PROTON PUMP INHIBITOR

Field of the Invention

This invention relates to novel chemical compounds having pharmaceutical utility. More particularly, it relates to novel heterocyclic chemical compounds useful in the treatment of peptic ulcers in mammals, to methods for their synthesis and to compositions and uses thereof in peptic ulcer treatment in mammals.

Background of the Invention and Prior Art

Peptic ulcers are one of the most prevalent diseases in industrialized nations. Control of gastric acid secretion is the main therapy for peptic ulcers. Acid secretion is in turn brought about by the interaction of three physiological stimulants, gastrin, acetylcholine and histamine with their respective parietal cell receptors. Prior to the discovery of histamine H_2-receptor antagonists such as cimetidine and ranitidine, peptic ulcer treatment consisted of antacid therapy and anticholinergic drugs (eg. dicyclomine HCl). However, with the advent of H_2-receptor antagonists, treatment with anticholinergic agents has been largely supplanted by histamine H_2-receptor antagonist therapy. The development of this class of therapeutic entities presents one of the most important advances in the field of medicinal chemistry.

Another major development in the treatment of peptic ulcers has been realized with the introduction of H^+/K^+-ATPase inhibitors e.g. omeprazole. The enzyme H^+/K^+ - ATPase, which is also known as the proton pump, is located in the membrane of gastric parietal cells and is responsible for the transport of protons from blood to lumen, which in turn results in decreasing the pH of stomach contents which leads to aggravation of peptic ulcers.

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Omeprazole itself is in fact a prodrug which under acidic conditions converts to the active drug, namely its corresponding sulfenamide. The mechanism of action of omeprazole is well-studied and is known to involve a nucleophilic attack of one (or two) thiol group(s) of the H^+/K^+-ATPase on the sulfur atom of the chemically active sulfenamide. The resulting chemical modification of the thiol group(s) of the enzyme (formation of a disulfide bond between the H^+/K^+-ATPase sulfur and the sulfur of the benzimidazole pyridinium salt) causes the observed inhibition of the proton pump. The complex cascade of molecular events that lead to the inhibition of the H^+/K^+-ATPase is shown in Figure 1.

As shown in Figure 1, the presence of acid is a prerequisite to the conversion of omeprazole to its chemically active sulfenamide. However, the resulting sulfenamide is a labile molecule which transforms further to a number of other compounds that are unreactive to nucleophilic attack by the H^+/K^+-ATPase thiol(s) and are therefore incapable of inhibiting the enzyme. These transformations are acid catalyzed. Accordingly, in a strict chemical sense, while acid is a prerequisite for the conversion of omeprazole to its active form, it also acts to its detriment. As a partial solution to this problem, omeprazole drug products are formulated to resist the acidic medium of the stomach by enteric coating. The coating is dissolved in the relatively neutral environment of the duodenum and omeprazole is absorbed into the blood stream which carries the prodrug to the proton pump. It should be emphasized however, that the conversion of the prodrug to the active enzyme inhibitor can only be achieved in acidic media which also results in substantial degradation of the active sulfenamide. In summary, the instability of omeprazole in acidic environments, which is a prerequisite to its activation into a proton pump inhibitor, is the major shortcoming of this drug.

Acid instability of omeprazole not only decreases the bioavailability of the drug, but also creates considerable difficulty in its formulation, adding to the cost of the final drug product.

These inherent problems are also observed in the large number of omeprazole analogues that have been synthesized to increase the acid stability of their corresponding sulfenamide. Two factors contribute to the instability of omeprazole in acidic media. First, as observed with other sulfoxides, omeprazole undergoes a characteristic acid catalyzed degradation known as the Pummerer rearrangement. Second, protonation of the trivalent nitrogen of sulfenamide followed by nucleophilic attack on the sulfur atom is another characteristic reaction of these compounds. Enzyme inhibition is observed only when the H^+/K^+-ATPase-S- acts as the nucleophile. On the other hand, sulfenamide degradation is caused when Cl- acts as the nucleophile. Accordingly, any slight gain in acid stability of the sulfenamide (or sulfoxide) that may be introduced by chemical modification (resistance to Cl- attack) is offset by a decrease in reactivity of the analogue to H^+/K^+-ATPase-S- attack. The net result is a less effective drug.

Another shortcoming of omeprazole is its variability of action in different patients. There is clinical evidence of a variable response to omeprazole as determined by inhibition of gastric acid release in peptic ulcer patients, attributable to a high first pass effect for the biotransformation of omeprazole, and the fact that the metabolism of omeprazole appears to be under polymorphic genetic control, resulting in variable amounts of drug reaching the systemic circulation following a given dose.

Summary of the Invention

It is an object of the present invention to provide novel pharmaceutical compounds, and compositions containing them, which are active as H^+/K^+-ATPase inhibitors, and hence useful in the treatment of peptic ulcers in mammals.

It is a further object of the invention to provide methods for the synthesis of such compounds.

The present invention is based upon the discovery of a class of new chemical compounds that are effective as H^+/K^+-ATPase inhibitors and are also acid stable. The new chemical compounds of the invention are characterized by an imidazo[1,2-*d*]-thiadiazole nucleus, with different substituents attached to the 3-position of the thiadiazolo heterocyclic ring structure.

Thus according to one aspect of the present invention, there are provided various 3-substituted 1,2,4-thiadiazolo[4,5-a]benzimidazole compounds and imidazo[1,2-*d*]-1,2,4-thiadiazole compounds corresponding to the general formula I:

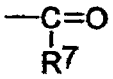


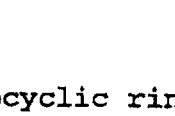
The groups represented by X and Z can be chosen from a wide variety of independent chemical groupings (hydrogen, lower alkyl, halo, nitro, amino, hydroxy, lower alkoxy, lower alkylamino, lower dialkylamino, etc) as more fully described hereinafter, to provide imidazo[*1,2-d*]-1,2,4-thiadiazoles. Alternatively, X and Z taken together can represent a benzene ring fused to the imidazo ring to

form 1,2,4-thiadiazolo[4,5-a]benzimidazole compounds, with the benzene ring thereof being optionally substituted with up to four substituents independently selected from a wide variety of chemical groupings (hydrogen, lower alkyl, halo, nitro, amino, hydroxy, lower alkoxy, lower alkylamino, lower dialkylamino, etc).

The group Y at the 3-position of the thiadiazole nucleus is generally an electron withdrawing group, and can be any of the following groups:

(1) groups of the formula:



in which R^7 represents hydrogen, hydroxy, lower alkyl, lower cycloalkyl, lower alkoxy, lower alkenyl, lower alkynyl, aryl, lower arylalkyl, heterocyclyl, hetero-cyclyloxy, heterocyclyl-lower alkylene, a group NR'R" where R' and R" are independently selected from hydrogen, lower alkyl, aryl and lower arylalkyl, or R' and R" when taken together form with the N-atom a five or six membered heterocyclic ring  wherein n = 4 or 5; and a group ANR'R", AOR wherein A is an amino acid residue or a peptide of 2 to 3 amino acid residues and R', R" have the same definition as above

(2) heterocyclyl, lower alkylene-heterocyclyl, lower alkylene-amino-heterocyclyl or amino-heterocyclyl, the heterocyclic ring being attached at any heteroatom or carbon atom which results in the creation of a stable structure, and the heterocyclic ring being optionally substituted with 1-3 substituents selected from lower alkyl; hydroxy; nitro; amino; lower alkylamino; di-lower alkylamino; lower alkoxy; lower alkyl substituted with 1-3

substituents s elected from hydroxy, lower alkylcarbamoyl, phenyl, halophenyl, heterocyclyl, carboxy and lower alkoxycarbonyl; lower acyl; lower alkocycarbonyl; lower alkyl-sulfonyl; amido; allyl; benzyl; phenyl optionally substituted with amino, halo hydroxy, lower alkoxy, lower alkyl, lower alkylamino or di-lower alkylamino; heterocyclyl optionally substituted with 1-3 substituents selected from nitro, hydroxy, lower alkoxy, lower alkyl, amino, halo, lower alkylamino, di-lower alkylamino; with the proviso that the heterocyclyl group Y is not 1-imidazolyl or substituted 1-imidazolyl;

(3) NR'R" or $-CH_2-NR'R"$ wherein R', R" have the same definition as above;

(4) ANR'R", AOR wherein A is an amino acid residue or a peptide of 2 to 3 amino acid residues and R', R" have the same definition as above

(5) lower 2-(alkoxycarbonyl)alkyl

(6) halo

(7) groups of formula R^8-CHOH- wherein R^8 is hydrogen, lower alkyl, aryl, lower arylalkyl, lower cycloalkyl, lower alkenyl, lower alkynyl or heterocyclyl, the heterocyclic ring being attached at any heteroatom or carbon atom which results in the creation of a stable structure,

(8) groups of formula R^9-C(=NOR^{10})- wherein R^{10} is hydrogen lower alkyl or lower arylalkyl, and R^9 is lower alkyl, aryl, lower arylalkyl, lower cycloalkyl, lower alkenyl, lower alkynyl or heterocyclyl, the heterocyclic ring being attached at any carbon atom which results in the creation of a stable structure;

(9) lower alkoxy, lower arylalkoxy, lower cycloalkoxy, lower heterocyclylalkoxy or heterocyclyloxy;

(10) lower alkylsulfonyl, lower alkylsulfinyl, arylsulfonyl, arylsulfinyl, lower arylalkylsulfonyl, lower arylalkylsulfinyl, heterocyclylsulfonyl,

heterocyclyl-sulfinyl; optionally substituted with 1 to 2 substituents selected from lower alkyl, halo, nitro, hydroxy, lower alkoxy, or groups of formula NR'R", OC(O)R', OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O)NR'R", NHC(O)OR' where R' and R" have the meanings given above;

(11) groups of the formula -C(=NOH)COOR^{11} wherein R^{11} is lower alkyl;

(12) hydrogen,, substituted lower alkyl, aryl, lower arylalkyl, lower cycloalkyl, each group being optionally substituted with 1 to 2 substituents selected from halo, nitro, amino, hydroxy, lower alkoxy, lower alkylamino, lower dialkylamino, NR'R", OC(O)R', OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O)NR'R", NHC(O)OR', with R' and R" having the meanings given above.

Brief Reference to the Drawings

FIGURE 1 is a diagrammatic representation of the mode of chemical interaction of omeprazole and H^+/K^+-ATPase;

FIGURE 2 is a similar diagrammatic representation of a proposed chemical interaction of compounds according to the invention with H^+/K^+-ATPase;

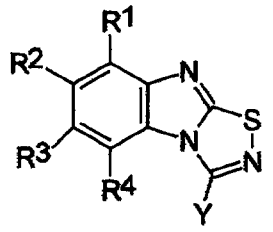
FIGURE 3 shows the chemical reaction of a thiadiazolobenzimidazole compound with phenethylmercaptan;

FIGURE 4 is a graphical representation of a specific synthesis route for the most preferred compound according to the present invention;

FIGURE 5 is a graphical presentation of the results of Example 40 below.

Description of the Preferred Embodiments

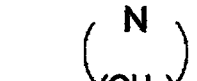
One class of preferred compounds according to the invention are 1,2,4-thiadiazolo[4,5-a]benzimidazoles corresponding to the following formula II :



(II)

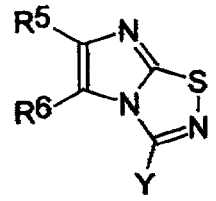
or pharmaceutically acceptable salts thereof, wherein:

R^1, R^2, R^3, R^4 are independently hydrogen, lower alkyl, halo, nitro, amino, hydroxy, lower alkoxy, lower alkylamino, lower dialkylamino, NR'R", OC(O)R', OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O)NR'R", NHC(O)OR', CONR'R".

R', R" are independently hydrogen, lower alkyl, aryl, lower arylalkyl or R' and R" in NR'R" when taken together with the N-atom, can form a five or six membered heterocyclic ring  wherein n = 4 or 5; and

Y is as previously defined.

A second class of preferred compounds according to the present invention is imidazo[1,2-*d*]-1,2,4-thiadiazole of the following formula III:



wherein R^5 and R^6 can have the same meanings as R^1, R^2, R^3 and R^4 in formula II above, and Y is as previously defined.

While it is not intended that the present invention should be limited to any particular theory or mode of action, it is believed that the compounds of the present invention interact to inhibit the action of the proton pump enzyme, by reacting with sulfhydryl groups on surface cysteine residues of the enzyme. This is generally illustrated in Fig. 2 of the accompanying drawings. The S-N bond in 1,2,4-thiadiazoles has a high energy content which originates, at least in part, from non-bonded electron repulsion between sulfur atom d orbitals and nitrogen atom p orbitals. 1,2,4-Thiazoles are therefore likely to be susceptible to nucleophilic attack. It has been reported over forty years ago that 1,2,4-thiadiazoles undergo S-N bond cleavage with reducing agents (Gordeler, Chem. Ber., **1954**, *87* , 57). The thiol groups of H^+/K^+-ATPase appear to act as reducing agents (nucleophiles), thereby become chemically modified as shown on Fig. 2, with resulting inhibition of the enzymatic activity. Group Y at the 3-position of the thiadiazole nucleus, because of its electron withdrawing nature, activates the adjacent bonds to facilitate this reaction.

A useful <u>in vitro</u> model for obtaining an indication of the reactivity of thiadiazole compound towards the proton pump enzyme for deactivation thereof is provided by the reactivity of the thiadiazole compound towards phenethyl-mercaptan. The chemical mechanism of this process, as applied to the thiadiazolobenzimidazole compounds of the present invention, is diagrammatically illustrated on Fig. 3 of the accompanying drawings. The first stage of reaction forms a disulfide compound by cleavage of the S-N bond of the thiadiazole ring. This disulfide X cannot be isolated, since it reacts very rapidly with a second mercaptan group to give the disulfide of phenethylmercaptan and intermediate XI. In connection with the actual enzyme, the second step

involving attack of another thiol group would not happen because of steric factors inhibiting the approach of two enzymes, or would lead to the formation of a disulfide bond in the event that another proximal thiol group is present. In both cases, this would lead to the inhibition of the enzyme. In some cases, intermediate XI further degrades to 2-mercaptobenzimidazole VIII or 1-cyano-2-mercaptobenzimidazole XII. A similar mechanism is followed by the imidazothiadiazoles of the present invention. Further description and discussion of this reaction and test method is included in the specific example section hereof.

Preferred compounds of formula II according to the invention are those in which R^1, R^2, R^3 and R^4 are each either hydrogen or lower alkoxy; and Y is (2-pyridyl) carbonyl or 2-pyridyl with the pyridyl ring in each case being optionally substituted with one to three substituents selected from methyl and methoxy, or lower alkoxy; Y is NR'R" where R' and R" are as previously defined, heterocyclyl (e.g. piperazino or morpholino), R^7CO where R^7 is lower alkyl, aryl, hydroxy or hydrogen.

Particularly preferred compounds of formula II are those belonging to the following sub-classes:

(a) R^1, R^3 and R^4 are hydrogen, R^2 is lower alkoxy, and Y is (2-pyridyl)carbonyl wherein the pyridine ring is either unsubstituted or optionally substituted with 1 - 3 substituents selected from methyl and methoxy;

(b) R^1, R^2, R^3 and R^4 are each hydrogen, and Y is lower alkoxy, heterocyclyl especially nitrogen heterocyclyl, or R^7CO wherein R^7 is alkyl, aryl, hydrogen or 2-pyridyl optionally substituted with up to 3 substituents selected from methyl and methoxy;

(c) R^1, R^2, R^3 and R^4 are each hydrogen, and Y is piperazino, morpholino, R^7CO wherein R^7 is lower alkyl, phenyl or hydroxy.

The preferred compounds according to the present invention show specificity for the mercaptan functional group demonstrated by the fact that the imidazo[1,2-*d*]-thiadiazole nucleus of these compounds show limited or no reactivity towards other nucleophiles present *in vivo* such as amines, hydroxide or iodide ions. In chemical model systems, the heterocyclic ring of 1,2,4-thiadiazolo[4,5-*a*]benzimidazole in particular is unreactive towards these nucleophiles.

One group of particularly preferred compounds of formula III according to the invention are those in which R^5 and R^6 are hydrogen, and Y is R^7CO wherein R^7 is lower alkyl, aryl, hydrogen, or 2-pyridyl optionally substituted with 1 to 3 substituents selected from methyl and methoxy.

Another group of particularly preferred compounds is those of formula II given above, in which R^1, R^2, R^3 and R^4 are hydrogen, and Y represents 4-substituted piperazinyl, r-substituted piperazinyl-methyl, or 2-pyridyl optionally substituted by amino. The most preferred such piperazinyl-methyl compound is that having a 1-phenyl-1-(4-chlorophenyl)-methyl substituent at the 4- position.

As used herein:

The term "lower", as applied for example to lower alkyl, means 1 to 8 carbon atoms.

The term "aryl", alone or in combination, means a phenyl or naphthyl radical which optionally carries one or more substituents selected from alkyl, alkoxy,

halogen, hydroxy, amino and the like, such as phenyl, *p*-tolyl, 4-methoxyphenyl, 4-(*tert*-butoxy)phenyl, 4-fluorophenyl, 4-chlorophenyl, 4-hydroxyphenyl, 1-naphthyl, 2-naphthyl and the like.

The term "arylalkoxy carbonyl", alone or in combination, means a radical of the formula -C(O)-O-arylalkyl, in which the term "arylalkyl" has the significance given below. An example of an arylalkoxycarbonyl radical is benzyloxycarbonyl.

The term "arylalkyl" means an alkyl radical in which one hydrogen atom is replaced by an aryl radical, such as benzyl, phenylethyl and the like.

The term "cycloalkylcarbonyl" means an acyl group derived from a monocyclic or bridged cycloalkanecarboxylic acid such as cyclopropanecarbonyl, cyclohexanecarbonyl, adamantanecarbonyl, and the like, or from a benz-fused monocyclic cycloalkanecarboxylic acid which is optionally substituted by, for example, alkylamino, such as 1,2,3,4-tetrahydro-2-naphthoyl, 2-acetamido-1,2,3,4-tetrahydro-2-naphthoyl.

The term "arylalkanoyl" means an acyl radical derived from an aryl-substituted alkanecarboxylic acid such as phenylacetyl, 3-phenylpropionyl, hydrocinnamoyl, 4-phenylbutyryl, (2-naphthyl)acetyl, 4-chlorohydrocinnamoyl, 4-aminohydrocinnamoyl, 4-methoxyhydrocinnamoyl, and the like.

The term "aroyl" means an acyl radical derived from an aromatic carboxylic acid. Examples of such radicals include aromatic carboxylic acid, an optionally substituted benzoic or naphthoic acids such as benzoyl, 4-chloro-benzoyl, 4-carboxybenzoyl, 4-[(benzyloxy)carbonyl]benzoyl, 1-naphthoyl, 2-naphthoyl, 6-carboxy-2-naphthoyl, 6-[(benzyloxy)carbonyl]-2-

naphthoyl, 3-benzyloxy-2-naphthoyl, 3-hydroxy-2-naphthoyl, 3-[(benzyloxy)formamido]-2-naphthoyl, and the like.

The term "heterocyclyl", as used herein except where noted, represents a stable 5- to 7-membered mono or bicyclic or stable 7- to 10-membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms, and from one to three heteroatoms selected from the group consisting of N, O, S, and wherein the nitrogen and sulfur heteroatoms may be optionally oxidized, and the nitrogen atom may optionally be quaternized, and including any bicyclic group in which any of the above defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic elements, commonly known as heterocyclyl include piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiper-azinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazoli-dinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzoxazolyl, furyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzothienyl, tetrahydroquinolinyl (e.g. 1,2,3,4-tetrahydro-2-quinolinyl, etc.), 1,2,3,4-tetrahydro-isoquinolinyl (e.g. 1,2,3,4-tetrahydro-1-oxo-isoquinolinyl etc.), quinoxalinyl, beta-carbolinyl, 2-benzofurancarbonyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, oxadiazolyl and the like. The heterocycle may be substituted in a manner which results in the creation of a stable structure.

"Amino acid residues" means any of the naturally occurring alpha-, beta-, and gamma-amino carboxylic acids, including their D and L optical isomers and racemic mixtures thereof, and the N-lower alkyl- and N-phenyl lower alkyl-derivatives of these amino acids. The amino acid residue is bonded through a nitrogen of the amino acid. The naturally occurring amino acids which can be incorporated into the present invention include, but are not limited to, alanine, arginine, asparagine, aspartic acid, cysteine, cystine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, ornithine, phenylalanine, proline, serine, threonine, thyroxine, tryptophan, tyrosine, valine, beta-alanine, and gamma-aminobutyric acid. Preferred amino acid residues include proline, leucine, phenylalanine, isoleucine, alanine, gamma-amino butyric acid, valine, glycine, and phenylglycine.

All alpha-amino acids except glycine contain at least one asymmetric carbon atom. As a result, they are optically active, existing in either D or L form as a racemic mixture. Accordingly, some of the compounds of the present invention may be prepared in optically active form, or as racemic mixtures of the compounds claimed herein.

The term "A" wherein A is an amino acid or peptide of 2 to 3 amino acid residues refers to an amino acid or a peptide diradical starting with the HN- radical on the left hand side of A and terminated by the -C(O) radical on the right hand side. For example, the amino acid glycine is abbreviated HAOH wherein A is $HN-CH_2-C(O)$.

The term "aryloxyalkanoyl" means an acyl radical of the formula aryl-O-alkanoyl.

The term "heterocyclyloxycarbonyl" means an acyl group derived from heterocyclyl-O-CO- wherein heterocyclyl is defined above.

The term "heterocyclylalkanoyl" is an acyl radical derived from a heterocyclyl-substituted alkane carboxylic acid wherein heterocyclyl has the same significance given above.

The term "heterocyclylalkoxycarbonyl" means an acyl radical derived from a heterocyclyl-substituted alkyl-O-COOH wherein heterocyclyl has the same significance given above.

The term "aminoalkanoyl" means an acyl radical derived from an amino-substituted alkanecarboxylic acid wherein the amino group can be a primary, secondary or tertiary amino group containing substituents selected from hydrogen, and alkyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl radicals and the like.

"Pharmaceutically acceptable, non-toxic salts" refers to pharmaceutically acceptable salts of the compounds of this invention which retain the biological activity of the parent compounds and are not biologically or otherwise undesirable (e.g. the salts are stable). Salts of the two types may be formed from the compounds of this invention: (1) salts of inorganic and organic bases from compounds of Formula I which have a carboxylic acid functional group. (2) Acid addition salts may be formed at the amine functional group of many of the compounds of this invention.

Pharmaceutically acceptable salts derived from inorganic bases include sodium, potassium, lithium, ammonium, calcium, magnesium, ferrous, zinc, copper, manganous, aluminum, ferric, manganic salts and the like. Particularly preferred are the ammonium, potassium,

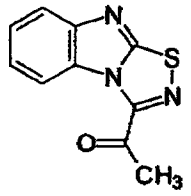
sodium, calcium and magnesium salts. Pharmaceutically acceptable, non-toxic salts derived from organic bases include salts of primary, secondary and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins. Such salts are exemplified by, for example, isopropopylamine, trimethyl-amine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, tromethamine, dicyclohexamine, lysine, arginine, histidine, caffeine, procaine, hydrabramine, choline, betaine, ethylenediamine, glucosamine, metylglucamine, theobromine, purines, piperazine, piperidine, *N*-ethylpiperidine, polyamine resins and the like. Particularly preferred organic non-toxic bases are isopropylamine, diethylamine, ethanolamine, piperidine, tromethamine, dicyclohexylamine, choline and caffeine.

Pharmaceutically acceptable acid addition salts are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

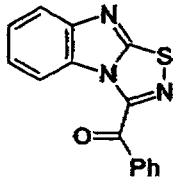
The term "animals" refers to humans as well as all other animal species, particularly mammals (e.g. dogs, cats, horses, cattle, pigs etc.), reptiles, fish, insects and helminths.

The specific, most preferred compounds according to the present invention are the following:

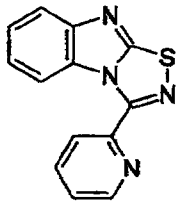
3-(1-oxoethyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole, which has the following chemical formula:



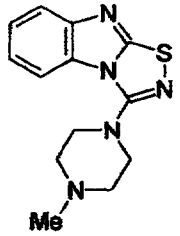
3-(1-oxophenylmethyl)-1,2,4-thiadiazolo[4,5-a] benzimidazole, which has the following chemical formula:



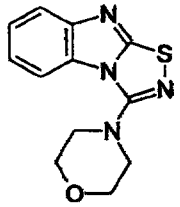
3-(2-pyridyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole, which has the following chemical formula:



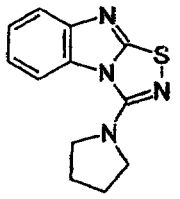
3-(4-methyl-1-piperazinyl)-1,2,4-thiadiazolo-[4,5-a]benzimidazole, which has the following chemical formula:



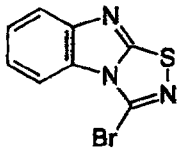
3-(4-morpholinyl)-1,2,4-thiadiazolo[4,5-a] benzimidazole, which has the following chemical formula:



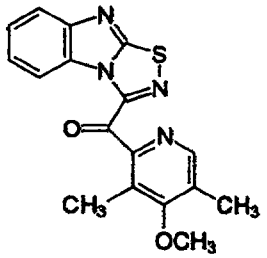
3-(1-pyrrolidinyl)-1,2,4-thiadiazolo[4,5-a] benzimidazole, which has the following chemical formula:



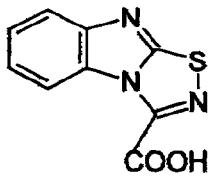
3-bromo-1,2,4-thiadiazolo[4,5-a]benzimidazole, which has the following chemical formula:



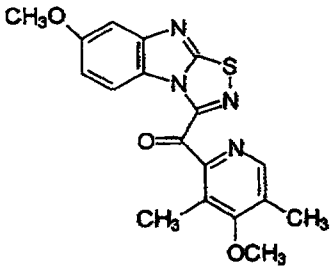
3-[(4-methoxy-3,5-dimethyl-2-pyridyl)oxomethyl]-1,2,4-thiadiazolo[4,5-a]benzimidazole, which has the following chemical formula:



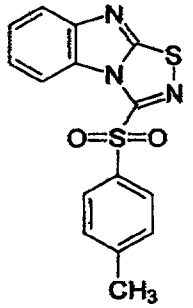
3-carboxy-1,2,4-thiadiazolo-[4,5-a]benzimidazole, which has the following chemical formula:



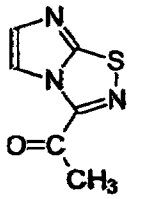
7-methoxy-3-[(4-methoxy-3,5-dimethyl-2-pyridyl) oxomethyl]-1,2,4-thiadiazolo[4,5-a]benzimidazole, which has the following chemical formula:



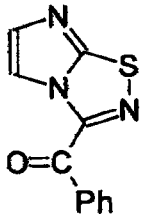
3-(4-methylphenylsulfonyl)-1,2,4-thiadiazolo [4,5-*a*]benzimidazole, which has the following chemical formula:



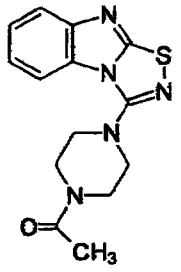
3-(1-oxoethyl)imidazo[1,2-*d*]-1,2,4-thiadiazole, which has the following chemical formula:



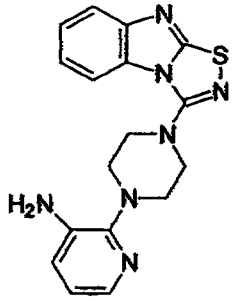
3-(oxophenylmethyl)imidazo[1,2-*d*]-1,2,4-thiadiazole, which has the following chemical formula:



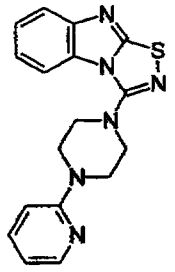
3-(4-acetyl-1-piperazinyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole, which has the following chemical formula:



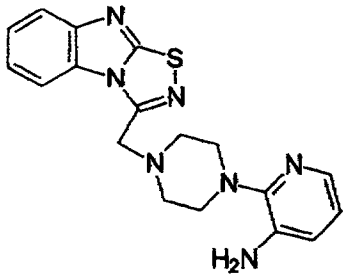
3-[4-(3-amino-2-pyridyl)piperazinyl]-1,2,4-thiadiazolo[4,5-a]benzimidazole, which has the following chemical formula:



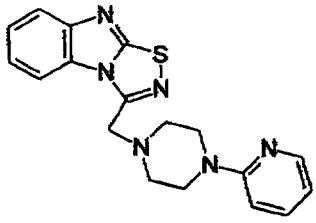
3-[4-(2-pyridyl)piperazinyl]1,2,4-thiadiazolo-[4,5-a]benzimidazole, which has the following chemical formula:



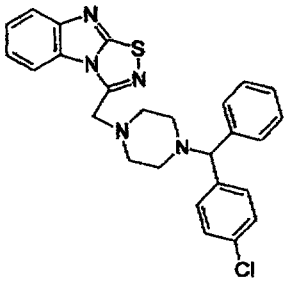
3-[4-(3-amino-2-pyridyl)piperazinyl-methyl]-1,2,4-thiadiazolo-[4,5-a]benzimidazole, which has the following chemical formula:



3-[4-(2-pyridyl)piperazinyl-methyl]-1,2,4-thiadiazolo-[4,5-a]benzimidazole, which has the following chemical formula:



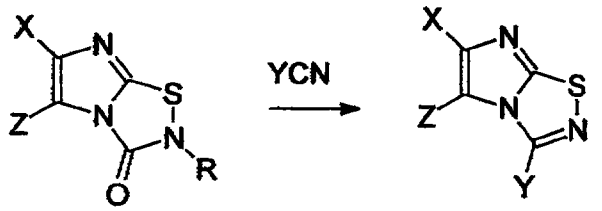
3-{[4-(1-(4-chlorophenyl)-1-phenylmethyl)-piperazinyl]methyl}-1,2,4-thiadiazolo[4,5-a]benzimidazole, which has the following chemical formula:



The present invention provides synthetic methods for preparing compounds according to the invention. Some of these methods involve conversion of one compound according to the invention into another, different such compound. The choice of method depends largely upon the desired Y group, i.e. the substituent on the 3-position in the final compound.

In a first process, the corresponding 3-oxo compound of formula IV, carrying a lower alkyl or lower arylalkyl

substituent at position 2 is reacted with YCN in an inert solvent. This method is appropriate for compounds in which Y is lower alkyl, aryl, arylalkyl, cycloalkyl, 1-haloalkyl, 1,1-dihaloalkyl, heterocyclyl, lower alkylsulfonyl or arylsulfonyl. The reaction can be represented as follows:



(IV)

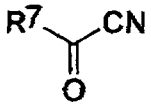
The appropriate nitrile compounds YCN wherein Y is lower alkyl, arylalkyl, cycloalkyl, 1-haloalkyl, 1,1-dihaloalkyl, or heterocyclyl are for the most part commercially available e.g. from Aldrich Chemical Co. Alternatively, they can be prepared by methods known in the Art (see for example Chapter 17 in Organic Functional Group Preparations, Vol. I by Sandler and Karo, Academic Press, 1983). Acetonitrile, benzonitrile, 2-cyanopyridine, cyclopentylcyanide, dibromoacetonitrile, 6-cyanopurine and p-toluenesulfonyl cyanide are some typical examples. The reaction normally takes place at elevated temperature between 70 to 140 °C in an inert solvent such as toluene, dimethylformamide for a period of 6 to 24 hours, preferably 16 hours. In some cases, YCN is used as the solvent. The product is isolated by conventional means.

Compounds of formula I in which Y is amino, lower alkylamino, lower dialkylamino, thioalkyl can also be prepared by using compounds of formula YCN wherein Y is amino, lower alkylamino, lower dialkylamino or lower thialkyl. Examples of YCN is this category are cyanamide, 1-piperidinecarbonitrile, methyl thiocyanate which are commercially available. Compounds YCN can also be synthesized from cyanogen bromide according to literature

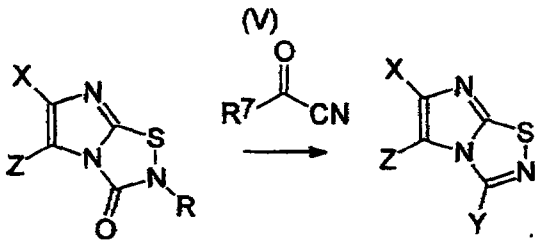
procedures (see p.174, Fieser and Fieser, Reagents in Organic Synthesis, John Wiley and Sons, 1967).

2-Alkyl-1,2,4-thiadiazolo[4,5-*a*]benzimidazole-3(2*H*)-ones of formula IV are prepared from alkyl isocyanate and 2-mercaptobenzimidazole according to the procedure of Martin et al., Tetrahedron, **1983**, *39*, 2311. 2-Alkylimidazo[1,2-*d*]-1,2,4-thiadiazole-3(2H)-ones of formula IV are prepared from alkyl isocyanate and 2-mercaptoimidazole according to the procedure of Tittlebach *et al.*, J. Prakt Chem. **1988**, *330*, 338-348. The 2-mercaptobenzimidazoles are either commercially available, or can be prepared by methods well known in the art or readily available in the literature. Commercially available 2-mercaptobenzimidazoles includes 5-methyl-2-mercaptobenzimidazole, 5-methoxy-2-mercaptobenzimidazole, 5-chloro-2-mercaptobenzimidazole. Suitable 2-mercaptobenzimidazole which are not commercially available can be prepared by known methods. Preparative method include those of Billeter *et al.*, Ber., **1887**, *20*, 231, Org. Synth., Coll. Vol. 4, 569, Futaki *et al.*, J. Pharm. Soc. Jpn., **1954**, *74*, 1365, Bucknall *et al.*, Nature, **1967**, *213*, 1099.

In a second, similar process, applicable for the preparation of compounds in which group Y in the final compound is R^7-C=O and R^7 is lower alkyl, aryl, lower arylalkyl, lower cycloalkyl, lower alkoxy, amino, lower alkylamino, lower dialkylamino, heterocyclyl, the heterocyclic ring being attached at any heteroatom or carbon atom which results in the creation of a stable structure, NR'R", ANR'R", AOR' wherein A is an amino acid residue or a peptide of 2 to 3 amino acid residues and R', R" have the same definition as above, a compound of general formula



is reacted with the corresponding 3-oxo compound carrying a lower alkyl or lower arylalkyl substituent at position 2, i.e. a compound of formula IV used in process A above, thus:



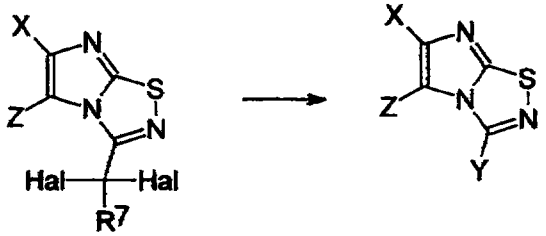
(IV)

The reaction may be carried out in an inert solvent such as dichloromethane, tetrahydrofuran or dimethylformamide. The reaction takes place at room temperature over a period of 3 to 48 hours, usually about 6 hours. The resulting solid is then isolated by conventional means.

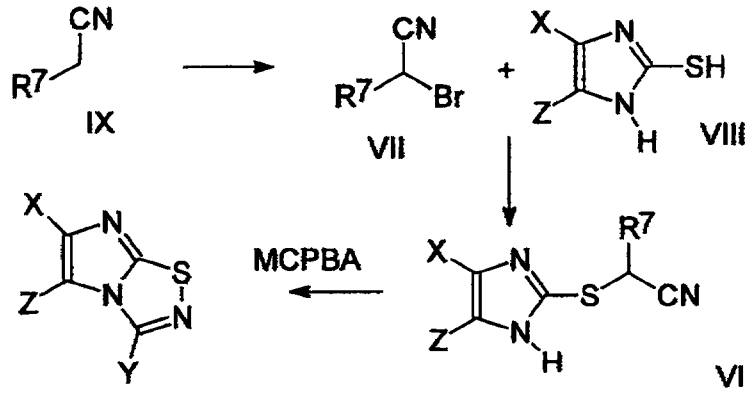
Most cyanoketones, cyanoester derivatives of formula V are commercially available. The cyanoketone derivatives used in this invention are either commercially available or can be prepared by methods known in the art. The commercially available cyanoketones include, benzoyl cyanide, acetyl cyanide, methoxycarbonyl cyanide. A list of commercially available cyanide derivatives is available (Chem Sources, U.S.A., 24th Ed., **1983**, Directories Publishing Company Inc., Ormont Beach, Fla.). Appropriate cyanoketones, cyanoesters which are not commercially available can be readily prepared by methods known in the art such as the ones described in Mathieu *et al.*, Formation of C-C Bonds, Vol I, p. 456-457, Georg Thieme Verlag, **1973**, Stuttgart. Other suitable methods include those of Koenig *et al.*, Tet. Lett., **1974**, 2275 and Ando *et al.*, Synthesis, **1983**, 637. These methods

include reacting an acid chloride with cuprous cyanide or potassium cyanide.

Alternatively, compounds of formula I in which Y is R^7-C=O wherein R^7 has the same definition as above can be prepared by the hydrolysis of compounds of formula I wherein Y is R^7-C(Hal)$_2$ and wherein Hal is a halogen, preferably chlorine, bromine or iodine. Such an hydrolysis can be carried out in a strongly acidic media or in aqueous silver nitrate, and can be represented thus:



A third process for making the same end products as in the case of the second process described above, involves, as a final step, reacting a 2-thioether diazole compound of formula VI with *m*-chloroperbenzoic acid (MCPBA) in an inert solvent, to effect cyclization to form the 1,2,4-thiadiazole ring, and can be represented as follows:



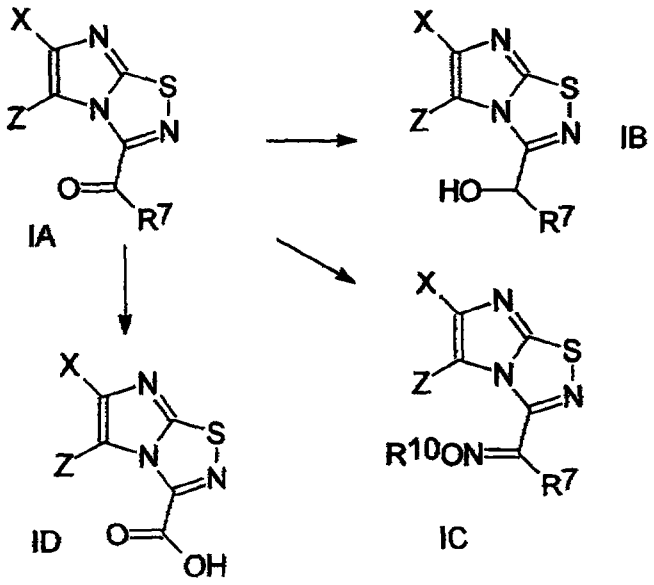
A bromoheterocyclylacetonitrile derivative (VII) can be reacted with 2-mercaptobenzimidazole (VIII) in base to give a compound of formula VI. Examples of those bases are sodium hydroxide or potassium hydroxide. The reaction takes place in a mixture of water and alcohol at

room temperature for about 1 to 16 hours, preferably 8 hours, the product compound VI is isolated by conventional means.

Compound VI reacts with *m*-chloroperbenzoic acid, in an inert solvent such as dichloromethane, or 1,2-dichloro-ethane to give the compound of formula I where Y is R^7-C=O. The reaction takes place at room temperature for about 3 to 8 hours, preferably 3 hours. The product is isolated by conventional means.

The bromoheterocyclylacetonitrile (VII) derivative is in turn prepared by reacting a compound of formula IX with *N*-bromosuccinimide in an inert solvent such as carbon tetrachloride.

A fourth process uses a compound of formula I in which Y is R^7-C=O (formula IA) as the starting material, and derivatizes it to a compound of formula I in which Y is -CHOH-R^7 (formula IB) or -C=(NOR^{10})-R^7 (formula IC), or -COOH (formula ID), thus:

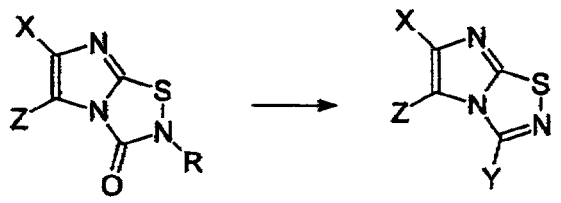


Compounds of formula IB can be prepared by the reduction of the corresponding compounds of formula IA wherein Y is R^7-C=O with sodium borohydride, or sodium cyanoborohydride in alcohol. Compound of formula IB is isolated by conventional means.

Compounds of formula IC can be prepared by reacting compound of formula I wherein Y is R^7-C=O with hydroxylamine derivatives. Examples of hydroxylamines are hydroxylamine, methoxylamine, ethoxylamine, benzyloxylamine. The conversion of a ketone to an oxime is well-documented in the art (see, for example, Sandler and Karo, Organic Functional Group Preparations, **1989**, Vol. III, Chapter 11).

Compounds of formula ID in which R^7 is hydroxy can be prepared by the base hydrolysis of the compounds of formula I wherein Y is R^7-C=O and R^7 is lower alkoxy. The reaction is carried out in 1M sodium hydroxide at room temperature in a mixture of water and an organic solvent such as methanol, ethanol, 1,4-dioxane or acetonitrile. The product is isolated by conventional means after neutralization of the base with diluted acid.

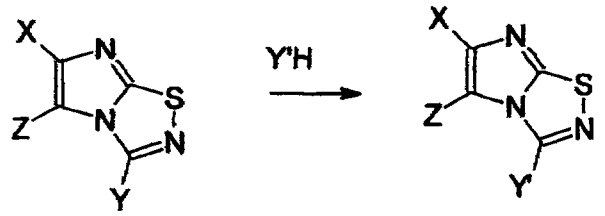
A fifth process, applicable to the preparation of compounds of formula I according to the invention in which Y represents halogen or halomethyl, uses the same starting compound of formula IV as used in process A and process B, and reacts it with a cyanogen halide or a haloacetonitrile, thus:



IV

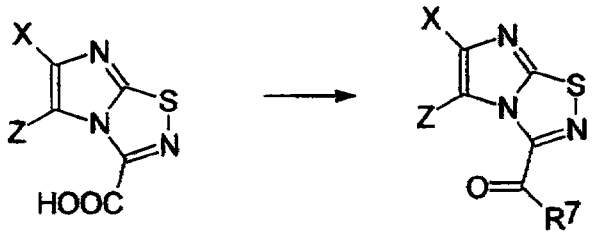
The reaction takes place in an inert solvent. The compound is isolated by conventional means.

A sixth process uses as starting materials the compounds of formula I where Y represents halogen, e.g. compounds prepared according to the fifth process above, and reacts them with a primary or secondary amine, or alcohol, to give a compound of formula I wherein Y is NR'R", AOR', ANR'R", OR'. R', R" have the same definition as above. This process proceeds best when Y in the starting material is bromine. It can be represented thus:



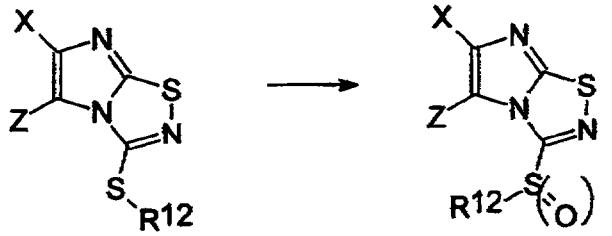
Nucleophiles such as lower alkoxides, aryloxides, lower arylalkoxides, lower cycloalkoxides, ammonia, lower alkylamines, lower dialkylamines, heterocyclic amines, HNR'R", HANR'R", HAOR', wherein A is an amino acid residue or a peptide of 2 to 3 amino acid residues, react with compounds of formula I wherein Y = bromide in an inert solvent to give compounds of formula I wherein Y is lower alkoxy, aryloxy, lower arylalkoxy, lower cycloalkoxy, amino, lower alkylamino, lower dialkylamino, NR'R", ANR R", AOR', wherein A is an amino acid residue or a peptide of 2 to 3 amino acid residues.

A seventh process uses as starting materials compounds of formula I according to the invention in which Y represents COOH (preparable by process D above), and reacts them with an amine to give a compound of formula I wherein Y is CO-R^7, wherein R^7 is NR'R", AOR', ANR'R", thus:



In this way, compounds of formula I in which Y is R^7-C=O and R^7 is NR'R", AOR , ANR R" can be prepared by reacting the carboxylic acid compound of formula I wherein Y is COOH with an amino acid amide HANR'R", or amines HNR R", or amino acid ester HAOR', in the presence of a dehydrating agent such as 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide (EDCI) and hydroxybenzotriazole in an inert solvent such as tetrahydrofuran, dimethylformamide, dichloromethane.

An eighth process applicable to the preparation of compounds of Formula 1 in which Y represents lower alkylsulfonyl, arylsulfonyl, heterocyclylsulfonyl, lower arylalkylsulfonyl, lower alkylsulfinyl, arylsulfinyl, heterocyclylsulfinyl or lower arylalkylsulfinyl comprises the reaction of the corresponding thioether compound with the predetermined stoichiometric amount of an oxidizing agent, thus:



where n is 1 or 2 and R^{12} represents lower alkyl, lower arylalkyl or aryl. A preferred oxidizing agent for use in this process is metachloroperbenzoic acid mCPBA, but there are many other, suitable such oxidizing agents.

A significant feature of the preferred compounds of this invention is that these compounds are heterocycles with molecular weight less than 450. Low molecular weight

compounds are generally more bioavailable. The spectrum of log P of these molecules, i.e. the partition coefficient between octanol and water, varies from 0.5 to 4.0 which covers the lipophilicity range of most known drugs.

One specific, preferred compound according to the present invention is 7-methoxy-3 -[(4-methoxy-3,5-dimethyl-2-pyridyl)oxomethyl]-1,2,4-thiadiazolo[4,5-a]benzimidazole. This molecule carries an electron-withdrawing group at the 3-position of the heterocyclic ring. It has limited solubility in water. A specific synthesis route for it, in accordance with the invention, is illustrated on Fig. 4 of the accompanying drawings. Its structure was proved by X-ray crystallography. ^{1}H and ^{13}C NMR, IR, mass spectrometry and elemental analysis provided additional evidence for the chemical identity of this compound. Further specific details of its preparation, characterization and properties are given in the specific examples below. It is active in the suppression of gastric acid secretion in animal model.

For the treatment of peptic ulcers, the compounds of the invention may be administered orally, topically, or parenterally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, etc., the compounds of the invention are effective in the treatment of humans.

For compositions, conventional non-toxic solid carriers include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate, and the like may be used. The active compound

as defined above may be formulated as liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, etc. an active compound as defined above and optional pharmaceutically adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol, and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain a minor amount of non-toxic auxiliary substances such as wetting or emulsifying agents and the like, for example, sodium acetate, sorbitan monolaurate, triethanolamine sodium acetate, triethanol-amine oleate, etc. Actual methods of preparing such dosage forms are known, or will be apparent to those skilled in this art: for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa, 15th Edition, 1975. The composition of formulation to be administered will, in any event, contain a quantity of the active compound(s) in an amount effective to alleviate the symptoms of the subject being treated.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard and soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions contain one or more agents from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with the non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. The excipients may be for example, inert

diluents, such as calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be coated by known techniques to delay the disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a long period. For monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredients are mixed with an inert solid diluent, for example, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with the excipient suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphate, for example lecithin, or condensation products of an alkene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecathyl-eneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more colouring agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with the dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional recipients, for example sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical composition of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphates, esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavouring and colouring agents. The pharmaceutical compositions may be

formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solutions and isotonic sodium chloride solution. In addition, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation or injectables.

Parenteral administration is generally characterized by injection, either subcutaneously, intramuscularly or intravenously. Injectables can be prepared in conventional forms, either as liquid solutions or suspension in liquid prior to injection, or as emulsions. Suitable excipients are for example, water, saline, dextrose, glycerol, ethanol or the like. In addition, if desired, the pharmaceutical compositions to be administered may also contain minor amounts of non-toxic auxiliary substance such as wetting or emulsifying agents, pH buffering agents and the like, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate, etc.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration of humans may contain from 0.5 mg to 5 gm of active agent compounded with an appropriate and convent amount of carrier material which may vary from about 5 to about 95% of the total composition. Dosage unit forms will generally contain

between from about 1 mg to about 500 mg of an active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, drug combination and the severity of the particular disease undergoing therapy.

The invention is further described and illustrated in the following specific examples.

SPECIFIC DESCRIPTION OF THE MOST PREFERRED EMBODIMENTS

Example 1

Preparation of bromo(2-pyridyl)acetonitrile

To a solution of (2-pyridyl)acetonitrile (12.0 g, 0.10 mole) in 150 ml of carbon tetrachloride, was added 18.1 g of N-bromosuccinimide (0.10 mole) at room temperature. The mixture was refluxed for 1.5 h. The resulting precipitate was removed by filtration and the solvent was removed under reduced pressure to give the crude product, which was recrystallized from hexane to yield 18.6 g (94 %) of the title compound as red crystals: mp 62-64°C; ^{1}H NMR (DMSO-d_6) δ 8.67 (d, 1H), 7.97 (t, 1H), 7.70 (d, 1H), 7.51 (td, 1H), 5.60(s,1H) ppm; IR (KBr): 3064, 2972, 1712, 1587, 1470, 1439, 1051, 993 cm^{-1}; MS *m/z* 196, 198 (M^+), 117 (M^+ - Br); HRMS calcd for $C_7H_5BrN_2$ 195.9630, found 195.9645.

Proceeding in a similar manner, the following compound was made:

bromo(4-methoxy-3,5-dimethyl-2-pyridyl)acetonitrile: mp 56-57°C; ^{1}H NMR ($CDCl_3$) δ 8.31 (s, 1H), 5.67 (s, 1H), 3.81 (s, 3H), 2.37 (s, 3H), 2.30 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 164.84, 150.19, 149.56, 128.28, 125.59, 115.49,

60.135, 27.99, 13.51, 11.05 ppm; IR (KBr): 3415, 2988, 2210, 1568, 1472, 1255, 997, 791 cm^{-1}; MS *m/z* 255, 257 (MH^+), 175 (M^+ - Br).

Example 2

Synthesis of [(2-benzimidazolyl)thio](2-pyridyl) acetonitrile

A mixture of 2-mercaptobenzimidazole (0.30 g, 3.0 mmole), bromo(2-pyridyl)acetonitrile (0.59 g, 3.0 mmole) and potassium carbonate (0.37 g 3.0 mmole) in 50 ml of dry *N,N*-dimethylformamide was heated at 60°C for 6 h. The solvent was evaporated. The residue was dissolved in ethyl acetate, washed with water and then saturated sodium chloride solution. The organic layer was dried over magnesium sulfate and evaporated to give a solid. The crude product was further purified by column chromatography on silica gel (100% ethyl acetate) to give 66 mg (10%) of the title compound as a solid; mp 166-167 °C; ^1H NMR (DMSO-d_6) δ 9.3 (m, 1H), 8.65 (m, 2H), 8.32 (m, 1H), 7.78 (br s, 4H), 4.81 (br s, 2H) ppm; IR: 2206, 1512, 1465, 1432, 1357, 1179, 740 cm^{-1}.

In a similar manner, by replacing 2-mercaptobenzimid-azole with 2-mercaptoimidazole, the following compound was made:
[(2-imidazolyl)thio](2-pyridyl)acetonitrile:
mp 203-204°C (dec); ^1H NMR ($CDCl_3$) δ 8.51 (d, 1H), 7.65 (t, 1H), 7.36 (d, 2H), 7.12 (d, 1H), 7.03 (dd, 1H), 6.33 (br s, 2H) ppm, ^{13}C NMR ($CDCl_3$) δ 154.08, 148.23, 145.76, 136.84, 134.95, 134.43, 119.15, 118.40, 109.32, 96.15 ppm; IR (KBr) 3344, 3225, 2202, 1643, 1493, 1485, 1427 cm^{-1};

Example 3

Synthesis of [(5-methoxy-2-benzimidazolyl)thio](4-methoxy-3,5-dimethyl-2-pyridyl)acetonitrile

To a solution of 2-mercapto-5-methoxybenzimidazole (15.1g, 0.14 mole) dissolved in 40 ml of 8.4% sodium

hydroxide, was added 170 ml of methanol, followed by bromo(4-methoxy-3,5-dimethyl-2-pyridyl)acetonitrile(21.4 g, 0.11 mole) at room temperature. The mixture was heated to reflux for 1 h under a nitrogen atmosphere. The resulting precipitate was removed by filtration and the methanol was evaporated. The residue obtained was extracted with chloroform, and the chloroform was washed 3 times with water and dried over magnesium sulfate. After evaporation of the solvent, the crude product was recrystallized from diethyl ether to give 22.6 g (90%) of the title compound as yellowish crystals: mp 193-197°C; ^1H NMR ($CDCl_3$) δ 8.25 (s,1H), 7.65 (dd, 1H), 7.30 (m, 1H), 6.90 (m, 1H), 6.30 (br s, 2H), 3.95 (s, 3H), 3.75 (s, 3H), 2.50 (s, 3H), 2.20 (s, 3H) ppm.

Example 4

Synthesis of 3-[oxo(2-pyridyl)methyl]imidazo[1, 2-*d*]-1,2,4-thiadiazole

To a solution of [(2-imidazolyl)thio](2-pyridyl) acetonitrile (30 mg, 0.14 mmole) in 5 ml of chloroform, was added portionwise 0.12 g of 60% *m*-chloroperbenzoic acid (0.42 mmol). The mixture was stirred at room temperature for 10 h. The resulting mixture was washed with water and saturated sodium bicarbonate solution. The organic phase was then treated with charcoal, and filtered to give the crude product. Chromatography on silica gel (100% ethyl acetate) affords 22 mg (84 %) of the title compound as a yellowish solid: mp 147-148°C; ^1H NMR ($CDCl_3$) δ 8.87 (d, 1H), 8.30 (m, 2H), 7.95 (m, 1H), 7.57 (m, 1H), 7.52 (m, 1H) ppm; IR (KBr): 1700, 1660 cm^{-1}; MS *m/z* 230 (M^+); HRMS calcd for $C_{10}H_6N_4OS$ 230.0262, found: 230.0267.

Example 5

Synthesis of 7-methoxy-3-[(4-methoxy-3,5-dimethyl-2-pyridyl)oxomethyl]-1,2,4-thiadiazolo[4,5-a]benzimidazole and 6-methoxy-3-[(4-methoxy-3,5-dimethyl-2-pyridyl) oxomethyl]-1,2,4-thiadiazolo[4,5-a]benzimidazole

To a solution of [(5-methoxy-2-benzimidazolyl)thio](4-methoxy-3,5-dimethyl-2-pyridyl)acetonitrile (5.31 g, 15 mmole) in 400 ml of chloroform, was added dropwise 60% *m*-chloroperbenzoic acid (8.62 g, 30 mmole) dissolved in 100 ml of chloroform at 0-5°C during a period of 1 h. After the addition was over, the reaction mixture was stirred at room temperature for 1 h. The resulting mixture was then washed with water and dried over magnesium sulfate. The solvent was evaporated to give the crude product. Chromatography on silica gel (ethyl acetate: hexane 1:1) yields 0.828 g (10%) of 7-methoxy-3-[(4-methoxy-3,5-dimethyl-2-pyridyl)oxomethyl]-1,2,4-thiadiazolo[4,5-a]benzimidazole as a yellowish solid and 0.828 g (10%) of 6-methoxy-3-[(4-methoxy-3,5-dimethyl-2-pyridyl)oxomethyl]-1,2,4-thiadiazolo[4,5-a]benzimidazole as a solid.

7-methoxy-3-[(4-methoxy-3,5-dimethyl-2-pyridyl)oxomethyl]-1,2,4-thiadiazolo[4,5-a]benzimidazole: mp 170-171°C; ^{1}H NMR (DMSO-d_6) δ 8.34 (s, 1H), 7.86 (d, 1H), 7.29 (d, 1H), 6.93 (dd, 1H), 3.84 (s, 6H), 2.42 (s, 3H), 2.31 (s, 3H) ppm; IR (KBr): 1684, 1654 cm^{-1}; MS *m/z* 369 (M^++1).

6-methoxy-3-[(4-methoxy-3,5-dimethyl-2-pyridyl)oxomethyl]-1,2,4-thiadiazolo[4,5-a]benzimidazole: mp 196-197°C; ^{1}H NMR (DMSO-d_6) δ 8.34 (s, 1H), 7.67 (d, 1H), 7.34 (d, 1H), 7.10 (dd, 1H), 3.84 (s, 3H), 3.74 (s, 3H), 2.44 (s, 3H), 2.31 (s, 3H) ppm; IR (KBr): 1684 cm^{-1}; MS *m/z* 369 (M^++ 1).

Example 6

Synthesis of dibromo(2-pyridyl)acetonitrile

To a solution of (2-pyridyl)acetonitrile (6.0 g, 50.8 mmol) in 120 mL carbon tetrachloride was added *N*-bromosuccinimide (18.5 g, 104 mmol) at room temperature. The resulting mixture was heated to reflux for 2 h.

After cooling, the precipitate was filtered. The carbon tetrachloride was evaporated to give 13.5 g (96%) of dibromo(2-pyridyl)acetonitrile as a dark-brown solid: mp 59-61°C; ^{1}H NMR ($CDCl_3$) δ 8.62 (d, 1H), 7.93 (d, 1H), 7.86 (dt, 1H), 7.35 (dt, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 155.23, 148.94, 138.24, 125.38, 120.55, 115.81, 30.81 ppm; HRMS calcd for $C_7H_4N_2Br_2$: 273.8741, found: 273.8730.

Example 7

Synthesis of 2-butyl-1,2,4-thiadiazolo[4,5-a]benzimidazole-3(2*H*)-one

The mixture of 2-mercaptobenzimidazole (29.30 g, 0.195 mole) and butyl isocyanate (48.3 mL, 0.33 mole) in a 500 ml of round-bottom flask equipped with a condenser was heated to 130-140 °C in an oil bath for 45 min. After the reaction mixture was cooled to room temperature, the solid was filtered, washed with hexane, and dried under vacuum to give 43.48 g (89 %) of 1-(butylcarbamoyl)-1,3-dihydrobenz-imidazole-2-thione as white crystals: mp 179-180°C.

To a solution of 1-(butylcarbamoyl)-1,3-dihydro-benzimidazole-2-thione (39.89 g, 0.16 mole) in 250 mL of chloroform, was added 25.57 g (0.16 mole) of bromine, in 110 mL of chloroform, at 0°C. After the addition was complete, triethylamine (44.6 mL, 0.32 mole), in 80 mL of chloroform, was added dropwise to the reaction mixture. The mixture was stirred at 0 °C for an additional 4 h, and then stirred at room temperature for 14 h. The resulting mixture was washed with water and then with a 10% sodium sulfate solution. The organic layer was dried over magnesium sulfate and evaporated to give the crude product. Recrystallization from methanol gave 27.10 g (69%) of 2-butyl-1,2,4-thiadiazolo[4,5-a]benzimidazole-3(2*H*)-one as colourless crystals: mp 153-154°C (lit.: 156-157°C, Martin *et al*. Tetrahedron **1983**, *39*, 2311).

In a similar manner, by replacing n-butyl isocyanate with other alkyl isocyanates, the following compounds are made:

2-ethyl-1,2,4-thiadiazolo[4,5-a]benzimidazole-3(2*H*)-one

2-isopropyl-1,2,4-thiadiazolo[4,5-*a*]benzimidazole-3(2*H*)-one

2-methyl-1,2,4-thiadiazolo[4,5-a]benzimidazole-3(2*H*)-one

2-phenyl-1,2,4-thiadiazolo[4,5-*a*]benzimidazole-3(2*H*)-one

2-benzyl-1,2,4-thiadiazolo[4,5-*a*]benzimidazole-3(2*H*)-one

Example 8

Synthesis of 3-[dibromo(2-pyridyl)methyl]-1,2,4-thiadiazolo [4,5-a]benzimidazole

A mixture of 2-butyl-1,2,4-thiadiazolo[4,5-a] benzimidazole-3(2*H*)-one (2.0 g, 8.1 mmol) and dibromo(2-pyridyl)acetonitrile (4.91 g, 17.8 mmol) in 50 mL of dichloromethane was heated to reflux for 16 h. After cooling to room temperature, the precipitate was filtered, washed with dichloromethane and dried to give 2.76 g (80%) of the title compound as a light-brown solid: mp 195°C (dec); ^{1}H NMR ($CDCl_3$) δ 8.25 (m, 2H), 7.96 (dt, 1H), 7.76 (d, 1H), 7.32 (m, 2H), 6.95 (t, 1H), 6.92 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 166.08, 157.95, 150.34, 148.28, 147.71, 138.31, 128.76, 124.79, 124.58, 122.94, 121.68, 119.49, 113.97, 54.37 ppm; HRMS calcd for $C_{14}H_8Br_2N_4S$: 421.8836, found: 421.8850.

Example 9

Synthesis of 3-(oxophenylmethyl)-1,2,4-thiadiazolo[4,5-a] benzimidazole

A mixture of 2-butyl-1,2,4-thiadiazolo[4,5-a] benzimidazole-3(2*H*)-one (6.0 g, 24.3 mmole) and benzoyl cyanide (6.36 g, 48.5 mmole) in 80 mL of dichloromethane was stirred at room temperature for 24 h. The precipitate was filtered and washed with dichloromethane. The crude product was recrystallized from acetone to give 6.48 g (96%) of 3-(oxophenylmethyl)-1,2,4-thiadiazolo[4,5-a] benzimidazole as yellow crystals: mp

190-191°C; ^{1}H NMR ($CDCl_3$) δ 8.35 (d, 3H), 7.82 (d, 1H), 7.73 (t, 1H), 7.59 (t, 2H), 7.50 (t, 1H), 7.36 (t, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 180.86, 163.69, 150.82, 146.70, 134.79, 134.34, 131.22 (2C), 129.46 (2C), 128.74, 125.82, 122.27, 119.49, 115.23 ppm; IR (KBr): 1671 cm^{-1}; HRMS calcd for $C_{15}H_9N_3OS$: 279.0466, found: 279.0475. Anal. Calcd for $C_{15}H_9N_3OS$: C, 64.50; H, 3.25; N, 15.04. Found: C, 63.93; H, 3.10; N, 14.53.

In a similar manner, by replacing benzoyl cyanide with pyruvonitrile, the following compound was made:

3-(1-oxoethyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole: mp 180-181°C; ^{1}H NMR ($CDCl_3$) δ 8.70 (d, 1H), 7.80 (d, 1H), 7.50 (t, 1H), 7.38 (t, 1H), 2.83 (s, 3H); ^{13}C NMR ($CDCl_3$) 187.02, 164.15, 150.69, 147.78, 129.63, 125.82, 122.26, 119.27, 115.94, 26.74 ppm; IR (KBr) 1703 cm^{-1}. HRMS calcd for $C_{10}H_7N_3OS$: 217.0310, found: 217.0318. Anal. Calcd for $C_{10}H_7N_3OS$: C, 55.29; H, 3.25; N, 19.34. Found: C, 55.31; H, 3.29; N, 19.46.

In a similar manner, by replacing benzoyl cyanide with other cyanides, the following compounds are made:
3-(1-oxopropyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole
3-(1-oxobutyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole
3-(1-oxo-2-phenylethyl)-1,2,4-thiadiazolo[4,5-a] benzimidazole
3-(cyclopentyloxomethyl)-1,2,4-thiadiazolo[4,5-a] benzimidazole
3-(1-oxo-2-phthalimidoethyl)-1,2,4-thiadiazolo[4,5-a] benzimidazole

Example 10

Synthesis of 3-methyl-1,2,4-thiadiazolo[4,5-a]benzimidazole

2-Butyl-1,2,4-thiadiazolo[4,5-a]benzimidazole-3(2*H*)-one (1.00 g, 4.04 mmol) was refluxed in 100 mL acetonitrile for 18 h. The solvent was then evaporated

and the residue was recrystallized from methanol to give 0.671 g (88%) of the title compound: mp 192-193°C; ^{1}H NMR ($CDCl_3$) δ 7.81 (dm, 2H), 7.47 (td, 1H), 7.34 (td, 1H), 2.92 (s, 3H) ppm; IR (KBr): 1564, 1481, 1453, 1430, 1304, 1208, 756, 745 cm^{-1}; MS *m/z* 189 (M^+), 148 (M^+-CH_3CN).

In a similar manner, by replacing acetonitrile with other alkyl nitriles, the following compounds are prepared:

3-ethyl-1,2,4-thiadiazolo[4,5-a]benzimidazole
3-isopropyl-1,2,4-thiadiazolo[4,5-a]benzimidazole
3-(2-methylpropyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole

Example 11

Synthesis of 3-[4-(methoxycarbonyl)phenyl]-1,2,4-thiadiazolo[4,5-a]benzimidazole

A mixture of 2-butyl-1,2,4-thiadiazolo[4,5-a] benzimidazole-3(2*H*)-one (0.3 g, 1.2 mmole) and methyl 4-cyanobenzoate (0.41 g, 2.5 mmole) in 7 mL of dichloromethane was heated to reflux for 20 h. The precipitate was filtered and washed with dichloromethane to give 0.16 g (48%) of 3-[4-(methoxycarbonyl)phenyl]-1,2,4-thiadiazolo [4,5-a]benzimidazole as a white solid: mp 204-206°C; ^{1}H NMR ($CDCl_3$) δ 8.33 (d, 2H), 7.98 (d, 2H), 7.83 (d, 1H), 7.49 (m, 2H), 7.20 (t, 1H), 4.02 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 165.96, 165.30, 151.08, 149.10, 133.16, 132.55, 130.24(2C), 128.69(3C), 125.34, 121.58, 119.96, 112.01, 52.56 ppm; IR (KBr): 1729, 1508, 1448, 1275, 733 cm^{-1}; HRMS calcd for $C_{16}H_{11}N_3O_2S$, 309.0572 found 309.05719.

Example 12

Synthesis of 3-(4-methylphenylsulfonyl)-1,2,4-thiadiazolo [4,5-a]benzimidazole

A mixture of 2-butyl-1,2,4-thiadiazolo[4,5-a] benzimidazole-3(2*H*)-one (10.0 g, 40.4 mmole) and p-toluenesulfonyl cyanide (14.7 g, 81.0 mmole) in 120 mL of dichloromethane was stirred at room temperature for 20 h. The precipitate was filtered and washed with dichloromethane to yield 12.2 g (91%) of 3-(4-methylphenylsulfonyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole as white powder: mp 231-234°C; ^{1}H NMR ($CDCl_3$) δ 8.53 (d, 1H), 8.04 (d, 2H), 7.82 (d, 1H), 7.56-7.44 (m, 4H), 2.53 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 163.72, 150.38, 147.97, 147.54, 132.48, 130.30(2C), 129.97(2C), 128.49, 126.14, 123.06, 119.70, 114.67, 21.93 ppm; IR (KBr): 1592, 1525, 1444, 1337, 1151, 1081, 735 cm^{-1}; HRMS calcd for $C_{15}H_{11}N_3O_2S_2$: 329.0293, found: 329.0300. Anal. Calcd for $C_{15}H_{11}N_3O_2S_2$: C, 54.70; H, 3.37; N, 12.76. Found: C, 54.29; H, 3.14; N, 14.59.

Example 13

Synthesis of 3-(methoxycarbonyl)-1,2,4-thiadiazolo[4,5-a] benzimidazole

A mixture of 2-butyl-1,2,4-thiadiazolo[4,5-a] benzimidazole-3(2*H*)-one (4.0 g, 16.2 mmole) and methyl cyanoformate (2.75 g, 32.4 mmole) in 30 mL of dichloromethane was stirred at room temperature for 21 h. The precipitate was filtered and washed with dichloromethane to give 3.36 g (84%) of 3-(methoxycarbonyl)-1,2,4-thiadiazolo [4,5-a]benzimidazole as a colourless solid: mp 208-209°C; ^{1}H NMR ($CDCl_3$) δ 8.61 (d, 1H), 7.82 (d, 1H), 7.51 (t, 1H), 7.31 (t, 1H), 4.17 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 164.02, 156.51, 150.67, 140.89, 129.34, 125.93, 122.41, 119.48, 115.41, 54.04 ppm; IR (KBr): 1733 cm^{-1}; HRMS calcd for $C_{10}H_7N_3O_2S$ 233.0259, found 233.0262. Anal. Calcd. for $C_{10}H_7N_3O_2S$: C, 51.50; H, 3.02; N, 18.02. Found: C, 51.41; H, 2.89; N, 18.16.

In a similar manner, by replacing methyl cyanoformate with other cyanoformates, the following compounds are made:

3-(ethoxycarbonyl)-1,2,4-thiadiazolo[4,5-*a*]benzimidazole

3-(butoxycarbonyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole

3-(isopropoxycarbonyl)-1,2,4-thiadiazolo[4,5-*a*]benzimidazole

3-[(benzyloxy)carbonyl]-1,2,4-thiadiazolo[4,5-*a*]benzimidazole

3-[(cyclopentyloxy)carbonyl]-1,2,4-thiadiazolo[4,5-a] benzimidazole

Example 14

Synthesis of 3-(2-pyridyl)-1,2,4-thiadiazolo[4,5-a] benzimidazole

A mixture of 2-butyl-1,2,4-thiadiazolo[4,5-a] benzimidazole-3(2*H*)-one (15.0 g, 60.7 mmole) and 2-cyanopyridine (13.3 g, 0.13 mole) in 150 mL of dichloromethane was stirred at room temperature for 72 h. The precipitate was filtered and washed with dichloromethane to give 10.4 g (68%) of 3-(2-pyridyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole as a white solid: mp 173-174°C; ^{1}H NMR ($CDCl_3$) δ 8.90 (d, 1H), 8.70 (d, 1H), 8.30 (d, 1H), 7.99 (t, 1H), 7.80 (d, 1H), 7.57 (t, 1H), 7.47 (t, 1H), 7.37 (t, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 166.10, 151.09, 150.11, 148.74, 147.73, 137.38, 130.50, 125.85, 125.24, 124.52, 121.41, 119.11, 116.33 ppm; IR (KBr): 3419, 3054, 1611, 1587, 1501, 1463, 1446, 727 cm^{-1}. HRMS calcd for $C_{13}H_8N_4S$ 252.0470, found 252.0882. Anal. Calcd for $C_{13}H_8N_4S$: C, 61.89; H, 3.20; N, 22.21. Found: C, 61.48; H, 3.30; N, 22.24.

Example 15

Synthesis of 3-amino-1,2,4-thiadiazolo[4,5-a]benzimidazole

To a cooled solution of 2-butyl-1,2,4-thiadiazolo[4,5-a]benzimidazole-3(2*H*)-one (2.00 g, 8.08 mmole) in 25 mL dichloromethane, cyanamide (0.728 g, 16.2 mmole) was added in one portion and the mixture was stirred for 48 h at room temperature. The resulting precipitate was filtered, slurried in methanol and subsequently washed with dichloromethane to give 1.01 g (66%) of 3-amino-1,2,4-thiadiazolo[4,5-a]benzimidazole as colourless crystals: mp 255-256°C; ^{1}H NMR (DMSO-d_6) δ 8.23 (d, 1H), 7.71 (d, 1H), 7.43 (t, 1H), 7.54 (s, 2H), 7.32 (t, 1H) ppm; IR (KBr): 3302, 3151, 1661, 1577, 1487, 1473, 1251, 1207, 810 cm^{-1}; HRMS calcd for $C_8H_6N_4S$ 190.0313, found 190.0293. Anal. Calcd for $C_8H_6N_4S$: C, 50.51; H, 3.18; N, 29.45. Found: C, 50.26; H, 3.26; N, 29.38.

Example 16

Synthesis of 3-bromo-1,2,4-thiadiazolo[4,5-a]benzimidazole

A mixture of 2-butyl-1,2,4-thiadiazolo[4,5-a]benzimidazole-3(2*H*)-one (5.0 g, 20.2 mmole) and cyanogen bromide (4.28 g, 40.4 mmole) in 100 mL of dichloromethane was stirred at room temperature for 26 h. The precipitate was filtered and washed with dichloromethane to yield 4.18 g (81%) of 3-bromo-1,2,4-thiadiazolo[4,5-a]benzimidazole as a white powder: mp 189-190°C; ^{1}H NMR ($CDCl_3$) δ 8.23 (d, 1H), 7.82 (d, 1H), 7.52 (t, 1H), 7.42 (d, 1H) ppm; ^{13}C NMR (1:1 $CDCl_3$:DMSO-d_6): δ 162.78, 149.67, 129.22, 125.53, 122.25, 119.48, 117.25, 111.27 ppm; IR (KBr): 3025, 2925, 1601, 1493, 1451, 1028, 757, 701 cm^{-1}; HRMS calcd for $C_8H_4N_3SBr$ 252.9309, found 252.9307. Anal. Calcd for $C_8H_4N_3SBr$: C, 37.81; H, 1.59; N, 16.54. Found: C, 37.44; H, 1.33; N, 16.57.

In a similar manner, by replacing cyanogen bromide with other cyanogen halides, the following compounds are made:

3-iodo-1,2,4-thiadiazolo[4,5-*a*]benzimidazole
3-chloro-1,2,4-thiadiazolo[4,5-*a*]benzimidazole

Example 17

Synthesis of 3-[oxo(2-pyridyl)methyl]-1,2,4-thiadiazolo [4,5-a]benzimidazole

To a solution of 3-[dibromo(2-pyridyl)methyl]-1,2,4-thiadiazolo[4,5-*a*]benzimidazole (2.02 g, 4.76 mmol) in 75 mL tetrahydrofuran was added a solution of silver nitrate (0.890g, 5.24 mmol) in 75 mL water. The suspension was stirred for 2 days and then basified to pH 6 with aqueous sodium bicarbonate. After the addition of 1 mL saturated aqueous sodium chloride, the mixture was filtered on celite and the celite was washed with ethyl acetate. After extraction with water, the ethyl acetate was dried and evaporated to give a crude residue which was purified by flash chromatography using a mixture of chloroform / methanol 10:0.1 as the eluent. 1.05 g (78%) of the title compound was obtained as a yellow solid: mp 182-186°C (dec); ^{1}H NMR ($CDCl_3$) δ 8.85 (m, 1H), 8.31 (dt, 1H), 8.19 (d, 1H), 8.01 (td, 1H), 7.83 (d, 1H), 7.63 (ddd, 1H), 7.50 (ddd, 1H), 7.35 (ddd, 1H) ppm; IR (film) 1673, 1511, 1444, 1235, 1057, 879, 733 cm^{-1}; MS *m/z* 280 (M+), 148 (M+ - (2-pyridyl)C(O)CN).

Example 18

Synthesis of 3-[bis(ethoxycarbonyl)methyl]-1,2,4-thiadiazolo[4,5-a]benzimidazole

A mixture of 3-bromo-1,2,4-thiadiazolo[4,5-*a*] benzimidazole (0.2 g, 0.78 mmole), diethyl malonate (0.15 g, 0.94 mmol) and triethylamine (0.13 mL, 0.94 mmole) in 8 mL of THF was refluxed under a nitrogen atmosphere for 36 h. The resulting mixture was extracted with ethyl acetate, washed with water and 10 % aqueous sodium sulfate. The organic layer was dried over magnesium sulfate to give the crude product, which was purified by flash chromatography (35% ethyl acetate : 65% hexane) to

afford 0.14 g (54%) of the title compound as a yellow oil:

^{1}H NMR ($CDCl_3$) δ 9.48 (s, 1H), 8.06 (d, 1H), 7.63 (d, 1H), 7.34-7.31 (m, 2H), 4.39 (q, 4H), 1.35 (t, 6H) ppm; IR (film): 1748 cm^{-1}. HRMS calcd for $C_{15}H_{15}N_3O_4S$ 333.0783, found 333.0794.

Example 19

Synthesis of 3-methoxy-1,2,4-thiadiazolo[4,5-a] benzimidazole

To a cooled mixture of 3-bromo-1,2,4-thiadiazolo[4,5-*a*]benzimidazole (4.55 g, 17.9 mmole) in 50 mL of methanol, sodium methoxide (0.967 g, 17.9 mmole) was added in one portion and stirred for 4 h at room temperature. The reaction mixture was evaporated to dryness under vacuum and the residue was taken-up in ethyl acetate and washed with water. The organic layer was dried with sodium sulfate, filtered and evaporated to yield 3.64 g (94%) of 3-methoxy-1,2,4-thiadiazolo[4,5-a]benzimidazole as colourless crystals: mp 172-175°C; ^{1}H NMR ($CDCl_3$) δ 7.83 (d, 1H), 7.75 (d, 1H), 7.42 (t, 1H), 7.27 (t, 1H), 4.32 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 163.2, 150.3, 148.1, 128.2, 124.9, 121.8, 119.2, 111.7, 57.5 ppm; IR (KBr): 3418, 2942, 1595, 1492, 1404, 1275, 1255, 1206, 1083, 755 cm^{-1}. Anal. Calcd for $C_9H_7N_3OS$: C, 52.67; H, 3.44; N, 20.49. Found: C, 52.28; H, 3.36; N, 20.45.

In a similar manner, by replacing sodium methoxide with other metal alkyloxides, the following compounds are made:

3-ethoxy-1,2,4-thiadiazolo[4,5-a]benzimidazole
3-propoxy-1,2,4-thiadiazolo[4,5-a]benzimidazole
3-isopropoxy-1,2,4-thiadiazolo[4,5-*a*]benzimidazole
3-butoxy-1,2,4-thiadiazolo[4,5-a]benzimidazole
3-*tert*-butoxy-1,2,4-thiadiazolo[4,5-a]benzimidazole
3-(cyclopentyloxy)-1,2,4-thiadiazolo[4,5-a]benzimidazole

Example 20

Synthesis of 3-(dimethylamino)-1,2,4-thiadiazolo[4,5-a] benzimidazole

To a cooled mixture of 3-bromo-1,2,4-thiadiazolo[4,5-a]benzimidazole (15.44 g, 0.0603 mole) in 100 mL dichloromethane, dimethylamine (40% solution in water) (5.44 g, 0.121 mole) was added dropwise. The reaction mixture was allowed to stir for 16 h at room temperature. It was then diluted with dichloromethane, washed with water, dried with sodium sulfate and evaporated under vacuum to give 10.47 g (80%) of 3-(dimethylamino)-1,2,4-thiadiazolo[4,5-a]benzimidazole as colourless crystals: mp 102-104°C; ^{1}H NMR ($CDCl_3$) δ 7.74 (t, 2H), 7.41 (t, 1H), 7.27 (t, 1H), 3.06 (s, 6H) ppm. Anal. Calcd for $C_{10}H_{10}N_4S$: C, 55.03; H, 4.62; N, 25.69. Found: C, 54.53; H, 4.90; N, 25.50.

In a similar manner, by replacing dimethylamine with other amines, the following compounds were made:

3-(ethylamino)-1,2,4-thiadiazolo[4,5-a]benzimidazole: mp 164.5-165°C (dec); ^{1}H NMR ($CDCl_3$) δ 7.78 (m, 2H), 7.65 (d, 1H), 7.43 (t, 1H), 7.21 (t, 1H) 3.68 (q, 2H), 1.45 (t, 3H) ppm.

3-(1-pyrrolyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole: mp 118-119°C; ^{1}H NMR ($CDCl_3$) 7.77 (t, 2H), 7.43 (t, 1H), 7.28 (t, 1H), 3.71 (m, 4H), 2.07 (m, 4H) ppm.

3-(4-morpholinyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole: mp 140-142°C; ^{1}H NMR ($CDCl_3$) δ 7.78 (d, 1H), 7.60 (d, 1H), 7.45 (t, 1H), 7.32 (t, 1H), 3.99 (m, 4H), 3.48 (m, 4H) ppm.

3-(1-piperazinyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole: mp 116-118°C; ^{1}H NMR ($CDCl_3$) δ 7.76 (d, 1H) , 7.63 (d, 1H), 7.42 (t, 1H), 7.30 (t, 1H), 3.41 (m, 4H), 3.15 (t, 4H), 2.00 (br s, 1H) ppm.

3-(4-methyl-1-piperazinyl)-1,2,4-thiadiazolo[4,5-a] benzimidazole: mp 158-158.5°C; ^{1}H NMR ($CDCl_3$) δ 7.77 (d, 1H), 7.64 (d, 1H), 7.42 (t, 1H), 7.32 (t, 1H), 3.49 (m, 4H), 2.70 (m, 4H), 2.43 (s, 3H) ppm.

3-[[2-(methoxycarbonyl)methyl]amino]-1,2,4-thiadiazolo[4,5-a]benzimidazole: mp 196-197°C. Anal. Calcd for $C_{11}H_{10}N_4O_2S$: C, 50.37; H, 3.84; N, 21.36. Found: C, 50.13; H, 3.96; N, 21.26.

In a similar manner, by replacing dimethylamine with other nucleophilic amines, the following compound is made:

3-(methylamino)-1,2,4-thiadiazolo[4,5-a]benzimidazole

Example 21

Synthesis of 3-[(hydroxyimino)phenylmethyl]-1,2,4-thiadiazolo[4,5-a]benzimidazole

To a solution of 0.5 g (1.79 mmol) of 3-(oxophenylmethyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole in 7 mL of ethanol was added 0.5 mL (6.46 mmol) of pyridine and 0.5 g (7.20 mmol) of hydroxylamine hydrochloride. The mixture was refluxed for overnight. The precipitate was collected by filtration, and washed with methanol and dichloromethane to give the crude product, which was recrystallized from methanol to yield 0.47 g (89%) of the title compound as white crystals. mp 247°-248°C; ^{1}H NMR (DMSO-d_6) δ 11.89 (s, 1H), 7.81 (d, 1H), 7.73 (dd, 2H), 7.45-7.53 (m, 5H), 7.32 (t, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 168.25, 155.24, 150.52, 147.95, 136.94, 135.67, 134.30(2C), 133.03, 131.52(2C), 130.35, 127.26, 124.28, 116.91 ppm; IR (KBr): 2731, 1549, 1475, 1450, 1251, 1194, 983, 753, 736 cm^{-1}. HRMS calcd for $C_{15}H_{10}N_4OS$ 294.0575, found 294.0583.

Example 22

Synthesis of 3-(1-hydroxyethyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole

To a suspension of 3-(1-oxoethyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole (729 mg, 3.36 mmol) in 200 mL methanol, was added sodium borohydride (140 mg, 3.69 mmol). The mixture was stirred for 30 min and 0.1 mL of water was added. The methanol was evaporated and the residue was partitioned between ethyl acetate and 0.1 M hydrochloric acid. The aqueous phase was extracted with ethyl acetate. The organic phases were combined, washed twice with brine, dried and evaporated. The crude residue was purified by chromatography using chloroform / methanol to give 3-(1-hydroxyethyl)-1,2,4-thiadiazolo[4,5-a] benzimidazole. mp 174-175°C; ^{1}H NMR ($CDCl_3$) δ 8.05 (d, 1H), 7.80 (d, 1H), 7.47 (td, 1H), 7.36 (td, 1H), 5.39 (q, 1H), 2.76 (d, 1H), 1.84 (d, 3H) ppm; IR (KBr): 3136, 1544, 1494, 1478, 1451, 1374, 1250, 1200, 1123, 1103, 1093, 752, 729, 711 cm^{-1}; MS *m/z* 219 (M^+), 148 (M^+ - $CH_3CH(OH)CN$).

Example 23

Synthesis of 3-carboxy-1,2,4-thiadiazolo[4,5-a]benzimidazole

To a 6 mL solution of 1N NaOH, 3-(methoxycarbonyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole (1.0 g, 4.3 mmole) in 6 mL of dioxane, was added. The reaction mixture was stirred at room temperature until completion. The resulting mixture was then acidified with 3N HCl to pH ~2.0, and stirred at room temperature for an additional 0.5 h. The solid was filtered, washed with water, and dried under vacuum at 60 °C for 24 h to yield 0.74 g (78 %) of the title compound as a colourless solid: mp 184-185°C (dec); ^{1}H NMR (DMSO-d_6) δ 13.79 (br s, 1H), 8.59 (d, 1H), 7.78 (d, 1H), 7.51 (t, 1H), 7.40 (t, 1H); IR (KBr) 3435, 1705 cm^{-1}; MS *m/z* 193 (M^+ - OH), 175 (M^+ - CO_2).

Example 24

Synthesis of sodium 3-carboxylato-1,2,4-thiadiazolo[4,5-a] benzimidazole

To a suspension of 3-carboxy-1,2,4-thiadiazolo[4,5-a]benzimidazole (10.00 g, 45.62 mmol) in methanol (150 ml) and water (100 ml), 1M NaOH (45.6 ml) was added over a period of 1 h. After 4 h, the solution turned clear and the methanol was removed under reduced pressure. The aqueous solution was extracted with chloroform, the aqueous phase was freeze-dried to give the title compound (10.4 g, 95%) as a white solid: mp 225-227°C; ^{1}H NMR (DMSO-d_6) δ 7.68 (d, 1H), 7.05 (d, 1H), 6.95 (t, 1H), 6.80 (t, 1H) ppm; ^{13}C NMR (DMSO-d_6) δ 167.20, 161.76, 149.68, 148.84, 129.52, 126.23, 122.74, 118.37, 116.06 ppm; IR (KBr): 3395, 3243, 1663, 1641, 1522, 1443, 1334, 827, 729 cm^{-1} .

Example 25

Preparation of 3-(4-methyl-1-piperazinyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole dihydrochloride

To a clear solution of 3-(4-methyl-1-piperazinyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole (6.07g, 22.21 mmol) in 100 ml of dichloromethane, hydrogen chloride gas was bubbled through for 40 min. The solution became turbid with time. The suspension was filtered and dried under vacuum to give the title compound as a fine white powder 7.60 g (99 %). mp 252-253°C(dec); ^{1}H NMR (DMSO-d_6 & D_2O) δ 7.85 (d, 2H), 7.60 (t, 1H), 7.51 (t, 1H), 3.86 (m, 2H), 3.56 (m, 6H), 2.91 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6 & D_2O) δ 164.39, 148.80, 144.27, 126.92, 126.12, 123.41, 117.08, 113.20, 51.19, 45.87, 42.32 ppm; IR (KBr): 3420, 1606, 1571, 1475, 1461, 1225, 981, 761 cm^{-1}.

Example 26

Preparation of 2-butylimidazo[1,2-d]-1,2,4-thiadiazole-3(2*H*)-one

2-Mercaptoimidazole (24.39 g, 0.244 mole) and butyl isocyanate (48.3 g, 0.487 mole) were combined in a round-

bottom flask and heated to 50 °C for 30 min or until the reaction was complete by TLC. The reaction mixture was then cooled to room temperature and the solidified mass was triturated with 50 mL of hexane for 30 min. The beige solid was filtered, washed with a minimum amount of hexane and dried under reduced pressure to yield 44.96 g (93%) of 1-(butylcarbamoyl)-1,3-dihydroimidazole-2-thione as beige crystals: mp 66-68°C.

To solution containing 1-(butylcarbamoyl)-1,3-dihydroimidazole-2-thione (4.73 g, 23.7 mmole) suspended in 15 mL of dichloromethane cooled to 0 °C under a nitrogen atmosphere, was added bromine (3.79 g, 23.7 mmole) dissolved in 15 mL of dichloromethane, in a dropwise manner. After the addition was complete, triethylamine (4.81 g, 47.5 mmole) dissolved in 15 mL dichloromethane was added such that the temperature of the reaction mixture never exceeded 0°C. The reaction mixture was maintained at 0°C for an additional 2 h and then stirred for 16 h at room temperature. It was then diluted with 150 mL of dichloromethane and washed twice with water and once with a saturated sodium chloride solution. The organic layer was then dried over magnesium sulfate and evaporated to dryness to yield 4.30 g (92%) of 2-butylimidazo[1,2-*d*]-1,2,4-thiadiazole-3(2*H*)-one as an off-white powder: mp 142-143°C; ^{1}H NMR ($CDCl_3$) δ 7.40 (d, 1H), 7.20 (d, 1H), 3.79 (t, 2H), 1.73 (m, 2H), 1.40 (m, 2H), 0.957 (t, 3H) ppm; IR (KBr) 1702 cm^{-1}.

In a similar manner, by replacing butyl isocyanate with other selected isocyanates, the following compounds are made:

2-methylimidazo[1,2-*d*]-1,2,4-thiadiazole-3(2*H*)-one
2-ethylimidazo[1,2-*d*]-1,2,4-thiadiazole-3(2*H*)-one
2-propylimidazo[1,2-*d*]-1,2,4-thiadiazole-3(2*H*)-one
2-isopropylimidazo[1,2-*d*]-1,2,4-thiadiazole-3(2*H*)-one

2-pentylimidazo[1,2-*d*]-1,2,4-thiadiazole-3(2*H*)-one
2-hexylimidazo[1,2-*d*]-1,2,4-thiadiazole-3(2*H*)-one
2-cyclohexylimidazo[1,2-*d*]-1,2,4-thiadiazole-3(2*H*)-one
2-benzylimidazo[1,2-*d*]-1,2,4-thiadiazole-3(2*H*)-one

Example 27

Synthesis of 3-(1-oxoethyl)imidazo[1,2-d]-1,2,4-thiadiazole-3(2*H*)-one

To a cooled solution of 2-butylimidazo[1,2-*d*]-1,2,4-thiadiazole-3(2*H*)-one (2.49 g, 12.6 mmole) in 5 mL of dichloromethane, pyruvonitrile (1.74 g, 25.2 mmole) was added dropwise and allowed to stir for 24 h. The precipitate was then collected by filtration, washed with dichloromethane and evaporated under reduced pressure to yield 0.662 g (31%) of 3-(1-oxoethyl)imidazo[1,2-*d*]-1,2,4-thiadiazole-3(2*H*)-one as yellow-green crystals: mp 142-144°C; ^{1}H-NMR ($CDCl_3$) δ 8.23 (s, 1H), 7.51 (s, 1H), 2.78 (s, 3H) ppm; IR (KBr): 3436, 3168, 3106, 1516, 1408, 1363, 1229, 1136, 730 cm^{-1}. Anal. Calcd for $C_6H_5N_3SO$: C, 43.11; H, 3.01; N, 25.13. Found: C, 43.11; H, 2.91; N, 25.27.

In a similar manner, by replacing pyruvonitrile with benzoyl cyanide, the following compound was made:

3-(oxophenylmethyl)imidazo[1,2-*d*]-1,2,4-thiadiazole-3(2*H*)-one: mp 166-168°C; ^{1}H NMR ($CDCl_3$) 8.44 (d, 2H), 8.40 (s, 1H), 7.70 (d, 1H), 7.58 (t, 3H) ppm.

In a similar manner, by replacing pyruvonitrile with other selected cyanide or nitriles, the following compounds are made:

3-(1-oxopropyl)imidazo[1,2-*d*]-1,2,4-thiadiazole-3(2*H*)-one
3-(1-oxobutyl)imidazo[1,2-*d*]-1,2,4-thiadiazole-3(2*H*)-one
3-(1-oxopentyl)imidazo[1,2-*d*]-1,2,4-thiadiazole-3(2*H*)-one
3-(1-oxohexyl)imidazo[1,2-*d*]-1,2,4-thiadiazole-3(2*H*)-one

3-(cyclopentyloxomethyl)imidazo[1,2-*d*]-1,2,4-thiadiazole-3(2*H*)-one

3-(1-oxo-2-phthalimidoethyl)imidazo[1,2-*d*]-1,2,4-thiadiazole-3(2*H*)-one

Example 28

Synthesis of 3-(methoxycarbonyl)imidazo[1,2-*d*]-1,2,4-thiadiazole

To a cooled solution of 2-butylimidazo[1,2-*d*]-1,2,4-thiadiazole-3(2*H*)-one (2.95 g, 15.0 mmole) in 25 mL dichloromethane, methyl cyanoformate (2.54 g, 30 mmole) was added dropwise and the mixture was stirred for 16 h at room temperature. The precipitate was filtered and subsequently washed with dichloromethane to give 2.18 g (80%) of 3-(methoxycarbonyl)imidazo[1,2-*d*]-1,2,4-thiadiazole as colourless crystals: mp 164.5-165°C; ^{1}H NMR ($CDCl_3$) δ 8.13 (s, 1H), 7.51 (s, 1H), 4.11 (s, 3H) ppm; IR (KBr): 3440, 1737, 1527, 1253, 1071 cm^{-1}. Anal. Calcd for $C_6H_5N_3O_2S$: C, 39.34; H, 2.75; N, 22.94. Found: C, 39.41; H, 2.51; N, 22.94.

In a similar manner, by replacing methyl cyanoformate with other cyanoformates, the following compounds are made:

3-(ethoxycarbonyl)imidazo[1,2-*d*]-1,2,4-thiadiazole

3-(propoxycabonyl)imidazo[1,2-*d*]-1,2,4-thiadiazole

3-(butoxycabonyl)imidazo[1,2-*d*]-1,2,4-thiadiazole

3-(isopropoxycarbonyl)imidazo[1,2-*d*]-1,2,4-thiadiazole

3-[(pentyloxy)cabonyl]imidazo[1,2-*d*]-1,2,4-thiadiazole

3-[(cyclopentyloxy)cabonyl]imidazo[1,2-*d*]-1,2,4-thiadiazole

3-[(benzyloxy)cabonyl]imidazo[1,2-*d*]-1,2,4-thiadiazole

Example 29

Synthesis of 3-bromoimidazo[1,2-*d*]-1,2,4-thiadiazole

To a cooled solution of 2-butylimidazo[1,2-*d*]-1,2,4-thiadiazole-3(2*H*)-one (4.78 g, 0.0242 mole) in 25 mL dichloromethane, cyanogen bromide (5.13 g, 0.0482 mole)

was added in one portion and the mixture was stirred for 16 h at room temperature. The precipitate was filtered, slurried in 10 mL of methanol and subsequently washed with dichloromethane to give 4.45 g (90%) of 3-bromoimidazo[1,2-*d*]-1,2,4-thiadiazole as a colourless powder: mp 220°C (dec); MS *m/z* 205, 203 (M^+). Anal. Calcd for $C_4H_2N_3SBr$ ½ H_2O: C, 22.55; H, 1.42; N, 19.72; O, 3.75; S, 15.02; Br, 37.50. Found: C, 22.79; H, 1.41; N, 19.42; O, 2.67; S, 14.61; Br, 38.20.

In a similar manner, by replacing cyanogen bromide with other cyanogen halides, the following compounds are made:

3-iodoimidazo[1,2-*d*]-1,2,4-thiadiazole

3-chloroimidazo[1,2-*d*]-1,2,4-thiadiazole

Example 30

Synthesis of 3-methylsulfonyl-1,2,4-thiadiazolo[4,5-a] benzimidazole

To a solution of 3-methylthio-1,2,4-thiadiazolo[4,5-*a*] benzimidazole (100mg, 0.45 mmole)in 10 mL dichloromethane was added *m*-chloroperbenzoic acid (287 mg, 0.95 mmole). The mixture was stirred at room temperature and the starting material was converted to the sulfoxide after a few hours; it was then further oxidized to the sulfone after 18h. The solvent was than evaporated and the residue purified by chromatography using chloroform/methanol 10:0.1 as the eluent to yield 50 mg (44%) of 3-methylsulfonyl-1,2,4-thiadiazolo[4,5-a]benzimidazole as white solid: mp 203-207°C (dec); ^1H NMR ($CDCl_3$) δ 8.31 (d,1H), 7.84 (d,1H), 7.54 (ddd, 1H), 7.43 (td, 1H), 3.63 (s,3H) ppm; IR (KBr) 1530, 1487, 1444,1324, 1315, 1193, 1147, 1141, 735 cm^{-1}, MS *m/z* 253 (M^+), 174 ($M^+ - CH_3SO_2$), 148 ($M^+ - CH_3SO_2CN$).

Example 31

Synthesis of 3-[4-(2-pyridyl)piperazinyl]-1,2,4-thiadiazolo [4,5-a]benzimidazole

To a cooled solution of 3-bromo-1,2-4-thiadiazolo [4,5-a]benzimidazole (0.30 g, 1.17 mmol) in 10 mL of dichloromethane, 2-pyridylpiperazine (0.54 mL, 3.51 mmol) was added dropwise and the mixture was allowed to stir for 16 h. The reaction mixture was diluted with 100 mL of dichloromethane and washed with water (2 x 30 mL) and then brine (1 x 25 mL). The organic layer was dried over sodium sulfate and evapratored to give a yellow oil which was purified by column chromatography (40% EtOAc; 60% hexane) to yield a white solid (0.27g, 68.5%); ^{1}H-NMR ($CDCl_3$) δ 3.58 (m, 4H, $2CH_2$), 3.82 (m, 4H, $2CH_2$), 6.75 (m, 2H, pyr-H), 7.30 (t, 1H, ArH), 7.44 (t, 1H, ArH), 7.55 (m, 1H, pyr-H), 7.68 (d, 1H, ArH), 7.79 (d, 1H, ArH), 8.24 (m, 1H, pyr-H), m.p. 176-177.5°C.

In a similar manner, by replacing 2-pyridylpiperazine with other piperazine derivatives, the following compounds were made:

3-[4-ethylpiperazinyl]-1,2,4-thiadiazolo[4,5-a] benzimidazole

^{1}H-NMR ($CDCl_3$) δ 1.15 (t, 3H, CH_3), 2.55 (q, 2H, CH_2), 2.70 (br. s, 4H, 2 CH_2), 3.49 (br.s, 4H, $2CH_2$), 7.25 (m, 1 H, ArH), 7.40 (m, 1H, ArH), 7.65 (d, 1H, ArH), 7.79 (d, 1H, ArH); m.p. 153-154.5°C.

3-[4-propylpiperazinyl]-1,2,4-thiadiazolo[4,5-a] benzimidazole

^{1}H-NMR ($CDCl_3$) δ 0.96 (t,3H, CH_3), 1.58 (m, 2H, CH_2), 2.45 (t, 2H, CH_2), 2.74 (br. s, 4H, $2CH_2$), 3.49 (br. s, 4 H, $2CH_2$), 7.26 (t, 1H, ArH), 7.30 (t, 1H, ArH), 7.64 (d, 1 H, ArH), 7.77 (d, 1H, ArH); m.p. 137-138°C.

3-[4-(2-hydroxyethyl)piperazinyl]-1,2,4-thiadiazolo[4,5-a] benzimidazole

^{1}H-NMR ($CDCl_3$) 2.65 (s, 1H, OH), 2.72 (t, 2H, CH_2) 2.84 (s, 4H, $2CH_2$), 3.51 (s, 4H, $2CH_2$) 3.70 (t, 2H, CH_2) 7.31

(t, 1H, ArH), 7.45 (t, 1H, ArH), 7.66 (d, 1H, ArH), 7.80 (d, 1H, ArH); m.p. 160-161.5°C.

3-[4-(3-chlorophenylpiperazinyl]-1,2,4-thiadiazolo[4,5-a] benzimidazole
^{1}H-NMR ($CDCl_3$) δ 3.37(m, 6H, $3CH_2$), 3.54 (m, 4H, $2CH_2$), 6.88 (d, 1H, ArH), 7.04 (dd, 1 H, ArH), 7.10 (br.s, 1H, ArH), 7.29 (t, 1H, ArH), 7.41 (t, 1H, ArH), 7.50 (t, 1H, ArH), 7.78 (d, 1H, ArH), 7.82 (d, 1H, ArH); m.p. 218.5-219.5°C.

3-[4-benzylpiperazinyl]-1,2-4-thiadiazolo[4,5-a] benzimidazole
^{1}H-NMR ($CDCl_3$) δ 2.76 (br.s, 4H, $2CH_2$), 3.49 (br.s, 4H, $2CH_2$), 3.66 (s, 2H, CH_2), 7.30-7.50 (m, 8H, ArH), 7.64 (d, 1H, ArH), 7.78 (d, 1H, ArH); m.p. 110-112.5°C.

3-[4-cinnamylpiperazine]-1,2-4-thiadiazolo[4,5-a] benzimidazole
^{1}H-NMR ($CDCl_3$) δ 2.81 (s, 4H, $2CH_2$), 3.32 (d, 2H, CH_2), 3.51 (s, 4H, $2CH_2$), 6.27-6.36 (m, 1H, CH), 6.60 (d, 1H, CH), 7.23 - 7.46 (m, 7H, ArH), 7.65 (d, 1 H, ArH), 7.79 (d, 1H, ArH); m.p. 120-121.5°C.

3-[4-(3-amino-2-pyridyl)piperazinyl]1,2,4-thiadiazolo[4,5-a]benzimidazole
^{1}H-NMR ($CDCl_3$) δ 3.42 (m, 4H, $2CH_2$), 3.55 (m, 4H, 2 CH_2), 3.88 (s, 2H, NH_2), 6.92 (dd, J=4.74 HZ, 7.69 Hz, 1H, pyr-H-4), 7.02 (dd, J = 1.57 Hz, 7.69 Hz, 1H, pyr-H-3), 7.30 (d, 1H), ArH), 7.44 (d, 1H, ArH), 7.76 (apparent br. t, 2H, ArH), 7.86 (dd, J = 1.57 Hz, 4.78 Hz, 1H, pyr-H); m.p. 176-177.5°C.

3-[4-(1-(4-chlorophenyl)-1-phenylmethyl)piperazinyl]-1,2,4-thiadiazolo[4,5-a]benzimidazole
^{1}H-NMR ($CDCl_3$) δ 2.68 (br.s, 4H, $2CH_2$), 3.49 (br.s, 4H, $2CH_2$), 4.35 (s, 1H, CH), 7.2-7.5 (m, 11H, ArH), 7.59 (d, 1H, ArH), 7.79 (d, 1H, ArH); m.p. 172.5-174°C.

Example 32

Synthesis of 3-[2-pyridylamino]-1,2,4-thiadiazolo[4,5-a] benzimidazole

To a cooled solution of 3-bromo-1,2,4-thiadiazolo[4,5-a]benzimidazole (0.30 g, 1.17 mmol) in 15 mL of dichloromethane, 2-aminopyridine (0.276 g, 2.93 mmol) was added dropwise and the mixture was allowed to stir for 48 h. The reaction mixture wad diluted with 100 mL of dichloromethane and washed with water (2 x 30 mL) and then brine (1 x 25 mL). The organic layer was dried over magnesium sulfate and evaporated to give a yellow solid (0.26 g, 83%) ^{1}H-NMR ($CDCl_3$) δ 6.59 (apparent 5, 1 H, pyr-H), 7.12 (apparent br. d, 1H, pyr-H), 7.28 (t, 1H, ArH), 7.38 (t, 1H, ArH), 7.51 (m, 2H, ArH & pyr-H), 7.70 (d, 1H, ArH), 8.28 (d, 1H, pyr-H); m.p. 155.5-157°C.

In a similar manner, by replacing 2-aminopyridine with other amine derivatives, the following compounds were made:

3-[3-pyridylamino]-1,2,4-thiadiazolo[4,5-a]benzimidazole
^{1}H-NMR ($CDCl_3$) δ 7.41 (t, 1H, ArH), 7.48 (t, 1H, ArH), 7.62 (dd, 1H, pyr-H), 7.75 (d, 1H, ArH), 8.34 (d, 1H, ArH), 8.44 (m, 2H, pyr-H), 9.02 (d,1H, pyr-H); m.p. 175-176°C.

3-[2-pyridylmethylamino]-1,2,4-thiadiazolo[4,5-a] benzimidazole
^{1}H-NMR ($CDCl_3$) δ 2.02 (s, 1H, NH), 4.84 (d, 2H, CH2), 7.22-7.56 (M, 4H, 2ArH & 2 Pyr-H), 7.75 (m, 2H, ArH & pyr-H), 7.85 (d, 1H, ArH), 8.66 (d, 1H, pyr-H); m.p. 155.5-157°C.

3-[N-methyl-(2-pyridylethyl)amino]-1,2,4-thiadiazolo[4,5-a] benzimidazole
^{1}H-NMR ($CDCl_3$) δ 3.11 (s, 3H, CH_3), 3.18 (t, 2H, CH_2), 3.87 9t, 2H, CH_2), 7.04-7.11 (m, 2H, pyr-H), 7.26 (m, 1 H, Ar-H), 7.40 (t, 1H, ArH), 7.52 (m, 1H, pyr-H), 7.63

(d, 1H, ArH), 7.74 (1H, d, ArH), 8.41 (d, 1H, pyr-H); m.p. 105-107 °C.

Example 33

Synthesis of 3-bromomethyl-1,2,4-thiadiazolo[4,5-a] benzimidazole

A solution of 2-butyl-1,2,4-thiadiazolo[4,5-a] benzimidazole-3(2H)-one (15 g, 60.65 mmol) and bromoacetonitrile (18.19 g, 151.6 mmol) in dichloromethane (150 mL) was stirred for 48 h. A white precipitate was formed and the insoluble solid was filtered to give 12.50 g (77%) of the title compound: ^{1}H NMR ($CDCl_3$) δ 4.79 (s, 2H, CH_2), 7.42 (t, 1H, ArH), 7.51 (t, 1H, ArH), 7.84 (d, 1H, ArH), 7.94 (d, 1H, ArH); mp 242-244°C.

Example 34

Synthesis of 3-{[4-ethylpiperazinyl]methyl}-1,2,4-thiadiazolo[4,5-a]benzimidazole

1-Ethylpiperazine (0.732 ml, 6.03 mmol) was added to a suspension of 3-bromomethyl-1,2,4-thiadiazolo[4,5-a] benzimidazole (704 mg, 2.62 mmol) in dichloromethane (20 mL). The mixture was left stirring at room temperature for 26 hr. The material was diluted with dichloromethane (150 mL), and washed with water (15 mL) and brine (15 mL). The organic layer was dried over sodium sulfate and evaporated to give a solid which was recrystallized from acetonitrile (600 gm, 75.9% yield).
^{1}H-NMR ($CDCl_3$) δ 1.06 (t, 3H, CH_3), 2.39 (q, 2H, CH_2) 2.44 (m, 4H, $2CH_2$), 2.70 (m, 4H, $2CH_2$), 3.90 (s, 2H, CH_2), 7.31 (t, 1H, ArH), 7.43 (t, 1H, ArH), 7.78 (d, 1H, ArH), 7.92 (d, 1H, ArH); m.p. 140-141.5°C.

In a similar manner, by replacing 1-ethylpiperazine with piperazine derivatives, the following compounds were made:

3-{[4-propylpiperazinyl]methyl}-1,2,4-thiadiazolo[4,5-a] benzimidazole

^{1}H-NMR ($CDCl_3$) δ 0.89 (t, 3H, CH_3), 1.51 (m, 2H, CH_2), 2.30 (t, 2H, CH_2), 2.50 (br.s, 4H, $2CH_2$), 2.70 (s, 4H, $2CH_2$), 3.99 (s, 2H, CH_2), 7.32 (t, 1H, ArH), 7.45 (t, 1H, ArH), 7.80 (d, 1H, ArH), 7.95 (d, 1H, ArH); m.p. 108-110°C.

3-{[4-(2-hydroxyethyl)piperazinyl]methyl}-1,2,4-thiadiazolo [4,5-a]benzimidazole
^{1}H-NMR ($CDCl_3$) δ 2.55 (M, 6H, $2CH_2$ of piperazine, CH_2), 2.70 (m, 4H, $2CH_2$), 3.61 (m, 2H, CH_2), 3.99 (s, 2H, CH_2), 7.32 (t, 1H, ArH), 7.45 (t, 1H, ArH), 7.78 (d, 1H, ArH), 7.91 (d, 1H, ArH); m.p. 165-166.5°C.

3-{[4-phenylpiperazinyl]methyl}-1,2,4-thiadiazolo[4,5-a] benzimidazole
^{1}H-NMR($CDCl_3$) 2.80 (m, 4H, $2CH_2$), 3.20 (m, 4H, $2CH_2$), 4.00 (s, 2H, CH_2), 6.90 (m, 3H, ArH), 7.25 (t, 4H, ArH), 7.50 (t, 1H, ArH), 7.80 (d, 1H, ArH), 8.00 (d, 1H, ArH); m.p. 197-197.5°C.

3-{[4-(4-amino)phenylpiperazinyl]methyl}-1,2,4-thiadiazolo [4,5-a]benzimidazole
^{1}H-NMR ($CDCl_3$) 2.82 (m, 4 H, 2 CH_2), 3.00 (m, 4H, $2CH_2$), 3.31 (s, 2H, NH_2), 4.01 (s, 2H, CH_2), 6.63 (d, 2H, ArH), 6.78 (d, 2H, ArH), 7.32 (t, 1H, ArH), 7.45 (t,1H, ArH), 7.80 (d, 1H, ArH), 7.98 (d, 1H, ArH); m.p. 199.5-200.5°C.

3-{[4-benzylpiperazinyl]methyl}-1,2,4-thiadiazolo[4,5-a] benzimidazole
^{1}H-NMR ($CDCl_3$) 2.50 (br.s, 4H, $2CH_2$), 2.68 (br.s, 4H, $2CH_2$), 3.49 (s. 2H, CH_2), 3.98 (S, 2H, CH2), 7.30 (t, 6H, ArH), 7.46 (t, 1H, ArH), 7.79 (d, 1H, ArH), 7.94 (d, 1H, ArH); m.p. 120.5-122°C.

3-{[4-cinnamylpiperazinyl]methyl}-1,2,4-thiadiazolo[4,5-a] benzimidazole

^{1}H-NMR ($CDCl_3$) δ 2.71 (m, 4H, $2CH_2$ 2.55 (m, 4H, $2CH_2$), 3.14 (d, 2H, CH_2), 3.98 (s, 2H, CH_2), 6.27 (d, 1H, CH), 6.49 (d, 1H, CH), 7.30-7.37 (m, 6H, ArH), 7.46 (t, 1H, ArH), 7.77 (d, 1H, ArH), 7.93 (d, 1H, ArH); m.p. 162-163°C.

3-{[4-(2-pyridyl)piperazinyl]methyl}-1,2,4-thiadiazolo [4,5-a]benzimidazole

^{1}H-NMR ($CDCl_3$)) δ 2.80 (m, 4H, $2CH_2$), 3.60 (m, 4H, $2CH_2$), 4.00 (s, 2H, CH_2), 6.60 (m, 2H, pyr-H), 7.31 (t, 1H, ArH), 7.45 (t, 2H, ArH), 7.80 (d, 1H, ArH); 7.98 (d, 1H, pyr-H), 8.18 (m, 1H, pyr-H); m.p. 214-214.5°C.

3-{4-(3-amino-2-pyridyl)piperazinyl]methyl}-1,2,4-thiadiazolo[4,5-a]benzimidazole

^{1}H-NMR ($CDCl_3$) δ 2.82 (br.s, 4H, 2 CH_2), 3.17 (br.s, 4H, $2CH_2$), 3.79 (s, 2H, NH_2), 4.07 (s, 1H, CH_2), 6.84 (m, 1H, pyr-H), 6.94 (m, 1 H, pyr-H), 7.30 (m, 1H, ArH), 7.50 (m, 1H, ArH), 7.79 (m, 2H, pyr-H, ArH), 8.0 (d, 1H, ArH); m.p. 214-215.5°C.

3-{[4-(4-methoxyphenyl)piperazinyl]methyl}-11,2,4-thiadiazolo[4,5-a]benzimidazole

^{1}H-NMR ($CDCl_3$) δ 2.80 (m, 4H, $2CH_2$), 3.10 (m, 4H, 2 CH_2), 3.80 (s, 3H, $0CH_3$), 4.10 (s, 2H, CH_2), 6.80 (m, 4H, ArH), 7.30 (t, 1H, ArH), 7.50 (t, 1H, ArH), 7.80 (d, 1 H, ArH), 8.00 (d, 1H, ArH); m.p. 202-204.5°C.

3-{[4-(1-(4-chlorophenyl)-1-phenylmethyl)piperazinyl] methyl}-1,2,4-thiadiazolo[4,5-a]benzimidazole

^{1}H-NMR ($CDCl_3$) δ 2.44 (br.s, 4H, 2 CH_2), 2.68 (br.s, 4H, 2 CH_2), 3.99 (s, 2H, CH_2), 4.18 (s, 1H, CH), 7.20-7.40 (m, 10H, ArH), 7.50 (t, 1H, ArH), 7.79 (d, 1H, ArH), 7.91 (d, 1H, ArH); m.p. 82-84°C.

Example 35

Synthesis of 3-dipropylaminomethyl-1,2,4-thiadiazolo[4,5-a] benzimidazole

Dipropylamine (0.64 mL, 4.67 mmol) was added to a suspension of 3-bromomethyl-1,2,4-thiadiazolo[4,5-] benzimidazole (0.5 g, 1.87 mmol) in dichloromethane (40 mL). The mixture was left stirring at room temperature for 26 h. The material was diluted with dichloromethane (100 mL), and washed with water (3 x 40 mL) and 10% sodium sulfate solution (15 mL). The organic layer was dried over magnesium sulfate and evaporated to give a solid which was recrystallized from acetonitrile (370 mg, 69% yield). ^{1}H-NMR ($CDCl_3$) δ 0.82 (t, 6H, $2CH_3$), 1.50 (m, 4H, $2CH_2$), 2.60 (m, 4H, $2CH_2$), 4.11 (s, 2H, CH_2), 7.31 (t, 1H, ArH), 7.44 (t, 1H, ArH), 7.78 (d, 1H, ArH), 8.03 (d, 1H, ArH); m.p. 70-5-72.5 °C.

In a similar manner, by replacing dipropylamine with other amine derivatives, the following compounds were made:

3-dimethylaminomethyl-1,2,4-thiadiazolo[4,5-a]benzimidazole

^{1}H-NMR ($CDCl_3$) δ 2.41 (s, 6H, 2 CH_3), 3.90 (s, 2H, CH_2), 7.32 (t, 1H, ArH), 7.44 (t, 1H, ArH), 7.76 (d, 1H, ArH), 7.99 (d, 1H, ArH); m.p. 134-135.5°C.

3-diethylaminomethyl-1,2,4-thiadiazolo[4,5-a]benzimidazole

^{1}H- NMR ($CDCl_3$) δ 1.07 (t, 6H, $2CH_3$), 2.73 (q, 4H, 2 CH_2), 4.08 (s, 2H, CH_2), 7.30 (m, 1H, ArH), 7.43 (m, 1H, ArH), 7.77 (d, 1H, ArH), 8.04 (d, 1H, ArH); m.p. 109-110.5°C.

3-dibutylaminomethyl-1,2,4-thiadiazolo[4,5-a]benzimidazole

^{1}H-NMR ($CDCl_3$) δ 0.85 (t, 6H, $2CH_3$), 1.26 (m, 4H, $2CH_2$), 1.43 (m, 4H, 2 CH_2) 2.65 (m, 4H, $2CH_2$) 4.10 (S, 2H, CH_2),

7.27 (t, 1H, ArH), 7.45 (t, 1H, ArH), 7.78 (d, 1H, ArH), 8.02 (d, 1H, ArH); m.p. 72-72.5°C.

3-(morpholinomethyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole
^{1}H-NMR ($CDCl_3$) δ 2.66 (m, 4H, 2 CH_2), 3.71 (m, 4H, 2 CH_2), 3.99 (s, 2H, CH_2) 7.33 (t, 1H, ArH), 7.45 (t, 1H, ArH), 7.80 (d, 1H, ArH), 7.91 (d, 1 H, ArH); m.p. 145-147 °C.

3-(imidazolylmethyl)1,2,4-thiadiazolo[4,5-a]benzimidazole
^{1}H,NMR ($CDCl_3$) δ 6.35 (s, 2H, CH_2), 7.48 (t, 1H, ArH), 7.54 (t, 1H, ArH), 7.72 (d, 1H, ArH), 7.84 (m, 2H, ArH, Imd-H), 8.14 (d, 1H, ArH), 9.12 (d, 1H, ArH); m.p. 226-227°C.

3-(1,2,4-triazolylmethyl)-1,2,4-thiadiazolo[4,5-a] benzimidazole
^{1}H-NMR ($CDCl_3$) δ 6.26 (s, 2H, CH_2), 7.39 (t, 1H, ArH), 7.50 (t, 1H,, ArH), 7.80 (d, 1H, ArH), 8.04 (d, 1H, ArH), 8.10 (s, 1H, H of triazole), 8.83 (s, 1 H, H of triazole); m.p. 204.5-206°C.

Example 36

Synthesis of 3-(2-pyrazinyl)-1,2,4-thiadiazolo[4,5-a] benzimidazole

A mixture of 2-butyl-1,2,4-thiadiazolo[4,5-] benzimidazole-3(2H)-one (300 mg, 1.213 mmol) and pyrazinecarbonitrile (319 mg, 3.03 mmol) in 8 mL of dicloromethane was stirred at room temperature for 36 hr. The precipitate was filtered and washed with dichloromethane to give 0.28 g (91%) of 3-(2-pyrazinyl)-1,2,4-thiadiazolo[4,5-]benzimidazole as a white solid; ^{1}H NMR ($CDCl_3$) δ 7.32 (t, 1H, ArH), 7.50 (t, 1H, ArH), 7.83 (d, 1H, ArH), 8.67 (d, 1 H, ArH), 8.87 (br.d, 2H, py-H), 9.59 (s, 1H, py-H); mp 255-256.5°C.

Example 37

Synthesis of 4-(2-pyridyl)piperazinylcarbonyl-1,2,4-thiadiazolo[4,5-a]benzimidazole

1,1-Carbonyldiimidazole (0.355 g, 2.19 mmol) was added to a solution of 2-carboxy-1,2,4-thiadiazolo[4,5-a] benzimidazole (0.3 g, 1.37 mmol) in DMF (10 mL). The resulting solution was stirred at 40 °C for 2 h. The reaction mixture gradually changed from a white suspension into a yellow solution. N-(2-pyridyl)piperazine (0.268 g, 1.64 mmol) was added to the reaction mixture. The resulting mixture was stirred at 40 °C for 3 h, and cooled. The material was diluted with dicloromethane (100 mL) wad washed with 1N HCl (40 mL), and then 5% NaOH (60 mL). The organic layer was dried over magnesium sulfate and evaporated to give the title compound as a solid (0.2 g, 40% yield).

^{1}H-NMR ($CDCl_3$) δ 3.69 (m, 2 H, CH_2), 3.79 (m, 2H, CH_2), 4.05 (m, 4 H, $2CH_2$), 6.70 (m, 2H, pyr-H), 7.30 (t, 1H, ArH), 7.40-7.60 (m, 2H, ArH and pyr-H), 7.80 (d, 1H, ArH), 8.00 (d, 1 H, ArH), 8.23 (m, 1H, pyr-H); m.p. 222-223.5°C.

In a similar manner, by replacing 4-(2-pyridyl) piperazine with other amine derivatives, the following compounds were made:

3-{4-(benzyl)piperazinylcarbonyl}-1,2,4-thiadiazolo[4,5-a] benzimidazole

^{1}H NMR ($CDCl_3$) δ 2.72 (m, 4H, 2 CH_2), 3.60 (s, 2H, CH_2), 3.92 (m, 4H, $2CH_2$), 7.31 (t, 7H, ArH), 7.46 (t, 1H, ArH), 7.80 (d, 1H, ArH), 7.98 (d, 1H, ArH); m.p. 230-5-231.5°C.

3-{4-methylpiperazinylcarbonyl}-1,2,4-thiadiazolo[4,5-a] benzimidazole

^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H, CH_3), 2.51 (t, 2H, CH_2), 2.60 (t, 2H, CH_2), 3.90 (t, 2H, CH_2), 3.96 (t, 2H, CH_2), 7.33 (t, 1H, ArH), 7.73 (t, 1H, ArH), 7.80 (d, 1 H, ArH), 7.98 (d, 1H, ArH).

Example 38

Synthesis of 3-(4-butylpiperazinyl)-1,2,4-thiadiazolo [4,5-a]benzimidazole

A mixture of potassium carbonate (700 mg, 5.06 mmol), butyl bromide (0.43 mL, 0.4 mmol), 3-piperazinyl-1,2,4-thiadiazolo[4,5-a]benzimidazole (798 mg, 3.07 mmol) in THF (15 mL) and DMSO (2 mL) was refluxed for 16 h. The solution was evaporated to dryness, the residue partitioned between dichloromethane and water. The organic layer was washed five times with water, dried over sodium sulfate and evaporated to give an oil. This oil was mixed with acetonitrile, an insoluble solid was formed which was filtered (595 mg). The solid was purified by chromatography to give the title compound which was recrystallized from hexane (5:95) (440 mg, 41%).

^{1}H-NMR ($CDCl_3$) δ 0.95 (t, 3H, CH_3), 1.30 (m, 2H, CH_2), 1.50 (m, 2 H, CH_2), 2.40 (t, 2H, CH_2), 2.7 (m, 4H, $2CH_2$), 3.5 (m, 4H, $2CH_2$), 7.3 (t, 1H, ArH), 7.4 (t, 1H, ArH), 7.65 (d, 1H, ArH), 7.8 (d, 1H, ArH); m.p. 121-122.5°C.

Example 39

Synthesis of 2-mercapto-5-(tert-butoxycarbonyl)amino-benzimidazole

A. A mixture of 2-mercapto-5-nitrobenzimidazole (10.0 g, 5 1.23 mmol) and iron fillings (8.0 g, 143.24 mmol) in ethanol (80 mL) and water (10 mL) was refluxed. Then, concentrated HCl (1.2 mL) was added dropwise in ca. 12 min. The resulting dark brown mixture was refluxed for a further 1.5 h then cooled in ice and neutralized with a saturated sodium bicarbonate solution to pH 7.0. The mixture was diluted with EtOH (50 mL), slurried with celite (0.82 g) and filtered over a bed of celite. The cake was washed with EtOH (3 x 100 mL). The combined filtrate was concentrated in vacuo to afford 9.2 g of a light brown solid. Crystallization from hot water gave the 2-mercapto-5-aminobenzimidazole (6.74 g, 80%) as a

light brown solid. ^{1}H-NMR (DMSO) δ 4.98 (br. s, 2H), 6.40-6.43 (m, 2H, Ar-H), 6.81-6.85 (d, J=9.0Hz, 1H, Ar-H), 12.06 (br. s, 1H). ^{13}C-NMR (DMSO) : 165.9 (CS), 144.9, 133.4, 123.6, 109.8, 94.4 IR (KBr, cm^{-1}): 3362, 3295, 3173, 1637, 1622, 1507.

B. A solution of 2-mercapto-5-aminobenzimidazole (22.0 g, 133.2 mmol) and di-tert-butyldicarbonate (30.52 g, 139.86 mmol) in anhydrous THF (200 mL) was stirred at room temperature for 16 h under a blanket of nitrogen.

THF was removed by evaporation under reduced pressure and the residue was crystallized from acetonitrile to afford the title compound (28.7 g, 80%) as a light yellow solid. ^{1}H-NMR (DMSO) : 1.50 (s, 9H), 7.00 (d, J=8.6 Hz, 1H, Ar-H), 7.11 (dd, J=8.6 and 1.8 Hz 1H, Ar-H), 7.53 (s, 1H, Ar-H), 9.41 (br.s, 1H), 12.41 (br.s, 2H). ^{13}C-NMR (DMSO) : 167.9 (CS), 152.9 (C=O), 134.9, 134.9, 132.5, 127.5, 113.3, 109.3, 99.5, 79.0 (C-O), 28.2 IR (KBr, cm^{-1}): 3300, 3127, 1724, 1706, 1623, 1530. M.p. 217.1-217.7°C. Elemental Analysis calc (found) %, C 54.32 (54.32); H 5.70 (5.71) and N 15.84 (15.85).

Example 40

Synthesis of 5'-(tert-butoxycarbonyl)amino-2-butyl-3-oxo-2,3-dihydro-1,2,4-thiadiazolo-[4,5-a]benzimidazole and 6'-(tert-butoxycarbonyl)amino-2-butyl-3-oxo-2,3-dihydro-1,2,4-thiadiazolo-[4,5-a]benzimidazole

A. To a slurry of 2-mercapto-5-(tert-butoxycarbonyl) aminobenzimidazole (11.46 g, 43.19 mmol) in o-xylene (50 mL) pre-heated to 100 °C was added n-butyl isocyanate (7.3 mL, 64.79 mmol) via syringe. The mixture was then heated at 145-150 °C for 1.5 h, then cooled to room temperature and diluted with hexane (200 mL). The solid was collected by suction filtration and dried under vacuum to afford 1-butylcarbonyl-2-mercapto-5-(tert-butoxycarbonyl)amino-benzimidazole (14.19 g, 95%). ^{1}H-NMR (DMSO) δ : 0.94 (t, J= 7.2 Hz, 3H), 1.20-1.60 (m, 4H,

$2CH_2$), 1.51 (s, 9H), 3.37-3.43 (m, 2H, CH_2N), 7.19-7.23 (dd, J=9.0 and 1.9 Hz, 1H, Ar-H), 7.64 (s, 1H), 7.96 (d, J=9.0 Hz, 1H, Ar-H), 9.59 (s, 1H), 10.22 (t, J=5.4 Hz, 1H, $NHCH_2$). Elemental Analysis calc (found %: C 56.0 (55.8); H 6.6 (5.7) and N 15.4 (15.3).

B. A slurry of 1-butylcarbamoyl-2-mercapto-5-(tert-butoxycarbonyl)aminobenzimidazole (12.90 g. 34.50 mmol) in chloroform (50 mL) was cooled to -5 °C and triethylamine (9.9 mL, 70.79 mmol) was added in one portion. The resulting clear solution was stirred at ca. 0 °C for 45 min., then bromine (1.82 mL, 35.4 mmol) in chloroform (40 mL) was added dropwise over ca. 1.5 h.

After stirring for a further 15 min at 0 °C, the mixture was allowed to warm to room temperature then diluted with chloroform (1.25 L). The organic phase was washed with brine (2 x 100 mL), dried over sodium sulfate, filtered and concentrated in vacuo. The residue was slurried in methanol (100 mL) and filtered. The off-white solid was collected and dried under vacuum to afford the title compounds as a mixture in ca. 85/15 ratio (by ^{1}H-NMR).

The proton NMR spectra obtained by heating the samples were helpful in the assignment of the peaks in the aromatic region corresponding to the 2 isomers.
Isomer 1 : ^{1}H-NMR (DMSO) δ : 0.95 (t, J=7.2 Hz, 3H), 1.36-1.43 (q, J=6.8 Hz, 2H, CH_2N), 1.53 (S, 3H), 1.65-1.73 (m, 2H, CH_2), 3.73-3.78 (t, J=6.8 Hz, 2H, CH_2,N), 7.38 (d, J=8.7 Hz, 1H, Ar-H), 7.80 (d, J=8.6 Hz, 1H, Ar-H), 7.98 (s, 1H, Ar-H), 9.53 (s, 1H)

Isomer 2 : ^{1}H-NMR (DMSO) δ : 0.95 (t, J=7.2 Hz, 3H), 1.36-1.43 (q, J=7.4 Hz, 2H, CH_2CH_3), 1.53 (S, 9H), 1.65-1.73 (m, 2H, CH_2), 3.73-3.78 (t, J=6.8 Hz, 2H, CH_2N), 7.38 (d, J=8.7 Hz, 1H, Ar-H), 7.63 (d, J=8.6 Hz, 1H, Ar-H), 8.34 (s, 1H, Ar-H), 9.60 (s, 1H).

Example 41

Synthesis of 5'amino-[3-(2-pyridyl)]-1,2,4-thiadiazolo [4,5-a]benzimidazole and 6'-amino-[3-(2-pyridyl)]-1,2,4-thiadiazolo[4,5-a]benzimidazole

A. To a slurry of products from Example 40, part B (1.0 g, 2.76 mmol) in chloroform (5.0 mL) was added 2-cyanopyridine (0.575 g, 5.52 mmol) in one portion. The resulting mixture was refluxed for 5 h, then stirred at room temperature for 16 h.

Chloroform was removed under reduced pressure and the residue was slurried with diethyl ether (10 mL) and filtered. The off-white solid was collected and dried under vacuum. Thus, 0.68 g (67%) of 5'-(tert-butoxycarbonyl)amino-[3-(2-pyridyl)]-1,2,4-thiadiazolo [4,5-a]benzimidazole and 6'-(tert-butoxycarbonyl)amino-[3-(2-pyridyl)]-1,2,4-thiadiazolo[4,5-a]benzimidazole in ca. 1:1 ratio were obtained.

^{1}H-NMR ($CDCl_3$) δ : 1.56 (s, 9H), 6.67 (br.s. 1H, NH), 7.23-7.32 (m, 1H, py-H), 7.54-6.60 (m, 1H, Ar-H), 7.66-7.69 (d, J=8.7 Hz, 0.5H, Ar-H), 7.79 (d, J=1.9 Hz, 0.5 H, Ar-H), 7.93-7.98 (t, J=8.0 Hz, 1H, py-H), 8.28-8.32 (m, 1H, py-H), 8.64 (d, J=9.0 Hz, 0.5 H, Ar-H), 8.86-8.89 (dd, J=4.8 and 0.9 Hz, 0.5 H, py-H), 8.98 (br.d, J=4.8 Hz, 0.5 H, py-H) and 9.20 (br. s, 0.5 H).

B. A slurry of the compounds obtained in Example 41, part A (1.0 g, 2.72 mmol) in a solution of HCl in MeOH (25 mL) were stirred at room temperature for 4.5 h. A further 25 mL of HCl in MeOH was added, and volatile materials were removed in vaccuo. The residue was slurried in diethyl ether and filtration afforded the title compounds as their light yellow HCl salts (0.99 g, 96.6%) in ca. a 1:1 mixture of isomers (by HPLC: 20 mM ammonium acetate/acetonitrile 80/20; C18 column). IR (KBr, cm^{-1}): 3419, 1611, 1551, 1527. Elemental Analysis:

calc. (found) %: C41.5 (41.0); H 3.2 (3.5) and N 18.6 (18.3).

Example 42

Synthesis of 1,2,4-thiadiazolo[4,5-a]benzimidazol-3-yl-L-leucyl isomylamide.

Potassium carbonate (544 mg, 3.94 mmol) was added to a solution of L-leucyl isoamylamide (0.788 g, 3.94 mmol) and 3-bromo-1,2,4-thiadiazolo[4,5-a]benzimidazole (1.0 g, 3.94 mmol) in THF (15 mL). The mixture was stirred at room temperature for 16 h and then refluxed for a further 8 h. The solvent was evaporated to dryness and the residue was partitioned between ethyl acetate (125 mL) and water (15 mL). The organic phase was washed with brine (10 mL), dried over sodium sulfate and evaporated to give a solid which was further purified by column chromatography (10% MeOH: $CHCl_3$) to give the title compound (715 mg).

^{1}H-NMR ($CDCl_3$) δ 0.92 (d, 6H, $2CH_3$), 0.92-1.10 (dd, 6H, $2CH_3$), 1.40-1.52 (m, 2H), 1.54-1.78 (m, 2H), 1.80-2.00 (m, 2H, CH_2), 3.34-3.45 (m, 2H, CH_2NH), 4.48-4.58 (m, 1H, -CH of leu), 6.56 (t, J=5.6 Hz, 1H, $NHCH_2$), 6.60 (d, J=8.3 Hz, 1H, NHCH), 7.15 (t, 1H, J=7.4 Hz, Ar-H), 7.34 (t, 1H, J=8.2 Hz, Ar-H), 7.64 (d, 1H, J=8.2 Hz, Ar-H), 7.77 (d, 1H, J=8.1 Hz, Ar-H),
^{13}C-NMR ($CDCl_3$) δ 172.5 (CO-CH), 164.4 (c-s), 150.4, 145.0, 127.8, 124.5, 121.3, 119.1, 110.2, 55.4 (CH-CO), 41.7, 38.4, 38.2, 25.8, 24.9, 23.0, 22.4, 22.1.
IR (thin film, cm^{-1}): 3241 (NH), 1660 (C=0), 1574.
M.p. 105-107 °C. Elemental Analysis: Calc. (found) %; C 61.10 (61.30), H 7.29 (7.05), N 18.75 (18.43).

Example 43

Synthesis of {1,2,4-thiadiazolo[4,5-a]benzimidazol-3-yl}-carbonyl-L-leucyl isoamylamide

1,1-Carbonyldimidazole (1.30 g, 8.03 mmol) was added to a suspension of 3-carboxy-1,2,4-thiadiazolo[4,5-a] benzimidazole (1.10 g, 5.02 mmol) in DMF (30 mL). The mixture was heated at 45 °C for 2 h at which time the mixture turned into a yellow solution. The solution was cooled to 0 °C, leucyl isoamylamide (1.21 g, 6.02 mmol) and DMF (5 mL) were added and the resulting mixture was stirred for 16 h at R.T. The mixture wad diluted with ether (400 mL), and the ethereal layer washed with 0.5 M HCl (25 mL), water (3 x 25 mL), and brine (925 mL). The ethereal layer was dried over sodium sulfate, and evaporated to give a solid (1.77 g) which was further purified by column chromatography to give 1.33 g of the desired material.

^{1}H-NMR ($CDCl_3$) δ 0.90 (d, 6H, J=6.5 Hz, $2CH_3$), 1.05 (dd, 6H, $2CH_3$), 1.38-1.48 (m, 2H), 1.54-1.68 (m, 1H), 1.72-1.85 (m, 3H), 3.22-3.38 (m, 2H, CH_2NH), 4.62-4.78 (m, 1H, CHCO), 6.30 (t, 1H, NH), 7.32 (t, 1H, J=7.3 Hz, Ar-H), 7.45 (t, 1H, J-7.4 Hz, Ar-H), 7.75 (d, 1H, J=8.0 Hz, Ar-H), 7.93 (d, 1H, J=8.4 Hz, Ar-H), 8.73 (d, 1H, J=8.3 Hz, NH).

^{13}C-NMR ($CDCl_3$) δ 170.8 (COCH), 164.4 (CS), 155.4, 150.5, 144.1, 129.4, 125.8, 122,2, 119.1, 116.3, 52.6 (CHCO), 41.4, 38.3, 38.2, 25.8, 24.9, 22.9, 22.4, 22.1.

IR (KBr, cm^{-1}): 3295 (NH), 1651 (C=0), 1527.

M.p. 164-167°C.

Example 44

Acid stability of 7-methoxy-3-[(4-methoxy-3,5-dimethyl-2-pyridyl)oxomethyl]-1,2,4-thiadiazolo[4,5-a]benzimidazole

To examine acid stability of the captioned compound, the compound was dissolved in a minimum volume of methanol and the resulting solution was added to a 6 molar solution of hydrochloric acid. The compound was found to be very stable in acid and was totally recovered after stirring for 48 hours at room temperature. Omeprazole, on the other hand, underwent complete

decomposition in a few minutes under the above conditions. 1,2,4-Thiadiazole derivatives are superior to omeprazole as a direct thiol trapping agent in acidic medium because they are stable in acid.

Example 45

Reaction of 3-[(4-methoxy-3,5-dimethyl-2-pyridyl) oxomethyl]-1,2,4-thiadiazolo[4,5-a]benzimidazole with 3-mercaptopropionic acid.

To a suspension of 250 mg of 3-[(4-methoxy-3,5-dimethyl-2-pyridyl)oxomethyl]-1,2,4-thiadiazolo[4,5-*a*] benzimidazole in 125 mL methanol and 38 mL 0.1 M hydrochloric acid was added 161 μL of 3-mercaptopropionic acid. After complete degradation of the starting material, the mixture was neutralized to pH 6 with aqueous sodium bicarbonate and extracted with ethyl acetate. The ethyl acetate was dried on anhydrous magnesium sulfate and evaporated. The crude material was purified by chromatography to give 93 mg of 2-imino-2-(2-mercapto-1-benzimidazolyl)-1-(4-methoxy-3,5-dimethyl-2-pyridyl) ethanone, 65 mg of 2-mercaptobenzimidazole and 61 mg of methyl 2-(4-methoxy-3,5-dimethyl-2-pyridyl)-2-oxoacetate. 2-Imino-2-(2-mercapto-1-benzimidazolyl)-1-(4-methoxy-3,5-dimethyl-2-pyridyl)ethanone: ^{1}H NMR ($CDCl_3$) δ 10.55 (br s, 1H, NH or SH), 10.35 (br s, 1H, NH or SH), 8.10 (d, 1H, J = 7 Hz, ArH), 7.80 (s, 1H, H6 of pyridyl), 7.35 - 7.20 (m, 2H, 2 X ArH), 7.10 (d, 1H, J = 7.9 Hz, ArH), 3.75 (s, 3H, OCH_3), 2.60 (s, 3H, $ArCH_3$), 2.15 (s, 3H, $ArCH_3$) ppm; IR (KBr) 3262, 1691, 1635, 1502, 1458, 1396, 1328, 1272, 1247, 1004, 746 cm^{-1}; MS (electrospray) *m/z* 341 (MH^+), 191 (MH^+ - 2-mercaptobenzimidazole). 2-Mercaptobenzimidazole: the material was found to be identical to an authentic sample purchased from Aldrich Chemical Co. by ^{1}H NMR, IR and TLC. Methyl 2-(4-methoxy-3,5-dimethyl-2-pyridyl)-2-oxoacetate: ^{1}H NMR ($CDCl_3$) δ 8.45 (s, 1H, ArH), 4.1 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 2.65 (s, 3H, $ArCH_3$), 2.4 (s, 3H, $ArCH_3$) ppm; IR (KBr) 1747, 1703, 1468, 1394,

1310, 1242, 1206, 1120, 1004, 740 cm^{-1}; MS *m/z* 224 (M^+ + H), 164 (M^+ - CO_2Me), 136 (M^+ - CO_2Me - CO).

Example 46

Reaction of 3-(dimethylamino)-1,2,4-thiadiazolo[4,5-a] benzimidazole with phenethyl mercaptan.

To a solution of 23 mg of 3-(dimethylamino)-1,2,4-thiadiazolo[4,5-a]benzimidazole in 10 mL of methanol was added 360 µL of phenethyl mercaptan. After 1 min, the reaction is complete. The solvent was evaporated and the crude material was purified by chromatography to give 15 mg of N^1,N^1-dimethyl-2-mercapto-1-benzimidazolylamidine: ^1H NMR (DMSO-d_6) δ 7.3-7.0 (m, 4H, 4 X ArH), 3.35 (br s, 2H, NH, SH), 2.88 (s, 6H, 2 X NCH_3) ppm; IR (KBr): 3210, 1641, 1475, 1452, 1407, 1319 cm^{-1}; MS *m/z* 220 (M+), 150 (M^+ - Me_2NC=NH).

Example 47

Reaction of 3-bromo-1,2,4-thiadiazolo[4,5-a]benzimidazole with phenethyl mercaptan.

To a suspension of 500 mg of 3-bromo-1,2,4-thiadiazolo [4,5-a]benzimidazole in 50 mL methanol was added 790 µL of phenethyl mercaptan. The solid rapidly dissolves. After completion of the reaction, the solvent was evaporated and the residue purified by chromatography to give 296 mg of 2-mercapto-1-benzimidazolecarbonitrile: ^1H NMR (DMSO-d_6): 12.85 (br s, 1H, SH), 7.5 - 7.2 (m, 4H, 4 X ArH) ppm; IR (KBr) 2259, 1509, 1459, 1303, 1189, 752 cm^{-1}; MS *m/z* 175 (M^+), 150 (M^+ - CN).

Example 48

Reaction of 3-methoxy-1,2,4-thiadiazolo[4,5-a]benzimidazole with phenethyl mercaptan.

To a solution of 23 mg of 3-methoxy-1,2,4-thiadiazolo [4,5-a]benzimidazole in 10 mL of methanol was

added 376 μL of phenethyl mercaptan. After 1 min, the reaction is complete. The methyl 2-mercapto-1-benzimidazolecarboxi-midate was identified as the major reaction product of the reaction: ^{1}H NMR (DMSO-d_6) δ 13.45 (br s, 1H, SH or NH), 9.8 (s, 1H, NH or SH), 7.7 (d, 1H, J = 8 Hz, ArH), 7.35 - 7.2 (m, 3H, 3 X ArH), 3.95 (s, 3H, OCH_3) ppm; IR (KBr): 3437, 3095, 1679, 1450, 1440, 1376, 1193, 735 cm^{-1}; MS *m/z* = 207 (M^+), 150 (M^+ - MeOC=NH).

Example 49

Reaction of 3-(oxophenylmethyl)-1,2,4-thiadiazolo[4,5-a] benzimidazole with phenethyl mercaptan

To a suspension of 26 mg of 3-(oxophenylmethyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole in 10 mL methanol was added 31 μL of phenethyl mercaptan. It was found that the substrate undergoes complete conversion to 2-mercaptobenz-imidazole by comparing with an authentic sample of 2-mercaptobenzimidazole purchased from Aldrich Chemical Co.

Example 50

Reaction of 3-[hydroxy(4-methoxy-3,5-dimethyl-2-pyridyl) methyl]-1,2,4-thiadiazolo[4,5-a]benzimidazole with phenethyl mercaptan.

To a suspension of 25 mg of 3-[hydroxy(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]-1,2,4-thiadiazolo[4,5-a] benzimidazole in 10 mL methanol was added 250 μL of phenethyl mercaptan. It was found that the substrate undergoes complete conversion to 2-mercaptobenzimidazole by comparing with an authentic sample of 2-mercaptobenz-imidazole purchased from Aldrich Chemical Co.

Example 51

Reaction of 3-[(4-methylphenyl)sulfonyl]-1,2,4-thiadiazolo [4,5-a]benzimidazole with phenethyl mercaptan.

To a suspension of 31 mg of 3-[(4-methylphenyl) sulfonyl]-1,2,4-thiadiazolo[4,5-a]benzimidazole in 10 mL methanol was added 313 μL of phenethyl mercaptan. It was found that the substrate undergoes complete conversion to 2-mercaptobenzimidazole by comparing with an authentic sample of 2-mercaptobenzimidazole purchased from Aldrich Chemical Co.

Example 52

Reaction of 3-[(4-methoxy-3,5-dimethyl-2-pyridyl) oxomethyl]-1,2,4-thiadiazolo[4,5-a]benzimidazole with phenethyl mercaptan

Phenethyl mercaptan (120 μL, 0.90 mmol) was added to a suspension of 3-[(4-4-methoxy-3,5-dimethyl-2-pyridyl) oxomethyl]-1,2,4-thiadiazolo[4,5-a]benzimidazole (300 mg, 0.887 mmol) in methanol (150 ml) and 0.1 M hydrochloric acid (38 mL). After stirring the mixture at room temperature for 51 h, the mixture was neutralized to pH 6 with aqueous sodium bicarbonate and extracted with ethyl ether. The ether layer was dried on sodium sulfate and evaporated. The crude material was purified by chromatography (elution gradient: 10% EtOAc : hexane to 30% EtOAc: hexane) to give 110 mg of diphenethyl disulfide (92% yield from phenethyl mercaptan), 63 mg of the methyl ester of 2-oxo-2-(4-methoxy-3,5-dimethyl-2-pyridyl)acetic acid (37.6% yield from consumed titled 1,2,4-thiadiazolo [4,5-a]benzimidazole), 44 mg of 3-[(4-methoxy-3,5-dimethyl-2-pyridyl)oxomethyl]-1,2,4-thiadiazolo[4,5-a]benzimidazole (14.6% recovered starting material) and 2-mercaptobenzi-midazole (46 mg, 40% yield from titled 1,2,4-thiadiazolo [4,5-a]benzimidazole).

Methyl 2-oxo-2-(4-methoxy-3,5-dimethyl-2-pyridyl)acetate: ^1H NMR ($CDCl_3$) δ 8.45 (s, 1H, ArH), 4.1 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 2.65 (s, 3H, $ArCH_3$), 2.4 (s, 3H, $ArCH_3$) ppm; IR (KBr) 1747, 1703, 1468, 1394, 1310,

1242, 1206, 1120, 1004, 740 cm^{-1}; MS m/z 224 (M^+ + H0, 164 (M^+ - CO_2Me), 136 (M^+ - CO_2Me - C0).

2-Mercaptobenzimidazole: the material was found to be identical to an authentic s ample purchased from Aldrich Chemical Co. by ^1H NMR, IR and TLC.

Diphenethyl disulfide: H-NMR ($CDCl_3$) δ: 3.03 (m, 8H, $2CH_2CH_2$), 7.27 (m, 6H, ArH), 7.30 (m, 4H, ArH), C-NMR ($CDCl_3$: 35.79, 40.27, 126,46, 128.57, 128.67, 140.08.

Example 53

Reaction of 3-(4-methyl-piperzinyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole with thiophenol

A solution of 3-(4-methylpiperazinyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole dihydrochloride (1.494 g. 4.31 mmol) and thiophenol (1.43 ml, 12.94 mmol) in methanol (400 ml) and 1N HCl (120 ml) was stirred at room temperature for 3.5 days. The material was evaporated to give a solid residue which was partitioned between ether (3 x 100 ml) and water (20 ml). The ethereal layer was dried over sodium sulfate and evaporated to give 753 mg of diphenyl disulfide (53.3% yield). The aqueous layer was neutralized by dropwise addition of 2N NaOH at 0 °C and then extracted with dichloromethane (3 x 100 ml). The dichloromethane layer was dried over sodium sulfate and evaporated to give 1-[imino-(5-methyl-piperazine-1-yl) methyl-1H-benzimidazole-2-thiol as a solid (1.13 g, 95.1% yield).

H-NMR (DMSO) δ: 2.19 (s, 3H, N-Me), 2.33 (br.s, 4H, $2CH_2CH_2$-), 3.24 (br. s, 4H, $2CH_2CH_2$-), 7.14-7.23 (m, 4H, ArH).

C-NMR (DMSO): 44.81, 45.11, 53.59, 109.52, 110.42, 123.09, 123.89, 131.47, 131.57, 149-34 (C=NH), 166.89 (CSH).

Example 54

Reaction of 3-benzoyl-1,2,4-thiadiazolo[4,5-a]benzimidazole with thiophenol

A solution of thiophenol (1.08 ml, 10.47 mmol), 3-benzoyl-1,2,4-thiadiazolo[4,5-a]benzimidazole (975 mg, 3.49 mmol) in methanol (400 ml) and 1N HCl solution (120 ml) was stirred at room temperature for 16 h. The solution was evaporated under reduced pressure to remove methanol; the aqueous mixture was neutralized to pH 7.0 with solid sodium bicarbonate and extracted with CH_2Cl_2. The organic layer was dried over sodium sulfate and evaporated to give a solid. This material was purified by column chromatography to give the following compounds:

Diphenyl disulfide (700 mg solid; R_1 = 0.69, 10% EtoAc : hexane) which has identical NMR to diphenyl disulfide from Aldrich Chemical.
H-NMR ($CDCl_3$): δ 7.3-7.35 (m, 2H, ArH), 7.35-7.45 (m, 4H, ArH); 7.63-7.68 (m, 4H, ArH), C-NMR ($CDCl_3$): 127.326, 127.703, 1 29.241, 137.219.

2-mercaptobenzimidazole (180 mg, 34.3% yield; R_1 = 0.46, 20% EtOAc : hexane) which has identical NMR to 2-mercaptobenzi-midazole from Aldrich Chemical.

Methyl benzoylformate (120 mg, 2 1% yield; R_1=0.57, 20% EtOAc : hexane) which has identical NMR to methyl benzoylformate from Aldrich Chemical. H-NMR ($CDCl_3$): 52.67, 128.86, 130.03, 1 32.44, 134.89, 164.01 (C=O), 185.98 (C=O), IR: 1740, 1687, cm^{-1}.

Example 55

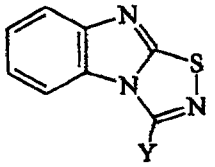
Reaction of 1,2,4-thiadiazolo[4,5-a]benzimidazole derivative with 2-mercaptoethanol. Determination of $t_{1/2}$ values.

Calculated amount of the 1,2,4-thiadiazolo[4,5-a] benzimidazole derivative (final solution strength = $5x10^{-3}$M) and phenol (118 mg, final solution strength = 5×10^{-3}M) were dissolved in of methanol (250 ml) in a

volumetric flask. 100 ml of the solution was transferred to a clean volumetric flask, and the resulting solution was stirred at R.T. 100 µl of 2-mercaptoethanol (final solution strength = 1.15×10^{-2}M) was added within 60 sec with the tip of the syringe inserted into the solution. The course of the reaction was monitored by HPLC (Hewlett Packard Model 1100) equipped with a PE express 3.3 cm, C18 column and an UV detector set at 254 nm. The column is eluted with 70% 50 mM ammonium acetate; 30% acetonitrile as the mobile phase.

Percentage reaction completion was calculated as follows:
At time 0, 100% starting material remained unreacted.
At time t, % of unreacted starting material
= $\{h_{sample}/h_{int.std}$ at time t$\}$ / $\{h_{sample}/h_{int.std}$ at time 0$\}$ * 100%. The % unreacted starting material was plotted against the time scale, t½ is the time point corresponding to 50% of unreacted starting material.

Reaction of tricyclic 1,2,4-thiadiazoles with mercaptoethanol at pH 7.0



Y Group	t½ at pH = 7.0
MeO	0.31 h
Me_2N	1.5 h
morpholino	2.4 h
4-methylpiperazinyl	6.7 h
phenyl	45 h
methyl	59 h
2-pyridyl	134 h
acetyl	110 h
morpholinomethyl	98 h
dimethylaminoethyl	64 h

Example 56

Effects of compounds of Formula I on Gastric Acid Secretions in Rats

Fasted, adult (140-240 g), male, Sprague-Dawley rats were fasted for 24 h from food, but not water, and then treated by oral gavage with 1 to 1.5 mL total volume of compound of Formula I (300 μmmol/Kg) on different days. Two hours later, rats were anesthetized with a combination of pentobartital and thiopental, the abdomen was opened and the pylorus was ligated, and tracheal, gastric, and peripheral venous canulas were placed. The stomachs were lavaged with 10 mL 0.9% saline every 10 min. for 30 min and the gastric effluent collected in receptacles to determine the basal acid secretion. Acid output was determined in each gastric effluent sample by back-titration to pH 7.0 using 0.02M NaOH. Then, 5 mL of an 8% peptone meal (pH 5.5) was instilled into the stomachs, mixed, and drained after 10 min each time for 2 hours. Acid output was determined in each gastric effluent containing the peptone meal by back-titration to pH 5.5 using 0.02 M NaOH.

In the controlled vehicle (n = 6), 8% peptone stimulated acid output is noted at 160 mmol/30 min after 1 hr., while rats dosed with 7-methoxy-3-[(4-methoxy-3,5-dimethyl-2-pyridyl)oxomethyl]-1,2,4-thiadiazolo[4,5-a] benzimidazole have an observed level of acid output at 20 μmmol/30 min after 1 h. 7-Methoxy-3-[(4-methoxy-3,5-dimethyl-2-pyridyl)oxomethyl]-1,2,4-thiadiazolo[4,5-a] benzimidazole demonstrated significant ($p < 0.05$) inhibition of meal-stimulated acid secretion at 300 μmol/kg doses.

Example 57

Effects of compounds of Formula I on Gastric Acid Secretions in Rats (Dose-dependent study)

Fasted, adult (140-240g), male, Sprague-Dawley rats were fasted for 24 h from food, but not water, and then treated by oral gavage with 1 to 1.5 mL total volume of 4 different doses (0.3, 3, 30, and 300 μmol/kg) of each compound on different days. Two hours later, rats were anesthetized with a combination of pentobartital and thiopental, the abdomen was opened and the pylorus was ligated, and tracheal, gastric, and peripheral venous canulas were placed. The stomachs were lavaged with 10 mL 0.9% saline every 10 min. for 30 min and the gastric effluent collected in receptacles. Acid output was determined in each gastric effluent sample by back-titration to pH 7.0 using 0.02M NaOH. Then, 5 mL of an 8% peptone meal (pH 5.5) was instilled into the stomachs, mixed, and drained after 10 min each time for 2 hours. Acid output was determined in each gastric effluent sample by back-titration to pH 7.0 using 0.02 M NaOH. After measuring basal acid output for at least 30 minutes, acid output was then measured during a 2 h intravenous infusion of histamine (5 mg/kg).

Figure 5 shows gastric acid output (mmol/min) after administration of vehicle and after administration of 4 doses of 7-methoxy-3-[(4-methoxy-3,5-dimethyl-2-pyridyl) oxomethyl]-1,2,4-thiadiazolo[4,5-a]benzimidazole (0.3, 3, 30, and 300 mmol/kg) in anesthetized rats.

7-methoxy-3-[(4-methoxy-3,5-dimethyl-2-pyridyl) oxomethyl]-1,2,4-thiadiazolo[4,5-a]benzimidazole demonstrated significant ($p < 0.05$) inhibition of histamine-stimulated acid secretion at 3, 30, 300 μmol/kg doses.

Example 58

***In Vitro* Inhibition of Gastric Acid Secretion By 3-(4-methyl-1-piperazinyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole dihydrochloride**

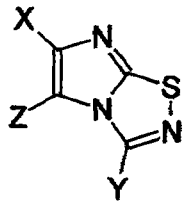
Acid secretion is measured indirectly by the accumulation of the weak base ^{14}C-aminopyrine in the isolated murine gastric glands of mouse. The assay is performed in polypropylene eppendorf tubes containing 0.5 mL of resuspended mouse gastric glands. In addition, tubes contain the tested drug, acid secretagogues (e.g. histamine, di-butyryl cyclic AMP (cAMP), carbachol) and ^{14}C-aminopyrine. Tubes are incubated for 60 min. at 37 °C and continuously rotated. The reaction is stopped by centrifugation of the gland suspension for five min. at 1500 g. Supernatant is aspirated leaving the pellet containing intact gastric glands. The pellet is washed extensively and digested overnight in 1 mL of Protosol (Amersham). After neutralisation with acetic acid and addition of scintillation fluid, the radioactivity is counted in a beta-counter (Beckman). The amount of radioactivity trapped in the pellet corresponds directly with the amount of acid being secreted. Each experimental point is done in triplicate. In each experiment, energy independent consumption was estimated with 0.1 mM of dinitrophenol and basal acid secretion in the absence of acid stimulants. These values were then subtracted from corresponding results in order to calculate basal or secretagogue stimulated acid secretion.

Mouse glands respond to a variety of conventional secretagogues and post-receptor mediators but not to gastrin. The maximum stimulation of acid secretion is achieved with 1 mM cAMP, 0.1 mM histamine, 0.1 mM IBMX, 10μM carbachol, 10 μM forskolin, 10 μM calcium ionophore A23187, 1 μM thapsigarin. Each experiment is repeated a number of times and all results are expressed as a % of the maximum stimulation. For the purpose of comparing the relative potency of the compounds, each experiment contains positive controls using omeprazole for post-receptor / cAMP mediated responses and ranitidine which inhibits histamine mediated acid secretion.

3-(4-Methyl-1-piperazinyl)-1,2,4-thiadiazolo[4,5-a] benzimidazole dihydrochloride completely inhibited cAMP and histamine stimulated acid secretion at 100 μM. Using the above procedure, the ED_{50} value for this compound was found to be 50 μM.

WHAT IS CLAIMED IS:

1. Imidazo[1,2-*d*]-thiadiazole compounds corresponding to the general formula I:

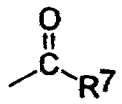


wherein X and Z are independently hydrogen, lower alkyl, halo, nitro, hydroxy, lower alkoxy, a group NR'R", OC(O)R', OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O)NR'R", NHC(O)OR' or CONR'R", with R' and R" being independently hydrogen, lower alkyl, aryl, lower arylalkyl or lower alkyl substituted with hydroxy, amino, lower alkylamino, carboxy or lower alkoxycarbonyl, or R' and R" in NR'R" when taken together forming a five or six membered ring heterocyclic ring selected from piperidinyl, pyrrolidinyl, morpholinyl and prolyl, the heterocyclic ring being optionally substituted with lower alkyl, carboxy, amino, phenyl, alkoxycarbonyl or di-lower alkylamino;

or X and Z taken together represent a benzene ring fused to the imidazo ring and being optionally substituted with up to four substituents independently selected from hydrogen, lower alkyl, halo, nitro, hydroxy, lower alkoxy, piperazinyl or a group NR'R", OC(O)R', OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O)NR'R", or NHC(O)OR', with R', R" being as defined above;

and Y is selected from :

(1) groups of the formula:



in which R^7 represents hydrogen, hydroxy, lower alkyl, lower cycloalkyl, lower alkoxy, lower

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in which R^7 represents hydrogen, hydroxy, lower alkyl, lower cycloalkyl, lower alkoxy, lower alkenyl, lower alkynyl, aryl, lower arylalkyl, heterocyclyl, N-substituted N-heterocyclyl, heterocyclyloxy, heterocyclyl-loweralkylene, a group NR'R" where R' and R" are independently selected from hydrogen, lower alkyl, aryl, lower arylalkyl, and alkylene, and a group ANR'R", AOR wherein A is an amino acid residue or a peptide of 2 to 3 amino acid residues and R', R" have the same definition as above

(2) heterocyclyl, lower alkylene-heterocyclyl, lower alkylene-amino-heterocyclyl, amino-lower alkylene-heterocyclyl or amino-heterocyclyl, the heterocyclic ring being attached at any heteroatom or carbon atom which results in the creation of a stable structure, and the heterocyclic ring being optionally substituted with 1-3 substituents selected from lower alkyl; hydroxy; nitro; amino; lower alkylamino; di-lower alkylamino; lower alkoxy; cinnamyl, lower alkyl substituted with 1-3 substituents selected from hydroxy, lower alkylcarbamoyl, phenyl, halophenyl, heterocyclyl, carboxy and lower alkoxycarbonyl; lower acyl; lower alkoxycarbonyl; lower alkyl-sulfonyl; amido; allyl; benzyl; phenyl optionally substituted with amino, halo, hydroxy, lower alkoxy, lower alkyl, lower alkylamino or di-lower alkylamino; heterocyclyl optionally substituted with 1-3 substituents selected from nitro, hydroxy, lower alkoxy, lower alkyl, amino, halo, lower alkylamino, di-lower alkylamino; with the proviso that the heterocyclyl group Y is not 1-imidazolyl or substituted 1-imidazolyl;

(3) NR'R" or $-CH_2-NR'R"$ wherein R', R" have the same definition as above;

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(4) ANR'R", AOR' wherein A is an amino acid residue or a peptide of 2 to 3 amino acid residues and R', R" have the same definition as above

(5) lower 2-(alkoxycarbonyl)alkyl

(6) halo

(7) groups of formula R^8-CHOH- wherein R^8 is hydrogen, lower alkyl, aryl, lower arylalkyl, lower cycloalkyl, lower alkenyl, lower alkynyl or heterocyclyl, the heterocyclic ring being attached at any heteroatom or carbon atom which results in the creation of a stable structure,

(8) groups of formula R^9-CH=NOR^{10} wherein R^{10} is hydrogen, lower alkyl or lower arylalkyl, and R^9 is lower alkyl, aryl, lower arylalkyl, lower cycloalkyl, lower alkenyl, lower alkynyl or heterocyclyl, the heterocyclic ring being attached at any carbon atom which results in the creation of a stable structure;

(9) lower alkoxy, lower arylalkoxy, lower cycloalkoxy, lower heterocyclyl alkoxy or heterocyclyloxy;

(10) lower alkylsulfonyl, lower alkylsulfinyl, arylsulfonyl, arylsulfinyl, lower alkyl-arylsulfonyl, lower alkyl-aryl sulfinyl, heterocyclyl-sulfonyl, heterocyclyl-sulfinyl; optionally substituted with 1 to 2 substituents selected from lower alkyl, halo, nitro, hydroxy, lower alkoxy, or groups of formula NR'R", OC(O)R', OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O)NR'R", NHC(O)OR' where R' and R" have the meanings given above;

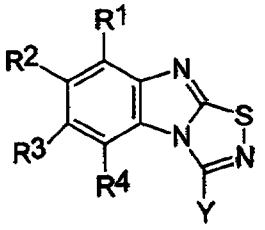
(11) groups of the formula -C(=NOH)COOR^{11} wherein R^{11} is lower alkyl

(12) hydrogen, substituted lower alkyl, aryl, lower arylalkyl, lower cycloalkyl, each group being optionally substituted with 1 to 3 substituents selected from lower alkyl, halo, nitro, amino, hydroxy, lower alkoxy, lower alkylamino, lower

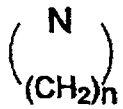
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dialkylamino, NR'R", OC(O)R', OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O)NR'R", NHC(O)OR', with R' and R" having the meanings given above.

2. Compounds according to claim 1, having the general formula:



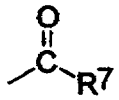
or pharmaceutically acceptable salts thereof, wherein R^1, R^2, R^3, R^4 are independently hydrogen, lower alkyl, halo, nitro, hydroxy, lower alkoxy, piperazinyl, or groups of the formula NR'R", OC(O)R', OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O)NR'R", NHC(O)OR' or CONR'R" in which R' and R" are independently hydrogen, lower alkyl, aryl, lower arylalkyl or NR'R" represents a five or six membered ring consisting of



wherein n = 4 or 5

and Y is selected from

(1) groups of the formula:



in which R^7 represents hydrogen, hydroxy, lower alkyl, lower cycloalkyl, lower alkoxy, lower alkenyl, lower alkynyl, aryl, lower arylalkyl, heterocyclyl, N-substituted N-heterocyclyl, heterocyclyloxy, heterocyclyl-loweralkylene, a group NR' R" where R' and R" are independently selected from hydrogen, lower alkyl, aryl, lower arylalkyl, and alkylene, and a group ANR'R", AOR wherein A is an amino acid residue

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or a peptide of 2 to 3 amino acid residues and R', R" have the same definition as above

(2) heterocyclyl, lower alkylene-amino-heterocyclyl amino-heterocyclyl, amino-lower alkylene-heterocyclyl or lower alkylene-heterocyclyl, the heterocyclic ring being attached at any heteroatom or carbon atom which results in the creation of a stable structure, and the heterocyclic ring being optionally substituted with 1-3 substituents selected from lower alkyl; hydroxy; nitro; amino; lower alkylamino; di-lower alkylamino; lower alkoxy; lower alkyl substituted with 1-3 substituents selected from hydroxy, lower alkylcarbamoyl, phenyl, halophenyl, heterocyclyl, carboxy and lower alkoxycarbonyl; lower acyl; lower alkoxycarbonyl; lower alkyl-sulfonyl; amido; allyl; benzyl; phenyl optionally substituted with amino, halo, hydroxy, lower alkoxy, lower alkyl, lower alkylamino or di-lower alkylamino; heterocyclyl optionally substituted with 1-3 substituents selected from nitro, hydroxy, lower alkoxy, lower alkyl, amino, halo, lower alkylamino, di-lower alkylamino; with the proviso that the heterocyclyl group Y is not 1-imidazolyl or substituted 1-imidazolyl;

(3) NR'R" or $-CH_2-NR'R"$ wherein R', R" have the same definition as above;

(4) ANR'R", AOR' wherein A is an amino acid residue or a peptide of 2 to 3 amino acid residues and R', R" have the same definition as above

(5) lower 2-(alkoxycarbonyl)alkyl

(6) halo

(7) groups of formula R^8-CHOH- wherein R^8 is hydrogen, lower alkyl, aryl, lower arylalkyl, lower cycloalkyl, lower alkenyl, lower alkynyl or heterocyclyl, the heterocyclic ring being

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attached at any heteroatom or carbon atom which results in the creation of a stable structure,

(8) groups of formula R^9-CH=NOR^{10} wherein R^{10} is hydrogen, lower alkyl or lower arylalkyl, and R^9 is lower alkyl, aryl, lower arylalkyl, lower cycloalkyl, lower alkenyl, lower alkynyl or heterocyclyl, the heterocyclic ring being attached at any carbon atom which results in the creation of a stable structure;

(9) lower alkoxy, lower arylalkoxy, lower cycloalkoxy, lower heterocyclyl alkoxy or heterocyclyloxy;

(10) lower alkylsulfonyl, lower alkylsulfinyl, arylsulfonyl, arylsulfinyl, lower alkyl-arylsulfonyl, lower alkyl-aryl sulfinyl, heterocyclyl-sulfonyl, heterocyclyl-sulfinyl; optionally substituted with 1 to 2 substituents selected from lower alkyl, halo, nitro, hydroxy, lower alkoxy, or groups of formula NR'R", OC(O)R', OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O)NR'R", NHC(O)OR' where R' and R" have the meanings given above;

(11) groups of the formula -C(=NOH)COOR^{11} wherein R^{11} is lower alkyl

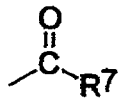
(12) hydrogen, aryl, lower arylalkyl, lower cycloalkyl, each group being optionally substituted with 1 to 3 substituents selected from lower alkyl, halo, nitro, amino, hydroxy, lower alkoxy, lower alkylamino, lower dialkylamino, NR'R", OC(O)R', OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O)NR'R", NHC(O)OR', with R' and R" having the meanings given above.

3. Compounds according to claim 2 wherein R^1, R^2, R^3 and R^4 each represents hydrogen or alkoxy.

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4. Compounds according to claim 2 wherein R^1, R^3 and R^4 are each hydrogen and R^2 is either hydrogen or methoxy.

5. Compounds according to claim 4 in which Y is a group of formula:



as defined in claim 2, and in which R^7 represents lower alkyl, lower arylalkyl, optionally substituted phenyl or naphthyl, heterocyclyl, hydroxy or lower alkoxy.

6. Compounds according to claim 5 wherein R^7 represents optionally substituted heterocyclyl.

7. Compounds according to claim 6 wherein R^7 represents 2-pyridyl either unsubstituted or substituted with 1 to 3 substituents selected from methyl and methoxy.

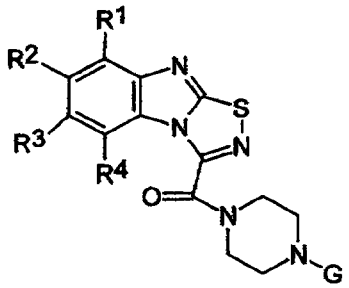
8. Compounds according to claim 7 wherein R^7 represents 3,5-dimethyl-4-methoxy-2-pyridyl.

9. A compound according to claim 8 which is 7-methoxy-3-[(4-methoxy-3,5-dimethyl-2-pyridyl)oxomethyl]-1,2,4-thiadiazolo[4,5-a]benzimidazole.

10. A compound according to claim 8 which is 3-[(4-methoxy-3,5-dimethyl-2-pyridyl)oxomethyl]-1,2,4-thiadiazolo [4,5-a]benzimidazole.

11. Compounds according to claim 5 wherein R^7 represents optionally substituted piperazine.

12. Compounds according to claim 2 of the general formula:



wherein R^1, R^2, R^3, and R^4 are independently lower alkyl, hydrogen, amino, lower alkylamino, di-lower alkylamino, hydroxy, lower alkoxy or piperazinyl, and G is alkyl (C_1 - C_6) optionally substituted with up to three substituents selected from hydroxy, lower alkylcarbamoyl, phenyl halophenyl, heterocyclyl, carboxy and lower alkoxycarbonyl.

13. Compounds according to claim 12 wherein G represents 4-methylpiperazinyl.

14. A compound according to claim 13 which is 3-(4-methylpiperazinylcarbonyl)-1,2,4-thiadiazolo[4,5-a] benzimidazole.

15. Compounds according to claim 12 wherein R' represents G represents 4-(2-pyridyl)piperazinyl.

16. A compound according to claim 15 which is 3-(4-(2-pyridyl)piperazinylcarbonyl)-1,2,4-thiadiazolo[4,5-a] benzimidazole.

17. Compounds according to claim 5 wherein R^7 represents optionally substituted phenyl or naphthyl.

18. Compounds according to claim 17 wherein R^7 represents phenyl.

19. A compound according to claim 18 which is 3-(oxophenylmethyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole.

20. A compound according to claim 12 which is 3-(4-benzyl)piperazinylcarbonyl)-1,2,4-thiadiazolo-[4,5-a] benzimidazole.

21. Compounds according to claim 5 wherein R^7 represents hydroxy.

22. A compound according to claim 21 which is 3-carboxy-1,2,4-thiadiazolo[4,5-*a*]benzimidazole.

23. Compounds according to claim 4 wherein Y is an optionally substituted heterocyclic group bonded directly to the thiadiazolo ring.

24. Compounds according to claim 23 wherein the heterocyclic moiety of group Y is selected from pyridyl, piperazinyl, morpholinyl, pyrrolidinyl and pyrazinyl.

25. A compound according to claim 24 which is 3-(2-pyridyl)-1,2,4-thiadiazolo[4,5-*a*]benzimidazole.

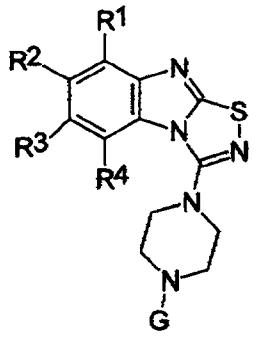
26. A compound according to claim 24 which is 3-(4-morpholinyl)-1,2,4-thiadiazolo[4,5-*a*]-benzimidazole.

27. A compound according to claim 24 which is 3-(1-pyrrolidinyl)-1,2,4-thiadiazolo[4,5-*a*]-benzimidazole.

28. A compound according to claim 23 which is 3-(4-acetyl-1-piperazinyl)-1,2,4-thiadiazolo[4,5-*a*] benzimidazole.

29. A compound according to claim 23 which is 3-(2-pyrazinyl)-1,2,4-thiadiazolo[4,5-]benzimidazole.

30. Compounds according to claim 2 having the general formula:



wherein R^1, R^2, R^3, and R^4 are independently lower alkyl, hydrogen, amino, lower alkylamino, di-lower alkylamino, hydroxy, lower alkoxy halo or piperazinyl, and G is alkyl (C_1 - C_6) optionally substituted with up to three substituents selected from hydroxy, lower alkylcarbamoyl, phenyl, halophenyl, heterocyclyl, carboxy and lower alkoxycarbonyl; allyl; benzyl; phenyl optionally substituted with amino, halo, hydroxy, lower alkoxy, lower alkyl, lower alkylamino or di-lower alkylamino; heterocyclyl optionally substituted with 1-3 substituents selected from nitro, hydroxy, lower alkoxy, lower alkyl, amino, halo, lower alkylamino, and di-lower alkylamino.

31. Compounds according to claim 30 wherein G represents optionally substitued lower alkyl.

32. A compound according to claim 31 which is 3-(4-methyl-1-piperazinyl)-1,2,4-thiadiazolo[4,5-a] benzimidazole.

33. A compound according to claim 31 which is 3-(4-ethyl-1-piperazinyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole.

34. A compound according to claim 31 which is 3-(4-propyl-1-piperazinyl)-1,2,4-thiadiazolo[4,5-a] benzimidazole.

35. A compound according to claim 31 which is 3-(4-butyl-1-piperazinyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole.

36. A compound according to claim 30 which is 3-(4-(2-hydroxyethyl)-1-piperazinyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole.

37. A compound according to claim 30 wherein G represents optionally substituted phenyl.

38. A compound according to claim 37 which is 3-(4-phenylpiperazinyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole.

39. A compound according to claim 37 which is 3-(4-(4-methoxyphenyl)piperazinyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole.

40. A compound according to claim 37 which is 3-(4-(3-chlorophenylpiperazinyl)-1,2,4-thiadiazolo[4,5-]benzimidazole.

41. A compound according to claim 30 wherein G represents benzyl.

42. A compound according to claim 42 which is 3-(4-benzylpiperazinyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole.

43. A compound according to claim 30 wherein G represents cinnamyl.

44. A compound according to claim 43 which is 3-(4-cinnamylpiperazinyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole.

45. A compound according to claim 30 wherein G represents 2-pyridyl.

46. A compound according to claim 45 which is 3-(4-(2-pyridyl)piperazinyl)-1,2,4-thiadiazolo[4,5-*a*]benzimida-zole.

47. A compound according to claim 30 wherein G represents 3-amino-2-pyridyl.

48. A compound according to claim 47 which is 3-(4-(3-amino-2-pyridyl)piperazinyl)-1,2,4-thiadiazolo[4,5-*a*] benzimidazole.

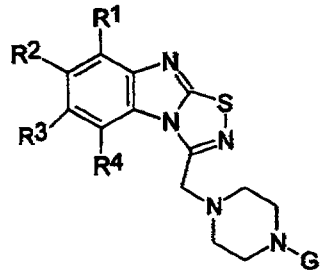
49. A compound according to claim 30 wherein G represents 2-pyrimidyl.

50. A compound according to claim 49 which is 3-(4-(2-pyrimidyl)piperazinyl)-1,2,4-thiadiazolo[4,5-*a*]benzimi-dazole.

51. A compound according to claim 30 wherein G represents (1-(4-chlorophenyl)-1-phenylmethyl).

52. A compound according to claim 51 which is 3-(4-(1-(4-chlorophenyl)-1-phenylmethyl)piperazinyl)-1,2,4-thiadiazolo[4,5-*a*]benzimidazole.

53. Compounds according to claim 2 and corresponding to the general formula:



wherein R^1, R^2, R^3, and R^4 are independently lower alkyl, hydrogen, amino, lower alkylamino, di-lower alkylamino, hydroxy, lower alkoxy, halo or piperazinyl, and G is alkyl (C_1 - C_6) optionally substituted with up to three

substituents selected from hydroxy, lower alkylcarbamoyl, phenyl, halophenyl, heterocyclyl, carboxy and lower alkoxycarbonyl; allyl; benzyl; phenyl optionally substituted with amino, halo, hydroxy, lower alkoxy, lower alkyl, lower alkylamino or di-lower alkylamino; heterocyclyl optionally substituted with 1-3 substituents selected from nitro, hydroxy, lower alkoxy, lower alkyl, amino, halo, lower alkylamino, and di-lower alkylamino.

54. Compounds according to claim 53 wherein G represents optionally substitued lower alkyl.

55. A compound according to claim 54 which is 3-((4-ethylpiperazinyl)methyl)-1,2,4-thiadiazolo[4,5-a]benzi-midazole.

56. A compound according to claim 54 which is 3-((4-propyl-1-piperazinyl)methyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole.

57. A compound according to claim 54 which is 3-((4-butylpiperazinyl)methyl)-1,2,4-thiadiazolo[4,5-a]benzimida-zole.

58. A compound according to claim 54 which is 3-((4-(2-hydroxyethyl)piperazinyl)methyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole.

59. A compound according to claim 53 wherein G represents optionally substituted phenyl.

60. A compound according to claim 59 which is 3-((4-phenylpiperazinyl)methyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole.

61. A compound according to claim 59 which is 3-((4-(4-methoxyphenyl)piperazinyl)methyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole.

62. A compound according to claim 59 which is 3-((4-(4-amino)-phenylpiperazinyl)methyl)-1,2,4-thiadiazolo[4,5-]benzimidazole.

63. A compound according to claim 53 wherein G represents benzyl.

64. A compound according to claim 63 which is 3-((4-benzylpiperazinyl)methyl)-1,2,4-thiadiazolo[4,5-a]benzimi-dazole.

65. A compound according to claim 53 wherein G represents cinnamyl.

66. A compound according to claim 65 which is 3-((4-cinnamylpiperazinyl)methyl)-1,2,4-thiadiazolo[4,5-a]benzi-midazole.

67. A compound according to claim 53 wherein G represents 2-pyridyl.

68. A compound according to claim 67 which is 3-((4-(2-pyridyl)piperazinyl)methyl)-1,2,4-thiadiazolo[4,5-a] benzimidazole.

69. A compound according to claim 53 wherein G represents 3-amino-2-pyridyl.

70. A compound according to claim 69 which is 3-((4-(3-amino-2-pyridyl)piperazinyl)methyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole.

71. A compound according to claim 53 wherein G represents 2-pyrimidyl.

72. A compound according to claim 71 which is 3-((4-(2-pyrimidyl)piperazinyl)methyl)-1,2,4-thiadiazolo[4,5-a] benzimidazole.

73. A compound according to claim 53 wherein G represents (1-(4-chlorophenyl)-1-phenylmethyl).

74. A compound according to claim 73 which is 3-((4-(1-(4-chlorophenyl)-1-phenylmethyl)piperazinyl)methyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole.

75. Compounds according to claim 4 wherein Y is halo.

76. Compounds according to claim 75 wherein Y is bromo.

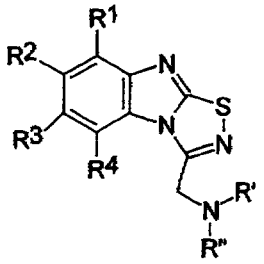
77. A compound according to claim 76 which is 3-bromo-1,2,4-thiadiazolo[4,5-a]benzimidazole.

78. Compounds according to claim 4 wherein Y is halomethyl.

79. A compound according to claim 78 which is 3-bromomethyl-1,2,4-thiadiazole[4,5-]benzimidazole.

80. A compound according to claim 4, which is 3-(4-methylphenylsulfonyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole.

81. Compounds according to claim 2 and having the general formula:



wherein R^1, R^2, R^3 and R^4 are independently lower alkyl, hydrogen, amino, lower alkylamino, di-lower alkylamino, hydroxy, lower alkoxy, halo or piperazinyl; and R' and R" are independently selected from lower alkyl, benzyl, phenyl, and lower alkyl substituted with hydroxy, amino, lower alkylamino, carboxy or lower alkoxycarbonyl, or R' and R" together with the N-group to which they are attached form an optionally substituted, saturated heterocyclic group selected from morpholinyl, piperidinyl, pyrrolidinyl and prolyl, the optional substituents thereon being selected from lower alkyl, carboxy, amino, phenyl, lower alkoxycarbonyl and di-lower alkylamino.

82. Compounds according to claim 81 wherein R' and R" are both lower alkyl.

83. A compound according to claim 82 which is 3-dimethylaminomethyl-1,2,4-thiadiazolo[4,5-a]benzimidazole.

84. A compound according to claim 82 which is 3-diethylaminomethyl-1,2,4-thiadiazolo[4,5-a]benzimidazole.

85. A compound according to claim 82 which is 3-dipropylaminomethyl-1,2,4-thiadiazolo[4,5-a]benzimidazole.

86. A compound according to claim 82 which is 3-dibutylaminomethyl-1,2,4-thiadiazolo[4,5-a]benzimidazole.

87. Compounds according to claim 81 wherein R' and R" with the N-atom to which they are attached form a morpholinyl ring structure.

88. A compound according to claim 87 which is 3-morpholinomethyl-1,2,4-thiadiazolo[4,5-a]benzimidazole.

89. Compounds according to claim 2 wherein Y represents phenyl optionally substituted with 1 - 3 substituents selected from lower alkyl, hydroxy, nitro, amino, lower alkylamino di-lower alkylamino and lower alkoxy.

90. A compound according to claim 89 which is 3-phenyl-1,2,4-thiadiazolo[4,5-a]benzimidazole.

91. A compound according to claim 89 which is 3-(2-nitrophenyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole.

92. A compound according to claim 89 which is 6-amino-3-phenyl-1,2,4-thiadiazolo[4,5-a]benzimidazole.

93. A compound according to claim 89 which is 7-amino-3-phenyl-1,2,4-thiadiazolo[4,5-a]benzimidazole.

94. Compounds according to claim 2 wherein Y represents 2-pyridyl optionally substituted with 1 - 3 substituents selected from lower alkyl, hydroxy, nitro, amino, lower alkylamino di-lower alkylamino and lower alkoxy.

95. A compound according to claim 94 which is 3-(2-pyridyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole.

96. Compounds according to claim 2 wherein Y represents 2-pyrazinyl optionally substituted with 1 - 3 substituents selected from lower alkyl, hydroxy, nitro,

amino, lower alkylamino di-lower alkylamino and lower alkoxy.

97. A compound according to claim 96 which is 3-(2-pyrazinyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole.

98. Compounds according to claim 2 wherein Y represents optionally substituted amino-pyridyl.

99. A compound according to claim 98 which is 3-[2-pyridylamino]-1,2,4-thiadiazolo[4,5-a]benzimidazole.

100. A compound according to claim 98 which is 3-[3-pyridylamino]-1,2,4-thiadiazolo[4,5-a]benzimidazole.

101. Compounds according to claim 2 wherein Y represents optionally substituted lower alkylene-amino-pyridyl.

102. A compound a ccording to claim 101 which is 3-[2-pyridylmethylamino]1,2,4-thiadiazolo[4,5-a]benzimidazole.

103. A compound according to claim 101 which is 3-[N-methyl-(2-pyridylethyl)amino]-1,2,4-thiadiazolo-[4,5-a] benzimidazole.

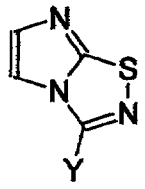
104. Compounds according to claim 2 wherein Y represents imidazolylmethyl.

105. A compound according to claim 104 which is 3-(imidazolylmethyl)-1,2,4-thiadiazolo[4,5-a]benzimidazole.

106. Compounds according to claim 2 wherein Y represents 1,2,4-triazolylmethyl.

107. A compound according to claim 106 which is 3-(1,2,4-triazolylmethyl)-1,2,4-thiadiazolo[4,5-a] benzimidazole.

108. Compounds according to claim 1 having the general formula III:

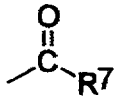


(III)

and pharmaceutically acceptable salts thereof, wherein R^5 and R^6 are independently selected from the group which are independently hydrogen, lower alkyl, halo, nitro, hydroxy, lower alkoxy, or groups of the formula NR'R", OC(O)R', OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O)NR'R", NHC(O)OR in which R' and R" are independently hydrogen, loweralkyl, aryl, lower arylalkyl or NR'R" represents a five or six membered ring consisting of  wherein n = 4 or 5

and Y is selected from :

(1) groups of the formula:



in which R^7 represents hydrogen, hydroxy, lower alkyl, lower cycloalkyl, lower alkoxy, lower alkenyl, lower alkynyl, aryl, lower arylalkyl, heterocyclyl, hetero-cyclyloxy, heterocyclyl-lower alkylene, a group NR'R" where R' and R" are independently selected from hydrogen, lower alkyl, aryl, lower arylalkyl, and alkylene, and a group ANR'R", AOR wherein A is an amino acid residue or a peptide of 2 to 3 amino acid residues and R', R" have the same definition as above

(2) heterocyclyl or lower alkylene-heterocyclyl, the heterocyclic ring being attached at any heteroatom or carbon atom which results in the creation of a stable structure, and the heterocyclic ring being optionally substituted with lower acyl, lower alkoxycarbonyl, lower alkyl-sulfonyl or amido, with the proviso that the heterocyclyl is not 1-imidazolyl or substituted 1-imidazolyl;

(3) NR'R" wherein R , R" have the same definition as above

(4) ANR'R", AOR wherein A is an amino acid residue or a peptide of 2 to 3 amino acid residues and R', R" have the same definition as above

(5) lower 2-(alkoxycarbonyl)alkyl

(6) halo

(7) groups of formula R^8-CHOH- wherein R^8 is hydrogen, lower alkyl, aryl, lower arylalkyl, lower cycloalkyl, lower alkenyl, lower alkynyl or heterocyclyl, the heterocyclic ring being attached at any heteroatom or carbon atom which results in the creation of a stable structure,

(8) groups of formula R^9-CH=NOR^{10} wherein R^{10} is hydrogen, lower alkyl or lower arylalkyl, and R^9 is lower alkyl, aryl, lower arylalkyl, lower cycloalkyl, lower alkenyl, lower alkynyl or heterocyclyl, the heterocyclic ring being attached at any carbon atom which results in the creation of a stable structure;

(9) lower alkoxy, lower arylalkoxy, lower cycloalkoxy, lower heterocyclylalkoxy, or heterocyclyoxy;

(10) lower alkylsulfonyl, lower alkylsulfinyl, arylsulfonyl, arylsulfinyl, lower alkyl-arylsulfonyl, lower alkyl-arylsulfinyl, heterocyclyl-sulfonyl, heterocyclyl-sulfonyl; optionally substituted with 1 to 2 substituents selected from lower alkyl, halo, nitro, hydroxy, lower alkoxy, or groups of formula NR'R", OC(O)R',

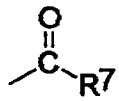
OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O)NR'R", NHC(O)OR' where R' and R" have the meanings given above;

(11) groups of the formula -C=NOH-COOR^{11} wherein R^{11} is lower alkyl;

(12) hydrogen, lower alkyl, aryl, lower arylalkyl, lower cycloalkyl, each group being optionally substituted with 1 to 2 substituents selected from halo, nitro, amino, hydroxy, lower alkoxy, lower alkylamino, lower dialkylamino, NR'R", OC(O)R', OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O)NR'R", NHC(O)OR', with R' and R" having the meanings given above.

109. Compounds according to claim 108 wherein R^5 and R^6 both represent hydrogen.

110. Compounds according to claim 109 wherein Y represents

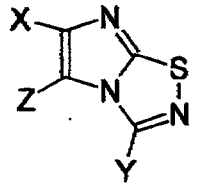


and R^7 represents lower alkyl, lower alkoxy or aryl.

111. A compound according to claim 110 which is 3-acetylimidazo[1,2-*d*]-1,2,4-thiadiazole.

112. A compound according to claim 110 which is 3-benzoylimidazo[1,2-*d*]-1,2,4-thiadiazole.

113. Process for preparing a bicyclic or tricyclic thiadiazole compound of the general formula:



(I)

wherein X and Z are independently hydrogen, lower alkyl, halo, nitro, hydroxy, lower alkoxy, a group NR'R",

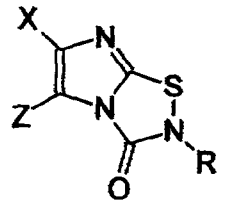
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OC(O)R', OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O)NR'R", or NHC(O)OR', with R' and R" being independently hydrogen, lower alkyl, aryl or lower arylalkyl, or R' and R" in NR'R" when taken together forming a five or six membered ring consisting of wherein n = 4 or 5;

or X and Z taken together represent a benzene ring fused to the imidazo ring and being optionally substituted with up to four substituents independently selected from hydrogen, lower alkyl, halo, nitro, hydroxy, lower alkoxy, or a group NR'R", OC(O)R', OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O) NR'R", or NHC(O)OR', with R', R" being as defined above;

and Y is selected from lower alkyl, lower arylalkyl, cycloalkyl, 1-haloalkyl, 1,1-dihaloalkyl, heterocyclyl, amino, lower alkylamino and lower dialkylamino, NR'R" with R', R" being as defined above, lower alkylthio, arylthio, lower arylalkylthio, lower alkylsulfonyl, lower arylalkyl-sulfonyl, arylsulfonyl, and groups of formula CO-R^7 where R^7 represents lower alkyl, lower cycloalkyl, lower alkoxy, aryl, lower arylalkyl, heterocyclyl, heterocyclyloxy, heterocyclyl-loweralkylene, a group NR'R" where R' and R" are as defined above; and a group ANR'R", AOR wherein A is an amino acid residue or a peptide of 2 to 3 amino acid residues and R', R" have the same definition as above;

which comprises reacting a compound of general formula IV:



(IV)

wherein X and Z have the meanings given above and R represents lower alkyl or lower arylalkyl, with a cyano reagent of the formula Y-CN, in which Y is as defined

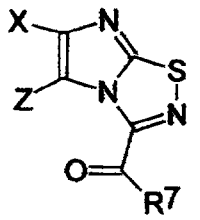
above, in solution in an inert solvent, and recovering the product of formula I so formed.

114. The process of claim 113 wherein the reaction takes place at a temperature of from about 25 to 140 °C.

115. The process of claim 114 wherein the solvent is dichloromethane, tetrahydrofuran, toluene or dimethylformamide.

116. The process of claim 113 wherein the cyano reagent is selected from acetonitrile, benzonitrile, 2-cyanopyridine, cyclopentylcyanide, dibromoacetonitrile, 6-cyanopurine, benzoyl cyanide, acetyl cyanide and methoxycarbonyl cyanide.

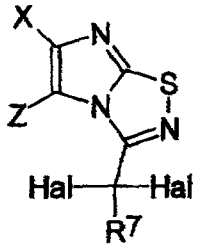
117. A process of preparing compounds of the general formula:



wherein X and Z are independently hydrogen, lower alkyl, halo, nitro, hydroxy, lower alkoxy, a group NR'R", OC(O)R', OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O)NR'R", NHC(O)OR' or CONR'R", with R' and R" being independently hydrogen, lower alkyl, aryl or lower arylalkyl, or R' and R" in NR'R" when taken together forming a five or six membered ring consisting of $(CH_2)_n$ wherein n = 4 or 5;
or X and Z taken together represent a benzene ring fused to the imidazo ring and being optionally substituted with up to four substituents independently selected from hydrogen, lower alkyl, halo, nitro, hydroxy, lower alkoxy, or a group NR'R", OC(O)R', OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O)NR'R", or NHC(O)OR', with R', R" being as defined above; and R^7 represents lower alkyl, lower

cycloalkyl, aryl, lower arylalkyl, heterocyclyl, and heterocyclyl-loweralkylene;

which comprises hydrolyzing a corresponding 3-dihalo compound of the general formula:

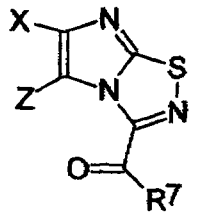


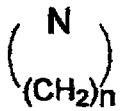
wherein X, Z and R^7 have the meanings given above and Hal represents chloride, bromide or iodide.

118. The process of claim 117 wherein the hydrolysis takes place using strong acid.

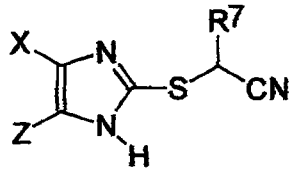
119. The process of claim 117 wherein the hydrolysis takes place using silver nitrate.

120. A process of preparing compounds of the formula:



wherein X and Z are independently hydrogen, lower alkyl, halo, nitro, hydroxy, lower alkoxy, a group NR'R", OC(O)R', OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O)NR'R", NHC(O)OR' or CONR'R", with R' and R" being independently hydrogen, lower alkyl, aryl or lower arylalkyl, or R' and R" in NR'R" when taken together forming a five or six membered ring consisting of  wherein n = 4 or 5; or X and Z taken together represent a benzene ring fused to the imidazo ring and being optionally substituted with

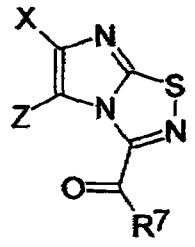
up to four substituents independently selected from hydrogen, lower alkyl, halo, nitro, hydroxy, lower alkoxy, or a group NR'R", OC(O)R', OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O)NR'R", or NHC(O)OR', with R', R" being as defined above;
and R^7 represents lower alkyl, lower cycloalkyl, aryl, lower arylalkyl, heterocyclyl, and heterocyclyl lower-alkylene;
which comprises rearranging a 2-thioether diazole of the general formula:



in which R^7, X and Z have the meanings given above with an oxidizing agent.

121. The process of claim 120 wherein the rearrangement is effected with m-chloroperbenzoic acid.

122. A process of converting compounds of the general formula:



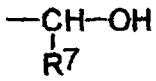
wherein X and Z are independently hydrogen, lower alkyl, halo, nitro, hydroxy, lower alkoxy, a group NR'R", OC(O)R', OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O)NR'R", or NHC(O)OR', with R' and R" being independently hydrogen, lower alkyl, aryl or lower arylalkyl, or R' and R" in NR'R" when taken together forming a five or six membered ring consisting of $(CH_2)_n$ wherein n = 4 or 5;
or X and Z taken together represent a benzene ring fused to the imidazo ring and being optionally substituted with up to four substituents independently selected from

hydrogen, lower alkyl, halo, nitro, hydroxy, lower alkoxy, or a group NR'R", OC(O)R', OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O)NR'R", or NHC(O)OR', with R', R" being as defined above;

and R^7 represents lower alkyl, lower cycloalkyl, lower alkoxy, aryl, lower arylalkyl, heterocyclyl, heterocyclyloxy, heterocyclyl-loweralkylene, a group NR'R" where R' and R" are independently selected from hydrogen, lower alkyl, aryl, lower arylalkyl, and alkylene, and a group ANR'R", AOR wherein A is an amino acid residue or a peptide of 2 to 3 amino acid residues and R', R" have the same definition as above;

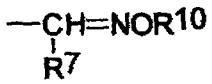
into other compounds of the formula given above but in which R^7 is different from R^7 in the starting material, which comprises:

(a) in the case where the 3-substituent group in the final product is to be



chemically reducing a compound of the above formula:

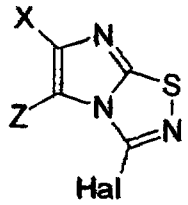
(b) in the case where the 3-substituent in the final product is to be



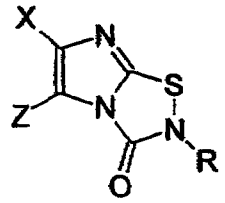
wherein R^{10} is hydrogen, lower alkyl or lower arylalkyl, reacting a compound of the above formula with a hydroxylamine derivative;

(c) in the case where the 3-substituent in the final product is to be -COOH, hydrolysing with alkali a compound of the above formula in which R^7 is alkoxide.

123. A process for preparing compounds of the formula:



wherein X and Z are independently hydrogen, lower alkyl, halo, nitro, hydroxy, lower alkoxy, a group NR'R", OC(O)R', OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O)NR'R", NHC(O)OR' or CONR'R", with R' and R" being independently hydrogen, lower alkyl, aryl or lower arylalkyl, or R' and R" in NR'R" when taken together forming a five or six membered ring consisting of $(CH_2)_n$ wherein n = 4 or 5;
or X and Z taken together represent a benzene ring fused to the imidazo ring and being optionally substituted with up to four substituents independently selected from hydrogen, lower alkyl, halo, nitro, hydroxy, lower alkoxy, or a group NR'R", OC(O)R', OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O)NR'R", or NHC(O)OR', with R', R" being as defined above;
and Hal represents, chloride, bromide or iodide, which comprises reacting a compound of the formula:

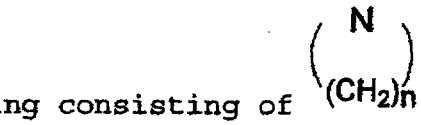


in which R represents lower alkyl or lower arylalkyl with a cyanohalogen Hal-CN.

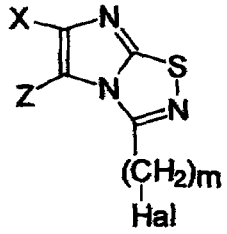
124. A process for preparing compounds of the formula



wherein X and Z are independently hydrogen, lower alkyl, halo, nitro, hydroxy, lower alkoxy, a group NR'R",

OC(O)R', OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O)NR'R", NHC(O)OR' or CONR'R", with R' and R" being independently hydrogen, lower alkyl, aryl or lower arylalkyl, or R' and R" in NR'R" when taken together forming a five or six membered ring consisting of  wherein n = 4 or 5; or X and Z taken together represent a benzene ring fused to the imidazo ring and being optionally substituted with up to four substituents independently selected from hydrogen, lower alkyl, halo, nitro, hydroxy, lower alkoxy, or a group NR'R", OC(O)R', OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O)NR'R", or NHC(O)OR', with R', R" being as defined above;

and Q represents NR'R", AOR', ANR'R"OR' where R' and R" are as defined above, or heterocyclic bonded directly to the thiadiazole ring or bonded thereto through the intermediary of a lower alkylene group, the heterocyclic ring in either case having one or two heterocyclic atoms and being optionally substituted with lower alkyl, hydroxy-lower alkyl, phenyl substituted lower alkyl, halophenyl-substituted lower alkyl, lower acyl, lower alkoxy-carbonyl, lower alkylsulfonyl, amino, amido, phenyl, halophenyl, benzyl, cinnanyl; which comprises reacting a compound of the formula



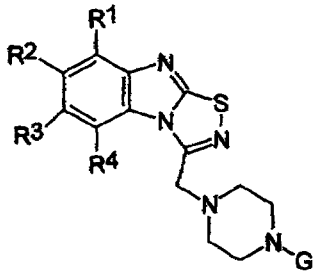
where Hal represents chloride, bromide or iodide and m is zero or 1, with an appropriately chosen primary or secondary amine, or an alcohol in the presence of a base.

125. The process of claim 124 wherein Hal represents bromide.

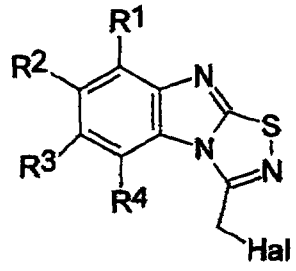
126. The process of claim 124 wherein the amine reactant is optionally substituted piperazine.

127. The process of claim 126 wherein the optionally substituted piperazine is 4-(1-(4-chlorophenyl)-1-phenyl-methyl)piperazine.

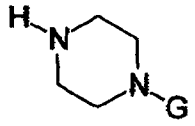
128. A process of preparing compounds of the general formula:



wherein R, R_2, R_3, and R_4 are independently lower alkyl, hydrogen, amino, lower alkylamino, di-lower alkylamino, hydroxy, lower alkoxy, halo or piperazinyl, and G is alkyl (C_1 - C_6) optionally substituted with up to three substituents selected from hydroxy, lower alkylcarbamoyl, phenyl, halophenyl, heterocyclyl, carboxy and lower alkoxycarbonyl; allyl; benzyl; phenyl optionally substituted with amino, halo, hydroxy, lower alkoxy, lower alkyl, lower alkylamino or di-lower alkylamino; heterocyclyl optionally substituted with 1-3 substituents selected from nitro, hydroxy, lower alkoxy, lower alkyl, amino, halo, lower alkylamino, and di-lower alkylamino, which comprises reacting a compound of the formula:



where Hal represents chloride, bromide or iodide, with a 4-substituted piperazine compound of formula;

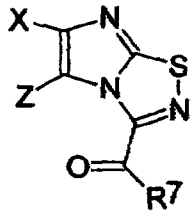


wherein G is as defined above.

129. The process of claim 128 wherein G is selected from 1-phenyl-1-(4-chlorophenyl)-methyl; 2-pyridyl; and 3-amino-2-pyridyl.

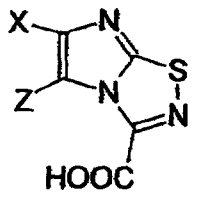
130. The process of claim 129 wherein R^1, R^2, R^3 and R^4 are hydrogen.

131. A process of preparing compounds of the formula:



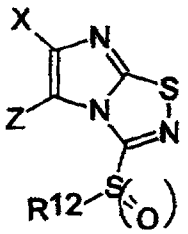
wherein X and Z are independently hydrogen, lower alkyl, halo, nitro, hydroxy, lower alkoxy, a group NR'R", OC(O)R', OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O)NR'R", or NHC(O)OR', with R' and R" being independently hydrogen, lower alkyl, aryl or lower arylalkyl, or R' and R" in NR'R" when taken together forming a five or six membered ring consisting of  wherein n = 4 or 5;
or X and Z taken together represent a benzene ring fused to the imidazo ring and being optionally substituted with up to four substituents independently selected from hydrogen, lower alkyl, halo, nitro, hydroxy, lower alkoxy, or a group NR'R", OC(O)R', OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O)NR'R", or NHC(O)OR', with R', R" being as defined above;
and R^7 is NR'R", AOR', or ANR'R" with R'and R" having the meanings given above, or nitrogen-containing heterocyclic atached at an N-atom and which results in the creation of

a stable structure, the heterocycle having one or two heterocyclic atoms and being optionally substituted with lower acyl, lower alkoxycarbonyl, lower alkylsulfonyl or amido; which comprises reacting a compound of the formula:



with an appropriately chosen amine in the presence of a dehydrating agent.

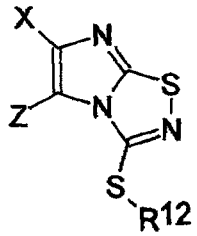
132. A process of preparing compounds of the formula:



wherein X and Z are independently hydrogen, lower alkyl, halo, nitro, hydroxy, lower alkoxy, a group NR'R", OC(O)R', OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O)NR'R", NHC(O)OR' or CONR'R", with R' and R" being independently hydrogen, lower alkyl, aryl or lower arylalkyl, or R' and R" in NR'R" when taken together forming a five or six membered ring consisting of  wherein n = 4 or 5; or X and Z taken together represent a benzene ring fused to the imidazo ring and being optionally substituted with up to four substituents independently selected from hydrogen, lower alkyl, halo, nitro, hydroxy, lower alkoxy, or a group NR'R", OC(O)R', OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O)NR'R", or NHC(O)OR', with R', R" being as defined above;

n is 1 or 2;

and R^{12} represents lower alkyl, lower arylalkyl or aryl, which comprises oxidizing a corresponding 3-thioether compound of the formula:



with an appropriately chosen stoichiometric amount of an oxidizing agent.

133. The process of claim 132 wherein the oxidizing agent is metachloroperbenzoic acid.

134. Pharmaceutical compositions for use in treating peptic ulcers in animals, comprising an effective dosage amount of an active ingredient of a compound of formula I as defined in claim 1, in association with a pharmaceutically acceptable carrier.

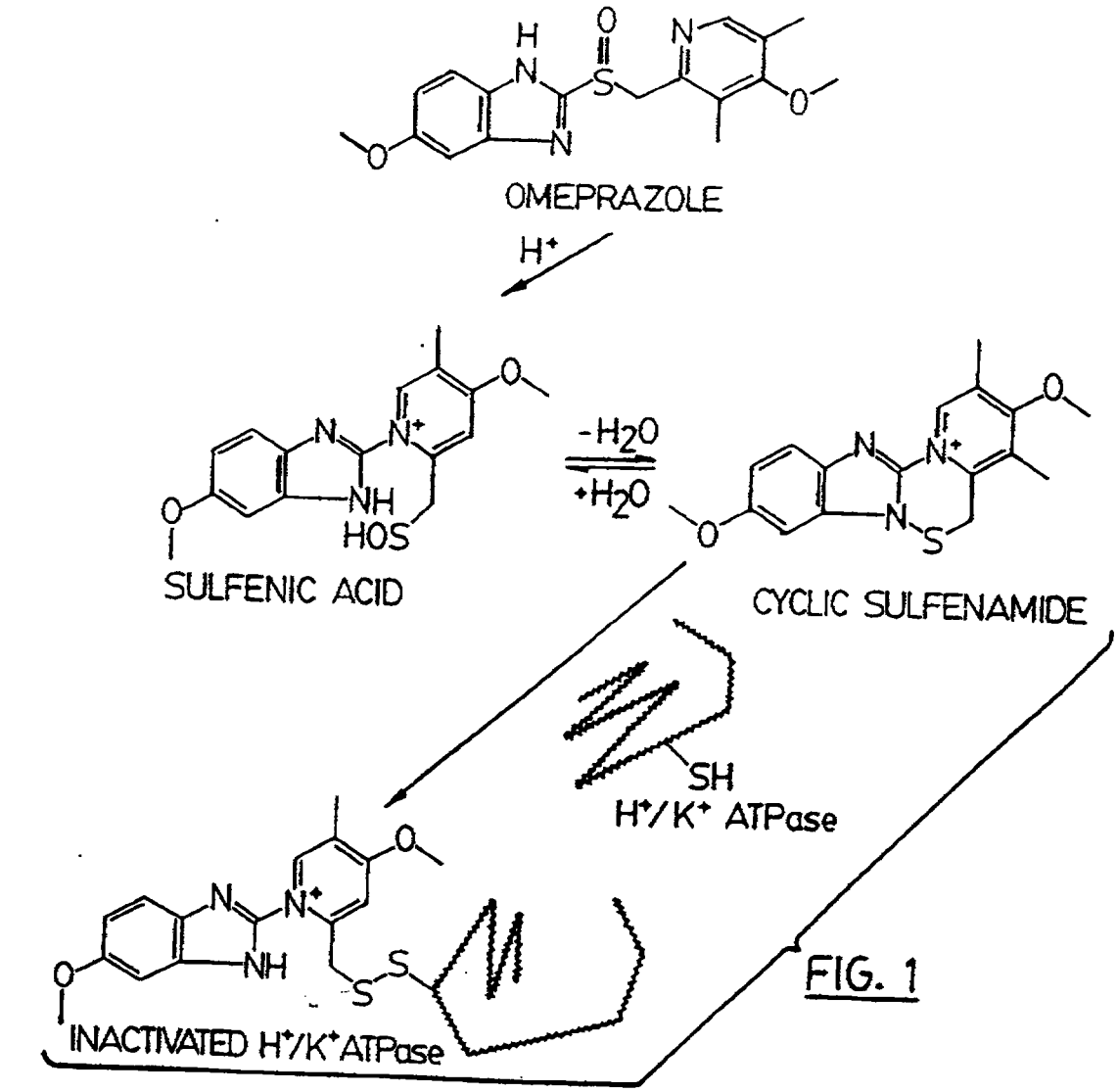

OMEPRAZOLE
H+
-H2O
+H2O
SULFENIC ACID
CYCLIC SULFENAMIDE
SH
H+/K+ ATPase
INACTIVATED H+/K+ATPase

FIG. 1

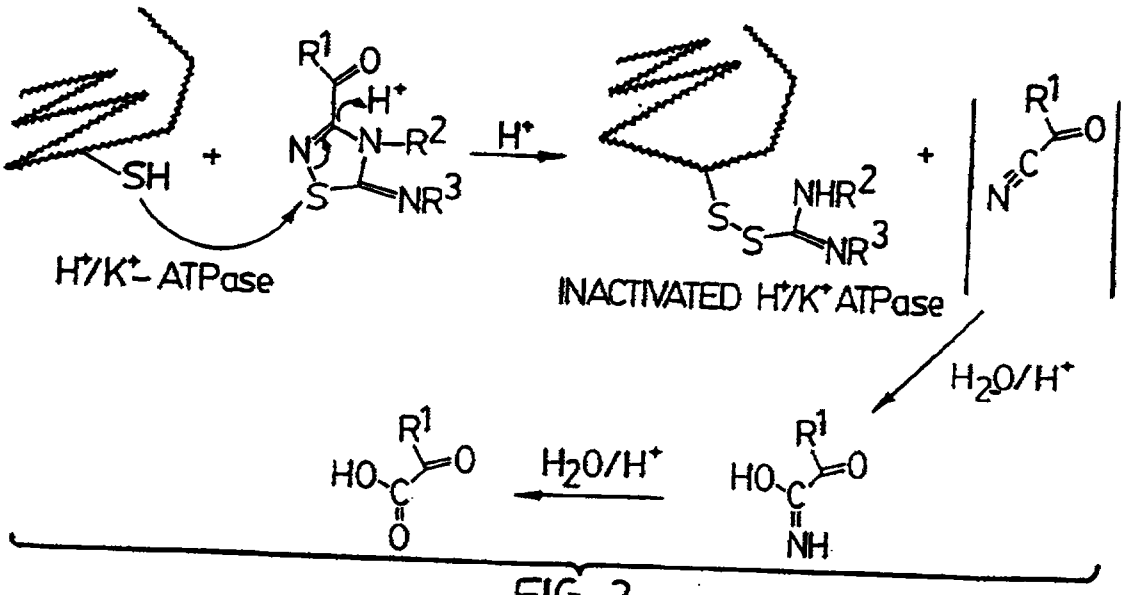

SH
H+/K+- ATPase
H+
NHR2
NR3
INACTIVATED H+/K+ATPase
H2O/H+
H2O/H+

FIG. 2

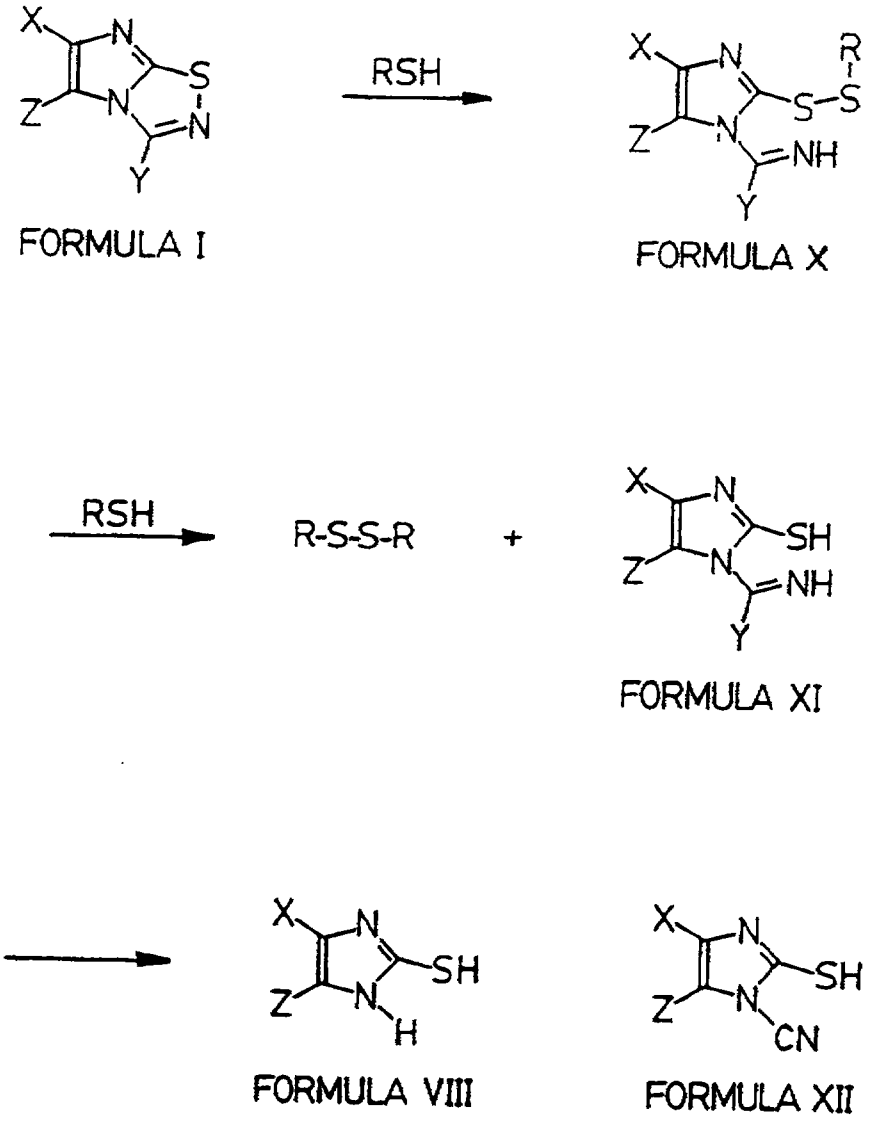

RSH
FORMULA I
FORMULA X
RSH
R-S-S-R
+
FORMULA XI
FORMULA VIII
FORMULA XII

FIG. 3

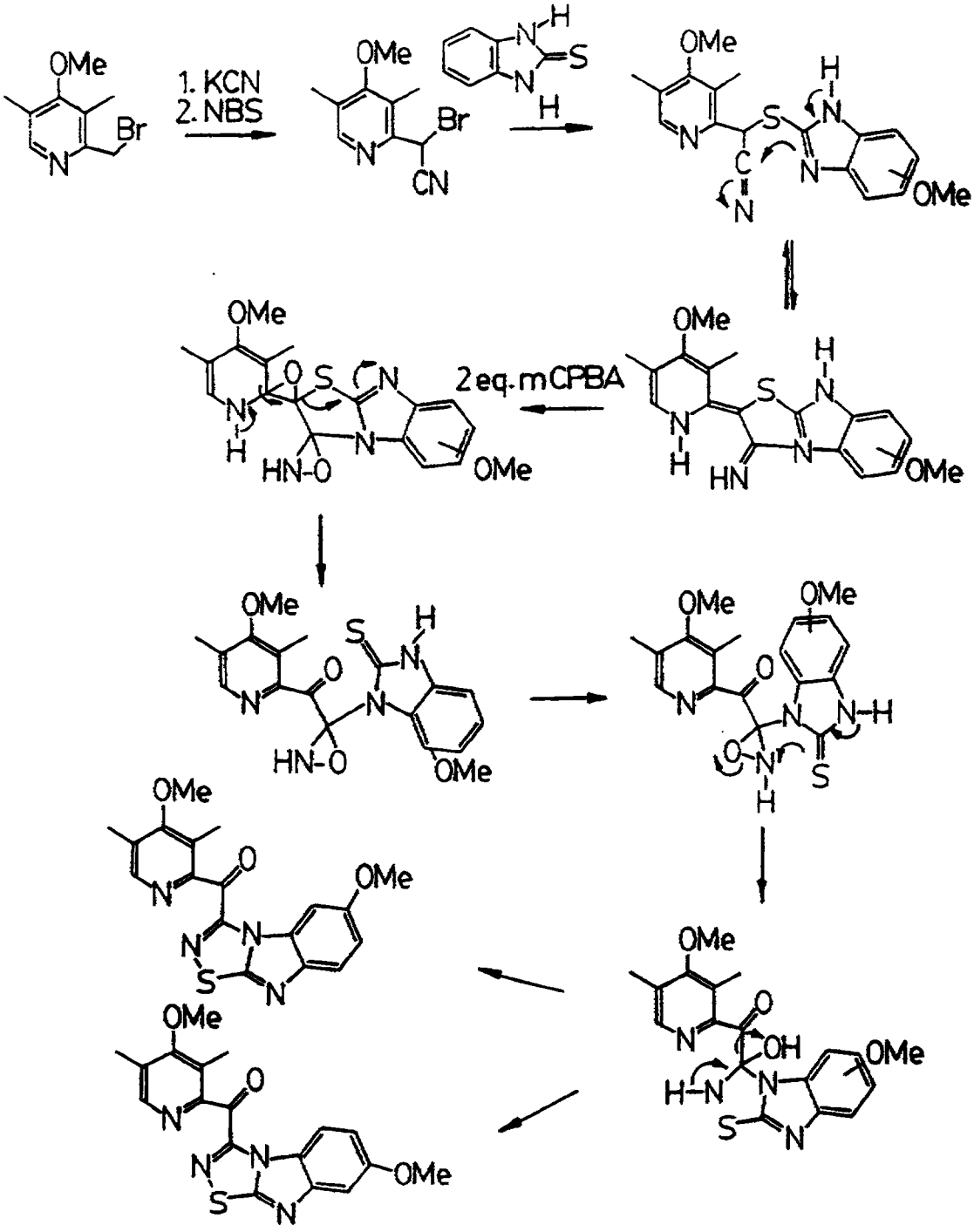


FIG. 4

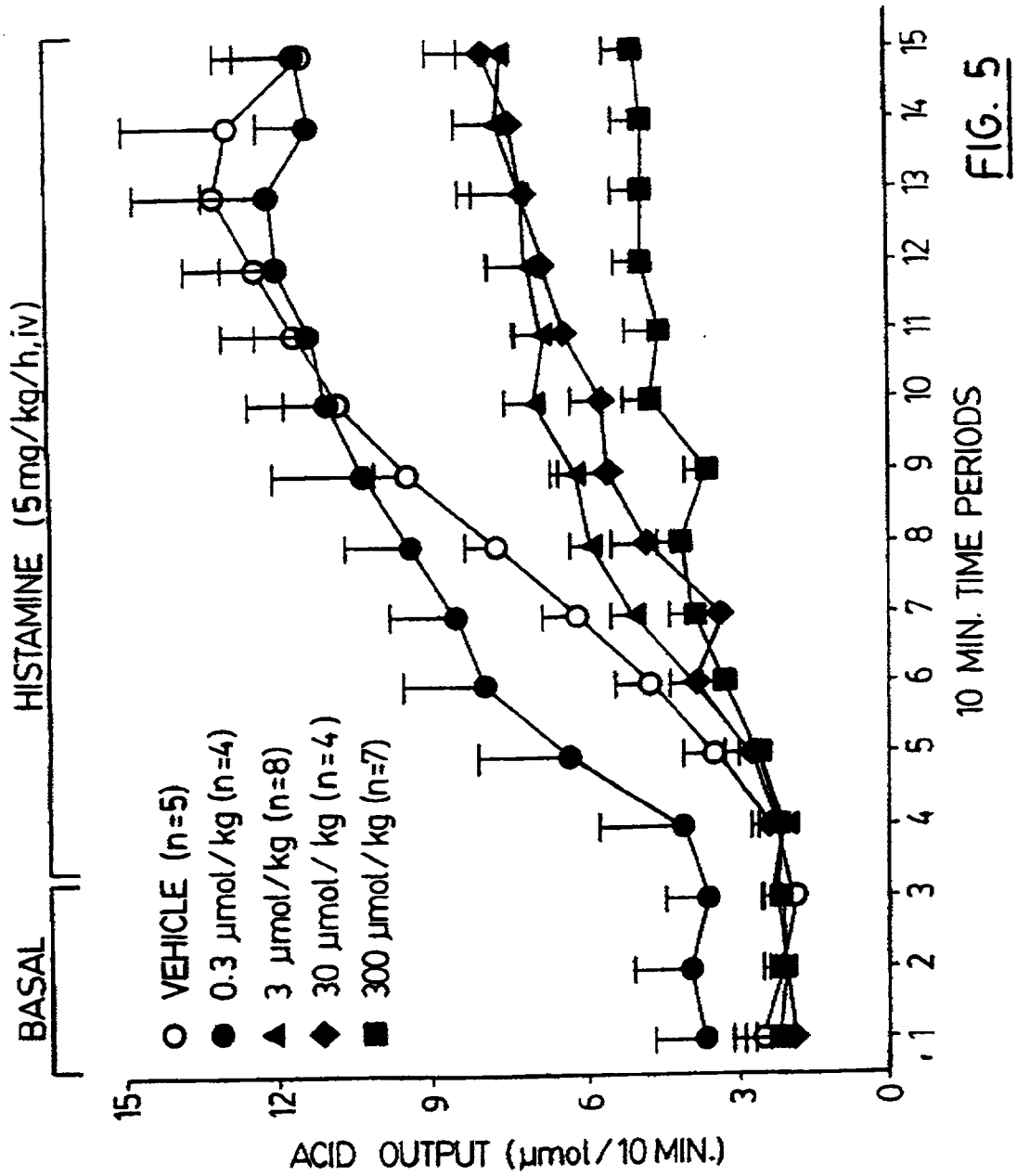
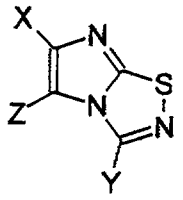

BASAL
HISTAMINE (5mg/kg/h,iv)
VEHICLE (n=5)
0.3 µmol/kg (n=4)
3 µmol/kg (n=8)
30 µmol/kg (n=4)
300 µmol/kg (n=7)
ACID OUTPUT (µmol/10 MIN.)
10 MIN. TIME PERIODS
0
3
6
9
12
15
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15

FIG. 5

* C L M S *

WHAT IS CLAIMED IS:

1. Imidazo[1,2-*d*]-thiadiazole compounds corresponding to the general formula I:

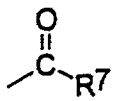


wherein X and Z are independently hydrogen, lower alkyl, halo, nitro, hydroxy, lower alkoxy, a group NR'R", OC(O)R', OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O)NR'R", NHC(O)OR' or CONR'R", with R' and R" being independently hydrogen, lower alkyl, aryl, lower arylalkyl or lower alkyl substituted with hydroxy, amino, lower alkylamino, carboxy or lower alkoxycarbonyl, or R' and R" in NR'R" when taken together forming a five or six membered ring heterocyclic ring selected from piperidinyl, pyrrolidinyl, morpholinyl and prolyl, the heterocyclic ring being optionally substituted with lower alkyl, carboxy, amino, phenyl, alkoxycarbonyl or di-lower alkylamino;

or X and Z taken together represent a benzene ring fused to the imidazo ring and being optionally substituted with up to four substituents independently selected from hydrogen, lower alkyl, halo, nitro, hydroxy, lower alkoxy, piperazinyl or a group NR'R", OC(O)R', OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O)NR'R", or NHC(O)OR', with R', R" being as defined above;

and Y is selected from :

(1) groups of the formula:



in which R^7 represents hydrogen, hydroxy, lower alkyl, lower cycloalkyl, lower alkoxy, lower alkenyl, lower

alkynyl, aryl, lower arylalkyl, heterocyclyl, N-substituted N-heterocyclyl, heterocyclyloxy, heterocyclyl-loweralkylene, a group NR'R" where R' and R" are independently selected from hydrogen, lower alkyl, aryl, lower arylalkyl, and alkylene, and a group ANR'R", AOR wherein A is an amino acid residue or a peptide of 2 to 3 amino acid residues and R', R" have the same definition as above

(2) heterocyclyl, lower alkylene-heterocyclyl, lower alkylene-amino-heterocyclyl, amino-lower alkylene-heterocyclyl or amino-heterocyclyl, the heterocyclic ring being attached at any heteroatom or carbon atom which results in the creation of a stable structure, and the heterocyclic ring being optionally substituted with 1-3 substituents selected from lower alkyl; hydroxy; nitro; amino; lower alkylamino; di-lower alkylamino; lower alkoxy; cinnamyl, lower alkyl substituted with 1-3 substituents selected from hydroxy, lower alkylcarbamoyl, phenyl, halophenyl, heterocyclyl, carboxy and lower alkoxycarbonyl; lower acyl; lower alkoxycarbonyl; lower alkyl-sulfonyl; amido; allyl; benzyl; phenyl optionally substituted with amino, halo, hydroxy, lower alkoxy, lower alkyl, lower alkylamino or di-lower alkylamino; heterocyclyl optionally substituted with 1-3 substituents selected from nitro, hydroxy, lower alkoxy, lower alkyl, amino, halo, lower alkylamino, di-lower alkylamino; with the proviso that the heterocyclyl group Y is not 1-imidazolyl or substituted 1-imidazolyl;

(3) NR'R" or $-CH_2-NR'R"$ wherein R', R" have the same definition as above;

(4) ANR'R", AOR' wherein A is an amino acid residue or a peptide of 2 to 3 amino acid residues and R', R" have the same definition as above

(5) lower 2-(alkoxycarbonyl)alkyl

(6) halo

(7) groups of formula R^8-CHOH- wherein R^8 is hydrogen, lower alkyl, aryl, lower arylalkyl, lower cycloalkyl, lower alkenyl, lower alkynyl or heterocyclyl, the heterocyclic ring being attached at any heteroatom or carbon atom which results in the creation of a stable structure,

(8) groups of formula R^9-CH=NOR^{10} wherein R^{10} is hydrogen, lower alkyl or lower arylalkyl, and R^9 is lower alkyl, aryl, lower arylalkyl, lower cycloalkyl, lower alkenyl, lower alkynyl or heterocyclyl, the heterocyclic ring being attached at any carbon atom which results in the creation of a stable structure;

(9) lower alkoxy, lower arylalkoxy, lower cycloalkoxy, lower heterocyclyl alkoxy or heterocyclyloxy;

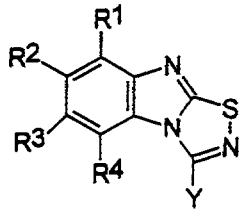
(10) lower alkylsulfonyl, lower alkylsulfinyl, arylsulfonyl, arylsulfinyl, lower alkyl-arylsulfonyl, lower alkyl-aryl sulfinyl, heterocyclyl-sulfonyl, heterocyclyl-sulfinyl; optionally substituted with 1 to 2 substituents selected from lower alkyl, halo, nitro, hydroxy, lower alkoxy, or groups of formula NR'R", OC(O)R', OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O)NR'R", NHC(O)OR' where R' and R" have the meanings given above;

(11) groups of the formula -C(=NOH)$COOR^{11}$ wherein R^{11} is lower alkyl

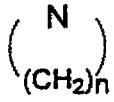
(12) substituted lower alkyl, aryl, lower arylalkyl, lower cycloalkyl, each group being optionally substituted with 1 to 2 substituents selected from lower alkyl, halo, nitro, amino, hydroxy, lower alkoxy, lower alkylamino, lower

dialkylamino, NR'R", OC(O)R', OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O)NR'R", NHC(O)OR', with R' and R" having the meanings given above.

2. Compounds according to claim 1, having the general formula:



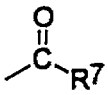
or pharmaceutically acceptable salts thereof, wherein R^1, R^2, R^3, R^4 are independently hydrogen, lower alkyl, halo, nitro, hydroxy, lower alkoxy, piperazinyl, or groups of the formula NR'R", OC(O)R', OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O)NR'R", NHC(O)OR' or CONR'R" in which R' and R" are independently hydrogen, lower alkyl, aryl, lower arylalkyl or NR'R" represents a five or six membered ring consisting of



wherein n = 4 or 5

and Y is selected from

(1) groups of the formula:



in which R^7 represents hydrogen, hydroxy, lower alkyl, lower cycloalkyl, lower alkoxy, lower alkenyl, lower alkynyl, aryl, lower arylalkyl, heterocyclyl, N-substituted N-heterocyclyl, heterocyclyloxy, heterocyclyl-loweralkylene, a group NR' R" where R' and R" are independently selected from hydrogen, lower alkyl, aryl, lower arylalkyl, and alkylene, and a group ANR'R", AOR wherein A is an amino acid residue

or a peptide of 2 to 3 amino acid residues and R', R" have the same definition as above

(2) heterocyclyl, lower alkylene-amino-heterocyclyl amino-heterocyclyl, amino-lower alkylene-heterocyclyl or lower alkylene-heterocyclyl, the heterocyclic ring being attached at any heteroatom or carbon atom which results in the creation of a stable structure, and the heterocyclic ring being optionally substituted with 1-3 substituents selected from lower alkyl; hydroxy; nitro; amino; lower alkylamino; di-lower alkylamino; lower alkoxy; lower alkyl substituted with 1-3 substituents selected from hydroxy, lower alkylcarbamoyl, phenyl, halophenyl, heterocyclyl, carboxy and lower alkoxycarbonyl; lower acyl; lower alkoxycarbonyl; lower alkyl-sulfonyl; amido; allyl; benzyl; phenyl optionally substituted with amino, halo, hydroxy, lower alkoxy, lower alkyl, lower alkylamino or di-lower alkylamino; heterocyclyl optionally substituted with 1-3 substituents selected from nitro, hydroxy, lower alkoxy, lower alkyl, amino, halo, lower alkylamino, di-lower alkylamino; with the proviso that the heterocyclyl group Y is not 1-imidazolyl or substituted 1-imidazolyl;

(3) NR'R" or $-CH_2-NR'R"$ wherein R', R" have the same definition as above;

(4) ANR'R", AOR' wherein A is an amino acid residue or a peptide of 2 to 3 amino acid residues and R', R" have the same definition as above

(5) lower 2-(alkoxycarbonyl)alkyl

(6) halo

(7) groups of formula R^8-CHOH- wherein R^8 is hydrogen, lower alkyl, aryl, lower arylalkyl, lower cycloalkyl, lower alkenyl, lower alkynyl or heterocyclyl, the heterocyclic ring being

attached at any heteroatom or carbon atom which results in the creation of a stable structure;

(8) groups of formula R^9-CH=NOR^{10} wherein R^{10} is hydrogen, lower alkyl or lower arylalkyl, and R^9 is lower alkyl, aryl, lower arylalkyl, lower cycloalkyl, lower alkenyl, lower alkynyl or heterocyclyl, the heterocyclic ring being attached at any carbon atom which results in the creation of a stable structure;

(9) lower alkoxy, lower arylalkoxy, lower cycloalkoxy, lower heterocyclyl alkoxy or heterocyclyloxy;

(10) lower alkylsulfonyl, lower alkylsulfinyl, arylsulfonyl, arylsulfinyl, lower alkyl-arylsulfonyl, lower alkyl-aryl sulfinyl, heterocyclyl-sulfonyl, heterocyclyl-sulfinyl; optionally substituted with 1 to 2 substituents selected from lower alkyl, halo, nitro, hydroxy, lower alkoxy, or groups of formula NR'R", OC(O)R', OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O)NR'R", NHC(O)OR' where R' and R" have the meanings given above;

(11) groups of the formula -C(=NOH)COOR^{11} wherein R^{11} is lower alkyl;

(12) aryl, lower arylalkyl, lower cycloalkyl, each group being optionally substituted with 1 to 3 substituents selected from lower alkyl, halo, nitro, amino, hydroxy, lower alkoxy, lower alkylamino, lower dialkylamino, NR'R", OC(O)R', OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O)NR'R", NHC(O)OR', with R' and R" having the meanings given above.

3. Compounds according to claim 2 wherein R^1, R^2, R^3, R^4 each represents hydrogen or alkoxy.

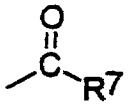
OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O)NR'R", NHC(O)OR' where R' and R" have the meanings given above;

(11) groups of the formula -C=NOH-COOR^{11} wherein R^{11} is lower alkyl;

(12) substituted lower alkyl, aryl, lower arylalkyl, lower cycloalkyl, each group being optionally substituted with 1 to 2 substituents selected from halo, nitro, amino, hydroxy, lower alkoxy, lower alkylamino, lower dialkylamino, NR'R", OC(O)R', OC(O)OR', OC(O)NR'R", NR'(COR'), NHC(O)NR'R", NHC(O)OR', with R' and R" having the meanings given above.

109. Compounds according to claim 108 wherein R^5 and R^6 both represent hydrogen.

110. Compounds according to claim 109 wherein Y represents

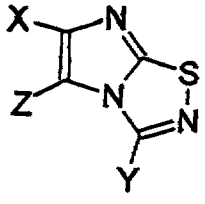


and R^7 represents lower alkyl, lower alkoxy or aryl.

111. A compound according to claim 110 which is 3-acetylimidazo[1,2-*d*]-1,2,4-thiadiazole.

112. A compound according to claim 110 which is 3-benzoylimidazo[1,2-*d*]-1,2,4-thiadiazole.

113. Process for preparing a bicyclic or tricyclic thiadiazole compound of the general formula:



(I)

wherein X and Z are independently hydrogen, lower alkyl, halo,nitro, hydroxy, lower alkoxy, a group NR'R",

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(54) Title: PROTON PUMP INHIBITOR



(I)

(57) Abstract

Novel thiadiazole compounds are provided, which are effective as proton pumps inhibitors, useful in treating peptic ulcers by inhibition of the proton pump enzyme H^+/K^+-ATPase. The compounds are 3-substituted 1,2,4-thiadiazole [4,5-*a*]benzimidazole and 3-substituted imidazo[1,2-*d*]-1,2,4-thiadiazoles corresponding to general formula (I) where X and Z either represented an optionally substituted benzene ring fused to the diazole nucleus, or represent a variety of independent chemical groupings (hydrogen, lower alkyl, halo, etc.) and Y is selected from a wide range, e.g. heterocyclics and carbonyl groups.