Chiral Pyrrolo[2,3-*d*]pyrimidine and Pyrimido[4,5-*b*]indole Derivatives: Structure−Activity Relationships of Potent, Highly Stereoselective A_1-Adenosine Receptor Antagonists[†,‡]

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Received January 3, 1996[⊗]

A series of 33 novel, mostly chiral pyrrolo[2,3-*d*]pyrimidine and pyrimido[4,5-*b*]indole derivatives has been synthesized and investigated in radioligand binding assays at the high-affinity adenosine receptor (AR) subtypes A_1 and A_{2a}. The compounds can be envisaged as adenine and hypoxanthine analogs lacking the nitrogen in the 7-position (7-deazaadenines and 7-deazahypoxanthines). 7-Deazaadenines were much more potent than 7-deazahypoxanthines at AR with A_1AR affinities in the low-nanomolar range, extraordinarily high selectivity for the rat brain A_1AR versus the A_{2a}AR (several thousandfold), and high stereoselectivity (up to 96-fold). Pyrimido[4,5-*b*]indoles were more potent A_1AR antagonists compared to pyrrolo[2,3-*d*]pyrimidines. Compound **34a** (APEPI) is one of the most potent and most selective non-xanthine A_1AR antagonists known to date (K_i = 2.8 nM, >2000-fold A_1-selective). A new class of very potent A_1AR antagonists has been identified, namely, 2-phenyl-7-deazaadenines bearing a substituent at the exocyclic amino group (N^4-substituted pyrrolo[2,3-*d*]pyrimidines). (*R*)-*N*-(1-Phenylethyl)-4-amino-5,6-dimethyl-2-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (DPEAP, **17a**) showed a K_i value of 6.7 nM at A_1AR and >4000-fold A_1 selectivity. Different binding modes are postulated for the N^4-substituted 4-aminopyrrolo[2,3-*d*]pyrimidines (e.g., **17a**) and the 7-substituted derivatives (e.g., **1a**), based on a comparison of steric, electronic, and hydrophobic properties of the two classes of compounds. Water solubility and lipophilicity have been determined for selected compounds. 4-Amino-5,6-dimethyl-2-(3-chlorophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (**4a**) showed the highest water solubility/A_1AR affinity ratio of 368 in the present series, over 2000-fold A_1 selectivity, and 64-fold stereoselectivity (*R* > *S*). Therefore, **4a** should be an interesting compound for *in vivo* evaluation.

Introduction

Adenosine receptors belong to the superfamily of purine receptors which are currently subdivided into P_1 (adenosine) and P_2 (ATP, ADP, and other nucleotide) receptors.[1] There is increasing evidence, however, that it is not the purine part which is essential for activity of natural and synthetic agonists at these receptors[2] but rather the ribose moiety. Therefore we have suggested to name this receptor family "riboside receptors" [3] in accordance with the originally proposed nomenclature for adenosine receptors by Londos and co-workers.[4] The riboside receptors could be subdivided into two subclasses, one activated by nucleosides, the other subclass activated by nucleotides. Four receptor subtypes for the nucleoside adenosine have been cloned so far from various species including humans.[5,6] Two receptor subtypes (A_1 and A_{2a}) exhibit high affinity for adenosine (generally in the low-nanomolar range), while the two other known subtypes (A_{2b} and A_3) are low-affinity receptors, typically showing affinity for adenosine in the low-micromolar range.[6] A_1- and A_3-adenosine receptor (AR) activation can lead to an inhibition of adenylate cyclase activity, while A_{2a}- and A_{2b}AR activation causes a stimulation of adenylate cyclase. Other second-messenger systems have been described for A_1AR, including coupling to calcium and potassium channels.[6] A_3ARs have been reported to be coupled to phosphoinositide turnover in some systems.[5]

All known AR agonists are derivatives of the physiological agonist adenosine. Adenine derivatives and analogs lacking the ribose moiety, however, have been shown to act as antagonists at AR.[7] We have been engaged in the search for and development of novel subtype-selective AR antagonists, especially for the high-affinity A_1- and A_{2a}AR subtypes.[8] Such AR antagonists are needed as pharmacological tools and are of considerable interest as drugs. A_1-antagonists are currently developed for the treatment of cognitive diseases, renal failure, and cardiac arrhythmias, while A_{2a}-antagonists may be beneficial for patients suffering from Morbus Parkinson.[9]

During our search for novel AR antagonists, we had found that 7-deazaadenines and 7-deazahypoxanthines with pyrrolo[2,3-*d*]pyrimidine or pyrimido[4,5-*b*]indole structure (see Chart 1) were potent and selective adenosine receptor antagonists.[10,11] 4-Aminopyrrolo[2,3-*d*]pyrimidines bearing a 2-phenyl ring had turned out to be particularly active at A_1AR and very selective for that receptor subtype.[11] The most potent compound was **1a** (ADPEP) with a K_i value at A_1AR of rat brain of 4.7 nM and ca. 789-fold selectivity for that receptor subtype

† Dedicated to Prof. Dr. G. Seitz, Marburg, on the occasion of his 60th birthday.

‡ Preliminary results were presented in Philadelphia at the 5th International Symposium on Adenosine and Adenine Nucleotides, 1994; abstract published in *Drug Dev. Res.* **1994**, *31*, 301.

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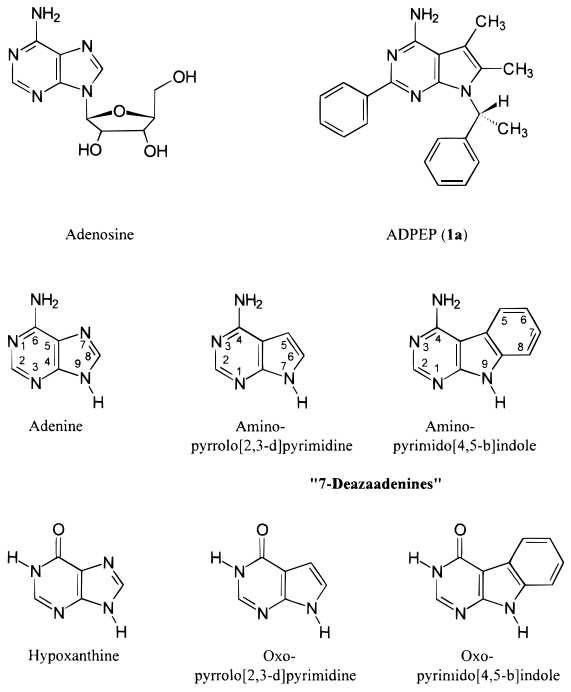
⊗ Abstract published in *Advance ACS Abstracts,* May 15, 1996.

S0022-2623(96)00011-8 CCC: $12.00

Chart 1. Basic Structure of Investigated 7-Deazaadenines and 7-Deazahypoxanthines



compared to the high-affinity A_2AR of rat striatum.[11] The compound exhibited stereoselectivity, the *R*-configurated stereoisomer **1a** being more potent than its *S*-enantiomer.

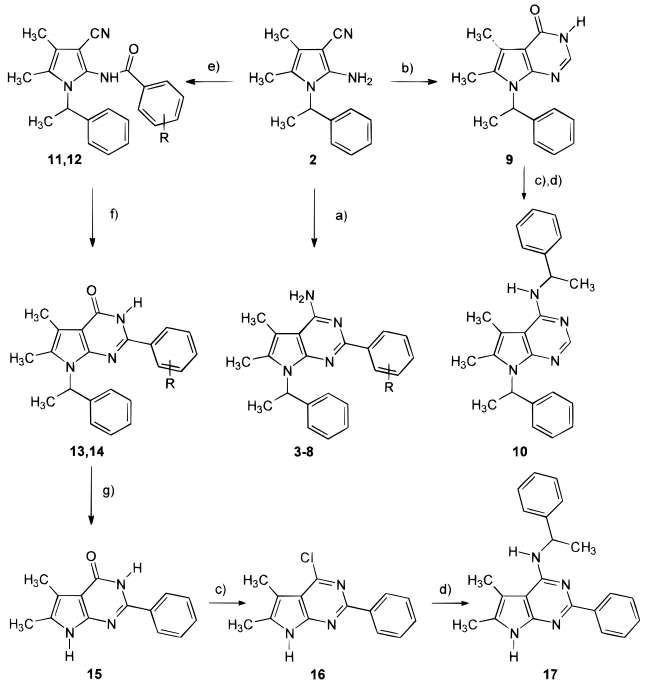
In the present study a new series of 7-deazaadenine and 7-deazahypoxanthine derivatives has been synthesized and investigated in A_1- and A_2AR binding assays. Our goal was to get more insight into structure−activity relationships of this potent class of non-xanthine AR antagonists and eventually to identify more potent and more selective compounds. In an earlier study most investigated compounds had been either achiral or racemic. We have now synthesized the enantiomers of a new series of chiral compounds to investigate the stereochemical requirements of this class of compounds for binding to AR. We were particularly interested in obtaining information about the binding mode of 7-deazaadenines to AR with respect to adenosine derivatives (AR agonists). Since potent AR antagonists often show high lipophilicity, low water solubility, and hence low bioavailibility, we also investigated physicochemical properties, especially water solubility of the compounds. These data may be useful for selecting compounds for *in vivo* studies.

Chemistry

Most of the products prepared were chiral, and in most cases both enantiomers were synthesized. All compounds with *R*-configuration were designated **a** and those with *S*-configuration **b** after the compound number.

N^4- Or 7-(1-phenylethyl)-substituted 5,6-dimethylpyrrolo[2,3-*d*]pyrimidines **3**−**10** and **13**−**17** (Scheme 1) were prepared starting from pyrrole derivative **2** (**2a**, *R*-enantiomer, or **2b**, *S*-enantiomer). Compound **2** was obtained in analogy to compounds **19**−**21** (see below; Scheme 2) in a one-pot reaction of 3-hydroxy-2-butanone, 1-phenylethylamine, and malonodinitrile.[11−14]

Scheme 1. Synthesis of Pyrrolo[2,3-*d*]pyrimidines[a]

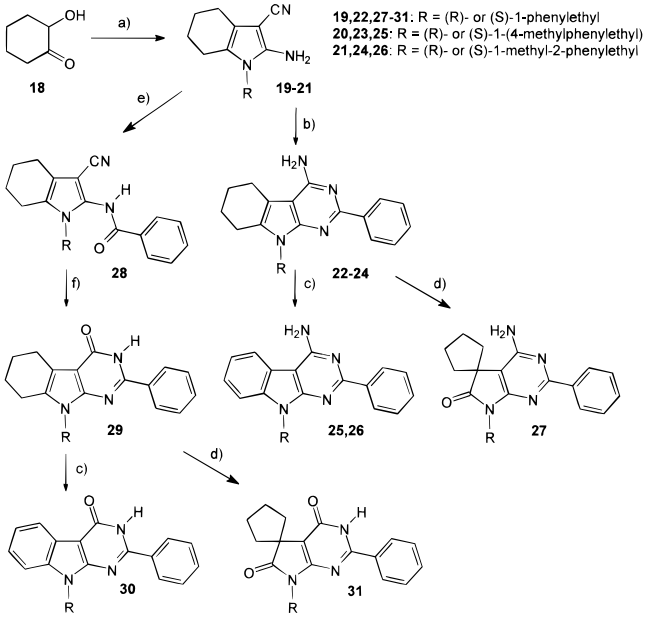


[a] For R, see Table 1 or 2. (a) Benzonitrile derivative (see Table 1), sodium methylate; (b) HCOOH; (c) $POCl_3$; (d) (*R*)- or (*S*)-1-phenylethylamine; (e) benzoyl chloride derivative (see Table 1); (f) P_2O_5, dimethylcyclohexylamine, H_2O; (g) polyphosphoric acid.

Pyrrolo[2,3-*d*]pyrimidin-4-one derivatives **13** and **14** were prepared by condensation of **2** with benzoyl chloride or *p*-chlorobenzoyl chloride, respectively. *N*7,N^4-Disubstituted pyrrolo[2,3-*d*]pyrimidines **10a**,**b** were synthesized from **2a**,**b** in three steps: Ring closure of **2** with formic acid yielded **9** which was treated with $POCl_3$ to afford the corresponding 4-chloro derivative. Substitution of the chlorine atom by (*R*)- or (*S*)-1-phenylethylamine could be achieved by heating the chloro derivative with a 10-fold excess of the amine for 96 h to yield **10**. 7-Unsubstituted N^4-substituted pyrrolo[2,3-*d*]pyrimidine **17**, an isomer of **1a**, was prepared from compound **13**. Dealkylation in the 7-position by heating with polyphosphoric acid[13] to **15** and subsequent reaction with $POCl_3$ yielded **16**. Substitution with a 10-fold excess of (*R*)- or (*S*)-1-phenylethylamine afforded **17**, requiring a reaction time of several days.

N-Substituted 2-aminotetrahydroindole-3-carbonitriles **19**−**21** (Scheme 2) were obtained in a one-pot reaction developed by Eger et al.[14] Hydroxycyclohexanone was condensed with an arylalkylamine in the presence of *p*-toluenesulfonic acid. Subsequent base-catalyzed cyclization with malononitrile yielded the desired products. The arylalkylamines used were chiral, and both enantiomers of each compound (**19**−**21**) were prepared starting from the *R*- or *S*-configurated amines, respectively. Reaction of **19**−**21** with benzonitrile and sodium methylate in 2-propanol yielded the 2-phenyltetrahydropyrimido[4,5-*b*]indolamine derivatives **22**−**24** in analogy to described procedures.[11,15] The 4-oxo analog **29** of the 4-aminotetrahydroindole **22** was prepared by condensation of **19** with benzoyl chloride to yield **28** and subsequent cyclization with phosphorus pentoxide in the presence of a mixture of dimethylcyclohexylamine and water at 190 °C.[16] Despite such drastic reaction conditions, the phenylethyl residue at N9 was stable, while treatment of similar compounds

Scheme 2. Synthesis of Pyrrolo[4,5-*b*]indoles and Spiro[cyclopentane-pyrrolo[2,3-*d*]pyrimidines][a]



[a] (a) RNH_2, $CH_2(CN)_2$; (b) benzonitrile, sodium methylate, 2-propanol; (c) Pd/C, 1-methylnaphthalene; (d) $NaIO_4$; (e) benzoyl chloride; (f) P_2O_5, dimethylcyclohexylamine, H_2O.

with polyphosphoric acid at 70 °C had led to dealkylation[13] (see above, compounds **13/15**). Dehydration of the tetrahydroindoles **23**, **24**, and **29** to obtain the desired aromatic indole derivatives **25**, **26**, and **30** was achieved catalytically with Pd/C at high temperatures. 1-Methylnaphthalene proved to be a suitable solvent for this reaction due to its high boiling point (244 °C). Solvents with lower boiling point such as decaline or mesitylene gave unsatisfactory results.[15] Reactions of tetrahydroindoles **22** and **29** with sodium periodate led to the corresponding spiro[cyclopentane-pyrrolo[2,3-*d*]-pyrimidine] derivatives in analogy to described reactions.[15]

Yields and analytical data, including optical rotation of enantiomers, are given in Table 1. ^1H and ^{13}C NMR spectral data were consistent with the proposed structures. Selected NMR data are given in the Experimental Section. Further ^1H and ^{13}C NMR data are available as Supporting Information.

Biological Evaluation

The compounds were tested in radioligand binding assays for affinity at A_1- and A_{2a}-adenosine receptors in rat cortical membrane and rat striatal membrane preparations, respectively. [^{3}H]-N^6-(*R*)-(Phenylisopropyl)adenosine ((*R*)-PIA) was used as A_1 ligand and [^{3}H]-5′-(*N*-ethylcarbamoyl)adenosine (NECA) as A_{2a} ligand in the presence of 50 nM N^6-cyclopentyladenosine, the latter to block A_1-receptors present in the striatal tissue.

Results and Discussion

Structure−Activity Relationships. The 2-phenyl substituent of 7-deaza-2-phenyladenines is known to contribute to a large extent to the high potency of the compounds at A_1AR as had been shown in a series of pyrrolo[2,3-*d*]pyrimidines.[11] This result could now be confirmed in a series of pyrimido[4,5-*b*]indole derivatives. Introduction of a 2-phenyl group into **32** resulted in a tremendous increase in A_1AR affinity (compounds **34a**,**b**).

The effects of substituents on the 2-phenyl ring of **1a** and its enantiomer **1b** were investigated. Substitution of the 2-phenyl group with chloro or methoxy functions generally reduced AR affinity. Meta- and ortho-chloro substitutions were better tolerated (ca. 2-fold decrease in A_1AR affinity) than para-chloro substitution, which led to a 10-fold reduction of A_1 affinity. Meta-chloro substitution, however, was favorable for high A_1 selectivity which was increased from 789-fold in **1a** to over 2000-fold in compound **4a**.

A regioisomer of **1a** in which the (*R*)-1-phenylethyl residue is attached to the exocyclic amino function rather than to the pyrrole nitrogen was prepared. The compound **17a** (DPEAP) exhibited high affinity to A_1-AR (K_i = 6.7 nM) and showed extraordinarily high A_1 selectivity (>4000-fold) and stereoselectivity (**17a/17b**: 96-fold; $R > S$).

A comparison of the steric and electronic properties of regioisomers **1a** and **17a** revealed excellent conformity, if the N^4 nitrogen atom of compound **17a** was aligned with the N7 of compound **1a** and N1 of one compound was aligned with N3 of the other one (see Figure 1, N^4/N7-binding model). Both compounds exhibited similarly high A_1AR affinity, A_1 selectivity, and stereoselectivity. We therefore postulate different binding modes for 7-substituted 4-aminopyrrolo[2,3-*d*]pyrimidines, such as **1a**, and N^4-substituted derivatives, such as **17a**. The postulated binding mode was tested by a molecular modeling study. At first we searched for low-energy conformations of compounds **1a** and **17a**. Then, the structures were aligned according to the proposed model, with N7 of **1a**/N^4 of **17a** and N1 of **1a**/N3 of **17a** superimposed. Figure 2, top, shows a comparison of the van der Waals volumes of **1a** and **17a** which are very similar for both compounds. In Figure 2, bottom, the molecular electrostatic potentials (MEP), which are also considered to be important for molecular recognition, of **1a** and **17a** are compared. Again, both compounds show a striking similarity when superimposed according to the N7/N^4 binding model. In addition, lipophilic properties of **1a** and **17a** were calculated and compared. The two compounds are regioisomers, and therefore, partition coefficients (*P* values) should be similar. In fact, calculation of log *P* values resulted in very similar numbers for compounds **1a** and **14a** (see Table 3).

Disubstitution with 1-phenylethyl at both nitrogen atoms, N^4 and N7, in a compound lacking the 2-phenyl group resulted in compounds with low AR affinity (**10a**,**b**) and loss of stereoselectivity. A similar effect had been observed in a series of analogous N^6,9-disubstituted adenine derivatives, another class of adenosine receptor antagonists.[17] At present it is not clear whether the lacking of the 2-phenyl group, the disubstitution, or both is responsible for the low activity of compounds **10a**,**b**.

7-Deazaadenines with pyrimido[4,5-*b*]indole structure were more potent than those with 5,6-dimethylpyrrolo-[2,3-*d*]pyrimidine structure, such as **1a**. The most potent compound of the whole series of 7-deazapurines was an analog of **1a**, **34a** (APEPI), with a K_i value at A_1AR of 2.6 nM and >2000-fold selectivity for A_1- versus

Table 1. Reagents, Yields, and Analytical Data of New Compounds Synthesized

compd[a]	reagent	amount [g (mmol)]	yield [g (%)]	formula	anal.	EI-MS (70 eV) *m/z* [M$^+$]	mp (°C)	$[\alpha]^{20}_D$[b] configuration R	S
3a,**b**	2-chlorobenzonitrile	1.4 (10)	2.0 (53)	$C_{22}H_{21}ClN_4$	C, H, N		152	+24	−23
4a,**b**	3-chlorobenzonitrile	1.4 (10)	1.9 (50)	$C_{22}H_{21}ClN_4$	C, H, N		168	+3	−3
5a,**b**	4-chlorobenzonitrile	1.4 (10)	2.0 (53)	$C_{22}H_{21}ClN_4$	C, H, N		150	−6	+6
6a,**b**	3,4-dichlorobenzonitrile	1.72 (10)	2.4 (58)	$C_{22}H_{20}Cl_2N_4$	C, H, N		152	+2	−2
7a	3-methoxybenzonitrile	1.3 (10)	2.8 (75)	$C_{23}H_{24}N_4O$	C, H, N		181	−21	
8a	4-methoxybenzonitrile	1.3 (10)	2.5 (67)	$C_{23}H_{24}N_4O$	C, H, N		156	−10	
9a,**b**	**2a** or **2b**	9.57 (40)	8.5 (79)	$C_{16}H_{17}N_3O$	C, H, N		245	+56	−54
10a,**b**	**9a** or **9b**	5.3 (20)	4.4 (59)	$C_{24}H_{26}N_4$	C, H, N		118	−110	+108
11a,**b**	benzoyl chloride	4.5 (32)	5.3 (51)	$C_{22}H_{21}N_3O$	C, H, N		215	+169	−164
12a,**b**	4-chlorobenzoyl chloride	5.6 (32)	6.0 (53)	$C_{22}H_{20}N_3O$	C, H, N		215	+163	−161
13a,**b**	**11a** or **11b**	2.75 (8)	1.4 (51)	$C_{22}H_{21}N_3O$	C, H, N	343.2	254	+82	−84
14a,**b**	**12a** or **12b**	3.0 (8)	1.3 (43)	$C_{22}H_{20}ClN_3O$	C, H, N	377.1	286	+79	−80
15	**13a** or **13b**	6.87 (20)	4.3 (90)	$C_{14}H_{13}N_3O$	C, H, N		312−315		
16	**15**	4.8 (20)	2.8 (55)	$C_{14}H_{12}N_3Cl$	C, H, N		177		
17a,**b**	(*R*)- or (*S*)-1-phenylethylamine	1.55 (6)	0.8 (39)	$C_{22}H_{22}N_4$	C, H, N		142	+18	−20
19a,**b**	(*R*)- or (*S*)-1-phenylethylamine	6.06 (20)	nd[c]		nd		(oil)	nd	nd
20a,**b**	(*R*)- or (*S*)-(1-(4-methylphenyl) ethyl)amine	6.75 (20)	9.6 (71)	$C_{18}H_{21}N_3$	C, H, N		128	+116	−112
21a,**b**	(*R*)- or (*S*)-1-methyl-2-phenylethylamine	1.35 (10)	nd		nd		(oil)	nd	nd
23a,**b**	**20a** or **20b**	1.65 (6)	1.2 (52)	$C_{25}H_{26}N_4$	C, H, N		153	+19	−19
24a,**b**	**21a** or **21b**	1.65 (6)	1.5 (65)	$C_{25}H_{26}N_4$	C, H, N	382.3	158−159	−200	+198
25a,**b**	**23a** or **23b**	0.95 (2.5)	0.68 (72)	$C_{25}H_{22}N_4$	C, H, N		150	+103	−106
26a,**b**	**24a** or **24b**	0.95 (2.5)	0.67 (71)	$C_{25}H_{22}N_4$	C, H, N		151	−113	+112
27a	**22a**	2.2 (6)	0.7 (30)	$C_{24}H_{24}N_4O$	C, H, N	384	200−201	+4.0	
28a,**b**	**19a** or **19b**	7.95 (30)	8.5 (77)	$C_{24}H_{23}N_3O$	C, H, N		234	+164	−160
29a,**b**	**28a** or **28b**	2.95 (8)	1.3 (44)	$C_{24}H_{23}N_3O$	C, H, N		275	+14	−16
30a,**b**	**29a** or **29b**	0.9 (4.2)	0.72 (80)	$C_{24}H_{19}N_3O$	C, H, N	365.2	257	+114	−110
31a	**29a**	2.2 (6)	0.9 (38)	$C_{24}H_{23}N_3O_2$	C, H, N	385.3	254−255	+160 ($CHCl_3$)	

[a] In cases where separate enantiomers were prepared, the *R*-enantiomer was designated **a** and the *S*-enantiomer **b** after the compound number. [b] Determined in DMSO unless otherwise noted. [c] nd = not determined.

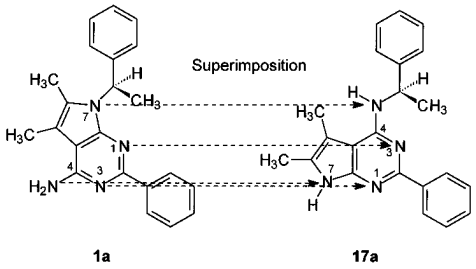


Figure 1. Different binding modes for N7-substituted (**1a**) and N^4-substituted (**17a**) pyrrolopyrimidine derivatives: the N7/N^4-binding model.

A_{2a}AR. The compound exhibited marked stereoselectivity, the *R*-enantiomer being 25-fold more potent than the *S*-enantiomer at A_1AR.

As had been observed earlier in the pyrrolo[2,3-*d*]-pyrimidine series, an (*R*)-1-phenylethyl substituent on the pyrrole nitrogen is superior to a phenyl substituent in that position in pyrimidoindoles as well (cp. **34a/33**). Para-methyl substitution of the phenylethyl substituent of **34a** and its enantiomer **34b** led to an about 5-fold decrease in A_1AR affinity and also decreased A_2AR affinity (compounds **25a**,**b**). It appears that the adenosine receptors cannot accommodate well an additional methyl group in the phenylethyl-binding receptor domain.

Exchange of the (*R*)-1-phenylethyl group in the 7-position of **34a** by (*R*)-phenylisopropyl in analogy to the potent A_1AR agonist (*R*)-PIA[18] led to a dramatic (>200-fold) decrease in A_1AR affinity (cp. **34a**/**26a**). Stereoselectivity of the phenylisopropyl derivatives **26a**,**b** was very low (only ca. 2-fold) and reversed (*S* > *R*) compared to the 1-phenylethyl-substituted analogs **34a**,**b**. Therefore, it appears very unlikely that the substituent at the pyrrole nitrogen of 7-deazaadenines binds to the same receptor region as the N^6-substituent of adenosine derivatives.

The exchange of the amino group in 7-deazaadenines for an oxo function leads to 7-deazahypoxanthines. The loss of the amino group resulted in a significant decrease in AR affinity of the compounds investigated (cp. **1a**,**b**/**13a**,**b**; **5a**,**b**/**14a**,**b**; **34a**,**b**/**30a**,**b**; **27a**/**31a**). The oxo analog **13a** of **1a**, for example, showed a more than 600-fold lower affinity than the amino compound **1a**. A_1AR selectivity and stereoselectivity, however, was retained. Stereoselectivity was *R* > *S* as observed with the amino analogs (cp. **13a**,**b**/**1a**,**b**). Para-chloro substitution of the 2-phenyl ring reduced A_1 affinity as in the amino series (compounds **5a**,**b**/**14a**,**b**).

Pyrimido[4,5-*b*]indoles, however, were less active than the corresponding 5,6-dimethylpyrrolo[2,3-*d*]pyrimidines in the 7-deazahypoxanthine series (cp. **13a**/**30a**), indicating different binding modes for 7-deazaadenines and 7-deazahypoxanthines. Also, a 1-phenylethyl substituent on the pyrrole nitrogen appeared to be less favorable for 7-deazahypoxanthines compared to a phenyl substituent (cp. **37**/**36**), in contrast to results in the 7-deazaadenine series. In 7-deazaadenines the introduction of a 2-phenyl ring had led to a tremendous increase in A_1AR affinity.[11] 2-Phenyl-substituted 7-deazahypoxanthine derivatives had not been investigated so far. We have now found that a 2-phenyl substituent in 7-deazahypoxanthine derivatives had a detrimental effect on AR affinity of the compounds (**13a**,**b**, **14a**,**b**, **30a**,**b**, **31a**). These results again indicate different binding modes for 7-deazahypoxanthines and 7-deazaadenines, at least for those derivatives that bear a substituent on the pyrrole nitrogen. Oxo analogs of N^4-

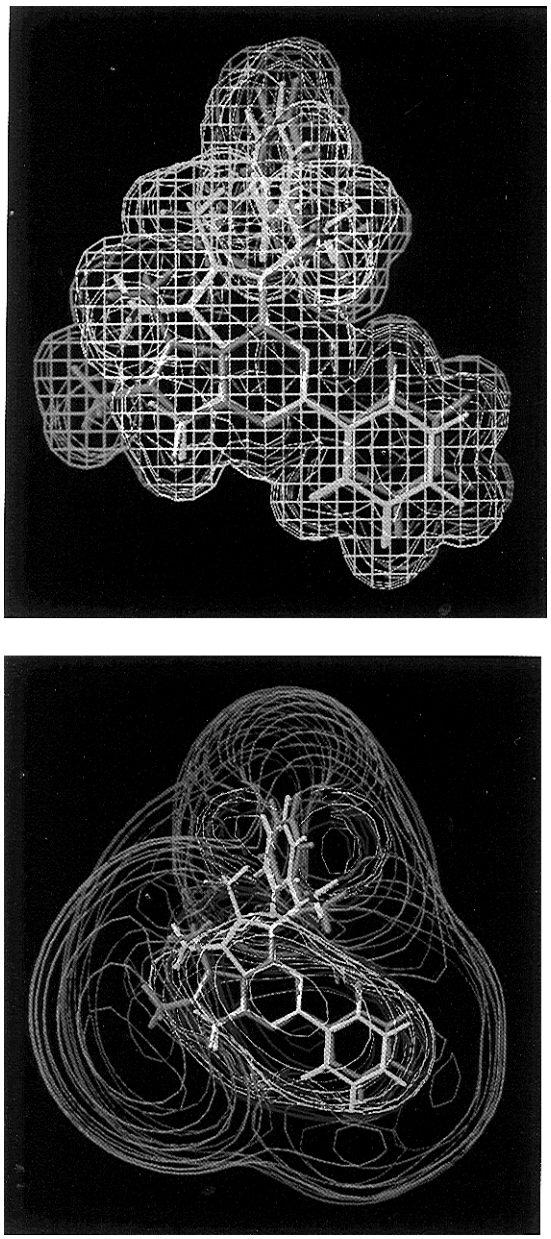


Figure 2. Comparison of (top) van der Waals volumes and (bottom) molecular electrostatic potentials (MEP) of **1a** in cyan and **17a** in magenta. (Bottom) Positive (+4.2 kJ/mol) MEP are shown in red for **1a**, in magenta for **17a**; negative MEP (−4.2 kJ/mol) are shown in blue for **1a**, in green for **17a**.

substituted pyrrolopyrimidines or pyrimidoindoles without a substituent on the pyrrole nitrogen, e.g., O^4-substituted oxo analogs of **17a**, however, have not been investigated so far. 7-Deazahypoxanthine analogs substituted at the pyrrole nitrogen are lacking an N-H function at the appropriate position (such as the N^4-H in **1a** or the N7-H in **17a**; see Figure 1) for hydrogen bonding to the receptors.

Spiro-7-deazahypoxanthines **31a** and **35**−**37** showed relatively low AR affinity. 7-Deazaadenine analog **27a** of 7-deazahypoxanthine derivative **31a** was relatively potent at A_1AR and quite selective but much less potent than the corresponding 5,6-dimethylpyrrolopyrimidine **1a** or the pyrimidoindole **34a**.

Adenosine receptor agonists (adenosine derivatives) bind to AR in a highly stereoselective manner. Stereochemistry at the ribose moiety is particularly important,[19] since the ribose is believed to play the essential role in mediating agonistic activity.[3,7] Not only is the ribose part recognized stereoselectively but also substituents at the exocyclic amino function (N^6) of adenosine. A typical example is the classical standard A_1AR agonist (*R*)-PIA which binds with ca. 50-fold higher affinity to A_1AR than its diastereomer (*S*)-PIA.[18] Among antagonists stereoselective binding has also been observed. The degree of stereoselectivity, however, was generally much lower than that observed with agonists. (*R*)-1,3-Dipropyl-8-(phenylisopropyl)xanthine, for example, was only 9-fold more potent than its *S*-enantiomer.[20] Chiral N^6-substituted adenines also showed only a moderate (<10-fold) degree of stereoselectivity.[17] 7-Deazaadenine derivative **1a** had been the first example of an AR antagonist exhibiting high (35-fold) stereoselectivity (*R* > *S*).[11] In the present study we have investigated the separate stereoisomers of a new series of 7-deazaadenines and 7-deazahypoxanthines. We found that not only is the 7-substituent of pyrrolo[2,3-*d*]pyrimidines recognized stereoselectively but also the N^4-substituent, as in **17a** (*R* > *S*). The highest degree of stereoselectivity was exhibited by compounds **4a** (64-fold) and **17a** (96-fold).

It has been postulated that ARs contain three binding domains for their ligands, a central aromatic binding domain, a hydrophobic binding domain, and a ribose binding domain[21] (for agonists) which can be occupied by lipophilic (often aromatic) substituents of AR antagonists. The structures of potent 7-deazaadenines are consistent with the proposed model. One important feature, particularly for A_1AR ligands, appears to be a hydrogen bond donor (N−H) and a hydrogen bond acceptor (e.g., =N−, =O) in a certain distance (**1a**, N^4−H and N3; **17a**, N7−H and N1; see Figure 1).

In contrast to AR antagonists, adenosine derivatives (AR agonists) probably can bind to A_1AR only in one binding mode, determined by the ribose moiety. A comparison of adenosine derivatives and 7-deazaadenines (antagonists) would at first sight lead to the conclusion that adenosines and N^4-substituted pyrrolo-[2,3-*d*]pyrimidines, such as **17a**, bind to AR in the same binding mode (Figure 1) with the heterocyclic ring systems and the amino substituents superimposed. Structure−activity relationships of adenosine derivatives, however, are not consonant with either of the two binding modes proposed for 7-deazaadenine derivatives such as **1a** and **17a** (see Figures 1 and 2) for the following reasons. (1) 7-Deazaadenosine is nearly inactive at AR,[19,22] while 7-deazaadenines, such as **17a**, are very potent. (2) PIA is a potent A_1AR agonist exhibiting a high degree of stereoselectivity (*R* > *S*), while (phenylisopropyl)-7-deazadenine **26** shows very low A_1 affinity and a low degree of stereoselectivity, which is reversed (*S* > *R*). Therefore we conclude that adenosine derivatives may bind to A_1AR in yet another binding mode, different from those for N7- and N^4-substituted 7-deazaadenines.

N^6,9-Disubstituted adenine derivatives, in which the ribose of adenosine is substituted by an alkyl or aryl function, are moderately potent A_1AR antagonists, e.g., N^6-cyclopentyl-9-methyladenine.[7] Structure−activity relationships indicate a similar binding mode for this class of compounds as for adenosine derivatives but, again, a different binding mode from 7-deazaadenines.[7,17]

Another related class of potent AR antagonists, which

has been described recently, is the 8-azaadenines. Independently from our model,[23] Biagi et al. postulated a similar binding model with two different binding modes for 2-phenyl-8-azaadenines.[24] In contrast to their hypothesis, however, we propose a third binding mode for adenosine derivatives different from the two binding modes postulated for 7-deazaadenines (Figures 1 and 2). The investigation of the third binding mode, that for adenosines with respect to 7-deazaadenines **1a** and **17a**, is currently under investigation.

In addition to the high-affinity AR subtypes A_1 and A_{2a}, at least two low-affinity AR subtypes exist, designated A_{2b} and A_3. The A_{2b}AR shows a high degree of homology to the high-affinity A_{2a}AR.[6] The relationship between the A_2AR subtypes is much closer than between A_1- and A_2AR. Therefore, it is likely that AR antagonists selective for A_1 versus A_{2a} are also selective versus the A_{2b}AR subtype. One 7-deazahypoxanthine, 9-phenyl-9*H*-pyrimido[4,5-*b*]indol-4(3*H*)-one (HPPI), a compound with reasonable A_{2a}AR affinity,[10] had been investigated as antagonist at rat A_{2b}AR.[25] In fact, the compound showed similar activity at A_{2a}AR (K_B = 2.5 μM) and A_{2b}AR (K_B = 3.4 μM) in functional assays (antagonism of NECA stimulation of adenylate cyclase in PC 12 (A_{2a}AR) and NIH 3T3 (A_{2b}AR) cell membranes).[25] To our knowledge, 7-deazaadenine and derivatives have not been investigated at the novel A_3AR subtype so far. Two 7-deazahypoxanthines, HPPI and its 5,6,7,8-tetrahydro derivative, showed less than 20% inhibition of radioligand binding at a concentration of 10 μM at rat A_3AR.[36]

Solubility and Lipophilicity. The application of *in vitro* assays for the development of AR ligands often leads to compounds with high receptor affinity but, at the same time, high lipophilicity and low water solubility. Due to their low bioavailability, such compounds may be inactive *in vivo* and therefore of no interest for drug development.[26] Bruns and Fergus proposed that the solubility-over-receptor affinity ratio (the so-called Bruns−Fergus index or BF index) should be >100 for a drug to exhibit *in vivo* activity.[27] We used the A_1AR binding protocol developed by Bruns and Fergus[27] to determine solubilities of the potent A_1-antagonists **5a**, **17a**, and **34a**. Solubilities of **1a** and racemic **4** had been determined earlier by the same method.[11] It had been shown that this biochemical method of solubility determination corresponds well with analytical methods, such as UV-photometry, and it has the advantage of being easily applicable to very insoluble compounds.[11,27] Stock solutions of compounds in DMSO were prepared and diluted into buffer to obtain a saturated solution in buffer containing 1% DMSO. The earlier somewhat surprising finding that a chloro substituent at the 2-phenyl ring could enhance solubility of 2-phenyl-7-deazaadenines[11] was confirmed in this study. Thus, the chloro-substituted derivatives **4a** and **5a** of **1a** showed about 10-fold higher water solubility compared to **1a**. The very potent and highly selective meta-chloro derivative **4a** exhibited a solubility/A_1 affinity ratio of 368 and was the best compound of the series with respect to the BF index. Pyrimidoindole analog **34a** of pyrrolopyrimidine **1a** was about 2-fold more soluble than **1a**. Since it was also more active at A_1AR, the BF index was improved from 55 in **1a** to 185 in **34a**. N^4-Substituted pyrrolopyrimidine **17a** exhibited even higher water solubility (1.5 μM) and an about 4-fold increase in the BF index compared to its isomer **1a**. With compounds **4a**, **17a**, and **34a**, we have now been successful in developing 7-deazaadenine derivatives with a BF index of >100. These compounds should be sufficiently soluble to exhibit activity *in vivo*.

Solubilities of the investigated 7-deazaadenines were in the low-micromolar range, or even below. In the AR assays, however, we had been able to measure competition with radioligands at membrane preparations up to much higher concentrations of test compounds. As reported in Table 2, concentrations up to 30 μM of most compounds, including **5a** and **17a**, could be used without any apparent problems due to limited solubility. In order to investigate whether the higher DMSO concentration (2.5% in the binding assays vs 1% for solubility determination) was the reason for this discrepancy, we determined solubilities of three selected compounds in buffer containing 2.5% DMSO. We found that the solubility was increased by the higher DMSO concentration, as expected. Compounds **5a**, **17a**, and **34a** all showed an about 3-fold increase in solubility in aqueous buffer solution containing 2.5% DMSO as compared to 1% DMSO (see Table 3). But this moderate increase in solubility could still not fully explain our observations. A further explanation could be the increase in solubility at higher temperatures, since solubility was determined at room temperature, while the A_1 binding assays were performed at 37 °C. Another explanation that has been forwarded was that supersaturated solutions may be formed.[27] Our observations, however, appear to indicate that the presence of membrane tissue in the assay mixture leads to the observed increase in solubility of the test compounds by acting as a kind of solubilizer.

Calculated partition coefficients for selected compounds (Table 3) show that water solubility and log *P* values cannot be correlated in the present series. Chloro-substituted derivatives **4a** and **5a** show a better water solubility than **1a** despite their higher lipophilicity.

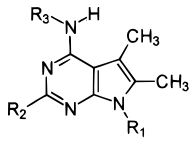
In conclusion, new A_1AR antagonists have been developed which should be promising candidates for *in vivo* studies.

Experimental Section

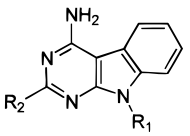
Synthetic Procedures. NMR spectra were performed on a Bruker WP-80 (^{1}H, 80 MHz; ^{13}C, 20 MHz), a Bruker AC-250 (^{1}H, 250 MHz; ^{13}C, 60 MHz), or a Varian Gemini 300 (^{1}H, 300 MHz; ^{13}C, 75 MHz) spectrometer, respectively. DMSO-d_6 was used as solvent, unless otherwise noted. The chemical shifts of the remaining protons of the deuterated solvents served as internal standards: δ (^{1}H, DMSO-d_6 = 2.50, $CDCl_3$ = 7.24; ^{13}C, DMSO-d_6 = 39.7, $CDCl_3$ = 77.0). All compounds were checked for purity by TLC on 0.2 mm aluminum sheets with silica gel 60 F_{254} (Merck); as eluent toluene, toluene:methanol (9:1), toluene:acetone:formic acid (60:39:1), or ethyl acetate, respectively, was used. Melting points were taken on a Büchi 510 melting point apparatus and are uncorrected. Electron ionization mass spectra were recorded on a Finnigan MAT 711A spectrometer. Optical rotation was measured with a Perkin-Elmer 241 spectrometer in a cuvette of 10 cm length, in a concentration of 1.00% in DMSO, unless otherwise noted. Elemental analyses, NMR spectra, and mass spectra were performed by the Institute of Chemistry, University of Tübingen, and the Institute of Organic Chemistry, University of Leipzig, respectively. Additional NMR data are available as Supporting Information.

Compounds **2a**,**b**, **19a**,**b**, and **22a**,**b** were obtained as described.[13−15] The synthesis of the final products **32**−**37** has

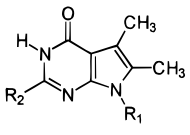
Table 2. Adenosine Receptor Affinities of Pyrrolo[2,3-*d*]pyrimidines and Pyrimido[4,5-*b*]indoles



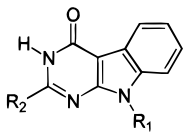
I
4-Amino-pyrrolo-[2,3-d]pyrimidines



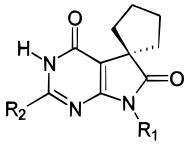
II
4-Amino-pyrimido-[4,5-b]indoles



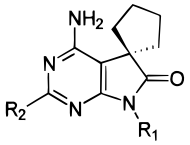
III
4-Oxo-pyrrolo-[2,3-d]pyrimidines



IV
4-Oxo-pyrimido-[4,5-b]indoles



V
Oxo-spiro-pyrrolo[2,3-d]-pyrimidines



VI
Amino-spiro-pyrrolo-[2,3-d]pyrimidines

compd	R_1	R_2	R_3	$K_i \pm$ SEM (μM): A_1-receptors vs [^{3}H]-(*R*)-PIA, rat brain cortex	$K_i \pm$ SEM (μM): A_2-receptors vs [^{3}H]NECA, rat striatum	A_1 selectivity, A_2/A_1
			4-Aminopyrrolo[2,3-*d*]pyrimidines (**I**)			
1a (ADPEP)	(*R*)-1-phenylethyl	phenyl	H	0.0047[2]	3.71[2]	789
1b	(*S*)-1-phenylethyl	phenyl	H	0.165[2]	81[2]	490
3a	(*R*)-1-phenylethyl	2-chlorophenyl	H	0.0096 ± 0.0010	5.2 ± 0.6	537
3b	(*S*)-1-phenylethyl	2-chlorophenyl	H	0.273 ± 0.028	>30 (35%)[a]	>110
4a	(*R*)-1-phenylethyl	3-chlorophenyl	H	0.0076 ± 0.0013	16.3 ± 4.9	2145
4b	(*S*)-1-phenylethyl	3-chlorophenyl	H	0.485 ± 0.015	>30 (20%)[a]	>62
5a	(*R*)-1-phenylethyl	4-chlorophenyl	H	0.050 ± 0.006	>30 (23%)[a]	>600
5b	(*S*)-1-phenylethyl	4-chlorophenyl	H	0.878 ± 0.153	>30 (3%)[a]	>34
6a	(*R*)-1-phenylethyl	3,4-dichlorophenyl	H	0.33 ± 0.07	>30 (8%)[a]	>91
6b	(*S*)-1-phenylethyl	3,4-dichlorophenyl	H	1.8 ± 0.1	>30 (2%)[a]	>17
7a	(*R*)-1-phenylethyl	3-methoxyphenyl	H	0.083 ± 0.012	>10 (41%)[a]	>120
8a	(*R*)-1-phenylethyl	4-methoxyphenyl	H	0.101 ± 0.004	>10 (23%)[a]	>99
10a	(*R*)-1-phenylethyl	H	(*R*)-1-phenylethyl	2.65 ± 0.51	>30 (13%)[a]	>11
10b	(*S*)-1-phenylethyl	H	(*S*)-1-phenylethyl	2.53 ± 0.61	>30 (11%)[a]	>12
17a (DPEAP)	H	phenyl	(*R*)-1-phenylethyl	0.0067 ± 0.0060	>30 (23%)[a]	>4478
17b	H	phenyl	(*S*)-1-phenylethyl	0.64 ± 0.07	>30 (43%)[a]	>47
			4-Aminopyrimido[4,5-*b*]indoles (**II**)			
25a	(*R*)-1-(4-methylphenyl)ethyl	phenyl		0.014 ± 0.001	21.4 ± 4.4	1529
25b	(*S*)-1-(4-methylphenyl)ethyl	phenyl		0.297 ± 0.005	≫30 (0%)[a]	≫101
26a	(*R*)-phenylisopropyl	phenyl		0.57 ± 0.17	>30 (25%)[a]	>53
26b	(*S*)-phenylisopropyl	phenyl		0.32 ± 0.29	>30 (15%)[a]	>94
32	(*rac*)-1-phenylethyl	H		1.13 ± 0.18	27.7 ± 5.9	25
33	phenyl	phenyl		0.022 ± 0.002	8.3 ± 2.0	377
34a (APEPI)	(*R*)-1-phenylethyl	phenyl		0.0026 ± 0.0008	6.2 ± 1.1	2385
34b	(*S*)-1-phenylethyl	phenyl		0.064 ± 0.017	>30 (15%)[a]	>469
			4-Oxopyrrolo[2,3-*d*]pyrimidines (**III**)			
13a	(*R*)-1-phenylethyl	phenyl		2.98 ± 0.8	>30 (10%)[a]	>10
13b	(*S*)-1-phenylethyl	phenyl		>30(12%)[a]	≫30 (0%)[a]	
14a	(*R*)-1-phenylethyl	4-chlorophenyl		>30 (17%)[a]	>30 (12%)[a]	
14b	(*S*)-1-phenylethyl	4-chlorophenyl		>30 (24%)[a]	>30 (5%)[a]	
			4-Oxopyrimido[4,5-*b*]indoles (**IV**)			
30a	(*R*)-1-phenylethyl	phenyl		>30 (19%)[a]	>30 (12%)[a]	
30b	(*S*)-1-phenylethyl	phenyl		>30 (16%)[a]	>30 (2%)[a]	
			Oxospiropyrrolo[2,3-*d*]pyrimidines (**V**)			
31a	(*R*)-1-phenylethyl	phenyl		>30 (21%)[a]	>30 (6%)[a]	
35	H	H		127 ± 6	346 ± 82	2.7
36	phenyl	H		1.3 ± 0.3	17.2 ± 13.4	13
37	(rac)-1-phenylethyl	H		3.4 ± 0.1	88.4 ± 9.4	26
			Aminospiropyrrolo[2,3-*d*]pyrimidines (**VI**)			
27a	(*R*)-1-phenylethyl	phenyl		0.18 ± 0.02	>30 (32%)[a]	>167

[a] Percent inhibition at the indicated concentration; IC_{50} could not be determined due to limited solubility.

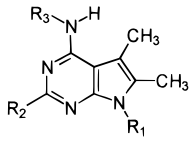
been described elsewhere.[15] In cases of chiral compounds, the *R*-configurated stereoisomer was designated **a** and the *S*-configurated stereoisomer **b** after the compound number.

2-Phenyl-Substituted Derivatives of 4-Amino-5,6-dimethyl-7*H*-7-(1-phenylethyl)pyrrolo[2,3-*d*]pyrimidines 3a,b, 4a,b, 5a,b, 6a,b, 7a, and 8a. General procedure: A suspension of 2.4 g (10 mmol) of **2a** or **2b**,[13] respectively, 1.1 g (20 mmol) of sodium methylate, and 10 mmol of the appropriate benzonitrile derivative (see Table 1) in 20 mL of 2-propanol was refluxed for 8 h. After cooling to about 30 °C, the mixture was diluted with EtOH to keep sodium methylate in solution. After cooling, the precipitated crystals were filtered and recrystallized from EtOH/H_2O. Reactants, yields, and some analytical data are given in Table 1. **3a**: ^{1}H NMR δ 1.94 (d, J = 7.3 Hz, 3H, CHCH_3), 2.08 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 6.08 (q, J = 7.3 Hz, 1H, CHCH$_3$), 6.53 (s, 2H, NH_2), 6.53−7.67 (m, 9H, aromatic).

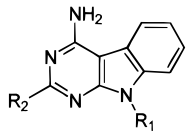
(*R*)- and (*S*)-5,6-Dimethyl-7*H*-7-(1-phenylethyl)pyrrolo-[2,3-*d*]pyrimidin-4(3*H*)-one (9a,b). A mixture of 9.57 g (40mmol) of **2a** or **2b**, respectively, and 50 mL of formic acid (85%) was refluxed for 5 h. After cooling, the precipitate was collected by filtration, washed until the washings showed a neutral pH value, and recrystallized from EtOH. Yield and some analytical data are given in Table 1.

(*R*,*R*)- and (*S*,*S*)-*N*,7-Bis(1-phenylethyl)-5,6-dimethyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (10a,b). A mixture of 5.3 g (20 mmol) of **9a** or **9b**, respectively, with 30 mL of $POCl_3$ was boiled for 1 h. Excess reagent was removed by distillation. For removing residues of $POCl_3$, the obtained oil was heated with H_2O and then extracted with CH_2Cl_2. The

Table 3. Solubility and Solubility/Affinity Ratio of Selected Pyrrolo[2,3-*d*]pyrimidines and Pyrimido[4,5-*b*]indoles



Pyrrolo[2,3-d]pyrimidines (**I**)



Pyrimido[4,5-b]indoles (**II**)

compd	R_1	R_2	R_3	solubility[a] (μM ± SEM) 1% DMSO	solubility[a] (μM ± SEM) 2.5% DMSO	ratio,[c] solubility/ A_1 affinity	calcd log *P* value
			Pyrrolo[2,3-*d*]pyrimidines (**I**)				
1a	(*R*)-1-phenylethyl	phenyl	H	0.26[11]	nd[b]	55	3.8
4a	(*R*)-1-phenylethyl	3-chlorophenyl	H	2.8[11]	nd	368	4.4
5a	(*R*)-1-phenylethyl	4-chlorophenyl	H	2.2 ± 0.6	7.2 ± 4.4	44	4.4
17a	H	phenyl	(*R*)-1-phenylethyl	1.5 ± 0.5	5.9 ± 3.8	224	3.5
			Pyrimido[4,5-*b*]indoles (**II**)				
34a	(*R*)-1-phenylethyl	phenyl		0.48 ± 0.11	1.5 ± 0.9	185	4.5

[a] Determined in 50 mM TRIS-HCl buffer, pH 7.4, containing the indicated amount of DMSO. [b] nd = not determined. [c] Solubility in buffer containing 1% (v/v) DMSO.

organic phase was dried with anhydrous Na_2SO_4 and evaporated *in vacuo*. The remaining oil was refluxed for 96 h with 24.2 g (200 mmol) of (*R*)- or (*S*)-1-phenylethylamine in 20 mL of EtOH. After removing excess solvent and reagent *in vacuo*, the residue was triturated with a few drops of EtOH. The crystalline product was filtered and recrystallized from EtOH/H_2O. Yield and some analytical data are given in Table 1. **10a**: ^{1}H NMR δ 1.56 (d, J = 7.0 Hz, 3H, N^4-CHCH_3), 1.90 (d, J = 7.23 Hz, 3H, N7-CHCH_3), 2.05 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 5.50 (m, 1H, N^4-C*H*CH_3), 6.09 (q, J = 7.3 Hz, 1H, N7-C*H*CH_3), 6.27 (d, J = 8.0 Hz, NH), 7.10−7.47 (m, 10H, aromatic), 8.00 (s, 1H, H-2).

(*R*)- and (*S*)-2-Benzamido-4,5-dimethyl-1-(1-phenylethyl)-1*H*-pyrrole-3-carbonitrile (11a,b), (*R*)- and (*S*)-2-(4-Chlorobenzamido)-4,5-dimethyl-1-(1-phenylethyl)-1*H*-pyrrole-3-carbonitrile (12a,b), and (*R*)- and (*S*)-4,5,6,7-Tetrahydro-2-benzamido-1*H*-1-(1-phenylethyl)indole-3-carbonitrile (28a,b). General procedure: To a solution of 30 mmol of **2a**, **2b**, **19a**, or **19b**, respectively, in 20 mL of CH_2Cl_2 was added 5 mL of pyridine followed by the addition of 32 mmol of the appropriate benzoyl chloride derivative upon cooling. After 1 h of stirring the mixture in an ice bath, 10 mL of petroleum ether (bp 40−60 °C) was added to complete the precipitation of the product. The precipitate was collected by filtration and recrystallized from EtOH/H_2O. Reagents, yields, and some analytical data are given in Table 1.

(*R*)- and (*S*)-5,6-Dimethyl-2-phenyl-7*H*-7-(1-phenylethyl)pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (13a,b), (*R*)- and (*S*)-2-(4-Chlorophenyl)-5,6-dimethyl-7*H*-7-(1-phenylethyl)pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (14a,b), and (*R*)- and (*S*)-5,6,7,8-Tetrahydro-2-phenyl-9*H*-9-(1-phenylethyl)pyrimido[4,5-*b*]indol-4(3*H*)-one (29a,b). General procedure: H_2O (4.5 g, 250 mmol) was added dropwise to a mixture of 22.7 g (160 mmol) of phosphorus pentoxide and 20.2 g (160 mmol) of *N*,*N*-dimethylcyclohexylamine with stirring and ice cooling.[16] The viscous mixture was heated (to ca. 220 °C) until a homogenous solution was obtained. After cooling to 190 °C, 8 mmol of the appropriate 2-benzamido-4,5-dimethyl-1-(1-phenylethyl)-1*H*-pyrrole-3-carbonitrile (**11a**, **11b**, or **12**, respectively) or compound **20a** or **20b**, respectively, was added with stirring. The temperature was kept at 190−200 °C for 4 h. After allowing to cool to 90 °C, a pH value of 12 was adjusted by the addition of 2 N NaOH (ca. 150 mL), in order to obtain a separated amine phase. The precipitate was collected by filtration, washed with H_2O and subsequently with petroleum ether (bp 40−60 °C), and recrystallized from EtOH. Reagents, yields, and some analytical data are given in Table 1. **13**: ^{1}H NMR δ 2.00 (d, J = 7.2 Hz, 3H, CHCH_3), 2.07 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 6.10 (q, J = 7.1 Hz, 1H, C*H*CH_3), 7.20−8.12 (m, 10H, aromatic), 11.95 (s, 1H, NH); ^{13}C NMR δ 9.75, 10.43 (CH_3), 19.44 (CHCH_3), 51.83 (CH), 105.05, 110.02 (C-4a, C-5), 126.26, 127.04, 127.15, 128.24, 128.46, 128.58 (aromatic CH), 130.53 (C-6), 132.88, 141.80 (aromatic C), 147.00, 149.00, 159.65 (C-7a, C-2, C-4).

5,6-Dimethyl-2-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (15). Compound **13** (6.87 g, 20 mmol) was suspended in 100 g of polyphosphoric acid and heated for 2 h to 70−80 °C. The hot suspension was poured into 100 mL of H_2O, and the solution was brought to a pH value of 10 by the addition of NH_3 solution (25%). The precipitated product was filtered off, washed with H_2O until the washings showed a neutral pH, and recrystallized from toluene. Yield and some analytical data are listed in Table 1.

4-Chloro-5,6-dimethyl-2-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (16). A mixture of 4.8 g (20 mmol) of **15** and 50 mL of $POCl_3$ was refluxed for 1 h. Excess reagent was removed *in vacuo*. The residue was poured on H_2O, collected by filtration, washed until neutral reaction, and recrystallized from toluene. Yield and analytical data are given in Table 1.

(*R*)- and (*S*)-*N*-(1-Phenylethyl)-5,6-dimethyl-2-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (17a,b). A solution of 1.55 g (6 mmol) of **16**, 9.7 g (80 mmol) of (*R*)- or (*S*)-phenylethylamine, respectively, and a catalytic amount of concentrated HCl in 15 mL of EtOH was refluxed for 120 h. Excess solvent and reagent were removed *in vacuo* by distillation. The resulting oil was purified by column chromatography on silica gel starting with toluene as eluent and continuing with toluene:methanol (9:1). The product was recrystallized from EtOH. **17a:** ^{1}H NMR δ 1.63 (d, J = 7.0 Hz, 3H, CHCH_3), 2.25 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 5.61 (m, 1H, C*H*CH_3), 6.25 (d, J = 7.3 Hz, 1H, NH), 7.18−8.29 (m, 10H, aromatic), 11.26 (s, 1H, NH); ^{13}C NMR δ $CDCl_3$ 11.23, 11.35 (CH_3), 23.38 (CHCH_3), 50.34 (CH), 102.97, 104.27 (C-4a, C-5), 126.68, 127.48, 128.50, 128.70 (aromatic CH), 128.83 (C-6),-129.51 (aromatic CH), 140.10, 145.62 (aromatic C), 151.70, 156.24, 157.36 (C-7a, C-4, C-2).

1-Substituted 4,5,6,7-Tetrahydro-2-aminoindole-3-carbonitriles 19a,b, 20a,b, and 21a,b. General procedure: A mixture of 5.65 g (50 mmol) of 2-hydroxycyclohexanone (**18**), 50 mmol of the appropriate amine[13,28] (see Table 1), and a catalytic amount of *p*-toluenesulfonic acid in 50 mL of cyclohexane was refluxed using a Dean−Stark trap. After separation of the calculated amount of H_2O, the solution was allowed to cool to ca. 50 °C. After the addition of 2 mL of piperidine, a solution of 3.3 g (50 mmol) of malononitrile in hot cyclohexane was added dropwise, to keep the solution slightly boiling. After cooling, the precipitate was collected by filtration and recrystallized from EtOH. Reagents, yields, and some analytical data are given in Table 1. In contrast to the previously described synthesis of racemic **19**,[15] which could be obtained in crystalline form, the enantiomers of **19** as well as the enantiomers of **21** were obtained as oils. These were used for the subsequent step without prior purification.

9-Substituted 5,6,7,8-Tetrahydro-2-phenyl-9*H*-pyrimido-[4,5-*b*]indol-4-amines 23a,b and 24a,b. General procedure: A mixture of **20a**, **20b**, **21a**, or **21b**, respectively, sodium methylate, and benzonitrile in 2-propanol was refluxed for 8−15 h. After cooling the solution to about 30 °C, a small amount of EtOH and H_2O was added to keep the sodium methylate in solution. The precipitate was collected by filtration, washed until the washings showed a neutral pH value, and recrystallized from EtOH. Amounts of reagents, yields, and some analytical data are given in Table 1.

9-Substituted 2-Phenyl-9*H*-pyrimido[4,5-*b*]indol-4-amines 25a,b and 26a,b and (*R*)- and (*S*)-2-Phenyl-9*H*-9-(1-phenylethyl)pyrimido[4,5-*b*]indol-4(3*H*)-one (30a,b). General procedure: A mixture of the appropriate tetrahydropyrimido[4,5-*b*]indole **23a**, **23b**, **24a**, **24b**, **29a**, or **29b**, respectively, and 0.1 g of Pd/C (10%) in 10 mL of 1-methylnaphthalene was refluxed for 4 h (**25**, **26**) or 5 h (**30**), respectively. The hot solution was filtered. For the isolation of **25** and **26**, the solvent was removed by distillation *in vacuo*. Compounds **25** were purified by column chromatography as described for **17**. Compounds **26** were crystallized by trituration of the resulting oil with a few drops of EtOH. Compounds **30** precipitated after cooling of the filtrate and were collected by filtration and recrystallized from EtOH. Amounts of reagents, yields, and some analytical data are given in Table 1. **25**: ^{1}H NMR δ 2.00 (d, J = 7.2 Hz, 3H, CHCH_3), 6.45 (q, J = 7.2 Hz, 1H, CHCH$_3$), 7.18−7.31 (m, 8H, aromatic), 7.29 (s, 2H, NH_2), 8.34 (m, 1H, H-5), 8.36 (s, 1H, 2-H); ^{13}C NMR δ 17.89 (CHCH$_3$), 20.53 (phenyl-CH$_3$), 50.54 (CH), 93.80 (C-4a), 110.96 (C-8), 120.22 (C-4b), 120.27 (C-6), 121.35 (C-5), 124.13 (C-7), 126.43, 127.77, 128.19, 128.96, 129.77 (aromatic CH), 136.23, 136.32, 138.02, 138.58 (C-8a, aromatic C), 156.17, 157.70, 159.61 (C-9a, C-4, C-2).

30: ^{1}H NMR (CDCl$_3$) δ 2.16 (d, J = 7.2 Hz, 3H, CHCH_3), 6.68 (q, J = 7.2 Hz, 1H, CHCH$_3$), 7.23−7.43 (m, 8H, aromatic), 7.64−7.66 (m, 3H, 2-phenyl-H), 8.28−8.41 (d, J = 7.4 Hz, 1H, H-5), 8.58−8.61 (m, 2H, 2-phenyl-H), 13.33 (s, 1H, NH); ^{13}C NMR δ 18.26 (CH$_3$), 51.57 (CH), 98.36 (C-4a), 111.71 (C-8), 120.83, 121.44, 122.13, (C-5, C-4b, C-6), 124.02 (C-7), 126.54, 127.32, 127.97, 128.53, 128.75, 131.59 (aromatic CH), 132.45 (aromatic C), 135.49 (C-8a), 140.79 (aromatic C), 153.28, 154.21, 159.16 (C-9a, C-4, C-2).

(*R*)-4′-Amino-2′-phenyl-7′-(1-phenylethyl)spiro[cyclopentane-1,5′-[5*H*]pyrrolo[2,3-*d*]pyrimidin]-6′(7′*H*)-one (27a) and (*R*)-2′-Phenyl-7′-(1-phenylethyl)spiro[cyclopentane-1,5′-[5*H*]pyrrolo[2,3-*d*]pyrimidine]-4′,6′(3′*H*,7′*H*)-dione (31a). General procedure: A suspension of **22a**[15] (2.2 g, 6 mmol) in 100 mL of MeOH or 2.2 g (6 mmol) of **29a** in 150 mL of MeOH, respectively, was mixed with a solution of 6.0 g of $NaIO_4$ (28 mmol) in 50 mL of H_2O, and the mixture was refluxed for 6 h. Then the solvent was removed *in vacuo*, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). After drying with anhydrous Na_2SO_4, the solution was evaporated to dryness. The remaining oil was crystallized with EtOH and recrystallized from MeOH (**27a**) or EtOH (**31a**). Yields and some analytical data are given in Table 1. **27a:** ^{1}H NMR δ 1.73−2.18 (m, 8H, -CH$_2$-), 1.93 (d, J = 7.6 Hz, 3H, CHCH_3), 5.67(q, J = 7.3 Hz, 1H, CHCH$_3$), 6.51 (s, 2H, NH_2), 7.24−8.26 (m, 10H, aromatic); ^{13}C NMR δ 17.52 (CH$_3$), 25.72, 32.59, 32.71 (C-2, C-3, C-4, C-5), 49.39 (CH), 51.92 (C-5′), 99.27 (C-4a′), 126.88, 127.30, 127.73, 128.56, 130.40 (aromatic CH), 138.04, 141.45 (aromatic C), 156.66 (C-7a′), 161.71, 162.70 (C-2, C-4′), 182.08 (C-6′).

31a: ^{1}H NMR δ 2.00 (d, J = 7.3 Hz, 3H, CHCH_3), 2.06−2.21 (m, 8H, -CH$_2$-), 5.78 (q, J = 7.3 Hz, 1H, CHCH$_3$), 7.25−8.31 (m, 10H, aromatic), 13.64 (s, 1H, NH); ^{13}C NMR δ CDCl$_3$ 17.57 (CH$_3$), 27.80, 35.84, 35.96 (C-2, C-3, C-4, C-5), 50.36 (CH), 52.88 (C-5′), 107.78 (C-4a′), 127.26, 127.43, 128.05, 128.39, 128.78 (aromatic CH), 131.91 (aromatic C), 132.22 (aromatic CH), 140.83 (aromatic C), 157.92, 160.01, 162.57 (C-7a′, C-4′, C-2′), 183.21 (C-6′).

Adenosine Receptor Assays. Inhibition of binding of [^{3}H]-(*R*)-*N*^{6}-(phenylisopropyl)adenosine ((*R*)-PIA) to A$_1$-adenosine receptors of rat cerebral cortical membranes and inhibition of [^{3}H]-5′-(*N*-ethylcarbamoyl)adenosine (NECA) to A$_2$-adenosine receptors of rat striatal membranes were assayed as described.[29−31] 2-Chloroadenosine (10 μM) was used in the A$_1$ binding assay and theophylline (5 mM) in the A$_2$ binding assay to define nonspecific binding. The A$_1$-selective adenosine receptor agonist *N*^{6}-cyclopentyladenosine (50 nM) was present to block A$_1$-adenosine receptors in the A$_2$ binding assay. Inhibition of the receptor−radioligand binding was determined by a range of five to six concentrations of the compounds in triplicate in at least three (A$_1$) or two (A$_2$) separate experiments. The Cheng−Prusoff equation[32] and K_D values of 1 nM for [^{3}H]-(*R*)-PIA and 8.5 nM for [^{3}H]NECA were used to calculate the K_i values from the IC_{50} values, determined by the nonlinear curve-fitting program InPlot, Version 4.03 (GraphPad, San Diego, CA). For selected compounds additional A$_1$AR binding studies with [^{3}H]cyclohexyladenosine ([^{3}H]CHA) as a radioligand were performed. A K_D value of 1 nM was used for [^{3}H]CHA for the calculation of K_i values.

Solubility Determination. Solubilities of selected compounds were determined according to the method of Bruns and Fergus.[27] A 10 mM solution of compounds in DMSO was prepared, diluted 1:100 in TRIS-HCl buffer, 50 mM, pH 7.4, and allowed to reach equilibrium with shaking overnight at room temperature. After centrifugation, the supernatant was filtered through cotton. Several dilutions of these saturated stock solutions were made in the buffer, on the basis of the estimated solubility and the known affinity of each compound. An A$_1$ binding assay was performed with [^{3}H]CHA as radioligand. Data analysis was performed as described above using a K_D value of 1 nM for [^{3}H]CHA. The solubility of each compound was then calculated by dividing the IC_{50} value of a compound, determined separately with [^{3}H]CHA as described above, by the fold dilution of the saturated solution required to give 50% inhibition of [^{3}H]CHA binding. Similar assays were performed using a 1:40 dilution of the 10 mM stock solution of the compounds to estimate their solubility in buffer, containing 2.5% DMSO.

Molecular Modeling. The molecular modeling studies were carried out on an Evans & Sutherland ESV 3/32 graphics workstation and a Silicon Graphics Iris Indigo workstation using the software package Sybyl, program versions 6.0 and 6.1,[33] and MOPAC 5.0.[34] Structures were built using Sybyl. Energy minimization was performed using the Sybyl force field. Conformational analysis was done using the Random Search option of Sybyl with 30° increments. Charges were calculated with the AM1 method as implemented in MOPAC 5.0 without changing the previously found geometries. A low-energy conformation of **1a** was used as a template for compound **17a**. Torsion angles of **17a** were adjusted in analogy to **1a** to get a maximal overlap of the (*R*)-1-phenylethyl residue. This conformation was again minimized by the Sybyl force field. Fitting of the obtained structures was carried out with the Multifit module in Sybyl, using the four nitrogens of both molecules for the fit. Approximate log *P* values were calculated as described by Broto et al.[35] by summarizing the f_i values of each atom. Nondefined f_i values for three fragmental codes were extrapolated according to the method of Broto.[35]

Acknowledgment. We thank Dr. Tom Scior (Strasbourg) who provided guidance on molecular modeling studies, Prof. Dr. W. Adam (Würzburg) for permission to use the computer facility of his laboratory, and Prof. Dr. G. Bringmann (Würzburg) for allowing us to work in his isotope laboratory. K. Eger was supported by the Deutsche Forschungsgemeinschaft. C. E. Müller is grateful for support by the Fonds der Chemischen Industrie.

Supporting Information Available: ^{1}H and ^{13}C NMR data of intermediate and final products synthesized (6 pages). Ordering information is given on any current masthead page.

References

(1) Fredholm, B. B.; Abbracchio, M. P.; Burnstock, G.; Daly, J. W.; Harden, T. K.; Jacobson, K. A.; Leff, P.; Williams, M. VI. Nomenclature and Classification of Purinoceptors. *Pharmacol. Rev.* **1994**, *46*, 143−156.

(2) (a) Dubyak, G. R.; El-Moatassim, C. Signal transduction via P2-purinergic receptors for extracellular ATP and other nucleotides. *Am. J. Physiol.* **1993**, *265*, C577−C606. (b) Lazarowski, E. R.; Harden, T. K. Identification of a Uridine Nucleotide-selective G-protein-linked Receptor That Activates Phospholipase C. *J. Biol. Chem.* **1994**, *269*, 11830−11836. (c) Seifert, R.; Schultz, G. Involvement of pyrimidinoceptors in the regulation of cell function by uridine and by uracil nucleotides. *Trends Pharmacol. Sci.* **1989**, *10*, 365−369.

(3) Müller, C. E.; Scior, T. Adenosine receptors and their modulators. *Pharm. Acta Helv.* **1993**, *68*, 77−111.

(4) Londos, C.; Cooper, D. M.; Wolff, J. Subclasses of external adenosine receptors. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 2551−2554.

(5) Linden, J. Cloned adenosine A3 receptors: pharmacological properties, species differences and receptor function. *Trends Pharmacol. Sci.* **1994**, *15*, 298−306.

(6) Collis, M. G.; Hourani, S. M. O. Adenosine receptor subtypes. *Trends Pharmacol. Sci.* **1993**, *14*, 360−366.

(7) (a) Ukena, D.; Padgett, W. L.; Hong, O.; Daly, J. W.; Daly, D. T.; Olsson, R. A. N^6-Substituted 9-methyladenines: a new class of adenosine receptor antagonists. *FEBS Lett.* **1987**, *215*, 203−208. (b) Thompson, R. D.; Secunda, S.; Daly, J. W.; Olsson, R. A. N^6,9-Disubstituted adenines: potent, selective antagonists at the A_1 adenosine receptor. *J. Med. Chem.* **1991**, *34*, 2877−2882. (c) Jacobson, K. A.; Siddiqi, S. M.; Olah, M. E.; Ji, X.-d.; Melman, N.; Bellamkonda, K.; Meshulam, Y.; Stiles, G. L.; Kim, H. O. Structure-activity relationships of 9-alkyladenine and ribose-modified adenosine derivatives at rat A_3 adenosine receptors. *J. Med. Chem.* **1995**, *38*, 1720−1735. (d) Lohse, M. J.; Klotz, K.-N.; Diekmann, E.; Friedrich, K.; Schwabe, U. 2′,3′-Dideoxy-N^6-cyclohexyladenosine: an adenosine derivative with antagonist properties at adenosine receptors. *Eur. J. Pharmacol.* **1988**, *156*, 157−160.

(8) (a) Müller, C. E.; Shi, D.; Manning, M., Jr.; Daly, J. W. Synthesis of paraxanthine analogs (1,7-disubstituted xanthines) and other xanthines unsubstituted at the 3-position: structure-activity relationships at adenosine receptors. *J. Med. Chem.* **1993,** *36*, 3341−3349. (b) Grahner, B.; Winiwarter, S.; Lanzner, W.; Müller, C. E. Synthesis and Structure-Activity Relationships of Deazaxanthines: analogs of potent A1- and A_2-adenosine receptor antagonists. *J. Med. Chem.* **1994**, *37*, 1526−1534. (c) Müller, C. E.; Grahner, B.; Heber, D. Amino-substituted 1,8-naphthyridines and pyrido[2,3-*d*]-pyrimidines: new compounds with affinity for A_1- and A_2-adenosine receptors. *Pharmazie* **1994**, *49*, 878−880. (d) Geis, U.; Grahner, B.; Pawlowski, M.; Drabczynska, A.; Gorczyca, M.; Müller, C. E. Tricyclic theophylline derivatives with high water solubility: structure-activity relationships at adenosine receptors, phosphodiesterases, and benzodiazepine binding sites. *Pharmazie* **1995**, *50*, 333−336.

(9) (a) Jacobson, K. A.; Trivedi, B. K.; Churchill, P. C.; Williams, M. Novel therapeutics acting via purine receptors. *Biochem. Pharmacol.* **1991**, *41*, 1399−1410. (b) Suzuki, F. Adenosine A1 antagonists; A new therapeutic approach to cognitive deficits and acute renal failure. *Drug News Perspect.* **1992**, *5*, 587−591. (c) Kanda, T.; Shiozaki, S.; Shimada, J.; Suzuki, F.; Nakamura, J. KF17837: a novel selective adenosine A_{2a} receptor antagonist with anticataleptic activity. *Eur. J. Pharmacol.* **1994**, *256*, 263−268.

(10) Daly, J. W.; Padgett, W. L.; Eger, K. 7-Deaza-9-phenyladenines a New Class of Adenosine Receptor Antagonists. *Biochem. Pharmacol.* **1988**, *37*, 3749−3753.

(11) Müller, C. E.; Hide, I.; Daly, J. W.; Rothenhäusler, K.; Eger, K. 7-Deaza-2-phenyladenines: structure-activity relationships of potent A_1 selective adenosine receptor antagonists. *J. Med. Chem.* **1990**, *33*, 2822−2828.

(12) (a) Roth, H. J.; Eger, K. Synthese von 2-Amino-3-cyano-pyrrolen. (Synthesis of 2-amino-3-cyanopyrroles.) *Arch. Pharm. (Weinheim, Ger.)* **1975**, *308*, 179−185. (b) Roth, H. J.; Eger, K. Synthese von Pyrrolo[2,3-*d*]pyrimidinen. (Synthesis of pyrrolo-[2,3-*d*]pyrimidines.) *Arch. Pharm. (Weinheim, Ger.)* **1975**, *308*, 252−258.

(13) Pichler, H.; Folkers, G.; Roth, H. J.; Eger, K. Synthese von 7-unsubstituierten 7*H*-Pyrrolo[2,3-*d*]pyrimidinen. (Synthesis of 7-unsubstituted 7H-pyrrolo[2,3-*d*]pyrimidines.) *Liebigs Ann. Chem.* **1986**, 1485−1505.

(14) Eger, K.; Pfahl, J. G.; Folkers, G.; Roth, H. J. Selected reactions on the o-aminonitrile system of substituted pyrroles. *J. Heterocycl. Chem.* **1987**, *24*, 425−430.

(15) Eger, K.; Lanzner, W.; Rothenhäusler, K. Synthesis of Substituted Indoles and Pyrimido[4,5-*b*]indoles by Dehydrogenation of Tetrahydroindoles and Tetrahydro-pyrimidoindoles. *Liebigs Ann. Chem.* **1993**, 465−470.

(16) Girgis, N. S.; Jörgensen, A.; Pedersen, E. B. Phosphorus Pentoxide in Organic Synthesis; XI. A New Synthetic Approach to 7-Deazahypoxanthines. *Synthesis* **1985**, 101−104.

(17) Thompson, R. D.; Manning, M., Jr.; Daly, J. W.; Olsson, R. A. N^6,9-Disubstituted adenines: effect on affinity for adenosine receptors of a chiral center in the 9-substituent. *Med. Chem. Res.* **1992**, *2*, 474.

(18) Schwabe, U.; Trost, T. Characterization of adenosine receptors in rat brain by (−)[^{3}H]N^6-phenylisopropyladenosine, a new ligand for R_i adenosine receptors. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1980**, *321*, 84−87.

(19) Bruns, R. F. Adenosine receptor activation in human fibroblasts: nucleoside agonists and antagonists. *Can. J. Physiol. Pharmacol.* **1980**, *58*, 673−691.

(20) Peet, N. P.; Lentz, N. L.; Meng, E. C.; Dudley, M. W.; Ogden, A.-M. L.; Demeter, D. A.; Weintraub, H. J. R.; Bey, P. A novel synthesis of xanthines: support for a new binding mode for xanthines with respect to adenosine at adenosine receptors. *J. Med. Chem.* **1990**, *33*, 3127−3130.

(21) Dooley, M. J.; Quinn, R. J. The three binding domain model of adenosine receptors: molecular modeling aspects. *J. Med. Chem.* **1992**, *35*, 211−216.

(22) Cristalli, G.; Grifantini, M.; Vittori, S.; Balduini, W.; Cattabeni, F. Adenosine and 2-chloroadenosine deaza-analogues as adenosine receptor agonists. *Nucleosides Nucleotides* **1985**, *4*, 625−639.

(23) Müller, C. E.; Geis, U.; Grahner, B.; Lanzner, W.; Eger, K. Pyrrolo[2,3-*d*]pyrimidines and pyrimido[4,5-*b*]indoles: Structure-activity relationships of potent adenosine receptor antagonists. *Drug Dev. Res.* **1994**, *31*, 301 (Abstract).

(24) (a) Biagi, G.; Giorgi, I.; Livi, O.; Scartoni, V.; Lucacchini, A.; Martini, C.; Tacchi, P. N(6)-Substituted 2-phenyl-9-benzyl-8-azaadenines. Affinity for adenosine A_1 and A_2 receptors. A comparison with 2-N-butyl analogous derivatives. *Farmaco* **1994**, *49*, 187−191. (b) Biagi, G.; Giorgi, I.; Livi, O.; Scartoni, V.; Lucacchini, A.; Martini, C.; Tacchi, P. Synthesis of new N(6)-substituted 2-phenyl-8-azaadenosines. Their affinity for adenosine A_1 and A_2 receptors. A comparison with the corresponding 2-phenyl-9-benzyl-8-azaadenines. *Farmaco* **1995**, *50*, 13−19.

(25) Brackett, L. E.; Daly, J. W. Functional characterization of the A_{2b} adenosine receptor in NIH 3T3 fibroblasts. *Biochem. Pharmacol.* **1994**, *47*, 801−814.

(26) Ceccarelli, S.; Altobelli, M.; D'Alessandro, A.; Paesano, A. A novel hydrophilic 8-cycloalkylxanthine derivative (IRFI 117) is a highly selective antagonist at A_1 adenosine receptors. *Res. Commun. Mol. Pathol. Pharmacol.* **1995**, *87*, 101−102.

(27) Bruns, R. F.; Fergus, J. H. Solubilities of adenosine antagonists determined by radioreceptor assay. *J. Pharm. Pharmacol.* **1989**, *41*, 590−594.

(28) (a) Ingersoll, A. W.; Burns, F. B. Solubility relationships among optically isomeric salts II. The camphorates of α para tolylethylamine. *J. Am. Chem. Soc.* **1932**, *54*, 4712−4715. (b) Leithe, W. Die Konfiguration der Ephedrin-Basen. (The configuration of the ephedrine bases.) *Chem. Ber.* **1932**, *65*, 660−666. (c) Pratesi, P.; La Manna, A. Azione di Alcune Basi Otticamente Attive sugli Acidi Canfocarbonici Enantiomorfi: L'Inversione di Effetto cinetico. (Actions of Some Optically Active Bases on Enantiomeric Camphoric Acids: The Inversion of the Kinetic Effect.) *Farmaco Ed. Sci.* **1956**, *11*, 33−45.

(29) Bruns, R. F.; Daly, J. W.; Snyder, S. H. Adenosine receptors in brain membranes: binding of N^6-cyclohexyl[^{3}H]adenosine and 1,3-diethyl-8-[^{3}H]phenylxanthine. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 5547−5551.

(30) Bruns, R. F.; Lu, G. H.; Pugsley, T. A. Characterization of the A_2 adenosine receptor labeled by [^{3}H]NECA in rat striatal membranes. *Mol. Pharmacol.* **1986**, *29*, 331−346.

(31) Jacobson, K. A.; Ukena, D.; Kirk, K. L.; Daly, J. W. [^{3}H]Xanthine amine congener of 1,3-dipropyl-8-phenylxanthine, an antagonist radioligand for adenosine receptors. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 4089−4093.

(32) Cheng, Y. C.; Prusoff, W. H. Relationship between the inhibition constant (K_i) and the concentration of inhibition which causes 50 percent inhibition (I_{50}) of enzyme reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099−3108.

(33) Tripos Associates, Inc. 1993, 1994 Molecular Modelling Software Sybyl, Version 6.0 and 6.1; St. Louis, MO 63144.

(34) Stewart, J. J. P. MOPAC Version 5.0 (QCPE No. 455).

(35) Broto, P.; Moreau, G.; Vandycke, C. Molecular structures: perception, autocorrelation descriptor and sar studies. System of atomic contributions for the calculation of the n-octanol/water partition coefficients. *Eur. J. Med. Chem.* **1984**, *19*, 71−78.

(36) Siddiqi, S. M.; Ji, X.-d.; Melman, N.; Olah, M. E.; Jain, R.; Evans, P.; Glashofer, M.; Padgett, W. L.; Cohen, L. A.; Daly, J. W.; Stiles, G. L.; Jacobson, K. A. A survey of nonxanthine derivatives as adenosine receptor ligands. *Nucleosides Nucleotides* **1996**, *15*, 693−717.

JM960011W