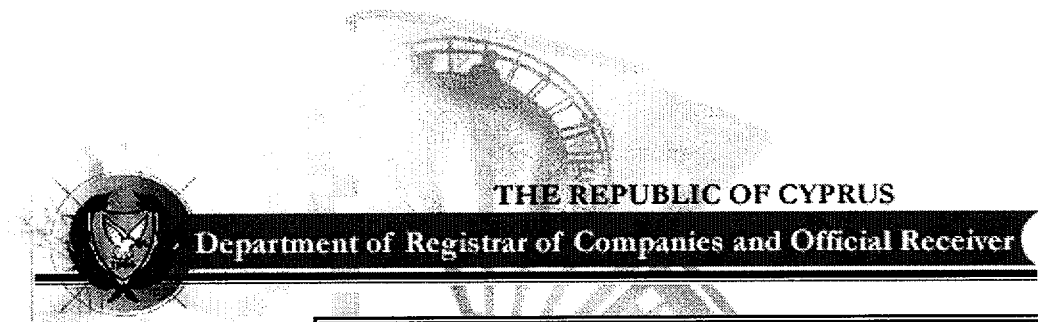




**ΚΥΠΡΙΑΚΟ ΓΡΑΦΕΙΟ ΔΙΠΛΩΜΑΤΩΝ
ΕΥΡΕΣΙΤΕΧΝΙΑΣ
THE PATENT OFFICE OF CYPRUS**

**ΑΡΙΘΜΟΣ ΔΗΜΟΣΙΕΥΣΗΣ CY1230
PUBLICATION NUMBER**

ΑΡΙΘΜΟΣ ΔΗΜΟΣΙΕΥΣΗΣ
ΓΡΑΦΕΙΟΥ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ
ΗΝΩΜΕΝΟΥ ΒΑΣΙΛΕΙΟΥ
UK PATENT OFFICE
PUBLICATION NUMBER GB1598630

Το έγγραφο που παρουσιάζεται πιο κάτω καταχωρήθηκε στο «Γραφείο Διπλωμάτων Ευρεσιτεχνίας» στην Αγγλία σύμφωνα με το Νόμο Κεφ. 266 πριν την 1^η Απριλίου 1998. Δημοσίευση έγινε μετέπειτα από το Γραφείο Διπλωμάτων Ευρεσιτεχνίας του Ηνωμένου Βασιλείου μόνο στην Αγγλική γλώσσα.

**The document provided hereafter was filed at "The Patent Office"
in England under the law CAP.266 before the 1st of April 1998.
It was published afterwards by the UK patent office only in English.**

PATENT SPECIFICATION

(11) 1 598 630

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- (21) Application No. 18923/80 (22) Filed 26 May 1978
 (62) Divided out of No. 1598628
 (31) Convention Application No. 803009
 (32) Filed 3 June 1977
 (31) Convention Application No. 826796
 (32) Filed 22 Aug. 1977
 (31) Convention Application No. 848959
 (32) Filed 7 Nov. 1977 in
 (33) United States of America (US)
 (44) Complete Specification published 23 Sept. 1981
 (51) INT CL³ C07C 129/12
 (52) Index at acceptance
 C2C 202 20Y 30Y 320 326 371 37Y 747 758 AA RH

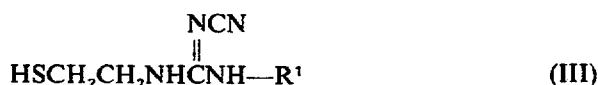


(54) N-CYANO-N'-ALKYNYL-N''-(2-MERCAPTOETHYL)-GUANIDINES

(71) We, BRISTOL-MYERS COMPANY, a Corporation organised and existing under the laws of the State of Delaware, United States of America, of 345 Park Avenue, State of New York, 10022, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed to be particularly described in and by the following statement:—

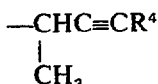
The present invention relates to certain N - cyano - N' - alkynyl - N'' - (2 - mercaptoethyl) - guanidines which are intermediates useful in the preparation of certain N - cyano - N' - [2 - [(4 - methyl - 5 - imidazolyl)methylthio] - ethyl] - N'' - alkynyl guanidines which are H₂ receptor blocking agents, which inhibit gastric acid secretion and which are useful in the treatment of ulcers.

Accordingly, the present invention provides a compound of the formula:

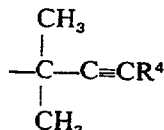


wherein R¹ is a straight or branched chain alkynyl group containing from 3 to 9 carbon atoms.

In a preferred embodiment, R¹ of the compound of formula III is



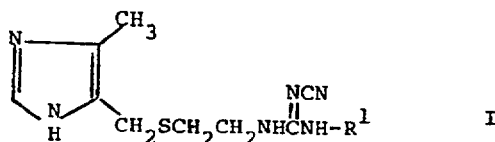
in which R⁴ is hydrogen or methyl; in another preferred embodiment R¹ is $-(\text{CH}_2)_n\text{C}\equiv\text{CR}^4$ in which n is an integer of from 1 to 6 and R⁴ is hydrogen or methyl; and in still another preferred embodiment R¹ is



in which R⁴ is hydrogen or methyl.

In a more preferred embodiment, R¹ of the compound of Formula III is a 2-butyn-1-yl, 3-butyn-1-yl, 4-pentyn-1-yl, 2-methyl-3-butyn-2-yl or 3-butyn-2-yl group.

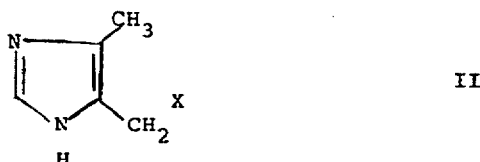
The compounds of the present invention are intermediates in the preparation of compounds of the formula:



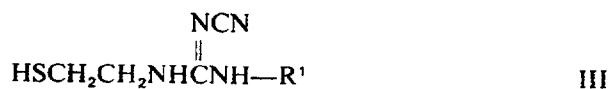
wherein R^1 is a straight or branched chain alkynyl group containing from 3 to 9 carbon atoms.

The compounds of Formula I are described and claimed in our co-pending patent application No. 23611/78, Serial No. 1,598,628.

The compounds of Formula I may be prepared by reacting a compound of the formula:

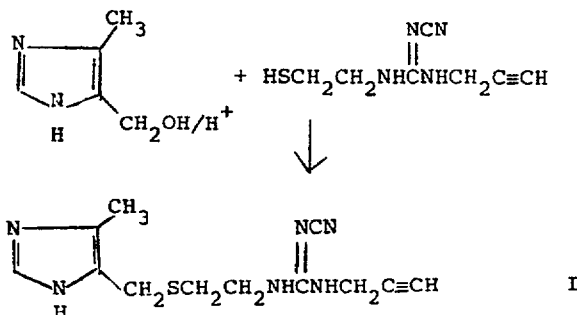


or an acid addition salt thereof, in which X is hydroxy or a leaving group with a compound of the formula:



wherein R^1 is as above defined.

This process is illustrated, by way of example, by the following reaction scheme:



The compounds of the present invention may be prepared by reacting a compound of the formula:



wherein P is a mercapto protecting group with a compound of the formula:



wherein $-\text{SR}$ is a leaving group, and thereafter removing the protecting group P from the resulting compound to produce the compound of the invention.

This process is illustrated by the scheme given below:



1) Heat
2) Deprotect



The present invention will be further described with reference to the following Examples.

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EXAMPLE 1

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N-Cyano-N'-propargyl-N''-(2-mercaptoethyl) guanidine

N-Cyano-N'-propargyl-S-methylisothiurea

(A) A solution of dimethyl cyanodithioiminocarbonate (16.00 g, 0.109 mole) and propargylamine (6.03 g, 0.109 mole) in acetonitrile (320 ml) was stirred at reflux for 4 hours, and then at 25°C for 12 hours. The mixture was cooled and filtered to yield N-cyano-N'-propargyl-S-methylisothiurea.

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N-Cyano-N'-propargyl-N''-(2-mercaptoethyl) guanidine

(B) A mixture of 1.136 g (10 m moles) of cysteamine hydrochloride, 1.53 g (10 m moles) of the product of step (A) above, and 0.055 g of hydroquinone in 10 ml DMF was slightly warmed to dissolve the compounds therein. To this solution was added 10 ml of an aqueous sodium hydroxide and nitrogen was bubbled through the solution. After standing at room temperature for 17 hours, the reaction mixture was evaporated to dryness to give a mixture of the title product and sodium chloride. The title product was extracted from this mixture with 10 ml ethanol.

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EXAMPLE 2

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N-Cyano-N'-(2-butyln-1-yl)-N''-(2-mercaptoethyl)-guanidine

N-Cyano-N'-(2-butyln-1-yl)-S-methylisothiurea

(A) A solution of dimethyl cyanodithioiminocarbonate (10.00 g, 0.0684 mole) and 2-butyln-1-ylamine (4.73 g, 0.0684 mole) in acetonitrile (200 ml) was stirred at 25°C for 0.5 hour, and then at reflux for 2.5 hours. The mixture was cooled and filtered to yield N-cyano-N'-(2-butyln-1-yl)-S-methylisothiurea.

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N-Cyano-N'-(2-butyln-1-yl)-N''-(2-mercaptoethyl) guanidine

(B) The general procedure of Example 1(B) was repeated except that the N-cyano-N'-propargyl-S-methylisothiurea utilized therein is replaced by an equimolar amount of N-cyano-N'-(2-butyln-1-yl)-S-methylisothiurea, and the title product is thereby produced.

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EXAMPLE 3

N-Cyano-N'-(3-butyln-1-yl)-N''-(2-mercaptoethyl)-guanidine

The general procedures of Example 1 steps A and B are repeated except that the propargylamine utilized in step A thereof is replaced by an equimolar amount of 3-butyln-1-ylamine, and the title compound is thereby produced.

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EXAMPLE 4

N-Cyano-N'-(4-pentyln-1-yl)-N''-(2-mercaptoethyl)-guanidine

The general procedures of Example 1 steps A and B are repeated except that the propargylamine utilized in step A thereof is replaced by an equimolar amount of 4-pentyln-1-ylamine, and the title compound is thereby produced.

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EXAMPLE 5

N-Cyano-N'-(2-methyl-3-butyln-2-yl)-N''-(2-mercaptoethyl)-guanidine

The general procedures of Example 1 steps A and B are repeated except that the propargylamine utilized in step A thereof is replaced by an equimolar amount of 1,1 - dimethylpropargylamine, and the title compound is thereby produced.

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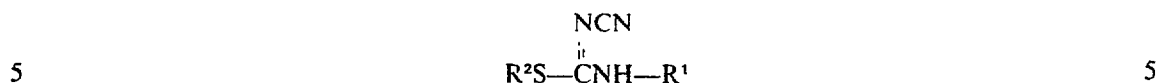
EXAMPLE 6

N-Cyano-N'-(3-butyln-2-yl)-N''-(2-mercaptoethyl)guanidine

The general procedures of Example 1 steps A and B are repeated except that

the propargylamine utilized in step A thereof is replaced by an equimolar amount of 1-methyl-propargylamine, and the title compound is thereby produced.

Our copending patent application No. 27637/79. Serial No. 1,598,629 describes and claims compounds of the formulae



wherein R¹ is as above defined and R² is C₁₋₉ alkyl, aryl, substituted aryl, aralkyl, —CH₂CN, —CH₂COOH or —CH₂COOR' wherein R' is C₁₋₉ lower alkyl.

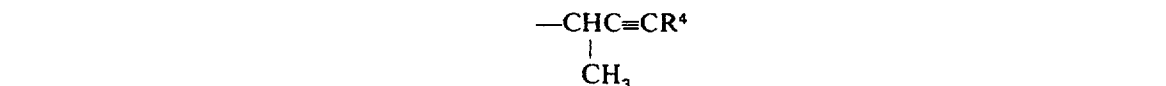
WHAT WE CLAIM IS:

1. A compound of the general formula:



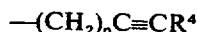
wherein R¹ is a straight or branched chain alkynyl group containing from 3 to 9 carbon atoms.

2. A compound as claimed in claim 1 wherein R¹ is



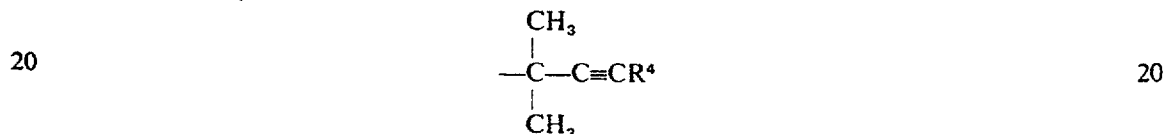
wherein R⁴ is H or CH₃.

3. A compound as claimed in claim 1 wherein R¹ is



wherein R⁴ is H or CH₃ and n is an integer of from 1 to 6, inclusive.

4. A compound as claimed in claim 1 wherein R¹ is



wherein R⁴ is H or CH₃.

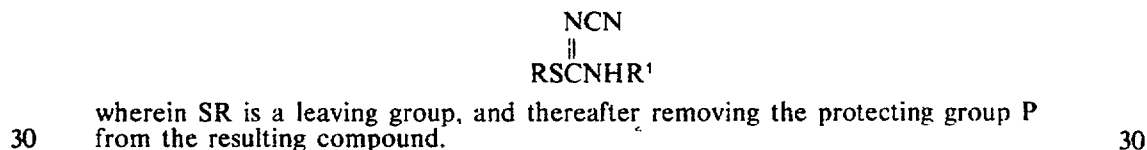
5. A compound as claimed in claim 2 or claim 3 wherein R⁴ is H.

6. A compound as claimed in claim 2 or claim 3 wherein R⁴ is CH₃.

25 7. A process for the preparation of a compound as claimed in claim 1 which process comprises reacting a compound of the formula: 25



wherein P is a mercapto protecting group with a compound of the formula:



wherein SR is a leaving group, and thereafter removing the protecting group P from the resulting compound.

8. A process for preparing a compound as claimed in claim 1 substantially as hereinbefore described with reference to any one of the Examples.

9. A compound as claimed in claim 1 whenever prepared by a process as claimed in claim 7 or claim 8.

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Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1981
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from
which copies may be obtained.