SPECIFICATION

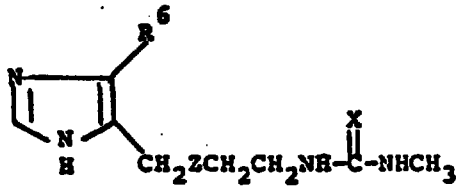
Substituted furans

This application relates to certain N-alkynyl-N'-[2-[(5-substituted-2-furyl)alkylthio]alkyl]-derivatives of N''-cyanoguanidine and of 1,1-diamino-2-(substituted)-ethylene which are histamine H_2-receptor blocking agents, which inhibit gastric acid secretion and which are useful in the treatment of ulcers; and to processes for, and intermediates in, their preparation.

The clinical objective in treatment of peptic ulcer disease is to decrease gastric acid secretion, based on the principle "no acid, no ulcer". Traditional peptic ulcer disease therapy involves control of diet and the use of antacids and anticholinergics.

There is evidence indicating that histamine may be the final common pathway for stimulation of gastric secretion. This effect of histamine is mediated via H_2 receptors and is not inhibited by the classical antihistamines, which are H_1-receptor blockers. A number of specific H_2-receptor blocking agents (H_2-receptor antagonists) are now known. These compounds inhibit basal acid secretion, as well as secretion by other known gastric acid stimulants, and are useful in the treatment of peptic ulcers.

Burimamide (*IIa*) was the first clinically effective H_2-receptor antagonist. It inhibits gastric secretion in animals and man, but oral absorption is poor.



II

IIa; R^6=H, Z=CH_2, X=S Burimamide

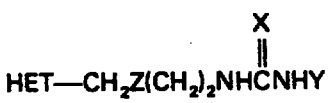
IIb; R^6=CH_3, Z=S, X=S Metiamide

IIc; R^6=CH_3, Z=S, X=NCN Cimetidine

Metiamide (*IIb*), a subsequently evaluated H_2 antagonist, is more potent than burimamide and is orally active in man. Clinical utility was limited, however, owing to toxicity (agranulocytosis). Cimetidine (*IIc*) is as effective an H_2 antagonist as metiamide, without producing agranulocytosis, and has recently been marketed as an anti-ulcer drug. The half-life of cimetidine is relatively short, thereby necessitating a therapeutic regimen of multi daily doses of 200—300 mg. tablets. There is thus a need for anti-ulcer agents which are longer acting and/or more potent than cimetidine.

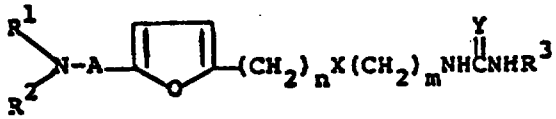
Reviews on the development of H_2 antagonists, including those discussed in the preceding paragraph, may be found in C. R. Ganellin, *et al., Federation Proceedings, 35*, 1924 (1976), in *Drugs of the Future, 1,* 13 (1976), and in references cited therein. Relevant patents are as follows:

Belgian Patent No. 841,814 (Farmdoc 90568X) discloses inhibitors of histamine-stimulated gastric secretion having the formula



in which HET is one of eight named heterocyclic rings (all of which contain at least one nitrogen, thereby excluding furyl) which may be substituted by (lower)alkyl, hydroxy, amino or halogen, Z is sulfur or CH_2, X is S, $CHNO_2$, NCN or NH, Y is NH_2, (lower)alkylamino, di(lower)alkylamino, (lower)alkoxy, phenylethyl, imidazolylethyl, allyl, trifluoroethyl or $(CH_2)_nR$ in which n is 1—12 and R is OH, (lower)alkoxy, NH_2 or (lower)alkylamino; provided that, when X is NH, Y is trifluoroethyl or $(CH_2)_nR$; and when X is NCN, Y may not be amino or alkylamino.

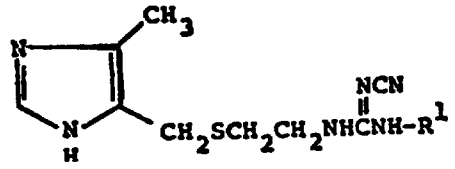
Belgian Patent No. 857,388 discloses histamine H_2-receptor inhibitors of the formula



in which R^1 and R^2 are the same or different and are hydrogen, (lower)alkyl, cycloalkyl, (lower)alkenyl, aralkyl or a (lower)alkyl group which is interrupted by an oxygen atom or by the group NR^4 in which R^4 is hydrogen or (lower)alkyl, or R^1 and R^2 together with the nitrogen atom form a heterocyclic ring optionally containing an oxygen atom or an NR^4 group; A is (lower)alkylene; m is 2—4; n is 1 or 2, or

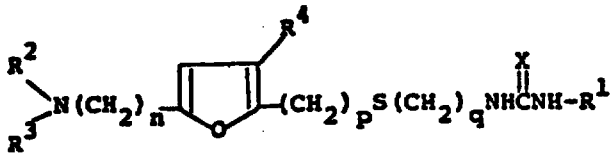
can be zero when X is sulfur or CH_2; X is oxygen, sulfur or CH_2; Y is sulfur, oxygen, NR^5 or CHR^6; R^5 is hydrogen, nitro, cyano, (lower)alkyl, aryl, alkylsulfonyl or arylsulfonyl; R^6 is nitro, arylsulfonyl or alkylsulfonyl; and R^3 is hydrogen, (lower)alkyl, (lower)alkenyl or alkoxyalkyl.

U.S. Patent No. 4,112,234 discloses histamine H_2-receptor inhibitors of the formula



wherein R^1 is a straight or branched chain alkynyl group containing from 3 to 9 carbon atoms, inclusive, and processes for the preparation thereof.

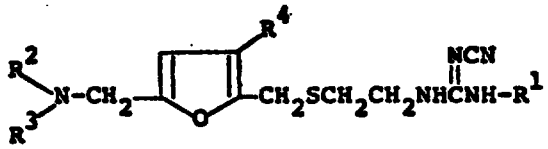
The present invention provides histamine H_2-receptor antagonists of Formula I which are effective inhibitors of gastric secretion in animals, including man, and which are useful in the treatment of peptic ulcer disease.



I

In Formula I, R^1 is a straight or branched chain alkynyl group containing from 3 to 9 carbon atoms, inclusive; R^2 and R^3 are the same or different and are hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl or Ar; R^4 is hydrogen or (lower)alkyl; *n* is an integer of from 1 to 6; *p* is 1 or 2 and *q* is 2 or 3, provided that the sum of *p* and *q* is 3 or 4; X is NR^5 or CHR^5; R^5 is cyano, nitro, SO_2Ar or SO_2-(lower)alkyl; and Ar is an optionally substituted phenyl group; and nontoxic, pharmaceutically acceptable salts thereof.

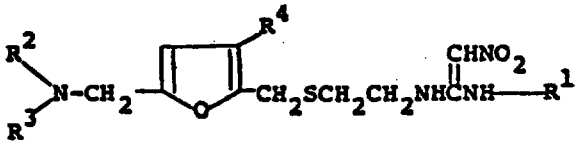
A preferred embodiment of the invention is a compound of the formula



Ia

wherein R^1, R^2, R^3 and R^4 are as described above, or a nontoxic, pharmaceutically acceptable salt thereof.

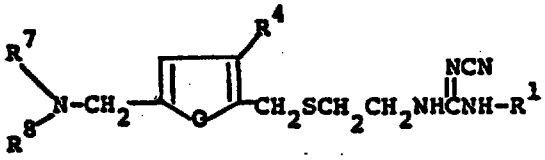
Another preferred embodiment of the invention is a compound of the formula



Ib

wherein R^1, R^2, R^3 and R^4 are as described above, or a nontoxic, pharmaceutically acceptable salt thereof.

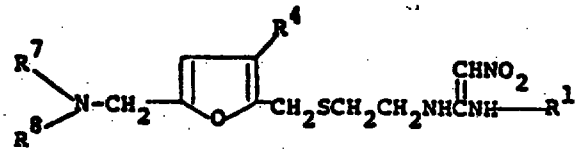
A more preferred embodiment of the invention is a compound of the formula



Ic

wherein R^1 and R^4 are as described above and R^7 and R^8 are the same or different and are hydrogen or (lower) alkyl, or a nontoxic, pharmaceutically acceptable salt thereof.

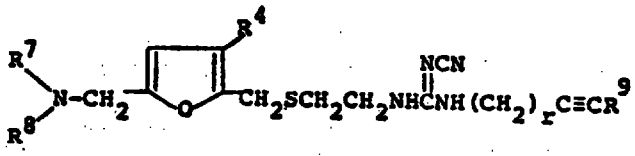
Another more preferred embodiment of the invention is a compound of the formula



Id

wherein R^1, R^4, R^7 and R^8 are as described above, or a nontoxic, pharmaceutically acceptable salt thereof.

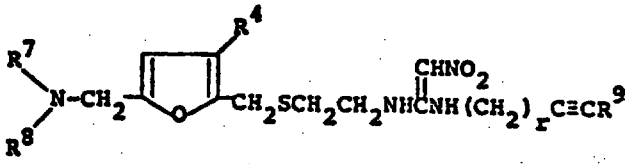
A still more preferred embodiment of the invention is a compound of the formula



Ie

wherein R^4, R^7 and R^8 are as described above, r is an integer of from 1 to 6, inclusive, and R^9 is hydrogen or methyl, or a nontoxic, pharmaceutically acceptable salt thereof.

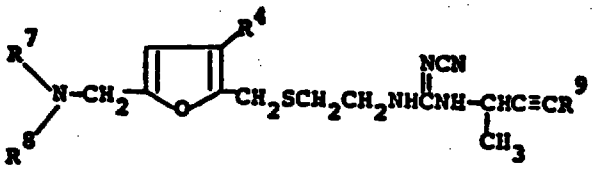
Another still more preferred embodiment of the invention is a compound of the formula



If

wherein R^4, R^7, R^8, R^9 and r are as described above, or a nontoxic, pharmaceutically acceptable salt thereof.

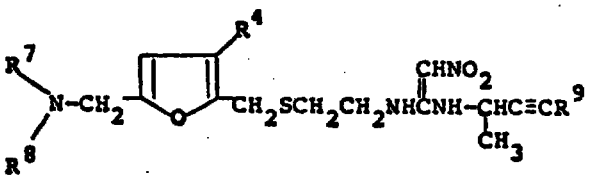
Another still more preferred embodiment of the invention is a compound of the formula



Ig

wherein R^4, R^7, R^8 and R^9 are as described above, or a nontoxic, pharmaceutically acceptable salt thereof.

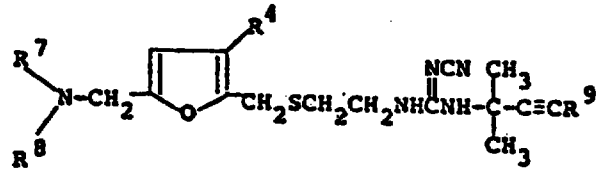
Another still more preferred embodiment of the invention is a compound of the formula



Ih

wherein R^4, R^7, R^8 and R^9 are as described above, or a nontoxic, pharmaceutically acceptable salt thereof.

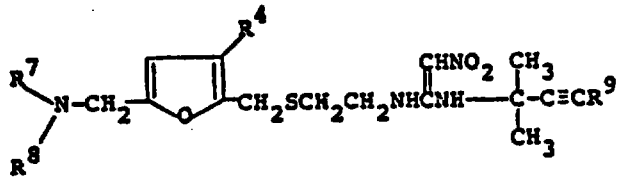
Another still more preferred embodiment of the invention is a compound of the formula



Ii

wherein R^4, R^71, R^8 and R^9 are as described above, or a nontoxic, pharmaceutically acceptable salt thereof.

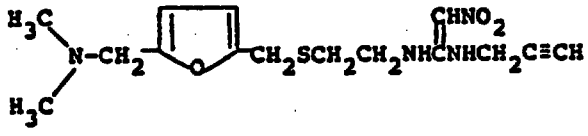
Another still more preferred embodiment of the invention is a compound of the formula



Ij

wherein R^4, R^7, R^8 and R^9 are as described above, or a nontoxic, pharmaceutically acceptable salt thereof.

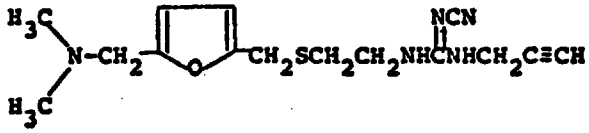
A most preferred embodiment is a compound of the formula



Ik

or a nontoxic pharmaceutically acceptable salt thereof.

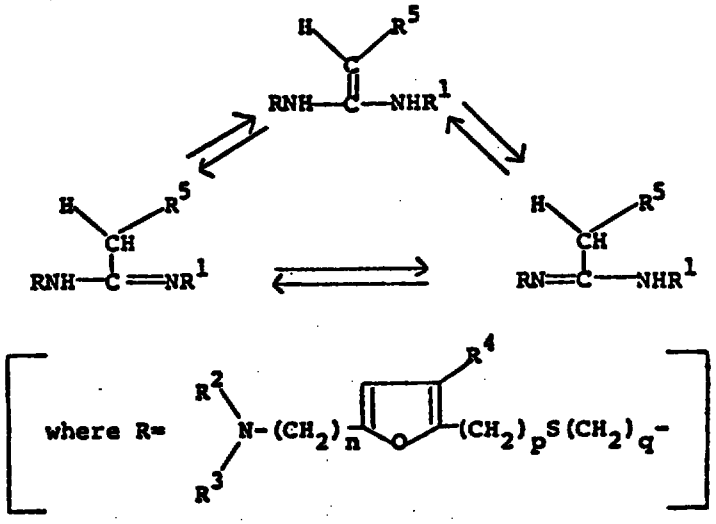
Another most preferred embodiment of the invention is the compound of the formula



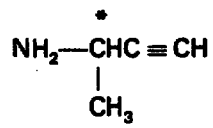
Im

or a nontoxic, pharmaceutically acceptable salt thereof.

Although the compounds of this invention have been shown as having the structure of Formula I, it will be appreciated by those skilled in the art that the compounds in which X is CHR^5 can exist in various tautomeric forms, as follows:



Also, the compounds in which X is CHR^5 may exist as two geometric isomers, i.e., cis/trans isomers about the double bond. In addition, all the compounds of formula *I* which contain a branched chain alkynyl group as substituent R^1 may exist as their d- or l-optical isomers as well as their racemic forms. Thus, for example, 3-amino-1-butyne of the formula

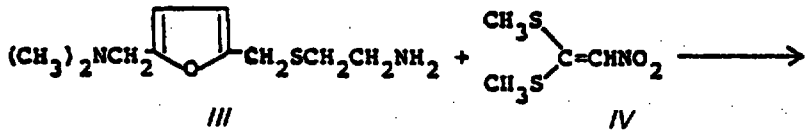


may be resolved into its d- and l- isomers as described in A. Marszak-Fleury, *Compt. rend.*, 242, 1046 (1956). The use of the d- or l-isomer of the alkynylamine in the preparation of a compound of Formula *I* produces the corresponding d- or l- isomer of the compound of Formula *I*. The present invention includes within its scope all possible tautomeric forms, geometric isomers and optical isomers of the compounds of Formula *I* as well as mixtures thereof.

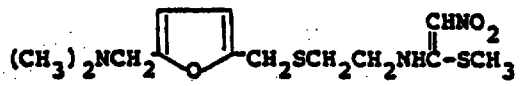
The compounds of the present invention may be prepared by various alternative reaction schemes.

as illustrated below for preferred compounds *Ik* and *Im*.

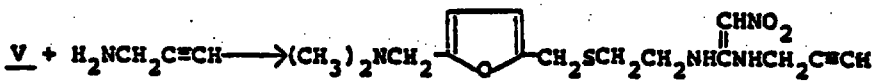
Scheme I



III *IV*



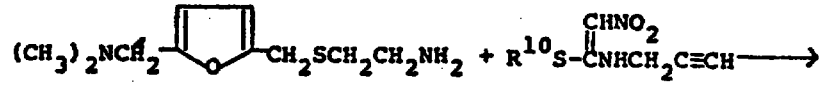
V



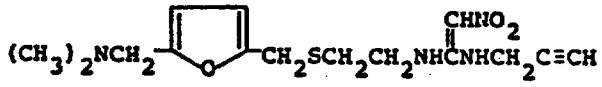
Ik

The compound of Formula *III* is prepared by the procedure described in Belgian Patent No. 857,388. Analogous and homologous compounds are prepared by procedures described in Belgian Patent No. 857,388 or by analogous procedures. The compound of Formula *IV* is prepared by procedures described in *Chem. Ber., 100,* 591 (1967) and *Acta Chem. Scand., 21,* 2797 (1967). The reaction steps of Scheme I are conducted in a non-reactive solvent at or above room temperature. The alkynylamines utilized as starting materials (propargylamine illustrated above) are either commercially available or may be prepared by procedures described in *Bull. Soc. Chim. Fr.,* 490 (1958), *Bull. Soc. Chim. Fr.,* 588 (1967), *Bull. Soc. Chim. Fr.,* 592 (1967), *Annales de Chimie (Paris), 3,* 656 (1958) and *J. Org. Chem., 21,* 791 (1956).

Scheme II

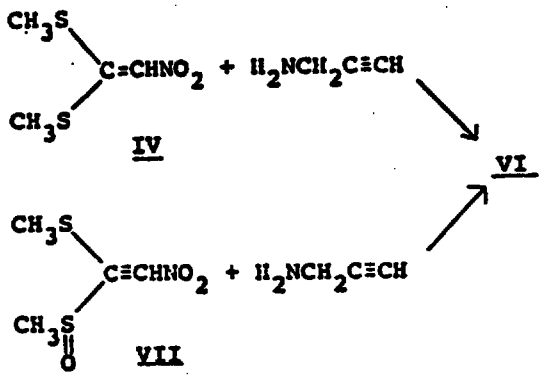


III *VI*



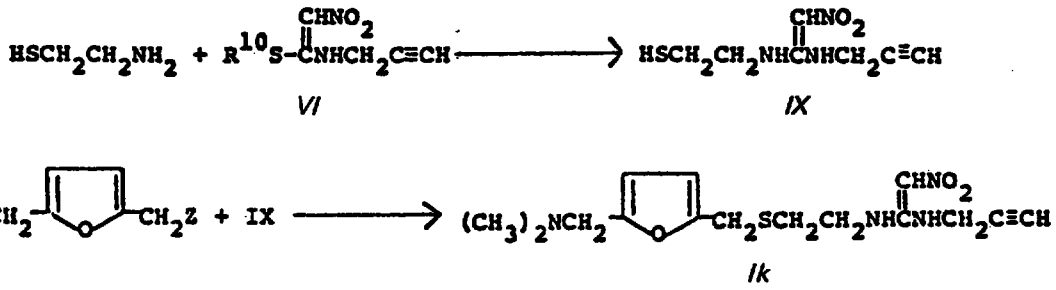
Ik

The reaction is conducted in a non-reactive solvent at or above room temperature. As will be appreciated by those skilled in the art, R^{10} may be any substituent such that —SR^{10} will be a suitable leaving group. Such leaving groups are conventional in the art. Thus, R^{10} may be (lower)alkyl, aryl or substituted aryl (e.g. p-nitrophenyl), or the like. The compounds of Formula *VI* may themselves be prepared by alternative procedures, such as illustrated below for the preparation of Compound *VI* wherein R^{10} is methyl.



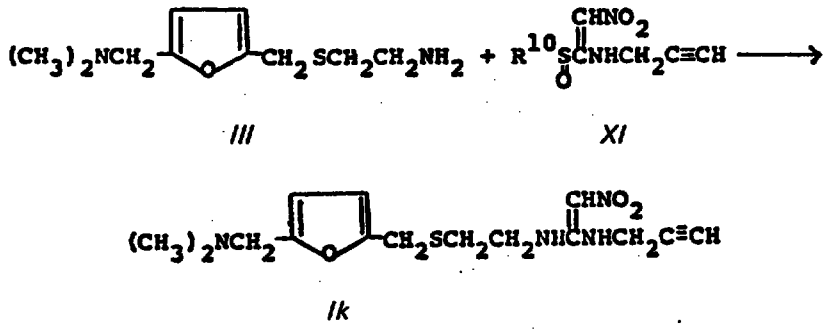
The compound of Formula *VII* is prepared by the procedures described in Belgian Patent No. 841,526 and analogous compounds may be prepared by analogous procedures. It will be apparent to those skilled in the art that, if the propargylamine utilized above is replaced by a different alkynylamine, there will be produced a compound of Formula *VI* which contains the different alkynyl group. That compound, in turn, can be reacted with a compound of Formula *III* to produce a compound of Formula *I* containing the different alkynyl group.

Scheme III



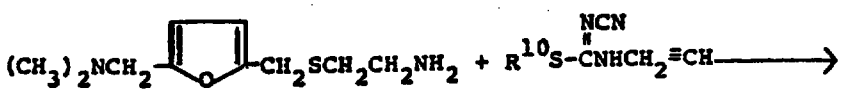
The reaction steps are conducted in a non-reactive solvent at or above room temperature. Compound *VI* is prepared as described above in Scheme II. Substituent Z in Compound *X* is a conventional leaving group. Suitable leaving groups "Z" for use in this reaction are well-known to those skilled in the art. They include, for example, fluoro, chloro, bromo, iodo, $-O_3SR^{11}$ wherein R^{11} is (lower)alkyl [e.g. methanesulfonate], $-O_3SR^{12}$ wherein R^{12} is aryl or substituted aryl [e.g. benzenesulfonate, p-bromobenzenesulfonate or p-toluenesulfonate], $-O_3SF$, acetoxy and 2,4-dinitrophenoxy. For convenience and economy it is normally preferred to utilize compound *X* in which Z is chloro. The compound of Formula *X*, and analogous compounds, may be prepared by procedures described in Belgian Patent No. 857,388.

Scheme IV



The reaction is conducted in a non-reactive solvent at or above room temperature. The compound of Formula *XI*, in which R^{10} is as described above, is prepared by oxidation of a compound of Formula *VI* by conventional means.

Scheme V



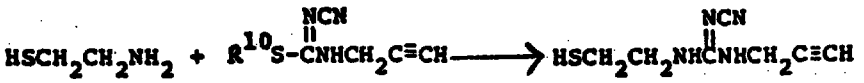
III XII



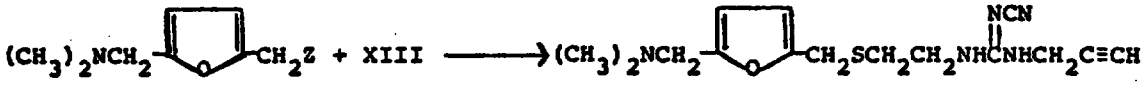
Im

The reaction is conducted in a non-reactive solvent at or above room temperature. The compounds of Formula *XII* may be prepared by procedures described in our U.S. Patent No. 4,157,347. For example, Compound *XII* in which R^{10} is methyl may be prepared by reacting dimethyl cyanodithioimidocarbonate with propargylamine. The dimethyl cyanodithioimidocarbonate may itself be prepared by procedures described in *J. Org. Chem., 32,* 1566 (1967). Analogous compounds may be prepared by analogous procedures.

Scheme VI



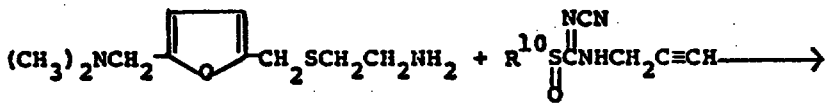
XII XIII



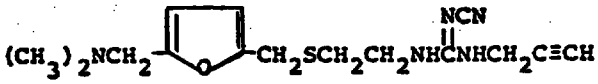
X Im

The reaction which is analogous to that described in Scheme *III* above, is conducted in a non-reactive solvent at or above room temperature. The compound of Formula *XII* and homologous and analogous compounds containing other alkynyl groups are described and claimed in our U.S. Patent No. 4,158,013.

Scheme VII



III XIV



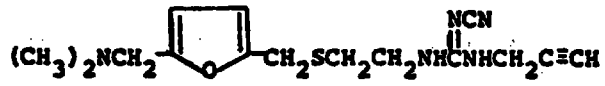
Im

The reaction, which is analogous to that described in Scheme *IV* above, is conducted in a non-reactive solvent at or above room temperature. The compounds of Formula *XIV* are prepared by oxidation of a compound of Formula *XII* by conventional means.

Scheme VIII



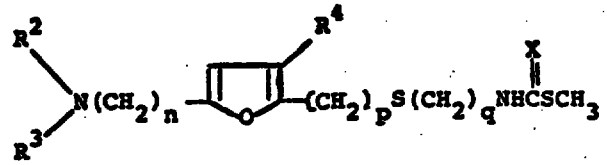
XV



Im

The reaction, which is analogous to that described in the second step of Scheme I above, is conducted in a non-reactive solvent at or above room temperature. The compound of Formula *XV* is prepared by the procedure described in Belgian Patent No. 857,388.

In view of Scheme VIII and the second step of Scheme I, above, this invention provides a process for preparing compounds of Formula *I* characterized by reacting a compound having formula *XX*



XX

wherein R^2, R^3, R^4, X, n, p and q are as defined in Formula I, with a compound having the formula

$$H_2NR^1$$

wherein R^1 is a straight or branched chain alkynyl group containing from 3 to 9 carbon atoms, in a non-reactive solvent at or above room temperature.

As used herein, the term nontoxic pharmaceutically acceptable acid addition salt means the mono- or di-salt of a compound of this invention with a nontoxic pharmaceutically acceptable organic or inorganic acid. Such acids are well known and include hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, maleic, fumaric, succinic, oxalic, benzoic, methanesulfonic, ethanedisulfonic, benzenesulfonic, acetic, propionic, tartaric, citric, camphorsulfonic, and the like. The salts are made by methods known in the art.

Substituent Ar is defined above as optionally substituted phenyl. As used herein it is intended that Ar include unsubstituted phenyl and phenyl containing 1 or 2 substituents independently selected from (lower)alkyl and halogen. The term "(lower)alkyl", as used herein, means a straight or branched chain alkyl group containing from 1 to 6 carbon atoms and "(lower)alkenyl and "(lower)alkynyl means groups having from 2 to 6 carbon atoms.

For therapeutic use, the pharmacologically active compounds of this invention will normally be administered as a pharmaceutical composition comprising as the (or an) essential active ingredient at least one such compound in the basic form or in the form of a nontoxic pharmaceutically acceptable acid addition salt, in association with a pharmaceutically acceptable carrier.

The pharmaceutical compositions may be administered orally, parenterally or by rectal suppository. A wide variety of pharmaceutical forms may be employed. Thus, if a solid carrier is used, the preparation may be tableted, placed in a hard gelatine capsule in powder or pellet form, or in the form of a troche or lozenge. If a liquid carrier is employed, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule, sterile solution for injection, or an aqueous or nonaqueous liquid suspension. The pharmaceutical compositions are prepared by conventional techniques appropriate to the desired preparation.

Preferably, each dosage unit will contain the active ingredient in an amount of from about 10 mg. to about 250 mg., and most preferably from about 20 mg. to about 200 mg. The active ingredient will preferably be administered in equal doses from two to four times a day. The daily dosage regimen will preferably be from 50 mg. to about 1000 mg., and most preferably from about 100 mg. to about 750 mg.

Histamine H_2-receptor antagonists have been shown to be effective inhibitors of gastric secretion in animals and man, Brimblecombe *et al., J. Int. Med. Res., 3,* 86 (1975). Clinical evaluation of the histamine H_2-receptor antagonist cimetidine has shown it to be an effective therapeutic agent in the treatment of peptic ulcer disease, Gray *et al., Lancet, 1* (8001), 4 (1977). The compounds prepared in Examples 1 and 2 below (hereinafter referred to as BL—5966 and BL—5993) have been compared, in various tests, with cimetidine and the structurally related compound of Formula *XVI*



XVI

(disclosed in Belgian Patent 857,388). BL—5966 has been shown to be more potent than either cimetidine or Compound *XVI* both as a histamine H_2 receptor antagonist in isolated guinea pig atria and as an inhibitor of gastric secretion in rats and dogs.

Histamine H_2-Receptor Antagonism-Isolated Guinea Pig Atria Assay

Histamine produces concentration-related increases in the contractile rate of isolated, spontaneously beating guinea pig right atria. Black *et al., Nature, 236,* 385 (1972), described the receptors involved in this effect of histamine as histamine H_2-receptors when they reported the properties of burimamide, a competitive antagonist of these receptors. Subsequent investigations by Hughes and Coret, *Proc. Soc. Exp. Biol. Med., 148,* 127 (1975) and Verma and McNeill, *J. Pharmacol. Exp. Ther., 200,* 352 (1977) support the conclusion of Black and coworkers that the positive chronotropic effect of histamine in isolated guinea pig right atria is mediated via histamine H_2-receptors. Black et al., *Agents and Actions, 3,* 133 (1973) and Brimblecombe et al., *Fed. Proc., 35,* 1931 (1976) have utilized isolated guinea pig right atria as a means for comparing the activities of histamine H_2-receptor antagonists. The present comparative studies were carried out using a modification of the procedure reported by Reinhardt et al., *Agents and Actions, 4,* 217 (1974).

Male Hartley strain guinea pigs (350—450 gm.) were sacrificed by a blow on the head. The heart was excised and placed in a Petri dish of oxygenated (95% O_2, 5% CO_2) modified Krebs solution (g./liter: NaCl 6.6, KCl 0.35, $MgSO_4 \cdot 7\,H_2O$ 0.295, KH_2PO_4 0.162, $CaCl_2$ 0.238, $NaHCO_3$ 2.1 and dextrose 2.09). The spontaneously beating right atrium was dissected free from other tissues and a silk thread (4—0) attached to each end. The atrium was suspended in a 20 ml. muscle chamber containing oxygenated modified Krebs solution maintained at 32°C. Atrial contractions were recorded isometrically by means of a Grass FT 0.03 force displacement transducer and recordings of contractile force and rate were made with a Beckman RP Dynograph.

A resting tension of 1 g. was applied to the atrium and it was allowed to equilibrate for 1 hour. At the end of the equilibration period a submaximal concentration of histamine dihydrochloride (3×10^{-6}M) was added to the bath and washed out to prime the tissue. Histamine was then added to the bath in a cumulative fashion using $\frac{1}{2}$ log 10 intervals to give final molar bath concentrations of 1×10^{-7} to 3×10^{-5}. The histamine-induced increase in atrial rate was allowed to plateau before the next successive concentration was added. The maximal response invariably occurred at the 3×10^{-5}M concentration. The histamine was washed out several times and the atrium allowed to return to control rate. The test compound (3×10^{-5}M) was then added and after a 30 minute incubation the histamine concentration-response was repeated adding higher concentrations as needed.

The histamine ED50 values (concentration of histamine which increased contractile rate 50% of maximum) and 95% confidence limits before and after the test compound were obtained by regression analysis as described by Finney *Probit Analysis,* 3rd ed., Cambridge (1971). Concentration-response curve displacement factors were calculated as follows:

$$\text{Displacement factor} = \frac{\text{ED50 Histamine + Compound}}{\text{ED50 Histamine Alone}}$$

The factors obtained for BL—5966, BL—5993 and Compound *XVI* were then expressed as ratios of the factor obtained for cimetidine.

$$\text{Activity Ratio} = \frac{\text{Test Compound Displacement Factor} - 1}{\text{Cimetidine Displacement Factor} - 1}$$

The results obtained from these studies are summarized in Table 1. Cimetidine and Compound *XVI* displaced the histamine concentration-response curve to the right by factors of 25.26 and 38.61, respectively, while BL—5966 and BL—5993 displaced the curve to the right by factors of 181.67 and 23.78, respectively. Based on the concentration-response curve displacement of factors, Compound *XVI* was about 1.55 times more active than cimetidine, BL—5966 was about 7.45 times more active than cimetidine and BL—5933 was about 0.94 times as active as cimetidine as histamine H_2-receptor antagonists in isolated guinea pig right atria. BL—5966 was about 4.80 times more active than Compound *XVI* in this model.

Relative Activity of Cimetidine, Compound XVI, BL–5966 and BL–5993 in Isolated Guinea Pig Right Atria

Compound	N	Concentration	Histamine ED50 With 95% Confidence Limits (μg/ml)	Concentration-Response Curve Displacement Factor	Activity Ratio Relative to Cimetidine
Histamine control	8	–	0.19 (0.15 – 0.24)	–	–
Cimetidine	8	3×10^{-5}M	4.80 (3.9 – 5.9)	25.26	1.0
Histamine control	2	–	0.31 (0.21 – 0.46)	–	–
Compound *XVI*	2	3×10^{-5}M	11.97 (5.00 – 29.20)	38.61	1.55
Histamine control	2	–	0.18 (0.15 – 0.22)	–	–
BL–5966	2	3×10^{-5}M	32.70 (20.10 – 63.93)	181.67	7.45
Histamine control	2	–	0.18 (0.14 – 0.23)	–	–
BL–5993	2	3×10^{-5}M	4.28 (2.70 – 7.00)	23.78	0.94

N = number of experiments

Determination of Gastric Antisecretory Activity in the Two Hour Pylorus Ligated (Shay) Rat

The pyloric ligation procedure in the rat was designed by Shay et al., *Gastroenterology, 5,* 53 (1945) for the study of perforating gastric ulcers; however, as the method became known, it was also employed as a means of studying rat gastric secretion, Shay et al., *Gastroenterology, 26,* 906 (1954), Brodie, D. A., *Am. J. Dig. Dis., 11,* 231 (1966). A modification of this procedure is presently used to evaluate compounds for gastric antisecretory activity.

Male Long Evans rats, 280—300 gm., are used. The animals are placed in individual cages and fasted for 24 hours with free access to water. Under ether anesthesia, the stomach is reached through a midline incision, and a cotton-thread ligature is placed around the pylorus. After wound closure, ether administration is stopped and either BL—5966, BL—5993, Compound *XVI*, cimetidine or vehicle is administered intraperitoneally in a volume of 1 mg/kg. All compounds are solubilized with one equivalent of HCl and brought to the proper volume with water. The animals are returned to their cages from which the water bottles have been removed and two hours later are sacrificed with ether. The stomach is removed and the two hour gastric collection is drained into a graduated test tube for volume determination. Titratable acidity is measured by titrating a one ml. sample to pH 7.0 with 0.02N NaOH, using an Autoburet and an electrometric pH meter (Radiometer). Titratable acid output is calculated in microequivalents by multiplying the volume in milliliters by the acid concentration in milliequivalents per liter. The percent inhibition of acid output is calculated as follows

$$\% \text{ Inhibition Acid Output} = \frac{\text{Acid Output-Control} - \text{Acid Output-Drug}}{\text{Acid Output-Control}} \times 100$$

The test results are summarized in Table 2. These results indicate that, in the two hour pylorus ligated rat preparation, BL—5966 is 5.81, BL—5993 is 0.83 and Compound *XVI* is 2.31 times as potent as cimetidine. It is also evident that BL—5966 is 2.52 times more potent than Compound XVI.

TABLE 2

Effect of BL–5966, BL–5993, Compound XVI and Cimetidine on Gastric Acid Output in the Two Hour Pylorus Ligated Rat

Compound	Dose (ip)[a] μ Mole/kg	Percent Inhibition Acid Output	ED50 μ Mole/kg	Potency Ratio
BL–5966	5	83		
	2.5	59	1.80	5.81
	1.25	36		
	0.625	27		
BL–5993	20	71	12.5	0.83
	10	34		
Compound *XVI*	20	89		
	10	77	4.52	2.31
	5	42		
Cimetidine	40	72		
	20	57		
	10	41	10.4	1.00
	5	53		
	2.5	9		

[a] At least 5 animals were employed at each dose.

Determination of Gastric Antisecretory Activity in the Gastric Fistula Dog

Thomas type [Thomas, J. E., *Proc. Soc. Exp. Biol. Med., 46,* 260 (1971)] stainless steel cannulae are inserted into the stomachs of beagle dogs (10—12 kg.) just orad to the pyloric gland area near the greater curvature to provide a chronic gastric fistula. Animals are allowed to recover for at least two months before any testing is done. Dogs are fasted overnight (~18 hours) with water *ad lib* prior to each experiment. The dogs are placed in a sling and an eight inch inside needle catheter (C. R. Baird, Inc.) with a two inch 17 gauge needle is inserted into a leg vein for purposes of drug administration. Gastric secretions are collected every 15 minutes by gravity drainage from the opened cannula. Basal secretions are collected for two consecutive 15 minute periods and if these prove to be excessive (>4 ml./15 min.; ph <5.0) the animal is not used. A modification of the procedure described by Grossman and Konturek, *Gastroenterology, 66,* 517 (1974) was followed. Immediately after the second basal collection, histamine (100 μg./kg./hr.) is infused for 90 minutes with a Harvard Infusion Pump in a volume of 6 ml./hr. At this time either BL—5966, cimetidine (solubilized with one equivalent of HCl and brought a proper volume with normal saline) or normal saline is injected rapidly (within 30 seconds) in a volume of 0.1 ml./kg. and then infusion of histamine continues for an additional 60 minutes (total time of infusion is 2.5 hours). Each 15 minute sample of gastric juice is measured to the nearest 0.5 ml. and titratable acidity against 0.02N NaOH (endpoint pH 7.0) is measured with an Autoburet and pH meter (radiometer). The percent inhibition of acid output is calculated as described in the pylorus ligated rat procedure.

The results of the tests are summarized in Table 3. It is evident that BL—5966 is 11.5 times more potent than cimetidine with respect to the inhibition of gastric acid output in gastric fistula dogs.

TABLE 3

Effect of BL—5966 and Cimetidine on Gastric Acid Output in the Gastric Fistula Dog

Compound	Dose (iv) μ Mole/kg	N	Percent Inhibition Acid Output	ED50 μ Mole/kg	Potency Ratio
BL—5966	0.375	2	90	0.12	11.5
	0.1875	3	46		
	0.0938	3	47		
	0.0469	3	32		
Cimetidine	3.0	8	73	1.32	1.0
	1.5	11	53		
	0.75	3	37		

N = number of dogs employed at each dose.

EXAMPLE 1

1-Nitro-2-(2-propynylamino)-2-[2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino]ethylene (BL—5966)

A. 1-Nitro-2-methylthio-2-[2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino]ethylene

A mixture of 2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamine (12.86 g, 60 mmole) [prepared by the procedure described in Belgian Patent 857,388] and 1,1-bis(methylthio)-2-nitroethylene (9.91 g, 60 mmole) [prepared according to the procedure described in *Chem. Ber., 100,* 591 (1967) and *Acta Chem. Scand., 21,* 2797 (1967)] in acetonitrile (150 ml) was stirred and heated to reflux temperature under a positive pressure of nitrogen for 15.5 hours. The solvent was removed by evaporation under reduced pressure and the crude product placed on silica gel and chromatographed using a gradient elution of methylene chloride-methanol. The appropriate fractions were combined to yield the title compound (12.6 g.).

B. 1-Nitro-2-(2-propynylamino)-2-[2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino]-ethylene (BL—5966)

A mixture of the product of Step A (3.04 g, 9.17 mmole) and distilled propargylamine (6 ml) in acetonitrile (30 ml) was stirred and heated to reflux temperature under a positive pressure of nitrogen

for 19 hours. The reaction mixture was evaporated under reduced pressure and the residue placed on solica gel and chromatographed using a gradient elution of methylene chloride-methanol. The appropriate fractions were combined and evaporated. The residue was dissolved in warm acetonitrile, treated with charcoaal then diluted with diethyl ether to give the title compound mp 125—127°.

Anal. Calcd for $C_{15}H_{22}N_4O_3S$: C, 53.23; H, 6.55; N, 16.56; S, 9.48.
Found: C, 53.25; H, 6.53; N, 16.95; S, 9.67.

EXAMPLE 2

1-Nitro-2-(2-propynylamino)-2-[2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino]ethylene (BL—5966)

A. 1-Methylthio-1-(2-propynylamino)-2-nitroethylene

A solution of propargylamine (1.10 g, 0.02 mole) in 22 ml of methanol was added dropwise to a stirred suspension of 1-methylsulfinyl-1-methylthio-2-nitroethylene [prepared according to the procedure described in Belgian Patent 841,526] at 25°. After 1 hour at ambient temperature, the solution was evaporated under reduced pressure, triturated under 20 ml of cold isopropyl alcohol and filtered to give the product. Recrystallization from isopropyl alcohol gave the title compound, mp. 131—132°.

B. 1-Nitro-2-(2-propynylamino)-2-[2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino]-ethylene (BL—5966)

A solution of the product of Step A is reacted with about an equimolar amount of 2-[(5-dimethylaminoethyl-2-furyl)methylthio]ethylamine to give, after workup and chromatography as in Example 1, the title compound.

The product prepared in Step A may alternatively be prepared by reacting about equimolar amounts of 1,1-bis-(methyl-thio)-2-nitroethylene and propargylamine in a non-reactive solvent.

EXAMPLE 3

N-Cyano-N'-(2-propyn-1-yl)-N''-[2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethyl]guanidine (BL—5993)

A mixture of N-cyano-N'-[2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethyl]-S-methylisothiourea (4.0 g, 12.8 mmole) [prepared according to the procedure described in Belgian Patent 857,388] and distilled propargylamine (4.0 ml) in methanol (20 ml) was stirred at reflux temperature under a positive pressure of nitrogen for 19 hours. The reaction mixture was evaporated under reduced pressure and the residual oil placed on silica gel and chromatographed using a gradient elution with methylene chloride-methanol. The appropriate fractions were combined to give product (2.04 g.). Recrystallization from acetonitrile with charcoal treatment gave the title compound, mp. 122—124°.

Anal. Calcd for $C_{15}H_{21}N_5OS$: C, 56.40; H, 6.63; N, 21.93; S, 10.04
Found: C, 56.35; H, 6.72; N, 22.07; S, 10.10

EXAMPLE 4

N-Cyano-N'-(2-propyn-1-yl)-N''-[2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethyl]guanidine (BL—5993)

A. N-Cyano-N'-(2-propyn-1-yl)-S-methylisothiourea

A solution of dimethyl cyanodithioimidocarbonate [prepared according to the procedure described in *J. Org. Chem., 32*, 1566 (1967)] (16.0 g., 0.019 mole) and propargylamine (6.03 g., 0.109 mole) in acetonitrile (320 ml.) was stirred at reflux for 4 hours, then at 25° for 12 hours. Workup gave the title compound (13.58 g, 81%), mp. 160—164°.

B. N-Cyano-N'-(2-propyn-1-yl)-N''-[2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethyl]guanidine (BL—5993)

The product of Step A is reacted with about an equimolar amount of 2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamine in a non-reactive solvent to give, after workup and chromatography as in Example 3, the title product.

EXAMPLE 5

1-Nitro-2-(2-propynylamino)-2-[2-[(5-methylaminomethyl-2-furyl)methylthio]ethylamino]ethylene

A mixture of 1-nitro-2-methylthio-2-[2-[(5-methylaminomethyl-2-furyl)metylthio]ethylamino]ethylene [prepared according to the procedure described in Belgian Patent 857,388] and propargylamine in acetonitrile is stirred and heated under a positive pressure of nitrogen to give, after workup and chromatography, the title compound.

EXAMPLE 6

N-Cyano-N'-(2-propyn-1-yl)-N''-[2-[(5-methylaminomethyl-2-furyl)methylthio]ethyl]guanidine

A mixture of N-cyano-N'-[2-[(5-methylaminomethyl-2-furyl)methylthio]ethyl]-S-methylisothiourea [prepared according to the procedure described in Belgian Patent 857,388] and propargylamine in methanol is stirred and heated under a positive pressure of nitrogen to give, after workup and chromatography, the title compound.

EXAMPLE 7

The general procedure of Example 1 is repeated except that the propargylamine utilized therein is replaced by an equimolar amount of

2-butyn-1-amine,
3-butyn-1-amine,
4-pentyn-1-amine,
3-amino-1-butyne and
1,1-dimethylpropargylamine, respectively,

and there is thereby produced

1-nitro-2-(2-butyn-1-ylamino)-2-[2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino]ethylene,
1-nitro-2-(3-butyn-1-ylamino)-2-[2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino]ethylene,
1-nitro-2-(4-pentyn-1-ylamino)-2-[2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino]-ethylene,
1-nitro-2-(3-butyn-2-ylamino)-2-[2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino]-ethylene and
1-nitro-2-(2-methyl-3-butyn-2-ylamino)-2-[2-[(5-dimethylaminomethyl-2-furyl)methylthio]-ethylamino]ethylene, respectively.

EXAMPLE 8

The general procedure of Example 3 is repeated except that the propargylamine utilized therein is replaced by an equimolar amount of

2-butyn-1-amine,
3-butyn-1-amine,
4-pentyn-1-amine,
3-amino-1-butyne and
1,1-dimethylpropargylamine, respectively,

and there is thereby produced

N-cyano-N'-(2-butyn-1-yl)-N''-[2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethyl]guanidine,
N-cyano-N'-(3-butyn-1-yl)-N''-[2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethyl]guanidine,
N-cyano-N'-(4-pentyn-1-yl)-N''-[2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethyl]guanidine,
N-cyano-N'-(3-butyn-2-yl)-N''-[2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethyl]guanidine and
N-cyano-N'-(2-methyl-3-butyn-2-yl)-N''-[2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethyl]-guanidine, respectively.

EXAMPLE 9

N-Cyano-N'-(2-butyn-1-yl)-N''-[2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethyl]guanidine

2-[(5-Dimethylaminomethyl-2-furyl)methylthio]ethylamine is reacted in a non-reactive solvent with about an equimolar amount of N-(2-butyn-yl)-N'-cyano-S-methylisothiourea [prepared according to the procedure described in U.S. Patent 4,112,234, and, after workup and chromatography, the title product is produced.

EXAMPLE 10

A solution of propargylamine in methanol is added dropwise to a stirred methanol suspension of an approximately equimolar amount of

1,1-bis(methylthio)-2-nitroethylene,
1,1-bis(ethylthio)-2-nitroethylene,
1,1-bis(benzylthio)-2-nitroethylene, and
1,1-bis(2,4-dinitrophenylthio)-2-nitroethylene,
respectively, and there is thereby produced
1-methylthio-1-(2-propynylamino)-2-nitroethylene,
1-ethylthio-1-(2-propynylamino)-2-nitroethylene,

1-benzylthio-1-(2-propynylamino)-2-nitroethylene and
1-(2,4-dinitrophenylthio)-1-(2-propynylamino)-2-nitroethylene, respectively.

Reaction of each of the above products with 2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamine produces in each case 1-nitro-2-(2-propynylamino)-2-[2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino]ethylene (BL—5966).

The 1,1-bis(methylthio)-2-nitroethylene, 1,1-bis(ethylthio)-2-nitroethylene and 1,1-bis(benzylthio)-2-nitroethylene starting materials are prepared by procedures described in *Chem. Ber., 100*, 591 (1967) and *Acta Chem. Scand., 21*, 2797 (1967). The 1,1-bis(2,4-dinitrophenylthio)-2-nitroethylene starting material is prepared by the reaction of 2,4-dinitrofluorobenzene and dipotassium nitrodithioacetate.

EXAMPLE 11

A solution of cysteamine hydrochloride in dimethylformamide is reacted with about an equimolar amount of

1-methylthio-1-(2-propynylamino)-2-nitroethylene,
1-ethylthio-1-(2-propynylamino)-2-nitroethylene,
1-benzylthio-1-(2-propynylamino)-2-nitroethylene and
1-(2,4-dinitrophenylthio)-1-(2-propynylamino)-2-nitroethylene,

respectively, in the presence of about one equivalent of base, and there is produced in each case 1-nitro-2-(2-propynylamino)-2-(2-mercaptoethyl)ethylene.

When the above product is reacted in a non-reactive solvent with 5-dimethylaminomethylfurfuryl chloride hydrochloride [prepared from thionyl chloride and 5-dimethylaminomethylfurfuryl alcohol, which itself is prepared according to the procedure described in *J. Chem. Soc.*, 4728 (1958)] and about one equivalent of base, there is produced 1-nitro-2-(2-propynylamino)-2-[2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino]ethylene (BL—5966).

Alternatively, the 1-nitro-2-(2-propynylamino)-2-(2-mercaptoethyl)ethylene may be reacted directly with 5-dimethylaminomethylfurfuryl alcohol in concentrated hydrochloric acid to produce 1-nitro-2-(2-propynylamino)-2-[2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino]ethylene (BL—5966).

EXAMPLE 12

N-Cyano-N'-(2-propyn-1-yl)-N''-[2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethyl]guanidine (BL—5993)

A solution of N-cyano-N'-(2-propyn-1-yl)-N''-(2-mercaptoethyl)-guanidine [prepared according to the procedure described in U.S. Patent 4,112,234] in ethanol is reacted with an ethanol solution of about an equimolar amount of 5-dimethylaminomethylfurfuryl chloride hydrochloride and about one equivalent of base, and the title product is thereby produced.

EXAMPLE 13

The general procedure of Example 1 is repeated except that the 2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamine utilized therein is replaced by an equimilar amount of

2-[(5-diethylaminomethyl-2-furyl)methylthio]ethylamine,
2-[(5-[[N-ethyl-N-methylamino]methyl]-2-furyl)methylthio]ethylamine,
2-[(5-[2-[dimethylamino]ethyl]-2-furyl)methylthio]ethylamine,
2-[(5-[3-[dimethylamino]propyl]-2-furyl)methylthio]ethylamine,
2-[(5-aminomethyl-2-furyl)methylthio]ethylamine and
2-[(5-[[1-pyrrolidinyl]methyl]-2-furyl)methylthio]ethylamine, respectively.

[each prepared by the procedure described in Belgian Patent 857,388], and there is thereby produced

1-nitro-2-(2-propynylamino)-2-[2-[(5-diethylaminomethyl-2-furyl)methylthio]ethylamino]ethylene,
1-nitro-2-(2-propynylamino)-2-[2-[(5-[[N-ethyl-N-methylamino]methyl]-2-furyl)methylthio]-ethylamino]ethylene,
1-nitro-2-(2-propynylamino)-2-[2-[(5-[2-[dimethylamino]ethyl]-2-furyl)methylthio]ethylamino]-ethylene,
1-nitro-2-(2-propynylamino)-2-[2-[(5-[3-[dimethylamino]propyl]-2-furyl)methylthio]ethylamino]-ethylene,
1-nitro-2-(2-propynylamino)-2-[2-[(5-aminomethyl-2-furyl)methylthio]ethylamino]ethylene and
1-nitro-2-(2-propynylamino)-2-[2-[(5-[(1-pyrrolidinyl)methyl]-2-furyl)methylthio]ethylamino]ethylene, respectively.

EXAMPLE 14

1-Nitro-2-(2-propynylamino)-2-{2-[(5-{[N-methyl-N-propargylamino]methyl}-2-furyl)methylthio]-ethylamino}ethylene

The reaction of furfuryl alcohol and N-methylpropargylamine hydrochloride with paraformaldehyde according to the general procedure of *J. Chem. Soc.*, 4728 (1958), and treatment of the product with cysteamine hydrochloride followed by neutralization, produces 2-{(5-{[N-methyl-N-propargylamino]methyl}-2-furyl)methylthio}ethylamine. When the latter product is reacted with 1,1-bis(methylthio)-2-nitroethylene and then with propargylamine according to the general procedure of Example 1, the title compound is produced.

EXAMPLE 15

The general procedure of Example 14 is repeated, except that the N-methylpropargylamine hydrochloride is replaced by an equimolar amount of

N-methylallylamine hydrochloride,
dipropargylamine hydrochloride,
allylamine hydrochloride,
N-methylaniline hydrochloride and
benzylamine hydrochloride, respectively,

and there is thereby produced

1-nitro-2-(2-propynylamino)-2-{2-[(5-{[N-methyl-N-allylamino]methyl}-2-furyl)methylthio]-ethylamino}ethylene,
1-nitro-2-(2-propynylamino)-2-{2-[(5-dipropargylaminomethyl-2-furyl)methylthio]ethylamino}-ethylene,
1-nitro-2-(2-propynylamino)-2-{2-[(5-allylaminomethyl-2-furyl)methylthio]ethylamino}ethylene,
1-Nitro-2-(2-propynylamino)-2-{2-[(5-{[N-methyl-N-phenylamino]methyl}-2-furyl)methylthio]-ethylamino}ethylene and
1-nitro-2-(2-propynylamino)-2-{2-[(5-benzylaminomethyl-2-furyl)methylthio]ethylamino}ethylene, respectively.

EXAMPLE 16

N-Cyano-N'-(2-propyn-1-yl)-N''-{2-[(5-{[N-ethyl-N-methylamino]methyl}-2-furyl)methylthio]ethyl}-guanidine

When an isopropyl alcohol solution of dimethyl cyanodithioimidocarbonate [prepared according to the procedure described in *J. Org. Chem.*, *32*, 1566 (1967)] is reacted with 2-{(5-{[N-ethyl-N-methylamino]methyl}-2-furyl)methylthio]ethylamine and the resultant N-cyano-N'-2-{(5-{[N-ethyl-N-methylamino]methyl}-2-furyl)methylthio]-ethyl}-S-methylisothiourea treated with propargylamine in the procedure of Example 2, there is produced N-cyano-N'-(2-propyn-1-yl)-N''-{2-[(5-{[N-ethyl-N-methylamino]methyl}-2-furyl)methylthio]ethyl}guanidine.

EXAMPLE 17

The general procedure of Example 16 is repeated except that the 2-[(5-{[N-ethyl-N-methylamino]methyl}-2-furyl)methylthio]ethylamine utilized therein is replaced by an equimolar amount of

2-[(5-diethylaminomethyl-2-furyl}-methylthio]ethylamine,
2-[(5-{2-[dimethylamino]ethyl}-2-furyl)methylthio]ethylamine,
2-{(5-{3-[dimethylamino]propyl}-2-furyl)methylthio]ethylamine,
2-[(5-aminomethyl-2-furyl)methylthio]ethylamine,
2-[(5-{[1-pyrrolidinyl]methyl}-2-furyl)methylthio]ethylamine,
2-[5-{[N-methyl-N-propargylamino]methyl}-2-furyl)methylthio]ethylamine,
2-[(5-{[N-methyl-N-allylamino]methyl}-2-furyl)methylthio]ethylamine,
2-[(5-dipropargylaminomethyl-2-furyl)methylthio]ethylamine,
2-[(5-allylaminomethyl-2-furyl)methylthio]ethylamine,
2-[(5-{[N-methyl-N-phenylamino]methyl}-2-furyl)methylthio]ethylamine and
2-[(5-benzylaminomethyl-2-furyl)methylthio]ethylamine,

respectively, and there is thereby produced

N-cyano-N'-(2-propyn-1-yl)-N''-{2-[(5-diethylaminomethyl-2-furyl)methylthio]ethyl}guanidine,
N-cyano-N'-(2-propyn-1-yl)-N''-{2-[(5-{2-[dimethylamino]ethyl}-2-furyl)methylthio]ethyl}guanidine,
N-cyano-N'-(2-propyn-1-yl)-N''-{2-[(5-{3-[dimethylamino]propyl}-2-furyl)methylthio]ethyl}guanidine,
N-cyano-N'-(2-propyn-1-yl)-N''-{2-[(5-aminomethyl-2-furyl)methylthio]ethyl}guanidine,

N-cyano-N'-(2-propyn-1-yl)-N''-[2-[(5-[[1-pyrrolidinyl]methyl]-2-furyl)methylthio]ethyl]guanidine,
N-cyano-N'-(2-propyn-1-yl)-N''-[2-[(5-[[N-methyl-N-propargylamino]methyl]-2-furyl)methylthio]-ethyl]guanidine,
N-cyano-N'-(2-propyn-1-yl)-N''-[2-[(5-[[N-methyl-N-allylamino]methyl]-2-furyl)methylthio]ethyl]-guaniidine,
N-cyano-N'-(2-propyn-1-yl)-N''-[2-[(5-dipropargylaminomethyl-2-furyl)methylthio]ethyl]guanidine,
N-cyano-N'-(2-propyn-1-yl)-N''-[2-[(5-allylaminomethyl-2-furyl)methylthio]ethyl]guanidine,
N-cyano-N'-(2-propyn-1-yl)-N''-[2-[(5-[[N-methyl-N-pheneylamino]methyl]-2-furyl)methylthio]ethyl]-guanidine and
N-cyano-N'-(2-propyn-1-yl)-N''-[2-[(5-benzylaminomethyl-2-furyl)methylthio]ethyl]guanidine,
respectively.

EXAMPLE 18

1-Nitro-2-(2-pyropynylamino)-2-[2-[2-(5-dimethylaminomethyl-2-furyl)ethylthio]ethylamino]ethylene

When 1-phthalimido-2-[2-(5-dimethylaminomethyl-2-furyl)ethylthio]ethane [prepared according to the procedure described in Belgian Patent 857,388] is treated with hydrazine, and the resulting substituted ethylamine is reacted according to the general procedure of Example 1, the title product is produced.

EXAMPLE 19

1-Nitro-2-(2-propynylamino)-2-[3-[(5-dimethylaminomethyl-2-furyl)-methylthio]propylamino]ethylene

When 1-phthalimido-3-[(5-dimethylaminomethyl-2-furyl)methylthio]propane [prepared according to the procedure described in Belgian Patent 857,388] is treated with hydrazine, and the resulting substituted propylamine is reacted according to the general procedure of Example 1, the title product is produced.

EXAMPLE 20

N-Cyano-N'-(2-propyn-1-yl)-N''-[2-[2-(5-dimethylaminomethyl-2-furyl)ethylthio]ethyl]guanidine

When 1-phthalimido-2-[2-(5-dimethylaminomethyl-2-furyl)ethylthio]ethane is treated with hydrazine and the resultant substituted ethylamine is reacted with dimethyl cyanodithioimidocarbonate there is produced N-cyano-N'-[2-[2-(5-dimethylaminomethyl-2-furyl)ethylthio]ethyl]-S-methylisothiourea, and when this is reacted with propargylamine according to the general procedure of Example 3 the title compound is produced.

EXAMPLE 21

N-Cyano-N'-(2-propyn-1-yl)-N''-[3-[(5-dimethylaminomethyl-2-furyl)methylthio]propyl]guanidine

When 1-phthalimido-3-[(5-dimethylaminomethyl-2-furyl)methylthio]propane is treated with hydrazine and the resultant substituted propylamine is reacted with dimethyl cyanodithioimidocarbonate there is produced N-cyano-N'-[3-[(5-dimethylaminomethyl-2-furyl)methylthio]propyl]-S-methylisothiourea, and when this is reacted with propargylamine according to the general procedure of Example 3 the title compound is produced.

EXAMPLE 22

1-Phenylsulfonyl-2-(2-propynylamino)-2-[2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino]-ethylene

Reaction of methyl phenyl sulfone with carbon disulfide under strongly basic conditions and treatment with methyl iodide yields 1-phenylsulfonyl-2,2-bis(methylthio)ethylene, a known compound which is described in *Bull. Soc. Chim. Fr.*, 673 (1973). When the latter compound is reacted with 2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamine according to the general procedure of Example 1, the title product is produced.

EXAMPLE 23

The general procedure of Example 22 is repeated except that the methyl phenyl sulfone utilized therein is replaced by an equimolar amount of

4-chlorophenyl methyl sulfone,
3,4-dichlorophenyl methyl sulfone,
4-methylphenyl methyl sulfone and
dimethyl sulfone, respectively,

[each prepared by the general procedure described in *Bull. Soc. Chim. Fr.*, 637 (1973)] and there is thereby produced

1-(4-chlorophenylsulfonyl)-2-(2-propynylamino)-2-[2-[(5-dimethylaminomethyl-2-furyl)methylthio]-ethylamino]ethylene,

1-(3,4-dichlorophenylsulfonyl)-2-(2-propynylamino)-2-{2-[(5-dimethylaminomethyl-2-furyl)-methylthio]ethylamino}ethylene,
1-(4-methylphenylsulfonyl)-2-(2-propynylamino)-2-{2-[(5-dimethylaminomethyl-2-furyl)methylthio]-ethylamino}ethylene and
1-(methylsulfonyl)-2-(2-propynylamino)-2-{2-[(5-dimethylaminomethyl-2-furyl)methylthio]-ethylamino}ethylene, respectively.

EXAMPLE 24

1-Cyano-2-(2-propynylamino)-2-{2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino}ethylene

When 2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamine is reacted with 1-cyano-2-ethoxy-2-propynylaminoethylene [prepared from propargylamine and 1-cyano-2,2-bis(ethoxy)ethylene, which itself is prepared by the procedure described in *J. Am. Chem. Soc., 71*, 47 (1949)], the title product is produced.

Alternatively, when 2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamine is reacted with 1-cyano-2,2-bis(methoxy)ethylene and the resultant 1-cyano-2-methoxy-2-{2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino}ethylene is reacted with propargylamine according to the general procedure of Example 1, the title product is produced.

EXAMPLE 25

1-Nitro-2-(2-propynylamino)-2-{2-[(3-methyl-5-dimethylaminomethyl-2-furyl)methylthio]ethylamino}-ethylene

A. 2-[(3-Methyl-5-dimethylaminomethyl-2-furyl)methylthio]ethylamine

The reaction of 3-methyl-2-furfuryl alcohol [prepared according to the procedure described in *J. Am. Chem. Soc., 72*, 2195 (1950)] and dimethylamine hydrochloride with paraformaldehyde according to the general procedure described in *J. Chem. Soc.*, 4728 (1958), and treatment of the resultant product with cysteamine hydrochloride, followed by neutralization, produces the title product.

B. 1-Nitro-2-(2-propynylamino)-2-{2-[(3-methyl-5-dimethylaminomethyl-2-furyl)methylthio]-ethylamino}ethylene

When the product of Step A is reacted according to the procedure of Example 1, Steps A and B, the title product is produced.

EXAMPLE 26

The general procedure of Example 25 is repeated except that the dimethylamine hydrochloride utilized therein is replaced by an equimolar amount of

methylamine hydrochloride,
ethylmethylamine hydrochloride,
N-methylpropargylamine hydrochloride and
diethylamine hydrochloride, respectively,

and there is thereby produced

1-nitro-2-(2-propynylamino)-2-{2-[(3-methyl-5-methylaminomethyl-2-furyl)methylthio]ethylamino}-ethylene,
1-nitro-2-(2-propynylamino)-2-{2-[(3-methyl-5-[N-ethyl-N-methylamino]methyl-2-furyl)methylthio]-ethylamino}ethylene,
1-nitro-2-(2-propynylamino)-2-{2-[(3-methyl-5-[N-methyl-N-propargylamino]methyl-2-furyl)methylthio]ethylamino}ethylene and
1-nitro-2-(2-propynylamino)-2-{2-[(3-methyl-5-diethylaminomethyl-2-furyl)methylthio]ethylamino}ethylene, respectively.

EXAMPLE 27

N-Cyano-N'-(2-propyn-1-yl)-N''-{2-[(3-methyl-5-dimethylaminomethyl-2-furyl)methylthio]ethyl}-guanidine

When an alcohol solution of dimethyl cyanodithioimidocarbonate is reacted with 2-[(3-methyl-5-dimethylaminomethyl-2-furyl)methylthio]ethylamine, and the resultant N-cyano-N'-{2-[(3-methyl-5-dimethylaminomethyl-2-furyl)methylthio]ethyl}-S-methylisothiourea is treated with propargylamine according to the general procedure of Example 3, the title compound is produced.

EXAMPLE 28

The general procedure of Example 27 is repeated except that the 2-[(3-methyl-5-dimethylaminomethyl-2-furyl)methylthio]ethylamine utilized therein is replaced by an equimolar amount of

2-[(3-methyl-5-methylaminomethyl-2-furyl)methylthio]ethylamine,
2-[(3-methyl-5-[N-ethyl-N-methylamino]methyl-2-furyl)methylthio]ethylamine,
2-[(3-methyl-5-[N-methyl-N-propargylamino]methyl-2-furyl)methylthio]ethylamine and
2-[(3-methyl-5-diethylaminomethyl-2-furyl)methylthio]ethylamine, respectively,

and there is thereby produced

N-cyano-N'-(2-propyn-1-yl)-N''-[2-[(3-methyl-5-methylaminomethyl-2-furyl)methylthio]ethyl]-guanidine,
N-cyano-N'-(2-propyn-1-yl)-N''-[2-[(3-methyl-5-[N-ethyl-N-methylamino]methyl-2-furyl)methylthio]-ethyl]guanidine,
N-cyano-N'-(2-propyn-1-yl)-N''-[2-[(3-methyl-5-[N-methyl-N-propargylamino]methyl-2-furyl)methylthio]ethyl]guanidine and
N-cyano-N'-(2-propyn-1-yl)-N''-[2-[(3-methyl-5-diethylaminomethyl-2-furyl)methylthio]ethyl]-guanidine, respectively.

EXAMPLE 29

N-Phenylsulfonyl-N'-(2-propyn-1-yl)-N''-[2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethyl]-guanidine

Reaction of N-phenylsulfonylimidodithiocarbonic acid dimethyl ester [prepared by the general procedure described in *Chem. Bber., 99*, 2885 (1966)] with 2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamine and reaction of the resultant product with excess propargylamine according to the general procedure of Example 3 yields the title product.

EXAMPLE 30

The general procedure of Example 29 is repeated except that the N-phenylsulfonylimidodithiocarbonic acid dimethyl ester is replaced by an equimolar amount of

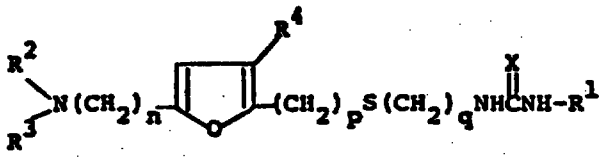
N-(4-chlorophenylsulfonyl)imidodithiocarbonic acid dimethyl ester,
N-(4-methylphenylsulfonyl)imidodithiocarbonic acid dimethyl ester and
N-methylsulfonylimidodithiocarbonic acid dimethyl ester, respectively,

and there is thereby produced

N-(4-chlorophenylsulfonyl)-N'-(2-propyn-1-yl)-N''-[2-[(5-dimethylaminomethyl-2-furyl)methylthio]-ethyl]guanidine,
N-(4-methylphenylsulfonyl)-N'-(2-propyn-1-yl)-N''-[2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethyl]guanidine and
N-methylsulfonyl-N'-(2-propyn-1-yl)-N''-[2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethyl]-guanidine, respectively.

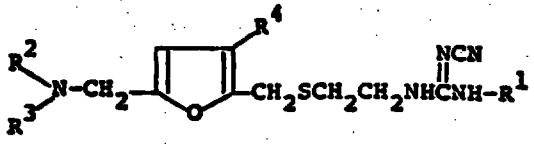
CLAIMS

1. A compound of the formula



wherein R^1 is a straight or branched chain alkynyl group containing from 3 to 9 carbon atoms, inclusive; R^2 and R^3 are the same or different and are hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl or Ar; R^4 is hydrogen or (lower)alkyl; n is an integer of from 1 to 6; p is 1 or 2 and q is 2 or 3, provided that the sum of p and q is 3 or 4; X is NR^5 or CHR^5; R^5 is cyano, nitro, SO_2Ar or SO_2— (lower)alkyl; and Ar is phenyl or phenyl containing one or two substituents indpendently selected from (lower)alkyl and halogen.

2. A compound as claimed in claim 1 having the formula:



wherein R^1, R^2, R^3 and R^4 are as defined in claim 1.

2-[(3-methyl-5-methylaminomethyl-2-furyl)methylthio]ethylamine,
2-[(3-methyl-5-[N-ethyl-N-methylamino]methyl-2-furyl)methylthio]ethylamine,
2-[(3-methyl-5-[N-methyl-N-propargylamino]methyl-2-furyl)methylthio]ethylamine and
2-[(3-methyl-5-diethylaminomethyl-2-furyl)methylthio]ethylamine, respectively,

and there is thereby produced

N-cyano-N'-(2-propyn-1-yl)-N''-[2-[(3-methyl-5-methylaminomethyl-2-furyl)methylthio]ethyl]-guanidine,
N-cyano-N'-(2-propyn-1-yl)-N''-[2-[(3-methyl-5-[N-ethyl-N-methylamino]methyl-2-furyl)methylthio]-ethyl]guanidine,
N-cyano-N'-(2-propyn-1-yl)-N''-[2-[(3-methyl-5-[N-methyl-N-propargylamino]methyl-2-furyl)methylthio]ethyl]guanidine and
N-cyano-N'-(2-propyn-1-yl)-N''-[2-[(3-methyl-5-diethylaminomethyl-2-furyl)methylthio]ethyl]-guanidine, respectively.

EXAMPLE 29

N-Phenylsulfonyl-N'-(2-propyn-1-yl)-N''-[2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethyl]-guanidine

Reaction of N-phenylsulfonylimidodithiocarbonic acid dimethyl ester [prepared by the general procedure described in *Chem. Bber., 99,* 2885 (1966)] with 2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamine and reaction of the resultant product with excess propargylamine according to the general procedure of Example 3 yields the title product.

EXAMPLE 30

The general procedure of Example 29 is repeated except that the N-phenylsulfonylimidodithiocarbonic acid dimethyl ester is replaced by an equimolar amount of

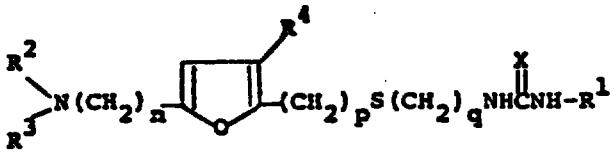
N-(4-chlorophenylsulfonyl)imidodithiocarbonic acid dimethyl ester,
N-(4-methylphenylsulfonyl)imidodithiocarbonic acid dimethyl ester and
N-methylsulfonylimidodithiocarbonic acid dimethyl ester, respectively,

and there is thereby produced

N-(4-chlorophenylsulfonyl)-N'-(2-propyn-1-yl)-N''-[2-[(5-dimethylaminomethyl-2-furyl)methylthio]-ethyl]guanidine,
N-(4-methylphenylsulfonyl)-N'-(2-propyn-1-yl)-N''-[2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethyl]guanidine and
N-methylsulfonyl-N'-(2-propyn-1-yl)-N''-[2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethyl]-guanidine, respectively.

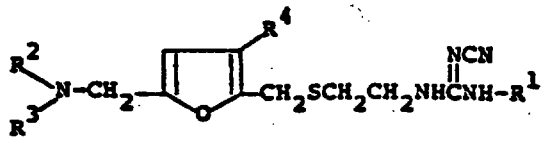
CLAIMS

1. A compound of the formula



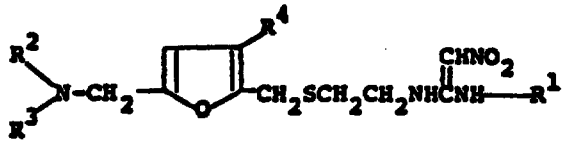
wherein R^1 is a straight or branched chain alkynyl group containing from 3 to 9 carbon atoms, inclusive; R^2 and R^3 are the same or different and are hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl or Ar; R^4 is hydrogen or (lower)alkyl; n is an integer of from 1 to 6; p is 1 or 2 and q is 2 or 3, provided that the sum of p and q is 3 or 4; X is NR^5 or CHR^5; R^5 is cyano, nitro, SO_2Ar or SO_2— (lower)alkyl; and Ar is phenyl or phenyl containing one or two substituents indpendently selected from (lower)alkyl and halogen.

2. A compound as claimed in claim 1 having the formula:



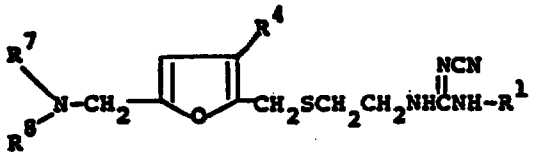
wherein R^1, R^2, R^3 and R^4 are as defined in claim 1.

3. A compound as claimed in claim 1 having the formula:



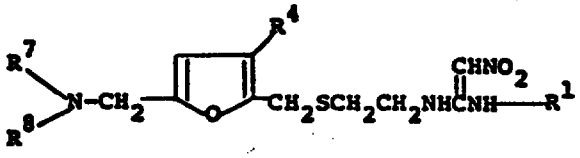
wherein R^1, R^2, R^3 and R^4 are as defined in claim 1.

4. A compound as claimed in claim 1 having the formula:



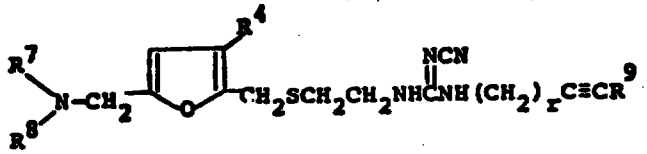
wherein R^1 is a straight or branched chain alkynyl group containing from 3 to 9 carbon atoms, inclusive; R^4 is hydrogen or (lower)alkyl; and R^7 and R^8 are the same or different and are hydrogen or (lower)alkyl.

5. A compound as claimed in claim 1 having the formula:



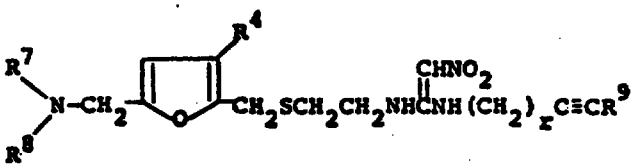
wherein R^1 is a straight or branched chain alkynyl group containing from 3 to 9 carbon atoms, inclusive; R^4 is hydrogen or (lower)alkyl; and R^7 and R^8 are the same or different and are hydrogen or (lower)alkyl.

6. A compound as claimed in claim 4 having the formula:



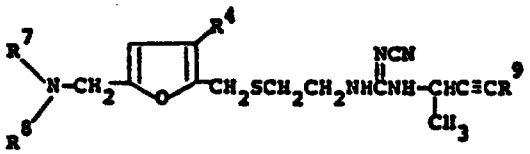
wherein R^4, R^7 and R^8 are as defined in claim 4, *r* is an integer of from 1 to 6, inclusive, and R^9 is hydrogen or methyl.

7. A compound as claimed in claim 5 having the formula:



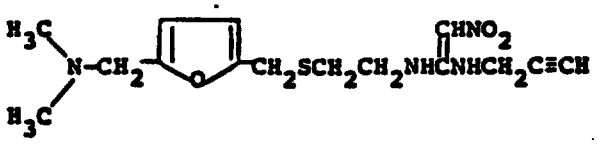
wherein R^4, R^7 and R^8 are as defined in claim 5, *r* is an integer of from 1 to 6, inclusive, and R^9 is hydrogen or methyl.

8. A compound as claimed in claim 4 having the formula:

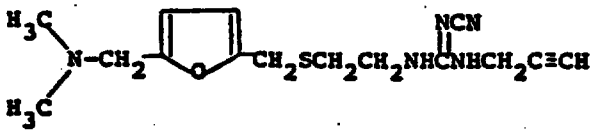


wherein R^4, R^7 and R^8 are as defined in claim 4 and R^9 is hydrogen or methyl.

9. A compound of the formula:

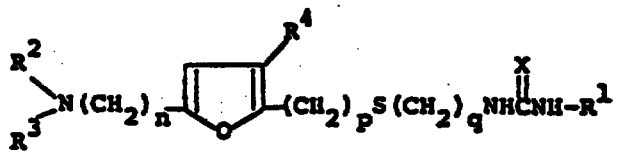


10. A compound of the formula:

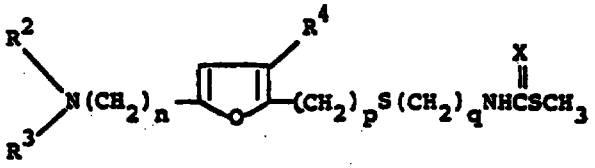


11. A nontoxic, pharmaceutically acceptable salt of a compound as claimed in any one of claims 1 to 10.

12. A process for preparing a compound having the formula:



wherein R^1, R^2, R^3, R^4, X, *n*, *p* and *q* are as defined in claim 1, or a nontoxic, pharmaceutically acceptable salt thereof, which comprises reacting a compound having the formula:



wherein R^2, R^3, R^4, X, *n*, *p* and *q* are as defined above, with a compound having the formula:

$$H_2NR^1$$

wherein R^1 is as defined above, in a non-reactive solvent at or above room temperature.

13. A process as claimed in claim 12 substantially as hereinbefore described with reference to any one of the Examples.

14. A compound as claimed in claim 1 whenever produced by a process as claimed in claim 12 or claim 13.

15. A pharmaceutical compositon which comprises as active ingredient at least one compound as claimed in any one of claims 1 to 10 or claim 14, or a pharmaceutically acceptable salt thereof as claimed in claim 11, together with a pharmaceutically acceptable diluent or carrier.

16. A pharmaceutical composition as claimed in claim 15 which is in unit dosage form.

17. A pharmaceutical composition as claimed in claim 16 wherein each unit dosage contains from 10 mg to 250 mg of the active iingredient.

18. A pharmaceutical composition as claimed in claim 17 wherein each unit dosage contains from 20 to 200 mg of the active ingredient.

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* C L M S *