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3*H*-[1,2,4]-Triazolo[5,1-*i*]purin-5-amine derivatives as adenosine A_{2A} antagonists

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Abstract—A novel series of 3-substituted-8-aryl-[1,2,4]-triazolo[5,1-*i*]purin-5-amine analogs related to Sch 58261 was synthesized in order to identify potent adenosine A_{2A} receptor antagonists with improved selectivity over the A_1 receptor, physiochemical properties, and pharmacokinetic profiles as compared to those of Sch 58261. As a result of structural modifications, numerous analogs with excellent in vitro binding affinities and selectivities were identified. Moreover, compound **27** displayed both superior in vitro and highly promising in vivo profiles.

Adenosine, a purine nucleoside, modulates physiological functions via interaction with specific cell surface receptors. Four adenosine receptor subtypes (A_1, A_{2A}, A_{2B}, and A_3) have been identified and belong to the family of G protein-coupled receptors (GPCR).[1]

The adenosine A_{2A} receptor (AR) is abundantly expressed in striatum, compared to the A_1 AR which is widely distributed throughout the brain.[2] The A_{2A} and A_{2B} receptors stimulate adenylate cyclase activity which controls intracellular AMP levels and plays an important role in regulating motor function.[3] A_{2A} AR agonists have been shown to inhibit locomotor activity and induce catalepsy in rodents.[4] In contrast, A_{2A} AR antagonists prevent the motor disturbances seen in dopamine D2 receptor null mice.[5] It has been discovered that dopamine deficiency in the brain can initiate the onset of Parkinson's disease (PD), a neurodegenerative motor disorder.[6] Consequently, A_{2A} AR antagonists may offer potential value as a new class of anti-symptomatic drugs for the treatment of PD.

Over the past few years, there has been extensive work done to synthesize novel xanthine and non-xanthine potent and selective A_{2A} AR antagonists. KW-6002, a xanthine based A_{2A} AR antagonist, has been reported to improve motor disability in the parkinsonian monkey without provoking dyskinesia.[7] In addition, numerous novel non-xanthine based selective A_{2A} AR antagonists have been identified as well.[8] Several years ago, SCH 58261, a pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine, was identified as a very potent but only moderately selective A_{2A} AR antagonist (A_{2A} $K_i = 4.3$ nM, $A_1/A_{2A} = 35$).[9] However, SCH 58261 exhibited poor physiochemical and pharmacokinetic (PK) profiles. Consequently, in order to identify novel A_{2A} AR antagonists with enhanced selectivity over A_1 and improved solubility and PK profiles, we conducted a structure–activity relationship (SAR) investigation where the pyrazole ring of SCH 58261 was replaced with an imidazole ring as shown in general structure **1**.

Using structure **1** as the scaffold, we varied the substituted side chains at N-3 and then we replaced the 2-furyl at C-8 with various arene moieties. Herein we report a summary of the results of our SAR investigation.

Keywords: Adenosine A_{2A} receptor; Antagonist.
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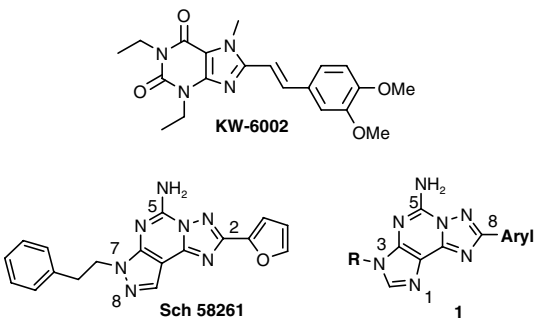
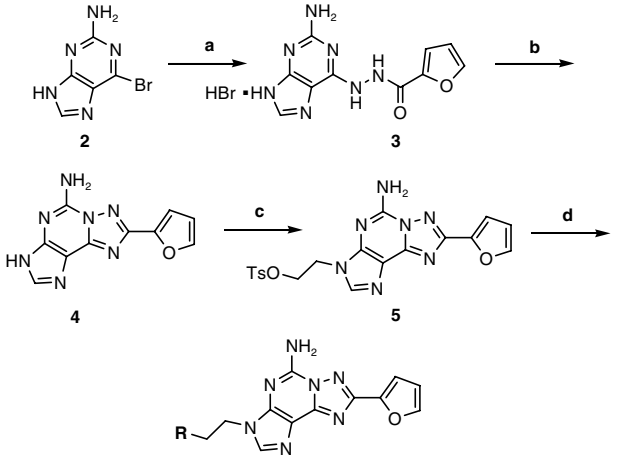


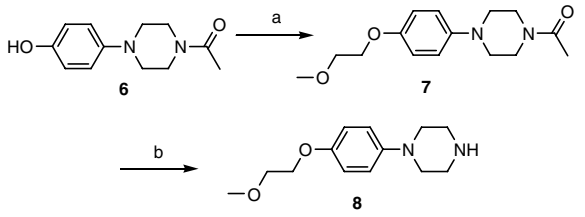
Compounds **21**–**45** were prepared according to the general route described in Scheme 1 or via a slightly modified route to accommodate the structural modifications described above. For example, the nucleophilic displacement of bromine on commercially available 2-amino-6-bromopurine (**2**) by 2-furoic hydrazide produced HBr salt **3**, which was treated with *N*,*O*-bis(trimethylsilyl)acetamide (BSA) to undergo a dehydrative rearrangement to produce imidazole tricycle **4**. Next, **4** was alkylated with ethylene glycol di-*p*-tosylate to give a 1:1 mixture of N-3 (**5**) and N-1 alkylated products. Desired tosylate **5** was isolated by column chromatography and coupled with piperazine and piperidine derivatives to give the reported analogs.

Piperazine **8**, incorporated in **27** and **39**–**45**, was prepared as shown in Scheme 2. Commercially available 1-acetyl-4-(4-hydroxyphenyl)-piperazine (**6**) was alkylated with 2-bromoethyl methyl ether to give intermediate **7** which was deacetylated via acid hydrolysis to yield **8**.

Piperazine **12**, used for the preparation of **28**, was prepared as shown in Scheme 3. Commercially available 1-bromo-2-fluoro-4-methoxybenzene (**9**) was demethylated with BBr_3 to give phenol **10** which was alkylated



Scheme 1. Reagents and conditions: (a) 2-furoic hydrazide, *n*-BuOH, 120 °C, 95%; (b) BSA, 100 °C, 95%; (c) $(p\text{-TsOCH}_2)_2$, NaH, DMF, 0 °C to rt, 20% (after purification); (d) R = aryl piperazine/aryl piperidine, DMF, 90 °C, sealed tube, 60%.



Scheme 2. Reagents and conditions: (a) 2-bromoethyl methyl ether, NaH, DMF, 60 °C, 80%; (b) 1—6 N HCl, 80 °C; 2—5 N NaOH, 95%.

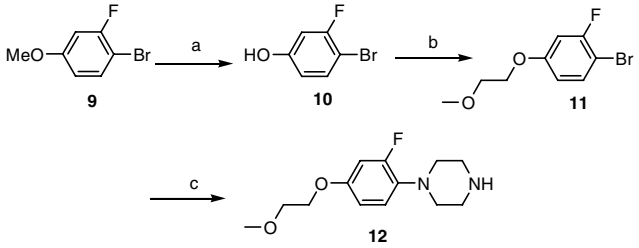
with 2-bromoethyl methyl ether to give intermediate **11**. Next, **11** and piperazine were coupled via Buchwald conditions to give **12**. The remainder of piperazines required to prepare compounds **21**, **26**, **29**, **30**, and **33**–**38** were either synthesized in a similar fashion or commercially available.

Piperidine **17**, used for the preparation of **31**, was prepared as shown in Scheme 4. Commercially available 4-bromophenol (**13**) was alkylated with 2-bromoethyl methyl ether to give intermediate **14** which was lithiated and added to the C-4 carbonyl of 4-oxo-piperidine-1-carboxylic acid benzyl ester to yield intermediate **15**. Next, **15** was deoxygenated to yield **16** which was deprotected via palladium catalyzed hydrogenolysis to give **17.** The piperidine required to prepare compound **32** was synthesized in a similar fashion. All compounds reported herein gave satisfactory analytical results.[10]

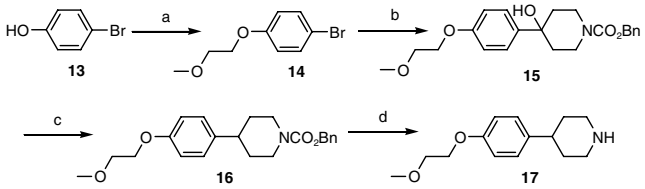
The in vitro results of the A_{2A} AR binding assays are expressed as inhibition constants (K_i, nM) and A_1/A_{2A} describes the selectivity over the A_1 AR.[11] All assays were performed in duplicate and reported as mean values. These compounds were not tested against the other known adenosine receptor subtypes, A_3 and A_{2B}.

Table 1 shows our initial SAR where the C-8 2-furanyl moiety is fixed and N-3 is substituted with alkyl and phenyl groups of varied size, chain length, and electronic nature. All of the compounds demonstrate acceptable potency for A_{2A} (K_i = 1–6.3 nM). However compound **21**, the phenyl piperazine analog, is the only one that is selective over A_1.

Table 2 shows our follow-up SAR where the C-8 2-furanyl moiety is fixed and the N-3 side chain has been varied with substituted aryl piperazines and piperidines. With the exception of compound **36** (thiazole), the balance of analogs exhibit binding affinities (subnanomo-

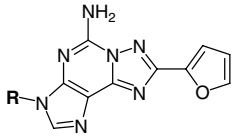


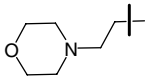
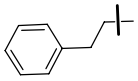
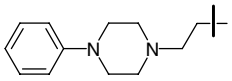
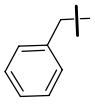
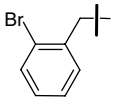
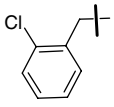
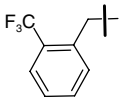
Scheme 3. Reagents and conditions: (a) BBr_3/CH_2Cl_2, Δ, 99%; (b) K_2CO_3, 2-bromoethyl methyl ether, CH_3CN, Δ, 98%; (c) piperazine, $Pd_2(dba)_3$, NaO^{t}Bu, BINAP, toluene, Δ, 70%.



Scheme 4. Reagents and conditions: (a) K_2CO_3, 2-bromoethyl methyl ether, CH_3CN, Δ, 95%; (b) 1—*n*-BuLi, −78 °C, THF; 2—4-oxo-piperidine-1-carboxylic acid benzyl ester, −78 °C to rt, 60%; (c) Et_3SiH, TFA, CH_2Cl_2, −78 °C to rt, 95%; (d) H_2, 5% Pd/C, MeOH/EtOAc, 1 atm, 98%.

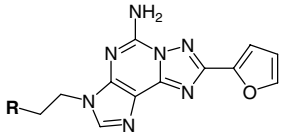
Table 1. Receptor affinity of N-3 substituted analogs



Compound	R	A_{2A} K_i (nM)	A_1/A_{2A}
18		5.9	50
19		6.3	37
20		4.1	33
21		1.7	182
22		1.5	17
23		4.6	7
24		1.7	9
25		4.6	30

lar) superior to that of analog **21**. Moreover, all of the compounds except **30** (2,4-difluorophenyl) are at least as selective as compound **21** ($A_1/A_{2A} \geqslant \approx 170$). Compounds **27**, **28**, **29**, and **31** are of particular note since all of them are extremely selective ($A_1/A_{2A} > 500$) and they all contain 4-alkoxy phenyl substituents. In addition, the replacement of piperazine with piperidine (compounds **27** and **31**) does not affect the in vitro potency and selectivity. Although **26** has the highest binding affinity and selectivity, after kinetic solubility and PK evaluations, compound **27** appeared to have the best overall physiochemical profile. Consequently, the [4-(2-methoxyethoxy)-phenyl]-1-piperazinyl-4-ethyl side chain was selected for the final SAR study.

Table 2. Receptor affinity of N-3 aryl piperidine/piperazine analogs



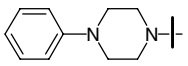
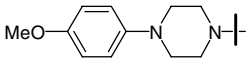
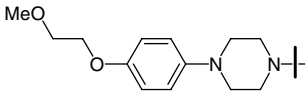
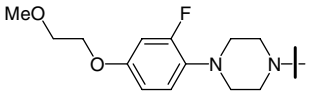
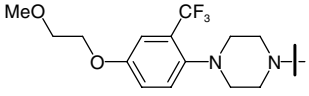
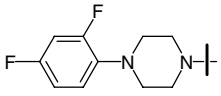
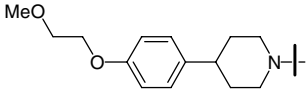
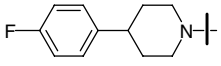
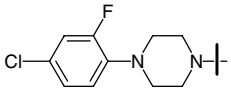
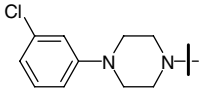
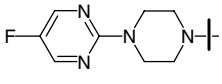
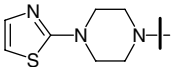
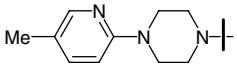
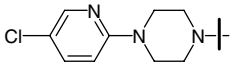
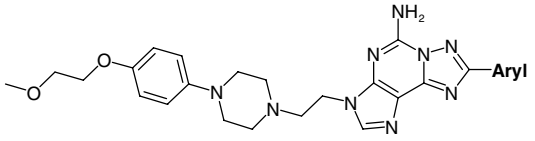
Compound	R	A_{2A} K_i (nM)	A_1/A_{2A}
21		1.7	182
26		0.1	1695
27		0.9	669
28		0.8	517
29		0.4	218
30		0.7	88
31		0.7	519
32		0.9	196
33		0.3	403
34		0.4	371
35		1.4	378
36		1.7	138
37		1.0	162
38		0.9	333

Table 3. Receptor affinity of C-8 aryl analogs



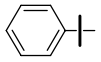
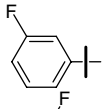
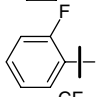
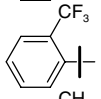
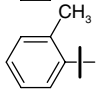
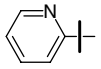
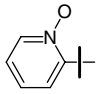
Compound	Aryl	A_{2A} K_i (nM)	A_1/A_{2A}
27		0.9	669
39		3.7	91
40		2.0	83
41		9.3	15
42		10.0	181
43		20.5	76
44		12.6	108
45		89.7	17

Table 3 shows the results of the SAR where the N-3 [4-(2-methoxyethoxy)-phenyl]-1-piperazinyl-4-ethyl moiety is fixed and the C-8 2-furanyl moiety has been replaced with various substituted aryl groups. Compared to the C-8 2-furanyl series, in general the C-8 substituted aryl derivatives are less potent and selective. Compounds **39** and **40** (phenyl and 3-fluorophenyl) retain good binding affinity but selectivity against A_1 is reduced 7-fold. The 2-substituted phenyl and pyridinyl ring derivatives (**41**–**45**) are 9- to 90-fold less potent and 4- to 40-fold less selective than antagonist **27**.

In summary, we have identified 3-substituted-8-aryl-3*H*-[1,2,4]-triazolo[5,1-*i*]purin-5-amines, a novel series of adenosine A_{2A} receptor antagonists which display excellent binding affinity and selectivity over the A_1 AR. Most of the N-3 substituted aryl piperazine and piperidine analogs demonstrate in vitro A_{2A} receptor binding affinity ($K_i < 1$ nM) and A_1 receptor selectivity ($A_1/A_{2A} = 300–1700$) profiles superior to those of SCH 58261. In addition, compound **27** has demonstrated superior PK profiles at an oral dose of 3.0 mg/kg (AUC = 524 ng h/mL) in addition to exhibiting in vivo activity at 3 mg/kg at 1 and 4 h (80% and 50%) as well as at 1 mg/kg at 1 and 4 h (55% and 50%) in the rat catalepsy model.[13] All studies were carried out in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals.

Acknowledgments

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References and notes

1. Fredholm, B. B.; Abbracchio, M. P.; Burnstock, G.; Daly, J. W.; Harden, T. K.; Jacobson, K. A.; Legg, P.; Williams, M. *Pharmacol. Rev.* **1994**, *46*, 143.
2. Svenningsson, P.; Le Moine, C.; Fisone, G.; Fredholm, B. B. *Prog. Neurobiol.* **1999**, *59*, 355.
3. Olah, M.; Stiles, G. L. *Pharmacol. Ther.* **2000**, *85*, 55.
4. (a) Shiozaki, S.; Ichikawa, S.; Nakamura, J.; Kitamura, S.; Yamada, K.; Kuwana, Y. *Psychopharmacology* **1999**, *147*, 90; (b) Shiozaki, S.; Ichikawa, S.; Nakamura, J.; Kuwana, Y. In *Effects of Adenosine Receptors*; Kase, H., Richardson, P. J., Jenner, P., Eds.; Academic Press: New York, 1999; pp 193–210.
5. Aoyama, S.; Kase, H.; Borreli, E. *J. Neurosci.* **2000**, *20*, 5848.
6. Ognini, E.; Fredholm, B. B. *Trends Pharmacol. Sci.* **1996**, *17*, 364.
7. Kanda, T.; Jackson, M. J.; Smith, L. A.; Pearce, R. K. B.; Nakamura, J.; Kase, H.; Kuwana, Y.; Jenner, P. *Exp. Neurol.* **2000**, *162*, 321.
8. (a) Baraldi, P. G.; Cacciari, B.; Romagnoli, R.; Spalluto, G.; Monopoli, A.; Ongini, E.; Varani, K.; Borea, P. A. *J. Med. Chem.* **2002**, *45*, 101; (b) Baraldi, P. G.; Cacciari, B.; Spalluto, G.; Bergonzoni, M.; Dionosotti, S.; Ongini, E.; Varani, K.; Borea, P. A. *J. Med. Chem.* **1998**, *41*, 2126; (c) Baraldi, P. G.; Cacciari, B.; Spalluto, G.; Borioni, A.; Viziano, M.; Dinisotti, S.; Ongini, E. *Curr. Med. Chem.* **1995**, *2*, 707; (d) Vu, C. B.; Pan, D.; Peng, B.; Sha, L.; Kumaravel, G.; Jin, X.; Phadke, D.; Engebr, T.; Huang, C.; Reilly, J.; Tam, S.; Petter, R. C. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4831; (e) Gatta, F. et al. *Eur. J. Med. Chem.* **1993**, *28*, 569; (f) Yao, G. et al. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 511.
9. Zocchi, C.; Ongini, E.; Conti, A.; Monopoli, A.; Negretti, A.; Baraldi, P. G.; Dionisotti, S. *J. Pharmacol. Exp. Ther.* **1996**, *276*, 398.
10. Compound **27**: ^{1}H NMR (DMSO-d_6,400 MHz): δ 2.58 (br s, 4H), 2.75 (t, 2H), 2.95 (br s, 4H), 3.26 (s, 3H), 3.58 (m, 2H), 3.96 (m, 2H), 4.27 (t, 2H), 6.70 (dd, 1H), 6.76–6.84 (m, 4H), 7.22 (m, 1H), 7.78 (br s, 2H), 7.92 (s, 1H), 8.05 (s, 1H).
11. 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.[12]
12. (a) Dionisotti, S.; Ongini, E.; Zocchi, C.; Kull, B.; Arslan, G.; Fredholm, B. B. *Br. J. Pharmacol.* **1997**, *121*, 353; (b) Klotz, K.-N.; Hessling, J.; Hegler, J.; Owman, C.; Kull, B.; Fredholm, B. B.; Lohse, M. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1997**, *357*, 1.
13. (a) Matasi, J. J.; Caldwell, J. P.; Zhang, H.; Fawzi, A.; Cohen-Williams, M. E.; Varty, G. B.; Tulshian, D. B. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3670; (b) Matasi, J. J.; Caldwell, J. P.; Zhang, H.; Fawzi, A.; Higgins, G. A.; Cohen-Williams, M. E.; Varty, G. B.; Tulshian, D. B. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3675.