Recent Developments in Adenosine A_{2A} Receptor Ligands

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Abstract The development of potent and selective agonists and antagonists of adenosine receptors (ARs) has been a target of medicinal chemistry research for several decades, and recently the US Food and Drug Administration has approved Lexiscan™, an adenosine derivative substituted at the 2 position, for use as a pharmacologic stress agent in radionuclide myocardial perfusion imaging. Currently, some other adenosine A_{2A} receptor (A_{2A}AR) agonists and antagonists are undergoing preclinical testing and clinical trials. While agonists are potent antiinflammatory agents also showing hypotensive effects, antagonists are being developed for the treatment of Parkinson's disease.

However, since there are still major problems in this field, including side effects, low brain penetration (for the targeting of CNS diseases), short half-life, or lack of in vivo effects, the design and development of new AR ligands is a hot research topic.

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This review presents an update on the medicinal chemistry of A_{2A}AR agonists and antagonists, and stresses the strong need for more selective ligands at the human A_{2A}AR subtype, in particular in the case of agonists.

Keywords Adenosine receptor · Adenosine A_{2A} receptor · A_{2A} agonists · A_{2A} antagonists · Nucleosides · Xanthines · Adenines · Nitrogen (poly)heterocyclic compounds

Abbreviations

ADA	Adenosine deaminase
Ado	Adenosine
AK	Adenosine kinase
AR	Adenosine receptor
CCPA	2-Chloro-N^6-cyclopentyladenosine
CHA	N^6-Cyclohexyladenosine
CHO	Chinese hamster ovarian
CNS	Central nervous system
CPA	N^6-Cyclopentyladenosine
HEAdo	2-(Hexyn-1-yl)adenosine
HENECA	2-Hexynyl-NECA
MECA	*N*-Methylcarboxamidoadenosine
NECA	*N*-Ethylcarboxamidoadenosine
PEAdo	2-Phenylethynyladenosine
PENECA	2-PhenylethynylNECA
PHPAdo	2-Phenylhydroxypropynyladenosine
PHPNECA	2-PhenyhydroxypropynylNECA
PIA	N^6-(2-Phenylisopropyl)adenosine
QSAR	Quantitative structure–activity relationships

1 Adenosine A_{2A} Receptor Agonists

1.1 Adenosine

The clinical utility of adenosine (Ado, **1**, Fig. 1) was recognized late in the 1980s by Belardinelli and Pelleg, and it soon became clear that the unmodified molecule is of restricted interest as a tool for the study of adenosine receptors due to its susceptibility to extensive metabolism by a number of enzymes (Klotz 2000). In fact, the observation that the activity of exogenous Ado on the mammalian cardiovascular system is of short duration because of the rapid uptake of Ado into red blood cells and tissues (Pfleger et al. 1969), its phosphorylation by adenosine kinase

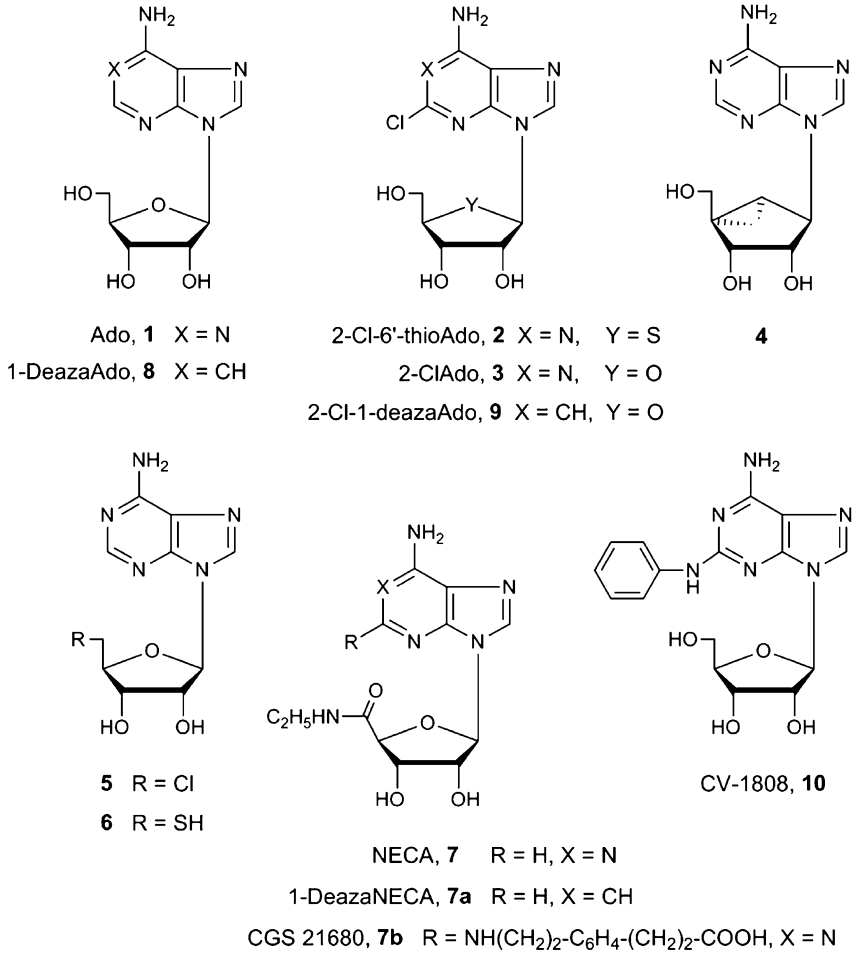

Fig. 1 A_{2A}AR agonists

(AK), and its conversion to inosine by adenosine deaminase (ADA) (Cristalli et al. 2001) led many labs to carry out several modifications of the Ado structure in order to find stable and selective ligands for the four adenosine receptor subtypes.

Almost all AR agonists known so far are derivatives of the physiological agonist Ado (Table 1). One exception is a set of substituted pyridines recently found to be agonists for human adenosine A_{2B} receptor (A_{2B}AR) (Beukers et al. 2004). Many attempts to modify the Ado structure led to the conclusion that the Ado scaffold must be conserved, although three positions in the molecule may be modified to increase affinity to specific receptor subtypes without destroying the agonistic efficacy: the 5′ position of the ribose and the 2 and N^6 positions of the purine (Cristalli et al. 2003). It must be underlined that any of these modifications render the agonists metabolically stable.

Table 1 Affinities of AR agonists in radioligand binding assays at A_1AR, $A_{2A}AR$, and A_3AR, and effects on adenylate cyclase activity at the $A_{2B}AR$

Cpd	K_i (A_1AR)[a]	K_i ($A_{2A}AR$)[a]	EC_{50} ($A_{2B}AR$)[b]	K_i (A_3AR)[a]
2	300 r	20 r	–	1,090 r
3	9.3 r	63 r	24,000 r	1,890 r
7	10 r	7.8 r	–	113 r
	63 r	16 r	3,100 h	10 h
	14 h	20 h	2,400 h	6.2 h
7a	51 r	580 r	16,000 h	703 r
7b	1,400 r	19 r		584 r
	290 h	27 h	88,800 h	67 h
8	115 r	2,900 r	–	–
9	226 r	163 r	–	2,480 r
10	400 r	100 r	–	–
11	977 r	68 r	–	–
	530 h	62 h	–	310 h
12	130 r	17 r	–	–
	221 h	9.3 h	3,490 h	54 h
13	48,000 h	270 h	>100,000 h	900 h
14	11,700 r	22 r	–	–
15	2,800 r	22 r	–	–
	1,730 h	92 h	–	83 h
16	701 r	109 r	–	–
	806 r[c]	246 r[c]	–	28 r[c]
	395 h	363 h	>100,000 h	16 h
17	98 r	2.2 r	–	–
	111 r[c]	5.2 r[c]	–	24 r[c]
	18 h	5.7 h	≈100,000 h	4.7 h
18	3.4 r	1.9 r	–	–
	3.9 r[c]	5.3 r[c]	–	0.98 r[c]
	0.67 h	7.0 h	2,400 h	3.3 h
19a	1.5 r[c]	1.0 r[c]	–	0.40 r[c]
	0.44 h	29 h	6,200 h	5.0 h
19b	2.5 r[c]	1.6 r[c]	–	24 r[c]
	0.67 h	1.8 h	920 h	1.4 h
20	332 r	14 r	–	–
21	618 r	757 r	–	–
23	0.6 r	462 r	–	–
26	356 h	1.0 h	2,780 h[d]	100 h
27	473 r	9.7 r	–	–
28	130 r	2.2 r	–	26 r
	160 r[c]	1.0 r[c]	–	18 r[c]
	60 h	6.4 h	6,100 h	2.4 h
29	2.5 r	0.9 r	–	–
	3.8 r	2.7 r	–	7.7 r
	2.7 h	3.1 h	1,100 h	0.42 h

(continued)

Table 1 (continued)

Cpd	K_i (A_1AR)[a]	K_i (A_{2A}AR)[a]	EC_{50} (A_{2B}AR)[b]	K_i (A_3AR)[a]
29a	5.9 r	2.6 r	–	–
	2.7 r[c]	16 r[c]	–	0.46 r[c]
	1.9 h	39 h	2,400 h	5.5 h
29b	4.0 r	0.5 r	–	–
	5.5 r[c]	1.8 r[c]	–	2.6 r[c]
	2.1 h	2.0 h	220 h	0.75 h
30	698 r	120 r	–	–
	1,000 r[c]	267 r[c]	–	768 r[c]
	560 h	620 h	>100,000 h	6.2 h
31	28 r	5.5 r	–	–
	77 h	0.2 h	–	45 h
32a	251 r	1.6 r	–	–
32b	951 r	70 r	–	–
33	>10,000 p	85 p	–	–
	380 r[c]	15 r[c]	–	46 r[c]
	189 h	24 h	>100,000 h	86 h
34	1,100 r	330 r	45,000 h	6.4 h
35	63 r	12 r	5,300 h	108 h
36	403 h	49 h	>100,000 h	16 h
37	1,700 h	720 h	>100,000 h	246 h
38	32% r	115 r	–	5,640 r
39	48% r	82 r	–	3,160 r
40	–	1,122 p	–	–
41	5,836 h	2,895 h	–	–

[a]Binding data from different species: rat (*r*), human (*h*) or pig (*p*) A_1AR, A_{2A}AR, and A_3AR, expressed as K_i (nM)

[b]Measurement of receptor-stimulated adenylate cyclase activity at rat (*r*) or human (*h*) A_{2B}AR, expressed as EC_{50} (nM)

[c]Unpublished data

[d]Binding data

1.2 Ribose-Modified Adenosine Derivatives

A variety of modifications of the Ado ribose ring in several positions were carried out in order to get information on the essential points of agonist activity, and possibly to obtain more active and stable compounds (Yan et al. 2003; Akkari et al. 2006). Most alterations of either the structure or the stereochemistry of the ribose resulted in a loss of receptor binding potency and possibly intrinsic activity (Siddiqi et al. 1995).

Compounds in which the furanose ring was modified have been synthesized in order to improve stability, since the glycosidic bonds of adenine riboside derivatives are subject to scission in vivo. Results have shown that the sugar moiety must be maintained as a ribose ring, but that in some cases the endocyclic oxygen ring atom can be replaced with a sulfur atom (**2**, Fig. 1) (Siddiqi et al. 1995) or a methylene

group (carbonucleoside). Comparison of 2-ClAdo (**3**) and the thio–ribosyl analog **2** showed a 3.2-fold higher affinity of the latter at the A_{2A}AR, whereas its adenosine A_1 receptor (A_1AR) affinity was reduced by 32-fold. In contrast, compounds **2** and **3** were of similar potency at the adenosine A_3 receptor (A_3AR) (Siddiqi et al. 1995). Carbonucleosides showed generally weak A_{2A}AR selectivity and low affinity for A_3AR. Carbocyclic modification of the agonists ribose resulted in nonglycosidic compounds that are potentially more biologically stable. The synthesis of a variety of methanocarba analogs of Ado was reported (**4**, Fig. 1) (Jacobson et al. 2000). These compounds contain a fused cyclopropane ring that constrains the pseudosugar ring in either a North (*N*) or South (*S*) conformation, with the aim of defining the role of sugar puckering in stabilizing the AR-bound conformation. Such modifications lead to compounds endowed with very low A_{2A}AR affinity and high A_1AR and A_3AR selectivity.

The 2′- and 3′-hydroxy groups of the ribose moiety appear to be essential for full agonist activity (Mathot et al. 1995; Siddiqi et al. 1995; van der Wenden et al. 1995; Vittori et al. 2000), whereas the substitution of the 5′-hydroxyl group of Ado is better tolerated, although the removal of this group results in a decrease in potency (van der Wenden et al. 1995). Moreover, 5′-modified Ados are also less expected to be incorporated into DNA due to their resistance to phosphorylation by AK (IJzerman and van der Wenden 1997).

Substitution of the 5′-hydroxyl group with a chlorine or a thiol group (**5** and **6**, Fig. 1) has been observed to increase affinity for ARs (Taylor et al. 1986; van der Wenden et al. 1998). However, it has been observed that the 5′-chloro-5′-deoxy modification of N^6-substituted Ados can increase A_1AR selectivity by reducing A_2 receptor potency (Taylor et al. 1986). A number of changes have been made to the riboses of a range of Ado analogs (Siddiqi et al. 1995). Most of the compounds with modified ribose in these studies were not substrates for ADA, and hence all were resistant to metabolism.

The introduction of an *N*-alkylcarboxamido group in position 5′ was well tolerated by all AR subtypes, and produced the most active compounds, such as NECA (**7**, Fig. 1) (Prasad et al. 1980), a nonselective AR agonist. On the other hand, *N*-ethylthiocarboxamidoAdo showed a decrease in affinity compared with NECA at all AR subtypes (de Zwart et al. 1999a). In particular, the 5′-*N*-ethyluronamide group enhances receptor affinity for all AR subtypes and it leads to a further increase in the agonist activity and/or selectivity, especially if other substituents are simultaneously present at position 2 of the Ado (Prasad et al. 1980; Hutchison et al. 1990; Cristalli et al. 1995; Baraldi et al. 1998a; de Zwart et al. 1999a). Structure–activity relationships showed that the 5′-*N*-ethyl-, 5′-*N*-methyl- and 5′-*N*-cyclopropylcarboxamido substitutions give the most potent agonists (Prasad et al. 1980).

1.3 Purine-Modified Adenosine Derivatives

In general, modification of the purine scaffold results in compounds with reduced receptor binding affinity compared with the corresponding Ado analogs

(Müller and Scior 1993; IJzerman et al. 1994). In particular, 1-deazaAdo (**8**) and its N^6-substituted derivatives are A_1AR selective, while the nitrogen atoms in the 3 and 7 positions are required for high affinity of Ado analogs at all subtypes (Bruns 1980; Cristalli et al. 1985; Siddiqi et al. 1995; de Zwart et al. 1998). On the other hand, 2-chloro-1-deazaAdo (**9**) showed an A_{2A}AR and A_3AR affinity similar to that of compound **3** (which is slightly A_1AR selective), and a reduced A_1AR activity, thus being slightly selective for the A_{2A}AR (Cristalli et al. 1988). Furthermore, **8** was reported to possess ADA inhibitory activity (Cristalli et al. 2001).

1.3.1 2- or N^6-Substituted Adenosine Derivatives

In the last 35 years, a significant number of C2-substituted Ado derivatives were synthesized and tested for their affinities at A_1AR and A_{2A}AR, and the first Ado derivative found to have some A_{2A}AR selectivity was CV-1808 (**10**, Fig. 1) (Bruns et al. 1986). A number of substitutions were made with amine (Francis et al. 1991), hydrazine (Niiya et al. 1992a, b; Viziano et al. 1995), alkoxyl (Daly et al. 1993; Matova et al. 1997), alkythio (Hasan et al. 1994; Cristalli 2000; Volpini et al. 2004), and alkynyl groups (Abiru et al. 1992, 1995; Cristalli et al. 1992; Matsuda et al. 1992; Volpini et al. 2002; Ohno et al. 2004), and the compounds with a phenylethyl (or cyclohexylethyl) group directly linked to the heteroatom (**11–15**, Fig. 2) or a triple bond (**16–18**) showed the highest A_{2A}AR affinities (Cristalli et al. 2007).

Substitutions with hydrazine led to 2-(N'-alkylidenehydrazino) and 2-(N'-aralkylidenehydrazino)Ado derivatives (Niiya et al. 1992a, b). Among these molecules, we should mention WRC-0470 (2-cyclohexylmethylidenehydrazinoAdo, also known as MRE-0470 or SHA-174 or Binodenoson, **13**) discovered at Nelson/Whitby Research and developed at Discovery Therapeutics, and now in clinical trial for myocardial perfusion imaging.

The alkynyl derivatives 2-phenylethynylAdo (PEAdo, **16**), 2-(hexyn-1-yl)Ado (HEAdo, **17**), (*R*, *S*)-2-phenylhydroxypropynylAdo ((*R*, *S*)-PHPAdo, **18**), and the corresponding diastereomers **19a** and **19b** were tested in binding studies on rat membrane A_1AR, A_{2A}AR (Cristalli et al. 1992), and A_3AR (Cristalli et al., unpublished results) and on the four human recombinant receptor subtypes, stably transfected into Chinese hamster ovarian (CHO) cells (the potency at the A_{2B}AR was measured with adenylate cyclase activity assays) (Volpini et al. 2002). All the compounds showed A_{2A}AR affinity in the low nanomolar range, and HEAdo was also shown to be slightly A_{2A}AR selective in rat membrane (A_1AR/A_{2A}AR $\approx$ 20 and A_3AR/A_{2A}AR $\approx$ 5). The phenylhydroxypropynyl derivatives are generally very potent, but are not selective at both rat and human AR subtypes. Partial and full reduction of the HEAdo triple bond led to *E*- and *Z*-alkenyl isomers **20** and **21** and 2-hexylAdo, respectively, among which the *trans* isomer **20** showed good A_{2A}AR affinity and modest selectivity (A_1AR/A_{2A}AR $\approx$ 24), while 2-hexylAdo proved to be inactive at both A_1AR and A_{2A}AR subtypes (Vittori et al. 1996). More recently, broad screening was carried out with the aim of characterizing the affinity and selectivity of 2-alkoxyAdo derivatives at A_3AR subtypes.

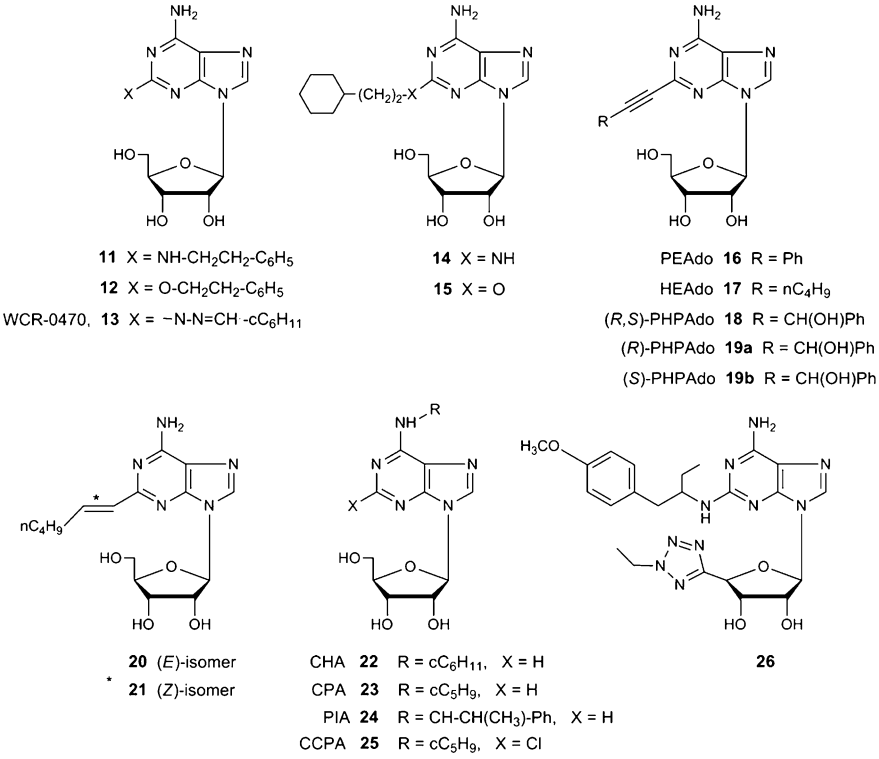

Fig. 2 A_{2A}AR agonists: various Ado derivatives

These single substitutions at the 2 position, previously found to contribute to the affinity for the rat A_{2A}AR, were also proven to be important for affinity and selectivity at the human A_{2A}AR ortholog (Gao et al. 2004).

In general, substitution of Ado at the N^6 position (and in particular disubstitution with bulky substituents at the C2 and N^6 positions) is detrimental to A_{2A}AR affinity (Müller and Scior 1993). In fact, the first known subtype-selective Ado derivatives modified at the N^6 position, such as N^6-cyclohexylAdo (CHA, **22**), N^6-cyclopentylAdo (CPA, **23**), and N^6-(2-phenylisopropyl)Ado (PIA, **24**) showed A_1AR selectivity (Daly 1982). Furthermore, substituents in this position were more recently also shown to enhance A_3AR affinity and selectivity (Knutsen et al. 1999; Volpini et al. 2002).

In a series of 1-deaza analogs of Ados, it turned out that 2-chloro substitution in addition to an N^6-cyclopentyl increases A_1AR selectivity (Cristalli et al. 1988). The respective modification in Ado led to the development of 2-chloro-N^6-cyclopentylAdo (CCPA, **25**) as the most potent and selective A_1AR ligand characterized in rat brain (Lohse et al. 1988; Klotz et al. 1989).

1.4 Ribose- and Purine-Modified Adenosine Derivatives

The majority of A_{2A}AR-selective agonists are 2-substituted Ado derivatives bearing an *N*-alkylcarboxamido modification at the ribose 5′ position, as in NECA (Hutchison et al. 1990; Cristalli et al. 1992, 1994b, 1995, 1996, 2003, 2007; Homma et al. 1992; Vittori et al. 1996; de Zwart et al. 1998; Müller 2000a). Also, Ado derivatives bearing bulky substituents in the C2 position and NECA derivatives with bulky substituents in the N^6 position are not selective versus A_1AR and A_3AR. N^6 and C2 substitution are helpful to improve A_3AR agonist activity, even if substitution at both N^6 and C2 with large substituents led to a large drop in affinity when combined (Baraldi et al. 1998a). This effect at A_{2A}AR had been observed in a series of Ado derivatives developed as A_{2A}AR agonists (Müller and Scior 1993). QSAR (quantitative structure–activity relationship) studies on different N^6-arylcarbamoyl, 2-arylalkynyl-N^6-arylcarbamoyl, and N^6-carboxamide Ado derivatives showed that the main determinants of the affinity at A_{2A}ARs were the bulkiness of the substituents attached at the 2 and 5′ positions and the stereoselectivity of the Ado derivatives (Gonzalez et al. 2005). Moreover, the synthesis and potential human A_{2A}AR agonistic activity of Ado derivatives containing an ethyl-substituted tetrazole moiety at the 4′ position of the ribose and an amino alcohol at the 2 position of the adenine core were reported (Bosch et al. 2004). The activities of these compounds were tested in radioligand binding assays using the four cloned human ARs. The compounds have also been profiled in cAMP assays using human receptors expressed on transfected CHO cells, and in functional assays using rat aorta, guinea pig aorta, and guinea pig tracheal rings. Results of these experiments show that substitution at the *para* position of the phenyl ring at the 2 side-chain by different groups greatly increases the affinity for A_{2A}AR. At the same time, the tested substituted derivatives have reduced affinity for A_1AR and A_3AR, thus greatly improving the A_1AR/A_{2A}AR and A_3AR/A_{2A}AR selectivity. Among the tested Ado derivatives, compound **26**, lacking the hydroxyl group in the side chain, was the most potent and selective in binding studies.

1.4.1 2-Substituted NECA Derivatives

The 4′-uronic acid ethyl ester analog of Ado, NECA, was reported in the early 1980s to be a potent coronary vasodilator and hypotensive (Prasad et al. 1980), and a good inhibitor of platelet aggregation induced by ADP (Cusack and Hourani 1981). However, NECA showed little or no A_2 selectivity in either functional or binding studies (Cristalli et al. 1994a, b; Klotz et al. 1999).

A series of 2-(arylalkylamino)-NECA derivatives were synthesized and evaluated for their A_1AR and A_{2A}AR binding profiles in rat brain membranes soon after the first Ado derivative with some A_{2A}AR selectivity, CV-1808 (**10**, Fig. 1), was reported. As in the case of arylalkylaminoAdos, the phenylethylamino analog of NECA **27** (Fig. 3) showed the highest rat A_{2A}AR affinity in the series and a greater than 2,000-fold separation between A_2 (coronary vasodilation) and A_1AR

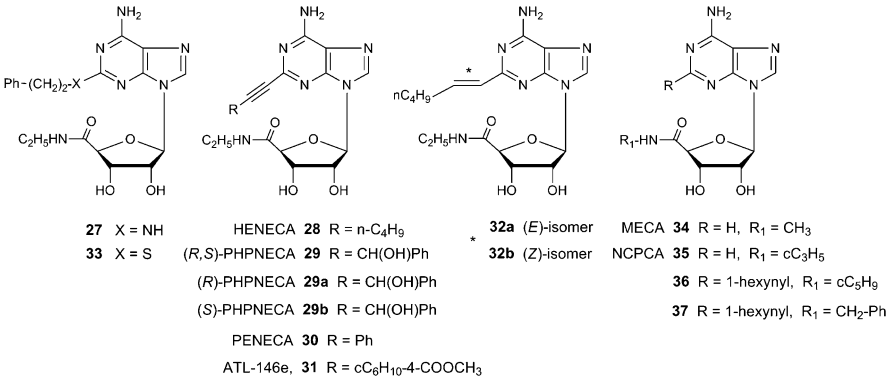

Fig. 3 A_{2A}AR agonists: NECA derivatives

(negative chronotropic effect) receptor-mediated events. Among these compounds, CGS 21680 (**7b**, Fig. 1) proved to be an A_{2A}AR-selective agonist that was 140-fold selective vs. A_1AR in a rat model (Hutchison et al. 1989). This molecule was selected for extensive biological evaluation (Hutchison et al. 1989) and tritiation for use as an A_{2A}AR-selective ligand for receptor binding (Jarvis et al. 1989). However, due to a similar affinity of CGS 21680 for A_3AR and the remarkable species variation observed for the A_1AR, with an over tenfold higher affinity of this compound for the human subtype (Klotz et al. 1998), it can no longer be considered an A_{2A}AR-selective agonist. In any case, it has been the ligand of choice to distinguish A_{2A}AR- and A_{2B}AR-mediated effects so far.

The synthesis and evaluation of 2-alkynyl derivatives of NECA, bearing from five to eight linear carbon atom chains, was driven by the same observations that led to the synthesis and testing of 2-alkynylAdos (Cristalli et al. 1992). Affinities for A_1AR and A_{2A}AR were determined in rat membranes using radioligand competition assays. All compounds showed good A_1AR and A_{2A}AR affinities (K_i in the nanomolar range) and moderate A_{2A}AR selectivity (Cristalli et al. 1992). Among this series of 2-substituted compounds tested at rat receptors, 2-hexynyl-NECA (HENECA, **28**, Fig. 3) exhibited 60-fold A_{2A}AR selectivity compared to the A_1AR subtype. The pharmacological profile of this compound was characterized by studies carried out by Monopoli and coworkers, using in vitro and in vivo models (Monopoli et al. 1994). In addition to the binding studies on both rat and bovine brain, which confirmed the moderate A_{2A}AR versus A_1AR selectivity, HENECA was administered intraperitoneally in conscious spontaneously hypertensive rats, and it caused a dose-dependent reduction in systolic blood pressure with minimal reflex tachycardia. It also appeared to penetrate the central nervous system, as shown by its protection against pentylenetetrazole-induced convulsions in rats (Monopoli et al. 1994). In another work, administration of HENECA i.p. induced Fos-like immunoreactivity in the rat nucleus accumbens shell, lateral septal nucleus, and dorso–medial striatum, similar to that induced by atypical neuroleptics (Pinna et al. 1997).

The therapeutic potential of HENECA for the treatment of cardiovascular and psychotic diseases led to the synthesis of a series of 2-alkynyl, 2-cycloalkynyl, 2-aralkynyl, and 2-heteroaralkynyl derivatives of NECA that were tested in binding and functional assays to evaluate their potency for the A_{2A}AR compared to A_1AR (Cristalli et al. 1994b; Cristalli et al. 1995). Results showed that good A_{2A}AR affinities of the compounds were obtained with large 2-substituents containing a relatively rigid spacer, but that the affinity was reduced by introducing the bulkier naphthyl ring at the 2 position.

High agonist potency was found by introducing an α-hydroxy group into the alkynyl chain of NECA derivatives and obtaining compounds like 2-phenylhydroxypropynylNECA ((*R*, *S*)-PHPNECA, **29**), which was endowed with subnanomolar affinity in binding studies (K_i A_1AR = 2.5 nM and K_i A_{2A}AR = 0.9 nM) and was 16-fold more potent than NECA (**7**) as a platelet aggregation inhibitor. The problem with these analogs is that they also possess good A_1AR affinity, resulting in low A_{2A}AR selectivity. The diastereoisomer separation of a PHPNECA racemic mixture was accomplished obtaining compounds **29a** and **29b**. Binding tests in rat membranes showed that the (*S*)-diastereomer **29b** is about fivefold more potent and selective than the (*R*)-diastereomer **29a** as an agonist of the A_{2A}AR receptor subtype (**29b**, K_i A_{2A}AR = 0.5 nM; **29a**, K_i A_{2A}AR = 2.6 nM, Table 1) (Camaioni et al. 1997).

Things changed in the late 1990s after the cloning of the four human AR subtypes and their stable transfection into CHO cells. In fact, it was then possible to carry out comparative studies in a similar cellular background, utilizing binding studies (A_1AR, A_{2A}AR, A_3AR) or adenylate cyclase activity assays (A_{2B}AR) (Klotz et al. 1998). Transfected CHO cells were employed to screen for some nucleosides previously considered A_{2A}AR selective, and following this screening none of the prototypical AR agonists exhibited high affinity and selectivity for the human A_{2A}AR subtype. Both NECA and CGS 21680, which were available as radioligands for this subtype, demonstrated reduced affinity at the human as compared to the rat receptor, whereas HENECA (**28**) also showed high affinity at human A_{2A}AR and A_3AR, with tenfold and 25-fold selectivity versus the A_1AR subtype, respectively (K_i A_1AR = 60 nM, K_i A_{2A}AR = 6.4 nM, and K_i A_3AR = 2.4 nM). Interestingly, the potency for A_{2B}AR receptor is comparable with that of **7** (**28**: EC_{50} A_{2B} = 6.1 μM against **7** EC_{50} A_{2B} = 2.4 μM) (Cristalli et al. 1998), and it was also confirmed that **29** is a highly potent, nonselective agonist at A_1AR, A_{2A}AR, and A_3AR subtypes with a K_i in the low nanomolar range at the three subtypes. In the A_{2B}AR functional test, it was found that **29** (EC_{50} A_{2B} = 1.1 μM) is twofold more potent than **7**, and the (*S*)-diastereomer **29b** showed an EC_{50} A_{2B} in the nanomolar range (EC_{50} = 220 nM). It must be underlined that this was the first case of a NECA derivative substituted in the 2 position with a bulky group and showing good potency at the human A_{2B}AR subtype (Klotz et al. 1999; Lambertucci et al. 2003; Vittori et al. 2004). On the other hand, CGS 21680 was about 100-fold weaker than (*R*, *S*)-PHPNECA at the same subtype, with EC_{50} A_{2B} = 89 μM (Cristalli et al. 1998). The substituent linked to the triple bond allowed modulation of selectivity at the A_3AR, and the presence of a phenyl ring conjugated to the triple

bond was detrimental for all the subtypes with the exception of the A_3AR; for example, PENECA (**30**) showed high potency and good selectivity for the A_3AR subtype (Klotz et al. 1999; Vittori et al. 2005). Anyway, the introduction of an alkyl spacer group restored high A_{2A}AR affinity and selectivity, as in phenylpentynyl–NECA.

Another A_{2A}AR agonist, apadenoson (ATL-146e, **31**, Fig. 3), was prepared following the literature activity on alkynyl derivatives. In fact, this molecule is a NECA derivative bearing in the 2 position a propynyl–cyclohexanecarboxylic acid methyl ester group, and binding assays are reported in which the affinity to recombinant human A_{2A}AR is measured as high- and low-affinity K_i values (0.2 and 67.9 nM, respectively) (Murphree et al. 2002).

Other developments include 2-(aralkenyl)-substituted Ado and NECA derivatives (Vittori et al. 1996), and (*E*)-isomers (**32a**, Fig. 3) were 15- to 50-fold more potent at A_{2A}AR than the corresponding (*Z*)-isomers (**32b**). Alkenyl–NECA derivatives, such as (*E*)-2-hexenyl-NECA (**32a**), displayed similar potency as A_{2A}AR agonists to the corresponding alkynyl derivatives, but showed higher selectivity versus A_1AR (Vittori et al. 1996). In this series, the *N*-ethylcarboxamido modification of the ribose was critical to increasing A_{2A}AR affinity. In addition, some 2-arylalkylthio analogs of NECA were synthesized and tested in radioligand binding studies, and the 2-phenylethylthio derivative (**33**) proved to be the most potent and selective agonist at the pig and rat A_{2A}AR (Volpini et al. 2004).

In conclusion, the affinities at the human and rat A_{2A}AR are ranked as follows: PHPNECA $\geqslant$ HENECA > NECA > CGS 21680 > PENECA, even though none of these compounds are selective towards both A_1AR and A_3AR subtypes at the same time. Thus, so far, no satisfactory A_{2A}AR-selective agonists are available. In 2001, four new derivatives that are structurally similar to the 2-alkynyl derivatives of NECA that were previously reported (Cristalli et al. 2003) were evaluated by competitive binding assays employing the A_{2A}AR in rat striatal membranes and A_1AR of rat cortex. Hence, the A_{2A}AR against A_1AR selectivity was evaluated, but no A_{2A}AR against A_3AR selectivity was reported (Rieger et al. 2001). As some 2-alkynyl derivatives of NECA had been previously reported to behave as potent A_3AR agonists, affinity at this receptor should be measured before claiming selectivity for the reported compounds.

1.4.2 Ribose- and Purine-Modified NECA Derivatives

A few modifications of the ribose moiety of NECA have been reported (Jacobson et al. 1995; Volpini et al. 1998, 1999; de Zwart et al. 1999a). The ethyl group of the *N*-alkylcarboxamido function was substituted by a methyl or a cyclopropyl group, and this modification seems to be the only one that is well tolerated by the rat A_{2A}AR (see compounds **34** (MECA) and **35** in Fig. 3 and Table 1, K_i A_{2A}AR = 330 and 12 nM, respectively) (de Zwart et al. 1999a). On the other hand, replacing the same ethyl substituent in the 5′ position of **28** with a cyclopentyl or benzyl group brought about a significant decrease in affinity at all of the receptor subtypes (see compounds **36** and **37** in Table 2, K_i A_{2A}AR = 49 and 720 nM, respectively)

(Volpini et al. 1999). Some deoxy and dideoxy derivatives of **34** have been described, and the general effect of these modifications is a reduced affinity at all receptor subtypes (Jacobson et al. 1995; Volpini et al. 1998). However, the removal of the 3′-hydroxy group seems to be better tolerated by the A_{2A}AR than the removal of the corresponding group in the 2′ position (Cristalli et al., unpublished results).

The only purine-modified analog of NECA that has been synthesized and tested so far is 1-deazaNECA (**7a**, Fig. 1) (Cristalli et al. 1988; Siddiqi et al. 1995). As in the case of the other 1-deazaAdo analogs, the affinity of 1-deazaNECA at all ARs is reduced in comparison to that of the parent compound NECA (**7**)—in fact it is about tenfold less active than NECA—but 1-deazaNECA is clearly more active than the parent compound 1-deazaAdo (**8**) as an inhibitor of platelet aggregation and as a stimulator of cyclic AMP accumulation. However, in contrast to 2-chloro-1-deazaAdo (**9**), which was the only 1-deaza analog showing slight A_{2A}AR-selectivity, the potency of 1-deazaNECA at A_1AR, A_{2B}AR, and A_3AR is diminished by a factor of about 5, whereas that at the A_{2A}AR subtype is about 60-fold lower than that of NECA. Hence, 1-deazaNECA proved to be a moderate A_{2A}AR agonist.

1.5 Agonist Radioligands

[^{3}H]NECA was introduced as a ligand for the A_2 receptor (K_d values of between 31 and 46 nM), but further studies demonstrated that it is a prototypical nonselective ligand (Gessi et al. 2000). It labels A_1AR, A_{2A}AR, and A_3AR with similar affinities, with a slight preference for the A_3AR subtype (Bruns et al. 1986). CGS 21680 was introduced as an A_2-selective agonist and it was also developed as a tritiated ligand (Jarvis et al. 1989), but (as reported above) this molecule is not an ideal tool for the characterization of A_{2A}ARs, particularly if differentiation from A_3AR is required. The tritiated compound displays a K_d value of 32 nM at the human A_{2A}AR and therefore shows a comparable potency to [^{3}H]NECA (Wan et al. 1990).

1.6 Partial Agonists

Recently, a series of 2,8-disubstituted Ado derivatives were synthesized and tested. Most of these compounds appeared to have A_{2A}AR affinities in the low micromolar or nanomolar range, and also displayed reduced intrinsic activities compared to the reference agonist CGS 21680 (**7b**); hence, they behaved as partial agonists (van Tilburg et al. 2003).

The introduction of 8-alkylamino substituents led to a reduction in A_{2A}AR affinity but also to an increase in selectivity versus the A_3AR subtype. In particular, the 8-methylamino and 8-propylamino derivatives of **17** (**38** and **39**, respectively, Fig. 4)

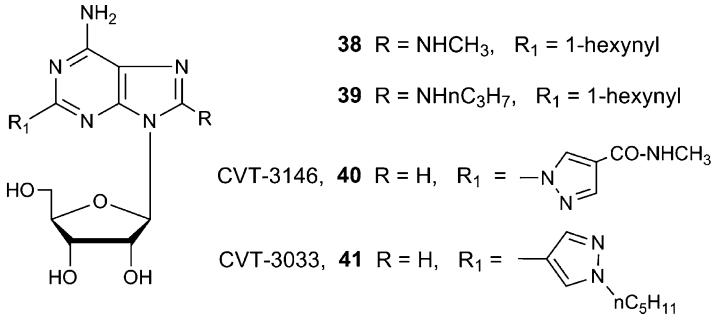

Fig. 4 A_{2A}AR partial agonists

showed K_i A_{2A}AR affinity values of 115 and 82 nM, respectively, and 49- and 26-fold selectivities for the A_{2A}AR versus the A_3AR.

Other Ado derivatives that were substituted at the 2 position with 1-pyrazolyl (Lexiscan, regadenoson, CVT-3146, **40**) or 4-pyrazolyl (CVT-3033, **41**) rings were found to be short-acting functionally selective coronary vasodilators with good potency, but they possessed low affinity for A_{2A}AR ($K_i = 1{,}122$ and 2,895 nM, respectively) (Zablocki et al. 2001). One of these, Lexiscan, appears to be a weak partial agonist in stimulating cAMP accumulation in PC12 cells but a full and potent agonist in inducing coronary vasodilation, a response that has a very large A_{2A}AR reserve (Gao et al. 2001; Eggbrecht and Gossl 2006; Gordi 2006).

Very recently, the US Food and Drug Administration (FDA) has approved injected Lexiscan for use as a pharmacologic stress agent in radionuclide myocardial perfusion imaging (MPI) (CVT 2008).

2 Adenosine A_{2A} Receptor Antagonists

In the last few years, A_{2A}AR antagonists have become attractive pharmacological tools due to their potential as novel drugs for the treatment of Parkinson's disease (PD) and restless legs syndrome, Alzheimer's disease, and their antidepressive and neuroprotective activities (Impagnatiello et al. 2000; Cacciari et al. 2003; Xu et al. 2005; Jacobson and Gao 2006; Moro et al. 2006; Schapira et al. 2006; Schwarzschild et al. 2006; Cristalli et al. 2007; Dall'Igna et al. 2007; Fuxe et al. 2007; Yu et al. 2008; Salamone et al. 2008). In addition, A_{2A}AR antagonists seem to protect against cellular death induced by ischemia, and may also be active as cognition enhancers, antiallergic agents, analgesics, positive inotropics, and even for the treatment of alcoholism and alcohol and cannabis abuse (Ledent et al. 1997; Richardson et al. 1997; Monopoli et al. 1998; Brambilla et al. 2003; Pedata et al. 2005; Melani et al. 2006; Ferré et al. 2007; Thorsell et al. 2007; Bilkei-Gorzo et al. 2008; Takahashi et al. 2008). A_{2A}ARs are expressed in high density in restricted areas of

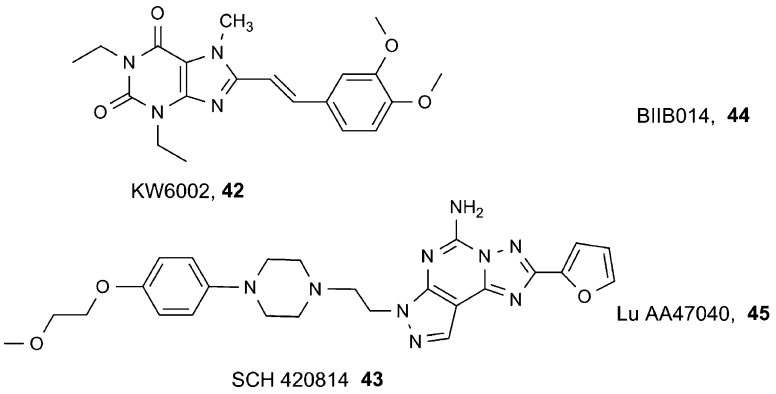

Fig. 5 A_{2A}AR antagonists in clinical trials

the brain, namely in the caudate-putamen (striatum), and there they are coexpressed with dopamine D_2 and cannabinoid CB_1 receptors (Carriba et al. 2007; Ferré et al. 2008). The restricted expression as well as the promising pharmacological potential of A_{2A}AR antagonists has led to extensive efforts to develop potent and selective A_{2A}AR antagonists (Yuzlenko and Kiec-Kononowicz 2006; Müller and Ferré 2007; Baraldi et al. 2008). Four different A_{2A}AR antagonists are currently being studied in clinical trials, istradefylline (KW-6002, **42**), preladenant (SCH-420814, **43**), BIIB014 (V2006, **44**), and Lu AA47040 (**45**). The structures of the latter two compounds have not been disclosed (Fig. 5).

Several heterocyclic classes of compounds have been studied as A_{2A}AR antagonists; these can generally be divided into xanthine and non-xanthine derivatives. The xanthine analogs represent the prototypical group of antagonists, and modifications of the xanthine scaffold resulted in a comprehensive collection of derivatives, among which several compounds showed distinct subtype selectivity. A second class of heterocyclic compounds can be envisaged as adenine-derived structures (Cacciari et al. 2003; Vu 2005; Moro et al. 2006; Müller and Ferré 2007). Very recently, other heterocyclic structures related to neither xanthine nor adenine derivatives have been described. These are based on lead structures identified by the screening of large compound libraries (Müller and Ferré 2007). The present review focuses on antagonists published in scientific articles. Thorough reviews on the patent literature have recently been published (Vu 2005; Müller and Ferré 2007).

2.1 Xanthine Derivatives

Years ago it was reported that caffeine was the "most widely consumed behaviorally active substance in the world" (Fredholm et al. 1999). In fact, the vast majority of people on our planet have enjoyed the CNS effects of the AR antagonist caffeine long before the physiological effects of Ado were discovered. Naturally occurring

xanthines like caffeine or theophylline generally have affinities at the micromolar level, with the highest affinity being at the A_{2A}AR, and this receptor subtype appears to be relevant to the activation caused by caffeine (Ledent et al. 1997; Svenningsson et al. 1997). Hence, the xanthine scaffold represented an important starting point for the development of antagonists of this family of receptors (Daly et al. 1991).

A large number of modifications at the 1, 3, 7 and 8 positions have been performed with the aim of obtaining potent and selective A_{2A}AR antagonists. The first xanthine derivative considered an A_{2A}AR antagonist was 3,7-dimethyl-1-propargylxanthine (DMPX, **46**, Fig. 6, Table 2), even though this compound proved to be poorly active (K_i rA_{2A} and hA_{2A} = 16 and 2 μM, respectively) and moderately selective against the A_1AR and A_{2B}AR subtypes (Daly et al. 1986, 1991). Nevertheless, this compound has been widely used in in vivo studies because of its good water solubility and bioavailability (Daly et al. 1986; Seale et al. 1988; Thorsell et al. 2007). Further studies on DMPX derivatives led to the 2-*O*-methyl-1-propargylxanthine derivative **47**, endowed with an affinity in the high nanomolar range (K_i A_{2A}AR = 105 nM) at the A_{2A}AR subtype and significant selectivity in comparison to the A_1AR (45-fold) (Müller and Stein 1996; Müller et al. 1998a).

Starting from these observations, a program to screen various 1,3,8-substituted xanthines led to the discovery of the first very potent and selective A_{2A}AR antagonists (Erickson et al. 1991; Jacobson et al. 1993a; Nonaka et al. 1994a; Müller and Stein 1996; Müller 2000b). In particular, 3-chlorostyrylcaffeine (CSC, **48**) showed

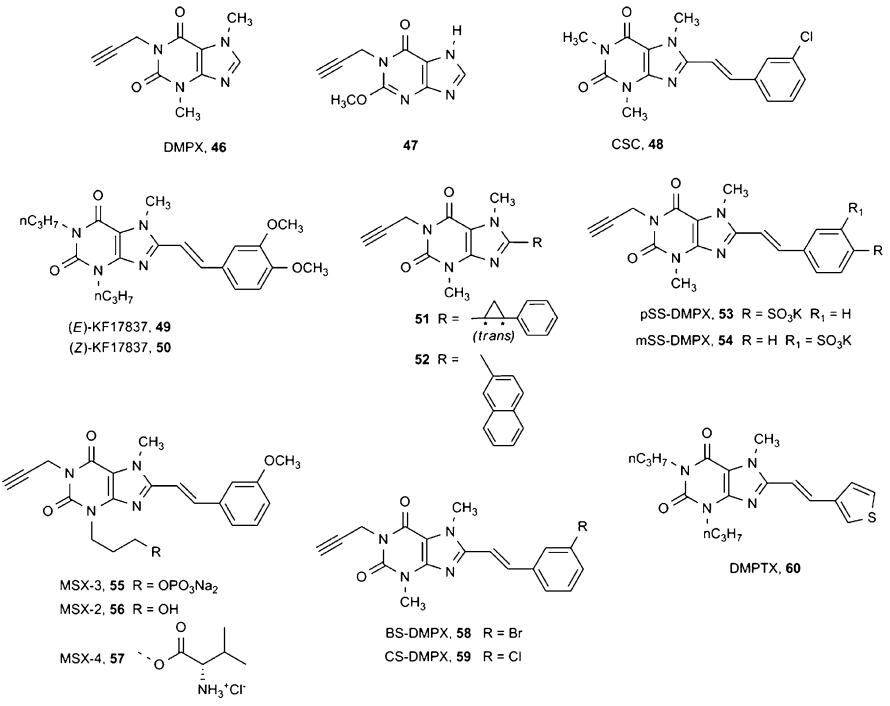

Fig. 6 A_{2A}AR antagonists: xanthines

Table 2 Affinities of AR antagonists in radioligand binding assays at A_1AR, $A_{2A}AR$ and A_3AR. For $A_{2B}AR$, radioligand binding assays values are reported where available; for some compounds, values are related to the effects on adenylate cyclase activity

Cpd	K_i (A_1AR)[a]	K_i ($A_{2A}AR$)[a]	K_i ($A_{2B}AR$)[a]	K_i (A_3AR)[a]
42	580 r	13 r	–	–
	2,830 h	36 h	1,800 h	>3,000 h
43	–	2.5 r	–	–
	>1000 h	1.1 h	>1,700 h	>1,000 h
46	45,000 r	16,000 r	2,500 m	–
	–	2,000 h	4,130 h	>10,000 h
47	4,700 r	105 r	–	–
48	28,000 r	54 r	–	–
49	62 r	1 r	–	–
50	>10,000 r	860 r	–	–
51	4,600 r	1,700 r	–	–
52	980 r	380 r	–	–
53	4,900 r	240 r	–	–
	–	–	–	>100,000 h
54	8,900r	300 r	–	–
	–	–	–	>100,000 h
56	900r	8 r	–	–
	2,500 h	5.0 h	–	>10,000 h
58	1,200 r	8.2 r	–	–
59	1,300 r	13 r	–	–
60	561 r	19 r	–	–
61	21 r	3.3 r	–	–
	4.4 h	0.43 h	25 h	85 h
62	270 r	21 r	–	–
63	3.3 r	1.2 r	–	–
64	121 r	2.3 r	–	–
	549 h	1.1 h	>10,000 h	>10,000 h
65	504 r	2.4 r	–	–
	350 h	1.2 h	>10,000 h	>10,000 h
66	444 r	1.7 r	–	–
	–	–	–	>10,000 h
67	741 r	0.94 r	–	–
	1,111 h	1.5 h	–	>10,000 h
68	1,815 r	0.048 r	–	–
	1,111 h	0.5 h	>10,000 h	>10,000 h
69	4,927 h	4.63 h	>10,000 h	>10,000 h
70	139 h	140 h	>10,000 h	>10,000 h
71	2,160 h	0.22 h	>10,000 h	>10,000 h
72	369 h	3.8 h	>10,000 h	>10,000 h
73	15 b	6.5 b	–	–
	–	–	–	>10,000 h
74	83 h	0.8 h	–	–
75	257 r	1.8 r	–	–
	774 h	1.6 h	28 h	743 h

(continued)

Table 2 (continued)

Cpd	K_i (A_1AR)[a]	K_i ($A_{2A}AR$)[a]	K_i ($A_{2B}AR$)[a]	K_i (A_3AR)[a]
76	1,270 p	14 p	–	–
77	320 r	1 r	–	–
78	100 r	1.1 r	–	–
79	208 h	1.4 h	865 h	476 h
80	12.5 r	1.2 r	–	–
	7.9 m	1.6 m	–	–
	9.0 h	1.8 h	>557 h	–
81	17 h	1.1 h	112 h	1,472 h
82	170 h	1.7 h	141 h	1,931h
83	24 h	3.7 h	380 h[b]	4,700 h
84	2,400 h	46 h	>30,000 h[b]	21,000 h
85	150 h	19 h	690 h[b]	3,100 h
86	23 h	1.7 h	569 h[b]	1,090 h
87	9.4 h	3.8 h	780 h[b]	17.6 h
88	5.8 h	2.2 h	521 h[b]	16 h
89	71.8 h	6.6 h	352 h	>10,000 h
90	–	26 r	–	–
	266 h	2.7 h	–	–
91	–	9.4 r	–	–
	60 h	0.4 h	–	–
94	–	90 r	–	–
	1,380 h	20 h	–	–

[a]Binding data from different species: rat (*r*), human (*h*), pig (*p*), bovine (*b*) or mouse (*m*) A_1AR, $A_{2A}AR$, $A_{2B}AR$, and A_3AR, expressed as K_i (nM)

[b]Effects on adenylate cyclase activity at the human (*h*) $A_{2B}AR$ expressed as K_i (nM)

high affinity at the $A_{2A}AR$ (54 nM) and high selectivity in comparison to the A_1AR subtype (560-fold) (Jacobson et al. 1993a). In addition, it is a relatively potent monoaminoxidase type B (MAO-B) inhibitor, which may contribute to its pharmacological effects in models of Parkinson's disease (Petzer et al. 2003; van den Berg et al. 2007). Another compound, (*E*)-1,3-dipropyl-8-(3,4-dimethoxystyryl)-7-methylxanthine ((*E*)-KF17837, **49**), proved to be potent in the nanomolar range at the $A_{2A}AR$ subtype (1 nM) and significantly selective in comparison to the A_1AR (62-fold) (Nonaka et al. 1994a). However, several problems have initially limited the use of these xanthine derivatives as pharmacological tools for studying the $A_{2A}AR$ subtype, in particular their low water solubility (Jackson et al. 1993) and the rapid photoisomerization that they undergo when exposed to daylight in dilute solution (Nonaka et al. 1993; Müller et al. 1998a). It should be noted that this isomerization process does not occur when styrylxanthines are administered orally as solid substances, but the phenomenon happens very rapidly during binding studies performed in buffer solution and in the presence of light (Müller et al. 1998a). In particular, after photoisomerization, (*E*)-KF17837 becomes a stable mixture of ca. 18% (*E*) and ca. 82% (*Z*, **50**) isomers, and the binding data change (K_i $A_{2A}AR$ = 7.9 nM, K_i A_1AR = 390 nM) (Nonaka et al. 1993). Another

problem associated with 8-styrylxanthine derivatives is their tendency to undergo light-induced dimerization ([2 + 2]-cycloaddition reaction) in the solid state, yielding weakly active cyclobutane derivatives (Hockemeyer et al. 2004).

To overcome this photoisomerization, the styryl moiety has been replaced with different functional groups (e.g., triple bond, cyclopropyl ring, **51**, a 2-naphthyl residue, **52**) (Müller et al. 1997c), or a tricyclic constrained structure (Kiec-Kononowicz et al. 2001; Drabczynska et al. 2003, 2004, 2006, 2007). In many cases, a significant loss of affinity was observed by such modifications. Substitution of the ethenyl group with an azo structure has also been performed. The compounds obtained retained selectivity but showed only moderate affinity (Müller et al. 1997b).

Different approaches have been utilized to improve the water solubility of styrylxanthines, such as the introduction of polar groups on the phenyl ring and the preparation of phosphate or amino-acid prodrugs. The introduction of a sulfonate group on the phenyl ring of the styryl moiety at the *para*- (**53**) or *meta*- (**54**) position led to water-soluble derivatives endowed with only high nanomolar affinity at the A_{2A}AR but retaining selectivity (Müller et al. 1998b). Tricyclic styryl-substituted imidazo[2,1-*i*]purin-5-one derivatives showed enhanced water-solubility but reduced A_{2A}AR affinity and selectivity (Müller et al. 2002). The prodrug approach has been much more successful. In fact, MSX-3 (**55**), which is the phosphate prodrug of MSX-2 (3-(3-hydroxypropyl)-8-(*m*-methoxystyryl)-1-propargylxanthine, **56**), is stable and highly soluble (15 mM) in aqueous solution but readily cleaved by phosphatases to liberate MSX-2, which showed a very high affinity (rat and human A_{2A}AR $K_i = 8$ and 5 nM, respectively) and selectivity for the A_{2A}AR (Sauer et al. 2000; Hockemeyer et al. 2004). Recently, an L-valine ester prodrug of MSX-2 has been described, named MSX-4 (**57**), which shows good water solubility as a hydrochloride as well as high stability in artificial gastric fluid and at physiological pH values, but is readily cleaved by esterases (Vollmann et al. 2008). It is expected that the L-amino acid ester prodrug can be absorbed via an active transport mechanism by L-amino acid carrier proteins.

All of these studies strongly suggest that the xanthine family should be reconsidered as A_{2A}AR antagonists. In fact, the antagonist KW-6002 (istradefylline: 1,3-diethyl-8-(3,4-dimethoxystyryl)-7-methylxanthine, **42**; human A_{2A}AR $K_i = 36$ nM) is already in Phase III clinical trials for the treatment of basal ganglia disorders such as Parkinson's disease (Knutsen and Weiss 2001; Weiss et al. 2003; Kalda et al. 2006). This compound showed a $(E)/(Z)$ stable equilibrium ratio of 19:81 with good affinity and selectivity but most importantly a very high anticataleptic activity (0.03 mg kg^{-1}, p.o.) in a mouse haloperidol model (Shimada et al. 1997).

Further modifications of all the positions of the xanthine nucleus were introduced and investigated. For example, the bioisosteric replacement of one of the alkenyl CH groups of the 8-styryl residue with nitrogen led to more potent and selective antagonists for the A_{2A}ARs, but the compounds were highly unstable in aqueous solution because of their imine (Schiff base) structure (Müller et al. 1997b). The introduction of a propargyl or an *n*-propyl residue at the 1 position in combination with the 8-styryl group seems to increase affinity at the A_{2A}AR subtypes

while retaining the selectivity. These studies led to the discovery of two compounds, named BS-DMPX (3,7-dimethyl-1-propargyl-8-(3-bromostyryl)xanthine, **58**) and CS-DMPX (3,7-dimethyl-1-propargyl-8-(3-chlorostyryl)xanthine, **59**), which could be considered lead compounds of this series (Müller et al. 1997a). Methyl substitution at the 3 and 7 positions appears to be desirable for achieving both affinity and selectivity at A_{2A}AR subtypes (Shamim et al. 1989; Erickson et al. 1991; Del Giudice et al. 1996). However, large substituents are also tolerated at the 3 position (Massip et al. 2006). The bioisosteric replacement of the phenyl ring with a thienyl moiety led to DPMTX ((*E*)-1,3-dipropyl-7-methyl-8-[2-(3-thienyl)ethenyl]xanthine, **60**) which showed high affinity and selectivity (Del Giudice et al. 1996). Regarding the substitutions at the 8 position, it has been demonstrated that an aromatic ring attached to an ethenyl group is essential for both affinity and selectivity at the A_{2A}AR (Erickson et al. 1991; Jacobson et al. 1993b; Del Giudice et al. 1996). 8-Styryl-9-deazaxanthine derivatives were nearly as potent as the corresponding xanthine derivatives at A_{2A}ARs (Grahner et al. 1994).

2.2 Adenine Derivatives and Related Heterocyclic Compounds

Due to the initial problems with xanthine derivatives, such as poor water solubility and photoisomerization, many scientists searched for alternative heterocyclic derivatives for use as lead compounds. The first promising A_{2A}AR antagonists with a non-xanthine structure were CGS 15943 (9-chloro-2-(2-furanyl)-[1,2,4]triazolo[1,5-*c*]quinazolin-5-amine, **61**, Fig. 7) (Williams et al. 1987; Francis et al. 1988; Kim et al. 1996; Baraldi et al. 2000) and CP-66713 (4-amino-8-chloro-1-phenyl-[1,2,4]triazolo[4,3-*a*]quinoxaline, **62**) (Sarges et al. 1990), compounds that were not very A_{2A}AR selective but were important as starting points for developing new non-xanthine structures as A_{2A}AR antagonists. All of these structures are reminiscent of the nucleobase adenine, a partial structure of Ado.

A few years later, the synthesis of 8FB-PTP (5-amino-8-(4-fluorobenzyl)-2-(2-furyl)pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine, **63**), a bioisoster of **61**, was reported (Gatta et al. 1993; Dionisotti et al. 1994). Here, the phenyl ring was replaced by a substituted pyrazole nucleus; this compound showed good affinity but no selectivity for A_{2A}ARs. Structure–activity relationship studies on the pyrazolo-triazolo-pyrimidine nucleus were carried out with the aim of determining the important features for high A_{2A}AR potency and selectivity, focusing on the presence of a free amino group at the 5 position and a furan ring at the triazole ring. The role of the substituents on the pyrazole ring was explored. Results showed that the substituents at the 7 and 8 positions were influential. In particular, substitutions at the 7 position gave selective compounds, whereas the same substitution at the 8 position resulted in potent but nonselective derivatives (Baraldi et al. 1994, 1996a, 2001). Furthermore, replacement of the pyrazole ring with a triazole led to affinity retention but also a complete loss of selectivity (Baraldi et al. 1996b). Recently, the pyrazole was replaced by an imidazole ring with great success (Silverman et al. 2007).

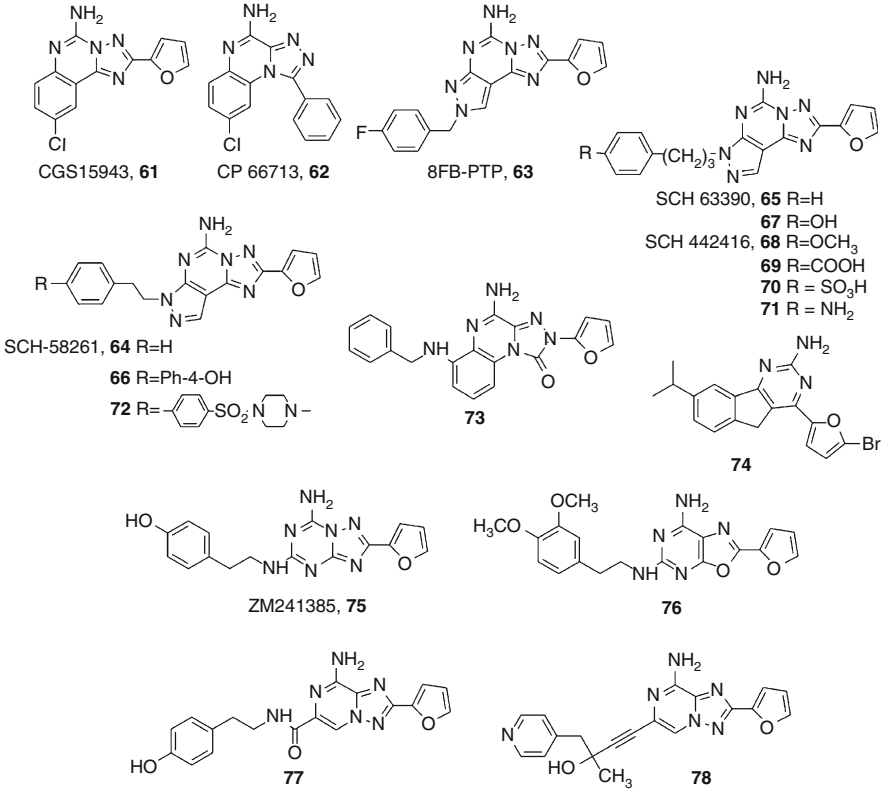

Fig. 7 A_{2A}AR antagonists: nonxanthine derivatives

Two selected compounds named SCH-58261 (5-amino-7-(2-phenylethyl)-2-(2-furyl)pyrazolo[4,3-*e*]1,2,4-triazolo[1,5-*c*]pyrimidine, **64**, Fig. 7) and SCH-63390 (5-amino-7-(3-phenylpropyl)-2-(2-furyl)pyrazolo[4,3-*e*]1,2,4-triazolo[1,5-*c*]pyrimidine, **65**) proved to be very potent and selective A_{2A}AR antagonists at both rat and human receptors (Baraldi et al. 1996a, b, 1998b; Zocchi et al. 1996a).

Problems with low water solubility affected even these non-xanthine compounds, and the poor bioavailability limited their use as pharmacological tools. To improve the hydrophilicities of these derivatives, polar functions were introduced on the phenyl ring located on the side chain of the pyrazole nucleus. The presence of a hydroxyl group at the phenyl ring in the *para* positions of compounds **64** and **65** led to compounds **66** (5-amino-7-[4-(4-hydroxyphenyl)ethyl]-2-(2-furyl)pyrazolo[4,3-*e*]1,2,4-triazolo[1,5-*c*]pyrimidine) and **67** (5-amino-7-[3-(4-hydroxyphenyl)propyl]-2-(2-furyl)pyrazolo[4,3-*e*]1,2,4-triazolo[1,5-*c*]pyrimidine), which showed slightly enhanced hydrophilicity and also a significant increase in both affinity and selectivity (Baraldi et al. 1998b). To understand the nature of the hydrogen bond, the phenolic hydroxy group was substituted with a methoxy group (thus reducing compound hydrophilicity), leading to

SCH-442416 (5-amino-7-[3-(4-methoxyphenyl)propyl]-2-(2-furyl)pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine, **68**). This derivative showed an increased potency and remarkable selectivity for the A_{2A}AR, and so it has been used as a tool for PET studies in its ^{11}C-labeled form (Todde et al. 2000). The introduction of oxygen-containing groups on the phenyl ring did not confer sufficient water solubility on the derivative, so it appeared necessary to introduce different functionalities to address this problem. Several polar functions such as carboxylic (**69**) and sulfonic acid (**70**) functions were introduced for this purpose and, as expected, an increased solubility was observed, especially in the case of the sulfonate. Unfortunately, a great loss of affinity and selectivity was observed at the same time. The introduction of an amino group at the *para* position of the phenyl ring gave compound **71** ($K_i = 0.22$ nM, $hA_1AR/hA_{2A}AR = 9820$), which yielded the best results in terms of affinity and selectivity, without improving the water solubility. Sulfonamido derivatives seem to exhibit a good balance between solubility and affinity (**72**) (Baraldi et al. 2002). Structure–activity relationships for this group of compounds indicated that the tricyclic structure of the pyrazolo-triazolo-pyrimidine, the presence of the furan ring, the exocyclic 5-amino group, and the arylalkyl substituent on the nitrogen at the 7 position are probably crucial to their affinities and selectivities for the A_{2A}AR subtype.

A recent series of pyrazolo-triazolo-pyrimidine derivatives was obtained by modifying the phenylethyl substituent of **64** with substituted phenylpiperazinethyl groups (Neustadt et al. 2007). Introduction of fluorine atoms into the phenyl ring enhanced the affinity to subnanomolar values and the compounds displayed potent peroral activity, but their solubility still remained poor. Further introduction of ether substituents led to derivatives with high affinities and selectivities for A_{2A}ARs and improved water solubilities. In particular, one of these compounds (SCH-420814, preladenant, **43**) exhibited high affinities for both rat and human A_{2A}ARs, with K_i values of 2.5 and 1.1 nM, respectively. In addition, the compound is very selective for human A_{2A}ARs over A_1AR, A_{2B}AR, and A_3AR. Interestingly, the compound did not show significant binding against a panel of 59 unrelated receptors, enzymes, and ion channels. preladenant is now in Phase II clinical trials for dyskinesia in Parkinson's disease (Neustadt et al. 2007). Recently, the pyrazole moiety in these tricyclic derivatives was replaced by an imidazole ring, yielding 3*H*-[1,2,4]triazolo[5,1-*i*]purin-5-amine derivatives. The isomer of SCH-420814 displayed promising in vitro and in vivo profiles (Silverman et al. 2007).

The triazoloquinoxaline (Colotta et al. 1999, 2000, 2003) and the indenopyrimidine (Matasi et al. 2005) series possess promising features as A_{2A}AR antagonists. The triazoloquinoxaline nucleus seems to be very sensitive to any kind of variation and modification: alkylation of the amino group, replacement of the amino group by a carbonyl function, and substitution on the phenyl ring all reduced A_{2A}AR affinity. In this class, only compound **73** (4-amino-6-benzylamino-1,2-dihydro-2-1,2,4-triazolo[4,3-*a*]quinoxalin-1-one) showed a favorable binding profile (Colotta et al. 1999, 2000, 2003). In contrast, the indenopyrimidine derivatives are very promising, and the derivative **74** shows affinity in the nanomolar range and good selectivity against the A_1AR subtype. It must be underlined that

binding data at A_{2B}AR and A_3AR are lacking, so it is not possible to fully assess this compound with regard to potentially being an ideal A_{2A}AR antagonist (Matasi et al. 2005). Anyway, these structures showed several problems, such as poor water solubility and (most importantly) complex and difficult synthetic accessibility.

Therefore, researchers focused their attention on simplified analogs like bicyclic systems, and the Zeneca group reported on a compound named ZM241385 (4-[2-[[7-amino-2-(2-furyl)[1,2,4]-triazolo[2,3-*a*][1,3,5]triazin-5-yl]amino]ethyl]phenol, **75**), which proved to be one of the most potent A_{2A}AR antagonists ever reported, and which had a favorable water solubility (Caulkett et al. 1995; Poucher et al. 1995; de Zwart et al. 1999b; Weiss et al. 2003; Moro et al. 2006). This compound also binds with high affinity to human A_{2B}AR, and its tritiated form is actually used in radioligand binding studies for this receptor subtype (Ji and Jacobson 1999).

In the last few years, Biogen Idec Inc. has developed a large series of triazolotriazine and triazolopyrimidine analogs bearing various substituents, and a few compounds have shown high potency and selectivity for the A_{2A}AR as compared with the A_1AR (Peng et al. 2004; Vu et al. 2004a, b, c, 2005; Yang et al. 2007). However, the lack of binding data for the A_{2B}AR and A_3AR prevents any comparison of the derivatives with other fully characterized compounds. Interestingly, some of these derivatives showed good oral efficacy in a rodent catalepsy model of Parkinson's disease (Peng et al. 2004; Vu et al. 2004a, b, c, 2005).

Among synthesized isosters of the triazolotriazine nucleus, some oxazolopyrimidines (**76**) (Holschbach et al. 2006) and triazolopyrazines (**77**, **78**) should be mentioned (Dowling et al. 2005; Yao et al. 2005). All of these compounds showed good A_{2A}AR potency and selectivity against the A_1AR, but full characterization at the four AR subtypes has not been completed. Some pyrazolopyrimidines have also been reported (Chebib et al. 2000), but in all cases the affinities and/or selectivities were only moderate.

A thieno[3,2-*d*]pyrimidine, VER-6623 (**79**, Fig. 8), showed a high affinity for A_{2A}AR ($K_i = 1.4$ nM), but it also had low or poor oral bioavailability (Weiss et al. 2003; Yang et al. 2007). Very recently, a potent A_1AR and A_{2A}AR dual antagonist, 5-[5-amino-3-(4-fluorophenyl)pyrazin-2-yl]-1-isopropylpyridine-2(1*H*)-one (ASP5854, **80**), was synthesized and tested in models of Parkinson's disease and cognition (Mihara et al. 2007). The binding affinities of **80** for human A_1AR and A_{2A}AR were 9.0 and 1.8 nM, respectively. This compound also showed antagonistic action on A_1AR and A_{2A}AR agonist-induced increases in intracellular Ca^{2+} concentration, and in vivo tests showed that this molecule improves motor impairment, is neuroprotective via A_{2A}AR antagonism, and also enhances cognitive function through A_1AR antagonism.

The development of A_{2A}AR antagonists also made use of non-xanthine imidazopyrimidine (purine)-type structures, and some of these derivatives (recently reported by several groups) seem to be very promising. Some compounds, like VER-6947 (**81**) and VER-7835 (**82**), show human A_{2A}AR K_i values of around 1 nM (Weiss et al. 2003), while some 6-(2-furanyl)-9*H*-purin-2-amino derivatives

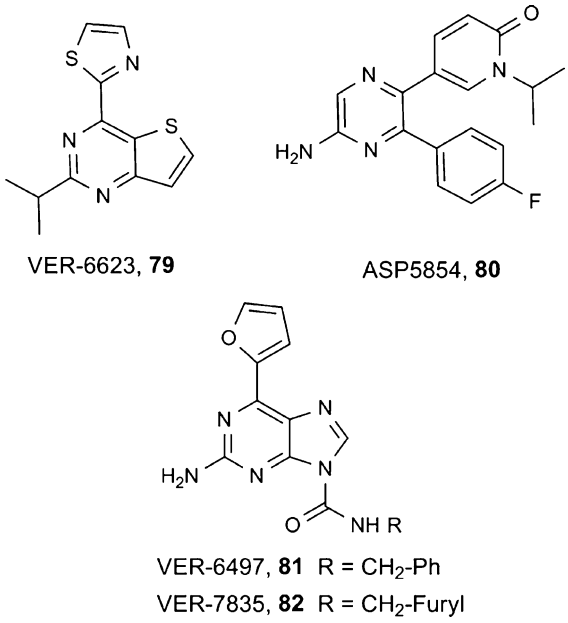

Fig. 8 A_{2A}AR antagonists: nonxanthine derivatives (2)

are endowed with A_{2A}AR affinities in the low nanomolar range and a good level of selectivity against the other receptor subtypes (Kiselgof et al. 2005).

In the late 1990s, Cristalli and coworkers reported the synthesis of a number of 9-ethylpurines bearing various substituents in the 2, 6 or 8 positions (Camaioni et al. 1998). 9-Ethyladenine showed micromolar affinities at the human A_1AR and A_{2A}AR subtypes, but the introduction of a bromine atom in the 8 position led to an enhancement of the binding affinity at all AR subtypes. Recently, rat model studies on the derivatives ANR-152 (9-ethyl-8-furyl-adenine, **83**, Fig. 9) and ANR-94 (8-ethoxy-9-ethyl-adenine, **84**) were reported. It should be noted that **83** was more potent at A_{2A}AR than at A_1AR, with poor selectivity against A_1AR, while the replacement of furan ring with an ethoxy function (**84**) (Klotz et al. 2003) led to a decrease in affinity but a significant increase in selectivity. Study results showed that both of these derivatives are able to ameliorate motor deficits in rat models of Parkinson's disease (Pinna et al. 2005).

The 2 and 8 positions of adenine were further explored through the introduction of alkynyl chains, and while the 2-alkynyl derivatives possessed good affinity and were slightly selective for the human A_{2A}AR, the affinities of the 8-alkynyl derivatives at the human A_1AR, A_{2A}AR, and A_{2B}AR proved to be lower than those of the corresponding 2-alkynyl derivatives, with improved binding data for the human A_3AR subtype (Volpini et al. 2005). The observation that the introduction at the 2 position of phenylethylamino or phenethoxy groups resulted in compounds with increased A_{2A}AR affinity (Camaioni et al. 1998) led to the synthesis of 9-ethyladenine derivatives substituted at the 2 position with phenylalkylamino

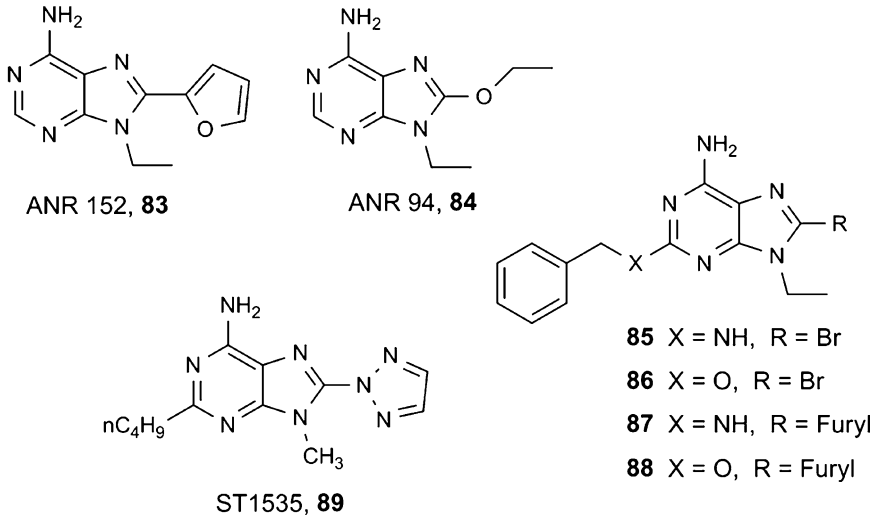

Fig. 9 A_{2A}AR antagonists: adenine derivatives

and phenylalkoxy groups and bearing a bromine atom in the 8 position (**85** and **86**, respectively) (Lambertucci et al. 2007b). This series was synthesized and tested in binding affinity assays at human ARs, and the new compounds showed good affinity and selectivity at A_{2A}AR. In particular, the introduction of a bromine atom at the 8 position increased the affinity of these compounds, leading to ligands with K_i values in the nanomolar range. Further substitution of the bromine atom of **85** and **86** with a 2-furyl group led to compounds **87** and **88** respectively, which maintained the A_{2A}AR affinity at low nanomolar levels, but with reduced selectivity versus A_1AR and A_3AR (Cristalli et al., unpublished results).

A new series of 2,6-substituted 9-propyladenines has been recently synthesized and reported (Lambertucci et al. 2007a). Results show that the introduction of bulky chains at the N^6 position of 9-propyladenine significantly increases binding affinities at the human A_1AR and A_3AR, while the presence of a chlorine atom at the 2 position results in unequivocal effects depending on the receptor subtype and/or on the substituent present in the N^6 position. In any case, the presence in the 2 position of a chlorine atom favors the interaction with the A_{2A}AR subtype. Among other adenine derivatives reported as A_{2A}AR antagonists, ST1535 (2-*n*-butyl-9-methyl-8-[1,2,3]triazol-2-yl-9*H*-purin-6-ylamine, **89**, Fig. 9) (Minetti et al. 2005) proved to be quite potent but barely selective against A_1AR. Nevertheless, this compound was selected for in vivo studies and was shown to induce a dose-related increase in locomotor activity.

Slee and colleagues developed a series of aminopyrimidine derivatives that were acylated at the amino group (2-amino-*N*-pyrimidin-4-yl acetamides) and showed high water solubility (Slee et al. 2008c). The lead compound **90** was optimized with regard to replacement of the metabolically problematic furan ring (Slee et al. 2008a), reducing its effects on hERG channels (Slee et al. 2008b); it showed high affinity at

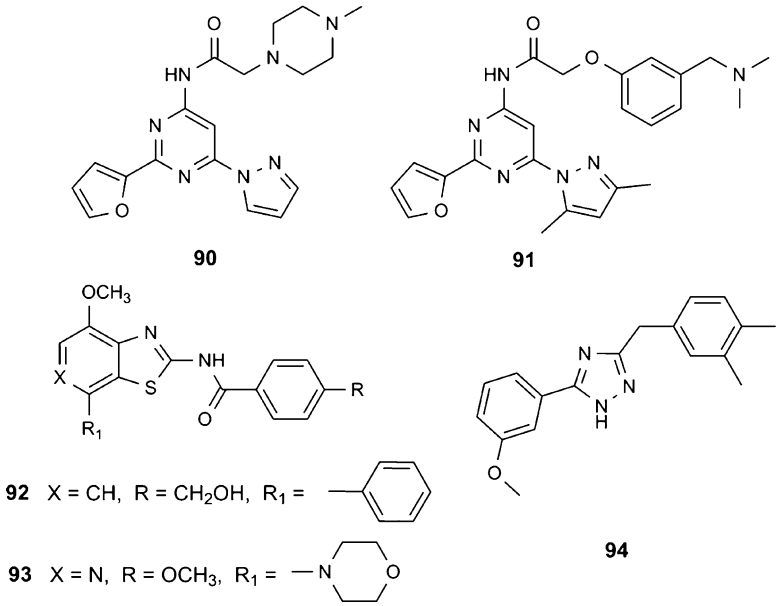

Fig. 10 Various heterocyclic compounds

both human and rodent A_{2A}ARs, as well as A_{2A}AR selectivity (Zhang et al. 2008) and efficacy in rodent catalepsy models after peroral application, yielding **91** as a new lead structure (Fig. 10).

2.3 Heterocyclic Compounds Unrelated to Adenine or Xanthine

Simplified heterocyclic compounds, such as benzothiazole (Flhor and Riemer 2006) and 1,2,4-triazole (Alanine et al. 2004) derivatives (**92**–**94**), have been reported by the Roche group. These derivatives have been identified by high-throughput screening of compound libraries and are structurally related to neither xanthine nor to adenine derivatives. These compounds appear to be promising new lead compounds for the development of A_{2A}AR antagonists for therapeutic applications (Müller and Ferré 2007).

2.4 Antagonist Radioligands

A number of A_{2A}AR antagonist radioligands have been developed, and again they can be divided into xanthine and non-xanthine derivatives. Among the xanthine derivatives, three biotin conjugates of 1,3-dipropyl-8-phenylxanthine were

reported in 1985 as being able to bind competitively to the ARs, but only in the absence of avidin. Results were interpreted in terms of the possible reorientation of the ligands at the receptor binding site (Jacobson et al. 1985). A few years later, a study on a radiolabeled amine-functionalized derivative of 1,3-dipropyl-8-phenylxanthine ([^{3}H]XAC) as an A_2 antagonist at human platelets was published. This molecule exhibited a K_d value at the nanomolar level, and it was reported as the first antagonist radioligand with high affinity at A_2ARs (Jacobson et al. 1986; Ukena et al. 1986). In the mid 1990s, the tritiated derivative of KF17837S (the equilibrium mixture of (*E*)- and (*Z*)-KF17837 isomers) was shown to bind to rat striatal membranes in a saturable and reversible way, with K_d values at low nanomolar concentrations (Nonaka et al. 1994b). In another study, ^{11}C-labeled (*E*)-KF17837 was synthesized and tested, and it was proposed as a potential positron emission tomography (PET) radioligand for mapping the A_{2A}ARs in the heart and the brain (Ishiwata et al. 1996, 1997). Further studies on radiolabeled xanthine derivatives as A_{2A}AR radioligands were carried out by preparing and testing an ^{11}C-labeled selective A_{2A}AR antagonist, (*E*)-8-(3-chlorostyryl)-1,3-dimethyl-7-[^{11}C]methylxanthine [^{11}C]CSC). This molecule was shown to accumulate in the striatum, and PET studies on rabbits showed a fast brain uptake of [^{11}C]CSC, reaching a maximum in less than 2 min (Marian et al. 1999). Few years later, iodinated and brominated styrylxanthine derivatives labeled with ^{11}C were tested as in vivo probes (Ishiwata et al. 2000c). [7-Methyl-^{11}C]-(*E*)-3,7-dimethyl-8-(3-iodostyryl)-1-propargylxanthine ([^{11}C]IS-DMPX) and [7-methyl-^{11}C]-(*E*)-8-(3-bromostyryl)-3,7-dimethyl-1-propargylxanthine ([^{11}C]BS-DMPX) showed K_i affinities of 8.9 and 7.7 nM respectively, and high $A_{2A}AR/A_1AR$ selectivity values. Unfortunately, biological studies proved that the two ligands were only slightly concentrated in the striatum, and that the two compounds were not suitable as in vivo ligands because of low selectivity for the striatal A_{2A}ARs and a high nonspecific binding (Ishiwata et al. 2000c). Another A_{2A}AR antagonist radioligand was prepared, [^{3}H]3-(3-hydroxypropyl)-7-methyl-8-(*m*-methoxystyryl)-1-propargylxanthine ([^{3}H]MSX-2). This molecule showed high affinity (K_d = 8.0 nM) for A_{2A}AR, with saturable and reversible binding, and also a selectivity of at least two orders of magnitude versus all other AR subtypes (Müller et al. 2000). A very interesting xanthine derivative that acts as A_{2A}AR radioligand was found in [^{11}C]KF18446 ([7-methyl-^{11}C]-(*E*)-8-(3,4,5-trimethoxystyryl)-1,3,7-trimethylxanthine, also named (^{11}C)TMSX) (Ishiwata et al. 2000a, b, 2002, 2003a, b). Ex vivo autoradiography for this molecule showed a high striatal uptake and a high uptake ratio of the striatum in comparison to other brain regions; [^{11}C]KF18446 was therefore proposed as a suitable radioligand for mapping A_{2A}ARs of the brain by PET (Mishina et al. 2007). In 2001, the synthesis and the testing of [^{11}C]KW-6002 as a PET ligand was reported. This molecule showed high retention in the striatum, but it also bound to extrastriatal regions, so its potential as a PET ligand appeared to require further investigation (Hirani et al. 2001).

Among nonxanthine derivatives, in 1995 the synthesis of [^{125}I]-4-(2-[[7-amino-(2-furyl)[1,2,4]-triazolo[2,3-*a*][1,3,5]triazin-5-yl]amino]ethyl)phenol ([^{125}I]ZM241

385) and its characterization as a radioligand in A_{2A}AR-expressing membranes was reported (Palmer et al. 1995). This molecule proved to be a highly selective antagonist radioligand for studying A_{2A}ARs within some species. [^{3}H]ZM241385 showed A_{2A}AR affinity at subnanomolar levels (Alexander and Millns 2001; DeMet and Chicz-DeMet 2002; Kelly et al. 2004; Uustare et al. 2005) and, as reported above, it later also proved to be a high-affinity ligand for A_{2B}AR receptors, and is actually used in radioligand binding studies of this receptor subtype (Ji and Jacobson 1999). Another important A_{2A}AR antagonist radioligand was obtained with [^{3}H]SCH-58261, which showed a K_d value of about 1 nM (Zocchi et al. 1996b). Biological results showed that this compound directly labels striatal A_{2A}ARs in vivo, and it could be an excellent tool for studying A_{2A}AR brain distribution and its occupancy of various antagonists. Additional studies suggested that [^{3}H]SCH-58261 is a useful tool for autoradiography studies, and indicated that it was the first available radioligand for the characterization of the A_{2A}AR subtype in platelets (Dionisotti et al. 1996, 1997; Zocchi et al. 1996b; Fredholm et al. 1998; El Yacoubi et al. 2001).

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