(54) Title: N-6 AND 5'-N SUBSTITUTED CARBOXAMIDOADENOSINE DERIVATIVES AS CARDIAC VASODILATORS AND ANTIHYPERTENSIVE AGENTS, AND PROCESS FOR MAKING SAID COMPOUNDS

(57) Abstract

Compounds of formula (I), wherein \( R_1 \) represents secondary alkyl; aralkyl; cycloalkyl; heteroaryl substituted alkyl; norbornyl; and substituted secondary alkyl, aralkyl, cycloalkyl, heteroaryl substituted alkyl, norbornyl; and para-substituted phenyl groups; and \( R_2 \) and \( R_3 \) are hydrogen or pharmacologically acceptable acyl groups. The compounds of the invention are useful as cardiovascular vasodilator or anti-hypertensive agents. The therapeutically useful compounds of the invention as well as similar 5'-N and N-6 substituted adenosine 5'-uronamides are prepared, in accordance with a novel process, from isopropylidene (or otherwise suitably blocked) inosine-5'-uronic acid. Isopropylideneinosine-5'-uronic acid is reacted with a suitable inorganic acid halide, such as thionyl chloride, to yield 6-halogeno-9-[2',3'-O-isopropylidene-\( \beta \)-D-ribofuranosyl]-5'-uronic acid halide-9\( \beta \)-purine. This intermediate is reacted with an amine of the general formula \( R_4 \), \( R_5 \)NH to give a 6-halogeno substituted, substituted uronic acid amide of formula (II), wherein X is halogen. Reaction of the latter intermediate with an amine of the formula \( R_1 \)-NH\(_2\) and removal of the isopropylidene (or other) blocking groups yields the compounds of the invention.
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N-6 AND 5'-N SUBSTITUTED CARBOXAMIDOADENOSINE DERIVATIVES
AS CARDIAC VASODILATORS AND ANTIHYPERTENSIVE AGENTS,
AND PROCESS FOR MAKING SAID COMPOUNDS

BACKGROUND OF THE INVENTION

1. Cross-Reference To Related Application

The present application is a continuation-in-part of application Serial No. 625,450, filed on June 28, 1984, by the same inventors, and assigned to the same assignee as the present application.

2. Field of the Invention

The present invention is directed to certain N-6 and 5'-N substituted carboxamidoadenosine derivatives which have beneficial cardiovascular and antihypertensive activity in mammals, including humans and domestic animals. The present invention is also directed to a process for making said compounds.

3. Brief Description of the Prior Art

Adenosine has been known for a long time to possess certain cardiovascular, and particularly coronary dilator, activity. In an effort to obtain adenosine analogs of greater potency, or longer duration of activity, or both, many analogs of this naturally occurring nucleoside have been synthesized and tested.

Moreover, numerous studies have been conducted in order to elucidate the biochemical mechanism of action of adenosine and its analogs, and several theories and hypotheses have been proposed regarding biochemical pathways and receptor sites.

For discussion of current theories regarding the foregoing, reference is made to the following articles and

In addition to the foregoing publications, German Offenlegungsschrift Nos. 2133273, 2426682, 1795761, 1913818, 2007273, 2238923, 2060189, 2244328, 1814711, 2136624, South African Patent Application No. 677630 (filed on December 20, 1967) and British Patent Specification No. 1,123,245 describe adenosine derivatives which have cardiovascular, coronary dilator, or antilipolytic activities. Still more adenosine derivatives having beneficial cardiovascular activity are described in another application for United States Letters Patent of the present inventors, Serial No. 601,435, filed on April 18, 1984.

Still further, published Japanese Patent Application Nos. 58-167599 and 58-167600 disclose adenosine 5'-carboxamide derivatives which have fibrinolysis
accelerating activity. United States Patent No. 4,029,334 discloses anti-hypertensive and anti-anginal adenosine 5'-carboxamide derivatives where the N^6 amino group is unsubstituted. United States Patent No. 4,167,565 discloses adenosine 5'-carboxamide derivatives which have substituents both in the N^6 and 5'-carboxamido position, and which are useful as poisons for certain noxious animals, such as rodents and coyotes.

In the cardiovascular and anti-hypertensive field, however, the therapeutic utility of the natural nucleoside adenosine and many of its analogs is limited because the desired beneficial effect is often of relatively short duration.

More particularly, the short duration of the beneficial cardiovascular effects of adenosine and those of its analogs which have an unsubstituted hydroxyl group at C-5 of the ribofuranose moiety is usually attributed to rapid penetration into cells followed by enzymatic conversion into less active or impermeant metabolites. For example, adenosine deaminase converts adenosine into inosine, which is a weak cardiovascular agonist. Alternatively, phosphorylation, catalyzed by adenosine kinase, forms adenylic acid (5'-AMP). Ionization of the phosphate group under physiological conditions prevents the escape of 5'-AMP from the cells in which it is formed. Thus trapped, 5'-AMP cannot exert its cardiovascular actions, which are mediated by cell surface receptors, as is discussed below.

Some known adenosine analogs, however, cannot be phosphorylated in the 5' position because the 5' position is effectively blocked. 5'-N-Ethylcarboxamidoadenosine [NECA] (Compound 1 in General Formula 1) is an example of such an adenosine analog incapable of phosphorylation by adenosine kinase. Nevertheless, this compound binds potently to certain adenosine receptor sites and exhibits substantial cardiovascular activity. Other examples of known derivatives of adenosine-5'-carboxamide (Compound 2), and of adenosine-5'-carboxylic acid (Compound 9) are shown below in
General Formulae 1 and 2. Generally speaking, in these compounds, the 5'-carboxylate or 5'-carboxamide group of the uronic acid moiety is substituted with lower alkyl or lower acyl groups. Some of the adenosine-5'-carboxamide derivatives shown in General Formula 1 are disclosed in Chemical Abstracts Volume 100, 68652c and 68653d (1984) and in the corresponding published Japanese Patent Application Nos. 58-167599 and 58-167600.

The biological activity of adenosine-5'-carboxamide derivatives, such as NECA, is thought to be due to the activation of adenylate cyclase through cell surface "R_a" or "A_2" receptors. Structure-activity studies show that the R_a receptor recognizes the alkyl uronamide moiety of NECA and its congeners. A second type of cell surface adenosine receptor designated "R_i" or "A_1" inhibits the catalytic activity of adenylate cyclase. Adenosine analogs possessing certain N-6 alkyl or aralkyl substituents, such as cyclohexyl or R-1-phenyl-2-propyl, are selective agonists at R_i receptors. Many mammalian and human cells contain both R_a and R_i receptors; examples of exceptions are fat cells which contain R_i receptors only, and blood platelets and human placenta, in which R_a receptors predominate.

Currently available agonists are only selective, not absolutely specific, for R_a and R_i receptors. Because the two types of receptors coexist in many organs, including brain and heart, even a selective agonist will activate both to a certain degree. A goal of pharmaceutical chemistry is the development of agonists which are as nearly specific as possible because unselectivity can be a source of side effects.

The prior art makes no prediction about receptor selectivity of adenosine analogs which contain, in the same molecule, the recognition groups which confer specificity for R_a and R_i receptors.
Compound 1 \( R_1 = R_3 = H, R_2 = \text{ETHYL} \)  
Compound 2 \( R_1 = R_2 = R_3 = H \)  
Compound 3 \( R_1 = R_3 = H, R_2 = \text{CYCLOPROPYL} \)  
Compound 4 \( R_1 = R_3 = H, R_2 = \text{CH}_3 \)  
Compound 5 \( R_1 = H, R_2 = R_3 = \text{CH}_3 \)  
Compound 6 \( R_1 = \text{CH}_3, R_3 = H, R_2 = \text{ETHYL} \)  
Compound 7 \( R_1 = \text{CH}_3, R_3 = H, R_2 = \text{BUTYL} \)  
Compound 8 \( R_1 = R_3 = H, R_2 = \text{BUTYL} \)  
Compound 9 \( R = H \)  
Compound 10 \( R = \text{CH}_3 \)  
Compound 11 \( R = \text{ETHYL} \)  
Compound 12 \( R = \text{n-PROPYL} \)  
Compound 13 \( R = \text{i-PROPYL} \)  
Compound 14 \( R = \text{n-BUTYL} \)  
Compound 15 \( R_1 = R_2 = \text{ETHYL}, R_3 = H \)  
Compound 16 \( R_1 = \text{PROPYL}, R_2 = \text{ETHYL}, R_3 = H \)  

Many of the known adenosine derivatives, including the above-noted N-6 substituted and the 5'-carboxamide derivatives, are less than satisfactory as cardiovascular or antihypertensive drugs for animal and human use. This is either because of low activity, short duration of the desired activity, undue toxicity, or undesirable side effects. Undesirable side effects of cardiovascularly active adenosine analogs often include cardiac depression.
In light of the foregoing, the pharmaceutical industry is still striving to obtain adenosine analogs having high cardiovascular and hypotensive potency coupled with other optimal physiological characteristics, such as relatively long duration of the desired activity, low toxicity, and minimal side effects. The compounds of the present invention constitute a step in this direction.

**SUMMARY OF THE INVENTION**

It is an object of the present invention to provide adenosine analogs which have potent and prolonged cardiovascular activity in mammals and humans, coupled with relatively low toxicity and minimal side effects.

It is another object of the present invention to provide adenosine analogs which have potent or prolonged anti-hypertensive activity in mammals and humans, coupled with relatively low toxicity and minimal side effects.

It is still another object of the present invention to provide a relatively efficient synthetic process for the preparation of the adenosine derivatives which meet the above-noted objectives.

The foregoing and other objects and advantages are attained by compounds of the General Formula 3, wherein $R_1$ represents secondary alkyl; hydroxy, lower alkoxy or halogen substituted secondary alkyl; aralkyl; aralkyl substituted in the aromatic nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups; cycloalkyl; hydroxy, lower alkoxy, lower alkyl or halogen substituted cycloalkyl; para-substituted phenyl; heteroaryl substituted alkyl; heteroaryl substituted alkyl substituted in the heteroaryl nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups; norbornyl, and hydroxy, alkyl or halogen substituted norbornyl groups.

The substituent $R_2$ and $R_3$ groups in the compounds of the present invention, as shown in General Formula 3, are hydrogen, or pharmacologically acceptable organic acyl groups, or inorganic acid radicals, such as $\text{NO}_2$ groups, which esterify the hydroxyl groups of the ribofuranose moiety. The $R_2$ and $R_3$ groups are preferably of the type which are
relatively readily hydrolyzed under physiological conditions. The $R_2$ and $R_3$ substituents need not be identical with one another.

Still further, in the compounds of General Formula 3, the substituent $R_4$ is straight chain lower alkyl having 1-4 carbon atoms; hydroxy, lower alkoxy or halogen substituted straight chain lower alkyl having 1-4 carbon atoms; cyclopropyl; secondary alkyl having 3-6 carbon atoms; hydroxy, lower alkoxy or halogen substituted secondary alkyl having 3-6 carbon atoms; alkenyl having 3 to 6 carbon atoms; aralkyl having 1 to 4 carbons in the alkyl chain; aralkyl having 1 to 4 carbons in the alkyl chain and substituted in the aryl nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups; heteroarylmethyl having 1 to 4 carbons in the alkyl chain; and heteroarylmethyl having 1 to 4 carbons in the alkyl chain and substituted in the heteroaryl nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups. $R_5$ is hydrogen, or straight chain lower alkyl having 1 to 4 carbons.
The compounds of the present invention are resistant to enzymatic phosphorylation and to deamination by adenosine deaminase. The compounds exhibit significant cardiovascular activity.

In accordance with a novel process of the invention, the compounds of General Formula 3 are obtained from 2',3'-Q-isopropylideneinosine-5'-uronic acid by treatment with a suitable inorganic acid halide, such as thionyl chloride, to yield the intermediate, 6-chloro-9-[2,3-Q-isopropylidene-R-D-ribofuranosyl-5-uronic acid chloride]-9H-purine. The intermediate, 6-chloro-9-[2,3-Q-isopropylidene-R-D-ribofuranosyl-5-uronic acid chloride]-9H-purine (or the corresponding bromide if, for example, thionyl bromide is used instead of thionyl chloride) is usually not isolated in a pure state.

The acid chloride moiety of 6-chloro-9-[2,3-Q-isopropylidene-R-D-ribofuranosyl-5-uronic acid chloride]-9H-purine (or the acid bromide of the corresponding bromo-analog) is significantly more readily displaced by nucleophilic reagents than the halide group in the 6 position of the purine moiety. Therefore, in accordance with the process of the present invention, 6-chloro-9-[2,3-Q-isopropylidene-R-D-ribofuranosyl-5-uronic acid chloride]-9H-purine is reacted with a first nucleophilic reagent having the formula R₄R₅-NH (General Formula 4) to yield an intermediate substituted carboxamide shown in General Formula 5, wherein the halide is retained in the 6 position of the purine moiety.

The intermediate of General Formula 5 is subsequently reacted with a nucleophile having the formula R₁-NH₂ (General Formula 6) and the isopropylidene blocking group is removed with acid to yield the compounds of the invention (General Formula 3), having free hydroxyl groups in the 2' and 3' positions of the ribofuranose moiety. Instead of the isopropylidene blocking group, other acid stable blocking groups can also be used to protect the 2'-OH and 3'-OH groups.
of the ribofuranose moiety during the step of treatment with the inorganic acid halide.

The groups \( R_1, R_4 \) and \( R_5 \) in General Formulae 4-6 are defined the same as in General Formula 3.

\[
R_4 - \text{NH} - R_5 \\
R_1 - \text{NH}_2
\]

GENERAL FORMULA 4  
GENERAL FORMULA 6

GENERAL FORMULA 5
DETAILED DESCRIPTION OF THE INVENTION

Certain derivatives of 5'-carboxamidoadenosine, wherein both the amino nitrogen (N-6) of the purine moiety and the amido nitrogen of the 5'-carboxamido moiety are substituted, have been found, in accordance with the present invention, to possess significant cardiovascular and/or anti-hypertensive activity. The compounds of the invention have the composition characterized by General Formula 3. The substituent R₁, R₂, R₃, R₄ and R₅ groups are defined above in the summary description of the present invention.

A preferred subclass of the compounds of the present invention consists of N-6 substituted derivatives of 5'-N-ethylcarboxamidoadenosine shown in General Formula 7, wherein the R₄ substituents of the N-6 amino nitrogen comprise: secondary alkyl; hydroxy, lower alkoxy or halogen substituted secondary alkyl; aralkyl; aralkyl substituted in the aromatic nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups; cycloalkyl; hydroxy, lower alkoxy, lower alkyl or halogen substituted cycloalkyl; para-substituted phenyl; heteroaryl substituted alkyl; heteroaryl substituted alkyl substituted in the heteroaryl nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups.

The R₂ and R₃ substituent groups on the 2' and 3' positions of the ribofuranose moiety are hydrogen, or pharmaceutically acceptable acyl groups, such as acetyl, propionyl, butyryl and benzoyl groups. Especially preferred, in this regard, are those acyl groups which are relatively readily split off the ribofuranose moiety under physiological conditions. The R₂ and R₃ substituent groups can also represent inorganic acid radicals, such as NO₂ groups, which esterify the hydroxyl groups of the ribofuranose moiety.

The R₄ substituent in the foregoing subclass of compounds, shown in General Formula 7, is hydrogen, methyl or ethyl.

Another preferred subclass of the compounds of the present invention consists of derivatives of 5'-carboxamidoadenosine, compounds of General Formula 8,
wherein both the N-6 and 5'-carboxamido nitrogens are monosubstituted with the substituents $R_1$ and $R_4$, respectively, and where the $R_2$ and $R_3$ substituents are defined the same as for the compounds of General Formula 7.

In this preferred subclass of compounds, shown in General Formula 8, the $R_1$ substituents are: secondary alkyl; hydroxy, lower alkoxy or halogen substituted secondary alkyl; aralkyl; aralkyl substituted in the aromatic nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups; cycloalkyl; hydroxy, lower alkoxy, lower alkyl or halogen substituted cycloalkyl; para-substituted phenyl; heteroaryl substituted alkyl; heteroaryl substituted alkyl substituted in the heteroaryl nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups.

The substituents $R_4$ of the preferred subclass shown in General Formula 8 are: straight chain lower alkyl having 1-4 carbon atoms; hydroxy, lower alkoxy or halogen substituted straight chain lower alkyl having 1-4 carbon atoms; cyclopropyl; secondary alkyl having 3-6 carbon atoms; hydroxy, lower alkoxy or halogen substituted secondary alkyl having 3-6 carbon atoms; alkenyl having 3 to 6 carbon atoms.

Specific examples of preferred compounds of this subclass (General Formula 8) are those where the $R_1$ (N-6) and $R_4$ (5'-carboxamido) substituents are as follows, with $R_2$ and $R_3$ being hydrogen:

- **Compound 17**: $R_1$ is 3-pentyl, $R_4$ is ethyl;
- **Compound 18**: $R_1$ is cyclohexyl, $R_4$ is ethyl;
- **Compound 19**: $R_1$ is (S)-1-phenyl-2-butyl, $R_4$ is ethyl;
- **Compound 20**: $R_1$ is 4-methoxy-phenyl, $R_4$ is ethyl;
- **Compound 21**: $R_1$ is 2-(3,4,5-trimethoxyphenyl)ethyl, $R_4$ is ethyl;
- **Compound 22**: $R_1$ is 3-phenyl-propyl, $R_4$ is ethyl;
- **Compound 23**: $R_1$ is (R)-1-phenylethyl, $R_4$ is ethyl;
- **Compound 24**: $R_1$ is 2-(2-pyridyl)ethyl, $R_4$ is ethyl;
- **Compound 25**: $R_1$ is (2-chlorophenyl)methyl, $R_4$ is ethyl;
- **Compound 26**: $R_1$ is (2-thienyl)methyl, $R_4$ is ethyl;
- **Compound 27**: $R_1$ is endo-2-norbornyl, $R_4$ is 2-hydroxyethyl;
Compound 28: $R_1$ is 3-pentyl, $R_4$ is methyl;
Compound 29: $R_1$ is 3-pentyl, $R_4$ is isopropyl;
Compound 30: $R_1$ is 3-pentyl, $R_4$ is 3-pentyl;
Compound 31: $R_1$ is 3-pentyl, $R_4$ is allyl;
Compound 32: $R_1$ is 3-pentyl, $R_4$ is (2-methyl)propyl;
Compound 33: $R_1$ is 3-pentyl, $R_4$ is cyclopropyl;
Compound 34: $R_1$ is (R)-1-phenyl-2-propyl, $R_4$ is ethyl.

A preferred subgroup within the subclass shown by General Formula 8 comprise compounds in which the 5'-carboxamido group is ethyl substituted. With reference to General Formula 8, specific examples of compounds of this subgroup are:

Compound 17: $R_1$ is 3-pentyl, $R_4$ is ethyl;
Compound 18: $R_1$ is cyclohexyl, $R_4$ is ethyl;
Compound 19: $R_1$ is (S)-1-phenyl-2-butyl, $R_4$ is ethyl;
Compound 20: $R_1$ is 4-methoxy-phenyl, $R_4$ is ethyl;
Compound 21: $R_1$ is 2-(3,4,5-trimethoxyphenyl)ethyl, $R_4$ is ethyl;
Compound 22: $R_1$ is 3-phenylpropyl, $R_4$ is ethyl;
Compound 23: $R_1$ is (R)-n-phenylethyl, $R_4$ is ethyl;
Compound 24: $R_1$ is 2-(2-pyridyl)ethyl, $R_4$ is ethyl;
Compound 25: $R_1$ is (2-chlorophenyl)methyl, $R_4$ is ethyl;
Compound 26: $R_1$ is (2-thienyl)methyl, $R_4$ is ethyl;
Compound 34: $R_1$ is (R)-1-phenyl-2-propyl, $R_4$ is ethyl.

Another preferred subclass of the cardiovascularly active or anti-hypertensive compounds of the present invention is shown by General Formula 9, where the substituents $R_1$, $R_2$ and $R_3$ signify the same groups as in the compounds of General Formula 8. The 5'-carboxamido substituent groups comprise, in this subclass of compounds, aralkyl having 1 to 4 carbons in the alkyl chain, unsubstituted or substituted in the aryl nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups; heteroarylmethyl having 1 to 4 carbons in the alkyl chain; and heteroarylmethyl having 1 to 4 carbons in the alkyl chain, unsubstituted or substituted in the heteroaryl nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups. Thus,
in the structure symbolized by General Formula 9, n is an integer having the values of 1 to 4, and Q is an aromatic nucleus, or aromatic heterocycle, and Z is one or more H, hydroxy, halogen, lower alkoxy or lower alkyl.

Specific examples of compounds of the subclass of General Formula 9 are:

**Compound 35:** \( R_1 \) is 3-pentyl and the 5'-carboxamido substituent is phenylmethyl;

**Compound 36:** \( R_1 \) is 3-pentyl and the 5'-carboxamido substituent is 2-methoxyphenylmethyl;

**Compound 37:** \( R_1 \) is 3-pentyl and the 5'-carboxamido substituent is 2-thienylmethyl;

**Compound 38:** \( R_1 \) is 3-pentyl and the 5'-carboxamido substituent is 2-phenylethyl.

(Compounds 17 through 34)

GENERAL FORMULA 7

GENERAL FORMULA 8
Yet another subclass of the compounds of the present invention is shown in General Formula 10. In this subclass of compounds, the N-6 amino group of the purine moiety is substituted with a 3-pentyl group, and the \( R_1 \) substituent of the 5'-carboxamido group is straight chain lower alkyl having 1-4 carbon atoms; hydroxy, lower alkoxy or halogen substituted straight chain lower alkyl having 1-4 carbon atoms; cyclopropyl; secondary alkyl having 3-6 carbon atoms; hydroxy, lower alkoxy or halogen substituted secondary alkyl having 3-6 carbon atoms; alkenyl having 3 to 6 carbon atoms; aralkyl having 1 to 4 carbons in the alkyl chain; aralkyl having 1 to 4 carbons in the alkyl chain and substituted in the aryl nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups; heteroarylationkyl having 1 to 4 carbons in the alkyl chain; and heteroarylationkyl having 1 to 4 carbons in the alkyl chain and substituted in the heteroaryl nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups. The second substituent on the 5'-carboxamido nitrogen, \( R_4 \), is hydrogen, or straight chain lower alkyl having 1 to 4 carbons. The \( R_2 \) and \( R_3 \) substituents on the hydroxykyl groups.
of the ribofuranose moiety are the same as described above in connection with the compounds of General Formulae 7, 8, and 9.

Specific examples of compounds of the subclass of General Formula 10, where the \( R_2 \) and \( R_3 \) substituents are hydrogen, are:

- **Compound 17**: \( R_1 \) is ethyl, \( R_4 \) is H;
- **Compound 28**: \( R_1 \) is methyl, \( R_4 \) is H;
- **Compound 29**: \( R_1 \) is isopropyl, \( R_4 \) is H;
- **Compound 30**: \( R_1 \) is 3-pentyl, \( R_4 \) is H;
- **Compound 31**: \( R_1 \) is allyl, \( R_4 \) is H;
- **Compound 32**: \( R_1 \) is (2-methyl)propyl, \( R_4 \) is H;
- **Compound 33**: \( R_1 \) is cyclopropyl, \( R_4 \) is H;
- **Compound 35**: \( R_1 \) is phenylmethyl, \( R_4 \) is H;
- **Compound 36**: \( R_1 \) is 2-methoxyphenylmethyl, \( R_4 \) is H;
- **Compound 37**: \( R_1 \) is 2-thienylmethyl, \( R_4 \) is H;
- **Compound 38**: \( R_1 \) is 2-phenylethyl, \( R_4 \) is H;
- **Compound 39**: \( R_1 \) is methyl, \( R_4 \) is methyl;
- **Compound 40**: \( R_1 \) is n-butyl, \( R_4 \) is methyl;
- **Compound 41**: \( R_1 \) is ethyl, \( R_4 \) is ethyl.

\[
\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3
\]

\[
\text{NH}
\]

\[
\text{R}_4
\]

\[
\text{R}_1\text{-N-C}==\text{O}
\]

\[
\text{O}
\]

\[
\text{O}
\]

\[
\text{R}_2\quad \text{R}_3
\]

(Compounds 17, 28-33, 35-41)

**GENERAL FORMULA 10**
The physical characteristics and biological activity of specific examples of the compounds of the present invention are noted below together with certain biological activity data. The tests showing the biological activity of the compounds of the present invention are discussed after description of the specific examples.

**SPECIFIC EXAMPLES**

**Ethyl N^6-(3-pentyl)adenosine-5'-uronamide** (Compound 17), mp 176-177; uv λ max(ε) 269nm (18.1X10^3) at pH 7. Anal. Calculated for C_{17}H_{26}N_{6}O_{4} (378.44): C, 53.96; H, 6.93; N, 22.21. Found: C, 53.82; H, 6.95; N, 22.17. Molar potency ratio (mpr) 3.3 ± 0.25; anti-hypertensive activity at 0.05mg/kg (22,20,22).

**Ethyl N^6-cyclohexyladenosine-5'-uronamide** (Compound 18), mp 133-135; uv λ max(ε) 270 (18.8X10^3) at pH 7. Anal. Calculated for C_{18}H_{26}N_{6}O_{4} (382.38): C, 55.37; H, 6.71; N, 21.52. Found: C, 55.34; H, 6.86; N, 21.42. Molar potency ratio (mpr) 1.5 ± 0.24; anti-hypertensive activity at 0.1mg/kg (13,17,15).

**Ethyl N^6-(S)-1-phenyl-2-butyladenosine-5'-uronamide** (Compound 19), mp 177-179; uv λ max(ε) 270nm (19.2X10^3) at pH 7; α_D^25 = +27; c=1 in 95% EtOH. Anal. Calculated for C_{22}H_{28}N_{6}O_{4} (440.51): C, 59.99; H, 6.41; N, 19.08. Found: C, 59.89; H, 6.37; N, 19.06. Anti-hypertensive activity at 0.1mg/kg (12,14,12).

**Ethyl N^6-4-methoxyphenyladenosine-5'-uronamide** (Compound 20), mp 189-190; uv λ max(ε) 287nm (19.4X10^3) at pH 7; Anal. Calculated for C_{19}H_{22}N_{6}O_{4} (414.42): C, 55.07; H, 5.35; N, 20.28. Found: C, 55.16; H, 5.45; N, 20.23. Anti-hypertensive activity at 10mg/kg (40,47,52).

**Ethyl N^6-2-(3,4,5-trimethoxyphenyl)ethyladenosine-5'-uronamide** (Compound 21), mp 154-155; uv λ max(ε) 270.5nm (15.7X10^3) at pH 7; Anal. Calculated for C_{23}H_{30}N_{6}O_{7} (502.53): C, 54.97; H, 6.02; N, 16.72. Found: C, 55.14; H, 6.13; N, 16.71. Anti-hypertensive activity at 10mg/kg (18,0,8).
Ethyl N^2-3-phenylpropyladenosine-5'-uronamide (Compound 22), mp 153-156; uv \( \lambda_{\max} (\varepsilon) \) 268nm(17.6X10^3) at pH 7; Anal. Calculated for C\(_{21}\)H\(_{26}\)N\(_6\)O\(_4\) (426.48): C, 59.14; H, 6.15; N, 19.71. Found: C, 59.24; H, 5.91; N, 19.85. Anti-hypertensive activity at 10mg/kg (39.40,39)+.

Ethyl N^6-(R)-1-phenyl-ethyladenosine-5'-uronamide (Compound 23), mp 144-147; uv \( \lambda_{\max} (\varepsilon) \) 270nm(19.9X10^3) at pH 7; Anal. Calculated for C\(_{20}\)H\(_{24}\)N\(_6\)O\(_4\) (412.45): C, 58.24; H, 5.87; N, 20.06. Found: C, 58.26; H, 6.00; N, 20.22. Anti-hypertensive activity at 1mg/kg, no detectable signal of blood pressure.

Ethyl N^6-2-(2-pyridyl)ethyladenosine-5'-uronamide (Compound 24), mp 126-127; uv \( \lambda_{\max} (\varepsilon) \) 268.5nm(20.5X10^3) at pH 7; Anal. Calculated for C\(_{19}\)H\(_{22}\)N\(_7\)O\(_4\) (413.44): C, 55.20; H, 5.61; N, 23.71. Found: C, 55.38; H, 5.82; N, 23.87. Anti-hypertensive activity at 10mg/kg (31,16,21)+.

Ethyl N^6-(2-chlorophenyl)methyladenosine-5'-uronamide (Compound 25), mp 134-136; uv \( \lambda_{\max} (\varepsilon) \) 267.5nm(19.4X10^3) at pH 7; Anal. Calculated for C\(_{19}\)H\(_{21}\)ClN\(_6\)O\(_4\).H\(_2\)O (450.89): C, 50.61; H, 5.14; N, 18.64. Found: C, 50.85; H, 5.04; N, 18.49. Anti-hypertensive activity at 5mg/kg, no detectable signal of blood pressure.

Ethyl N^6-2-thienylmethyladenosine-5'-uronamide (Compound 26), mp 164-165; uv \( \lambda_{\max} (\varepsilon) \) 268.5nm(21.2X10^3) at pH 7. Anal. Calculated for C\(_{17}\)H\(_{20}\)N\(_6\)O\(_4\)S (404.45): C, 50.49; H, 4.98; N, 20.78. Found: C, 50.46; H, 5.21; N, 20.81. Anti-hypertensive activity at 5mg/kg (22,32,29)+.

2-Hydroxyethyl N^6-endo-2-norbornyladenosine-5'-uronamide (Compound 27), mp 132-134; uv \( \lambda_{\max} (\varepsilon) \) 270.5nm(18.5X10^3) at pH 7; Anal. Calculated for C\(_{19}\)H\(_{26}\)N\(_6\)O\(_5\).H\(_2\)O (420.48): C, 54.27; H, 6.71; N, 19.99. Found: C, 54.22; H, 6.66; N, 19.90. Anti-hypertensive activity at 1mg/kg (8,33,36)*.

Methyl N^6-3-pentyladenosine-5'-uronamide (Compound 28), mp 126-128; uv \( \lambda_{\max} (\varepsilon) \) 269nm(18.5X10^3) at pH 7; Anal. Calculated for C\(_{16}\)H\(_{24}\)N\(_6\)O\(_4\) (364.41): C, 52.74; H, 6.64; N, 23.06. Found: C, 52.66; H, 6.70; N, 23.16. Anti-hypertensive activity at 0.5mg/kg (14,17,17).
Isopropyl N^2-3-pentyladenosine-5'-uronamide (Compound 29), mp 191-193; uv λ max(ε) 269nm(18.3X10^3) at pH 7; Anal. Calculated for C_{18}H_{28}N_{6}O_{4} (392.46): C, 55.09; H, 7.19; N, 21.41. Found: C, 55.03; H, 7.37; N, 21.27. Anti-hypertensive activity at 0.5mg/kg (11,24,18).

3-Pentyl N^6-3-pentyladenosine-5'-uronamide (Compound 30), mp 211-212; uv λ max(ε) 270nm(17.9X10^3)k at pH 7; Anal. Calculated for C_{20}H_{32}N_{6}O_{4} (420.52): C, 57.13; H, 7.67; N, 19.98. Found: C, 57.35; H, 7.76; N, 19.81. Anti-hypertensive activity at 20mg/kg (6,21,17).

Allyl-N^6-3-pentyladenosine-5'-uronamide (Compound 31), mp 169-170; uv λ max(ε) 269nm(19.2X10^3) at pH 7; Anal. Calculated for C_{18}H_{26}N_{6}O_{4} (390.45): C, 55.37; H, 6.71; N, 21.52. Found: C, 55.24; H, 6.97; N, 21.31. Anti-hypertensive activity at 2.5mg/kg (15,15,20).

(2-Methyl)-propyl N^6-3-pentyladenosine-5'-uronamide (Compound 32), mp 206-207; uv λ max(ε) 268.5nm(16.9X10^3) at pH 7; Anal. Calculated for C_{19}H_{30}N_{6}O_{4} (406.49): C, 56.14; H, 7.44; N, 20.67. Found: C, 56.22; H, 7.46; N, 20.76. Anti-hypertensive activity at 10mg/kg (15,19,13).

Cyclopropyl N^6-3-pentyladenosine-5'-uronamide (Compound 33), mp 181-183; uv λ max(ε) 269nm(20.0X10^3) at pH 7; Anal. Calculated for C_{18}H_{26}N_{6}O_{4} (390.45): C, 55.37; H, 6.71; N, 21.52. Found: C, 55.11; H, 6.65; N, 21.66. Anti-hypertensive activity at 0.25mg/kg (21,21,28), molar potency ratio (mpr) 2.3.

Ethyl N^6-(R)-1-phenyl-2-propyladenosine-5'-uronamide (Compound 34), mp 157-158; uv λ max(ε) 270nm(18.0X10^3) at pH 7. Ω_D^{25} = -104.5. Anal. Calculated for C_{21}H_{26}N_{6}O_{4} (426.48): C, 59.14; H, 6.15; N, 19.71. Found: C, 58.91; H, 6.10; N, 19.64. Molar potency ratio (mpr) 4.3 ± 0.60.

Phenylmethyl N^6-3-pentyladenosine-5'-uronamide (Compound 35), mp 174-175; uv λ max(ε) 269nm(17.4X10^3) at pH 7; Anal. Calculated for C_{22}H_{28}N_{6}O_{4} (440.51): C, 59.99; H, 6.41; N, 19.08. Found: C, 59.76; H, 6.34; N, 19.07. Anti-hypertensive activity at 5mg/kg (18.26,22).
2-Methoxyphenylmethyl N^6-3-pentyladenosine-5'-uronamide (Compound 36), mp 176-178; uv $\lambda_{\text{max}}(\varepsilon)\text{269.5nm}(18.9\times 10^3)$ at pH 7; Anal. Calculated for C_{23}H_{30}N_6O_5 (470.53): C, 58.71; H, 6.43; N, 17.86. Found: C, 58.53; H, 6.68; N, 17.65. Anti-hypertensive activity at 10mg/kg (12,18,18).

2-Thienylmethyl N^6-3-pentyladenosine-5'-uronamide (Compound 37), mp 160-161; uv $\lambda_{\text{max}}(\varepsilon)\text{237nm}(10.1\times 10^3)$, 269.0nm(17.4\times 10^3) at pH 7; Anal. Calculated for C_{20}H_{26}N_6O_4S (446.53): C, 53.80; H, 5.87; N, 18.82. Found: C, 53.62; H, 6.00; N, 19.00. Anti-hypertensive activity at 5mg/kg (16,16,14).

2-Phenylethyl N^6-3-pentyladenosine-5'-uronamide (Compound 38), mp 203-204; uv $\lambda_{\text{max}}(\varepsilon)\text{268.5nm}(18.8\times 10^3)$ at pH 7; Anal. Calculated for C_{23}H_{30}N_6O_4 (453.53): C, 60.78; H, 6.65; N, 18.49. Found: C, 60.88; H, 6.67; N, 18.50. Anti-hypertensive activity at 40mg/kg (17,13,15).

Dimethyl N^6-3-pentyladenosine-5'-uronamide (Compound 39), mp 168-169; uv $\lambda_{\text{max}}(\varepsilon)\text{269nm}(18.7\times 10^3)$ at pH 7; Anal. Calculated for C_{17}H_{26}N_6O_4 (378.44): C, 53.96; H, 6.93; N, 22.21. Found: C, 53.71; H, 7.11; N, 22.34. Anti-hypertensive activity at 2.5mg/kg (25,23,17).

Methyl, n-butyl N^6-3-pentyladenosine-5'-uronamide (Compound 40), mp 139-141; uv $\lambda_{\text{max}}(\varepsilon)\text{270nm}(19.2\times 10^3)$ at pH 7; Anal. Calculated for C_{20}H_{32}N_6O_4 (420.52): C, 57.13; H, 7.67; N, 19.98. Found: C, 57.26; H, 7.50; N, 19.92. Anti-hypertensive activity at 1mg/kg (31,21,27).

Diethyl N^6-3-pentyladenosine-5'-uronamide (Compound 41), mp 148-150; uv $\lambda_{\text{max}}(\varepsilon)\text{269nm}(19.0\times 10^3)$ at pH 7; Anal. Calculated for C_{17}H_{30}N_6O_4 (406.49): C, 56.14; H, 7.44; N, 20.67. Found: C, 56.42; H, 7.29; N, 20.67. Anti-hypertensive activity at 1mg/kg (10,13,11).

Dimethyl N^6-2-(2-chlorophenyl)-ethyladenosine-5'-uronamide (Compound 42), mp 129-131; uv $\lambda_{\text{max}}(\varepsilon)\text{268.5nm}(20.2\times 10^3)$ at pH 7; Anal. Calculated for C_{20}H_{23}ClN_6O_4 (446.90): C, 53.75; H, 5.19; N, 18.81. Found: C, 53.91; H, 5.37; N, 18.59. Anti-hypertensive activity at 5mg/kg (20,19,13).
PROCESS FOR MAKING THE COMPOUNDS OF THE INVENTION

The compounds of the present invention are prepared in accordance with a novel process of the invention from a suitably blocked derivative of inosine-5'-uronic acid, such as 2',3'-Q-isopropylideneinosine-5'-uronic acid (Compound 43). 2',3'- Q-isopropylideneinosine-5'-uronic acid (Compound 43) is readily obtained from inosine by treatment with acetone to block the 2'-and 3'-hydroxy groups of the ribofuranose moiety, followed by oxidation with chromic acid, in accordance with the published procedure of R. R. Schmidt and H. J. Fritz, Chemische Berichte., 103, 1867 (1970).

2',3'-Q-isopropylideneinosine-5'-uronic acid (Compound 43) is treated in accordance with the process of the present invention, with a suitable inorganic acid halide, such as thionyl chloride, to convert, in the same reaction step, the uronic acid moiety into a uronic acid halide and to introduce a halogen substituent into the 6 position of the purine moiety. In this regard, it is noted that the blocking groups of the 2' and 3' hydroxyl groups must be capable of withstanding the conditions of this reaction, which is advantageously conducted in neutral solvents, such as chloroform, in the presence of dimethylformamide or other dialkylamides. The isopropylidene blocking group serves well for this purpose. Nevertheless, other ketal, acetal or even acyl blocking groups are also suitable. Instead of thionyl chloride, other inorganic acid halides, such as thionyl bromide, may also be used. The product of the just-described first step of the novel reaction sequence is 6-chloro-9-

[2,3-Q-isopropylidene-β-D-ribofuranosyl 5-uronic acid chloride]-9H-purine (Compound 44).

The reaction sequence leading to the compounds of the present invention, using the example of 6-chloro-9-

[2,3-Q-isopropylidene-β-D-ribofuranosyl 5-uronic acid chloride]-9H-purine (Compound 44) as the important intermediate, is shown in Reaction Scheme 1.
GENERAL FORMULA 5

1. GENERAL FORMULA 6

2. AQUEOUS ACID

REACTION SCHEME 1
6-chloro-9-[2,3-O-isopropylidene-D-ribofuranosyl-5-uronic acid chloride]-9H-purine (Compound 44) is preferably not isolated in a pure state. Rather, it is reacted with an amine of the General Formula 4 to displace the halide of the uronic acid moiety and to provide compounds of the General Formula 5, wherein the halogen in the 6 position of the purine nucleus is retained. This selective displacement of the "acid chloride" group is readily conducted in neutral solvents, such as chloroform, preferably at low temperature.

The intermediates of General Formula 5 may be isolated in a purified state. They are subsequently reacted with a nucleophilic amine of General Formula 6 in a suitable solvent, such as ethyl alcohol, to displace the halogen substituent in the 6 position of the purine nucleus. The displacement reaction is preferably conducted in the presence of an acid acceptor, such as triethyl amine. The blocking groups of the 2' and 3' hydroxyls of the ribofuranose moiety are thereafter removed to provide the compounds of the invention (General Formula 3). Removal of the isopropylidene blocking groups is affected, for example, by heating with aqueous hydrochloric acid. These steps are illustrated in the continuation of Reaction Scheme 1. In the formulae shown in Reaction Scheme 1, the definition of the substituent R groups is the same as was given above in connection with the respective general formulae.

Specific examples of the steps of the novel process of the present invention for the preparation of ethyl N^6-(3-pentyl)adenosine-5'-uronamide (Compound 17) and of N,N-dimethyl N^6-(3-pentyl)adenosine-5'-uronamide (Compound 39) are given below.

Actually, the invention of the herein-disclosed novel process is broader than the preparation of the herein-disclosed compounds having beneficial cardiovascular or anti-hypertensive properties. In a broad sense, a multitude of N-6 and 5'-N substituted adenosine 5'-uronamides can be synthesized in accordance with the process of the
present invention. The compounds which are obtainable by the process of the present invention include, in addition to the compounds described above, those compounds wherein the carboxamido nitrogen is mono or di substituted with alkyl, alkenyl, cycloalkyl, aralkyl, and heterocyclyl groups. The carboxamido nitrogen (5'-N) can also be a member of a saturated heterocyclic ring, such as a piperidine or morpholine ring.

An alternative process for the preparation of at least some of the compounds of the present invention comprises the steps of oxidizing N-6 substituted adenosine derivatives which are suitably protected (for example, by isopropylidene or benzyl groups) on the 2' and 3' hydroxyl groups. The step of oxidation is conducted in analogy to the procedure published by R. R. Schmidt and H. J. Fritz in Chemische Berichte, 103, 1867 (1970). The N-6 substituted adenosine derivatives can be obtained by reaction of 6-chloro-9-2-D-ribofuranosyl-9H-purine with the suitable amine.

The resulting uronic acid is then converted to the corresponding acid halide by treatment, for example, with thionyl chloride, in analogy to the process which was described above. The resulting uronic acid halide is thereafter reacted with a primary amine bearing the desired R₄ and R₅ substituents. After removal of the protecting groups from the ribofuranosyl moiety, the compounds of the present invention are obtained.

6-Chloro-9-[2,3-O-isopropylidene-5-ethylcarboxamido-2-D-ribofuranosyl]-9H-purine (Compound 45)

A mixture of 2',3'-O-isopropylideneinosine-5'-uronic acid (6.5 g, 20 mmols), thionyl chloride (4 ml, 53.3 mmols), dry dimethylformamide (1.5 ml, 40 mmols), and dry chloroform (250 ml) was refluxed for 4 to 5 hours. The chloroform was removed in vacuo to give a syrup. The syrup was dissolved in dry chloroform (80 ml), and the resulting solution was added to a mixture of ethylamine (14 ml) and dry chloroform (150 ml) at 10°C. The mixture was stirred for one hour at 10°C, and then poured into cold water (300 ml). The resulting
organic layer was separated and washed in succession with aqueous hydrochloric acid (10%, 2 X 200 ml), aqueous sodium bicarbonate solution (saturated, 1 X 200 ml) and water (1 X 100 ml), and dried over magnesium sulfate. The chloroform solvent was removed in vacuo to give 6.3 g (85% yield) of a slightly yellow solid. The product is usable in the subsequent reaction steps without further purification.

**Ethyl N⁵-(3-pentyl)adenosine-5'-uronamide (Compound 17)**

A mixture of 6-chloro-9-[2,3-O-isopropylidene-5-ethylcarboxamido-β-D-ribofuranosyl]-9H-purine (Compound 45) (6.3 g, 17.1 mmols), 3-pentylamine (1.6 g, 18.4 mmols), triethylamine (4.7 ml, 34 mmols) and absolute ethanol (200 ml) was refluxed for about 48 hours, or until thin layer chromatography indicated complete reaction. The ethanol was removed in vacuo and the product purified by chromatography on a silica gel column eluted with chloroform/aceton 16:1. Evaporation of fractions containing product yielded a syrup which was heated for 1.5 hours with aqueous hydrochloric acid (1.0 N, 100 ml) at 70%. Upon cooling, it yielded Compound 17 as white crystals. Recrystallization from ethanol yielded white needles (4.5 g, 70% yield). The physical characteristics and analytical data of Compound 17 were described above.

**Dimethyl N⁵-(3-pentyl)adenosine-5'-uronamide (Compound 39) from 2',3'-O-isopropylideneinosine-5'-uronic acid (Compound 43)**

A mixture of 2',3'-O-isopropylideneinosine-5'-uronic acid (5.0 g; 15.5 mmols) thionyl chloride (2.5 ml; 33.3 mmols) dry dimethylformamide (1.25 ml; 18.1 mmols) and dry chloroform (170 ml) was refluxed for 5 hours. The solvents were removed in vacuo to give a syrup. The syrup was dissolved in dry chloroform (50 ml) and the resulting solution was added to a mixture of dimethylamine (20 ml, 302 mmols) and dry chloroform (150 ml) at 0°C. The mixture was stirred for 15 minutes after the addition was complete, and thereafter poured into cold water (300 ml). The organic phase was separated and washed successively with water (1 X
100 ml), 10% aqueous hydrochloric acid solution (2 x 100 ml), saturated aqueous sodium bicarbonate solution, and was thereafter dried with anhydrous magnesium sulfate. The chloroform solvent was removed in vacuo to give a syrup. The syrup was refluxed for 48 hours (or until thin layer chromatography indicated complete reaction) with 3-pentyamine (2.3 ml; 20 mmols), triethylamine (2.8 ml, 20 mmols) and anhydrous ethanol (100 ml). The solvent and volatile reagents were removed in vacuo to give a syrup (blocked nucleoside). The blocked (isopropylidene) nucleoside was purified by C-18 high performance, low pressure liquid chromatography (HPLPLC), methanol-water (70%) being used as the eluent. The solvent was removed in vacuo from the appropriate fractions, to yield a light yellow solid which was thereafter heated at 70°C for 1.5 hours in 2N aqueous hydrochloric acid (100 ml). Cooling and neutralization with solid sodium bicarbonate yielded Compound 39 as a white syrup, which was crystallized from methanol/water to give 4.0 g (68%) of colorless needles. The physical characteristics and analytical data of Compound 39 were described above.

**BIOLOGICAL ACTIVITY AND PHARMACOLOGICAL PROPERTIES**

The cardiovascular and anti-hypertensive activities of the compounds of the present invention were determined in bioassays conducted on dogs and spontaneously hypertensive rats.

More particularly, in one type of assay in which the activity of the compounds of the present invention was determined, the compounds to be tested are infused intracoronarily into either open-chest anesthetized or conscious dogs. Adenosine has a demonstrable coronary dilator effect under these conditions. The concentration of the test compound in coronary plasma which causes half-maximal vasodilation is designated ED-50.

More specifically, ED-50 is determined in the following manner. Late diastolic coronary conductance (LDCC) of the experimental dog is monitored through suitable
instrumentation. Late diastolic coronary conductance is measured at maximum coronary vasodilation (peak reactive hyperemia), and is designated $\text{LDCC}_{\text{max}}^\text{a}$. Late diastolic coronary conductance is also measured at basal coronary vasodilation, and is designated $\text{LDCC}_0$.

The difference between instantaneously measured late diastolic coronary conductance ($\text{LDCC}$) and basal late diastolic coronary conductance ($\text{LDCC}_0$) is expressed as a fraction of the difference between maximum late diastolic coronary conductance ($\text{LDCC}_{\text{max}}$) and basal late diastolic coronary conductance ($\text{LDCC}_0$). Thus, $\Delta \text{LDCC}$ is defined by Equation I.

$$\Delta \text{LDCC} = \frac{\text{LDCC} - \text{LDCC}_0}{\text{LDCC}_{\text{max}} - \text{LDCC}_0} \quad \text{EQUATION I}$$

As the concentration of the test compound is varied, and the corresponding $\Delta \text{LDCC}$ is obtained through measurements and the above-summarized calculations, data of an "$\Delta \text{LDCC}$ versus concentration" function or plot are obtained.

$\text{ED-50}$ is derived from these data by log-logit transformation of the "$\Delta \text{LDCC}$ versus concentration" plot; namely by solving the linear regression of logit ($\Delta \text{LDCC}$) on log (concentration) for $\Delta \text{LDCC}=0.5$.

When $\text{ED-50}$ of a tested compound is compared to $\text{ED-50}$ of adenosine in the same dog, as is set forth in EQUATION II, then the resulting molar potency ratio (mpr) provides good comparison of the cardiovascular activity of the tested compound with cardiovascular activity of other compounds in the same or other experimental dogs. Thus, molar potency ratio (mpr) is a useful measure of the cardiovascular vasodilatory effect, and hence of the utility of the tested compounds. The greater the vasodilatory effect of a tested compound, the larger the corresponding molar potency ratio (mpr).

$$\text{MPR} = \frac{\text{ED-50 (adenosine)}}{\text{ED 50 (tested compound)}} \quad \text{EQUATION II}$$
For a more detailed description of the bioassay used for determining molar potency ratios, reference is made to an article written by Olsson et al., and titled "Coronary Vasoreactivity of Adenosine in the Conscious Dog", Circulation Research, 45, 468 (1979).

Molar potency ratios of the specific examples of the compounds of the present invention are listed above next to the detailed description of the specific compounds. These data demonstrate that the compounds are cardiovascularly active.

In another assay for the anti-hypertensive activity of the compounds of the invention, blood pressure of unanesthetized, unheated spontaneously hypertensive rats (SHR) is measured indirectly (through a tail cuff) usually at 2, 4, and 6 hours after oral administration of a single dose of the compounds of the invention. Reduction in mean blood pressure by more than ten percent (10%) indicates anti-hypertensive activity. The test itself is well established in the art and need not be described here in further detail.

The data obtained in the hypertensive rat (SHR) assay are indicated next to the description of the compounds. In the data, the percentage reduction of blood pressure in 2, 4, and 6 hours after the single oral dose is indicated in parentheses. A * sign after the data shows that the measured reduction of blood pressure occurred 1, 2, and 3 hours after the oral dose; a + sign indicates that the measured reduction occurred in 1, 2, and 2.5 hours after the oral dose. The data demonstrate the anti-hypertensive activity of the compounds of the invention.

An assay for the affinity of some of the compounds of the present invention for R_a receptors employs a modification of the radioligand displacement method described by Fox and Kurpis in The Journal of Biological Chemistry, Volume 258, pages 6952-55 (1983). Briefly, this method comprises the steps of incubating [3H]NECA and the analogs to be tested, with human placenta membrane particles, a source of R_a
receptors. The particles are then filtered, washed with a buffer to remove unbound ligand, and then the amount of bound radioligand is measured. By varying the concentration of the competing analog, one may estimate an index of binding affinity, IC-50, the concentration of which causes half-maximum displacement of [\( ^3H \)]NECA. Using [\( ^3H \)]NECA in this assay instead of [\( ^3H \)]-2-chloroadenosine is a modification of the original method.

The compounds of the present invention were found to compete weakly, or not at all, with [\( ^3H \)]ethyladenosine-5'-uronamide at \( R_a \) receptor sites of human placenta.

The foregoing indicates that the compounds of the present invention are selective to \( R_a \) receptors of the cardiovascular system. Such selectivity would not be expected on the basis of prevailing prior art theory.

Further advantages of the compounds of the present invention include their inability to undergo phosphorylation in the 5' position, and their stability to acid. Therefore, the therapeutic effect of the compounds of the present invention is unlikely to be eliminated by the action of phosphorylating enzymes, and the compounds are unlikely to be incorporated into DNA or RNA. As is known, incorporation into RNA or DNA is likely to cause teratogenic, mutagenic, or carcinogenic effects.

Moreover, because the compounds of the present invention are stable to acid (they survive heating with 1N aqueous HCl for 1.5 hours at 70°C), they are capable of surviving the acidic conditions prevailing in the stomach. Therefore, they are suitable as drugs for oral administration to humans and animals.

Various modifications of the herein-disclosed invention, in terms of structural modifications of the invented compounds and also in terms of making or using the same, may become readily apparent to those skilled in the art in light of the above disclosure. For example, the compounds of the
present invention may be administered as pharmaceutically acceptable salts.

Inasmuch as the compounds of the present invention are useful as cardiac vasodilators, cardiovascular, and particularly as anti-hypertensive agents in mammals, domestic animals, and humans, various modes of administering the compounds will be apparent to a person having average skill in the art. Such modes of administering the compounds include oral and topical administration, and intravenous infusion. One having average skill in the art may readily prepare suitable formulations for the above-mentioned and other modes of administering the compounds of the invention.

In light of the foregoing, the scope of the present invention should be interpreted solely from the following claims, as such claims are read in light of the disclosure.
WHAT IS CLAIMED IS:

1. Compounds of the formula

\[
\begin{align*}
&\text{R}_1-\text{NH} \\
&\text{N} & \text{N} \\
&\text{R}_5 \\
&\text{R}_4-\text{HNC}=\text{O} \\
&\text{O} & \text{O} \\
&\text{R}_2 & \text{R}_3
\end{align*}
\]

wherein:

\( \text{R}_1 \) represents secondary alkyl; hydroxy, lower alkoxy or halogen substituted secondary alkyl; aralkyl; aralkyl substituted in the aromatic nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups; cycloalkyl; hydroxy, lower alkoxy, lower alkyl or halogen substituted cycloalkyl; para-substituted phenyl; heteroaryl substituted alkyl; heteroaryl substituted alkyl substituted in the heteroaryl nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups; norbornyl, and hydroxy, alkyl or halogen substituted norbornyl groups;

\( \text{R}_2 \) and \( \text{R}_3 \) are hydrogen, pharmacologically acceptable acyl groups, or inorganic acid radicals, and are identical with one another, or are different from one another;

\( \text{R}_4 \) is straight chain lower alkyl having 1-4 carbon atoms; hydroxy, lower alkoxy or halogen substituted straight chain lower alkyl having 1-4 carbon atoms; cyclopropyl;
secondary alkyl having 3-6 carbon atoms; hydroxy, lower alkoxy or halogen substituted secondary alkyl having 3-6 carbon atoms; alkenyl having 3 to 6 carbon atoms; aralkyl having 1 to 4 carbons in the alkyl chain; aralkyl having 1 to 4 carbons in the alkyl chain and substituted in the aryl nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups; heteroarylmethyl having 1 to 4 carbons in the alkyl chain; and heteroarylmethyl having 1 to 4 carbons in the alkyl chain and substituted in the heteroaryl nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups, and

R₅ is hydrogen, or straight chain lower alkyl having 1 to 4 carbons.

2. Compounds of Claim 1 wherein R₂ and R₃ are both hydrogen.

3. Compounds of Claim 1 wherein R₂ and R₃ are both acetyl.

4. Compounds of Claim 1 wherein R₂ and R₃ are both NO₂ groups.

5. Compounds of the formula
wherein:

\( R_1 \) represents secondary alkyl; hydroxy, lower alkoxy or halogen substituted secondary alkyl; aralkyl; aralkyl substituted in the aromatic nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups; cycloalkyl; hydroxy, lower alkoxy, lower alkyl or halogen substituted cycloalkyl; para-substituted phenyl; heteroaryl substituted alkyl; heteroaryl substituted alkyl substituted in the heteroaryl nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups;

\( R_2 \) and \( R_3 \) are hydrogen, pharmacologically acceptable acyl groups, or inorganic acid radicals, and are identical with one another, or are different from one another, and

\( R_4 \) is hydrogen, methyl or ethyl.

6. Compounds of Claim 5 wherein \( R_4 \) is methyl or ethyl.

7. Compounds of Claim 5 wherein \( R_2 \) and \( R_3 \) are hydrogen.

8. Compounds of Claim 5 wherein \( R_1 \) is phenylalkyl; phenylalkyl substituted in the aromatic nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups; pyridylalkyl; pyridylalkyl substituted in the pyridine nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups; thienylalkyl; or thienylalkyl substituted in the thiophene nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups.
9. Compounds of the formula

\[
\begin{align*}
\text{R}_1 - \text{N}-\text{H} \\
\text{N} & \quad \text{N} \\
\text{R}_4 & \quad \text{NH} = \text{O} \\
\text{O} & \quad \text{O} \\
\text{R}_2 & \quad \text{R}_3
\end{align*}
\]

wherein:

- \( \text{R}_1 \) represents secondary alkyl; hydroxy, lower alkoxy or halogen substituted secondary alkyl; aralkyl; aralkyl substituted in the aromatic nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups; cycloalkyl; hydroxy, lower alkoxy, lower alkyl or halogen substituted cycloalkyl; para-substituted phenyl; heteroaryl substituted alkyl; heteroaryl substituted alkyl substituted in the heteroaryl nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups;

- \( \text{R}_2 \) and \( \text{R}_3 \) are hydrogen, pharmacologically acceptable acyl groups, or inorganic acid radicals, and are identical with one another, or are different from one another, and

- \( \text{R}_4 \) represents straight chain lower alkyl having 1-4 carbon atoms; hydroxy, lower alkoxy or halogen substituted straight chain lower alkyl having 1-4 carbon atoms; cyclopropyl; secondary alkyl having 3-6 carbon atoms; hydroxy, lower alkoxy or halogen substituted secondary alkyl having 3-6 carbon atoms; alkenyl having 3 to 6 carbon atoms.
10. Compounds of Claim 9 wherein R₁ is endo-2-norbornyl, R₄ is 2-hydroxyethyl.
11. The compound of Claim 10 wherein R₂ and R₃ are hydrogen.
12. Compounds of Claim 9 wherein R₂ and R₃ are hydrogen.
13. Compounds of the formula

\[
\text{R}_1 - \text{N} - \text{H}
\]

\[
\text{CH}_3\text{CH}_2\text{-NHCO}=\text{O}
\]

wherein:

R₁ represents secondary alkyl; hydroxy, lower alkoxy or halogen substituted secondary alkyl; aralkyl; aralkyl substituted in the aromatic nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups; cycloalkyl; hydroxy, lower alkoxy, lower alkyl or halogen substituted cycloalkyl; para-substituted phenyl; heteroaryl substituted alkyl; heteroaryl substituted alkyl substituted in the heteroaryl nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups, and

R₂ and R₃ are hydrogen, pharmaceutically acceptable acyl groups, or inorganic acid radicals, and are identical with one another, or are different from one another.
14. Compounds of Claim 13 wherein R₁ is cyclohexyl.
15. The compound of Claim 14 wherein R₂ and R₃ are hydrogen.
16. Compounds of Claim 13 wherein R₁ is (S)-1-phenyl-2-butyl.
17. The compound of Claim 16 wherein R₂ and R₃ are hydrogen.
18. Compounds of Claim 13 wherein R₁ is 4-methoxyphenyl.
19. The compound of Claim 18 wherein R₂ and R₃ are hydrogen.
20. Compounds of Claim 13 wherein R₁ is 2-(3,4,5-trimethoxyphenyl)-ethyl.
21. The compound of Claim 20 wherein R₂ and R₃ are hydrogen.
22. Compounds of Claim 13 wherein R₁ is 3-phenylpropyl.
23. The compound of Claim 22 wherein R₂ and R₃ are hydrogen.
24. Compounds of Claim 13 wherein R₁ is (R)-1-phenyl-ethyl.
25. The compound of Claim 24 wherein R₂ and R₃ are hydrogen.
26. Compounds of Claim 13 wherein R₁ is 2-(2-pyridyl)ethyl.
27. The compound of Claim 26 wherein R₂ and R₃ are hydrogen.
28. Compounds of Claim 13 wherein R₁ is (2-chloro-phenyl)-methyl.
29. The compound of Claim 28 wherein R₂ and R₃ are hydrogen.
30. Compounds of Claim 13 wherein R₁ is (2-thienyl)methyl.
31. The compound of Claim 30 wherein R₂ and R₃ are hydrogen.
32. Compounds of Claim 13 wherein R₁ is (R)-1-phenyl-2-propyl.
33. The compound of Claim 32 wherein $R_2$ and $R_3$ are hydrogen.

34. Compounds of the formula:

\[
\begin{align*}
R_1&-\text{NH} \\
\text{N} &= \text{N} \\
\text{N} &= \text{N} \\
\text{N} &= \text{N} \\
\text{N} &= \text{N} \\
Z-\text{Q-}(\text{CH}_2)_n-\text{NHC}=O \\
\text{O} &= \text{O} \\
\text{O} &= \text{O} \\
R_2 &= R_3
\end{align*}
\]

wherein:

- $R_1$ represents secondary alkyl; hydroxy, lower alkoxy or halogen substituted secondary alkyl; aralkyl; aralkyl substituted in the aromatic nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups; cycloalkyl; hydroxy, lower alkoxy, lower alkyl or halogen substituted cycloalkyl; para-substituted phenyl; heteroaryl substituted alkyl; heteroaryl substituted alkyl substituted in the heteroaryl nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups;

- $R_2$ and $R_3$ are hydrogen, pharmacologically acceptable acyl groups, or inorganic acid radicals, and are identical with one another, or are different from one another;

- $n$ is an integer having the values of 1 to 4;

- $Q$ is an aromatic nucleus, or aromatic heterocycle, and
Z is one or more H, hydroxy, halogen, lower alkoxy or lower alkyl.

35. Compounds of Claim 34 wherein \( R_2 \) and \( R_3 \) are hydrogen.

36. Compounds of the formula

\[
\begin{align*}
\text{CH}_3&-\text{CH}_2-\text{CH} & -\text{CH}_2-\text{CH}_3 \\
\text{NH} & & \\
\text{N} & \text{N} & \text{N} \\
\text{N} & & \\
\text{R}_1\text{-N-C=O} & & \\
\text{O} & \text{O} & \\
\text{R}_2 & \text{R}_3 \\
\end{align*}
\]

wherein:

- \( R_1 \) represents straight chain lower alkyl having 1-4 carbon atoms; hydroxy, lower alkoxy or halogen substituted straight chain lower alkyl having 1-4 carbon atoms; cyclopropyl; secondary alkyl having 3-6 carbon atoms; hydroxy, lower alkoxy or halogen substituted secondary alkyl having 3-6 carbon atoms; alkenyl having 3 to 6 carbon atoms; aralkyl having 1 to 4 carbons in the alkyl chain; aralkyl having 1 to 4 carbons in the alkyl chain and substituted in the aryl nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups; heteroaryllalkyl having 1 to 4 carbons in the
alkyl chain; and heteroarylalkyl having 1 to 4 carbons in the alkyl chain and substituted in the heteroaryl nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups;

R₂ and R₃ are hydrogen, pharmacologically acceptable acyl groups, or inorganic acid radicals, and are identical with one another, or are different from one another, and
R₄ is hydrogen, or straight chain lower alkyl having 1 to 4 carbons.

37. Compounds of Claim 36 wherein R₁ is ethyl, R₄ is H.
38. The compound of Claim 37 wherein R₂ and R₃ are hydrogen.
39. Compounds of Claim 36 wherein R₁ is methyl, R₄ is H.
40. The compound of Claim 39 wherein R₂ and R₃ are hydrogen.
41. Compounds of Claim 36 wherein R₁ is isopropyl, R₄ is H.
42. The compound of Claim 41 wherein R₂ and R₃ are hydrogen.
43. Compounds of Claim 36 wherein R₁ is 3-pentyl, R₄ is H.
44. The compound of Claim 43 wherein R₂ and R₃ are hydrogen.
45. Compounds of Claim 36 wherein R₁ is allyl, R₄ is H.
46. The compound of Claim 45 wherein R₂ and R₃ are hydrogen.
47. Compounds of Claim 36 wherein R₁ is (2-methyl)propyl, R₄ is H.
48. The compound of Claim 47 wherein R₂ and R₃ are hydrogen.
49. Compounds of Claim 36 wherein R₁ is cyclopropyl, R₄ is H.
50. The compound of Claim 49 wherein R₂ and R₃ are hydrogen.
51. Compounds of Claim 36 wherein R₁ is phenylmethyl, R₄ is H.
52. The compound of Claim 51 wherein R₂ and R₃ are hydrogen.

53. Compounds of Claim 36 wherein R₁ is 2-methoxyphenylmethyl, R₄ is H.

54. The compound of Claim 53 wherein R₂ and R₃ are hydrogen.

55. Compounds of Claim 36 wherein R₁ is 2-thienylmethyl, R₄ is H.

56. The compound of Claim 55 wherein R₂ and R₃ are hydrogen.

57. Compounds of Claim 36 wherein R₁ is 2-phenylethyl, R₄ is H.

58. The compound of Claim 56 wherein R₂ and R₃ are hydrogen.

59. Compounds of Claim 36 wherein R₁ is methyl, R₄ is methyl.

60. The compound of Claim 59 wherein R₂ and R₃ are hydrogen.

61. Compounds of Claim 36 wherein R₁ is n-butyl, R₄ is methyl.

62. The compound of Claim 61 wherein R₂ and R₃ are hydrogen.

63. Compounds of Claim 36 wherein R₁ is ethyl, R₄ is ethyl.

64. The compound of Claim 63 wherein R₂ and R₃ are hydrogen.
65. Compounds of the formula

wherein:

$R_1$ and $R_2$ are hydrogen, pharmacologically acceptable acyl groups, or inorganic acid radicals, and are identical with one another, or are different from one another.

66. The compound of Claim 65 wherein $R_1$ and $R_2$ are hydrogen.
67. A process for preparing compounds of the formula

\[
\begin{array}{c}
\text{R}_1 - \text{N} - \text{R}_2 \\
\text{N} \\
\text{N} \\
\text{R}_5 \\
\text{R}_5 - \text{NC}=\text{O} \\
\text{O} \\
\text{O} \\
\text{R}_3 \quad \text{R}_4 \\
\end{array}
\]

wherein:

\( \text{R}_1 \) and \( \text{R}_2 \) are hydrogen; alkyl; alkenyl; hydroxy, cycloalkyl, alkoxy or halogen substituted alkyl; aralkyl; substituted aralkyl; cycloalkyl; alkyl, aryl, hydroxy, alkoxy or halogen substituted cycloalkyl; aryl; heterocyclyl; hydroxy, alkyl, alkoxy or halogen substituted aryl; or hydroxy, alkyl, alkoxy or halogen substituted heterocyclyl groups, and are identical with one another, or are different from one another; or the \( \text{R}_1 \) and \( \text{R}_2 \) groups, jointly with the \( N-6 \) substituent of the purine moiety, form a piperidine or morpholine ring;

\( \text{R}_3 \) and \( \text{R}_4 \) are hydrogen, ketal, acetal, acyl groups or inorganic acid radicals and are identical with one another, or are different from one another;
$R_5$ is hydrogen; alkyl; alkenyl; cycloalkyl; aralkyl; heterocyclyl; substituted alkyl, alkenyl, cycloalkyl, aralkyl and heterocyclyl, and

$R_6$ is lower alkyl or lower secondary alkyl;

the process comprising the steps of:

reacting a derivative of inosine-5'-uronic acid which is protected on the 2' and 3' hydroxyl group of the ribofuranose moiety with ketal, acetal, benzyl, acyl groups or with inorganic acid radicals, with an inorganic acid halide, to obtain a uronic acid halide compound of the formula

![Chemical structure](image)

wherein $X$ is a halogen and $R_7$ and $R_8$ are acyl, or benzyl groups, or jointly form an acetal or ketal group, or are inorganic acid radicals;

reacting said uronic acid halide with an amine of the formula $R_5-\text{NH}-R_6$ to obtain a 6-halogeno substituted uronic acid amide of the formula
and subsequently reacting said 6-halogeno substituted uronic acid amide with an amine of the formula \( R_1 R_2 - NH \).

68. The process of Claim 67 wherein \( X \) is chlorine.

69. The process of Claim 68 wherein the inorganic acid halide is thionyl chloride.

70. The process of Claim 69 wherein the step of reacting with thionyl chloride is conducted in the presence of a dialkylamide.

71. The process of Claim 69 wherein the step of reacting with thionyl chloride is conducted in the presence of dimethylformamide.

72. The process of Claim 71 wherein the \( R_7 \) and \( R_8 \) groups form an isopropylidene group.

73. The process of Claim 67 wherein the \( R_7 \) and \( R_8 \) groups form an isopropylidene group.
74. The process of Claim 73 wherein $R_5$ is straight chain lower alkyl having 1-4 carbon atoms; hydroxy, lower alkoxy or halogen substituted straight chain lower alkyl having 1-4 carbon atoms; cyclopropyl; secondary alkyl having 3-6 carbon atoms; hydroxy, lower alkoxy or halogen substituted secondary alkyl having 3-6 carbon atoms; alkenyl having 3 to 6 carbon atoms; aralkyl having 1 to 4 carbons in the alkyl chain; aralkyl having 1 to 4 carbons in the alkyl chain and substituted in the aryl nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups; heteroarylaralkyl having 1 to 4 carbons in the alkyl chain; and heteroarylaralkyl having 1 to 4 carbons in the alkyl chain and substituted in the heteroaryl nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups, and $R_6$ is hydrogen, or straight chain lower alkyl having 1 to 4 carbons.

75. The process of Claim 67 wherein $R_5$ is straight chain lower alkyl having 1-4 carbon atoms; hydroxy, lower alkoxy or halogen substituted straight chain lower alkyl having 1-4 carbon atoms; cyclopropyl; secondary alkyl having 3-6 carbon atoms; hydroxy, lower alkoxy or halogen substituted secondary alkyl having 3-6 carbon atoms; alkenyl having 3 to 6 carbon atoms; aralkyl having 1 to 4 carbons in the alkyl chain; aralkyl having 1 to 4 carbons in the alkyl chain and substituted in the aryl nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups; heteroarylaralkyl having 1 to 4 carbons in the alkyl chain; and heteroarylaralkyl having 1 to 4 carbons in the alkyl chain and substituted in the heteroaryl nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups, and $R_6$ is hydrogen, or straight chain lower alkyl having 1 to 4 carbons.

76. A process of administering to humans or animals of the mammalian species a vasodilator or anti-hypertensive compound in a therapeutically effective dose to achieve a
vasodilatory or anti-hypertensive effect, the compound having the formula

\[
\begin{align*}
R_1 &-\text{NH} \\
N &| \\
N &| \\
N &| \\
O & \\
O & \\
O & \\
R_2 & \quad R_3
\end{align*}
\]

wherein:

- \( R_1 \) represents secondary alkyl; hydroxy, lower alkoxy or halogen substituted secondary alkyl; aralkyl; aralkyl substituted in the aromatic nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups; cycloalkyl; hydroxy, lower alkoxy, lower alkyl or halogen substituted cycloalkyl; para-substituted phenyl; heteroaryl substituted alkyl; heteroaryl substituted alkyl substituted in the heteroaryl nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups; norbornyl, and hydroxy, alkyl or halogen substituted norbornyl groups;
$R_2$ and $R_3$ are hydrogen, pharmacologically acceptable acyl groups, or inorganic acid radicals, and are identical with one another, or are different from one another;

$R_4$ is straight chain lower alkyl having 1-4 carbon atoms; hydroxy, lower alkoxy or halogen substituted straight chain lower alkyl having 1-4 carbon atoms; cyclopropyl; secondary alkyl having 3-6 carbon atoms; hydroxy, lower alkoxy or halogen substituted secondary alkyl having 3-6 carbon atoms; alkenyl having 3 to 6 carbon atoms; aralkyl having 1 to 4 carbons in the alkyl chain; aralkyl having 1 to 4 carbons in the alkyl chain and substituted in the aryl nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups; heteroarylalkyl having 1 to 4 carbons in the alkyl chain; and heteroarylalkyl having 1 to 4 carbons in the alkyl chain and substituted in the heteroaryl nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups, and

$R_5$ is hydrogen, or straight chain lower alkyl having 1 to 4 carbons.

77. The process of Claim 76 wherein in the formula of the administered compounds $R_2$ and $R_3$ are hydrogen.

78. The process of Claim 76 wherein in the formula of the administered compound $R_4$ is ethyl and $R_5$ is hydrogen.

79. The process of Claim 76 wherein in the formula of the administered compound $R_1$ is 3-pentyl.

80. The process of Claim 79 wherein in the formula of the administered compound $R_2$ and $R_3$ are hydrogen.

81. The process of Claim 76 wherein the compound is administered in the form of a pharmaceutically acceptable salt.
INTERNATIONAL SEARCH REPORT

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC*: C 07 H 19/16; A 61 K 31/70

II. FIELDS SEARCHED

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Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched

III. DOCUMENTS CONSIDERED TO BE RELEVANT*

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* Special categories of cited documents: 10
  "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
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  "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
  "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.
  "A" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search 21st August 1985

Date of Mailing of this International Search Report 20 SEP. 1985

International Searching Authority
EUROPEAN PATENT OFFICE

Signature of Authorized Officer
G.L.M. Krudenberg
### III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

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Form PCT ISA 210 (extra sheet) (January 1985)
### OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. **Claim numbers 7,8,9** because they relate to subject matter not required to be searched by this Authority, namely:

   **PCT Rule 39.1(iv):** Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. **Claim numbers** because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. **Claim numbers** because they are dependent claims and are not drafted in accordance with the second and third sentences of **PCT Rule 6.4(a).**

### OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This International Searching Authority found multiple inventions in this international application as follows:

1. **As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.**

2. **As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:**

3. **No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:**

4. **As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.**

   **Remark on Protest:**
   - [ ] The additional search fees were accompanied by applicant’s protest.
   - [ ] No protest accompanied the payment of additional search fees.

*Form PCT/ISA/210 (supplemental sheet (2)) (January 1985)*
This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDF file on 10/09/85.

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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