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2,6-Diaryl-4-acylaminopyrimidines as potent and selective adenosine A_{2A} antagonists with improved solubility and metabolic stability

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ABSTRACT

In this report, the strategy and outcome of expanding SAR exploration to improve solubility and metabolic stability are discussed. Compound **35** exhibited excellent potency, selectivity over A_1 and improved solubility of >4 mg/mL at pH 8.0. In addition, compound **35** had good metabolic stability with a scaled intrinsic clearance of 3 mL/min/kg (HLM) and demonstrated efficacy in the haloperidol induced catalepsy model.

Adenosine is considered to be one of the human body's most important neuromodulators, in both the central and peripheral nervous systems.[1] The effects of this purine nucleoside are modulated via four receptor subtypes: A_1, A_{2A}, A_{2B} and A_3.[2] These four subtypes belong to the family of seven trans-membrane G-protein coupled receptors (GPCRs).[3] Adenosine A_{2A} receptors are highly distributed in the central nervous system and are found in abundance in the basal ganglia, a region of the brain associated with motor function.[4] A number of A_{2A} receptor antagonists have been shown to improve motor disabilities in animal models of Parkinson's disease.[5] Parkinson's disease is a debilitating motor disorder arising from the progressive degeneration of dopaminergic neurons in the nigrostriatal pathway.[6] Unfortunately, current dopamine replacement therapies for Parkinson's disease suffer from poor long term control and undesirable side effects, namely dyskinesia (involuntary movements). A number of companies have progressed A_{2A} antagonists into clinical trials including KW-6002 (istradefylline) from Kyowa Hakko Kogyo, which showed efficacy in alleviating symptoms of the disease in Phase II clinical trials.[7] In addition, Schering-Plough has progressed SCH 420814 into Phase II clinical trials (Fig. 1).[8]

Previously, we reported on a series of non-xanthine based A_{2A} antagonists which incorporated a pyrimidine core. A number of compounds from our initial exploration, including compound **1**, showed good in vivo efficacy in rat models of Parkinson's disease.[8] However, as this series of compounds contained an unsubstituted furan ring, we sought to replace this heterocycle (Fig. 2).[9] It has been well documented that unsubstituted furan rings can be metabolized to form reactive intermediates, which in turn can form protein adducts leading to liver toxicity.[10] A number of heterocycles were surveyed in the context of the right hand side methyl piperazine. Although compound **2** was less active than the starting lead **1**, replacement of the furan with a dimethyl pyrazole was tolerated and significantly decreased binding against the A_1 receptor. In addition, we found that by removing the bulky right hand side methyl piperazine (**3**), the potency against the A_{2A} receptor was increased. We hoped to further benefit from these findings by utilizing the dimethyl pyrazole as a furan replacement and eliminating the need for a bulky right hand side substituent. In an effort to further increase potency, an SAR exploration was undertaken to replace the left hand side heterocycle with previously unexplored substituted phenyl groups.

Compounds **8**–**35** were prepared from intermediate **4**[9] according to the general synthesis outlined in Scheme 1. Compounds **8**–**22** were prepared in one step by Suzuki coupling with suitable

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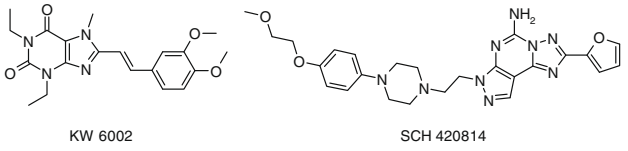
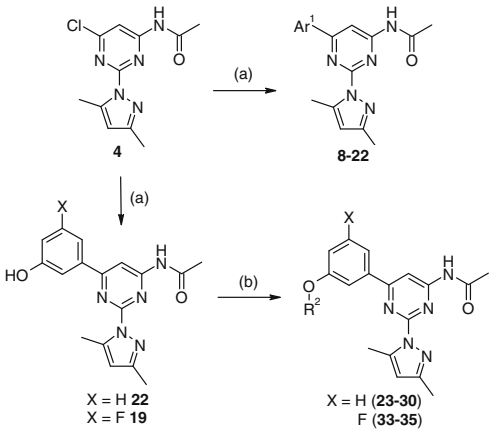


Figure 1. Examples of A_{2A} antagonists in clinical development.

commercially available boronic acids. For compounds **23**–**30** and **33**–**35**, intermediate **4** was first reacted with either 3-hydroxyphenylboronic acid (**23**–**30**) or 3-fluoro-5-hydroxyphenylboronic acid (**33**–**35**) by Suzuki coupling to yield intermediates **22** and **19**, respectively. The resulting intermediates were reacted with alcohols via a Mitsunobu reaction to yield final compounds. Likewise, compounds **31**–**32** were prepared by coupling intermediate **4** with 3-(hydroxymethyl)phenylboronic acid, followed by Mitsunobu reaction with the appropriate alcohol in a similar fashion to compounds 23–30 and 33–35.

Replacement of the left hand side heterocycle with a simple phenyl group (**8**) showed modest A_{2A} activity but poor selectivity over the A_1 receptor (K_i of 87 nM and A_1/A_{2A} of 7). However, encouraged that some potency remained, we further explored various substituents. By the addition of a methoxy group (**9–11**), potency and selectivity were greatly increased. In particular, substitution in the *ortho* (**9**) and *meta* (**10**) positions gave very potent compounds with K_is of 2 and 1 nM, respectively, and selectivity of ~70-fold over A_1. A further boost in potency came upon the addition of another methoxy substituent, as in the case of 3,5-dimethoxy phenyl (**18**). Compound **18** not only showed an increase in potency (K_i of 0.2 nM) but the A_1 selectivity was 111-fold. In addition to having very good potency and selectivity, compound **18** was potent in an A_{2A} functional assay (cAMP IC_{50} of 29 nM).[11] Due to the promising in vitro profile, compound **18** was selected for in vivo efficacy evaluation. The haloperidol induced catalepsy (HIC) model in rat was used as the primary assay to screen compounds for efficacy.[12] Compound **18** showed good efficacy in the HIC model with a minimum efficacious dose of 1 mg/kg p.o., however, it was determined to have poor aqueous solubility (<0.1 mg/mL at pH 8.0).[13] In addition, upon further profiling, compound **18** showed time dependant inhibition of *CYP*3A4. Compound **21** also showed promising potency and selectivity with a K_i of 3 nM and selectivity of 164-fold over A_1. Unfortunately, compound **21** also exhibited poor aqueous solubility of <0.1 mg/mL at pH 8.0. From this initial survey, we determined that *meta* substitution off of the phenyl ring was preferred. Also, the incorporation of a hydrogen bond acceptor, as in the case of the 3-methoxyphenyl and 3,5-dimethoxyphenyl, increased A_{2A} potency. However, poor solubility of the most promising compounds, and the inhibition of a major *CYP* enzyme for compound **18**, prevented further development. As such, an SAR exploration was initiated to improve solubility while maintaining potency at A_{2A}. The idea was to introduce a basic center off of the phenyl group, while maintaining the preferred *meta* substitution pattern and a hydrogen bond acceptor at that site, in the form of an oxygen atom (see Table 2).



Scheme 1. Reagents and conditions: (a) $Ar^1B(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, 1,4-dioxane, 100 °C, 12 h, 60–90%; (b) R^2OH, DEAD, PPh_3, THF, rt, 12 h, 70–85%.

By replacing the methoxy group with an *N*-dimethylamino ethoxy (**23**), we obtained a potent and selective compound. Solubility testing at pH 8.0 revealed that incorporation of an amine did in fact increase the solubility significantly to >4 mg/mL. To reduce the number of rotatable bonds in an attempt to improve drug like properties,[14] cyclized analogues of compound **23** were made, exploring ring size and substitution off of the basic nitrogen. The methyl pyrrolidine compound **24**, showed an increase in A_{2A} potency and selectivity over A_1 as compared to the straight chain analogue **23**. Extending the substitution off of the pyrrolidine to ethyl (**25**) and isopropyl (**26**) resulted in similar potency as the methyl version (**24**) but a slight loss of selectivity from 191-fold over A_1 to 167-fold was observed. As the six membered piperidine compounds did not significantly increase potency or selectivity (**27**), the single enantiomers of compound **24** were made. The S enantiomer (**30**) showed slightly better potency than the R enantiomer (**29**) with a K_i of 2 nM versus 4 nM. A more significant improvement was seen in the selectivity over A_1 as the S isomer was 320-fold selective, double the selectivity of the R isomer. Further in vitro profiling of compound **24** revealed similar human functional activity to compound **18** (cAMP IC_{50} of 42 nM). Unfortunately, this compound showed poor metabolic stability in human liver microsomes with a scaled intrinsic clearance value of 54 mL/min/kg.[15] As this series proved to have good potency and selectivity while greatly improving the solubility (compound **24** >4 mg/mL at pH 8.0), we turned to improving the poor metabolic stability. From our initial survey, we determined that fluorine atoms were well tolerated off of the phenyl ring (**19–21**). The addition of an electron withdrawing group such as a fluorine atom may help to stabilize the electronic rich phenyl group, thereby improving the metabolic stability (see Table 3).

The 3-fluoro-5-(N-methyl-3-pyrrolidol) compound **33**, showed good potency with a K_i of 1 nM and selectivity of 135-fold over A_1. The addition of a 3-fluorine atom did not adversely affect the potency or the selectivity when compared to compound **24**. The

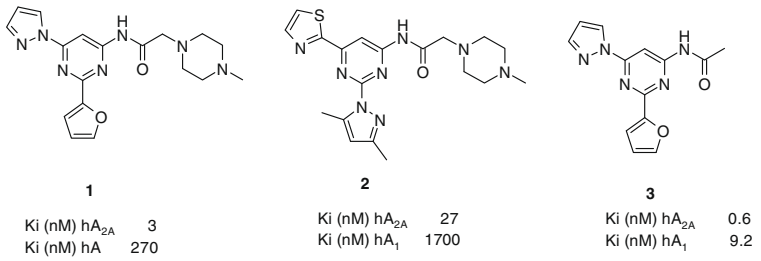


Figure 2. Potent A_{2A} antagonists