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2-SUBSTITUTED PI SYSTEM DERIVATIVES OF ADENOSINE THAT ARE CORONARY VASODILATORS ACTING VIA THE A_{2A} ADENOSINE RECEPTOR

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ABSTRACT

Compound **20** (CVT-3146 - a 2-[(N-1-(4-N-methylcarboxamidopyrazolyl)] adenosine derivative) and compound **31** (CVT-3033 - a 2-[(4-(1-N-pentylpyrazolyl)] adenosine derivative), were found to be short acting functionally selective coronary vasodilators (CV t_{0.5} = 5.2 ± 0.2 and 3.4 ± 0.5 min, respectively - rat isolated heart 50% reversal time) with good potency (EC₅₀s = 6.4 ± 1.2 nM and 67.9 ± 16.7 nM, respectively), but they possess low affinity for the ADO A_{2A} receptor (K_i = 1122 ± 323 nM and 2138 ± 952 nM, respectively; pig striatum).

INTRODUCTION

Initially, A_{2A} adenosine (ADO) agonists, such as CGS-21680 and YT-146 (Compounds **1** and **2**, respectively Fig. 1) were developed for there peripheral vasodilator effect for the treatment of hypertension (1–3). In the last decade, another use for A_{2A} ADO agonists is as coronary vasodilators in conjunction with radionuclide imaging of the heart or echocardiography to detect and provide prognostic assessment of underperfused areas of myocardium. Currently, adenosine is used in

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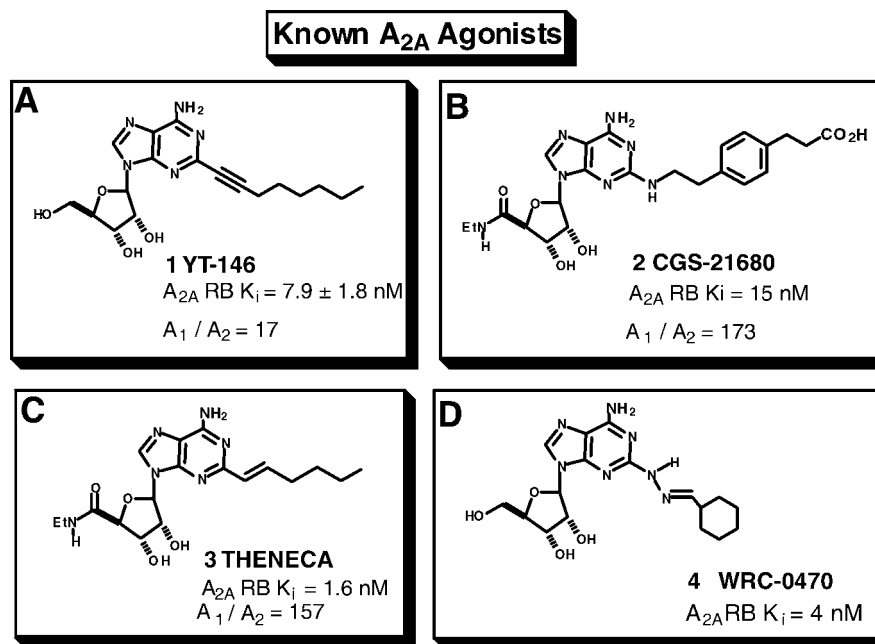


Figure 1. Examples of compounds from the three classes of Ado A_{2A} agonists that contain a lipophilic 2-substituent, and their affinity for the rat brain (RB, forebrain) Ado A_{2A} receptor: pi system linker – compound **1** (YT-146) (2) and compound **3** (THENECA) (10) Panels A and C; heteroatom linker – compound **2** (CGS-21680) (1) panel B; and pi system and heteroatom linker – compound **4** (WRC-470) (6) panel D. The K_i for THENECA is from reference 10.

“pharmacological stress” tests during myocardial imaging with excellent diagnostic and prognostic value, however, a high percentage of patients that receive adenosine experience a number of drug related side effects (4–5). We and others (6–9) have hypothesized that a selective A_{2A} Ado agonist may have fewer side effects than adenosine itself. Therefore, our goal was to synthesize a coronary (not peripheral) vasodilator that is functionally selective for the A_{2A} Ado receptor, and test that it’s effect is rapid in onset but short in duration.

There are three classes of Ado A_{2A} agonists based on different 2-substituted adenosine derivatives with illustrative examples shown in Figure 1. The first class contains a pi system at the 2-position, exemplified by the acetylenic and trans double bonds of YT-146² and THENECA (10) respectively (Compounds **1** and **3**), that are used to extend a hydrophobic chain into a putative lipophilic pocket in the Ado A_{2A} receptor. A second class of A_{2A} Ado agonists contain a 2-heteroatom alkyl linker to a hydrophobic group that is exemplified by CGS-21680 (compound **2**, Fig. 1) (1). A third class of 2-substituted A_{2A} adenosine agonists contains both a 2-heteroatom linker and a pi system, and it is exemplified by WRC-0470 (compound **4**, Fig. 1) (6). All of the agonists shown in Figure 1 have high affinity for the A_{2A} receptor, and possess low affinity for the A₁ receptor (note: WRC-470, compound **4**, has been shown to be functionally selective for the ADO A_{2A} receptor compared to A₁ receptor (6)).

Our four classes of A_{2A} Ado agonists that are 2-substituted pi system derivatives of adenosine have design features related to those shown in Figure 1 where the trajectory of the hydrophobic 2-substituent from the purine ring of adenosine approximates one of the three classes described above. The first class, a 2-propargyl phenyl ether Ado derivatives, has the same linker as YT-146 (**4**), but a different hydrophobic element than YT-146 (**4**) or (S)-PHPNECA (**10**) (**5**) shown in Figure 2 (Panel A). The propargyl phenyl ether has only a hydrogen bond acceptor in the ether oxygen, whereas the (S)-PHPNECA (**5**) has both a hydrogen bond acceptor and a donor in the hydroxyl group. This structural difference may impart different biological properties (see modeling section below). In class two (Panel B), the 2,5-thienyl class of A_{2A} Ado agonists has a hydrophobic group with a 164° trajectory relative to the 180° trajectory of the acetylene linker (Fig. 2, Panel B). Class three is a 2-[(4-(1-N-substituted pyrazolyl)] adenosine series (C-Pyrazole class, Fig. 2, Panel C) that has the same 152° trajectory as that of the THENECA (**3**) derivative shown in Figure 1. Similarly, the 2-[(N-1-(4-substituted pyrazolyl)] adenosine series (N-pyrazole class **4**) has a 152° trajectory, but also contains a 2-heteroatom linker and a pi system like WRC-470 (**4**). This class was designed by envisioning a 5-membered pyrazole ring obtained through closing the hydrazone as illustrated in Figure 2 (Panel D).

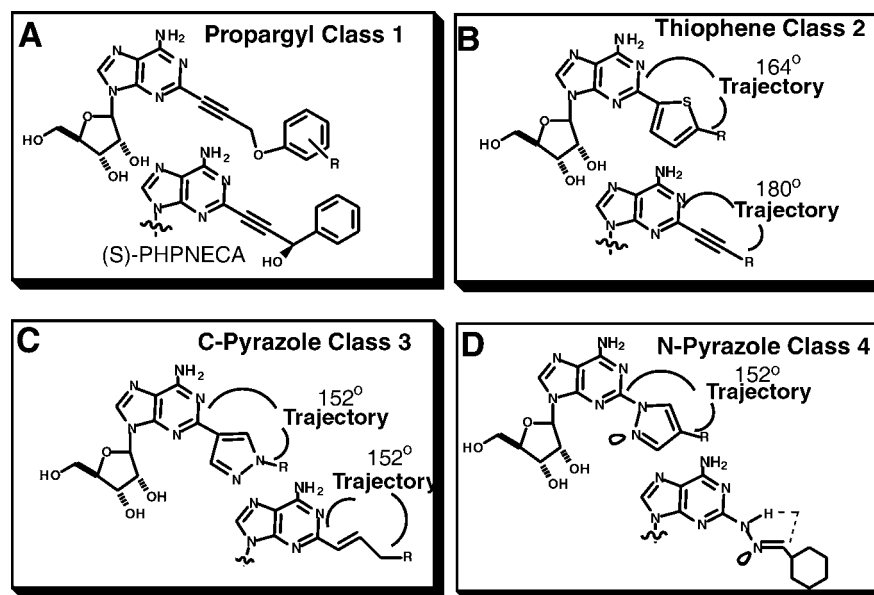
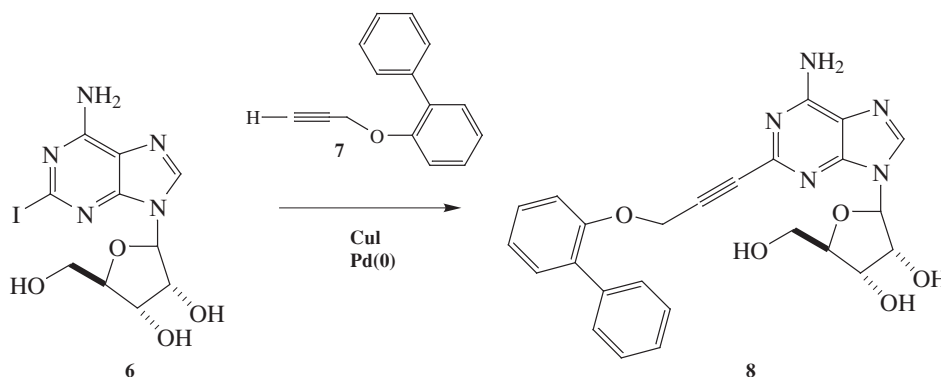


Figure 2. Our four classes of Ado A_{2A} agonists that are 2-substituted pi system derivatives of adenosine: propargyl phenyl ether class 1 is related to (S)-PHPNECA (Cristalli et al (10)); 5-substituted thiophene class 2 presents a lipophilic substituent at a 164° trajectory that is compared to the 180° trajectory of the acetylene class 1; C-pyrazole class 3 has an identical trajectory to THENECA; N-pyrazole class 4 can be viewed as a constrained hydrazone mimetic.



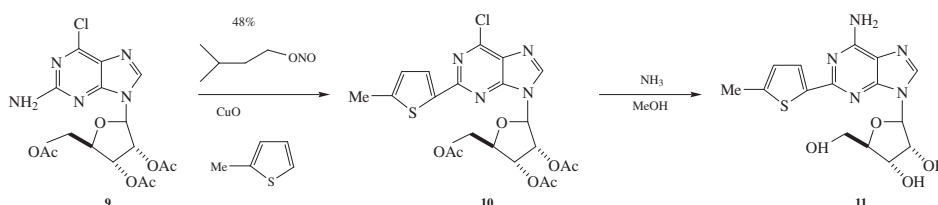


Scheme 1.

CHEMISTRY

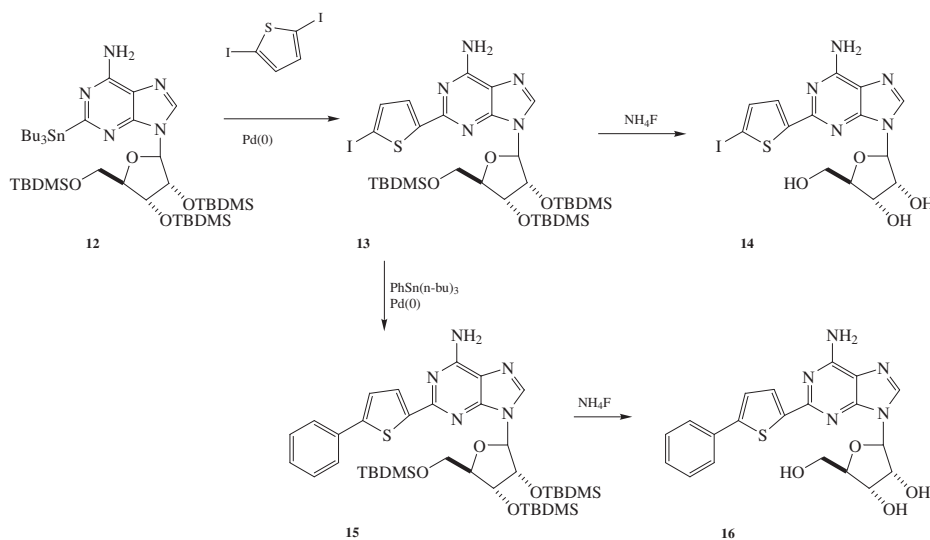
The synthesis of new compounds and intermediates from the 2-propargyl phenyl ether, 2-thienyl, and 2-(1-N-pyrazolyl) adenosine series are illustrated in Schemes 1–4. Members of the 2-(4-pyrazolyl) and 2-(N-1-pyrazolyl) adenosine series are described elsewhere (8,9). The preparation of the propargyl phenyl ether class utilizes a palladium mediated coupling reaction between the previously described iodo derivative (11,12) **6** and the propargyl phenyl ether **7** as shown in Scheme 1. The iodo derivative **6** is derived from guanosine in four steps involving introduction of a 6-chloro group (POCl₃), diazotization of the 2-amino group, and a *in situ* radical trapping to introduce the 2-iodo group (11,12). The propargyl phenyl ethers were all prepared in greater than 85% yield through the reaction of propargyl bromide with the corresponding phenolic compounds in the presence of potassium carbonate as base.

The 2-thienyl adenosine series was prepared through diazotization of the previously described 2-amino derivative (11,12) **9**, and a *in situ* radical trapping to introduce the 2-(5-methylthienyl) group of compound **10** as shown in Scheme 2 (13). Introduction of the 6-amino group and deprotection was accomplished through treatment with ammonia in methanol to yield compound **11**. The 2-(5-iodothieryl) and 2-(5-phenylthienyl) adenosine derivatives **14** and **16** respectively were prepared from the previously described 2', 3', 5'-trisilylated 2-stannyl derivative (14) **12** through a palladium mediated Stille coupling involving 2,5-diiodothiophene as



Scheme 2.

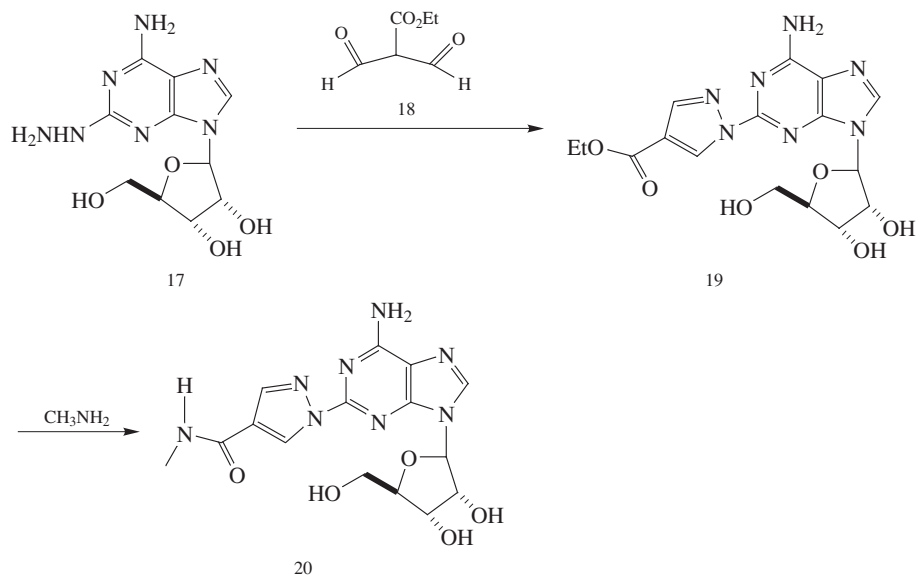




Scheme 3.

shown in Scheme 3. The 2-(5-iodothiophenyl) adenosine derivative **13** was converted to the triol **14** by treatment with ammonium fluoride (15). A second Stille coupling between 2-(5-iodothiophenyl) adenosine derivative **13** and commercially available tributylphenyl stannane resulted in 2-(5-phenylthiophenyl) adenosine derivative **15** that was deprotected by treatment with ammonium fluoride to yield compound **16**.

The preparation of the new compounds of the 2-(N-1-pyrazolyl) adenosine series is shown in Scheme 4. The 2-hydrazino adenosine derivative (16) **17** was



Scheme 4.

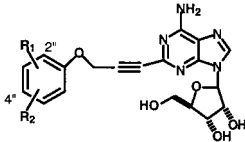
condensed with the known dialdehyde (17) **18** in a 1:1 mixture of acetic acid: methanol at 80°C to generate the ester **19**. The ester was converted to various amides by direct amine displacement or conversion to the acid and standard dehydrative coupling (see experimental for details).

RESULTS AND DISCUSSION

Our goal was to obtain a short acting coronary vasodilator that is functionally selective for the A_{2A} Ado receptor. Four classes of 2-substituted pi system derivatives of adenosine were evaluated for the affinity of individual members for both pig brain (PB) and rat brain (RB) A_{2A} Ado receptor, and their time to achieve 50% reversal of coronary vasodilatation (CV t_{0.5}) in isolated rat hearts (Tables 1–3). The CV t_{0.5} was used as the principle screen for compound selection for further characterization with respect to selective affinity (Table 4), and more importantly functional selectivity for A_{2A} Ado receptor mediated effects as opposed to A₁ Ado receptor mediated effects. The objective was to obtain a compound with a CV t_{0.5} that was two to three times longer than that of adenosine (CV t_{0.5} = 1.60 min) with the purpose to have an agent to be administered as a bolus, and still produce a coronary vasodilatation suitable for distribution and uptake of radionuclide agent by the myocardium. Based on this criteria, compounds **20** and **31** were chosen for further characterization with respect to selectivity (Tables 3 and 4, respectively). A detailed discussion of the structure activity relationships (SAR) that led to this choice follows.

The affinity of individual members of the 2-propargyl phenyl ether class for the A_{2A} Ado receptor, and their CV t_{0.5} are shown in Table 1. The unsubstituted propargyl phenyl ether derivative **21** and the phenylmethylenedioxy derivative **22**

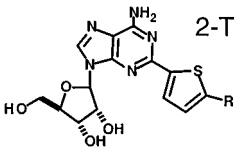
Table 1. Affinity of Propargyl Ether Class 1 for Ado A_{2A}

				Propargyl Phenyl Series 1	
Compd #	R ₁	R ₂	PB K _i A _{2A} nM	Rat t _{0.5}	Min t _{0.9}
21	H	H	14 ± 2	17.5	23.2
22	3,4-OCH ₂ O-	H	18	NT	NT
23	4-CN	H	93 ± 14	16.7	25.6
8	2-Ph	H	230 ± 45	NT	NT
24	2-CH ₂ Ph	H	58 ± 47	16.1	21.8
25	4-Ph	H	1030 ± 145	NT	NT
26	3-But	5-But	> 10,000	NT	NT

PB stands for Pig Brain (striatum).



Table 2. Affinity for Ado A_{2A} and Time for 50% Reversal of Coronary Vasodilation (CV $t_{0.5}$) in Isolated Rat Hearts



2-Thiophene Series 2

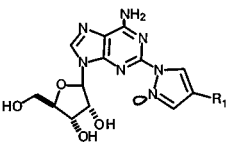
Cmpd #	R ₁	PB K _i A _{2A} nM	Rat $t_{0.5}$	Min $t_{0.9}$
27	H	1000 ± 175	3.4 ± 0.2	9.2 ± 2.2
11	5-Me	692 ± 102	5.1 ± 0.1	10.1 ± 0.3
14	5-I	> 10,000	—	—
16	5-Ph	> 10,000	—	—

PB stands for Pig Brain (striatum). The compounds were given as a bolus at approximately three times the EC₅₀.

had the highest affinities for the A_{2A} Ado receptor when compared to all of the compounds tested with K_i's of 14 ± 2 nM and 18 nM, respectively (PB, Table 1). A 2''-phenyl compound **8** had four times the affinity of the 4''-phenyl compound **25**, and a 2''-benzyl compound **24** had four times the affinity of compound **8**. Thus, it appears that a lipophilic substituent at the 2'' position was well tolerated. The sterically demanding 3,5-ditert-butylphenyl derivative **26** was not well tolerated by the A_{2A} Ado receptor demonstrating a limit to the tolerance for large lipophilic groups. Compounds **21**, **23**, and **24** had high affinities (<100 nM PB) for the A_{2A} Ado receptor, and their CV $t_{0.5}$'s were greater than ten times that of adenosine.

The affinity of individual members of the 2-thienyl class for the A_{2A} Ado receptor, and their CV $t_{0.5}$ are shown in Table 2. Both the unsubstituted 2-thienyl

Table 3. Affinity for Ado A_{2A} and Time for 50% Reversal of Coronary Vasodilation (CV $t_{0.5}$) in Isolated Rat Hearts

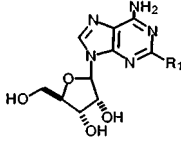
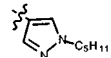
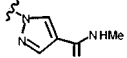
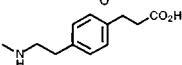


N-Pyrazole Series 4

Cmpd #	R ₁	PB K _i A _{2A}	nM RB K _i A _{2A}	Rat Heart $t_{0.5}$	Min $t_{0.9}$
19	-CO ₂ Et	60 ± 29	1280 ± 430	14.8 ± 3.6	15.0 ± 1.6
20	-CONHMe	1122 ± 323	290 ± 10	5.2 ± 3.6	11.5 ± 2.7
28	-CONHEt	380 ± 130	60 ± 10	—	—
29	-CONHPr	120 ± 20	50 ± 20	—	—
30	-CONHc-Pent	140 ± 20	50 ± 10	—	—
32	-(Ph-4-Me)	490 ± 156	190 ± 50	14.2 ± 2.8	19.3 ± 4.6

PB stands for Pig Brain (striatum), and RB stands for Rat Brain (forebrain). The compounds were given as a bolus at approximately three times the EC₅₀.

Table 4. The Selective Affinity of Compounds **20** (CVT-3146) and **31** (CVT-3033) for Human Ado Receptors Versus **2** (CGS-21680)

Cmpd	R ₁			
		HEK h-A _{2A} nM	A ₁ /A _{2A}	CHO h-A ₁ nM
31		2895	2.0	5836
20		1269	13.0	> 16460
2		609	5.8	> 3540

The affinity for human Ado receptor A_{2A} was tested in human embryonic kidney cells (HEK) using [³H]-ZM241385. The affinity for human Ado receptor A₁ was tested in chinese hamster ovary cells (CHO) using [³H]-CPX.

derivative **27** and the 2-(5-methylthienyl) derivative **11** had low affinity for the A_{2A} Ado receptor; however, their CV t_{0.5}'s were approximately two to three times that of adenosine. These compounds were not further evaluated, because compound **11** was positive in the Ames test. Surprisingly, the 2-(5-iodothienyl) compound **14** and the 2-(5-phenylthienyl) compound **16** were not active at 10,000 nM (PB, Table 2). This series requires further investigation to test the trajectory from the purine ring of 162° with a more flexible lipophilic substituent, but the positive Ames test on a related member precludes further exploration of this series for drug development purposes.

The affinity of individual members of the 2-(N-1-pyrazolyl) adenosine class for the A_{2A} Ado receptor, and their CV t_{0.5} are shown in Table 3. Again, the high affinity ester derivative **19** had a long CV t_{0.5} (>nine times adenosine). Conversion of the ethyl ester of **19** to the N-methylamide of **20** resulted in a large decrease in affinity, but a more favorable CV t_{0.5} (three times adenosine). A trend is developing wherein high affinity compounds took a longer time to achieve CV t_{0.5} than low affinity compounds. We hypothesize that the lower affinity compounds may have a more favorable off rate from the receptor leading to a shorter pharmacodynamic effect in the heart. Compounds **28**, **29**, and **30** suggest that by replacing the N-methylamide of **20** by amides containing a larger lipophilic group the affinity for the A_{2A} Ado receptor is returned to the level of ethyl ester **19** (RB data Table 3). The importance of the nature of the heteroatoms within the 2-heterocyclic substituent is made apparent in comparison of 4-methylphenyl derivative **32** and 2-(5-phenylthienyl) Ado derivative **16** (Table 2). Compound **16** has poor affinity (>10,000 nM, Table 2), but the similarly substituted 2-(1-N-pyrazolyl) **32** has an affinity of 490 ± 156 nM (Table 3). We hypothesize that the 2-pyrazolyl nitrogen may accept a hydrogen bond from the receptor, and orient the phenyl substituent in



the case of compound **32**. This interaction would not be expected from the sulfur of the thienyl group found in compound **16**.

The SAR of the 2-(4-pyrazolyl) adenosine class for the A_{2A} Ado receptor has been previously described (8). The lead compound that has been further characterized for selective affinity and functional selectivity is the 2-[(4-(1-N-pentyl pyrazolyl)] adenosine derivative **31** (Table 4), and its affinity for the A_{2A} Ado receptor is $K_i = 2138 \pm 952$ and $K_i = 2590 \pm 320$ (PB and RB, respectively). The trend appears to hold, because the low affinity compound **31** had a CV $t_{0.5}$ twice that of adenosine (2.97 ± 0.2 min).

The two lead compounds **20** and **31** were further evaluated for their selective affinity for the human A_{2A} Ado receptor versus the human A_1 Ado receptor (Table 4). One well known side effect of the use of adenosine as a pharmacological stress agent in patients is the negative dromotropic effects (AV block) of adenosine that is mediated through activation of the A_1 Ado receptor in the AV nodal cells (4,5). Thus, a focus was placed on obtaining a functionally selective agent that would induce coronary vasodilatation without negative dromotropic effects (i.e. prolongation of AV nodal conduction time). These pharmacological studies will be described in complete detail elsewhere (18). The N-pyrazole compound **20** has a more favorable selectivity with respect to affinity A_{2A}/A_1 than the C-pyrazole compound **31** (Table 4), but both compounds were found to be functionally selective for coronary vasodilatation in isolated rat hearts without any negative dromotropic effects observed at high concentrations ($500 \times EC_{50}$ for vasodilatation) (18). In spite of their relatively low affinity for the Ado A_{2A} receptor, both compound **20** and compound **31** had favorable EC_{50} 's relative to adenosine for coronary vasodilatation, EC_{50} 's = 6.4 nM and 68 nM respectively (Ado $EC_{50} = 59$ nM). Previously, Belardinelli (19) and Shryock have described in detail the high receptor reserve of the A_{2A} receptor mediated coronary vasodilatation. Further details regarding the exploitation of this A_{2A} receptor reserve will be described in subsequent papers (18). Compound **20** was further evaluated for its selectivity by testing the affinity against other human Ado receptor subtypes, A_{2B} (HEK cell membranes with [3H]-DPCPX) and A_3 (CHO cell membranes with [^{125}I]ABMECA), where it demonstrated low affinity for these subtypes (only 22% of the competitive ligand was displaced in both cases).

MOLECULAR MODELING

The design of the four series of compounds exploited similar vectors for lipophilic substituents at the 2-position of the purine ring as the selective A_{2A} agonists described in Figure 1. The propargyl phenyl ether derivative **21** presents a lipophilic group to the Ado A_{2A} receptor in a different manner than (S)-PHPNECA (10) as illustrated in Figure 3 panel A by the superimposition of the respective compounds (Sybyl Fit algorithm). It is noteworthy that the propargyl phenyl ether derivative **21** was found to have a 44 fold higher affinity for the A_{2A} Ado receptor when compared to the A_1 Ado receptor, but the (S)-PHPNECA (10) was found to

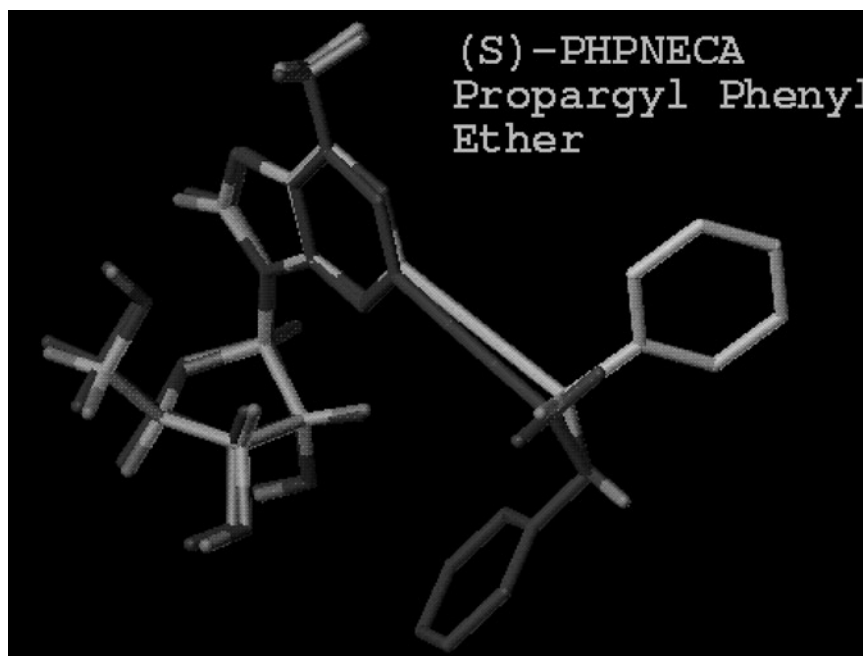


Figure 3, Panel A. A superimposition of (S)-PHPNECA from Cristalli et al (10) and the unsubstituted propargyl phenyl ether **21** demonstrates an overlay of the oxygen hydrogen bond acceptor regions, but a distinctly different presentation of the lipophilic phenyl groups to the receptor.

have similar affinity for both receptors. The difference in selectivity may be due to the presence of a hydrogen bond donor in (S)-PHPNECA, a different presentation of the lipophilic phenyl ring to the receptor, or both changes.

The 2-(N-1-pyrazolyl) adenosine class 4 (Fig. 2, Panel D) provides the same 152° trajectory as the THENECA (**3**) derivative, and the overlay of compound **29** from this class with THENECA is shown in Figure 3 Panel B (Sybyl Fit algorithm). Both compounds have high affinity for the A_{2A} Ado receptor, but it is apparent that the trajectory of the lipophilic substituent alone does not solely dictate activity based on the SAR in Table 3.

The 2-(N-1-pyrazolyl) adenosine series (class 4) was designed by envisioning a 5-membered pyrazole ring obtained through closing the hydrazone group of compound **4** (WRC-470) as illustrated in Figure 2, Panel D. Analysis of the H NMR of compound **4** shows a mixture of the E and Z hydrazones with the E being the predominant isomer ($>5:1$). Conformational searching of the E and Z hydrazones resulted in two local minima for each isomer wherein the hydrazone pi system is coplanar with the aromatic purine ring (Fig. 4, Panels A and B). A torsional search demonstrated a very small barrier to rotation about the purine-2-nitrogen bond that is attributed to a lack of ortho hydrogens on the purine ring. The 2-(N-1-pyrazolyl) series SAR suggests that the 2-pyrazolyl nitrogen and the lipophilic group are key

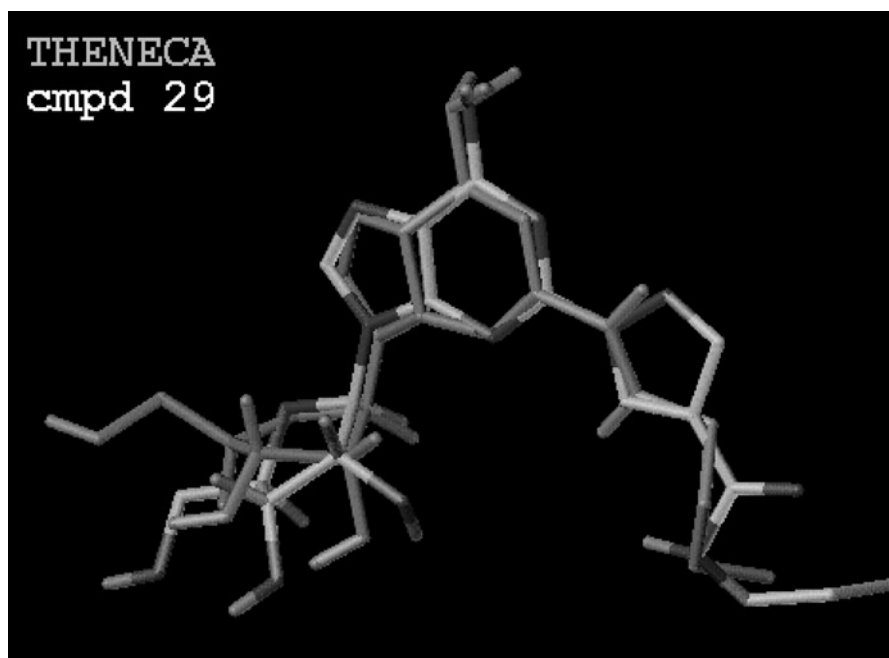


Figure 3, Panel B. An overlay of compound **29** (Rat Brain Ado A_{2A} K_i = 50 nM) and THENECA (Rat Brain Ado A_{2A} K_i = 1.6 nM) suggests a similar presentation of both lipophilic groups to the receptor.

binding elements. Therefore, an attempt was made to superimpose the two nitrogens of the pyrazole ring with the two nitrogens of the hydrazone plus achieve overlap of the lipophilic substituents. Only the lower energy *Z* hydrazone conformation of compound **4** (Fig. 4 Panel B) and compound **20** would fit this requirement. Thus, the 2-[(N-1-(4-substituted pyrazolyl))] adenosine series may be a constrained mimetic of the *Z*-hydrazone of compound **4**.

SUMMARY

We accomplished our goal to obtain a short acting coronary vasodilator that is functionally selective for the A_{2A} Ado receptor with the discovery of two new compounds: **20** (CVT-3146-a 2-[(N-1-(4-N-methylcarboxamidopyrazolyl))] adenosine derivative) and compound **31** (CVT-3033 - a 2-[(4-(1-N-pentylpyrazolyl))] adenosine derivative) with coronary vasodilatation CV $t_{0.5}$'s = 5.2 ± 0.2 and 3.4 ± 0.5 min, respectively - rat isolated heart 50% reversal time, with good potency - EC_{50} s = 6.4 ± 1.2 nM and 67.9 ± 16.7 nM, respectively, but they possess low affinity for the A_{2A} ADO receptor (K_i = 1122 ± 323 nM and 2138 ± 952 nM, respectively; pig striatum). We hypothesize that the low affinity compounds still produce the desired coronary vasodilatation because of the high receptor reserve of the A_{2A}

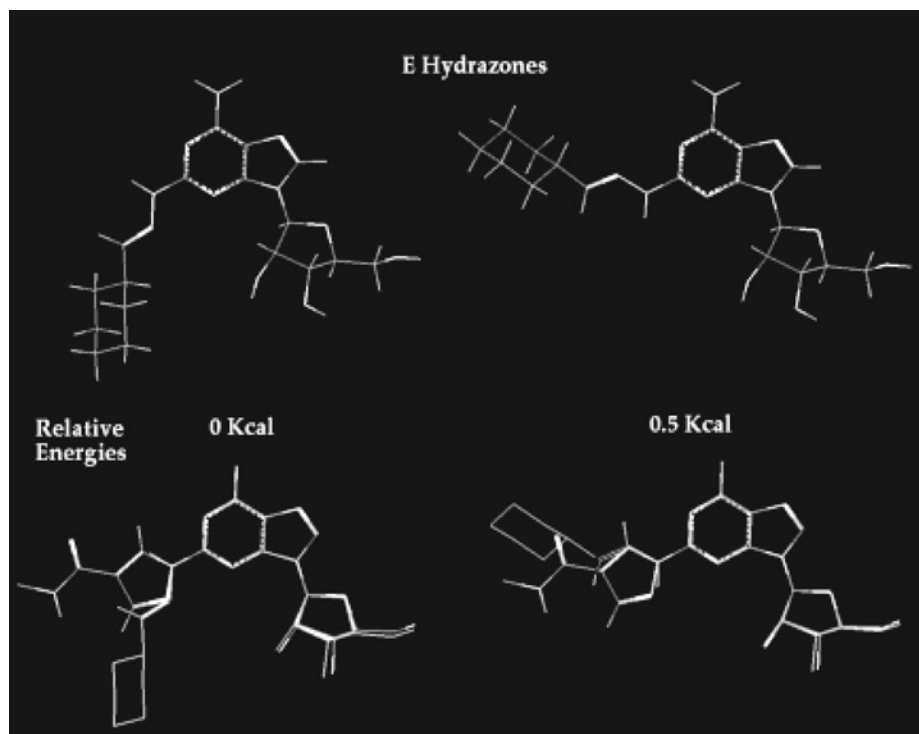


Figure 4, Panel A. Two local minima were found for the E hydrazone and superimposition was done with compound **20**; however, neither conformation affords an overlay of key binding elements (i.e. lipophilic substituents and two nitrogens of pyrazole and hydrazone).

Ado receptor for this effect, and it (i.e. low affinity) may contribute to the short duration of action through increasing their off rates from the receptor. Compounds **20** and **31** are currently being evaluated for their *in vivo* vasodilatation to further assess their potential as pharmacological stress agents, and the results will be published in due course.

EXPERIMENTAL

2-phenyl-1-prop-2-ynyloxybenzene (7). To a solution of propargyl bromide (80% solution in toluene, 0.50 mL, 3.36 mmol) in acetone (15 mL) at 23°C was added 2-phenyl phenol (0.316 g, 1.86 mmol) and potassium carbonate (1.05 g, 7.61 mmol). After being stirred in a sealed reaction vial at 65°C for 14 hours, the reaction was concentrated *in vacuo*, and the residue purified by flash chromatography (ethyl acetate: hexane: 9:1) to afford compound **7** in 95% yield. ¹H NMR (CDCl₃) δ 2.45–2.55 (m, 1 H), 4.60–4.70 (m, 2 H), 6.90–7.43 (m, 9 H).

Synthesis of (4S,2R,3R,5R)-2-[6-amino-2-(3-phenoxyprop-1-ynyl)purin-9-yl]-5-(hydroxymethyl)oxolane-3,4-diol (compound 8). To a solution of

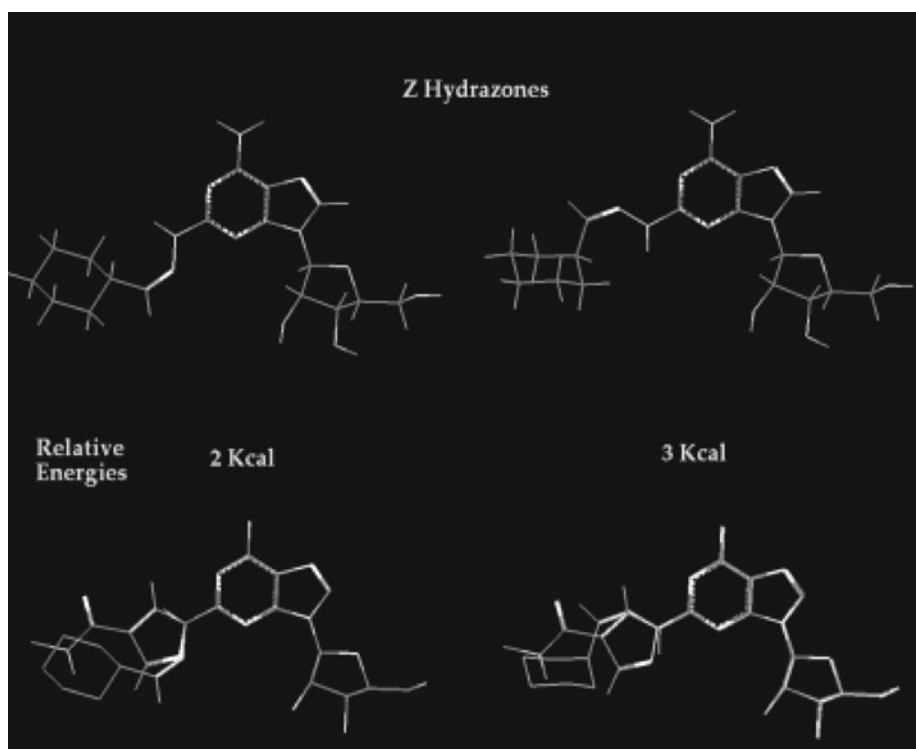


Figure 4, Panel B. Two local minima were found for the Z hydrazone and superimposition was done with compound **20**. Only the lower energy conformation affords an overlay wherein the two nitrogens of the pyrazole plus the two lipophilic substituents coincide.

(4S,2R,3R,5R)-2-(6-amino-2-iodopurin-9-yl)-5-(hydroxymethyl)oxolane-3,4-diol **6** (0.05 g, 0.13 mmol) and 2-phenyl-1-prop-2-ynyloxybenzene **7** (0.03 mL, 0.16 mmol) in DMF (1 mL) and triethylamine (0.021 mL, 0.16 mmol) at 23°C was added copper iodide (0.005g, 0.026 mmol) and dichlorobis(triphenylphosphine) palladium(II) (0.022 g, 0.031 mmol). After being stirred in a sealed reaction vial at 80°C for 6 hours, the reaction was concentrated *in vacuo* and the residue was purified by preparatory thin layer chromatography (methylene chloride: methanol 9:1) to afford 9.6 mg of compound **8** (20% yield). ¹H NMR (CDCl₃:CD₃OD 9:1) δ 3.02–3.04 (m, 1 H), 3.07 (s, 1 H), 3.55, 3.74 (dd, 2 H), 4.02 (s, 1 H), 4.11–4.13 (m, 1 H), 4.48–4.52 (m, 1 H), 4.72 (s, 2 H), 5.65 (d, 1 H), 6.75–6.82 (m, 3 H), 7.08–7.12 (m, 2 H), 7.94 (s, 1 H).

(4S,2R,3R,5R)-2-[6-amino-2-(3-phenoxyprop-1-ynyl)purin-9-yl]-5-(hydroxymethyl)oxolane-3,4-diol (21**).** Compound **21** was prepared in a manner similar to that employed in the synthesis of compound **8**. ¹H NMR (CDCl₃:CD₃OD 9:1) δ 3.02–3.04 (m, 1 H), 3.07 (s, 1 H), 3.55, 3.74 (dd, 2 H), 4.02 (s, 1 H), 4.11–4.13 (m, 1 H), 4.48–4.52 (m, 1 H), 4.72 (s, 2 H), 5.65 (d, 1 H), 6.75–6.82 (m, 3 H), 7.08–7.12 (m, 2 H), 7.94 (s, 1 H). , 4.48–4.52 (m, 1 H), 4.72 (s, 2 H), 5.65

(d, 1 H), 6.90–7.00 (m, 1 H), 7.10–7.15 (m, 1 H), 7.15–7.32 (m, 5 H), 7.35–7.45 (m, 2 H), 7.94 (s, 1 H).

4-(3-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl} prop-2-ynyloxy)benzenecarbonitrile (23). Compound 23 was prepared in a manner similar to that employed in the synthesis of compound 8. ¹H NMR (CDCl₃:CD₃OD 9:1) δ3.55 (d, 1 H), 3.70 (d, 1 H), 4.05–4.07 (m, 1 H), 4.10–4.12 (m, 1 H), 4.48 (dd, 1 H), 4.80 (s, 2 H), 5.65 (d, 1 H), 6.90 (d, 2 H), 7.45 (d, 2 H), 7.95 (s, 1 H).

(4S,2R,3R,5R)-2-{6-amino-2-[3-(4-phenylphenoxy)prop-1-ynyl]purin-9-yl}-5-(hydroxymethyl)oxolane-3,4-diol (25). Compound 25 was prepared in a manner similar to that employed in the synthesis of compound 8. ¹H NMR (CDCl₃:CD₃OD 9:1) δ3.02–3.04 (m, 1 H), 3.07 (s, 1 H), 3.55, 3.74 (dd, 2 H), 4.02 (s, 1 H), 4.11–4.13 (m, 1 H), 4.48–4.52 (m, 1 H), 4.72 (s, 2 H), 5.65 (d, 1 H), 6.90–7.00 (m, 1 H), 7.10–7.15 (m, 1 H), 7.15–7.32 (m, 5 H), 7.35–7.45 (m, 2 H), 7.94 (s, 1 H).

(4S,2R,3R,5R)-2-(6-amino-2-{3-[2-benzylphenoxy]prop-1-ynyl} purin-9-yl)-5-(hydroxymethyl)oxolane-3,4-diol (24). Compound 24 was prepared in a manner similar to that employed in the synthesis of compound 8. ¹H NMR (CDCl₃:CD₃OD 9:1) δ3.02–3.04 (m, 1 H), 3.07 (s, 1 H), 3.55, 3.74 (dd, 2 H), 3.92 (s, 2 H), 4.02 (s, 1 H), 4.11–4.13 (m, 1 H), 4.48–4.52 (m, 1 H), 4.72 (s, 2 H), 5.65 (d, 1 H), 6.80–6.88 (m, 1 H), 6.96–7.01 (m, 2 H), 7.15–7.22 (m, 6 H), 7.94 (s, 1 H).

(4S,2R,3R,5R)-2-(6-amino-2-{3-[2-benzylphenoxy]prop-1-ynyl} purin-9-yl)-5-(hydroxymethyl)oxolane-3,4-diol (22). Compound 22 was prepared in a manner similar to that employed in the synthesis of compound 8. ¹H NMR (CDCl₃:CD₃OD 9:1) δ3.02–3.04 (m, 1 H), 3.07 (s, 1 H), 3.55, 3.74 (dd, 2 H), 3.92 (s, 2 H), 4.02 (s, 1 H), 4.11–4.13 (m, 1 H), 4.48–4.52 (m, 1 H), 4.72 (s, 2 H), 5.65 (d, 1 H), 6.80–6.88 (m, 1 H), 6.96–7.01 (m, 2 H), 7.15–7.22 (m, 6 H), 7.94 (s, 1 H).

(4S,2R,3R,5R)-2-(6-amino-2-{3-[3,5-bis(tert-butyl)phenoxy]prop-1-ynyl} purin-9-yl)-5-(hydroxymethyl)oxolane-3,4-diol (26). Compound 26 was prepared in a manner similar to that employed in the synthesis of compound 8. ¹H NMR (CDCl₃:CD₃OD 9:1) δ1.22 (s, 9 H), 3.02–3.04 (m, 1 H), 3.07 (s, 1 H), 3.55, 3.74 (dd, 2 H), 4.02 (s, 1 H), 4.11–4.13 (m, 1 H), 4.48–4.52 (m, 1 H), 4.72 (s, 2 H), 5.65 (d, 1 H), 6.78 (s, 2 H), 6.99 (s, 1 H), 7.94 (s, 1 H).

{(2R,3R,4R,5R)-3,4-diacetyloxy-5-[6-chloro-2-(5-methyl(2-thienyl)) purin-9-yl]oxolan-2-yl}methyl acetate (10). To a suspension of 2-Amino-6-chloro-9-(2',3',5'-tri-*O*-acetyl)-D-ribofuranosyl-purine 9 (0.17 g, 0.40 mmol) in 2 mL 2-methylthiophene (20.0 mmol), was added isoamyl nitrite (0.25 mL, 1.80 mmol), Cu (I) Oxide (0.060 g, 0.42 mmol) and the mixture was allowed to stir at 115°C for 3 h. The reaction mixture was filtered, concentrated under vacuo and the residue was purified using preparative thin layer chromatography



(EtOAc:Hexanes 1:1) to afford **10** in 51% yield. ^1H NMR (CDCl_3) δ 2.0 (s, 3 H), 2.05 (s, 3 H), 2.1 (s, 3 H), 2.5 (s, 3 H), 4.30 (m, 1 H), 4.40–4.55 (m, 2 H), 5.90 (t, 1 H), 6.0 (t, 1 H), 6.1 (d, 1 H), 6.8 (d, 1 H), 7.85 (d, 1 H), 8.1 (s, 1 H).

(4S,2R,3R,5R)-2-[6-amino-2-(5-methyl(2-thienyl))purin-9-yl]-5-(hydroxymethyl)oxolane-3,4-diol (11). Compound **10** (0.05 g, 0.10 mmol) was dissolved in 5 mL methanolic ammonia (saturated at 0°C), and the mixture was allowed to stir at 40°C for 24 h. After concentration in vacuo, the residue was purified using preparative thin layer chromatography (10% MeOH/DCM) to afford **11** in 78% yield. ^1H NMR (CD_3OD) δ 2.5 (s, 3 H), 3.75 (d, 1 H), 3.85 (d, 1 H), 4.15 (d, 2 H), 4.45 (m, 1 H), 4.85 (m, 1 H), 6.0 (d, 1 H), 6.75 (d, 1 H), 7.7 (d, 1 H), 8.25 (s, 1 H).

(4S,3R,5R)-2-(6-amino-2-(2-thienyl)purin-9-yl)-5-(hydroxymethyl)oxolane-3,4-diol (27). Compound **27** was synthesized in a manner similar to that employed in the synthesis of **11** using thiophene instead of methylthiophene (81% yield). ^1H NMR (CD_3OD) δ 3.75 (d, 1 H), 3.85 (d, 1 H), 4.15 (d, 2 H), 4.45 (m, 1 H), 4.85 (m, 1 H), 6.0 (d, 1 H), 7.10 (d, 1 H), 7.5 (d, 1 H), 7.9 (d, 1 H), 8.25 (s, 1 H).

9-[(2R,3R,4R,5R)-3,4-bis(1,1,2,2-tetramethyl-1-silapropoxy)-5-[(1,1,2,2-tetramethyl-1-silapropoxy)methyl]oxolan-2-yl]-2-(5-iodo(2-thienyl))purine-6-ylamine (13). A mixture of compound **12** (0.05 g, 0.056 mmol), 2,5-diiodopyrazole (0.05 g, 0.14 mmol), $\text{Pd}(\text{PPh}_3)_4$ (0.02 g, 15 mol %) and CuI (0.04 g, 0.2 mmol) in DMF (1 mL) was stirred at 90°C for 16 h. The reaction was concentrated in vacuo, and the residue was purified by preparative thin layer chromatography (methylene chloride: methanol 10:1) to afford compound **13**: ^1H NMR (CDCl_3) δ 0.00 (s, 3 H), 0.01 (s, 3 H), 0.04 (s, 3 H), 0.07 (s, 3 H), 0.11 (s, 3 H), 0.14 (s, 3 H), 0.78 (s, 9 H), 0.83 (s, 9 H), 0.91 (s, 9 H), 3.80 (d, 1 H), 4.05 (d, 1 H), 4.11–4.12 (m, 1 H), 4.32–4.33 (m, 1 H), 4.80 (d, 1 H), 5.55 (bs, 2 H, D_2O exchangeable), 5.95 (d, 1 H), 7.21 (d, 2 H), 7.50 (d, 2 H), 8.10 (s, 1 H).

(4S,2R,3R,5R)-2-[6-amino-2-(5-iodo(2-thienyl))purin-9-yl]-5-(hydroxymethyl)oxolane-3,4-diol(14). A solution of triTBDMS derivative **13** (0.015 g, 0.054 mmol) in 0.5 M solution of NH_4F in methanol (5 mL) was refluxed for 16 h. The reaction mixture was concentrated, and the residue was purified by preparative TLC (methanol-dichloromethane 9:1) to afford **14**; ^1H NMR (CD_3OD) δ 3.65 (d, $J = 11.2$ Hz, 1 H), 3.81 (d, $J = 11.2$ Hz, 1 H), 4.15–4.16 (m, 1 H), 4.25–4.26 (m, 1 H), 4.78 (dd, 1 H), 5.72 (d, 1 H), 7.15 (s, 2 H), 7.45 (d, 2 H), 7.80 (s, 1 H).

9-[(2R,3R,4R,5R)-3,4-bis(1,1,2,2-tetramethyl-1-silapropoxy)-5-[(1,1,2,2-tetramethyl-1-silapropoxy)methyl]oxolan-2-yl]-2-(5-phenyl(2-thienyl))purine-6-ylamine(15). A mixture of compound **13** (0.02 g, 0.056 mmol), tri *n*-butylphenyltin (0.05 g), $\text{Pd}(\text{PPh}_3)_4$ (0.02 g, 15 mol %) and CuI (0.04 g, 0.2 mmol) in DMF (1 mL) was stirred at 90°C for 16 h. The reaction was concentrated in vacuo,



and the residue was purified by preparative thin layer chromatography (methylene chloride: methanol 10:1) to afford compound **15**: ^1H NMR (CDCl_3) δ 0.00 (s, 3H), 0.01 (s, 3 H), 0.04 (s, 3 H), 0.07 (s, 3 H), 0.11 (s, 3 H), 0.14 (s, 3 H), 0.78 (s, 9 H), 0.83 (s, 9 H), 0.91 (s, 9 H), 3.80 (d, 1 H), 4.05 (d, 1 H), 4.11–4.12 (m, 1 H), 4.32–4.33 (m, 1 H), 4.80 (d, 1 H), 5.55 (bs, 2 H, D_2O exchangeable), 5.95 (d, 1 H), 7.25–7.4 (m, 5 H), 7.65 (d, 2 H), 7.85 (d, 1 H), 8.12 (s, 1 H).

(4S,2R,3R,5R)-2-[6-amino-2-(5-phenyl(2-thienyl))purin-9-yl]-5-(hydroxymethyl)oxolane-3,4-diol (16). A solution of triTBDMS derivative **15** (0.05 g) in 0.5 M solution of NH_4F in methanol (5 mL) was refluxed for 16 h. The Reaction mixture was concentrated, and residue was purified by preparative TLC (methanol-dichloromethane 9:1) to afford **16**; ^1H NMR (CD_3OD) δ 3.65 (d, $J = 11.2$ Hz, 1 H), 3.81 (d, $J = 11.2$ Hz, 1 H), 4.15–4.16 (m, 1 H), 4.22–4.26 (m, 1 H), 4.74 (dd, 1 H), 5.74 (d, 1 H), 7.10–7.25 (m, 5 H), 7.45 (d, 2 H), 7.74 (d, 2 H), 7.87 (s, 1 H).

Ethyl 1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazole-4-carboxylate (19). To a suspension of 2-hydrazinoadenosine **17** (0.025 g, 0.08 mmol) in a 1:1 mixture of MeOH/AcOH was added (ethoxycarbonyl)malondialdehyde (0.019 g, 0.12 mmol), and the mixture was heated heart at 80°C for 3 h. The precipitate formed was collected by filtration, and washed with EtOH and ether to afford compound **19** in 91% yield. ^1H NMR ($\text{DMSO}-d_6$) δ 1.25 (t, 3 H), 3.5 (m, 1 H), 3.6 (m, 1 H), 3.8 (d, 1 H), 4.15 (d, 1 H), 4.55 (m, 1H), 5.0 (t, 1 H), 5.2 (d, 1 H), 5.5 (d, 1 H), 5.9 (d, 1H), 7.15–7.3 (m, 5 H), 7.8 (br s, 2 H), 8.1 (s, 1H), 8.4 (s, 1 H), 8.9 (s, 1H).

(1-{9-[(4S,2R,3R,5R)-3,4-Dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazol-4-yl)-N-methylcarboxamide (20). Compound **19** (0.05 mg, 0.12 mmol) was added to 4 mL methylamine (40% sol. In water). The mixture heated at 65°C in for 24 h. After concentration in vacuo, the residue was purified using prep. TLC (10% MeOH:DCM) to afford compound **20** 75% yield. $^1\text{HNMR}$ (CD_3OD) δ 2.90 (s, 3 H), 3.78 (m, 1 H), 3.91 (m, 1 H), 4.13 (d, 1 H), 4.34 (d, 1 H), 4.64 (m, 1 H), 6.06 (d, 1 H), 8.11 (s, 1 H), 8.38 (s, 1 H), 9.05 (s, 1 H).

(1-{9-[(4S,2R,3R,5R)-3,4-Dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazol-4-yl)-N-ethylcarboxamide (28). Compound **19** (0.10 g, 0.13 mmol) was suspended in 10 mL ethylamine, and the mixture was heated at reflux in a sealed tube for 24 h. The solvent was evaporated and the residue was dissolved in 1 mL MeOH and treated with 10 mL ethyl ether. The precipitate formed was collected by filtration, and washed with ether to afford compound **28** in 61% yield. MS 405.35 ($M + 1$). ^1H NMR (CD_3OD) δ 1.00 t, 3 H), 3.00 (m, 1 H), 3.41 (d, 1 H), 3.60 (d, 1 H), 3.80 (d, 2 H) 4.00 (m, 1 H), 4.25 (m, 1 H), 5.80 (d, 1 H), 7.95 (s, 1 H), 8.25 (s, 1 H), 8.80 (s, 1 H).



(1-{9-[(4S,2R,3R,5R)-3,4-Dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazol-4-yl)-N-(cyclopentylmethyl)carboxamide (30). Compound **19** (0.5 g, 1.2 mmol) was dissolved in dry DMF, TBDMSCl (1.5 g, 10 mmol) and imidazole (.068 g, 10 mmol) were added, and the mixture was heated at 80°C for 24 h. The solvent was evaporated, and the residue was purified by flash column (20:1, DCM:MeOH) to afford the trisilyl protected form of compound **12** in 88% yield. MS 748.71 (M + 1).

The trisilyl derivative (0.8 g, 1 mmol) was suspended in 1 mL of water, and treated with 4 mL 1N KOH/MeOH. The mixture was allowed to stirred at RT for 72. The solvent was removed under reduced pressure, and the residue was suspended in 5 mL of water and acidified to pH 5 with 1N HCl. The resulting precipitate was filtered and washed with water and ethyl ether to afford the trisilyl acid **20**.

The trisilyl derivative acid (0.14 g, 0.2 mmol) was then dissolved in 5 mL dichloromethane. To the solution was added HBT_U (0.19 g, 0.4 mmol), HOBt (.076 g, 4 mmol), N-methylmorpholine (0.04 g, 0.4 mmol) and cat. DMAP. The mixture was allowed to stir at RT for 24 h. The mixture was then washed with 10% citric acid, saturated NaHCO₃, brine, and dried over MgSO₄. The solvent was removed, and the residue (without further purification) was treated with 5 mL 0.5 N NH₄F/MeOH. The solution was heated at reflux for 24 h. The solvent was evaporated, and the residue was purified by preparative TLC (10 1, DCM:MeOH) to afford compound **30** in 90% yield (one step). MS 445.26 (M + 1). ¹H NMR (CD₃OD) δ 1.50–1.82 (m, 8 H), 3.40 (m, 1 H), 3.61 (d, 1 H), 3.85 (d, 1 H), 4.15 (d, 2 H) 4.45 (m, 1 H), 4.85 (m, 1 H), 5.95 (d, 1 H), 8.10 (s, 1 H), 8.25 (s, 1 H), 8.98 (s, 1 H).

REFERENCES

1. a) Hutchison, A. J.; Webb, R. L.; Oei, H. H.; Ghai, G. R.; Zimmerman, M. B.; Williams, M. J. *Pharmacol. Exp. Ther.* **1989**, *251*, 47–55. b) Hutchison, A. J.; Williams, M. J.; de Jesus, R.; Yokoyama, R.; Oei, H. H.; Ghai, G. R.; Webb, R. L.; Zoganas, H. C.; Stone, G. A.; Jarvis, M. F. *J. Med. Chem.* **1990**, *33*, 1919–1924.
2. a). Abiru, T.; Yamaguchi, T.; Watanabe, Y.; Kogi, K.; Aihara, K.; Matsuda, A., *Eur. J Pharmacol.* **1991**, *196*, 69–76. b) Kogi, K.; Uchibori, T.; Aihara, K.; Yamaguchi, T.; Abiru T., *Jpn J Pharmacol.* **1991**, *57*, 153–65.
3. a) Chern, Y.; Lai, H. L.; Fong, J. C.; Liang, Y., *Mol. Pharmacol.* **1993**, *44*, 950–958. b) Palmer, T. M.; Gettys, T. W.; Jacobson, K. A.; Stiles, G. L., *Mol. Pharmacol.*, **1994**, *45*, 1082–94.
4. Verani, M. S. *Cor. Art. Dis.* **1992**, *3*, 1145–1151.
5. Verani, M. S.; Mahmonian, Y. Y. *Am. J. Cardiol. Imaging* **1994**, *3*, 223–230.
6. Glover, D. K.; Ruiz, M.; Yang, J. Y.; Koplan, B. A.; Allen, T. R.; Smith, W. H.; Watson, D. D.; Barrett, R. J.; Beller, G. A. *Circulation* **1996**, *94*, 1726–1732.
7. Linden, J.; Sullivan, G. W.; Ross, S. C.; Kron, I. L.; McPherson, J. A.; Sarembock, I. J.; Macdonald, T. L.; Okusa, M. D. *Drug. Dev. Res.*, **2000**, *50*, 68 (Purine 2000 conference, abstract #078).



8. Palle, V. P.; Elzein, E. O.; Gothe, S. A.; Li, Z.; Gao, Z.; Meyer, S.; Blackburn, B.; Belardinelli, L.; Zablocki, J. A. *Drug. Dev. Res.*, **2000**, *50*, 64 (Purine 2000 conference, abstract #062).
9. Elzein, E. O.; Palle, V. P.; Gothe, S. A.; Li, Z.; Gao, Z.; Meyer, S.; Blackburn, B.; Belardinelli, L.; Zablocki, J. A. *Drug. Dev. Res.*, **2000**, *50*, 64 (Purine 2000 conference, abstract #061).
10. Cristalli, G.; Camaioni, E.; Di Francesco, E.; Vittori, S.; Volpini, R. *Persp. In Receptor Res.* 1996, 165–180.
11. Miyashita, Y.; Abiru, T.; Watanabe, Y.; Yamaguchi, T.; Matsuda, A., US Patent 5,189, 027, 1993.
12. Nair, V.; Turner, G. A.; Buenger, G. S.; Chamberlain, S. D., *J. Org. Chem.* **1988**, *53*, 3051–3057.
13. Matsuda, A.; Satoh, K.; Tanaka, H.; Miyasaka, T. *Synthesis*, **1984**, 963–965.
14. Kato, K.; Hayakawa, H.; Tanaka, H.; Kumamoto, H.; Miyasaka, T. *Tetrahedron Lett.* **1995**, *36*, 6507–6510.
15. Zhang, W.; Robins, M. J. *Tetrahedron Lett.* **1992**, *33*, 1177–1180.
16. Niiya, K.; Thompson, R. D.; Silvia, S. K.; Olsson, R. A., *J. Med. Chem.*, **1992**, *35*, 4562–4566.
17. Bertz, S. H.; Dabbagh, G.; Cotte, P. *J. Org. Chem.* **1982**, *47*, 2216–2217.
18. Belardinelli, L.; Gao, Z.; Li, Z.; Zablocki, J.; Palle, V.; Elzein, E. Manuscript in preparation.
19. Shryock, J. C.; Snowdy, S.; Baraldi, P. G.; Cacciari, B.; Spalluto, G.; Monopoli, A.; Ongini, E.; Baker, S. P.; Belardinelli, L. *Circulation* **1998**, *98*, 711–718.



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