Adenosine $A_{2A}$ Receptor Antagonists and Parkinson’s Disease

Brian C. Shook* and Paul F. Jackson

Johnson & Johnson Pharmaceutical Research and Development, L.L.C., Welsh and McKean Roads, P.O. Box 776, Spring House, Pennsylvania 19477, United States

**ABSTRACT:** This Review summarizes and updates the work on adenosine $A_{2A}$ receptor antagonists for Parkinson’s disease from 2006 to the present. There have been numerous publications, patent applications, and press releases within this time frame that highlight new medicinal chemistry approaches to this attractive and promising target to treat Parkinson’s disease. The Review is broken down by scaffold type and will discuss the efforts to optimize particular scaffolds for activity, pharmacokinetics, and other drug discovery parameters. The majority of approaches focus on preparing selective $A_{2A}$ antagonists, but a few approaches to dual $A_{2A}/A_{1}$ antagonists will also be highlighted. The in vivo profiles of compounds will be highlighted and discussed to compare activities across different chemical series. A clinical report and update will be given on compounds that have entered clinical trials.

**KEYWORDS:** Adenosine, $A_{2A}$ receptor antagonist, $A_{1}$ receptor antagonist, Parkinson’s disease, catalepsy, 6-OHDA, MPTP

Parkinson’s disease (PD) is a chronic, progressive neurological disease that affects $\sim 1\%$ of the population over the age of 65.\(^1\) It is characterized by progressive impairment in motor function that is often accompanied by disturbances in mood and cognitive function. The majority of motor impairments of PD are caused by a gradual loss of dopamine (DA) producing neurons in the ventral midbrain and concomitant loss of DA input to forebrain (striatal) motor structures.\(^2,3\) The loss of DA input to the neostriatum leads to dysregulation of striatal function and the classic motor symptoms of PD, such as resting tremor, muscular rigidity, and bradykinesia.

The majority of treatments aim to restore dopamine signaling and thereby reduce the severity of the motor symptoms. Dopamine replacement therapy using L-DOPA, the precursor to dopamine, remains the gold-standard treatment for PD. Other approaches include inhibition of DA turnover using monoamine oxidase type B (MAO-B) inhibitors,\(^4\) catechol O-methyl-transferase (COMT) inhibitors,\(^5\) and inhibition of dopamine reuptake\(^6\) or direct agonists of postsynaptic dopamine receptors. Although the dopamine targeted therapies work well to address the PD related motor disturbances, they all produce undesirable side effects (dyskinesias, hallucinations, on–off effects) that become more severe and problematic with continued treatment. Also, the aforementioned therapies typically show reduced efficacy as motor functions deteriorate and the disease progresses. Moreover, these treatments do not alter disease progression and do not address the mood, postural instability, or cognitive disturbances that frequently accompany PD.

The dopamine replacement agents have significant limitations which influenced researchers to find nondopamine based treatments for PD. One nondopaminergic approach that has received considerable attention is modulation of adenosine receptors which is the topic highlighted in this Review.\(^8\) Adenosine is a neuromodulator that coordinates responses to dopamine and other neurotransmitters in areas of the brain that are responsible for motor function, mood, and learning and memory.\(^9\) Adenosine comprises four distinct receptor subtypes designated $A_{1}$, $A_{2A}$, $A_{2B}$, and $A_{3}$ belonging to the G protein-coupled receptor superfamily.\(^10\) Adenosine $A_{1}$ and $A_{3}$ receptors are coupled to inhibitory G proteins, while $A_{2A}$ and $A_{2B}$ receptors are coupled to stimulatory G proteins. Autoradiography studies in rodents showed that the greatest densities of $A_{2A}$ receptors are found in the striatum\(^11\) which closely matches the distribution in humans based on PET imaging.\(^12\)

As described above, loss of dopamine input into the neostriatum is a hallmark of PD and causes many of the cardinal motor symptoms of this disorder. In the striatum adenosine $A_{2A}$ receptors colocalize and physically associate with dopamine $D_2$ receptors.\(^3,3\) $A_{2A}$ and $D_2$ receptors have opposing effects on adenylate cyclase and cAMP production in cells, such that activation of $A_{2A}$ receptors inhibits dopamine $D_2$ receptor signaling. Conversely, $A_{2A}$ receptor antagonists enhance $D_2$ dependent signaling as shown by induction of immediate early gene c-fos expression in the striatopallidal pathway\(^13\) and facilitate other $D_2$ mediated responses. Of importance to PD, pharmacological blockade of $A_{2A}$ receptors has shown dramatic beneficial effects in preclinical animal models of PD, showing potentiation of dopamine-mediated responses in dopamine depleted (6-OHDA-treated)\(^14\) animals and dramatic relief of parkinsonian symptoms in MPTP-treated\(^15\) nonhuman primates.\(^16\) $A_{2A}$ antagonists facilitate dopamine receptor signaling and thereby normalize motor function in animal models of dopamine dysregulation. As a result of these
findings, the adenosine A2A receptor has become a sought after target for treating PD. Blockade of A2A signaling by selective A2A receptor antagonists\(^1\) was shown to be beneficial for not only enhancing the therapeutic effects of L-DOPA but also reducing dyskinesia from long-term L-DOPA treatment.\(^1\)8

The adenosine A1 receptor is also expressed in the striatum; based on anatomical and in vivo microdialysis studies, A1 receptors appear to be localized presynaptically of dopamine axon terminals where they inhibit dopamine release.\(^1\)9 A1 receptor antagonists facilitate dopamine release in the striatum, and like A2A receptors potentiate dopamine mediated responses. Antagonism of both the A2A and A1 would be synergistic: inhibition of the A1 receptor will facilitate dopamine release, while inhibition of the A2A receptor will enhance postsynaptic responses to dopamine. Interestingly, the A1 receptor is also concentrated in neocortical and limbic system structures that are important for cognitive function. Pharmacological inhibition of A1 receptors enhances neurotransmitter release in the hippocampus\(^1\)0 and enhances performance in animal models of learning and memory.\(^1\)1 Antagonism of A1 receptors could present a potential liability, as it is known that some A1 antagonists have cardiovascular\(^1\)2 and diuretic\(^1\)3 liabilities.

The major unmet medical needs of PD are as follows: improved symptomatic treatment without inducing adverse effects (primarily dyskinesia) associated with long-term L-DOPA or dopamine agonist therapy; opportunity to slow disease progression by protecting midbrain dopamine and other neurons from degeneration; treatment of disease comorbidities, including cognitive dysfunction, anxiety, and depression. Based on published preclinical and human clinical data, the majority of approaches focus on selective antagonism of A2A receptors while a few approaches suggest that a dual A2A/A1 receptor antagonist may be better suited to address many of these unmet needs. There have been a number of excellent reviews on A2A receptor antagonists reported in the literature,\(^2\)4 but the following Review will highlight the work done on this target in the past five years. The \(K_i\) values represented in the figures refer to binding affinities unless noted otherwise. Updates on key compounds that have entered the clinic will also be highlighted.

![Xanthine based A2A antagonists](image1.png)

**Figure 1.** Xanthine based A2A antagonists.

![Pyrazolo[4,3-c]-1,2,4-triazolo[1,5-c]pyrimidines](image2.png)

**Figure 2.** Pyrazolo[4,3-c]-1,2,4-triazolo[1,5-c]pyrimidines.

### XANTHINE BASED A2A ANTAGONISTS

Adenosine A2A receptor antagonists have been traditionally categorized as xanthine based or nonxanthine based derivatives. Caffeine (1) and theophylline (2) are two of the oldest known adenosine antagonists, and both have weak affinity for A2A and A1 (Figure 1).\(^2\)5 Numerous efforts to identify xanthine based derivatives have been explored but will not be discussed in this Review.\(^2\)6 However, istradefylline (3), KW-6002, is a xanthine based, selective A2A antagonist that showed efficacy in numerous preclinical models of PD\(^2\)7 and was investigated in several clinical trials for PD.\(^2\)8 Istradefylline completed phase III clinical trials in 2009, but it was not approved by the FDA due to lack of efficacy.\(^2\)9 There are two active phase III studies using istradefylline (clinicaltrials.gov identifier: NCT00955526 and NCT00957203). More recent efforts have focused on nonxanthine based scaffolds to identify viable selective A2A and dual A2A/A1 receptor antagonists.

### TRICYCLIC A2A ANTAGONISTS

Schering-Plough identified a new series of nonxanthine based derivatives that led to SCH-58261 (4) as a potent A2A antagonist with moderate 35-fold selectivity over the A1 receptor (Figure 2).\(^3\)0 SCH-58261 showed efficacy in rodent models of PD after intraperitoneal (i.p.) administration, but it suffers from poor solubility and is not active when dosed orally. There have been numerous efforts to increase the selectivity and pharmacokinetic (PK) properties of this particular scaffold. A series of biaryl substituted pyrazolo[4,3-c]-1,2,4-triazolo[1,5-c]pyrimidines was also prepared.\(^3\)1 The methoxy biaryl compound 5 had very potent affinity for A2A and is significantly more selective (2124-fold) selective against the A1 receptor compared to 4. This compound showed 30 and 5% inhibition of rat catalepsy at 1 and 4 h, respectively, at 1 mg/kg, and exhibited very poor plasma exposure. Efforts to replace the methoxyaryl substituent with heterocycles such as pyridines and pyrazines resulted in compounds that retained potency and selectivity, but generally suffered from poor solubility and poor exposures in rat after oral dosing. Contracting the biaryl substituent into a quinoline,
More recently a variety of fused heterocyclic derivatives of the tricyclic scaffold were prepared that had comparable $A_{2A}$ binding affinities with respect to the aryl piperazines 7 and 8 but were generally much less selective against the $A_1$ receptor. The tetrahydroisoquinoline derivative 9 had excellent binding affinity and was 68-fold selective versus $A_1$ (Figure 4). The compound had moderate plasma exposure in rats and reversed catalepsy in rat by 50% and 58% at 1 and 4 h, respectively, after a 3 mg/kg dose, p.o. A related azaisoquinoline 10 had a >5-fold higher exposure in rat compared to 9 and reversed catalepsy in rat by 85% and 30% at 1 and 4 h, respectively. A variety of substituted isoindolines and benzazepines were also prepared.

Replacing the pyrazole ring, present in the previously described scaffolds, with an imidazole ring gave a series of 3H-1,2,4-triazolo[5,1-i]purin-5-amines (Figure 5). Compounds 11 and 12 contain the optimal aryl piperazine substituents present in the pyrazolopyrimidines 7 and 8. Both 11 and 12 have good affinities for $A_{2A}$ while maintaining good selectivity versus $A_1$ (88- and 669-fold, respectively), albeit considerably lower than the selectivities obtained from 7 and 8. Compound 12 (1 mg/kg, p.o.) showed 55% and 50% inhibition of catalepsy in rat at 1 and 4 h, respectively, but in general the compounds from this series were inferior to the corresponding compounds from the pyrazolopyrimidine scaffold. Efforts to replace the furan substituent with substituted aryls resulted in compounds having good $A_{2A}$ potency but were much less selective versus $A_1$ receptors.

A series of methylene amine substituted arylindenopyrimidines was reported as dual $A_{2A}/A_1$ receptor antagonists (Figure 6).
Compound 15 was the original lead compound that was potent in both A2A and A1 functional assays and had an ED50 of 5.0 mg/kg, p.o. in the haloperidol-induced catalepsy model in mice. Compound 15 suffered from poor solubility, and it was found to be Ames positive. A variety of heterocyclic furan replacements were prepared that generally maintained good in vitro potency but lost in vivo activity. Replacing the furan with phenyl gave 16 that had good in vitro potency and comparable in vivo activity (ED50 = 8.0 mg/kg, p.o.) reversing catalepsy in mice. Compound 16 was negative in the Ames screen, but it still suffered from poor solubility. A variety of amines were incorporated at the 9-position of the scaffold to increase solubility and resulted in the synthesis of 17 that had good in vitro potency and had an ED50 of 3.8 mg/kg, p.o. in the mouse catalepsy model. Moving the pyrrolidine to the 8-position gave compound 18 that was equipotent at A2A, more potent at A1, and had significantly increased potency in vivo (ED50 = 0.2 mg/kg, p.o.) in the mouse catalepsy model. Further characterization of 18 showed that it was active in rat catalepsy (ED50 = 0.5 mg/kg, p.o.), and had minimum effective doses of 1.0, 1.0, and 10 mg/kg for reserpine-induced akinesia model in mice, 6-OHDA lesion model in rats, and reversing motor disability in MPTP-treated marmosets, respectively. 38

Further evaluation revealed that metabolism of 18 resulted in the formation of reactive metabolites that were attributed to some adverse events seen in the 28-day GLP toxicology studies in nonhuman primates. 39 The development of 18 was discontinued based on these findings, and the focus was to identify a suitable backup compound devoid of the metabolic liabilities associated with compound 18.

A variety of ethylamine derivatives were prepared in a pyrazolo[4,3-e]-1,2,4-triazolo[4,3-c]pyrimidon-3-one series (Figure 8). 40 The ethylenedimethylamino analogue 22 has good binding affinity for A2A and is >269-fold selective versus A1 receptors. In general, analogues had good binding affinities but were not able to reverse haloperidol-induced catalepsy in rat at 10 mg/kg, p.o., and showed very low exposures in rat brain. A series of thiazolotriazolopyrimidines was developed with multiple compounds having sub-nanomolar binding affinities. 41 Compound 23 had potent A2A binding affinity and exhibited good selectivity against A1 receptors. Compound 23 also showed very potent functional (cAMP) activity (Ki = 0.1 nM) and was able to reverse both haloperidol-induced catalepsy and akinesia in mice after a 10 mg/kg dose, p.o.

**BICYCLIC A2A ANTAGONISTS**

Substituted 1,2,4-triazolo[1,5-c]pyrimidines are a bicyclic system related to preladenant without the fused pyrazole ring (Figure 9). 42 A variety of linkers were explored including O, S, NH, NMe, and NEt corresponding to compounds 24–28 while keeping the optimized aryl piperazine, present in preladenant, fixed. 39 In general, the binding affinities for A2A were good for all of the linkers with good selectivity versus A1, but the O and S

![Figure 6. Arylindenopyrimidines.](image6.png)

![Figure 7. Substituted arylindenopyrimidines.](image7.png)

![Figure 8. Pyrazolo[4,3-e]-1,2,4-triazolo[4,3-c]pyrimidon-3-one and thiazolotriazolopyrimidines.](image8.png)
Figure 9. Substituted 1,2,4-triazolo[1,5-c]pyrimidines.

Figure 10. Substituted purinones.

A series of thieno[3,2-d]pyrimidine-4-methanone derivatives was prepared as adenosine A2A receptor antagonists with modest selectivity over A1 (Figure 11). The most potent compound 34 was potent at both A2A and A1, and was found to be active in haloperidol-induced hypolocomotion model in mice when dose at 30 mg/kg, i.p. Removing the ketone linker and directly attaching the heterocycle to the pyrimidine core afforded a series of 4-aryltetrazolo[3,2-d]pyrimidines having good affinity for A2A receptors. Compound 35 was moderately potent for A2A (Kᵢ = 69 nM), but it did not reverse haloperidol-induced hypolocomotion in mice following i.p. administration of 30 mg/kg. Interestingly, replacing the 2-phenyl substituent with 2-thiophenyl resulted in a significant increases in A2A binding affinity (Kᵢ = 1.6 nM) and selectivity over A1. Compound 36 was also able to reverse hypolocomotion in mice at 30 mg/kg, i.p. A similar aminopyrimidine 37 was identified that had good receptor binding for A2A but was moderately selective versus A1. Efforts to identify other bicyclic templates identified pyrazolo[3,4-d]pyrimidines 38 and 39 and 6-arylpyrimidines 40 and 41. The pyrazolo analogues 38 and 39 both show good affinity for A2A and were both able to reverse haloperidol-induced hypolocomotion in mice at 30 mg/kg, i.p. None of the analogues within this series, however, were active when given orally. Interestingly, the 6-arylpyrimidine 40 had much weaker affinity for A2A but was effective in reversing hypolocomotion in mice when dosed at 10 mg/kg, i.p., and 1 mg/kg, p.o. No plasma or brain exposures were reported to explain this unexpected result. The benzyl analogue 41 was also active in vivo at 30 mg/kg, i.p., but not active when dosed orally.

A variety of substituted benzyl analogues were prepared that had good A2A activity but were not able reverse haloperidol-induced hypolocomotion when dosed orally. Inactivity was attributed to low solubility and poor PK profiles and led to the synthesis of heterocyclic compounds such as the 2-pyridyl analogue 42. Despite good in vivo activity and increased solubility, 43 was not active in vivo as 30 mg/kg, p.o. Further optimization of this scaffold led to the discovery of vipadenant (44) (V2006/BIBB-014) which was evaluated in phase II clinical trials. Vipadenant showed excellent binding affinity for A2A and had
modest selectivity against A1 and A2B, $K_i = 63$ nM, while it showed good selectivity against A3, $K_i = 1005$ nM. When tested in vivo in the mouse and rat haloperidol-induced hypolocomotion models, 44 had a minimum effective dose of 0.1 and 1 mg/kg, respectively. Vipadenant was able to increase contralateral rotations in 6-OHDA lesioned rats when dosed orally in combination with apomorphine at 3 and 10 mg/kg. 24a The compound also showed reversal of motor disability in MPTP-treated marmosets without dyskinesias at a minimum effective dose of <5 mg/kg, p.o. 24a The excellent in vivo data and a favorable safety profile helped progress this compound through phase II clinical trials. Despite positive phase II clinical results, in July 2010 Vernalis and Biogen have discontinued the development of vipadenant due to some preclinical toxicology findings that showed adverse side effects. 50

A series of triazolo-9H-purines was reported as A2A antagonists having moderate selectivity versus A1 (Figure 13). 55 The in vitro activities for A2A and A1 are reported as functional activity, not binding affinity. The unsubstituted furan proved to be the optimal substituent for A2A potency and selectivity versus A1. The basicity of amine substituent was the key to obtain in vivo activity in the haloperidol-induced catalepsy model in mice. Very basic amines such as pyrrolidines and piperidines had good in vitro potency but were not able to reverse catalepsy in vivo at 10 mg/kg, p.o. The morpholine compound 47 was much less basic, based on calculated pK$a$ values, than the corresponding pyrrolidines and piperidines and had a reported oral ED$_{50}$ of 1.3 mg/kg in the mouse catalepsy model. A variety of less basic amines were explored to determine the scope and to identify if the basicity was indeed a real trend. Compounds 48 and 49 were even more

![Figure 11. Thieno[3,2-d]pyrimidines, pyrazolo[3,4-d]pyrimidines, and 6-arylpurines.](image1)

![Figure 12. Benzyl substituted triazolo[4,5-d]pyrimidines.](image2)

![Figure 13. Triazolo-9H-purines.](image3)
potent in vitro than 47 and significantly reversed catalepsy at 10 mg/kg, p.o. Further characterization of 48 showed that it had an ED_{50} of <1 mg/kg, p.o., but suffered from a suboptimal PK profile that was attributed to the furan. Efforts to substitute the 5-position of the furan with methyl, ethyl, isopropyl, cyclopropyl, —CHF_2, chlorine, and bromine generally resulted in slight decreases of in vitro potency, but dramatic decreases of in vivo activity. Replacing the furan with various 5-membered heterocycles resulted in a very large decrease of in vitro potency. Interestingly, the furan could be replaced with a 3-cyanoanilino group and maintain good A_2A activity. Compound 50 was ~6-fold less potent than the corresponding furan analogue, but maintained good activity in vivo (ED_{50} < 1 mg/kg) and had a superior PK profile.

A series of 2-aminimidazopyridines 51 and 52 resulted from the optimization of a high throughput screen hit (Figure 15).^{56} Compound 51 showed good binding affinity for A_2A with 93-fold selectivity over A_1. A variety of amidines were explored in the 6-position but generally suffered from poor microsomal stability. Moving the amide substituent to the 5-position resulted in compounds with similar binding affinities, but in general led to better microsomal stability. Compound 52 was a potent binder for A_2A and showed moderate plasma and brain exposure when dosed orally, but it was not evaluated in animal models of PD.

A 4-morpholino-benzothiazole based series of compounds was reported as dual A_2A/A_1 receptor antagonists (Figure 18).^{64} Compound 59 had potent affinity for both A_2A and A_1, and significantly reversed haloperidol-induced catalepsy in mice at 3.2 mg/kg, p.o. Further optimization of the pyrazine scaffold led to the identification of 60 (ASP-5854) that has been characterized extensively in numerous animal models of PD and cognition.^{65} ASP-5854 reversed CGS21680-induced and haloperidol-induced catalepsy in mice with ED_{50} values of 0.15 and 0.07 mg/kg, p.o., respectively, and had a minimum effective dose of 0.1 mg/kg to reverse haloperidol-induced catalepsy in rats. In rhesus monkeys, ASP-5854 gave >85% occupancy of A_3A receptors in the striatum and reversed haloperidol-induced catalepsy with an ED_{50} of 0.1 mg/kg, p.o.^{66} ASP-5854 effectively potentiated L-DOPA-induced rotation in 6-OHDA lesioned rats with a minimum effective dose of 0.03 mg/kg, p.o. Statistical significance was reached in MPTP-treated mice and MPTP-treated marmosets at 0.1 and 1 mg/kg, p.o., respectively.^{51,67} ASP-5854 produced positive results in scopolamine-induced memory deficits in the mouse Y-maze test and rat passive avoidance test, both models of cognition, with minimum effective doses of 0.3 and 0.1 mg/kg, p.o., respectively.^{61} The selective A_2A antagonist KW-6002 (3) was also tested in parallel for comparison in these models and was significantly less effective having a minimum effective dose of 10 mg/kg, p.o. in the mouse Y-maze test and no effect in the rat passive avoidance test up to 10 mg/kg, p.o. These results suggest that a dual A_2A/A_1 may provide added benefit to PD patients to address the cognitive impairments associated with the disease.

### MONOCYCLIC A_2A ANTAGONISTS

An aminopyrazine based series of compounds was reported as dual A_2A/A_1 receptor antagonists (Figure 18).^{64} Compound 59 had potent affinity for both A_2A and A_1, and significantly reversed haloperidol-induced catalepsy in mice at 3.2 mg/kg, p.o. Further optimization of the pyrazine scaffold led to the identification of 60 (ASP-5854) that has been characterized extensively in numerous animal models of PD and cognition.^{65} ASP-5854 reversed CGS21680-induced and haloperidol-induced catalepsy in mice with ED_{50} values of 0.15 and 0.07 mg/kg, p.o., respectively, and had a minimum effective dose of 0.1 mg/kg to reverse haloperidol-induced catalepsy in rats. In rhesus monkeys, ASP-5854 gave >85% occupancy of A_3A receptors in the striatum and reversed haloperidol-induced catalepsy with an ED_{50} of 0.1 mg/kg, p.o.^{66} ASP-5854 effectively potentiated L-DOPA-induced rotation in 6-OHDA lesioned rats with a minimum effective dose of 0.03 mg/kg, p.o. Statistical significance was reached in MPTP-treated mice and MPTP-treated marmosets at 0.1 and 1 mg/kg, p.o., respectively.^{51,67} ASP-5854 produced positive results in scopolamine-induced memory deficits in the mouse Y-maze test and rat passive avoidance test, both models of cognition, with minimum effective doses of 0.3 and 0.1 mg/kg, p.o., respectively.^{61} The selective A_2A antagonist KW-6002 (3) was also tested in parallel for comparison in these models and was significantly less effective having a minimum effective dose of 10 mg/kg, p.o. in the mouse Y-maze test and no effect in the rat passive avoidance test up to 10 mg/kg, p.o. These results suggest that a dual A_2A/A_1 may provide added benefit to PD patients to address the cognitive impairments associated with the disease.

---

**Figure 14.** Aminomethyl substituted thieno[2,3-d]pyrimidines.

**Figure 15.** 2-Aminomethyl substituted thieno[2,3-d]pyrimidines.
A variety of carboxamides of 2-amino-4-phenyl-thiazoles were prepared as adenosine A\(_{2A}\) receptor antagonists (Figure 19).\(^6\) A lead optimization effort identified that the cyclopropyl amide was the optimal amide substituent. Further evaluation into the substitution at the 5-position of the thiazole led to the 5-methyl-[1,2,4]-oxadiazole compound \(^{61}\) which had good affinity for A\(_{2A}\) and A\(_1\). Compound \(^{61}\) also showed good activity in the haloperidol-induced hypolocomotion model in mice with an ED\(_{50}\) of 7 mg/kg. A series of related substituted 2-amino-5-benzoyl-4-(2-furyl)thiazoles was designed from a high throughput screening hit.\(^6\) Lead optimization led to compound \(^{62}\) which had good affinity for A\(_{2A}\) and excellent selectivity versus A\(_1\). Interestingly, a simple methyl substitution (\(^{63}\)) dramatically decreases the binding affinity for A\(_{2A}\). No in vivo evaluation of \(^{62}\) was reported.

A series of trisubstituted pyrimidines was reported to have potent A\(_{2A}\) activity (Figure 20).\(^7\) Compound \(^{64}\) was a potent A\(_{2A}\) antagonist, but it lacked the desired selectivity versus A\(_1\) and had poor metabolic stability that was attributed to the unsubstituted furan moiety. SAR studies resulted in the synthesis of the thiazole compounds \(^{65}\) and \(^{66}\) that maintained potency for A\(_{2A}\). Interestingly, replacing the benzylidene, present in \(^{65}\), with an oxygen atom resulted in the selective compound \(^{66}\). Compound \(^{66}\) was further optimized by replacing the thiazole with the dimethylpyrazole to give compound \(^{67}\) that was very potent for A\(_{2A}\) and had excellent selectivity versus A\(_1\). Despite the increase in selectivity, \(^{67}\) suffered from poor solubility, so basic amines were appended to the phenol ring to increase solubility and improve PK properties. A number of the amino alkyl compounds had good binding affinities for A\(_{2A}\) and good selectivity versus A\(_1\), but had significant hERG liabilities. Compound \(^{68}\) had the best hERG profile (patch clamp IC\(_{50}\) = 1.2 \(\mu\)M) and showed oral activity in the haloperidol-induced catalepsy in rats with a minimal effective dose of 10 mg/kg.

A series of 2-amino-N-pyrimidin-4-ylacetamides was prepared with compound \(^{69}\) being the representative example (Figure 21).\(^7\) Compound \(^{69}\) had a high affinity for A\(_{2A}\) and was 99-fold selective versus A\(_1\). Tissue distribution studies showed very good exposure (2700 ng/g) in rat brain at 2 h after a 10 mg/kg oral dose. The compound effectively reversed haloperidol-induced catalepsy in rats at 10 mg/kg, p.o. Like \(^{64}\), compound \(^{69}\) had metabolic liabilities that were associated with the unsubstituted furan, so there was an effort to find a suitable furan replacement.\(^7\) A variety of combinations consisting of 5- and 6-membered heterocycles were made to replace the furan and pyrazole substituents. Compounds \(^{70}\) and \(^{71}\) were identified as the most promising compounds having good binding affinities and good selectivity versus A\(_1\). Further evaluation of \(^{70}\) showed it to be a potent inhibitor of hERG with an IC\(_{50}\) of 950 nM (patch clamp). The basicity of the piperazine was enhancing the hERG

---

**Figure 16.** Substituted 4-morpholino-benzothiazoles.

**Figure 17.** 4-Aryl and 4-morpholino substituted benzofurans.

**Figure 18.** Pyridone substituted pyrazines.

**Figure 19.** Heterocyclic substituted 2-amino-thiazoles.

---

562  
dx.doi.org/10.1021/cn2000537 | ACS Chem. Neurosci. 2011, 2, 555–567
activity, so various replacements were prepared in effort to decrease the hERG liability. Although the hERG inhibition could not be completely eliminated, removal of one of the basic amines decreased the hERG activity. Several compounds within the series showed activity in haloperidol-induced catalepsy in rats.

A related series of 2,6-diaryl-4-acylaminopyrimidines was developed with improved solubility and metabolic stability (Figure 22). Compound 72 was potent for A_{2A} and was 218-fold selective against A_{1}. More importantly, the addition of the fluorine atom significantly increased metabolic stability, decreased intrinsic clearance, and reduced CYP inhibition compared to the corresponding des-fluoro analogue (not shown). Further characterization of 72 showed that it significantly reversed haloperidol-induced catalepsy in rats at 30 mg/kg, p.o.

Another related compound 73 was able to reverse catalepsy in rats at 10 mg/kg, p.o. Compound 73 also showed the ability to potentiate L-DOPA-induced rotational behavior in the 6-OHDA lesioned rat at 10 and 30 mg/kg oral doses.

Analogues of pyrimidine-4-carboxamides have been reported to display good potency for A_{2A} and with good selectivity over other adenosine receptor subtypes (Figure 23). Compound 74 is a representative example having binding affinities of 1.7, 43, 460, and 1740 nM for A_{2A}, A_{1}, A_{2B}, and A_{3}, respectively. Compound 75 also had a minimum effective dose of 0.1 mg/kg in the haloperidol-induced hypolocomotion model in mice. Related pyridine 75 and triazine 76 have also been reported, but they are significantly less potent than the corresponding pyrimidines.

**SUMMARY**

Adenosine A_{2A} receptor antagonists continue to be a sought after target for the treatment of PD. There have been a variety of chemical scaffolds reported with interesting SAR features that showed dramatic activity differences, both in vitro and in vivo, from subtle modifications. Despite the relentless research efforts to identify potent compounds, there still remains the challenge of achieving selectivity, solubility, and acceptable pharmacokinetic/pharmacodynamic properties to progress into the clinic. There have been a number of compounds that are in or have been in clinical trials including istradefylline (3), preladenant (8),...
The progression through the clinic with positive trial results indicates the viability of A2A antagonists to treat PD patients with potential advantages over the current standard treatments. Two examples of efforts to identify dual A2A/A1 were also described as having the potential to provide added benefit to PD patients, via A1 antagonism, to address the cognitive impairments that worsen as the disease progresses. Idenopryridimidine 18 and ASP-5854 (60) are potent A2A/A1 receptor antagonists that showed very potent activity across a number of PD models. ASP-5854 also showed potent and effective activity in a number of rodent cognition models, while the selective A2A antagonist istradefylline showed no or marginal effects in these models. The continued research to identify selective A2A and dual A2A/A1 antagonists should provide some new and interesting opportunities for PD patients for years to come.

**AUTHOR INFORMATION**

**Corresponding Author**

*E-mail: bshook@its.jnj.com. Telephone: 215-628-7047.

**ABBREVIATIONS**

6-OHDA, 6-hydroxydopamine; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PD, Parkinson’s disease; DA, dopamine; L-DOPA, levodopa; MAO-B, monoamine oxidase type B; COMT, catechol-o-methyltransferase; cAMP, cyclic adenosine monophosphate; PK, pharmacokinetics

**ACKNOWLEDGMENT**

The table of contents graphic represents a positron emission tomography (PET) picture of adenosine A2A receptors in rat striatum using 11C-TMSX, an A2A receptor antagonist. We thank Dr. Paul Acton and Carlos Cotto for performing the PET experiments.

**REFERENCES**


Selective lesion of central dopamine or moradrenaline neuron systems in the neonatal rat: motor behavior and monoamine alteration at adult stage. Behav. Brain Res. 33, 267–277.


