethylamino)methyl}benzene-4-sulfonyl]-6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-[2-acetamido-4-methyl-5-thiazolylsulfonyl]-6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-(thiophene-2-sulfonyl)-6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-(thiophene-2-sulfonyl)-2-[[[(4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole,
1-(thiophene-2-sulfonyl)- 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-(thiophene-2-sulfonyl)- 6-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-(thiophene-2-sulfonyl)-]- 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-

pyridyl]methyl]sulfinyl]-1H-benzimidazole,
1-(phenylmethylsulfonyl)-5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-(n-propanesulfonyl)-5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-(n-butanesulfonyl)-5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-(isopropylsulfonyl)-5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-[(N,N-dimethylamino)benzene-4-sulfonyl]-5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-(phenylmethylsulfonyl)-6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-(n-propanesulfonyl)-6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-(n-butanesulfonyl)-6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-(isopropylsulfonyl)-6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-[(N,N-dimethylamino)benzene-4-sulfonyl]-6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-(pyridine-3-sulfonyl)-2-[[(3-methyl-4-methoxypropoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-[4-(morpholin-4-yl)phenylsulfonyl]-2-[[[(4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole,
1-benzenesulfonyl-2-[[(3-chloro-4-morpholino-2-pyridyl)methyl]sulfinyl]-5-methoxy-(1H)-benzimidazole,
1-benzenesulfonyl-2-[[[(4-(3-methoxypropoxy)-3-methyl-2-

pyridyl]methyl]sulfinyl]-1H-benzimidazole,
1-benzenesulfonyl-2-[(3-methoxyphenyl)methylsulfinyl]-1H-benzimidazole,
1-benzenesulfonyl-2-[(3-methoxyphenyl)methylsulfinyl]imidazolo[5,4-c]pyridine,
1-benzenesulfonyl-2-[(3-methoxyphenyl)methylsulfinyl]imidazolo[4,5-c]pyridine,
1-benzenesulfonyl-2-[(3-methoxyphenyl)methylsulfinyl]-5-nitro-benzimidazole,
1-benzenesulfonyl-2-[{2-(dimethylamino)phenyl}methylsulfinyl]-1H-benzimidazole,
1-benznesulfonyl-2-[[[4-(2,2,3,3,4,4,4-heptafluorobutyl)oxy]-2-pyridyl]methyl]sulfinyl]-1H-thieno[3,4-d]imidazole,
1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]- 2-[(3-methoxyphenyl)methylsulfinyl]imidazolo{5,4-c]pyridine,
1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]- 2-[{2-(dimethylamino)phenyl}methylsulfinyl]-1H-benzimidazole,
1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]- 5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]- 6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-2-[[[(4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole,
1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-6-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,

1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]- 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole,

1-(benzotriazol-1-yl)methyl-5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,

1-(benzotriazol-1-yl)methyl-6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,

1-(benzotriazol-1-yl)methyl-2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole,

diethyl [5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]benzimidazol-1-yl]phosphate,

1-(4-acetaminobenzenesulfonyl)-5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,

1-(4-acetaminobenzenesulfonyl)-6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,

The compounds of the invention wherein the R_{15} group is an arylsulfonyl group, can be prepared by the reacting the 2-pyridylmethylsulfinyl-1H-benzimidazole derivatives (or structurally related compounds) having a free NH group within the imidazole moiety, with an arylsulfonyl chloride. In the broad sense the benzimidazole or structurally related compound which is the starting material having the free NH group, can be described by **Formula 1** wherein the R_{15} group would be H. Similarly, in the broad sense the arylsulfonyl chloride reagent is described by the formula $R_{21}(R_{17})SO_2Cl$ where the R_{21} and R_{17} groups are defined as in connection with **Formula 1**. **Reaction Scheme 1** discloses a process for preparing examplary preferred compounds of the invention by reacting the 2-pyridylmethylsulfinyl-1H-benzimidazole derivative of **Formula 13** with a benzenesulfonyl chloride derivative of **Formula 14** in the presence of a suitable base. The reaction is typically conducted in an inert organic solvent, such as dichloromethane in the

presence of an organic base, such as triethylamine. For compounds of **Formula 13** and **Formula 14** the R_1 - R_3 , R_6 - R_9 and R_{17} groups are defined as in connection with **Formula 1**. As it can be seen in **Reaction Scheme 1**, the benzenesulphonylation reaction may give rise to two isomeric or tautomeric products depending on the nature and positions of the R_6 - R_9 substituents on the benzimidazole ring. The two isomeric products (which may be merely taumers) are shown in **Formulas 15** and **16**.

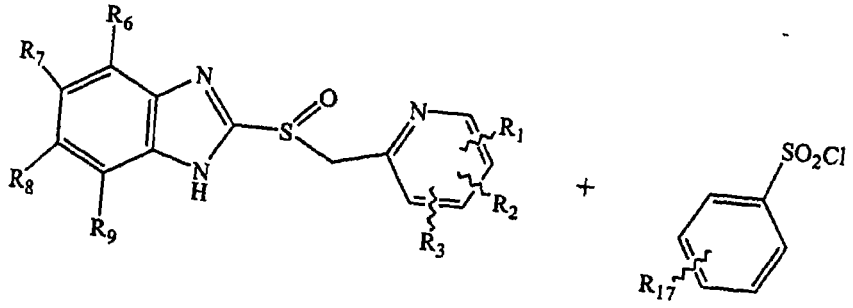
The benzenesulfonyl chloride derivatives of **Formula 14** can be obtained in accordance with procedures well known in the art.

Those skilled in the art will recognize the 2-pyridylmethylsulfinyl-1H-benzimidazole derivatives of **Formula 13** as the proton pump inhibitors generally known in the art and described for example in United States Patent No. 4,686,230 (*Rainer et. al.*) and in published international application WO 97/48380 (*Astra Aktiobiolag*). Starting materials within the scope of **Formula 13** include the known drugs LANSOPRAZOLE (United States Patent No. 4,628,098), OMEPRAZOLE (United States Patent Nos. 4,255,431 and 4,255,431), PANTOPRAZOLE (United States Patent No. 4,758,579) and RABEPRAZOLE (United States Patent No. 5,045,552) Thus, the starting compounds of **Formula 13** can be prepared in accordance with the state-of-the-art, for example as described in United States Patent Nos. 4,686,230, 4,628,098, 4,255,431, 4,758,579, 5,045,552, international application WO 97/48380, Journal of Medicinal Chemistry, 32, 1970-1977 (1989), Chem. Pharm. Bull. 38, 2853-2858 (1990), J. Med. Chem., 34, 1049-1062 (1991), Journal of Medicinal Chemistry, 35, 1049-1057 (1992), and Journal of Medicinal Chemistry, 35, 438-450 (1992), all of which are specifically incorporated herein by reference.

Although this is not shown in the reaction scheme, to obtain compounds of the invention where with reference to **Formula 1** R_{15} is $R_{21}(C_6H_4)SOY$ and

Y is $=NR_{16}$, a reagent of the formula $R_{21}(C_6H_4)S(O)(Cl)NR_{16}$ is used instead of the reagent of **Formula 14**, to react with the compounds of **Formula 13**. The reagent of the formula $R_{21}(C_6H_4)S(O)(Cl)NR_{16}$ can be obtained in accordance with methods known in the art, for example as described in the treatise COMPREHENSIVE ORGANIC FUNCTIONAL GROUP TRANSFORMATIONS, Volume 7, Editors-in-Chief A. R. Katritzky, O. Meth-Cohn and C. W. Rees (Pergamon).

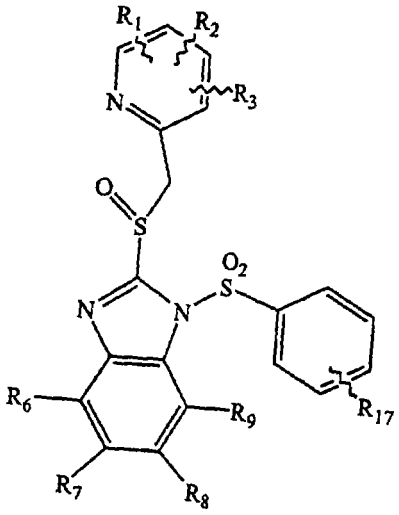
07 FEB 2003



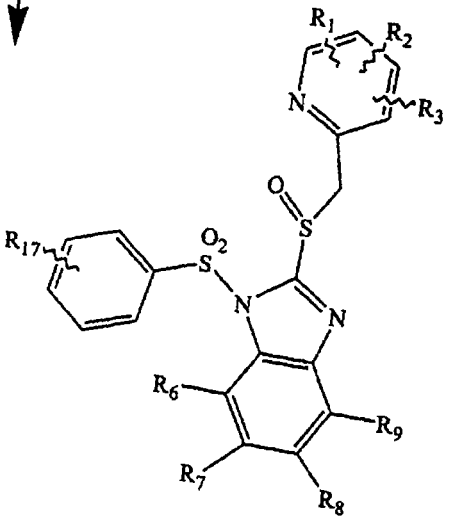
Formula 13

Formula 14

BASE



Formula 15

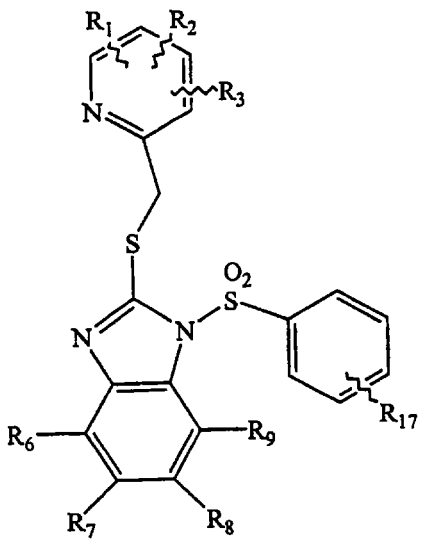


Formula 16

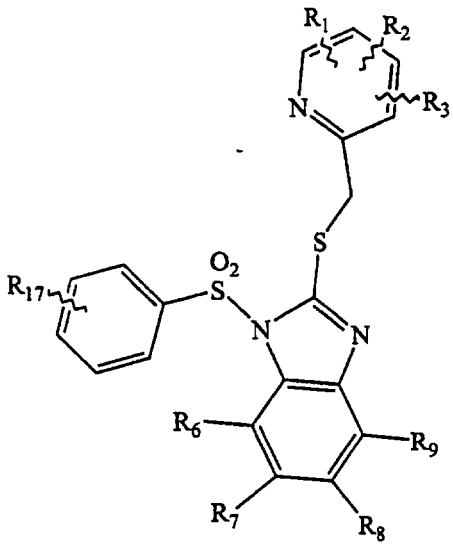
Reaction Scheme 1

Instead of using the free benzimidazole compounds of **Formula 13**, their suitable salts such as the sodium, potassium, magnesium (and other) salts can be reacted with the benzenesulfonyl chloride derivative of **Formula 13**, to also provide the exemplary compounds of the invention in accordance with **Formulas 15** and **16**.

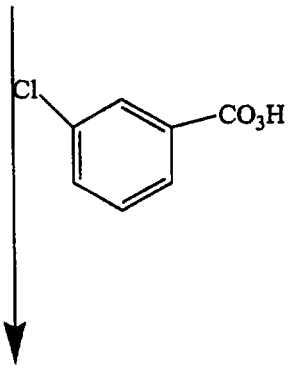
Reaction Scheme 2 discloses an alternative method for preparing the exemplary compounds of the invention, shown in **Formulas 15** and **16**. This reaction involves the oxidation of the corresponding 1-(*N*)-benzenesulfonyl-benzimidazolyl, 2-pyridylmethyl sulfide compounds of **Formulas 17** and **18** to the corresponding sulfoxides. Those skilled in the art will recognize that **Formulas 17** and **18** represent isomeric compounds which may be different or identical (tautomeric) with one another depending on the nature and position of the R_6 - R_9 substituents. The oxidation reaction can be performed with oxidizing agents known in the art for forming sulfoxides, for example hydrogen peroxide, *m*-chloroperoxybenzoic acid and iodosobenzene may serve for this purpose. The oxidation reaction is normally conducted in an aprotic neutral solvent, such as dichloromethane. The sulfide compounds of **Formulas 17** and **18** can be obtained by performing a benzenesulphonylation reaction (in analogy to the reaction of **Scheme 1**) on the sulfide compounds having a free benzimidazole NH group, or their suitable salt. The latter sulfides (**Formulas 17** and **18**) can be obtained in accordance with the state-of-the-art.



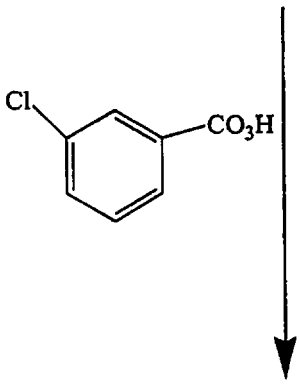
Formula 17



Formula 18



Formula 15



Formula 16

Reaction Scheme 2

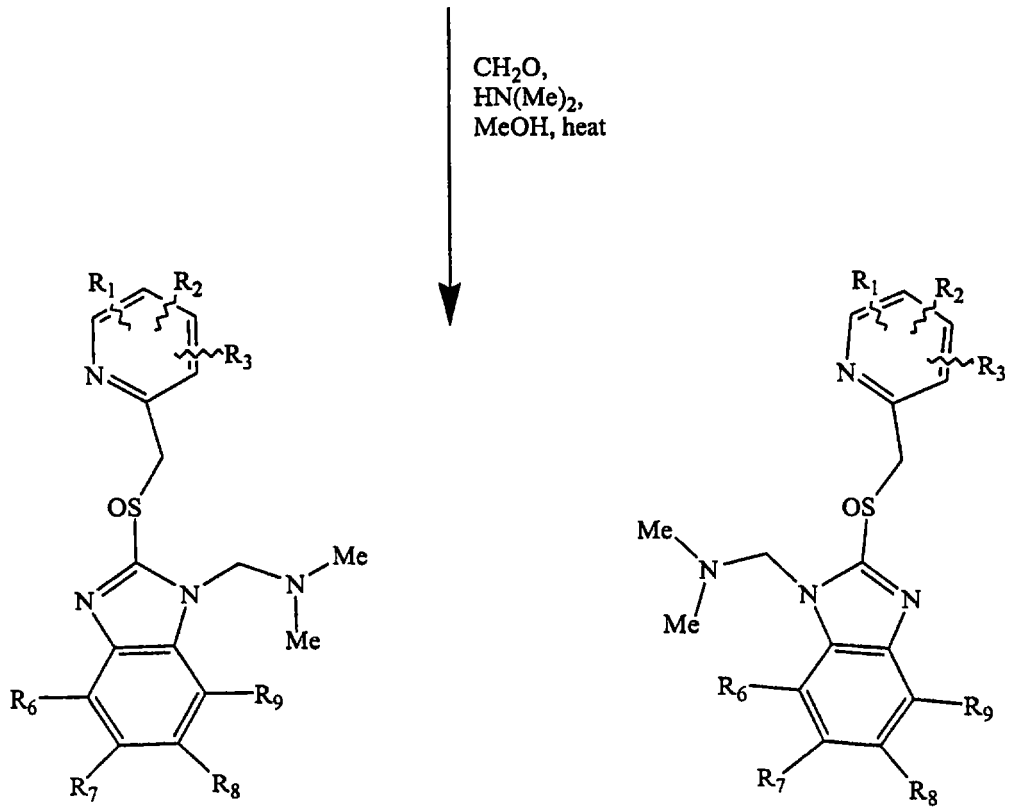
The compounds of the invention where the physiologically labile R_{15} group is $R_{16}(R_{17})SO$ (sulfinyl), as defined in connection with **Formula 1**, can be made in reactions which are analogous to the reactions shown in **Scheme 1**, except that instead of an arylsulfonyl chloride an arylsulfinyl chloride of formula $R_{16}(R_{17})SOCl$ is used. The arylsulfinylation reaction is usually conducted in the presence of an organic base, in a solvent such as dioxane, tetrahydrofuran, or an alcohol. The arylsulfinyl chloride of formula $R_{16}(R_{17})SOCl$ can be made from the corresponding sulfinic acid or salt having the formula $R_{16}(R_{17})SO_2Na$, by treatment with thionyl chloride. In view of their close analogy to the sulfonylation reactions of **Scheme 1**, the sulfinylation reactions are not shown in a scheme.

The compounds of the invention where the physiologically labile R_{15} group together with the 2-pyridylmethylsulfinyl-1H-benzimidazole derivatives (or structurally related compounds) form a *Mannich* base, can be made under conditions which are generally applicable and known in the art for forming *Mannich* bases. A specific detailed description for forming *Mannich* base type prodrugs is provided by *Bundgaard et al.* in **Methods in Enzymology 112**, p347 -359 which is incorporated herein by reference. Generally speaking, the preparation of *Mannich* base type prodrugs of this invention involves heating a mixture of an amine of the formula $R_{19}R_{20}NH$ with an aldehyde or ketone of the formula $OC(R_{18})_2$ in an alcohol, water, dioxane or other suitable solvent. The symbols R_{18} - R_{20} are defined as in connection with **Formula 1**.

Reaction Scheme 3 illustrates the preparation of exemplary *Mannich* base type compounds of the invention from the 2-pyridylmethylsulfinyl-1H-benzimidazole derivatives of **Formula 13** using formaldehyde as the aldehyde and dimethylamine as the amine. As it can be seen in the reaction scheme, this reaction also may provide two isomeric products of **Formula 19** and **20**,

respectively. The two products may be identical (tautomeric) depending on the nature and position of the R_6 - R_9 substituents.

Formula 13



Formula 19

Formula 20

Reaction Scheme 3

07 FEB 2003

The compounds of **Formula 19** and **Formula 20** can be and preferably are prepared by an alternative method including a reaction of N-halomethyl dialkylamines with a sodium salt of **Formula 13**, or a tetraammonium salt of **Formula 13**, or with a compound of **Formula 13** in the presence of sodium tert-butoxide. N-chloromethyl dialkylamines were prepared as described by *Boehme et al.*, (Chemische Berichte, vol., 93, pp1305-1309 (1960) and Chemische Berichte, vol., 95, pp 1849-1858(1962)), and a tetra(alkyl)ammonium salt of **Formula 13** was prepared by a method described in United States Patent No. 5,021,433. For example, tetrabutylammonium salt of 2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl] sulfinyl]-5-methoxy-1H-benzimidazole was prepared as described in the United States Patent No. 5,021,433 and used *in situ*. Tetrabutylammonium salt of 2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-5-methoxy-1H-benzimidazole was reacted with 1-chloromethyl-N,N-dimethylamine in dichloromethane to give a mixture of 1-(N,N-dimethylamino)methyl-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-5-methoxy-1H-benzimidazole and 1-(N,N-dimethylamino)methyl-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-6-methoxy-1H-benzimidazole. 1-(Heteroaryl-N-methyl)-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-(5 and 6-methoxy)-1H-benzimidazole was synthesized by a similar method. For example, a mixture of 1-(benzotriazol-1-yl)methyl-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-5-methoxy-1H-benzimidazole and 1-(benzotriazol-1-yl)methyl-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-6-methoxy-1H-benzimidazole was prepared by a reaction of sodium salt of 2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-5-methoxy-1H-benzimidazole with 1-chloromethyl-1H-benzotriazole.

Another method for preparing the compounds of **Formula 19** and

Formula 20 is using a reaction of 1-chloromethyl-2-[(2-pyridyl)methylsulfinyl]-1H-benzimidazole compounds with dialkylamines such as morpholine, dimethylamine, pyrrolidine, and piperidine. 1-Chloromethyl-2-[(2-pyridyl)methylsulfinyl]-1H-benzimidazole compounds were prepared by a method described in European Pat., No. 279,149 (*Alminger et al.*). For example, a mixture of 1-chloromethyl-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-chloromethyl-6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole was reacted with morpholine to give a mixture of 1-(morpholin-4-yl)methyl-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-(morpholin-4-yl)methyl-6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole.

A significant advantage of the compounds of the present invention is that they can release the active forms of the proton pump inhibitors spontaneously by hydrolysis in the mammalian (including human) body. Hydrolysis can occur chemically or enzymatically. Because the compounds of this invention spontaneously release the active form of the proton pump inhibitor drugs by *in vivo* hydrolysis, they can attain longer duration of effective drug concentration in the body. Thus, the compounds of the present invention are prodrugs which are converted to active drugs by hydrolysis in the body, providing long duration of effective concentration. The long duration of inhibitory activity by spontaneous hydrolysis of the compounds of this invention allows more effective inhibition of gastric acid secretion, which enables better therapy of acid related disease as defined on p.1. and p.2. Compounds of this invention can be administered for inhibiting gastric acid secretion orally. The typical daily dose of the compounds will depend on various factors such as the individual requirement of each patient. In general,

oral and parenteral dosages will be in the range of 5 to 100 mg per day.

Those skilled in the art will readily understand that for oral administration the compounds of the invention are admixed with pharmaceutically acceptable excipients which *per se* are well known in the art. Specifically, a drug to be administered systemically, it may be confected as a powder, pill, tablet or the like or as a syrup or elixir suitable for oral administration. Description of the subtances normally used to prepare tablets, powders, pills, syrups and elixirs can be found in several books and treatise well known in the art, for example in Remington's Pharmaceutical Science, Edition 17, Mack Publishing Company, Easton, Pennsylvania.

Compounds of the present invention can be combined with certain amounts of known proton pump inhibitors, *e. g.* LANSOPRAZOLE, OMEPRAZOLE, PANTOPRAZOLE, or RABEPRAZOLE, to provide a drug-prodrug combination, and the combination administered for inhibition of gastric acid secretion. Thus, initially the proton pump inhibitor (drug) inhibits gastric acid secretion of the patient. The aforesaid known and widely used proton pump inhibitors have 60-90 minutes of plasma half-life. As the effective concentration of the proton pump inhibitor (drug) is decreased by metabolism, the compounds of the present invention (prodrug) continuosly undergoes hydrolysis and provides and maintains new active inhibitor concentration in the mammalian, including human body.

A disadvantage of the presently used proton pump inhibitors is that for therapy by injection in a liquid form they must be reconstituted from a lyophilized powder in a medium having the high pH of approximately 9.5. The prodrugs of the present invention overcome the disadvantage of requiring a reconstituting medium having such high pH, because the compounds of the present invention can be reconstituted to form an injectable liquid in a medium of approximately pH 6.0 to 8.5. It will be readily appreciated by those skilled

in the art that for administration in liquid form by injection the liquid that reconstitues the drug is a pharmaceutically acceptable aqueous solution that *per se* is known in the art. Such pharmaceutically acceptable solutions utilized for administration of drugs in injectable form are described for example in the treatise PHARMACEUTICAL DOSAGE FORMS (Parenteral Medications, Volume 1, Edited by K. E. Avis, H. A. Lieberman and L. Lachman (1992).

Among the benefits of the pre-proton pump inhibitor (P-PPI) type of drugs of the present invention is their ability to provide more effective treatment of erosive esophagitis and of less severe reflux diseases as well. This is because effective treatment of erosive esophagitis (and to a lesser extent of lesser reflux diseases) requires prevention of the reflux of gastric contents at pH 3.0 or still lower pH. The current PPI drugs allow several acidic excursions to pH < 2.0 per day, resulting in a moderate to weak amelioration of symptoms. However, healing would require elevation to pH > 4.0 for about 16 hours per day or longer. When, as in current usual treatment by PPIs, the other 8 hours contain episodic acidity to pH 3.0 or less, the patients tend to continue to complain of pain. The more effective and more continues acid suppression by the drugs of the present invention is likely to result in substantially better treatment of this disease, as well as faster healing of all acid related erosions or ulcers.

The pre-proton pump inhibitor (P-PPI) type of drugs of the present invention provide improved dual therapy for *H. pylori* eradication. This is because the PPI's synergize with cell division dependent antibiotics such as amoxicillin (cell wall biosynthesis) and clarithromycin (protein synthesis) by elevating gastric surface pH to enable a larger fraction of the bacterial population to be in dividing phase during presentation of the antibiotic to the gastric lumen. However, their effect on intragastric pH is limited by their dwell time in the plasma. The pre-proton pump inhibitor (P-PPI) type of drugs

of the present invention can continuosly elevate intragastric pH close to neutrality on current once a day therapy. Therefore, 100% eradication of the bacteria is expected in dual therapy with the prodrugs of the invention (for example a pro-drug of OMEPRAZOLE in accordance with the invention) plus an effective antibiotic, such as amoxicillin.

Even monotherapy for *H. pylori* eradication is likely to be successful with the pre-proton pump inhibitor (P-PPI) type of drugs of the present invention. This is because in the absence of acid, the enzyme *H. pylori* urease elevates environmental pH to > 8.3, which is toxic to the organism. PPI's in current formulation inhibit growth or present of the organism in the antrum, due to elevation of antral pH to close to neutrality. Elevation of 24 hour pH to neutrality, as it can be accomplished with the drugs of the present invention, is likely to result in "self eradication" of the bacteria.

Approximately 30% of patients with gastrointestinal distress appear with symptoms without quantitative underlying disease (non-ulcer dyspepsia). The most likely cause for these symptoms is upper gastrointestinal afferent nerve sensitivity to gastric acid. Only acid ablation ameliorates these symptoms and this can be attained with the drugs of the present invention.

By way of concrete examples, the following tests and results are described. Certain compounds of the invention have been tested in one or more standard laboratory tests that demonstrate gastric antisecretory activity. The compounds of the invention did not directly inhibit the K^+ -dependent ATP hydrolysis of gastric H,K-ATPase. However, after hydrolysis the compounds of this invention showed strong inhibition of gastric H,K-ATPase activity. This is consistent with the knowledge that the compounds obtained by hydrolysis *e. g.* LANSOPRAZOLE, OMEPRAZOLE, PANTOPRAZOLE and RABEPRAZOLE are well known H,K-ATPase inhibitors. For example, 1-benzenesulfonyl-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-

pyridyl)methylsulfinyl]-1H-benzimidazole was tested for inhibitory activity of gastric H,K-ATPase. Initially this compound did not inhibit gastric H,K-ATPase. However, gastric H,K-ATPase activity was spontaneously inhibited as hydrolysis of this compound in aqueous solution at pH 7.4 proceeded. After 5.75 hr -hydrolysis at pH 7.4, this compound inhibited 91% of gastric H,K-ATPase activity, same as 5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole (OMEPRAZOLE) which was the product of the hydrolysis. It was determined that 1-benzenesulfonyl-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole was hydrolyzed to 5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole (OMEPRAZOLE) with a half-life ($t_{1/2}$) 3 ± 0.5 hr at 37 °C at pH 7.4.

When a mixture of 2-{4-[(5-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-pyridyl)acetamide and 2-{4-[(6-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-pyridyl)acetamide was orally administrated to male rat, 5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole (OMEPRAZOLE) was continuously released to the plasma for more than 4 hours as a result of the hydrolysis of 2-{4-[(5-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-pyridyl)acetamide and 2-{4-[(6-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-pyridyl)acetamide. As a control experiment, when OMEPRAZOLE was administrated to male rat, OMEPRAZOLE Has completely disapperead from the plasma within 1.5 hr. Bioavailability of 2-{4-[(5-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-pyridyl)acetamide was much higher than that of

OMEPRAZOLE after oral administration.

When a mixture of 2-{4-[(5-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-pyridyl)acetamide and 2-{4-[(6-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-pyridyl)acetamide was orally administrated to male rat, gastric acid secretion was significantly and continuously inhibited. After 5 hours of oral administration, a mixture of 2-{4-[(5-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-pyridyl)acetamide and 2-{4-[(6-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-pyridyl)acetamide provided maximum 90% of inhibition of gastric acid secretion stimulated by histamine, while OMEPRAZOLE provided only about 45% of inhibition. There is a report that 50-60% of inhibition of gastric acid output is obtained after 4 to 6 hours of intravenous administration of OMEPRAZOLE (*Katashima, et al.*, Drug metabolism and Disposition, vol., 23, 718-723, 1995). Probably, lower inhibition (45 %) of gastric acid production after administration of OMEPRAZOLE in this experiment, compared to the reported data (50-60 %) obtained by Katashima. et al, is due to the different method of administration. However, it is well known that oral potency of OMEPRAZOLE without enteric-coating is significantly lower than that found after i.v. or i.d. administration in both rat and dog (*Larsson et al.*, Scand. J. Gastroenterology, vol. 20 (suppl. 108), 23-35, 1985). The compounds of this invention do not need enteric-coating for protection from acid-catalyzed decomposition. Furthermore, the compounds of this invention provide continuous inhibition of gastric acid secretion. Maximum inhibition by the compound of 2-{4-[(5-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-

pyridyl)acetamide and 2-{4-[(6-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-pyridyl)acetamide obtained after 5 hours shows that the compounds of the invention are continuously converted to the corresponding PPI in vivo, which inhibits gastric acid secretion.

SPECIFIC EMBODIMENTS AND EXPERIMENTAL DESCRIPTION

Preparation of Intermediates

Reference Example 1: Preparation of [(morpholin-4-yl)alkoxy]benzene-4-sulfonyl chloride

[(morpholin-4-yl) alkoxy] benzene-4-sulfonyl chloride was prepared by chlorosulfonylation of 4-[(phenoxy)alkoxy]morpholine using chlorosulfonic acid in the presence of dichloromethane or chloroform. In this reaction, chloroform or dichloromethane was important to avoid the cleavage of ether linkage of alkoxybenzene moiety by chlorosulfonic acid.

[3-(Morpholin-4-yl) propoxy] benzene-4-sulfonyl chloride was prepared by chlorosulfonylation of 4-(3-phenoxypropyl)morpholine using chlorosulfonic acid in the presence of dichloromethane or chloroform. For example, to a solution of 2.2 g (10 mmole) of N-(3-phenoxypropyl) morpholine in 20 ml of chloroform, 2 ml of chlorosulfonic acid (30 mmole) was slowly added at −10 °C and stirred for 30 min. The reaction mixture was stirred at room temperature for 5 hr. Chloroform was removed from lower layer. Lower layer was treated with chopped-ice to give solids. To a mixture of ice and solid product, 10 g of sodium phosphate (tribasic) was added and stirred with cooling. Chlorosulfonyl compound was extracted with dichloromethane (300 ml). Dichloromethane extract was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. 1.6 g of [3-(morpholin-4-yl) propoxy] benzene-4-sulfonyl chloride was obtained.

[2-(Morpholin-4-yl)ethoxy]benzene-4-sulfonyl chloride was prepared using N-(2-phenoxyethyl) morpholine by similar reaction described above. For example, 7.2 g of N-(2-phenoxyethyl)morpholine HCl salt was resuspended in 20 ml of dichloromethane and 7 ml of chlorosulfonic acid was slowly introduced with cooling by ice-jacket. The reaction mixture was stirred at 0 °C for 2 hr, then, at room temperature overnight. Dichloromethane (350 ml) was added to the reaction mixture and excess chlorosulfonic acid was destroyed by adding icy water(about 100 g). Aqueous layer was adjusted to pH 8.5 by concentrated sodium carbonate solution with cooling by ice. Dichloromethane was dried over anhydrous magnesium sulfate and evaporated under reduced pressure to give 8.1 g of [2-(morpholin-4-yl)ethoxy]benzene-4-sulfonyl chloride. M.P. 48-50 °C.

N-(2-Phenoxyethyl) morpholine was prepared by a modified method of Grail. et al (Journal of American Chemical Society, 1952, 74, 1313-1315). For example, 9.2 g of phenol and 18.6 g of N-(2-chloroethyl)morpholine HCl salt were dissolved in 120 ml of isopropanol and 12 g of potassium hydroxide was added with cooling. The reaction mixture was refluxed for 12 hours. Solid (KCl) was filtered off. The filtrate was distilled off. The residual material was treated with 150 ml of 1 N NaOH, then, extracted with dichloromethane (200 ml). Dichloromethane layer was again washed with a solution of 0.1 N sodium carbonate in 10% NaCl solution. Dichloromethane layer was dried over anhydrous magnesium chloride, and evaporated under reduced pressure. Residual syrup was dissolved in 100 ml of 1.5 N HCl solution, and washed with 100 ml of chloroform. Aqueous layer was treated with 100 ml of toluene and water was removed by Dean-Stark apparatus by distillation. Residual toluene layer was cooled to give crystalline solid, which was collected by filtration. 12 g of N-[(2-phenoxy)ethyl]morpholine HCl salt (50% yield)was obtained.

N-[3-(Phenoxy)propyl] morpholine was prepared by a reaction of 3-(phenoxy)propyl bromide with morpholine. For example, 3-(phenoxy)propyl bromide (7.8 ml, 50 mmole) was added to morpholine (8 ml) in toluene (50 ml) and refluxed overnight. NaOH solution (2 g of NaOH in 20 ml of water) was added and additionally refluxed for 4 hr. Toluene was removed by distillation under reduced pressure. Residue was treated with dichloromethane(200 ml) and water(200 ml). Dichloromethane layer was dried and concentrated. Residue was treated with dichloromethane-heptane to give 7 g of 4-[3-(phenoxy)propyl] morpholine.

[2-{2-(Morpholin-4-yl)ethoxy}ethoxy]benzene-4-sulfonyl chloride was prepared using 4-[2-[2-(phenoxy)ethoxy]ethyl]morpholine by a similar reaction described above. For example, 2-(phenoxy)ethanol (4.0 ml) was added to 5.4 g of N-(2-chloroethyl)morpholine hydrochloride and 6 g of sodium tert-butoxide in 70 ml of toluene. The reaction mixture was refluxed for 16 hr. EtOAc (100 ml) was added and washed with water (200 ml). Organic layer was separated, and again, extracted with 0.5 N HCl solution (120 ml). Aqueous layer was washed again with chloroform (30 ml), then, was adjusted to pH 10.5 by adding NaOH solution. The product, [2-[2-(morpholin-4-yl)ethoxy]ethoxy]benzene, was extracted with dichloromethane (200 ml) from water. Organic layer was again washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The product, [2-[2-(morpholin-4-yl)ethoxy]ethoxy]benzene, was obtained as a yellow syrup (5.4 g). TLC analysis showed over 99% purity and the structure was confirmed by NMR. The syrupy product was used in situ for preparing [2-{2-(morpholin-4-yl)ethoxy}ethoxy]benzene-4-sulfonyl chloride.

5.0 g of 2-[2-(morpholin-4-yl)ethoxy]ethoxybenzene was dissolved in 70 ml of dichloromethane. In ice bath, chlorosulfonic acid (7 ml) was slowly added. The reaction mixture was stirred at room temperature overnight. Two layers

were separated. Chloroform layer, upper layer, was removed. Pale brown syrup, lower layer, was added to 100 g of chopped ice. Dichloromethane (200 ml) was added, and concentrated sodium carbonate solution was slowly added upto pH 9 under 4 °C with good stirring. Dichloromethane layer was separated, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. Yellow syrup was obtained, which was dried in vacuo. 3.8 g of [2-{2-(morpholin-4-yl)ethoxy}ethoxy]benzene-4-sulfonyl chloride was obtained.

Reference Example 2: Preparation of [2-(dimethylamino)ethoxy]phenyl-4-sulfonyl chloride

2 g of N,N-dimethyl-N-[(2-phenoxy)ethyl]amine was dissolved in 10 ml of dichloromethane and 3 ml of chlorosulfonic acid was slowly added under ice cooling. The mixture was stirred at room temperature for 3 hr and poured into ice. Dichloromethane (100 ml) was added and aqueous layer was neutralized by concentrated sodium carbonate solution with keeping temperature under 4 °C. Dichloromethane layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. 0.8 g of [2-(dimethylamino)ethoxy]phenyl-4-sulfonyl chloride was obtained.

Reference Example 3: Preparation of N-[4-(chlorosulfonyl)phenyl]urea

N-[4-(chlorosulfonyl)phenyl]urea was prepared by a known method (R. J. W. Cremlyn, D. Leonard, and R. Motwani (1973) J. Chem. Soc., Perkin I 500-503).

Chlorosulfonic acid (4.4 ml) was added to phenylurea (2.7 g) in an ice bath, then, warmed to 60 °C for 3 hr. The syrup was poured on chopped ice with good mixing. Solid was separated and dried in vacuo. 2.3 g of product was obtained. M.P. 138-141 °C.

Reference Example 4: Preparation of N-[(p-chlorosulfonyl)phenyl]morpholine

N-[(p-Chlorosulfonyl)phenyl] morpholine was synthesized by a modified

method of Cremlyn, et al. (R. J. Cremlyn, J. P. Bassin, S. Farouk, M. Potterton, and T. Mattu. (1992) Phosphorus, Sulfur, and Silicon, Vol., 73, pp. 107-120).

10 g of 4-phenyl morpholine in 50 ml of chloroform was added to 25 ml of chlorosulfonic acid in a ice-jacket. The reaction mixture was stirred at reflux for 7 hr. Brown syrup was poured into dichloromethane (150 ml) and chopped ice (100 g) with stirring, and neutralized by saturated sodium phosphate, tribasic, with ice-cooling. Collect dichloromethane layer, dried over anhydrous magnesium sulfate. Organic solvent was evaporated under reduced pressure to give yellow solid, which was dried in vacuo. 6.1 g of product was obtained. M. P. 154-156 °C.

Reference Example 5: Preparation of pyridine-3-sulfonyl chloride

Pyridine-3-sulfonyl chloride was prepared by a method of Alo, et al. (B. I. Alo, O. B. Familoni, F. Marsais, and G. Queguiner, (1992) Journal of Heterocyclic Chemistry, vol. 29, pp 61-64.)

24 g of phosphorus pentachloride was added to a suspension of 15 g of pyridine-3-sulfonic acid in 30 ml of phosphorus oxychloride and heated at 120 °C for 12 hr. The reaction mixture was concentrated by distillation under reduced pressure, and treated with toluene. Solid obtained was collected and dried in vacuo. 16.7 g of product was obtained. M. P. 138-141 °C

Reference Example 6: Preparation of m-(chlorosulfonyl)benzo-15-crown-5-ether

To an ice-cold solution of benzo-15-crown-5-ether (536.6 mg, 2 mmole) in 5 ml of chloroform and cooled in ice-bath, 0.3 ml of chlorosulfonic acid (4.5 mmole) was slowly added. The reaction mixture was stirred in ice bath for 2 hr, then, 5 hr at room temperature. The reaction mixture was added to chopped ice and extracted with dichloromethane (50 ml). Combined organic layer was dried over magnesium chloride, and evaporated. 374 mg of product was

obtained. M.P. 79-84 °C

m-(Chlorosulfonyl)benzo-18-crown-6-ether was prepared using same method as described above. Yield was about 46%. M. P. 108-110 °C

Reference Example 7: Preparation of 2-[p-(chlorosulfonyl)phenoxy]-N-(2-pyridyl)acetamide

1.32 g of 2-(phenoxyacetyl)aminopyridine HCl salt (5 mmole) was resuspended in 10 ml of dichloromethane and 2 ml of chlorosulfonic acid was added in ice-bath to give clear solution. The solution was stirred at room temperature for 3 hr. The reaction mixture was added to ice-water with good stirring to give white solids. The solids were filtered, washed with acetonitrile, and dried in vacuo. 0.65 g of solid was obtained. M. P. 170-175 °C (decomposition)

Reference Example 8: Preparation of N-[p-(chlorosulfonyl)phenylmethyl]-N,N-dimethylamine HCl salt

1.5 ml of N,N-dimethylbenzylamine (10 mmole) was dissolved in 6 ml of dichloromethane and 2 ml of chlorosulfonic acid was added in ice bath cooling. The reaction mixture was warmed to 40 °C for 40 min, and stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure and poured into ice to give solids, which were collected and dried in vacuo. 1.6 g (59.2%) of N-(p-chlorosulfonylphenylmethyl)-N,N-dimethylamine HCl salt was obtained.

Reference Example 9: Preparation of 2-[p-(chlorosulfonyl)phenoxy]acetamide

3.0 g of 2-(phenoxy)acetamide was dissolved in 10 ml of dichloromethane and 6 ml of chlorosulfonic acid was slowly added at 0 °C. The reaction mixture was stirred at room temperature for 10 hr. Dichloromethane was evaporated under reduced pressure. Residual material was poured on chopped ice. Solid was collected by filtration and dried in vacuo. 3.9 g of product was obtained. M.P. 166-171 °C (decomposition)

Reference Example 10: Preparation of N-(p-chlorosulfonylphenylmethyl) pyridinium chloride

p-(Chloromethyl)benzenesulfonyl chloride (2.2 g) was dissolved in acetonitrile (20 ml)-dichloromethane (20 ml) and pyridine (1.9 ml) was added. The reaction mixture was refluxed for 3 hr. Brown syrup was separated from solvent, and was lyophilized in vacuo. Reddish brown product (2.9 g) was obtained. M.P. 105-108 °C.

Reference Example 11: Preparation of p-(dimethylamino)benzenesulfonyl chloride

N,N-Dimethylaniline (8 ml) was dissolved in 20 ml of chloroform, and chlorosulfonic acid (20 ml) was slowly added with cooling. The reaction mixture was refluxed for 6 hr. The reaction mixture was cooled and poured on ice (100 g). Dichloromethane (120 ml) was added and aqueous layer was neutralized by concentrated sodium carbonate solution with keeping temperature below 4 °C. Organic layer was again washed with ice-cold 0.1 N sodium bicarbonate solution, and dried over anhydrous magnesium sulfate. Organic layer was concentrated under reduced pressure. Residual material was crystallized from ethyl ether-heptane to give yellowish green solid. p-(Dimethylamino)benzenesulfonyl chloride (4.2 g) was obtained. M. P. 108-111 °C

Reference Example 12: Preparation of N-(carbamoylmethyl)-2-[4-(chlorosulfonyl)phenoxy]acetamide

a) Preparation of N-(carbamoylmethyl)-2-(phenoxy)acetamide

Glycinamide HCl salt (5 g) was resuspended in 200 ml of dichloromethane and 14 ml of triethylamine at 4 °C. Phenoxyacetyl chloride (6 ml) was slowly added with good stirring. The reaction mixture was stirred at room temperature for 3 hr, then, refluxed for 3 hr. The reaction mixture was cooled to give crystalline solid, which was collected by filtration. Filtered solid was washed

with water, and dried in vacuo to give 7.5 g of product, N-(carbamoylmethyl)-2-(phenoxy)acetamide . The filtrate was washed with water, and 0.1 N sodium carbonate solution. The filtrate was concentrated, and treated with ether to give additional product, 1.2 g of N-(carbamoylmethyl)-2-(phenoxy)acetamide .
M.P. 138-140 °C

b) Preparation of N-(carbamoylmethyl)-2-[4-(chlorosulfonyl)phenoxy]acetamide

N-(carbamoylmethyl)-2-(phenoxy)acetamide (2.08 g) was resuspended in 30 ml of dichloromethane and chlorosulfonic acid (6 ml) was slowly added with cooling. The reaction mixture was stirred at room temperature for 2 hr. Two layers separated after standing for 10 min without stirring. Upper layer was decanted. Lower layer was poured to chopped ice (60 g) with good mixing to give white solid, which was collected by filtration and washed with ice-cold water. The solid was dried in vacuo to give 2.78 g of N-(carbamoylmethyl)-2-[4-(chlorosulfonyl)phenoxy]acetamide .
M.P. 97-100 °C (decomposition)

EXAMPLE 1

1-Benzenesulfonyl-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole and 1-Benzensulfonyl-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole

Method A: 5-Methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole(172 mg, 0.5 mmole) was dissolved in 20 ml of dichloromethane and 0.140 ml of triethylamine. The solution was cooled to 0-4 °C in an ice bucket. Benzenesulfonyl chloride (96 mg, 0.55 mmole) was slowly added and stirred at 0-4 °C with thin layer chromatography monitoring (developing solvent system: chloroform-methanol (10:1) and acetonitrile-chloroform (1:1)). After the reaction was complete, the organic

layer was washed with an aqueous solution composed of 0.1 M NaCl, and 0.1 M sodium phosphate, pH 8.5. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residual material was crystallized from dichloromethane-ethyl ether-heptane to provide 127 mg of product. M. p. 87-89 °C (decomposition). Heptane was introduced to the remaining organic layer to provide a second crop of product (104 mg). After combining the solids, 231 mg of the product (yield 95%) was obtained. The product was composed of an mixture of 1-benzensulfonyl-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole and 1-benzensulfonyl-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole (3:2 ratio by NMR)

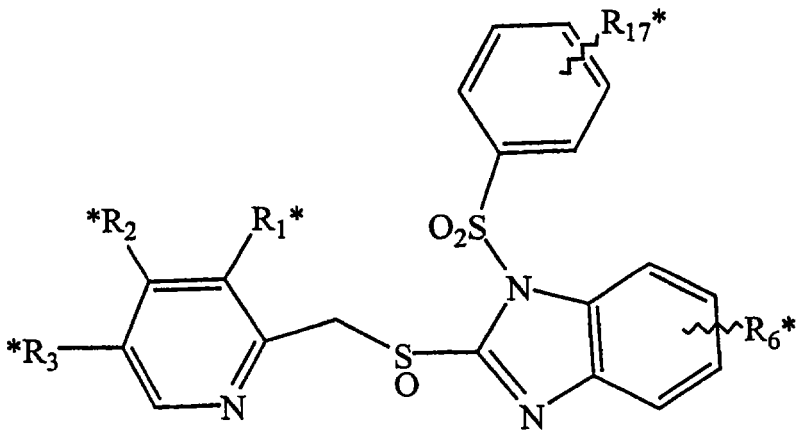
1H NMR ($CDCl_3$, δ: 8.10-8.15 (m, 3H), 7.45-7.80(m, 5H), 7.0-7.1(m, 1H), 4.8-5.0(2q, 2AB total 2H), 3.83 and 3.92 (2s, total 3H), 3.75(s, 3H), 2.31(s, 3H), 2.23(s, 3H)

Method B: A mixture of 1-benzenesulfonyl-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylthio]-1H-benzimidazole and 1-benzenesulfonyl-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylthio]-1H-benzimidazole was prepared by reacting 5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylthio]-1H-benzimidazole with benzenesulfonyl chloride as in method A. 1-Benzenesulfonyl-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylthio]-1H-benzimidazole was isolated by silica gel column chromatography and used in the next step as follows. 1-Benzenesulfonyl-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylthio]-1H-benzimidazole (318 mg, 1 mmole) in 30 ml of dichloromethane was cooled to – 20 °C. A dichloromethane solution (5 ml) containing m-chloroperbenzoic acid (equivalent to 1 mmole from 60% purity) was slowly added. The reaction was monitored by thin layer chromatography. After 5 hours the organic layer was washed with an aqueous solution of 0.1 M

sodium bicarbonate and 50 mM sodium thiosulfate. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Residual material was solidified from dichloromethane-ethyl ether-heptane to provide 397 mg of product (yield 82%), 1-benzenesulfonyl-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole and 1-benzensulfonyl-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole.

EXAMPLES 2-19

The compounds listed under Examples 2-19 below were prepared using the method A as described in Example 1. 2-Pyridylmethylsulfinyl benzimidazole compounds were reacted with the corresponding arylsulfonyl chloride to give the corresponding 1-arylsulfonyl-2-pyridylmethylsulfinyl benzimidazoles as shown in Table 1 with reference to **Formula 21**.



Formula 21

TABLE 1

#	R_6*	R_1*	R_2*	R_3*	R_{17}*	Yield (%)	m.p. (°C)
2	5-OCH_3[1]	$-CH_3$	$-OCH_3$	$-CH_3$	4-Cl	81	76-78
3	5-OCH_3[1]	$-CH_3$	$-OCH_3$	$-CH_3$	4-Br	73	84-86
4	5-OCH_3[1]	$-CH_3$	$-OCH_3$	$-CH_3$	4-F	85	70-72
5	5-OCH_3[1]	$-CH_3$	$-OCH_3$	$-CH_3$	4-CH_3	79	64-66
6	5-OCH_3	$-CH_3$	$-OCH_3$	$-CH_3$	4-OCH_3	83	85-87
7	5-OCH_3[1]	$-CH_3$	$-OCH_3$	$-CH_3$	3-CF_3	67	65-67
8	5-OCH_3[1]	$-CH_3$	$-OCH_3$	$-CH_3$	4-OCF_3	78	63-64
9	H	$-CH_3$	OCH_2CF_3	H	H	78	80-83
10	H	$-CH_3$	OCH_2CF_3	H	4-Cl	79	90-92
11	H	$-CH_3$	OCH_2CF_3	H	4-Br	71	105-107
12	H	$-CH_3$	OCH_2CF_3	H	4-F	73	85-87
13	H	$-CH_3$	OCH_2CF_3	H	4-CH_3	67	125-126
14	H	$-CH_3$	OCH_2CF_3	H	4-OCH_3	78	94-9[illegible]
15	H	$-CH_3$	OCH_2CF_3	H	3-CF_3	67	123-125
16	H	$-CH_3$	OCH_2CF_3	H	4-OCF_3	78	125-126
17[2]	5-$OCHF_2$	OCH_3	OCH_3	H	H	92	51-54
18[2]	5-$OCHF_2$	OCH_3	OCH_3	H	4-OCH_3	87	67-69
19[2]	5-$OCHF_2$	OCH_3	OCH_3	H	4-OCF_3	87	61-63

[1] signifies a 3:2 ratio of 5-OCH_3 and 6-OCH_3

[2] signifies a 5:4 ratio of 5-$OCHF_2$ and 6-$OCHF_2$

EXAMPLE 20

5-Difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole, sodium salt sesquihydrate (432 mg, 1 mmole) was suspended in 30 ml of dichloromethane in the presence of anhydrous sodium carbonate (100 mg). 4-Chlorobenzenesulfonyl chloride (211 mg, 1 mmole) was added to the suspension and stirred at 4 °C overnight. The organic layer was separated by filtration and concentrated under reduced pressure. The residual solid was crystallized from dichloromethane-ethyl ether-heptane. 417 mg of isomer, 1-(4-chlorobenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole and 1-(4-chlorobenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole (5:4 ratio by NMR), was obtained. Yield 74.5% M.P. 82-83 °C.

1H NMR (CDCl3, δ: 8.05-8.15(m, 2H), 8.0(d, 1H), 7.78-7.81(m, 1H), 7.45-7.6(m, 2H), 7.2-7.3(m, 1H), 6.80-6.81(d, 1H), 6.5-6.6(d, 1H), 4.9-5.0(q, 2H), 3.93(s, 3H).

EXAMPLES 21-24

The compounds listed in Table 2, with reference to **Formula 20,** were prepared using the method described in Example 20.

TABLE 2

%	R_6*	R_1*	R_2*	R_3*	R_{17}*	Yield(%)	m.p. (°C)
21[1]	5-$OCHF_2$	OCH_3	OCH_3	H	4-Br	87	80-82
22[1]	5-$OCHF_2$	OCH_3	OCH_3	H	4-F	78	67-70
23[1]	5-$OCHF_2$	OCH_3	OCH_3	H	4-CH_3	88	73-75
24[1]	5-$OCHF_2$	OCH_3	OCH_3	H	3-CF_3	83	62-66

[1] signifies a 5:4 ratio of 5-$OCHF_2$ and 6-$OCHF_2$

EXAMPLE 25

1-(Pyridine-3-sulfonyl)-5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-(pyridine-3-sulfonyl)-6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole

5-Methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole (344 mg) was dissolved in 20 ml of dichloromethane and 1 ml of triethylamine. Pyridine-3-sulfonyl chloride (195 mg) was added and stirred in ice-bath for 3 hr. Dichloromethane layer was washed with an aqueous solution composed of 0.1 M NaCl and 0.1 M sodium bicarbonate. Dichloromethane layer was dried over anhydrous magnesium sulfate. Solvent was removed under reduced pressure. Residual material was precipitated by dichloromethane-ethyl ether-heptane to provide 372 mg of product, which were a mixture of 1-(pyridine-3-sulfonyl)-5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-(pyridine-3-sulfonyl)-6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole (3:1 ratio by NMR).

M.P. 136-138 °C (decomposition)

NMR ($CDCl_3$, δ): 2.27 (s, 3H), 2.35 (s, 3H), 3.82 (s, 3H), 3.86 & 3.93 (2s, total 3H), 5.04-5.17 (q, AB, 2H), 7.01-7.02 (dd, 1H), 7.47-7.56 (m, 2H), 7.67-7.71 (d, 1H), 8.15 (s, 1H), 8.51-8.55 (dd, 1H), 8.85-8.88 (d, 1H), 9.34 (s, 1H)

EXAMPLE 26

1-(Pyridine-3-sulfonyl)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole

2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (370 mg) was dissolved in 20 ml of dichloromethane and 1 ml of triethylamine. Pyridine-3-sulfonyl chloride (195 mg) was added and stirred in ice-bath for 5 hr. Dichloromethane layer was washed with an aqueous solution

composed of 0.1 M NaCl and 0.1 M sodium bicarbonate. Dichloromethane layer was dried over anhydrous magnesium sulfate. Solvent was removed under reduced pressure. Residual material was precipitated by dichloromethane-ethyl ether-heptane to provide 348 mg of 1-(pyridine-3-sulfonyl)-2-[(3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole.

M.P. 118-120 °C (decomposition)

NMR ($CDCl_3$, δ): 2.35 (s, 3H), 4.38-4.49 (q, 2H), 4.98-5.22 (q, AB, 2H), 6.73 (d, 1H), 7.41-7.56 (m, 3H), 7.80-8.02 (dd, 2H), 8.23 (s, 1H), 8.52 (dd, 1H), 8.87 (dd, 1H), 9.36 (s, 1H)

EXAMPLE 27

1-(Pyridine-3-sulfonyl)-5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-(pyridine-3-sulfonyl)-6-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole

5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole (383 mg) was dissolved in 20 ml of dichloromethane and 1 ml of triethylamine. Pyridine-3-sulfonyl chloride (195 mg) was added and stirred in ice-bath for 5 hr. Dichloromethane layer was washed with an aqueous solution composed of 0.1 M NaCl and 0.1 M sodium bicarbonate. Dichloromethane layer was dried over anhydrous magnesium sulfate. Solvent was removed under reduced pressure. Residual material was precipitated by dichloromethane-ethyl ether-heptane to provide 397 mg of a mixture of 1-(pyridine-3-sulfonyl)-5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-(pyridine-3-sulfonyl)-6-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole (ratio 3:2 by NMR).

M.P. 127-128 °C (decomposition)

EXAMPLE 28

Preparation of 1-(morpholin-4-yl)phenylsulfonyl-5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-(morpholin-4-yl)phenylsulfonyl-6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole

270.8 mg of 4-(p-chlorosulfonyl)phenyl morpholine was added to 344 mg of 5-Methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole in 20 ml of dichloromethane and 0.5 ml of triethylamine. The reaction mixture was stirred at room temperature overnight. Dichloromethane layer was washed with water, and dried over anhydrous magnesium sulfate. Organic layer was evaporated. Residual material was lyophilized in vacuo to give 425 mg of the titled product (1:1 ratio by NMR).

m.p.; 76-79 °C (decomposition)

EXAMPLE 29

Preparation of N-[4-[[5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]benzimidazol-1-yl]sulfonyl]phenyl]urea and N-[4-[[6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]benzimidazol-1-yl]sulfonyl]phenyl]urea

128 mg of N-[4-(chlorosulfonyl)phenyl]urea was added to 172 mg of 5-Methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole in a mixture of 0.5 ml of triethylamine and 10 ml of dichloromethane-acetonitrile (50/50). The reaction mixture was stirred at room temperature overnight. Dichloromethane (20 ml) was added and washed with water, and 0.1 M sodium bicarbonate solution. Organic layer was dried over anhydrous magnesium sulfate and evaporated. Residue was dissolved in 2 ml of dichloromethane and ethyl ether was added for crystallization. Crystals were collected and dried. 190 mg of product was obtained. The product was composed of a mixture of N-[4-[[5-methoxy-2-

[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]benzimidazol-1-yl]sulfonyl]phenyl]urea and N-[4-[[6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]benzimidazol-1-yl]sulfonyl]phenyl]urea (4:3 ratio by NMR).

m.p.; 154-158 °C (decomposition)

NMR ($CDCl_3$, δ): 2.19 (s, 3H), 2.20 & 2.21 (2s, total 3H), 3.69 & 3.70 (2s, total 3H), 3.76 & 3.89 (2s, total 3H), 4.75-4.94 (q, AB, 2H), 5.6-5.7 (br, NH_2), 6.95-7.08 (d, 1H), 7.05 (s, 1H), 7.43-7.86 (m, 5H), 8.12 (s, 1H), 9.0 (br, NH)

EXAMPLE 30

Preparation of N-(4-{[2-({[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}phenyl)urea

2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (185 mg) dissolved in 30 ml of dichloromethane and 0.4 ml of triethylamine was added to 128 mg of N-[4-(chlorosulfonyl)phenyl]urea. The reaction mixture was stirred at room temperature overnight. The reaction mixture was washed with water and 0.1 N sodium bicarbonate solution. Organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Residue was dissolved in 2 ml of dichloromethane and ethyl ether was added for precipitation. 125 mg of the titled product was obtained.

M.P. 115 °C (decomposition)

NMR ($CDCl_3$, δ): 2.25 (s, 3H), 4.37-4.42 (q, 2H), 4.6-4.85 (q, AB, 2H), 6.67 (d, 1H), 7.35-7.42 (m, 2H), 7.61-7.75 (m, 3H), 7.89-8.05 (m, 2H), 8.27-8.38 (m, 2H)

EXAMPLE 31

Preparation of 15-[(5-methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]-1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene and 15-[(6-

methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]- 1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene

170 mg of 5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole

and 190 mg of m-(chlorosulfonyl) benzo-15-crown-5-ether were dissolved in 0.2 ml of triethylamine and 20 ml of dichloromethane. The reaction mixture was stirred at room temperature overnight. Organic layer was washed with water and dried over anhydrous magnesium sulfate. Solvent was removed to give syrup, which was lyophilized. 210 mg of the titled product, a mixture of 15-[(5-methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]- 1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene and 15-[(6-methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]-1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene (1:1 ratio by NMR), was obtained. Lyophilized product showed M.P. 76-80 °C with decomposition.

NMR ($CDCl_3$, δ): 2.21 (s, 3H), 2.31 (s, 3H), 3.68-3.73 (m, 8H), 3.74 (s, 3H), 3.84-3.87 (m, 4H), 3.90 (s, 3H), 4.10-4.13 (m, 4H), 4.81-4.95 (2q, 2AB, 2H), 6.84 (d, 1H), 7.00-7.07 (dd, 1H), 7.25 (d, 1H), 7.42-7.72 (m, 3H), 8.15 (s, 1H)

EXAMPLE 32

Preparation of 15-{[2-({[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}-1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene

2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (185 mg) dissolved in 20 ml of dichloromethane and 0.2 ml of triethylamine was added to 190 mg of m-(chlorosulfonyl) benzo-15-crown-5-ether. The reaction mixture was stirred at room temperature overnight. Organic layer was

washed with water and dried over anhydrous magnesium sulfate. Solvent was removed to give syrup, which was lyophilized. 231 mg of the titled product was obtained. Lyophilized product showed M.P. 76-80 °C with decomposition.
NMR ($CDCl_3$, δ): 2.33 (s, 3H), 3.66-3.73 (m, 8H), 3.83-3.87 (m, 4H), 4.10-4.12 (m, 4H), 4.35-4.41 (q, 2H), 4.84-5.05 (q, AB, 2H), 6.61 (d, 1H), 6.86 (d, 1H), 7.37-7.45 (m, 2H), 7.56 (s, 1H), 7.71-7.74 (dd, 2H), 7.95 (d, 1H), 8.23 (d, 1H)

EXAMPLE 33

Preparation of 2-{4-[(5-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-pyridyl)acetamide and 2-{4-[(6-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-pyridyl)acetamide

170 mg of 2-[p-(chlorosulfonyl)phenoxy]-N-(2-pyridyl)acetamide was added to 172 mg of 5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole dissolved in dichloromethane (15 ml) and triethylamine (0.4 ml). The reaction mixture was stirred at room temperature overnight. The reaction mixture was washed with water. Organic layer was dried over anhydrous magnesium sulfate, and evaporated. Residual material was lyophilized in vacuo to give 244 mg of the titled product, which was a mixture of 2-{4-[(5-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-pyridyl)acetamide and 2-{4-[(6-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-pyridyl)acetamide (2:1 ratio by NMR).
M.P. 76-80 °C
NMR ($CDCl_3$, δ): 2.21 & 2.23 (2s, total 3H), 2.32 (s, 3H), 3.74 & 3.75 (2s, total 3H), 3.83 & 3.93 (2s, total 3H), 4.65 (s, 2H), 4.83-4.92 (q, AB, 2H), 6.99-7.11 (m, 5H), 7.46 (d, 1H), 7.68-7.88 (m, 2H), 8.75 (br, NH)

EXAMPLE 34

Preparation of 2-(4-{[2-({[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}phenoxy)-N-(2-pyridyl)acetamide

2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (185 mg) dissolved in 20 ml of dichloromethane and 0.2 ml of triethylamine was added to 170 mg of 2-[p-(chlorosulfonyl)phenoxy]-N-(2-pyridyl)acetamide. The reaction mixture was washed with water. Organic layer was dried over anhydrous magnesium sulfate, and evaporated. Residual material was lyophilized to give 237 mg of the titled product. M.P. 78-81 °C.

NMR ($CDCl_3$, δ): 2.31 (s, 3H), 4.34-4.40 (q, 2H), 4.71 (s, 2H), 4.84-5.05 (q, AB, 2H), 6.62 (d, 1H), 7.09 (d, 2H), 7.29-7.47 (m, 2H), 7.62-7.80 (m, 2H), 7.98 (d, 1H), 8.11 (d, 2H), 8.20-8.29 (m, 4H), 8.92 (br, NH)

EXAMPLE 35

Preparation of 2-{4-[(5-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-pyridyl)acetamide and 2-{4-[(6-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-pyridyl)acetamide

5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole (192 mg) dissolved in 20 ml of dichloromethane and 0.2 ml of triethylamine was added to 170 mg of 2-[(p-chlorosulfonyl)phenoxyacetyl]aminopyridine. The reaction mixture was washed with water. Organic layer was dried over anhydrous magnesium sulfate, and evaporated. Residual material was lyophilized to give 187 mg of the titled product, which was a mixture of 2-{4-[(5-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-

pyridyl)acetamide and 2-{4-[(6-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-pyridyl)acetamide (2:1 ratio by NMR).

M.P. 95-101 °C

NMR ($CDCl_3$, δ): 3.90 (s, 3H), 3.93 (s, 3H), 4.67 (s, 2H), 4.85-5.00 (2q, 2AB, 2H; s like, 1H), 6.52-6.80 (m, 2H), 7.08 (m, 3H), 7.29-7.40 (d, 1H), 7.58-7.80 (m, 2H), 7.97-8.16 (m, 3H), 8.22 (d, 1H), 8.30 (d, 1H), 8.82 (br, NH)

EXAMPLE 36

Preparation of 1-[4-(3-(morpholin-4-yl) propoxy) benzenesulfonyl]-5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-[4-(3-(morpholin-4-yl) propoxy) benzenesulfonyl]-6-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole

180 mg of 4-(3-(morpholin-4-yl) propoxy) benzenesulfonyl chloride was added to a solution of 190 mg of 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole in 10 ml of dichloromethane and 0.5 ml of triethylamine. The reaction mixture was stirred overnight, and washed with water. Organic layer was concentrated and lyophilized in vacuo. 210 mg of the titled mixture was obtained (1:1 ratio by NMR).

EXAMPLE 37

Preparation of 1-[4-[3-(morpholin-4-yl) propoxy] benzenesulfonyl]-5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-[4-[3-(morpholin-4-yl) propoxy] benzenesulfonyl]-6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole

200 mg of 4-[3-(morpholin-4-yl) propoxy] benzenesulfonyl chloride was added to a solution of 200 mg of 5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-

pyridyl)methyl]sulfinyl]-1H-benzimidazole in 10 ml of dichloromethane and 0.5 ml of triethylamine. The reaction mixture was stirred overnight, and washed with water. Organic layer was concentrated and treated with ethyl ether to give solids. Solids were crystallized from dichloromethane and ether. 210 mg of the titled product, 1:1 ratio of 5-methoxy and 6-methoxy compound, was obtained.

M.P. 98-102 °C (decomposition)

NMR ($CDCl_3$, δ): 1.97-2.05 (m, 2H), 2.09 (s, 3H), 2.20 (s, 3H) 3.05-3.15 (m, 6H), 3.58 (s, 3H), 3.65-3.80 (m, 4H), 3.81 & 3.92 (2s, total 3H), 3.82-3.95 (t, 2H), 4.73-4.94 (q, AB, 2H), 6.89-6.91 (d, 2H), 7.4-7.6 (m, 3H), 7.79-8.0 (m, 2H), 8.17 (s, 1H)

EXAMPLE 38

Preparation of 1-[[(N,N-dimethylamino)methyl]benzene-4-sulfonyl]-5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-[[(N,N-dimethylamino)methyl]benzene-4-sulfonyl]-6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole

120 mg of N-[[p-(chlorosulfonyl)phenyl]methyl]-N,N-dimethylamine was added to 172 mg of 5-Methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole dissolved in 20 ml of dichloromethane and 0.5 ml of triethylamine. The reaction mixture was stirred at room temperature for 16 hr. Dichloromethane layer was washed with water, and 0.1 N sodium bicarbonate solution. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Residual material was lyophilized in vacuo to give 245 mg of the titled product (1:1 ratio by NMR).

EXAMPLE 39

Preparation of 1-[2-acetamido-4-methyl-5-thiazolylsulfonyl]-5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole

172 mg of 5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole was dissolved in 10 ml of dichloromethane and 0.4 ml of triethylamine, and 128 mg of 2-acetamido-4-methyl-5-thiazolyl sulfonyl chloride was added. The reaction mixture was stirred at room temperature for 15 hr. Product spot was shown at slightly higher position than 5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole in thin layer chromatography (developing solvent: dichloromethane-acetonitrile-methanol = 100:10:5). Product was separated by silica gel column chromatography. 145 mg of the titled product was isolated.

EXAMPLE 40

Preparation of 1-(thiophene-2-sulfonyl)-5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-(thiophene-2-sulfonyl)-6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole

172 mg of 5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole was dissolved in 10 ml of dichloromethane and 0.2 ml of triethylamine. 95 mg of thiophene-2-sulfonyl chloride was added. . The reaction mixture was stirred at room temperature for 16 hr. Dichloromethane layer was washed with water and concentrated under reduced pressure. Residual material was crystallized from acetonitrile-ethyl ether-hexane. 225 mg of the titled product, a mixture of 1-(thiophene-2-sulfonyl)-5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-(thiophene-2-sulfonyl)-6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole (7:1 ratio by NMR), was obtained.

M.P. 86-90 °C

NMR ($CDCl_3$, δ): 2.20 (s, 3H), 2.30 (s, 3H), 3.73 (s, 3H), 3.83 & 3.91 (2s, total 3H), 4.80-4.92 (q, AB, 2H), 7.00-7.10 (m, 2H), 7.47 (s, 1H), 7.67-7.69 (m, 2H),

7.97-7.99 (d, 1H), 8.13 (s, 1H)

EXAMPLE 41

Preparation of 1-(phenylmethylsulfonyl)-5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-(phenylmethylsulfonyl)-6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole

172 mg of 5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole was dissolved in 10 ml of dichloromethane and 0.2 ml of triethylamine. 95 mg of phenylmethylsulfonyl chloride was added. . The reaction mixture was stirred at room temperature for 36 hr. Dichloromethane layer was washed with water and concentrated under reduced pressure. Residual material was lyophilized in vacuo to give 205 mg of the titled product, a mixture of 1-(phenylmethylsulfonyl)-5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-(phenylmethylsulfonyl)-6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole (2:1 ratio by NMR)

M.P. 130 °C (decomposition)

EXAMPLE 42

Preparation of 1-(n-propanesulfonyl)-5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-(n-propanesulfonyl)-6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole

103 mg of 5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole was dissolved in 2 ml of chloroform and 0.1 ml of triethylamine. 1-Propanesulfonyl chloride (0.042 ml) was slowly added in ice bath. The reaction mixture was stirred at room temperature for 3 hr. Organic layer was washed with cold 0.1 N sodium bicarbonate solution. Chloroform layer was dried

over anhydrous magnesium sulfate, and concentrated under reduced pressure. Residual material was solidified from chloroform-ethyl ether-hexane to give 128 mg (95%) of the titled product (3:2 ratio).

M.P. 96-100 °C

EXAMPLE 43

Preparation of 1-(n-butanesulfonyl)-5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-(n-butanesulfonyl)-6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole

103 mg of 5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole was dissolved in 2 ml of chloroform and 0.1 ml of triethylamine. 1-Butanesulfonyl chloride (0.042 ml) was slowly added in ice bath. The reaction mixture was stirred at room temperature for 3 hr. Organic layer was washed with cold 0.1 N sodium bicarbonate solution. Chloroform layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Residual material was solidified from chloroform-ethyl ether-hexane to give 130 mg (93%) of the titled product (3:2 ratio).

M.P. 54-56 °C

EXAMPLE 44

Preparation of 1-(isopropylsulfonyl)-5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and -(isopropylsulfonyl)-6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole

103 mg of 5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole was dissolved in 2 ml of chloroform and 0.1 ml of triethylamine. Isopropylsulfonyl chloride (0.042 ml) was slowly added in ice bath. The reaction mixture was stirred at room temperature for 24 hr. Organic layer was concentrated under reduced pressure and applied to silica gel column

chromatography. 78 mg of the titled product was isolated (1:1 ratio).

M.P. 105-108 °C (decomposition)

EXAMPLE 45

1-[(N,N-dimethylamino)benzene-4-sulfonyl]-5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-[(N,N-dimethylamino)benzene-4-sulfonyl]-6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole

120 mg of p-(N,N-dimethylamino)benzenesulfonyl chloride was added to 172 mg of 5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole dissolved in 20 ml of dichloromethane and 0.5 ml of triethylamine. The reaction mixture was stirred at room temperature for 16 hr. Dichloromethane layer was washed with water and 0.1 N sodium carbonate solution. Organic layer was dried over anhydrous magnesium sulfate and was concentrated under reduced pressure. Residual material was lyophilized in vacuo to give 215 mg of the titled product (1:1 ratio).

M.P. 92-96 °C

NMR ($CDCl_3$, δ): 2.24 (s, 3H), 2.30 (s, 3H), 3.02 (s, 3H), 3.03 (s, 3H), 3.75 (s, 3H), 3.83 & 3.92 (2s, total 3H), 4.77-4.94 (2q, AB & A'B', total 2H), 6.57-6.61 (m, 2H), 6.96-7.07 (m, 1H), 7.48 & 7.68 (2d, total 1H), 7.85-7.90 (m, 3H), 8.22 (s, 1H)

EXAMPLE 46

Preparation of N-(4-{[2-({[4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}phenyl)urea

128 mg of N-[4-(chlorosulfonyl)phenyl]urea was added to 191 mg of 2-[(3-methyl-4-methoxypropoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole sodium salt in a mixture of 0.1 ml of triethylamine and 10 ml of dichloromethane-

acetonitrile (50/50). The reaction mixture was stirred at room temperature overnight. Dichloromethane (20 ml) was added and washed with water, and 0.1 M sodium bicarbonate solution. Organic layer was dried over anhydrous magnesium sulfate and evaporated. Residue was dissolved in minimum amounts of acetonitrile and ethyl ether was added for crystallization. Crystals were collected and dried. 190 mg of the titled product was obtained.

NMR ($CDCl_3$, δ): 2.03-2.07 (m, 2H), 2.18 (s, 3H), 3.34 (s, 3H), 3.52-3.54 (t, 2H), 4.05-4.08 (t, 2H), 4.76-5.00 (q, AB, 2H), 5.50-5.61 (br, -NH2), 6.69 (d, 1H), 7.33-7.37 (m, 3H), 7.51 (d, 1H), 7.65 (d, 1H), 7.81 (d, 2H), 7.98 (d, 1H), 8.17 (d, 1H), 8.97 (s, -NH-)

EXAMPLE 47

Preparation of 1-(pyridine-3-sulfonyl)-2-[[[3-methyl-4-(3-methoxypropoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole

100 mg of pyridine-3-sulfonyl chloride was added to 191 mg of 2-[[[3-methyl-4-(3-methoxypropoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole sodium salt in a mixture of 0.15 ml of triethylamine and 10 ml of dichloromethane. The reaction mixture was stirred at room temperature overnight. Dichloromethane (20 ml) was added and washed with water, and 0.1 M sodium bicarbonate solution. Organic layer was dried over anhydrous magnesium sulfate and evaporated. Residue was dissolved in minimum amounts of acetonitrile and ethyl ether was added for precipitation. Solids was collected and dried to give 127 mg of the titled product.

NMR ($CDCl_3$, δ): 1.97-2.10 (m, 2H), 2.21 (s, 3H), 3.35 (s, 3H), 3.51-3.57 (t, 2H), 4.04-4.07 (t, 2H), 4.82-5.14 (q, AB, 2H), 6.73 (d, 1H), 7.41-7.56 (m, 3H), 7.80-8.02 (dd, 2H), 8.23-8.87 (m, 3H), 9.34 (s, 1H)

EXAMPLE 48

Preparation of 2-(4-{[2-({[4-(3-methoxypropoxy)-3-methyl-2-

pyridyl]methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}phenoxy)-N-(2-pyridyl)acetamide

170 mg of 2-[p-(chlorosulfonyl)phenoxy]-N-(2-pyridyl)acetamide was added to 191 mg of 2-[[[4-(3-methoxypropoxy)-3-methyl-2- pyridyl]methyl]sulfinyl]-1H-benzimidazole sodium salt in dichloromethane (15 ml) and triethylamine (0.1 ml). The reaction mixture was stirred at room temperature overnight. The reaction mixture was washed with water. Organic layer was dried over anhydrous magnesium sulfate, and evaporated. Residual material was lyophilized in vacuo to give 244 mg of the titled product.

M.P. 78-81 °C (decomposition)

NMR ($CDCl_3$, δ): 2.00-2.10 (m, 2H), 2.27 (s, 3H), 3.35 (s, 3H), 3.52-3.57 (t, 2H), 4.06-4.10 (t, 2H), 4.64 (s, 2H), 4.83-5.02 (q, AB, 2H), 6.67 (d, 1H), 7.07-7.10 (m, 3H), 7.32-7.49 (m, 3H), 7.70-7.82 (m, 2H), 7.99 (d, 1H), 8.14-8.30 (m, 4H), 8.77 (br, NH)

EXAMPLE 49

Preparation of 1-[4-(morpholin-4-yl)phenylsulfonyl]-2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole

136 mg of 4-[(p-chlorosulfonyl)phenyl] morpholine was added to 191 mg of 2-[[[4-(3-methoxypropoxy)-3-methyl –2-pyridyl]methyl]sulfinyl]-1H-benzimidazole sodium salt in dichloromethane (15 ml) and triethylamine (0.1 ml). The reaction mixture was stirred at room temperature overnight. The reaction mixture was washed with water. Organic layer was dried over anhydrous magnesium sulfate, and evaporated. Residual material was lyophilized in vacuo to give 224 mg of the titled product.

M.P. 93-96 °C (decomposition)

NMR ($CDCl_3$, δ): 2.02-2.06 (m, 2H), 2.26 (s, 3H), 3.2-3.3 (m, 4H), 3.35 (s, 3H), 3.50-3.53 (t, 2H), 3.75-3.80 (m, 4H), 4.04-4.08 (t, 2H), 4.71-4.79 (q, AB, 2H),

6.71 (d, 1H), 7.26-7.5 (m, 4H), 7.8-8.1 (m, 2H), 8.27 (d, 1H)

EXAMPLE 50

Preparation of 1-[{2-(morpholin-4-yl)ethoxy}phenyl-4-sulfonyl]-2-[[[(4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole

136 mg of 4-[2-[(p-chlorosulfonyl)phenoxy]ethyl]morpholine was added to 191 mg of 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole sodium salt in dichloromethane (15 ml) and triethylamine (0.1 ml). The reaction mixture was stirred at room temperature overnight. The reaction mixture was washed with water. Organic layer was dried over anhydrous magnesium sulfate, and evaporated. Residual material was lyophilized in vacuo to give 234 mg of the titled product.

NMR ($CDCl_3$, δ): 2.05-2.10 (m, 2H), 2.27 (s, 3H), 2.56 (m, 4H), 2.79-2.82 (t, 2H), 3.35 (s, 3H), 3.53-3.56 (t, 2H), 3.69-3.72 (m, 4H), 4.07-4.10 (t, 2H), 4.12-4.15 (t, 2H), 4.81-4.99 (q, AB, 2H), 6.68 (d, 1H), 6.95 (d, 2H), 7.36-7.46 (m, 2H), 7.81 (d, 1H), 7.99 (d, 1H), 8.06 (d, 2H), 8.21 (d, 1H)

EXAMPLE 51

Preparation of 1-(thiophene-2-sulfonyl)-2-[[[(4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole

92 mg of thiophene-2-sulfonyl chloride was added to 191 mg of 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole sodium salt in dichloromethane (15 ml) and triethylamine (0.1 ml). The reaction mixture was stirred at room temperature overnight. The reaction mixture was washed with water. Organic layer was dried over anhydrous magnesium sulfate, and evaporated. Residual material was lyophilized in vacuo to give 215 mg of the titled product.

M.P. 147-150 °C

NMR ($CDCl_3$, δ): 2.00-2.08 (m, 2H), 2.27 (s, 3H), 3.35 (s, 3H), 3.53-3.56 (s, 3H), 4.07-4.10 (t, 2H), 4.83-5.00 (q, AB, 2H), 6.67 (d, 1H), 7.08-7.10 (t, 1H), 7.42-7.49 (m, 2H), 7.68-7.70 (d, 1H), 7.82-7.84 (d, 1H), 8.00-8.03 (m, 2H), 8.18 (d, 1H)

EXAMPLE 52

Preparation of 1-benzenesulfonyl-2-[[[(4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole

94 mg of benzenesulfonyl chloride was added to 191 mg of 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole sodium salt in dichloromethane (15 ml) and triethylamine (0.1 ml). The reaction mixture was stirred at room temperature overnight. The reaction mixture was washed with water. Organic layer was dried over anhydrous magnesium sulfate, and evaporated. Residual material was crystallized from acetonitrile-ethyl ether. 210 mg of the titled product was obtained.

M.P. 126-128 °C

NMR ($CDCl_3$, δ): 1.97-2.09 (m, 2H), 2.27 (s, 3H), 3.34 (s, 3H), 3.52-3.57 (t, 3H), 4.05-4.10 (t, 3H), 4.81-5.03 (q, AB, 2H), 6.66 (d, 1H), 7.38-7.53 (m, 4H), 7.61-7.65 (t, 1H), 7.80 (d, 1H), 8.00 (d, 1H), 8.11-8.16 (m, 3H)

EXAMPLE 53

Preparation of 2-{4-[(5-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}acetamide and 2-{4-[(5-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}acetamide

5-Methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole (344 mg) was dissolved in 40 ml of dichloromethane and 1 ml of triethylamine. 2-[p-(chlorosulfonyl)phenoxy]acetamide(250 mg) was added. The reaction mixture was stirred at room temperature overnight. The reaction was

monitored by thin layer chromatography (developing solvent: chloroform-acetonitrile-methanol (100:10:7)). Solid was collected by filtration, washed with small amounts of dichloromethane, and dried in vacuo to give 415 mg of the titled product (3:2 ratio of 5-methoxy / 6-methoxy compound).

M.P. 159-161 °C (decomposition)

NMR (DMSO-d6, δ): 2.13 (s, 3H), 2.25 (s, 3H), 3.69 (s, 3H), 3.78 & 3.88 (2s, total 3H), 4.56 (s, 2H), 4.82-5.04 (2q, AB, 2H), 7.05-7.18 (m, 3H), 7.34-7.40 (m, 1H), 7.60-7.90 (m, 2H), 8.12-8.18 (m, 2H)

EXAMPLE 54

Preparation of 2-(4-{[2-({[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}phenoxy)acetamide

2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (370 mg) was dissolved in 20 ml of dichloromethane and 1 ml of triethylamine. 2-[p-(chlorosulfonyl)phenoxy]acetamide(250 mg) was added. The reaction mixture was stirred at room temperature for 24 hr. Solid was collected, washed with dichloromethane, and dried in vacuo. 378 mg of the titled product was obtained.

M.P. 162-166 °C (decomposition)

NMR (DMSO-d6, δ): 2.21 (s, 3H), 4.55 (s, 2H), 4.86-5.15 (q, 2H and q, 2H) 6.99 (d, 1H), 7.16 (d, 2H), 7.39-7.58 (m, 2H), 7.79 (d, 1H), 7.97-8.03 (m, 2H), 8.17 (d, 2H)

EXAMPLE 55

Preparation of 2-{4-[(5-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}acetamide and 2-{4-[(6-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}acetamide

5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole (383 mg) was dissolved in 20 ml of dichloromethane and 1 ml of triethylamine. 2-[p-(chlorosulfonyl)phenoxy]acetamide(250 mg) was added. The reaction mixture was stirred at room temperature for 24 hr. Solid was collected, washed with dichloromethane, and dried in vacuo. 413 mg of the titled product (1:1 ratio) was obtained.

M.P. 125-128 °C (decomposition)

EXAMPLE 56

Preparation of 2-(4-{[2-({[4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}phenoxy)acetamide

2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole sodium salt (382 mg) was added in dichloromethane (45 ml) and triethylamine (0.1 ml). 2-[p-(chlorosulfonyl)phenoxy]acetamide(250 mg) was added. The reaction mixture was stirred at room temperature overnight. The reaction mixture was washed with water. Organic layer was dried over anhydrous magnesium sulfate, and evaporated. Residual material was crystallized from acetonitrile-ethyl ether. 437 mg of the titled product was obtained.

M.P. 148-153 °C (decomposition)

NMR (DMSO-d6, δ): 1.93-1.97 (m, 2H), 2.18 (s, 3H), 3.35 (s, 3H), 3.46 (t, 2H), 4.06 (t, 2H), 4.56 (s, 2H), 4.83-5.13 (q, AB, 2H), 6.85 (d, 1H), 7.16 (d, 2H), 7.41-7.60 (m, 2H), 7.79 (d, 1H), 7.89 (d, 1H), 8.00-8.02 (d, 1H), 8.16-8.18 (d, 2H)

EXAMPLE 57

Preparation of 1-[{2-(morpholin-4-yl)ethoxy}phenyl-4-sulfonyl]-2-[(3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole

2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (370 mg) was dissolved in 20 ml of dichloromethane and 1 ml of

triethylamine. [2-(Morpholin-4-yl)ethoxy]phenyl-4-sulfonyl chloride (273 mg) was added and stirred at room temperature overnight. Dichloromethane layer was washed with an aqueous solution composed of 0.1 M NaCl and ice-cooled 0.1 N sodium bicarbonate solution. Dichloromethane layer was dried over anhydrous magnesium sulfate. Solvent was removed under reduced pressure. Residual material was lyophilized to provide 515 mg of the titled product.

NMR ($CDCl_3$, δ): 2.33 (s, 3H), 2.50-2.52 (m, 4H), 2.78-2.81 (t, 2H), 3.70-3.74 (m, 4H), 4.12-4.15 (t, 2H), 4.84-5.02 (q, AB, 2H), 6.63 (d, 1H), 6.96 (d, 2H), 7.38-7.49 (m, 2H), 7.81 (d, 1H), 7.99 (d, 1H), 8.04 (d, 2H), 8.26 (d, 1H)

EXAMPLE 58

Preparation of 1-[{2-(morpholin-4-yl)ethoxy}phenyl-4-sulfonyl]-5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-[{2-(morpholin-4-yl)ethoxy}phenyl-4-sulfonyl]-6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole

137 mg of [2-(Morpholin-4-yl)ethoxy]phenyl-4-sulfonyl chloride was added to 172 mg of 5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole in dichloromethane (15 ml) and triethylamine (0.4 ml). The reaction mixture was stirred at room temperature overnight. The reaction mixture was washed with an aqueous solution composed of 0.1 M NaCl and 0.1 M sodium bicarbonate. Organic layer was dried over anhydrous magnesium sulfate, and evaporated. Residual material was lyophilized in vacuo to give 224 mg of the titled product (1:1 ratio).

NMR ($CDCl_3$, δ): 2.22 (s, 3H), 2.30 (s, 3H), 2.50-2.51 (m, 4H), 2.79 (t, 2H), 3.69-3.74 (m, 4H; s, 3H), 3.82 & 3.91 (2s, total 3H), 4.12 (t, 2H), 4.78-4.94 (q, AB, 2H), 6.93-7.08 (m, 3H), 7.46 (s, 1H), 7.68-7.86 (dd, 1H), 8.00-8.04 (m, 2H), 8.17 (s, 1H)

EXAMPLE 59

Preparation of 1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-2-[(3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole

2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (185 mg) was dissolved in 20 ml of dichloromethane and 0.5 ml of triethylamine. 2-[2-(Morpholin-4-yl)ethoxy]ethoxyphenyl-4-sulfonyl chloride (163 mg) was added and stirred at room temperature overnight. Dichloromethane layer was washed with an aqueous solution composed of 1 M NaCl and 0.1 N $NaHCO_3$. Dichloromethane layer was dried over anhydrous magnesium sulfate. Solvent was removed under reduced pressure. Residual material was separated by preparative TLC. 198 mg of the titled product was obtained.

NMR ($CDCl_3$, δ): 2.30 (s, 3H), 2.48 (m, 4H), 2.58 (t, 2H), 3.64-3.77 (m, 8H), 4.10 (t, 2H), 4.34-4.40 (q, 2H), 4.81-5.01 (q, AB, 2H), 6.62 (d, 1H), 6.94 (d, 2H), 7.35-7.47 (m, 2H), 7.78 (d, 1H), 7.96 (d, 1H), 8.02 (d, 2H), 8.22 (d, 1H)

EXAMPLE 60

Preparation of 1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]- 5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole

162 mg of [2-{2-(morpholin-4-yl)ethoxy}ethoxy]benzene-4-sulfonyl chloride was added to 172 mg of 5-Methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole in dichloromethane (15 ml) and triethylamine (0.5 ml). The reaction mixture was stirred at room temperature overnight. The reaction mixture was washed with an aqueous solution composed of 1 M NaCl and 0.1 M sodium bicarbonate. Organic layer was dried over anhydrous magnesium sulfate, and evaporated. Residual material was dried in

vacuo to give 254 mg of the titled product (1:1 ratio).

NMR ($CDCl_3$, δ): 2.21 (s, 3H), 2.29 (s, 3H), 2.49-2.53 (m, 2H), 2.69-2.78 (m, 4H), 3.67-3.89 (m, 8H; s, 3H; s, 3H), 4.07-4.13 (m, 2H), 4.76-4.93 (q, AB, 2H), 6.92-7.00 (m, 2H), 7.23 (d, 1H), 7.44 (d, 1H), 7.65-7.85 (dd, 1H), 7.98-8.03 (m, 2H), 8.15 (s, 1H)

EXAMPLE 61

Preparation of 1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-2-[[[(4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole

2-[(3-Methyl-4-methoxypropoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole sodium salt (191mg) was dissolved in 20 ml of dichloromethane and 0.1 ml of triethylamine. 2-[2-(Morpholin-4-yl)ethoxy]ethoxyphenyl-4-sulfonyl chloride (163 mg) was added and stirred at room temperature overnight. Dichloromethane layer was washed with an aqueous solution composed of 1 M NaCl and 0.1 N $NaHCO_3$. Dichloromethane layer was dried over anhydrous magnesium sulfate. Solvent was removed under reduced pressure. Residual material was lyophilized to give 253 mg of the titled product.

NMR ($CDCl_3$, δ): 1.99-2.03 (m, 2H), 2.21 (s, 3H), 2.46 (t, 2H), 2.55 (t, 2H), 2.67 (t, 2H), 3.29 (s, 3H), 3.48-3.53 (m, 2H), 3.64-3.68 (m, 6H), 3.73-3.74 (m, 2H), 4.02-4.07 (m, 4H), 4.74-4,97 (q, AB, 2H), 6.62 (d, 1H), 6.89-6.92 (d, 2H), 7.31-7.42 (m, 2H), 7.75 (d, 1H), 7.93 (d, 1H), 8.02 (d, 2H), 8.13 (d, 1H)

EXAMPLE 62

Preparation of N-(carbamoylmethyl)-2-{4-[(5-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}acetamide and N-(carbamoylmethyl)-2-{4-[(6-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}acetamide

Method 1) 5-Methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole (172 mg) was dissolved in 20 ml of dichloromethane. Sodium tert-butoxide (55 mg) and N-(carbamoylmethyl)-2-[4-(chlorosulfonyl)phenoxy]acetamide (160 mg) was added. The reaction mixture was stirred at 30 °C for 36 hr. The reaction mixture was filtered. The filtrate was concentrated and treated with ethyl ether to give precipitates. Solid was collected, and dried in vacuo. 253 mg of the titled product (1:1 ratio) was obtained.

Method 2) 5-Methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole (172 mg) was dissolved in 20 ml of dichloromethane and 0.4 ml of triethylamine. N-(carbamoylmethyl)-2-[4-(chlorosulfonyl)phenoxy]acetamide (160 mg) was added. The reaction mixture was stirred at 30 °C for 36 hr. The reaction mixture was treated with additional 80 ml of dichloromethane, and washed with 7% NaCl solution and 0.1 N sodium bicarbonate solution. Dichloromethane layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residual material was lyophilized to give 213 mg of the titled product (1:1 ratio).

NMR (DMSO-d6, δ): 2.14 (s, 3H), 2.25 (s, 3H), 3.34 (br, -NH, -NH2), 3.66 (d, 2H), 3.70 (s, 3H), 3.88 (s, 3H), 4.67 (s, 2H), 4.81-5.08 (q, AB, 2H), 7.05-7.22 (m, 3H), 7.35 (s, 1H), 7.89 (dd, 1H), 8.14-8.18 (m, 2H), 8.32 (s, 1H)

EXAMPLE 63

Preparation of N-(carbamoylmethyl)-2-(4-{[2-({[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}phenoxy)acetamide

2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (185 mg) was dissolved in 20 ml of dichloromethane and 0.5 ml of triethylamine, and N-(carbamoylmethyl)-2-[4-(chlorosulfonyl)phenoxy]acetamide (158 mg) was added. The reaction mixture was stirred at room temperature for 24

hr. Dichloromethane (100 ml) was added to the reaction mixture. The reaction mixture was washed with saturated NaCl solution, and 0.1 N sodium bicarbonate solution. Dichloromethane layer was separated and dried over anhydrous magnesium sulfate. Dichloromethane was evaporated under reduced pressure to give syrupy material, which was lyophilized in vacuo. 237 mg of the titled product was obtained.

NMR (DMSO-d6, δ): 2.23 (s, 3H), 3.36 (br, -NH2, -NH), 3.66 (d, 2H), 4.67 (s, 2H), 4.84-5.17 (m, 2H and q, AB, 2H), 6.99-8.35 (m, 10H, aromatic H)

EXAMPLE 64

Preparation of N-(carbamoylmethyl)-2-(4-{[2-({[4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}phenoxy)acetamide

2-[[[(4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole sodium salt (190 mg) was dissolved in 20 ml of dichloromethane and 0.5 ml of triethylamine, and N-(carbamoylmethyl)-2-[4-(chlorosulfonyl)phenoxy]acetamide (160 mg) was added. The reaction mixture was stirred at room temperature for 24 hr. Dichloromethane (100 ml) was added to the reaction mixture. The reaction mixture was washed with saturated NaCl solution, and 0.1 N sodium bicarbonate solution. Dichloromethane layer was separated and dried over anhydrous magnesium sulfate. Dichloromethane was evaporated under reduced pressure to give syrupy material, which was lyophilized in vacuo. 215 mg of the titled product was obtained.

NMR (DMSO-d6, δ): 1.94-1.97 (m, 2H), 2.19 (s, 3H), 3.22 (s, 3H), 3.46 (t, 2H), 3.67 (d, 2H), 4.06 (t, 2H), 4.68 (s, 2H), 4.84-5.14 (q, AB, 2H), 6.85 (d, 1H), 7.21 (d, 2H), 7.42-7.55 (m, 2H), 7.80 (d, 1H), 7.91 (d, 1H), 8.02(d, 1H), 8.18(d, 2H)

EXAMPLE 65

Preparation of 1-[(benzotriazol-1-yl)methyl]- 5-methoxy-2-[[(3,5-dimethyl-4-

methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-[(benzotriazol-1-yl)methyl]- 6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole

5-Methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole (172 mg) was dissolved in 20 ml of dichloromethane. Sodium tert-butoxide (55 mg) and 1-(chloromethyl)-1H-benzotriazole (85 mg) was added. The reaction mixture was stirred at 30 °C for 3 days. TLC analysis (developing solvent; chloroform-methanol 15:1) showed major one spot of 1-[(benzotriazol-1-yl)methyl]- 5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole above 5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole. The titled product was purified by preparative thin layer chromatography. 195 mg of product, a mixture of 1-[(benzotriazol-1-yl)methyl]- 5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole and 1-[(benzotriazol-1-yl)methyl]- 6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole was obtained (3:2 ratio).

NMR ($CDCl_3$, δ): 2.21 (s, 3H), 2.24 (s, 3H), 3.70 (s, 3H), 3.79 & 3.86 (2s, total 3H), 4.85-5.08 (q, AB, 2H), 6.65 (d, 2H, N-CH_2-N), 6.89-8.12 (m, 8H)

EXAMPLE 66

Preparation of 1-[(benzotriazol-1-yl)methyl-2-[[[(4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole

2-[[[(4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole sodium salt (190 mg) was dissolved in 20 ml of dichloromethane. 1-(Chloromethyl)-1H-benzotriazole (85 mg) was added. The reaction mixture was stirred at 30 °C for 3 days. TLC analysis showed one spot of product. The reaction mixture was filtered. The filtrate was concentrated under reduced pressure, and treated with ethyl ether-heptane for precipitation. Precipitated solids were collected

and dried to give pure 1-[(benzotriazol-1-yl)methyl-2-[[[(4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (212 mg).

NMR ($CDCl_3$, δ): 2.05-2.08 (m, 2H), 2.21 (s, 3H), 3.34 (s, 3H), 3.54 (t, 2H), 4.08 (t, 2H), 4.86-5.16 (q, AB, 2H), 6.69-6.70 (d, 2H, N-CH_2-N), 7.00-8.15 (m, 10H)

EXAMPLE 67

Preparation of diethyl [5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]benzimidazol-1-yl]phosphate

5-Methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole (172 mg) was dissolved in 50 ml of dichloromethane and 0.5 ml of triethylamine. Diethyl chlorophosphate (87 mg) was added. The reaction mixture was stirred at room temperature for 18 hr. The reaction mixture was washed with saturated NaCl solution, and 0.1 N sodium bicarbonate solution twice times. Dichloromethane layer was separated and dried over anhydrous magnesium sulfate. Dichloromethane was evaporated under reduced pressure to give syrupy material, 215 mg of product. Syrupy product was slowly decomposed.

NMR ($CDCl_3$, δ): 1.28-1.38 (m, 6H), 2.10 (s, 3H), 2.19(s, 3H), 3.60 (s, 3H), 3.83 (s, 3H), 4.20-4.28 (m, 4H), 4.72-4.87 (q, AB, 2H), 6.91 (d, 1H), 7.7 (d, 1H), 7.92 (s, 1H), 8.18 (s, 1H)

CHEMICAL STABILITY

The chemical stability of the compounds of the invention has been followed kinetically at low concentration at 37 °C in a buffer solution composed of 0.2 M NaCl, 50 mM sodium phosphate, pH 7.4, 2% bovine albumin serum, 5-10% methanol. The compounds of Example 1 and Example 19 were measured to have a half-life ($t_{1/2}$) 3 hr ± 0.5 hr and 3.5 hr ± 0.3 hr, respectively. The compound of Example 1 has slightly higher solubility in aqueous buffer than the compound of Example 19. The solubility of these compounds was found to affect their rate of

hydrolysis.

Acid stability of the compounds was assayed in 95% methanol containing 0.1 N HCl. Approximately 90% of the compound of Example 1 was still present intact (without decomposition) after 2.25 hour in this solution.

BIOLOGICAL ASSAY

Inhibition of ATPase activity was measured using isolated hog gastric vesicles. The gastric H,K-ATPase (10 μg) was incubated at 37 °C in a solution (1 ml) composed of 0.25 M sucrose, 20 mM Pipes/Tris, pH 7.4, 0.15 M KCl, 2 mM $MgCl_2$, valinomycin 2 μg/ml, and various concentration of compounds of the invention. At timed intervals, ATP was added (up to 2 mM) and incubated for 15 minutes and amount of released phosphate ion was measured. As a control experiment the prior art drug without a labile group on the benzimidazole nitrogen (*e. g.* OMEPRAZOLE or LANSOPRAZOLE) was used for measuring inhibition of enzyme activity. Initially (before it underwent hydrolysis), the samples having 10, 20, 50, and 100 μM of the compound of Example 1 failed to inhibit enzyme activity. After 80 minutes however, the sample having 10 μM of the compound of Example 1 inhibited 10% and the sample having 50 μM inhibited 50%. In samples having 10 μM of OMEPRAZOLE (control) and 10 μM of the compound of Example 1, the same level of inhibition was obtained after 5.75 hours of hydrolysis.

RELATIVE PLASMA CONCENTRATION OF OMEPRAZOLE IN MALE RAT

Male adult rats of the Sprague-Dawley strain were used for determining the concentration of OMEPRAZOLE in the plasma. All rats were derived of food but not of water for one day. Example compounds (2 mg/kg of rat weight) were orally administrated to male rats (weighing 250 g to 270 g) and blood samples (0.3 ml) were taken at timed intervals. Blood samples were centrifuged and plasma was taken out. Plasma was extracted with 0.5 ml of dichloromethane. Dichloromethane layer was evaporated by nitrogen/air blowing. The residual materials were

dissolved in 0.5 ml of 40% acetonitrile in 10 mM phosphate buffer (pH 7.4). Amounts of OMEPRAZOLE were determined by HPLC analysis. As a control, OMEPRAZOLE (4 mg/kg of rat weight) was orally administrated.

TABLE 3 : Relative concentration of OMEPRAZOLE released in the plasma (arbitrary unit)

min	EXAMPLE 29	EXAMPLE 33	EXAMPLE 37	omeprazole
20	4.5	2.5	1.67	28
40	14	34	14.36	4
60	8.5	13	3.5	2
80	3.5	4	1.88	1
100	2.5	2	1.88	N/D*
120	1.875	2	1.5	N/D*
140	0.625	1.5	1.5	
160	0.6	1	1	
180	0.6	1	1	
210	1.5	1	0.7	
240	0.5	1	0.7	
270	0.5	0.5	0.7	
300	0.2	0.5	0.4	
330	0.1	0.3	0.2	
360	0.05	0.3	0.1	
390	N/D	0.2	0.1	
430		0.1	N/D	

* N/D : non-detectable.

TIME COURSES OF INHIBITORY EFFECT ON GASTRIC ACID SECRETION OF THE CONSCIOUS MALE RAT

Male rats (the Sprague-Dawley strain) are used. OMEPRAZOLE (2 mg) or Example 33 compound (1 mg) was resuspended in 1 ml of 15% sugar and 20 mM sodium phosphate buffer, pH 7.4. OMEPRAZOLE (2 mg/kg) or compound of Example 33 (1 mg/kg) was orally administrated. At timed intervals (2, 3.5, and 5

hr), the abdomen of the rat was incised and the pylorus was ligated under light ether anethesia. Histamine (2 mg/kg) was intravenously injected for acid stimulation. Immediately the abdomen was closed. One hour later, the stomach was removed after ligation of the esophagus. The gastric juice was collected and acid output was quantified by titration using 0.1 N NaOH solution. As a control experiment, 1 ml of 15% sugar and 20 mM phosphate buffer solution was orally administrated without any compounds (inhibitors). Acid output was quantified by same method as described above, showing maximum histamine-stimulated gastric acid secretion. Percentage inhibition was calculated from the fractional responses elicited by test compound and a control experiment. Further calculations are base. on group mean responses from 3-4 rats.

TABLE 4: Inhibition of gastric acid secretion at the timed intervals

Time course	OMEPRAZOLE (2 mg/kg, p.o.)	Example 33 (1 mg/kg, p.o.)
2 hr	90 %	84 %
3.5 hr	46 %	71 %
5 hr	45 %	91 %

The compound of Example 33 showed long duration of inhibition compared to OMEPRAZOLE. Maximum inhibition by the compound of Example 33 was obtained after 5 hours, which shows that the compound of the invention is continuously converted to the corresponding PPI in vivo and inhibits gastric acid secretion.

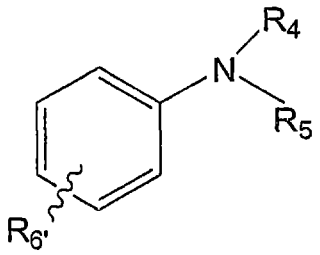
WHAT IS CLAIMED IS :

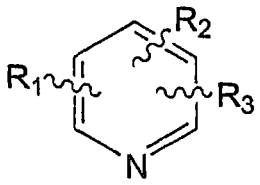
1. A compound of the formula

$$Het_1 - X - S(O) - Het_2$$

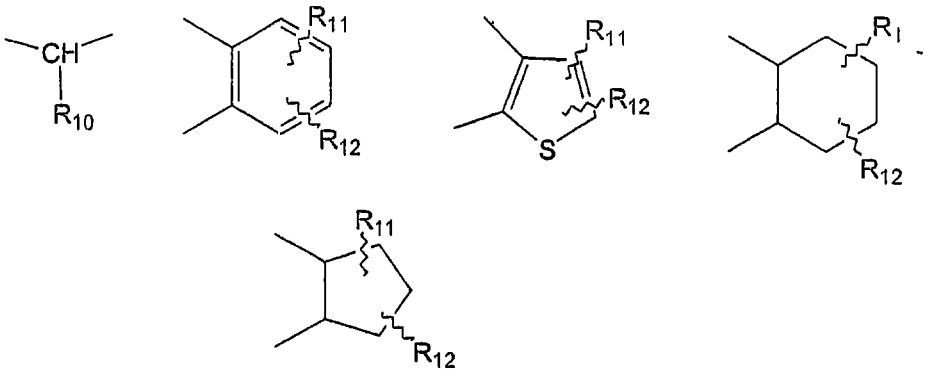
wherein

Het_1 is selected from the group consisting of the structures shown by the formulas below

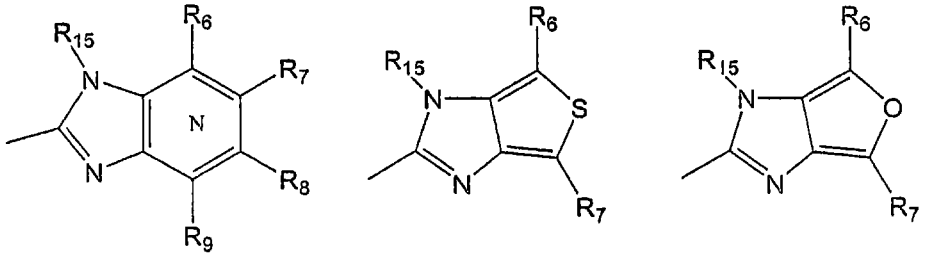




X is selected from the group consisting of the structures shown by the formulas below



and Het_2 is selected from the group consisting of the structures shown by the formulas below



where N in the benzimidazole moiety represents that one of the ring carbons may be exchanged for an unsubstituted N atom;

R_1, R_2 and R_3 are independently selected from hydrogen, alkyl of 1 to 10 carbons, fluoro substituted alkyl of 1 to 10 carbons, alkoxy of 1 to 10 carbons, fluoro substituted alkoxy of 1 to 10 carbons, alkylthio of 1 to 10 carbons, fluoro substituted alkylthio of 1 to 10 carbons, alkoxyalkoxy of 2 to 10 carbons, amino, alkylamino and dialkylamino each of the alkyl groups in said alkylamino and dialkyl amino groups having 1 to 10 carbons, halogen, phenyl, alkyl substituted phenyl, alkoxy substituted phenyl, phenylalkoxy, each of the alkyl groups in said alkyl substituted phenyl, alkoxy substituted phenyl and phenylalkoxy having 1 to 10 carbons, piperidino, morpholino or two of the R_1, R_2 and R_3 groups jointly forming a 5 or 6 membered ring having 0 or 1 heteroatom selected from N, S and O;

R_4 and R_5 are independently selected from hydrogen, alkyl of 1 to 10 carbons, fluoro substituted alkyl of 1 to 10 carbons, phenylalkyl, naphthylalkyl and heteroarylalkyl, alkyl in said phenylalkyl, naphthylalkyl and heteroarylalkyl groups having 1 to 10 carbons;

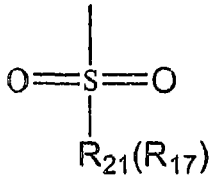
$R_{6'}$ is hydrogen, halogen, alkyl of 1 to 10 carbons, fluoro substituted alkyl of 1 to 10 carbons, alkoxy having 1 to 10 carbons or fluoro substituted alkoxy having 1 to 10 carbons;

R_6 through R_9 are independently selected from hydrogen, alkyl of 1 to 10 carbons, halogen substituted alkyl of 1 to 10 carbons, alkoxy of 1 to 10 carbons, halogen substituted alkoxy of 1 to 10 carbons, alkylcarbonyl, alkoxycarbonyl the alkyl group in said alkylcarbonyl and alkoxycarbonyl having 1 to 10 carbons, oxazolyl, imidazolyl, thiazolyl, pyrazolyl, or any two adjacent ones of the R_6 through R_9 groups may form a ring that may optionally include a heteroatom selected from N, O and S;

R_{10} is hydrogen, alkyl of 1 to 10 carbons;

R_{11} and R_{12} are independently selected from hydrogen, halogen, alkyl of 1 to 10 carbons and halogen substituted alkyl of 1 to 10 carbons;

R_{15} has the formula below



where

R_{17} is alkyl of 1 to 10 carbons, halogen substituted alkyl of 1 to 10 carbons, alkoxy having 1 to 10 carbons, halogen substituted alkoxy of 1 to 10 carbons, alkylthio having 1 to 10 carbons, halogen substituted alkylthio of 1 to 10 carbons, alkoxy carbonyl having 1 to 10 carbons, halogen substituted alkoxy carbonyl having 1 to 10 carbons, F, Cl, Br, I, NO_2 , CN, OCOalkyl, NH_2 , alkylamino and dialkylamino where in said OCOalkyl, alkylamino and dialkylamino groups each of said alkyl group has 1 to 10 carbons, carbamoyl, N-substituted carbamoyl, alkylcarbonyl having 1 to 10 carbons, (alkoxycarbonyl)alkoxy groups of each of said alkoxy group has 1 to 10 carbons, (alkoxycarbonyl)alkyl groups of each of said alkoxy or alkyl group has 1 to 10 carbons, (carbamoyl)alkoxy having 1 to 10 carbons, (N-alkylcarbamoyl)alkoxy having 1 to 10 carbons, (N,N-dialkylcarbamoyl)alkoxy having 1 to 10 carbons, (N-substituted or unsubstituted carbamoyl)poly(alkoxy) having 1 to 10 carbons, (N-substituted or unsubstituted carbamoyl)alkyl having 1 to 10 carbons, [N-(heteroaryl)carbamoyl]alkyl having 1 to 10 carbons, [N-(heteroaryl)carbamoyl]alkoxy having 1 to 10 carbons, [N-(substituted heteroaryl)carbamoyl]alkoxy having 1 to 10 carbons, [N-(substituted aryl)carbamoyl]alkoxy having 1 to 10 carbons, poly(alkoxy) group of each of said alkoxy group has 1 to 10 carbons, cyclic polyalkoxy, guanidinyl group, ureido group, dialkylamino-poly(alkoxy) group, [N-(carbamoylalkyl)carbamoyl]alkoxy, [N-(carbamoylalkyl)carbamoyl]alkyl, [N-[[N-(heteroaryl) carbamoyl]alkyl]carbamoyl]alkoxy, [N-[[N-(substituted heteroaryl) carbamoyl]alkyl]carbamoyl]alkoxy, (sulfonato)alkyl, (sulfonato)alkoxy, N-[sulfonato)alkyl]amido, (substituted)maleimido-, (substituted)succinimido [(tri-alkyl)ammonium]-alkoxy, and

R_{21} is (aryl)alkyl, (heteroaryl)alkyl, phenyl, naphthyl or heteroaryl where

heteroaryl has 1 to 3 heteroatoms independently selected from N, O and S, said phenyl, naphthyl or heteroaryl groups being unsubstituted or substituted with 1 to 5 R_{17} groups,

or to a pharmaceutically acceptable salt of said compound.

2. A compound in accordance with Claim 1 where $\mathbf{Het_1}$ represents a substituted pyridyl group.

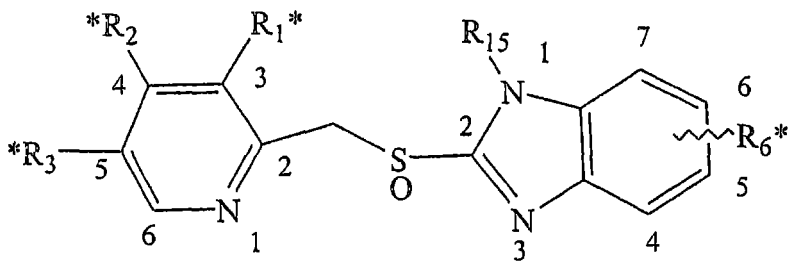
3. A compound in accordance with Claim 1 where $\mathbf{Het_2}$ represents a a susbtituted benzimidazole group.

4. A compound in accordance with Claim 1 where **X** represents a CH_2 group.

5. A compound in accordance with Claim 1 where $\mathbf{R_{21}}$ is phenyl, pyridyl, thiophenyl, thiazolyl, or imidazolyl.

07 FEB 2003

6. A compound of the formula



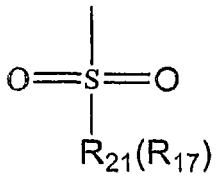
wherein R_1* is methyl, methoxy or chloro;

R_2* is methoxy, 2,2,2-trifluoroethoxy, 4-morpholino, ethylthio, (2,2,3,3,4,4,4-heptafluoroctyl)oxy; or $CH_3O(CH_2)_3O$;

R_3* is H or methyl;

R_6* is H, methoxy or difluoromethoxy group in the 5 or in the 6 position of the benzimidazole moiety; and

R_{15} has the formula below



where

R_{17} is alkyl of 1 to 10 carbons, halogen substituted alkyl of 1 to 10 carbons, alkoxy having 1 to 10 carbons, halogen substituted alkoxy of 1 to 10

carbons, alkylthio having 1 to 10 carbons, halogen substituted alkylthio of 1 to 10 carbons, alkoxy carbonyl having 1 to 10 carbons, halogen substituted alkoxy carbonyl having 1 to 10 carbons, F, Cl, Br, I, NO_2 , CN, OCOalkyl, NH_2 , alkylamino and dialkylamino where in said OCOalkyl, , alkylamino and dialkylamino groups each of said alkyl group has 1 to 10 carbons, further R_{17} is carbamoyl, N-substituted carbamoyl, alkylcarbonyl having 1 to 10 carbons, (alkoxycarbonyl)alkoxy groups of each of said alkoxy group has 1 to 10 carbons, (alkoxycarbonyl)alkyl groups of each of said alkoxy or alkyl group has 1 to 10 carbons, (carbamoyl)alkoxy having 1 to 10 carbons, (N-alkylcarbamoyl)alkoxy having 1 to 10 carbons, (N,N-dialkylcarbamoyl)alkoxy having 1 to 10 carbons, (N-substituted or unsubstituted carbamoyl)poly(alkoxy) having 1 to 10 carbons, (N-substituted or unsubstituted carbamoyl)alkyl having 1 to 10 carbons, [N-(heteroaryl)carbamoyl]alkyl having 1 to 10 carbons, [N-(heteroaryl)carbamoyl]alkoxy having 1 to 10 carbons, [N-(substituted heteroaryl)carbamoyl]alkoxy having 1 to 10 carbons, [N-(substituted aryl)carbamoyl]alkoxy having 1 to 10 carbons, poly(alkoxy) group of each of said alkoxy group has 1 to 10 carbons, cyclic polyalkoxy, guanidinyl group, ureido group, dialkylamino-poly(alkoxy) group, [N-(carbamoylalkyl)carbamoyl]alkoxy, [N-(carbamoylalkyl)carbamoyl]alkyl, [N-[[N-(heteroaryl) carbamoyl]alkyl]carbamoyl]alkoxy, [N-[[N-(substituted heteroaryl) carbamoyl]alkyl]carbamoyl]alkoxy, [(tri-alkyl)ammonium]-alkoxy, (sulfonato)alkyl, (sulfonato)alkoxy, N-[sulfonato)alkyl]amido, (substituted)maleimido-, (substituted)succinimido, and

R_{21} is (aryl)alkyl, (heteroaryl)alkyl, phenyl, naphthyl or heteroaryl having 1 to 3 heteroatoms indpendently selected from N, O and S, said phenyl, naphthyl or heteroaryl groups being unsubstituted or substituted with 1 to 5 R_{17} groups,

or to a pharmaceutically acceptable salt of said compound.

7. A compound in accordance with Claim 6 where $\mathbf{R_{21}}$($\mathbf{R_{17}}$) is phenyl, thienyl or pyridyl, substituted or unsubstituted with the $\mathbf{R_{17}}$ group.

8. A compound in accordance with Claim 7 where $\mathbf{R_{17}}$ is selected from Cl, Br, F, lower alkyl, lower alkoxy, trifluoromethyl, trifluoromethoxy, di-(lower alkyl)amino, lower alkoxycarbonyl, carbamoyl, guanidinyl, ureido, (carbamoyl)alkoxy, [N-(heteroaryl)carbamoyl]alkoxy, morpholinyl, (morpholin-4-yl)alkoxy, [(morpholin-4-yl)alkoxy]alkoxy, (di-(lower

07 FEB 2003

alkyl)amino)alkoxy, [N-[(carbamoyl) alkyl]carbamoyl]alkoxy, poly(alkoxy), sodium(sulfonato)alkoxy, (trimethylammonium)alkoxy, and cyclic tetra- or penta-ethyleneoxy wherein the terms lower alkyl and lower alkoxy each define groups having 1 to 6 carbons.

9. A compound in accordance with Claim 7 where R_{21} is unsubstituted or where R_{17} is selected from Cl, Br, F, lower alkyl, lower alkoxy, trifluoromethyl, di-(lower alkyl)amino, lower alkoxycarbonyl, carbamoyl, guanidinyl, ureido, (carbamoyl)methoxy, [N-(pyridyl)carbamoyl]methoxy, morpholinyl, (morpholin-4-yl)alkoxy, [(morpholin-4-yl)alkoxy]alkoxy, 2-(dimethylamino)ethoxy, [N-[(carbamoyl) methyl]carbamoyl]methoxy, poly(alkoxy), and cyclic tetra- or penta-ethyleneoxy group wherein the terms lower alkyl and lower alkoxy each define groups having 1 to 6 carbons.

10. A compound in accordance with Claim 6, selected from the group consisting of:

1-benzenesulfonyl-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,

1-benzenesulfonyl-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,

1-benzenesulfonyl-5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,

1-benzenesulfonyl-6-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,

1-benzenesulfonyl-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole,

1-(p-chlorobenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,

1-(p-chlorobenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,

1-(p-chlorobenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,

1-(p-chlorobenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,

1-(p-chlorobenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole,

07 FEB 2003

1-(p-bromobenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-bromobenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-bromobenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-bromobenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-bromobenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-fluorobenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-fluorobenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-fluorobenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-fluorobenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-fluorobenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-methylbenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-methylbenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-methylbenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-methylbenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-methylbenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-methoxybenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-methoxybenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,

1-(p-methoxybenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl) methylsulfinyl]-1H-benzimidazole,
1-(p-methoxybenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl) methylsulfinyl]-1H-benzimidazole,
1-(p-methoxybenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-pyridyl) methylsulfinyl]-1H-benzimidazole,
1-(3-trifluoromethylbenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-p yridyl)methylsulfinyl]-1H-benzimidazole,
1-(3-trifluoromethylbenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-p yridyl)methylsulfinyl]-1H-benzimidazole,
1-(3-trifluoromethylbenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyr idyl)methylsulfinyl]-1H-benzimidazole,
1-(3-trifluoromethylbenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-pyr idyl)methylsulfinyl]-1H-benzimidazole,
1-(3-trifluoromethylbenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-p yridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-trifluoromethoxybenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-trifluoromethoxybenzenesulfonyl)-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-trifluoromethoxybenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-p yridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-trifluoromethoxybenzenesulfonyl)-6-difluoromethoxy-2-[(3,4-dimethoxy-2-p yridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-trifluoromethoxybenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-dimethylaminobenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-p yridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-dimethylaminobenzenesulfonyl)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyr idyl)methylsulfinyl]-1H-benzimidazole,
1-(p-dimethylaminobenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-p yridyl)methylsulfinyl]-1H-benzimidazole,
1-(p-ethoxycarbonylbenzenesulfonyl)-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-p yridyl)methylsulfinyl]-1H-benzimidazole,

1-(p-ethoxycarbonylbenzenesulfonyl)-2-[(3-methyl-4-(2',2',2'-trifluoroethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-(pyridine-3-sulfonyl)-5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-(pyridine-3-sulfonyl)-6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-(pyridine-3-sulfonyl)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole,
1-(pyridine-3-sulfonyl)-5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-(pyridine-3-sulfonyl)-6-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-[4-[(morpholin-4-yl)phenyl]sulfonyl]-5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-[4-[(morpholin-4-yl)phenyl]sulfonyl]-6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
N-[4-[[5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]benzimidazol-1-yl]sulfonyl]phenyl]urea,
N-[4-[[6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]benzimidazol-1-yl]sulfonyl]phenyl]urea,
N-(4-{[2-({[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}phenyl)urea,
N-(4-{[2-({[4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}phenyl)urea,
N-(4-{[2-{[(3,4-di(methoxy)-2-pyridyl)methyl]sulfinyl}-5-(difluoromethoxy)-benzimidazol-1-yl]sulfonyl}phenyl)urea,
N-(4-{[2-{[(3,4-di(methoxy)-2-pyridyl)methyl]sulfinyl}-6-(difluoromethoxy)-benzimidazol-1-yl]sulfonyl}phenyl)urea,
15-{[2-({[4-(3-methoxypropoxy-3-methyl-2-pyridyl]methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}-1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene
15-{[2-({[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}-1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene
15-[(5-methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl}benzimi

dazol-1-yl)sulfonyl]-
1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene
15-[(6-methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl}benzimi
dazol-1-yl)sulfonyl]-
1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene
15-[(5-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl}benzimi
dazol-1-yl)sulfonyl]-
1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene
15-[(6-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl}benzimi
dazol-1-yl)sulfonyl]-
1,2,3,4,5,6,7,8,9,10,11,12,13-tridecahydrobenzo[a][15]annulene
2-{4-[(5-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl}benzi
midazol-1-yl)sulfonyl]phenoxy}acetamide,
2-{4-[(5-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl}benzi
midazol-1-yl)sulfonyl]phenoxy}-N-(2-pyridyl)acetamide,
N-(carbamoylmethyl)-2-{4-[(5-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-pyridyl)
methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}acetamide,
2-{4-[(6-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl}benzi
midazol-1-yl)sulfonyl]phenoxy}acetamide,
2-{4-[(6-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl}benzi
midazol-1-yl)sulfonyl]phenoxy}-N-(2-pyridyl)acetamide,
N-(carbamoylmethyl)-2-{4-[(6-methoxy-2-{[(3,5-dimethyl-4-methoxy-2-pyridyl)
methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}acetamide,
2-(4-{[2-({[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl}sulfinyl)benzimi
dazol-1-yl]sulfonyl}phenoxy)acetamide,
2-(4-{[2-({[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl}sulfinyl)benzimi
dazol-1-yl]sulfonyl}phenoxy)-N-(2-pyridyl)acetamide,
N-(carbamoylmethyl)-2-(4-{[2-({[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]m
ethyl}sulfinyl)benzimidazol-1-yl]sulfonyl}phenoxy)acetamide,
2-{4-[(5-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl}benzi
midazol-1-yl)sulfonyl]phenoxy}acetamide,
2-{4-[(5-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl}benzi
midazol-1-yl)sulfonyl]phenoxy}-N-(2-pyridyl)acetamide,
N-(carbamoylmethyl)-2-{4-[(5-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-pyridyl)

methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}acetamide,
2-{4-[(6-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}acetamide,
2-{4-[(6-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}-N-(2-pyridyl)acetamide,
N-(carbamoylmethyl)-2-{4-[(6-(difluoromethoxy)-2-{[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl}benzimidazol-1-yl)sulfonyl]phenoxy}acetamide,
2-(4-{[2-({[4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}phenoxy)acetamide,
2-(4-{[2-({[4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}phenoxy)-N-(2-pyridyl)acetamide,
N-(carbamoylmethyl)-2-(4-{[2-({[4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methyl}sulfinyl)benzimidazol-1-yl]sulfonyl}phenoxy)acetamide,
1-[[4-{3-(morpholin-4-yl) propoxy}
phenyl]sulfonyl]-5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-[[4-{3-(morpholin-4-yl) propoxy}
phenyl]sulfonyl]-6-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-[[4-{3-(morpholin-4-yl) propoxy}
phenyl]sulfonyl]-5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-[[4-{3-(morpholin-4-yl) propoxy}
phenyl]sulfonyl]-6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-[[4-{3-(morpholin-4-yl) propoxy}
phenyl]sulfonyl]-2-[(3-methyl-4-methoxypropoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-[[4-{3-(morpholin-4-yl) propoxy}
phenyl]sulfonyl]-2-[(3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl)methylsulfinyl]-1H-benzimidazole,
1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-2-[[[(4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole,
1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-5-(difluoromethoxy)-2-[[(3,4-di

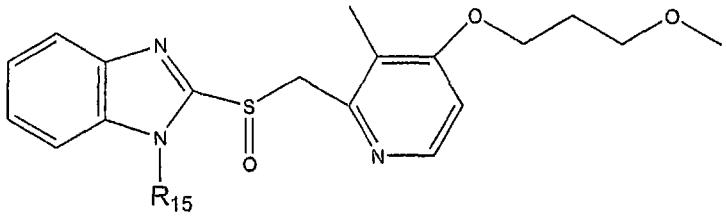
07 FEB 2003

methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]]-1H-benzimidazole,
1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-6-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]]-1H-benzimidazole,
1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-
2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole,
1-[{(N,N-dimethylamino)methyl}benzene-4-sulfonyl]-5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-[2-acetamido-4-methyl-5-thiazolylsulfonyl]-5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-(thiophene-2-sulfonyl)-5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-[{(N,N-dimethylamino)methyl}benzene-4-sulfonyl]-6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-[2-acetamido-4-methyl-5-thiazolylsulfonyl]-6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-(thiophene-2-sulfonyl)-6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-(thiophene-2-sulfonyl)-2-[[[(4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole,
1-(thiophene-2-sulfonyl)-
5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-(thiophene-2-sulfonyl)-
6-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-(thiophene-2-sulfonyl)-]-
2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole,
1-(phenylmethylsulfonyl)-5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)met

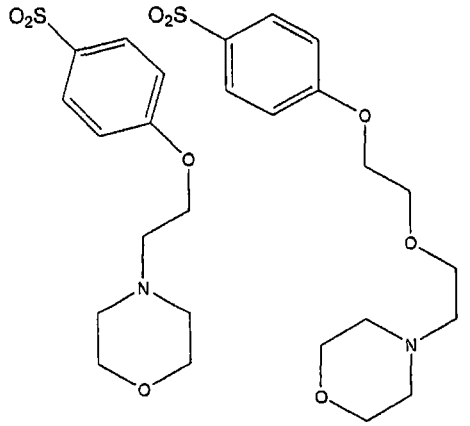
hyl]sulfinyl]-1H-benzimidazole,
1-[(N,N-dimethylamino)benzene-4-sulfonyl]-5-methoxy-2-[[(3,5-dimethyl-4-meth oxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-(phenylmethylsulfonyl)-6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)met hyl]sulfinyl]-1H-benzimidazole,
1-[(N,N-dimethylamino)benzene-4-sulfonyl]-6-methoxy-2-[[(3,5-dimethyl-4-meth oxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-(pyridine-3-sulfonyl)-2-[[(3-methyl-4-methoxypropoxy-2-pyridyl)methyl]sulfin yl]-1H-benzimidazole,
1-[4-(morpholin-4-yl)phenylsulfonyl]-2-[[[(4-(3-methoxypropoxy)-3-methyl-2-py ridyl]methyl]sulfinyl]-1H-benzimidazole,
1-benzenesulfonyl-2-[[(3-chloro-4-morpholino-2-pyridyl)methyl]sulfinyl]-5-meth oxy-(1H)-benzimidazole,
1-benzenesulfonyl-2-[[[(4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfin yl]-1H-benzimidazole,
1-benzenesulfonyl-2-[(3-methoxyphenyl)methylsulfinyl]-1H-benzimidazole,
1-benzenesulfonyl-2-[(3-methoxyphenyl)methylsulfinyl]imidazolo[5,4-c]pyridine,
1-benzenesulfonyl-2-[(3-methoxyphenyl)methylsulfinyl]imidazolo[4,5-c]pyridine,
1-benzenesulfonyl-2-[(3-methoxyphenyl)methylsulfinyl]-5-nitro-benzimidazole,
1-benzenesulfonyl-2-[{2-(dimethylamino)phenyl}methylsulfinyl]-1H-benzimidaz ole,
1-benzenesulfonyl-2-[[[4-(2,2,3,3,4,4,4-heptafluorobutyl)oxy]-2-pyridyl]methyl]s ulfinyl]-1H-thieno[3,4-d]imidazole,
1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-
2-[(3-methoxyphenyl)methylsulfinyl]imidazolo{5,4-c]pyridine,
1-[4-[2-(morpholin-4-yl)ethoxy]phenylsulfonyl]-
2-[{2-(dimethylamino)phenyl}methylsulfinyl]-1H-benzimidazole,
1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-
5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimid azole,
1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-
6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimid azole,
1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-2-[[[(4-(3-methoxypr

opoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole,
1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-6-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-[[2-{2-(morpholin-4-yl)ethoxy}ethoxy]phenyl-4-sulfonyl]-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole,
1-(4-acetaminobenzenesulfonyl)-5-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole,
1-(4-acetaminobenzenesulfonyl)-6-methoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole.

11. A compound of the formula

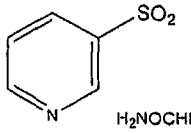


where R_{15} is selected from the groups (1) through (9) shown below:

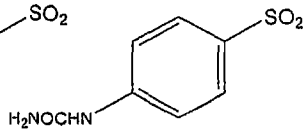


(1)

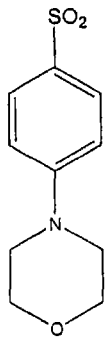
(2)



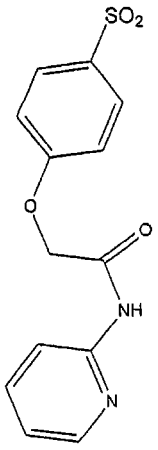
(3)



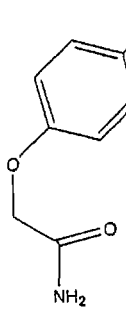
(4)



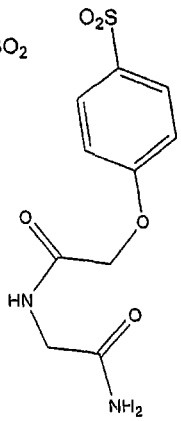
(5)



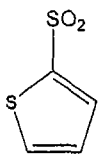
(6)



(7)

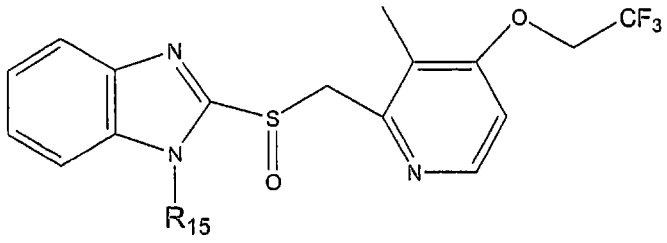


(8)

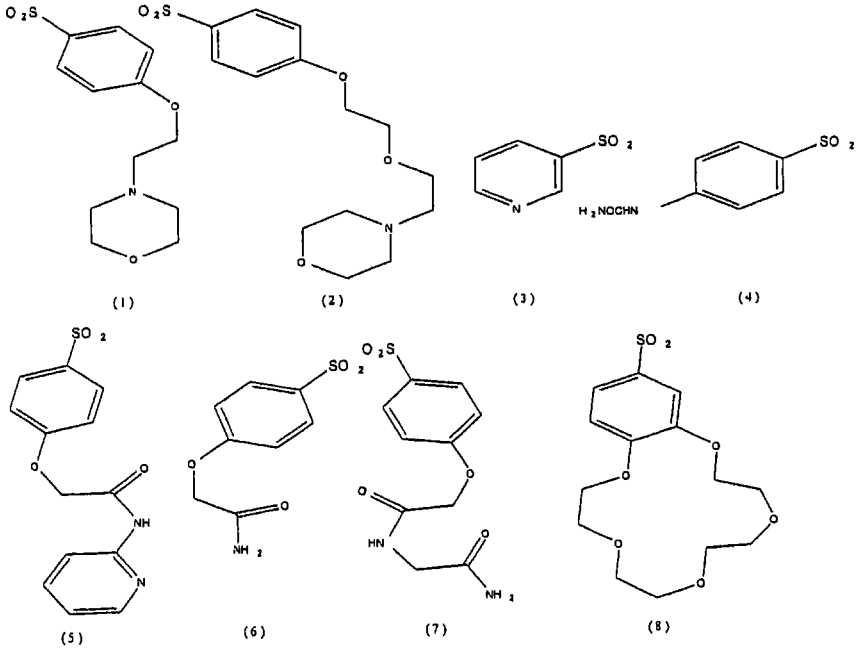


(9)

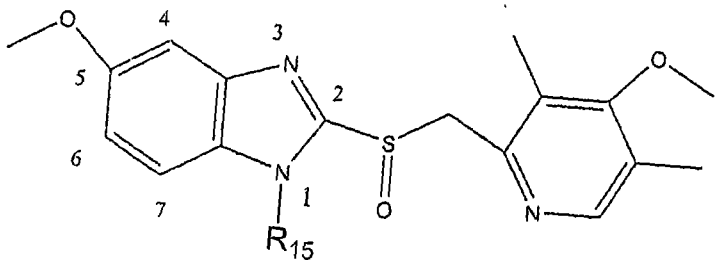
12. A compound of the formula



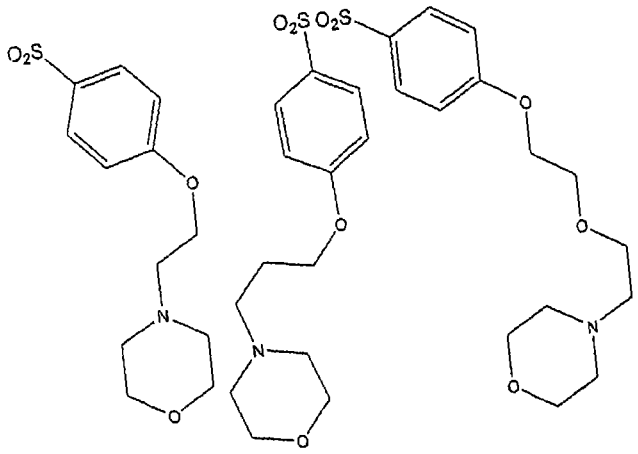
where R_{15} is selected from the groups (1) through (8) shown below:



13. A compound of the formula



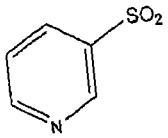
where $\mathbf{R}_{15}$ is selected from the groups (1) through (15) shown below:



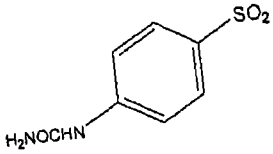
(1)

(2)

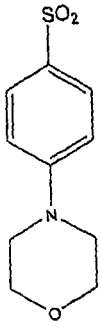
(3)



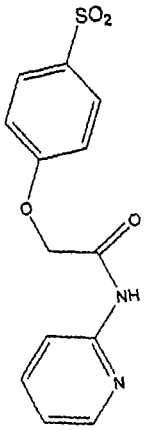
(4)



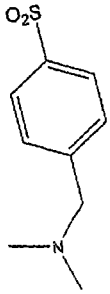
(5)



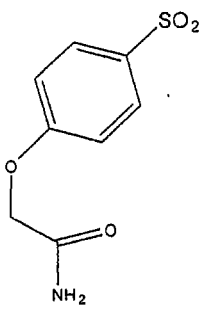
(6)



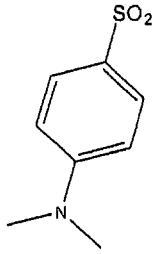
(7)



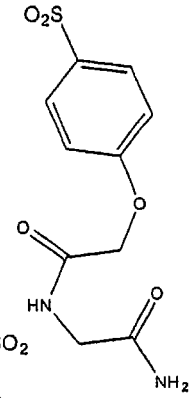
(8)



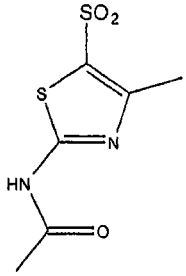
(9)



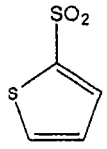
(10)



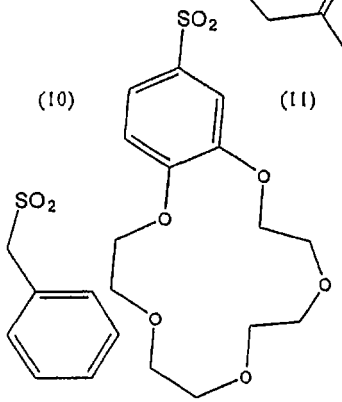
(11)



(12)



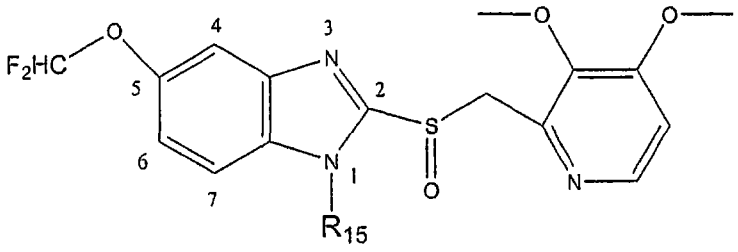
(13)



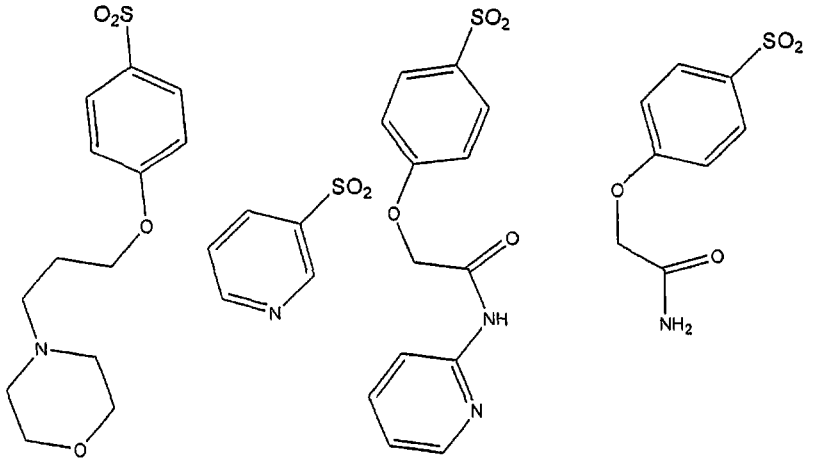
(14) (15)

and isomers of the compounds of the formula where the R_{15} group is linked to the nitrogen in the 3-position of the benzimidazole ring.

14. A compound of the formula



where $\mathbf{R_{15}}$ is selected from the groups (1) through (4) shown below:



(1) (2) (3) (4)

and isomers of the compounds of the formula where the $\mathbf{R_{15}}$ group is linked to the nitrogen in the 3-position of the benzimidazole ring.

15. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a prodrug of a proton pump inhibitor in accordance with Claim 1.

16. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a prodrug of a proton pump inhibitor in accordance with Claim 6.

17. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a prodrug of a proton pump inhibitor in accordance with Claims 10, 11, 12, 13 or 14.

18. A pharmaceutical composition in accordance with Claims 10, 11, 12, 13, 14, 15, 16, or 17, said composition comprising a liquid adapted for injection to a mammal, said liquid having a pH not exceeding 8.5 pH units.