Pure Appl. Chem., Vol. 73, No. 9, pp. 1411–1420, 2001.

New developments in A_1 and A_2 adenosine receptor antagonists*

K. Kieć-Kononowicz[1,†], A. Drabczyńska[1], E. Pękala[1], B. Michalak[1], C. E. Müller[2], B. Schumacher[2], J. Karolak-Wojciechowska[3], H. Duddeck[4], S. Rockitt[4], and R. Wartchow[4]

[1]Jagiellonian University, Medical College, Department of Chemical Technology of Drugs, Medyczna 9, Pl 30-688 Kraków, Poland; [2]Pharmaceutical Institute Poppelsdorf, University of Bonn, Kreuzbergweg 26, D-53115 Bonn, Germany; [3]Institute of General and Ecological Chemistry, Technical University of Łódź, Żwirki 36, Pl 30-924 Łódź, Poland; [4]University of Hannover, Institute of Organic Chemistry, Schneiderberg 1B, D-30167 Hannover, Germany

Abstract: The aim of this article is to briefly present progress in the development of the potent adenosine receptor (AR) antagonists with high selectivity for either A_1, A_{2A}, or A_{2B} ARs. The structural requirements for each AR subtype were discussed as well as their potential therapeutic use. In the search for new AR antagonists, series of imidazo-, pyrimido-, and diazepino-purindione derivatives as well as oxazolo-, oxazino-, and oxazepino-purindiones were designed, synthesized, and preliminarily evaluated in pharmacological studies. Oxygen-containing tricyclic derivatives were shown to be moderately potent AR antagonists exhibiting selectivity either for A_1 or A_{2A} ARs. Tricyclic purindiones with nitrogen in the third ring were generally more A_{2A} AR selective. The compounds tested *in vivo* according to the Antiepileptic Drug Development Program of the National Institutes of Health (USA) were generally active as anticonvulsants in chemically induced seizures.

The endogenous nucleoside adenosine is an autacoid produced in many organs and tissues, exhibiting diverse potent physiological actions in the cardiovascular, nervous, pulmonary, renal, and immune systems. Extracellular adenosine either released from cells or ATP hydrolysis regulates several physiological functions by activation on specific cell membrane receptors. The combination of pharmacological studies and molecular cloning revealed the existence of four distinct adenosine receptor (AR) subtypes, which are identified and classified as A_1, A_{2A}, A_{2B}, and A_3, all belonging to the G protein-coupled, 7-transmembrane-segment receptors superfamily. Whereas the adenosine A_1 and A_3 receptor subtypes are coupled to the G_i protein, inhibiting adenylate cyclase, A_{2A} and A_{2B} subtypes stimulate this enzyme via G_s. A_1 and A_3 ARs may also be coupled to other second messenger systems, such as activation of phospholipase C (PLC), and A_1 ARs can also lead to a stimulation of K^+ channels or an inhibition of Ca^{2+} channels [1].

Moreover, ARs are involved in interactions with receptors for other neurotransmitters and/or neuromodulators, namely receptors for neuropeptides (CGRP and VIP), ionotropic (NMDA) and

*Plenary lecture presented at the Hungarian–German–Italian–Polish Joint Meeting on Medicinal Chemistry, Budapest, Hungary, 2–6 September 2001. Other presentations are published in this issue, pp. 1387–1509.

†Corresponding author

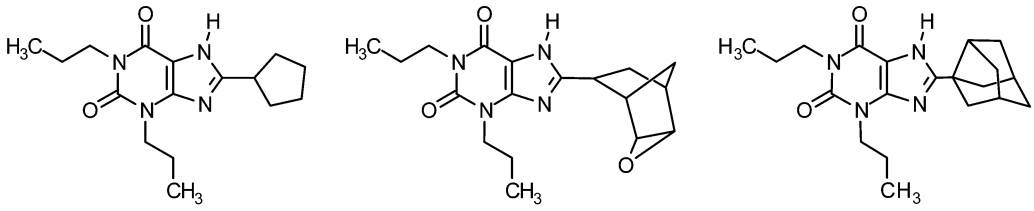
metabotropic (mGlu I and III) glutamate receptors, GABA and nicotinic autofacilitatory, muscarinic, and dopamine receptors [2–4].

ARs have been cloned from several mammalian species [1], including humans (human recombinant ARs were expressed in mammalian cell lines—CHO, HEK [5–7]). It was found that, for example, the human A_1 AR differs by 18 amino acids from the dog A_1 sequence and 16 amino acids from the rat A_1 sequence, the human A_{2A} AR differs by 28 amino acids from the dog A_{2A} sequence [7]. ARs have become important targets for drug development.

Selective interaction with AR subtypes offers very broad therapeutic potentials, including the regulation of the electrophysiological properties of the heart, kidney functions, immune system (including inflammatory activity), some central nervous system functions, and cell growth [8–12].

The main interest of this work concerns current developments of selective A_1 and A_2 AR antagonists.

The A_1 AR is found in high density in the brain (cortex, hippocampus) and in lower density in peripheral organs and tissues such as heart, kidney, lung, and fat cells. Adenosine A_1 antagonists have the main therapeutic potentials as kidney-protective diuretics and agents for the treatment of dementias, including Alzheimer's disease, depression, cardiac failure, and asthma [9,13]. During the past 20 years, a large number of A_1 AR antagonists have been developed including bi- or tricyclic heterocyclic derivatives [13–15]. Important classes of A_1-selective antagonists comprise xanthine derivatives with bulky 8-substituents, adenine derivatives with bulky N^6-substituents, 7-deaza and 7-deaza-8-aza analogs of adenine, pyrazolo[1,5-a]pyridines, and other heterocyclic compounds (Fig. 1).



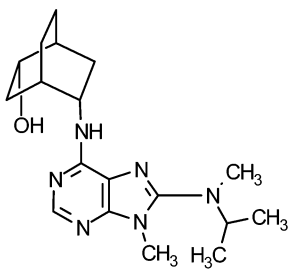
DPCPX (CPX)

0.9	3.0
450	129
–	51
5300	3960

BG-9719 (CVT-124)

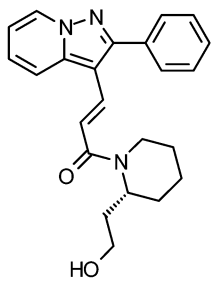
0.5	0.5
1000	1000
–	200
4500	4000

KW-3902



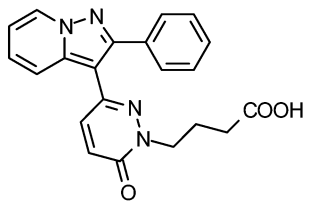
WRC-0571

1	
52	
–	
6500	



FK-453

17.2	
11300	



FK-838

Fig. 1 Selective antagonists at A_1 AR. K_i values in nM (left: rat; right: human) for A_1, A_{2A}, A_{2B}, and A_3 receptors are shown in that order below the structure and name of the compound. Data are taken from [14–18].

BG-9719, **KW-3902**, and **FK-838** are under development as drugs for treating renal failure (diuretics) [17,18] and **CPX** for the treatement of cystic fibrosis [19]. Due to the greater solubility in water of **FK-838** sodium salt, this compound has shown improved oral bioavailability as compared to **FK-453**, although **FK-453** affinity and selectivity toward A_1 ARs was better (A_1 – pK_i = 8.18; A_{2A} – pK_i = 5.92 for **FK 838** and A_1 – pK_i = 9.31; A_{2A} – pK_i = 5.90 for **FK 453**) [17].

The analysis of structure–activity relationships of xanthines, the major group of A_1-adenosine receptor antagonists, revealed the main requirements for their activity (Fig. 2).

Although potent A_1 AR antagonists with high selectivity for the A_1 AR subtype have been developed in the last years, some of the compounds considered to be selective may not be as selective in humans as in rats and may not be very selective vs. the new AR subtypes A_3 or A_{2B}. Low water solubility of many A_1 AR antagonists remains a problem.

Recent developments in A_1 AR-selective antagonists include [20] mainly non-xanthine groups of compounds: thiazoles [21,22], thiadiazoles [21], 3-benzoylothiophenes [23], pyrazolopyridines [17], 3-arylotriazinobenzimidazolones (ATBIs) [24], 7-deazaadenines [25] and triazolo-quinazoline [26], -quinoxaline [27], -pyridazine [28], and -pyrimidine [29] derivatives.

Several theoretical studies aimed at understanding the way ligands interact with the A_1 AR binding site [32,33] were recently supplemented by Da Settimo's model [24]. In this approach, molecular modeling studies were performed based on a set of pharmacophoric elements of the well-known A_1 AR antagonists from different chemical classes and on a rhodopsin-based model of the bovine adenosine A_1 receptor. It was hypothesized that within the A_1 AR binding cleft exist three putative hydrogen bonding sites (HB_1 acceptor, HB_2 and HB_3 donors) and three lipophilic pockets (L_1, L_2, L_3).

Another way to analyze adenosine A_1 receptor activity uses selective irreversible antagonists of this AR subtype [30,31]. Irreversible adenosine A_1 receptor antagonists (Fig. 3) may be valuable research tools for A_1 ARs in *in vivo* experiments ("receptor knock-down" tools) used to measure receptor reserve and to identify ligand binding sites.

A_{2A} ARs, similarly as A_1 ARs belong to the so-called high-affinity subtypes of ARs because they are stimulated by low (nanomolar) concentrations of adenosine. A_{2A} AR antagonists are promising new drugs for the treatment of Parkinson's disease [34,35]. Central A_{2A} ARs are mainly located in parts of the basal ganglia such as striatum and are able to modulate the actions of dopamine receptors [36–38]. Furthermore, A_{2A} AR antagonists may be useful in the treatment of dementia, and other neurodegenerative disorders, alcohol withdrawal, ischemic conditions (such as stroke, cardiac ischemia), migraine, and pain [39–42].

A variety of xanthine derivatives, mainly 8-substituted, has shown A_{2A} AR antagonist properties [34,42]. Introduction of a styryl group in the 8-position was critical in obtaining compounds with selec-

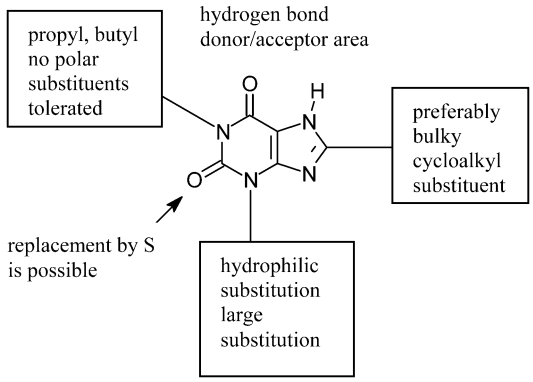


Fig. 2 Structure–activity relationships of xanthines as A_1 AR antagonists [14].

tive A_{2A} AR antagonistic properties. As a result, the structurally related **KF 17837** and its *N*,*N*-diethyl analog **KW 6002** (Fig. 4), were discovered. Despite having similar *in vitro* profiles (Fig. 4), these two structurally similar xanthines appeared to have dramatically different *in vivo* potencies, as measured by the attenuation of haloperidol-induced catalepsy in mice, with **KW-6002** being clearly more potent (ED_{50} = 0.03 mg/kg and 2.7 mg/kg for **KW-6002** and **KF-17837**, respectively). This divergence in *in vivo* activity may be due to differences in pharmacokinetics, pharmacodynamics, metabolism, and/or bioavailability. **KW-6002** is undergoing phase II clinical trials for the potential treatment of Parkinson's disease and, since June 2000, for the treatment of depression [43,44].

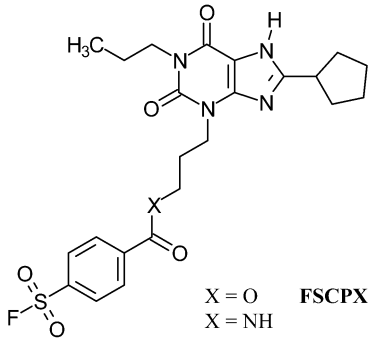
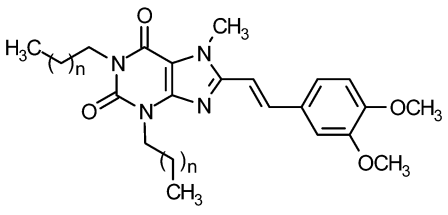
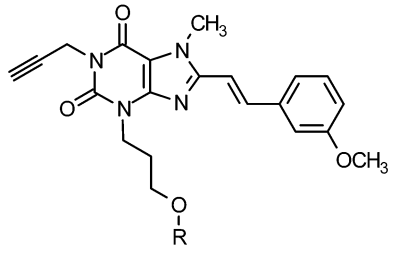


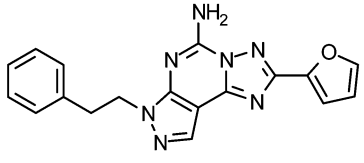
Fig. 3 Irreversible adenosine A_1 receptor antagonists [30,31].



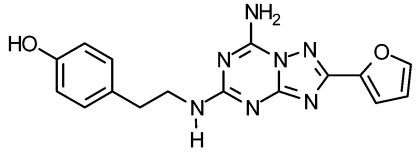
	n = 0 **KW-6002**	n = 1 **KW-17837**
A_1	150	62
A_{2A}	2.2	1.0
A_{2B}	–	
A_3	–	



	R = H **MSX-2**	R = – PO_3Na_2 **MSX-3**
A_1	900 (2500)	
A_{2A}	8 (8)	
A_{2B}	inactive	
A_3	inactive	



SCH 58261
121
2.3
–
> 100000



ZM 241385
2000
0.3
–
> 100000

Fig. 4 A_{2A} receptor antagonists. K_i values in nM (rat, in parentheses, human)[15,34,45,46].

In order to obtain further A_{2A}-selective antagonists with high water solubility at physiological pH values, useful as pharmacological tools and potential drugs [45–47], water-soluble prodrugs (e.g., **MSX-3** from 8-styrylxanthine derivative **MSX-2** [39]) were obtained. **MSX-2** has also been prepared in tritiated form as a radioligand for labeling A_{2A} ARs. The main drawback specific for this class of compounds is their low stability. In dilute solution they suffer from sensitivity to photoisomerization: the active (E)-configurated 8-styrylxanthines form isomeric mixtures in which often the less active or even inactive (Z)-isomer dominates.

Among highly potent and selective nonxanthine antagonists for A_{2A} ARs are derivatives of pyrazolotriazolopyrimidine **SCH 58261** and triazolotriazine **ZM 241385** (Fig. 4); both compounds have been tritiated for use as radioligands. [^{3}H]**ZM 241385**, an excellent radioligand for A_{2A} receptors, is of sufficiently high affinity at recombinant A_{2B} receptors for use as radioligand when these receptors are expressed in systems lacking A_{2A} receptors [44,48].

Second-generation pyrazolotriazolopyrimidines have been reported as potent and selective A_{2A} receptor antagonists [50]. Based on these results [^{11}C]**SCH 442416**, a new non-xanthine ligand was obtained and has been shown to be applicable for diagnostic positron tomography studies for *in vivo* measurement of A_{2A} ARs [51].

Steric, electrostatic, and hydrophobic properties of the typical A_{2A} AR antagonists were discussed [34,52]. Important features for A_{2A} affinity and selectivity are: voluminous, frequently aromatic substituent; hydrogen bond acceptor; and hydrogen bond donor (the latter does not appear in A_{2A}-selective 8-styrylxanthine derivatives [34].

The A_{2B} receptor subtype is a low-affinity receptor, adenosine-exhibiting activity at this subtype at concentrations greater than 10 μM [1]. It is the least investigated subtype of ARs in consequence of lack of suitable, potent, and selective ligands for detailed study [9]. Recently it has been proposed that A_{2B} AR antagonists may have potential for use in the treatment of asthma, myocardial reperfusion injury, allergic reactions, autoimmune and inflammatory bowel diseases, and non-insulin dependent diabetes and retinopathy [16,53].

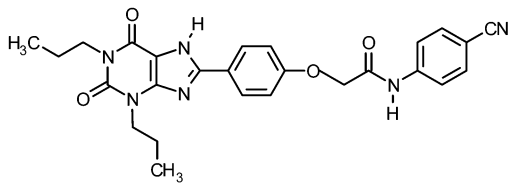
It is hypothesized that structurally related to **CGS 15943** 2-alkyl-8-aryl-9-methyl adenines (e.g., **compounds 1** and **2**) cause inhibition of hepatic glucose production via the A_{2B} receptor. These compounds are in preclinical study for the treatment of non-insulin dependent diabetes. However, the compounds are not A_{2B} selective.

The first potent antagonists at human A_{2B} AR were found in the group of 1,3-dialkylxanthines [54]. More selective and potent A_{2B} AR antagonists have been reported nowadays among 8-phenyl xanthine derivatives [53,55] (Fig. 5). **MRS 1754** and **MRS 1706** may be the first selective pharmacological probes needed to investigate the physiological role of this AR subtype and in tritiated form may be suitable tools for pharmacological A_{2B} receptor tests [55]. However, the compounds exhibit only low selectivity vs. rat A_1 ARs.

Structural predictions of adenosine A_{2B} antagonist affinity were done using molecular field analysis [56]. A pharmacophore model was developed using known A_{2B} antagonists, mainly xanthines. It was stated that a hydrogen bond donor in the 7-position of xanthine is essential for the biological activity. The presence of more negative charges on the N-1 increases biological activity, bulky aromatic substitutions on the 8-position improve activity.

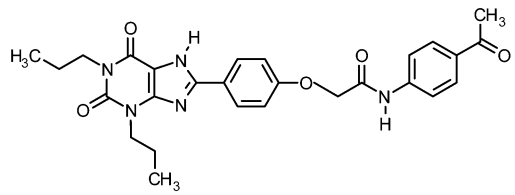
To develop new ligands for A_{2A} ARs, two series of tricyclic compounds have been prepared: the group of oxygen- or nitrogen-containing annelated theophylline derivatives (Fig. 6). So, oxazolo- (**1**), oxazino- (**2**), and oxazepino-purindiones (**3**) were obtained in the former group and imidazo- (**4**), pyrimido- (**5**), and diazepino-purindiones (**6**) were obtained as the latter group of compounds. The new compounds could be envisaged as bioisosteric analogs of 8-styryl xanthines. In contrast to styrylxanthines however, they cannot isomerize in dilute solution, due to their sterically fixed structure.

Compounds from groups **1**, **4**, **5**, and **6** were obtained with the described methods [57,58] from 8-unsubstituted xanthines via 2- or 3-step procedures involving bromination of theophylline. The start-



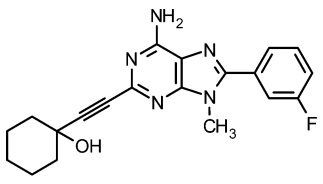
MRS 1754

16.8	403
612	503
	1.97
	570

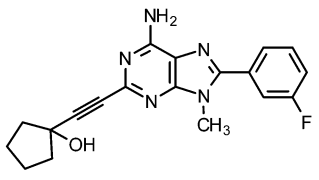


MRS 1706

37.6	157
548	112
	1.39
	230



Compound 1



Compound 2

Fig. 5 Antagonists at A_{2B} ARs. K_i values in nM (left: rat; right: human) for A_1, A_{2A}, A_{2B}, and A_3 receptors are shown in that order below the structure and name of compound. Data are taken from [55].

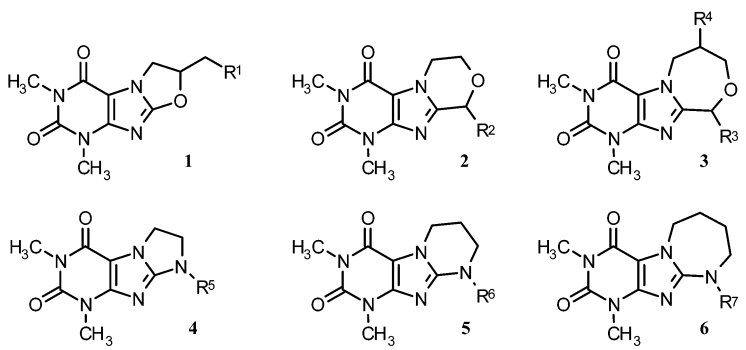


Fig. 6 Structures of the investigated tricyclic compounds.

ing material for the syntheses of compounds **2**, **3** was 8-(hydroxybenzyl)theophylline received from 5,6-diamino-1,3-dimethyluracil.

Spatial properties of the obtained compounds were examined by X-ray structure determination. Conformational analysis of the oxygen containing groups **1**, **2**, and **3** performed by ^{1}H-NMR method in solution or by AM1 and *ab initio* calculations allowed to state that oxazoline ring is practically coplanar, while oxazine (**2**) and oxazepine (**3**) rings may adopt various conformations [57].

For chiral recognition of the compounds possessing in their structures chiral centers, the dirhodium method was successfully applied. The way of complexation was studied as well in solution as in solid state. It was shown by IR and NMR studies that compounds from groups **1**, **2**, **3**, and **5** prefer a side-on complexation of the central imidazole unit to the chiral dirhodium complex in solution, whereas carbonyl groups are involved in the solid state [56,57].

Physicochemical properties of the obtained compounds were examined on basis of theoretical (pK_a, log *P*, log *D*) calculations and practical experiments (HPLC, TLC).

The synthesized compounds were evaluated in *in vitro* receptor binding studies for the affinity at A_1 and A_{2A} ARs in assays at rat brain membrane preparations (using [^{3}H] **CCPA** for A_1, [^{3}H] **MSX-2** for A_{2A} AR) (Table 1).

Selected compounds additionally investigated in binding assays at human recombinant A_1, A_{2A}, A_{2B}, and A_3 ARs (with [^{3}H] **ZM 241 385** used for hA_{2B} and [^{3}H] **PSB-11** [59] for hA_3 ARs) were shown to be A_{2A} selective vs. all other AR subtypes (Fig. 7). The most potent and selective ligands

Table 1 Pharmacological characterization of group **5** compounds.

No.	R6	*In vitro*		*In vivo*	
		$K_i \pm$ SEM (μM)			
		A_1	A_{2A}	ASP	Positive tests
5a	-H	>25	5.22	3	
5b	-methyl	>25	4.30	4	
5c	-ethyl	>25	2.65	1	ScMet
5d	-*n*-propyl	3.87	1.29	1	ScMet
5e	-*n*-butyl	4.32	1.75	4	MES, ScMet
5f	-*n*-pentyl	3.16	3.06	2	MES, ScMet
5g	-*n*-hexyl	2.87	0.82	1	ScMet
5h	-cyclopentyl	5.31	1.00	1	ScMet
5j	-cyclohexyl	>25	0.81	2	ScMet
5k	-4-hydroxycyclohexyl	>25	2.04	3	ScMet
5l	-cyclooctyl	>25	0.57	2	MES
5m	-4-methylcyclohexyl	>25	0.24	2	ScMet
5n	-vinyl	>25	>25	2	ScMet
5o	-methoxyethyl	5.05	1.34	1	ScMet
5p	-methoxypropyl	>25	3.12	1	ScMet
5r	-cyclopropylmethyl	2.39	0.98	1	ScMet

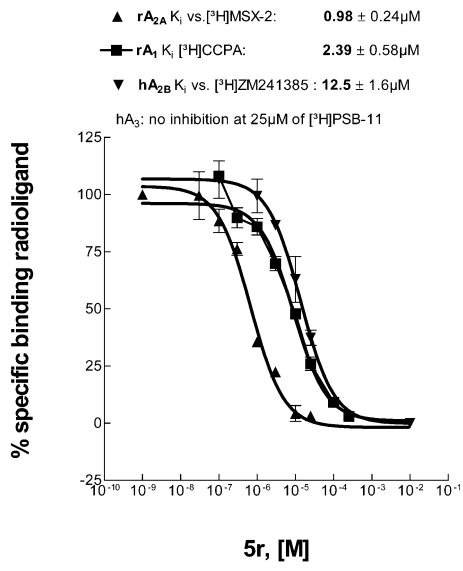


Fig. 7 Affinity of **5h** at A_1, A_{2A}, A_{2B}, and A_3 ARs.

investigated for their antagonistic properties [60] in the radioligand binding studies in the presence of Na^+ ions were classified as antagonists for A_{2A} AR.

The compounds were also tested *in vivo* according to the National Institutes of Health's Antiepileptic Drug Development Program in Bethesda, Maryland, USA (Table 1) [61,62]. They were generally active as anticonvulsants mainly in chemical induced seizures (ScMet). Some of them (with shorter substituents **5b**–**5d**) exhibited neurotoxicity (clonic seizures, tonic extension, and death). The most potent butyl **5e** and methoxyalkyl derivatives **5o**, **5r** were advanced for further investigations.

Structure–AR activity relationships for **1**–**6** revealed that oxygen-containing tricylic derivatives **1**, **2**, and **3** are moderately potent AR antagonists exhibiting selectivity either for A_1 or A_{2A} ARs; tricyclic purindiones with nitrogen in the third ring are generally more A_{2A} selective; and cycloalkyl substituents increase A_{2A} affinity and selectivity (Table 1). The most potent compound of the present series is *N*-(methylcyclohexyl)-substituted pyrimido-purindione **5m** (K_i A_{2A} = 240 nM, >100-fold selectivity), the compound was slightly less potent at human as compared to rat A_{2A} ARs (Fig. 8). There was no apparent correlation between anticonvulsant activity and AR affinity.

Concluding, new classes of tricyclic AR antagonists were identified and characterized, which can be envisaged as configurationally stable analogs of 8-styrylxanthines. Further efforts to optimize the affinity and selectivity of these new classes of AR antagonists applying also QSAR methods are in progress.

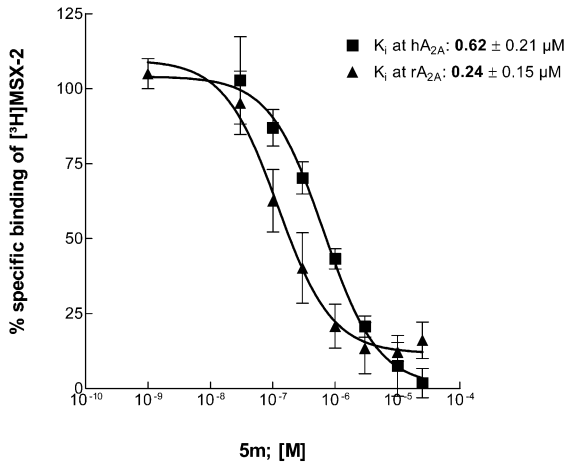


Fig. 8 Comparison of the **5m** affinity at human and rat A_{2A} ARs.

ACKNOWLEDGMENTS

This study was partly supported by the Polish State Committee for Scientific Research grants No. 4 P05F 014 18 and 4 P05F 024 21, and by the Deutsche Forschungsgemeinschaft (GRK-677). The authors are grateful to Prof. J. P. Stables for providing anticonvulsant tests data through the Antiepileptic Drug Development Program, National Institutes of Health, Bethesda, Maryland, USA.

REFERENCES

1. B. Fredholm, G. Arslan, L. Halldner, B. Kull, G. Schulte, U. Ådén, P. Svenningsson. *Drug Dev. Res.* **52**, 274–282 (2001).
2. J. A. Ribeiro, D. Cunha-Reis, L. V. Lopes, J. E. Coelho, A. R. Costenla, P. Correia-de-Sá, R. A. Cunha, A. de Mendonça, A. M. Sebastião. *Drug Dev. Res.* **52**, 337–345 (2001).

3. F. Ciruela, M. Escriche, M. M. Soloviev, E. J. Canela, J. Burgeño, J. Mallol, W.-Y. Chan, C. Luis, R. A. J. McIlhinney, R. Franco. *Drug Dev. Res.* **52**, 316–322 (2001).
4. J. A. Ribeiro. *Eur. J. Pharmacol.* **375**, 101–113 (1999).
5. K.-N. Klotz, J. Hessling, C. Owman, B. Kull, B. B. Fredholm, M. J. Lohoe. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **357**, 1–9 (1998).
6. G. Schulte and B. B. Fredholm. *Mol. Pharmacol.* **58**, 477–482 (2000).
7. M. A. Jacobson, C. J. Luneau, R. G. Johnson, C. A. Salvatore. U.S. Patent 6166 181, Filed 18 May 1998, Issued 26 Dec. 2000.
8. S. M. Kaiser and R. J. Quinn. *Drug Discov. Today* **4**, 542–551 (1999).
9. S.-A. Poulsen and R. J. Quinn. *Bioorg. Med. Chem.* **6**, 619–641 (1998).
10. M. P. DeNinno. *Annu. Rep. Med. Chem.* **33**, 111–120 (1998).
11. A. H. Dickenson, R. Suzuki, A. J. Reeve. *CNS Drugs* **13**, 77–85 (2000).
12. V. Shneyvays, N. Safran, I. Halili-Rutman, A. Shainberg. *Drug Dev. Res.* **50**, 324–337 (2000).
13. C. E. Müller. *Exp. Opin. Ther. Patents* **7**, 419–440 (1997).
14. C. E. Müller. *Il Farmaco* **56**, 77–80 (2001).
15. B. T. Liang, D. Stewart, K. A. Jacobson. *Drug Dev. Res.* **52**, 366–378 (2001).
16. H. Harada, O. Asano, Y. Hoshino. S. Yoshikawa, M. Matsukura, Y. Kabasawa, J. Niijima, Y. Kotake, N. Watanabe, T. Kawata, T. Inoue, T. Horizoe, N. Yasuda, H. Minami, K. Nagata, M. Murakami, J. Nagaoka, S. Kobayashi, I. Tanaka, S. Abe. *J. Med. Chem.* **44**, 170–179 (2001).
17. A. Akahane, H. Katayama, T. Mitsunaga, T. Kato, T. Kinoshita, Y. Kita, T. Kusunoki, T. Terai, K. Yoshida, Y. Shiokawa. *J. Med. Chem.* **42**, 779–783 (1999).
18. K. Yao, N. Heyne, C. M. Erley, T. Risler, H. Osswald. *Eur. J. Pharmacol.* **414**, 99–104 (2001).
19. L. A. Sorbera, L. Martin, J. Castañer. *Drugs Fut*. **25**, 1011–1016 (2000).
20. C. Neely. U.S. Patent 6117 998, Filed 15 April 1998, Issued 12 Sept. 2000.
21. J. E. van Muijlwijk-Koezen, H. Timmerman, R. C. Vollinga, J. Frijtag, D. Künzel, M. de Groote, S. Visser, A. P. IJzerman. *J. Med. Chem.* **44**, 749–762 (2001).
22. E. W. van Tilburg, P. A. M. van der Klein, M. de Groote, M. W. Beukers, A. P. IJzerman. *Bioorg. Med. Chem. Lett.* **11**, 2017–2019 (2001).
23. A. P. Kourounakis, P. A. M. van der Klein, A. P. IJzerman. *Drug Dev. Res.* **49**, 227–237 (2000).
24. F. Da Settimo, G. Primofiore, S. Taliani, A. M. Marini, C. La Motta, E. Novellino, G. Greco, A. Lavecchia, L. Trincavelli, C. Martini. *J. Med. Chem.* **44**, 316–327 (2001).
25. S. Hess, C. E. Müller, W. Frobenius, U. Reith, K.-N. Klotz, K. Eger. *J. Med. Chem.* **43**, 4636–4646 (2000).
26. L. Bertelli, G. Biagi, J. Giorgi, O. Livi, C. Manera, V. Scartoni, A. Lucacchini, G. Giannaccini, P. L. Barili. *Eur. J. Med. Chem.* **35**, 333–441 (2000).
27. V. Colotta, D. Catarzi, F. Varano, L. Cecchi, G. Filacchioni, C. Martini, L. Trincavelli, A. Lucacchini. *J. Med. Chem.* **43**, 1158–1164 (2000).
28. G. Biagi, J. Giorgi, O. Livi, C. Manera, V. Scartoni, L. Betti, G. Giannaccini, A. Lucacchini. *Il Farmaco* **54**, 615–623 (1999).
29. L. Betti, G. Biagi, G. Giannaccini, I. Giorgi, O. Livi, A. Lucacchini, C. Manera, V. Scartoni. *Eur. J. Med. Chem.* **34**, 867–875 (2000).
30. A. R. Beauglehole, S. P. Baker, P. J. Scammells. *J. Med. Chem.* **43**, 49733–49780 (2000).
31. J. E. van Muijlwijk-Koezen, H. Timmerman, R. P. van der Sluis, A. C. van de Stolpe, W. M. P. B. Menge, M. W. Beukers, P. H. van der Graaf, M. de Groote, A. P. IJzerman. *Bioorg. Med. Chem. Lett.* **11**, 815–818 (2001).
32. M. J. Dooley, M. Kono, F. Suzuki. *Bioorg. Med. Chem.* **4**, 923–934 (1996).
33. I. Doytchinova and S. Petrova. *Med. Chem. Res.* **8**, 143–152 (1998).
34. C. E. Müller. *Drugs Fut.* **25**, 1043–1052 (2000).
35. W. Hauber, J. Nagel, R. Sauer, C. E. Müller. *NeuroReport* **9**, 1803–1806 (1998).
36. P. J. Richardson, H. Kase, P. G. Jenner. *Trends Pharmacol. Sci.* **189**, 338–344 (1997).

37. J. Strömberg, P. Popoli, C. E. Müller, S. Ferré, K Fuxe. *Eur. J. Neurosci*. **12**, 4033–4037 (2000).
38. S. Ferré, P. Poppoli, L. Gimenéz-Llort, R. Rimondini, C. E. Müller, J. Strömberg, S. O. Ögren, K. Fuxe. *Parkinson & Related Disorders* **7**, 235–241 (2001).
39. C. E. Müller, R. Sauer, Y. Maurinsh, R. Huertas, F. Fülle, K.-N. Klotz, J. Nagel, W. Hauber. *Drug Dev. Res.* **45**, 190–197 (1998).
40. J. Sawynok. *Curr. Opin. CPNS Invest. Drugs* **1**, 27–38 (1999).
41. M. El Yacoubi, C. Ledent, M. Parmentier, M. Daoust, J. Costentin, J.-M. Vaugeois. *Neuropharmacology* **40**, 424–432 (2001).
42. E. Ongini, A. Monopoli, B. Cacciari, P. G. Baraldi. *Il Farmaco* **56**, 87–90 (2001).
43. L. J. S. Knutsen and S. M. Weiss. *Curr. Opin. Invest. Drugs* **2**, 668–673 (2001).
44. X. Rabasseda, L. A. Sorbera, L. Martin, P. A. Leeson, J. Castañer. *Drugs Fut.* **26**, 20–24 (2001).
45. C. E. Müller, J. Sandoval-Ramirez, U. Schobert, U. Geis, W. Frobenius, K.-N. Klotz. *Bioorg. Med. Chem.* **6**, 707–719 (1998).
46. R. Sauer, J. Maurinsh, U. Reith, F. Fülle, K.-N. Klotz, C. E. Müller. *J. Med. Chem.* **43**, 440–448 (2000).
47. C. E. Müller, J. Maurinsh, R. Sauer. *Eur. J. Pharm. Sci.* **10**, 259–265 (2000).
48. X. D. Ji and K. A. Jacobson. *Drug Des. Discov.* **16**, 217–226 (1999).
49. P. H. Stephen and P. J. Millns. *Eur. J. Pharmacol.* **411**, 205–210 (2001).
50. P. G. Baraldi, B. Cacciari, G. Spalluto, M. Bergonzoni, S. Donisotti, E. Ongini, K. Varani, P. A. Borea *J. Med. Chem.* **41**, 2126–2233 (1998).
51. S. Todde, R. M. Moresco, P. Simonelli, P. G. Baraldi, B. Cacciari, G. Spalluto, K. Varani, A. Monopoli, M. Mataresse, A. Carpinelli, F. Magni, M. G. Kienle, F. Fazio. *J. Med. Chem.* **43**, 440–448 (2000).
52. P. G. Baraldi, P. A. Borea, M. Bergonzoni, B. Cacciari, E. Ongini, M. Recantini, G. Spalluto. *Drug Dev. Res.* **46**, 126–133 (1999).
53. J. M. Linden. U.S. Patent 6117 878, Filed 24 Feb. 1998, Issued 12 Sept. 2000.
54. K. A. Jacobson, A. P. IJzerman, J. Linden. *Drug Dev. Res.* **47**, 45–53 (1999).
55. Y.-C. Kim, X.-D. Ji, N. Melman, J. Linden, K. A. Jacobson. *J. Med. Chem.* **43**, 1165–1172 (2000).
56. Y. Song, I. M. Coupar, M. N. Iskander. *Quant. Struct. – Act. Relat*. **20**, 23–30 (2001).
57. S. Rockitt, H. Duddeck, A. Drabczyńska, K. Kieć-Kononowicz. *Eur. J. Org. Chem.* 3489–3496 (2000).
58. S. Rockitt, R. Wartchow, H. Duddeck, A. Drabczyńska, K. Kieć-Kononowicz. *Z. Naturforsch.* **56b**, 319–324 (2001).
59. C. E. Müller. *Mini-Reviews Med. Chem*. **1**, 433–443 (2001).
60. Z. G. Gao and A. P. IJzerman. *Biochem. Pharmacol.* **60**, 669–676 (2000).
61. R. L. Krall, J. K. Penry, B. G. White, H. J. Kupferberg, E. A. Swinyard. *Epilepsia* **19**, 400–428 (1978).
62. R. J. Porter, J. J. Cereghino, G. D. Gladding, H. J. Kupferberg, B. Scoville, B. G. White. *Cleveland Clin. Q*. **51**, 293–305 (1984).