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Potent and selective adenosine A_{2A} receptor antagonists: 1,2,4-Triazolo[1,5-*c*]pyrimidines

Bernard R. Neustadt [a,*], Hong Liu [a], Jinsong Hao [a], William J. Greenlee [a], Andrew W. Stamford [a], Carolyn Foster [a], Leyla Arik [a], Jean Lachowicz [a], Hongtao Zhang [a], Rosalia Bertorelli [b], Silva Fredduzzi [b], Geoffrey Varty [a], Mary Cohen-Williams [a], Kwokei Ng [a]

[a] *Departments of Chemical Research, CNS Pharmacology, Drug Metabolism and Pharmacokinetics, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033-1310, USA*
[b] *Schering-Plough Research Institute, San Raffaele Science Park, 20132 Milan, Italy*

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ABSTRACT

Antagonism of the adenosine A_{2a} receptor offers great promise in the treatment of Parkinson's disease. In the course of exploring pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine A_{2A} antagonists, which led to clinical candidate SCH 420814, we prepared 1,2,4-triazolo[1,5-*c*]pyrimidines with potent and selective (vs A_1) A_{2a} antagonist activity, including oral activity in the rat haloperidol-induced catalepsy model. Structure–activity relationships and plasma levels are described for this series.

Parkinson's disease (PD) is a very serious neurological disorder, and current methods of treatment fail to achieve long-term control. Since adenosine A_{2A} receptor antagonists have been shown to restore the deficits caused by degeneration of the striatonigral dopamine system, which is compromised by the loss of striatal neurons in this disease, A_{2A} antagonism affords a possible treatment for PD.[1] The A_{2A} antagonist KW-6002 (istradefylline) was shown to be effective in animal models of PD, and recent clinical studies demonstrated efficacy in alleviation of symptoms of the disease.[2]

Adenosine A_{2A} receptor antagonists of several structural types have been described. In our previous report[3] we have summarized these,[4] as well as our development of the pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine SCH 420814 **1a** as a potential agent for the treatment of Parkinson's disease.[5] As part of the exploration of this series, several structural types of 1,2,4-triazolo[1,5-*c*]pyrimidines were evaluated. The activity of a set of 7-aryl-1,2,4-triazolo[1,5-*c*]pyrimidines of type **2** has been described.[6] In the present report, we describe a series of 1,2,4-triazolo[1,5-*c*]pyrimidines **3** bearing a 7-substituent linked through a heteroatom.[7] These compounds are high affinity adenosine A_{2A} receptor antagonists with high selectivity versus the A_1 receptor. In addition, oral activity has been demonstrated in the rat haloperidol-induced catalepsy model. Other workers have described compounds of type **3** with cyclic linker groups,[8,9] as well as limited efforts with chain linker groups.[10] We explored both alkyl and piperazino-alkyl linker groups in depth, together with efforts to replace the 2-furanyl substituent found in the majority of reported adenosine A_{2A} receptor antagonists.

We began our studies with a simple alkyl linker. Synthetic methods were developed to explore a full range of heteroatoms **X** in structure **3**, as shown in Scheme 1. For O and N heteroatoms, intermediates **7** and **8** were prepared in a straight-forward manner. For S as the heteroatom, intermediate **9** was prepared in two steps, while a keto-ester **6** was employed for the carbon attachment in **10**. Formation of hydrazides **11** was unsuccessful under nucleophilic displacement conditions and required the seldom employed acid-catalyzed conditions. Final Dimroth-mediated cyclization to **12**, **13**, **14**, and **15** was achieved by heating **11** with bis-trimethylsilylacetamide as previously disclosed.[3]

Utilizing this methodology[11] we prepared the set of targets **12a–e** shown in Table 1. A receptor binding assay with human A_{2A} receptors showed that each of heteroatoms provided a potent antagonist, but only **12c** with the NMe group provided the desired high selectivity versus the adenosine A_1 receptor.[12] Compound **12c**, however, showed no detectable plasma level upon oral administration in rats.[13]

Additional structure–activity relationships were developed in relation to chain length (compounds **13a–b**), aromatic substitution (**14**), and N-substitution (**15a–b**). While receptor affinity is reduced with the shorter chain of **13a**, affinity is retained with the longer chain of **13b**, but receptor selectivity is reduced. Substitution of

* Corresponding author. Tel.: +1 908 740 3495; fax: +1 908 740 7152.
E-mail address: bernard.neustadt@spcorp.com (B.R. Neustadt).

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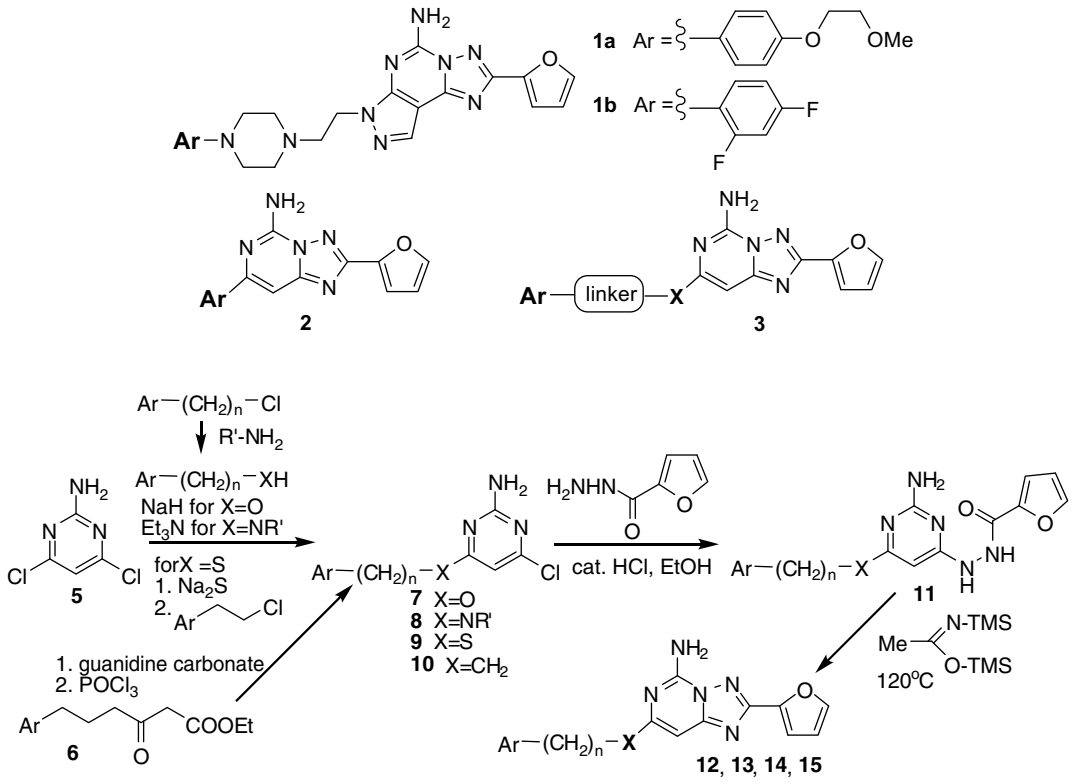
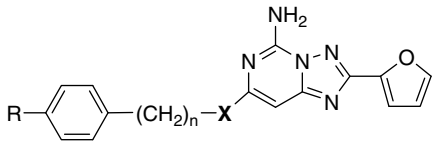


Scheme 1. Synthetic methods for preparation of compounds **12**, **13**, **14**, and **15**.

Table 1
Structure–activity relationships for aralkyl compounds



Compound	X	*n*	R	A_{2A} K_i[a] (nM)	A_{2A}/A_1[a]
12a	O	2	OMe	2.8	58
12b	NH	2	OMe	5.8	20
12c	NMe	2	OMe	1.8	473
12d	S	2	OMe	1.6	58
12e	CH_2	2	OMe	11.5	31
13a	NMe	1	OMe	46	40
13b	NMe	3	OMe	5.7	76
14	NMe	2	F	2.0	248
15a	NEt	2	F	3.0	525
15b	NCH_2CH_2OMe	2	F	1.0	566

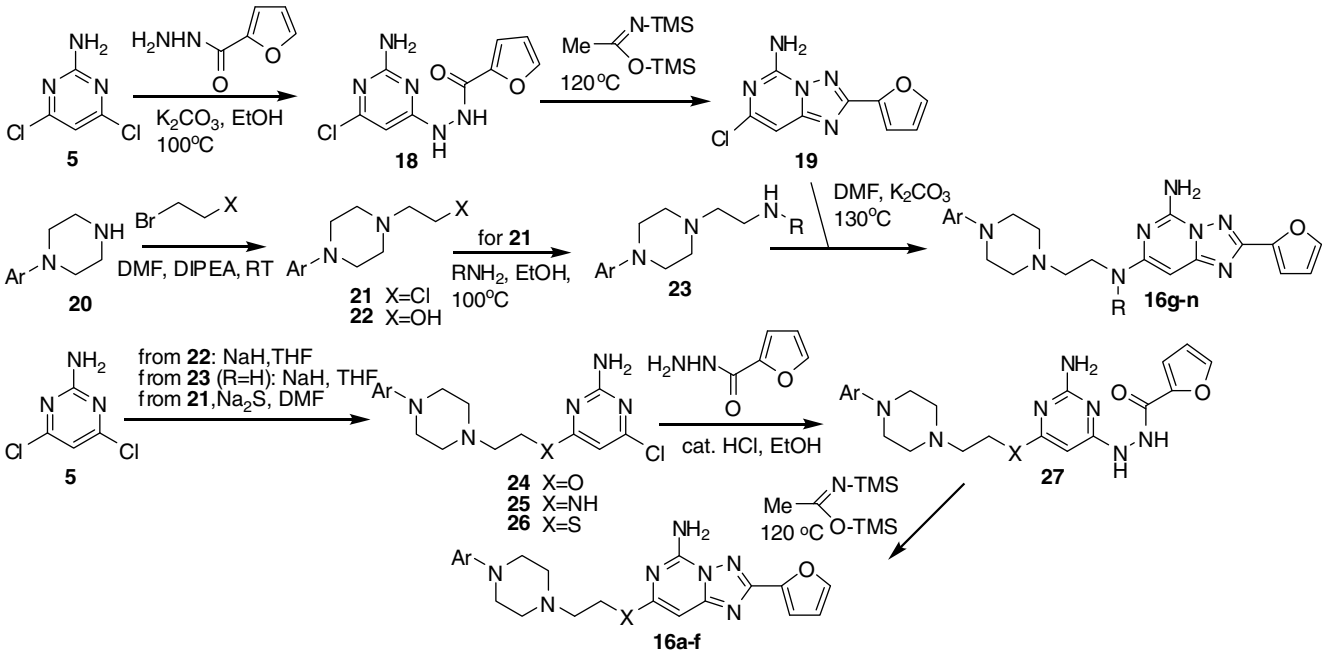
[a] Average of duplicate determinations, human receptors.

fluoro for methoxy (**14**) retained both attributes, while larger N-substitution was tolerated, as seen in **15a** and **15b**. Nevertheless, following oral administration of selected analogs, for example, **15b**, to rats at the dose of 3 mg/kg, plasma levels of the compounds were below the limit of detection.[14]

To improve bioavailability, we investigated aryl-piperazine derivatives related to **1a** and **1b**.[3] These compounds were prepared by the methods shown in Scheme 2.[10] Compounds **16e** and **16g** have been described in a previous paper.[10] Assessment of compounds **16a–h** resulted in identification of significant plasma levels (**16b**, **16d**, and **16h**) as shown in Table 2. Plasma levels of the 4-(methoxyethoxy)phenyl compounds were uniformly superior to those of the 2,4-difluorophenyl analogs, and brain/plasma ratios of these analogs typically approached unity. Compounds **16d** and **16g** were of particular interest because of their in vivo activity (*vide infra*). We further explored elaboration of the *N*-methyl moiety and demonstrated that functionalized alkyl groups were very well tolerated (**16i–n**).

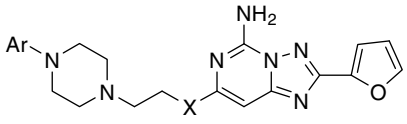
Encouraged by these results, we employed the aryl-piperazine moieties present in **16a–n** to explore SAR for the 2-furanyl group (Table 3), which is a common structural feature of reported A_{2A} antagonists. A 5-chloro substituent on the furan ring resulted in a significant loss in receptor affinity (**17a** vs **16b**), as did replacement with an unsubstituted phenyl group (**17b** vs **16h**). However, appropriate substitution on the phenyl group, such as 3-CN, restored affinity and receptor selectivity (**17d**), in addition to providing good plasma levels in the rat following oral administration. Certain aza-heterocycles were well tolerated as replacements for the furan (**17e** and **17f**). In general, the active compounds did not possess oral anti-cataleptic activity superior to that of furan derivative **16g** (Table 4).

We were particularly desirous of demonstrating in vivo activity in the rat haloperidol-induced catalepsy model.[15] Compounds **1a** and **1b** have shown potent and robust activity in this assay.[3] Activity of compounds from the current series is shown in Table 4. After oral administration (3 mg/kg) compounds **16d** and **16g** showed substantial activity at the 1-h time point, but for **16g** this activity was attenuated at four hours. The *N*-cyclopropylmethyl derivatives **16m** and **16n** were active at 3 mg/kg, but **16m** showed attenuated activity at four hours. The non-furan compounds **17c** and **17d**, in spite of high potency and good plasma and brain levels, failed to show pronounced in vivo activity. Reasons for the lack of in vivo activity of **17c** and **17d** are not understood; possibilities include unfavorable striatal distribution or high non-specific binding to brain tissue. Finally, comparison with **1a** and **1b** shows that the most potent compounds of this



Scheme 2. Synthetic methods for preparation of compounds **16**.

Table 2
Structure–activity relationships for aryl-piperazine compounds



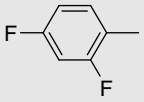
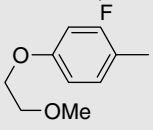
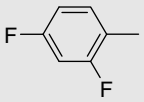
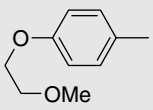
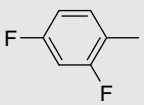
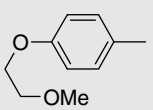
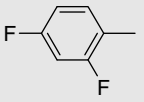
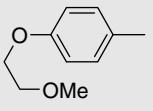
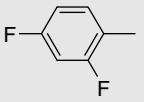
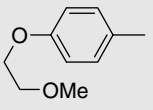
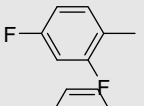
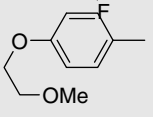
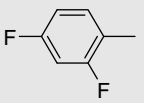
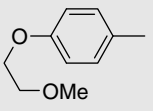
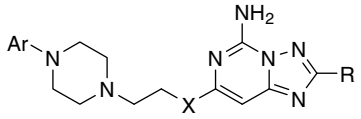
Compound	X	Ar	A_{2A} K_i[a] (nM)	A_{2A}/A_1[a]	Rat plasma AUC at 3 mg/kg, ng h/ml[b]
16a	O		6.0	275	187
16b	O		2.8	405	943
16c	S		1.4	365	229
16d	S		1.5	965	910
16e	NH		1.5	262	<LOQ
16f	NH		9.5	145	103

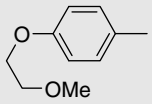
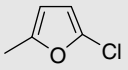
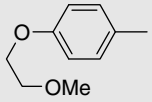
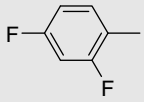
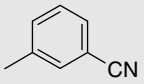
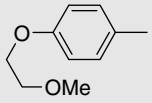
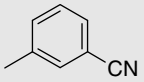
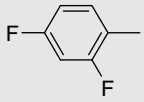
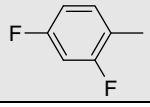
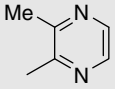
Table 2 (*continued*)

Compound	X	Ar	A_{2A} K_i[a] (nM)	A_{2A}/A_1[a]	Rat plasma AUC at 3 mg/kg, ng h/ml[b]
16g	NMe		1.0	1580	53
16h	NMe		2.5	694	521
16i	NEt		0.9	312	50
16j	NEt		1.5	102	230
16k	NCH_2CH_2OMe		0.5	1059	<LOQ
16l	NCH_2-CH_2OMe		0.7	338	355
16m	NCH_2-*c*-Pr		0.3	831	17
16n	NCH_2-*c*-Pr		0.8	234	245

[a] Average of duplicate determinations, human receptors.
[b] LOQ at each time point 10 ng/ml.

Table 3
Activity of compounds with furan moiety modified or replaced



Compound	X	Ar	R	A_{2A} K_i[a] (nM)	A_{2A}/A_1[a]	Rat plasma AUC at 3 mg/kg, ng h/ml
17a	O			40	40	6
17b	NMe			25	56	
17c	NMe			1.8	620	1295
17d	NMe			0.7	1071	546
17e	NMe			0.3	7000	
17f	NMe			0.3	7368	

[a] Average of duplicate determinations, human receptors.

Table 4
Activity of compounds in the rat haloperidol-induced catalepsy model

Compound	Hetero-link	Dose, mg/kg	Rat catalepsy, % inhibition[a]	
			1 h	4 h
16a	O	3.0	25	0
16b	O	1.0	45	25
16c	S	3.0	50	45
		1.0	25	5
16d	S	3.0	65	65
		1.0	50	15
16g	NMe	3.0	75	35
		1.0	50	30
16h	NMe	1.0	15	0
16k	NCH_2CH_2OMe	3.0	56	57
16l	NCH_2CH_2OMe	3.0	57	37
		1.0	29	6
16m	NCH_2-*c*-Pr	3.0	65	41
		1.0	40	34
16n	NCH_2-*c*-Pr	3.0	65	77
		1.0	7	32
17c	NMe	3.0	35	14
17d	NMe	3.0	29	31
1a	—	1.0	77	70
		0.3	60	60
		0.1	25	25
1b	—	1.0	75	80
		0.3	75	NT

[a] Average for $n = 3$. Maximum reduction attainable is 60–80%.

series were nevertheless several-fold less potent than **1a** and **1b** in vivo.

In summary, we have shown potent and selective adenosine A_{2A} receptor antagonist activity for 1,2,4-triazolo[1,5-*c*]pyrimidines bearing either an aralkyl or arylpiperazino-alkyl chain in the 7-position. Compounds of the latter series achieved significant rat plasma levels. Successful replacements for the widely-employed furanyl moiety were demonstrated. In vivo activity was observed for a number of compounds, although the level of potency seen in tricyclic compounds **1a** and **1b** was not achieved.

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