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Bioorganic & Medicinal Chemistry Letters 15 (2005) 2119–2122
Bioorganic & Medicinal Chemistry Letters

6-(2-Furanyl)-9*H*-purin-2-amine derivatives as A_{2A} adenosine antagonists

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Received 10 January 2005; revised 8 February 2005; accepted 9 February 2005
Available online 19 March 2005

Abstract—Structure–activity relationships have been investigated through substitutions at the 9-position of the 2-amino-6-(2-furanyl) purine (**5**) to identify novel and selective A_{2A} adenosine receptor antagonists. Several potent and selective antagonists were identified. In particular, compounds **20**, **25**, and **26** show very high affinity with excellent selectivity.

The purine nucleoside, adenosine, is known to act via four major receptor subtypes, A_1, A_{2A}, A_{2B}, and A_3 which have been characterized according to their primary sequences.[1] Adenosine A_{2A} receptors are abundant in the caudate–putamen, nucleus accumbens and olfactory tubercle in several species.[2] In the caudate–putamen, adenosine A_{2A} receptors are localized on several neurons and have been shown to modulate the neurotransmission of γ-aminobutyric acid (GABA), acetylcholine, and glutamate.[3] These actions of the A_{2A} receptor contribute to the control of motor behavior.[4] A_{2A} agonists inhibit locomotor activity and induce catalepsy in rodents.[5] In contrast, adenosine A_{2A} antagonists prevent the motor disturbances of dopamine D2 receptor null mice.[6] Recently, an A_{2A} antagonist, KW-6002, was found to have antiparkinsonian activity in the parkinsonian monkey without producing hyperactivity and provoking dyskinesia.[7] These results suggest that A_{2A} antagonists have potential to be a new class of antisymptomatic drugs for Parkinson's disease.

In the past ten years, great efforts have been devoted to identify potent and selective A_{2A} adenosine antagonists. SCH 58261, that displayed single-digit nanomolar potency and modest selectivity (A_{2A} $K_i = 4.3$ nM, $A_1/A_{2A} = 35$) has been widely used as a tool for characterizing the adenosine A_{2A} receptor subtype.[8] However, SCH 58261 suffered from several drawbacks including low selectivity, poor solubility, and pharmacokinetic profile. Based on these observations, we undertook a structure–activity relationship (SAR) investigation to identify a novel A_{2A} receptor antagonist using SCH 58261 as a template. Our plan was to replace the tricyclic core of SCH 58261 with purine moiety such as in **1**, and investigate the SAR via substitution at N-9. In this communication, we report the results of this investigation.

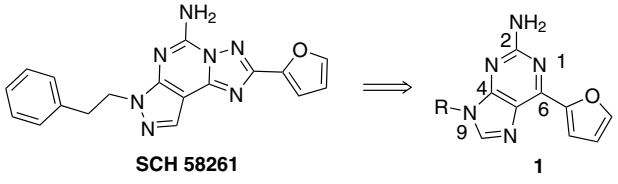
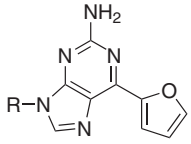


Table 1. Receptor binding of phenyl alkyl analogues



Compound	R	A_{2A} K_i (nM)	A_1/A_{2A}
	SCH 58261	4.3	35
6	C_6H_5–	68.5	3
7	$C_6H_5CH_2$–	34.9	86
8	$C_6H_5CH_2CH_2$–	270.5	7
9	$C_6H_5CH_2CH_2CH_2$–	6.8	27
10	C_6H_5CH(Me)-	381.0	5

Keywords: Adenosine receptor; Antagonist; 2-Furanyl; 9-*H* Purin.
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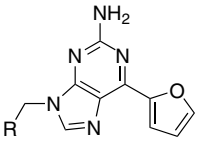
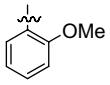
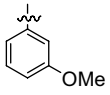
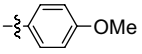
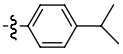
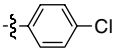
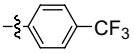
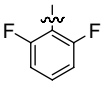
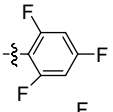
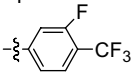
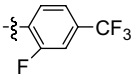
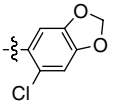
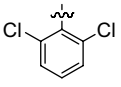
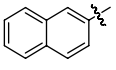
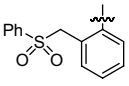
doi:10.1016/j.bmcl.2005.02.031

Table 2. Receptor binding of substituted benzyl analogues



Compound	R	A_{2A} K_i (nM)	A_1/A_{2A}
11		22.0	31
12		12.3	163
13		7.7	104
14		10.0	135
15		21.5	63
16		20.5	98
17		4.5	162
18		26	58
19		8.7	185
20		2.8	418
21		6.3	106
22		7.1	195
24		5.6	223
25		1.4	466
26		3.1	574

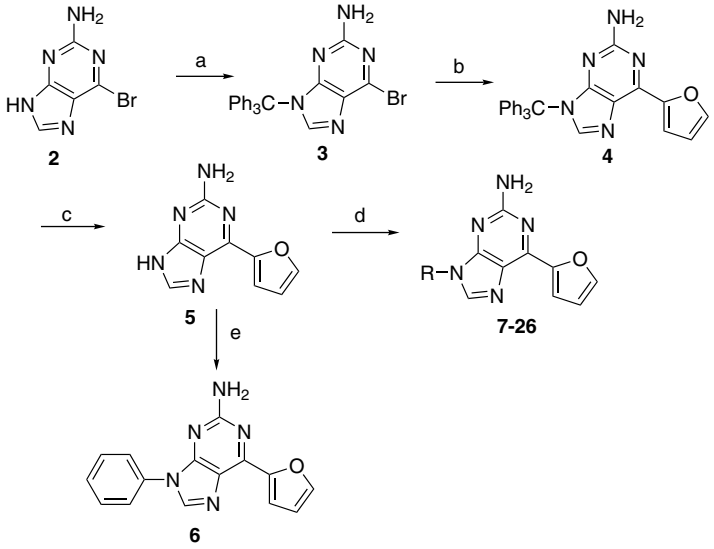
Compounds presented in Tables 1 and 2 were prepared from commercially available 2-amino-6-bromopurine **2** using general procedure described in Scheme 1. Accordingly, compound **2** was protected with triphenylmethyl to give compound **3** as a major product along with a small amount of a dialkylated derivative in 85% combined yield. Bromide **3** was then subjected to Stille coupling[9] to produce compound **4**, which upon deprotection under acidic conditions and neutralization produced compound **5** in 70–80% yield. Compound **5**, 6-(2-furanyl)-9H-purin-2-amine, was utilized to prepare analogues with general structure **1**. Alkylation of **5** with various benzyl halides produced compounds described in Tables 1 and 2. The benzyl halides were all commercially available. Compound **6** was prepared using procedure described in Scheme 1.

Compound **5** was subjected to cross-coupling reaction using phenylboronic acid and cupric acetate[10] to produce **6**. All compounds gave satisfactory analytical results.[11]

The results of the A_{2A} adenosine receptor binding assays[12] are expressed as inhibition constants (K_i, nM). The A_1/A_{2A} describes the selectivity over A_1 adenosine receptor. Table 1 shows the SAR of compounds where N-9 was substituted with phenyl **6** and phenyl alkyls **7**–**9** derivatives. Substitution with either phenyl (**6**) or phenethyl (**8**) moieties resulted in the significant loss of affinity. The benzyl compound **7** shows significant increase in the selectivity with moderate decrease in A_{2A} adenosine receptor affinity. Introduction of a methyl substituent at the benzylic site in compound **10** was detrimental to A_{2A} receptor binding. Compound **9** with three carbon linker exhibited binding and selectivity very similar to SCH 58261. Since a benzyl substituent at N-9 produced a significant increase in selectivity over A_1 adenosine receptor, the SAR of a variety of substituted benzyl derivatives was investigated in detail and results are presented in Table 2.

The monosubstituted derivatives represented by compounds **11**–**16** exhibited A_{2A} adenosine receptor binding affinities in a very narrow range of 8–22 nM. The *para*-substituted derivatives in general were more selective over A_1 receptor subtype. It was found that the nature of the substituents on the benzyl was critical for the selectivity of A_{2A} over A_1 adenosine receptor. The lipophilic substituents produced compounds with significantly greater selectivity. Hence disubstituted compounds containing either two fluorine atoms as in **17**, or a combination of fluorine and trifluoromethyl as in **19** and **20** produced the best potency and selectivity. Similarly, naphthalene derivatives **24** and **25** were also very potent and selective. The trisubstituted compound **18** was significantly less potent and selective. The phenyl sulfone derivative **26** was the only monosubstituted compound identified to be selective with very high affinity for A_{2A} adenosine receptor.

In summary, we have identified 6-(2-furanyl)-9*H*-purin-2-amine derivatives as a novel class of compounds with high A_{2A} receptor antagonist affinities. Compared to SCH 58261, several compounds in this series are more potent and selective. Some of these compounds show better solubility and pharmacokinetic profiles than SCH 58261.



Scheme 1. Reagents and conditions: (a) Ph_3CCl, Et_3N, CH_2Cl_2, rt; (b) 2-(tributylstannyl)furan, $Pd(PPh_3)_2Cl_2$, CuI, THF, reflux; (c) HCl; (d) RX, K_2CO_3, DMF, rt; (e) $PhB(OH)_2$, $Cu(OAc)_2$, pyridine, CH_2Cl_2.

In particular, compounds **20**, **25**, and **26** show very high affinity (K_i = 2.8, 1.4, 3.1 nM, respectively) with excellent selectivity over A_1 adenosine receptor.

Acknowledgments

We would like to thank Dr. William Greenlee for his support and encouragement of this work. We would also like to thank Zheng Tan for her help in the preparation of this manuscript.

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11. For compound **20**: ^{1}H NMR ($CDCl_3$): δ 7.84 (s, 1H), 7.81 (d, J = 3.4 Hz, 1H), 7.49 (dd, J = 1.8, 0.8 Hz, 1H), 7.41–7.37 (m, 3H), 6.65 (dd, J = 3.4, 1.8 Hz, 1H), 5.39 (s, 2H), 5.13 (br s, 2H); MS m/z (ES) 378 $[M+1]^+$. For compound **25**: 1H NMR ($CDCl_3$): δ 7.75–7.86 (m, 5H), 7.72 (dd, J = 1.8, 0.8 Hz, 1H), 7.67 (br s, 1H), 7.49 (ddd, J = 9.9, 3.5, 3.5 Hz, 2H), 7.37 (dd, J = 8.4, 1.8 Hz, 1H), 6.63 (dd, J = 3.4, 1.8 Hz, 1H), 5.44 (s, 2H), 5.21 (br s, 2H); MS m/z (ES) 342 $[M+1]^+$. For compound **26**: ^{1}H NMR ($CDCl_3$): δ 7.81–7.75 (m, 3H), 7.69 (dd, J = 1.8, 0.8 Hz, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.52 (dd, J = 7.8, 7.8 Hz, 2H), 7.30 (ddd, J = 14.1, 7.4, 2H), 7.20 (dd, J = 13.6, 7.4 Hz, 2H), 7.01 (d, J = 7.8 Hz, 1H), 6.61 (dd, J = 3.4, 1.8 Hz, 1H), 5.37 (s, 2H), 5.19 (br s, 2H), 4.64 (s, 2H); MS m/z (ES) 446 $[M+1]^+$.
12. 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 before.[13] Briefly, 5 μg HEK cell membranes expressing human adenosine A_{2A} receptors were incubated with different concentrations of compounds and 1 nM [^{3}H]SCH 58261 in 200 μL assay buffer containing 2.7 mM KCl, 1.1 mM KH_2PO_4, 137 mM NaCl, 7.6 mM Na_2HPO_4, 10 mM $MgCl_2$, 0.04% methyl cellulose, 20 μg/mL adenosine deaminase, and 4% dimethyl sulfoxide. Adenosine A_1 binding assays were performed on 10 μg CHO cell membranes expressing human adenosine A_1 receptors and 1 nM [^{3}H]DPCPX in 200 μL assay buffer. Reactions were carried out for 60 min at room temperature (23 °C) and were terminated by rapid filtration over GF/B filters. Filters were washed seven times with 1 mL cold (4 °C) distilled water, air dried, and radioactivity retained on filters were counted in Packard's TopCount NXT microplate scintillation counter. Compounds were tested at 10 different concentrations ranging from 0.1 nM to 3 μM. Non-specific binding for adenosine A_{2A} and A_1 receptors

were determined in the presence of 10 μM CGS 15943 and 10 μM NECA, respectively. Assays were performed in duplicates and compounds were tested twice. Data were fitted in one site competition binding model for IC_{50} determination using the program GraphPad Prism (GraphPad Software, Inc., San Diego, CA) and K_i values were calculated using Cheng and Prusoff's formula.[14]

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