

A₁ Adenosine Receptor Antagonists, Agonists, and Allosteric Enhancers

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Contents

1	Introduction.....	28
2	A ₁ Adenosine Receptor Antagonists.....	28
2.1	KW3902.....	29
2.2	BG9928.....	37
2.3	SLV320.....	43
3	A ₁ Adenosine Receptor Agonists.....	45
3.1	Intravenous Antiarrhythmic Agents: Tecadenoson, Selodenoson, Phenylsulfide, Phenylethers, PJ-875.....	47
3.2	Insulin-Sensitizing Agents: GR79236, ARA, CVT-3619.....	49
3.3	Angina Agents: Capadenoson (Nonnucleoside: BAY 68-4986).....	52
4	Allosteric Enhancers.....	52
4.1	Neuropathic Pain: T-62.....	52
5	Conclusion.....	53
	References.....	54

Abstract Intense efforts of many pharmaceutical companies and academicians in the A₁ adenosine receptor (AR) field have led to the discovery of clinical candidates that are antagonists, agonists, and allosteric enhancers. The A₁AR antagonists currently in clinical development are KW3902, BG9928, and SLV320. All three have high affinity for the human (h) A₁AR subtype (hA₁ K_i < 10 nM), > 200-fold selectivity over the hA_{2A} subtype, and demonstrate renal protective effects in multiple animal models of disease and pharmacologic effects in human subjects. In the A₁AR agonist area, clinical candidates have been discovered for the following conditions: atrial arrhythmias (tecadenoson, selodenoson and PJ-875); Type II diabetes and insulin sensitizing agents (GR79236, ARA, RPR-749, and CVT-3619); and angina

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(BAY 68–4986). The challenges associated with the development of any A₁AR agonist are to obtain tissue-specific effects but avoid off-target tissue side effects and A₁AR desensitization leading to tachyphylaxis. For the IV antiarrhythmic agents that act as ventricular rate control agents, a selective response can be accomplished by careful IV dosing paradigms. The treatment of type II diabetes using A₁AR agonists in the clinic has met with limited success due to cardiovascular side effects and a well-defined desensitization of full agonists in human trials (GR79236, ARA, and RPR 749). However, new partial A₁AR agonists are in development, including CVT-3619 (hA₁AR K_i = 55 nM, hA_{2A}:hA_{2B}:hA₃ > 200:1,000:20, CV Therapeutics), which have the potential to provide enhanced insulin sensitivity without cardiovascular side effects and tachyphylaxis. The nonnucleosidic A₁AR agonist BAY 68–4986 (capadenoson) represents a novel approach to angina wherein both animal studies and early human studies are promising. T-62 is an A₁AR allosteric enhancer that is currently being evaluated in clinical trials as a potential treatment for neuropathic pain. The challenges associated with developing A₁AR antagonists, agonists, or allosteric enhancers for therapeutic intervention are now well defined in humans. Significant progress has been made in identifying A₁AR antagonists for the treatment of edema associated with congestive heart failure (CHF), A₁AR agonists for the treatment of atrial arrhythmias, type II diabetes and angina, and A₁AR allosteric enhancers for the treatment of neuropathic pain.

Keywords A₁ adenosine receptor agonists · A₁ adenosine receptor antagonists · Acutely decompensated heart failure · Adenine · Cardiorenal syndrome · Congestive heart failure · Anti-arrhythmic agents · Tecadenoson · Selodenoson · Insulin sensitizing agents · CVT-3619 · Angina · Capadenoson · Allosteric enhancers · Neuropathic pain · Type II diabetes · BG9928 · KW3902 · SLV320

Abbreviations

ACE	Angiotensin-converting enzyme
ADHF	Acutely decompensated heart failure
ALT	Alanine aminotransferase
APD	Action potential duration
AR	Adenosine receptor
ARA	(1 <i>S</i> , 2 <i>R</i> , 3 <i>R</i>)-3-((trifluoromethoxy)methyl)-5-(6-(1-(5-(trifluoromethyl)pyridine-2-yl)pyrrolidin-3-ylamino)-9 <i>H</i> -purin-9-yl)cyclopentane-1,2-diol
ARB	Angiotensin II receptor blocker
AST	Aspartate aminotransferase
AUC	Area under the curve
(A–V) node	Atrioventricular
BG9719	(8-(3-Oxa-tricyclo[3.2.1.0 ^{2,4}]oct-6-yl)-1,3-dipropyl-3,7-dihydropurine-2,6-dione)

BG9928	(3-(4-(2,6-Dioxo-1,3-dipropyl-2,3,6,7-tetrahydro-1 <i>H</i> -purin-8-yl)bicyclo[2.2.2]octan-1-yl)propanoic acid)
cAMP	Cyclic AMP
Capadenoson	(BAY 68–4986) (2-amino-6-((2-(4-chlorophenyl)thiazol-4-yl)methylthio)-4-(4-(2-hydroxyethoxy)phenyl)pyridine-3,5-dicarbonitrile)
CHA	<i>N</i> ⁶ -Cyclohexyl adenosine
CHF	Congestive heart failure
CHO	Chinese hamster ovary
CK	Creatinine kinase
CL	Total body clearance
<i>C</i> _{max}	Maximal plasma concentration
CPA	<i>N</i> ⁶ -Cyclopentyl adenosine
CrCl	Creatinine clearance
CV	Cardiovascular
CVT-3619	(2 <i>S</i> , 3 <i>S</i> , 4 <i>R</i>)-2-((2-fluorophenylthio)methyl)-5-(6-((1 <i>R</i> , 2 <i>R</i>)-2-hydroxycyclopentylamino)-9 <i>H</i> -purin-9-yl)tetrahydrofuran-3,4-diol
DPCPX	1,3-Dipropyl-8 cyclopentylxanthine
ED ₅₀	50% Efficient dose
F (%)	% Oral bioavailability
GFR	Glomerular filtration rate
GR79236	(3 <i>R</i> , 4 <i>S</i> , 5 <i>R</i>)-2-(6-((1 <i>S</i> , 2 <i>S</i>)-2-hydroxycyclopentylamino)-9 <i>H</i> -purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol
HF	Heart failure
HSL	Hormone sensitive lipase
IP	Intraperitoneal
IPC	Ischemic preconditioning
IV	Intravenous
KW3902	(3-Noradamantyl-1,3-dipropylxanthine)
<i>L</i> -(NAME)	<i>N</i> -o-Nitro- <i>L</i> -arginine methyl ester
MRT	Mean residence time
NEFA	Nonesterified fatty acids
PVST	Paroxysmal supraventricular tachycardia
RCM	Radiocontrast media
RPF	Renal plasma flow
SAR	Structure–activity relationship
Selodenoson	(2 <i>S</i> , 3 <i>S</i> , 4 <i>R</i>)-5-(6-(Cyclopentylamino)-9 <i>H</i> -purin-9-yl)- <i>N</i> -ethyl-3,4-dihydroxytetrahydrofuran-2-carboxamide)
(S–A)	Sinoatrial
SLV320	(4-(2-Phenyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-ylamino)cyclohexanol)
<i>t</i> _{1/2}	Half-life
T-62	(2-Amino-4,5,6,7-tetrahydrobenzo[<i>b</i>]thiophen-3-yl)(4-chlorophenyl)methanone
Tecadenoson	(2 <i>R</i> , 3 <i>S</i> , 4 <i>R</i>)-2-(Hydroxymethyl)-5-(6-((<i>R</i>)-tetrahydrofuran-3-ylamino)-9 <i>H</i> -purin-9-yl)tetrahydrofuran-3,4-diol)

TG's	Triglycerides
T2D	Type II diabetes
UNaV	Urinary sodium excretion
UV	Urine volume
V_{ds}	Volume of distribution

1 Introduction

The A_1 adenosine receptor (AR), a member of the P_1 family of seven-transmembrane adenosine receptors, couples to G_i to decrease the secondary messenger cAMP. The P_1 family of adenosine receptors consists of the members A_1 , A_{2A} , A_{2B} , and A_3 , which have high sequence homology with many conserved residues at the active sites; however, sufficient differences are found for each active site such that selective agonists and antagonists have been generated for each receptor subtype (Akhari et al. 2006; Dhalla et al., 2003; Fredholm et al. 2001; Jacobson and Gao 2006). The major goal of this review is twofold: to highlight the structure–affinity relationships (SAR) of A_1 AR antagonists, agonists, and allosteric enhancers, and to give an overview of the A_1 AR antagonists, agonists, and allosteric enhancers currently under development for various indications.

2 A_1 Adenosine Receptor Antagonists

From the earliest reports on the physiologic effects of theophylline and adenosine to the three active clinical programs today (see Fig. 1), the study of AR ligands has a long and rich history (Baraldi et al. 2008; Jacobson and Gao 2006). There are a number of excellent reviews on A_1 AR antagonists (Baraldi et al. 2008; Hess 2001; Moro et al. 2006; van Galen et al. 1992; Yuzlenko and Kieć-Kononowicz 2006). Because these reviews discuss the historical development of this class of molecules, their structure–activity relationships (SARs), pharmacology, and therapeutic applications, a comprehensive review of A_1 AR antagonists will not be presented here. It is important to note that a number of A_1 AR antagonists have entered clinical trials; however, problems with high lipophilicity and corresponding low water solubility and bioavailability have limited their clinical development (Hess 2001). This section of our review will present brief overviews of the most advanced A_1 adenosine receptor (A_1 AR) antagonists that are promising drug candidates currently in clinical trials. The discussion will address SARs around the lead molecules, highlights of pharmacology in healthy animals and disease models, and top-line human clinical trial results.

The 1,3-dialkylxanthine core has been the mainstay of A_1 AR antagonists since the isolation of theophylline in 1886 (Kossel 1888) (Fig. 1). One hundred years passed before replacement of the methyl substituents with *n*-propyl chains and

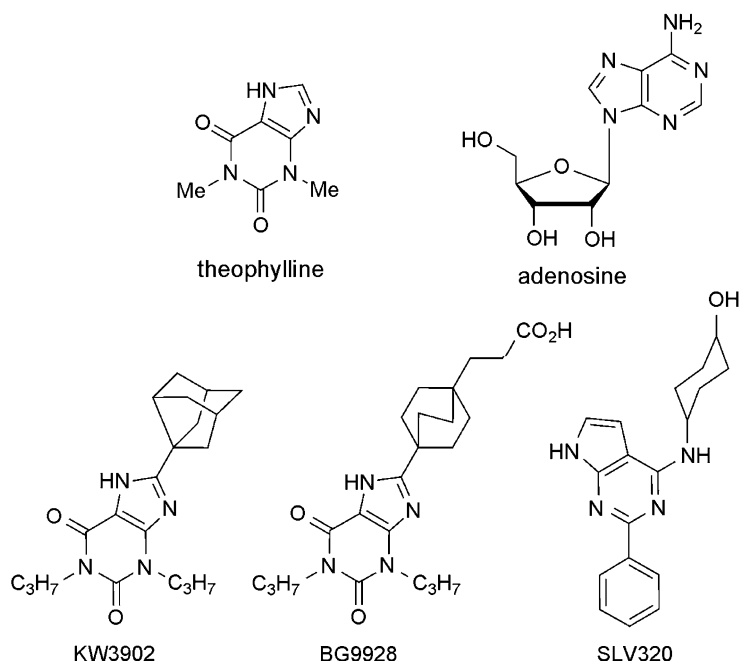


Fig. 1 Dialkylxanthine and adenine-based adenosine A₁ receptor ligands

the installation of cyclopentane at the C8 position led to the discovery of 1,3-dipropyl-8-cyclopentyl xanthine (DPCPX), which has been used as a radioligand and pharmacologic probe for the *in vivo* effects of A₁AR antagonism in living systems (Shamim et al. 1988). Since then, significant effort has been directed toward garnering improvements in activity and selectivity on the well-optimized 1,3-dipropylxanthine, and has led to the discovery of two molecules that are in active clinical development programs: KW3902 (3-noradamantyl-1,3-dipropylxanthine) (Suzuki et al. 1992) and BG9928 (3-(4-(2,6-dioxo-1,3-dipropyl-2,3,6,7-tetrahydro-1H-purin-8-yl)bicyclo[2.2.2]octan-1-yl)propanoic acid) (Kiesman et al. 2006a). A structurally distinct nonxanthine series based upon the adenine substructure of adenosine itself has also been developed and is represented by clinical candidate SLV320 (4-(2-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)cyclohexanol) (Kalk et al. 2007). All three of these A₁AR antagonists display high affinity for the A₁AR and significant selectivity over the A_{2A}AR (Table 1).

2.1 KW3902

To further characterize the hydrophobic interactions between the 8 position in the xanthine series and the A₁AR binding site, Shimada et al. (1991, 1992) investigated substitutions of the 8-cyclopentyl ring in DPCPX **1** (Table 2). Clipping the cyclopentyl ring into two ethyl groups **2** led to a loss of guinea pig (gp)A₁ affinity but

Table 1 Binding affinities for selected A₁ adenosine receptor antagonists

	K_i (nM) ^a					
	rA ₁	rA _{2A}	hA ₁	hA _{2A}	hA _{2B}	hA ₃
KW3902	0.2 ^b	170 ^b	8	673	296	4,390
BG9928	1.3	2,440	7	6,410	90	>10,000
SLV320	2.5 ^c	501 ^c	1 ^c	398 ^c	3980 ^c	200 ^c

^aReceptor binding experiments using cloned human receptors in CHO (hA₁, 0.3 nM [¹²⁵I]-aminobenzyladenosine ([¹²⁵I]ABA)) or HEK293-derived cell membranes (hA_{2A}, 0.7 nM [¹²⁵I]-ZM241385; hA_{2B}, 0.5 nM [¹²⁵I]-3-(4-aminobenzyl)-8-phenyloxyacetate-1-propyl-xanthine; and hA₃, 0.6 nM [¹²⁵I]-ABA); rA₁ binding measured as inhibition of [³H]-DPCPX to rat forebrain membranes; rA_{2A} binding measured as inhibition of [³H]-ZM241385 in rat striatal membranes (Kiesman et al. 2006a)

^brA₁ binding measured as inhibition of [³H]-CHA to rat forebrain membranes; rA_{2A} binding measured as inhibition of [³H]-CGS21680 in rat striatal membranes (Suzuki et al. 1992)

^cReceptor binding experiments using cloned human receptors in CHO (hA₁: [³H]-DPCPX or HEK293-derived cell membranes (hA_{2A}: [³H]-CGS21680; hA_{2B}: [³H]-DPCPX; hA₃: [³H]-AB-MECA or rat cerebral cortex (rA₁: [³H]-CCPA, or striatal membranes (rA_{2A}: [³H]-CGS21680 (Kalk et al. 2007)

had no effect on rat (r)A_{2A} binding. When compared to **1**, dicyclopropyl substitution **3** showed enhanced potency and selectivity versus gpA₁ and rA_{2A} receptors, respectively, while the addition of *gem*-dimethyl substitution **4** led to diminished gpA₁ affinity but a remarkable decrease in rA_{2A} binding (>170-fold decrease). Bicyclo- and tricycloalkane systems **5**, **7**, **8** were then examined to determine if restrictions in conformational flexibility around the cyclopentyl ring in **1** effected the antagonist activity. Interestingly, the 3-noradamantyl system **8** stood out, with increases in gpA₁ affinity ($K_i = 1.3$ nM and high selectivity over the rA_{2A} receptor (890-fold; Nonanka et al. 1996). Introduction of a methylene linker between the bulky polycyclic alkane in the 8 position gave compound **9** significantly reduced gpA₁ affinity (>65-fold).

Animal Studies

The diuretic activity of KW3902 was examined in saline-loaded, conscious Wistar rats (Suzuki et al. 1992). The antagonist was orally administered in a saline suspension and the urine collected and analyzed for sodium content. Urine volume (UV) and urinary sodium excretion (UNaV) both increased in a dose-dependent manner, with maximal effects observed between 0.1 and 0.4 mg kg⁻¹ (Fig. 2).

During the development of intravenously (IV) injectable formulations for KW3902, which has a solubility in water of <1 µg mL⁻¹, Hosokawa et al. (2002) investigated the effects of a lipid emulsion and liposome formulation on the pharmacokinetics of KW3902 and its metabolite (M1-KW3902) in comparison to a 1 N NaOH–DMSO-containing formulation (Fig. 3). They reported no

Table 2 Structure–activity relationships for 8-substituted 1,3-dipropylxanthines

Cmpd	R	K_i (nM) ^a		
		gpA ₁	rA _{2A}	rA _{2A} /gpA ₁
1		6.4 ± 0.35 (0.49 ± 0.06) ^b rat (17 ± 6.5) ^c dog	590 ± 48 – –	92 – –
2		19 ± 1.0	570 ± 44	30
3		3.0 ± 0.21 (0.919 ± 0.04) ^b rat	430 ± 5.8 –	140 –
4		22	>100,000	>4,500
5		3.83 ± 0.32	440 ± 42	120
6		31	2,300	74
7		13 ± 2.8	5,100 ± 1,100	390
8		1.3 ± 0.12 (0.19 ± 0.042) ^b , rat 10 ± 2.6 ^c dog	380 ± 30 (170 ± 16) ^c (rat) –	290 890 (rat) –
9		880	>100,000	>110

^agpA₁ binding was carried out with *N*⁶-[³H]cyclohexyladenosine ([³H]-CHA) in guinea pig (gp) forebrain membranes and rA_{2A}, binding was carried out with *N*-[³H]ethyladenosine-5'-uronamide in the presence of 50 nM cyclopentyladenosine in rat (r) striatal membranes (Shimada et al. 1991)

^brA₁ binding measured as inhibition of [³H]-CHA to rat forebrain membranes (Shimada et al. 1992)

^crA_{2A} binding measured as inhibition of [³H] CGS21680 in rat striatal membranes and dA₁ (dog) measured with [³H]-CHA in dog forebrain membranes (Nonanka et al. 1996). All K_i measurements are given as mean ± SEM for 3–5 determinations

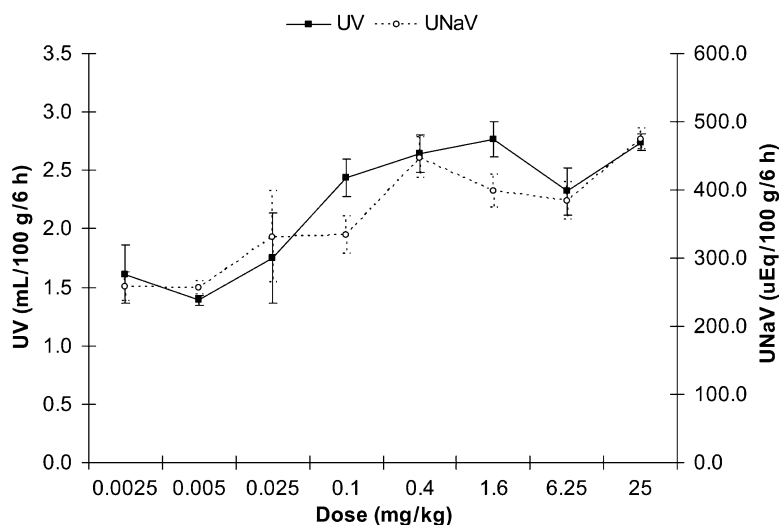


Fig. 2 Dose-response for urine volume (UV) in mL $100\text{ g}^{-1}6\text{ h}^{-1}$ (mean \pm SEM) and urinary sodium excretion (UNaV) in $\mu\text{Eq } 100\text{ g}^{-1}6\text{ h}^{-1}$ (mean \pm SEM) over 6 h following oral doses of KW3902 ranging from 0.0025 to 25 mg kg^{-1} in male rats

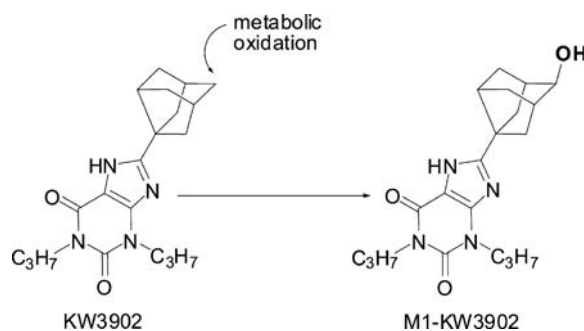


Fig. 3 Chemical structure of the metabolite of KW3902, M1-KW3902

significant differences in elimination half-life ($t_{1/2}$), area under the curve (AUC), total body clearance (CL), and mean residence time (MRT) for all of the formulations investigated. Table 3 summarizes the pharmacokinetic parameters measured for KW3902 and M1-KW3902 in the 1 N NaOH–DMSO formulation. The lipid formulation, however, did prevent the precipitation of KW3902 after IV injection, and it was suggested that this formulation may be used in further clinical studies.

The renal protective activity of KW3902 was investigated in a rat model of glycerol-induced acute renal failure (Suzuki et al. 1992). The antagonist was administered intraperitoneally (IP), and after 30 min glycerol (50% v/v in sterile saline; 0.8 mL 100 g^{-1}) was injected subcutaneously. After a subsequent 24-h hold time, blood was collected and serum creatinine and urea nitrogen were determined

Table 3 Pharmacokinetic parameters of KW3902 and metabolite M1-KW3902 after IV administration of KW3902 to rats

	Free KW3902		Metabolite M1-KW3902	
	0.1 mg kg ⁻¹	1 mg kg ⁻¹	0.1 mg kg ⁻¹	1 mg kg ⁻¹
<i>t</i> _{1/2} (h)	1.0 ± 1.1	1.6 ± 0.6	4.7 ± 1.2	7.9 ± 3.9
AUC _{0-∞} (ng h ⁻¹ mL ⁻¹)	72 ± 50	561 ± 18	486 ± 113	4,916 ± 2,457
CL (L h ⁻¹ kg ⁻¹)	1.87 ± 1.11	1.79 ± 0.06	–	–
MRT (h)	1.5 ± 1.9	1.5 ± 0.3	7.3 ± 1.7	11.3 ± 5.6
<i>V</i> _{ds} (L kg ⁻¹)	1.66 ± 1.10	2.72 ± 0.51	–	–

Values represent the means ± standard deviation of three experiments.

*t*_{1/2}, Half-life; *AUC*, area under the curve; *CL*, total body clearance; *MRT*, mean residence time; *V*_{ds}, volume of distribution

Table 4 Renal protective activity of KW3902 in rats^a

Dose (mg kg ⁻¹ , IP)	Serum creatinine			Serum urea		
	Concentration (mg dL ⁻¹)			nitrogen (mg dL ⁻¹)		
	Vehicle	Treated	% Inhibition	Vehicle	Treated	% Inhibition
0.01	4.03 ± 0.23	1.83 ± 0.08 ^b	55	130.5 ± 7.0	45.2 ± 3.9 ^b	65
0.1	2.89 ± 0.18	1.40 ± 0.14 ^c	52	138.4 ± 9.8	48.1 ± 7.0 ^c	65
1	3.75 ± 0.43	2.00 ± 0.14 ^c	47	123.2 ± 14.2	66.4 ± 6.3 ^c	46

^aAll values are the means ± SEM; significant difference from vehicle-treated group

^b*P* < 0.01

^c*P* < 0.001

(Table 4). Typically after glycerol injection, serum creatinine and urea nitrogen increase seven- to tenfold in rats. Pretreatment with KW3902 significantly reduced (50–60%) the negative renal effects of glycerol-induced acute renal failure (Suzuki et al. 1992).

The mechanism of the protective effects of A₁AR antagonism on two additional nephrotoxic models of acute renal failure in vivo, including renal accumulation of gentamicin (Yao 2000) and radiocontrast media (RCM) (Yao et al. 2001), were examined. From these studies, it was suggested that KW3902 inhibited the action of endogenous adenosine and increased renal blood flow, which led to suppression of intrarenal accumulation of gentamicin, whereas in RCM-induced nephropathy, it prevented the drop in glomerular filtration rate (GFR); a marker for kidney function that occurs in *N*-o-nitro-*L*-arginine methyl ester (*L*-NAME) hypertensive rats. In the RCM model, it is unclear whether the action of the antagonist reduces RCM uptake and cellular toxicity by inhibiting sodium transport in the proximal tubule or by another mechanism.

Adenosine has been found, through its actions on A₂ARs (presumably A_{2A}ARs), to play a protective role in the ischemic preconditioning of multiple organs, including the liver (Peralta et al. 1999), heart (Forman et al. 1993), and lung (Khimenko et al. 1995). Magata (Magata et al. 2007) recently reported that blockade of the A₁AR with KW3902 attenuated hepatic ischemia-reperfusion injury in dogs. Two

groups of female beagles ($n=6$) underwent a 2 h total hepatic vascular exclusion; one group served as the control and the other received $1 \mu\text{g kg}^{-1} \text{min}^{-1}$ of KW3902 via continuous intraportal infusion for 60 min prior to ischemia. It was noted that although peripheral IV infusion of KW3902 was effective in earlier studies (Nonaka et al. 1996), no beneficial effects were seen in the hepatic ischemia-reperfusion model by this route of administration. Thus, treatment by KW3902 via the portal vein proved beneficial in a number of outcomes in the study. The two-week survival of the control group was 16.7% versus 83.3% ($P < 0.05$) for the treated group. Serum alanine aminotransferase (ALT) levels were significantly inhibited by the A_1 AR antagonist; the control group rose rapidly to $12,625 \pm 1,010 \text{ U L}^{-1}$ after 6 h of reperfusion, while the treated animals peaked at 24 h at $2,352 \pm 452 \text{ U L}^{-1}$. In addition, the number of infiltrating neutrophils in the hepatic tissue of the KW3902 group (41.17 ± 11.01 at 60 min) was significantly lower than that of the control group (63.6 ± 23.6 at 60 min) (Fig. 4).

Treatment with KW3902 in the liver ischemia-reperfusion model prevented the bradycardia seen in the control animals just after reperfusion, significantly increased adenine nucleotide levels in the ischemic tissues, and regulated the microcirculatory disturbances, resulting in greater hepatic tissue blood flow. It was concluded that for adenosine to protect the liver from ischemia-reperfusion injury it is necessary to block A_1 AR activation.

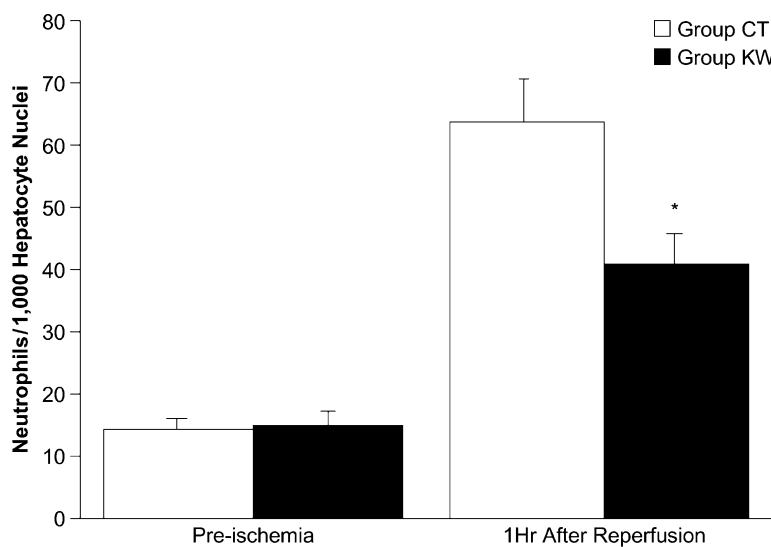


Fig. 4 The number of infiltrated neutrophils in liver tissue. Data are expressed as mean \pm SEM. Group CT, negative control ($n = 6$); group KW, treated KW3902 ($n = 6$). * $P < 0.05$ versus group CT. Reprinted with permission from Magata et al. (2007)

Clinical Studies

Building upon the earlier studies of the renal effects of another A₁AR antagonist, BG9719 (8-(3-oxa-tricyclo[3.2.1.0^{2,4}]oct-6-yl)-1,3-dipropyl-3,7-dihydropurine-2,6-dione) (Gottlieb et al. 2002), in patients with congestive heart failure (CHF), Dittrich and colleagues (Dittrich et al. 2007) examined the renal vasodilatory effects of 30 mg doses of KW3902 in patients with ambulatory heart failure (HF). The two-way crossover study followed patients with CHF with mild renal impairment (median GFR 50 mL min⁻¹) and compared IV administration of placebo or KW3902 oil emulsion followed by IV furosemide (80 mg). GFR and renal plasma flow were assessed by iothalamate and *para*-aminohippurate clearances over 8 h. After a three- to eight-day washout period, subjects crossed over to either active treatment or placebo, again followed by furosemide. Renal plasma flow (Fig. 5) and GFR increased by 48% ($P < 0.05$ vs. placebo) and 32% ($P < 0.05$ vs. placebo), respectively, over baseline for 8 h postKW3902 administration, supporting the conclusion that blockade of the A₁AR leads to vasodilation and increases in filtration rates in patients with HF with reduced kidney function. There also appeared to be a persistent positive effect on GFR (approx. 10 mL min⁻¹ increase in GFR over previous baseline) seen in the crossover patients who received KW3902 in the first dose. The pharmacokinetics of the parent compound or its metabolites could not account for the change in the baseline GFR values.

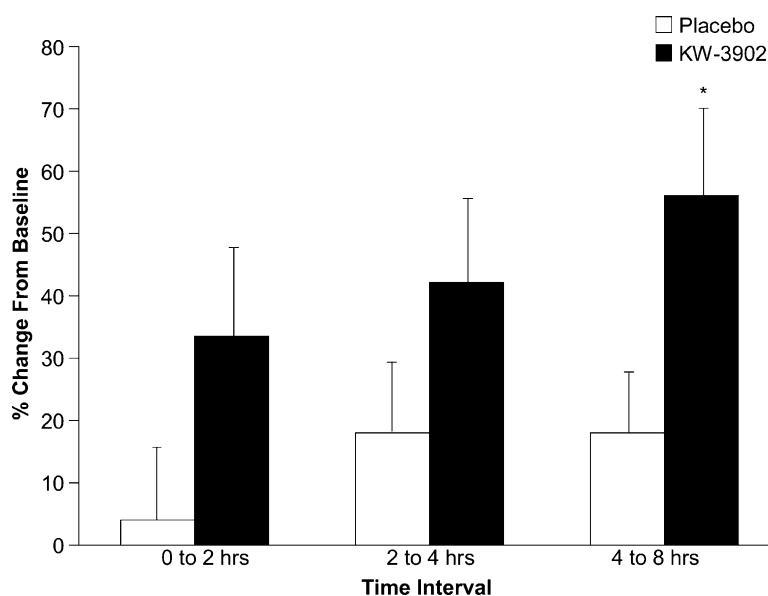


Fig. 5 Renal plasma flow (RPF). The percent change in RPF from baseline for KW-3902 and placebo in the presence of furosemide ($n = 23$). Values shown are for all subjects mean \pm SEM. P values reflect analysis of RPF percent change between KW-3902 and placebo using log RPF values (* $P < 0.05$). Reprinted with permission from Dittrich et al. (2007)

In a related clinical investigation, Givertz et al. (2007) examined the dose-dependent effects of KW3902 on diuresis and renal function in two subsets of patients with acutely decompensated heart failure (ADHF) with either renal impairment or diuretic resistance. In the first protocol, patients with volume overload and creatinine clearance (CrCl) of 20–80 mL min⁻¹ received either placebo or one of four doses (2.5, 15, 30, or 60 mg) of KW3902 as a 2 h IV infusion for up to three days of treatment. All four doses increased urine output during the 6 h period following administration (Fig. 6). There were no significant differences in systolic blood pressure or heart rate in any of the treatment groups. A transient decrease in serum creatinine was noted on day 2 of treatment for all dose levels (−0.03 to −0.08 mg dL⁻¹ for KW3902 arms vs. +0.04 mg dL⁻¹ for placebo). This effect was maintained on day 4 (or the day of discharge), except for the 60 mg dose level.

In the diuretic-resistant population, single infusions of KW3902 (10, 30, or 60 mg) were given to patients with an average baseline CrCl of 34 mL min⁻¹. Urine output increased for all dose levels (ranging from +22 to +24 mL h⁻¹), whereas the placebo arm saw a decrease in urine output (−29 mL h⁻¹). The CrCl data for this subset of patients was complex. In general, the placebo arm had decreases in CrCl over 24 h with similar trending from the 60 mg dose treatment group. However, the 10 and 30 mg doses showed increases in CrCl over the 24 h period. The inverted relationship between KW3902 dose and renal function (CrCl) at high doses bears some resemblance to the dose–response relationship seen at higher doses of the A₁AR antagonist BG9719 (Gottlieb et al. 2002). Whether these similarities are due

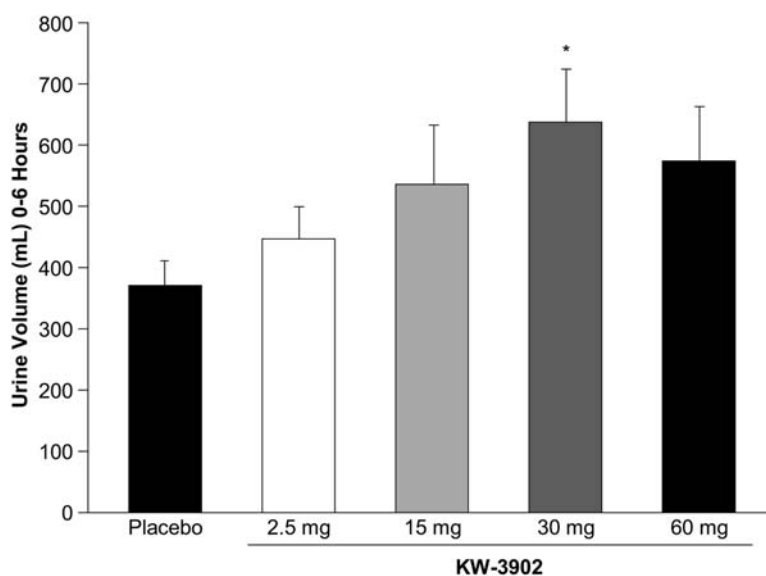


Fig. 6 Urine output in first 6 h after administration of KW3902. Cumulative urine volume (mean ± SEM) 6 h after initiation of placebo or KW-3902 in patients with acutely decompensated heart failure (ADHF) with renal impairment (* $P = 0.02$ vs. placebo). Reprinted with permission from Givertz et al. (2007)

to cross-activity against the other adenosine receptors in the kidney at high doses or in other tissues is unclear and may require further study. Phase III clinical trials of KW3902 in patients with ADHF are currently underway, and limited releases of the data have recently appeared (Novacardia Press Release 2007).

2.2 BG9928

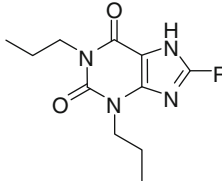
At the same time that formulation development began on KW3902, another selective A₁AR antagonist, BG9719, which possessed adequate pharmacologic activity, was used to demonstrate proof of concept for A₁AR antagonism in animals (Pfister et al. 1997) and humans (Gottlieb et al. 2000, 2002). However, the poor pharmaceutical properties of this molecule (low aqueous solubility and a tendency to rearrange to inactive products in both acidic and basic media) led Kiesman et al. (Kiesman et al. 2006a, b) to design more pharmaceutically acceptable antagonists by exploring the placement of polar substituents on linearly substituted 8-cycloalkyl 1,3-dipropylxanthines. For structurally related imidazolines, see Vu et al. (2006). The binding affinities of selected 8-cyclohexyl and 8-bicyclo[2.2.2]octyl xanthines are listed in Table 5.

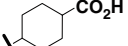
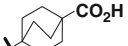
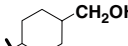
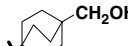
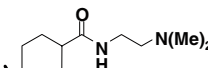
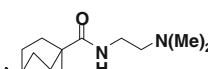
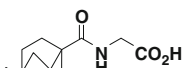
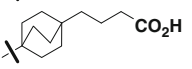
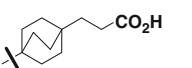
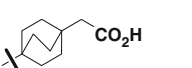
The bicyclo[2.2.2]octyl analogs **11**, **13**, **15** had better A₁AR binding affinities than the related cyclohexyl variants **10**, **12**, **14**, and maintained similar A_{2A}AR activity. A significant improvement in receptor selectivity ($hA_{2A}/hA_1 = 161$ vs. 22) came with the replacement of the dimethylamino functional group in **15** with the carboxylic acid in **16**. Further optimization of the bridgehead chain led to the propionic acid **18**, BG9928, and single-digit nanomolar ($rA_1 = 1.3$ nM and $hA_1 = 7.4$ nM) activity and high receptor selectivities ($rA_{2A}/rA_1 = 1,880$; $hA_{2A}/hA_1 = 915$).

The functional antagonist activity of BG9928 (Kiesman et al. 2006a) was confirmed by examining the blockade or increasing doses of the compound on the inhibitory effects of *N*⁶-cyclopentyl adenosine (CPA) on the beat rates of isolated rat atria. Administration of the antagonist restored the atrial beat rates to their maxima and effectively blocked the negative chronotropic activity of CPA ($EC_{50} = 16.1 \pm 7.7$ nM). In a separate set of isolated rat atria experiments, BG9928 was found to have a pA₂ (antagonist potency) of 9.8.

Animal Studies

Single oral doses of BG9928 administered to male Sprague–Dawley rats (Fig. 7) led to increases in urine volume (UV) and sodium excretion (UNaV) with a 50% efficient dose (ED_{50}) of approximately $15 \mu\text{g kg}^{-1}$ (Kiesman et al. 2006a; Ticho et al. 2003). The increases in urinary potassium excretion were proportional to volume increases, confirming the potassium-neutral diuresis commonly observed with A₁AR antagonists. The dose–response relationships are similar to those seen with KW3902 (Fig. 2); however, the magnitude of the pharmacodynamic effect is smaller

Table 5 Structure–activity relationships for 1,4-linearly-substituted 8-cycloalkylxanthines


Cmpd	K_i (nM) ^a or % of specific radioligand binding ^b					
	R	hA ₁	hA _{2A}	hA _{2B}	hA ₃	hA _{2A} /hA ₁
10		(31%)	(75%)	(69%)	(88%)	–
11		33	1,070	(48%)	(100%)	32
12		41	313	(18%)	(77%)	8
13		16	414	(27%)	(73%)	26
14		12	168	(16%)	(91%)	14
15		6	132	(3%)	(79%)	22
16		49	7,880	(53%)	(70%)	161
17		29 (4.0) rat	– (50%) rat	127 –	(26%) –	– (~250) rat
18		7.4 (1.3) rat	6,410 (2,440) rat	90 –	>10,000 –	915 (1,880) rat
19		(22.5) rat	(8,960) rat	–	–	(398) rat

^aReceptor binding experiments using cloned human receptors in CHO (hA₁, 0.3 nM [¹²⁵I]-aminobenzyladenosine (¹²⁵IABA) or HEK293-derived cell membranes (hA_{2A}, 0.7 nM [¹²⁵I]-ZM241385; hA_{2B}, 0.5 nM [¹²⁵I]-3-(4-aminobenzyl)-8-phenyloxyacetate-1-propyl-xanthine; and hA₃, 0.6 nM [¹²⁵I]-ABA); rA₁ binding measured as inhibition of [³H]-DPCPX to rat forebrain membranes; rA_{2A} binding measured as inhibition of [³H] ZM241385 in rat striatal membranes. All K_i values were calculated from binding curves generated from the mean of four determinations per concentration (seven antagonist concentrations), with variation in individual values of <15% (Kiesman et al. 2006a)

^bData are presented as percent of radioligand bound in the presence of target compound relative to control

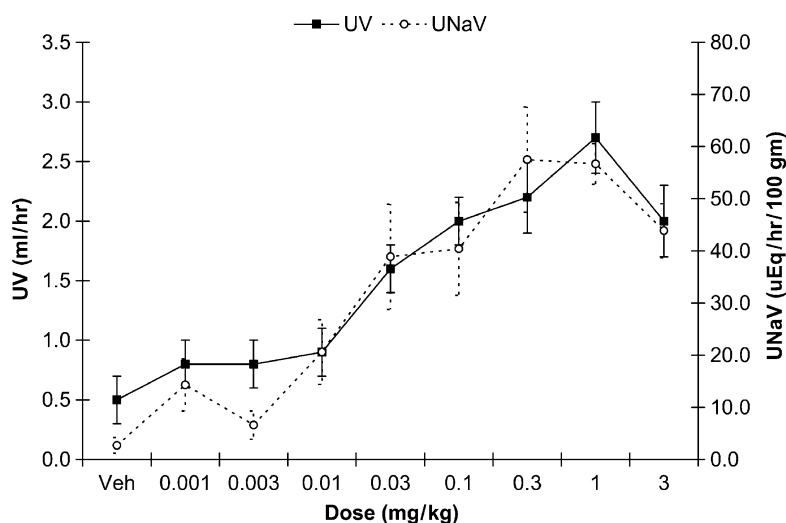


Fig. 7 Dose-response for urine volume (UV) in mL h^{-1} (mean \pm SEM) and urinary sodium excretion (UNaV) in $\mu\text{Eq h}^{-1} 100 \text{ g}^{-1}$ (mean \pm SEM) over 4 h following single oral doses of vehicle (0.5% carboxymethyl cellulose suspension, $n=3$) or BG9928 ranging from 0.001 to 3 mg kg^{-1} in rats (0.001 mg kg^{-1} , 0.003 mg kg^{-1} , 0.01 mg kg^{-1} , each $n=4$; 0.03 mg kg^{-1} , 0.1 mg kg^{-1} , 0.3 mg kg^{-1} , each $n=5$; 1.0 mg kg^{-1} , 3.0 mg kg^{-1} , each $n=3$). Adapted with permission from Kisman et al. (2006a)

Table 6 Pharmacokinetic parameters of BG9928 following single oral dose administration

	<i>F</i> (%)	<i>t</i> _{1/2} (h)	CL ($\text{mL min}^{-1} \text{ kg}^{-1}$)	<i>V</i> _{ds} (L kg^{-1})
Rat	99	3.14 \pm 0.14	1.56 \pm 0.26	0.32 \pm 0.02
Dog	78	6.40 \pm 4.0	11.8 \pm 0.6	2.64 \pm 1.29
Monkey	94	11.1 \pm 4.2	5.82 \pm 0.45	4.25 \pm 0.70

$n = 3$ male rats, 4 male dogs, and 4 male cynomolgus monkeys

F(%), Percent bioavailability; *t*_{1/2}, half-life; CL, total body clearance; *V*_{ds}, volume of distribution

in the BG9928 study than in the KW3902 study because the rats in the BG9928 model were not saline-loaded prior to treatment.

The single oral-dose pharmacokinetic profile of 1 mg kg^{-1} BG9928 was assessed in the rat, dog, and cynomolgus monkey (Table 6). Bioavailability was nearly complete in the rat and cynomolgus monkey, slightly lower in the dog, and followed the clearance difference amongst the species. Elimination half-lives were similar in the rat and dog (3–6 h), and longer in the cynomolgus monkey (11 h).

A rat model was designed to mimic the sodium-retentive state of patients with CHF (Ticho et al. 2003). Rats were given an oral dose of 100 mg kg^{-1} furosemide and placed on a low-sodium diet for up to six days. One group ($n = 8$) then received a single IV bolus of 30 mg kg^{-1} furosemide, while the other group ($n = 9$) received IV furosemide and 1 mg kg^{-1} of BG9928. The results are depicted in Fig. 8.

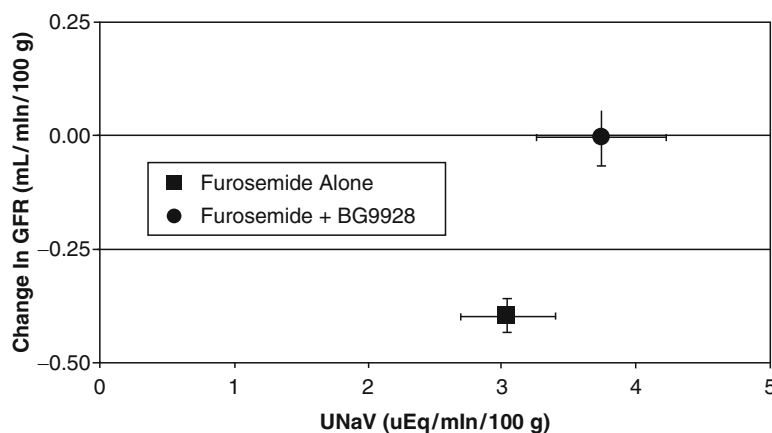


Fig. 8 Renal protective (mean \pm SEM change in glomerular filtration rate [GFR]) and natriuretic (mean \pm SEM) urinary sodium excretion (UNaV) effect of 1 mg kg^{-1} BG9928 administered IV in combination with furosemide (30 mg kg^{-1} IV) ($n = 9$, *circles*) compared with furosemide alone (30 mg kg^{-1} IV) ($n = 8$, *squares*) in low-sodium-retention rats. Reprinted with permission from Ticho et al. (2003)

Furosemide increased natriuresis and reduced GFR by approximately 50% over baseline. The addition of BG9928 not only further increased the natriuresis ($+0.71 \mu\text{Eq min}^{-1} 100 \text{ gm}^{-1}$) but also maintained the GFR, therefore preserving renal function. Similar data were presented for a Phase II proof-of-concept clinical trial for BG9719, a precursor compound to BG9928 (Gottlieb et al. 2002).

The interplay of A_1 AR antagonism and ischemic preconditioning (IPC), specifically the effects of DPCPX, BG9719, and BG9928, in an in vivo dog model of myocardial infarction was examined (Auchampach et al. 2004). The study was composed of three arms in which the dogs ($n = 6\text{--}12$) were subjected to 60 min of left anterior descending coronary artery occlusion, followed by 3 h of reperfusion. Infarct size was assessed by triphenyltetrazolium chloride staining. In protocol 1, the dogs received vehicle or 1 mg kg^{-1} of the antagonist as a pretreatment, followed by continuous infusion at $10 \mu\text{g kg}^{-1} \text{ min}^{-1}$ over the occlusion time. In protocol 2, the dogs received the same pretreatment as before but also received four 5-min occlusion/reperfusion preconditioning cycles. In protocol 3, the antagonists were not administered until 10 min prior to release of the occlusion and continued for 1 h into the reperfusion. Figure 9 summarizes the infarct size measurements across all three protocols.

Pretreatment with DPCPX or BG9928 reduced the myocardial infarct size by 51% and 49%, respectively, and none of the three antagonists blocked the protection of the myocardium afforded by the brief multiple-cycle IPC. In the most challenging experiment, it was found that treatment with either DPCPX or BG9928 just prior to reperfusion, a situation that more closely resembles clinical intervention in the course of treatment for myocardial infarction, reduced the infarct sizes by 43%

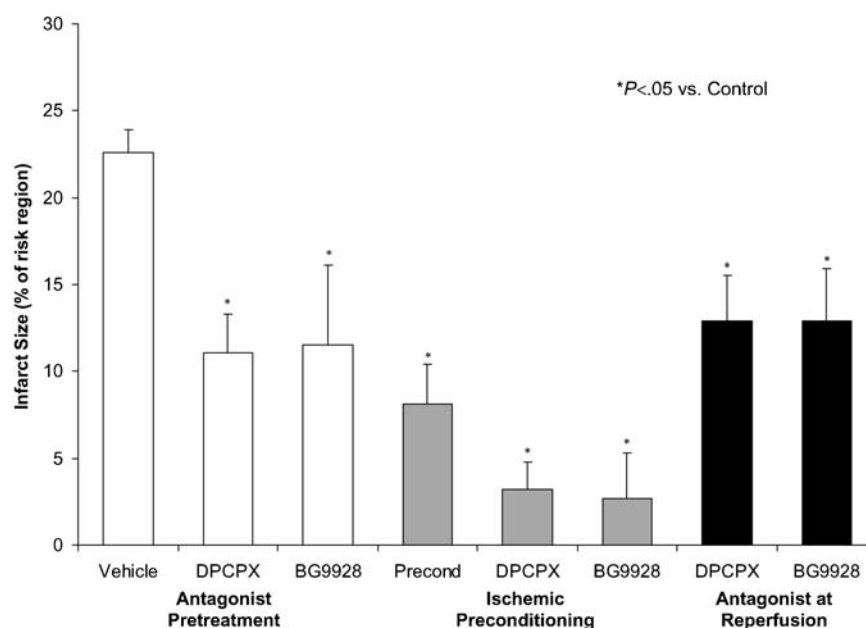


Fig. 9 Myocardial infarct size data (infarct size expressed as a percent of the area at risk) from antagonist pretreatment (protocol 1), ischemic preconditioning (protocol 2), and antagonist at reperfusion (protocol 3). $P < 0.05$ vs. control Adapted with permission from Auchampach et al. (2004)

and 45%, respectively. The study concluded that treatment with BG9928 provided cardioprotective effects that reduced infarct size and did not interfere with the protective effects of multiple-cycle IPC.

Clinical Studies

Greenberg et al. (2007) described the results of a placebo-controlled dose-escalation study designed to assess the pharmacokinetics and clinical effects of oral BG9928 in patients with HF. The study was conducted in 50 patients with HF, an ejection fraction of $\leq 40\%$ documented in the past 12 months, and who were on standard therapy including angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blocker (ARB) therapy and diuretics.

The pharmacokinetics of oral BG9928 in humans compared favorably to data from the earlier animal studies (Kiesman et al. 2006a) (Table 6). BG9928 was rapidly absorbed, with a t_{\max} of 1.5–3.1 h and similar C_{\max} , $t_{1/2}$, and clearances for days 1, 6, and 10. Steady-state AUC was reached by day 6, and the elimination half-life (14–25 h) was consistent with once-daily dosing. Patients received BG9928 (3, 15, 75, or 225 mg) or placebo orally for ten days and were evaluated for changes in sodium excretion (primary endpoint), potassium excretion, creatinine clearance,

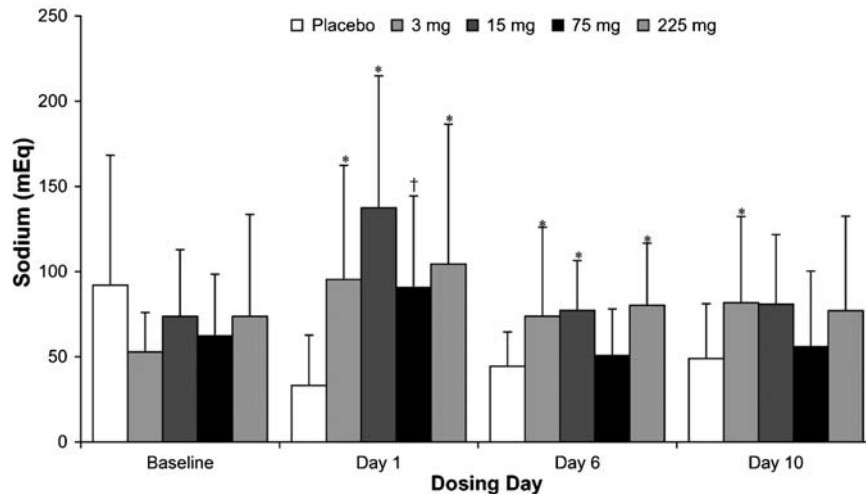


Fig. 10 Cumulative urinary sodium excretion (mEq) over the interval of 0–8 h at baseline and after placebo or BG9928 administration on days 1, 6, and 10. * $P < 0.05$ vs. placebo; † $P < 0.055$ vs. placebo; $n = 10$ per group except for 15 and 75 mg dose groups on day 10 ($n = 9$ per group). Reproduced with permission from Greenberg et al. (2007)

and body weight. In humans, BG9928 increased sodium excretion compared with placebo and maintained the natriuresis over the ten-day study period (Fig. 10) with little kaliuresis. These data followed the same trends seen in the previous rat and monkey studies (Kiesman et al. 2006a; Ticho et al. 2003) (Fig. 7).

Use of ACE inhibitors, ARBs, and diuretics in patients with HF can adversely affect renal function and depress GFR. Despite the significant increases in natriuresis, adjusted CrCl was unchanged over the study period for all of the treatment groups (Fig. 11), suggesting that BG9928 may have had a protective effect on renal function.

Patients who received daily doses of greater than 3 mg had a reduction in body weight (−0.6, −0.7, −0.5 kg) versus a net weight gain of +0.3 kg for the placebo group at the end of the study (Fig. 12).

Patients receiving BG9928 also showed favorable directional trends in other measures of clinical status, including New York Heart Association functional class (five BG9928-treated patients improved by one level); Cody edema score (mean change from day 1 to day 11: 0 for placebo and up to −0.6 for the treated groups; a negative number indicates an improvement in HF signs); and physician's global assessment. Thus, positive effects were observed for all treated groups. However, there were no significant differences in clinical status for the short duration of the trial. This is the first clinical assessment of chronic oral dosing of an A₁ AR antagonist in humans. Future studies are planned to examine clinical status and renal preservation with both oral and parenteral BG9928 in patients with HF.

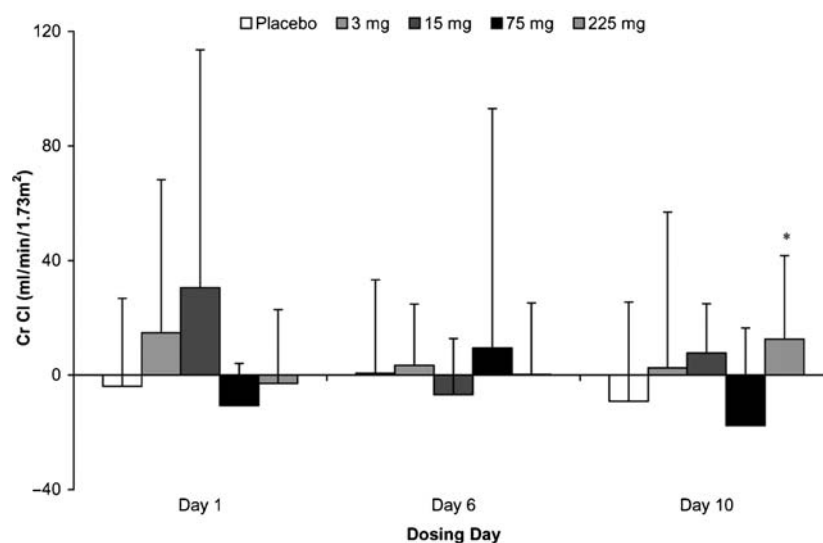


Fig. 11 Absolute change from baseline in adjusted creatinine clearance (CrCl) ($\text{ml min}^{-1} 1.73 \text{ m}^{-2}$) for the interval of 2–24 h after placebo or BG9928 administration on days 1, 6, and 10. * $P < 0.05$ vs. placebo; $n = 7$ –10 per group. Reproduced with permission from Greenberg et al. (2007)

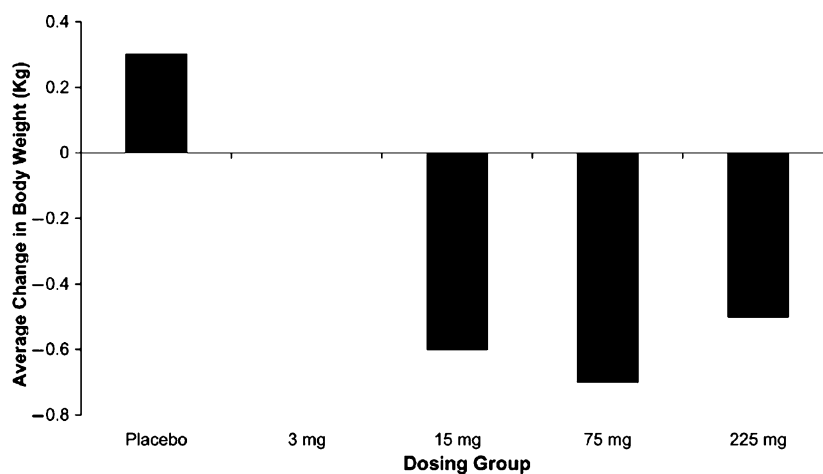
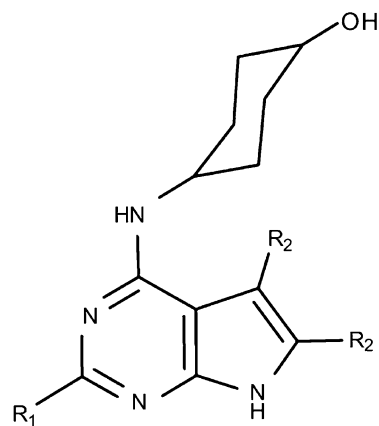


Fig. 12 Average change in body weight (kg) from baseline to day 11 after placebo or BG9928 administration. $n = 10$ per group. Reproduced with permission from Greenberg et al. (2007)

2.3 SLV320

Unlike the two xanthine-based A₁AR antagonists described in the preceding sections, SLV320 (see Fig. 1) contains an *N*⁶-substituted-7-deazapurine core (specifically a 2-phenyl-pyrrolopyrimidine) with an *N*⁶-*trans*-cyclohexanol side chain. The

Fig. 13 Structure of pyrrolopyrimidine series**Table 7** Structure–activity relationships for pyrrolopyrimidines

Compd	R ₁	R ₂	K _i (nM) or % of specific radioligand binding ^a				
			hA ₁	hA _{2A}	hA _{2B}	hA ₃	hA _{2A} /hA ₁
20	Ph	Me	~22	933	138	22	42
21	4-Pyridyl	H	8.0	131	1,031	(54%)	16
22	3-Chlorophenyl	H	8.0	531	530	419	66
23	3-Fluorophenyl	H	1.8	206	802	270	114
24	Ph	H	3.7	630	2,307	630	170

^aReceptor binding experiments performed using membranes from yeast cells containing cloned human receptors (hA₁, [³H]-DPCPX) or HEK293-derived cell membranes (hA_{2A}, [³H]-CGS21680; hA_{2B}, [³H]-DPCPX; and hA₃, 0.6 nM [¹²⁵I]-AB-MECA) (Castelhano et al. 2005)

published SAR data around the pyrrolopyrimidine series (Fig. 13, Table 7) are only described within a series of patent filings (Castelhano et al. 2005). Dimethyl analog **20** had equipotent A₁ and A₃ AR affinities, a result that contrasts strikingly with those for the earlier xanthine systems (Tables 2 and 2.5). Removal of the two methyl groups (R₂ = Me) from compound **20** led to a tenfold increase in affinity for the A₁AR **24** and a significant reduction in A₃AR binding (22–630 nM) (Table 7). Substitution on the phenyl ring has small effects upon A₁AR activity and, in general, decreased selectivity versus the A_{2A}AR.

The functional antagonist activity of SLV320 was confirmed in experiments involving transient A₁AR-mediated bradycardia in anesthetized rats. Bolus injections of adenosine (100 µg kg⁻¹) lowered the heart rate in rats, and subsequent pretreatment both IV and orally with the antagonist caused a dose-dependent increase back to baseline in heart rate, with ED₅₀ values of 0.25 and 0.49 mg kg⁻¹, respectively. Similar to the results for BG9928 (Greenberg et al. 2007; Ticho et al. 2003), no significant hemodynamic effects were seen in anesthetized rats (heart rate, systolic arterial pressure, or diastolic arterial pressure) with single IV bolus doses of between 0.1 and 5 mg kg⁻¹.

In a model of chronic renal failure and myocardial fibrosis, rats were subjected to either sham operations or removal of 5/6 of their kidneys (5/6 NX animals) (Kalk

Table 8 Plasma analytes, GFR, and albumin excretion at the end of the 5/6 NX study

Parameter	Sham	Sham + SLV320	5/6NX	5/6 NX +SLV320
CK (U L ⁻¹)	481 ± 159	255 ± 31	1,267 ± 324	196 ± 64 ^d
AST (U L ⁻¹)	41 ± 2	41 ± 1	60 ± 5 ^a	35 ± 1 ^d
ALT (U L ⁻¹)	36 ± 1	31 ± 1	43 ± 1 ^a	32 ± 1 ^d
Creatinine (mg L ⁻¹)	4.7 ± 0.3	4.3 ± 0.2	7.3 ± 0.3 ^b	7.6 ± 0.42 ^b
GFR (mL min ⁻¹ 100 g ⁻¹)	0.45 ± 0.05	0.52 ± 0.02	0.32 ± 0.02 ^a	0.31 ± 0.01 ^a
Urinary albumin excretion (mg 24 h ⁻¹)	0.06 ± 0.02	0.07 ± 0.02	2.31 ± 0.39 ^b	1.08 ± 0.19 ^{b,c}

Values given as mean ± SEM

^a $P < 0.05$ versus sham^b $P < 0.001$ versus sham^c $P < 0.05$ versus sham^d $P < 0.001$ versus 5/6 NX

CK, Creatinine kinase; AST, aspartate aminotransferase; ALT, serum alanine aminotransferase; GFR, glomerular filtration rate

et al. 2007). The effects of SLV320 on markers for cardiomyopathy and clinical chemistry were examined. Treatment with the A₁AR antagonist completely abolished higher creatinine kinase (CK) plasma levels as well as elevated ALT and aspartate aminotransferase (AST) in the nephrectomized animals (Table 8). The creatinine levels and GFR measurements of the 5/6 NX animals showed diminished renal function, as expected, when compared to the sham group. Treatment with SLV320 did not significantly lower creatinine or increase GFR. In addition, although albuminuria was higher in the 5/6 NX group, treatment with SLV320 led to a 50% reduction in albumin excretion and exerted beneficial effects on renal disease progression.

No significant differences in cardiac histology were seen between the arms of the study; however, immunohistochemistry uncovered a significant increase in collagen I and III in the untreated 5/6 NX group compared to the SLV320-treated group (Fig. 14). This study was the first to demonstrate that an A₁AR antagonist inhibited markers of myocardial fibrosis without changes in blood pressure. The experiments also agree with two previous studies (Amann et al. 1998a, b) that concluded that uremia promotes cardiac fibrosis independently of hypertension.

It was recently reported that the clinical development of the oral form of SLV320 was suspended and little information is available on the results of human clinical trials with the intravenous product.

3 A₁ Adenosine Receptor Agonists

Agonism at A₁ARs may provide benefit for the following disease states: paroxysmal supraventricular tachycardia (PSVT)—break the atrial arrhythmia to return to sinus rhythm (Belardinelli and Lerman 1990; Belardinelli et al. 1995; DiMarco

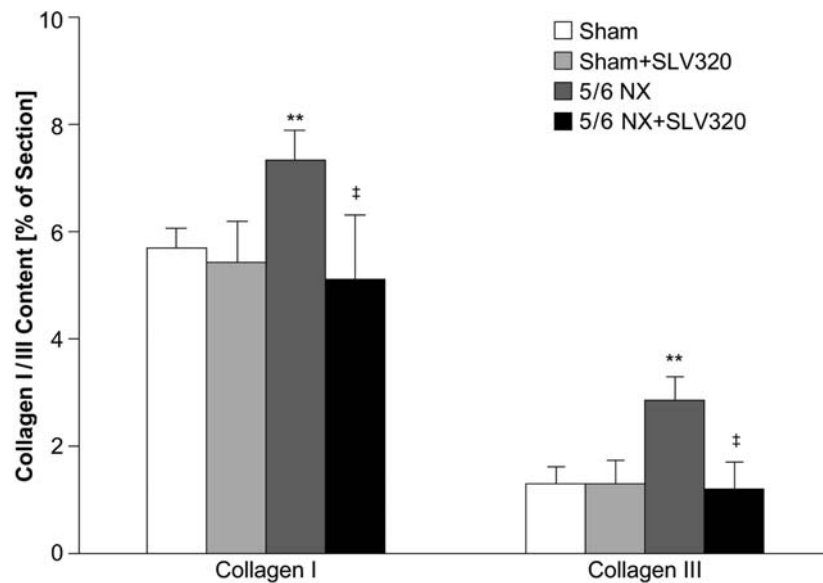


Fig. 14 Collagen I and III in rat hearts from nephrectomized rats versus normal controls. Values are given as mean \pm SEM. Unpaired *t*-test was applied to detect significant differences between the study groups. ***P* < 0.001 vs. sham; ‡*P* < 0.001 vs. 5/6 NX. Reprinted with permission from Kalk et al. (2007)

et al. 1985; Lerman and Belardinelli 1991), atrial fibrillation (AF)—provide ventricular rate control (Wang et al. 1996; Zablocki et al. 2004), type II diabetes (T2D)—lower nonesterified fatty acid (NEFA) levels and triglycerides (TG's), as well as enhancing insulin sensitivity (Fatholahi et al. 2006; Gardner et al. 1994; Hoffman et al. 1986; Roden et al. 1996), and angina (Liu et al. 1991; Miura and Tsuchida 1999; Mizumura et al. 1996). The A₁AR is found in the A–V and S–A nodes, where stimulation by an A₁AR agonist results in negative dromotropic and chronotropic effects, respectively (Belardinelli et al. 1995; Wang et al. 1996). These cardiovascular (CV) effects are often side effects of A₁AR agonists that are being pursued for the other indications. Multiple full A₁AR agonists, tecadenoson (2*R*, 3*S*, 4*R*)-2-(hydroxymethyl)-5-(6-((*R*)-tetrahydrofuran-3-ylamino)-9*H*-purin-9-yl)tetrahydrofuran-3,4-diol), selodenoson (2*S*, 3*S*, 4*R*)-5-(6-(cyclopentylamino)-9*H*-purin-9-yl)-*N*-ethyl-3,4-dihydroxytetrahydrofuran-2-carboxamide) and PJ-875 are being pursued as intravenous clinical agents for the treatment of atrial arrhythmias, and the progress of these compounds will be highlighted below. In addition to the full A₁AR agonists, CV Therapeutics has reported on orally bioavailable partial A₁AR agonists that slow AV nodal conduction without causing third-degree AV block. For T2D, although both full and partial agonists will lower NEFA levels, a partial A₁AR agonist has the potential to do so with fewer side effects (Song et al. 2002; Srinivas et al. 1997; Stephenson 1997; Wu et al. 2001). Partial A₁AR agonists have the potential to

provide for a selective targeted response, avoiding CV side effects (Wu et al. 2001). Plus, partial A₁AR agonists may be able to avoid receptor desensitization due to overstimulation that can lead to tachyphylaxis. In T2D, overstimulation of hormone-sensitive lipase (HSL) due to enhanced beta-adrenergic agonism on adipocytes leads to elevated NEFA levels within T2D patients from the 0.4–0.5 mM range up to the 0.8–1.2 mM range. Elevated NEFA levels have been shown to decrease skeletal muscle uptake of glucose, lower insulin release from the pancreas, and increase glucose production in the liver (Boden et al. 2005; Dhalla et al. 2007a; Ferrannini et al. 1983; Green 1987; Itani et al. 2002; Sako and Grill 1990). Decreasing NEFA levels through A₁AR agonism has an insulin-sensitizing effect in animal models. Several full A₁AR agonists (GR79236, ARA, and RPR749) have been evaluated in animal models and in clinical trials for the treatment of T2D, and the progress and challenges of these compounds will be described. CVT-3619 (2*S*, 3*S*, 4*R*)-2-((2-fluorophenylthio)methyl)-5-(6-((1*R*, 2*R*)-2-hydroxycyclopentyl-amino)-9*H*-purin-9-yl)tetrahydrofuran-3,4-diol), a partial agonist, is in preclinical development. The SAR leading up to the discovery of this partial agonist, as well as its efficacy in animal models of T2D, will be highlighted. The last indication for A₁AR agonists that we describe in this review is the treatment of angina. One A₁AR agonist (BAY 68–4986) is currently under clinical evaluation, and the progress of this compound will be described.

3.1 Intravenous Antiarrhythmic Agents: Tecadenoson, Selodenoson, Phenylsulfide, Phenylethers, PJ-875

The first A₁AR agonists to enter clinical development with the exception of adenosine were the IV antiarrhythmic agents, tecadenoson (Ellenbogen et al. 2005; Peterman and Sanoski 2005; Prystowsky et al. 2003) and selodenoson (Bayes et al. 2003; ClinicalTrials.gov 2005) (Fig. 15). The N⁶ lipophilic substituents are the key structure features that impart high affinity and selectivity for the A₁AR: N⁶-(*R*)-3-tetrahydrofuranyl for tecadenoson (A₁AR *K*_i = 3 nM) and N⁶-cyclopentyl for selodenoson (A₁AR *K*_i = 6 nM). Both compounds are similar in structure to N⁶-cyclopentyl adenosine (CPA), but key structural differences are found in each molecule relative to CPA that impart beneficial pharmacological and pharmaceutical properties. For tecadenoson, the furan oxygen is favorable for imparting enhanced binding selectivity and additional solubility. For selodenoson, the 5'-*N*-ethyl carboxamide is favorable for both A₁AR and A₃ AR affinities, and it enhances oral activity. In Phase I clinical trials, both compounds were found to be safe and well tolerated at their specified IV bolus or infusion doses. With regards to efficacy, tecadenoson demonstrated favorable conversion (90%) of acute PSVT at the 300–600 µg bolus dose without significant adverse events. The A₁AR, which is highly expressed in atrial and AV nodal tissues, exerts its effects in the heart through lowering cAMP and direct activation of the inward rectifying potassium current, IK(Ado) (Belardinelli et al. 2005). In addition, A₁AR activation in the heart inhibits the

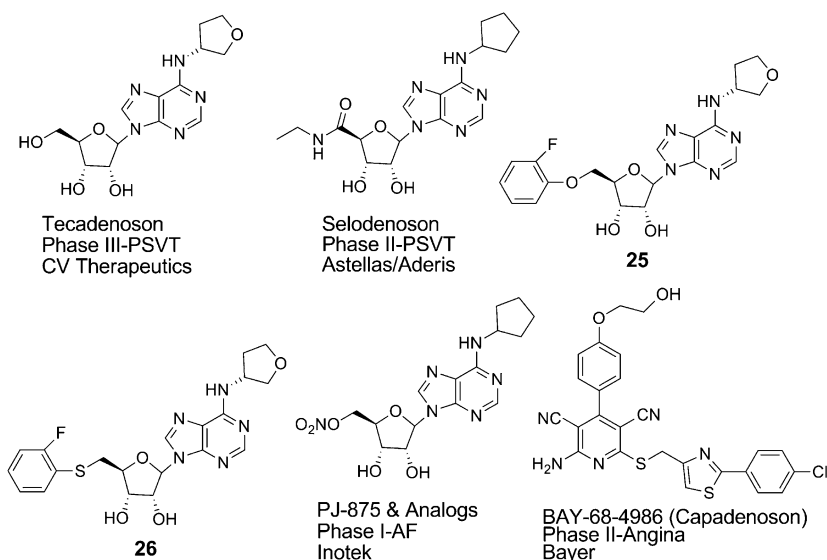


Fig. 15 Antiarrhythmic and antianginal A₁AR agonists

catecholamine-stimulated ion currents such as pacemaker current and L-type calcium currents (Belardinelli et al. 2005). The result of A₁AR activation in the heart is prolongation of the AV nodal refractory period, reducing sinoatrial pacemaker rate and shortening the action potential duration (APD), it is not unexpected to have some atrial fibrillation (AF) after PSVT conversion, and this was found to be extremely low with tecadenoson (<1%), but the incidence of AF with adenosine following IV bolus is reported to be 11% and 15% in different studies (Ellenbogen et al. 2005).

Selodenoson was evaluated for the treatment of AF in a dose-ranging infusion study where it was infused for 15 min at doses of 2, 4, 6, 8, 10, and 12 $\mu\text{g kg}^{-1}$, where it provided for effective ventricular rate control in a dose-dependent manner with minimal side effects (Bayes et al. 2003). CV Therapeutics' scientists have described a number of partial A₁AR agonists as potential oral antiarrhythmic agents that do not cause high-degree AV block at high concentrations (Morrison et al. 2004). These partial agonists were obtained by incorporating aromatic ethers and sulfides at the 5' position of the full agonist tecadenoson, a strategy that is known to decrease intrinsic activity with respect to GTP shift and induction of [³⁵S]GTP γ S binding to G-protein (Yan et al. 2003). The 5' substitution caused a significant drop in affinity for the A₁AR when compared to tecadenoson, and the 5'-aromatic ethers had greater affinity and potency for the A₁AR than the corresponding 5'-sulfides. Comparing the two lead molecules from both series (**25** and **26**) (Fig. 15), the 2-fluorophenyl ether analog **25** displayed higher affinity for the A₁AR ($K_i = 12 \text{ nM}$) and sixfold greater potency ($\text{EC}_{50} = 200 \text{ nM}$) in slowing AV

nodal conduction than the 2-fluorophenyl sulfide **26** without causing third-degree AV block. In addition, compound **25** exhibited greater oral bioavailability (81%) relative to **26**. To our knowledge, compound **25** is the most potent partial A₁ AR agonist known to date; however, after oral administration, a small amount of the extremely potent full A₁ AR agonist tecadenoson was generated; thus, compound **25** was unacceptable for further clinical development as an oral partial A₁ AR agonist for chronic use. PJ-875 is a third A₁ AR agonist in clinical development for AF from Inotek (DailyDrugNews.com 2008). The structure of PJ-875 has not been publicly disclosed; however, Inotek's patent application focuses on a 5'-nitrate ester of CPA with high A₁ AR affinity (A₁ AR K_i = 1 nM) and a 5'-nitrate ester of tecadenoson (A₁ AR K_i = 10 nM) (Jagtap et al. 2005). In Phase I clinical trials, PJ-875 did not have serious side effects, and Phase II clinical trials are planned (DailyDrugNews.com 2008).

The initial clinical trials with full A₁ AR agonists in a controlled IV setting demonstrate that it may be possible to obtain antiarrhythmic properties with minimal CNS side effects. In addition, CV Therapeutics has discovered that the antiarrhythmic properties of a full A₁ AR agonist, tecadenoson, can be augmented by coadministration of a subtherapeutic dose of a short-acting beta-blocker, esmolol, to achieve pronounced ventricular rate control effects in animal models (Belardinelli and Dhalla 2003). This combination approach of beta-blocker and A₁ AR agonist will be interesting to watch in the clinic. Due to the pronounced CV effects at low doses of full A₁ AR agonists, it is clear that a partial A₁ AR agonist may be required to achieve tissue selectivity for other indications such as T2D.

3.2 *Insulin-Sensitizing Agents: GR79236, ARA, CVT-3619*

The therapeutic use of A₁ AR agonists as antilipolytic agents has been tried in the clinic; however, the CV effects mediated by the A₁ AR agonists are a potential obstacle to the successful use of A₁ AR agonists for this indication. A second challenge associated with the use of A₁ AR agonists as antilipolytic agents is the development of acute tolerance to the antilipolytic effects due to receptor desensitization (Dhalla et al. 2007a; IJzerman et al. 1995). One potential solution is to discover a partial A₁ AR agonist that is capable of eliciting a greater effect in the adipocytes than in the heart (i.e., tissue selectivity). By definition, a partial agonist is a low-efficacy ligand that, in contrast to the full agonist, elicits only a submaximal biological response, and is hence less prone to receptor desensitization.

GR79236 ((3*R*, 4*S*, 5*R*)-2-(6-((1*S*, 2*S*)-2-hydroxycyclopentylamino)-9*H*-purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol) and ARA ((1*S*, 2*R*, 3*R*)-3-((trifluoromethoxy)methyl)-5-(6-(1-(5-(trifluoromethyl)pyridine-2-yl)pyrrolidin-3-ylamino)-9*H*-purin-9-yl)cyclopentane-1,2-diol) (Fig. 16), the two full A₁ AR agonists, have demonstrated that A₁ AR agonism can have a pronounced effect on NEFA and TG levels in both acute and chronic animal models, thus establishing the potential of this approach for the treatment of T2D (Bigot et al. 2004; Merkel et al. 1995).

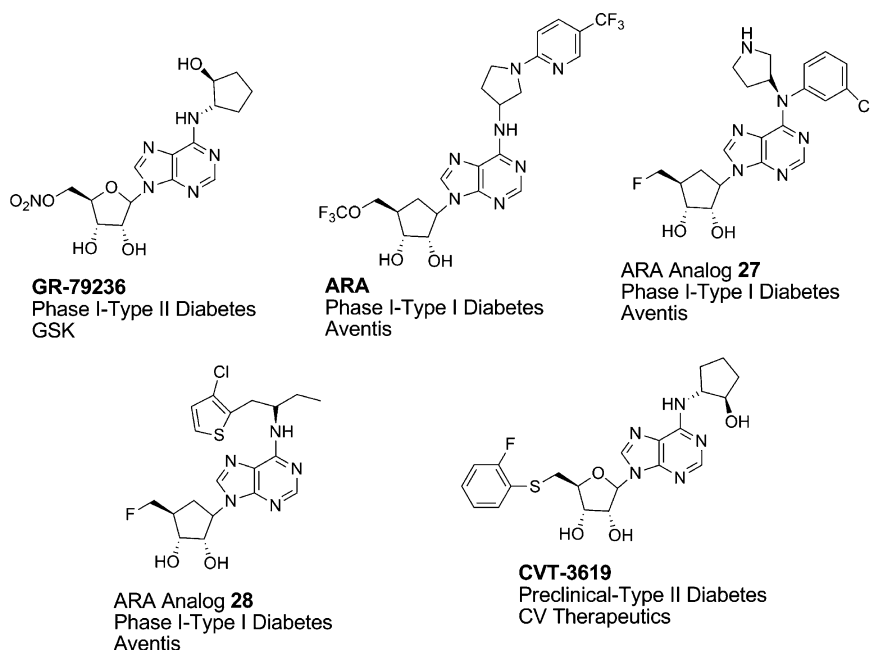


Fig. 16 Antidiabetic and insulin-sensitizing A₁AR agonists

Plus, the use of these full A₁AR agonists in clinical trials has resulted in a better understanding of the desensitization of the A₁AR and some potential limitations of using a full A₁AR agonist in a chronic setting. In early in vitro studies, GR79236 demonstrated that it inhibited catecholamine-induced lipolysis in adipocytes at low concentrations (Green et al. 1990; Qu et al. 1997; Webster et al. 1996). In addition, GR79236 was demonstrated to reduce NEFA levels by 50% in normal fasted rats (Qu et al. 1997). However, in a fructose-fed rat model of noninsulin-dependent diabetes, GR79236 (1 mg kg⁻¹ per day for eight days oral administration) did not enhance insulin sensitivity, but it did significantly lower NEFA and TGs (Webster et al. 1996). ARA, a full A₁AR agonist, has both animal data and clinical trial data supporting its effects on NEFA (Bigot et al. 2004). ARA is a C-sugar wherein the ribose oxygen is replaced by a carbon, and the ribose 5'-hydroxyl group was replaced by fluoro (as in compounds **27** and **28**) or a trifluoromethoxy group, as in ARA (Fig. 16). Compound **28** has lower affinity for the A₁AR with its unusual disubstituted N6 substituent containing an anilino moiety and a 3-pyrrolidinyl group. This is expected, since in most models of A₁AR agonist binding to the receptor, the N–H on N6 is involved in a key hydrogen-bonding interaction to the asparagine 254 side chain (IJzerman et al. 1995). ARA exhibited high affinity and selectivity for the A₁AR agonist ($K_i = 1.7$ nM and 4.5 nM in rat brain and rat adipocytes, respectively) (Zannikos et al. 2001). ARA demonstrated some tissue selectivity, being less potent (100- to 200-fold) in inducing A₁AR-mediated bradycardia than

in inducing A₁AR inhibition of lipolysis in rat and human adipocytes. This selective effect is most likely due to the high density and/or efficiency of A₁AR coupling in adipocytes. Although ARA was effective at lowering plasma FFA when administered intravenously to fasted healthy volunteers in a Phase I clinical study, the rapid appearance of tolerance to its FFA-lowering ability was clearly evident (Zannikos et al. 2001).

These clinical findings support the need for a partial A₁AR agonist.

Partial A₁AR agonists were considered as an alternative to full agonists to avoid receptor desensitization. CVT-3619 ((2*S*, 3*S*, 4*R*)-2-((2-fluorophenylthio)methyl)-5-(6-((1*R*, 2*R*)-2-hydroxycyclopentylamino)-9*H*-purin-9-yl) tetrahydrofuran-3,4-diol) (Fig. 16), a selective partial A₁AR agonist devoid of CV effects, is being developed by CV Therapeutics as an antilipolytic agent (Dhalla et al. 2007a; Fatholai et al. 2006). This clinical candidate was obtained by further optimization of the 5'-phenylsulfide derivatives of tecadenoson (described earlier). The binding affinity of CVT-3619 for rat epididymal adipocytes was 14 nM (K_i , high affinity). CVT-3619 reduced forskolin-induced cAMP accumulation in both epididymal and inguinal adipocytes, with EC₅₀ values of 5.9 nM and 44 nM, respectively. The maximal effect of CVT-3619 at reducing cAMP levels in adipocytes was similar to that of CPA, suggesting that CVT-3619 is a full agonist with respect to reduction of cAMP. Plus, CVT-3619 reduced the forskolin-stimulated release of NEFA from both epididymal and inguinal adipocytes, with EC₅₀ values of 47 nM and 170 nM, respectively. However, CVT-3619 was found to be a partial agonist with respect to forskolin (1 μ M)-stimulated NEFA release from epididymal and inguinal adipocytes, with only 42 and 58%, respectively, of CPA's effect. Most likely, the presence of a large receptor reserve and/or a higher efficacy of coupling of A₁AR in the adipocytes can explain the fact that CVT-3619 reduced the cAMP content of epididymal adipocytes with an EC₅₀ value that was lower than the K_i value from the binding assay, and the EC₅₀ value to reduce the release of NEFA was also much lower than the K_i . Furthermore, the high A₁AR receptor reserve in the adipocyte relative to the heart can explain the 1,000-fold functional selectivity of CVT-3619 to decrease epididymal adipose tissue lipolysis in the rat (EC₁₅ = 30 nM) relative to the atrial rate (both A₁AR-mediated effects) (Fatholai et al. 2006). With respect to CV side effects, CVT-3619 (10 nM–30 μ M) caused only a small increase in S–H interval (6 ms) without causing second- or higher-degree AV block; however, CPA significantly prolonged the S–H interval (38 ms) and caused second- or higher-degree AV block at concentrations >30 nM. In normal, overnight-fasted awake rats, at doses of 2.5, 5 and 10 mg kg⁻¹, CVT-3619 lowered FFA by 31%, 47% and 57% from baseline, respectively (Dhalla et al. 2007b). In addition, CVT-3619 significantly reduced serum TG levels and increased insulin sensitivity in rats (Dhalla et al. 2007b). The ED₅₀ of insulin to inhibit lipolysis was potentiated fourfold by a single dose (0.5 mg kg⁻¹) of CVT-3619, suggesting that CVT-3619 increases insulin sensitivity in adipose tissue. The antilipolytic effects of CVT-3619 in rats (given twice daily) were well maintained for up to six weeks of treatment, and no tachyphylaxis or receptor desensitization were observed. Based on the above data, CVT-3619 is in preclinical development by CV Therapeutics as a partial A₁AR agonist for the potential treatment of T2D

in order to avoid CV effects and receptor desensitization. For more information on the effects of partial A₁AR agonists in diabetes and obesity, the reader is referred to Chap. 9 of this volume, "A₁ Adenosine Receptor: Role in Diabetes and Obesity" (Dhalla et al.).

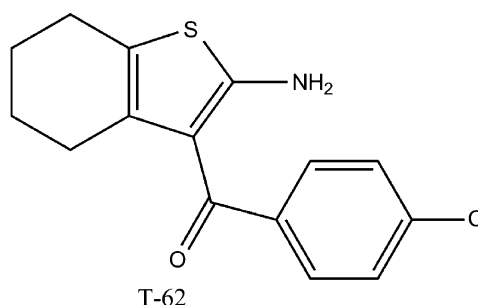
3.3 Angina Agents: Capadenoson (Nonnucleoside: BAY 68–4986)

Bayer chemists were first to make a key discovery that a heterocyclic class of compounds devoid of a ribose moiety can function as agonists at the adenosine receptor, although the first compounds were nonselective (Erguden et al. 2007). IJzerman and colleagues followed this with a further elaboration of the heterocyclic class of agonists in order to introduce some receptor selectivity (Chang et al. 2005). The Bayer chemists then reported the development of a compound from this very novel class of compounds. The oral A₁AR agonist capadenoson (BAY 68–4986), 2-amino-6-((2-(4-chlorophenyl)thiazol-4-yl)methylthio)-4-(4-(2-hydroxyethoxy)phenyl)pyridine-3,5-dicarbonitrile (Fig. 15), was evaluated in a Phase II double-blinded, placebo-controlled multicenter study in patients with stable angina and coronary heart disease studying doses of 1, 2.5, 5, 10 and 20 mg. A 10 mg dose of capadenoson significantly reduced heart rate at peak exercise compared to placebo. Capadenoson is currently under going further studies and is anticipated to finish Phase III clinical trials by 2009 (Bays et al. 2007).

4 Allosteric Enhancers

4.1 Neuropathic Pain: T-62

A different approach to A₁AR agonism is to use the endogenous adenosine levels to activate the receptor coupled with an allosteric enhancer of the A₁AR. This approach has the theoretical advantage of fewer side effects, since it relies on adenosine being produced at the target tissue. In some disease states, adenosine release is a natural compensatory process to help the tissue restore balance. The A₁AR allosteric enhancer will take advantage of this local adenosine release and provide activation of a local A₁AR. The SAR of A₁AR allosteric enhancers has evolved over many years, with major contributions from IJzerman and Baraldi (Baraldi et al. 2007; Van der Klein et al. 1999). The common structural theme that has emerged is a 2-amino-3-acyl-thiophenyl core as exemplified by the lead compound in the area, T-62 (2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophen-3-yl)(4-chlorophenyl)methanone; (Fig. 17), a compound discovered by Baraldi et al. and developed by King Pharmaceuticals for neuropathic pain (Baraldi et al. 2007; Obata et al. 2003; Pan et al. 2001). T-62 demonstrated efficacy for reducing pain

Fig. 17 Allosteric A₁AR enhancer

hypersensitivity in a plantar surgical injury rat model (0.3–1 mcg intrathecal administration) in a dose-dependent manner. The dose of T-62 required for an antihyperalgesic effect was reduced by half when clonidine was coadministered, and this effect was 40% of the maximum possible effect. T-62 is under clinical evaluation in patients with postherpetic neuralgia experiencing pain. It will be interesting to see how the lead compound T-62 does in clinical trials of neuropathic pain, since it may drive further research in the area of A₁AR allosteric enhancers.

5 Conclusion

A considerable body of research over the past 20 years in the A₁AR field has resulted in the identification of clinical candidates for A₁AR antagonism, agonism, and allosteric modification. From a pharmacological perspective, the developmental path for A₁AR antagonists should theoretically be easier due to the challenges associated with developing A₁AR agonists, such as receptor desensitization and the risk of pronounced CV and CNS side effects. With two of the three active A₁AR antagonist clinical programs (KW3902 and BG9928) in Phase III human clinical trials, there is optimism in the cardiology community that an A₁AR antagonist will be available for patient use in the coming years (Dohadwala and Givertz 2008). Partial A₁AR agonism with CVT-3619, for example, may represent a way to avoid both CV and CNS side effects, which makes CVT-3619 an interesting compound to watch as it proceeds to the clinic. BAY 68–4986 opens up the A₁AR agonist field with the advent of nonribose partial agonists that possess a longer half-life for chronic agents that are no longer limited by the high polarity of the ribose ring. The A₁AR allosteric enhancer T-62 has demonstrated promising results in animal models of neuropathic pain, and is currently undergoing clinical evaluation. Based on these important scientific and clinical advances, therapeutics that target the A₁AR (A₁AR antagonists, A₁AR agonists, and allosteric enhancers) may show long-awaited clinical success in the near future.

References

- Akhari R, Burbiel JC, Hockemeyer J, Muller CE (2006) Recent progress in the development of adenosine receptor ligands as anti-inflammatory drugs. *Curr Top Med Chem* 6:1375–1399
- Amann K, Breitbart M, Ritz E, Mall G (1998a) Myocyte/capillary mismatch in the heart of uremic patients. *J Am Soc Nephrol* 9:1018–1022
- Amann K, Kronenberg G, Gehlen F, Wessels S, Orth S, Munter K (1998b) Cardiac remodeling in experimental renal failure—an immunohistochemical study. *Nephrol Dial Transplant* 13:1958–1966
- Auchampach JA, Jin X, Moore J, Wan TC, Kreckler LM, Ge ZD, Narayanan J, Whalley E, Kiesman W, Ticho B, Smits G, Gross GJ (2004) Comparison of three different A₁ adenosine receptor antagonists on infarct size and multiple cycle ischemic preconditioning in anesthetized dogs. *J Pharmacol Exp Ther* 308:846–856
- Baraldi PG, Iaconinoto MA, Moorman AR, Carrion MD, Cara CL, Preti D, Lopez OC, Fruttarolo F, Tabrizi MA, Romagnoli R (2007) Allosteric enhancers for A₁ adenosine receptor. *Minirev Med Chem* 7:559–569
- Baraldi PG, Tabrizi MA, Gessi S, Borea PA (2008) Adenosine receptor antagonists: translating medicinal chemistry and pharmacology into clinical utility. *Chem Rev* 108:238–263
- Bayes M, Rabasseda X, Prous JR (2003) Gateways to clinical trials. *Methods Find Exp Clin Pharmacol* 25:831–855
- Bays M, Rabasseda X, Prous JR (2007) Gateways to clinical trials. *Method Find Exp Clin Pharmacol* 29(5):359–373
- Belardinelli L, Dhalla A (2003) Method of treating arrhythmias comprising administration of an A₁ adenosine agonist with a beta blocker, calcium channel blocker, or a cardiac glycoside. US Patent WO03088978
- Belardinelli L, Lerman BB (1990) Electrophysiological basis for use of adenosine in the diagnosis and treatment of cardiac arrhythmias. *Br Heart J* 63:3–34
- Belardinelli L, Shryock JC, Song Y, Wang D, Srinivas M (1995) Ionic basis of the electrophysiological actions of adenosine on cardiomyocytes. *FASEB J* 5:359–365
- Belardinelli L, Shryock JC, Wu L, Song Y (2005) Use of preclinical assays to predict risk of drug-induced torsades de pointes. *Heart Rhythm* 2(2 Suppl):S16–22
- Bigot A, Stengelin S, Johne G, Herling A, Muller G, Hock FJ, Myers MR (2004) Novel adenosine analogues and their use as pharmaceutical agents. US Patent WO04003002
- Boden G, She P, Mozzoli M, Cheung P, Gumireddy K, Reddy P, Xiang X, Luo Z, Ruderman N (2005) Free fatty acids produce insulin resistance and activate the proinflammatory nuclear factor- κ B pathway in rat liver. *Diabetes* 54:3458–3465
- Castelhano AI, McKibben B, Witter DJ (2005) Compounds specific to adenosine A₁ receptor and uses thereof. US Patent 6,878,716
- Chang LC, Von Kuenzel JK, Mulder-Krieger T, Spanjersberg RF, Roerink F, Van Den Hout G, Beukers MW, Brussee J, IJzerman AP (2005) A series of ligands displaying a remarkable agonistic–antagonistic profile at the adenosine A₁ receptor. *J Med Chem* 48(6):2045–2053
- ClinicalTrials.gov (2005) Aderis Pharmaceuticals: safety and efficacy study of an A₁-adenosine receptor agonist to slow heart rate atrial fibrillation. <http://www.clinicaltrials.gov/ct/show/NCT00040001?order=1>
- DailyDrugNews.com (2008) Inotek begins a Phase I trial of INO-8875 for the treatment of glaucoma (Daily Essentials, 20 June 2008). <http://www.dailydrugnews.com>
- Dhalla AK, Shryock JC, Shreenivas R, Belardinelli L (2003) Pharmacology and therapeutic application of A₁ adenosine receptor ligands. *Curr Top Med Chem* 3:369–385
- Dhalla AK, Wong MY, Voshol PJ, Belardinelli L, Reaven GM (2007a) A₁-adenosine receptor partial agonist lowers plasma FFA and improves insulin resistance induced by high-fat diet in rodents. *Am J Physiol Endocrinol Metab* 292:E1358–E1363

- Dhalla AK, Melissa S, Smith M, Wong M, Shryock JC, Beraldinelli L (2007b) Antilipolytic activity of a novel partial A₁ adenosine receptor agonist devoid of cardiovascular effects: comparison with nicotinic acid. *J Pharmacol Exp Ther* 321:327–333
- DiMarco JP, Sellers TD, Lerman BB, Greenberg ML, Berne RM, Belardinelli L (1985) Diagnostic and therapeutic use of adenosine in patients with supraventricular tachycardias. *J Am Coll Cardiol* 6:417–425
- Dittrich HC, Gupta D, Hack TC, Dowling T, Callahan J, Thomson S (2007) The effect of KW-3902, an adenosine A₁ receptor antagonist, on renal function and renal plasma flow in ambulatory patients with heart failure and renal impairment. *J Cardiac Fail* 13:609–617
- Dohadwala MM, Givertz MM (2008) Role of adenosine antagonism in cardiorenal syndrome. *Cardiovasc Ther* 26:276–286
- Ellenbogen KA, O'Neill G, Prystowsky EN, Camm JA, Meng L, Lieu HD, Jerling M, Shreenivas R, Beraldinelli L, Wolff AA (2005) Trial to evaluate the management of paroxysmal supraventricular tachycardia during an electrophysiology study with Tecadenoson. *Circulation* 111:3202–3208
- Erguden JK, Karig G, Rosentreter U, Albrecht B, Henninger K, Hutter J, Diedrichs N, Nell P, Arndt S, Hubsch W, Knorr A, Schlemmer KH, Brohm P (2007) Substituted phenylaminothiazoles and use thereof. US Patent WO0773855
- Fatholahi M, Xiang Y, Wu Y, Li Y, Wu L, Dhalla AK, Belardinelli L, Shryock JC (2006) A novel partial agonist of the A₁-adenosine receptor and evidence of receptor homogeneity in adipocytes. *J Pharmacol Exp Ther* 317:676–684
- Ferrannini E, Barrett EJ, Bevilacqua S, DeFronzo RA (1983) Effect of fatty acids on glucose production and utilization in man. *J Clin Invest* 72:1737–1747
- Forman M, Velasco CE, Jackson EK (1993) Adenosine attenuates reperfusion injury following regional myocardial ischemia. *Cardiovasc Res* 27:9–17
- Fredholm BB, IJzerman AP, Jacobson KA, Klotz, KN, Linden J (2001) International Union of Pharmacology. XXXV: nomenclature and classification of adenosine receptors. *Pharmacol Rev* 53:527–552
- Gardner CJ, Twissell DJ, Coates J, Strong P (1994) The effects of GR79236 on plasma fatty acid concentrations, heart rate and blood pressure in the conscious rats. *Eur J Pharmacol* 257:117–121
- Givertz MM, Massie BM, Fields TK, Pearson LL, Dittrich HC, on behalf of the CKI-201 and CKI-202 investigators (2007) The effects of KW-3902, an adenosine A₁-receptor antagonist, on diuresis and renal function in patients with acute decompensated heart failure and renal impairment or diuretic resistance. *J Am Coll Cardiol* 50:1551–1560
- Gottlieb SS, Skettino SL, Wolff A, Beckman E, Fisher ML, Freudenberger R, Gladwell T, Marshall J, Cines M, Bennett, D, Liitschwager EB (2000) Effects of BG9719 (CVT-124), an A₁-adenosine receptor antagonist, and furosemide on glomerular filtration rate and natriuresis in patients with congestive heart failure. *J Am Coll Cardiol* 35:56–59
- Gottlieb SS, Brater C, Thomas I, Havranek E, Bourge R, Goldman S, Dyer F, Gomez M, Bennett D, Ticho B, Beckman E, Abraham WT (2002) BG9719 (CVT-124), an A₁ adenosine receptor antagonist, protects against the decline in renal function observed with diuretic therapy. *Circulation* 105:1348–1353
- Green A (1987) Adenosine receptor down-regulation and insulin resistance following prolonged incubation of adipocytes with an A₁ adenosine receptor agonist. *J Biol Chem* 262:15702–15707
- Green A, Johnson JL, Milligan G (1990) Down-regulation of G_i subtypes by prolonged incubation of adipocytes with an A₁ adenosine receptor agonist. *J Biol Chem* 265:5206–5210
- Greenberg B, Thomas I, Banish D, Goldman S, Havranek E, Massie B, Zhu Y, Ticho B, Abraham WT (2007) Effects of multiple oral doses of an A₁ adenosine antagonist, BG9928, in patients with heart failure. *J Am Coll Cardiol* 50:600–606
- Hess S (2001) Recent advances in adenosine receptor antagonist research. *Expert Opin Ther Patents* 11:1533–1561

- Hoffman BB, Chang H, Dall'Agilo E, Reaven GM (1986) Desensitization of adenosine receptor-mediated inhibition of lipolysis. The mechanism involves the development of enhanced cyclic adenosine monophosphate accumulation in tolerant adipocytes. *J Clin Invest* 78:185–190
- Hosokawa T, Yamauchi M, Yamamoto Y, Iwata K, Mochizuki H, Kato Y (2002) Role of the lipid emulsion on an injectable formulation of lipophilic KW-3902, a newly synthesized adenosine A₁-receptor antagonist. *Biol Pharm Bull* 25:492–498
- IJzerman AP, van der Wenden NM, van Galen PJM, Jacobson KA (1995) Molecular modeling of adenosine A₁ and A_{2a} receptors. In: Belardinelli L, Pelleg A (eds) *Adenosine and adenine nucleotides: from molecular biology to integrative physiology*. Kluwer, Boston, MA, pp 27–37
- Itani SI, Ruderman NB, Schmieder F, Boden G (2002) Lipid-induced insulin resistance in human muscle is associated with changes in diacylglycerol protein kinase C and IKK α . *Diabetes* 51:2005–2011
- Jacobson KA, Gao ZG (2006) Adenosine receptors as therapeutic targets. *Nat Rev Drug Disc* 5:247–264
- Jagtap P, Szabo C, Salzman AL (2005) Purine derivatives as adenosine A₁ receptor agonists and methods of use thereof. WO Patent Appl 2005/117910
- Kalk P, Eggert B, Relle K, Godes M, Heiden S, Sharkovska Y, Fischer Y, Ziegler D, Bielenberg GW, Hoher B (2007) The adenosine A₁ receptor antagonist SLV320 reduces myocardial fibrosis in rats with 5/6 nephrectomy without affecting blood pressure. *Br J Pharmacol* 151:1025–1032
- Khimenko PL, Moore TM, Hill LW, Wilson PS, Coleman S, Rizzo A, Taylor AE (1995) Adenosine A₂ receptors reverse ischemia-reperfusion lung injury independent of beta-receptors. *J Appl Physiol* 78:990–996
- Kiesman WF, Zhao J, Conlon PR, Dowling JE, Petter RC, Lutterodt F, Jin X, Smits G, Fure M, Jayaraj A, Kim J, Sullivan GW, Linden J (2006a) Potent and orally bioavailable 8-bicyclo[2.2.2]octylxanthines as adenosine A₁ receptor antagonists. *J Med Chem* 49:7119–7131
- Kiesman WF, Zhao J, Conlon PR, Petter RC, Jin X, Smits G, Lutterodt F, Sullivan GW, Linden J (2006b) Norbornylactone-substituted xanthines as adenosine A₁ receptor antagonists. *Bioorg Med Chem* 14:3654–3661
- Kossel A (1888) Über eine neue Base aus dem Pflanzenreich. *Chem Ber* 21:2164–2167
- Lerman BB, Belardinelli L (1991) Cardiac electrophysiology of adenosine. Basis and clinical concepts. *Circulation* 83:1499–1509
- Liu GS, Thornton J, Van Winkle DM, Stanely AW, Olsson RA, Downey JM (1991) Protection against infarction afforded by preconditioning is mediated by A₁ adenosine receptors in rabbit heart. *Circulation* 84:350–356
- Magata S, Taniguchi M, Suzuki T, Shimamura T, Fukai M, Furukawa H, Fujita M, Todo S (2007) The effect of antagonism of adenosine A₁ receptor against ischemia and reperfusion injury of the liver. *J Surg Res* 139:7–14
- Merkel LA, Hawkins ED, Colussi DJ, Greenland BD, Smits GJ, Perrone MH, Cox BF (1995) Cardiovascular and antilipolytic effects of the adenosine agonist GR79236. *Pharmacology* 51:224–36
- Mizumura T, Auchampach JA, Linden J, Burns RF, Gross GJ (1996) PD 81,723 an allosteric enhancer of the A₁ adenosine receptor, lowers the threshold for ischemic preconditioning in dogs. *Circ Res* 79:415–423
- Miura T, Tsuchida A (1999) Adenosine and preconditioning revisited. *Clin Exp Pharm Physiol* 26:92–99
- Moro S, Gao Z.-G, Jacobson KA, Spalluto G (2006) Progress in the pursuit of therapeutic adenosine receptor antagonists. *Med Res Rev* 26:131–159
- Morrison CF, Elzein E, Jiang B, Ibrahim P, Maa T, Wu L, Zeng D, Fong I, Lustig D, Leung K, Zablocki J (2004) Structure–affinity relationships of 5'-aromatic ethers and 5'-aromatic sulfides as partial A₁ adenosine agonists, potential supraventricular anti-arrhythmic agents. *Bioorg Med Lett* 14:3793–3797

- Nonaka H, Ichimura M, Takeda M, Kanda T, Shimada J, Suzuki F, Kase H (1996) KW-3902, a selective high affinity antagonist for adenosine A₁ receptors. *Br J Pharmacol* 117:1645–1652
- Novacardia, Inc. (2007) Pilot phase 3 results of Novacardia's KW-3902 for acute congestive heart failure. In: Heart Failure Congress 2007, Hamburg, Germany, 9–12 June 2007 (see <http://www.medicalnewstoday.com/articles/73876.php>)
- Obata H, Li X, Eisenach JC (2003) A synergistic effect of intrathecal administration of T62 and clonidine in the rat postoperative pain model. In: 33rd Annu Meet Soc Neurosci Proc, New Orleans, LA, 8–12 Nov 2003, Abstract 589.7
- Pan H.-L, Xu Z, Leung E, Eisenach JC (2001) Allosteric adenosine modulation to reduce allodynia. *Anesthesiology* 95:416
- Peralta C, Hotter G, Closa D, Prats N, Xaus C, Gelpi E, Rosello-Catafau J (1999) The protective role of adenosine in inducing nitric oxide synthesis in rat liver ischemia preconditioning is mediated by activation of adenosine A₂ receptors. *Hepatology* 29:126–132
- Peterman C, Sanoski CA (2005) Tecadenoson: a novel, selective A₁ adenosine receptor agonist. *Cardiol Rev* 13:315–321
- Pfister JR, Bellardinelli L, Lee G, Lum RT, Milner P, Stanley WC, Linden J, Baker SP, Schreiner G (1997) Synthesis and biological evaluation of the enantiomers of the potent and selective A₁-adenosine antagonist 1,3-dipropyl-8-[2-(5,6-epoxynorbornyl)]-xanthine. *J Med Chem* 40:1773–1778
- Prystowsky EN, Niazi I, Curtis AB, Wilber DJ, Bahnson T, Ellenbogen K, Dhalla A, Bloomfield DM, Gold M, Kadish A, Fogel RI, Gonzalez MD, Belardinelli L, Shreenivas R, Wolff AA (2003) Termination of paroxysmal supraventricular tachycardia by tecadenoson (CVT-510), a novel A₁-adenosine receptor agonist. *J Am Coll Cardiol* 42:1098–1102
- Qu X, Cooney G, Donnelly R (1997) Short-term metabolic and haemodynamic effects of GR79236 in normal and fructose-fed rats. *Eur J Pharmacol* 338:269–276
- Roden, M, Price, TB, Perseghin, G, Petersen, KF, Rothman, DL, Cline, GW, Shulman, GI (1996) Mechanism of free fatty acid-induced insulin resistance in humans. *J Clin Invest* 97: 2859–2865
- Sako Y, Grill VE (1990) A 48-hours lipid infusion in the rat time-dependently inhibits glucose-induced insulin secretion and B cell oxidation through a process likely coupled to fatty acid oxidation. *Endocrinology* 127:1580–1589
- Shamim MT, Ukena D, Padgett WL, Hong O, Daly JW (1988) 8-Aryl-and 8-cycloalkyl-1,3-dipropylxanthines: further potent and selective antagonists for A₁-adenosine receptors. *J Med Chem* 31:613–617
- Shimada J, Suzuki F, Nonaka H, Karasawa A, Mizumoto H, Ohno T, Kubo K, Ishii A (1991) 8-(Dicyclopropylmethyl)-1,3 dipropylxanthine: a potent and selective adenosine A₁, antagonist with renal protective and diuretic activities. *J Med Chem* 34:466–469
- Shimada J, Suzuki F, Nonaka H, Ishii A (1992) 8-Polycycloalkyl-1,3-dipropylxanthines as potent and selective antagonists for A₁-adenosine receptors. *J Med Chem* 35:924–930
- Song Y, Wu L, Shryock JC, Beralinelli, L (2002) Selective attenuation of isoproterenol-stimulated arrhythmic activity by a partial agonist of adenosine A₁ receptor. *Circulation* 105:118–123
- Srinivas M, shryock JC, Dennis DM, Baker SP, Beraldinelli L (1997) Differential A₁ adenosine receptor reserve for two actions of adenosine on guinea pig atrial myocytes. *Mol Pharmacol* 52:683–691
- Stephenson RP (1997) A modification of receptor theory. *Br J Pharmacol* 120:106–120
- Suzuki F, Shimada J, Mizumoto H, Karasawa A, Kubo K, Nonaka H, Ishii A, Kawakita T (1992) Adenosine A₁ antagonists. 2. Structure–activity relationships on diuretic activities and protective effects against acute renal failure. *J Med Chem* 35:3066–3075
- Ticho B, Whalley E, Gill A, Lutterodt F, Jin X, Auchampach J, Smits G (2003) Renal effects of BG9928, an A₁ adenosine receptor antagonist, in rats and nonhuman primates. *Drug Dev Res* 58:486–492
- Van der Klein PAM, Kourounakis AP, IJzerman AP (1999) Allosteric modulation of the adenosine A₁ receptor. Synthesis and biological evaluation of novel 2-amino-3-benzoylthiophenes as allosteric enhancers of agonist binding. *J Med Chem* 42:3629–3635

- van Galen PJM, Stiles GL, Michaels G, Jacobson KA (1992) Adenosine A₁ and A₂ receptors: structure–function relationships. *Med Res Rev* 12:423–471
- Vu CB, Kiesman WF, Conlon PR, et al (2006) Tricyclic imidazoline derivatives as potent and selective adenosine A₁ receptor antagonists. *J Med Chem* 49:7132–7139
- Wang D, Shryock JC, Belardinelli L (1996) Cellular basis for the negative dromotropic effect of adenosine on rabbit single atrioventricular nodal cell. *Circ Res* 78:697–706
- Webster JM, Heseltine L, Taylor R (1996) In vitro effect of adenosine agonist GR79236 on insulin sensitivity of glucose utilization in rat soleus and human rectus abdominus muscle. *Biochim Biophys Acta* 1316:109–113
- Wu L, Belardinelli L, Zablocki JA, Palle V, Shryock JC (2001) A partial agonist of the A₁-adenosine receptor selectively slows AV conduction in guinea pig hearts. *Am J Physiol Heart Cir* 280:H334–H343
- Yan L, Burbiel JC, Maass A, Muller CE (2003) Adenosine receptor agonists from basic medicinal chemistry to clinical development. *Expert Opin Emerg Drugs* 8:537–576
- Yao K (2000) Effect of KW-3902, a selective adenosine A₁-receptor antagonist, on accumulation of gentamicin in the proximal renal tubules in rats. *Yakugaku Zasshi* 120:801–805
- Yao K, Heyne N, Erley CM, Risler T, Osswald H (2001) The selective adenosine A₁ receptor antagonist KW-3902 prevents radiocontrast media-induced nephropathy in rats with chronic nitric oxide deficiency. *Eur J Pharmacol* 414:99–104
- Yuzlenko O, Kieć-Kononowicz K (2006) Potent adenosine A₁ and A_{2A} receptors antagonists: recent developments. *Curr Med Chem* 13:3609–3625
- Zablocki JA, Wu L, Shryock J, Belardinelli L (2004) Partial A(1) adenosine receptor agonists from a molecular perspective and their potential use as chronic ventricular rate control agents during atrial fibrillation (AF). *Curr Top Med Chem* 4:839–54
- Zannikos PN, Rohatagi S, Jensen BK (2001) Pharmacokinetic-pharmacodynamic modeling of the antilipolytic effects of an adenosine receptor agonist in healthy volunteers. *J Clin Pharmacol* 41:61–69

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