Bioorganic & Medicinal Chemistry Letters 20 (2010) 2864–2867

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

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

ARTICLE INFO

Article history:
Received 20 January 2010
Revised 2 March 2010
Accepted 8 March 2010
Available online 11 March 2010

Keywords:
A_{2A} antagonists
A_1 antagonists
Adenosine antagonists
Parkinson's disease
Catalepsy
Dopamine

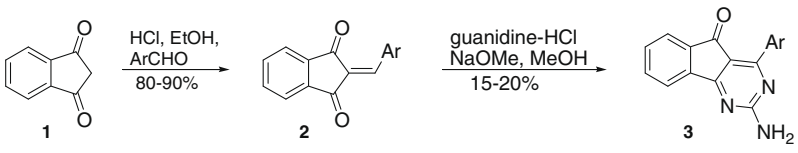
ABSTRACT

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]

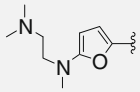
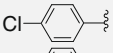
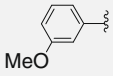


Scheme 1. Synthesis of arylindenopyrimidines.

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

0960-894X/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2010.03.042

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

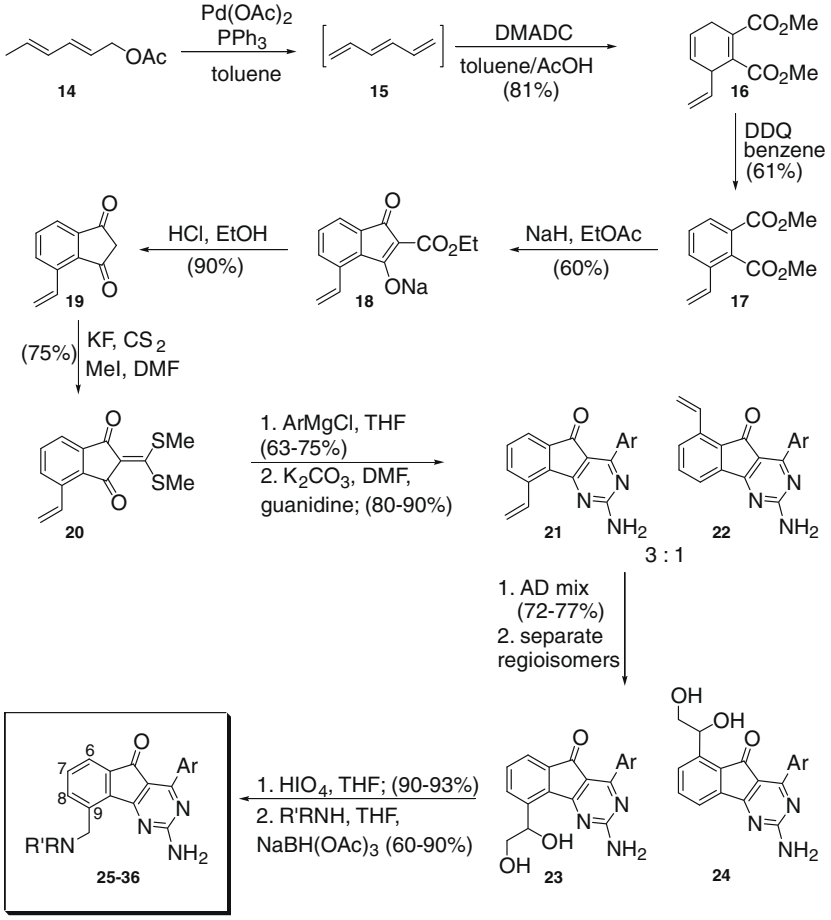
Compound	HetAr	A_{2A} K_i (nM)	A_1 K_i (nM)	Mouse catalepsy 10 mg/kg, po
4		0.1	0.4	Active ED_{50} = 5.0 mg/kg
5		0.2	0.5	Inactive
6		10.5	40.0	Active ED_{50} = 17.1 mg/kg
7		0.6	3.2	Active ED_{50} not determined
8		0.5	6.9	Inactive
9		4.6	16.4	Inactive
10		0.1	1.1	Active ED_{50} = 8.0 mg/kg
11		5.5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