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Methylene amine substituted arylindenopyrimidines as potent adenosine A_{2A}/A_1 antagonists

Brian C. Shook *, Stefanie Rassnick, Daniel Hall, Kenneth C. Rupert, Geoffrey R. Heintzelman, Kristen Hansen, Devraj Chakravarty, James L. Bullington, Robert H. Scannevin, Brian Magliaro, Lori Westover, Karen Carroll, Lisa Lampron, Ronald Russell, Shawn Branum, Kenneth Wells, Sandra Damon, Scott Youells, Xun Li, Mel Osbourne, Keith Demarest, Yuting Tang, Kenneth Rhodes, Paul F. Jackson

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

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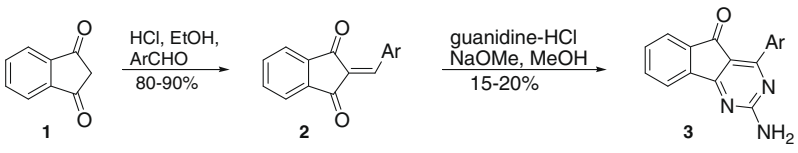
ABSTRACT

A novel series of arylindenopyrimidines were identified as A_{2A} and A_1 receptor antagonists. The series was optimized for in vitro activity by substituting the 8- and 9-positions with methylene amine substituents. The compounds show excellent activity in mouse models of Parkinson's disease when dosed orally.

Parkinson's disease (PD) is a chronic, progressive neurological disease that affects ~1% of the population over the age of 65.[1] It is characterized by loss of dopamine neurons in areas of the brain that are important for motor function, mood, and cognition. Although the primary symptom of PD is motor dysfunction, the disease also has comorbidities associated with it including anxiety, depression, and cognitive impairment.

Adenosine is a neuromodulator that coordinates responses to dopamine and other neurotransmitters in areas of the brain that are responsible for motor function, learning and memory.[2] Adenosine is comprised of four distinct sub-types designated A_1, A_{2A}, A_{2B}, and A_3.[3] Both A_{2A} and A_1 receptors are highly expressed in the brain, particularly striatum, while A_{2B} and A_3 receptors are not.[4] Literature reports have shown that A_{2A} antagonists may be useful in the treatment of PD.[5] In fact, several selective A_{2A} antagonists have advanced into clinical development.[6]

There have been several reports published suggesting that adenosine A_1 antagonists may improve learning and memory.[2c,d] This would suggest that a dual A_{2A}/A_1 antagonist may offer improved benefit to PD patients as it is known that cognitive deficiencies increase as the disease progresses. Unfortunately, it is unknown what balance of A_1 versus A_{2A} antagonism would be ideal for PD patient benefit. We would like to report herein a novel series of arylindenopyrimidines as dual A_{2A}/A_1 antagonists for the potential treatment of PD.[7]



Scheme 1. Synthesis of arylindenopyrimidines.

* Corresponding author.
E-mail address: bshook@its.jnj.com (B.C. Shook).

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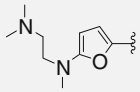
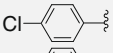
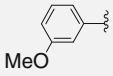
Table 1
In vitro activity for A_{2a} and A_1 functional assays, and in vivo results for mouse catalepsy at 10 mg/kg, po

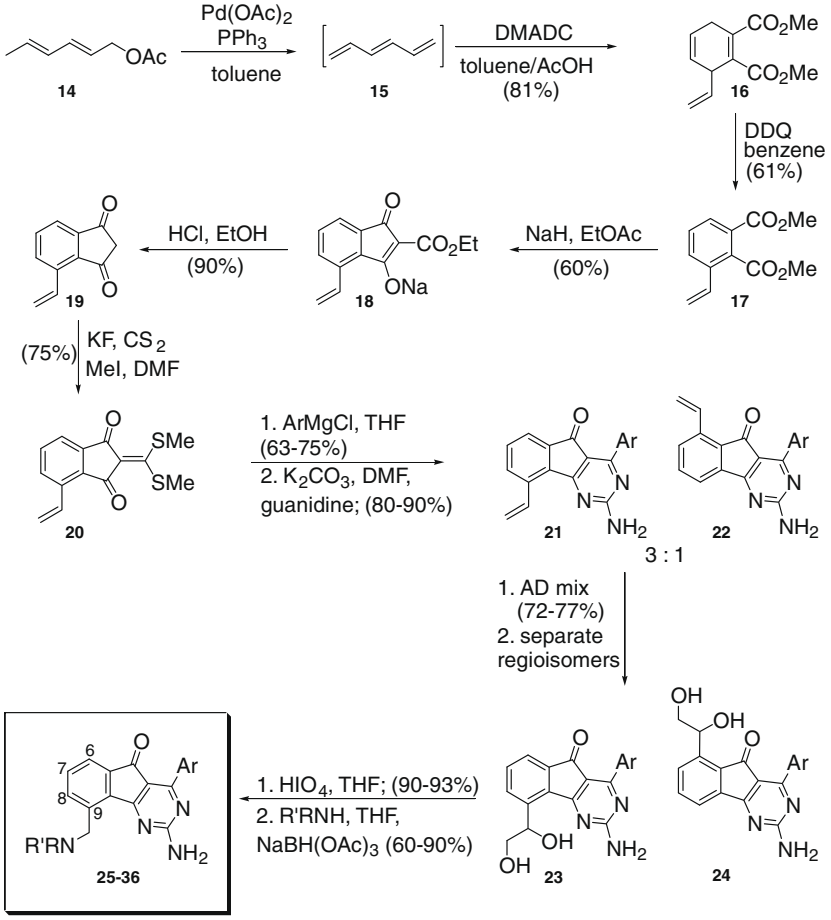
Compound	HetAr	A_{2A} K_i (nM)	A_1 K_i (nM)	Mouse catalepsy 10 mg/kg, po
4		0.1	0.4	Active ED_{50} = 5.0 mg/kg
5		0.2	0.5	Inactive
6		10.5	40.0	Active ED_{50} = 17.1 mg/kg
7		0.6	3.2	Active ED_{50} not determined
8		0.5	6.9	Inactive
9		4.6	16.4	Inactive
10		0.1	1.1	Active ED_{50} = 8.0 mg/kg
11		5.5	11.6	Inactive
12		1.6	2.5	Inactive
13		32.5	172	Inactive

Initial screening hits lead to a series of arylindenopyrimidines that were potent A_{2A}/A_1 antagonists generalized by structure **3** (Scheme 1). These compounds were prepared in two steps starting from the commercially available indanedione **1**. Condensation with the appropriate aldehyde gave the intermediate benzylidene **2**[8] that was then reacted with guanidine under basic conditions to give the corresponding amino pyrimidine **3**.[7]

A variety of aryl and heteroaryl aldehydes were incorporated to explore the scope and generality of the aryl and heteroaryl substituents (Table 1). Although most substitution was tolerated the 2-substituted furan **4** had superior functional in vitro and in vivo activity. This compound reversed haloperidol induced catalepsy in mouse[9] with an ED_{50} of 5.0 mg/kg. Further characterization of this compound revealed that it was Ames[10] positive. Ames liabilities are not uncommon for unsubstituted furans and we tried to exploit this liability to increase solubility of this series. Amine substitution, compound **6**, on the furan did eliminate the Ames liability, but also caused decreased in vivo activity. Simple substitution with chlorine, compound **5**, or methyl, not shown, also eliminated the Ames liability, but both compounds were inactive in vivo. Other heterocycles like thiophene **7** and thiazole **8** showed decreased or no in vivo activity.

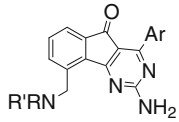
Generally compounds bearing phenyl or substituted phenyl **10–13**, had no Ames liability while maintaining good functional in vitro potency, some also had in vivo activity. Our attention then turned to other parts of the molecule to optimize for in vivo activity, PK properties, and solubility. It is worth noting that the NH_2 of the amino pyrimidine must be unsubstituted as a single methyl substituent completely eliminates any in vitro activity.

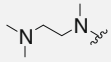
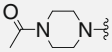
The focus was to substitute the 'A' ring of the arylindenopyrimidine core to explore where and what substituents were tolerated. The plan was to diversify the compounds later on in the synthesis



Scheme 2. Synthesis of arylindenopyrimidines substituted in the 9-position.

Table 2
A_{2A}/A_1 antagonists substituted in the 9-position



Compound	NRR′	Ar	A_{2A} K_i (nM)	A_1 K_i (nM)	Mouse catalepsy ED_{50} (mg/kg), po
25		Ph	40.1	119	Inactive
26		Ph	18.3	107	Inactive
27		Ph	14.3	40.8	5.0
28		Ph	11.3	94.2	7.8
29		Ph	7.9	34.1	10.7
30		Ph	8.6	95.2	Inactive
31		Ph	3.3	32.9	5.6
32		4-F-Ph	3.8	155	1.3
33		3-CN-Ph	5.4	75.0	1.7
34		Ph	2.5	116	3.8
35		4-F-Ph	3.6	85.0	0.8
36		Ph	11.3	140	Inactive

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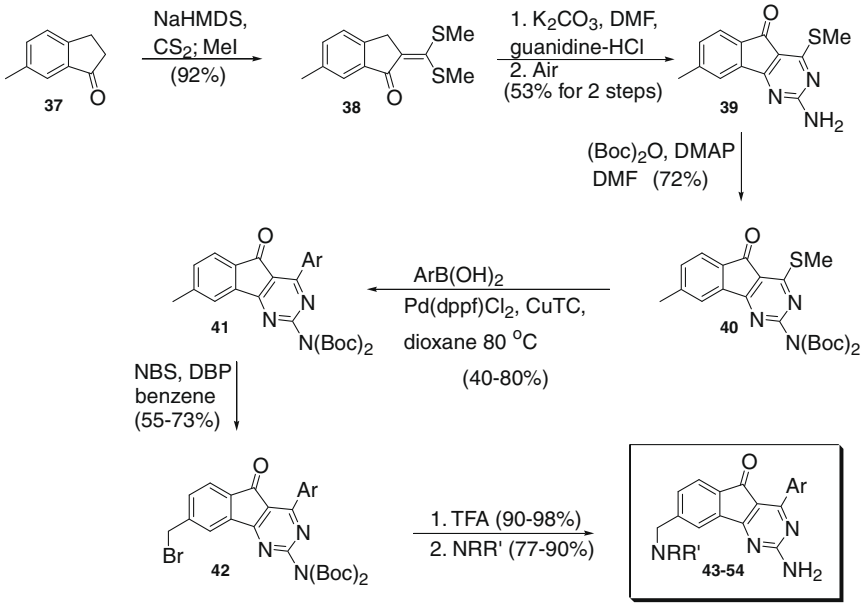
to maximize the efficiency, so ideally the core needed to be made that had a handle on the A-ring to develop the SAR. Unfortunately there are not many indanediones that are commercially available, so **19** was synthesized having a vinyl group for manipulation later on in the synthesis (Scheme 2). The indanedione was prepared starting from the commercially available 2,4-hexadienyl acetate **14** which was treated with $Pd(OAc)_2$ to generate the 1,3,5-hexatriene **15** in situ. The triene reacted nicely with dimethylacetylene dicarboxylate (DMADC) to generate **16**, that is, subsequently oxidized to the corresponding phthalic ester **17** using DDQ. The phthalic ester was then reacted under Claisen condensation conditions using ethyl acetate to give the stable sodium salt **18**.[11] Finally, decarboxylation under acidic conditions afforded the vinyl indanedione **19**.

The diketone **19** reacted with CS_2 under mild conditions and was subsequently trapped with MeI to afford the dithioketene acetal **20** (Scheme 2).[12] Aryl Grignards reacted smoothly with **20** in a 1,4-fashion followed by reaction with guanidine to give the corresponding amino pyrimidines **21** and **22** in a 3:1 ratio, respectively.[7] At this point the regioisomers were not separable via column chromatography, so the vinyl substituents were dihydroxylated using AD-mix to give the corresponding diols **23** and **24**.[13] The diols were very separable via chromatography and each was carried on individually at this point, the less abundant regioisomer **24** will not be shown. The diol **23** was oxidized with periodic acid[14] to give the corresponding aldehyde, not shown, that is, reacted with a variety of amines under reductive amination[15] conditions to afford target molecules **25**–**36**. Analogous compounds substituted in the 6-position were not active in the A_{2A} functional in vitro assay.

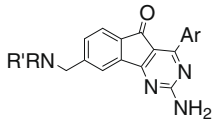
Table 2 illustrates a number of compounds that were synthesized having various amino and aryl substituents. Each has good functional in vitro potency for both A_{2A} and A_1, and most have some in vivo activity in mouse catalepsy, which was the primary animal model.[9] Acyclic amino substituents had good in vitro potency, but generally lacked in vivo activity as exemplified in compounds **25** and **26**. Cyclic amino groups, however, showed good in vitro and in vivo activity. The morpholine and pyrrolidine analogs, **31**–**33** and **34**–**36**, respectively, represent optimal substitution for in vivo potency, with compound **35** having an ED_{50} = 0.8 mg/kg. Most substitution on the aryl group resulted in decreased activity both in vitro and in vivo, but the 4-fluoro and 3-cyano groups were well tolerated and increased potency in vivo for compounds **32**, **33**, and **35**.

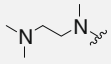
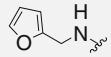
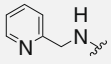
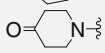
At this point the SAR was extensively explored various substitutions at carbons 6 and 9, but the SAR needed to be completed for analogs substituted at carbons 7 and 8. Analogous chemistry



Scheme 3. Synthesis of arylindenopyrimidines substituted in the 8-position.

Table 3
A_{2A}/A_1 antagonists substituted in the 8-position



Compound	NRR'	Ar	A_{2A} K_i (nM)	A_1 K_i (nM)	mouse catalepsy ED_{50} (mg/kg), po
43		Ph	7.8	20.0	Inactive
44		Ph	5.3	12.5	1.2
45		Ph	5.4	26.3	1.6
46		Ph	3.0	20.4	0.3
47		4-F-Ph	9.9	95.7	0.6
48		Ph	9.3	86.2	1.7
49		4-F-Ph	29.8	225	3.5
50		Ph	12.9	114	0.7
51		Ph	5.9	73.0	0.3
52		Ph	1.0	1.8	1.7
53		Ph	4.1	17.0	0.2
54		4-F-Ph	12.8	66.2	1.6

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allowed us to make some methylene amine analogs at positions 7 and 8 similar to those in compounds **25**–**36**. We quickly identified that substitution was tolerated on carbon 8 giving good in vitro potency for A_{2A} and A_1 while it decreased activity on carbon 7. It was decided to design a regioselective synthesis to access the desired target compounds having substitution at carbon 8 because separation of 7 and 8 substituted regioisomers was difficult and sometimes not possible (Scheme 3).

The commercially available 6-methyl indanone **37** was reacted with CS_2 under basic conditions to afford the dithioketene acetal **38**.[16] Compound **38** reacted with guanidine to form an intermediate amino pyrimidine, not shown, that was then oxidized to the corresponding ketone by passing air through the solution to give **39**.[7] The amino pyrimidine was di-Boc protected using excess $(Boc)_2O$ and DMAP to give **40**. The aryl substituent was installed via a modified Suzuki reaction under Liebeskind-type conditions using the methylthioether as the coupling partner to afford **41**.[17] Compound **41** underwent benzyl bromination to afford the corresponding bromide **42**. Removal of the Boc groups with TFA followed by alkylation with a variety of amines gave the desired target compounds **43**–**54**.

Table 3 illustrates several dual A_{2A}/A_1 antagonists having comparable activity to those shown in Table 2. One obvious difference however is the increased in vivo potency of the analogs substituted in the 8-position over those in the 9-position. For example, the piperidine analog **46** had an ED_{50} = 0.3 mg/kg compared to its regioisomer **29** having an ED_{50} = 5.0 mg/kg. Another example is seen in the pyrrolidine analog **53** which had an ED_{50} = 0.2 mg/kg while its regioisomer **34** had an ED_{50} = 3.8 mg/kg. Also, the homopiperazine **30** was inactive in the 9-position, but the 8-position regioisomer **50** had an ED_{50} = 0.7 mg/kg. This effect was general for most of the analogs prepared in both of the positions. Again, acyclic analogs like **43** lacked in vivo efficacy similarly to compounds **25** and **26**. Interestingly, when a heteroaryl group was attached to the acyclic amine chain the in vivo activity returned as seen for compounds **44** and **45**.

In summary, it was shown that methylene amine arylindenopyrimidines substituted at carbons 8 and 9 had potent functional in vitro activity for both A_{2A} and A_1. These analogs also demonstrated very potent activity in an animal model of PD.

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