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Optimization of arylindenopyrimidines as potent adenosine A_{2A}/A_1 antagonists

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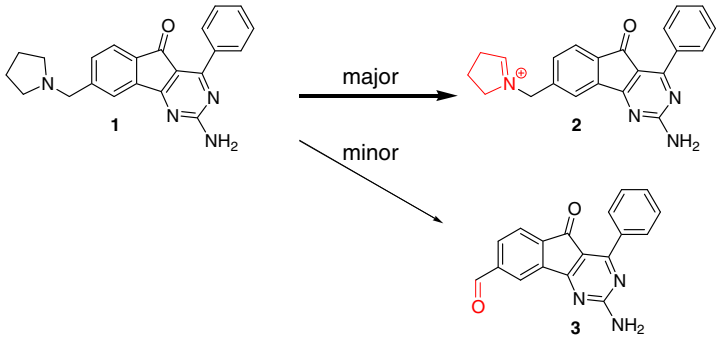
ABSTRACT

Two reactive metabolites were identified in vivo for the dual A_{2A}/A_1 receptor antagonist **1**. Two strategies were implemented to successfully mitigate the metabolic liabilities associated with **1**. Optimization of the arylindenopyrimidines led to a number of amide, ether, and amino analogs having comparable in vitro and in vivo activity.

Adenosine receptors are members of the G-protein-coupled receptor super family.[1] The adenosine receptors have been divided into four different subtypes A_1, A_{2A}, A_{2B}, and A_3.[1] The A_{2A} receptor, which is highly expressed in the striatum,[2] is a much sought after target in the pharmaceutical industry because of its potential to treat Parkinson's disease (PD) and other neurodegenerative disorders.[3]

We have previously reported a series of methylene amine substituted arylindenopyrimidines as dual adenosine A_{2A}/A_1 antagonists.[4] Parkinson's disease severely affects motor function but the disease is also associated with anxiety, depression, and cognitive impairment.[5] Therefore the idea of a dual antagonist could offer improved benefit over the traditional selective A_{2A}



Scheme 1. In vivo metabolism of compound **1**.

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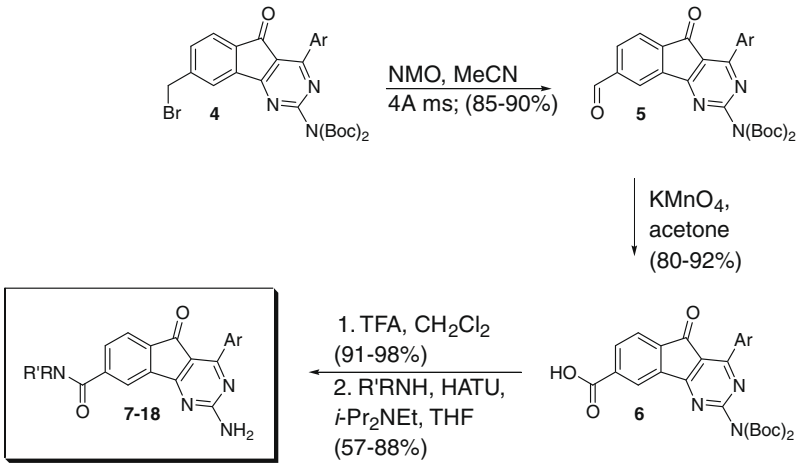


Scheme 2. Synthesis of amides **7**–**18**.

antagonist because of its inherent A_1 activity which is known to show positive effects in animal models of learning and memory.[5c,d]

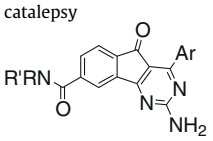
We have reported that **1** was a potent A_{2A}/A_1 antagonist that had very potent activity in haloperidol induced catalepsy in mice (ED_{50} = 0.2 mg/kg) as well as other animal models of PD.[4] Further characterization of this compound however, showed the formation of two reactive intermediates, **2** and **3**, that were formed in vivo (Scheme 1). The major metabolite was the iminium ion **2** which was formed via oxidation alpha to the nitrogen inside the pyrrolidine ring followed by elimination. Members of our DMPK group were able to identify this iminium ion and successfully trap it with cyanide. The minor metabolite **3** was formed through an analogous oxidation at the benzylic position followed by elimination of pyrrolidine. These metabolites did not prove to be liabilities until some adverse events were detected in the 28 day non-human primate studies.

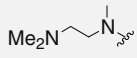
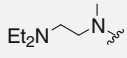
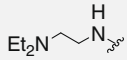
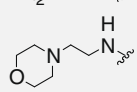
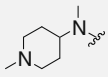
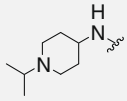
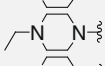
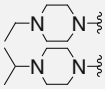
At this point the focus was to address this issue and eliminate the potential for these metabolites to be formed. The strategy consisted of two approaches to manipulate the current scaffold while maintaining good functional in vitro and in vivo activity.[6] One approach was to oxidize the benzylic position of the methylene amines, to form the corresponding amides, which would eliminate the benzylic oxidation and also decrease the electron rich nature of the pyrrolidine making it less susceptible to ring oxidation. The second approach was to convert the benzylic carbon to heteroatoms like oxygen and nitrogen, to eliminate benzylic oxidation, while moving the solubilizing group out further in hope to eliminate the iminium ion formation.

The first approach took advantage of a common intermediate **4** used to synthesize **1** and a number of its analogs (Scheme 2).[4] The benzyl bromide **4** was oxidized to the corresponding aldehyde **5** using *N*-methylmorpholine-*N*-oxide (NMO).[7] Further oxidation of the aldehyde with $KMnO_4$ gave the carboxylic acid **6**. Deprotection of the amino group using TFA followed by amide coupling using HATU afforded the desired amide analogs **7**–**18**.

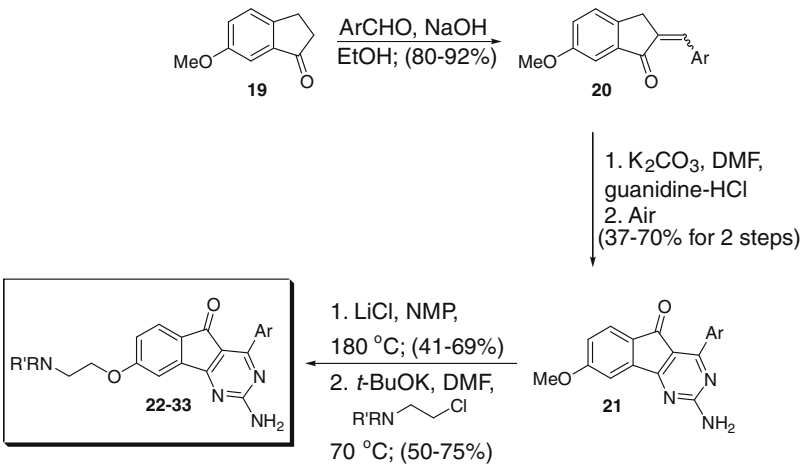
A wide variety of amides were prepared and most substitution was tolerated as seen in Table 1. Both acyclic and cyclic amides gave desired functional activity for both A_{2A} and A_1. For the acyclic analogs **7**–**12** both secondary and tertiary amides maintained good in vitro acitivity. The majority of cyclic analogs prepared were substituted piperazines as these kept a tertiary amine present for solubility. The cyclic analogs also maintained good in vitro activity, and a number of these compounds showed very good activity in our primary animal model of mouse catalepsy,[8] comparable to that of compound **1**. One difference, however, is that the amides typically had lower brain concentrations in rat compared to those having methylene amine substituents. For example, the brain C_{max} for **1** was 3.6 μM while the brain C_{max} for **14** was 0.6 μM. The decreased brain exposure, however, did not dramatically decrease its in vivo potency. Most importantly, the amides did not have the metabolic liability associated with **1**. As we previously reported for the methylene amines,

Table 1
A_{2A}/A_1 antagonists having an amide linker. In vitro activity for A_{2A} and A_1 functional assays, and ED_{50}'s for mouse catalepsy



Compound	NRR′	Ar	A_{2A} K_i (nM)	A_1 K_i (nM)	Mouse catalepsy ED_{50} (mg/kg), po
7		Ph	12.4	208	<1.0
8		Ph	7.8	94.7	<1.0
9		Ph	13.5	45.2	ND
10		Ph	28.4	215	ND
11		Ph	18.6	258	<1.0
12		Ph	16.8	119	0.4
13		Ph	32.5	12.3	ND
14		Ph	8.2	58.4	0.4
15		4-F-Ph	11.1	101	<1.0
16		Ph	14.9	67.4	<1.0
17		4-F-Ph	32.1	191	ND
18		Ph	20.7	84.1	ND

ND = not determined.



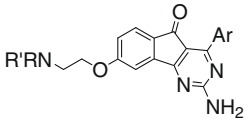
Scheme 3. Synthesis of ethers **22**–**33**.

only phenyl, 4-fluoro and 3-cyano substituents were tolerated on the aromatic ring of the amide analogs.

The second strategy was implemented next by introducing a heteroatom to replace the methylene in **1**. The commercially available 6-methoxyindanone **19** was condensed with a variety of aryl aldehydes under basic conditions to afford the benzylidenes **20** (Scheme 3).[4,9] Similar to our previous Letter, **20** was reacted with guanidine to form an intermediate dihydroaminopyrimidine that, upon aromatization to the aminopyrimidine, was oxidized up to the corresponding ketone **21**.[10] Removal of the methyl ether was achieved using LiCl[11] in NMP at 180 °C to give the intermediate phenols, not shown. The use of BBr_3 was ineffective in removing the methyl ether. Lastly, the phenol was alkylated with a variety of aminoethyl chlorides using *t*-BuOK[12] in DMF to give the desired ethers **22**–**33**.

Like the amides, most of the ether linkages were tolerated (Table 2), but there is a consistent ~3- to 10-fold decrease in potency with compounds having a 4-fluoro substituent (compounds **23**, **25**, **27**, **30**, and **32**). Several of the compounds showed excellent activity in vivo having ED_{50}'s <1.0 mg/kg. Interestingly, **32** was significantly less potent in vitro for A_{2A} than the other analogs tested in vivo, yet it still remains quite good at reversing mouse catalepsy

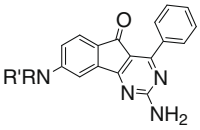
Table 2
A_{2A}/A_1 antagonists having an ether linker. In vitro activity for A_{2A} and A_1 functional assays, and ED_{50}'s for mouse catalepsy

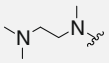
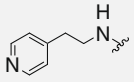
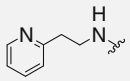
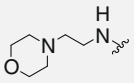
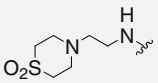
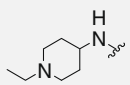
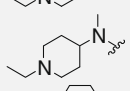
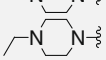
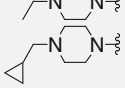


Compound	NRR'	Ar	A_{2A} K_i (nM)	A_1 K_i (nM)	Mouse catalepsy ED_{50} (mg/kg), po
22	Me_2N–	Ph	17.3	33.3	<3.0
23	Me_2N–	4-F-Ph	37.3	37.4	ND
24	Et_2N–	Ph	7.9	103	<1.0
25	Et_2N–	4-F-Ph	50.6	414	ND
26	*i*-Pr_2N–	Ph	13.7	187	<1.0
27	*i*-Pr_2N–	Ph	76.6	468	ND
28		Ph	35.3	194	ND
29		Ph	6.5	48.2	<1.0
30		4-F-Ph	18.1	203	<1.0
31		Ph	19.3	159	<1.0
32		Ph	117	600	0.8
33		Ph	35.1	334	Not active at 10 mg/kg

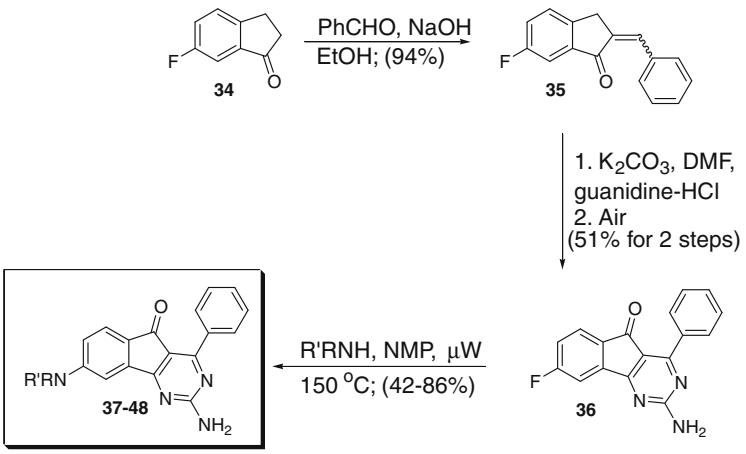
ND = not determined.

Table 3
A_{2A}/A_1 antagonists having an amino linker. In vitro activity for A_{2A} and A_1 functional assays, and ED_{50}'s for mouse catalepsy



Compound	NRR'	A_{2A} K_i (nM)	A_1 K_i (nM)	Mouse catalepsy ED_{50} (mg/kg), po
37		4.7	57.3	ND
38		0.9	12.7	ND
39		0.9	15.4	ND
40		4.4	32.7	<1.0
41		3.1	46.7	Not active at 3 mg/kg
42		12.5	142	Not active at 3 mg/kg
43		4.9	16.4	ND
44		2.9	32.4	ND
45		2.7	35.6	<1.0
46		11.4	256	<1.0
47		23.2	253	ND
48		10.0	137	ND

ND = not determined.



Scheme 4. Synthesis of amines **37**–**48**.

having an ED_{50} = 0.8 mg/kg. This may be due to increased brain exposure of the ether analogs. Unlike the amides, the ethers showed much improved brain exposure comparable to that of **1**. Compound **29** had a brain C_{max} of 4.1 μM and an extremely potent ED_{50} <0.1 mg/kg in the mouse catalepsy model. The ether substituted analogs showed superior metabolic stability compared to **1**.

Finally, the ether linker was replaced with an amino linker using similar chemistry. The commercially available 6-fluoroindanone **34** was condensed with benzaldehyde under basic conditions to afford the benzylidene **35** (Scheme 4). The aminopyrimidine **36** was formed analogously to **21** using guanidine and air. The fluoride was then displaced, in the microwave, using a number of different primary and secondary amines to give the target compounds **37**–**48**. The attempted the displacement on the 4-fluoro analogs, resulted in competing reactions giving mixtures of products, so the focus was on the phenyl substituent.

Similarly to the ethers and amides, the amino analogs were also well tolerated (Table 3). In general, most of the compounds showed superior in vitro activity for A_{2A} than the amides and ethers, and most showed increased A_1 activity as well. Although a limited number of compounds were tested in vivo, **40**, **45**, and **46**, did show comparable activity to the previously described analogs. No brain concentrations were determined for this set of analogs. Again, it is worth noting that the compounds in Table 3 did not show the metabolic liabilities present in **1**.

In summary, it was shown that amide, ether and amino substituted arylindenopyrimidines have potent functional in vitro activity for both A_{2A} and A_1. Several analogs of each set also demonstrate very potent activity in the mouse catalepsy model.

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