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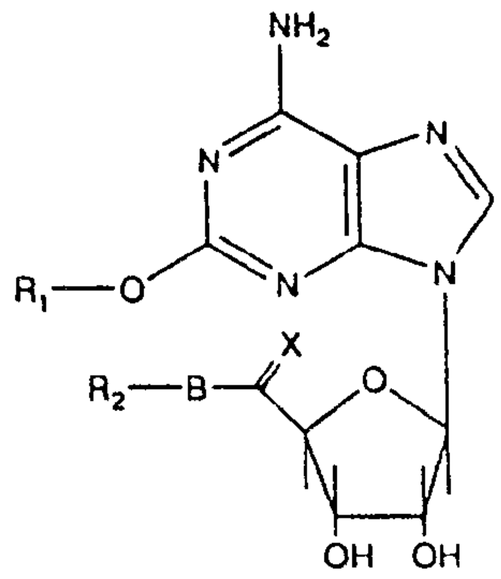
(54) Titre : DERIVES DE 2-ARALKOXY ET DE 2-ALKOXYADENOSINE COMME VASODILATATEURS CORONAIRES ET AGENTS ANTIHYPERTENSEURS

(54) Title: 2-ARALKOXY AND 2-ALKOXY ADENOSINE DERIVATIVES AS CORONARY VASODILATORS AND ANTIHYPERTENSIVE AGENTS



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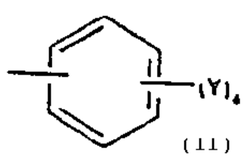

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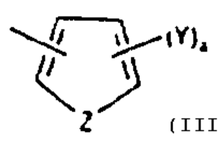

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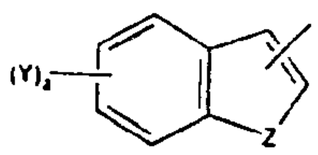

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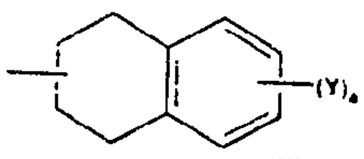

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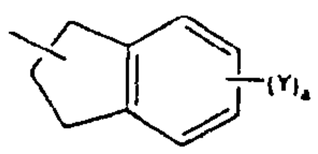

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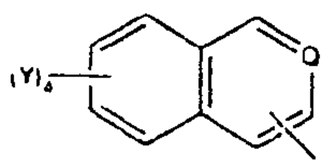

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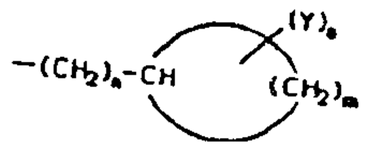

(VIII)

(57) Abrégé/Abstract:
Compounds are disclosed having the formula: (see formula I) wherein R_1 is selected from the group, consisting of branched, straight-chained or cyclic hydrocarbyl radicals, having from one to six carbon atoms, and radicals represented by the general

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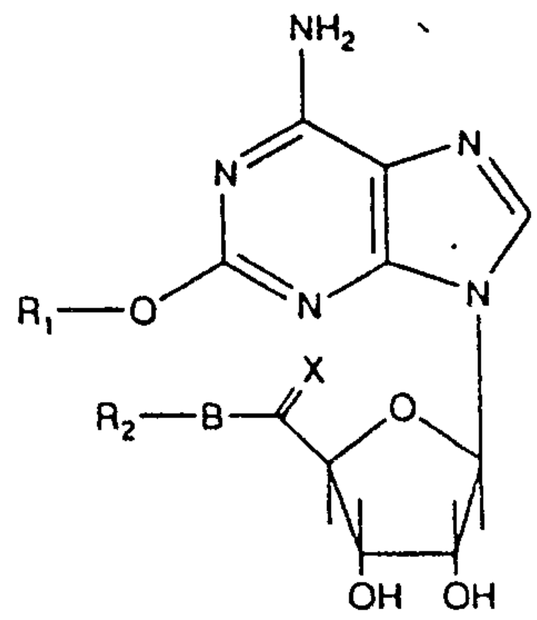
(57) Abrégé(suite)/Abstract(continued):
formulae: (see formulae II to (VIII) wherein Y is selected from the group consisting of lower alkyl, lower alkoxy, carboxy-lower alkyl and halogen; Z is oxygen, sulfur or -NH, Q is -CH or nitrogen; a is zero or an integer of from one to three; n is zero or an integer of from one to three; and m is an integer of from three to six; and wherein, when R_1 is a hydrocarbyl radical, it may be substituted with one or two radicals represented by the above general formula or substituted with $-OR_3$, wherein R_3 is hydrogen or lower alkyl, having from one to ten carbon atoms; R_2 is selected from the group consisting of hydrogen and straight chain, branched and cyclic hydrocarbyl radicals having from one to four carbon atoms, and optionally substituted with a hydroxyl radical; and wherein X is two hydrogen atoms or oxygen and B is selected from oxygen and nitrogen, and pharmaceutically acceptable salts thereof, with the proviso that when X is two hydrogen atoms, B is oxygen, and with the further proviso that when R_3 is present or R_1 is a branched or straight-chained hydrocarbyl radical, then R_1 must be substituted with one of the above radicals, and with the still further proviso that when B is oxygen, then R_1 cannot be a phenyl or a substituted phenyl radical. Pharmaceutical preparations using these compounds and a method for inducing an adenosine response mediated by the adenosine A_2 receptor by administering these compounds are also disclosed.

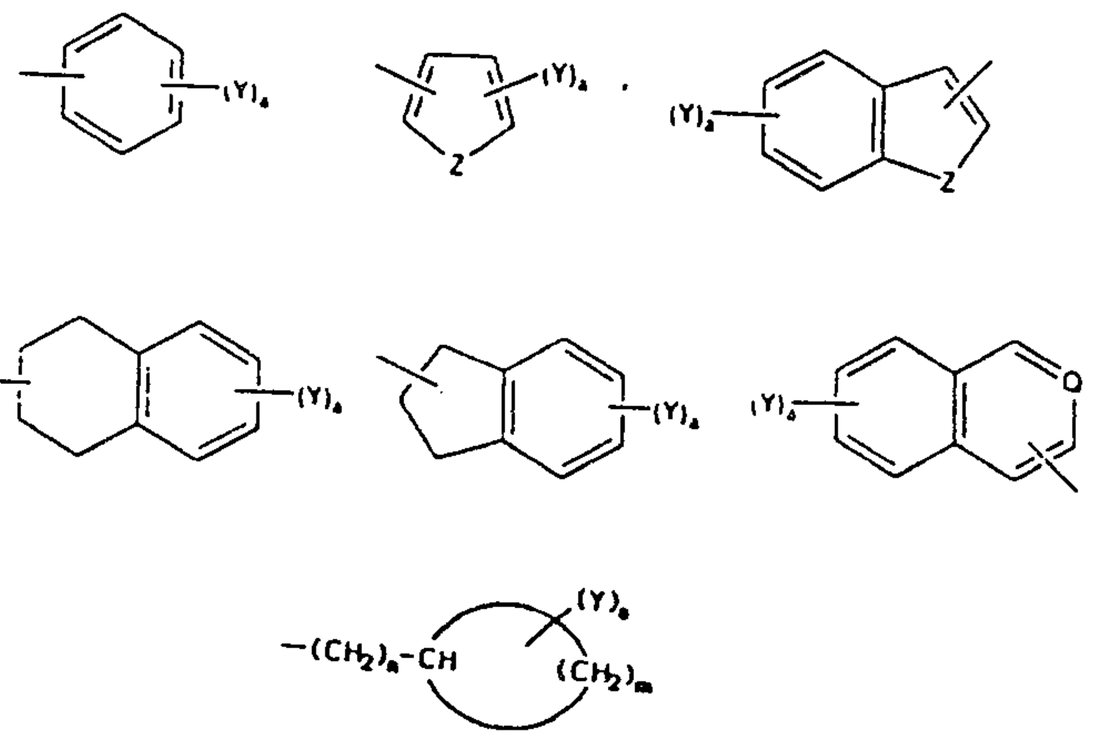
2-ARALKOXY AND 2-ALKOXY ADENOSINE DERIVATIVES AS CORONARY VASODILATORS AND ANTIHYPERTENSIVE AGENTS

ABSTRACT

Compounds are disclosed having the formula:



wherein R_1 is selected from the group, consisting of branched, straight-chained or cyclic hydrocarbyl radicals, having from one to six carbon atoms, and radicals represented by the general formulae:



wherein Y is selected from the group consisting of lower alkyl, lower alkoxy, carboxy-lower alkyl and halogen; Z is oxygen, sulfur or -NH, Q is -CH or nitrogen; a is zero or an integer of from one to three; n is zero or an integer of from one to three; and m is an integer of from three to six; and

wherein, when R_1 is a hydrocarbyl radical, it may be substituted with one or two radicals represented by the above general formula or substituted with $-OR_3$, wherein R_3 is hydrogen or lower alkyl, having from one to ten carbon atoms; R_2 is selected from the group consisting of hydrogen and straight chain, branched and cyclic hydrocarbyl radicals having from one to four carbon atoms, and optionally substituted with a hydroxyl radical; and

wherein X is two hydrogen atoms or oxygen and B is selected from oxygen and nitrogen, and pharmaceutically acceptable salts thereof, with the proviso that when X is two hydrogen atoms, B is oxygen, and with the further proviso that when R_3 is present or R_1 is a branched or straight-chained hydrocarbyl radical, then R_1 must be substituted with one of the above radicals, and with the still further proviso that when B is oxygen, then R_1 cannot be a phenyl or a substituted phenyl radical.

Pharmaceutical preparations using these compounds and a method for inducing an adenosine response mediated by the adenosine A_2 receptor by administering these compounds are also disclosed.

2-ARALKOXY AND 2-ALKOXY ADENOSINE DERIVATIVES AS CORONARY VASODILATORS AND ANTIHYPERTENSIVE AGENTS

Background of the Invention

Field of the Invention

The present invention is directed to certain 2-substituted adenosine 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.

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 publications: Adenosine Receptors: Targets for Future Drugs, by John W. Daly, Journal of Medicinal Chemistry, 25, 197 (1982); Cardiovascular Effects of Nucleoside Analogs, by Herman H. Stein and Pitambar Somani, Annals New York Academy of Sciences, 225, 380 (1979); Coronary Dilatory Action of Adenosine Analogs: a Comparative Study, by G. Raberger, W. Schutz and O. Kraupp. Archives internationales de Pharmacodynamie et de Therpie 230, 140-149 (1977); chapter 6 of the book titled: Regulatory Function of Adenosine, (pages

77-96), R. M. Berne, T. W. Rall and R. Rubio editors, Martinus Nijhoff publishers, The Hague/Boston/London; and Ethyl Adenosine-5'-carboxylate. A Potent Vasoactive Agent in the Dog, by Herman H. Stein, Journal of Medicinal Chemistry, 16 1306 (1973); R.N. prasad *et al.*, "Modification of the 5' Position of Purine Nucleosides. 1. Synthesis and Biological Properties of Alkyl Adenoside-5'-carboxylates," *J. Med. Chem.* 19: 1180-1186 (1976); and R.N. Prasad *et al.*, "Modification of the 5' Position of Purine Nucleosides. 2. Synthesis and Some Cardiovascular Properties of Adenosine-5'-(*N*-substituted)carboxamides," *J. Med. Chem.*23:313-319 (1980).

Adenosine receptors have been subdivided into two subtypes: A_1 receptors, which inhibit adenylate cyclase, and A_2 receptors, which stimulate adenylate cyclase. It is throght that coronary vasodilation is mediated by A_2 recptor activation [see, e.g., Haleen, S., et. al., Life Sci., 36, 127-137 (1985)]. In order to minimize side effects associated with activation of A_1 receptors, it is a goal of pharmaceutical research to identify compounds highly selective for A_2 receptors.

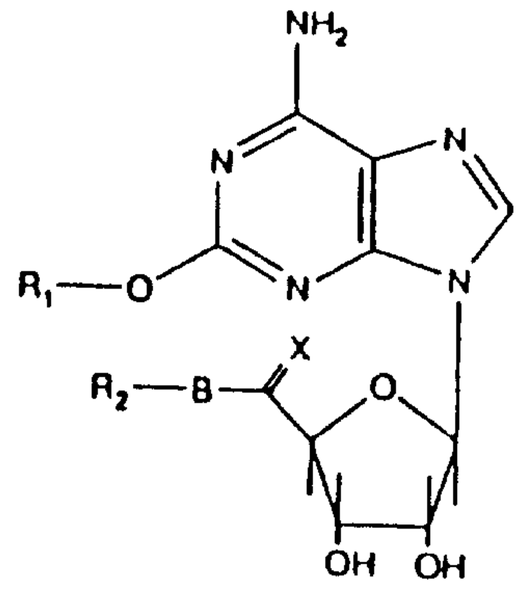
Among a series of related compounds, one early compound claimed to possess coronary vasodilatory activity was 2-phenylaminoadenosine (CV-1808) [see Marumoto, R., et. al., Chem. Pharm. Bull., 23, 759 (1975)]. More recently, a series of N^6-substituted adenosine derivatives were disclosed as having high A_2 affinity and selectivity [see Trivedi, B. K.,

et. al., J. Med. Chem., 31, 271-273 (1988), and Bridges, A., et. al., J. Med. Chem.,31, 1282-1285 (1988)]. Another series of 2,5'-disubstituted adenosine derivatives have been disclosed as A_2 agonists (European Patent Publication EP-277-917-A).

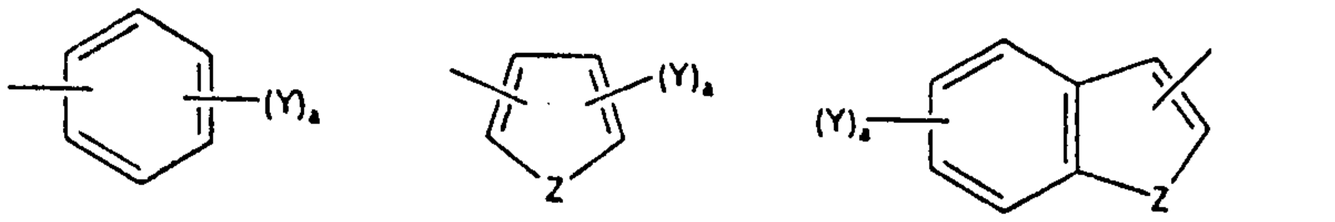
Many of the known adenosine derivatives are less than satisfactory as theraupeutics agents, due to low activity, short duration of effect, toxicity or undesirable side effects. In this light, there is a continuing interest in identifying agents which possess an desired profile of highly selective and potent adenosine A_2 receptor activity with minimal toxicity. The compounds of the present invention constitute a step in this direction.

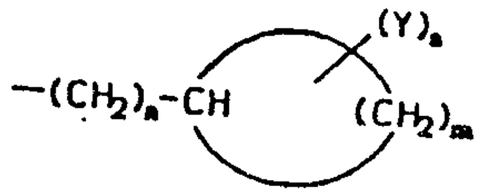
Summary of the Invention

There have now been discovered certain novel compounds having activity as A_2 adenosine receptor agonists and having the structural formula:



wherein R_1 is selected from the group, consisting of branched, straight-chained or cyclic hydrocarbyl radicals, having from one to six carbon atoms, and radicals represented by the general formulae:





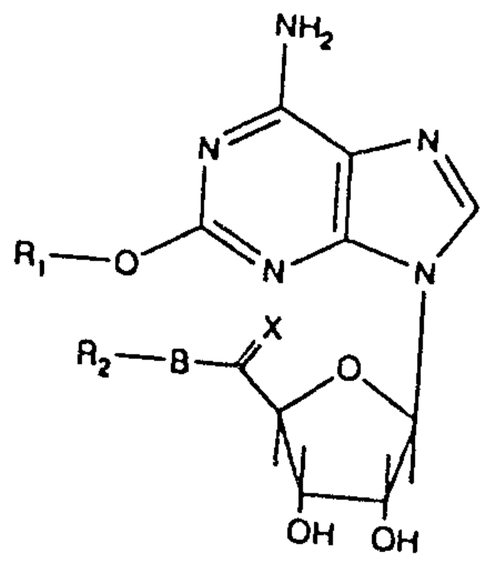
wherein Y is selected from the group consisting of lower alkyl, lower alkoxy, carboxy-lower alkyl and halogen; Z is oxygen, sulfur or -NH, Q is -CH or nitrogen; a is zero or an integer of from one to three; n is zero or an integer of from one to three; and m is an integer of from three to six; and

wherein, when R_1 is a hydrocarbyl radical, it may be substituted with one or two radicals represented by the above general formula or substituted with $-OR_3$, wherein R_3 is hydrogen or lower alkyl, having from one to ten carbon atoms; R_2 is selected from the group consisting of hydrogen and straight chain, branched and cyclic hydrocarbyl radicals having from one to four carbon atoms, and optionally substituted with a hydroxyl radical; and

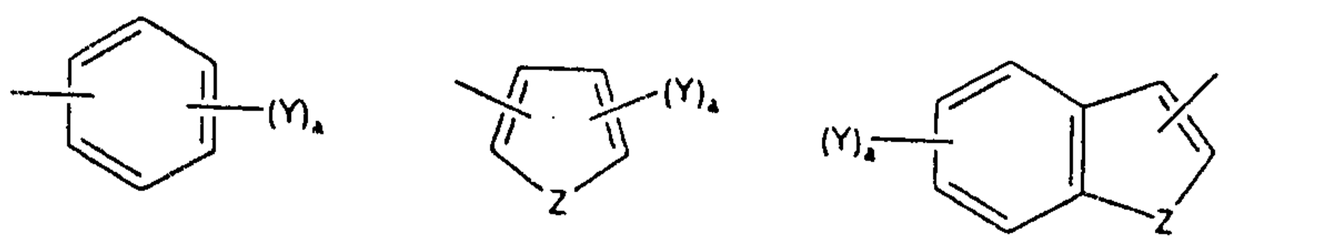
wherein X is two hydrogen atoms or oxygen and B is selected from oxygen and nitrogen, with the proviso that when X is two hydrogen atoms, B is oxygen, and with the further proviso that when R_3 is present or R_1 is a branched or straight-chained hydrocarbyl radical, then R_1 must be substituted with one of the above radicals, and with the still further proviso that when B is oxygen, then R_1 cannot be a phenyl or a substituted phenyl radical.

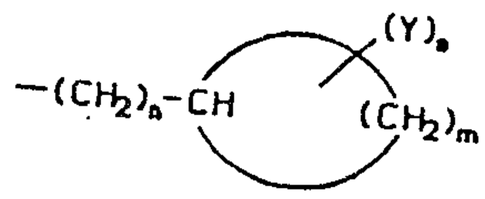
Detailed Description of the Invention

Certain derivatives of adenosine have been found in accordance with the present invention to selectively activate A_2 adenosine receptors and to possess significant cardiovascular and/or vasodilatory anti-hypertensive activity. The compounds used in the present invention are selected from the group of stereoisomers or mixtures thereof of compounds having activity as adenosine A_2 receptor agonists are represented by the formula:



wherein R_1 is selected from the group, consisting of branched, straight-chained or cyclic hydrocarbyl radicals, having from one to six carbon atoms, and radicals represented by the general formulae:





wherein Y is selected from the group consisting of lower alkyl, lower alkoxy, carboxy-lower alkyl and halogen; Z is oxygen, sulfur or -NH; Q is -CH or nitrogen; a is zero or an integer of from one to three; n is zero or an integer of from one to three; and m is an integer of from three to six; and

wherein, when R_1 is a hydrocarbyl radical, it may be substituted with one or two radicals represented by the above general formula or substituted with $-OR_3$, wherein R_3 is hydrogen or lower alkyl, having from one to ten carbon atoms; R_2 is selected from the group consisting of hydrogen and straight chain, branched and cyclic hydrocarbyl radicals having from one to four carbon atoms, and optionally substituted with a hydroxyl radical; and

wherein X is two hydrogen atoms or oxygen and B is selected from oxygen and nitrogen, with the proviso that when X is two hydrogen atoms, B is oxygen, and with the further proviso that when R_3 is present or R_1 is a branched or straight-chained hydrocarbyl radical, then R_1 must be substituted with one of the above radicals, and with the still further proviso that when B is oxygen, then R_1 cannot be a phenyl radical or a substituted phenyl radical.

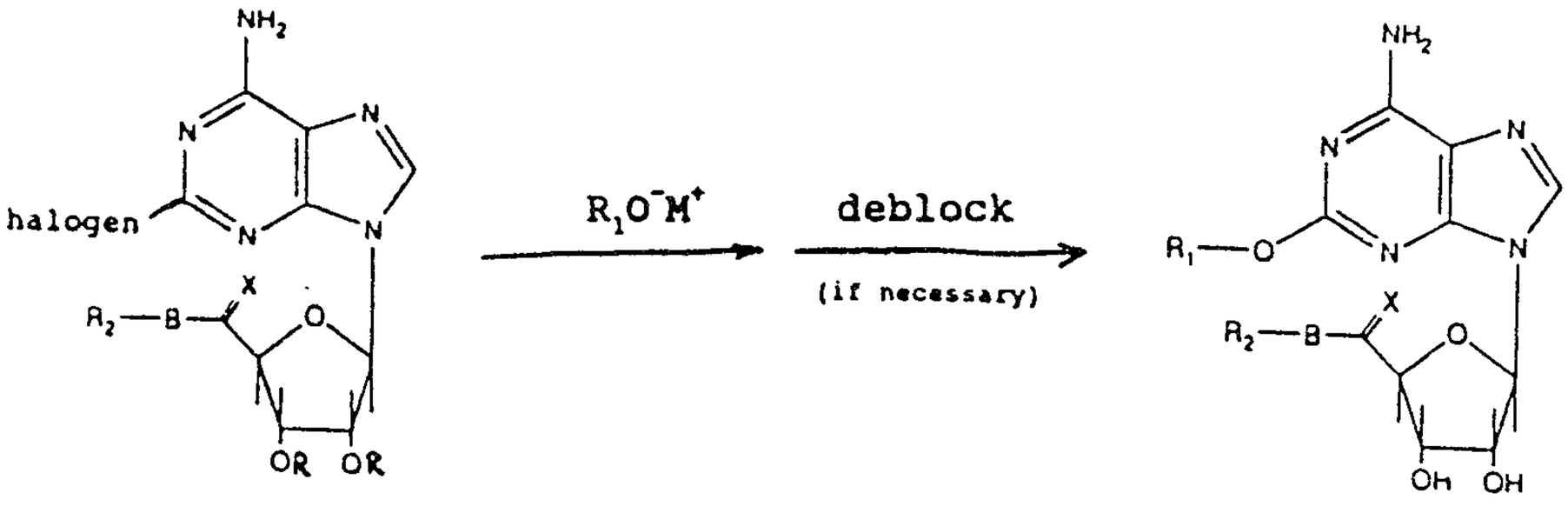
As used herein, the term "lower" as in "lower alkyl" refers to compounds having from 1 to 10 carbon atoms. The preferred lower alkyl radicals have from 1 to 4 carbon atoms. As used herein, the term "halogen" refers to bromide, chloride, fluoride and iodide radicals. Compounds falling within the scope of this invention are as follows:

2-benzyloxyadenosine
2-(2-phenylethoxy)adenosine
2-(5-phenylpentoxy)adenosine
2-cyclopentyloxyadenosine
2-cyclohexyloxyadenosine
2-(2-phenylethoxy)-5'-(N-ethylcarboxamido)adenosine
2-[2-(4-fluorophenyl)ethoxy]-5'-(N-ethylcarboxamido)adenosine
2-(3-phenylpropoxy)adenosine
2-cyclohexylethoxyadenosine
2-(4-phenylbutoxy)adenosine
2-(3,4,5-trimethoxyphenylethoxy)adenosine
2-[2-(2-thienyl)ethoxy]adenosine
2-[2-(3-thienyl)ethoxy]adenosine
2-(4-phenylbutoxy)adenosine
2-(2-pyridylethoxy)adenosine
2-(2-cyclohexylethoxy)adenosine
2-[2-(2-methylphenyl)ethoxy]adenosine
2-[2-(2-methoxyphenyl)ethoxy]adenosine
2-[2-(3-methoxyphenyl)ethoxy]adenosine
2-[2-(4-methoxyphenyl)ethoxy]adenosine
2-[2-(4-fluorophenyl)ethoxy]adenosine
2-[2-(3-indolyl)ethoxy]adenosine
2-[2-(1-naphthyl)ethoxy]adenosine
2-[2-(2-naphthyl)ethoxy]adenosine
2-(2,2-diphenylethoxy)adenosine
2-(4-biphenylethoxy)adenosine
2-(4-aminophenylethoxy)adenosine
2-(4-hydroxyphenylethoxy)adenosine
2-(2-indanyloxy)adenosine
2-2R-(1,2,3,4-tetrahydronaphthyloxy)adenosine

2-2S-(1,2,3,4-tetrahydronaphthyloxy)adenosine
2-(2-phenyl-1-propoxy)adenosine
2-(-2-phenyl,2R-hydroxyethoxy)adenosine
2-(-2-phenyl,2S-hydroxyethoxy)adenosine
2-(-2-phenyl,2R-methoxyethoxy)adenosine
2-(-2-phenyl,2S-methoxyethoxy)adenosine
2-(2R-phenyl,1-butoxy)adenosine
2-(2S-phenyl,1-butoxy)adenosine
2-[(4-carboxyethylphenyl)ethyoxy]adenosine
2-[(2-butylphenyl)ethoxy]adenosine

The invention is further illustrated by the following examples which are illustrative of various aspects of the invention, and are not intended as limiting the scope of the inventions defined by the appended claims.

The invention also encompasses a method of preparation of the subject compounds, pharmaceutical compositions of the subject compounds and a method for inducing an adenosine A_2 response by administering the subject compounds to a patient. The general method of preparation of the above compounds comprises the reaction of a 2-haloadenosine derivative shown below with an alkali metal salt of R_1OH.



R= H, blocking group

In a preferred embodiment, the invention comprises a commercial package comprising a container containing a compound having activity as an A_2 adenosine receptor agonist according to the subject invention and written subject matter which states that the compound is for use in inducing an adenosine response mediated by an adenosine A_2 receptor in an animal. In a further preferred embodiment, the invention comprises a commercial package comprising a container containing a composition which comprises a compound having activity as an A_2 adenosine receptor agonist according to the subject invention in admixture with a pharmaceutically acceptable carrier and written subject matter which states that the composition is for use in inducing an adenosine response mediated by an adenosine A_2 receptor in an animal.

Details of the synthesis, together with modifications and variations specifically tailored for particular compounds, are set out more fully in the specific examples which follow.

Example 1

Preparation of 2-(3-phenyl-1-propoxy)adenosine.

To a cold (10° C) solution of 3-phenyl-1-propanol (6 mL, 44.4 mmoles) and 70 mL of dry tetrahydrofuran was added n-butyllithium 1.6 M in hexanes (25 mL, 40.0 mmoles) via syringe. The above solution was stirred for 15 minutes at room temperature followed by the addition of 2-chloro-2', 3'-O-isopropylideneadenosine (3.0 g, 8.8 mmoles). The mixture was refluxed for 4 days (HPLC showed less than 5% starting material). The solvents were removed in vacuo to give a dark brown syrup. Water (50 mL) was added and the pH adjusted to 7 with 4 N HCl. The aqueous phase was extracted with ethyl acetate (4 x 50 mL) and the organic extracts dried over magnesium sulfate. The drying agent was filtered off and the solvents removed in vacuo to afford a brown syrup. This was purified by flash chromatography on silica gel (40-60μ) using a step gradient of chloroform to 2% methanol in chloroform. The fractions that showed product were collected and the solvents removed in vacuo to give a light brown syrup (blocked nucleoside). The syrup was dissolved in 80 mL of methanol. To this solution was added 10 mL water and 10 mL 98% formic acid and boiled until HPLC showed no blocked nucleoside. Sodium bicarbonate was added until a pH of 7 was achieved. The solvents were removed in vacuo. To the residue was added 2-propanol and the insoluble salts were filtered off. The 2-propanol was removed in vacuo and the product purified by preparative HPLC on a C-18 column, using a linear gradient of 50-70% methanol in water to yield 700 mg (20%) of a colorless solid. The characteristic NMR spectral peaks are: (60 MHz, DMSO-d_6) δ 1.95 (m, 2H), 2.63 (m, 2H),

3.5-5.4 (m, 8H), 4.15 (t, 2H), 5.78 (d, 2H), 7.20 (m, 7H), 8.15 (s, 1H). m.p. 100-102° C.

The above procedure was attempted using sodium hydride in place of n-butyllithium, which gave less than 5% yield by HPLC.

Example 2

Preparation of 2-[2-(4-fluorophenyl)ethoxy]adenosine.

The general procedure of Example 1 was followed, using the following reactants: 4-Fluorophenyl alcohol (4.2 mL, 33.5 mmoles); 1.6 M n-butyllithium (20.0 mL, 31.9 mmoles); 2-chloro-2',3'-O-ethoxymethylideneadenosine (3.0 g, 8.4 mmoles). All conditions were identical with the exception of the hydrolysis and final purification conditions. Hydrolysis was achieved using concentrated acetic acid (5 mL). Final purification was done in the same manner, using a linear gradient of 50-68% methanol to yield 1.3 g (36%) of colorless solid. The characteristic NMR spectral peaks are: (60 MHz, DMSO-d_6) δ 3.12 (t, 2H), 3.55-5.55 (m, 8H), 4.58 (t, 2H), 5.88 (d, 1H), 7.05-7.41 (m, 6H), 8.08 (s, 1H). m.p. 148-150° C.

Example 3

Preparation of 2-Cyclopentyloxyadenosine.

The general procedure of Example 1 was followed, using cyclopentanol in place of 3-phenyl-1-propanol. The characteristic NMR spectral peaks are: (60 MHz, DMSO-d_6) δ 1.80 (s, 8H), 3.50-5.48 (m, 9H), 5.80 (d, 1H), 7.20 (s, 2H), 8.14 (s, 1H). m.p. 147-150° C.

Example 4

Preparation of 2-Cyclohexyloxyadenosine.

The general procedure of Example 1 was followed, using cyclohexanol in place of 3-phenyl-1-propanol. The character-

istic NMR spectral peaks are: (60 MHz, DMSO-d_6) δ 1.00-2.10 (m, 10H), 3.42-5.52 (m, 9H), 5.71 (d, 1H), 7.15 (s, 2H), 8.02 (s, 1H). m.p. 147° C.

Example 5

Preparation of 2-(2-Cyclohexylethoxy)adenosine.

The general procedure of Example 1 was followed, using 2-cyclohexylethanol in place of 3-phenyl-1-propanol. The characteristic NMR spectral peaks are: (60 MHz, DMSO-d_6) δ 0.88-1.95 (m, 13H), 3.50-5.60 (m,8H), 4.64 (t, 2H), 5.89 (d, 1H), 7.20 (s, 2H), 8.10 (s, 1H). m.p. 185-187° C.

Example 6

Preparation of 2-benzyloxyadenosine.

The general procedure of Example 1 was followed, using benzyl alcohol in place of 3-phenyl-1-propanol. The characteristic NMR spectral peaks are: (60 MHz, DMSO-d_6) δ 3.40-5.45 (m, 8H), 5.27 (s, 2H), 5.66 (d, 1H), 7.32 (m, 7H), 8.09 (s, 1H). m.p. 172-175° C.

Example 7

Preparation of 2-(2-phenylethoxy)adenosine.

The general procedure of Example 1 was followed, using phenethyl alcohol in place of 3-phenyl-1-propanol. The characteristic NMR spectral peaks are: (60 MHz, DMSO-d_6) δ 3.00 (t, 2H), 3.45-5.45 (m, 10H), 5.77 (d, 1H), 7.29 (s, 7H), 8.13 (s, 1H). m.p. 95-97° C.

Example 8

Preparation of 2-[2-(2-methoxyphenyl)ethoxy]adenosine.

The general procedure of Example 1 was followed, using 2-(2-methoxyphenyl)ethanol in place of 3-phenyl-1-propanol. The characteristic NMR spectral peaks are: (60 MHz, DMSO-d_6) δ 3.03 (t, 2H), 3.6-5.6 (m, 10H), 3.8 (s, 3H), 5.86 (d, 1H), 6.8-7.52 (m, 6H), 8.17 (s, 1H). m.p. 126-130° C.

Example 9

Preparation of 2-[2-(3-methoxyphenyl)ethoxy]adenosine.

The general procedure of Example 1 was followed, using 2-(3-methoxyphenyl)ethanol in place of 3-phenyl-1-propanol. The characteristic NMR spectral peaks are: (60 MHz, DMSO-d_6) δ 3.0 (t, 2H), 3.6-5.65 (m, 10H), 3.76 (s, 3H), 5.86 (d, 1H), 6.7-7.5 (m, 6H), 8.18 (s, 1H). m.p. 103-105° C.

Example 10

Preparation of 2-[2-(4-methoxyphenyl)ethoxy]adenosine.

The general procedure of Example 1 was followed, using 2-(4-methoxyphenyl)ethanol in place of 3-phenyl-1-propanol. The characteristic NMR spectral peaks are: (60 MHz, DMSO-d_6) δ 2.95 (t, 2H), 3.5-5.52 (m, 8H), 3.74 (s, 3H), 4.4 (t, 2H), 5.86 (d, 1H), 6.86 (d, 2H), 7.25 (d, 2H), 7.33 (2, 2H), 8.2 (s, 1H).

Example 11

Preparation of 2-[2-(2-methylphenyl)ethoxy]adenosine.

The general procedure of Example 1 was followed, using 2-methylphenylethanol in place of 3-phenyl-1-propanol. The characteristic NMR spectral peaks are: (60 MHz, DMSO-d_6) δ 2.33 (s, 3H), 3.04 (t, 2H), 3.5-5.55 (m, 8H), 4.45 (t, 2H), 5.85 (d, 1H), 7.2 (s, 4H), 7.3 (s, 2H), 8.19 (s, 1H). m.p. 166-168° C.

Example 12

Preparation of 2-[2-(3,4,5-trimethoxyphenyl) ethoxy]adenosine.

The general procedure of Example 1 was followed, using 3,4,5-trimethoxyphenylethanol in place of 3-phenyl-1-propanol. The characteristic NMR spectral peaks are: (60 MHz, DMSO-d_6) δ 2.95 (t, 2H), 3.5-5.58 (m, 8H), 4.45 (t, 2H), 5.72 (d, 1H), 6.65 (s, 2H), 7.28 (s, 2H), 8.16 (s, 1H). m.p. 110-112° C.

Example 13

Preparation of 2-[2-(2-thienyl)ethoxy]adenosine.

The general procedure of Example 1 was followed, using 2-(2-thienyl)ethanol in place of 3-phenyl-1-propanol. The characteristic NMR spectral peaks are: (60 MHz, DMSO-d_6) δ 3.19 (t, 2H), 3.5-5.5 (m, 8H), 4.44 (t, 2H), 5.8 (d, 1H), 6.88-7.43 (m, 5H), 8.26 (s, 1H). m.p. 104-106° C.

Example 14

Preparation of 2-[2-(3-thienyl)ethoxy]adenosine.

The general procedure of Example 1 was followed, using 2-(3-thienyl)ethanol in place of 3-phenyl-1-propanol. The characteristic NMR spectral peaks are: (60 MHz, DMSO-d_6) δ 3.1 (t, 2H), 3.3-5.6 (m, 8H), 4.5 (t, 2H), 5.85 (d, 1H), 7.0-7.58 (m, 5H), 8.22 (s, 1H). m.p. 99-102° C.

Example 15

Preparation of 2-[2-(1-naphthyl)ethoxy]adenosine.

The general procedure of Example 1 was followed, using 2-(1-naphthyl)ethanol in place of 3-phenyl-1-propanol. The characteristic NMR spectral peaks are: (60 MHz, DMSO-d_6) δ 3.45-5.5 (m, 10H), 4.5 (t, 3H), 5.84 (d, 1H), 7.42 (s, 2H), 7.35-8.38 (m, 7H), 8.2 (s, 1H). m.p. 125-130° C.

Example 16

Preparation of 2-[2-(3-indolyl)ethoxy]adenosine.

The general procedure of Example 1 was followed, using 2-(3-indolyl)ethanol in place of 3-phenyl-1-propanol. The characteristic NMR spectral peaks are: (60 MHz, DMSO-d_6) δ 3.24 (t, 2H), 3.52-3.58 (m, 8H), 4.54 (t, 2H), 5.88 (d, 1H), 6.9-7.7 (m, 7H), 8.12 (s, 1H), 10.12 (s, 1H). m.p. 138-140° C.

Example 17

Preparation of 2-(2-phenyl-1-propoxy)adenosine.

The general procedure of Example 1 was followed, using 2-phenyl-1-propanol in place of 3-phenyl-1-propanol. The characteristic NMR spectral peaks are: (60 MHz, DMSO-d_6) δ 1.36 (d, 3H), 3.1-5.55 (m, 11H), 5.85 (d, 1H), 7.35 (s, 7H), 8.2 (s, 1H). m.p. 135° C.

Example 18

Preparation of 2-[(2R)-phenyl-1-butoxy]adenosine.

The general procedure of Example 1 was followed, using (2R)-phenyl-1-butanol in place of 3-phenyl-1-propanol. The characteristic NMR spectral peaks are: (60 MHz, DMSO-d_6) δ 0.82 (t, 3H), 1.7 (m, 2H), 3.0 (m, 1H), 3.45-5.5 (m, 8H), 4.4 (d, 2H), 5.82 (d, 1H), 7.32 (s, 6H), 8.16 (s, 1H). m.p. 155° C.

Example 19

Preparation of 2-[(2S)-phenyl-1-butoxy]adenosine.

The general procedure of Example 1 was followed, using (2S)-phenyl-1-butanol in place of 3-phenyl-1-propanol. The characteristic NMR spectral peaks are: (60 MHz, DMSO-d_6) δ 0.8 (t, 3H), 1.73 (m, 2H), 2.95 (m, 1H), 3.6-5.57 (m, 8H), 4.4 (d, 2H), 5.89 (d, 1H), 7.32 (s, 6H), 8.22 (s, 1H). m.p. 108-110° C.

Example 20

Preparation of 2-(4-phenyl-1-butoxy)adenosine.

The general procedure of Example 1 was followed, using 4-phenyl-1-butanol in place of 3-phenyl-1-propanol. The characteristic NMR spectral peaks are: (60 MHz, DMSO-d_6) δ 1.75 (m, 4H), 2.61 (m, 2H), 3.5-5.55 (m, 10H), 5.81 (d, 1H), 7.27 (s, 7H), 8.16 (s, 1H). m.p. 93-96° C.

Example 21

Preparation of 2-(5-phenyl-1-pentoxy)adenosine.

The general procedure of Example 1 was followed, using 5-phenyl-1-pentanol in place of 3-phenyl-1-propanol. The characteristic NMR spectral peaks are: (60 MHz, DMSO-d_6) δ 1.35-2.07 (m, 6H), 2.72 (t, 2H), 3.6-5.58 (m, 8H), 4.33 (t, 2H), 5.88 (d, 1H), 7.23 (s, 7H), 8.1 (s, 1H). m.p. 102-104° C.

Example 22

Preparation of 2-(2-phenyl)ethoxy-5'-N-ethylcarboxamido-adenosine.

To a mixture of 2-phenylethanol (3.14 mL, 26.3 mmoles) in dry tetrahydrofuran (50 mL) was added n-butyllithium (16.4 mL, 26.2 mmoles) dropwise. This mixture was allowed to stir 15 min. at room temperature. The 2-chloro-5'-N-ethylcarboxamidoadenosine (1.5 g, 4.38 mmoles) was added in one portion and the mixture refluxed for 72 hours. Water (50 mL) was added. The precipitate was filtered off and the filtrate extracted with ethyl acetate (4 x 50 mL). The organic phases were dried with magnesium sulfate. The drying agent was removed by filtration and the solvents removed <u>in vacuo</u> to give a foam. Purification on a preparative HPLC C-18 column, using a linear gradient of 50-70% methanol/water gave a colorless solid. The characteristic NMR spectal peaks are: (60 MHz, DMSO-d_6) δ 1.07 (t, 3H), 3.39 (m, 4H), 4.1-4.77 (m, 5H), 5.5-5.78 (m, 2H), 5.9 (d, 1H), 7.32 (s, 5H), 7.46 (s, 2H), 8.2 (s, 1H), 8.9 (t, 1H). m.p. 130-133° C.

Example 23

Preparation of 2-(3-cyclohexyl)propoxyadenosine.

The general procedure of Example 1 was followed, using 3-cyclohexyl-1-propanol in place of 3-phenyl-1-propanol. The characteristic NMR spectral peaks are: (60 MHz, DMSO-d_6) δ 0.7-1.9 (m, 15H), 3.55-5.55 (m, 10H), 5.8 (d, 1H), 7.23 (s, 2H), 8.14 (s, 1H).

Example 24

Preparation of 2-[2-(2-naphthyl)ethoxy]adenosine.

The general procedure of Example 1 was followed, using 2-(2-naphthyl)ethanol in place of 3-phenyl-1-propanol. The characteristic NMR spectral peaks are: (60 MHz, DMSO-d_6) δ 3.3 (t, 2H), 3.42-5.5 (m, 8H), 4.67 (t, 2H), 5.84 (d, 1H), 7.22-8.05 (m, 7H), 7.89 (s, 2H), 8.18 (s, 1H).

Example 25

Assays of the cardiovascular potency of the above compounds at the A_1 receptors of the SA node and at the A_2 receptor of the coronary artery employed perfused hearts from female Sprague-Dawley guinea pigs in an isolated Langendorff heart preparation. An assay consists of an infusion of a spectophotometrically standardized solution of test compound directly into the aortic cannula at rates increasing stepwise every 5 minutes. Collection of the total cardiac effluent during the first half of each infusion period provides a measure of coronary flow (A_2 effect). The concentration of test compound required to produce a half-maximal increase in coronary flow is determined. Registration of the ECG assesses the effect of the test compound on SA node (stimulus to Q interval, A_1 effect). The concentration of test compound required to produce a half-maximal prolongation of stimulus to Q interval is determined. Table I summarizes the resultant data, using adenosine as a reference compound. The ratio of A_1 and A_2 effects of test compounds are calculated to provide the selectivity ratio.

TABLE I

Example	Coronary Blood Flow Increase (A_2) EC_{50} (nM)	SQ Prolongation (A_1) EC_{50} (nM)	Selectivity (A_1/A_2)
Adenosine	49.7	3162	63.6
6	419.3	6310	15
7	2.8	19953	7126
3	91.7	79433	866
4	656.9	100000	152
22	1.3	14962	11509
1	61.3	19953	326
13	3.7	11885	3212
14	3.4	18836	5540
20	9.9	7356	743
15	5.1	8414	1650
17	9.0	53088	5899
12	22.0	47315	2151
5	1.0	8630	8630
11	3.8	25119	6610
9	2.6	16218	6238
18	373.7	18836	50
19	31.4	27384	872
8	32.0	35481	1109
21	6.4	4597	718
2	0.9	25606	29432
16	9.8	14125	1441
10	1.4	19724	14089
23	2.2	3758	1708
24	0.5	11416	22832

This data shows the high degree of potency and selectivity of the subject compounds in increasing coronary blood flow at low concentrations while having comparatively little effect on the SQ prolongation. The ratios calculated show the marked A_2 selectivity of the subject compounds.

It is essential that the compounds herein be capable of binding selectively to A_2 adenosine receptors, e.g., in a human. 2-phenylethoxy-5'-(N-ethylcarboxamido)adenosine and 2-(4-fluorophenyl) ethoxyadenosine 2-[2-(4-methoxyphenyl) ethoxy] adenosine and 2-[2-(2-naphthyl) ethoxy] adenosine are particularly preferred compounds because of the high affinity and selectivity for A_2 adenosine receptors. It is believed that the compounds herein will be useful as cardiac vasodilators in humans and other animals.

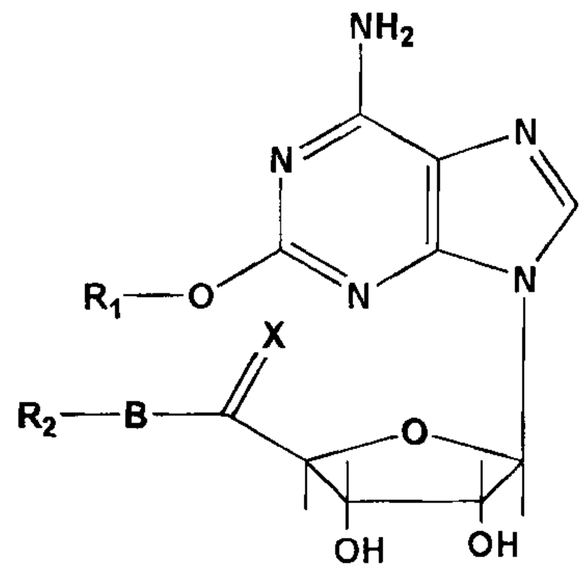
Various modifications of the herein disclosed invention, in terms of structural modifications of the invented compounds and also in terms of making or using the same, may become readily apparent to those skilled in the art in light of the above disclosure. For example, the compounds of the present invention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

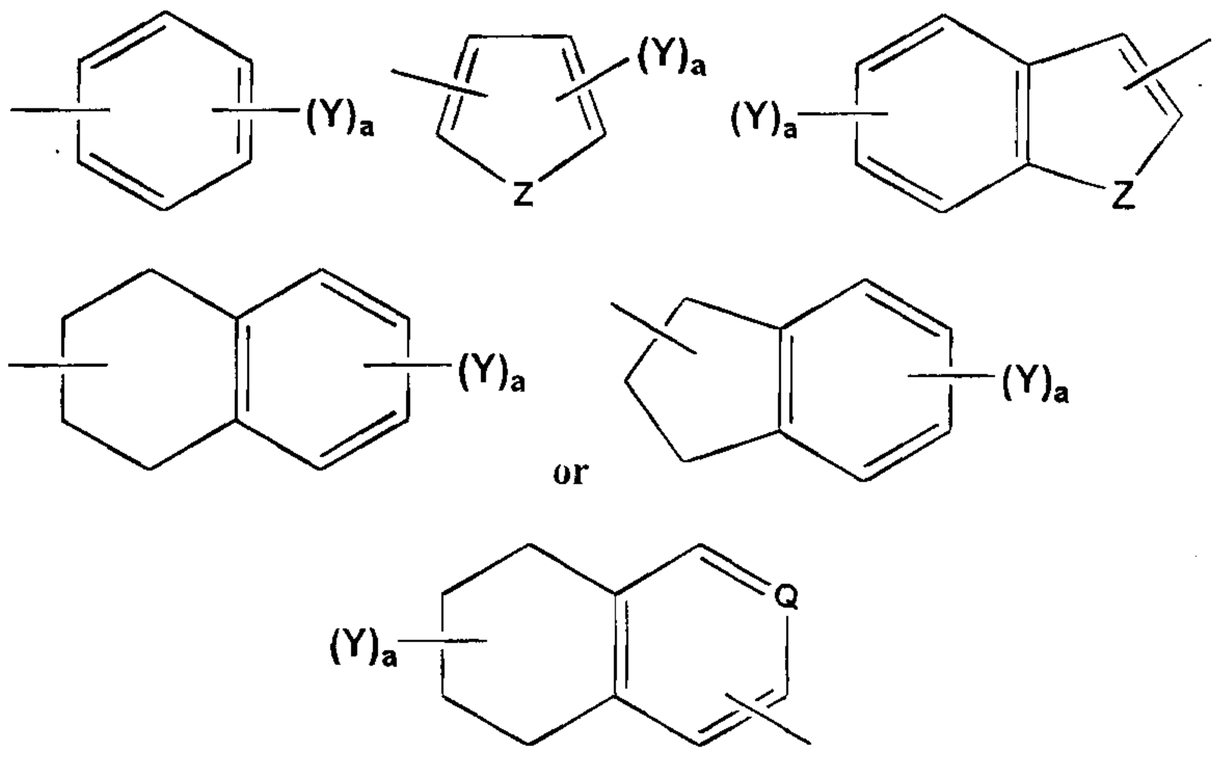
In light of the foregoing, the scope of the present invention should be interpreted solely from the following claims, as such claims are read in light of the disclosure.

We Claim :

1. A compound selected from the group of stereoisomers or mixtures thereof of compounds having the formula:



wherein R_1 is a radical represented by the general formulae:



wherein Y is selected from the group consisting of lower alkyl, lower alkoxy, carboxy-lower alkyl, and halogen; Z is oxygen, sulfur or -NH; Q is -CH or nitrogen; a is zero or an integer from one to three;

or R_1 is a branched- or straight-chain hydrocarbyl radical having from one to six carbon atoms and substituted with one or two radicals represented by the above general formulae;

R_2 is selected from the group consisting of hydrogen and straight, branched or cyclic hydrocarbyl radicals having from 1 to 4 carbon atoms; and

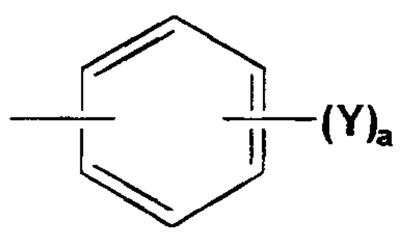
X is two hydrogen atoms or an oxygen; and

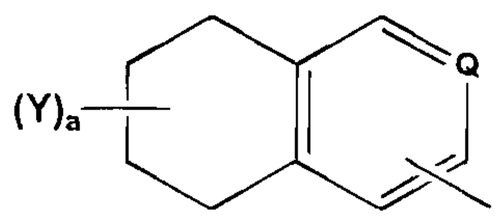
B is selected from the group consisting of oxygen and NH;

with the proviso that when X is two hydrogen atoms, B is oxygen; and

with the further proviso that when B is oxygen, then R_1 cannot be a phenyl or substituted phenyl.

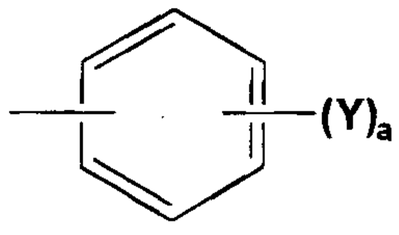
2. A compound of claim 1 wherein R_1 is a radical selected from the group consisting of the following radicals:

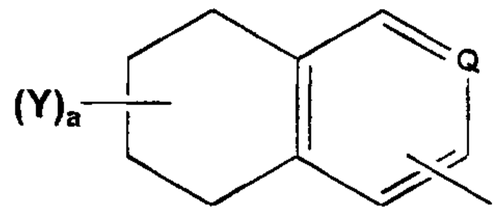




wherein Q is -CH or nitrogen, Y is selected from the group consisting of halogen, lower alkyl and lower alkoxy, and a is an integer of from zero to 3.

3. A compound of claim 1, wherein R_1 is a branched- or straight-chain hydrocarbyl radical having from one to six carbon atoms and substituted with a radical selected from the group consisting of one of the following radicals:





wherein Q is -CH or nitrogen, Y is selected from the group consisting of halogen, lower alkyl and lower alkoxy, and a is an integer of from zero to 3.

4. A compound of claim 3 wherein a is zero.

5. A compound of claim 3 wherein Y is halogen.

6. A compound of claim 3 wherein Q is -CH.

7. A compound of claim 1 wherein R_1 is phenylethyl.

8. A compound of claim 1 wherein R_1 is 4-fluorophenylethyl.

9. A compound of claim 1 wherein R_1 is 4-methoxyphenylethyl.

10. A compound of claim 1 wherein R_1 is 2-(2-naphthyl)ethyl.

11. The compound of claim 1 wherein X is two hydrogen atoms, B is oxygen and R_2 is hydrogen.

12. A compound of claim 1 wherein X is oxygen and B is NH.

13. A compound of claim 12 wherein R_2 is a straight chain alkyl radical.

14. A compound of claim 13 wherein R_2 is ethyl.

15. A compound of claim 13 wherein R_2 is ethyl and R_1 is phenylethyl.

16. 2-(2-phenyl)ethoxyadenosine.

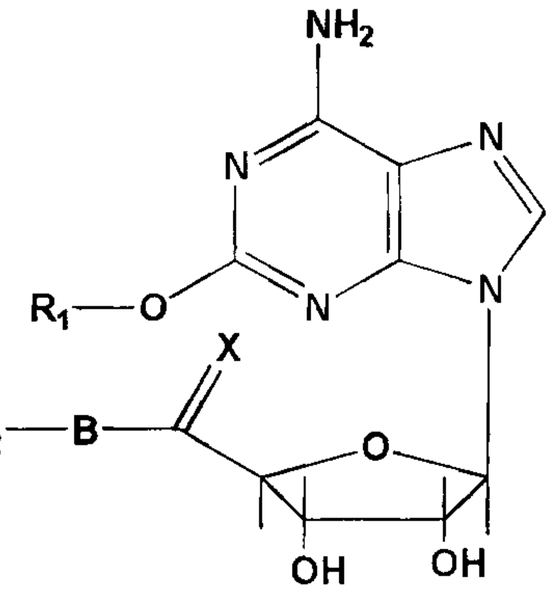
17. 2-(2-phenyl)ethoxy-5'-N-ethylcarboxamidoadenosine.

18. 2-[2-(4-fluorophenyl)ethoxy]adenosine.

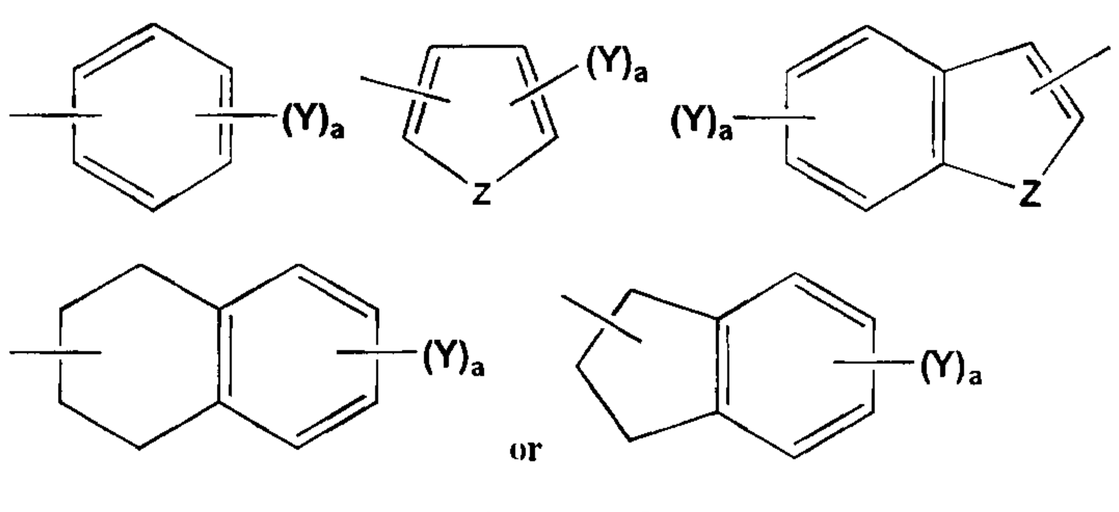
19. 2-[2-(4-methoxyphenyl)ethoxy]adenosine.

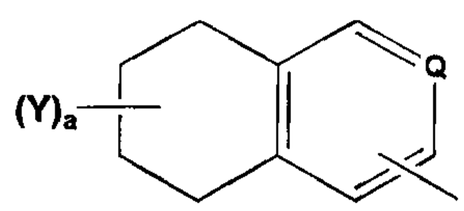
20. 2-[2-(2-naphthyl)ethoxy]adenosine.

21. A pharmaceutical composition, comprising an active ingredient of the formula:



wherein R_1 is a radical represented by the general formulae:





wherein Y is selected from the group consisting of lower alkyl, lower alkoxy, carboxy-lower alkyl, and halogen; Z is oxygen, sulfur or -NH; Q is -CH or nitrogen; a is zero or an integer from one to three;

or R_1 is a branched- or straight-chain hydrocarbyl radical having from one to six carbon atoms and substituted with one or two radicals represented by the above general formulae;

R_2 is selected from the group consisting of hydrogen and straight, branched or cyclic hydrocarbyl radicals having from 1 to 4 carbon atoms; and

X is two hydrogen atoms or an oxygen; and

B is selected from the group consisting of oxygen and NH;

with the proviso that when X is two hydrogen atoms, B is oxygen; and

with the further proviso that when B is oxygen, then R_1 cannot be a phenyl or substituted phenyl;

and a pharmaceutically acceptable carrier.

22. The composition of claim 21, wherein said active ingredient is 2-(2-phenyl)ethoxyadenosine.

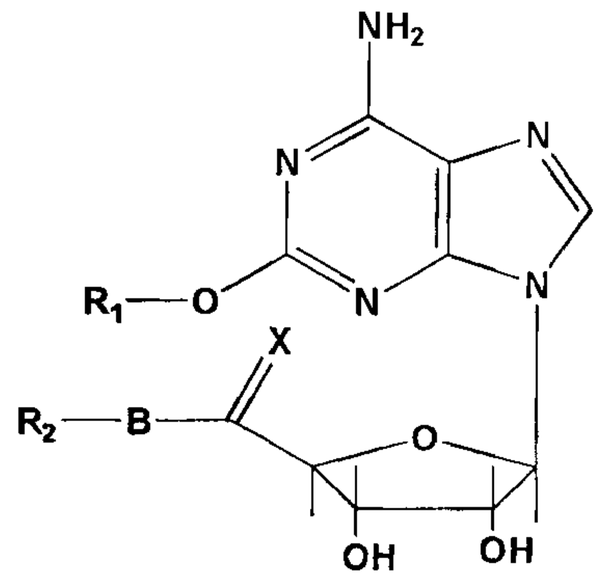
23 .The composition of claim 21, wherein said active ingredient is 2-(2-phenyl)ethoxy-5'-N-ethylcarboxamidoadenosine.

24. The composition of claim 21, wherein said active ingredient is 2-[2-(4-fluorophenyl)ethoxy]adenosine.

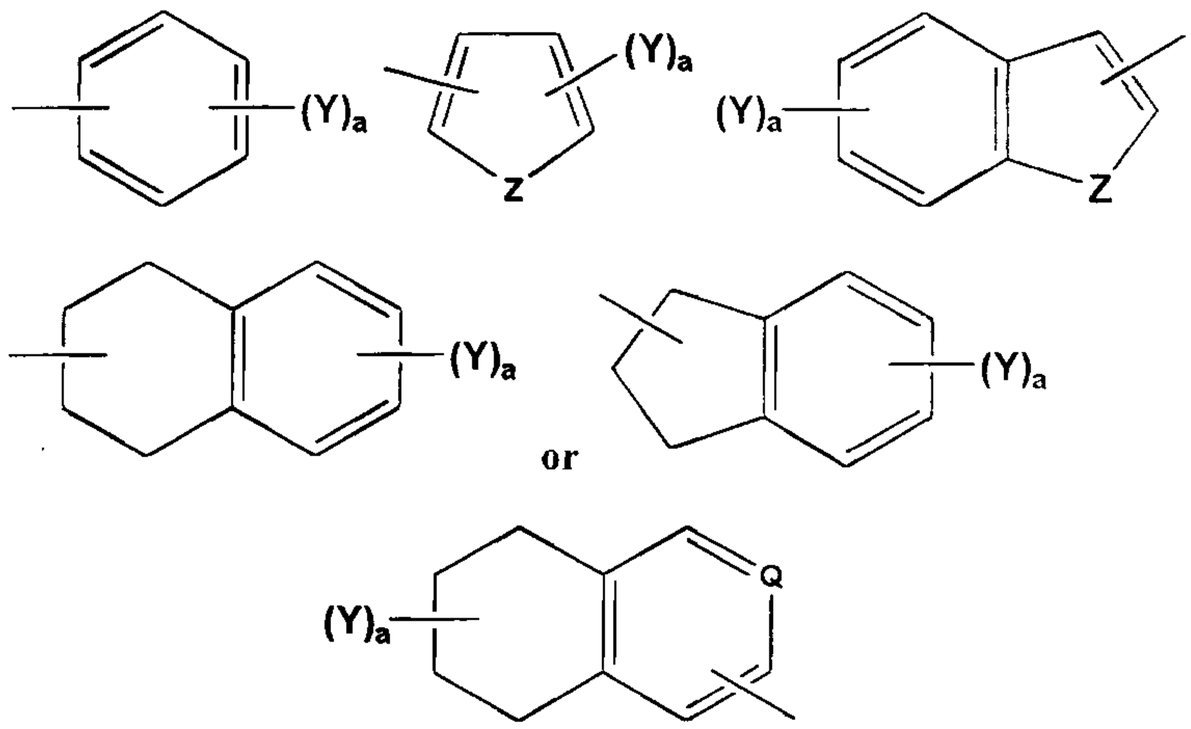
25. The composition of claim 21, wherein said active ingredient is 2-[2-(4-methoxyphenyl)ethoxy]adenosine.

26. The composition of claim 21, wherein said active ingredient is 2-[2-(2-naphthyl)ethoxy]adenosine.

27. For use in inducing an adenosine response mediated by an adenosine A_2 receptor in a human or animal, an effective amount of a compound having the formula:



wherein R_1 is a radical represented by the general formulae:



wherein Y is selected from the group consisting of lower alkyl, lower alkoxy, carboxy-lower alkyl, and halogen; Z is oxygen, sulfur or -NH; Q is -CH or nitrogen; a is zero or an integer from one to three;

or R_1 is a branched- or straight-chain hydrocarbyl radical having from one to six carbon atoms and substituted with one or two radicals represented by the above general formulae;

R_2 is selected from the group consisting of hydrogen and straight, branched or cyclic hydrocarbyl radicals having from 1 to 4 carbon atoms; and

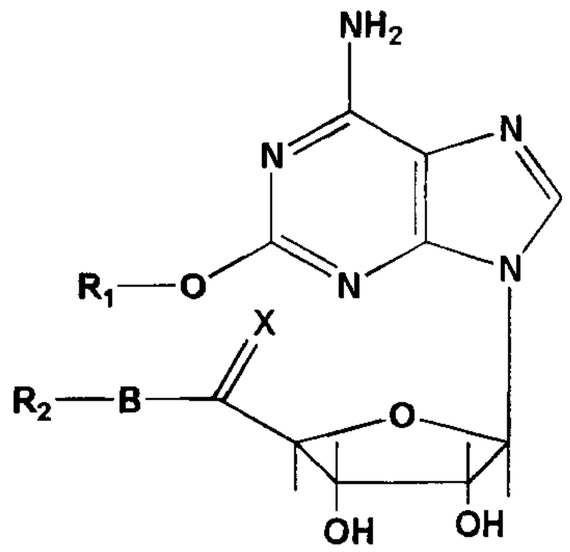
X is two hydrogen atoms or an oxygen; and

B is selected from the group consisting of oxygen and NH;

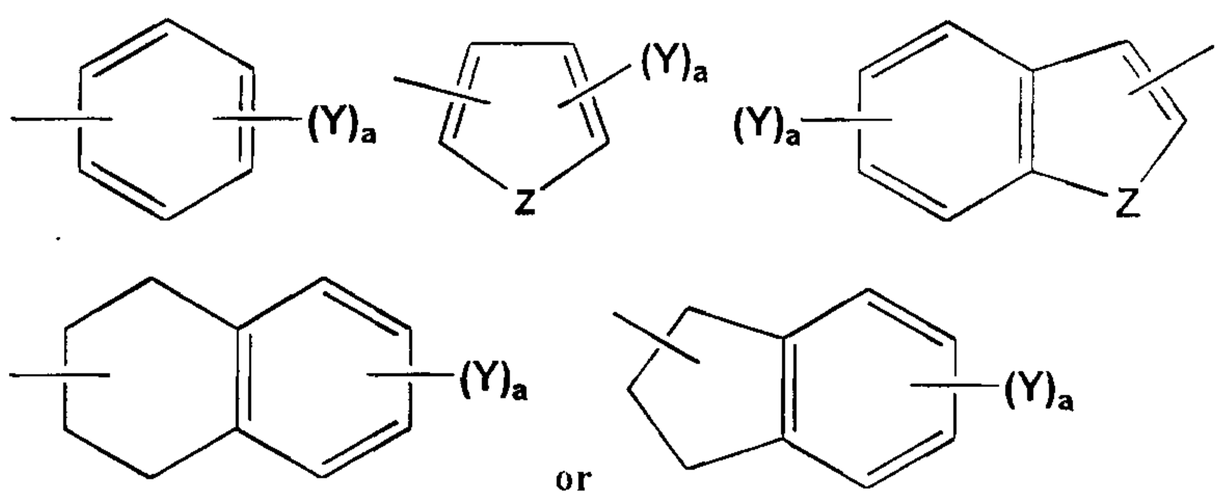
with the proviso that when X is two hydrogen atoms, B is oxygen; and

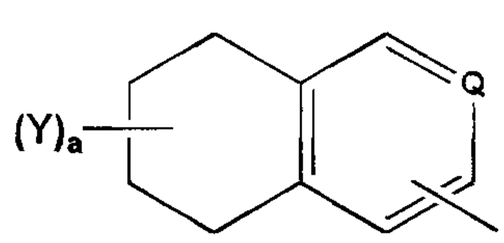
with the further proviso that when B is oxygen, then R_1 cannot be a phenyl or substituted phenyl.

28. A process for the manufacture of compounds selected from the group of stereoisomers or mixtures thereof of compounds having the formula:



wherein R_1 is selected from the group, consisting of branched, straight-chained or cyclic hydrocarbyl radicals, having from one to six carbon atoms, and radicals represented by the general formulae:





wherein Y is selected from the group consisting of lower alkyl, lower alkoxy, carboxy-lower alkyl, and halogen; Z is oxygen, sulfur or -NH; Q is -CH or nitrogen; a is zero or an integer from one to three;

or R_1 is a branched- or straight-chain hydrocarbyl radical having from one to six carbon atoms and substituted with one or two radicals represented by the above general formulae;

R_2 is selected from the group consisting of hydrogen and straight, branched or cyclic hydrocarbyl radicals having from 1 to 4 carbon atoms; and

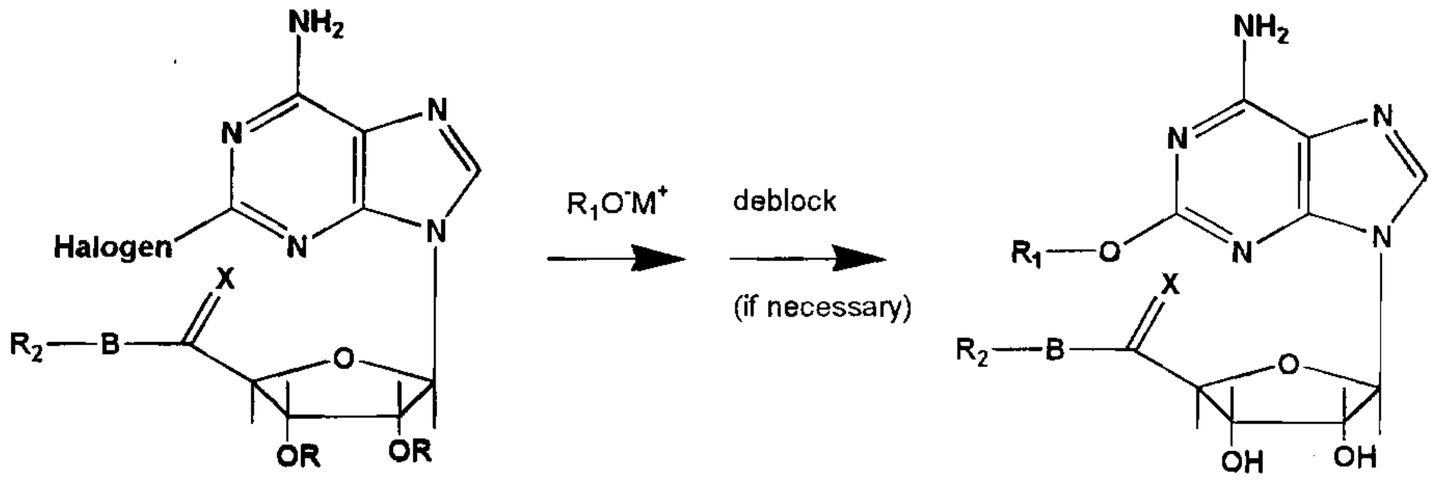
X is two hydrogen atoms or an oxygen; and

B is selected from the group consisting of oxygen and NH;

with the proviso that when X is two hydrogen atoms, B is oxygen; and

with the further proviso that when B is oxygen, then R_1 cannot be a phenyl or substituted phenyl, comprising

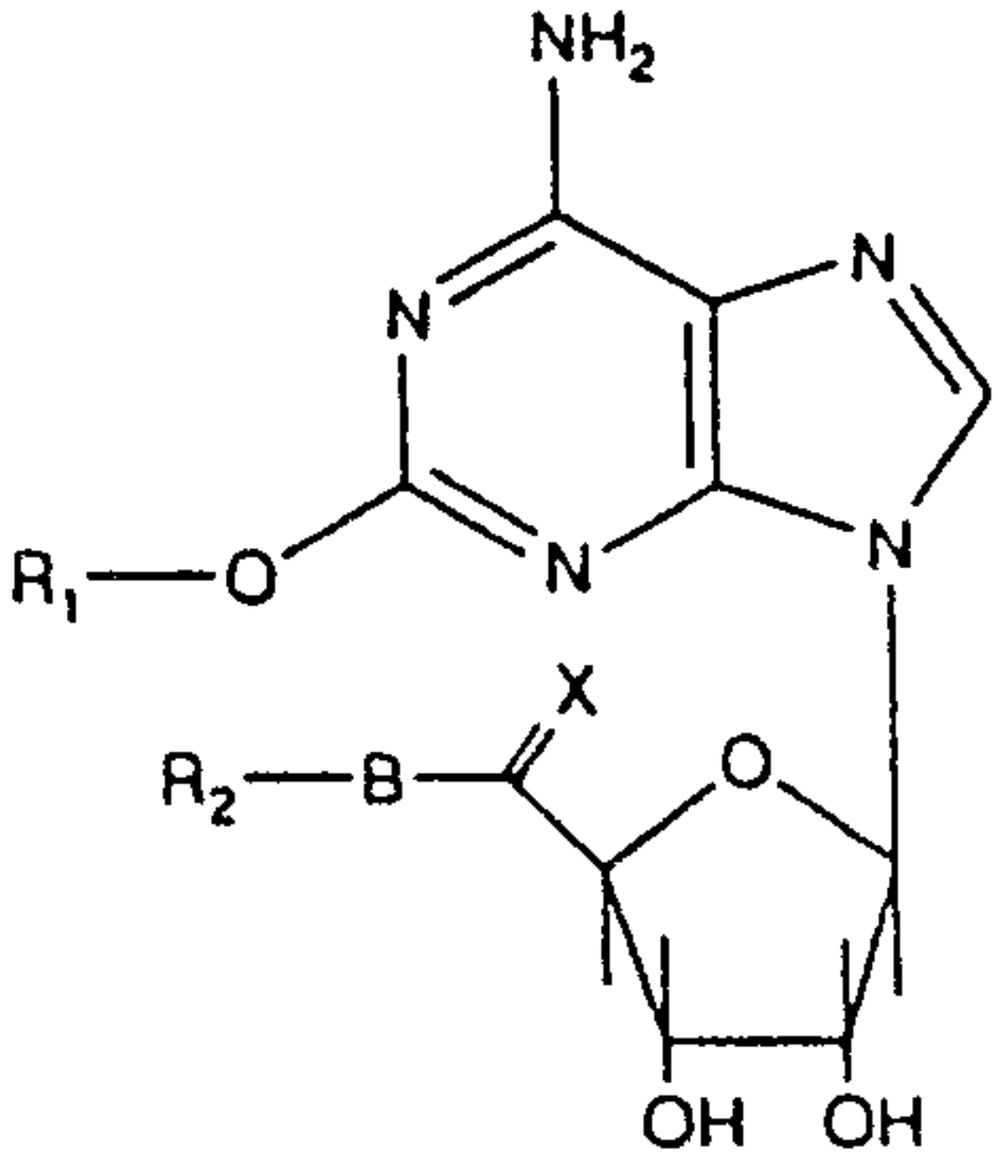
the reaction of a 2-haloadenosine derivative shown below with an alkali metal salt of R_1OH:



R = H, blocking group

29. A commercial package comprising a container containing compound according to any one of Claims 1-20 and written subject matter which states that the compound is for use in inducing an adenosine response mediated by an adenosine A_2 receptor in an animal.

30. A commercial package comprising a container containing composition according to any one of Claims 21-26 and written subject matter which states that the composition is for use in inducing an adenosine response mediated by an adenosine A_2 receptor in an animal.



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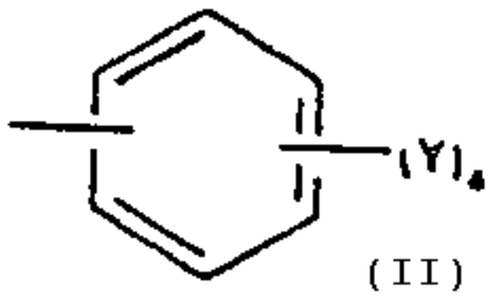

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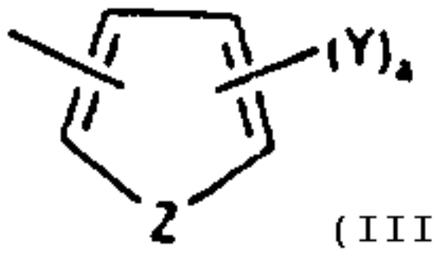

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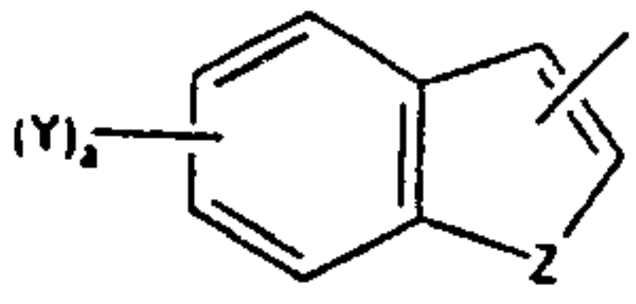

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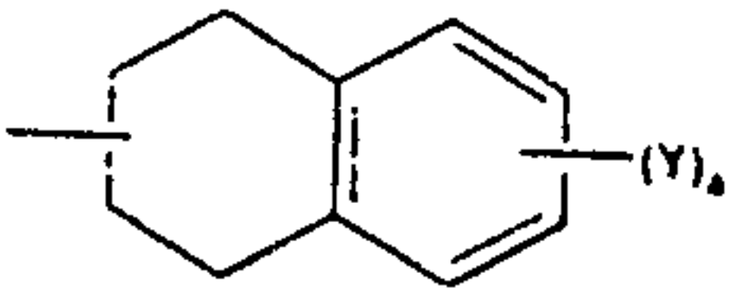

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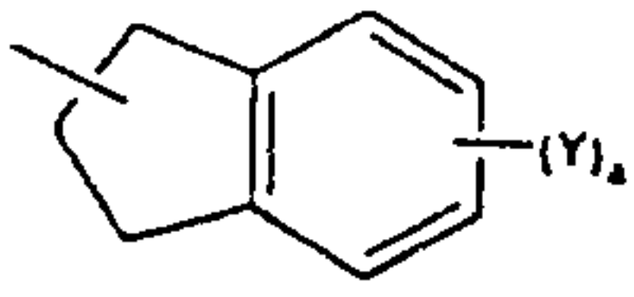

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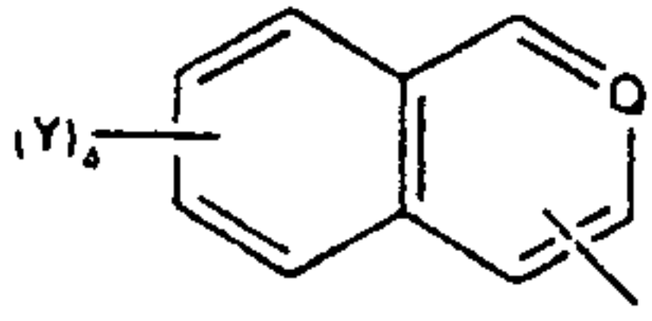

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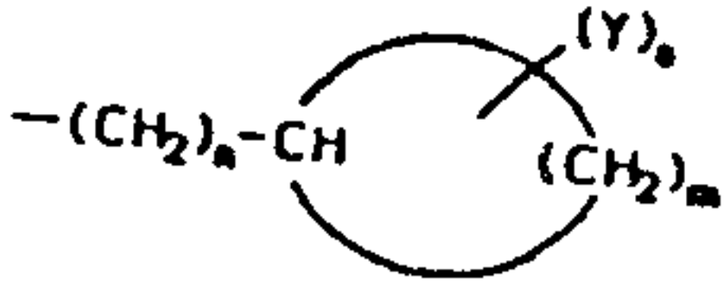

(VIII)