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Article

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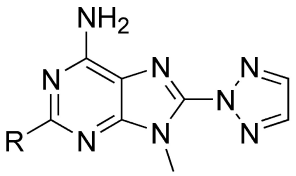
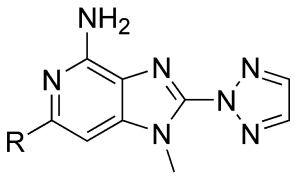


Series A

R = H, -CH_3, -$(CH_2)_2CH_3$, -$CH(CH_3)CH_3$, -$(CH_2)_3CH_3$, -$(CH_2)_4CH_3$, -$(CH_2)_2Ph$



Series B

R = H, -CH_3

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2-*n*-Butyl-9-methyl-8-[1,2,3]triazol-2-yl-9*H*-purin-6-ylamine and Analogues as A_{2A} Adenosine Receptor Antagonists. Design, Synthesis, and Pharmacological Characterization

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Two types of adenosine receptor ligands were designed, i.e., 9*H*-purine and 1*H*-imidazo[4,5-*c*]pyridines, to obtain selective A_{2A} antagonists, and we report here their synthesis and binding affinities for the four adenosine receptor subtypes A_1, A_{2A}, A_{2B} and A_3. The design was carried out on the basis of the molecular modeling of a number of potent adenosine receptor antagonists described in the literature. Three compounds (**25b**−**d**) showed an interesting affinity and selectivity for the A_{2A} subtype. One of them, i.e., ST1535 (2-*n*-butyl-9-methyl-8-[1,2,3]triazol-2-yl-9*H*-purin-6-ylamine, **25b**) (K_i A_{2A} = 6.6 nM, K_i A_1/A_{2A} = 12; K_i A_{2B}/A_{2A} = 58; K_i A_3/A_{2A} > 160), was selected for in vivo study and shown to induce a dose-related increase in locomotor activity, suggestive of an A_{2A} antagonist type of activity.

Introduction

Adenosine is an endogenous modulator which, among other effects, mediates a general depression of the central nervous system, vasodilatation and inhibition of platelet aggregation.[1] It acts at specific membrane G-protein receptors[2] positively (A_{2A}, A_{2B})[1] or negatively (A_1, A_3)[1] linked to adenylate cyclase. The discovery of selective ligands facilitated the defining of tissue distribution and the role of each receptor subtype. Receptors A_{2A} are densely distributed in the central nervous system (striatum, nucleus accumbens and olfactory tubercles) where they play an important role in the regulation of mood and motor activity.[1] Available evidence provided the basis for the formulation of a theory according to which selective A_{2A} adenosine receptor antagonists can be useful in the treatment of Parkinson's disease.[3]

A number of potent and subtype selective A_{2A} antagonists, of various structures, including xanthines and nonxanthines, are reported in the literature.[4] The most important xanthine-based adenosine A_{2A} receptor antagonist is KW-6002 (((*E*)-1,3-diethyl-8-(3,4-dimethoxystyryl)-7-methyl-3,7-dihydro-1*H*-purine-2,6-dione, **1**).[5] SCH 58261 (5-amino-7-(2-phenylethyl)-2-(2-furyl)pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine, **2**)[6] and ZM 241385 (4-[2-[[7-amino-2-(2-furyl)[1,2,4]-triazolo[2,3-*a*]-[1,3,5]triazin-5-yl]amino]ethyl]phenol, **3**),[7] which has been derived from the prototype CGS 15943 (5-amino-9-chloro-2-(furyl)-1,2,4-triazolo[1,5-*c*]quinazoline, **4**) (Figure 1)[8] are considered as the reference ligands. Adenosine receptor antagonists with a purine ring have also been reported.[9]

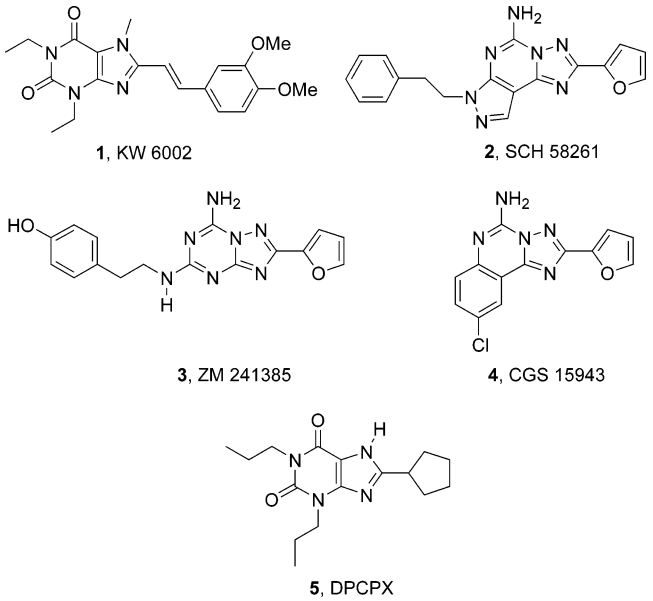

Figure 1. Reference compounds with different A_1/A_{2A} selectivity.

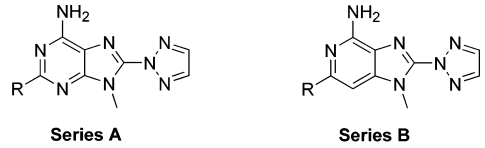

Figure 2. General formula of series A−B.

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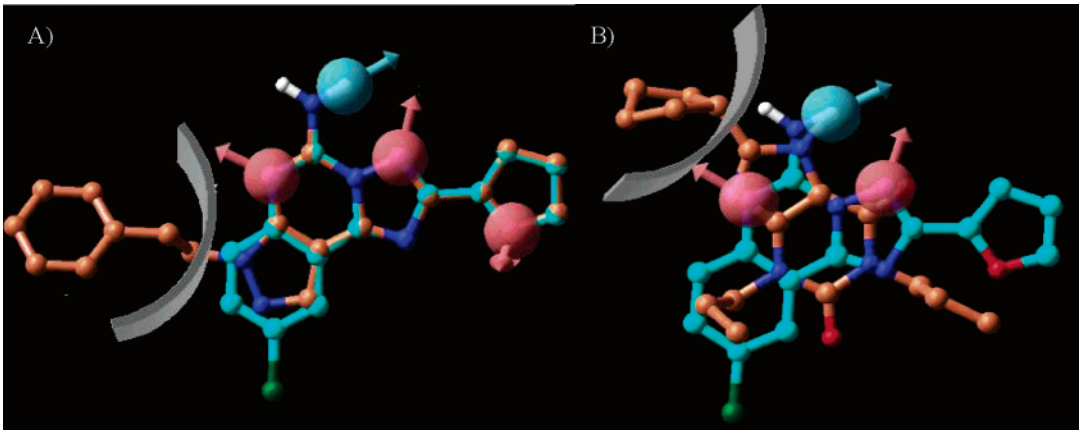
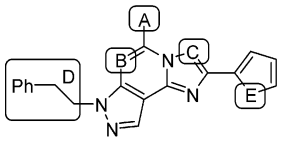


Figure 3. Proposed alignment between: (A) SCH 58261 (orange) and CGS 15943 (light blue). (B). DPCPX (orange) and CGS 15943 (light blue). Heteroatoms are colored as atom type. Pharmacophoric features are highlighted as follows: red vectors are H-bond acceptors, blue vectors are H-bond donors (as visualized using software Phase, Schrodinger Inc.), gray solids represent steric clashes, respectively, in A_1 and A_{2A} receptors.



SCH 58261

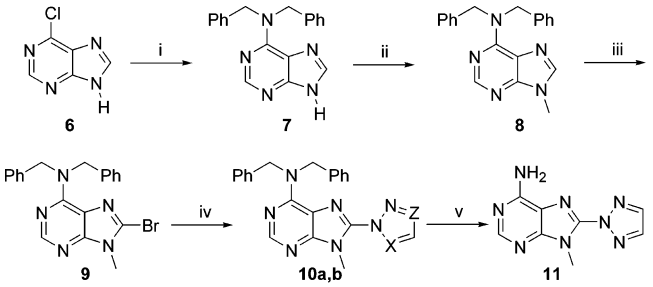
A: H-bond donor (NHR; R=H or small hydrophobic group)
B: H-bond acceptor
C: H-bond acceptor
D: hydrophobic / aromatic zone
E: H-bond acceptor
B, **C** and **E**: part of an aromatic planar system

Figure 4. Pharmacophoric model visualized on SCH 58261.

The present paper describes a study aimed at generating new A_{2A} antagonist ligands on the basis of the available structure−activity knowledge for the A_{2A} receptor. We designed two different series (Figure 2): series A (9*H*-purine derivatives), series B (1*H*-imidazo-[4,5-*c*]pyridine derivatives). We report here the synthesis of compounds of these series and their binding affinities for the four adenosine receptor subtypes. Series A was explored more extensively than B. In the case of the former series we synthesized a number of 2-alkyl-substituted compounds and three of them (**25b**−**d**) showed good affinity and a varying degree of selectivity for A_{2A} adenosine receptor subtype.

Molecular Modeling. The molecular design of the new series of adenosine A_{2A} antagonists was carried out using 52 structures from the literature; in particular we used three classes with different selectivity for A_1 and A_{2A} subtypes where the best compounds were DPCPX (1,3-dipropyl-8-cyclopentylxanthine, **5**)[10] A_1 selective antagonist (K_i $A_1/A_{2A} = 2.1\ 10^{-3}$), CGS 15943 A_1/A_{2A} mixed antagonist (K_i $A_1/A_{2A} = 5.3$) and SCH 58261 A_{2A} selective antagonist (K_i $A_1/A_{2A} = 52.6$) (Figure 1). The reference molecules were built and optimized using semiempirical quantomechanic method AM1 (ChemX software, Chemical Design Ltd, Oxford Molecular Group, the Magdalene Centre, Oxford Science Park, Oxford OX4 4GA UK); we also obtained electrostatic potential maps which we used to compare the electronic features of the molecules and to invesigate the different alignments between compounds related or unrelated to the xanthine ring system.[1,11] In Figure 3A,B are shown our proposed superimpositions between SCH 58261 (orange) and CGS 15943 (light blue) (Figure 3A) and DPCPX (orange) and CGS 15943 (light blue) (Figure 3B). These alignments identified three common pharmacophoric points showing one H-bond donor and two H-bond acceptors that represent the minimum requirement to interact with both A_1 and A_{2A} receptors. An exclusion zone, representing an unfavorable steric interaction in the A_{2A} active site, is visualized as a gray solid in Figure 3B. An additional exclusion zone, representing an unfavorable steric interaction in the A_1 active site, is visualized as a gray solid in Figure 3A. Finally the furan ring on both CGS 15943 and SCH 58261 represents an additional pharmacophoric point (H-bond acceptor) (Figure 3A) relative to DPCPX. In the case of CGS 15943 and SCH 58261 a variation of the position or type of the heteroatom negatively modulates the potency but does not modify the selectivity for the A_1/A_{2A} subtypes. Figure 4 shows the final pharmacophoric model visualized on SCH 58261. On the basis of previous considerations, we planned some novel structures belonging to two classes of compounds (Figure 2) that contain all required pharmacophoric groups. In particular group D

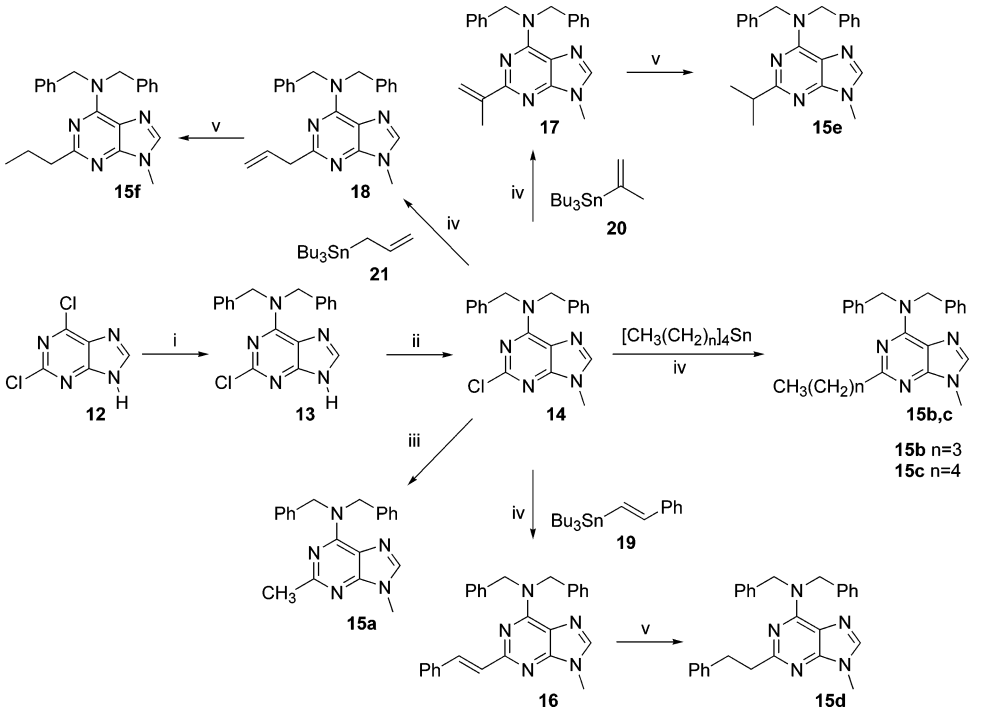
Scheme 1[a]



10a X=N Z=CH
10b X=CH Z=N

[a] (i)EtOH, Bn_2NH, iPr_2EtN, rfx (80 °C), 20 h. (ii) DMF, K_2CO_3, CH_3I, rt, 12 h. (iii) MeOH, THF, sodium acetate buffer (pH 4), Br_2, rt, 20 h. (iv) DMF, NaH, 1*H*-1,2,3-triazole, rfx (100 °C). (v) CH_2Cl_2, CF_3SO_3H, rfx (40 °C), 5 h.

Scheme 2[a]



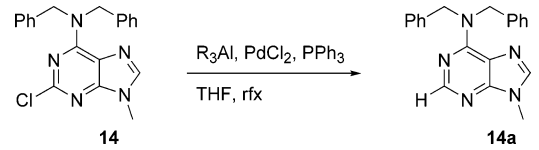
[a] (i) EtOH, Bn_2NH, iPr_2EtN, rfx (80 °C), 20 h. (ii) DMF, K_2CO_3, CH_3I, rt, 12 h. (iii) THF, $Al(CH_3)_3$, $PdCl_2$, PPh_3, rfx (50 °C), 24 h. (iv) NMP, $Pd(PPh_3)_4$, rfx (120 °C). (v) EtOH, H_2, Pd/C, rt.

(Figure 4) is an alkyl or arylalkyl chain useful in modulating selectivity versus A_{2A} subtype receptor, and group E (Figure 4) can be a 1,2,3 triazole or oxazole ring useful for improving the solubility profile and for providing one more H-bond acceptor relative to furan.

Chemistry. Synthesis of 9*H*-Purine Derivatives (series A). The synthesis of 2-unsubstituted 9-methyl-8-[1,2,3]triazol-2-yl-9*H*-purin-6-ylamine (**11**) is described in Scheme 1. Dibenzyl-(9-methyl-9*H*-purin-6-yl)-amine (**8**) was prepared by double substitution at the 6 and 9 positions of commercially available 6-chloro-9*H*-purine (**6**) with dibenzylamine and methyl iodide.[12] Selective bromination of **8** with bromine in the presence of sodium acetate buffer (pH 4) gave the bromo derivative **9**,[13] which, upon treatment with 1*H*-1,2,3-triazole, produced a mixture of the two regioisomers **10a**,**b**[14] that were separated by flash chromatography on silica gel. Finally, acid-catalyzed debenzylation of **10a** yielded **11**,[15] whereas deprotection of compound **10b** under the same conditions yielded an untractable mixture of compounds.

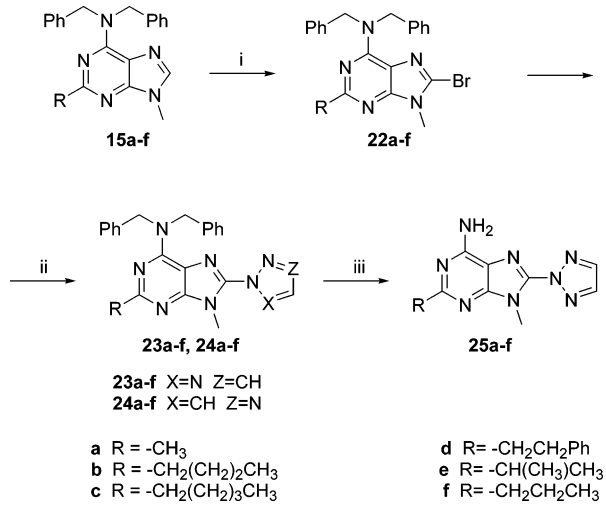
The synthesis of the 2-alkyl-adenines (**15a**−**f**) is described in Scheme 2. 2-Chloro-6-dibenzylamine-9-methyl-9*H*-purine (**14**) was obtained by sequential substitution with dibenzylamine and methylation of 2,6-dichloro-9*H*-purine (**12**) according to the literature.[12] Cross-coupling reaction of **14** with trimethylaluminum in the presence of palladium catalyst ($PdCl_2$) and triphenylphosphine gave **15a**.[16] Instead, reductive dehalogenation took place when triisopropylaluminum and tributylaluminum were used (Scheme 3). Therefore, compounds **15b**,**c** and **16**−**19** were synthesized by Stille's reaction with the corresponding organostannanes (Scheme 2).[17] Catalytic hydrogenation of **16**, **17** and **18** gave **15d**, **15e** and **15f**, respectively (Scheme 2). As described in Scheme 4 compounds **15a**−**f** were subsequently bromurated (**22a**−**f**)[13] and substituted

Scheme 3[a]



[a] R = $CH(CH_3)CH_3$ or $CH_2(CH_2)_2CH_3$.

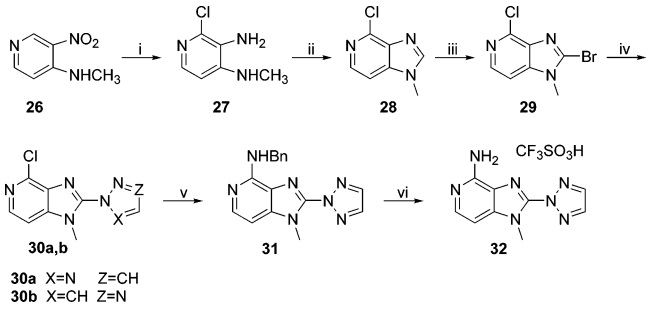
Scheme 4[a]



[a] (i) MeOH, THF, sodium acetate buffer (pH 4), Br_2, rt. (ii) DMF,NaH or K_2CO_3, 1*H*-1,2,3-triazole, rfx (100 °C). (iii) CH_2Cl_2, CF_3SO_3H, rfx (40 °C).

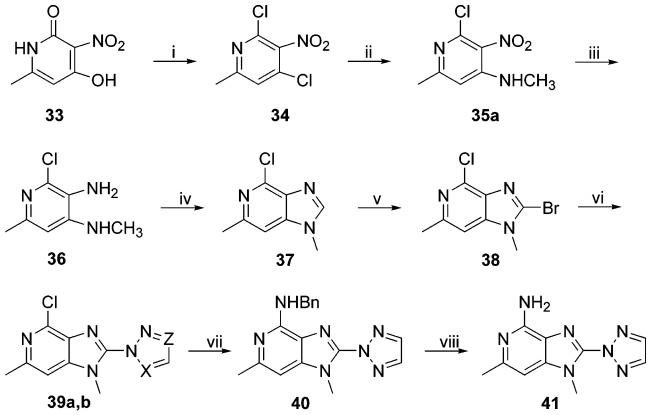
with 1*H*-1,2,3-triazole to give **23a**−**f** and **24a**−**f.**[14,18] The substitution reaction with commercially available 1*H*-1,2,3-triazole provided in each case a mixture of regioisomers (N-1 and N-2 triazolyl derivatives). **23b** and **24b** only were separated by flash chromatography on silica

Scheme 5[a]



[a] (i) HCl 12 N, $SnCl_2 \cdot 2H_2O$, 90 °C, 1 h. (ii) DMF, $CH(OEt)_3$, HCl 12 N, rt, 12 h. (iii) (1) THF, BuLi, −78 °C, 1 h (2) Br_2, −65 °C, 2 h. (iv) DMF, K_2CO_3, 1*H*-1,2,3-triazole, rfx (100 °C), 20 h. (v) $BnNH_2$, MW 460 W, 5 min. (vi) CH_2Cl_2, CF_3SO_3H, rfx (40 °C), 1.5 h.

Scheme 6[a]



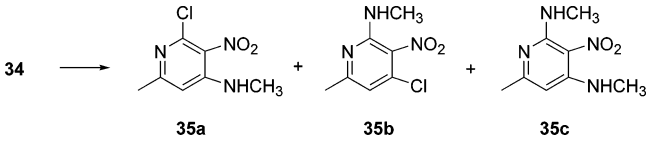
[a] (i) *N*,*N*-diethylaniline, $POCl_3$, rfx (100 °C), 3 h. (ii) EtOH, Na_2CO_3, $MeNH_2$ (40% aq), rt, 24 h. (iii) MeOH, HCl 12 N, Fe, rt, 24 h. (iv) DMF, $CH(OEt)_3$, HCl 12N, rt, 24 h. (v) THF, LDA, NBS, −78 °C, 2 h. (vi) DMF, K_2CO_3, 1*H*-1,2,3-triazole, rfx (100 °C), 20 h. (vii) $BnNH_2$, MW 460 W, 5 min. (viii) CH_2Cl_2, CF_3SO_3H, rfx (40 °C), 2 h.

gel and identified by ^{1}H NMR spectra[19] whereas **24a**,**c**−**f** were not isolated. **23a**−**f** were deprotected (**25a**−**f**) under the same conditions used for **10a**.[15]

Synthesis of 1*H*-Imidazo[4,5-*c*]pyridine Derivatives (series B). The synthesis of 1-methyl-2-[1,2,3]-triazol-2-yl-1*H*-imidazo[4,5-*c*]pyrid-4-ylamine triflate (**32**)-is described in Scheme 5. Methyl-(3-nitro-pyridin-4-yl)amine (**26**) was prepared from commercially available 4-hydroxy-3-nitropyridine, using the literature procedure.[20] **26** was reductively chlorinated to 2-chloro-N^4-methylpyridine-3,4-diamine (**27**) with stannous chloride in hot 12 N HCl that after treatment with triethyl orthoformate yielded 4-chloro-1-methyl-1*H*-imidazo[4,5-*c*]pyridine (**28**).[21] Selective bromination of **28** was carried out by deprotonation with BuLi and subsequential quenching with bromine. Substitution of **29** with 1*H*-1,2,3-triazole gave a mixture of the two regioisomers (**30a**,**b**),[14] that were used in the next step without further purification. Treatment of **30a**,**b** with benzylamine gave 4-benzyl-(1-methyl-2-[1,2,3]triazol-2-yl-1*H*-imidazo[4,5-*c*]pyridin-4-yl)amine (**31**) that was deprotected under the same conditions used for **10a**.[15]

The synthesis of 1,6-dimethyl-2-[1,2,3]triazol-2-yl-1*H*-imidazo[4,5-*c*]pyridin-4-ylamine (**41**) is described in Scheme 6. 2,4-dichloro-6-methyl-3-nitropyridine (**34**)

Scheme 7



was prepared from commercially available 4-hydroxy-6-methyl-3-nitro-1*H*-pyridin-2-one (**33**) and $POCl_3$[22] and further treated with methylamine in refluxing ethanol to give a mixture of regioisomers **35a**,**b**,**c** (Scheme 7).[23] The position of the amine substituent was established by NOE experiments (Figure 5). Saturation of the signal at 6.57 ppm (H-5 proton) of compound **35a** resulted in 3% enhancement of the resonance at 2.42 ppm (methyl in C-6) and 5.5% enhancement of the resonance at 3.10 ppm (methyl binding with NHCH_3 in C-4), whereas saturation of the signal at 6.48 ppm (H-5 proton) of compound **35b** resulted in 2% enhancement of the resonance at 2.99 ppm (CH_3 in C-6) and absence of NOE effect between H-5 proton and NHCH_3 in C-2. Reduction of **35a** with iron powder and further cyclization with $CH(OEt)_3$ produced 4-chloro-1,6-dimethyl-1*H*-imidazo-[4,5-*c*]pyridine (**37**).[21] Bromination of **37** with LDA/NBS gave **38** (Scheme 6). Compound **41** was obtained by using the same route and conditions described for **29** (Schemes 5, 6).

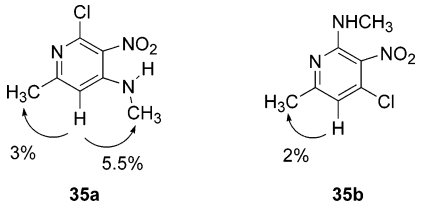


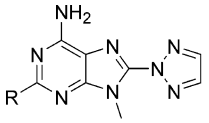
Figure 5. 1D- NOE experiments.

Results

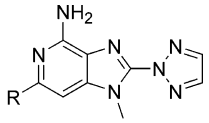
Table 1 reports the affinity[K_i (nM)] values of the studied compounds for the A_1, and cloned human A_{2A} and A_{2B} receptors (*h*-A_{2A}, *h*-A_{2B}), expressed in CHO-K1 (A_1) and HEK-293 (A_{2A}, A_{2B}) cells (human embryo kidney cells). Radioligand [^{3}H]-DPCPX was used for competition binding assays on receptors A_1 and *h*-A_{2B}, whereas [^{3}H]-CGS21680 was used for *h*-A_{2A}.

Compounds **11** and **32** exhibit the same affinity toward the adenosine A_{2A} receptor but an appreciably different selectivity toward A_1; in particular **11** is 100 times more selective toward A_1 while **32** is 20 times more selective toward A_{2A}. Moreover **25b**−**d** exhibit elevated affinity toward the adenosine A_{2A} receptor. The affinity of these compounds, relative to that of other products with an adenine-type structure, denotes that 2-substitution of the adenine ring system with relatively long $(CH_2)_n$-CH_3, where $n > 2$ (see **25b** and **25c**) or bulky $(CH_2)_2$-Ph, (see **25d**) alkyl chains favors affinity toward the A_{2A} receptor, whereas relatively short $(CH_2)_n$-CH_3, ($n \leq 2$, see **25a** and **25f**) or branched alkyl chains (see **25e**) are less effective. Reported in the same table are affinity values with regard to the adenosine receptor subtypes A_{2B} and A_1, of some of the synthesized compounds and their selectivity ratios (K_i A_1/A_{2A}) and (K_i A_{2B}/A_{2A}). It can be observed that compounds **25b**−**d** and **32** possess, to a varying degree, significantly selective affinity for A_{2A} adenosine receptor. Compounds **25b**−**d**

Table 1. Affinity K_i (nM) and Selectivity for the Adenosine Receptors



11; 25a-f



32; 41

compounds	R	affinity[a] K_i (nM) A_{2A}	A_{2B}	A_1	A_1/A_{2A}	A_{2B}/A_{2A}
11	H	46.3	b	0.4	0.01	
25a	CH_3	70.4	b	10.4	0.15	
25b (ST1535)	$(CH_2)_3CH_3$	6.6	352.3	71.8	11.92	58.53
25c	$(CH_2)_4CH_3$	3.3	153.0	26.2	7.84	45.81
25d	$(CH_2)_2Ph$	4.7	2330.0	80.0	17.02	495.74
25e	$CH(CH_3)_2$	481.3	b	2270.0	4.72	
25f	$(CH_2)_2CH_3$	83.7	18.0	266.0	3.18	0.22
32	H	51.6	518.0	1056.3	20.48	10.04
41	CH_3	120.0	140.0	340.0	2.83	1.17
CGS 21680		51.3	b	>10000	>1949	
ZM 241385		0.1	b	307.9	4430.7	
alloxazine		935.0	3.8	>100000	>107.0	0.004
DPCPX		56	b	6.5	0.12	
KW6002[26]		2.2		>1000	>454	

[a] K_i values represent replicate determinations and SEM are tipically within ±20%. [b] Not tested.

Table 2. Values of Affinity and Selectivity, Expressed as K_i (nM), for the Adenosine A_3 Receptors[a]

receptors	**25b** 1 μM	**25b** K_i (nM)	**25c** 1 μM	**25c** K_i (nM)	reference compounds	IC_{50} (nM)	K_i (nM)
A_3 *(h)*		>1000		760	IB-MECA	1.2	0.84
$ADO_{transporter}$	24		34		NBTI	0.30	
α_1 (nonselective)	–[b]	–	–		prazosin	0.86	
α_2 (nonselective)	–		–		yohimbine	95	
β_1	–		–		atenolol	1.770	
β_2	–		–		ICI 118551	2.3	
BZD (central)	–		–		diazepam	12	
D1	–		–		SCH 23390	0.66	
D2	–		–		(+)butaclamol	8.9	
D3	–		–		(+)butaclamol	5.1	
D4 *(h)*	–		–		clozapine	156	
D5 *(h)*	–		–		SCH 23390	0.61	
GABAa	–		–		muscimol	16	
GABA b	–		–		baclofen	50	
$GABA_{transporter}$	–		–		nipecotic acid	10.100	
AMPA	–		–		L-glutamate	613	
kainate	–		–		kainic acid	77	
PCP	–		–		MK-801	2.0	
P2X	–		–		α,β-MeATP	14	
P2Y	–		–		dATPα S	22	
NMDA	–		–		CGS 19755	967	
H_1 (central)	–		–		pyrilamine	1.3	
M_1	–		–		pirenzepine	22	
M_2	–		–		methoctramine	34	
M_3	–		–		4-DAMP	3.5	
M_4	–		–		4-DAMP	1.9	
M_5	–		–		4-DAMP	2.0	
$choline_{transporter}$	–		–		hemicholinium-3	12	
opiate[c]	–		–		naloxone	1.6	
$5\text{-}HT_{1A}$	–		–		8-OH-DPAT	0.66	
$5\text{-}HT_{2A}$	–		–		ketanserin	2.7	
$5\text{-}HT_{2C}$ *(h)*	–		–		mesulergine	1.9	
$5\text{-}HT_3$ *(h)*	–		–		MDL 72222	9.3	
$5\text{-}HT_4$	–		–				
$5\text{-}HT_{5A}$ *(h)*	–		–		serotonin	79	
$5\text{-}HT_6$ *(h)*	–		–		serotonin	421	
NE transporter	–		–		protriptyline	1.1	
DA transporter	–		–		GBR 12909	5.0	
5-HT transporter					imipramine	4.4	

[a] For the test compounds, the results are expressed as percent inhibition of control specific binding (mean values; $n = 2$). [b] – Symbol indicates an inhibition of less than 10%. [c] = nonselective.

show a better affinity than compound **32** vs A_{2A} receptor and **25b**,**d** are generally more selective than **25c**. The in vivo examination (locomotor activity, vide infra) was restricted to **25b** because of practical reasons related to the synthesis of the two compounds. The overall yield of **25b** is in fact 11% vs 0.6% of **25d**. Due to the number

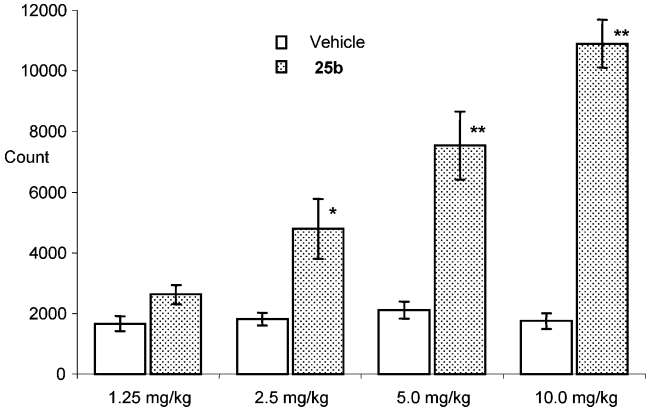


Figure 6. Effect of **25b** (1.25 mg/kg to 10 mg/kg po) on spontaneous locomotor activity in rats. The mean ± SE of 12 rats for each treatment group are shown. ANOVA with Student-Neuman-Keuls post hoc analysis: *: $p < 0.01$ and **: $p < 0.001$ vs corresponding vehicle group.

of animals to be observed it was not practical to proceed with **25d** although the profile of this compound compares favorably with that of **25b**.

Furthermore, the affinity of compounds **25b** and **25c** for A_3 adenosine receptors and an array of 35 unrelated enzymes or receptors was evaluated (Table 2). In these binding studies, compounds of interest were initially tested at a concentration of 1 μM. Compounds that displaced more than 50% of the specific radioligand were evaluated at eight different concentrations to determine their IC_{50} value. Compounds **25b** and **25c** displayed low to negligible affinity for the A_3 subtype and had no affinity for the other receptors ($IC_{50} > 1000$ nM).

Effect on Locomotor Activity. Motor activity increasing effects were observed in rats after A_{2A} receptor antagonists administration whereas an activation of adenosine A_{2A} receptors reduce locomotion.[24] Rat locomotor activity was therefore studied to indirectly evaluate the functional profile at adenosine A_{2A} receptor of selected compound. Rat spontaneous locomotor activity was dose-relatedly and significantly increased by oral administration of **25b** (Figure 6). The increase in motor activity is the protypic effect of adenosine receptor antagonism due to an inhibition of central adenosine A_{2A} receptor; this effect and the selectivity for the A_{2A} receptor (Tables 1 and 2) suggest that the **25b** binding to adenosine A_{2A} receptor is of the antagonistic type.

SAR Analysis. By comparing **11** and **32** we can assume that A_1 receptor needs the N_3 atom as further pharmacophoric determinant with respect to A_{2A} receptor. Moreover the elongation of the alkyl chain has the same effect on both receptors, indicating a steric clash with short or branched chains (**25a**, **25e** and **25f**) and a more favorable interaction with long or bulky chains. In this case affinity gain for the A_{2A} is more evident than for the A_1 receptor.

Experimental Section

Instrumentation. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC 200 spectrometer; chemical shifts (δ scale) are reported in parts per million (ppm) relative to the central peak of the solvent. Coupling constants (J values) are given in Hertz (Hz). EI-MS spectra (70 eV) were taken on a Fisons Trio 1000. Molecular ions (M^+) and base peaks only are given. Melting points were determined on a Büchi SMP-510 capillary melting point apparatus and are uncorrected. Column chromatography purifications were performed in flash conditions using Merck 230−400 Mesh silica gel. Thin-layer chromatography (TLC) was carried out with silica gel plates. Elemental analyses were performed by REDOX, Milan, Italy, and were within ±0.4 of the theoretical values (C, H, N). The solvents used for purification were purchased from Carlo Erba (Italy) with the exception of DMF and dichloromethane that were purchased from Fluka. All reactants were purchased from Aldrich.

Dibenzyl-(9*H*-purin-6-yl)amine (7). Diisopropylethylamine (1.2 mL, 7.15 mmol) and dibenzylamine (1.4 mL, 7.15 mmol) were added to a solution of **6** (1 g, 6.50 mmol) in absolute ethanol (37 mL). The mixture was stirred at reflux temperature for 20 h (after 1 h a white precipitate formed). The solvent was removed under reduced pressure and the residue washed with cold water. The solid was filtered and dried under vacuum to yield 1.8 g (89%) of **7**; mp 182 °C (water); ^{1}H NMR ($CDCl_3$) δ 5.45 (br, 4H), 7.31 (s, 10H), 7.97 (s, 1H), 8.48 (s, 1H); MS (EI) *m/e* 316 $(M + 1)^+$, 224, 91.

Dibenzyl-(2-chloro-9*H*-purin-6-yl)amine (13). The title compound was obtained by the same procedure as for **7**, with **12** as starting material. Yield 95%; mp 250−252 °C (water); ^{1}H NMR ($CDCl_3$) δ 4.94 (br, 2H), 5.55 (br, 2H), 7.32 (s, 10H), 7.89 (s, 1H); MS (EI) *m/e* 351−349 (M^+), 260−258, 91.

Synthesis of Compounds 8 and 14. General Procedure. K_2CO_3 (2.5 g, 17.94 mmol) was added to a solution of **7** or **13** (17.42 mmol) in hot DMF (45 mL). The solution was then cooled to 0 °C and treated dropwise with CH_3I (1.5 mL, 24.39 mmol). The mixture was stirred at room temperature for 12 h. The solvent was evaporated under reduced pressure. The solid obtained was washed with water and collected by filtration.

Dibenzyl-(2-chloro-9-methyl-9*H*-purin-6-yl)amine (14). Yield 78%, mp 144−146 °C (ethanol); ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 3H), 4.93 (br, 2H), 5.50 (br, 2H), 7.31 (s, 10H), 7.67 (s, 1H); MS (EI) *m/e* 365−363 (M^+), 274−272, 91.

Dibenzyl-(2,9-dimethyl-9*H*-purin-6-yl)amine (15a). 2 M trimethylaluminum in toluene (6 mL, 12 mmol), $PdCl_2$ (27 mg, 0.15 mmol) and PPh_3 (79 mg, 0.3 mmol) were added to a solution of **14** (1.07 g, 2.94 mmol) in anhydrous THF (30 mL), under nitrogen. The reaction mixture was refluxed for 48 h. The excess of trialkylaluminum was destroyed by small additions of water and ethanol. Aluminum hydroxide was filtered through paper, and the liquid mixture was extracted with dichloromethane. The organic phase was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography (cyclohexanes−ethyl acetate 1:1) afforded 900 mg (89%) of desired compound (**15a**) in crystalline form: mp 117−118 °C (cyclohexanes−ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 2.62 (s, 3H), 3.81 (s, 3H), 5.31 (br, 4H), 7.30 (s, 10H), 7.65 (s, 1H); MS (EI) *m/e* 343 (M^+), 252, 91.

Synthesis of Compounds 15b,c and 16−18. General Procedure. The appropriate alkyl-stannane (3.8 mmol) and $Pd(PPh_3)_4$ (140 mg) were added to a solution of **14** (700 mg, 1.93 mmol), in anhydrous NMP (*N*-methylpyrrolidinone) (4 mL), under nitrogen. The reaction mixture was stirred at 120 °C (8 h for compounds **15b**, **15c** and **17**, 2 h for **16** and 20 h for **18**). The reaction mixture was cooled, diluted with water and extracted with dichloromethane. The organic phase was washed with brine and dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure, thus obtaining a dark liquid. The residue was purified by flash chromatography, (cyclohexanes−ethyl acetate 7:3) giving **15b**,**c** and **16**−**18** in the form of solid or oily material.

Dibenzyl-(2-*n*-butyl-9-methyl-9*H*-purin-6-yl)amine (15b). Yield 90%; mp nondeterminable − rubber-like substance; ^{1}H NMR ($CDCl_3$) δ 0.91 (t, 3H, $J = 8.0$ Hz), 1.3−1.5 (m, 2H), 1.7−1.9 (m, 2H), 2.88 (t, 2H, $J = 7.6$ Hz), 3.84 (s, 3H), 5.27 (br, 4H), 7.30 (s, 10H), 7.65 (s, 1H); MS (EI) *m/e* 385 (M^+), 294, 238, 91.

Dibenzyl-(9-methyl-2-styryl-9*H*-purin-6-yl)amine (16). Yield 84%; mp nondeterminable − rubber-like substance; ^{1}H NMR ($CDCl_3$) δ 4.26 (s, 3H), 5.14 (br, 2H), 5.62 (br, 2H), 7.36

(br, 15H), 7.65 (s, 1H), 7.71 (s, 1H), 7.96 (s, 1H); MS (EI) *m/e* 431 (M^+), 340, 91.

Synthesis of Compounds 15d−f. General Procedure. Alkyl derivatives (**16**−**18**) (0.27 mmol) were placed in an autoclave with ethanol (5 mL). The mixture was heated until complete dissolution, and then 10% palladium on graphite (50 mg) was added. The mixture was stirred overnight under 4 atm of H_2. The catalyst was filtered through Celite, and the residue was washed with dichloromethane. The organic phases were dried over anhydrous sodium sulfate and evaporated under reduced pressure, to yield **15d**−**f**.

Dibenzyl-(9-methyl-2-phenethyl-9*H*-purin-6-yl)-amine (15d). Quantitative yield; mp 144 °C (ethanol); ^{1}H NMR ($CDCl_3$) δ 3.16 (s, 4H), 3.81 (s, 3H), 5.2 (br, 4H), 7.2−7.3 (m, 15H), 7.66 (s, 1H); MS (EI) *m/e* 433 (M^+), 342, 91.

Synthesis of Compounds 9 and 22a−f. General Procedure. Bromine (0.7 mL, 13.6 mmol) was added dropwise, at 0°, to **8** or **15a**−**f** (1.6 mmol) dissolved in a mixture of MeOH (7 mL), THF (7 mL) and acetate buffer pH=4 (7 mL) (obtained by dissolving 4 g of sodium acetate in 100 mL of water and by adjusting to pH 4 with glacial acetic acid). The reaction was stirred at room temperature until the starting products disappeared (about 12 h). Excess of bromine was eliminated with sodium metabisulfite and the reaction brought to pH 8 by addition of saturated solution of Na_2CO_3. The aqueous phase was extracted with dichloromethane. The organic phases were dried over anhydrous sodium sulfate and evaporated under reduced pressure, to give a residue that was used for the following reaction without further purification.

Dibenzyl-(8-bromo-2-*n*-butyl-9-methyl-9*H*-purin-6-yl)-amine (22b). Quantitative yield; mp 89−87°C (dichloromethane); ^{1}HNMR ($CDCl_3$) δ 0.90 (t, 3H, J = 8.0 Hz), 1.2−1.4 (m, 2H), 1.6−1.8 (m, 2H), 2.79 (t, 2H, J = 8.0 Hz), 3.75 (s, 3H), 5.31 (s, 4H), 7.28 (s, 10H); MS (EI) *m/e* 465−463 (M^+), 374−372, 91.

Dibenzyl-(8-bromo-9-methyl-2-phenethyl-9*H*-purin-6-yl)amine (22d). Quantitative yield; mp nondeterminable − rubber-like substance; ^{1}H NMR ($CDCl_3$) δ 3.15 (s, 4H), 3.78 (s, 3H), 4.99 (br, 2H), 5.41 (br, 2H), 7.2−7.3 (m, 15H); MS (EI) *m/e* 422−420, 91.

Synthesis of Compounds 10a, 23a, 23c−f, 30a,b and 39a,b. General Procedure. 1*H*-1,2,3-triazole (0.18 mL, 2.5 mmol) was added dropwise to a suspension of anhydrous DMF (2 mL) and NaH (80% in paraffin, 92 mg, 2.5 mmol) under nitrogen. The mixture was stirred for 1 h and to it was added, dropwise, a solution of crude bromoderivatives (1.7 mmol) in anhydrous DMF (5 mL) and stirred at 100 °C for 12 h. The solvent was removed under reduced pressure, and water was added to the residue. The aqueous phase was extracted with dichloromethane, and the organic phases were dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography (cyclohexanes−ethyl acetate). N-2-triazolyl derivatives of compounds **10a**, **23a** and **23c**−**f** were isolated by flash chromatography whereas their regioisomers were not eluted under the conditions used. **30a**,**b** and **39a**,**b** could not be separated by chromatography and were used in the following reaction as a mixture of the two regioisomers.

Dibenzyl-(9-methyl-2-phenethyl-8-[1,2,3]triazol-2-yl-9*H*-purin-6-yl)amine (23d). Yield 20%; mp 173 °C (cyclohexanes−ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 3.1−3.2 (m, 2H), 3.2−3.3 (m, 2H), 4.10 (s, 3H), 5.00 (br, 2H), 5.53 (br, 2H), 7.2−7.3 (m, 15H), 7.96 (s, 2H); MS (EI) *m/e* 500 (M^+), 409, 91.

Synthesis of Compounds 23b and 24b. K_2CO_3 (5.32 g, 28 mmol) and 1*H*-1,2,3-triazole (1.6 mL, 28 mmol) were added to a solution of **22b** (18 mmol) in anhydrous DMF (300 mL), under nitrogen. The mixture was refluxed for 20 h at 100 °C. The solvent was removed under reduced pressure, and water was added to the residue. The aqueous phase was extracted with dichloromethane, and the organic phases were dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography (dichloromethane-acetone 98:2) giving **23b** and **24b** as white solids.

Dibenzyl-(2-*n*-butyl-9-methyl-8-[1,2,3]triazol-2-yl-9*H*-purin-6-yl)amine (23b). Yield 30%, mp 114 °C (dichloromethane−acetone); ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 3H, J = 8.0 Hz), 1.3−1.4 (m, 2H), 1.7−1.9 (m, 2H), 2.84 (t, 2H, J = 8.0 Hz), 3.97 (s, 3H), 5.01 (br, 2H), 5.45 (br, 2H), 7.29 (s, 10H), 7.94 (s, 2H); MS (EI) *m/e* 452 (M^+), 361, 333, 91.

Dibenzyl-(2-*n*-butyl-9-methyl-8-[1,2,3]triazol-1-yl-9*H*-purin-6-yl)amine (24b). Yield 50%; mp 139 °C (dichloromethane−acetone); ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 3H, J = 8.0 Hz), 1.3−1.5 (m, 2H), 1.7−1.9 (m, 2H), 2.86 (t, 2H, J = 8.0 Hz), 4.12 (s, 3H), 5.06 (br, 2H), 5.36 (br, 2H), 7.31 (s, 10H), 7.81 (d, 1H, J = 0.8 Hz), 8.24 (d, 1H, J = 0.8 Hz); MS (EI) *m/e* 452 (M^+), 361, 333, 91.

Synthesis of Compounds 11, 25a−f, 32 and 41. General Procedure. CF_3SO_3H (0.37 mL, 3.3 mmol) was added dropwise to a solution of **10a**, **23a**−**f**, **31** or **40** (0.33 mmol) in anhydrous dichloromethane (3 mL), under nitrogen at 0 °C. The mixture was refluxed for 6 h, then cooled and diluted with water, basified (pH 10) with 30% NaOH and extracted with dichloromethane. The organic phase was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography (cyclohexanes−ethyl acetate 3:7) to give a white solid that was crystallized by ethanol.

2-*n*-Butyl-9-methyl-8-[1,2,3]triazol-2-yl-9*H*-purin-6-ylamine (25b). Yield 55%; mp 182 °C (ethanol); ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 3H, J = 7.25 Hz), 1.3−1.5 (m, 2H), 1.7−1.9 (m, 2H), 2.85 (t, 2H, J = 7.9 Hz), 4.07 (s, 3H), 5.56 (br, 2H), 8.00 (s, 2H); MS (EI) *m/e* 272 (M^+), 257, 243, 230. Anal. ($C_{12}H_{16}N_8 \cdot 0.3$ EtOH) C,H,N.

9-Methyl-2-phenetyl-8-[1,2,3]triazol-2-yl-9H-purin-6-ylamine (25d). Yield 5%; mp 164 °C (ethanol); ^{1}H NMR ($CDCl_3$) δ 3.18 (s, 4H), 4.07 (s, 3H), 5.65 (br, 2H), 7.2−7.3 (m, 5H), 8.01 (s, 2H); MS (EI) *m/e* 320(M^+), 303, 243, 216. Anal. ($C_{16}H_{16}N_8$) C,H,N.

2-Chloro-N^4-methyl-pyridine-3,4-diamine (27). A solution of **26** (10 g, 65.3 mmol), prepared according to the literature,[20] in 12 N HCl (50 mL) was heated to 90 °C. To this hot solution was added $SnCl_2 \cdot 2H_2O$ (72.5 g, 0.32 mmol) in five portions over a 60-s period. This solution was stirred at 90 °C for 1 h, cooled to 0 °C, diluted with 100 mL of water and reduced in vacuo to dryness. The residue was dissolved in 100 mL of water and stirred in an ice bath whereas 2 N ammonia solution was added dropwise until a precipitate formed. The pH was adjusted to 8.5−9 and the resulting emulsion centrifuged. The solid residue was redissolved in water and centrifuged. The operation was repeated three times. The combined solid residues were stirred overnight in 50 mL of dichloromethane. The centrifuged aqueous phases were extracted three times with dichloromethane, then the combined organic phases were dried over anhydrous sodium sulfate and evaporated under reduced pressure, yielding 6.2 g (60%) of desired compound **(27)** (pink crystals); mp 165 °C (dichloromethane); ^{1}H NMR ($CDCl_3$) δ 2.92 (d, 3H, J = 4.8 Hz), 3.45 (br, 2H), 4.26 (br, 1H), 6.45(d, 1H, J = 5.3 Hz), 7.78 (d, 1H, J = 5.3 Hz); MS (EI) *m/e* 159−157 (M^+), 143−141, 116−114.

Synthesis of Compounds 28 and 37. General Procedure. To a solution of **27** or **36** (15.2 mmol) in triethyl orthoformate (97 mL) and DMF (added with stirring until the turbidity disappeared) was added 12 N HCl solution (1.7 mL), under nitrogen. The mixture was stirred at room temperature for 12 h. The solvent was evaporated under reduced pressure and the brown oily residue purified by flash chromatography (cyclohexane−ethyl acetate 2:8) provided a white solid.

4-Chloro-1-methyl-1*H*-imidazo[4,5-*c*]pyridine (28). Yield 68%; mp 168−170 °C (cyclohexane- ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 3.91 (s, 3H), 7.33 (d, 1H, J = 5.6 Hz), 7.98 (s, 1H), 8.24 (d, 1H, J = 5.6 Hz); MS (EI) *m/e* 169−167 (M^+), 132, 105.

2-Bromo-4-chloro-1-methyl-1*H*-imidazo[4,5-*c*]pyridine (29). 2.5 M BuLi in hexane (8 mL, 20 mmol) was added dropwise to a solution of **28** (1.5 g, 9 mmol) in anhydrous THF (25 mL), under nitrogen at −78 °C. The solution was stirred at this temperature for 1 h, then bromine (2 mL, 40 mmol) was carefully added dropwise, over a period of 30 min. This

solution was stirred at −78 °C for 2 h and cooled slowly at 0 °C, and then a saturated solution of sodium metabisulfite was added dropwise until the bromine was completely destroyed. The solution was basified (pH 9) with 2 N Na_2CO_3. The solution was extracted with dichloromethane. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure. A brownish solid was obtained which crystallized in water giving 1.4 g (64%) of desired compound (**29**) in the form of white crystals: mp 207−209 °C (water); ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 3H), 7.25 (d, 1H, J = 6,1 Hz), 8.23 (d, 1H, J = 6.1 Hz); MS (EI) *m/e* 249−247−245 (M^+), 212−210, 131, 105.

Synthesis of Compounds 31 and 40. General Procedure. Crude **30a**,**b** or **39a**,**b** (5.5 mmol), in a flat-bottomed, long-necked flask, was suspended in benzylamine (5 mL). The reaction mixture was placed inside a microwave oven (frequency of irradiation: 2.450 MHz) and irradiated at 460 W until the benzylamine boiled (about 1−2 min) and then cooled at r.t. The irradiation was repeated until the starting material disappeared, as monitored by TLC. Cooling after the last cycle yielded a yellow waxy mass that was purified by flash chromatography [gradient: cyclohexanes−ethyl acetate 4:6 (100 mL), cyclohexanes−ethyl acetate 2:8 (100 mL), ethyl acetate].

4-Benzyl-(1-methyl-2-[1,2,3]triazol-2-yl-1*H*-imidazo[4,5-c]pyridin-4-yl)amine (31). Yield 29%; mp 180−184 °C (ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 4.00 (s, 3H), 4.8 (br, 1H), 5.87 (br, 2H), 6.71 (d, 1H, J = 5.9 Hz), 7.3−7.4 (m, 5H), 7.98 (s, 2H), 8.04 (d, 1H, J = 5.9 Hz); MS (EI) *m/e* 305 (M^+), 215, 200.

2,4-Dichloro-6-methyl-3-nitropyridine (34). 33 (1 g, 5.88 mmol) and diethylaniline (0.94 mL, 5.88 mmol) were heated at reflux in $POCl_3$ (4.5 mL) for 3 h. After cooling the solution was poured into ice−water (50 mL) and stirred at room temperature for 2.5 h. The mixture was extracted with ethyl acetate, and the organic phases were washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was dissolved in ethyl acetate and passed through a glass funnel packed with a layer of silica gel (2 cm thick) and Celite (2 cm thick). The filtrate was evaporated under reduced pressure to give 1.2 g (98%) of desired compound (**34**) which was used for the following reaction without further purification: mp 74−75 °C (ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 2.62 (s, 3H), 7.31 (s, 1H); MS (EI) *m/e* 210−208−206 (M^+), 180−178−176, 171, 164−162−160.

(4-Chloro-6-methyl-3-nitro-pyridin-2-yl)methylamine (35a). To an ice-cooled mixture of **34** (600 mg, 2.90 mmol) in ethanol (6 mL) were added sodium carbonate (768 mg, 7.25 mmol) and a 40% w/w water solution of methylamine (0.3 mL) dropwise. The resulting mixture was stirred at room-temperature overnight. The solvent was evaporated, and water was added to the residue. The aqueous phase was extracted with ethyl acetate, and the organic phases were washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography (cyclohexanes−ethyl acete 8:2) yielding 74 mg (13%) of the desired compound (**35a**): mp 148−150 °C (cyclohexanes−ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 3H), 3.10 (d, 3H, J = 4.8 Hz), 6.57 (s, 1H), 7.27 (br, 1H); MS (EI) *m/e* 203−201 (M^+), 173−171, 166.

2-Chloro-6,*N*^{4}-dimethylpyridine-3,4-diamine (36). Powdered Fe (56 mg) was added to a solution of **35a** (100 mg, 0.5 mmol) in MeOH (2 mL) and 1 N HCl solution (9.8 mL). The mixture was stirred at room-temperature overnight and then basified (pH 10) with 1 N NaOH solution and filtered through a Celite cake, which was washed with several portions of ethyl acetate and MeOH. The layers were separated, and the aqueous phase was extracted with additional ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure, to give a residue (**36**) that was used for the following reaction without further purification.Yield 80%; mp nondeterminable − rubber-like substance; ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3H), 2.88 (d, 3H, J = 5.2 Hz), 3.29 (br, 2H), 4.29 (br, 1H), 6.29 (s, 1H); MS (EI) *m/e* 173−171 (M^+), 158−156, 143−141, 109−107.

2-Bromo-4-chloro-1,6-dimethyl-1*H*-imidazo[4,5-*c*]pyridine (38). 2 M LDA (lithium diisopropylamide) in THF/heptane/ethylbenzene (1.2 mL, 2.4 mmol) was added dropwise to a solution of **37** (1.33 mmol) in anhydrous THF (3.3 mL), under nitrogen at −78 °C. The solution was stirred at this temperature for 30 min, then NBS (*N*-bromosuccinimide) (470 mg, 2.65 mmol) was added. This solution was stirred at room temperature for 1 h, and then a saturated NH_4Cl solution was added. The mixture was extracted with dichloromethane, the organic phases washed with brine and dried over anhydrous sodium sulfate and then evaporated under reduced pressure. The residue was purified by flash chromatography (ethyl acetate) yielding 132 mg (38%) of desired compounds **(38)**; mp 133−134 °C (ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 2.60 (s, 3H), 3.76 (s, 3H), 7.02 (s, 1H); MS (EI) *m/e* 263−261−259 (M^+), 248−246−244, 182−180.

Pharmacology. Compounds **11**, **25a**−**f**, **32** and **41** which represent the two planned series A and B, were tested for their affinity to human A_1, A_{2A} and A_{2B} adenosine receptors. **25b** and **25c** only were tested for their affinity to human A_3 adenosine receptors.

Affinity toward the Adenosine A_1 Receptor. The interactive capacity of each product toward the adenosine A_1 receptor was evaluated using membranes from human recombinant CHO cells which stably express the human A_1 subtype.

These membranes were incubated with [^{3}H]-DPCPX at a concentration of 1 nM in a buffer comprised of 50 mM Tris (pH 7.4), 120 mM NaCl; 5 mM KCl; 10 mM $MgCl_2$; 2 mM $CaCl_2$, 2 U/mL of adenosine deaminase for 60 min at 22 °C. Nonspecific binding was measured in the presence of DPCPX (8-cyclopentyl-1,3-dipropylxantine) at a concentration of 1 μM.

Affinity toward the Adenosine A_{2A} Receptor. The interactive capacity of each product toward the adenosine A_{2A} receptor was evaluated using membranes from human recombinant HEK 293 cells (human embryo kidney cells) stably expressing the human A_{2A} receptor subtype exclusively.

These membranes were incubated with [^{3}H]-CGS21680 at a concentration of 6 nM in a buffer comprised of 50 mM Tris (pH 7.4), 120 mM NaCl; 10 mM $MgCl_2$; 2 mM $CaCl_2$, 2 U/mL of adenosine deaminase for 90 min at 22 °C. Nonspecific binding was measured in the presence of NECA (10 μM).

Affinity toward the Adenosine A_{2B} Receptor. The interactive capacity of each product toward the adenosine A_{2B} receptor was evaluated using membranes from human recombinant HEK 293 stably expressing the human A_{2B} receptor subtype exclusively.

These membranes were incubated with [^{3}H]-DPCPX at a concentration of 5 nM in a buffer comprised of 50 mM Tris (pH 7.4), 120 mM NaCl; 10 mM $MgCl_2$; 2 mM $CaCl_2$, 2 U/mL of adenosine deaminase for 120 min at 22 °C. Nonspecific binding was measured in the presence of NECA (100 μM).

Affinity toward the Adenosine A_3 Receptor. For this study, membranes from human recombinant HEK-293 cells, which express the human A_3 subtype, were used according to the method described in the literature.[25] Experimental conditions required the use of [^{125}I]AB-MECA as a radioligand at a concentration of 0.1 nM, an incubation time of 90 min at a temperature of 22 °C, and IB-MECA (1 μM) for the determination of nonspecific binding.

Spontaneous Locomotor Activity in Rats. The effect of **25b** on motor performance was examined in 344 male Fischer rats. The fasting animals (12 rats per group) were given either **25b** (1.25, 2.5, 5 and 10 mg/kg po) or vehicle (0.3% Tween 80, 10% sucrose and saline). Rats were individually placed in Plexiglas activity cage (40 × 40 cm) with photocells on the walls. The photocells were connected through an interface to a computer. The consecutive interruption of photocell beams was taken as locomotion count. Rats were placed in the activity cage for 30 min and then treated with either vehicle or test compound. Locomotor activity was recorded for 90 min after the administration of the test compound.

Supporting Information Available: Spectroscopic data of compounds **8**, **9**, **10a**, **15c**,**e**,**f**, **17**, **18**, **22a**,**c**,**e**,**f**, **23a**,**c**,**e**,**f**, **30a**,**b**, **37**, **39a**,**b**, **40**. Spectroscopic data and elemental analysis of compounds **11**, **25a**,**c**,**e**,**f**, **32**, **41**. Elemental analysis of compounds **25b**,**d**. This material is available free of charge via Internet at http://pubs.acs.org.

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