

# PATENT SPECIFICATION

(11) 1 598 629

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## (54) N-CYANO-N'-ALKYNYL-S-SUBSTITUTED ISOTHIUREAS

(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:—

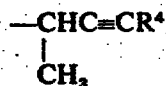
The present invention relates to certain N-cyano-N'-alkynyl-S-substituted isothioureas which are intermediates useful in the preparation of certain N-cyano-N'-[2 - [(4 - methyl - 5 - imidazolyl)methylthio] - ethyl]-N'-alkynylguanidines which are H<sub>2</sub> receptor blocking agents, which inhibit gastric acid secretion and which are useful in the treatment of ulcers.

Accordingly, the present invention provides a compound of the formula



wherein R<sup>1</sup> is a straight or branched chain alkynyl group containing from 3 to 9 carbon atoms and R<sub>2</sub> is C<sub>1-9</sub> alkyl, aryl, substituted aryl, aralkyl, —CH<sub>2</sub>CN, —CH<sub>2</sub>COOH or —CH<sub>2</sub>COOR' wherein R' is C<sub>1-9</sub> lower alkyl.

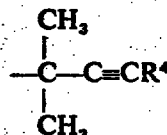
In a preferred embodiment, R<sup>1</sup> of the compound of formula III is



in which R<sup>4</sup> is hydrogen or methyl; in another preferred embodiment R<sup>1</sup> is



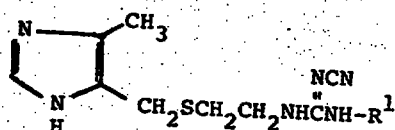
in which n is an integer of from 1 to 6 and R<sup>4</sup> is hydrogen or methyl; in another preferred embodiment R<sup>1</sup> is



in which R<sup>4</sup> is hydrogen or methyl.

In a more preferred embodiment, R<sup>1</sup> is a propargyl, 2-butyne-1-yl, 3-butyne-1-yl, 2-methyl-3-butyne-2-yl, or 4-pentyne-1-yl group.

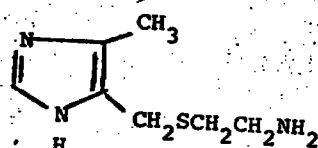
The compounds of the present invention are intermediates in the preparation of compounds of the formula



wherein R<sup>1</sup> is a straight or branched chain alkynyl group containing from 3 to 9 carbon atoms, or non-toxic pharmaceutically acceptable acid addition salts thereof.

The compounds of formula I are described and claimed in our copending patent application No. 23611/78. Serial No. 1,598,628.

The compounds of formula I and salts thereof may be prepared by reacting a

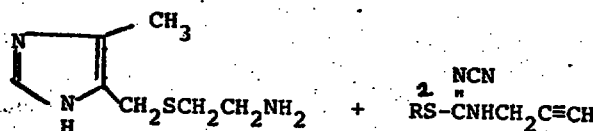
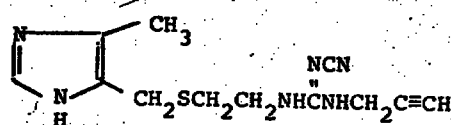


or an acid addition salt thereof, with a compound of the formula



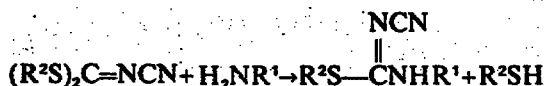
wherein R<sup>1</sup> and R<sup>2</sup> are as above defined, and, if desired, converting the resulting compound of formula I in basic form or an acid addition salt thereof to the corresponding non-toxic pharmaceutically acceptable acid addition salt or free base form.

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



wherein R<sup>2</sup> is as above defined

The compounds of the present invention may be prepared by the reaction of an appropriately substituted cyanodithioiminocarbonate with an alkynylamine having from 3 to 9 carbon atoms. The general reaction scheme is given below:—



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

#### EXAMPLE 1

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

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. Workup gave the title compound (13.58 g, 81%), mp 160—164°C.

#### EXAMPLE 2

##### N-(2-Butyn-1-yl)-N'-cyano-S-methylisothiurea

A solution of dimethyl cyanodithioiminocarbonate (10.00 g, 0.0684 mole) and 2-butyn-1-yl-amine (4.73 g, 0.0684 mole) in acetonitrile (200 ml) was stirred at reflux for 2.5 hours. The mixture was cooled, then filtered to yield the title compound, mp 180—183°C.

#### EXAMPLE 3

##### N-(1,1-Dimethylpropargyl)-N'-cyano-S-methylisothiurea

The general procedure of Example 2 is repeated except that the 2-butyn-1-yl-amine utilized therein is replaced by an equimolar amount of 1,1-dimethylpropargylamine, and the title product is thereby produced.

#### EXAMPLE 4

##### N-(1-Methylpropargyl)-N'-cyano-S-methylisothiurea

The general procedure of Example 2 is repeated except that the 2-butyn-1-yl-amine utilized therein is replaced by an equimolar amount of 1-methylpropargylamine, and the title product is thereby produced.

#### EXAMPLE 5

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

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 the title compound (13.58 g, 81%), mp 160—164°C.

#### EXAMPLE 6

##### N-Cyano-N'-(2-butyn-1-yl)-S-methylisothiurea

A solution of dimethyl cyanodithioiminocarbonate (10.00 g, 0.0684 mole) and 2-butyn-1-yl-amine (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, then filtered to yield the title compound, mp 180—183°C.

#### EXAMPLE 7

##### N-Cyano-N'-(3-butyn-1-yl)-S-methylisothiurea

The general procedure of Example 5 is repeated, except that the propargylamine utilized therein is replaced by an equimolar amount of 3-butyn-1-yl-amine, and the title compound is thereby produced.

#### EXAMPLE 8

##### N-Cyano-N'-(4-pentyn-1-yl)-S-methylisothiurea

The general procedure of Example 5 is repeated, except that the propargylamine utilized therein is replaced by an equimolar amount of 4-pentyn-1-yl-amine, and the title compound is thereby produced.

#### EXAMPLE 9

##### N-Cyano-N'-(2-methyl-3-butyn-2-yl)-S-methylisothiurea

The general procedure of Example 5 is repeated, except that the propargylamine utilized therein is replaced by an equimolar amount of 1,1-dimethylpropargylamine, and the title compound is thereby produced.

## EXAMPLE 10

## N-Cyano-N'-(3-butyn-2-yl)-S-methylisothiurea

The general procedure of Example 5 is repeated, except that the propargylamine utilized therein is replaced by an equimolar amount of 1-methyl-propargylamine, and the title compound is thereby produced.

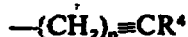
## WHAT WE CLAIM IS:—

1. A compound of the formula



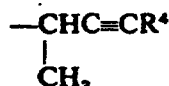
wherein R<sup>1</sup> is a straight or branched chain alkynyl group containing from 3 to 9 carbon atoms, inclusive, and R<sup>2</sup> is C<sub>1-9</sub>alkyl, aryl, substituted aryl, aralkyl, —CH<sub>2</sub>CN, —CN<sub>2</sub>COOH or —CH<sub>2</sub>COOR' where R' is C<sub>1-9</sub>alkyl.

2. A compound as claimed in claim 1 in which R<sup>1</sup> is



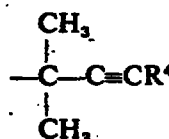
wherein n is an integer of from 1 to 6, inclusive, and R<sup>4</sup> is hydrogen or methyl.

3. A compound as claimed in claim 1 in which R<sup>1</sup> is



wherein R<sup>4</sup> is hydrogen or methyl.

4. A compound as claimed in claim 1 in which R<sup>1</sup> is



wherein R<sup>4</sup> is hydrogen or methyl.

5. A compound as claimed in claim 1 wherein R<sup>1</sup> is a propargyl, 2-butyn-1-yl, 3-butyn-1-yl, 2-methyl-3-butyn-2-yl, or 4-pentyn-1-yl group.

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

7. A compound as claimed in claim 1 whenever prepared by a process as claimed in claim 6.

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## EXAMPLE 10

N-Cyano-N'-(3-butyne-2-yl)-S-methylisothiourea

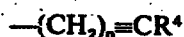
The general procedure of Example 5 is repeated, except that the propargylamine utilized therein is replaced by an equimolar amount of 1-methyl-propargylamine, and the title compound is thereby produced.

## WHAT WE CLAIM IS:—

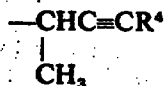
1. A compound of the formula



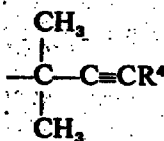
wherein R<sup>1</sup> is a straight or branched chain alkynyl group containing from 3 to 9 carbon atoms, inclusive, and R<sup>2</sup> is C<sub>1-9</sub>alkyl, aryl, substituted aryl, aralkyl, —CH<sub>2</sub>CN, —CN<sub>2</sub>COOH or —CH<sub>2</sub>COOR' where R' is C<sub>1-9</sub>alkyl.

2. A compound as claimed in claim 1 in which R<sup>1</sup> is

wherein n is an integer of from 1 to 6, inclusive, and R<sup>4</sup> is hydrogen or methyl.

3. A compound as claimed in claim 1 in which R<sup>1</sup> is

wherein R<sup>4</sup> is hydrogen or methyl.

4. A compound as claimed in claim 1 in which R<sup>1</sup> is

wherein R<sup>4</sup> is hydrogen or methyl.

5. A compound as claimed in claim 1 wherein R<sup>1</sup> is a propargyl, 2-butyne-1-yl, 3-butyne-1-yl, 2-methyl-3-butyne-2-yl, or 4-pentyne-1-yl group.

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

7. A compound as claimed in claim 1 whenever prepared by a process as claimed in claim 6.

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