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The discovery and synthesis of novel adenosine receptor (A_{2A}) antagonists

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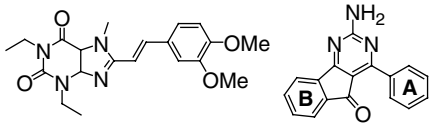
Abstract—In high throughput screening of our file compounds, a novel structure **1** was identified as a potent A_{2A} receptor antagonist with no selectivity over the A_1 adenosine receptor. The structure–activity relationship investigation using **1** as a template lead to identification of a novel class of compounds as potent and selective antagonists of A_{2A} adenosine receptor. Compound **26** was identified to be the most potent A_{2A} receptor antagonist (K_i = 0.8 nM) with 100-fold selectivity over the A_1 adenosine receptor.

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 in 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} adenosine receptor could contribute to motor behavior.[4] For instance, A_{2A} agonists have been shown to inhibit locomotor activity and induce catalepsy in rodents.[5] In contrast, adenosine A_{2A} antagonists prevent the motor disturbances of dopamine D_2 receptor null mice.[6]

Recently, evaluation of A_{2A} receptor antagonist, KW-6002, exhibited antiparkinsonian activity in the parkinsonian monkey without producing hyperactivity and provoking dyskinesia,[7] suggesting that A_{2A} receptor antagonists have potential to be a new class of antisymptomatic drug for Parkinson's disease. A number of A_{2A} selective adenosine receptor antagonists[8] have been developed using purine as a template. In our quest to discover A_{2A} receptor antagonists, screening of our file compounds identified a novel nonpurine structure **1** as a potent A_{2A} antagonist (K_i = 1.7 nM). However, it had no selectivity over the A_1 adenosine receptor. We began the SAR using Compound **1** as a starting point to improve selectivity of this novel class of compounds over the A_1 adenosine receptor. Our strategy was to achieve the selectivity via modifications of rings **A** and **B** as well as the amino moiety. We also planned to address the role of ketone functionality of lead **1**. It was quickly realized that the amino functionality was essential for A_{2A} receptor affinity, since either alkylation or acylation produced compounds with significantly reduced affinity for the A_{2A} adenosine receptor.



KW-6002 1

It was also established that reduction of the ketone to a methylene as in **6b** or its replacement with the ether linkage to compound **6c** produced compounds with A_{2A} affinity similar to **1** without any improvement in the selectivity over A_1 adenosine receptor (see Table 1). Based on these results, the SAR was focused only in the methylene series represented by **6b**. Hence, both

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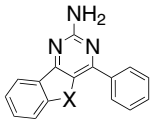
Table 1. Modification of the five-membered ring (indenyl ring)

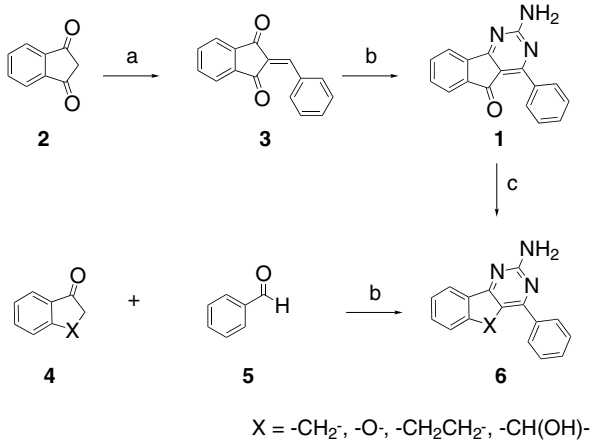


Compound	R	A_{2A} K_i (nM)	A_1/A_{2A}
1	–(C=O)–	1.7	1.4
6a	–(CHOH)–	168.3	
6b	$–CH_2–$	11.2	1.2
8	–(NH)–	40.5	9.7
6c	–O–	9.0	2
6d	$–CH_2CH_2–$	172	<1

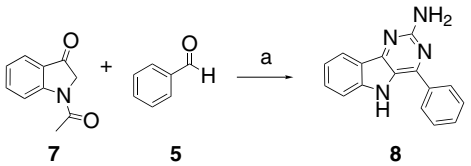
rings **A** and **B** of **6b** were modified. Compounds shown in Table 1 were prepared according to the procedures described in Schemes 1 and 2. An aldol condensation at room temperature between ketone derivatives **2** or **4** with benzaldehyde **5** in the presence of a catalytic amount of sodium hydroxide produced the benzylidene adduct, which was not isolated.

This adduct was heated to reflux in ethanol with a solution of salt free guanidine hydrochloride under basic condition to produce **1** and **6**. Sodium borohydride reduction of **1** produced compound **6a** in quantitative yield. Compound **7**, prepared as described in the literature,[9] was converted to compound **8** under the reaction conditions shown in Scheme 2.

Some of the starting indanones and derivatives were purchased from commercial sources and used in these reactions. Those that were not commercially available were prepared as shown in Schemes 3 and 4. Using the Doebner modification of the Knoevenagel condensation between substituted aldehydes **9** and malonic acid in pyridine in presence of piperidine afforded cinnamic acid derivatives **10**. After catalytic hydrogenation with 10% palladium on carbon, the carboxylic acids were then converted to the acyl chlorides. Cyclization of the acyl chlorides using aluminum trichloride provided the required indanones **11**.



Scheme 1. Reagents and conditions: (a) benzaldehyde, NaOH, EtOH; (b) guanidine, HCl, NaOH, EtOH; (c) $NaBH_4$, MeOH.



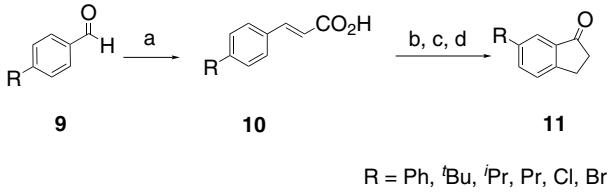
Scheme 2. Reagents and conditions: (a) guanidine, HCl, NaOH, EtOH.

Indanone derivative **14** was prepared from 6-bromo-1-indanone **12** using Scheme 4. Sodium borohydride reduction of **12** in methanol followed by protection of the resulting alcohol as silyl ether, and a standard palladium-catalyzed amination gave **13** in 78% yield.

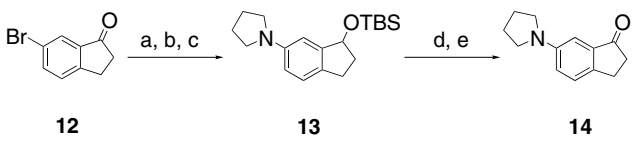
Compound **13** was deprotected and then treated under Swern oxidation conditions to give **14**. This ketone was then condensed with various aldehydes following the method in Scheme 1 to provide compounds presented in Table 3. All compounds gave satisfactory analytical results.[10]

The results of A_{2A} adenosine receptor binding assay[11] are expressed as inhibition constants (K_i nM). The A_1/A_{2A} describes their selectivity over A_1 adenosine receptor. Results in Table 1 show that the modification of the indenylene ring does not result in improvement of selectivity over the A_1 adenosine receptor. No significant change in affinity for A_{2A} adenosine receptor was observed when ketone **1** was converted to either methylene **6b** or ether derivative **6c**. Reduction of ketone **1** to compound **6a** or the ring expanded derivative **6d** produced a significant drop in affinity for the A_{2A} adenosine receptor where as amino derivative **8** showed a moderate decrease in affinity.

Initial SAR had established that substitution at the 8-position of these derivatives was optimal for A_{2A} affinity



Scheme 3. Reagents and conditions: (a) $HO_2CCH_2CO_2H$, piperidine, pyridine; (b) H_2, 10% Pd/C, MeOH; (c) $(COCl)_2$, CH_2Cl_2; (d) $AlCl_3$, CH_2Cl_2.



Scheme 4. Reagents and conditions: (a) $NaBH_4$, MeOH; (b) TBSCl, imidazole, DMF; (c) pyrrolidine, $Pd(OAc)_2$, $P(^tBu)_3$, NaO^tBu, toluene; (d) TBAF, THF; (e) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2.

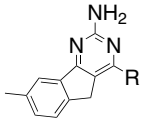
and moderate selectivity. With this knowledge, we directed our efforts around the 8-methyl derivative.

The SAR of the modifications of ring **A** is summarized in Table 2. These results showed that the replacement of phenyl with furan or substituted furans is well tolerated by the A_{2A} adenosine receptor. There is a moderate to significant improvement in selectivity for these derivatives. Among these, the 2-furanmethanol derivative, compound **19** was identified to be the most potent A_{2A} adenosine receptor antagonist with almost 100-fold selectivity over the A_1 receptor. The 2- or 4-pyridyl derivatives (**20** and **21**) exhibited a significant drop in A_{2A} receptor affinity. These results suggested that the furan was a favorable substitute for the phenyl. We focused on the 5-bromo-2-furnyl derivative **18** for further SAR since A_{2A} receptor affinities were similar for all furan derivatives.

The A_{2A} adenosine receptor affinities for derivatives of the modified ring **B** are presented in Table 3. These results showed that the introduction of substituents at the 8-position is well tolerated by the A_{2A} adenosine receptor and can be substituted with a variety of susbtituents. There is no significant increase in selectivity over A_1 receptor for these derivatives when compared with compound **18**. Compound **26** was found to have higher affinity for A_{2A} adenosine receptor and slightly improved selectivity. The selectivity against A_{2B} and A_3 adenosine receptors was not determined. This current class of compounds does not contain purine as a template, which makes them structurally different than known class[14] of A_{2A} adenosine receptor antagonists in the literature namely SCH-58261 and ZM-241385.

In summary, 4-aryl-5*H*-indeno[1,2-*d*]pyrimidin-2-ylamine derivatives were identified as a novel class of A_{2A} receptor antagonists. Compared to our initial nonselective lead **1**, several compounds in this series with moderate to high selectivity were identified. In particular, compounds **19** and **26** show very high affinity (K_i = 2.6, 0.8 nM, respectively) with approximately 100-fold selectivity over A_1 receptor.

Table 2. Optimization of substituents at position 4 (ring **A**)



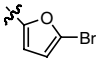
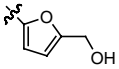
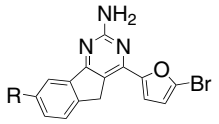
Compound	R	A_{2A} K_i (nM)	A_1/A_{2A}
15		11	9
16		6.7	29.4
17		7.1	25.7
18		4.2	48.8
19		2.6	94.1
20		154.2	5.5
21		56.9	9.0

Table 3. Optimization of substituents at position 8 (ring **B**)



Compound	R	A_{2A} K_i (nM)	A_1/A_{2A}
22	$-C_6H_5$	10.9	68
23	$-C(CH_3)_3$	8.1	26
24		3.9	32
25	–Cl	1.0	70
26	$-CH(CH_3)_2$	0.8	103
27	$-CH_3$	4.2	49
28	$-OCH_3$	1.6	21
29	$-CH_2CH_3$	2.6	42

Acknowledgements

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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. (a) Svenningsson, P.; Le Moine, C.; Fisone, G.; Fredholm, B. B. *Prog. Neurobiol.* **1999**, *59*, 355; (b) Schiffmann, S. N.; Libert, F.; Vassart, G.; Dumont, J. E.; Vanderhaeghen, J. J. *Brain Res.* **1990**, *519*, 333.
3. (a) Ochi, M.; Koga, K.; Kurokawa, M.; Kase, H.; Nakamura, J.; Kuwana, Y. *Neuroscience* **2000**, *100*, 53; (b) Mori, A.; Shindou, T.; Ichimura, M.; Nonka, H.; Kase, H. *J. Neurosci.* **1996**, *16*, 605.
4. Kuwana, Y.; Shiozaki, S.; Kanda, T.; Kurokawa, M.; Koga, K.; Ochi, M.; Ikeda, K.; Kase, H.; Jackson, M. J.; Smith, L. A.; Pearce, R. K. B.; Jenner, P. *Adv. Neurol.* **1999**, *80*, 121.
5. (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, in Adenosine Receptors and Parkinson's Disease*; Kase, H., Richardson, P. J., Jenner, P., Eds.; Academic, 1999; 193–210.
6. Aoyama, S.; Kase, H.; Borreli, E. *J. Neurosci.* **2000**, *20*, 5848.
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.

9. Sugasawa, T.; Adachi, M.; Sasakura, K.; Kitagawa, A. *J. Org. Chem.* **1979**, *44*, 578.
10. Compound **19**: ^{1}H NMR (DMSO-d_6, 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). Compound **26**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.90 (s, 1H), 7.55 (d, 1H), 7.39 (d, 1H), 7.19 (d, 1H), 6.52 (d, 1H), 5.25 (s, 2H), 4.02 (s, 2H), 3.04 (m, 1H), 1.32 (d, 6H).
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 before.[12] 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. Filteres 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. Nonspecific 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.[13]
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. J. *Arch. Pharmacol.* **1998**, *357*, 1.
13. Cheng, Y.; Prusoff, W. H. *Biochem. Pharmacol.* **1973**, *22*, 3099.
14. (a) Zocchi, C.; Ongini, E.; Conti, A.; Monopoli, A.; Negretti, A.; Baraldi, P. G.; Dionisotti, S. *J. Pharmacol. Exp. Ther.* **1996**, *276*, 398; (b) Jones, G.; James, R.; Hargreaves, R. B. U.S. Patent 5,380,714, 1995.