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(71) Applicant (for all designated States except US): **ADE-
NOBIO B.V.** [US/US]; Burgemeester Haspelslaan 131,
NL-1181 NC Amstelveen (NL).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **GORNY, Philippe**
[US/US]; Paris (FR).

(74) Agent: **RYAN, John, W.**; Dechert, LLP, 1775 I Street,
NW, Washington, DC 20006-2401 (US).

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(54) Title: STABLE AND ACTIVE COMPLEXES OF ADENOSINE AND ADENOSINE PHOSPHATES WITH AMINOALCOHOLS FOR THE TREATMENT OF PULMONARY ARTERY HYPERTENSION, CARDIAC FAILURE AND OTHER DISEASES

(57) Abstract: The invention is directed to compositions and methods which permit the oral use of adenosine and adenosine phosphates for cardiovascular applications such as pulmonary artery hypertension, cardiac failure and other diseases. Certain compositions in accordance with the invention have enhanced AMP gastrointestinal bioavailability and thus efficacy. The invention prolongs the activity of adenosine and adenosine phosphates when administered intravenously. In particular, the invention contemplates methods of treating several human (as well as animal) cardiovascular and neurological medical conditions that could be improved by an effective amount of adenosine, ATP or AMP combined with dialkylaminoalcohols and their salts.



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**Stable and Active Complexes of Adenosine and Adenosine Phosphates with
Aminoalcohols for the Treatment of Pulmonary Artery Hypertension, Cardiac Failure
and Other Diseases.**

Field of the Invention

The present invention relates to stable and active complexes of adenosine, adenosine monophosphate and adenosine triphosphate with aminoalcohols, alkylamino-alkanols, dialkylamino-alkanols, and their salts for treating cardiovascular and neurological and other diseases including, but not limited to, pulmonary artery hypertension, cardiac failure and cerebral vasospasm.

Description of the Prior Art

1. Adenosine

Adenosine is a ubiquitous purine that is a modulator of numerous physiological activities, particularly within the cardiovascular and nervous systems. Adenosine has a variety of extracellular and intracellular effects. The effects of adenosine appear to be mediated by specific cell surface receptor proteins (A1, A2a, A2b, and A3). Adenosine modulates diverse physiological functions including, arterial vasodilation, reduction of cardiac rate, down regulation of several brain activities, inhibition of acute inflammation, stimulation of gluconeogenesis, and inhibition of lipolysis. Adenylate cyclase mediates many of adenosine's effects, e.g., the opening of potassium channels and the reduction of flux through calcium channels.

1.1 Adenosine is a potent arterial vasodilator.

Adenosine constantly modulates vascular tone, significantly under ischemic conditions, thus contributing to the protection of a large number of tissues (heart, brain, liver, kidney, stomach, etc.). Currently, adenosine vasodilating properties are used for ischemic heart disease diagnosis (e.g., as an adjunct to thallium-201 myocardial perfusion scintigraphy in patients unable to exercise adequately) and occasionally for cardioprotection during revascularization procedures.

- ❖ Acting via A₂ receptors adenosine increases cyclic AMP which promotes vasodilatation by both decreasing intracellular calcium and directly inhibiting myosin light chain kinase phosphorylation.
- ❖ Adenosine has a preferential vasodilator effect on the pulmonary circulation in human.
Morgan JM- Adenosine as a vasodilator in primary pulmonary hypertension. Circulation. 1991 Sep;84(3):1145-9. This effect is confined to the pulmonary arterial tissues for dosages in the 50µg/kg/mn range given in perfusion for 15 minutes.
Fullerton DA- Adenosine effectively controls pulmonary hypertension after cardiac operations- Ann Thorac Surg. 1996 Apr;61(4):1118-23. At dosages of 140µg/kg/mn for 6mn (*Adenoscan prescribing information*) a systemic vasodilating effect is observed and hypotension can be seen in 2% of patients.
Due to its very short half-life, less than 5 seconds, usage of adenosine is currently limited to IV acute testing in order to determine those patients who may respond to calcium channel blockers or other vasodilating therapies prescribed in pulmonary artery hypertension.
- ❖ Adenosine induces collateral circulation via inducing growth factors and triggering ischemic preconditioning, both of which induce ischemic tolerance in advance. Adenosine is also known to reduce the release of noradrenaline, production of endothelin, and attenuate the activation of renin-angiotensin system, all of which are believed to cause cardiac hypertrophy and remodelling. Exogenous adenosine is further known to reduce the severity of ischemia and reperfusion injury. Finally, adenosine is reported to counteract neurohumoral factors, i.e., cytokine systems, known to be related to the pathophysiology of cardiac failure. *Kitakaze M, Hori M- Adenosine therapy: a new approach to chronic heart failure. Expert Opin Investig Drugs 2000 Nov;9(11):2519-35.*
- ❖ Intra-arterial (133)Xe cerebral blood flow (CBF) measurements suggest that intracarotid adenosine, in a dose that lacks significant systemic side effects, profoundly increases CBF, whereas nitroprusside has no effect. *Joshi S et al- In nonhuman primates intracarotid adenosine, but not sodium nitroprusside, increases cerebral blood flow. Anesth Analg. 2002 Feb; 94(2):393-9.*
- ❖ In the heart, adenosine has been shown to suppress pacemaker activity and slow atrio-ventricular conduction. It is currently used by intravenous bolus administration to treat supraventricular tachycardia.

1.2 Adenosine is a neuromediator.

In most brain areas, high extracellular adenosine concentrations, through A1 and A2 adenosine receptors, decrease neuronal activity. See *Dunwiddie TV, Masino SA, Neuroscience 2001, 107(4):653-63*. See also, *The role and regulation of adenosine in the central nervous system. Annu. Rev. Neurosci. 2001; 24:31-55*.

- ❖ Adenosine is also thought to play a key role in the induction of sleep. Investigations into the relationship between adenosine and sleep surged following the discovery that caffeine's stimulating characteristics stem from its ability to prevent adenosine from binding to cells and launching distinct actions. Now a large body of work has revealed the details of how, under normal circumstances, adenosine promotes sleep. Many studies in animals have shown that blocking adenosine's actions in the brain increases alertness, while injections of adenosine or similar compounds induce apparently normal sleep. See *Porkka-Heiskanen T., et al., Adenosine: A mediator of the sleep-inducing effects of prolonged wakefulness. Science 276(May 23):1265, 1997*.
- ❖ Adenosine also participates in many local regulatory mechanisms, such as those occurring in synapses, in the central nervous system (CNS) and at neuroeffector junctions in the peripheral nervous system. In the CNS, adenosine is known to inhibit the release of a variety of neurotransmitters, such as noradrenaline, dopamine, serotonin, glutamate and GABA, to depress neurotransmission, to reduce neuronal firing, to induce spinal analgesia, and to possess anxiolytic properties.
- ❖ Adenosine can also function as an inhibitory modulator of seizure activity, of particular importance in epilepsy and convulsions of the alcohol withdrawal syndrome. For review, see *Ph. De Witte, E. Pinto, M. Ansseau and P. Verbanck. Alcohol and withdrawal: from animal research to clinical issues, Neuroscience & Biobehavioral Reviews, 2003;27:189-197*. This likely represents an adaptive response to seizure severity induced by repeated episodes of withdrawal.
- ❖ The identification of adenosine as a transactivator of the Trk tyrosine kinase receptor suggests that it can replace neurotrophins as a potential treatment for a wide range of neurological disorders, including Alzheimer disease, cerebral ischemia, hyperalgesia, and Parkinson's disease. See *Lee FS, Rajagopal R, Chao MV. Distinctive features of Trk neurotrophin receptor transactivation by G protein-coupled receptors. Cytokine Growth Factor Rev. 2002 Feb; 13(1):11-7*. Indeed, adenosine activates the Trk receptor tyrosine kinase and mediates neuronal cell survival in the absence of neurotrophins. Adenosine also offsets impaired cholinergic signalling. The regulation

of the cholinergic calcium signalling in astroglial cells is thought to play a crucial role in the pathogenesis of Alzheimer's disease. Various study results suggest that impaired cholinergic signalling, the cardinal symptom of Alzheimer's disease, can be reinforced at the second messenger level by an alternative intracellular Ca²⁺ mobilizing path, which can be brought into play by the concomitant activation of A1 purinoceptors. See Ferroni S, Marchini C, Ogata T, Schubert P., *J Neurosci Res.* 2002 Jun 1;68(5):615-21, *Recovery of deficient cholinergic calcium signalling by adenosine in cultured rat cortical astrocytes*. Therefore, it is thought that adenosine can stop and prevent neurons from calcium dysregulation.

1.3 Adenosine has anti-inflammatory properties.

Adenosine signalling strongly affects inflammatory cell function. (Ohta, A. & Sitkovsky, M. *Role of G-protein-coupled receptors in downregulation of inflammation and protection from tissue damage. Nature* 414, 916-920 (2001)) thus resulting in:

- ❖ Inhibition of leucocytes migration and free radical production. Cronstein BN. *Adenosine, an endogenous anti-inflammatory agent, J Appl Physiol* 1994 Jan;76(1):5-13.
- ❖ Down-regulation of pro-inflammatory cytokines such as TNF-alpha, IL-6, IFN-gamma, IL-12, and the up-regulation of the anti-inflammatory cytokine IL-10. Zdenek Zidek *Adenosine cyclic AMP pathways and cytokine expression- Review- European Cytokine Network. Vol. 10, Issue 3, September 1999: 319-28.*
- ❖ A2 receptor stimulation also inhibits NFkappaB activity, whereas activation of other adenosine receptors have no effect (activation of NFkappaB induces gene programs leading to transcription of factors that promote inflammation, such as leukocyte adhesion molecules, cytokines, and chemokines).

Despite its role in multiple biological functions and pharmacological processes, the very short plasmatic half-life of adenosine (less than 5 sec.) restricts its therapeutic use to massive bolus injections by the intravenous route for treating supraventricular tachycardia with the risk of serious A1 related adverse-effects such as chest-pain, AV block, and bronchoconstriction.

2. AMP

The purine nucleotide AMP is a natural “adenosine precursor” which ultimately converts into adenosine by ecto-5'-nucleotidase on the extra-cellular surface of all cells. Ecto-5'-nucleotidase is a ubiquitous wide spread enzyme that hydrolyzes a variety of nucleotides, but has greatest affinity for AMP that it efficiently converts to adenosine. The vasodilating effects of AMP are mentioned in the *Monographs of Commercialized AMP Products Cardiomone and Adenyl*.

3. ATP

ATP is a naturally occurring nucleotide which is present in every cell. Extracellular ATP appears to be involved in the regulation of a variety of biological processes via P2 receptors divided into P2X ligand-gated ion channel and P2Y G-protein-coupled receptors families.

3.1 ATP potentiates cytostatic agents.

- ❖ In *in vitro* and *in vivo* animal studies, ATP has been shown to inhibit the growth of several solid carcinoma tumours (colon, pancreas, esophagus) and of several cancer cell lines (prostate, breast, melanoma, myeloid cells). See *Agteresch HJ & al., Adenosine Triphosphate. Established and potential clinical applications. Drugs 1999 Aug; 58(2):211-232*. The underlying predominant mechanism is not clear but increased membrane permeability (not observed in untransformed cells) seems predominant. Potentiation effects of cytostatic agents were also observed in several *in vitro* and animal studies (melanoma, ovarian carcinoma) and some human studies (myeloid leukaemia, glioma).
- ❖ ATP infusion in patients with advanced cancer is feasible but is limited by dyspnoea and chest tightness. A Phase II trial in patients with non-small cell lung cancer showed that it reduces or inhibits weight loss. See *Haskell CM & al., Phase I trial of extracellular ATP in patients with advanced cancer. Med Pediatr Oncol 1996; 27(3):165-73*. This effect has also been observed in mice with human pancreatic carcinoma.

Cachexia is caused by elevated lipolysis, protein breakdown and gluconeogenesis. It is also correlated with lower ATP levels. It was suggested that the administration of extracellular ATP inhibits Cori cycle (i.e. the gluconeogenesis from lactate followed

by reconversion of glucose to lactate in peripheral tissue), activity which is a potential means of inhibiting weight loss.

3.2 ATP is the universal source of cell energy.

ATP is depleted during exercise, in chronic fatigue syndrome and in heart failure. See Steele DS, Duke AM. *Metabolic factors contributing to altered Ca²⁺ regulation in skeletal muscle fatigue* Acta Physiol Scand. 2003 Sep;179(1):39-48 / Harmer AR & al- *Skeletal muscle metabolic and ionic adaptations during intense exercise following sprint training in humans* J Appl Physiol. 2000 Nov;89(5):1793-803/ Forsyth LM. *Therapeutic effects of oral NADH on the symptoms of patients with chronic fatigue syndrome.* Ann Allergy Asthma Immunol. 1999 Feb;82(2):185-91 / Ventura-Clapier R. *Metabolic myopathy in heart failure.* News Physiol Sci. 2002 Oct; 17:191-6./ *Energy metabolism in heart failure.* Physiol. 2004 Feb 15;555(Pt 1):1-13. Epub 2003 Dec 05.

3.3 ATP is a potent vasodilating agent.

ATP exerts its vasodilating effects mainly through P2Y receptors and ATP-sensitive potassium channel openers. *Van Aken H et al- Haemodynamic and cerebral effects of ATP-induced hypotension.* Br J Anaesth. 1984 Dec;56(12):1409-16.

Despite possessing numerous and very important physiological and pharmacological activities, adenosine and adenosine triphosphate (ATP) have both a very short plasma half-life (less than 5 seconds) and therefore cannot be used orally. Although having a longer half life, adenosine monophosphate (AMP) has a poor gastrointestinal bioavailability which restricts its medical applications. Further, when administered intravenously, the effects of adenosine and ATP are limited in duration (e.g. less than one minute after adenosine bolus injection). Thus, there is a need for improved compositions and methods which take advantage of the pharmacological effects of adenosine and adenosine phosphates while having improved stability when administered orally (as well as intravenously).

Given that adenosine and adenosine phosphates possess numerous physiological and pharmacological activities significant research has been devoted in the pursuit of harnessing their pharmacological effects in therapeutic compositions and methods. For example, U.S. Patent No. 3,993,639 (the '639 patent) describes heptaminol adenosine-5'-monophosphate.

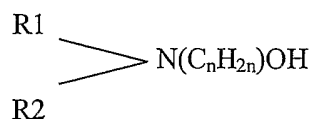
This compound has interesting properties in the cardiovascular domain, particularly in the treatment of venous vascular insufficiencies (phlebology). However the '639 patent document does not teach nor suggest the formation of complexes between adenosine and tertiary amines such as dialkylaminoalkanols nor pharmaceutical compositions between adenosine monophosphate and tertiary amines as dialkylaminoalkanols nor that primary amine heptaminol might improve adenosine-5'-monophosphate bioavailability. Thus, no properties of such complexes, e.g. enhanced capacity to cross the gastrointestinal barrier, are described or suggested.

The present invention provides compositions and method which permit the oral use of adenosine and adenosine phosphates for cardiovascular applications such as pulmonary artery hypertension, cardiac failure and other diseases. The invention also enhances AMP gastrointestinal bioavailability and efficacy. The invention further permits prolonged activity of those substances when administered intravenously. In addition, the invention contemplates method of treating several human (as well as animal) cardiovascular and neurological medical conditions that could be improved by an effective amount of adenosine, ATP or AMP combined with dialkylaminoalcohols and their salts.

SUMMARY OF THE INVENTION

One embodiment of the invention includes compositions comprising complexes of adenosine or an adenosine phosphate with a dialkylamino-alkanol.

Another embodiment of the invention includes compositions comprising complexes of adenosine or an adenosine phosphate with a dialkylamino-alkanol having the formula:



where R1 and R2 are lower alkyl and n is an integer of 2 to 16.

Another embodiment of the invention is a composition comprising complexes of adenosine or an adenosine phosphate with dimethylamino isopropanol.

An additional embodiment of the invention is a composition comprising complexes of either adenosine or an adenosine phosphate with any one of dimethylamino ethanol, diethylamino ethanol, diethylamino isopropanol, methylethylamino ethanol, dimethylamino propanol, dimethylaminoisopropanol, dimethylaminobutanol, dibutylaminoethanol, dipropyl aminoethanol, or diisopropylamino ethanol.

Embodiments of the present invention also contemplate a composition comprising a mole ratio of either adenosine or an adenosine phosphate to dimethylaminoalkanol of about 1:1 to 1:10.

The present invention further contemplates a pharmacologically active salt of complexes of adenosine or an adenosine phosphate with a dialkylamino-alkanol.

One embodiment of the instant invention contemplates methods of treating cardiovascular and cerebrovascular diseases, systemic arterial hypertension, cardiac failure, ischemic heart disease, peripheral arterial diseases, cerebral vasospasm, pulmonary arterial hypertension, inflammatory diseases, thrombosis, pathology of sleep, neurodegenerative disease, malignant tumor growth inhibition and enhancement of cancer chemotherapy using complexes of adenosine or adenosine phosphates by oral or parenteral routes.

Another embodiment of the instant invention comprises novel compositions which allow adenosine and adenosine phosphates to cross the gastrointestinal barrier after oral administration.

A further embodiment of the invention prolongs adenosine and adenosine phosphate activity and efficacy when administered intravenously.

Additional embodiments of the present invention contemplate methods of crossing the blood brain barrier by incorporating adenosine and adenosine phosphate complexes into nanoparticles or liposome systems.

Embodiments of the present invention also contemplate an adenosine or adenosine phosphates complexes with amino-alkanol, or alkylamino-alkanol or dialkylamino-alkanol for use in methods of treating neurological diseases such as the pathology of sleep, psychological

disorders, neurodegenerative diseases and more particularly Alzheimer disease , pain, dependence withdrawal and epilepsy.

Embodiments of the present invention also contemplate an ATP complex with amino-alkanol, or alkylamino-alkanol or dialkylamino-alkanol for use in methods of treating malignant tumor growth, enhancement of cancer chemotherapy, weight loss, and fatigue syndrome.

Embodiments of the present invention provide methods of sustained release delivery of adenosine, ATP and AMP into the circulation when those substances are combined with a dialkylamino-alkanol and are administered via the IV route.

These and other embodiments of the present invention, which will become better understood during the course of the following detailed description, have been achieved by the inventor's discovery of stable complexes produced by the reaction of adenosine and/or adenosine phosphates with certain amino alcohols. These complexes have many therapeutic properties which are further described throughout the Detailed Description below.

BRIEF DESCRIPTION OF THE FIGURES AND DRAWINGS

Figure 1 shows the synthesis of compound 330A1 and of compound 330A2 currently named Adb011 (adenosine with 4-acetamidobenzoic acid and dimethylaminopropanol).

Figure 2 shows the synthesis of adenosine triphosphate with 4-acetamidobenzoic acid (p-aminobenzoic acid derivative) and dimethylaminopropanol (Adb311) and that of adenosine monophosphate with 4-acetamidobenzoic acid and dimethylaminopropanol (Adb111).

Figure 3a shows the synthesis of adenosine with adipic acid and dimethylaminoisopropanol (Adb013).

Figures 3b and 3c show the synthetic pathways of adenosine with acetyl salicylic acid and dimethylaminoisopropanol (Adb-012) and that of adenosine monophosphate with acetyl salicylic acid and dimethylaminoisopropanol (Ad-112).

Figure 3d shows an NMR of compounds Adb-012.

Figure 3e shows an NMR of compounds Adb-112.

Figure 4 to 9 are the infrared curves for 3 compounds compared to their components. The curves illustrate the novelty of the complexes since those latter have a different infrared spectrum and drawing.

Figure 10 shows mean values of blood pressure in 5 rats receiving 50 mg/kg Adb011 and 5 rats receiving vehicle (control group).

Figure 11 shows mean values of blood pressure in 4 rats receiving 10 mg/kg Adb011 intravenously and 3 rats receiving vehicle (control group).

Figures 12 show the effects of Adb011 given orally in rats with acute and chronic pulmonary artery hypertension.

Figures 13 show the effect on blood pressure of Adb111 and AMP given orally in normal rats at comparable dosages.

Figures 14 shows the effect on blood pressure of compound 330A1 (salt of the complexes) given either orally or IV in normal rats.

DETAILED DESCRIPTION OF THE INVENTION

For simplicity and illustrative purposes, the principles of the present invention are described by referring to various exemplary embodiments thereof. Although the preferred embodiments of the invention are particularly disclosed herein, one of ordinary skill in the art will readily recognize that the same principles are equally applicable to, and can be implicated in other compositions and methods, and that any such variation would be within such modifications that do not part from the scope of the present invention. Before explaining the disclosed embodiments of the present invention in detail, it is to be understood that the invention is not limited in its application to the details of any particular embodiment shown, since of course the invention is capable of other embodiments. The terminology used herein is for the purpose of description and not of limitation. Further, although certain methods are described with reference to certain steps that are presented herein in certain order, in many instances, these steps may be performed in any order as may be appreciated by one skilled in the art, and the methods are not limited to the particular arrangement of steps disclosed herein.

The present invention relates to novel adenosine, adenosine monophosphate and adenosine triphosphate complexes. The inventors of the instant invention have surprisingly discovered complexes of adenosine and adenosine phosphates with amino-alcohols that are stable when administered orally or intravenously. These complexes are useful in the treatment of pulmonary artery hypertension, cardiac failure and other diseases due to their

ethanol, dimethylaminoisopropanol, diethylaminoethanol, diethylaminoisopropanol, methylethylamino ethanol, dimethylaminopropanol, dimethylaminobutanol, dibutylaminoethanol, dipropylaminoethanol, and diisopropylaminoethanol.

Acceptable acids for forming salts include any pharmacologically acceptable acids or their derivatives including, but not limited to, hydrochloric acid, sulphuric acid, phosphoric acid, acetyl salicylic acid, d-tartratic acid, maleic acid, fumaric acid, succinic acid, citric acid, trans cinnamic acid, salicylic acid, 5-amino-salicylic acid, sulfasalazine, adipic acid, methane sulfonic acid, acetic acid, hyaluronic acid, and p-aminobenzoic acid. Other acids include arylacetic acid derivatives such as diclofenac, sulindac. Acids can also be selected from arylpropionic acid derivatives such as: flurbiprofen, ibuprofen, ketoprofen, and naproxen.

Most of the salts with amines are hygroscopic. However, the p-aminobenzoic acid salt and more specifically the 4-acetamidobenzoic acid of the adenosine-dimethylamino isopropanol complex (or AMP or ATP-dimethylamino isopropanol complexes) is a solid and is the presently preferred salt. It is prepared by mixing the aminoalcohol and the acid mole for mole and then heating slightly. The salt thus formed is then dry mixed with adenosine (or AMP, or ATP) in a mole ratio of, for example, either 1:1 or 3:1 (salt to adenosine or AMP or ATP). The complex is then formed, for example, by dissolving in water and can be recovered there from if desired by evaporation. The preferred ratio of adenosine (or ATP) to aminoalcohol is 1:3.

The adenosine complexes of the instant invention have pharmacological activities including the ability to lower systemic blood pressure, the lowering of pulmonary arterial blood pressure, the ability to vasodilate arteries and fight against ischemic heart diseases, cardiac failure, peripheral arterial disease and cerebral vasospasm, the ability to down regulate acute inflammation, promoting sleep, and the ability to restore various neurodegenerative deficits.

The adenosine monophosphate complexes of the instant invention also have vasodilating properties and can be used in similar indications.

The adenosine triphosphate complexes of the instant invention have pharmacological activities including, vasodilation, the ability to inhibit various tumor growth, the ability to enhance the efficacy of cancer chemotherapy, the ability to fight muscular fatigue including that of heart failure, the ability to fight weight loss.

Most of these different pharmacological effects are thought to be mediated by adenosine and ATP specific receptors. For this purpose molecules of the present invention may be provided in any form enabling oral administration (in particular in the form of gel

capsules, drinkable solutions or emulsions, powders, gels, lozenges, tablets), nasally (for example solutions administered in the form of drops or sprays), in the form of collyrium (eye drops or solutions) by the pulmonary route (solutions in pressurized aerosol dispensers), rectally (suppositories) cutaneously (for example ointments or transdermal devices also known as patches) or transmucosally for example sublingually (solutions in pressurized dispensers or tablets that crumble in the mouth) or vaginally (particularly vaginal creams or suppositories) or by the intravenous, subcutaneous, intramuscular routes (injectables suspensions or solutions).

Delivery of the complexes into the brain can be done via nanoparticles made of safe ingredients below 400 nanometers or using liposomes and PEGlyated immunoliposomes systems.

EXAMPLE. 1

a. Complexing of adenosine with para-aminobenzoic acid and dimethylaminoisopropanol (Adb011).

The synthesis of this compound follows a two step process:

- Step 1: synthesis of compound 330A1 (Figure 1).

The suspension of compounds 330A0 (4-acetamidobenzoic acid, a para-aminobenzoic acid derivative) and 330B0 (dimethylaminoisopropanol) in water is stirred for 2 hours at 50°C. The solvent is evaporated under vacuum. The residue is taken up and evaporated three times in acetonitrile. The residue is taken up in cold acetonitrile, crystallization is observed. The solid is filtered and dried under vacuum. Compound 330A1 (salt) is obtained as a white solid (approximately 6g.) The yield is approximately 76% the purity of compound 330A1 is controlled by RMN 1H and is approximately greater than 95%. See Figure 1 for quantities and for chemical structures.

- Step 2: synthesis of final compound 330A2 currently named Adb011 (Figure 1). Compounds 330A1 (salt) and 320A0 (adenosine) are added to water at room temperature (RT). The mixture is stirred at RT for three hours. The formation of a precipitate is observed (paste). Water is added until stirring is observed again. The mixture is evaporated under vacuum to yield 2.1 g. of compound 330A2 as a white solid. Yield is approximately 100%. The purity of compound 330A2 is controlled by

RMN 1H and is approximately greater than 95%. See Figure 1 for quantities and chemical structures.

b. Complexing of adenosine triphosphate with para-aminobenzoic acid and dimethylaminopropanol (Adb311)

This complex is produced by the same process as shown above, see Figure 2.

c. Complexing of adenosine monophosphate with para-aminobenzoic acid and dimethylaminopropanol (Adb111)

This complex is produced by the same process as shown above, see Figure 2.

d. Complexing of adenosine with adipic acid and dimethylaminopropanol (Adb013)

This complex is produced by the same process as shown above, but different intermediary product. See Figure 3a.

e. Complexing of adenosine with acetyl salicylic acid and dimethylaminopropanol (Adb-012).

This complex is produced by the same process as shown above, but different intermediary product. See Figure 3b.

f. Complexing of adenosine monophosphate with acid acetyl salicylic and dimethylaminopropanol (Adb-112)

This complex is produced by the same process as shown above, but different intermediary product. See Figure 3c.

One of skill in the art will recognize that the above components can be replaced by substitute or equivalent components (see Fig 3 / Fig 1 & 2). For example, other amino alcohols may be used in varying proportions. One of skill in the art would further recognize that changes in the amino alcohols and their ratios could affect the characteristic of the resulting compound.

EXAMPLE 2. Infrared spectrum analysis of adenosine, AMP and ATP complexes.

The following spectra were recorded on the same apparatus with the same operating protocol.

1. Spectrum of the complexes (Adb011, Adb111, Adb 311).
2. Spectrum of the mixtures adenosine/salt, AMP/salt, ATP/salt: 1/3. (Salt of the example is 330A1).
3. Comparison of the spectra was then analysed by the computer.

Between wave number 2800cm^{-1} and 1800cm^{-1} , no difference is shown between Adb011, Adb111, Adb311 and their original components. Between $3600\text{-}3200\text{cm}^{-1}$, and $1700\text{-}500\text{cm}^{-1}$, curves of the three compounds and that of their original components are very different. See Figures 4 to 9

This experiment confirms the formation of complexes between aminoalcohol-acetamidobenzoic acid salt and adenosine or AMP or ATP.

EXAMPLE 3. The effect of oral administration of Adb011 on blood pressure of normotensive Wistar rats.

The experiment was performed in 10 male Wistar rats (340 to 410 g.; 5 in the treated group and 5 in the control group). Animals were maintained for two weeks of adaptation in humidity and temperature controlled room and were fed a standard diet (U.A.R, Villemoisson, France). Each animal, (control or treated) was anaesthetized with sodium pentobarbital (6%, 0.9 ml/Kg body weight). The left carotid artery was cannulated with a PE50 polyethylene catheter connected to a pressure transducer (MacLabs, ADInstruments, Hastings, UK). Blood pressure was monitored continuously and recorded. Adb011 was administered orally by gavage at the dose of 50 mg/kg (in Arabic syrup 5%).

Results are reported as mean \pm SEM of n experiments. Multiple measurement analysis was performed using ANOVA, followed by Bonferroni-Dunn test. Statistical significance was accepted for p values less than 0.05. The results are shown in Figure 10.

Figure 10 shows mean values of blood pressure (\pm SEM) in 5 rats receiving 50 mg/kg Adb011 p.o. (n+5) and 5 rats receiving vehicle (control group). Blood pressure began to decrease after 30 minutes of Adb-011 administration. It reached a significant maximal decrease of -13.9 mmHg between 70 and 100 min. (with respect to vehicle values, $p < 0.05$)

ANOVA multiple measurement analysis followed by a Bonferroni-Dunn test) and returned to normal after 110-120 minutes. In the control group, blood pressure slightly decreased due to anesthesia conditions.

In conclusion, orally administered Adb-011 effectively lowered blood pressure in rats for up to 110-120 min beginning 30 minutes after administration suggesting that it crosses the gastrointestinal barrier and delivers adenosine in the body for up to two hours See Figure 10.

EXAMPLE 4. Effects of Abd011 by the IV route on systemic arterial pressure in rats.

The experiment is similar to example 3.

Experimental protocol

Animals were divided in two groups:

-*Adb-011* ($n=4$): receiving IV a bolus of Adb-011 (10 mg/kg in suspension with distilled water 30 mg/ml)

-*Control* ($n=3$): receiving IV (distilled water)

Figure 11 shows mean values of blood pressure (\pm SEM) in the treated group (Adb011-10mg) and control group (vehicle). In the treated group, blood pressure began to decrease after 15min of the Adb011 administration and reached a significant maximal decrease of 48 mmHg at 15 minutes. In the control group, blood pressure slightly decreased beginning after the administration of sodium pentobarbital and then leveled off.

Results demonstrate that Adb011 administered IV has a very strong and prolonged effect on mean arterial blood pressure which is still very low two hours after injection. Given that Adb-011 is a slow releasing form of adenosine, one should also compare these results with the well documented duration of activity of natural adenosine administered under the same conditions and which is less than one minute.

EXAMPLE 5. The effect of oral administration of Adb011 on chronic pulmonary hypertension caused by hypoxia on rats.

The adenosine compound (Adb-011) was tested for its ability to reduce pulmonary artery pressure in hypoxic rats (rats exposed to chronic hypoxia, $P_b=380$ mmHg, for 14 days). Animals were divided in three groups:

- Adb-011 chronic treatment ($n=5$): receiving by gavage Adb-011 (50 mg/kg in suspension with Arabic syrup, 20 mg/ml) twice a day (morning and evening) for 14 days.

- Control (n=6): receiving by gavage vehicle (suspension of Arabic syrup 20 mg/kg).
- Adb-011 acute treatment (n=6): receiving by gavage vehicle for 14 days and orally treated with a single dose of Adb-011 on the last day (day of surgery).

Rats were placed in a chamber where air was circulated at a pressure of 380 Torr, which corresponds to an altitude of 5500 meters. The chamber was open twice a day for ~30 minutes to treat animals and to replace food and water.

On the day of surgery the animals were removed from the chamber and anesthetized with pentobarbital sodium (60 mg/kg ip). A polyethylene catheter (PE-50) was placed in the aortic arch via the left carotid artery. An introducer was advanced in the right ventricle via the right jugular vein. Adequate placement of both catheters was established by the pressure waveform. Both catheters were connected to a pressure transducer (Biopac MP30, BIOPAC Systems, Inc.). The time-lag between last dose of Adb-011 (in group 1) and blood pressure measurement was 14 hours.

Results and conclusions: Adb-011 given twice a day significantly decreased pulmonary hypertension ((by 21.5 mmHg) and right ventricular hypertrophy (-75 mg) induced by chronic hypoxia, with no effect on systemic pressure. Acute administration of Adb-011 in rats with fixed pulmonary hypertension was also able to reduce pulmonary artery pressure (-22 mmHg). See Figure 12. Results of all measurements are shown in Table 1.

Table 1

	HxC	HxA	HxC+A 15 min	HxC+A 60 min
RVp (mmHg)	74.80 ± 3.43	53.30 ± 4.61 *	75.17 ± 0.95	52.83 ± 3.83 #
HR (beat/min)	358 ± 21	364 ± 15	352 ± 12	329 ± 4
MABP (mmHg)	109 ± 6	113 ± 2	107 ± 5	92 ± 5 #
Cardiac output (mL/min/kg)	182 ± 14	162 ± 8	164 ± 11	
SVR	0.61 ± 0.05	0.70 ± 0.03	0.68 ± 0.06	
SV (mL/kg)	0.51 ± 0.04	0.45 ± 0.02	0.47 ± 0.03	
SaO2 (%)	77 ± 7	92 ± 1 *	82 ± 4	
CaO2 (mL O2 / dL of blood)	25.1 ± 2.2	29.2 ± 0.9	27.3 ± 1.4	
CvO2 (mL O2 / dL of blood)	18.2 ± 2.2	21.2 ± 1.0	19.0 ± 1.5	
C(a-v)O2 (mL O2 / dL blood)	6.8 ± 0.3	8.0 ± 0.4	8.3 ± 0.5	
VO2 (mL/min/kg)	12.28 ± 0.52	12.81 ± 0.29	13.38 ± 0.61	
BW (g)	293 ± 2	294 ± 5	303 ± 3	
RVw (mg)	437 ± 24	362 ± 10 *	436 ± 21	
(LV+S)w	644 ± 26	729 ± 56	675 ± 21	
Fulton' ratio	0.681 ± 0.039	0.506 ± 0.033	0.645 ± 0.019	

p < 0.05, HxA vs HxC, HxC+A 15min; # p < 0.05, HxC+A 60 min vs HxC+A 15 min.

HxC: Hypoxic control group; HxA: hypoxic adenosine group; HxC+A: hypoxic treated by Adb-011 the day of the surgery

RVp : Right ventricular pressure; HR : heart rate; MABP: mean arterial blood pressure; SVR : systemic vascular resistance; SV: stroke volume; SaO2: arterial oxygen saturation; CaO2: arterial O2 content; CvO2: Venous O2 content; C(a-v)O2: arterial -venous O2 difference; VO2: Oxygen consumption; BW: body weight; RVw: right ventricular weight; (LV+S)w: left ventricular + septum weight

EXAMPLE 6. The effect of oral administration of Adb111 (AMP complex) on blood pressure of normotensive Wistar rats and comparison with AMP.

The experiment is similar to example 3.

Experimental protocol

Animals were divided in five groups:

-Adb-111-I (n=5): receiving by gavage Adb-111 (100 mg/kg in suspension with Arabic syrup 30 mg/ml).

-AMP-I (n=5): receiving by gavage Adenosine monophosphate (100 mg/kg in suspension with Arabic syrup 30 mg/ml).

- Adb-111-II* ($n=5$): receiving by gavage Adb-111 (300 mg/kg in suspension with Arabic syrup 30 mg/ml).
- AMP-II* ($n=5$): receiving by gavage Adenosine monophosphate (300 mg/kg in suspension with Arabic syrup 30 mg/ml).
- Control* ($n=4$): receiving by gavage Arabic syrup 30 mg/ml alone.

In the two groups treated by Adb 111-100mg and Adb111-300mg, blood pressure began to decrease after 45 min of the Adb-111 administration and returned to normal values after 180 min.

In the two groups treated by AMP-100mg and AMP-300mg, blood pressure began to decrease after 45 min of the AMP administration and returned to normal values after 120 min. The decrease was maximal in between 75 and 120 min for Adb111-100mg / and after 60 min and 90 min for Adb111-300mg.

The drop in Adb111 groups is significant when compared to blood pressure values in the control group ($p < 0.05$). It is also significant and longer in duration when compared to AMP curves. Indeed no differences were shown between Adb-111 and AMP at the beginning of the experiment but after 45 minutes the effect was stronger with Adb-111 and ultimately lasted longer. The mean arterial blood pressure was significantly lower in Adb111-100mg/kg between 90 and 135 minutes and in Adb111-300 between 75 and 150.

Given that Adb111 provides 3.3 times less AMP than natural AMP at the same dosage, one should actually compare Adb111-300mg to AMP-100mg. Under those conditions the difference between the two products appears even more clearly and is more significant. In the control group, blood pressure decreased only slightly likely due to anesthesia conditions. See figure 13.

In conclusion, orally administered Adb-111 effectively lowered blood pressure in rats for up to 165 min beginning 45 minutes after oral administration thus suggesting that it crosses the gastrointestinal barrier and delivers adenosine monophosphate in the circulation for up to two hours.

Oral AMP also lowered blood pressure in rats for 60 minutes but to a much lesser extent. This indicates that Adb111 crosses the GI and is more capable than natural AMP to achieve active circulating pharmacological concentrations. Overall, Adb111 shows a better bioavailability and efficacy over natural AMP at comparable doses. See Figure 13.

EXAMPLE 7. The effect of oral and IV 330A1 (preferred salt of the complexes) on blood pressure of normotensive Wistar rats.

The experiment is similar to example 3.

Animals were divided in four groups:

-330A1 -I (n=4): receiving by gavage the product (50 mg/kg in suspension with Arabic syrup 30 mg/ml)

-Control - (n=4)I: receiving by gavage Arabic syrup 30 mg/ml alone

-330A1 -II: receiving the product IV (10 mg/kg in suspension with distilled water 30 mg/ml)

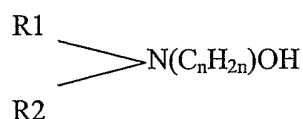
-Control-II (n=4): receiving IV distilled water

Results can be seen in Fig 14. They demonstrate that 330A1 has a minor effect on mean arterial blood pressure, not very different from control and thus does not account for Adb011 and Adb 111 strong effects on mean arterial blood pressure. These are likely to be due to the release of adenosine and AMP respectively.

While the invention has been described with reference to certain exemplary embodiments thereof, those skilled in the art may make various modifications to the described embodiments of the invention without departing from the scope of the invention. The terms and descriptions used herein are set forth by way of illustration only and are not meant as limitations. In particular, although the present invention has been described by way of examples, a variety of compositions and methods would practice the inventive concepts described herein. Although the invention has been described and disclosed in various terms and certain embodiments, the scope of the invention is not intended to be, nor should it be deemed to be, limited thereby and such other modifications or embodiments as may be suggested by the teachings herein are particularly reserved, especially as they fall within the breadth and scope of the claims here appended. Those skilled in the art will recognize that these and other variations are possible within the scope of the invention as defined in the following claims and their equivalents.

What is claimed is:

1. A composition comprising a complex of adenosine or an adenosine phosphate with an amino-alkanol.
2. The composition of claim 1, wherein the amino-alkanol is dialkylamino-alkanol.
3. The composition of claim 1, wherein the composition comprises the complex of adenosine triphosphate with an amino-alkanol, alkylamino-alkanol or dialkylamino-alkanol.
4. The composition of claim 2, wherein the dialkylamino-alkanol has the formula:



where R1 and R2 are lower alkyl and/or H and n is an integer of 2 to 16.

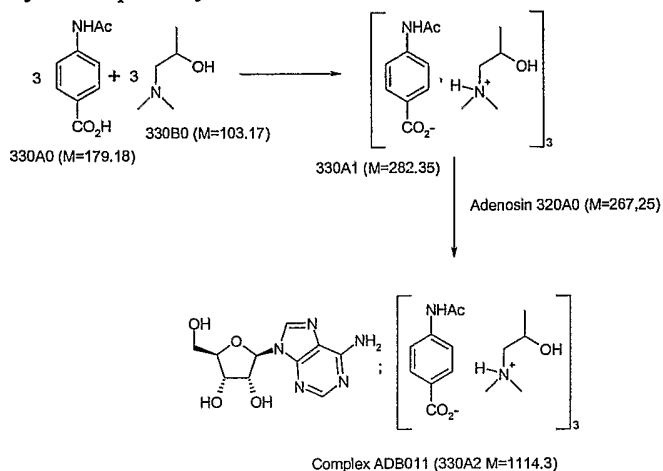
5. The composition of claim 1, wherein the amino-alkanol is dimethylaminoisopropanol.
6. The composition of claim 1, wherein the amino-alkanol is any one of dimethylaminoethanol, diethylaminoethanol, diethylaminoisopropanol, methylethylaminoethanol, dimethylamino propanol, dimethylaminobutanol, dibutylaminoethanol, dipropylaminoethanol, or diisopropylaminoethanol.
7. The composition of claim 1, wherein the mole ratio of adenosine or adenosine phosphate to amino-alkanol is about 1:1 to 1:10.
8. A composition comprising the pharmacologically active salt of a complex of adenosine or adenosine phosphate with an amino-alkanol.
9. The composition of claim 8, wherein the amino-alkanol is dialkylamino-alkanol.
10. The composition of claim 8, wherein the salt is formed with para-aminobenzoic acid or its derivatives.

11. The composition of claim 10, wherein the salt is 4-acetamidobenzoic acid.
12. The composition of claim 8, wherein the salt is formed with aspirin.
13. A method of treating an illness comprising: administering to a patient a composition comprising a complex of adenosine or an adenosine phosphate and an amino-alkanol.
14. The method of claim 13, wherein the composition comprises a complex of adenosine or an adenosine phosphate and a dialkylamino-alkanol.
15. The method of claim 14, wherein the composition comprises a complex of adenosine or an adenosine phosphate and dimethylaminoisopropanol.
16. The method of claim 13, wherein the composition is administered orally.
17. The method of claim 13, wherein the composition is administered intravenously.
18. The method of claim 13, wherein the illness is a cardiovascular or cerebrovascular disease.
19. The method of claim 13, wherein the illness is a neurological disease.
20. The method of claim 13, wherein the illness is an inflammatory disorder.
21. A method of treating an illness comprising: administering to a patient a composition comprising the pharmacologically active salt of a complex of adenosine or an adenosine phosphate with an amino-alkanol.
22. The method of claim 21, wherein the composition comprises the pharmacologically active salt of a complex of adenosine or an adenosine phosphate and a dialkylamino-alkanol.
23. The method of claim 22, wherein the composition comprises the pharmacologically active salt of a complex of adenosine or an adenosine phosphate and dimethylaminoisopropanol.

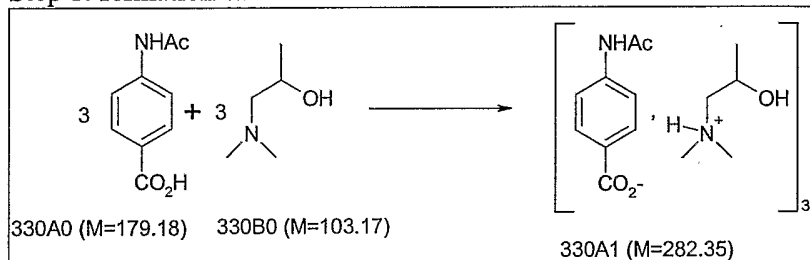
24. The method of claim 21, wherein the composition is administered orally.
25. The method of claim 21, wherein the composition is administered intravenously.
26. The method of claim 21, wherein the illness is a cardiovascular or cerebrovascular disease.
27. The method of claim 21, wherein the illness is a neurological disease.
28. The method of claim 21, wherein the illness is an inflammatory disorder.
29. The method of claim 21, wherein the illness is a malignant tumor, a weight loss, a fatigue syndrome or wherein the therapeutic goal is the enhancement of cancer chemotherapy.

Figure 1. Adb-011 synthesis (330A2)

Synthetic pathway :



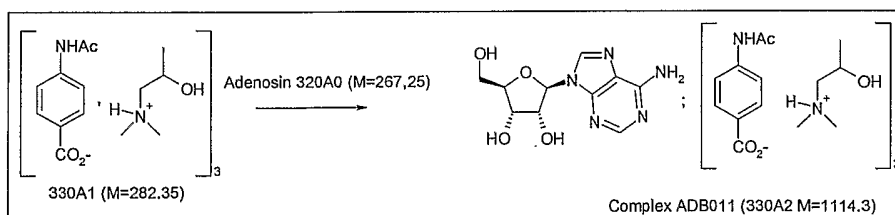
Step 1: formation of 330A1



Quantities:

Nom	MW g/mol	nbre de mole	rapport molaire	masse introduite en g	densité	volume ml	Rdt Théo. g
330A0	179,2	2,79E-02	1,00	5,00			
330B0	103,2	0,03	1,0	2,9	1,082	2,7	
H2O	18,0	1,40	50,0	25,1	1,000	25,1	
330A1	282,35						7,88

Step 2: formation of 330A2 (Adb011)

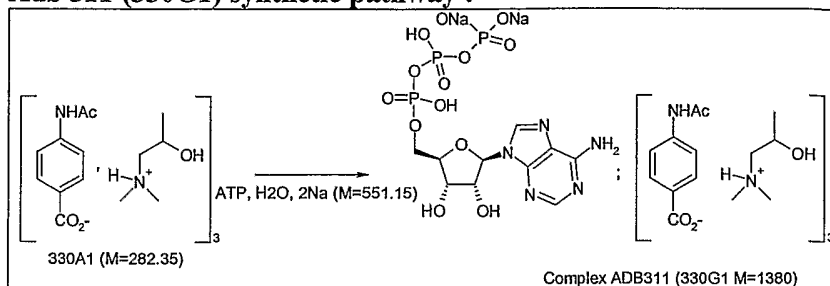


Quantities:

Nom	MW g/mol	nbre de mole	rapport molaire	masse introduite en g	densité	volume ml	Rdt théo. g
320A0	267,3	1,87E-03	1,00	0,50			
330A1	282,4	0,01	3,0	1,6			
H2O	18,0	0,09	50,0	1,7	1,000	1,7	
330A2	1114,3						2,08

Figure 2. Adb311 & 111 synthesis

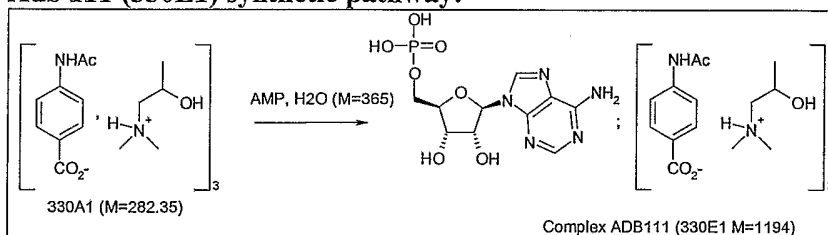
Adb 311 (330G1) synthetic pathway :



Quantities:

Nom	MW g/mol	nbre de mole	rapport molaire	masse introduite en g	densité	volume ml	Rdt théo. g
ATP, H ₂ O, 2Na	551,2	9,07E-04	1,00	0,50			
330A1	282,4	0,00	3,0	0,8			
H ₂ O	18,0	0,05	50,0	0,8	1,000	0,8	
330G1	1380						1,25

Adb 111 (330E1) synthetic pathway:

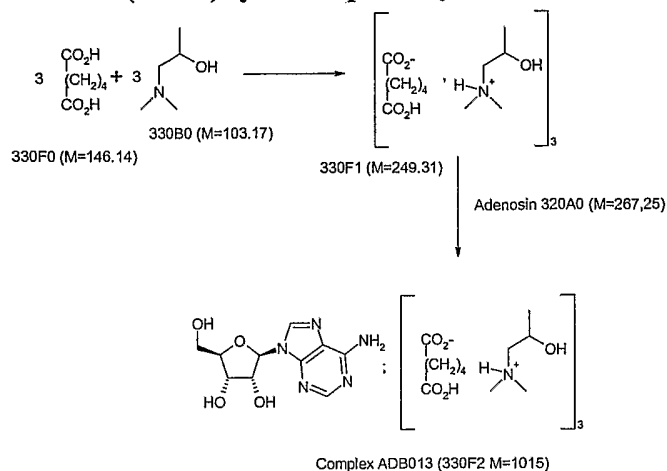


Quantities:

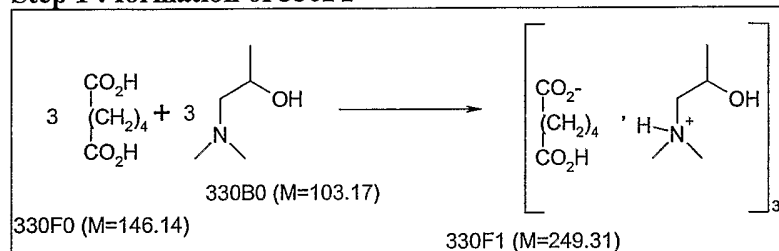
Nom	MW g/mol	nbre de mole	rapport molaire	masse introduite en g	densité	volume ml	Rdt théo. g
AMP, H ₂ O	365,0	1,37E-03	1,00	0,50			
330A1	282,4	0,00	3,0	1,2			
H ₂ O	18,0	0,07	50,0	1,2	1,000	1,2	
330E1	1194						1,64

Figure 3a. Adb013 synthesis (330F0= Adipic acid)

Adb 013 (330F2) synthetic pathway:



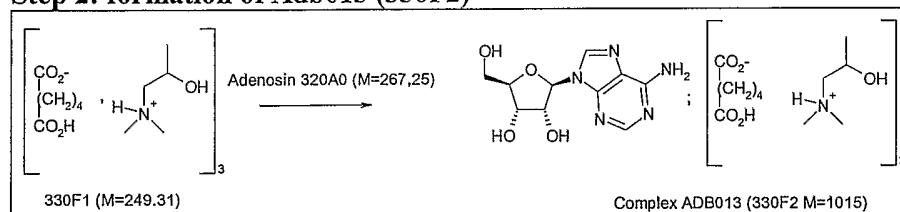
Step 1 : formation of 330F1



Quantities:

Nom	MW g/mol	nbre de mole	rapport molaire	masse introduite en g	densité	volume ml	Rdt Théo. g
330F0	146,1	3,42E-02	1,00	5,00			
330B0	103,2	0,03	1,0	3,5	1,082	3,3	
H2O	18,0	1,71	50,0	30,8	1,000	30,8	
330F1	249,31						8,53

Step 2: formation of Adb013 (330F2)



Quantities:

Nom	MW g/mol	nbre de mole	rapport molaire	masse introduite en g	densité	volume ml	Rdt théo. g
320A0	267,3	1,87E-03	1,00	0,50			
330F1	249,3	0,01	3,0	1,4			
H2O	18,0	0,09	50,0	1,7	1,000	1,7	
330F2	1015						1,90

Figure 3b Adb-012 synthesis (330D0 = acetyl salicylic acid)

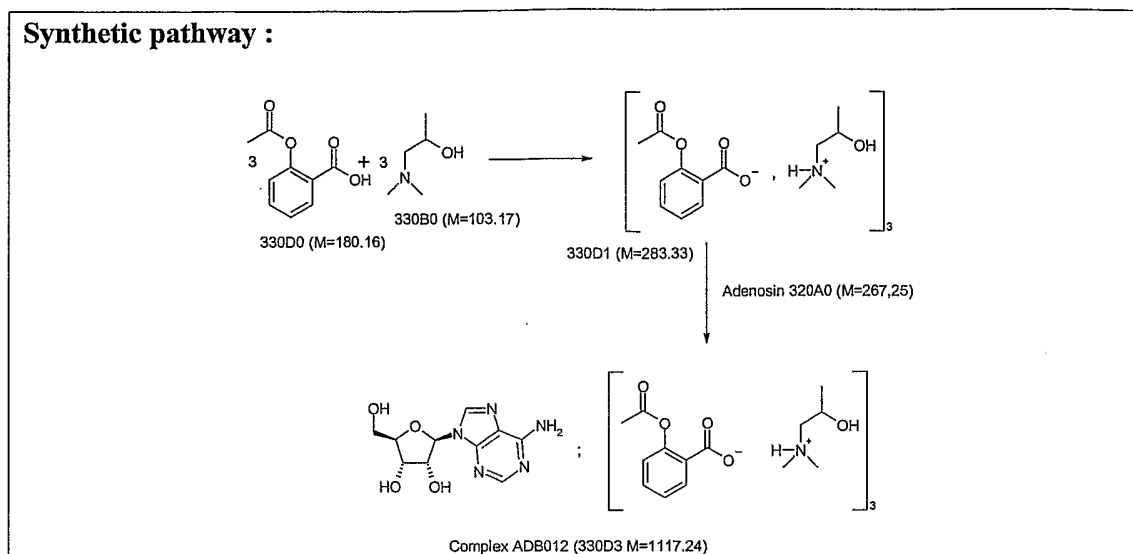
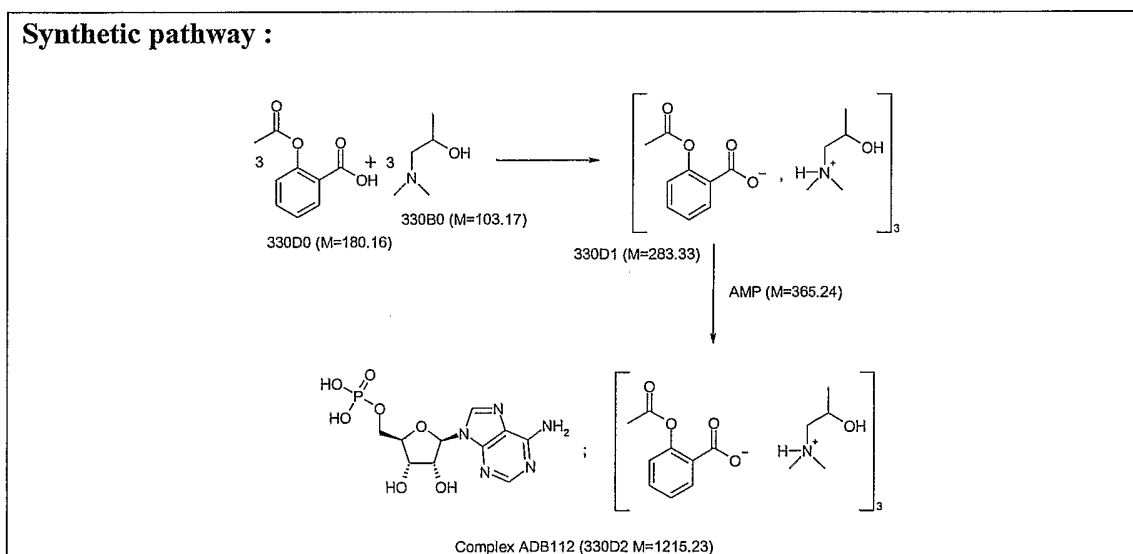


Figure 3c Synthesis of Adb-112



330D0= acetyl salicylic acid

Figure 3d NMR 1H of Adb-012

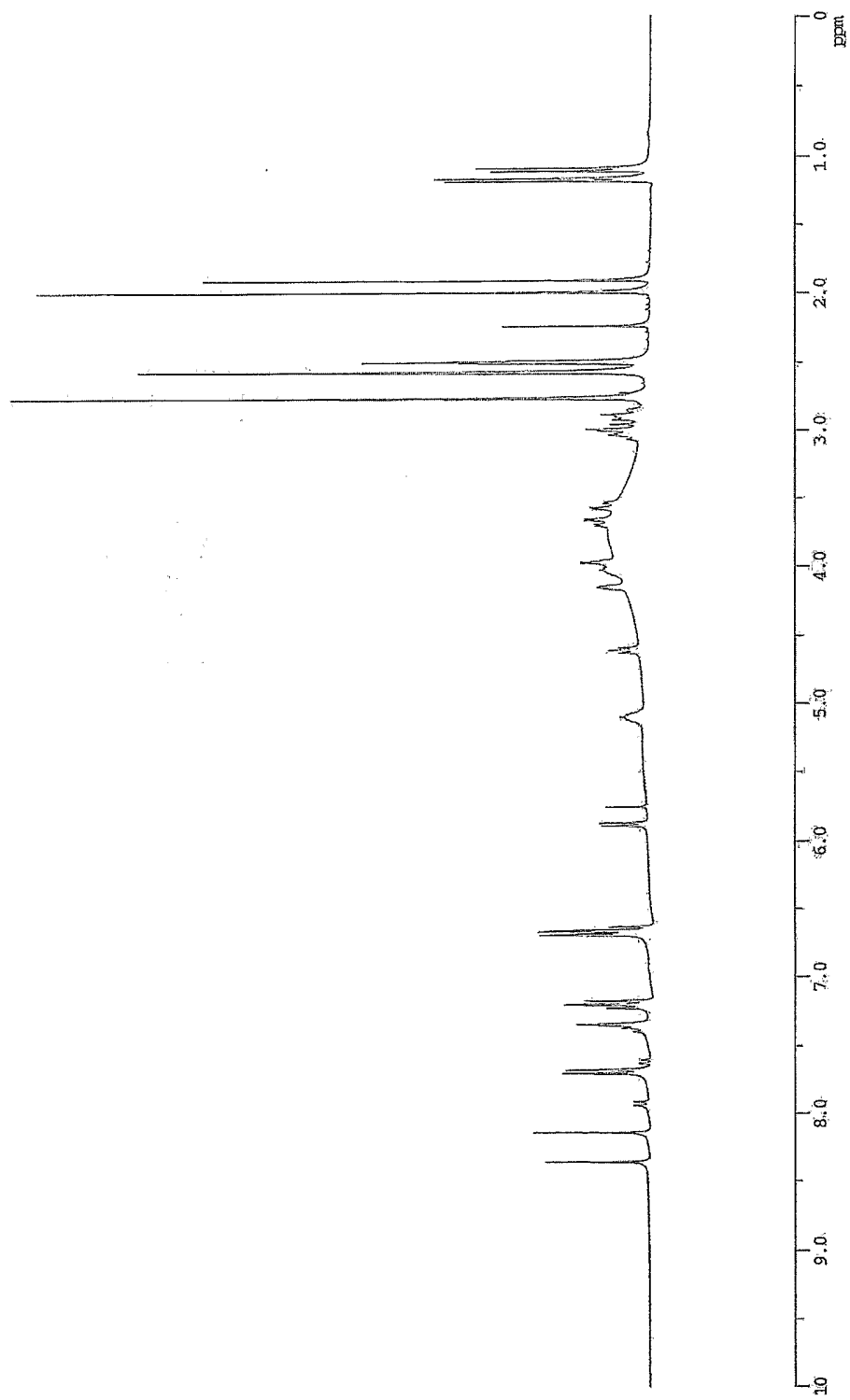


Figure 3e NMR 1H of Adb-112 (DMSO)

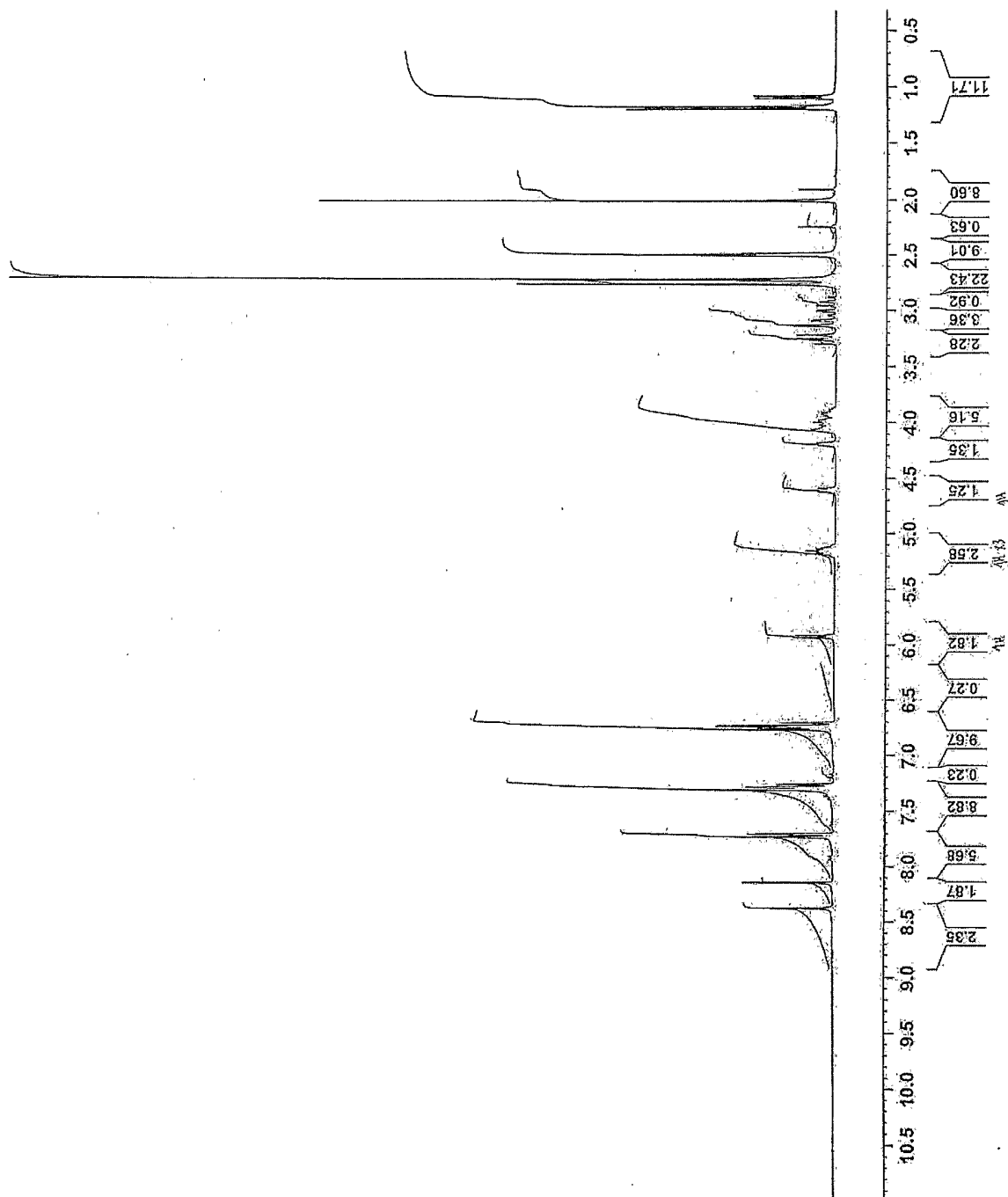


Figure 4. Infra-Red spectrum of ADB011:

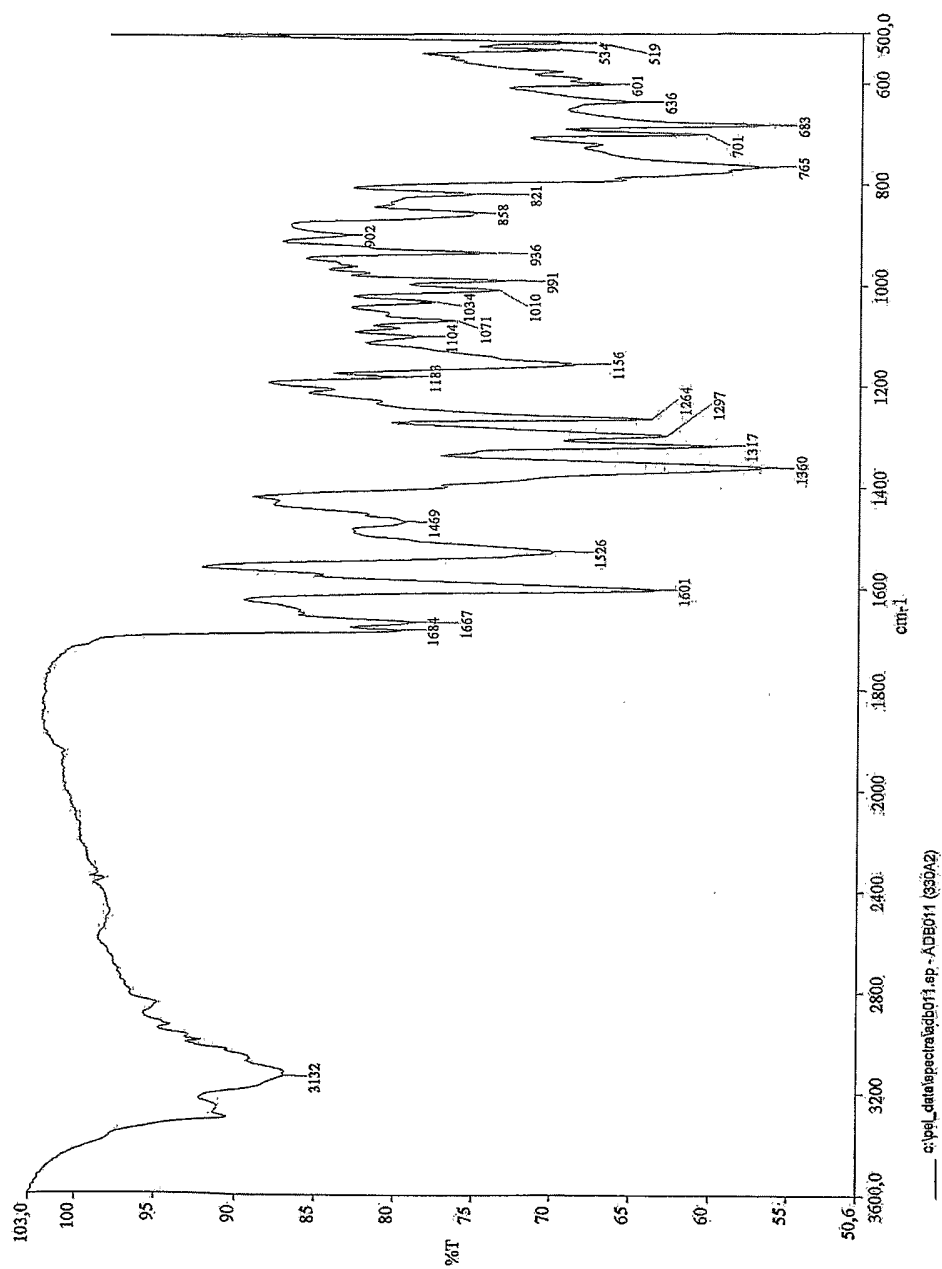


Figure 5. Infra-Red spectrum of ADB111:

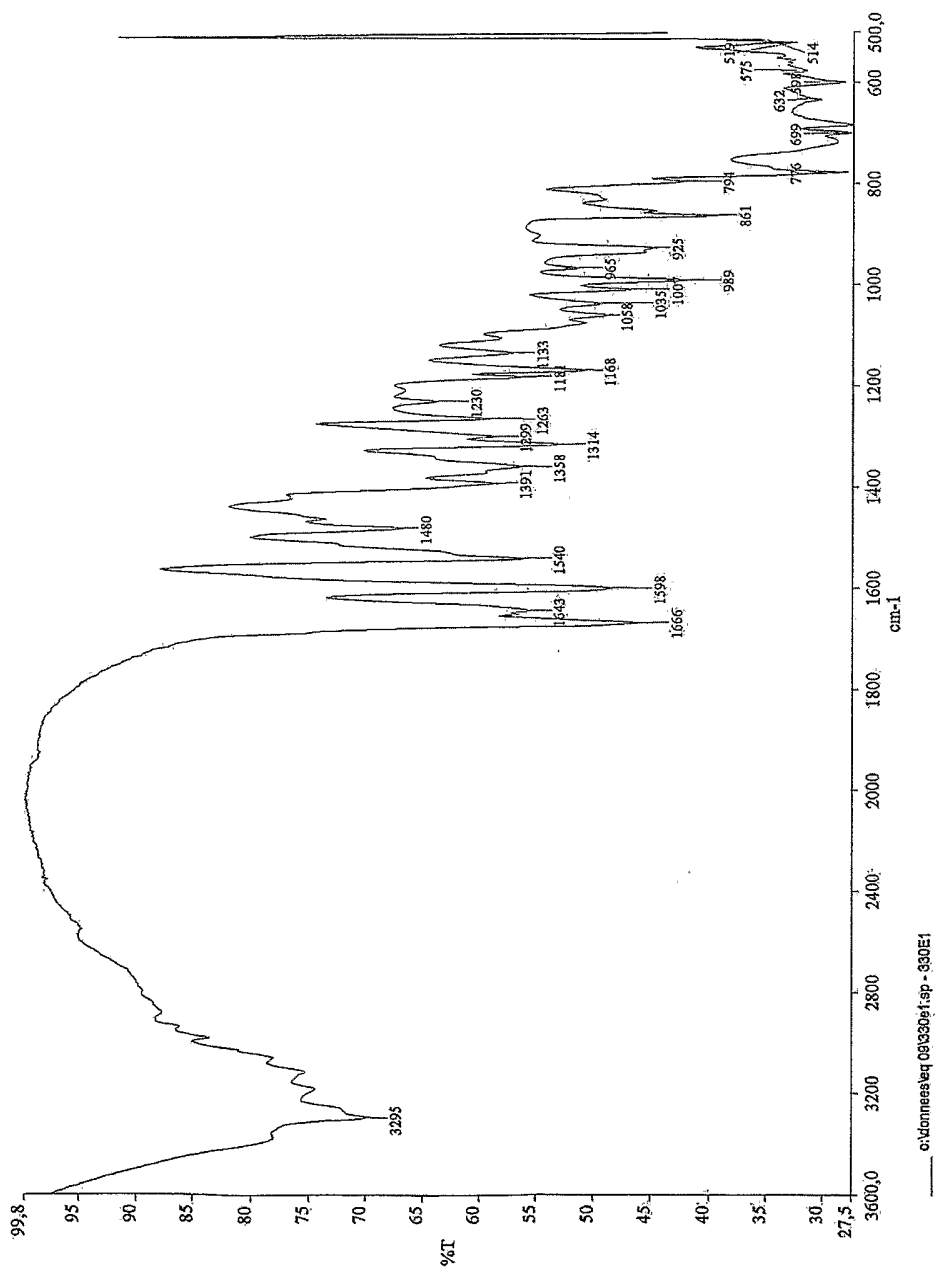


Figure 6. Infra-Red spectrum of ADB311:

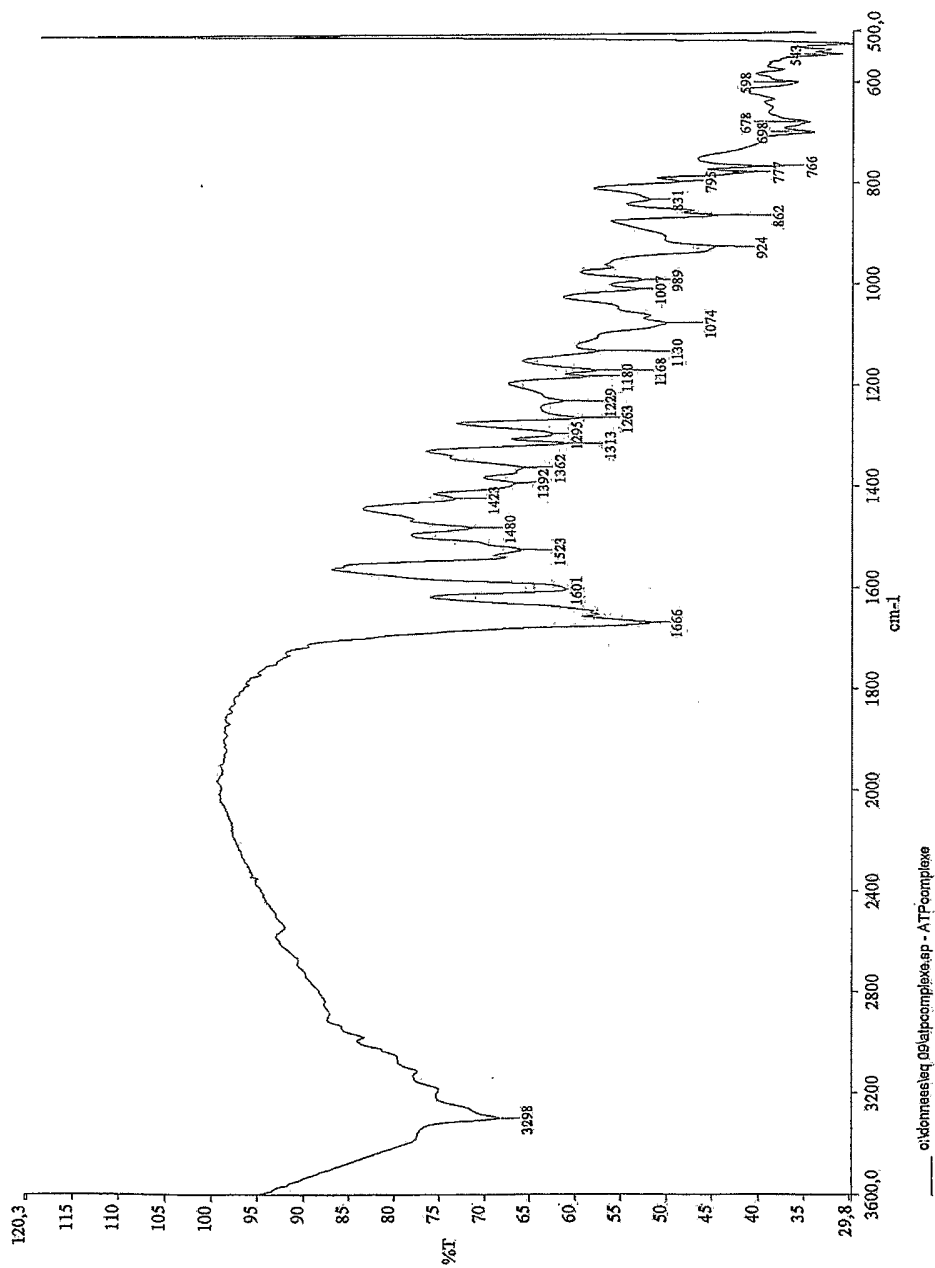


Figure 7. Infra-Red spectrum of the difference between the two spectra, that of ADB011 and that of the mixture adenosine/salt (330A1): 1/3.

Conclusion: Between wave number 2800cm^{-1} and 1800cm^{-1} , no difference is shown between ADB011 and its original components. Between $3600\text{-}3200\text{cm}^{-1}$, and $1700\text{-}500\text{cm}^{-1}$, curves are very different.

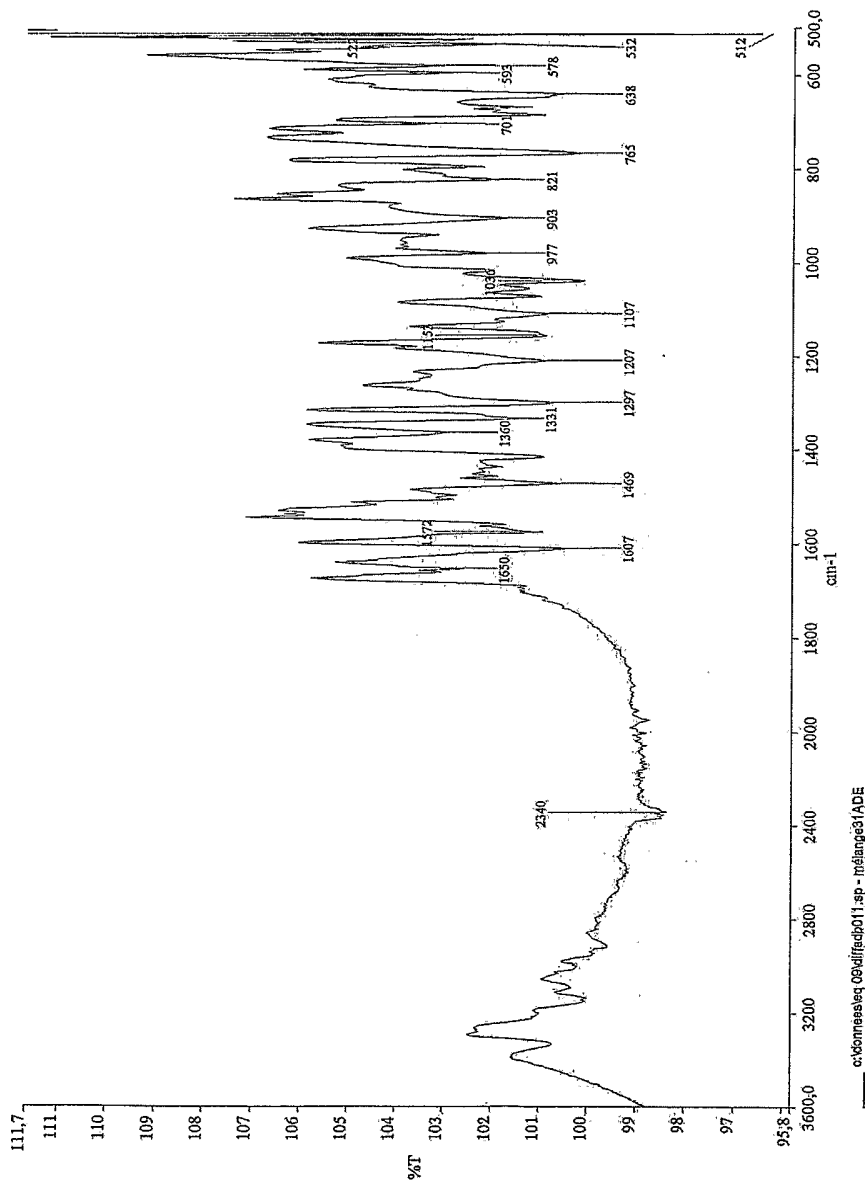


Figure 8. Infra-Red spectrum of the difference between the two spectra: ADB111 (complex AMP with salt) and mixture AMP/salt (330A1): 1/3.

Conclusion: Between wave number 2800cm⁻¹ and 1800cm⁻¹, no difference is shown between ADB111 and its original components. Between 3600-3200cm⁻¹, and 1700-500cm⁻¹, curves are very different.

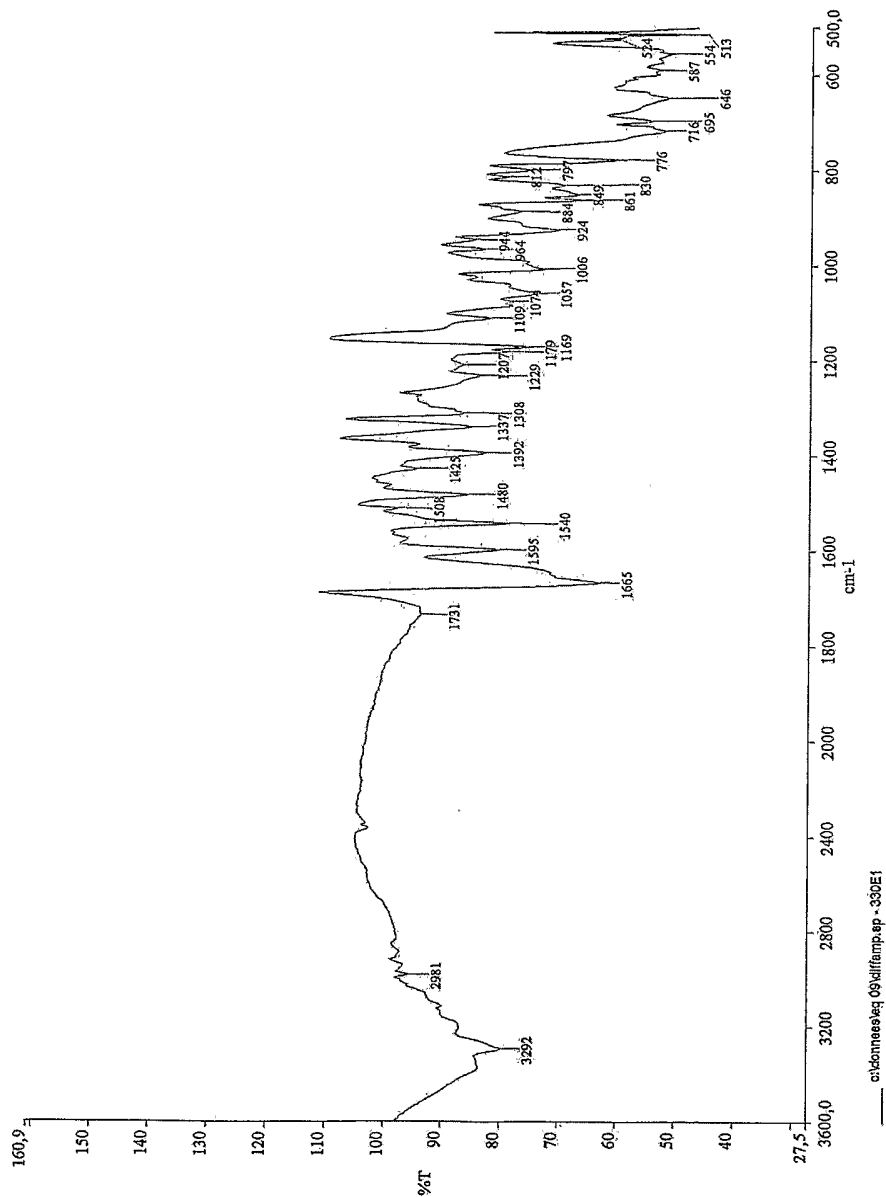


Figure 9. Infra-Red spectrum of the difference between the two spectra: ADB311 (complex ATP with salt) and mixture ATP/salt(330A1): 1/3.

Conclusion: Between wave number 2800cm^{-1} and 1800cm^{-1} , no difference is shown between ADB311 and its original components. Between $3600\text{-}3200\text{cm}^{-1}$, and $1700\text{-}500\text{cm}^{-1}$, curves are very different.

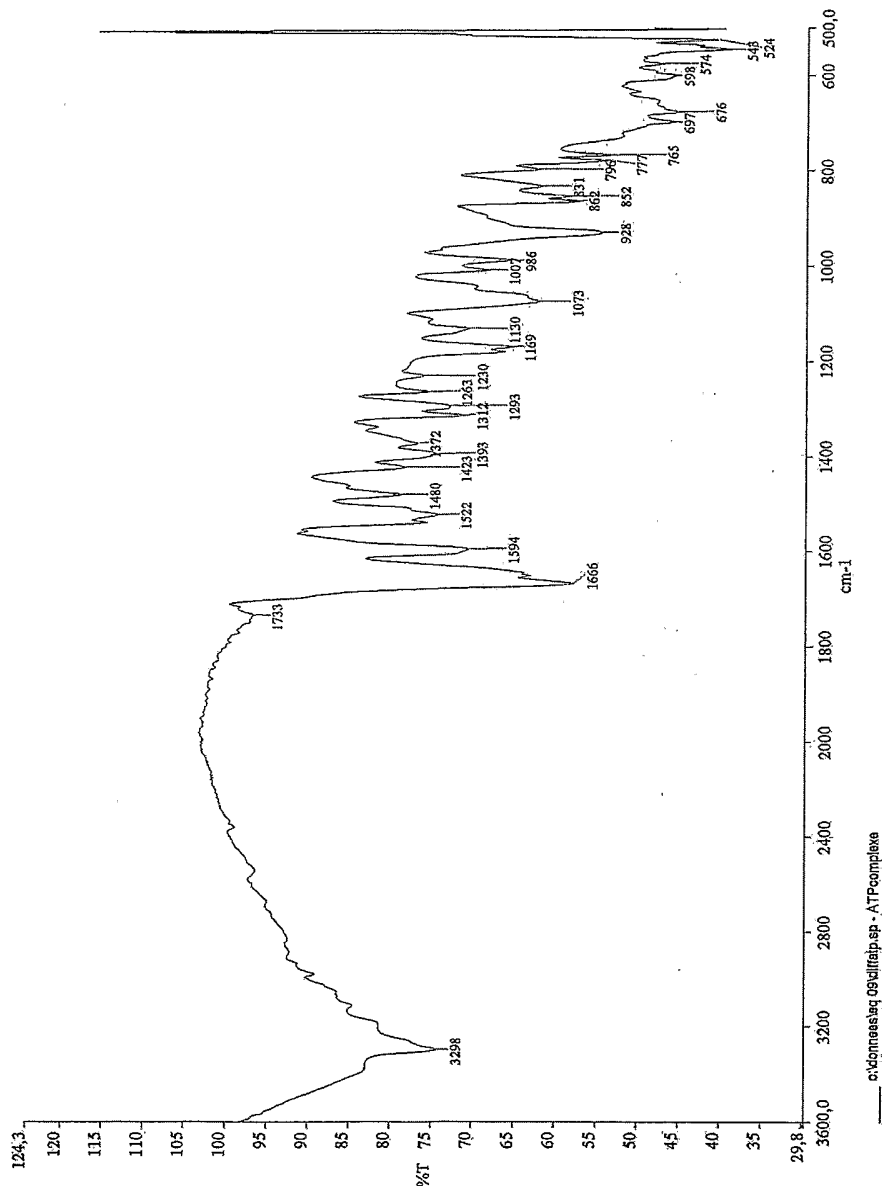
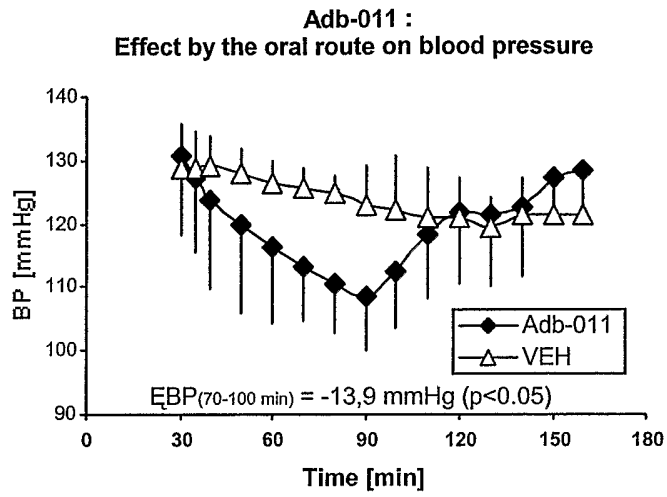


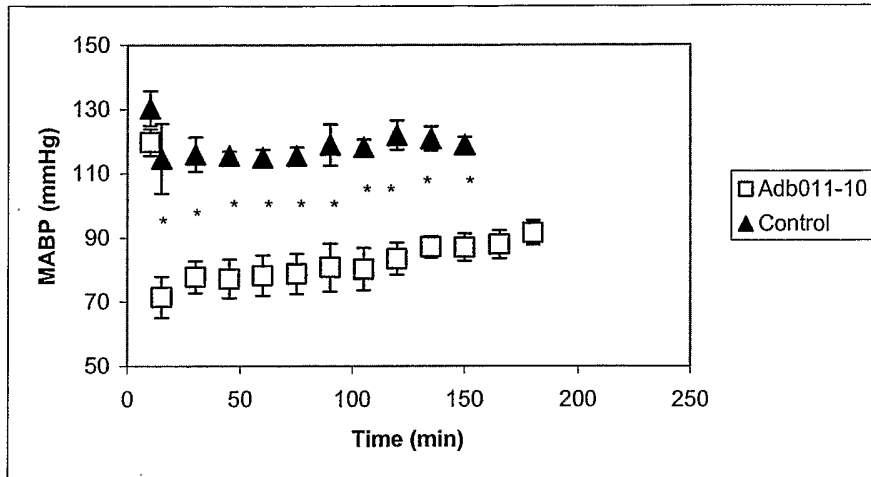
Figure 10. Adb011 : Effects by the oral route on blood pressure



Blood pressure lowering action of oral Adb-011 (p value was calculated by ANOVA multiple measurement analysis followed by Bonferroni-Dunn test).

Figure 11. Effects of Adb011 (complex of adenosine with salt) IV-10mg bolus administration on systemic arterial blood pressure

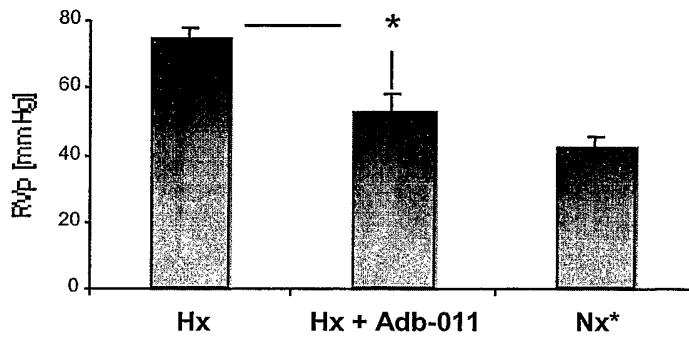
The lowering effect of Adb011 is still strong after two hours. One should compare this to the less than one minute lowering arterial pressure effect of adenosine after a 6mg to 12mg bolus injection in animals and humans (Adenocor, Adenocard monographs).



MAPB (Mean Arterial Blood Pressure) Blood pressure lowering action of oral Adb011-10mg/kg. (p value was calculated by t-test), * p<0.05 Adb011 vs Control

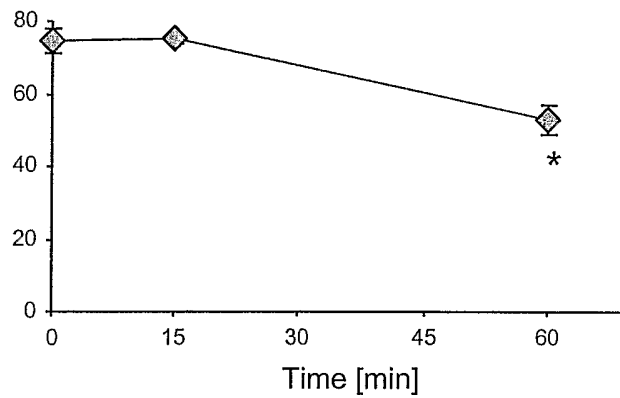
Figure 12

Chronic Adb-011 administration to hypoxic rats with established pulmonary artery hypertension



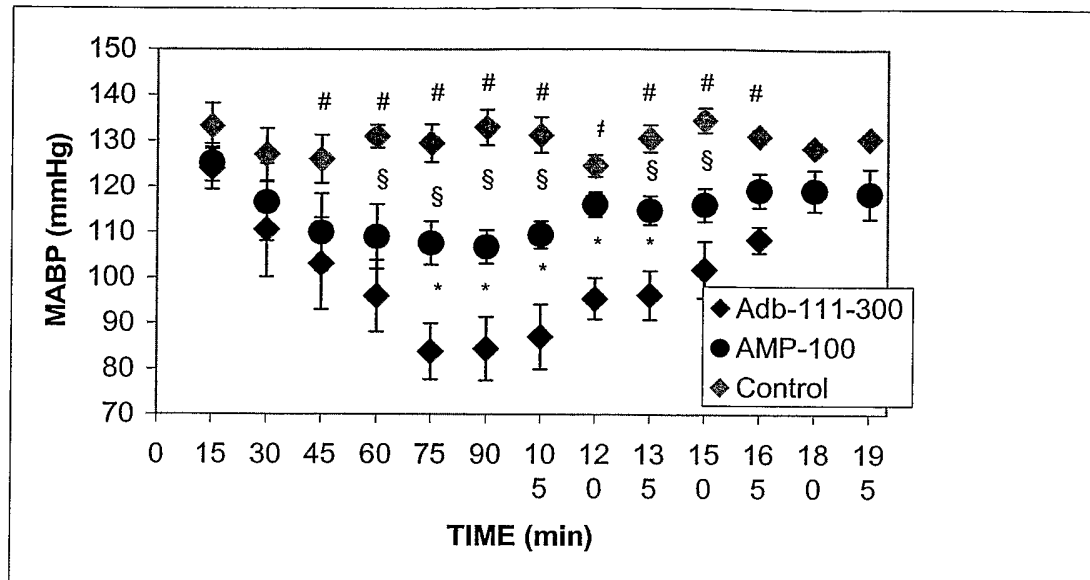
*Effect of orally given Adb-011 (50 mg/kg twice-a-day for 14 days) on right ventricular pressure of hypoxic rats. Values are given as mean \pm SEM. * indicates $p < 0.05$ (Mann Whitney U test). Hx indicates hypoxic rats. Normoxic(Nx) values were from data in Rpt Adb-011 2004/1.*

Acute Adb-011 administration to hypoxic rats with established pulmonary artery hypertension



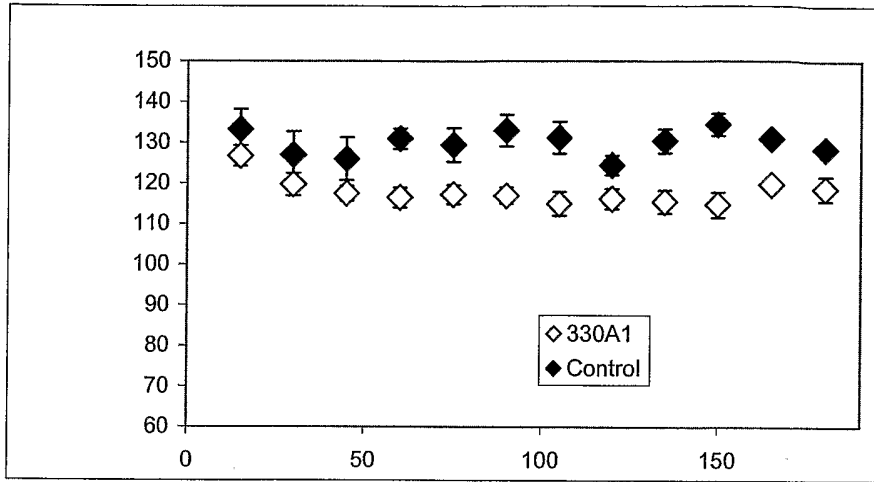
*Effect of a single oral dose of Adb-011 (50 mg/kg) on right ventricular pressure of hypoxic rats. Values are given as mean \pm SEM. * indicates $p < 0.05$ (Mann Whitney U test).*

Figure 13. Adb-111 : Effects by the oral route on systemic arterial pressure in rats. Comparison with oral Adenosine monophosphate

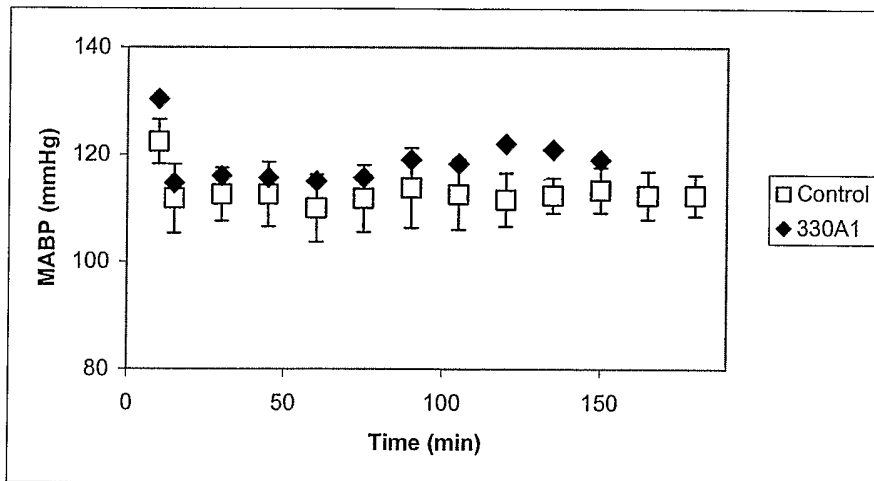


MAPB (Mean Arterial Blood Pressure) Blood pressure lowering action of oral Adb111-300mg/kg. (p value was calculated by t-test) , * p<0.05 Adb111-300 vs AMP-100; § p<0.05 AMP-100 vs control; # p<0.05 Adb111-300 vs control

Figure 14. Effects of orally and intravenously given 330A1 on systemic arterial blood pressure



MAPB (Mean Arterial Blood Pressure) Blood pressure lowering action of oral 330A1-50mg/kg



MAPB (Mean Arterial Blood Pressure) Blood pressure lowering action of IV 330A1-10mg/kg

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/003670

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/7076 A61P9/10 A61P25/00 A61P29/00 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BIOSIS, EMBASE, SCISEARCH, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	<p>GB 879 259 A (RIKER LABORATORIES, INC) 11 October 1961 (1961-10-11)</p> <p>page 3, left-hand column, line 46 - line 65; claims 1,17; example 17</p> <p style="text-align: center;">----- -/--</p>	<p>1,2,4, 6-9,13, 14, 16-19, 21,22, 24-27</p>

Further documents are listed in the continuation of box C

Patent family members are listed in annex.

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- *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
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *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 when the document is taken alone
- *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
- *G* document member of the same patent family

Date of the actual completion of the international search

18 July 2005

Date of mailing of the international search report

01/08/2005

Name and mailing address of the ISA

European Patent Office, P. B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx 31 651 epo nl,
Fax. (+31-70) 340-3016

Authorized officer

Hoff, P

INTERNATIONAL SEARCH REPORT

 International Application No
 PCT/US2005/003670

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	US 3 993 639 A (MAUVERNAY ET AL) 23 November 1976 (1976-11-23) cited in the application	1,7,8, 13, 16-18, 21, 24-26,29
Y	the whole document	2-6, 9-12,14, 15,19, 20,22, 23,27,28
Y	----- US 3 646 007 A (PAUL GORDON) 29 February 1972 (1972-02-29) cited in the application the whole document	2-6, 9-12,14, 15,19, 20,22, 23,27,28
X	----- DATABASE REGISTRY 'Online! 17 May 1986 (1986-05-17), XP002336568 retrieved from STN RN: 102185-19-3 abstract	1,3,4,7, 8
A	----- DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; "N-(1,5-Dimethyl-5-hydroxyhexyl)adenosine- 5'-phosphoramidate sodium salt" XP002336570 retrieved from STN Database accession no. 1984:22972 abstract & JP 58 140100 A2 (YAMASA SHOYU CO., LTD., JAPAN) 19 August 1983 (1983-08-19) -----	1-29

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/003670

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 13-29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.:
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. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. 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 claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2005/003670

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