Communications to the Editor

Discovery of 6-Oxo-3-(2-phenylpyrazolo[1,5-*a*]pyridin-3-yl)-1(6*H*)-pyridazinebutanoic Acid (FK 838): A Novel Non-Xanthine Adenosine A₁ Receptor Antagonist with Potent Diuretic Activity

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Introduction. Adenosine is a purine nucleoside that is widely distributed throughout the body and exerts a wide variety of physiological functions through interaction with extracellular receptors.[1] To date, four distinct adenosine receptor subtypes (A₁, A₂ₐ, A₂ᵦ, and A₃) have been cloned and characterized pharmacologically.[2] Numerous adenosine receptor ligands have been synthesized and studied as adenosine receptor agonists and antagonists and have thus resulted in clinically examined compounds.[3] Despite such efforts over several decades, the only compound approved is adenosine itself, which is currently used for the treatment and diagnosis of cardiac arrhythmias[4] and for the diagnosis of ischemic heart diseases.[5] In the field of adenosine antagonists, perhaps the major reason adenosine ligands have not succeeded in addressing significant medical need is the poor bioavailability of hitherto described analogues, mainly due to hydrophobicity and low solubility in water. For this reason, it is highly desirable to develop a selective, potent, and bioavailable non-xanthine adenosine receptor antagonist.[6]

Recent reports have demonstrated that 1,3-dipropyl-8-cyclopentylxanthine (DPCPX, **1**; Figure 1) and related xanthines, which are potent and selective adenosine A₁ receptor antagonists, have diuretic and saliuretic properties.[7] However, the solubility of these dipropylxan-
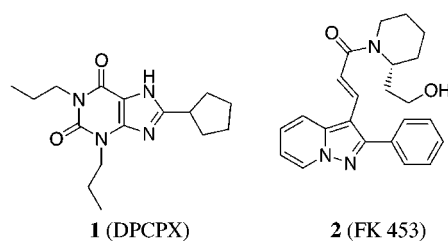

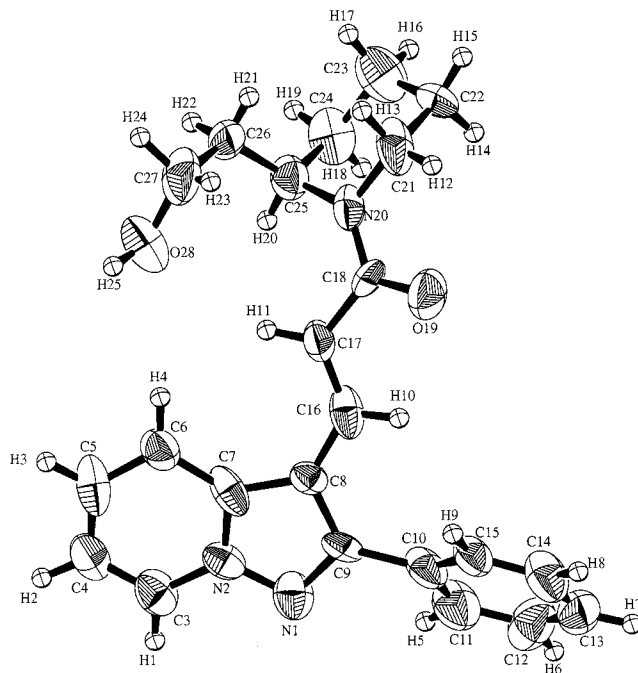**Figure 1.** Structures of adenosine A₁ antagonists **1** and **2**.

Figure 2. X-ray structure of **2**.

thines in water is extremely low, due to greater hydrophobicity. Recently, we described the discovery of (*E*)-(2*R*)-1-[3-(2-phenylpyrazolo[1,5-*a*]pyridin-3-yl)acryloyl]-2-piperidineethanol (FK 453, **2**; Figure 1), a novel non-xanthine adenosine A₁ receptor antagonist, as a diuretic and renal vasodilator.[8] Interestingly, **2** was originally identified as a potent diuretic, and later the exact mechanism of action was identified to be selective for
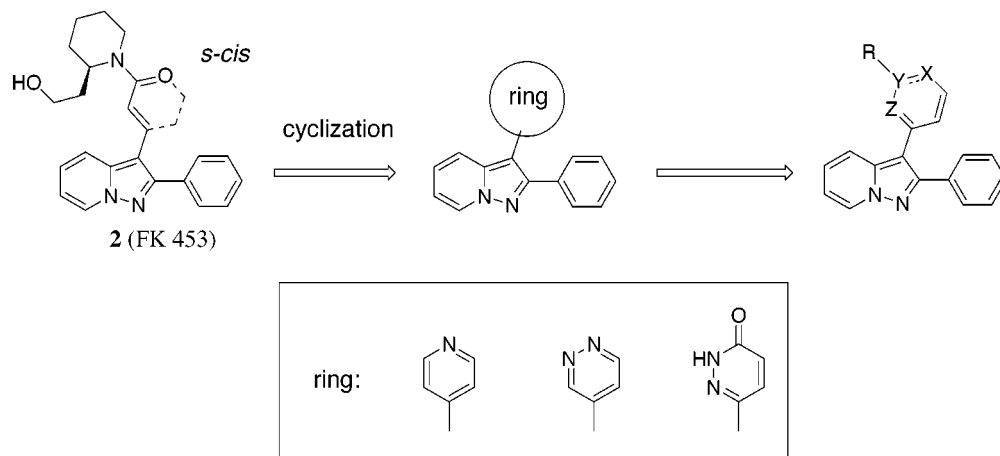
Figure 3. Design of 3-heteroaryl-2-phenylpyrazolo[1,5-*a*]pyridines.

Scheme 1[a]
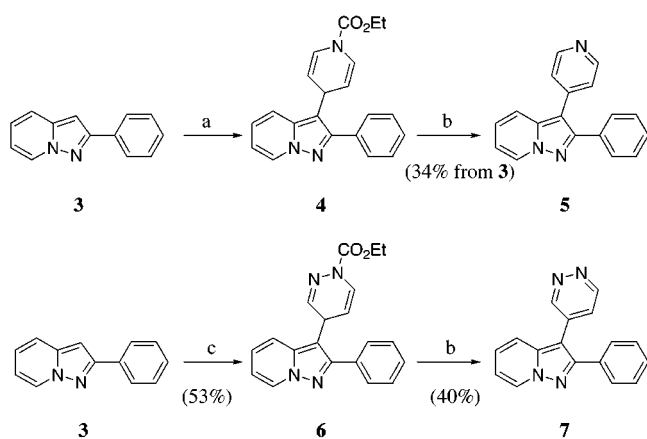
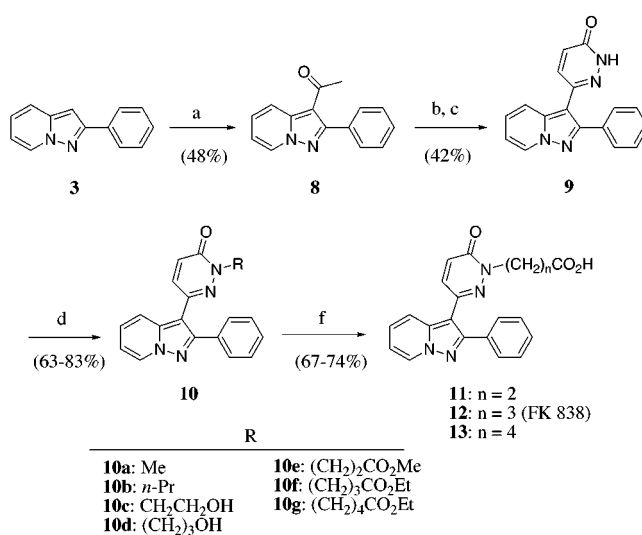[a] (a) ClCO$_2$Et, pyridine; (b) air, *t*-BuOK, *t*-BuOH; (c) ClCO$_2$Et, pyridazine.

Scheme 2[a]

R	
10a: Me	**10e**: (CH$_2$)$_2$CO$_2$Me
10b: *n*-Pr	**10f**: (CH$_2$)$_3$CO$_2$Et
10c: CH$_2$CH$_2$OH	**10g**: (CH$_2$)$_4$CO$_2$Et
10d: (CH$_2$)$_3$OH	

[a] (a) Concd H$_2$SO$_4$, Ac$_2$O; (b) HCOCO$_2$H·H$_2$O; (c) NH$_2$NH$_2$·H$_2$O; (d) RX or methyl acrylate, NaH or Triton B; (f) aq NaOH.

adenosine A$_1$ receptor antagonism; i.e., **2** was not found through in vitro receptor binding assay but through in vivo assay. Nevertheless, **2** was extraordinarily potent and highly selective for binding to the adenosine A$_1$ receptor subtype in the receptor binding assay. The pyrazolo[1,5-*a*]pyridine-based structure of **2** was completely different from known xanthine and non-xanthine adenosine A$_1$ receptor antagonists, and therefore **2** was a structurally unique adenosine receptor antagonist. Although **2** was a potent diuretic in several species, including humans,[9] the oral bioavailability of **2** was relatively low due to a rapid first-pass effect in the liver and to the poor solubility in water, which also resulted in problems in the preparation of intravenous formulations which are essential for the treatment of acute renal failure, a possible clinical indication for **2**.[10] In addition, **2** was readily converted to the less active *cis* isomer in solution due to a facile photochemical *trans–cis* isomerization process.[8a]

To overcome these problems and to obtain compounds with more potent in vivo activity, we initiated a search for a new series of pyrazolo[1,5-*a*]pyridine diuretics. In this paper we describe the rational design, synthesis, and pharmacological evaluation of a series of 3-heteroaryl-2-phenylpyrazolo[1,5-*a*]pyridines with an improved pharmacokinetic profile, greater water solubility, and superior in vivo potency.

Design. In structure–activity relationship (SAR) studies of **2**, the (*E*)-acryloyl moiety was found to be

indispensable for potent diuretic activity (unpublished results). Compounds in which the (*E*)-acryloyl moiety was replaced by (*Z*)-acryloyl, propionyl, or propioloyl were essentially inactive. Therefore, it was quite clear that the conformation of the acryloyl part of **2** was very important. The X-ray crystal structure of **2** (Figure 2) clearly indicated that the (*E*)-acryloyl moiety adopted the *s-cis* conformation. Furthermore, the double bond of the acryloylamide of **2** was almost in the same plane as the pyrazolo[1,5-*a*]pyridine ring (torsion angle of C7–C8–C16–C17: −9°), and the carbonyl group (C18–O19) and the double bond of the acryloyl moiety (C16–C17) were slightly twisted (torsion angle of C16–C17–C18–O19: −24°), while the phenyl ring was rotated 45° clockwise to the pyrazolo[1,5-*a*]pyridine ring (C8–C9–C10–C15). On the basis of these findings, we then designed new compounds in which position 3 of the 2-phenylpyrazolo[1,5-*a*]pyridine was substituted by heteroaryl groups such as 4-pyridyl, 4-pyridazinyl, and 6-oxo-1(6*H*)-pyridazin-3-yl, in which the double bond and carbonyl group of acryloyl moiety of **2** were mimicked by a ring system (Figure 3). These compounds were predicted to be stable to light and to be potentially more hydrophilic if suitable substituents were introduced to the heteroaryl groups.

Table 1. Diuretic Activity in Rats and Clog *P* Value of **5**, **7**, **9**, and **2**
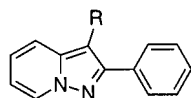
| | | | | diuretic activity in rats[a] | | |
compd	R	clog P^b	dose (mg/kg)	UV (mL/kg)	Na$^+$ (μequiv/kg)	K$^+$ (μequiv/kg)
5		4.10	vehicle	10.8 ± 0.7	1750 ± 27	405 ± 78
			10	34.2 ± 0.4**	5110 ± 290**	975 ± 8*
7		2.89	vehicle	18.5 ± 0.4	2000 ± 250	427 ± 34
			1.0	23.8 ± 2.3	2800 ± 300	569 ± 49
			3.2	29.5 ± 3.9	3770 ± 370*	667 ± 33**
			10	38.0 ± 2.1**	5110 ± 150*	907 ± 56**
9		2.95	vehicle^c	15.7	1670	449
			10	33.3 ± 3.9^d	4640 ± 410^d	826 ± 41^d
2 (FK453)		3.24	vehicle	16.3 ± 1.4	2080 ± 190	615 ± 85
			0.32	18.0 ± 1.0	2350 ± 160	727 ± 58
			1.0	24.6 ± 0.5**	3290 ± 190**	833 ± 10
			3.2	31.9 ± 1.4**	4110 ± 260**	831 ± 40
			10	44.4 ± 2.0**	5820 ± 200**	1070 ± 100*

^{a} After deprivation of food for 18 h, compounds suspended in 0.5% methyl cellulose solution were administered orally to saline (20 mL/kg, po)-loaded male Sprague–Dawley rats ($n = 3$), and urine was collected for 6 h; see ref 8b for details. Values are expressed as means $\pm$ SEM. *$p < 0.05$. **$p < 0.01$. UV: urine volume. ^{b} Calculated by MacLogP. ^{c} $n = 1$. ^{d} Statistical evaluation was not performed.
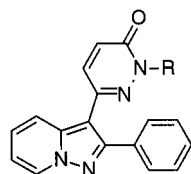
Chemistry. Compounds **5** and **7** were prepared according to the route shown in Scheme 1. The starting material **3**, which was obtained by a modification of the reported method,[11] was treated with ethyl chloroformate and pyridine to afford dihydropyridine **4**, which was then converted to pyridine **5** using potassium *tert*-butoxide in *tert*-butyl alcohol. Analogously, **7** was obtained from the reaction of **3** with ethyl chloroformate and pyridazine, followed by the treatment with *tert*-butoxide in *tert*-butyl alcohol.

Pyridazinone derivatives **9**, **10a**–**10d**, **11**, **12**, and **13** were prepared as shown in Scheme 2. Friedel–Crafts reaction of **3** using acetic anhydride in the presence of a catalytic amount of concentrated sulfuric acid afforded **8**, which was then treated with glyoxylic acid monohydrate. The intermediate adduct was cyclized with hydrazinemonohydrate to give pyridazinone **9**. Alkylation of **9** was performed by standard methods. For example, **9** was alkylated with alkyl halides or methyl acrylate in the presence of bases such as sodium hydride or Triton B, to afford **10a**–**10g**. Esters **10e**–**10g** were hydrolyzed with aqueous sodium hydroxide to give carboxylic acids **11**, **12**, and **13**, respectively.

Results and Discussion. The diuretic activity of the test compounds was evaluated orally in saline-loaded rats (Tables 1 and 2). As shown in Table 1, **5**, **7**, and **9** increased urine and sodium output at 10 mg/kg, and the efficacy of these compounds in diuresis and natriuresis was the same as that of **2** (2–3-fold of each control value). These results indicated that the acryloyl moiety of **2**, which was very important for diuretic activity, could be changed to a heteroaryl group. In a dose–response study, **7** was less active than **2**. The minimum effective doses of **2** and **7** in diuretic activity were 1.0 and 3.2 mg/kg, respectively. We compared the clog *P* values of the compounds shown in Table 1 as a parameter of hydrophobicity. The order of hydrophobicity was **5** > **2** > **9** > **7** (Table 1). After consideration of the ease of synthesis of analogues, we selected **9** as a new lead and started a lead optimization study.

The diuretic activity and clog *P* values of pyridazinone derivatives **10a**–**10d** and **11**–**13** are summarized in Table 2. Substitution at N^1 of the pyridazinone was tolerated for diuretic activity. Regardless of the variety of substituents, all compounds in Table 2 increased urine and sodium output at 10 mg/kg. Comparison of clog *P* values showed that compounds containing functional groups such as hydroxyl and carboxylic acid were more hydrophilic than **2** or **10b**. Carboxylic acids **11** and **12** had suitable clog *P* values (1.95 and 2.48) and potent diuretic activity and were actually soluble in water, if used as the sodium salt form. Both **11** and **12** increased urine and sodium output in a dose-dependent manner. The minimum effective doses of **11** and **12** in diuretic activity were 3.2 and 0.1 mg/kg, respectively. **12** was 10 times more potent than **2**, when comparing the minimum effective dose.

To identify the mechanism of action of **12**, receptor binding assays for **1**, **2**, and **12** were performed using rat and human A$_1$ and rat A$_{2A}$ adenosine receptors (Table 3). While affinity and selectivity of **1** and **2** for the A$_1$ adenosine receptor was potent and good, **12** was less active and less selective for the A$_1$ adenosine receptor compared with **1** and **2**. However, **12** still had considerable affinity and selectivity for A$_1$ adenosine receptors. Compound **12**, as well as **1** and **2**,[8d] also inhibited the Na$^+$ transport in rabbit proximal convoluted tubule in vitro via adenosine A$_1$ receptor (unpublished results). These results suggest that the diuretic activity of **12** results from adenosine A$_1$ receptor antagonism. To clarify the discrepancy between in vitro and in vivo activity, i.e., **12** was more potent than **2** in diuretic activity in rats, but **2** was more potent than **12** at the adenosine A$_1$ receptor, the solubility of **2** and **12** in water at 37 °C and the oral bioavailabilities of **2** and **12** in rats were determined (Table 3). The solubility of **2** in water was only 11.9 μg/mL, while **12** had greater solubility (10 mg/mL) in water, when the sodium salt was used. Similarly, the oral bioavailability of **2** in rats was 8.8% and that of **12** was 78% (free acid) and 100%

Table 2. Diuretic Activity in Rats and Clog P Value of **10a**–**10d**, **11**–**13**, and **2**

				diuretic activity in rats[a]		
compd	R	clog P^b	dose (mg/kg)	UV (mL/kg)	Na$^+$ (μequiv/kg)	K$^+$ (μequiv/kg)
10a	Me	2.88	vehicle^c	15.7	1660	449
			10	30.0 ± 3.2^d	4870 ± 290^d	891 ± 78^d
10b	*n*-Pr	3.93	vehicle^c	15.7	1660	449
			10	36.8 ± 2.9^d	5510 ± 80^d	972 ± 19^d
10c	(CH$_2$)$_2$OH	1.42	vehicle	19.5 ± 1.9	2150 ± 11	590 ± 37
			10	$40.4 \pm 1.1^*$	5930 ± 440	$942 \pm 20^*$
10d	(CH$_2$)$_3$OH	1.95	vehicle	17.3 ± 1.2	2090 ± 110	615 ± 2
			10	$37.9 \pm 0.1^{**}$	$5160 \pm 67^{**}$	964 ± 157
11	(CH$_2$)$_2$CO$_2$H	1.95	vehicle	15.2 ± 1.3	2850 ± 300	621 ± 52
			1.0^e	19.1 ± 0.9	3350 ± 120	790 ± 53
			$3.2e$	$28.1 \pm 1.8^{**}$	$4860 \pm 310^{**}$	$904 \pm 42^*$
			10^e	$31.4 \pm 2.1^{**}$	$5260 \pm 420^{**}$	$901 \pm 58^*$
12	(CH$_2$)$_3$CO$_2$H	2.48	vehicle	16.2 ± 1.1	2280 ± 160	566 ± 64
(FK 838)			0.032^e	15.6 ± 1.1	2390 ± 150	657 ± 62
			0.1^e	$26.4 \pm 2.6^*$	$3860 \pm 240^{**}$	$818 \pm 52^*$
			1.0^e	$35.8 \pm 0.6^{**}$	$5260 \pm 160^{**}$	$967 \pm 15^{**}$
			10^e	$38.6 \pm 2.9^{**}$	$5680 \pm 220^{**}$	$1150 \pm 49^{**}$
13	(CH$_2$)$_4$CO$_2$H	3.00	vehicle	18.8 ± 2.8	2190 ± 170	502 ± 29
			10^e	$36.3 \pm 1.7^*$	$4510 \pm 330^*$	977 ± 135
2		3.24	vehicle	16.3 ± 1.4	2080 ± 190	615 ± 85
(FK453)			0.32	18.0 ± 1.0	2350 ± 160	727 ± 58
			1.0	$24.6 \pm 0.5^{**}$	$3290 \pm 190^{**}$	833 ± 10
			3.2	$31.9 \pm 1.4^{**}$	$4110 \pm 260^{**}$	831 ± 40
			10	$44.4 \pm 2.0^{**}$	$5820 \pm 200^{**}$	$1070 \pm 100^*$

$^{a-d}$ See corresponding footnotes in Table 1. ^{e} Sodium salt was used.

Table 3. Binding Affinities of **12**, **2**, and **1** at A$_1$ and A$_{2A}$ Adenosine Receptors and Pharmacokinetic Profiles of **12** and **2**

	adenosine receptor binding (pK_i)^a		solubility in water	
compd	A$_1$	A$_{2A}$	(μg/mL)^b	BA (%)^c
12 (FK 838)	8.18 ± 0.09	5.92 ± 0.03	10000^d	78 $(100)^d$
2 (FK 453)	9.31 ± 0.09 $(9.31 \pm 0.76)^e$	5.90 ± 0.16	11.9	8.8
1 (DPCPX)	9.55 ± 0.04	6.82 ± 0.05		

^{a} A$_1$ binding was carried out with [^{3}H]DPCPX in rat cortical membranes, and A$_{2A}$ binding was carried out with [^{3}H]CGS 21680 in rat striatal membranes. Values are means $\pm$ 95% confidence limits determined from at least three independent experiments. See ref 12 for details. Data from ref 12. ^{b} Solubility at 37 °C. ^{c} Oral bioavailability in fasted rats. Compounds were suspended in 0.5% methyl cellulose solution, and 3.2 mg/kg **12** and 10 mg/kg **2** were administered orally ($n = 3-4$). ^{d} Sodium salt was used. ^{e} Data in parentheses is for A$_1$ receptors from human cortical membranes; see ref 12.

(sodium salt). These results can clearly explain the above discrepancy. **12** was more hydrophilic and soluble in water than **2**, and the improved oral bioavailability of **12** resulted in more potent diuretic activity, despite relatively low affinity for adenosine A$_1$ receptors. Due to the greater solubility in water, **12** can be used not only orally but also intravenously. Furthermore, **12** was stable to light in solution.

Bioisosteric replacement has been used for several decades as a rational approach to drug design.[13] It is notable that the acryloyl moiety of **2** can be replaced by a heteroaryl group, especially by the 6-oxo-1(6*H*)-pyridazin-3-yl group, which can be a novel example of a bioisostere. In comparison of structures, the butanoic acid moiety of **12** corresponds to the 2-piperidineethanol moiety of **2**. Further study will be necessary to improve in vitro receptor binding affinity and selectivity of **12**, by modification of the butanoic acid moiety.

In summary, based upon an X-ray crystal structure of **2** (FK 453), we designed and synthesized a new series of pyrazolo[1,5-*a*]pyridines, in which heterocyclic groups were introduced instead of the acryloylamide of **2**. Compound **12** displayed the most potent diuretic activity and was a potent and selective adenosine A$_1$ receptor antagonist with good oral availability and solubility in water. Among the many adenosine A$_1$ receptor antagonists reported, **12** can be classified as the first of a new generation of adenosine A$_1$ receptor antagonists, which are useful for the treatment of diseases such as hypertension and renal failure. Compond **12** (FK 838) is undergoing phase 2 clinical trials as a diuretic antihypertensive agent. Further investigations of the SAR and optimization of this class of adenosine A$_1$ receptor antagonist will be reported subsequently.

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