PCT WORLD INTELLECTUAL PROPE
International Bu

INTERNATIONAL APPLICATION PUBLISHED UNDER WO 9605187A1

(51) International Patent Classification 6 :
C07D 277/48, A61K 31/425

A1

(11) International Publication Number: WO 96/05187

(43) International Publication Date: 22 February 1996 (22.02.96)

(21) International Application Number: PCT/JP95/01596

(22) International Filing Date: 9 August 1995 (09.08.95)

(30) Priority Data:
9416459.7 15 August 1994 (15.08.94) GB

(71) Applicant *(for all designated States except US)*: FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP).

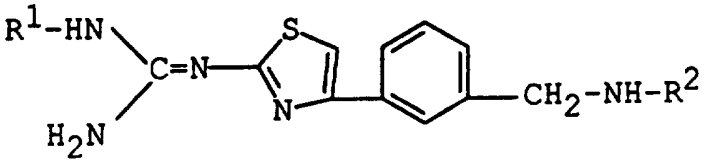
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: KATSURA, Yousuke [JP/JP]; 3-22-9, Miyayamacho, Toyonaka-shi, Osaka 560 (JP). TOMISHI, Tetsuo [JP/JP]; 5-24-11, Niina, Minoo-shi, Osaka 562 (JP). NISHINO, Shigetaka [JP/JP]; 1-26-3-C-1808, Tsukuda, Nishiyodogawa-ku, Osaka-shi, Osaka 555 (JP). OHNO, Mitsuko [JP/JP]; 5-14-2-407, Oyodonaka, Kita-ku, Osaka-shi, Osaka 531 (JP).

(74) Agent: SEKI, Hideo; Fujisawa Pharmaceutical Co., Ltd., Osaka Factory, 1-6, Kashima 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532 (JP).

(81) Designated States: AU, BR, CA, CN, FI, HU, JP, KR, MX, NO, NZ, RU, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: (4-(3-AMINOMETHYLPHENYL)THIAZOL-2-YL)-GUANIDINES AS H2-RECEPTOR ANTAGONISTS



(I)

(57) Abstract

New compounds of formula (I), wherein R^1 is lower alkoxy, lower alkoxy(lower)alkyl, cyano(lower)alkyl, phenyl, phenyl(lower)alkyl, [2-(lower)alkoxyphenyl] (lower)alkyl, diphenyl(lower)alkyl, phenoxy(lower)alkyl, phenyl(lower)alkoxy(lower)alkyl, cyclo(lower)alkenyl(lower)alkyl, protected amino(lower)alkyl or adamantyloxy(lower)alkyl, and R^2 is hydrogen, lower alkanoyl or carbamoyl, and a pharmaceutically acceptable salt thereof which are useful as a medicament.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**GB**	United Kingdom	**MR**	Mauritania
AU	Australia	**GE**	Georgia	**MW**	Malawi
BB	Barbados	**GN**	Guinea	**NE**	Niger
BE	Belgium	**GR**	Greece	**NL**	Netherlands
BF	Burkina Faso	**HU**	Hungary	**NO**	Norway
BG	Bulgaria	**IE**	Ireland	**NZ**	New Zealand
BJ	Benin	**IT**	Italy	**PL**	Poland
BR	Brazil	**JP**	Japan	**PT**	Portugal
BY	Belarus	**KE**	Kenya	**RO**	Romania
CA	Canada	**KG**	Kyrgystan	**RU**	Russian Federation
CF	Central African Republic	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CG	Congo			**SE**	Sweden
CH	Switzerland	**KR**	Republic of Korea	**SI**	Slovenia
CI	Côte d'Ivoire	**KZ**	Kazakhstan	**SK**	Slovakia
CM	Cameroon	**LI**	Liechtenstein	**SN**	Senegal
CN	China	**LK**	Sri Lanka	**TD**	Chad
CS	Czechoslovakia	**LU**	Luxembourg	**TG**	Togo
CZ	Czech Republic	**LV**	Latvia	**TJ**	Tajikistan
DE	Germany	**MC**	Monaco	**TT**	Trinidad and Tobago
DK	Denmark	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**US**	United States of America
FI	Finland	**ML**	Mali	**UZ**	Uzbekistan
FR	France	**MN**	Mongolia	**VN**	Viet Nam
GA	Gabon				

(4-(3-AMINOMETHYLPHENYL)THIAZOL-2-YL)-GUANIDINES AS H2-RECEPTOR ANTIGONISTS

TECHNICAL FIELD

This invention relates to NEW COMPOUNDS and pharmaceutically acceptable salts thereof which are useful as a medicament.

BACKGROUND ART

Some thiazole derivatives have been known as described, for example, in EP 0 545 376 A1.

DISCLOSURE OF INVENTION

This invention relates to new compounds and pharmaceutically acceptable salts thereof.

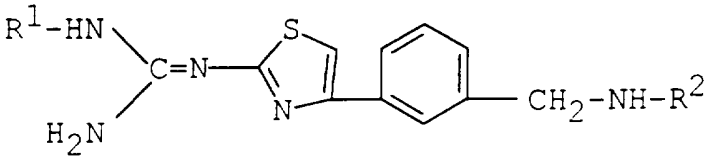
One object of this invention is to provide new thiazole derivatives and pharmaceutically acceptable salts thereof which possess antiulcer activity, H_2-receptor antagonism and antimicrobial activity against pathogenic microorganisms such as Helicobacter pylori.

Another object of this invention is to provide processes for the preparation of said thiazole derivatives and salt thereof.

A further object of this invention is to provide a pharmaceutical composition comprising, as an active ingredient, said thiazole derivatives of pharmaceutically acceptable salts thereof.

Still further object of this invention is to provide a method for the prophylactic or therapeutic treatment of ulcer in human being or animals.

The thiazole derivatives of this invention are new and can be represented by the following general formula (I) :



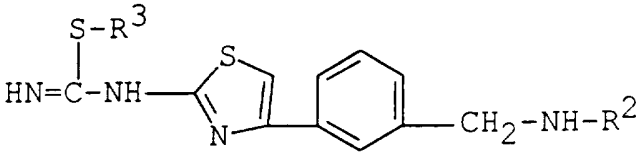
(I)

wherein R^1 is lower alkoxy, lower alkoxy(lower)alkyl, cyano(lower)alkyl, phenyl, phenyl(lower)alkyl, [2-(lower)alkoxyphenyl](lower)alkyl, diphenyl(lower)alkyl, phenoxy(lower)alkyl, phenyl(lower)alkoxy(lower)alkyl, cyclo(lower)alkenyl(lower)alkyl, protected amino(lower)alkyl or adamantyloxy(lower)alkyl, and

R^2 is hydrogen, lower alkanoyl or carbamoyl.

The object compound (I) or a salt thereof can be prepared by processes as illustrated in the following reaction schemes.

Process (1)

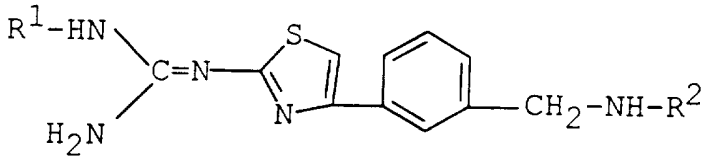


(II)
or a salt thereof

R^1-NH_2

(III)

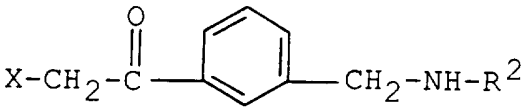
or a salt thereof



(I)

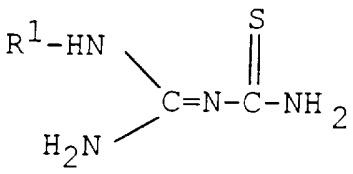
or a salt thereof

Process (2)



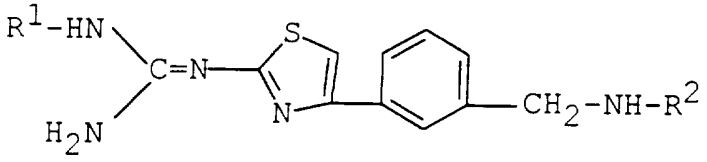
(IV)

or a salt thereof



(V)

or a salt thereof



(I)

or a salt thereof

wherein R^1 and R^2 are each as defined above,
R^3 is lower alkyl, and
X is a leaving group.

Suitable pharmaceutically acceptable salts of the object compound (I) are conventional non-toxic salts and may include a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g., sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g., calcium salt, magnesium salt, etc.), an ammonium salt; a salt with an organic base, for example, an organic amine salt (e.g., triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.); an inorganic acid addition salt (e.g., hydrochloride, hydrobromide, hydriodide, sulfate, phosphate, etc.); an organic carboxylic or sulfonic acid addition salt (e.g., formate, acetate, trifluoroacetate, maleate, tartrate, fumarate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.); a salt with a basic or acidic amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.).

In the above and subsequent descriptions of the present specification, suitable examples and illustration of the various definitions which the present invention intends to include within the scope thereof are explained

in detail as follows.

The term "lower" is used to intend a group having 1 to 6 carbon atom(s), unless otherwise provided.

The term "higher" is used to intend a group having 7 to 20 carbon atoms, unless otherwise provided.

Suitable "lower alkyl" and "lower alkyl moiety" in the terms "lower alkoxy(lower)alkyl", "cyano(lower)alkyl", "phenyl(lower)alkyl", "[2-(lower)alkoxyphenyl](lower)-alkyl", "diphenyl(lower)alkyl", "phenoxy(lower)alkyl", "phenyl(lower)alkoxy(lower)alkyl", "cyclo(lower)alkenyl(lower)alkyl", "protected amino(lower)alkyl" and "adamantyloxy(lower)alkyl" may include straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, tert-pentyl, hexyl, and the like, and in which more preferable example may be C_1-C_4 alkyl.

Suitable "lower alkoxy" and "lower alkoxy moiety" in the terms" lower alkoxy(lower)alkyl", "[2-(lower)alkoxyphenyl](lower)alkyl" and "phenyl(lower)alkoxy(lower)alkyl" may include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy, pentyloxy, t-pentyloxy, hexyloxy and the like.

Suitable "cyclo(lower)alkenyl moiety" in the term "cyclo(lower)alkenyl(lower)alkyl" may include cyclohexenyl, cyclohexadienyl and the like.

Suitable "halogen" may include fluorine, bromine, chlorine and iodine.

Suitable "leaving group" may include acid residue, lower alkoxy as exemplified above, and the like.

Suitable "acid residue" may include halogen as exemplified above, acyloxy and the like.

Suitable "protected amino" may include acylamino or an amino group substituted by a conventional protecting group such as mono (or di or tri)aryl(lower)alkyl, for example,

mono(or di or tri)phenyl(lower)alkyl (e.g., benzyl, trityl, etc.) or the like.

Suitable "acyl" and "acyl moiety" in the terms "acylamino" and "acyloxy" may include carbamoyl, aliphatic acyl group and acyl group containing an aromatic ring, which is referred to as aromatic acyl, or heterocyclic ring, which is referred to as heterocyclic acyl.

Suitable example of said acyl may be illustrated as follows :

Carbamoyl; Thiocarbamoyl;

Aliphatic acyl such as lower or higher alkanoyl (e.g., formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl, icosanoyl, etc.);

lower or higher alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, t-pentyloxycarbonyl, heptyloxycarbonyl, etc.);

lower or higher alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl, etc.);

lower or higher alkoxysulfonyl (e.g., methoxysulfonyl, ethoxysulfonyl, etc.);

cyclo(lower)alkylcarbonyl (e.g., cyclopentylcarbonyl, cyclohexylcarbonyl, etc.); or the like;

Aromatic acyl such as

aroyl (e.g., benzoyl, toluoyl, naphthoyl, etc.);

ar(lower)alkanoyl [e.g., phenyl(lower)alkanoyl (e.g., phenylacetyl, phenylpropanoyl, phenylbutanoyl, phenylisobutanoyl, phenylpentanoyl, phenylhexanoyl, etc.), naphthyl(lower)alkanoyl (e.g., naphthylacetyl, naphthylpropanoyl, naphthylbutanoyl, etc.), etc.];

ar(lower)alkenoyl [e.g., phenyl(lower)alkenoyl (e.g.,

phenylpropenoyl, phenylbutenoyl, phenylmethacryloyl, phenylpentenoyl, phenylhexenoyl, etc.), naphthyl(lower)alkenoyl (e.g., naphthylpropenoyl, naphthylbutenoyl, etc.), etc.];

ar(lower)alkoxycarbonyl [e.g., phenyl(lower)alkoxycarbonyl (e.g., benzyloxycarbonyl, etc.), etc.];

aryloxycarbonyl (e.g., phenoxycarbonyl, naphthyloxycarbonyl, etc.);

aryloxy(lower)alkanoyl (e.g., phenoxyacetyl, phenoxypropionyl, etc.);

arylglyoxyloyl (e.g., phenylglyoxyloyl, naphthylglyoxyloyl, etc.);

arylsulfonyl (e.g., phenylsulfonyl, p-tolylsulfonyl, etc.); or the like;

Heterocyclic acyl such as heterocycliccarbonyl;

heterocyclic(lower)alkanoyl (e.g., heterocyclicacetyl, heterocyclicpropanoyl, heterocyclicbutanoyl, heterocyclicpentanoyl, heterocyclichexanoyl, etc.);

heterocyclic(lower)alkenoyl (e.g., heterocyclicpropenoyl, heterocyclicbutenoyl, heterocyclicpentenoyl, heterocyclichexenoyl, etc.); heterocyclicglyoxyloyl; or the like;

in which suitable "heterocyclic moiety" in the terms "heterocycliccarbonyl", "heterocyclic(lower)alkanoyl", heterocyclic(lower)alkenoyl" and "heterocyclicglyoxyloyl" ad mentioned above means, in more detail, saturated or unsaturated, monocyclic or polycyclic heterocyclic group containing at least one hetero-atom such as an oxygen, sulfur, nitrogen atom and the like.

And, especially preferable heterocyclic group may be heterocyclic group such as

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl,

pyrazolyl, pyridyl, dihydropyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), for example, indolyl, isoindolyl, indolinyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl, (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.), etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, sydnonyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl (e.g., 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.), dihydrothiazinyl, etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolidinyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-

membered) heteromonocyclic group containing 1 to 2 sulfur atom(s), for example, thienyl, dihydrodithiinyl, dihydrodithionyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom, for example, furyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, dihydrooxathiinyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s), for example, benzothienyl, benzodithiinyl, etc.;

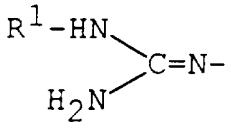
unsaturated condensed heterocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, benzoxathiinyl, etc.; and the like.

Suitable "lower alkanoyl" may include formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl and the like.

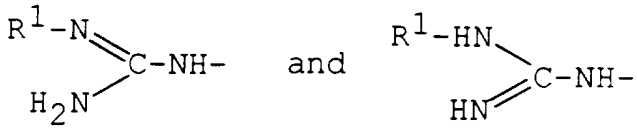
It is to be noted that the object compound (I) may include one or more stereoisomer(s) due to asymmetric carbon atom(s) and double bond(s) and all such isomers and mixture thereof are included within the scope of this invention.

Regarding the object compound (I), it is to be understood that they include tautomeric isomers.

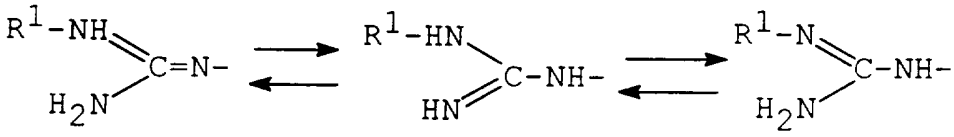
That is, a group of the formula :



can be also alternatively represented by its two tautomeric formulas :



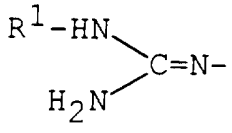
That is, the said three groups are in the state of equilibrium and such tautomerism can be represented by the following equilibrium.



And it is obvious to be any person skilled in the arts that the tautomeric isomers are easily convertible reciprocally and are included within the same category of the compound per se.

Accordingly, the tautomeric forms of the object compound (I) are clearly included within the scope of the present invention.

In the present specification, the object and starting compounds including the group of such tautomeric isomers are represented by using one of the expressions therefor, that is the formula :



only for the convenient sake.

The processes for preparing the object compound is explained in detail in the following.

Process (1)

The compound (I) or a salt thereof can be prepared by reacting the compound (II) or a salt thereof with the compound (III) or a salt thereof.

This reaction is usually carried out in a solvent such as water, alcohol (e.g., methanol, ethanol, etc.), benzene, N,N-dimethylformamide, tetrahydrofuran, toluene, methylene chloride, ethylene dichloride, chloroform, dioxane, diethyl ether or any other solvents which do not adversely affect the reaction, or the mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under warming to heating.

When the starting compound is in liquid, it can be used also as a solvent.

Process (2)

The compound (I) or a salt thereof can be prepared by reacting the compound (IV) or a salt thereof with the compound (V) or a salt thereof.

This reaction is usually carried out in a solvent such as water, alcohol (e.g., methanol, ethanol, etc.), benzene, N,N-dimethylformamide, tetrahydrofuran, toluene, methylene chloride, ethylene dichloride, chloroform, dioxane, diethyl ether or any other solvents which do not adversely affect the reaction, or the mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under warming to heating.

The reaction may be also carried out in the presence of an inorganic or an organic base such as an alkali metal (e.g., sodium, potassium, etc.), an alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, etc.), an alkali metal hydrogencarbonate (e.g., sodium hydrogencarbonate, potassium hydrogencarbonate, etc.), alkali metal carbonate (e.g. sodium carbonate, potassium carbonate, etc.), tri(lower)alkylamine (e.g., trimethylamine, triethylamine, diisopropylethylamine, etc.), alkali metal hydride (e.g., sodium hydride, etc.), alkali metal (lower)alkoxide (e.g. sodium methoxide, sodium ethoxide, etc.), pyridine, lutidine, picoline, dimethylaminopyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, N,N-di(lower)alkylaniline or the like.

When the base and/or the stating compound are in liquid, they can be used also as a solvent.

The new thiazole derivatives (I) and pharmaceutically acceptable salts thereof possess antiulcer activity, H_2-receptor antagonism, and especially antimicrobial activity against pathogenic microorganisms such as Helicobacter pylori, and are useful for a prophylactic or therapeutic treatment of gastritis, ulcer (e.g. gastric ulcer, duodenal ulcer, anastomotic ulcer, etc.), Zollinger-Ellison Syndrome, reflux esophagitis, upper gastrointestinal bleeding, and the like.

In order to illustrate the usefulness of the object compound (I), the pharmacological test data of some representative compounds of the compound (I) are shown in the following.

Test compound

(a) 4-(3-Acetylaminomethylphenyl)-2-[(amino)[2-(1-

cyclohexen-1-yl)ethylamino]methyleneamino]thiazole

(b) 4-(3-Acetylaminomethylphenyl)-2-[(amino)[2-(2-methoxyphenyl)ethylamino]methyleneamino]thiazole

Test A (H_2-receptor antagonism in isolated guinea-pig atrium) :

Test Method

The atrial strip isolated from guinea-pig was suspended under an initial tension 0.3 to 0.6 g in an organ bath containing Tyrode solution at 30°C, aerated 95% O_2 - 5% CO_2 gas.

The beating rate and amplitude of contraction of the atrium were recorded by means of a transducer and a polygraph. Histamine (1×10^{-6} g/ml) was added to the bathing fluid and the increase in beating rate after dosing was measured. Addition of test compound (1×10^{-6} g/ml) was made 30 minutes after washing out histamine. Inhibitory effect of test compound was calculated by comparing histamine-induced increases in beating rate before and 30 minutes after dosing with the test compound.

Test Result

Test Compound	inhibition (%)
(a)	100

Test B (in vitro Antimicrobial Activities)

Test Method

In vitro antimicrobial activity was determined by the agar dilution method. Test strain was precultured in Brucella Agar with 3% horse serum and 2% starch at 37°C for 3 days, and 10^7 cfu/ml were inoculated with a multipoint

replicater onto Brucella agar plus 7% horse blood plate containing serial 2-fold dilutions of Test compound and incubated at 37°C for 3 days.

Incubation was carried out in an atmosphere of 10% CO_2.

MIC was read after incubation as the lowest Test compound concentration that inhibited macroscopic colonial growth. The data shown below are mean MIC against clinical isolated.

Test Result

M.I.C. (μg/ml)

Test Strain	Test Compound
	(b)
Helico bacter pylori 8007	0.0125

The object compound (I) or its pharmaceutically acceptable salts can usually be administered to mammals including human being in the form of a conventional pharmaceutical composition such as oral dosage form (e.g., capsule, micro-capsule, tablet, granule, powder, troche, syrup, aerosol, inhalation, suspension, emulsion, etc.), injection dosage form or suppository, or the like.

The pharmaceutical composition of this invention can contain various organic or inorganic carrier materials, which are conventional used for pharmaceutical purpose, such as excipient (e.g. sucrose, starch, mannit, sorbitol, lactose, glucose, cellulose, talc, calcium phosphate, calcium carbonate, etc.), binding agent (e.g. cellulose, methyl cellulose, hydroxypropylcellulose, polypropylpyrrolidone, gelatin, gum arabic, polyethyleneglycol, sucrose, starch, etc.), disintegrator (e.g. starch, carboxymethyl cellulose, calcium salt of

carboxymethyl cellulose, hydroxypropylstarch, sodium glycole-starch, sodium bicarbonate, calcium phosphate, calcium citrate, etc.), lubricant (e.g. magnesium stearate, talc, sodium laurylsulfate, etc.), flavoring agent (e.g. citric acid, menthol, glycine, orange powders, etc.), preservative (e.g. sodium benzoate, sodium bisulfite, methylparaben, propylparaben, etc.), stabilizer (e.g. citric acid, sodium citrate, acetic acid, etc.), suspending agent (e.g. methyl cellulose, polyvinylpyrrolidone, aluminum stearate, etc.), dispersing agent, aqueous diluting agent (e.g. water), base wax (e.g. cacao butter, polyethyleneglycol, white petrolatum, etc.).

While the dosage of the compound (I) will vary depending upon the age and condition of the patient, an average single dose of about 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound (I) may be effective for treating ulcer. In general, amounts between 0.1 mg/body and about 1,000 mg/body may be administered per day.

Preferred embodiments of the object compound (I) are as follows.

R^1 is lower alkoxy, ethoxy(lower)alkyl, cyano(lower)alkyl, phenyl, phenyl(lower)alkyl, (2-methoxyphenyl)(lower)alkyl (more preferably 2-(2-methoxyphenyl)ethyl)), diphenyl(lower)alkyl, phenoxy(lower)alkyl, phenyl(lower)alkoxy(lower)alkyl, cyclo(lower)alkenyl(lower)alkyl, acylamino(lower)alkyl [more preferably carbamoylamino(lower)alkyl, or aroylamino(lower)alkyl (more preferably benzoylamino(lower)alkyl)] or adamantyloxy(lower)alkyl, and

R^2 is hydrogen, lower alkanoyl (more preferably acetyl) or carbamoyl.

The following Examples are given for the purpose of illustrating the present invention in more detail.

Example 1

A suspension of 4-(3-acetylaminomethylphenyl)-2-(2-methyl-1-isothioureido)thiazole hydriodide (3.0 g) and 2-phenoxyethylamine (5.0 g) in ethanol (100 ml) was refluxed for 38 hours. The solvent was removed under reduced pressure and the residue was dissolved in a mixture of water (100 ml)and tetrahydrofuran (30 ml). The mixture was adjusted to pH 10 with 30% potassium carbonate solution and then was extracted with ethyl acetate (200 ml). The extract was dried over magnesium sulfate and the solvent was removed under reduced pressure. The residue was chromatographed on a silica gel column eluting with a mixture of chloroform:methanol = 20:1. Recrystallization from a mixture of ethyl acetate and methanol afforded 4-(3-acetylaminomethylphenyl)-2-[(amino)(2-phenoxyethylamino)methyleneamino]thiazole (0.46 g).

mp : 164-165°C

IR (Nujol) : 3450, 3300, 1660, 1630, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 1.88 (3H, s), 3.59 (2H, t, J=5.5Hz), 4.10 (2H, t, J=5.5Hz), 4.27 (2H, d, J=5.8Hz), 6.91-7.02 (3H, m), 7.12-7.18 (2H, m), 7.22-7.35 (3H, m), 7.55 (2H, br s), 7.66-7.70 (2H, m), 8.35 (1H, t, J=5.8Hz)

Elemental Analysis Calcd. for $C_{21}H_{23}N_5O_2S$:
C 61.59, H 5.66, N 17.10
Found : C 61.30, H 5.65, N 16.80

Example 2

The following compounds were obtained according to a

similar manner to that of Example 1.

(1) 4-(3-Acetylaminomethylphenyl)-2-[(amino)(2-ethoxyethylamino)methyleneamino]thiazole
mp : 123-125°C
IR (Nujol) : 3470, 3300, 1650, 1590 cm^{-1}
NMR (DMSO-d_6, δ) : 1.13 (3H, t, J=7.0Hz), 1.89 (3H, s), 3.33-3.54 (6H, m), 4.28 (2H, d, J=5.8Hz), 7.13-7.17 (2H, m), 7.29-7.41 (3H, m), 7.65-7.80 (2H, m), 8.36 (1H, t, J=5.8Hz)
Elemental Analysis Calcd. for $C_{17}H_{23}N_5O_2S$: C 56.49, H 6.41, N 19.38
Found : C 56.78, H 6.55, N 19.07

(2) 4-(3-Acetylaminomethylphenyl)-2-[(amino)[2-(2-methoxyphenyl)ethylamino]methyleneamino]thiazole
mp : 155-156°C
IR (Nujol) : 3310, 3280, 1620 cm^{-1}
NMR (DMSO-d_6, δ) : 1.88 (3H, s), 2.77-2.85 (2H, t, J=7.0Hz), 3.37-3.43 (2H, m), 3.80 (3H, s), 4.28 (2H, d, J=5.8Hz), 6.84-6.99 (2H, m), 7.14-7.24 (4H, m), 7.32 (1H, t, J=7.6Hz), 7.44 (2H, br s), 7.63-7.68 (2H, m), 8.36 (1H, t, J=5.8Hz)
Elemental Analysis Calcd. for $C_{22}H_{25}N_5O_2S$: C 62.39, H 5.95, N 16.54
Found : C 62.39, H 6.07, N 16.35

(3) 4-(3-Acetylaminomethylphenyl)-2-[(amino)[2-(1-cyclohexen-1-yl)ethylamino]methyleneamino]thiazole
mp : 136-137°C
IR (Nujol) : 3330, 1660, 1600 cm^{-1}
NMR (DMSO-d_6, δ) : 1.40-1.65 (4H, m), 1.88 (3H, s), 1.90-2.00 (4H, m), 2.08-2.18 (2H, m), 3.26-3.31 (2H, m), 4.28 (2H, d, J=5.8Hz), 5.46(1H, br s), 7.13-7.17 (2H, m), 7.33 (1H, t, J=7.7Hz), 7.40

(2H, br s), 7.66-7.70 (2H, m), 8.36 (1H, t, J=5.8Hz)

Elemental Analysis Calcd. for $C_{21}H_{27}N_5OS$:
C 63.45, H 6.85, N 17.62
Found : C 63.43, H 6.83, N 17.36

(4) 4-(3-Acetylaminomethylphenyl)-2-[(amino)(3,3-diphenylpropylamino)methyleneamino]thiazole
mp : 162-163°C
IR (Nujol) : 3400, 3230, 1640, 1600 cm^{-1}
NMR (DMSO-d_6, δ) : 1.88 (3H, s), 2.20-2.40 (2H, m), 3.00-3.20 (2H, m), 4.06 (1H, t, J=7.7Hz), 4.26 (2H, d, J=5.8Hz), 7.13-7.36 (14H, m), 7.47 (2H, br s), 7.66-7.69 (2H, m), 8.35 (1H, t, J=5.8Hz)

(5) 4-(3-Acetylaminomethylphenyl)-2-[(amino)(2-cyanoethylamino)methyleneamino]thiazole
mp : 150-151 °C
IR (Nujol) : 3250, 3100, 2230, 1640 cm^{-1}
NMR (DMSO-d_6, δ) : 1.89 (3H, s), 2.76 (2H, t, J=6.3Hz), 3.41-3.50 (2H, m), 4.29 (2H, d, J=5.9Hz), 7.16 (1H, d, J=7.6Hz), 7.21 (1H, s), 7.34 (1H, t, J=7.6Hz), 7.69-7.72 (4H, m), 8.36 (1H, t, J=5.9Hz)

(6) 4-(3-Acetylaminomethylphenyl)-2-[(amino)[2-(1-adamantyloxy)ethylamino]methyleneamino]thiazole
mp : 85-89°C (dec.)
IR (Nujol) : 3270, 1640 cm^{-1}
NMR (DMSO-d_6, δ) : 1.57 (6H, br s), 1.70 (6H, br s), 1.89 (3H, s), 2.09 (3H, br s), 3.29-3.34 (2H, m), 3.46-3.50 (2H, m), 4.29 (2H, d, J=5.8Hz), 7.15-7.17 (2H, m), 7.32 (1H, t, J=7.8Hz), 7.41 (2H, br s), 7.69-7.70 (2H, m), 8.37 (1H, t, J=5.8Hz)

(7) 4-(Acetylaminomethylphenyl)-2-[(amino)(2-phenylpropylamino)methyleneamino]thiazole
mp : 68-70°C
IR (Nujol) : 3270, 1610 cm^{-1}
NMR (DMSO-d_6, δ) : 1.25 (3H, d, J=6.9Hz), 1.88 (3H, s), 2.95-3.06 (1H, m), 3.39-3.42 (2H, m), 4.28 (2H, d, J=5.8Hz), 7.13-7.36 (10H, m), 7.60-7.68 (2H, m), 8.37 (1H, t, J=5.8Hz)

(8) 4-(3-Acetylaminomethylphenyl)-2-[(amino)(2-phenylethylamino)methyleneamino]thiazole
mp : 118-119°C
IR (Nujol) : 3450, 3270, 1650, 1590 cm^{-1}
NMR (DMSO-d_6, δ) : 1.88 (3H, s), 2.83 (2H, t, J=7.3Hz), 3.40-3.50 (2H, m), 4.28 (2H, d, J=5.9Hz), 7.14-7.36 (8H, m), 7.47 (2H, br s), 7.63-7.69 (2H, m), 8.35 (1H, t, J=5.9Hz)
Elemental Analysis Calcd. for $C_{21}H_{21}N_5OS$:
C 64.10, H 5.89, N 17.80
Found : C 63.88, H 5.94, N 17.56

(9) 4-(3-Acetylaminomethylphenyl)-2-[(amino)(benzylamino)methyleneamino]thiazole
mp : 124-125°C
IR (Nujol) : 3450, 3320, 1630 cm^{-1}
NMR (DMSO-d_6, δ) : 1.88 (3H, s), 4.27 (2H, d, J=5.8Hz), 4.44 (2H, d, J=5.8Hz), 7.13-7.16 (2H, m), 7.27-7.37 (6H, m), 7.56 (2H, br s), 7.62-7.67 (2H, m), 8.35 (1H, t, J=5.8Hz)

(10) 4-(3-Acetylaminomethylphenyl)-2-[(amino)(3-phenylpropylamino)methyleneamino]thiazole
mp : 135-136°C
IR (Nujol) : 3450, 3300, 1640, 1580 cm^{-1}
NMR (DMSO-d_6, δ) : 1.79-1.88 (5H, m), 2.66 (2H, t,

J=7.3Hz), 3.16-3.25 (2H, m), 4.27 (2H, d, J=5.8Hz), 7.14-7.36 (8H, m), 7.46 (2H, br s), 7.67-7.70 (2H, m), 8.34 (1H, t, J=5.8Hz)

Elemental Analysis Calcd. for $C_{22}H_{25}N_5OS$: C 64.84, H 6.18, N 17.18

Found : C 64.61, H 6.19, N 16.97

Example 3

A suspension of 4-(3-acetylaminomethylphenyl)-2-(2-methyl-1-isothioureido)thiazole hydriodide (5.2 g) and 2-(2-methoxyphenyl)ethylamine (7.0 ml) in methylene chloride (100 ml) was refluxed for 40 hours. The solvent was removed under reduced pressure and the residue was dissolved in a mixture of water (100 ml) and tetrahydrofuran (20 ml). The mixture was adjusted to pH 9 with 30% potassium carbonate solution and then was extracted with ethyl acetate (150 ml). The extract was dried over magnesium sulfate and then the solvent was removed under reduced pressure. The residue was chromatographed on silica gel column eluting with a mixtue of ethyl acetate:methanol = 100:1. The appropriate fraction was collected and the solvent was removed under reduced pressure. The residue was crystallized from ethyl acetate. Recrystallization from a mixture of ethanol and diisopropyl ether afforded 4-(3-acetylaminomethylphenyl)-2-[(amino)[2-(2-methoxyphenyl)ethylamino]methyleneamino]-thiazole (1.6 g).

mp : 155-156°C

IR (Nujol) : 3310, 3280, 1620 cm^{-1}

NMR (DMSO-d_6, δ) : 1.88 (3H, s), 2.77-2.85 (2H, t, J=7.0Hz), 3.37-3.43 (2H, m), 3.80 (3H, s), 4.28 (2H, d, J=5.8Hz), 6.84-6.99 (2H, m), 7.14-7.24 (4H, m), 7.32 (1H, t, J=7.6Hz), 7.44 (2H, br s), 7.63-7.68 (2H, m), 8.36 (1H, t, J=5.8Hz)

Elemental Analysis Calcd. for $C_{22}H_{25}N_5O_2S$:

C 62.39, H 5.95, N 16.54
Found : C 62.39, H 6.07, N 16.35

At the same time, by this reaction the following compound was obtained as by-product.

4-(3-Acetylaminomethylphenyl)-2-[3-(2-(2-methoxyphenyl)ethyl)ureido]thiazole
mp : 145-146°C
IR (Nujol) : 3340, 3240, 1670, 1630 cm^{-1}
NMR (DMSO-d_6, δ) : 1.88 (3H, s), 2.76 (2H, t, J=7.0Hz), 3.34-3.45 (2H, m), 3.79 (3H, s), 4.28 (2H, d, J=5.8Hz), 6.46 (1H, t, J=4.6Hz), 6.89 (1H, t, J=7.3Hz), 6.97 (1H, d, J=7.6Hz), 7.15-7.25 (3H, m), 7.35 (1H, t, J=7.6Hz), 7.40 (1H, s), 7.69-7.73 (2H, m), 8.36 (1H, t, J=5.8Hz), 10.60 (1H, s)
Elemental Analysis Calcd. for $C_{22}H_{24}N_4O_3S$:
C 62.24, H 5.70, N 13.20
Found : C 62.44, H 5.66, N 13.20

Example 4

The following compound (Compound A) and by-product (Compound B) were obtained according to a similar manner to that of Example 3.

Compound A :
4-(3-Acetylaminomethylphenyl)-2-[(amino)(2-benzoylaminoethylamino)methyleneamino]thiazole
mp : 126-127°C
IR (Nujol) : 3300, 1640 cm^{-1}
NMR (DMSO-d_6, δ) : 1.88 (3H, s), 3.42 (4H, br s), 4.28 (2H, d, J=5.8Hz), 7.12-7.17 (2H, m), 7.31 (1H, t, J=7.9Hz), 7.44-7.52 (3H, m), 7.50-7.70 (4H, m), 7.84-7.88 (2H, m), 8.37 (1H, t,

J=5.8Hz), 8.62 (1H, t, J=5.8Hz)

Compound B :

4-(3-Acetylaminomethylphenyl)-2-[(imidazolidin-2-ylidene)amino]thiazole

mp : 228-229°C

IR (Nujol) : 3300, 1640 cm^{-1}

NMR (DMSO-d_6) : 1.89 (3H, s), 3.59 (4H, s), 4.30 (2H, d, J=5.9Hz), 7.13-7.18 (2H, m), 7.33 (1H, t, J=8.0Hz), 7.66 (2H, br s), 7.77-7.81 (2H, m), 8.37 (1H, t, J=5.9Hz)

Example 5

A suspension of N-(2-benzyloxyethyl)phthalimide (7.5 g) and hydrazine hydrate (1.33 g) in ethanol (100 ml) was refluxed for 2 hours. 4-(3-acetylaminomethylphenyl)-2-(2-methyl-1-isothioureido)thiazole hydriodide (3.0 g) was added to the reaction mixtur and then the mixtue was efluxed for 24 hours. The solvent was removed under reduced pressure and the residue was dissolved in a mixtue of water (100 ml) and tetrahydrofuran (40 ml). The mixtue was adjusted to pH 10 with 30% potassium carbonate solution and then was extracted with ethyl acetate (150 ml). The extract was dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel column eluting with a mixtue of chloroform:methanol = 50:1. Recrystallization from a mixture of ethanol and diisopropyl ether afforded 4-(3-acetylaminomethylphenyl)-2-[(amino)(2-benzyloxyethylamino)methyleneamino]thiazole (0.48 g).

mp : 143-144°C

IR (Nujol) : 3480, 3290, 1650, 1590 cm^{-1}

NMR (DMSO-d_6, δ) : 1.88 (3H, s), 3.41-3.44 (2H, m), 3.57 (2H, t, J=4.8Hz), 4.28 (2H, d, J=5.8Hz), 4.54 (2H, s), 7.12-7.16 (2H, m), 7.25-7.36 (8H,

m), 7.42 (2H, br s), 7.68-7.72 (2H, m), 8.36 (1H, t, J=5.8Hz)

Elemental Analysis Calcd. for $C_{22}H_{25}N_5O_2S$:
C 62.39, H 5.95, N 16.54
Found : C 62.20, H 5.94, N 16.34

Example 6

The following compound was obtained according to a similar manner to that of Example 5.

4-(3-Acetylaminomethylphenyl)-2-[(amino)(2-uureidoethylamino)methyleneamino]thiazole

mp : 167-168°C

IR (Nujol) : 3290, 3160, 1660, 1610 cm^{-1}

NMR (DMSO-d_6, δ) : 1.89 (3H, s), 3.12-3.23 (4H, m), 4.29 (2H, d, J=5.9Hz), 5.56 (2H, s), 6.10 (1H, t, J=5.3Hz), 7.14-7.17 (2H, m), 7.34 (1H, t, J=7.7Hz), 7.63-7.70 (4H, m), 8.37 (1H, t, J=5.9Hz)

Elemental Analysis Calcd. for $C_{16}H_{21}N_7O_2S$:
C 51.18, H 5.64, N 26.11
Found : C 51.45, H 5.69, N 26.09

Example 7

A solution of 3-(acetylaminomethyl)acetophenone (700 mg) and bromine (610 mg) in dioxane (10 ml) was stirred at room temperature for 5 hours. Methanol (20 ml), [(phenylamino)(aminomethylene]thiourea (700 mg) and potassium carbonate (1.11g) were added to the reaction mixture. The mixture was heated at 55°C for 2 hours. The solvent was removed under reduced pressureand the residue was dissolved in a mixtue of water (60 ml) and tetrahydrofuran (40 ml). The mixture was adjusted to pH 10 with 30% potassium carbonate solution and then was extracted with ethyl acetate (150 ml). The extract was

dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was crystallized from ethyl acetate. Recrystallization from a mixtue of ethanol and water afforded 4-(3-acetylaminomethylphenyl)-2-[(amino)(phenylamino)methyleneamino]thiazole (450 mg).

mp : 185-186°C

IR (Nujol) : 3420, 3290, 1650 cm^{-1}

NMR (DMSO-d_6, δ) : 1.89 (3H, s), 4.30 (2H, d, J=5.8Hz), 7.011 (1H, t, J=7.3Hz), 7.18 (1H, d, J=7.8Hz), 7.27-7.40 (5H, m), 7.52 (2H, d, J=7.6Hz), 7.72-7.76 (2H, m), 7.86 (2H, br s), 8.38 (1H, t, J=5.8Hz), 8.90 (1H, br s)

Elemental Analysis Calcd. for $C_{19}H_{19}N_5OS$:
C 62.44, H 5.24, N 19.16
Found : C 62.45, H 5.28, N 19.01

Example 8

The following compound was obtained according to a similar manner to that of Example 7.

4-(3-Acetylaminomethylphenyl)-2-[(amino)(ethoxyamino)methyleneamino]thiazole hydrochloride

mp : 115-117°C

IR (Nujol) : 3250, 1660, 1620 cm^{-1}

NMR (DMSO-d_6, δ) : 1.29 (3H, t, J=7.0Hz), 1.90 (3H, s), 4.00 (2H, q, J=7.0Hz), 4.30 (2H, d, J=5.9Hz), 7.25 (1H, d, J=7.7Hz), 7.40 (1H, t, J=7.7Hz), 7.69 (1H, s), 7.76-7.79 (2H, m), 8.44 (1H, t, J=5.9Hz)

Example 9

A mixture of 4-(3-acetylaminomethylphenyl)-2-[(amino)[2-(1-adamantyloxy)ethylamino]methyleneamino]-thiazole (500 mg) and 4N hydrogen chloride-dioxane (7 ml) in methanol (10 ml) was stirred at room temperature for 30

minutes. The solvent was removed under reduced pressure and the residue was crystallized frm a mixture of methanol and diisopropyl ether. Recrystallization from a mixture of ethanol and diisopropyl ether afforded 4-(3-acetylaminomethylphenyl)-2-[(amino)[2-(1-adamantyloxy)-ethylamino]methyleneamino]thiazole hydrochloride (320 mg).

mp : 133-135°C

IR (Nujol) : 3270, 1680, 1640 cm^{-1}

NMR (DMSO-d_6, δ) : 1.50-1.53 (6H, m), 1.62-1.66 (6H, m), 1.89 (3H, s), 2.04 (3H, br s), 3.45-3.65 (4H, m), 4.31 (2H, d, J=5.7Hz), 7.25 (1H, d, J=7.8Hz), 7.39 (1H, t, J=7.8Hz), 7.73-7.82 (3H, m), 8.44 (1H, t, J=5.7Hz), 8.56 (2H, br s)

Example 10

A suspension of 4-(3-acetylaminomethylphenyl)-2-[(amino)[2-(2-methoxyphenyl)ethylamino]methyleneamino]-thiazole (600 mg) and conc-hydrochloric acid (5 ml) in ethanol (50 ml) was refluxed for 4 days. After cooling, the resulting precipitate was collected by filtration to afford 4-(3-aminomethylphenyl)-2-[(amino)[2-(2-methoxyphenyl)ethylamino]methyleneamino]thiazole dihydrochloride (500 mg).

mp : 157-159°C (dec.)

IR (Nujol) : 3310, 1670, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 2.92 (2H, t, J=6.6Hz), 3.60-3.70 (2H, m), 3.75 (3H, s), 4.06 (2H, q, J=5.6Hz), 6.83-6.97 (2H, m), 7.16-7.28 (2H, m), 7.45-7.48 (2H, m), 7.74 (2H, br s), 8.07 (1H, s), 8.56 (4H, br s)

Example 11

A suspension of 4-(3-aminomethylphenyl)-2-[(amino)[2-(2-methoxyphenyl)ethylamino]methyleneamino]thiazole dihydrochloride (450 mg) and potassium isocyanate (100 mg)

in water (10 ml) was stirred at room temperature for 8 hours. The mixture was adjusted to pH 10 with 30% potassium carbonate solution. The resulting precipitate was collected by filtration. Recrystallization from a mixture of ethanol and water afforded 2-[(amino)[2-(2-methoxyphenyl)ethylamino]methyleneamino]-4-(3-ureidomethylphenyl)thiazole (220 mg).

mp : 167-168°C

IR (Nujol) : 3350, 1660, 1620 cm^{-1}

NMR (DMSO-d_6, δ) : 2.83 (2H, t, J=7.4Hz), 3.39-3.50 (2H, m), 3.79 (3H, s), 4.21 (2H, d, J=5.9Hz), 5.54 (2H, s), 6.44 (1H, d, J=5.9Hz), 6.87 (1H, t, J=7.5Hz), 6.9 (1H, d, J=8.0Hz), 7.17-77.22 (4H, m), 7.33 (1H, t, J=7.6Hz), 7.61-7.75 (4H, m)

Example 12

The following compound was obtained according to a similar manner to that of Example 7.

4-(3-Acetylaminomethylphenyl)-2-[(amino)[2-(2-methoxyphenyl)ethylamino]methyleneamino]thiazole

mp : 155-156°C

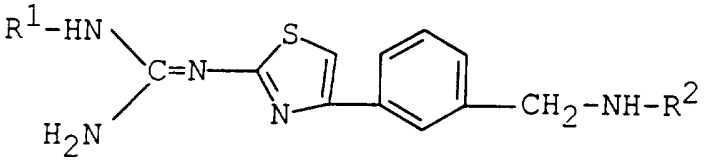
IR (Nujol) : 3310, 3280, 1620 cm^{-1}

NMR (DMSO-d_6, δ) : 1.88 (3H, s), 2.77-2.85 (2H, t, J=7.0Hz), 3.37-3.43 (2H, m), 3.80 (3H, s), 4.28 (2H, d, J=5.8Hz), 6.84-6.99 (2H, m), 7.14-7.24 (4H, m), 7.32 (1H, t, J=7.6Hz), 7.44 (2H, br s), 7.63-7.68 (2H, m), 8.36 (1H, t, J=5.8Hz)

Elemental Analysis Calcd. for $C_{22}H_{25}N_5O_2S$:
C 62.39, H 5.95, N 16.54
Found : C 62.39, H 6.07, N 16.35

C L A I M S

1. A compound of the formula :



wherein R^1 is lower alkoxy, lower alkoxy(lower)alkyl, cyano(lower)alkyl, phenyl, phenyl(lower)alkyl, [2-(lower)alkoxyphenyl](lower)alkyl, diphenyl(lower)alkyl, phenoxy(lower)alkyl, phenyl(lower)alkoxy(lower)alkyl, cyclo(lower)alkenyl(lower)alkyl, protected amino(lower)alkyl or adamantyloxy(lower)alkyl, and

R^2 is hydrogen, lower alkanoyl or carbamoyl, and a pharmaceutically acceptable salt thereof.

2. A compound of claim 1, wherein

R^1 is lower alkoxy, ethoxy(lower)alkyl, cyano(lower)alkyl, phenyl, phenyl(lower)alkyl, (2-methoxyphenyl)(lower)alkyl [2-(lower)alkoxyphenyl](lower)alkyl, diphenyl(lower)alkyl, phenoxy(lower)alkyl, phenyl(lower)alkoxy(lower)alkyl, cyclo(lower)alkenyl(lower)alkyl, acylamino(lower)alkyl or adamantyloxy(lower)alkyl, and

R^2 is hydrogen, acetyl or carbamoyl.

3. A compound of claim 2, wherein

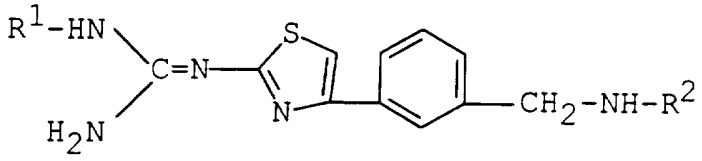
R^1 is lower alkoxy, ethoxy(lower)alkyl,

cyano(lower)alkyl, phenyl, phenyl(lower)alkyl, 2-[2-(lower)alkoxyphenyl](lower)alkyl, diphenyl(lower)alkyl, phenoxy(lower)alkyl, phenyl(lower)alkoxy(lower)alkyl, cyclo(lower)alkenyl(lower)alkyl, carbamoylamino(lower)alkyl, aroylamino(lower)alkyl or adamantyloxy(lower)alkyl.

4. A compound of claim 3, wherein
R^1 is lower alkoxy, ethoxy(lower)alkyl, cyano(lower)alkyl, phenyl, phenyl(lower)alkyl, [2-(lower)alkoxyphenyl](lower)alkyl, diphenyl(lower)alkyl, phenoxy(lower)alkyl, phenyl(lower)alkoxy(lower)alkyl, cyclo(lower)alkenyl(lower)alkyl, carbamoylamino(lower)alkyl, benzoylamino(lower)alkyl or adamantyloxy(lower)alkyl.

5. A compound of claim 4, wherein
R^1 is [2-(lower)alkoxyphenyl](lower)alkyl and
R^2 is acetyl.

6. A process for preparing a compound of the formula :



wherein R^1 is lower alkoxy, lower alkoxy(lower)alkyl, cyano(lower)alkyl, phenyl, phenyl(lower)alkyl, [2-(lower)alkoxyphenyl](lower)alkyl,

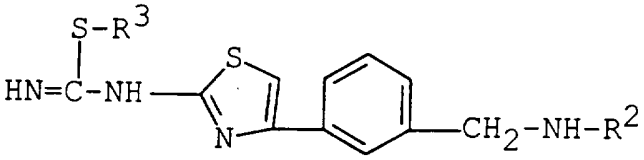
diphenyl(lower)alkyl, phenoxy(lower)alkyl, phenyl(lower)alkoxy(lower)alkyl, cyclo(lower)alkenyl(lower)alkyl, protected amino(lower)alkyl or adamantyloxy(lower)alkyl, and

R^2 is hydrogen, lower alkanoyl or carbamoyl,

or a salt thereof

which comprises

(1) reacting a compound of the formula :



wherein R^2 is as defined above, and

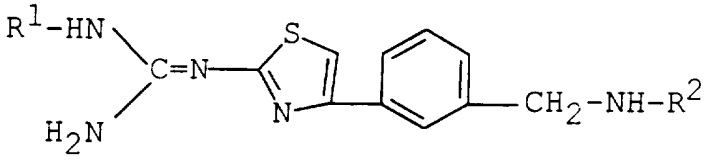
R^3 is lower alkyl,

or a salt thereof with a compound of the formula :

$$R^1 - NH_2$$

wherein R^1 is as defined above,

or a salt thereof to give a compound of the formula :

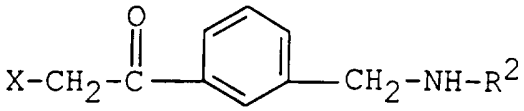


wherein R^1 and R^2 are each as defined above,

or a salt thereof,

or

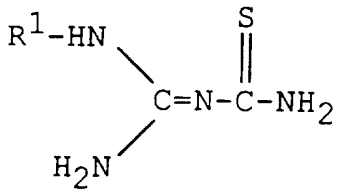
(2) reacting a compound of the formula :



wherein R^2 is as defined above, and

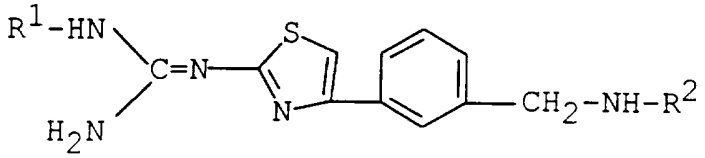
X is a leaving group,

or a salt thereof with a compound of the formula :



wherein R^1 is as defined above,

or a salt thereof to give a compound of the formula :



wherein R^1 and R^2 are each as defined above,

or a salt thereof.

7. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture

with pharmaceutically acceptable carriers.

8. A use of a compound of claim 1 or a pharmaceutically acceptable salt thereof as antiulcer agent, antimicrobial agent or H_2-receptor antagonist.

9. A method for the prophylactic or therapeutic treatment of ulcer which comprises administering a compound of claim 1 or a pharmaceutically acceptable salt thereof to human or animals.

10. A process for preparing a pharmaceutical composition which comprises admixing a compound of claim 1 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

Inter ...nal Application No
PCT/JP 95/01596

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D277/48 A61K31/425

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP-A-0 545 376 (FUJISAWA PHARMACEUTICAL CO., LTD.) 9 June 1993 cited in the application see claims 1-4,9-13; examples 2,6,14,16-19 ---	1-10
Y	EP-A-0 003 640 (IMPERIAL CHEMICAL INDUSTRIES LIMITED) 22 August 1979 see page 12, line 19 - page 13, line 6; claims 1-10 ---	1-10
Y	DATABASE WPI Week 8505 Derwent Publications Ltd., London, GB; AN 85-029005 & JP-A-59 225 172 (YAMANOUCHI PHARM. K. K.) , 18 December 1984 * compounds of formula I * see abstract -----	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
15 December 1995	18.01.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Herz, C

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. onal Application No
PCT/JP 95/01596

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-545376	09-06-93	AU-A-	2983792	10-06-93
		CA-A-	2084640	07-06-93
		CN-A-	1079469	15-12-93
		HU-A-	65776	28-07-94
		JP-A-	6321921	22-11-94
		ZA-A-	9208876	15-07-93
EP-A-3640	22-08-79	US-A-	4315009	09-02-82