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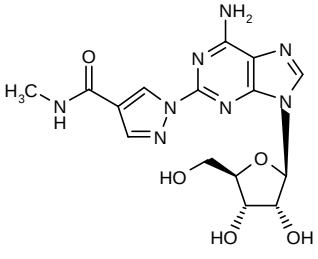
Regadenoson

Prop INN

Adenosine A_{2A} Agonist
Adjunct for Myocardial Perfusion Imaging

CVT-3146

2-[4-(*N*-Methylcarbamoyl)-1*H*-pyrazol-4-yl]adenosine
6-Amino-2-[4-(methylcarbamoyl)-1*H*-pyrazol-1-yl]purine-9-yl-β-D-ribofuranoside



$C_{15}H_{18}N_8O_5$
Mol wt: 390.3582
CAS: 313348-27-5
EN: 288324

Abstract

Coronary vasodilators such as adenosine and dipyridamole, commonly used in pharmacological stress testing, stimulate adenosine A_{2A} receptors. However, both agents also nonselectively stimulate A_1, A_{2B} and A_3 receptor subtypes, resulting in a high incidence of adverse events. Research efforts continue in an attempt to develop novel pharmacological stress agents with fewer unwanted side effects, more selective A_{2A} receptor-agonist effects and which can be administered as a bolus instead of by infusion to produce selective vasodilatation with a rapid onset and short duration of action. Regadenoson is a novel low-affinity A_{2A} receptor agonist that acts more selectively on coronary arteries to cause vasodilatation and increase coronary blood flow. The agent was demonstrated to have a longer duration of coronary vasodilating effects compared to adenosine, while being devoid of the significant hypotension and other adverse events associated with the latter. In clinical trials, regadenoson produced maximal hyperemia which was maintained for a duration optimal for radionuclide perfusion imaging. The agent is in phase III development for use as an adjunctive pharmacological agent in myocardial perfusion imaging for the diagnosis of coronary artery disease.

Synthesis

Regadenoson can be prepared by two related ways:

1) Acylation of guanosine (I) with Ac_2O gives the triacetate (II), which is treated with $POCl_3$ to yield the 6-chloropurine (III). Reaction of compound (III) with pentyl nitrite and diiodomethane affords the 6-chloro-2-iodopurine (IV), which is treated with ammonia in methanol to provide 2-iodoadenosine (V). The reaction of compound (V) with hydrazine hydrate in refluxing ethanol gives 2-hydrazinoadenosine (VI) (1), which is cyclized with (ethoxycarbonyl)malondialdehyde (VII) in a 1:1 mixture of acetic acid/methanol at 80 °C to provide the pyrazoloadenosine (VIII). Finally, this compound is treated with methylamine in water (1-3). Scheme 1.

2) Esterification of 1*H*-pyrazole-4-carboxylic acid (IX) in a conventional way gives the methyl ester (X), which is treated with methylamine to yield *N*-methyl-1*H*-pyrazole-4-carboxamide (XI). Finally, this compound is condensed with 2-iodoadenosine (V) in the presence of a strong base (4). Scheme 2.

Introduction

Physiological stress testing is commonly used to diagnose and characterize coronary artery disease. The procedure measures blood flow to the heart during rest and exercise in conjunction with the administration of radionuclide agents and myocardial perfusion imaging via single photon emission computed tomography (SPECT), echocardiography, positron emission tomography (PET) or cardiovascular magnetic resonance imaging (MRI). However, due to poor physical conditioning and/or medical conditions such as peripheral vascular disease or arthritis, many patients are unable to exercise adequately. The alternative diagnostic method for these patients is pharmacological stress testing in which a pharmacological agent is administered to temporarily increase coronary blood flow, thus mimicking the increase observed

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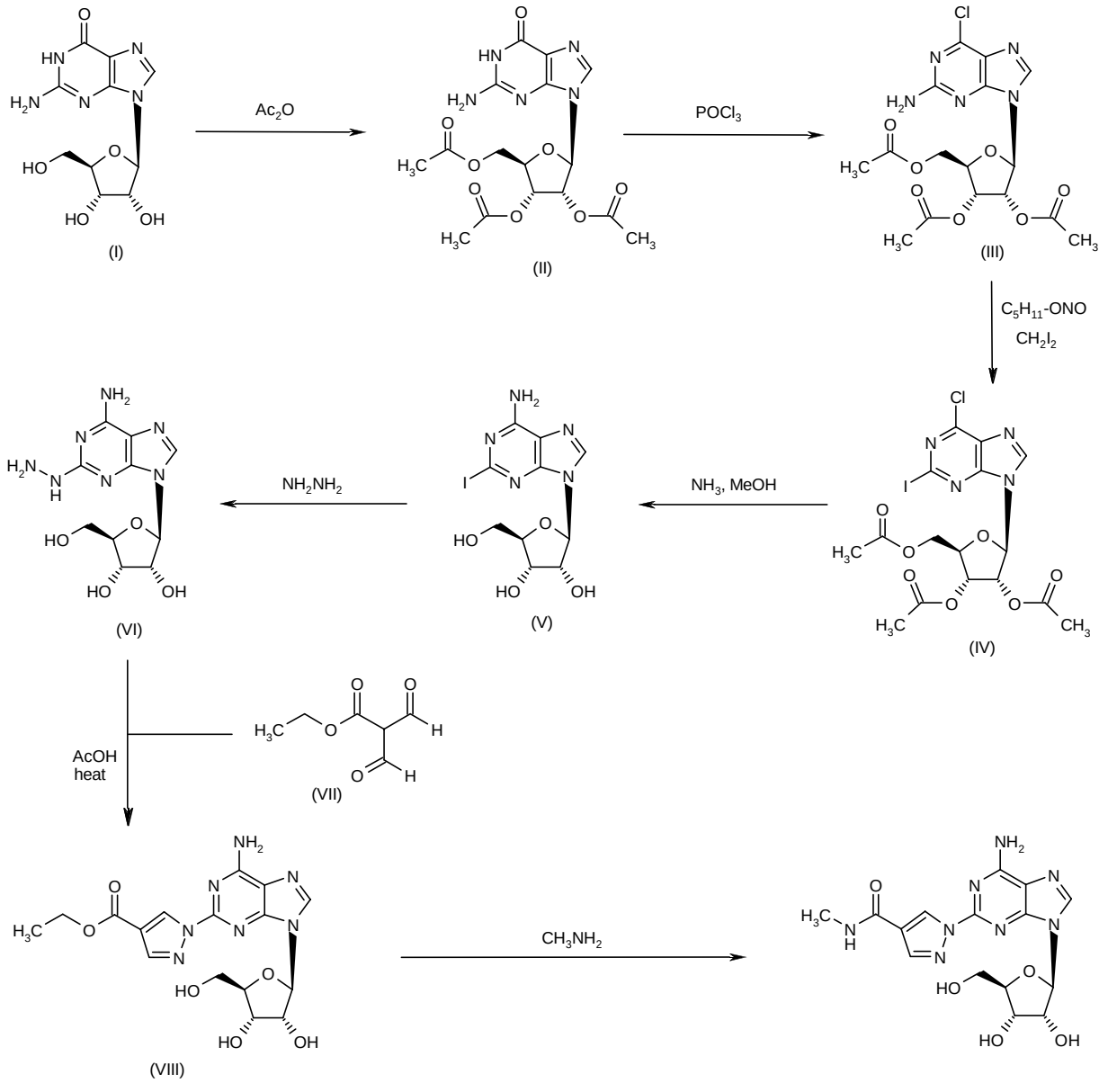
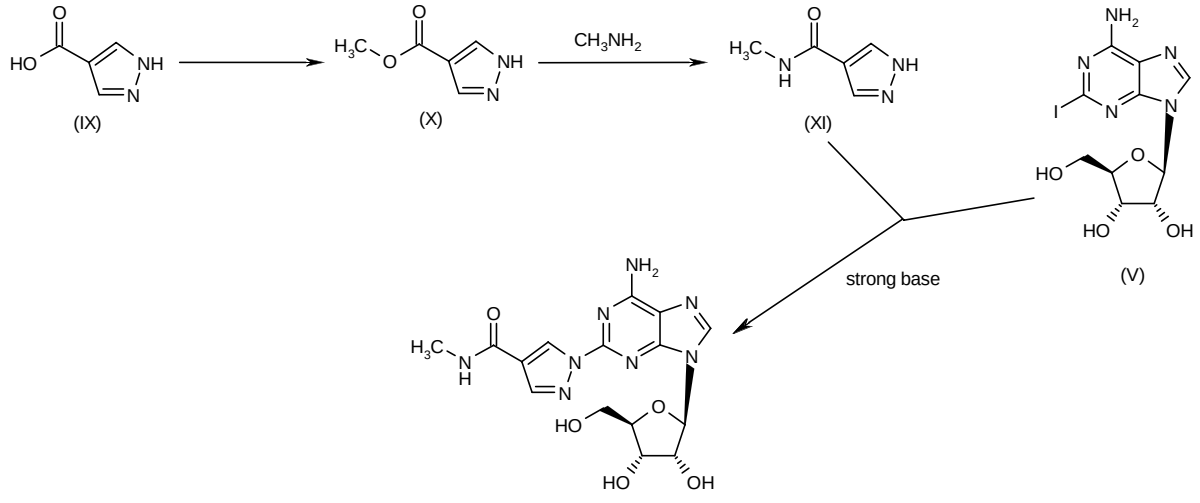
Scheme 1: Synthesis of Regadenoson



during exercise. Intravenous coronary vasodilators, such as adenosine and dipyridamole, that stimulate adenosine A_{2A} receptors on arteriolar vascular smooth muscle cells to cause hyperemic coronary blood flow have been used for more than 20 years in pharmacological stress testing. However, both agents also nonselectively stimulate adenosine A_1, A_{2B} and A_3 receptors, resulting in a high incidence of adverse events, including bronchospasm, dyspnea, chest pain, headache, dizziness and high-grade atrioventricular nodal block. In addition, the duration of coronary vasodilatation induced by adenosine is extremely short and it must be infused intravenously for 4-6 min (5-8).

Hence, researchers have focused their efforts on developing novel pharmacological stress agents with more selective A_{2A} receptor agonism. These novel agents should be suitable for bolus administration instead of via an infusion pump and produce selective vasodilatation with a rapid onset and short duration of action and without unwanted side effects. Unfortunately, the use of potent, high-affinity A_{2A} agonists is limited since the high affinity for the receptor results in an excessively prolonged duration of action, which can lead to significant hypotension. Regadenoson (CVT-3146) is a novel low-affinity adenosine A_{2A} receptor agonist that appears to act

Scheme 2: Synthesis of Regadenoson



more selectively on coronary arteries to cause vasodilatation and increase coronary blood flow. The 2-(*N*-pyrazolyl)adenosine derivative has been shown to have a longer duration of coronary vasodilating effects compared to adenosine, but is devoid of the significant hypotension associated with the latter. Regadenoson was therefore chosen for further development as a pharmacological stress testing agent (2, 3, 9-12).

Pharmacological Studies

Regadenoson was shown in binding and functional studies to be selective for the adenosine A_{2A} receptor (K_i = 0.29 ± 0.01 and 1.12 ± 0.32 μM in rat forebrain and pig striatum, respectively) as compared to A_1, A_{2B} and A_3 receptor subtypes. The agent was discovered to be a weak partial agonist in inducing cAMP accumulation in PC12 cells *in vitro* (EC_{50} = 291 nM), but acted as a potent full agonist in inducing coronary vasodilatation in isolated perfused rat and guinea pig hearts (EC_{50} = 6.4 ± 1.2 and 18.6 ± 6.0 nM, respectively) (2, 3, 9).

Results from experiments conducted in conscious dogs demonstrated the efficacy of regadenoson as a coronary dilator and indicated that the agent is more selective for coronary *versus* peripheral vasodilatation as compared to adenosine. The agent (0.1-5 μg/kg i.v.) dose-dependently increased coronary blood flow (ED_{50} = 0.34-0.45 μg/kg; maximal increase = 205-221%), with comparable efficacy but superior potency compared to adenosine (10-267 μg/kg; ED_{50} = 47-51 μg/kg; maximal increase = 163-227%) (11-13). At a dose of 2.5 μg/kg (10-s i.v. injection), 84% of the maximal hyperemic response was achieved following 20 s of coronary occlusion. The increase in coronary blood flow remained 2-fold above baseline for 97 s, which was significantly longer than with adenosine (24 s at 267 μg/kg). Minimal and transient increases in heart rate and decreases in mean arterial blood pressure were observed following administration of regadenoson, although no atrioventricular block was observed. In contrast, adenosine produced a greater decrease in total peripheral resistance and a greater increase in lower body flow. While regadenoson had no effect on renal blood flow, dose-dependent vasodilatation was observed with adenosine (13-16).

The selectively of regadenoson (1 μg/kg by i.v. bolus) for coronary vasculature was further demonstrated in a study using anesthetized dogs to examine the differential effects on blood flow velocity in different vascular beds. The greatest increase in average peak blood flow velocity occurred in the left circumflex coronary artery (3.1-fold increase) as compared to the brain arterial vasculature (1.4-fold), forelimb artery (1.2-fold) and pulmonary artery (1.1-fold). Treatment with regadenoson caused a small, transient increase in heart rate (16 beats/min) and a decrease in mean arterial pressure (12 mmHg) (17). Further experiments in anesthetized instrumented dogs confirmed the short-lasting and potent coronary vasodilating effects of regadenoson (18).

The effects of regadenoson (2.5 μg/kg for 30 s) and adenosine (280 μg/kg/min for 4.5 min) on the biodistribution and clearance of two radiotracers used in perfusion imaging (1.5 mCi thallium-201 and 25 mCi Tc99m-sestamibi) were also examined in anesthetized dogs. Similar hemodynamic effects, heart uptakes and heart/liver ratios were observed with both agents. Both tracers were cleared from blood monoexponentially for adenosine and regadenoson. However, Tc99m-sestamibi was cleared significantly faster than thallium-201 with regadenoson (clearance half-time = 1.35 ± 0.4 min *vs.* 1.59 ± 0.07 min).

When hearts were excised 5 min after tracer injection and *ex vivo* SPECT images compared, results indicated that regadenoson administered as a bolus in the presence of a critical coronary stenosis produced marked flow heterogeneity and showed significant perfusion deficits with both tracers. During regadenoson stress, thallium-201 produced larger perfusion deficits and tracked flow better than Tc99m-sestamibi (19, 20).

Clinical Studies

A randomized, double-blind, placebo-controlled, ascending-dose, crossover phase I trial in 36 healthy male subjects examined the tolerability and pharmacokinetics of a single dose of regadenoson (0.1, 0.3, 1, 3, 10, 20 or 30 μg/kg by i.v. bolus). Results showed that the agent was well tolerated at doses up to 10 μg/kg both in the supine and standing positions, and that it was associated with potent, short-lasting coronary vasodilating effects. The maximum tolerated dose (MTD) was 20 μg/kg supine and 10 μg/kg standing. Adverse events were generally mild to moderate and short-lived. Dose-limiting adverse events consisted of palpitations, flushing, nausea, vomiting, hyperventilation and headache, and syncope/near syncope at 20 μg/kg standing. No significant alterations in laboratory values were observed with treatment. Dose-dependent increases in heart rate were seen (25-60 beats/min). Using a 3-compartment open model, the initial, intermediate and terminal $t_{1/2}$ values were determined to be 2-4 min, 30 min and 2 h, respectively. Clearance, $t_{1/2}$ and steady-state volume of distribution values were not dose-dependent. There was no correlation between clearance and body weight. It was concluded that weight-adjusted dosing is not required with regadenoson (21).

An open-label phase II trial involving 23 patients undergoing coronary catheterization examined the magnitude and duration of the effects of regadenoson (10-500 μg by i.v. bolus). Dose-dependent and rapid increases in coronary blood flow velocity were observed, which were near peak at 30-40 s after onset of the bolus. The duration of the increase in coronary blood flow velocity was also dose-dependent (4 ± 4.9 min at 300 μg and 6.9 ± 7.6 min at 500 μg). The maximum increase in heart rate (18.7 ± 4 beats/min) and decrease in systolic blood pressure (8.7 ± 7.6 mmHg) were observed with the higher dose. Few adverse events were observed and they were mild and self-limiting and included nausea, flushing and headache (22).

The safety, tolerability and hemodynamic efficacy of regadenoson (200 or 500 μg by i.v. bolus) were evaluated in 36 patients undergoing pharmacological stress SPECT myocardial imaging. Adverse events were noted in 72% of the patients but were generally mild to moderate (96%) and resolved within 15 min (91%). A similar incidence of chest discomfort (33%), headache (25%) and abdominal pain (11%) was recorded for both doses. However, flushing, dyspnea and dizziness were more frequent in the 500-μg group. One serious adverse event requiring hospitalization, *i.e.*, exacerbation of migraine headache, was reported. In 7 and 5 patients, respectively, S-T and T wave abnormalities were seen with treatment. No second- or third-degree atrioventricular block or serious arrhythmias were reported. Peak effects on systolic blood pressure (–5.9 ± 10.7 mmHg) and heart rate (+21.9 ± 10.4 beats/min) occurred at 4 min and within 2 min, respectively; systolic blood pressure did not fall below 90 mmHg. The mean changes in heart rate were greater with the higher dose (23). Efficacy results from this trial comparing regadenoson by i.v. bolus and adenosine by infusion have also been reported. Regadenoson proved to be similar to adenosine in terms of detecting and measuring myocardial ischemia in these patients (24).

Regadenoson is currently undergoing phase III trials for potential use as a pharmacological stress agent in cardiac perfusion imaging studies (25).

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CV Therapeutics, Inc. (US); Fujisawa Healthcare, Inc. (US) (exclusive licensee for North America).

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