Brief Articles

Discovery and Characterization of 4′-(2-Furyl)-*N*-pyridin-3-yl-4,5′-bipyrimidin-2′-amine (LAS38096), a Potent, Selective, and Efficacious A_{2B} Adenosine Receptor Antagonist

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A novel series of *N*-heteroaryl 4′-(2-furyl)-4,5′-bipyrimidin-2′-amines has been identified as potent and selective A_{2B} adenosine receptor antagonists. In particular, compound **5** showed high affinity for the A_{2B} receptor (K_i = 17 nM), good selectivity (IC_{50}: A_1 > 1000 nM, A_{2A} > 2500 nM, A_3 > 1000 nM), displayed a favorable pharmacokinetic profile in preclinical species, and showed efficacy in functional in vitro models.

Introduction

Adenosine is a mediator that functions as regulator of cardiovascular homeostasis, tissue protection during ischemia reperfusion, and as modulator of inflammatory processes.[1,2] The initial observation that adenosine induced bronchoconstriction in asthmatics and that high levels of this mediator were detected in their bronchoalveolar lavage led to its early implication in the pathophysiology of human asthma.[3,4]

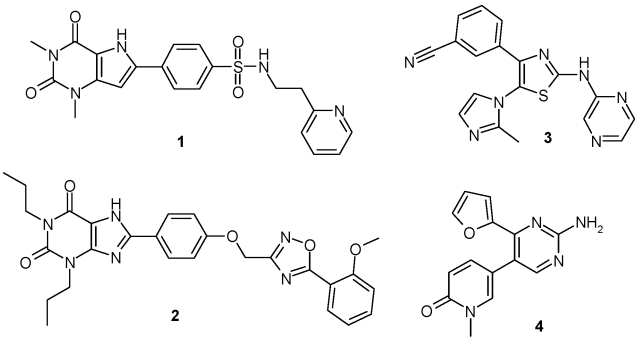
Adenosine potentiates the IgE-dependent degranulation of human mast cells through a mechanism believed to be mediated by the A_{2B} receptor, one of the four adenosine receptors.[4,5] A_{2B} is a low affinity receptor for adenosine that is mainly expressed in the gastrointestinal tract, urinary bladder, and lung tissue.[6] Among immune cell lineages, A_{2B} is expressed in mast cells, neutrophils, monocytes, macrophages, dendritic cells, and T cells.[7,8]

Characterization of mice deleted in the A_{2B} gene has shown no major deficiencies and suggests a potential anti-inflammatory role of the A_{2B} receptor.[9,10] This is in contrast with a large body of previous evidence demonstrating the overall pro-inflammatory properties of this receptor, suggesting a potential tissue or cell specific dual role in the context of inflammatory disease.[11]

A_{2B} receptors are responsible for the adenosine-mediated release of several inflammatory cytokines from mast cells, airway and bronchial epithelial cells, fibroblasts, smooth muscle cells, intestinal epithelial cells, and monocytes.[5,11,12] Therefore, A_{2B} antagonists have the potential to become a new pharmacological drug class for the treatment of asthma.[13]

Chart 1 shows some A_{2B} antagonists reported in the literature. The recently disclosed xanthine-type structures **1** and **2**, which topologically have similar features, displayed an excellent in vitro profile but suffered from low oral absorption in rats.[14] Additionally, diarylheterocycles such as compounds **3** and **4** have been reported to be potent A_{2B} antagonists, but selectivity remained as a challenge. In particular, compound **3** has been reported to show a good oral bioavailability.[15]

Chart 1. Structure of Some Selected A_{2B} Adenosine Receptor Antagonists



We have recently discovered a number of *N*-heteroaryl 4′-(2-furyl)-4,5′-bipyrimidin-2′-amines as potent and selective A_{2B} adenosine receptor antagonists.[16] Herein we report some of the SAR we developed and the characterization of the lead compound LAS38096.

From an initial SAR optimization it was found that 2-furyl and 3-pyrimidinyl formed a good substitution pattern at the pyrimidine central core, not only to keep good potency in antagonizing the A_{2B} receptor, but more importantly, to improve selectivity against the other adenosine receptor subtypes (A_{2A}, A_1, and A_3).

Chemistry

Compounds **5**−**14** were prepared according to the synthetic sequence outlined in Scheme 1. Thus, treatment of 4-methylpyrimidine **15** with LiHMDS followed by condensation with ethyl-2-furoate **16** provided ketone **17**.

Further treatment with neat dimethylformamide dimethylacetal followed by condensation with guanidine in the presence of potassium carbonate provided the key aminopyrimidine derivative **18**. Compound **5** was obtained by palladium-catalyzed *N*-arylation of pyrimidine **18** with 3-bromopyridine in the

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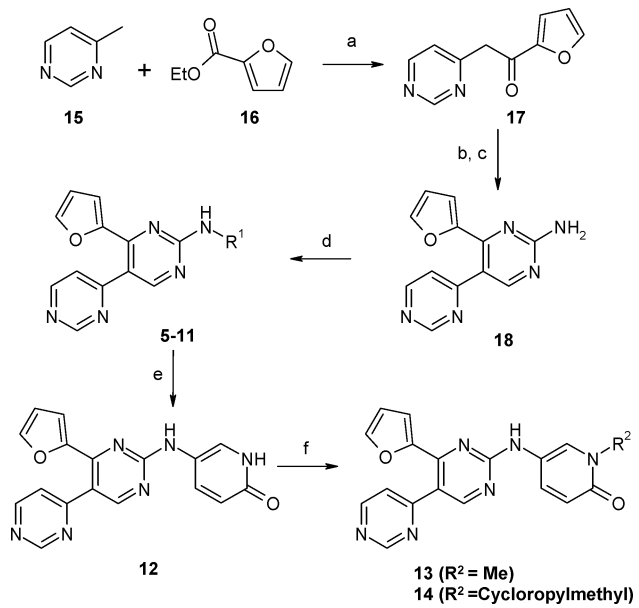
Scheme 1[a]



[a] Reagents and conditions: (a) LiHMDS, THF, rt, 2 h, 85%; (b) DMF−DMA, 100 °C, 2 h, 75%; (c) guanidine·HCl, K_2CO_3, DMF, 70 °C, 20 h, 61%; (d) for **5**, **6**, and **9**−**11**, $Pd_2(dba)_3$, R^1Br, Cs_2CO_3, xantphos, dioxane, 20 h, 100 °C, 40−75%; for **7**, $Pd(AcO)_2$, 2-chloropyrazine, Na*t*-BuO, 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl, toluene, 110 °C, 20 h, 33%; for **8**, CuI, 5-bromo-2-methoxypyridine, *N*,*N*′-dimethylethylenediamine, K_2CO_3, dioxane, 18 h, 110 °C, 69%; (e) compound **8**, HBr (aq), 110 °C, 5 h, 60%; (f) NaH, DMF, R^2Br, rt to 80 °C, 2 h, 40−57%.

presence of Xantphos as ligand.[17] Compounds **5**, **6**, and **9**−**11** were prepared in a similar manner. Compounds **7** and **8** were prepared using a Pd- or Cu-catalyzed *N*-arylation, respectively, using different ligands. Acid-catalyzed demethylation of compound **8** provided pyridone **12** that was transformed into the *N*-alkylated pyridones **13** and **14** by reaction with the corresponding alkyl bromides in the presence of a base such as sodium hydride.

Results and Discussion

As depicted in Table 1, a number of selected analogues were prepared, showing good binding affinities for the A_{2B} receptor in the radioligand assay, as well as good selectivity versus A_1, A_{2A}, and A_3 adenosine receptors. Initially we introduced unsubstituted nitrogen-containing heterocycles in R^1 such as pyridine, pyrimidine or pyrazine (compounds **5**−**7**). Among these, 3-pyridyl derivative **5** was found to show high potency and selectivity. Substitution by a methoxy group (compounds **8** and **9**) led to a drop in potency while keeping good selectivity. We speculated that the nitrogen atoms of the 3-pyridyl or the 3-pyrimidinyl rings were having a positive interaction with the receptor, so we prepared compounds **10** and **11** to evaluate the effect of substitution by a hydrogen bond acceptor. For cyano derivative **10**, even though affinity for the A_{2B} receptor dropped, we observed an excellent selectivity versus A_3. *N*-Oxide **11** had a 2-fold decrease in affinity compared to that of the corresponding reduced analogue **5**. Finally, we explored the introduction of a pyridone moiety (compounds **12**−**14**) and compound **12** was found to be one of the most potent (K_iA_{2B}: 16 nM) and selective compounds within the series (IC_{50} A_1 > 10 000 nM, IC_{50} A_{2A} > 2500 nM, IC_{50} A_3 > 1000 nM). Alkylation at the pyridine nitrogen had a slightly detrimental effect on A_3 selectivity (compound **13**) and on A_{2B} potency for the more lipophilic analogue **14**.

Additional profiling revealed that compound **12** displayed relatively low systemic exposures in rat oral and intravenous pharmacokinetic studies. On the basis of the good binding profile, compound **5** (LAS38096) was selected for further characterization in functional cellular assays, pharmacokinetics, as well as in vitro efficacy studies.

To further characterize the affinity of **5** against human and mouse adenosine receptors, the compound was evaluated in intracellular cAMP assays. Among other signaling pathways, agonist stimulation of A_{2B} receptors results in rapid increases of intracellular cAMP levels.[18a] Thus, we decided to test the effect of **5** over the increase in cAMP levels induced by the adenosine analog NECA in human HEK293 cells (expressing A_{2B} receptors) and CHO cells transfected with the mouse A_{2B} receptor.

Compound **5** was capable of inhibiting A_{2B} mediated NECA dependent increases in intracellular cAMP with IC_{50} of 321 nM and 349 nM in cells expressing human and mouse receptors respectively (Table 2). These results demonstrate that compound **5** is a functional A_{2B} receptor antagonist which displays a similar affinity for the human and mouse receptors.

Given that a role of the A_3 receptor in mouse models of allergy has been previously suggested[19] we decided to evaluate the affinity of **5** for this receptor to rule out any potential A_3-dependent effect in the context of murine efficacy models.

In contrast to A_{2B}, agonist stimulation of the A_3 receptor downregulates an adenylate cyclase-dependent increase in intracellular cAMP.[18b] In agreement with radioligand binding studies performed with the human A_3 receptor, **5** did not significantly block the murine A_3 receptor in a cellular assay measuring intracellular cAMP levels in cells transfected with this receptor (less than 5% inhibition at a concentration of 10 μM of compound **5**).

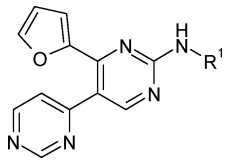
Among other inflammatory cytokines, the A_{2B} receptor mediates the NECA-induced release of IL-6 in airway epithelial cells, bronchial smooth muscle cells, primary human fibroblasts, intestinal epithelial cells, osteoblasts, pituitary folliculostellate cells, and atroglioma/astrocytoma cells.[11] Therefore, we decided to evaluate the effect of **5** in an in vitro model of primary mouse and human dermal fibroblasts.

Results depicted in Figure 1 show that incubation in the presence of 10 μM NECA induced the synthesis of IL-6 both in mouse and in human cells about 3-fold over nonstimulated cells. Under those conditions, **5** was capable of inhibiting the NECA-dependent production of IL-6 dose dependently with IC_{50} values of 340 nM and 640 nM in human and mouse fibroblasts, respectively. This confirms the anti-inflammatory properties of compound **5** in the context of a cellular in vitro model of IL-6 production.

The pharmacokinetic parameters of compound **5** in mouse, rat, and dog are summarized in Table 3. Regardless of the species, compound **5** was absorbed rapidly (t_{max} < 1 h), with the longest t_{max} observed in the dog. The AUC in mouse (4 μM·h) was four times lower than in the other two species studied. Compound **5** exhibited good bioavailability (75 and 80% for the rat and dog, respectively). The half-life in rat and dog was short (<1 h), resulting from a moderate-to-high plasma clearance and a low-to-moderate volume of distribution.

The encouraging oral bioavailability exhibited by **5** has subsequently allowed additional characterization of the efficacy of the compound in vivo in an allergic mouse model. Therefore, mice treated with compound **5** showed significantly less bronchial hyperresponsiveness, mucus production, and OVA-

Table 1. Adenosine Receptor Affinity of *N*-Heteroaryl 4′-Furyl-4,5′-bipyrimidin-2′-amines



cmpd	R^1	K_i[a] (nM) or % inhibition of radioligand binding at indicated concentration (nM) ±SEM[b]			
		hA_{2B}	hA_{2A}	hA_1	hA_3
5	3-pyridyl	17 ± 4	>2500 (40% ± 5)	>1000 (14% ± 4)	>1000 (36% ± 4)
6	3-pyrimidinyl	24 ± 0	>2500 (29% ± 32)	>10 000 (45 ± 6)	>1000 (42% ± 9)
7	2-pyrazinyl	116 ± 11	>2500 (21% ± 0.4)	>10 000 (30% ± 3)	>1000 (18% ± 6)
8	6-methoxypyridin-3-yl	115 ± 25	>2500 (21% ± 3)	>10 000 (25% ± 9)	>1000 (29% ± 2)
9	2-methoxypyrimidin-5-yl	39 ± 10	>2500 (25% ± 1)	>10 000 (45% ± 5)	>1000 (32% ± 4)
10	5-cyanopyridin-3-yl	69 ± 10	>2500 (37% ± 0)	>10 000 (22% ± 8)	>1000 (24% ± 5)
11	1-oxidopyridin-3-yl	34 ± 2	>2500 (24% ± 0.2)	>10 000 (38% ± 5)	>1000 (35% ± 4)
12	6-oxo-1,6-dihydropyridin-3-yl	16 ± 1	>2500 (25% ± 1.5)	>10 000 (31% ± 5)	>1000 (15% ± 1)
13	1-methyl-6-oxo-1,6-dihydropyridin-3-yl	28 ± 9	>2500 (20% ± 2)	>10 000 (17% ± 4)	>1000 (28% ± 21)
14	1-cyclopropylmethyl-6-oxo-1,6-dihydropyridin-3-yl	119 ± 39	>2500 (38.5% ± 1)	>10 000 (28% ± 2)	>1000 (29% ± 7)

[a] Values are reported as the mean of at least two independent determinations. Radioligand binding assay with ^{3}H-DPCPX as ligand and membranes from HEK293 cells transfected with human A_{2B} receptor. [b] Expressed as IC_{50}. Radioligand binding assays: A_{2A}, with ^{3}H-ZM241385 in HeLa cells; A_1, with ^{3}H-DPCPX in CHO cells; A_3, with ^{3}H-NECA in HeLa cells.

Table 2. Selectivity Profile of **5** in Intracellular cAMP Assays

	human A_{2B}	mouse A_{2B}
IC_{50} cAMP (nM) ± SEM[a]	321 ± 41	349 ± 76

[a] IC_{50} values are reported as the mean of at least four experiments.

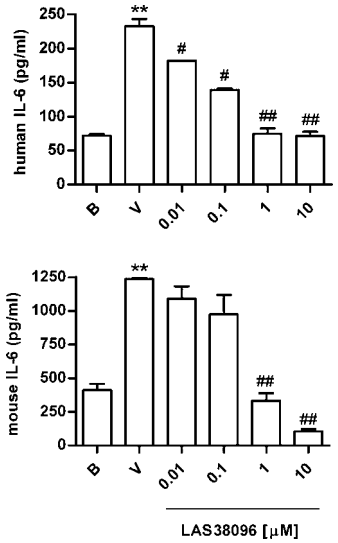


Figure 1. Effect of compound **5** on NECA-induced IL-6 synthesis by cultured dermal fibroblasts of human or mouse origin. Results are representative of three independent experiments performed in duplicate. B, basal (samples not treated with NECA); V, vehicle (samples treated with NECA and DMSO). $**p < 0.01$ vs basal (B), $\#p < 0.05$ vs vehicle (V), $\#\#p < 0.01$ vs vehicle (V).

specific IgE levels and a slight decrease in eosinophil infiltration and Th2 cytokine levels.[20]

In agreement with these results, additional published studies have also shown that selective A_{2B} antagonists are active in the context of functional murine in vivo models of allergy and pulmonary inflammation.[21] Overall, these results suggest that blockade of the A_{2B} receptor may provide clinical benefits in the treatment of chronic respiratory diseases.

Table 3. Pharmacokinetic Parameters of **5** in Mouse (only p.o.), Rat and Dog after Intravenous (i.v.) and Oral (p.o.) Administration

parameter	mouse[a]	rat[a]	dog[b]
p.o. dose (mg kg^{-1})	10	10	10
i.v. dose[c] (mg kg^{-1})		1	1
C_{max} (μM), p.o.	13 (9)	11 (4)	6
t_{max} (h), p.o.	0.3	0.3 (0)	1.3
AUC[d] (μM.h), p.o.	4	16 (8)	15
$t_{1/2}$ (h), i.v.		0.2 (0)	0.8
MRT[c] (h), p.o.		1.4 (0.2)	1.8
MRT (h) i.v.		0.3 (0)	0.7
Cl[e] (mL $min^{-1}kg^{-1}$), i.v.		25 (3)	28
V_{ss}[f] (L kg^{-1}), i.v.		0.5 (0)	1.1
F[g] (%)		75 (37)	81

[a] Results expressed as the mean ± SD in parenthesis ($n = 3$). [b] Results expressed as the mean ($n = 2$). [c] MRT = Mean residence time. [d] AUC = area under the curve. [e] Cl = total plasma clearance. [f] V_{ss} = volume of distribution at steady state. [g] F = bioavailability.

In conclusion, we have identified a novel series of *N*-heteroaryl 4′-furyl-4,5′-bipyrimidin-2′-amines as potent A_{2B} adenosine receptor antagonists and selective versus A_{2A}, A_1, and A_3 receptors. Optimization of the series SAR led to the identification of **5** (LAS38096), which displayed a favorable pharmacokinetic profile in preclinical species and showed efficacy in functional in vitro and in vivo models of allergy and inflammation.

On the basis of its favorable in vitro pharmacology, efficacy, and pharmacokinetic profile, compound **5** was advanced into preclinical in vivo safety and toxicology studies.

Experimental Section

Synthesis of Compound 5 (LAS38096). 1-(2-Furyl)-2-pyrimidin-4-ylethanone (17). To a solution of 4-methylpyrimidine (0.93 g, 9.9 mmol) and ethyl 2-furoate (1.54 g, 11 mmol) in anhydrous THF (8 mL) at 0 °C was added dropwise via syringe pump (1 h) a solution of lithium bis(trimethylsilyl)amide (20 mL, 20 mmol, 1 M solution in hexanes). The resulting mixture was stirred at room temperature for 2 h. The precipitate was collected

by filtration, washed with a saturated aqueous solution of ammonium chloride and water, and dried under vacuum to yield the title compound as a yellow solid (1.59 g, 85%).

3-(Dimethylamino)-1-(2-furyl)-2-pyrimidin-4-ylprop-2-en-1-one. A suspension of 1-(2-furyl)-2-pyrimidin-4-ylethanone **17** (1.59 g, 8.45 mmol) in *N*,*N*-dimethylformamide dimethyl acetal (4.5 mL, 33.8 mmol) was heated to 100 °C for 2 h. The mixture was allowed to cool to room temperature, the solvent was evaporated under reduced pressure, and the residue was partitioned between ethyl acetate and a saturated solution of ammonium chloride. The aqueous phase was extracted with ethyl acetate, and the organic extracts were washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure to provide the title compound as a red oil (1.54 g, 75%).

4′-(2-Furyl)-4,5′-bipyrimidin-2′-amine (18). A mixture of 3-(dimethylamino)-1-(2-furyl)-2-pyrimidin-4-ylprop-2-en-1-one (1.54 g, 6.33 mmol), K_2CO_3 (5.24 g, 38 mmol), and guanidine hydrochloride (1.81 g, 19 mmol) in DMF (12 mL) was heated to 70 °C for 20 h and then allowed to cool to room temperature. Water was added, and the precipitate was collected by filtration and washed copiously with water. The solid was dried under vacuum to yield the title compound (920 mg, 61%).

4′-(2-Furyl)-*N*-pyridin-3-yl-4,5′-bipyrimidin-2′-amine (5). An oven-dried resealable Schlenk tube was charged with 4,5-bis-(diphenylphosphino)-9,9-dimethylxanthene (Xantphos, 25.4 mg, 0.044 mmol), 3-bromopyridine (96.3 mL, 1 mmol), Cs_2CO_3 (456 mg, 1.4 mmol), 4′-(2-furyl)-4,5′-bipyrimidin-2′-amine (compound **19**; 263 mg, 1.1 mmol) and dioxane (5 mL). The Schlenk tube was subjected to three cycles of evacuation−backfilling with argon, and tris(dibenzylideneacetone)dipalladium-(0) [$Pd_2(dba)_3$; 18.3 mg, 0.02 mmol] was added. After three new cycles of evacuation−backfilling with argon, the Schlenk tube was capped and placed in a 100 °C oil bath. After 20 h, the mixture was cooled, 10 mL of water was added, and the solid was collected by filtration to give the title compound as a yellowish solid (211 mg, 67%).

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Supporting Information Available: General experimental details, experimental procedures, and characterization data for **5**−**14**, table of combustion analysis and HPLC data for key compounds, and detailed description of pharmacokinetic and efficacy assays. This material is available free of charge via the Internet at http://pubs.acs.org.

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