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Bioorganic & Medicinal Chemistry Letters 18 (2008) 1778–1783
Bioorganic & Medicinal Chemistry Letters

# Synthesis of *N*-pyrimidinyl-2-phenoxyacetamides as adenosine $A_{2A}$ receptor antagonists

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Received 13 December 2007; revised 12 February 2008; accepted 13 February 2008
Available online 16 February 2008

**Abstract**—A series of *N*-pyrimidinyl-2-phenoxyacetamide adenosine $A_{2A}$ antagonists is described. SAR studies led to compound **14** with excellent potency ($K_i$ = 0.4 nM), selectivity ($A_1/A_{2A}$ > 100), and efficacy (MED 10 mg/kg po) in the rat haloperidol-induced catalepsy model for Parkinson's disease.


Adenosine is an important modulator of physiological functions. Four adenosine receptors ($A_1$, $A_{2A}$, $A_{2B}$, $A_3$) have been identified, all of which belong to the family of seven trans-membrane G-protein coupled receptors (GPCRs).[1] In the central nervous system the $A_{2A}$ receptor is highly expressed in the stratium, where it is co-localized with dopamine $D_2$ receptors on striatopallidal output neurons.[2] Several pharmacological studies suggest that the $A_{2A}$ receptor is involved in motor activity. In particular, adenosine $A_{2A}$ receptor antagonists have been demonstrated to restore the deficits caused by degeneration of the striatonigral dopamine system, and therefore offer a possible treatment for Parkinson's disease.[3] Extensive work has been done to achieve potent and selective adenosine $A_{2A}$ receptor antagonists in the past decade.[4] Examples (Fig. 1) include non-xanthine-based SCH 58261[5] and ZM 241385,[6] and xanthine-based KW-6002 (istradefylline), which was shown to be effective in Parkinson's disease animal models. More recently, KW-6002 showed efficacy in the alleviation of Parkinson's disease symptoms in human clinical trials.[7]

Efforts in our laboratory to develop non-xanthine-based $A_{2A}$ antagonists led us to a series of pyrimidine-based potent $A_{2A}$ antagonists.[8] However, the initial compounds suffered from a lack of selectivity over the adenosine $A_1$ receptor[9,10] as exemplified by compound **1** ($A_{2A}$ $K_i$ = 0.6 nM, $A_1$ $K_i$ = 9.2 nM, 17-fold selectivity, Fig. 2). Furthermore, we wanted to replace the furan moiety in the molecule in view of the potential metabolic liabilities.[11] SAR studies showed that the right hand acetamide can be changed with a little loss of potency. When a fluorobenzyl group was appended to the acetyl group, modest selectivity was observed (compound **2**, $A_{2A}$ $K_i$ = 16 nM, $A_1$ $K_i$ = 410 nM, 26-fold selectivity). Surprisingly, changing the benzylic carbon to an oxygen resulted in a large gain in selectivity (compound **3**, $A_{2A}$ $K_i$ = 7.5 nM, $A_1$ $K_i$ = 650 nM, 87-fold selectivity).

In order to explore the influence of the substituents on the phenol ring, we prepared a focused library (Scheme 1).

The results (Table 1) showed that substitutions are well tolerated, with potency ranging from 7 to 36 nM.

*Keywords*: Parkinson's disease; $A_{2A}$ adenosine receptor antagonists.
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doi:10.1016/j.bmcl.2008.02.032

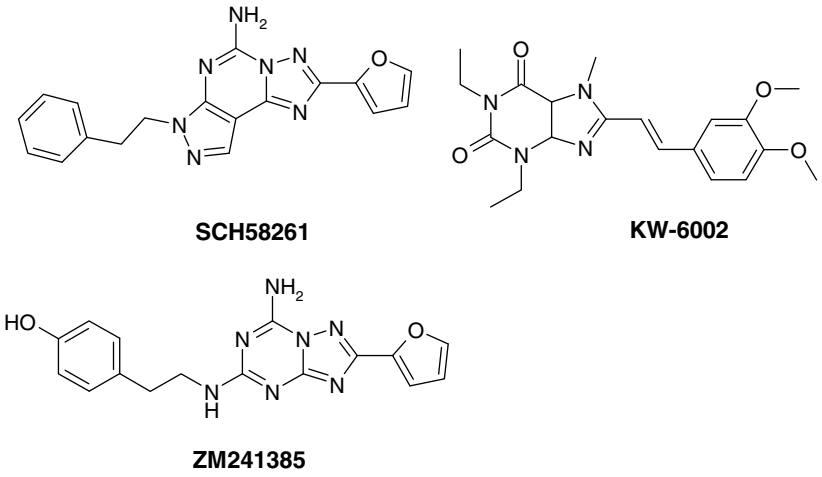



**Figure 1.** Representative $A_{2A}$ antagonists.

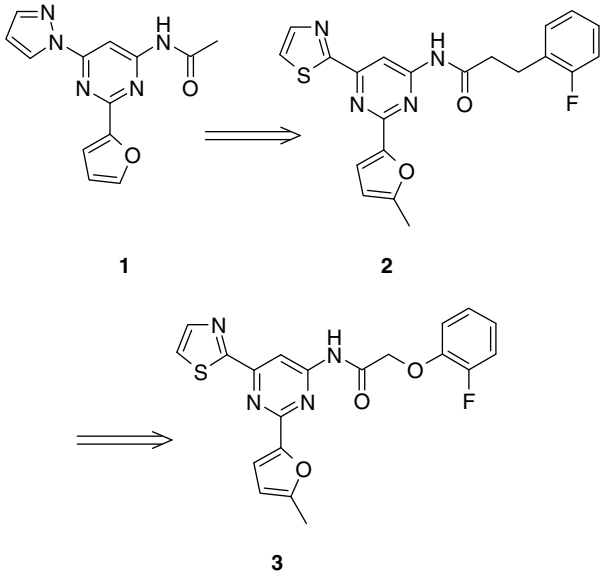
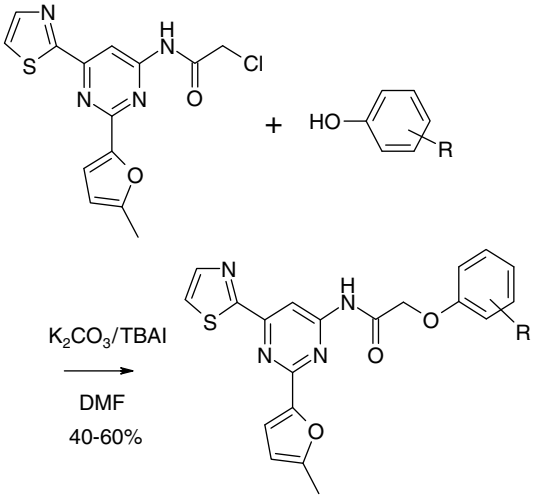
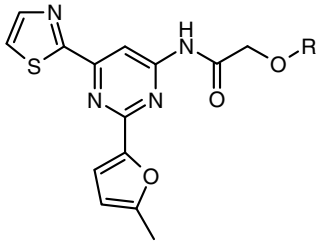


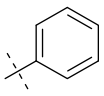
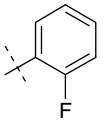
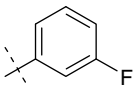
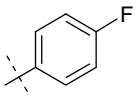
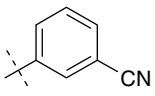
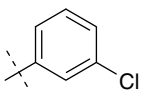
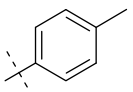

**Figure 2.**




**Scheme 1.** Focused phenoxy library synthesis.

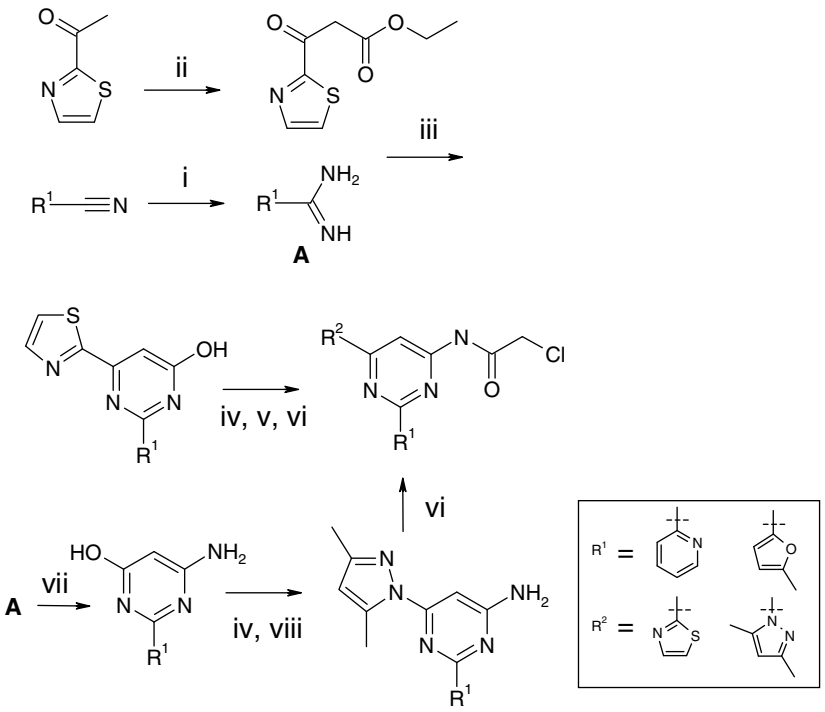
**Table 1.** Focused phenoxy library binding affinities



| Compound | R | $K_i$ (nM) $hA_{2A}$[a] | $K_i$ (nM) $hA_1$[b] |
|---|---|---|---|
| **4** |  | 7.4 | 1100 |
| **3** |  | 7.5 | 650 |
| **5** |  | 11 | 2200 |
| **6** |  | >10,000 | 1300 |
| **7** |  | 6.8 | 4300 |
| **8** |  | 14 | 1500 |
| **9** |  | 36 | 2100 |

[a] Displacement of specific [$^3$H]-ZM241385 binding at human $A_{2A}$ expressed in HEK293.

[b] Displacement of specific [$^3$H]-DPCPX binding at human $A_1$ receptors expressed in HEK293 cells. Data are expressed as geometric means of at least three runs with a standard deviation less than or equal to 20%.




**Scheme 2.** Reagents and conditions: (i) NaOMe, (1.1 equiv), $NH_4Cl$, MeOH, rt 6–12 h, 96%; (ii) diethyl carbonate (5 equiv), NaH, 80 °C, 12 h, 56%; (iii) KO*t*-Bu, (1.5 equiv), *t*-BuOH, 90 °C, 12 h, 50%; (iv) $POCl_3$, DIPEA, 90 °C, 3–12 h, 66%; (v) $NH_4OH$, MeOH, 80 °C, 12 h, 53%; (vi) chloroacetyl chloride, pyridine, DCM, rt, 2–12 h, 60–85%; (vii) ethyl cyanoacetate, NaOMe, EtOH, 67%; (viii) $N_2H_4$, EtOH, 90 °C; pentane-2,4-dione, 0–90 °C, 2 h, 72%.

However, the selectivity was best with substituents at the meta position (compounds **5**, **7**).

Next we chose to explore the variations of the two heterocycles at the pyrimidine C-2 and C-6 positions (Scheme 2).

We chose not to use an unsubstituted furan because of its potential metabolic liabilities. The 5-methyl-2-furyl group was used in this exercise since the methyl substitution on the furan substantially decreases the likelihood of oxidative metabolism of the furan ring.[11] The results (Table 2) showed that all the heterocyclic combinations led to potent antagonists ($K_i$ 1.8–12 nM); however, the methylfuran/dimethylpyrazole combination provided the best selectivity (compound **10**, $K_i$ 3.7 nM, 2600-fold selectivity).

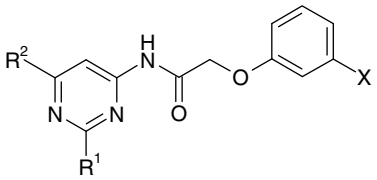
Compound **10**, although potent and selective, had poor solubility (0.08 mg/mL, pH 5.0), as did most of its close analogs. In order to improve solubility, we explored the option of appending a basic amine to the phenol ring (Scheme 3).

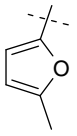
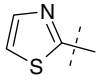
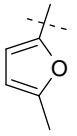
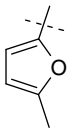
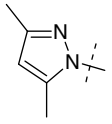
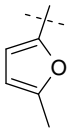
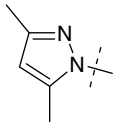
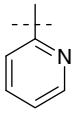
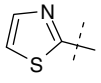
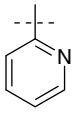
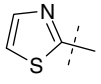
We were pleased to find that this exercise led to a group of antagonists with retained excellent potency and selectivity (Table 3).

For the mono meta-substituted benzyl amino compounds, it was clear that small amino groups were favorable for $A_{2A}$ activity. The binding affinity ranged from 0.3 nM (compounds **15**, **16**) to 0.7 nM (compound **18**), and selectivity was 100- to 230-fold. Larger amino groups (e.g., compound **17**) gave slightly decreased potency, but selectivity improved to 500-fold. A variety of other modifications were tolerated, including addition of a second meta-substituent (compounds **19**, **20**, **21**), extension of the methylene spacer (compounds **22**, **23**), and migration of the aminoalkyl group to the ortho position, with or without additional substituents in the para position (compounds **24**, **25**, **26**, **28**). For the *ortho*-aminoalkyl series, addition of a second ortho substituent did result in a slight decrease in potency (compound **27**). With the aminoalkyl group in the para position, both the potency and selectivity were excellent with or without additional substitutions (compounds **29**–**31**). Aromatic heterocycles were also tolerated as phenyl replacements. Pyrimidine **32** was potent but had somewhat poorer selectivity than the better phenyl compounds. Pyridine **33**, however, showed excellent potency and selectivity.

Despite the generally high potency and selectivity for this class of compounds, a number of deficiencies were revealed upon screening through secondary assays. For example, the para-substituted aminoalkyl compounds (**29**, **30**) were found to be cytotoxic in cellular assays, while the ortho-substituted compounds and the heterocycle-substituted compounds displayed CYP inhibition (e.g., compound **26**, CYP3A4 $IC_{50}$ = 1600 nM; compound **33**, CYP3A4 $IC_{50}$ = 1100 nM, CYP2D6 $IC_{50}$ = 50 nM)). The ortho-substituted aminoalkyl compounds showed significant hERG inhibition (compound

**Table 2.** Results of C-2 and C-6 heterocycle survey



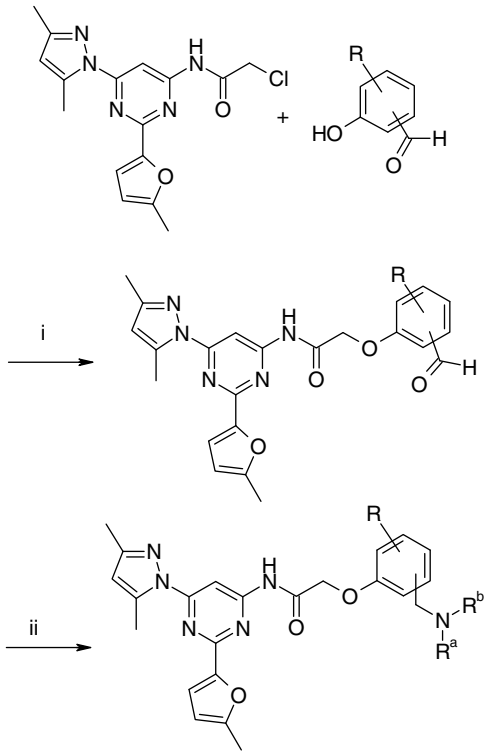
| Compound | $R^1$ | $R^2$ | X | $hA_{2A}$ $K_i$ (nM) | $hA_1$ $K_i$ (nM) |
|---|---|---|---|---|---|
| **5** |  |  | F | 12 | 2200 |
| **7** |  |  | CN | 6.8 | 4300 |
| **10** |  |  | F | 3.7 | 9700 |
| **11** |  |  | CN | >10,000 | 25,000 |
| **12** |  |  | F | 3.6 | 180 |
| **13** |  |  | CN | 1.8 | 87 |

See Table 1 footnotes.

**28**, hERG dofetolide competition binding assay $K_i$ = 180 nM).[12] Ultimately, compound **14** demonstrated the best overall profile for compounds in this series (hERG patch-clamp $IC_{50}$ = 1200 nM, CYP3A4 and CYP2D6 $IC_{50}$ > 6000 nM).[13]

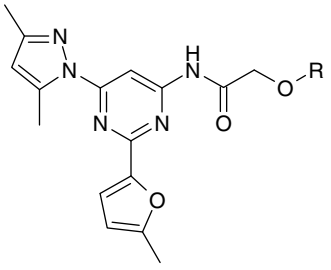
Compound **14** was chosen for further evaluation. Compound **14** demonstrated improved solubility (0.21 mg/mL, pH 5) compared with non-basic analogs (e.g., compound **10**), and was active at the rat $A_{2A}$ receptor ($K_i$ = 9.4 nM). When evaluated in a rat pharmacokinetics study, it showed $F\%$ = 19%, $V_d$ = 20 L/kg and a half life of 0.8 h. Although plasma clearance was rapid (330 mL/min kg), levels in the brain were high, even after 4 h (360 ng/g). In the rat haloperidol-induced catalepsy model for Parkinson's disease, compound **14**, dosed orally, showed significant inhibition of catalepsy with a minimum effective dose of 10 mg/kg.

In summary, we prepared a series of potent and selective adenosine $A_{2A}$ antagonists based on the *N*-pyrimidinyl-2-phenoxyacetamide scaffold. The strategy of introducing a solubilizing group onto the phenoxy moiety succeeded in producing compounds with high potency and selectivity, in addition to improved solubility. The leading compound **14** was evaluated in vivo and exhibited efficacy in the rat haloperidol-induced catalepsy model with a minimum effective dose of 10 mg/kg.



**Scheme 3.** Reagents: (i) DMF, $K_2CO_3$, TBAI, 40–60%; (ii) EtOH, amine, $BH_3$/pyridine, 60–90%.

**Table 3.** Binding affinities for aminoalkyl-substituted compounds



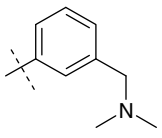
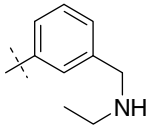
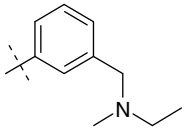
| Compound | R | $hA_{2A}$ $K_i$ (nM) | $hA_1$ $K_i$ (nM) |
|---|---|---|---|
| **14** |  | 0.4 | 60 |
| **15** |  | 0.3 | 68 |
| **16** |  | 0.3 | 68 |

**Table 3** (*continued*)

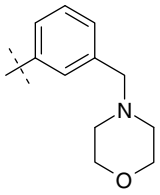
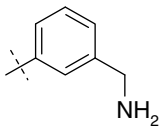
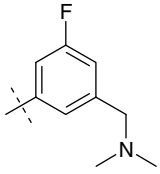
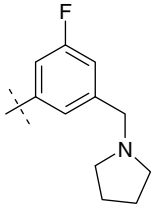
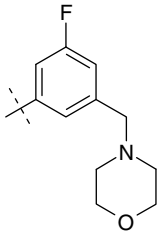
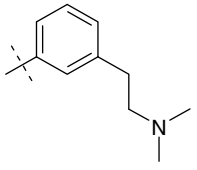
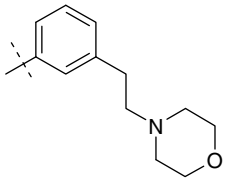
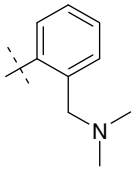
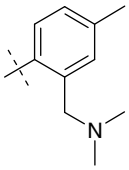
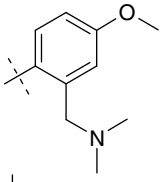
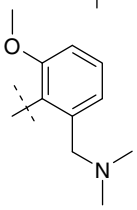
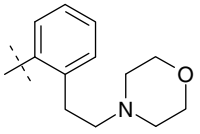
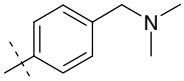
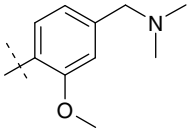
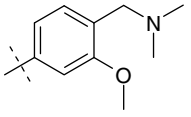
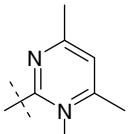
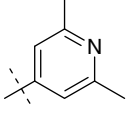
| Compound | R | $hA_{2A}$ $K_i$ (nM) | $hA_1$ $K_i$ (nM) |
|---|---|---|---|
| **17** |  | 1.2 | 600 |
| **18** |  | 0.7 | 73 |
| **19** |  | 0.5 | 140 |
| **20** |  | 0.5 | 120 |
| **21** |  | 1.4 | 480 |
| **22** |  | 0.5 | 78 |
| **23** |  | 2.3 | 540 |
| **24** |  | 1.0 | 270 |

**Table 3** (*continued*)

| Compound | R | $hA_{2A}$ $K_i$ (nM) | $hA_1$ $K_i$ (nM) |
|---|---|---|---|
| **25** |  | 1.0 | 270 |
| **26** |  | 0.9 | 200 |
| **27** |  | 5.7 | 1400 |
| **28** |  | 1.2 | 1200 |
| **29** |  | 0.3 | 120 |
| **30** |  | 0.2 | 100 |
| **31** |  | 0.3 | 150 |
| **32** |  | 3.7 | 95 |
| **33** |  | 0.7 | 740 |

See Table 1 footnotes.

## Acknowledgments

We are indebted to Shawn Ayube, Chris DeVore, Paddi Ekhlassi, and John Harman for analytical support.

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