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2-(2-Furanyl)-7-phenyl[1,2,4]triazolo[1,5-*c*]pyrimidin-5-amine analogs: Highly potent, orally active, adenosine A_{2A} antagonists. Part 1

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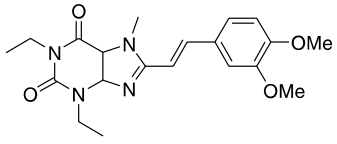
Abstract—The structure–activity relationship of this novel class of compounds based on 2-(2-furanyl)-7-phenyl[1,2,4]-triazolo[1,5-*c*]pyrimidin-5-amine, **1**, and its analogs was evaluated for their in vitro and in vivo adenosine A_{2A} receptor antagonism. Several compounds displayed oral activity at 3 mg/kg in a rat catalepsy model. Specifically, compound **8g** displayed an excellent in vitro profile, as well as a highly promising in vivo profile.

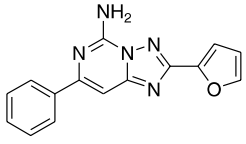
1. Introduction

Adenosine is a modulator of physiological functions through activation of numerous cell surface receptors. Four adenosine receptors (A_1, A_{2A}, A_{2B}, and A_3) belonging to the family of G protein-coupled receptors have been characterized according to their primary sequences.[1] A_1 and A_3 are coupled to inhibitory G protein while A_{2A} and A_{2B} are coupled to stimulatory G protein. Adenosine A_{2A} receptors (AR) are abundant in specific regions of the brain, such as the striatum, caudate-putamen, nucleus accumbens, and olfactory tubercle.[2] In the caudate-putamen A_{2A} AR are localized on several neurons and have been shown to modulate the neurotransmission of γ-aminobutyric acid acetylcholine and glutamate.[3] These actions of the A_{2A} AR could contribute to motor behavior.[4] For example, A_{2A} AR agonists have been shown to inhibit locomotor activity and induce catalepsy in rodents.[5] In contrast, A_{2A} AR antagonists prevent the motor disturbances seen in dopamine D_2 receptor null mice.[6]

Recently, KW-6002, an A_{2A} AR antagonist, has been reported to exhibit anti-parkinsonian activity in the parkinsonian monkey without producing hyperactivity and provoking dyskinesia.[7] These results suggest that A_{2A} AR antagonists potentially represent a novel class of anti-symptomatic drugs for the treatment of Parkinson's disease.



KW-6002



1

Several selective A_{2A} AR antagonists of various structural classes have been developed.[8] Based upon these compounds SAR and our previous work, we proposed to develop an SAR using structure **1** as a template to identify novel A_{2A} AR antagonists.[9]

The compounds shown in Table 1 were prepared using the general procedures described in Scheme 1. Initially, the Pd-catalyzed coupling of commercially available 2-amino-4,6-dichloropyrimidine with aryl boronic acids yielded chlorides **2** which underwent displacement with 2-furoic hydrazide to produce **3**. Dehydrative rearrangement[10] of **3** in *N*′,*O*′-bis(trimethylsilyl)acetamide

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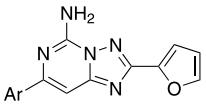
Table 1. Optimization of C-7 arene substituents



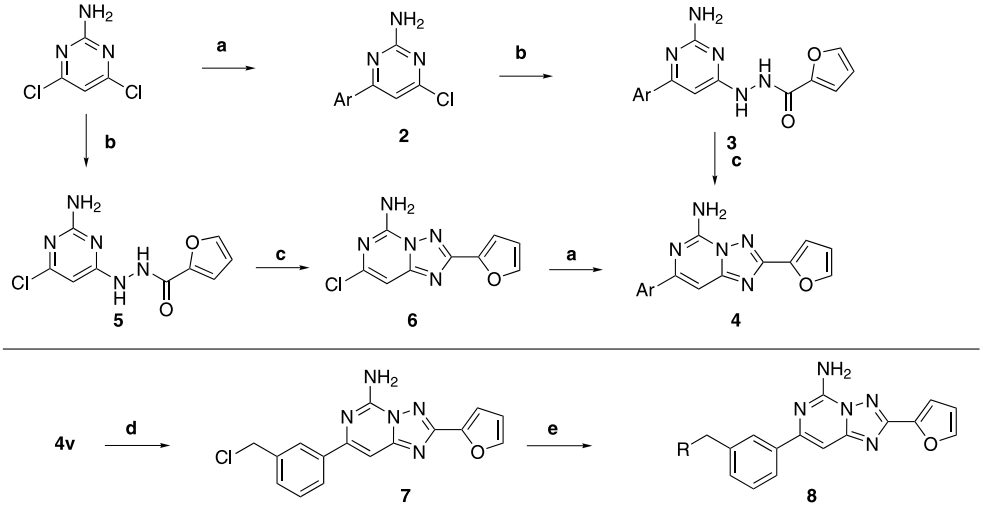
Compound	Ar	A_{2A} K_i (nM)	A_1/A_{2A}
1	Ph	7.0	3
4a	2-CH_3-Ph	22.0	12
4b	3-CH_3-Ph	3.7	13
4c	4-CH_3-Ph	8.4	19
4d	2-CH_3O-Ph	4.3	27
4e	3-CH_3O-Ph	5.0	20
4f	4-CH_3O-Ph	7.3	103
4g	2,4-$(CH_3O)_2$-Ph	2.9	98
4h	3,4-$(CH_3O)_2$-Ph	7.3	64
4i	2,5-$(CH_3O)_2$-Ph	4.5	65
4j	2,6-$(CH_3O)_2$-Ph	1700	1
4k	2,3-$(CH_3O)_2$-Ph	21.7	27
4l	3,4,5-$(CH_3O)_3$-Ph	4.5	69
4m	2,3,4-$(CH_3O)_3$-Ph	4.5	17
4n	2-Thiophene	4.4	15
4o	4-Pyridine	1.9	66
4p	3-Pyridine	6.6	65
4q	2-Pyridine	1.4	34
4r	3-(^{i}Pr)-Ph	4.7	31
4s	3-(Ph)-Ph	5.5	82
4t	3-(NH_2)-Ph	5.0	11
4u	3-(CN)-Ph	5.4	14
4v	3-(CH_2OH)-Ph	2.8	135

(BSA) produced structures of type **4**. Alternatively, 2-amino-4,6-dichloropyrimidine can be displaced with 2-furoic hydrazide to form **5** followed by the dehydrative rearrangement to provide **6** as an advanced intermediate.[11] Subsequent Pd-catalyzed couplings of **6** with various aryl boronic acids yielded compounds **4a**–**v**.

Synthesis of compounds shown in Table 2 originated from the 3-(hydroxymethyl)phenyl analog (**4v**). Conversion of **4v** to its corresponding chloride (**7**), followed by displacement with the requisite amine, led to compounds **8a-q** as shown in Table 2. Requisite amines that were not commercially available were prepared as shown in Scheme 2. The appropriately substituted bromophenols (**9**) were alkylated to form their corresponding methoxyethoxyphenyl bromides (**10**). Piperidines were prepared by the lithiation of the aryl bromides **10** followed by addition to 4-oxo-piperidine-1-carboxylic acid benzyl ester, deoxygenation, and benzyl deprotection to yield piperidines **11**. Piperazines (**12**) were prepared using a Pd-catalyzed amination with aryl bromides **10** and piperazine. All compounds reported herein gave satisfactory analytical results.[12]

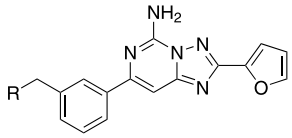
The in vitro results of the A_{2A} AR binding assays[13] are expressed as inhibition constants (K_i, nM) and A_1/A_{2A} describes the selectivity over the A_1 AR. All assays were performed in duplicate and reported as mean values. These compounds were not tested against the other known adenosine receptor subtypes, A_3 and A_{2B}. Results in Table 1 show that compound **1** had a high affinity for A_{2A} AR but was not selective over A_1 AR. The tolyl analogs (**4a**–**c**) retained the affinity for A_{2A} AR but failed to improve desired selectivity. The methoxy phenyl analogs (**4d**–**m**) provided compounds with high affinity for A_{2A} AR with moderate to good selectivity over A_1 AR. One exception was compound **4j** which had very poor affinity for A_{2A} AR, suggesting that orthogonality between the arene and the triazolopyrimidine ring system was not tolerated. Heteroaromatic analogs (**4n**–**q**) also retained single-digit nanomolar potency for A_{2A} AR with no improvement in selectivity over the A_1 AR.

Meta-substituted compounds, **4r**–**v**, retained single-digit nanomolar A_{2A} AR affinity and acceptable selectivity over A_1; particularly compound **4s**, which was 82-fold selective. Results of compound **4s** demonstrated the possibility of exploring the SAR via modifications of the side chains at the *meta*-position of



Scheme 1. Reagents: (a) aryl boronic acid, $Pd(PPh_3)_4$, K_2CO_3, CH_3CN/H_2O (23–70%); (b) 2-furoic hydrazide, BuOH; (c) BSA (28%); (d) Et_3N, $SOCl_2$, CH_2Cl_2; (e) KI, K_2CO_3, CH_3CN, amine.

Table 2. Receptor affinity and in vivo activity of side chain variants



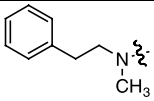
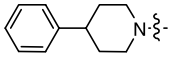
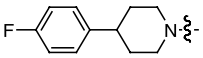
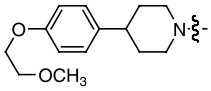
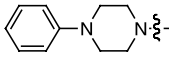
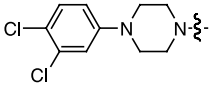
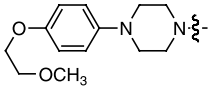
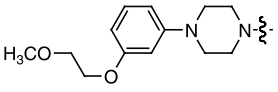
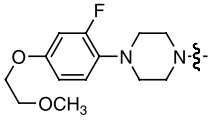
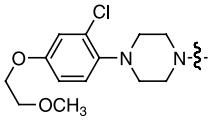
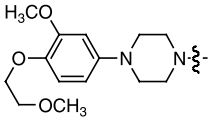
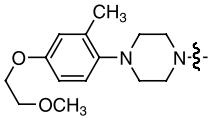
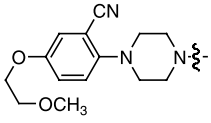
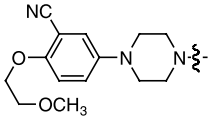
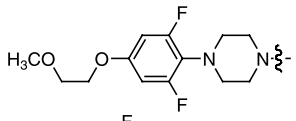
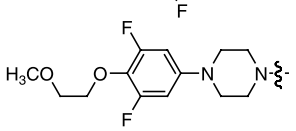
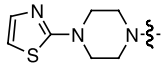
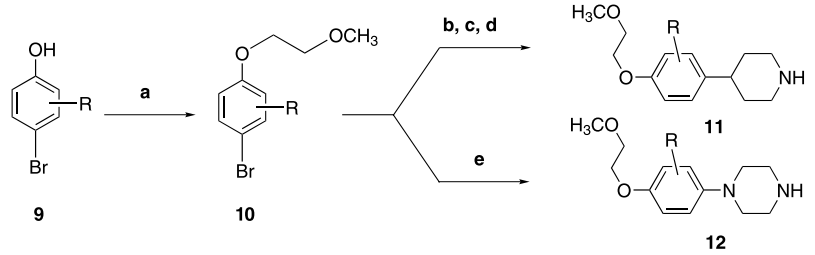
Compound	R	A_{2A} K_i (nM)	A_1/A_{2A}	Anti-cataleptic activity 1 h/4 h
8a		3.6	135	NT
8b		4.6	69	NT
8c		7.4	115	20/20
8d		8.9	202	0/0
8e		4.6	69	NT
8f		10.5	3	NT
8g		2.8	601	40/65
8h		4.0	115	29/53
8i		2.7	642	20/0
8j		2.9	204	12/15
8k		3.3	134	33/39
8l		2.7	72	NT
8m		3.6	85	NT
8n		1.1	314	14/9

Table 2 (*continued*)

Compound	R	A_{2A} K_i (nM)	A_1/A_{2A}	Anti-cataleptic activity 1 h/4 h
8o		6.4	71	NT
8p		2.2	338	28/47
8q		2.4	192	20/10



Scheme 2. Reagents: (a) $CH_3OCH_2CH_2Br$, K_2CO_3, acetone (80%); (b) i—*n*-BuLi, THF, ii—4-oxo-piperidine-1-carboxylic acid benzyl ester; (c) Et_3SiH, TFA, CH_2Cl_2 (72%); (d) 10% Pd/C, H_2, EtOAc/EtOH (99%); (e) $Pd(OAc)_2$, NaO^tBu, $Pd(^tBu)_3$, toluene.

compound **1**. The result of this work is summarized in Table 2.

Side chain modifications (Table 2) produced several compounds with high affinity for A_{2A} AR and excellent selectivity over A_1 AR. Substitution of the *meta*-position of the phenyl with either 4-(phenyl)-piperidine (**8b–d**) or 4-(phenyl)-piperazine derivatives (**8e–q**) was well tolerated. The incorporation of the methoxethoxy substituent, as in **8g** (A_1/A_{2A} = 601) and **8h** (A_1/A_{2A} = 115), seemed particularly beneficial in terms of selectivity over A_1 when compared with phenylpiperazine analog **8e** (A_1/A_{2A} = 69).

Several compounds from Table 2 were assessed for their bioavailability and anti-cataleptic activity in the rat at an oral dose of 3.0 mg/kg. In general, piperazine analogs displayed better bioavailability than piperidine analogs. Many of these compounds showed modest to high activity in the rat catalepsy assay at a 3 mg/kg dose. Brain concentration of some of these compounds was measured at 6 h and found to be in 40–50 ng range. Generally, there was no apparent correlation between their bioavailability and anti-cataleptic activity. Receptor occupancy studies are planned to understand this discrepancy.

The exploration of SAR of 2-(2-furanyl)-7-phenyl[1,2,4]triazolo[1,5-*c*]pyrimidin-5-amine analogs resulted in a novel class of A_{2A} AR antagonists. Compared to compound **1**, several analogs with high selectivity for A_1 AR with retention of A_{2A} binding affinity were identified. Several of these compounds demonstrated oral activity at 3 mg/kg in a rat catalepsy model. Among these compounds, **8g** displayed optimum binding, selectivity, and anti-cataleptic activity.

2. Catalepsy procedure

The rodent model for Parkinson's Disease is the rat catalepsy assay where the dopamine D_2 receptor antagonist, haloperidol (1 mg/kg, subcutaneous), is administered. After 30 min, rats were placed facing upwards on a wire screen inclined at 60°. The time taken for the rat to move one limb was measured, with a cut-off time of 120 s. Rats showing >75 s of immobility (catalepsy) were used for subsequent A_{2A} antagonist studies. Test compounds were administered orally and catalepsy was retested at 1 and 4 h after administration. Male CD rats (Charles River Laboratories) weighing 200–240 g were used for all studies. Upon arrival at our holding facility, rats were housed 4 per cage, with food and water available ad libitum. Rats were maintained on a 12-h light/dark cycle (light on 07:00; lights off 19:00). All studies were carried out in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals.

Acknowledgment

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12. Compound **1**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.66 (s, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.14 (d, J = 3.4 Hz, 1H), 6.60 (br s, 2H), 6.53 (d, J = 3.4 Hz, 1H), 5.39 (t, J = 5.8 Hz, 1H), 4.51 (d, J = 5.8 Hz, 2H), 3.98 (s, 2H), 2.41 (s, 3H); *8g*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.0 (s, 1H), 7.86 (m, 1H), 7.62 (dd, 1H), 7.41–7.45 (m, 3H), 7.3 24 (d, 1H), 6.82–6.85 (m, 4H), 6.58 (dd, 1H), 6.28 (br s, 52H), 4.06 (t, 2H), 3.72 (t, 3H); 3.66 (s, 2H), 3.43 (s, 3H), 3.00–3.12 (m, 4H); 2.65–2.67 (m, 4H).
13. Adenosine A_{2A} and A_1 binding assays: [^{3}H]SCH-58261 and [^{3}H]DPCPX binding assays for adenosine A_{2A} and A_1 receptors, respectively, were performed as described previously.[14]
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