Biochimica et Biophysica Acta 1808 (2011) 1290–1308

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamem

Review

Recent developments in adenosine receptor ligands and their potential as novel drugs ☆

Christa E. Müller [a,*], Kenneth A. Jacobson [b]

[a] PharmaCenter Bonn, Pharmaceutical Institute, Pharmaceutical Chemistry I, University of Bonn, An der Immenburg 4, D-53121 Bonn, Germany
[b] Molecular Recognition Section, Laboratory of Bioorganic Chemistry, National Institute of Diabetes & Digestive & Kidney Diseases, National Institutes of Health, Bldg. 8A, Rm. B1A-19, Bethesda, MD 20892-0810, USA

ARTICLE INFO

Article history:
Received 12 July 2010
Received in revised form 14 December 2010
Accepted 15 December 2010
Available online 23 December 2010

Keywords:
Adenosine receptor
Agonist
Antagonist
Clinical trial
Medicinal chemistry
G protein-coupled receptor

ABSTRACT

Medicinal chemical approaches have been applied to all four of the adenosine receptor (AR) subtypes (A_1, A_{2A}, A_{2B}, and A_3) to create selective agonists and antagonists for each. The most recent class of selective AR ligands to be reported is the class of A_{2B}AR agonists. The availability of these selective ligands has facilitated research on therapeutic applications of modulating the ARs and in some cases has provided clinical candidates. Prodrug approaches have been developed which improve the bioavailability of the drugs, reduce side-effects, and/or may lead to site-selective effects. The A_{2A} agonist regadenoson (Lexiscan®), a diagnostic drug for myocardial perfusion imaging, is the first selective AR agonist to be approved. Other selective agonists and antagonists are or were undergoing clinical trials for a broad range of indications, including capadenoson and tecadenoson (A_1 agonists) for atrial fibrillation, or paroxysmal supraventricular tachycardia, respectively, apadenoson and binodenoson (A_{2A} agonists) for myocardial perfusion imaging, preladenant (A_{2A} antagonist) for the treatment of Parkinson's disease, and CF101 and CF102 (A_3 agonists) for inflammatory diseases and cancer, respectively. This article is part of a Special Issue entitled: "Adenosine Receptors".

Contents

☆ This article is part of a Special Issue entitled: "Adenosine Receptors".

* Corresponding author. Pharmazeutisches Institut, Pharmazeutische Chemie I, An der Immenburg 4, D-53121 Bonn, Germany. Tel.: +49 228 73 2301; fax: +49 228 73 2567.
E-mail address: christa.mueller@uni-bonn.de (C.E. Müller).

0005-2736/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbamem.2010.12.017

1. Introduction

Extracellular adenosine acts on a family of four cell surface receptors termed adenosine receptors (ARs) of which there exist four subtypes: A_1, A_{2A}, A_{2B}, and A_3 [1,2]. The ARs are G protein-coupled receptors (GPCRs) and consist of a single polypeptide chain that transverses the membrane from the extracellular side beginning at the N terminus to form seven transmembrane helices (TMs). The A_1 and A_3 receptors preferentially couple to G_i protein to inhibit adenylate cyclase and consequently the production of cyclic AMP (cAMP), and the A_{2A} and A_{2B} subtypes stimulate the production of cAMP by coupling to G_s or G_o. These two subtype pairs also share higher sequence identity: the human A_1 and A_3ARs are 49% identical, and the human A_{2A} and A_{2B}ARs are 59% identical.

The human A_{2A}AR became the first non-rhodopsin, non-adrenergic GPCR for which an X-ray crystallographic structure was reported [3]. The availability of this physically determined structure has aided in recent drug discovery efforts [4,5], as did theoretical homology models previously. The initial structure of the A_{2A}AR contained ZM241385 (**53**), only one of the many known potent antagonists of nanomolar affinity. There is now an effort to crystallize the receptor with other ligands and to crystallize other AR subtypes. Another structural issue to be considered in drug discovery is the phenomenon of GPCR dimerization, which can have a major effect on the pharmacological behavior. The ARs have been proposed to participate in both homo- and heterodimerization or even oligomerization [6,7]. For example, a well-established $A_{2A}AR/D_2$ dopamine receptor heterodimer occurs in the striatum and is the target of drug discovery for antagonists to treat Parkinson's disease [8–10].

The effects of activation of ARs tend to be cytoprotective in many organs and tissues under a wide variety of physiological conditions. The levels of extracellular adenosine can rise substantially in response to stress, such as hypoxic stress, and the resultant activation of ARs acts to adapt to the stress [1,2]. Extracellular adenosine concentrations may rise as a result of the release of the breakdown of extracellular ATP or from intracellular sources, which leads to the activation of ARs in the vicinity. These protective responses may take the form of decreased energy demand (e.g. bradycardia), increased energy supply (e.g. vasodilation or angiogenesis), ischemic preconditioning (e.g. in the heart or brain), inhibition of the release of excitotoxic neurotransmitters, suppression of cytokine-induced apoptosis, or reduced inflammatory response [1,2].

Medicinal chemical approaches have been applied to all four of the AR subtypes to create selective agonists and antagonists for each (see Figs. 1–9 and Tables 1–3). The most recent class of selective AR ligands to be reported is the class of A_{2B}AR agonists [11–13]. The availability of these selective ligands has facilitated research on therapeutic applications of modulating the ARs and in some cases has provided clinical candidates. It must be kept in mind that there is a marked species dependency of ligand affinity at the ARs, and that the same ligand (especially antagonists of the A_3AR) could be selective for a given subtype in one species (e.g. human) and lose or reverse that selectivity in another species (e.g. rat) [14,15,17–20]. Therefore, caution must be used when characterizing new ligands and when using them in pharmacological experiments. In addition to receptor subtype selectivity, major considerations in the design of new ligands have been bioavailability and metabolic stability.

Synthetic adenosine agonists are under development as therapeutic agents. The half-life of adenosine in circulation is very short (~1 s), due to the action of enzymes that convert it to inosine (adenosine deaminase) or phosporylate it to 5′-AMP (adenosine kinase), or due to its uptake through nucleoside transporters (such as the equilibrative transporter ENT1) [1,2,21]. Therefore, analogues of adenosine for selective activation of ARs tend to prevent these processes and thereby lengthen the half-life. For example, the A_3-selective agonist IB-MECA (**29**) has a half-life of 8–9 h in man [22]. Adenosine itself is in use as an AR agonist for the treatment of paroxysmal supraventricular tachycardia (through the A_1 receptor) and in radionuclide myocardial perfusion imaging (through the A_{2A} receptor). For those applications, the short half-life of adenosine is advantageous. There are many selective and potent synthetic AR agonists that have been introduced as research tools and for consideration to be used in humans. So far, only one synthetic adenosine agonist (A_{2A}AR agonist regadenoson, **19**, Lexiscan™) is in clinical use, and that, so far, is for a diagnostic purpose rather than therapeutic use. One major consideration in the development of AR agonists is that desensitization of the receptor can occur after agonist binding, resulting in downregulation of the receptor. Thus, AR responses can desensitize rapidly, typically on the scale of less than one hour [23].

Synthetic adenosine antagonists have also been explored for potential therapeutic applications. Various early analogues of the xanthines, which greatly increased the AR subtype-selectivity over the naturally occurring alkylxanthines, tended to be hydrophobic and poorly water-soluble and consequently of low bioavailability [24–26]. More recently introduced AR antagonists and prodrug approaches have overcome some of these issues [e.g. 25–28].

The introduction of numerous radioligands for the ARs has aided in the drug discovery process. Thus, the primary screen of newly synthesized compounds in many AR drug discovery efforts has consisted of convenient radioligand binding assays [24]. Furthermore, both agonist and antagonist ligands containing positron-emitting radioisotopes have been introduced for 3-dimensional in vivo imaging of the receptors [29]. Such ligands for positron emission tomography (PET) might prove useful for diagnostic as well as research purposes. Now fluorescent ligands have been introduced for characterization of the ARs [30–32]. Some of these spectroscopic probes are suitable for compound screening and avoid the use of radioisotopes.

2. Adenosine receptor agonists

The structure–activity relationship (SAR) of adenosine derivatives as AR agonists has been exhaustively probed. Nearly all of the known AR agonists are derivatives of purine nucleosides, either adenosine (**1**) or xanthosine (Figs. 1–4 and Table 1). Therefore, in screens of structurally diverse chemical libraries, most of the hits will typically provide antagonists, rather than agonists. One exception to that generalization is the class of 2-aminopyridine-3,5-dicarbonitrile derivatives that act as agonists at ARs with varied degrees of subtype selectivity [33–35].

2.1. A_1-selective agonists

The SAR of adenosine ligands at the A_1AR was recently reviewed [36]. The earliest synthetic analogues of adenosine, such as N^6-[(*R*)-phenylisopropyl]adenosine (**2**, *R*-PIA), to be characterized at the ARs tended to be selective for the A_1AR (Fig. 1). In general, substitution of adenosine at the N^6-position with a wide range of alkyl, cycloalkyl, and arylalkyl groups increases selectivity for the A_1AR. In addition, any modification at the N^6-position precludes the action of adenosine deaminase, which rapidly degrades adenosine itself, in vivo.

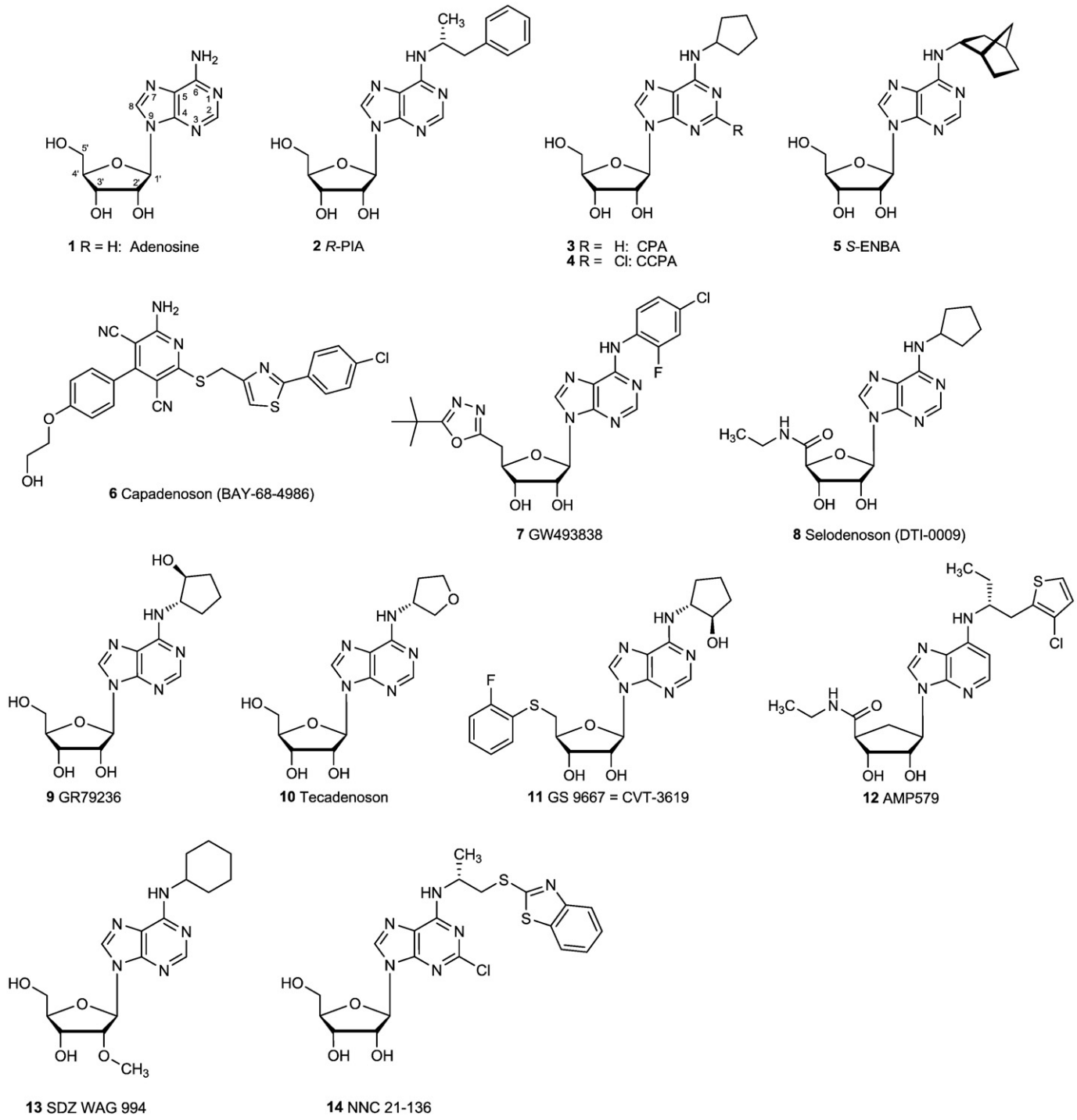

Fig. 1. A_1 adenosine receptor agonists.

N^6-Cycloalkyl substitution has been the most successful and general means of achieving selectivity for the A_1AR. N^6-Cyclopentyladenosine (**3**, CPA) and its 2-chloro analogue (**4**, CCPA) are among the most potent and selective A_1AR in wide use as pharmacological agents. As with many other N^6-substituted adenosine analogues, these two derivatives display considerable affinity at the A_3AR. In fact, CCPA was shown to act as an antagonist of the human A_3AR with a K_i value of 35 nM [37]. It was noted that the bicyclic analogue *S*-ENBA (**5**) has subnanomolar affinity at the A_1AR and has less residual affinity than CPA (**3**) or CCPA (**4**) for other AR subtypes [19]. Bayer Co. (Germany) discovered 2-amino-3,5-dicyanopyridine derivatives, e.g. capadenoson (**6**), as non-nucleoside-derived adenosine receptor agonists [33,36]. Besides **6** several A_1-selective adenosine derivatives, including GW493838 (**7**), selodenoson (**8**), GR79236 (**9**), tecadenoson (**10**), and CVT-3619 (GS9667, **11**) have been evaluated in clinical trials for various indications (see below).

2.2. A_{2A}-selective agonists

The SARs of ligands at the A_{2A}AR have been reviewed recently [38,39]. Substitution of adenosine at the 2-position, especially with (thio)ethers, secondary amines, and alkynes, has resulted in many synthetic analogues selective for the A_{2A}AR. The presence of a 5′-*N*-alkyluronamide modification, as found in the potent nonselective agonist NECA, a 5′-*N*-ethyluronamide, tends to maintain or enhance

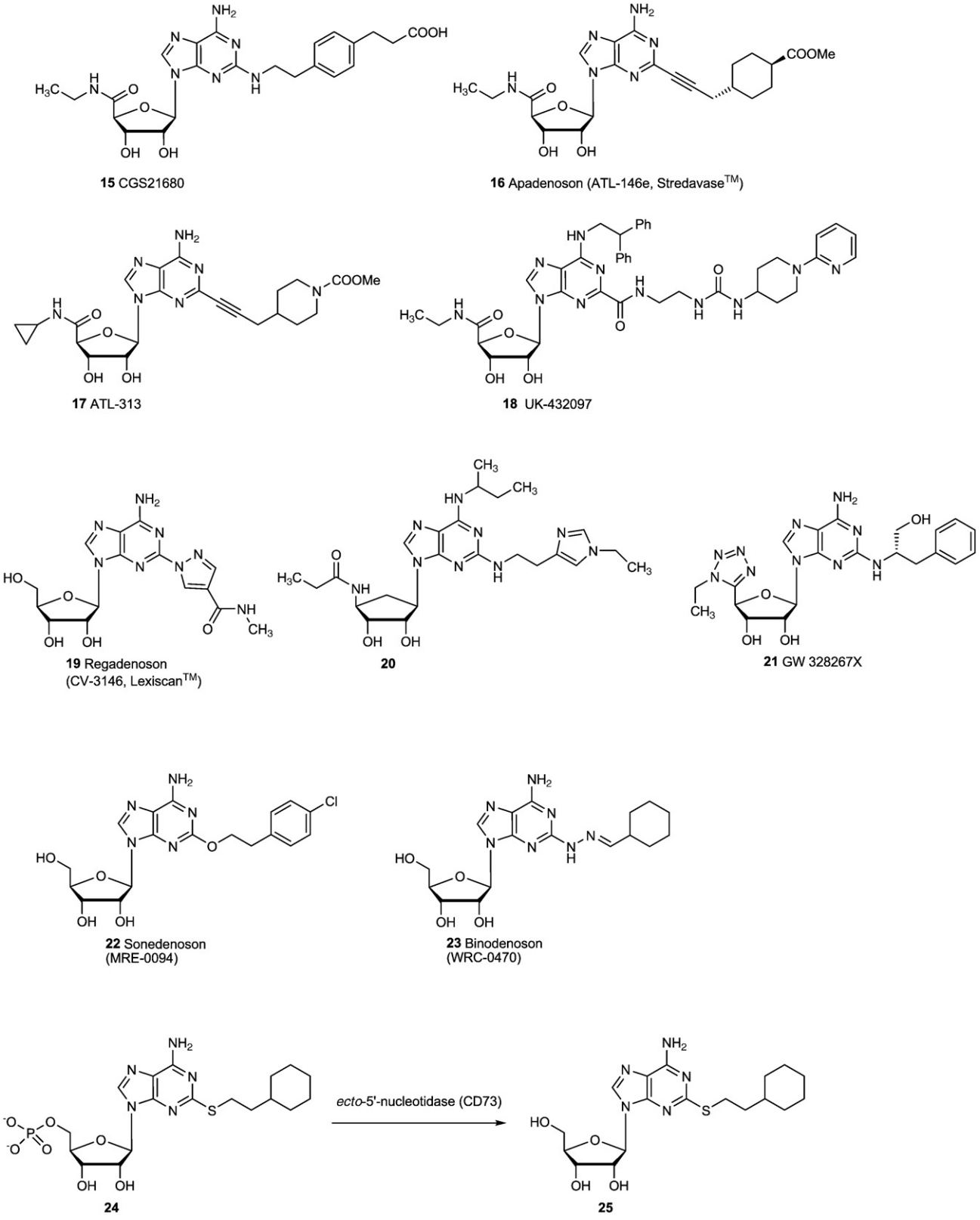

Fig. 2. A_{2A} adenosine receptor agonists.

the selectivity for the A_{2A}AR. These two modifications are present in the widely used A_{2A}AR agonist CGS21680 (**15**) (Fig. 2). The 2-(2-phenylethyl)amino modification of adenosine was particularly conducive to enhanced affinity at the A_{2A}AR and is present in an extended chain in CGS21680 (**15**). The carboxylate group at the terminal position of CGS21680 was found to act as a general site for chain extension and derivatization with bulky groups, including fluorescent groups and dendrimeric polymers [40,41], without losing high affinity of binding to the receptor. In receptor docking of agonist structures [42,43], this chain is pointing toward the extracellular face of the receptor, which has relaxed structural constraints relative to the main TM binding site. The 2-(2-cyclohexylethyl)amino modification of

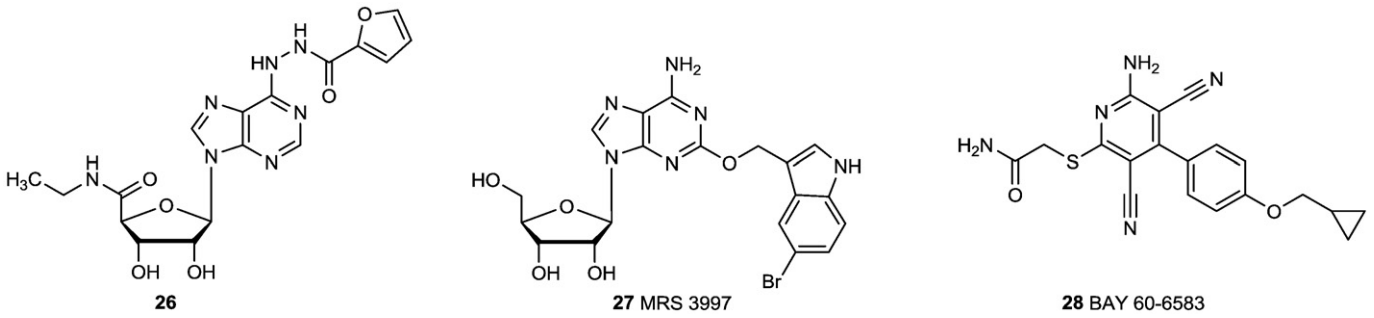

Fig. 3. A_{2B} adenosine receptor agonists.

adenosine also favored high affinity at the A_{2A}AR. Extended substituents are also present at the 2-position of the more recently introduced A_{2A}AR, such as apadenoson (ALT-146e, **16**) and ATL-313 (**17**), which are 5′-uronamide modified analogues.

Certain N^6-position substitutions have also been found to increase the affinity at the A_{2A}AR. An example of this is the class of N^6-(2,2-diphenylethyl)adenosine analogues, such as UK-432097 (**18**). Regadenoson (Lexiscan™, **19**) [191] has been introduced as a diagnostic for stress testing due to its vasodilatatory effects, and apadenoson (**16**) is developed for the same application.

An inverse amide structure in the 4′-position as in the C2,N^6-substituted adenosine analogue **20**, which is additionally lacking the oxygen atom in the ribose-analogous cyclopentane ring, is also well tolerated by the A_{2A}AR. Furthermore, the 4′-hydroxymethylene group in adenosine derivatives can be exchanged for a tetrazolyl residue as in GW328267X (**21**) (Fig. 2).

Several A_{2A}-selective agonists including UK-432097 (**18**), sonedenoson (**22**), and binodenoson (**23**) have been clinically evaluated (see below). A major problem with the systemic application of A_{2A} agonists as anti-inflammatory therapeutics has been their potent hypotensive effects. Recently, efforts have been undertaken to obtain A_{2A} agonists which show site-specific action. A_{2A} agonists, such as **18** have been developed for the treatment of bronchial inflammation (constructive pulmonary disease, COPD) by inhalation with limited systemic

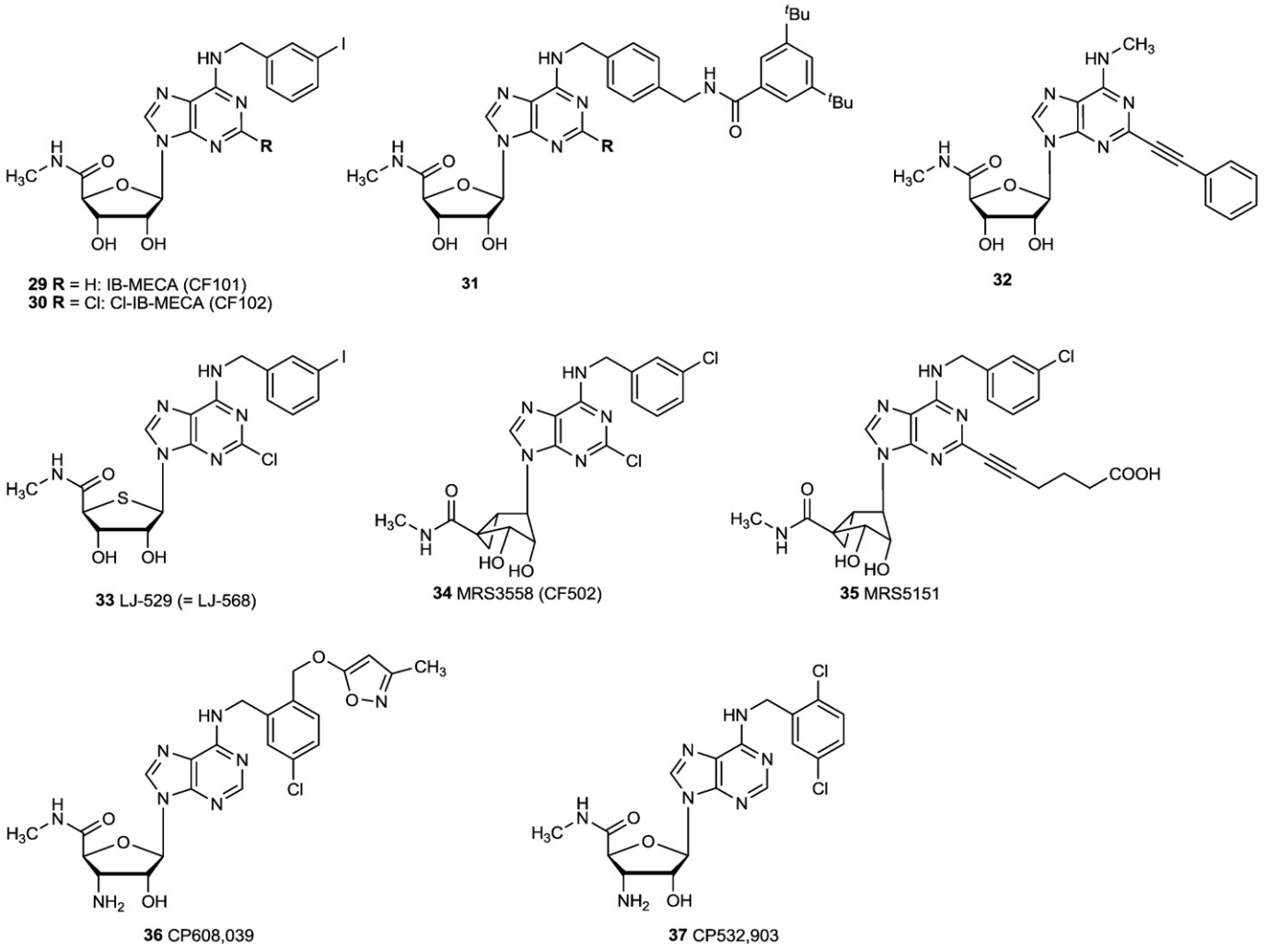

Fig. 4. A_3 adenosine receptor agonists.

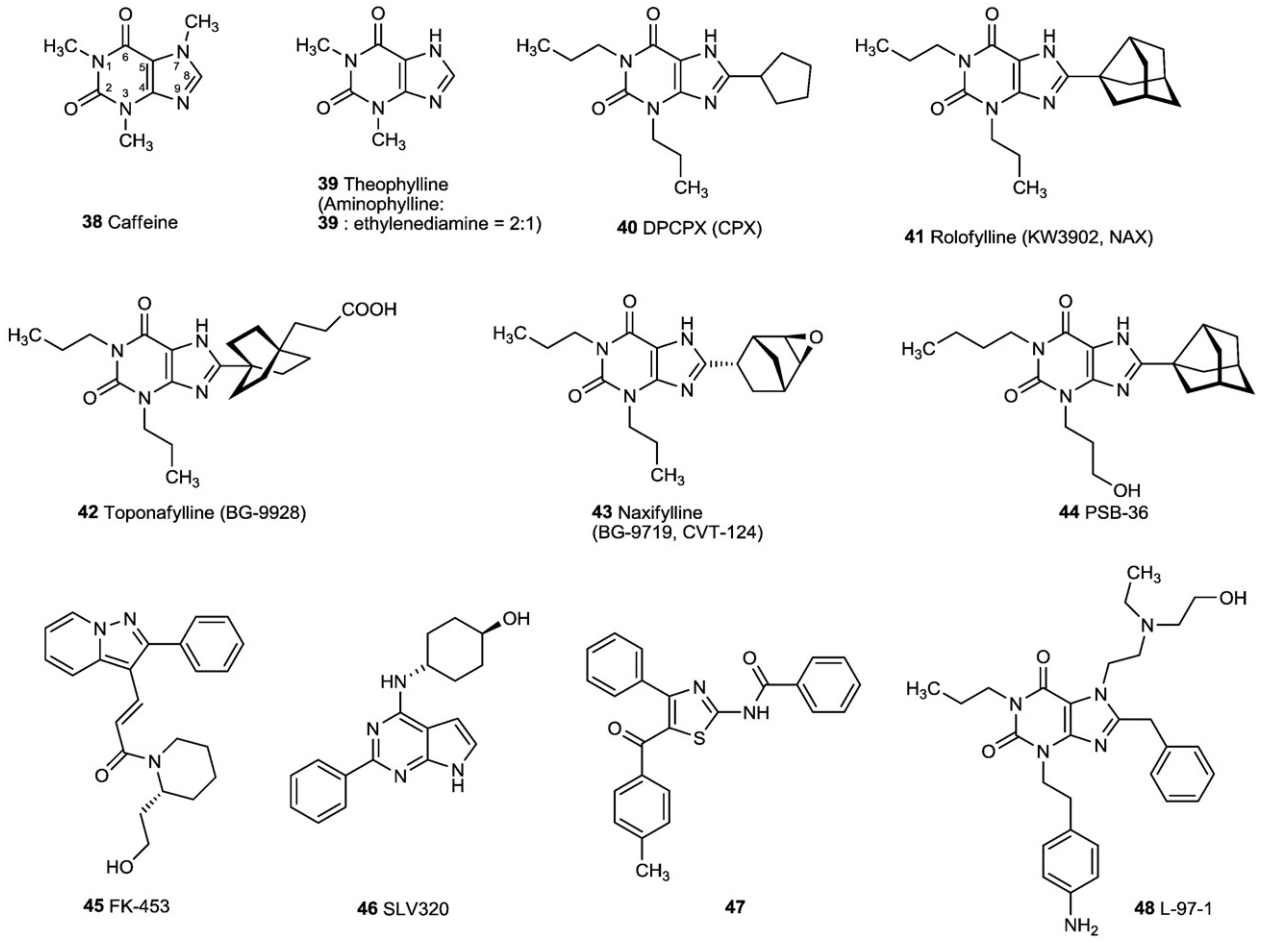

Fig. 5. A_1 adenosine receptor antagonists.

exposure [44]. In another approach 5′-phosphate prodrugs of A_{2A} agonists have been prepared (e.g. **24**) which are to be preferably cleaved releasing the A_{2A} agonist **25** at sites of inflammation where *ecto*-5′-nucleotidase (CD73) is highly expressed [45].

2.3. A_{2B}-selective agonists

The SAR of adenosine agonists at the A_{2B}AR was recently reviewed [11,13]. Substitution of adenosine at the N^6-position with a narrow range of aryl groups increases affinity at the A_{2B}AR. Also, very specific modification of the 5′- and C2-positions complements this increased affinity at the A_{2B}AR (e.g. compound **26**) (Fig. 3). Thus, combinations of narrowly defined modifications have resulted in compounds that interact selectively with A_{2B}AR [11,46] or that activate the A_{2B}AR along with the A_{2A}AR (MRS3997, **27**) [47].

BAY 60-6583 (**28**) is one of the 2-aminopyridine-3,5-dicarbonitrile derivatives found to activate the ARs [33]. This compound appears to be an A_{2B}AR-selective agonist [48,49].

2.4. A_3-selective agonists

The SAR of ligands at the A_3AR was recently reviewed [50]. Substitution with an N^6-benzyl group or substituted benzyl group increases selectivity for the A_3AR in both human and rat (e.g. **29**, **33**) (Fig. 4). Even bulky substituents as in compound **31** are well tolerated [51]. The N^6-methyl (e.g. compound **32**) and ethyl groups also favor A_3AR in human [52]. As with A_{2A}AR agonists, the NECA-like 5′-uronamide modification has also been found to be conducive to selectivity in A_3AR agonists. IB-MECA (**29**) and its 2-chloro analogue Cl-IB-MECA (**30**) are prototypical and widely used agonists of the A_3AR. Cl-IB-MECA (**30**) is more A_3AR selective (~2000-fold compared to the A_1AR) than IB-MECA (~50-fold compared to the A_1AR). The 4′-thioadenosine derivative LJ-529 (**33**), which is otherwise equivalent to Cl-IB-MECA, acts as a highly potent and selective A_3AR agonist with a subnanomolar affinity [53].

The ribose ring is normally freely twisting in solution and can adopt a range of conformations. The North conformation of the ribose ring was found to be the preferred conformation for binding to the A_3AR. It is possible to chemically freeze this preferred conformation in analogues containing a [3.1.0]bicyclohexane ring system in place of the ribose 5-membered ring. This observation was utilized in the design of more potent and selective analogues such as MRS3558 (**34**), which displays nanomolar affinity at the A_3AR [54]. The selectivity of MRS3558 for the A_3AR is evident in a comparison of human ARs and rat ARs, but at the mouse ARs only 10-fold selectivity for the A_3AR vs. the A_1AR was observed. A third (alkynyl) substituent at the 2 position in MRS5151 (**35**) remedied this issue of species-dependent selectivity [55].

Recently, a PAMAM dendrimer conjugate of a chemically functionalized AR agonist was reported to bind to and activate the A_3AR selectively with nanomolar affinity [56]. Such macromolecular receptor ligands can display pharmacological properties that are qualitatively different in comparison to the monomeric agonists.

3. Adenosine receptor antagonists

The prototypical AR antagonists were alkylxanthine derivatives. The stimulants caffeine (**38**) and theophylline (**39**) are natural products that behave as weak and nonselective AR antagonists

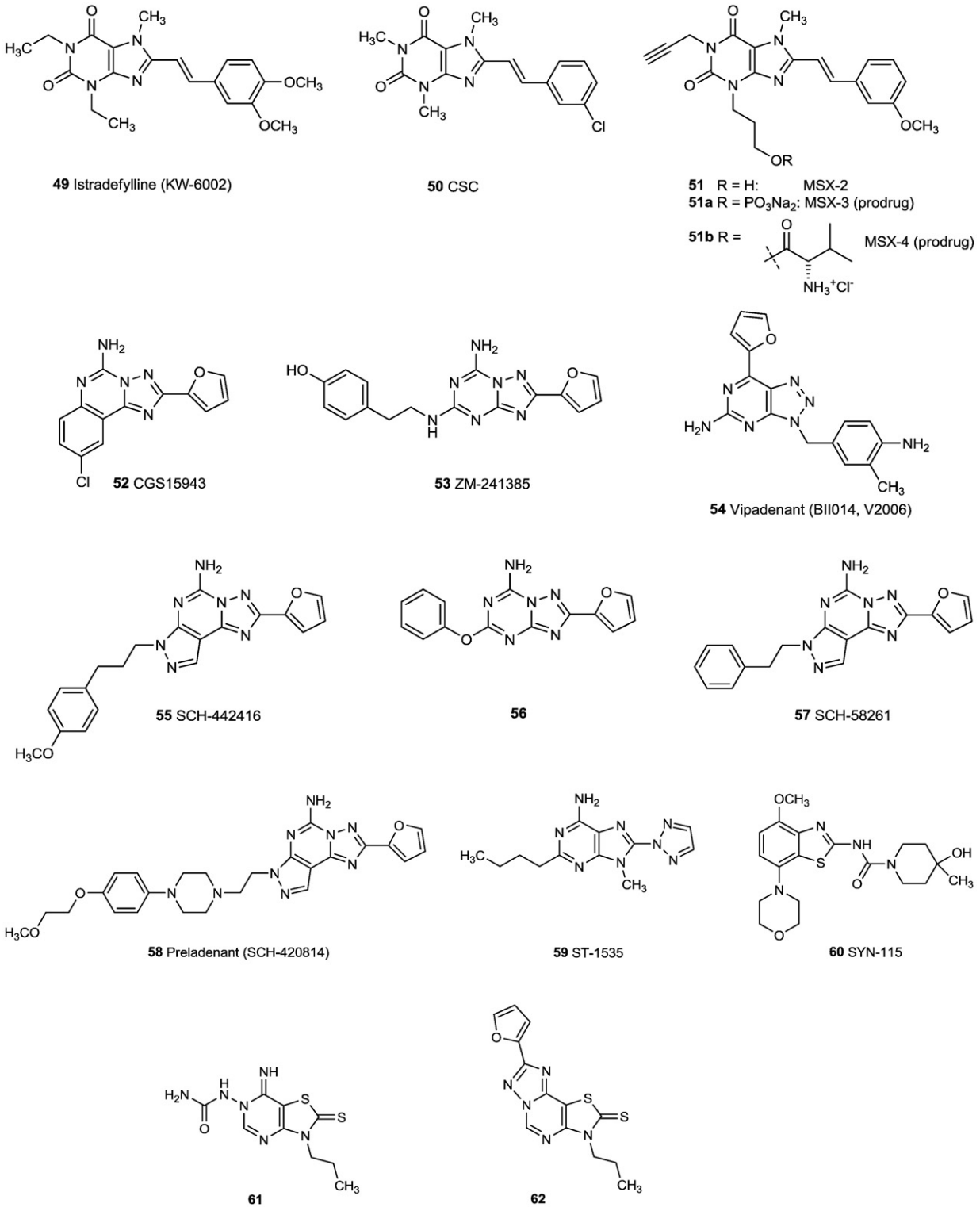

Fig. 6. A_{2A} adenosine receptor antagonists.

(Fig. 5). The structure–activity relationship (SAR) of xanthine derivatives as AR antagonists has been exhaustively probed. The effects of receptor subtype selectivity of substitution at the 1-, 3-, 7-, and 8-positions have been explored in detail [15]. However, many newer, highly selective AR antagonists are more chemically diverse than the xanthines and contain nonpurine heterocyclic core structures (Figs. 5–8 and Table 2). Various classes of AR antagonists and their synthetic methods have been reviewed [21,24,57,58].

3.1. A_1-selective antagonists

A_1-selective AR antagonists have recently been reviewed [36,59]. In general, modifications of the xanthine core structure at the 8-position with aryl or cycloalkyl groups have led to high affinity and selectivity for the A_1AR. Highly selective xanthine antagonists of the A_1AR have been reported. Many contain a cycloalkyl substitution at the 8-position. For example, the 8-cyclopentyl derivative DPCPX or alternately abbreviated

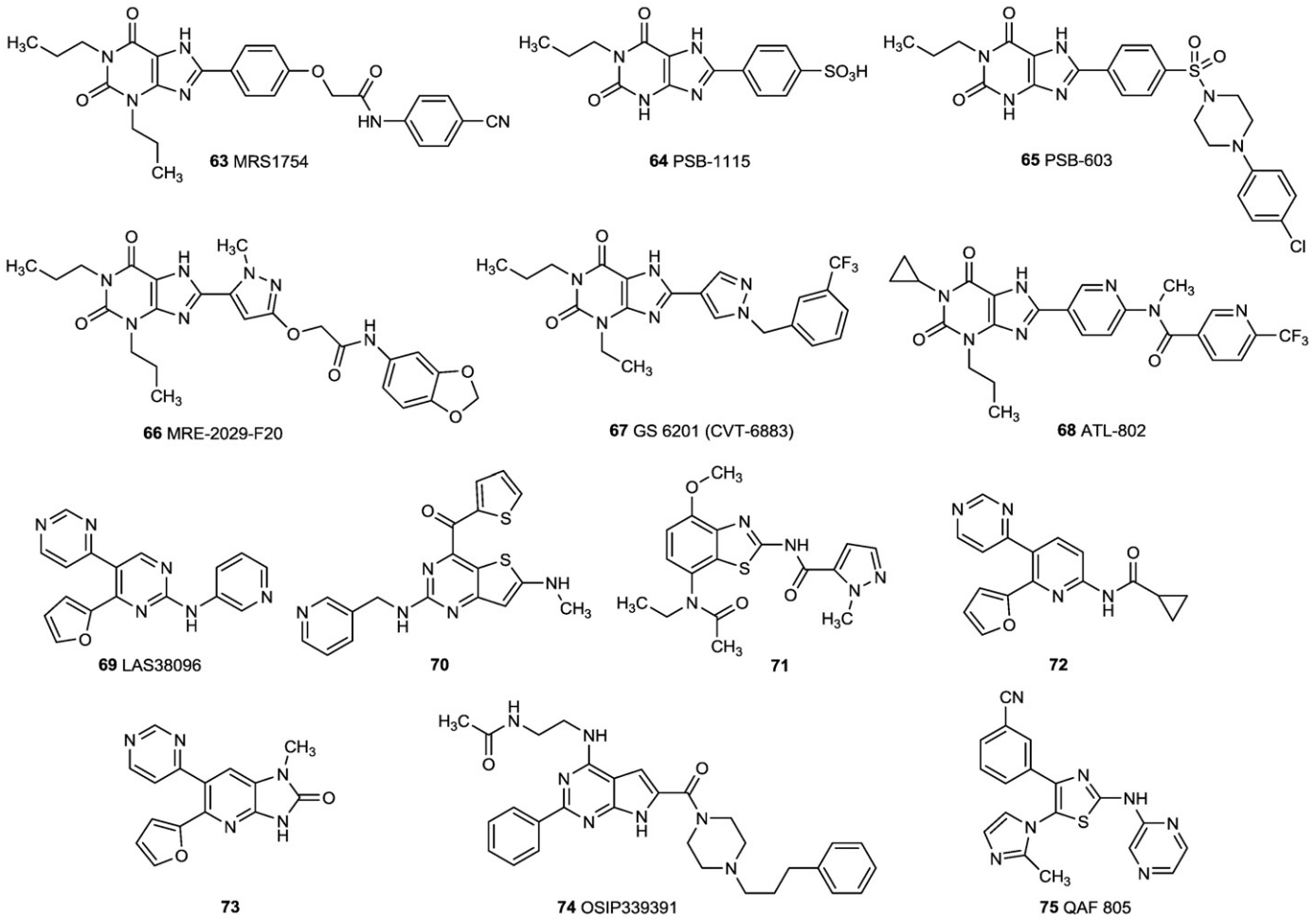

Fig. 7. A_{2B} adenosine receptor antagonists.

CPX (**40**, 8-cyclopentyl-1,3-dipropylxanthine) (Fig. 5) is highly selective and of nanomolar affinity at the rat A_1AR and is still selective, to a lesser degree, at the human A_1AR. A bicycloalkyl group is present in the 8-(3-noradamantyl) group of rolofylline (**41**, KW-3902, MK-7418) [60]. Another 8-bicycloalkyl xanthine analogue naxifylline (BG9719, **42**) was even more selective for the A_1AR, with a K_i ratio human A_{2A} /A_1 of 2400 compared with a ratio of 150 for KW-3902 (**41**). While BG9719 is highly selective for A_1AR compared to the human A_{2B}AR, the selectivity of the related A_1AR antagonist BG 9928 (**42**) is only ~10-fold. The 3-(3-hydroxypropyl)-substituted 1-butyl-8-noradamantylxanthine (**44**, PSB-36) shows a particularly high affinity and A_1-selectivity [25]. Phosphate prodrugs of 3-(3-hydroxypropyl)xanthine derivatives show greatly improved water-solubility [25,62].

A variety of A_1-selective antagonists with a non-xanthine structure has been developed [18,36,59], including the pyrazolopyridine derivative FK-453 (**45**) and the 7-deazaadenine derivative SLV320 (**46**), both of which have been evaluated in clinical trials. Recently, a 2-aminothiazole derivative (**47**) showing high A_1 affinity and selectivity has been developed [63].

3.2. A_{2A}-selective antagonists

Recent developments in the field of A_{2A} antagonists have been described [64–66]. Modification of xanthines at the 8-position with alkenes (notably styryl groups) has led to selectivity for the A_{2A}AR. The 8-styrylxanthine istradefylline (**49**, KW6002) was among the first A_{2A}AR antagonists reported (Fig. 6). Some 8-styrylxanthine derivatives, such as CSC (**50**, 8-(3-chlorostyryl)caffeine), were later found to inhibit monoamine oxidase-B in addition to the A_{2A}AR [67]. The phosphate prodrug MSX-3 (**51a**) and the L-valine ester prodrug MSX-4 (**51b**) have been prepared as water-soluble prodrugs of the potent and selective A_{2A} antagonist MSX-2 (**51**) [26,27]. Both are now broadly used as pharmacological tools in particular for in vivo studies [e.g. 67–70].

Substituting various heterocyclic ring systems in place of the xanthine core has led to exceptionally high affinity and selectivity at the A_{2A}AR. An early example of a heterocyclic structure proposed as an A_{2A}AR antagonist was the triazoloquinazoline CGS15943 (**52**), which was later demonstrated to be only slightly selective. Later refinement of the triazoloquinazoline by addition of a third ring or alteration of the pattern of N inclusion in the heterocyclic system greatly improved the A_{2A}AR selectivity. The triazolotriazine ZM241385 (**53**), the triazolopyrimidine vipadenant (**54**, BII014, V2006), and the pyrazolotriazolopyrimidine SCH442416 (**55**) are examples of highly potent A_{2A}AR antagonists of later generation. ZM241385 (**53**) also binds to the human A_{2B}AR with moderate affinity, and in both tritiated and iodinated form has been used as a radioligand at that receptor [71]. A recently described analogue (**56**) shows somewhat higher selectivity [72].

The affinity of SCH 442416 (**55**) at the human A_{2A}AR was originally reported as K_i 0.048 nM [73], however later reports of binding assays have placed it in the low nanomolar range (4.1 nM in [32]). Related compounds include SCH 58261 (**57**) and preladenant (SCH 420814, **58**). The latter is undergoing clinical trials for the treatment of Parkinson's disease (see below).

Examples for further non-xanthine A_{2A} antagonists are the adenine derivative ST-1535 (**59**) and the benzothiazole derivative

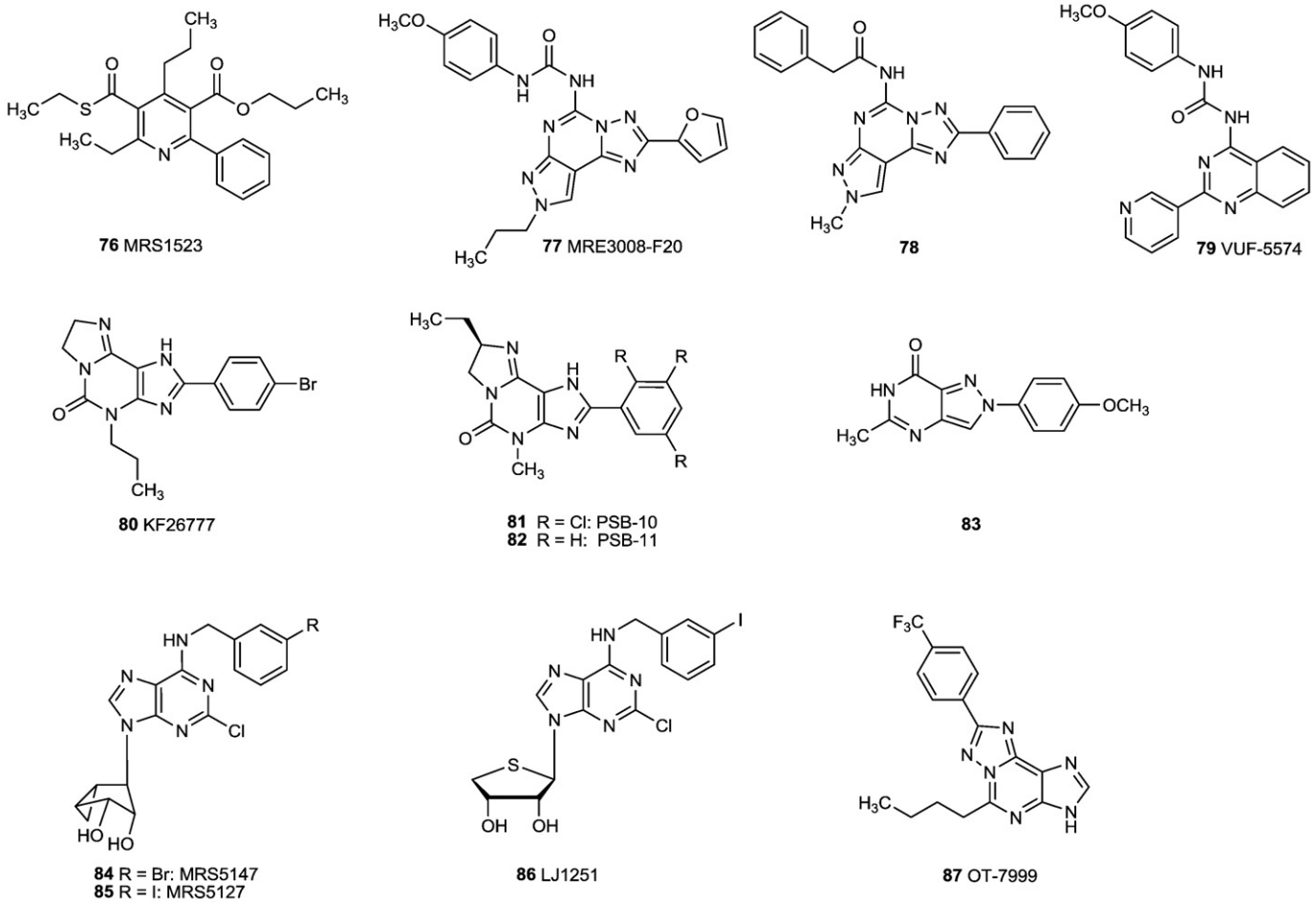

Fig. 8. A_3 adenosine receptor antagonists.

SYN-115 (**60**), both of which are being clinically evaluated. Very recently, benzofurans [74], 7-imino-2-thioxo-thiazolo[4,5-*d*]pyrimidines [75] (e.g. **61**) and the related thiazolotriazolopyrimidinethiones [76] (e.g. **62**) have been described as new potent A_{2A}-selective AR antagonists.

3.3. A_{2B}-selective antagonists

A_{2B} AR antagonists have recently been reviewed [12,13]. Certain modifications of the xanthine core structure at the 8-position with aryl groups have been found to result in selectivity for the A_{2B}AR [15].

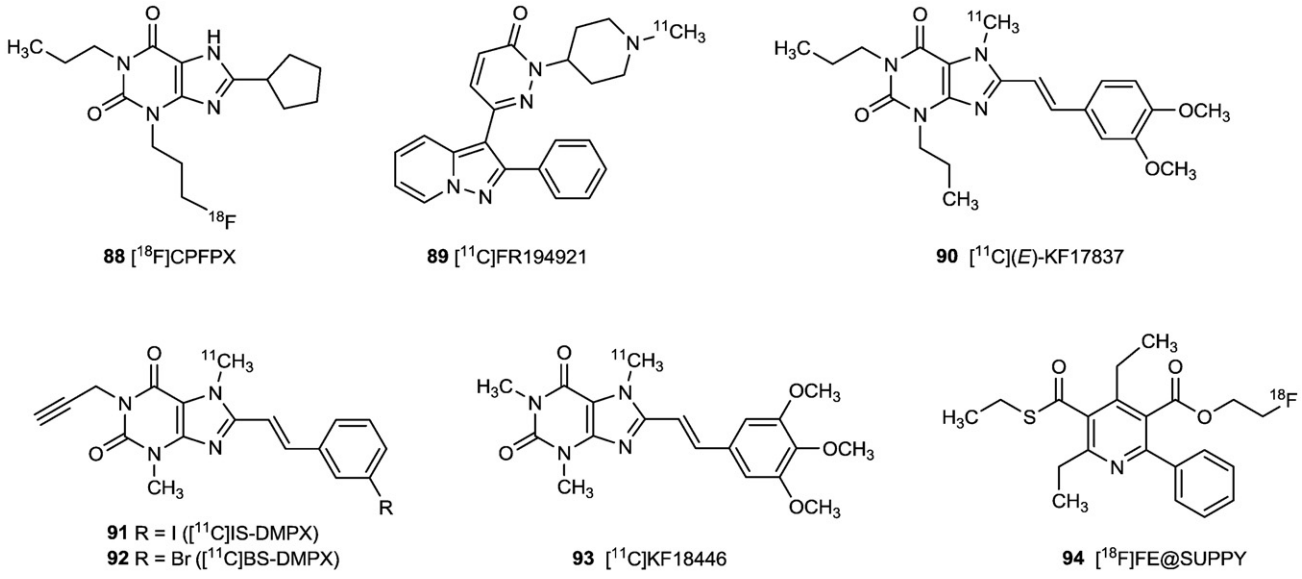

Fig. 9. Radioligands for positron emission tomography (PET) studies.

Table 1
Adenosine receptor affinities of agonists.

		K_i (nM)[a]			
		A_1	A_{2A}	A_{2B}[b]	A_3
1	Adenosine[c] [35]	ca. 100 (h) 73 (r)	310 (h) 150 (r)	15,000 (h) 5100 (r)	290 (h) 6500 (r)
A_1-selective agonists					
2	*R*-PIA	2.04 (h) [128] 1.2 (r) [129]	220 (r) [129]	150,000 (h) [130] 19,000 (m) [131]	33 (h) [132] 158 (r) [133]
3	CPA [109]	2.3 (h)	794 (h)	18,600 (h)	72 (h)
4	CCPA	0.83 (h) [109] 1.3 (r) [134] 0.1 (rb) [134]	2270 (h) [109] 950 (r) [134]	18,800 (h) [109]	38 (h) [109] 237 (r) [134] 37.7 (rb) [134]
5	(*S*)-ENBA [19]	0.34 (r)	477 (r)	nd[d]	282 (h) 915 (r)
6	Capadenoson (BAY68-4986)	nd	nd	nd	nd
7	GW493838	nd	nd	nd	nd
8	Selodenoson (DTI-0009)	nd	nd	nd	nd
9	GR79236 [109]	3.1 (r)	1300 (h)	nd	nd
10	Tecadenoson [109]	6.5 (p)	2315 (h)	nd	nd
11	CVT-3619 (GS 9667) [135]	55 (h)	>10,000 (h)	>50,000 (h)	>1000 (h)
12	AMP579 [136]	5.0 (r)	56 (r)	nd	nd
13	SDZ WAG 994 [137]	23 (p)	25,000 (p)	Inactive (p)	nd
14	NNC 21-0136 [93]	10 (r)	630 (r)	nd	nd
A_{2A}-selective agonists					
15	CGS21680	289 (h) [109] 1800 (r) [134] 120 (rb) [134]	27 (h) [109] 19 (r) [134]	>10,000 (h) [109] >10,000 (r) [134]	67 (h) [109] 584 (r) [134] 673 (rb) [134]
16	Apadenoson (ATL-146e) [109]	77 (h)	0.5 (h)	nd	45 (h)
17	ATL-313	nd	nd	nd	nd
18	UK-432097 [44]	nd	4 (h)	nd	nd
19	Regadenoson (CV-3146) [109]	>10,000 (h)	290 (h)	>10,000 (h)	>10,000 (h)
20	[138]	>10,000 (h)	5.4 (h)	9866 (h)	1640 (h)
21	GW328267X [138]	882 (h)	2.3 (h)	51 (h)	4.2 (h) (antagonist)
22	Sonedenoson (MRE-0094) [139]	>10,000 (h)	490 (h)	>10,000 (h)	nd
23	Binodenoson (WRC-0470) [45]	48,000 (h)	270 (h)	430,000 (h)	903 (h)
25	[45]	400 (r)	372 (r) 50 (m)	nd	3640 (h)
A_{2B}-selective agonists					
26	[46]	1050 (h)	1550 (h)	82 (h)	>5000 (h)
27	MRS3997 [47]	253 (h)	150 (h)	128 (h)	90 (h)
28	BAY 60-6583	>10,000 (h)[c], [140]	>10,000 (h)[c], [140]	3–10 (h) [140] 330 (m)[e], [141] 750 (d)[e], [141] 340 (rb)[e], [141]	>10,000 (h)[c], [140]
A_3-selective agonist					
29	IB-MECA (CF101) [109]	51 (h)	2900 (h)	11,000 (h)	1.8 (h)
30	Cl-IB-MECA (CF102)	220 (h) [109] 280 (r) [134] 35 (m) [134]	5360 (h) [109] 470 (r) [134] ~10,000 (m) [134]	>10,000 (h) [134] >10,000 (m) [134]	1.4 (h) [109] 0.33 (r) [134] 0.18 (m) [134]
31	[51]	245 (h)	>10,000 (h)	nd	2.25 (h)
32	[52]	32,800 (h)	41,700 (h)	>30,000 (h)	0.44 (h)
33	LJ529 [142]	193 (h)	223 (h)	nd	0.38 (h)
34	MRS3558 (CF502)	260 (h) [109] 105 (r) [134] 15.8 (m) [134]	2330 (h) [109] 1080 (r) [134] 10,400 (m) [134]	>10,000 (h) [109]	0.29 (h) [109] 1.0 (r) [134] 1.49 (m) [134]
35	MRS5151 [143]	14,900 (h) 10,500 (m)	~10,000 (h) >10,000 (m)	nd	2.38 (h) 24.4 (m)
36	CP608,039 [144]	7300 (h) 1750 (rb)	nd	nd	5.8 (h) 83 (rb)
37	CP532,903 [103]	898 (m)	>10,000 (m)	>10,000 (m)	9.0 (m)

[a] h = human; d = dog; m = mouse; p = pig; r = rat; rb = rabbit.
[b] Most data are from functional studies.
[c] Data from functional studies.
[d] nd = no data available.
[e] Data from radioligand binding studies versus the antagonist radioligand [^{3}H]MRS1754.

The first antagonist to be reported was MRS1754 (**63**) (Fig. 7). Later, groups at Univ. of Bonn, Germany (PSB-1115 (**64**), PSB-603 (**65**)), Univ. of Ferrara, Italy (MRE-2029-F20, **66**), at CV Therapeutics (now Gilead Sciences, CVT-6883, GS6201, **67**) and at Adenosine Therapeutics (now Clinical Data Inc., ATL802, **68**) improved on the degree of selectivity and/or the water solubility of the xanthines as A_{2B}AR

Table 2
Adenosine receptor affinities of antagonists.

		K_i (nM)[a]			
		A_1	A_{2A}	A_{2B}	A_3
Non-selective antagonists					
38	Caffeine	10,700 (h) [145] 44,900 (h) [67] 41,000 (r) [146] 44,000 (r) [147] 47,000 (gp) [20] 44,000 (c) [20]	23,400 (h) [67] 9560 (h) [145] 45,000 (r) [147] 32,500 (r) [148] 48,000 (r) [145]	33,800 (h) [14] 10,400 (h) [149] 20,500 (h) [150] 30,000 (r) [131] 13,000 (m) [131]	13,300 (h) [145] >100,000 (r) [133]
39	Theophylline	6770 (h) [127] 14,000 (r) [151] 8740 (r) [145] 7060 (gp) [152] 4710 (rb) [152] 9050 (s) [152] 6330 (c) [152]	1710 (h) [127] 6700 (h) [145] 22,000 (r) [151] 25,300 (r) [145]	9070 (h) [149] 74,000 (h) [150] 15,100 (r) [149] 5630 (m) [141] 11,000 (gp) [153] 17,700 (rb) [141] 38,700 (d) [141]	22,300 (h) [145] 86,400 (h) [127] >100,000 (r) [133] 85,000 (r) [154] >100,000 (d) [155]
A_1-selective antagonists					
40	DPCPX (CPX)	3.0 (h) [25] 0.50 (r) [25] 1.0 (r) [149] 0.18 (r) [152] 1.06 (gp) [152] 3.9 (gp) [20] 0.21 (rb) [152] 0.10 (s) [152] 0.05 (c) [152] 0.29 (c) [20] 11.4 (d) [155]	129 (h) [127] 60 (h) [25] 157 (r) [148] 500 (r) [149]	51 (h) [25] 63.8 (h) [149] 186 (r) [149] 200 (r) [153] 86.2 (m) [141] 145 (gp) [153] 96.0 (rb) [141] 147 (d) [141] 132 (d) [153]	795 (h) [156] 243 (h) [25] 509 (h) [155] 3960 (h) [127] >10,000 (r) [25] 43,000 (r) [155] 708 (rb) [155] 115 (d) [155]
41	Rolofylline (KW3902, NAX)	0.72 (h) [61] 8.0 (h) [157] 0.19 (r) [158] 12.6 (r) [61]	108 (h) [61] 673 (h) [157] 380 (r) [158] 510 (r) [61]	296 (h) [157]	4390 (h) [157]
42	Toponafylline (BG-9928)	7.4 (h) [157] 3.9 (mk) [159] 1.3 (r) [157] 29 (d) [159]	6410 (h) [157] 943 (mk) [159] 2440 (r) [157] 4307 (d) [159]	90 (h) [157]	>10,000 (h) [157]
43	Naxifylline (BG9719, CVT-124)	0.45 (h) [61] 12 (h) [158] 0.67 (r) [61]	1100 (h) [61] 1660 (h) [158] 1250 (r) [61]	611 (h) [158] 1010 (m) [141] 470 (rb) [141] 742 (d) [141]	4810 (h) [158]
44	PSB-36	0.7 (h) [25] 0.124 (r) [25]	980 (h) [25] 552 (r) [25]	187 (h) [25]	2300 (h) [25] 6500 (r) [25]
45	FK-453	18 (h) [109]	1300 (h) [109]	980 (h) [109]	>10,000 (h) [109]
46	SLV320	1.00 (h) [160] 2.51 (r) [160]	398 (h) [160]	3981 (h) [160] 501 (r) [160]	200 (h) [160]
47	Thiazole derivative	57.4 (h) [63] 4.83 (r) [63]	6250 (h) [63] >1000 (r) [63]	>1000 (r) [63]	2160 (h) [63]
48	L-97-1	580 (h) [161]	>100,000 (h) [161]	>100,000 (h) [161]	nd[b]
A_{2A}-selective antagonists					
49	Istradefylline (KW6002)	841 (h)[c] 230 (r)[c]	12 (h) [162] 91.2 (h)[c] 2.2 (r) [163] 4.46 (r) [164]	>10,000 (h)[c]	4470 (h)[c]
50	CSC (K_i MAO-B = 80.6 nM) [164]	28,000 (r) [165]	54 (r) [165]	8200 [165]	>10,000 (r) [133]
51	MSX-2	900 (r) [26] 2500 (h) [26]	8.04 (r) [26,148] 5.38 (h)[d], [26] 14.5 (h)[e], [26]	>10,000 (h) [26]	>10,000 (h) [26]
52	CGS15943	3.5 (h) [18] 6.4 (r) [18]	1.2 (h) [18]	32.4 (h) [141] 9.07 (m) [141]	35 (h) [18]
53	ZM-241385	774 (h) [109]	1.6 (h) [109]	75 (h) [109]	743 (h) [109]
54	Vipadenant (BIIB014, V2006)	68 (h) [166]	1.3 (h) [166]	63 (h) [166]	1005 (h) [166]
55	SCH-442416	1110 (h) [109]	4.1 (h) [32]	>10,000 (h) [109]	>10,000 (h) [109]
56		2720 (r) [72]	18.3 (r) [72]	3420 (h) [72]	489 (h) [72]
57	SCH-58261	725 (h) [109]	5.0 (h) [109]	1110 (h) [109]	1200 (h) [109]
58	Preladenant (SCH-420814)	>1000 (h) [65]	0.9 (h) [65]0	>1000 (h) [65]	>1000 (h) [65]
59	ST-1535	71.8 (h) [167]	6.6 (h) [167]9	352.3 (h) [167]	>1000 (h) [167]
60	SYN-115	nd	nd	nd	nd
61		2.8 (h) [75]	0.0038 (h) [75] 0.14 (h) cAMP [75]	nd	nd
62		228.4 (h) [76]	0.38 (h) [76]	nd	nd

Table 2 (*continued*)

		K_i (nM)[a]			
		A_1	A_{2A}	A_{2B}	A_3
A_{2B}-selective antagonists					
63	MRS1754	403 (h) [168] 16.8 (r) [168]	503 (h) [168] 612 (r) [168]	1.97 (h) [168] 12.8 (r) [168] 16.6 (r) [153] 3.39 (m) [141] 9.12 (gp) [153] 1.79 (rb) [141] 12.8 (d) [141] 12.3 (d) [153]	570 (h) [168]
66	MRE-2029-F20	200 (h) [169]	>1000 (h) [169]	5.5 (h) [169]	>1000 (h) [169]
65	PSB-603	>10,000 (h) [14] >10,000 (r) [14]	>10,000 (h) [14] >10,000 (r) [14]	0.553 (h) [14] K_D 0.403 (h) [14] K_D 0.351 (m) [14]	>10,000 (h) [14]
67	GS 6201 (CVT-6883)	1940 (h) [170]	3280 (h) [170]	22 (h) [170]	1070 (h) [170]
64	PSB-1115	>10,000 (h) [156] 2200 (r) [151]	24,000 (r) [151]	53.4 (h) [156]	>10,000 (h) [156]
68	ATL 802	369 (h) [168] 9583 (m) [168]1	654 (h) [168] 8393 (m) [168]	2.36 (h) [168] 8.58 (m) [168]	>1000 (h) [168] >10,000 (m) [168]
69	LAS38096	2821 (h) [171,172]	>1000 (h) [171,172]	17 (h) [171,172]	1043 (h) [171,172]
70		nd	965 (h) [173]	3.5 (h) [173]	nd
71		100 (h) [174]	51 (h) [174]	8 (h) [174] 21 (h) cAMP [174]	nd
72		931 (h) [174]	239 (h) [174]	4 (h) [174]	3754 (h) [174]
73		2444 (h) [175]	2126 (h) [175]	11 (h) [175]	>1000 (h) [175]
74	OSIP	37 (h) [176]	328 (h) [176]	0.41 (h) [176]	450 (h) [176]
75	QAF805	186 (h) [177]	1775 (h) [177]	3.4 (h) [177]	10.2 (h) [177]
A_3-selective antagonists					
76	MRS1523	>10,000 (h) [134] 15,600 (r) [134]	3660 (h) [134] 2050 (r) [134]	>10,000 (h) [134] >10,000 (m) [134]	18.9 (h) [109] 113 (r) [134] 731 (m) [134]
77	MRE3008-F20	1200 (h) [109]	141 (h) [109]	2100 (h) [109]	0.82 (h) [109]
78		562 (h) [178]	778 (h) [178]	>10,000 (h) [178]	0.108 (h) [178]
79	VUF-5574	≥10,000 (r) [179]	≥10,000 (r) [179]	nd	4.03 (h) [179]
80	KF26777	1800 (h) [180]	470 (h) [180]	620 (h) [180]	0.20 (h) [180]
81	PSB-10	1700 (h) [181] 805 (r) [28]	2700 (h) [181] 6040 (r) [28]	nd	0.441 (h) [28]
82	PSB-11	1640 (h) [181] 440 (r) [181]	1280 (h) [181] 2100 (r) [181]	2100 (m) [28]	2.34 (h) [181] KD 4.9 (h) [182]
83		>1000 (h) [183]	>1000 (h) [183]	>1000 (h) [183]	1.2 (h) [183]
84	MRS5147	1760 (h) [55]	1600 (h) [55]	nd	0.73 (h) [55]
85	MRS5127	3040 (h) [55]	1080 (h) [55]	nd	1.44 (h) [55]
86	LJ1251	2490 (h) [184]	341 (h) [184]	nd	4.16 (h) [184]
87	OT7999	>10,000 (h) [50]	>10,000 (h) [50]	>10,000 (h) [50]	0.95 (h) [50]

[a] h = human; c = cow; d = dog; gp = guinea pig; m = mouse; r = rat; rb = rabbit; s = sheep; a few A_{2B} data are from functional (cAMP) studies.
[b] nd = no data available.
[c] Unpublished data (Müller et al.).
[d] Recombinant receptors (expressed in CHO cells).
[e] Native receptors (post-mortem brain).

Table 3
Adenosine receptor affinities of ligands used for positron emission tomography.

		K_i (nM)[a]			
		A_1	A_{2A}	A_{2B}	A_3
88	CPFPX	1.26 (h) [29] 0.63 (r) [29] 1.37(p) [29] 0.18 (c) [29]	940 (h) [29] 812 (r) [29]	nd[b]	nd
89	FR194921	2.91 (h) [185] 4.96 (r) [185] 6.49 (m) [185]	>100 (h,r,m) [185]	nd	>100 (h) [185]
90	(*E*)-KF17837	390 (r) [186]	7.9 (r) [186] (*E*/*Z*) 1.0 (r) [186] (*E*)	1500 (h) [186]	nd
91	IS-DMPX	8.9 (r) [123]	>8000 (r) [123]	nd	nd
92	BS-DMPX	1200 (r) [187]	8.2 (r) [187]	>10,000 (h) [188]	>10,000 (h) [188]
93	KF18446	nd	5.9 (r) [124]	nd	nd
94	FE@SUPPY	6050 (r) [189]	9670 (r) [189]	nd	9.67 (h) [189]

[a] h = human; pig; m = mouse; p = pig; r = rat; a few A_{2B} data are from functional (cAMP) studies.
[b] nd = no data available.

antagonists. For example, GS-6201 (CVT-6883, **67**) has a selectivity of 88-fold vs. A_1, 149-fold vs. A_{2A}, and 49-fold vs. A_3ARs (human species).

PSB-603 (**65**) shows a particularly high affinity and selectivity, not only in humans, but also in rodents. PSB-1115 (**64**) exhibits high water-solubility and is therefore useful for in vivo studies, however its A_{2B} affinity and selectivity is lower than that for other A_{2B} antagonists. Besides xanthines, 2-aminopyrimidine derivatives, such as LAS38096 (**69**), 2-aminothiazolopyrimidines (e.g. **70**), benzothiazoles (e.g. **71**) [174], pyridine derivatives (e.g. **72**, **73**) [171,175], have been developed as A_{2B} antagonists. Compound **72** was shown to be metabolically unstable.

3.4. A_3-selective antagonists

Review articles on A_3AR antagonists have been previously published [16,17,77]. After it was recognized that the xanthines tended to be less potent as antagonists at the A_3AR in comparison to the other AR subtypes, chemically diverse sources were examined for possible interactions with the A_3AR. In an initial broad screen, several classes of nonxanthine antagonists were identified for the A_3AR: 1,4-dihydropyridines, pyridines, and flavones. The pyridine derivative MRS1523 (**76**) (Fig. 8) has become a useful tool since it shows relatively high affinity not only for the human but also for the rat A_3 receptor. Later it was noted that the potent nonselective AR antagonist CGS15943 (**52**) could be modified to produce A_3AR selectivity, two of the most potent and selective compounds at human A_3 receptors being MRE3008-F20 (**77**) and **78**. The urea-substituted quinazoline derivative VUF5574 (**79**) also possesses high A_{2B} affinity and selectivity. Some tricyclic xanthines (**80–82**) have been found to be very potent and selective antagonists at human A_3 receptors showing increased water-solubility due to a basic nitrogen atom in the additional imidazole ring. Recently described A_3-selective antagonists include pyrazolopyrimidinones (e.g. **83**). Many A_3 antagonists are much more potent at human as compared to rat A_3 ARs.

The principles for converting selective A_3AR agonists into selective A_3AR antagonists are based on either a conformationally constrained ribose-like ring or one that is truncated at the 4′-position (i.e., missing the ribose CH_2OH group entirely). Thus, the nucleoside derivatives MRS5147 (**84**) and its 3-iodo analogue MRS5127 (**85**) are highly selective A_3AR ligands generally across species. MRS5127 (**84**) was recently reported as a radioligand selective for the A_3AR [78]. The truncated 4′-thioadenosine derivative LJ-1251 (**86**), which acts as a A_3AR antagonist across species, was shown to lower intraocular pressure when applied topically [79,80].

4. Adenosine receptor ligands for diagnostic and therapeutic use

A selection of clinically used or evaluated AR ligands is collected in Table 4.

4.1. Agonists

Adenosine (**1**) itself for a long time was the only adenosine agonist to be used in humans. It is in widespread use in the treatment of paroxysmal supraventricular tachycardia (Adenocard®) due to its activation of A_1 receptors, and as a diagnostic for myocardial perfusion imaging (Adenoscan®, Astellas Pharma, Inc.) utilizing its A_{2A}-activating effects resulting in vasodilation. In addition, adenosine is being evaluated in several clinical trials for the treatment of inflammation, neuropathic and perioperative pain, and cardioprotection.

AMP579 (**12**) is a mixed agonist at A_1 and A_{2A}ARs. It was in clinical trials for myocardial ischemic preconditioning and reperfusion injury. It was tolerated in patients with end-stage renal disease, but in a placebo-controlled trial of patients undergoing primary percutaneous transluminal coronary angioplasty it failed to reduce infarct size [81,82]. Recently it was also shown to activate the A_{2B}AR, which may account for its cardioprotective properties in the rabbit heart [83].

A_1AR agonists are useful in preclinical models of cardiac arrythmia and ischemia and in pain. Adenosine agonists are also of interest for the treatment of sleep disorders [84,85]. A_{2A} agonists exhibit anti-inflammatory and immunosuppressive effects [86]. Activation of the A_{2B} AR protects against vascular injury [87]. A_3AR agonists have been proposed for the treatment of a wide range of autoimmune inflammatory conditions, such as rheumatoid arthritis, inflammatory bowel diseases, psoriasis, etc. [88–90], and also for cardiac and brain ischemia.

4.1.1. A_1-selective agonists

A_1-selective (partial) agonists have been clinically evaluated for the treatment of paroxysmal supraventricular tachycardia, atrial fibrillation, or angina pectoris (capadenoson (**6**), selodenoson (**8**), tecadenoson (**10**), and PJ-875), hypertriglyceridemia and type II diabetes (GR79236 (**9**), RPR-749, and GS9667/CVT-3619 (**11**)) and neuropathic pain (GW493838 (**7**), GR79236 (**9**)). Partial agonists are usually preferred to avoid receptor desensitization and to possibly achieve a certain tissue selectivity of the effects. The A_1AR agonist SDZ WAG94 (**13**) was one of the first agonists of this subtype to progress to clinical trials, i.e. for consideration for treatment of diabetes [91].

A_1AR agonists have antiischemic effects in the heart and brain. Recently, A_1AR activation was shown to mediate neuroprotective effects through microglial cells [92]. Various A_1AR agonists have been shown to be neuroprotective in ischemic and seizure models. However, the peripheral side effects of A_1AR agonists could be severe. The A_1AR agonist NNC-21-0136 (**14**) was previously in clinical development for the treatment of stroke and other neurodegenerative conditions [93]. It was found empirically to provide some degree of in vivo selectivity for the CNS in comparison to peripheral cardiovascular actions of adenosine that was not based on subtype selectivity.

Other A_1AR-selective agonists are intended for activation of the receptor at peripheral locations. The A_1AR-selective adenosine derivative GR79236 (**9**) has analgesic and anti-inflammatory actions in humans and animals [94]. The A_1AR-selective agonist GW493838 (**7**) was also under evaluation for pain management. RPR749 (Aventis) and its methylated metabolite are orally active and selective adenosine A_1AR agonists that inhibit lipolysis in adipocytes and lower plasma triglyceride levels [95]. GS-9667 (**11**, CVT-3619), a partial agonist of the A_1AR, is in development as an antilipolytic agent. It acts as a full agonist of the A_1AR in the inhibition of adenylate cyclase in adipocytes, which have a large receptor reserve and/or higher efficacy of coupling of the receptor to G_i. However, it is a partial agonist in the cardiovascular system and therefore lacks cardiovascular side effects.

A_1AR agonists are of interest for use in treating cardiac arrhythmias, and it recently was suggested that a partial agonist of this subtype would have advantages over a full agonist for this use [96]. The A_1AR-selective agonist selodenoson (formerly DTI-0009, **8**) has been in clinic trials for treatment of acute and chronic control of tachycardia and topical treatment of diabetic foot ulcers (Aderis Pharmaceuticals). It was formulated for intravenous administration to control heart rate during acute attacks and for oral administration in the chronic management of atrial fibrillation. The nonnucleoside AR agonist BAY 68-4986 (capadenoson, **6**) is under investigation for atrial fibrillation and for the treatment of angina.

4.1.2. A_{2A}-selective agonists

The 2-substituted A_{2A}AR agonists apadenoson (**16**, ATL-146e), binodenoson (**23**, MRE-0470 or WRC-0470), and sonedenoson (**22**, MRE0094) have been cardiovascular clinical candidates [97–99]. Such

Table 4
Therapeutic drugs, imaging agents, and clinical candidates that act through adenosine receptors.

Compound	Selectivity	Company	Indication or use (phase)[a]
Agonists			
Adenosine (**1**) (Adenocard, Adenoscan)	A_1, A_{2A}	Astellas	Paroxysmal supraventricular tachycardia (approved), myocardial perfusion imaging (approved), other uses in testing
AMP579 (**12**)	A_1, A_2	Aventis	Myocardial infarction (discontinued)
Apadenoson (**16**, Stedivaze, BMS068645, ATL146e)	A_{2A}	Clinical Data	Myocardial perfusion imaging (III)
ATL-1222	A_{2A}	Clinical Data	Acute inflammatory conditions (preclinical)
ATL-313 (**17**)	A_{2A}	Clinical Data	Ophthalmic disease (preclinical)
BAY 60-6583 (**28**)	A_{2B}	Bayer	Atherosclerosis (preclinical)
Binodenoson (**23**, WRC-0470, MRE-0470)	A_{2A}	Aderis, King	Myocardial perfusion imaging (III)
BVT.115959	A_{2A}	Biovitrum	Diabetic neuropathic pain (II)
Capadenoson (**6**, BAY68-4986, nonnucleoside)	A_1	Bayer Schering	Atrial fibrillation, chronic treatment (II)
Cl-IB-MECA (**30**, CF102)	A_3	Can-Fite	Liver cancer (I–II)
CP608,039 (**36**)	A_3	Pfizer	Cardiac ischemia (discontinued)
GS 9667 (**11**, CVT-3619)	A_1	Gilead	Hypertriglyceridemia associated with diabetes (I)
GR79236 (**9**)	A_1	GlaxoSmithKline	Pain, hyperlipidemia (I, discontinued)
GW493838 (**7**)	A_1	GlaxoSmithKline	Peripheral neuropathic pain (II, discontinued)
IB-MECA (**29**, CF101)	A_1	Can-Fite	Rheumatoid arthritis, psoriasis, dry eye, and other autoimmune inflammatory diseases (II), glaucoma (II)
MRS3558 (**34**, CF502)	A_3	Can-Fite	Autoimmune inflammatory diseases (preclinical)
NNC-21-0136 (**14**)	A_1	Novo Nordisk	Stroke, neurodegeneration (discontinued)
INO 8875 (PJ-875)	A_1	Inotek Pharmaceuticals	Glaucoma (II); atrial fibrillation (discontinued)
Regadenoson (**19**, Lexiscan, CV-3146)	A_{2A}	Gilead and Astellas	Myocardial perfusion imaging (approved)
RPR749	A_1	Aventis	Hyperlipidemia (I)
SDZ WAG 94 (**13**)	A_1	Sandoz/Novartis	Diabetes
Selodenoson (**8**)	A_1	Aderis	Atrial fibrillation (II)
Sonedenoson (**22**, MRE-0094)	A_{2A}	King	Diabetic foot ulcers, wound healing (II)
Tecadenoson (**10**, CVT-510)	A_1	Gilead	Paroxysmal supraventricular tachycardia (III)
UK 432097 (**18**)	A_{2A}	Pfizer	COPD (II)
Antagonists			
ATL 844	A_{2B}	Clinical Data and Novartis	Asthma and/or diabetes
Naxifylline (**43**, BG-9719)	A_1	Biogen-Idec	Heart failure (renal function) (discontinued)
Caffeine (**38**)		McMaster University	Apnea
CPFPX (**88**)	A_1	Research Center Jülich, Germany	PET imaging (^{18}F)
FK-453 (**45**)	A_1	Astellas	Acute renal failure
GS 6201 (**67**, CVT-6883)	A_{2B}	Gilead	Asthma (I)
Istradefylline (**49**, KW6002)	A_{2A}	Kyowa-Hakko Kogyo	Parkinson's disease (III, discontinued)
KF26777 (**80**)	A_3	Kyowa-Hakko Kogyo	Asthma (preclinical)
LAS38096 (**69**)	A_{2B}	Almirall	Anti-inflammatory (preclinical)
LAS101057 [192]	A_{2B}	Almirall	Antiasthmatic (I)
L-97-1 (**48**)	A_1	Endacea	Sepsis (preclinical)
MRE2029-F20 (**66**)	A_{2B}	King	Anti-inflammatory (preclinical)
OSIP339391 (**74**)	A_{2B}	OSI	Asthma (preclinical)
OT-7999 (**87**)	A_3	Otsuka	Glaucoma (preclinical)
Preladenant (**58**, SCH-420814)	A_{2A}	Schering-Plough	Parkinson's disease (III)
SCH-442416 (**55**)	A_{2A}	Schering-Plough	PET imaging (^{11}C)
QAF805 (**75**)	A_{2B}, A_3	Novartis	Asthma (I)
Rolofylline (**41**, KW3902, NAX)	A_1	NovaCardia and Merck	Heart failure (renal function) (discontinued)
SLV320 (**46**)	A_1	Solvay	Heart failure (renal function)
ST-1535 (**59**)	A_{2A}	Sigma-Tau	Parkinson's disease (I)
SYN-115 (**60**)	A_{2A}	Synosia Therapeutics /UCB (after Synosia Therapeutics)	Parkinson's disease (II), addiction
Theophylline/aminophylline (**39**)	A_1	King Faisal University	Recovery after anaesthesia
Toponafylline (**42**, BG-9928)	A_1	Biogen-Idec	Heart failure (renal function) (IIb)
Vipadenant (**54**, BIIB014, V2006)	A_{2A}	Vernalis and Biogen-Idec	Parkinson's disease (II)

[a] Many of the clinical trials indicated are no longer current.

agonists are of interest for use as vasodilatory agents in cardiac imaging (like adenosine itself, marketed as Adenoscan®) and in suppressing inflammation [100]. Regadenoson (**19**, CVT-3146, Lexiscan®) is already approved for diagnostic imaging [101]. The A_{2A}-agonist BVT.115959 (Biovitrum; structure not disclosed) has been claimed to show higher A_{2A} affinity at pH 7.0 as compared to pH 7.4 and is currently in phase II for the treatment of diabetic neuropathic pain. Since decreased pH values are found in pathological, e.g. inflamed tissues, this would result in tissue-selective effects and reduced side-effects. Two selective A_{2A} agonists developed by Adenosine Therapeutics (now Clinical Data) are in preclinical development for acute inflammatory conditions (ATL-1222, structure not disclosed) and ophthalmic disease (ATL-313, **17**).

4.1.3. A_3-selective agonists

The two A_3AR agonists that are currently in clinical trials contain the 5′-*N*-methyluronamide modification and have nanomolar affinity at the receptor. Thus CF101 (**29**, Can-Fite Biopharma) and Cl-IB-MECA (**30**, CF102) are in trials for autoimmune inflammatory disorders and for liver cancer, respectively. CF101 (**29**) was recently demonstrated to be efficacious in clinical trials of rheumatoid arthritis, psoriasis, and dry eye disease [102]. Further clinical trials are planned for glaucoma and osteoarthritis. Two other A_3AR agonists CP-608,039 (**36**) and its N^6-(2,5-dichlorobenzyl) analogue CP-532,903 (**37**) [103] were previously under development for cardioprotection. MRS3558 (**34**, CF502) is in preclinical development for the treatment of autoimmune diseases.

4.2. Antagonists

The non-selective AR antagonists caffeine (**38**) and theophylline (**39**) have been used as drugs for various indications. Caffeine (**38**) is mainly applied for CNS stimulation to restore alertness and to counteract fatigue, for the treatment of pain (e.g. headache, migraine) typically in combination with analgesics such as acetylsalicylic acid and/or paracetamol/acetaminophen, and for the treatment of apnoea in premature babies [104]. Theophylline or its salt aminophylline (**39**) are mainly applied for the treatment of bronchial asthma and COPD as a second-line treatment [105], although their use is now limited as a result of side effects on the central nervous system and the renal system. Theophylline may also be used for the prevention of sleep apnea in adults and for apnea of prematurity as a substitute for caffeine. A clinical study is currently performed using aminophylline for recovery after sevoflurane anaesthesia, since sevoflurane indirectly leads to an activation of A_1ARs.

A large number of synthetic AR antagonists that are much more potent and selective than the prototypical alkylxanthines have been introduced, although none have yet been approved for clinical use. Potent and selective AR antagonists display therapeutic potential as kidney protective (A_1), antifibrotic (A_{2A}), neuroprotective, antiasthmatic (A_{2B}), and antiglaucoma (A_3) agents [105–108].

4.2.1. A_1 receptor antagonists

Various A_1AR antagonists, xanthines and non-xanthines, have been or are currently being explored for clinical applications [109] for heart failure, and for improving renal function and treatment of acute renal failure. The xanthine derivative BG9719 (**43**), containing an epoxide ring, is highly selective, while the selectivity of the more water-soluble, metabolically more stable toponafylline (**42**) for the human A_1AR compared to the human A_{2B}AR is roughly 10. The 8-cyclopentyl derivative DPCPX (**40**), also known as CPX, which is selective for the A_1AR in the rat with nanomolar affinity but less selective at the human AR subtypes, has been in clinical trials for cystic fibrosis through a non-AR related mechanism [110]. The highly selective A_1AR antagonist L-97-1 (**48**, Endacea Inc.) is relatively well water-soluble and in late preclinical development for the treatment of asthma and sepsis [111]. As in the cases of DPCPX (**40**), rolofylline (**41**), naxifylline (BG 9719, **42**), and others a persistent problem in the development of A_1AR antagonists has been low water-solubility and low bioavailability [18,112]; thus, A_1AR antagonists, e.g. toponafylline (**43**) and L-97-1 (**48**), with good water solubility are preferable clinical candidates.

Nonxanthine antagonists of the A_1AR have also been shown to have high receptor subtype selectivity, e.g. FK453 (**45**) [113] and SLV 320 (**46**, Solvay Pharmaceuticals) [114]. For example, SLV 320 is in clinical trials as an intravenous treatment for acute decompensated heart failure with renal impairment.

4.2.2. A_{2A} receptor antagonists

Several selective A_{2A} antagonists have been evaluated in clinical trials for the treatment of Parkinson's disease. The first one has been istradefylline (**49**, KW6002), which did not reach the endpoint of phase III clinical trials, but additional trials are planned [115]. The non-xanthine derivatives preladenant (**58**, SCH420814; phase III), vipadenant (**54**, BII014, V2006; phase II), ST-1535 (**59**; phase I), as well as SYN-115 (**60**, phase II). Further potential indications include other neurodegenerative diseases, such as Alzheimer's disease, restless legs syndrome, depression, and addiction.

4.2.3. A_{2B} receptor antagonists

Modification of xanthines at the 8 position with certain aryl groups has given rise to preclinical candidates that are selective for the A_{2B}AR (e.g. **67**, GS-6201, CVT-6883, Gilead Sciences). GS-6201 is the first selective A_{2B} antagonist to be clinically evaluated for the treatment of asthma. Other A_{2B}-selective xanthine and nonxanthine derivatives include ATL844 (structure not disclosed), MRE2029-F20 (**66**), LAS38096 (**69**), LAS101057, and OSIP339391 (**74**), which are intended for treatment of asthma and/or inflammatory diseases. The aminothiazole derivative QAF 805 (**75**), a mixed A_{2B}/A_3-antagonist, has failed to attenuate bronchial hyperresponsiveness to inhaled AMP in a phase 1b clinical trial in asthmatics [116], but has also been investigated for other indications.

4.2.4. A_3 adenosine receptor antagonists

Cyclized derivatives of xanthines, such as PSB-11 (**82**), are A_3AR-selective, and similar compounds have been explored by Kyowa Hakko (e.g. **80**). Selective A_3AR antagonists, such as the heterocyclic derivatives OT-7999 (**87**), are being studied for the treatment of glaucoma [117], and other such antagonists are under consideration for treatment of cancer, stroke, and inflammation [10,118]. No A_3AR antagonists have yet reached human trials.

5. Radioligands for in vivo PET imaging of adenosine receptors

With the established relevance of ARs to human disease states, it has been deemed useful to develop high affinity imaging ligands for these receptors, for eventual diagnostic use in the CNS and in the periphery. Ligands for in vivo positron emission tomographic (PET) imaging of A_1, A_{2A}, and A_3ARs have been developed (Fig. 9 and Table 3). For example, the xanthine [^{18}F]CPFPX (**88**), similar in structure to DPCPX and the nonxanthine [^{11}C]FR194921 (**89**) have been developed as centrally-active PET tracers for imaging of the A_1AR in the brain [119].

^{11}C-labeled (*E*)-KF17837 (**90**) was proposed as a potential PET radioligand for mapping the adenosine A_{2A} receptors in the heart and brain [120,121]. ^{11}C labeled (*E*)-8-(3-chlorostyryl)-1,3-dimethyl-7-[^{11}C]methylxanthine ([^{11}C]CSC, **50**) proved 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 [122]. Further styrylxanthine derivatives labeled with ^{11}C were tested as in vivo probes [123]. [7-Methyl-^{11}C]-(*E*)-3,7-dimethyl-8-(3-iodostyryl)-1-propargylxanthine ([^{11}C]IS-DMPX, **91**) and [7-methyl-^{11}C]-(*E*)-8-(3-bromostyryl)-3,7-dimethyl-1-propargylxanthine ([^{11}C]BS-DMPX, **92**) showed K_i affinities of 8.9 and 7.7 nM respectively, and high A_{2A}/A_1 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} receptors and a high degree of nonspecific binding [123]. A useful A_{2A} PET ligand for in vivo imaging proved to be [^{11}C]KF18446 (**93**), also named (^{11}C)TMSX [124]. Ex vivo autoradiography for this molecule showed a high striatal uptake and a high uptake ratio of the striatum to the other brain regions. In 2001 the synthesis and evaluation of [^{11}C]KW-6002 (**49**) was reported. This molecule showed high retention in the striatum but it bound also to extra-striatal regions [190]. [^{11}C]SCH442416 (**55**) has recently been explored as a PET agent in the non-invasive in vivo imaging of the human A_{2A}AR [73,125].

Recently, an A_3AR PET ligand, [^{18}F]FE@SUPPY (**94**), based on a series of pyridine A_3AR antagonists, was introduced [126]. Several nucleoside derivatives that bind with nanomolar affinity at the A_3AR and that contain ^{76}Br for PET imaging were recently reported, including the antagonist MRS5147 (**84**) [127].

6. Concluding remarks

In conclusion, selective agonists and antagonists for all four adenosine receptor subtypes have been developed and diagnostic and therapeutic applications are being explored. The first selective AR agonist, the A_{2A} agonist regadenoson (Lexiscan®), has been approved as a diagnostic drug for myocardial perfusion imaging. Many other selective agonists and antagonists for the various receptor subtypes are undergoing clinical trials for a broad range of indications.

Although some trials of the selective ligands have been discontinued, the most advanced drugs so far have been capadenoson and tecadenoson (A_1 agonists for atrial fibrillation, or paroxysmal supraventricular tachycardia, respectively), apadenoson and binodenoson (A_{2A} agonists for myocardial perfusion imaging), preladenant (A_{2A} antagonist) for the treatment of Parkinson's disease, and CF101 and CF102 (A_3 agonists for inflammatory diseases and cancer, respectively).

Acknowledgements

KAJ acknowledges support from the Intramural Research Program of the NIH, National Institute of Diabetes & Digestive & Kidney Diseases. CEM is grateful for support by BMBF (BioPharma - Neuroallianz), DFG, DAAD, European Commission (ERANET Neuron), and the State of North-Rhine Westfalia (NRW International Research Graduate Schools BIOTECH-PHARMA and Chemical Biology).

References

[1] B.B. Fredholm, A.P. IJzerman, K.A. Jacobson, J. Linden, C.E. Müller, Nomenclature and classification of adenosine receptors — an update. Pharmacol. Rev., (in press).
[2] B.B. Fredholm, A.P. IJzerman, K.A. Jacobson, K.N. Klotz, J. Linden, International Union of Pharmacology. XXV. Nomenclature and classification of adenosine receptors, Pharmacol. Rev. 53 (2001) 527–552.
[3] V.P. Jaakola, M.T. Griffith, M.A. Hanson, V. Cherezov, E.Y. Chien, J.R. Lane, A.P. IJzerman, R.C. Stevens, The 2.6 angstrom crystal structure of a human A_{2A} adenosine receptor bound to an antagonist, Science 322 (2008) 1211–1217.
[4] V. Katritch, V.-P. Jaakola, J.R. Lane, J. Lin, A.P. IJzerman, M. Yeager, I. Kufareva, R.C. Stevens, R. Abagyan, Structure-based discovery of novel chemotypes for adenosine A_{2A} receptor antagonists, J. Med. Chem. 53 (2010) 1799–1809.
[5] J. Carlsson, L. Yoo, Z.G. Gao, J. Irwin, B. Shoichet, K.A. Jacobson, Structure-based discovery of adenosine A_{2A} receptor ligands, J. Med. Chem. 53 (2010) 3748–3755.
[6] R. Franco, V. Casadó, A. Cortés, K. Pérez-Capote, J. Mallol, E. Canela, S. Ferré, C. Lluis, Novel pharmacological targets based on receptor heteromers, Brain Res. Rev. 58 (2008) 475–482.
[7] M. Canals, D. Marcellino, F. Fanelli, F. Ciruela, P. de Benedetti, S.R. Goldberg, K. Neve, K. Fuxe, L.F. Agnati, A.S. Woods, S. Ferré, C. Lluis, M. Bouvier, R. Franco, Adenosine A_{2A}-dopamine D_2 receptor–receptor heteromerization: qualitative and quantitative assessment by fluorescence and bioluminescence energy transfer, J. Biol. Chem. 278 (2003) 46741–46749.
[8] P. Carriba, G. Navarro, F. Ciruela, S. Ferré, V. Casadó, L. Agnati, A. Cortés, J. Mallol, K. Fuxe, E.I. Canela, C. Lluis, R. Franco, Detection of heteromerization of more than two proteins by sequential BRET–FRET, Nat. Meth. 5 (2008) 727–733.
[9] S. Ferré, R. Baler, M. Bouvier, M.G. Caron, L.A. Devi, T. Durroux, K. Fuxe, S.R. George, J.A. Javitch, M.J. Lohse, K. Mackie, G. Milligan, K.D. Pfleger, J.P. Pin, N.D. Volkow, M. Waldhoer, A.S. Woods, R. Franco, Building a new conceptual framework for receptor heteromers, Nat. Chem. Biol. 5 (2009) 131–134.
[10] S. Ginés, J. Hillion, M. Torvinen, S. Le Crom, V. Casadó, E.I. Canela, S. Rondin, J.Y. Lew, S. Watson, M. Zoli, L.F. Agnati, P. Verniera, C. Lluis, S. Ferré, K. Fuxe, R. Franco, Dopamine D_1 and adenosine A_1 receptors form functionally interacting heteromeric complexes, Proc. Natl Acad. Sci. USA 97 (2000) 8606–8611.
[11] P.G. Baraldi, M.A. Tabrizi, F. Frutarollo, R. Romagnoli, D. Preti, Recent improvements in the development of A_{2B} adenosine receptor agonists, Purinergic Signal. 5 (2009) 3–19.
[12] R.V. Kalla, J. Zablocki, Progress in the discovery of selective, high affinity A_{2B} adenosine receptor antagonists as clinical candidates, Purinergic Signal. 5 (2009) 21–29.
[13] G. Ortore, A. Martinello, A_{2B} receptor ligands: past, present and future trends, Curr. Top. Med. Chem. 10 (2010) 923–940.
[14] T. Borrmann, S. Hinz, D.C.G. Bertarelli, W. Li, N.C. Florin, A.B. Scheiff, C.E. Müller, 1-Alkyl-8-(piperazine-1-sulfonyl)phenylxanthines: development and characterization of adenosine A_{2B} receptor antagonists and a new radioligand with subnanomolar affinity and subtype specificity, J. Med. Chem. 52 (2009) 3994–4006.
[15] C.E. Müller, K.A. Jacobson, Xanthines as adenosine receptor antagonists. In Methylxanthines. In Handbook of Experimental Pharmacology, B.B. Fredholm, ed., Springer, 200 (2011) 151–199.
[16] C.E. Müller, A_3 adenosine receptor antagonists, Mini-Rev. Med. Chem. 1 (2001) 417–427.
[17] C.E. Müller, Medicinal chemistry of adenosine A3 receptor ligands, Curr. Top. Med. Chem. 3 (2003) 445–462.
[18] C.E. Müller, A_1-adenosine receptor antagonists, Exp. Opin. Ther. Pat. 7 (1997) 419–440.
[19] Z.G. Gao, J. Blaustein, A.S. Gross, N. Melman, K.A. Jacobson, N^6-Substituted adenosine derivatives: selectivity, efficacy, and species differences at A_3 adenosine receptors, Biochem. Pharmacol. 65 (2003) 1675–1684.
[20] D. Ukena, K.A. Jacobson, W.L. Padgett, C. Ayala, M.T. Shamim, K.L. Kirk, R.A. Olsson, J.W. Daly, Species differences in structure–activity relationships of adenosine agonists and xanthine antagonists at brain A_1 adenosine receptors, FEBS Lett. 209 (1986) 122–128.
[21] C.E. Müller, T. Scior, Adenosine receptors and their modulators, Pharm. Acta Helv. 68 (1993) 77–111.
[22] A.R. van Troostenburg, E.V. Clark, W.D. Carey, S.J. Warrington, W.D. Kerns, I. Cohn, M.H. Silverman, S. Bar-Yehuda, K.L. Fong, P. Fishman, Tolerability, pharmacokinetics, and concentration-dependent hemodynamic effects of oral CF101, an A_3 adenosine receptor agonist, in healthy young men, Int. J. Clin. Pharmacol. Ther. 42 (2004) 534–542.
[23] E.C. Klaasse, A.P. IJzerman, W.J. de Grip, M.W. Beukers, Internalization and desensitization of adenosine receptors, Purinergic Signal. 4 (2008) 21–37.
[24] C.E. Müller, B. Stein, Adenosine receptor antagonists: structures and potential therapeutic applications, Curr. Pharm. Des. 2 (1996) 501–530.
[25] S. Weyler, F. Fülle, M. Diekmann, B. Schumacher, S. Hinz, K.N. Klotz, C.E. Müller, Improving potency, selectivity, and water-solubility of adenosine A1 receptor antagonists: xanthines modified at position 3 and related pyrimido[1,2,3-*cd*] purinediones, ChemMedChem 1 (2006) 891–902.
[26] R. Sauer, J. Maurinsh, U. Reith, F. Fülle, K.N. Klotz, C.E. Müller, Water-soluble phosphate prodrugs of 1-propargyl-8-styrylxanthine derivatives, A_{2A}-selective adenosine receptor antagonists, J. Med. Chem. 43 (2000) 440–448.
[27] K. Vollmann, R. Qurishi, J. Hockemeyer, C.E. Müller, Synthesis and properties of a new water-soluble prodrug of the adenosine A_{2A} receptor antagonist MSX-2, Molecules 13 (2008) 348–359.
[28] C.E. Müller, M. Thorand, R. Qurishi, M. Diekmann, K.A. Jacobson, W.L. Padgett, J.W. Daly, Imidazo[2,1-*i*]purin-5-ones and related tricyclic water-soluble purine derivatives: potent A2A- and A3-adenosine receptor antagonists, J. Med. Chem. 45 (2002) 3440–3450.
[29] M.H. Holschbach, R.A. Olsson, Applications of adenosine receptor ligands in medical imaging by positron emission tomography, Curr. Pharm. Des. 8 (2002) 2345–2352.
[30] Y. Cordeaux, S.J. Briddon, S.P.H. Alexander, B. Kellam, S.J. Hill, Agonist-occupied A_3 adenosine receptors exist within heterogeneous complexes in membrane microdomains of individual living cells, FASEB J. 22 (2008) 850–886.
[31] R.C. Middleton, S.J. Briddon, Y. Cordeaux, A.S. Yates, C.L. Dale, M.W. George, J.G. Baker, S.J. Hill, B. Kellam, New fluorescent adenosine A_1 receptor agonists that allow quantification of single living cells, J. Med. Chem. 50 (2007) 782–793.
[32] M. Kecskés, T.S. Kumar, L. Yoo, Z.G. Gao, K.A. Jacobson, Novel Alexa Fluor-488 labeled antagonist of the A_{2A} adenosine receptor: application to a fluorescence polarization-based receptor binding assay, Biochem. Pharmacol. 80 (2010) 506–511.
[33] U. Rosentreter, R. Henning, M. Bauser, T. Kramer, A. Vaupel, W. Hubsch, K. Dembowsky, O. Salcher-Schrauf-Stetter, J.P. Stasch, T. Krahn, E. Petzborn, Substituted 2-thio-3,5-dicyano-4-aryl-6-aminopyridines and the use thereof. WO Pat. 2001/025210.
[34] M.W. Beukers, L.C. Chang, J.K. von Frijtag Drabbe Künzel, T. Mulder-Krieger, R.F. Spanjersberg, J. Brussee, A.P. IJzerman, New, non-adenosine, high-potency agonists for the human adenosine A_{2B} receptor with an improved selectivity profile compared to the reference agonist N-ethylcarboxamidoadenosine, J. Med. Chem. 47 (2004) 3707–3709.
[35] L. Yan, J.C. Burbiel, A. Maaß, C.E. Müller, Adenosine receptor agonists: from basic medicinal chemistry to clinical development, Exp. Opin. Emerg. Drugs 8 (2003) 537–576.
[36] W.F. Kiesman, E. Elzein, J. Zablocki, A_1 adenosine receptor antagonists, agonists, and allosteric enhancers, Handb. Exp. Pharmacol. 193 (2009) 25–58, Review.
[37] Z.G. Gao, K.A. Jacobson, 2-Chloro-N^6-cyclopentyladenosine, adenosine A_1 receptor agonist, antagonizes the adenosine A_3 receptor, Eur. J. Pharmacol. 443 (2002) 39–42.
[38] G. Cristalli, C.E. Müller, R. Volpini, Recent developments in adenosine A_{2A} receptor ligands, Handb. Exp. Pharmacol. 193 (2009) 59–98.
[39] M. Clementina, S. Giuseppe, A_{2A} receptor ligands: past, present and future trends, Curr. Top. Med. Chem. 10 (2010) 902–922.
[40] F. Brand, A. Klutz, K.A. Jacobson, B.B. Fredholm, G. Schulte, Adenosine A_{2A} receptor dynamics studied with the novel fluorescent agonist Alexa488-APEC, Eur. J. Pharmacol. 590 (2008) 36–42.
[41] Y. Kim, B. Hechler, Z.G. Gao, C. Gachet, K.A. Jacobson, PEGylated dendritic unimolecular micelles as versatile carriers for ligands of G protein-coupled receptors, Bioconjug. Chem. 20 (2009) 1888–1898.
[42] A.A. Ivanov, D. Barak, K.A. Jacobson, Evaluation of homology modeling of G protein-coupled receptors in light of the A_{2A} adenosine receptor crystallographic structure, J. Med. Chem. 52 (2009) 3284–3292.
[43] F.F. Sherbiny, A.C. Schiedel, A. Maaß, C.E. Müller, Homology modelling of the human adenosine A_{2B} receptor based on X-ray structures of bovine rhodopsin, the β2-adrenergic receptor and the human adenosine A_{2A} receptor, J. Comput. Aided Mol. Des. 23 (2009) 807–828.
[44] S.J. Mantell, P.T. Stephenson, S.M. Monaghan, G.N. Maw, M.A. Trevethick, M. Yeadon, D.K. Walker, M.D. Selby, D.V. Batchelor, S. Rozze, H. Chavaroche, A. Lemaitre, K.N. Wright, L. Whitlock, E.F. Stuart, P.A. Wright, F. Macintyre, SAR of a series of inhaled A_{2A} agonists and comparison of inhaled pharmacokinetics in a preclinical model with clinical pharmacokinetic data, Bioorg. Med. Chem. Lett. 19 (2009) 4471–4475.
[45] A. El-Tayeb, J. Iqbal, A. Behrenswert, M. Romio, M. Schneider, H. Zimmermann, J. Schrader, C.E. Müller, Nucleoside-5′-monophosphates as prodrugs of adenosine A_{2A} receptor agonists activated by ecto-5′-nucleotidase, J. Med. Chem. 52 (2009) 7669–7677.

[46] P.G. Baraldi, D. Preti, M.A. Tabrizi, F. Fruttarolo, R. Romagnoli, M.D. Carrion, L.C. Lopez Cara, A.R. Moormann, K. Varani, P.A. Borea, Synthesis and biological evaluation of novel 1-deoxy-1-[6-[((hetero)arylcarbonyl)hydrazine]-9*H*-purin-9-yl]-N-ethyl-β-D-ribofuranuronamide derivatives as useful templates for the development of A_{2B} adenosine receptor agonists, J. Med. Chem. 50 (2007) 374–380.

[47] H. Adachi, K.K. Palaniappan, A.A. Ivanov, N. Bergman, Z.G. Gao, K.A. Jacobson, Structure–activity relationships of 2,N^6,5′-substituted adenosine derivatives with potent activity at the A2B adenosine receptor, J. Med. Chem. 50 (2007) 1810–1827.

[48] M.V. Cohen, J.M. Downey, Adenosine: trigger and mediator of cardioprotection, Basic Res. Cardiol. 103 (2008) 203–215.

[49] T. Eckle, T. Krahn, A. Grenz, D. Köhler, M. Mittelbronn, C. Ledent, K.A. Jacobson, H. Osswald, L.F. Thompson, K. Unertl, H.K. Eltzschig, Cardioprotection by ecto-5′-nucleotidase (CD73) and A_{2B} adenosine receptors, Circulation 115 (2007) 1581–1590.

[50] K.A. Jacobson, A.M. Klutz, D.K. Tosh, A.A. Ivanov, D. Preti, P.G. Baraldi, Medicinal chemistry of the A_3 adenosine receptor: agonists, antagonists, and receptor engineering, HEP Adenosine Receptors in Health and Disease, in: C. Wilson, J. Mustafa (Eds.), Handb. Exp. Pharmacol., 193, Springer, 2009, pp. 123–159.

[51] S.M. Devine, A. Gregg, H. Figler, K. McIntosh, V. Urmaliya, J. Linden, C.W. Pouton, P.J. White, S.E. Bottle, P.J. Scammels, Synthesis and evaluation of new N^6-substituted adenosine-5′-N-methylcarboxamides as A_3 adenosine receptor agonists, Bioorg. Med. Chem. 18 (2010) 3078–3087.

[52] R. Volpini, M. Buccioni, D. Dal Ben, C. Lambertucci, C. Lammi, G. Marucci, A.T. Ramadori, K.N. Klotz, G. Cristalli, Synthesis and biological evaluation of 2-alkynyl-N6-methyl-5′-N-methylcarboxamidoadenosine derivatives as potent and highly selective agonists for the human adenosine A_3 receptor, J. Med. Chem. 52 (2009) 7897–7900.

[53] L.S. Jeong, D.Z. Jin, H.O. Kim, D.H. Shin, H.R. Moon, P. Gunaga, M.W. Chun, Y.C. Kim, N. Melman, Z.-G. Gao, K.A. Jacobson, N^6-Substituted D-4′-thioadenosine-5′-methyluronamides: potent and selective agonists at the human A_3 adenosine receptor, J. Med. Chem. 46 (2003) 3775–3777.

[54] S. Tchilibon, B.V. Joshi, S.K. Kim, H.T. Duong, Z.G. Gao, K.A. Jacobson, (N)-Methanocarba 2,N^6-disubstituted adenine nucleosides as highly potent and selective A3 adenosine receptor agonists, J. Med. Chem. 48 (2005) 1745–1758.

[55] A. Melman, B. Wang, B.V. Joshi, Z.G. Gao, S. de Castro, C.L. Heller, S.K. Kim, L.S. Jeong, K.A. Jacobson, Selective A_3 adenosine receptor antagonists derived from nucleosides containing a bicyclo[3.1.0]hexane ring system, Bioorg. Med. Chem. 16 (2008) 8546–8556.

[56] A.M. Klutz, Z.G. Gao, J. Lloyd, A. Shainberg, K.A. Jacobson, Enhanced A3 adenosine receptor selectivity of multivalent nucleoside–dendrimer conjugates, J. Nanobiotechnol. 6 (2008) 12.

[57] P.G. Baraldi, M.A. Tabrizi, S. Gessi, P.A. Borea, Adenosine receptor antagonists: translating medicinal chemistry and pharmacology into clinical utility, Chem. Rev. 108 (2008) 238–263.

[58] S. Moro, Z.G. Gao, K.A. Jacobson, G. Spalluto, Progress in the pursuit of therapeutic adenosine receptor antagonists, Med. Res. Rev. 26 (2006) 131–159.

[59] S. Schenone, C. Brullo, F. Musumeci, O. Bruno, M. Botta, A1 receptors ligands: past, present, and future trends, Curr. Top. Med. Chem. 10 (2010) 878–901.

[60] M.T. Slawski, M.M. Givertz, Rolofylline: a selective adenosine 1 receptor antagonist for the treatment of heart failure, Exp. Opin. Pharmacother. 10 (2009) 311–322.

[61] J.R. Pfister, L. Belardinelli, G. Lee, R.T. Lum, P. Milner, W.C. Stanley, J. Linden, S.P. Baker, G. Schreiner, Synthesis and biological evaluation of the enantiomers of the potent and selective A1-adenosine antagonist 1,3-dipropyl-8-[2-(5,6-epoxynorbornyl)]xanthin, J. Med. Chem. 40 (1997) 1773–1778.

[62] C.E. Müller, Prodrug approaches for enhancing the bioavailability of drugs with low solubility, Chem. Biodivers. 6 (2009) 2071–2083.

[63] A. Scheiff, S.G. Yerande, A. El-Tayeb, W. Li, G.S. Inamdar, K.K. Vasu, V. Sudarsanam, C.E. Müller, 2-Amino-5-benzoyl-4-phenylthiazoles: development of potent and selective adenosine A_1 receptor antagonists, Bioorg. Med. Chem. 18 (2010) 2195–2203.

[64] C.E. Müller, S. Ferré, Blocking striatal adenosine A_{2A} receptors: a new strategy for basal ganglia disorders, Recent Pat. CNS Drug Discov. 2 (2007) 1–21.

[65] C.E. Müller, S. Ferré, Blocking striatal adenosine A_{2A} receptors: a new strategy for basal ganglia disorders, Frontiers in CNS Drug Discov 1 (2010) 304–341.

[66] U. Shah, R. Hogson, Recent progress in the discovery of adenosine A_{2A} receptor antagonists for the treatment of Parkinson's disease, Curr. Opin. Drug Discov. Devel. 13 (2010) 466–480.

[67] O.M. Abo-Salem, A.M. Hayallah, A. Bilkei-Gorzo, B. Filipek, A. Zimmer, C.E. Müller, Antinociceptive effects of novel A_{2B} adenosine receptor antagonists, J. Pharmacol. Exp. Ther. 308 (2004) 358–366.

[68] A. Bilkei-Gorzo, O.M. Abo-Salem, A.M. Hayallah, K. Michel, C.E. Müller, A. Zimmer, Naunyn Schmiedebergs Arch. Pharmacol. 377 (2008) 65–76.

[69] A.M. Mott, E.J. Nunes, L.E. Collins, R.G. Port, K.S. Sink, J. Hockemeyer, C.E. Müller, J.D. Salamone, The adenosine A_{2A} antagonist MSX-3 reverses the effects of the dopamine antagonist haloperidol on effort-related decision making in a T-maze cost/benefit procedure, Psychopharmacology 204 (2009) 103–112.

[70] L.T. Worden, M. Shahriari, A.M. Farrar, K.S. Sink, J. Hockemeyer, C.E. Müller, J.D. Salamone, The adenosine A_{2A} antagonist MSX-3 reverses the effort-related effects of dopamine blockade: differential interaction with D1 and D2 family antagonists, Psychopharmacology 203 (2009) 489–499.

[71] S.P. Alexander, P.J. Millns, [^{3}H]ZM241385 — an antagonist radioligand for adenosine A_{2A} receptors in brain, Eur. J. Pharmacol. 411 (2001) 205–210.

[72] G. Pastorin, S. Federico, S. Paoletta, M. Corradino, F. Cateni, B. Cacciari, K.-N. Klotz, Z.-G. Gao, K.A. Jacobson, G. Spalluto, S. Moro, Synthesis and pharmacological characterization of a new series of 5,7-disubstituted-[1,2,4]triazolo[1,5-*a*][1,3,5] triazine derivatives as adenosine receptor antagonists: a preliminary inspection of ligand–receptor recognition process, Bioorg. Med. Chem. 18 (2010) 2524–2536.

[73] S. Todde, R.M. Moresco, P. Simonelli, P.G. Baraldi, B. Cacciari, G. Spalluto, K. Varani, A. Monopoli, M. Matarrese, A. Carpinelli, F. Magni, M.G. Kienle, F. Fazio, Design, radiosynthesis, and biodistribution of a new potent and selective ligand for in vivo imaging of the adenosine A_{2A} receptor system using positron emission tomography, J. Med. Chem. 43 (2000) 4359–4362.

[74] O. Saku, M. Saki, M. Kurokawa, K. Ikeda, S-i. Uchida, T. Takizawa, N. Uesaka, Synthetic studies on selective adenosine A_{2A} receptor antagonists. Part II: synthesis and structure–activity relationships of novel benzofuran derivatives, Bioorg. Med. Chem. Lett. 20 (2010) 3768–3771.

[75] P.M. Luthra, C.B. Mishra, P.K. Jha, S.K. Barodia, Synthesis of novel 7-imino-2-thioxo-3,7-dihydro-2*H*-thiazolo[4,5-*d*]pyrimidine derivatives as adenosine A2A receptor antagonists, Bioorg. Med. Chem. 20 (2010) 1214–1218.

[76] C.B. Mishra, S.K. Barodia, A. Prakash, J.B.S. Kumar, P.M. Luthra, Novel 8-(furan-2-yl)-3-substituted thiazolo[5,4-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine-2(3*H*)-thione derivatives as potential adenosine A2A receptor antagonists, Bioorg. Med. Chem. 18 (2010) 2491–2500.

[77] S. Moro, F. Deflorian, M. Bacilieri, G. Spalluto, Ligand-based homology modeling as attractive tool to inspect GPCR structural plasticity, Curr. Pharm. Des. 12 (2006) 2175–2185.

[78] J.A. Auchampach, E. Gizewski, T.C. Wan, S. de Castro, G.G. Brown, K.A. Jacobson, Synthesis and pharmacological characterization of [^{125}I]MRS5127, a high affinity, selective agonist radioligand for the A_3 adenosine receptor, Biochem. Pharmacol. 79 (2010) 967–973.

[79] L.S. Jeong, S. Pal, S.A. Choe, W.J. Choi, K.A. Jacobson, Z.G. Gao, A.M. Klutz, X. Hou, H.O. Kim, H.W. Lee, S.K. Lee, D.K. Tosh, H.R. Moon, Structure activity relationships of truncated D- and L-4′-thioadenosine derivatives as species-independent A_3 adenosine receptor antagonists, J. Med. Chem. 51 (2008) 6609–6613.

[80] Z. Wang, C.W. Do, M.Y. Avila, K. Peterson-Yatorno, R.A. Stone, Z.G. Gao, B.V. Joshi, P. Besada, L.S. Jeong, K.A. Jacobson, M.M. Civan, Nucleoside-derived antagonists to A_3 adenosine receptors lower mouse intraocular pressure and act across species, Exp. Eye Res. 90 (2010) 146–154.

[81] P.N. Zannikos, B.K. Jensen, B.X. Boutouyrie, L. Tripp, L. Yongyi, T. McGowan, S.A. Waldman, H.E. Greenberg, Pharmacokinetics and safety of single intravenous infusions of the adenosine agonist, AMP 579, in patients with end-stage renal insufficiency, J. Clin. Pharmacol. 40 (2000) 745–751.

[82] S.L. Kopecky, R.J. Aviles, M.R. Bell, J.K. Lobl, D. Tipping, G. Frommell, K. Ramsey, A.E. Holland, M. Midei, A. Jain, M. Kellett, R.J. Gibbons, A randomized, double-blinded, placebo-controlled, dose-ranging study measuring the effect of an adenosine agonist on infarct size reduction in patients undergoing primary percutaneous transluminal coronary angioplasty: the ADMIRE (AmP579 Delivery for Myocardial Infarction REduction) study, Am. Heart J. 146 (2003) 146–152.

[83] Y. Liu, X. Yang, X.-M. Yang, S. Walker, K. Förster, M.V. Cohen, T. Krieg, J.M. Downey, AMP579 is revealed to be a potent A_{2b}-adenosine receptor agonist in human 293 cells and rabbit hearts, Basic Res. Cardiol. 105 (2010) 129–137.

[84] T. Porkka-Heiskanen, L. Alanko, A. Kalinchuk, D. Stenberg, Adenosine and sleep, Sleep Med. Rev. 6 (2002) 321–332.

[85] D. Elmenhorst, P.T. Meyer, O.H. Winz, A. Matusch, J. Ermert, H.H. Coenen, R. Basheer, H.L. Haas, K. Zilles, A. Bauer, Sleep deprivation increases A_1 adenosine receptor binding in the human brain: a positron emission tomography study, J. Neurosci. 27 (2007) 2410–2415.

[86] T.M. Palmer, M.A. Trevethick, Suppression of inflammatory and immune responses by the A2A adenosine receptor: an introduction, Br. J. Pharmacol. 153 (2008) S27–S34.

[87] D. Yang, M. Koupenova, D.J. McCrann, K.J. Kopeikina, H.M. Kagan, B.M. Schreiber, K. Ravid, The A2b adenosine receptor protects against vascular injury, Proc. Natl Acad. Sci. USA 105 (2008) 792–796.

[88] J. Guzman, J.G. Yu, Z. Suntres, A. Bozarov, H. Cooke, N. Javed, H. Auer, J. Palatini, H.H. Hassanain, A.J. Cardounel, A. Javed, I. Grants, J.E. Wunderlich, F.L. Christofi, Inflamm. Bowel Dis. 12 (2006) 766–789.

[89] V.L. Kolachala, R. Bajaj, M. Chalasani, S.V. Sitaraman, Purinergic receptors in gastrointestinal inflammation, Am. J. Physiol. Gastrointest. Liver Physiol. 294 (2008) G401–G410.

[90] L. Madi, S. Cohen, A. Ochayin, S. Bar-Yehuda, F.R. Barer, P. Fishman, Over-expression of A_3 adenosine receptor in peripheral blood mononuclear cells in rheumatoid arthritis: involvement of nuclear factor-kappaB in mediating receptor level, J. Rheumatol. 34 (2007) 20–26.

[91] J. Ishikawa, H. Mitani, T. Bandoh, M. Kimura, T. Totsuka, S. Hayashi, Hypoglycemic and hypotensive effects of 6-cyclohexyl-2′-O-methyl-adenosine, an adenosine A_1 receptor agonist, in spontaneously hypertensive rat complicated with hyperglycemia, Diab. Res. Clin. Pract. 39 (1998) 3–9.

[92] C. Lauro, R. Cipriani, M. Catalano, F. Trettel, G. Chece, V. Brusadin, L. Antonilli, N. van Rooijen, F. Eusebi, B.B. Bredholm, C. Limatola, Adenosine A1 receptors and microglial cells mediate CX3CL1-induced protection of hippocampal neurons against Glu-induced death, Neuropsychopharmacology 35 (2010) 1550–1559.

[93] L.J. Knutsen, J. Lau, H. Petersen, C. Thomsen, J.U. Weis, M. Shalmi, M.E. Judge, A.J. Hansen, M.J. Sheardown, N-Substituted adenosines as novel neuroprotective A_1 agonists with diminished hypotensive effects, J. Med. Chem. 42 (1999) 3463–3477.

[94] N.J. Giffin, F. Kowacs, V. Libri, P. Williams, P.J. Goadsby, H. Kaube, Effect of the adenosine A_1 receptor agonist GR79236 on trigeminal nociception with blink reflex recordings in healthy human subjects, Cephalalgia 23 (2003) 287–292.

[95] B. Shah, S. Rohatagi, C. Natarajan, S. Kirkesseli, R. Baybutt, B.K.I. Jensen, Pharmacokinetics, pharmacodynamics, and safety of a lipid-lowering adenosine A1 agonist, RPR749, in healthy subjects, Am. J. Ther. 11 (2004) 175–189.

[96] J.A. Zablocki, L. Wu, J. Shryock, L. Belardinelli, Partial A_1 adenosine receptor agonists from a molecular perspective and their potential use as chronic ventricular rate control agents during atrial fibrillation (AF), Curr. Top. Med. Chem. 4 (2004) 839–854.

[97] A.S. Awad, L. Huang, H. Ye, E.T. Duong, W.K. Bolton, J. Linden, M.D. Okusa, Adenosine A_{2A} receptor activation attenuates inflammation and injury in diabetic nephropathy, Am. J. Physiol. Renal. Physiol. 290 (2006) F828–F837.

[98] A. Desai, C. Victor-Vega, S. Gadangi, M.C. Montesinos, C.C. Chu, B.N. Cronstein, Adenosine A_{2A} receptor stimulation increases angiogenesis by down-regulating production of the antiangiogenic matrix protein thrombospondin 1, Mol. Pharmacol. 67 (2005) 1406–1413.

[99] J.E. Udelson, G.V. Heller, F.J. Wackers, A. Chai, D. Hinchman, P.S. Coleman, V. Dilsizian, M. DiCarli, R. Hachamovitch, J.R. Johnson, R.J. Barrett, R.J. Gibbons, Randomized, controlled dose-ranging study of the selective adenosine A_{2A} receptor agonist binodenoson for pharmacological stress as an adjunct to myocardial perfusion imaging, Circulation 109 (2004) 457–464.

[100] M.D. Cerqueira, Advances in pharmacologic agents in imaging: new A_{2A} receptor agonists, Curr. Cardiol. Rep. 8 (2006) 119–122.

[101] A.E. Iskandrian, T.M. Bateman, L. Belardinelli, B. Blackburn, M.D. Cerqueira, R.C. Hendel, H. Lieu, J.J. Mahmarian, A. Olmsted, S.R. Underwood, J. Vitola, W. Wang, Adenosine versus regadenoson comparative evaluation in myocardial perfusion imaging: results of the ADVANCE phase 3 multicenter international trial, J. Nucl. Cardiol. 14 (2007) 645–658.

[102] I. Avni, H.J. Garzozi, I.S. Barequet, F. Segev, D. Varssano, G. Sartani, N. Chetrit, E. Bakshi, D. Zadok, O. Tomkins, G. Litvin, K.A. Jacobson, S. Fishman, Z. Harpaz, M. Farbstein, S. Bar-Yehuda, M.H. Silverman, W.D. Kerns, I. Cohn, P. Fishman, Treatment of dry eye syndrome with orally-administered CF101: data from a phase 2 clinical trial, Ophthalmology 117 (2010) 1287–1293.

[103] T.C. Wan, Z.D. Ge, A. Tampo, Y. Mio, M.W. Bienengraeber, W.R. Tracey, G.J. Gross, W.M. Kwok, J.A. Auchampach, The A3 adenosine receptor agonist CP-532,903 [N^6-(2,5-dichlorobenzyl)-3′-aminoadenosine-5′-*N*-methylcarboxamide] protects against myocardial ischemia/reperfusion injury via the sarcolemmal ATP-sensitive potassium channel, J. Pharmacol. Exp. Ther. 324 (2008) 234–243.

[104] M. Skouroliakou, F. Bacopoulou, S.L. Markantonis, Caffeine versus theophylline for apnea of prematurity: a randomized controlled trial, J. Paediatr. Child Health 45 (2009) 587–592.

[105] R. Polosa, S.T. Holgate, Adenosine receptors as promising therapeutic targets for drug development in chronic airway inflammation, Curr. Drug Targets 7 (2006) 699–706.

[106] S.S. Gottlieb, Adenosine A_1 antagonists and the cardiorenal syndrome, Curr. Heart Fail. Rep. 5 (2008) 105–109.

[107] J. Che, E.S. Chan, B.N. Cronstein, Adenosine A2A receptor occupancy stimulates collagen expression by hepatic stellate cells via pathways involving protein kinase A, Src, and extracellular signal-regulated kinases 1/2 signaling cascade or p38 mitogen-activated protein kinase signaling pathway, Mol. Pharmacol. 72 (2007) 1626–1636.

[108] H. Yang, M.Y. Avila, K. Peterson-Yantorno, M. Coca-Prados, R.A. Stone, K.A. Jacobson, M.M. Civan, The cross-species A_3 adenosine-receptor antagonist MRS 1292 inhibits adenosine-triggered human nonpigmented ciliary epithelial cell fluid release and reduces mouse intraocular pressure, Curr. Eye Res. 30 (2005) 747–754.

[109] K.A. Jacobson, Z.G. Gao, Adenosine receptors as therapeutic targets, Nat. Rev. Drug Discov. 5 (2006) 247–264.

[110] N. Arispe, J. Ma, K.A. Jacobson, H.B. Pollard, Direct activation of cystic fibrosis transmembrane conductance regulator channels by 8-cyclopentyl-1,3-dipropylxanthine (CPX) and 1,3-diallyl-8-cyclohexylxanthine (DAX), J. Biol. Chem. 273 (1998) 5727–5734.

[111] C.N. Wilson, Adenosine receptors and asthma in humans, Br. J. Pharmacol. 155 (2008) 475–486.

[112] S. Hess, Recent advances in adenosine receptor antagonist research, Exp. Opin. Ther. Pat. 11 (2001) 1533–1561.

[113] T. Terai, Y. Kita, T. Kusonoki, T. Shimazaki, T. Ando, H. Horiai, A. Akahane, Y. Shiokawa, K. Yoshida, A novel non-xanthine adenosine A_1 receptor antagonist, Eur. J. Pharmacol. 279 (1995) 217–225.

[114] B. Hocher, Adenosine A_1 receptor antagonists in clinical research and development, Kidney Int. 78 (2010) 438–445.

[115] P.A. LeWitt, M. Guttman, J.W. Tetrud, P.J. Tuite, A. Mori, P. Chaikin, N.M. Sussman, Adenosine A_{2A} receptor antagonist istradefylline (KW6002) reduces "off" time in Parkinson's disease: a double-blind, randomized, multicenter clinical trial (6002-US-005), Ann. Neurol. 63 (2008) 295–302.

[116] S.J. Pascoe, H. Knight, R. Woessner, QAF805, an A_{2B}/A_3 antagonist, does not attenuate AMP challenge in subjects with asthma, Proc. Am. Thorac. Soc. (2007) A682.

[117] T. Okamura, Y. Kurogi, K. Hashimoto, S. Sato, H. Nishikawa, K. Kiryu, Y. Nagao, Structure–activity relationships of adenosine A3 receptor ligands: new potential therapy for the treatment of glaucoma, Bioorg. Med. Chem. Lett. 14 (2004) 3775–3779.

[118] P.A. Borea, S. Gessi, S. Bar-Yehuda, P. Fishman, A_3 adenosine receptor: pharmacology and role in disease, Handb. Exp. Pharmacol. 193 (2009) 297–327.

[119] A. Bauer, K. Ishiwata, Adenosine receptor ligands and PET imaging in the CNS, Handb. Exp. Pharmacol. (2009) 617–642.

[120] K. Ishiwata, J. Noguchi, H. Toyama, Y. Sakiyama, N. Koike, S. Ishii, K. Oda, K. Endo, F. Suzuki, M. Senda, Synthesis and preliminary evaluation of [^{11}C]KF17837, a selective adenosine A_{2A} antagonist, Appl. Radiat. Isot. 47 (1996) 507–511.

[121] J. Noguchi, K. Ishiwata, S. Wakabayashi, T. Nariai, S. Shumiya, S. Ishii, H. Toyama, K. Endo, F. Suzuki, M. Senda, Evaluation of carbon-11-labeled KF17837: a potential CNS adenosine A2a receptor ligand, J. Nucl. Med. 39 (1998) 498–503.

[122] T. Márián, I. Boros, Z. Lengyel, L. Balkay, G. Horváth, M. Emri, E. Sarkadi, A.J. Szentmiklósi, I. Fekete, L. Trón, Preparation and primary evaluation of [^{11}C]CSC as a possible tracer for mapping adenosine A_{2A} receptors by PET, App. Radiat. Isot. 50 (1999) 887–893.

[123] K. Ishiwata, J. Shimada, W.F. Wang, H. Harakawa, S. Ishii, M. Kiyosawa, F. Suzki, M. Senda, Evaluation of iodinated and brominated [^{11}C]styrylxanthine derivatives as in vivo radioligands mapping adenosine A_{2A} receptor in the central nervous system, Ann. Nucl. Med. 14 (2000) 247–253.

[124] K. Ishiwata, J. Noguchi, S. Wakabayashi, J. Shimada, N. Ogi, T. Nariai, A. Tanaka, K. Endo, F. Suzuki, M. Senda, ^{11}C-labeled KF18446: a potential central nervous system adenosine A_{2A} receptor ligand, J. Nucl. Med. 41 (2000) 345–354.

[125] R.M. Moresco, S. Todde, S. Belloli, P. Simonelli, A. Panzacchi, M. Rigamonti, M. Galli-Kienle, F. Fazio, In vivo imaging of adenosine A_{2A} receptors in rat and primate brain using [^{11}C]SCH442416, Eur. J. Nucl. Med. Mol. Imaging 32 (2005) 405–413.

[126] W. Wadsak, L.K. Mien, K. Shanab, D.E. Ettlinger, D. Haeusler, K. Sindelar, R.R. Lanzenberger, H. Spreitzer, H. Viernstein, B.K. Keppler, R. Dudczak, K. Letter, M. Mitterhauser, Preparation and first evaluation of [^{18}F]FEQSUPPY: a new PET tracer for the adenosine A_3 receptor, Nucl. Med. Biol. 35 (2008) 61–66.

[127] D.O. Kiesewetter, L. Lang, Y. Ma, A.K. Bhattacharjee, Z.G. Gao, B.V. Joshi, A. Melman, S. Castro, K.A. Jacobson, Synthesis and characterization of [^{76}Br]-labeled high affinity A_3 adenosine receptor ligands for positron emission tomography, Nucl. Med. Biol. 36 (2009) 3–10.

[128] L. Yan, J.C. Burbiel, A. Maaß, C.E. Müller, Adenosine receptor agonists: from basic medicinal chemistry to clinical development, Exp. Opin. Emerg. Drugs 8 (2003) 537–576.

[129] J.W. Daly, W.L. Padgett, S.I. Secunda, R.D. Thompson, R.A. Olsson, Structure–activity relationships for 2-substituted adenosines at A_1 and A_2 adenosine receptors, Pharmacology 46 (1993) 91–100.

[130] R.F. Bruns, Adenosine receptor activation in human fibroblasts: nucleoside agonists and antagonists, Can. J. Physiol. Pharmacol. 58 (1980) 673–691.

[131] L.E. Brackett, J.W. Daly, Functional characterization of the A2b adenosine receptor in NIH 3T3 fibroblasts, Biochem. Pharmacol. 47 (1994) 801–814.

[132] C.A. Salvatore, M.A. Jacobson, H.E. Taylor, J. Linden, R.G. Johnson, Molecular cloning and characterization of the human A_3 adenosine receptor, Proc. Natl Acad. Sci. 90 (1993) 10365–10369.

[133] P.J. van Galen, A.H. van Bergen, C. Gallo-Rodriguez, N. Melman, M.E. Olah, A.P. IJzerman, G.L. Stiles, K.A. Jacobson, A binding site model and structure–activity relationships for the rat A_3 adenosine binding site, Mol. Pharmacol. 45 (1994) 1101–1111.

[134] Liang, et al., in: Borea (Ed.), A_3 Adenosine Receptors From Cell Biology to Pharmacology, 2010, pp. 257–280.

[135] E. Elzein, J. Zablocki, A_1 adenosine receptor agonists and their potential therapeutic applications, Expert Opin. Investig. Drugs 17 (2008) 1901–1910.

[136] G.J. Smits, M. McVey, B.F. Cox, M.H. Perrone, K.L. Clark, Cardioprotective effects of the novel adenosine A1/A2 receptor agonist AMP 579 in a porcine model of myocardial infarction, J. Pharmacol. Exp. Ther. 286 (1998) 611–618.

[137] M. Prashad, K. Prasad, O. Repie, A practical synthesis of SDZ WAG 994 by selective methylation of N^6-cyclohexyladenosine, Synth. Commun. 26 (1996) 3967–3977.

[138] D. Beattie, A. Brearley, Z. Brown, S.J. Charlton, B. Cox, R.A. Fairhurst, J.R. Fozard, P. Gedeck, P. Kirkham, K. Meja, L. Nanson, J. Neef, H. Oakman, G. Spooner, R.J. Taylor, R.J. Turner, R. West, H. Woodward, Synthesis and evaluation of two series of 4′-aza-carbocyclic nucleosides as adenosine A_{2A} receptor agonists, Bioorg. Med. Chem. Lett. 20 (2010) 1219–1224.

[139] M.D. Valls, B.N. Cronstein, M.C. Montesinos, Adenosine receptor agonists for promotion of dermal wound healing, Biochem. Pharmacol. 77 (8) (2009) 1117–1124.

[140] A. Kuno, S.D. Critz, L. Cui, V. Solodushko, X.M. Yang, T. Krahn, B. Albrecht, S. Philipp, M.V. Cohen, J.M. Downey, Protein kinase C protects preconditioned rabbit hearts by increasing sensitivity of adenosine A2b-dependent signaling during early reperfusion, J. Mol. Cell. Cardiol. 43 (2007) 262–271.

[141] J.A. Auchampach, L.M. Kreckler, T.C. Wan, J.E. Maas, D. van der Hoeven, E. Gizewski, J. Narayanan, G.E. Maas, Characterization of the A_{2B} adenosine receptor from mouse, rabbit, and dog, J. Pharmacol. Exp. Ther. 329 (2009) 2–13.

[142] L.S. Jeong, H.W. Lee, K.A. Jacobson, H.O. Kim, D.H. Shin, J.A. Lee, Z.G. Gao, C. Lu, H.T. Duong, P. Gunaga, S.K. Lee, D.Z. Jin, M.W. Chun, H.R. Moon, Structure–activity relationships of 2-chloro-N^6-substituted-4′-thioadenosine-5′-uronamides as highly potent and selective agonists at the human A_3 adenosine receptor, J. Med. Chem. 49 (2006) 273–281.

[143] A. Melman, Z.G. Gao, D. Kumar, T.C. Wan, E. Gizewski, J.A. Auchampach, K.A. Jacobson, Design of (*N*)-methanocarba adenosine 5′-uronamides as species-independent A_3 receptor-selective agonists, Bioorg. Med. Chem. Lett. 18 (2008) 2813–2819.

[144] W.R. Tracey, W.P. Magee, J.J. Oleynek, R.J. Hill, A.H. Smith, D.M. Flynn, D.R. Knight, Novel N^6-substituted adenosine 5′-N-methyluronamides with high selectivity for human adenosine A3 receptors reduce ischemic myocardial injury, Am. J. Physiol. Heart Circ. Physiol. 285 (2003) H2780–H2787.

[145] K.A. Jacobson, A.P. IJzerman, J. Linden, 1,3-Dialkylxanthine derivatives having high potency as antagonists at human A2B adenosine receptors, Drug Dev. Res. 47 (1999) 45–53.

[146] B. Grahner, S. Winiwarter, W. Lanzner, C.E. Müller CE, Synthesis and structure–activity relationships of deazaxanthines: analogs of potent A_1- and A_2-adenosine receptor antagonists, J. Med. Chem. 37 (1994) 1526–1534.

[147] J.W. Daly, I. Hide, C.E. Müller, M. Shamim, Caffeine analogs: structure–activity relationships at adenosine receptors, Pharmacology 42 (1991) 309–321.

[148] C.E. Müller, J. Maurinsh, R. Sauer, Binding of [^{3}H]MSX-2 (3-(3-hydroxypropyl)-7-methyl-8-(*m*-methoxystyryl)-1-propargylxanthine) to rat striatal membranes — a new, selective antagonist radioligand for A_{2A} adenosine receptors, Eur. J. Pharm. Sci. 10 (2000) 259–265.

[149] S.-A. Kim, M.A. Marschall, N. Melman, H.S. Kim, C.E. Müller, J. Linden, K.A. Jacobson, Structure–activity relationships at human and rat A_{2B} adenosine receptors of xanthine derivatives substituted at the 1-, 3-, 7-, and 8-positions, J. Med. Chem. 45 (2002) 2131–2138.

[150] D.C.G. Bertarelli, M. Diekmann, A.M. Hayallah, D. Rüsing, J. Iqbal, B. Preiss, E.J. Verspohl, C.E. Müller, Characterization of human and rodent native and recombinant adenosine A_{2B} receptors by radioligand binding studies, Purinergic Signal. 2 (2006) 559–571.

[151] C.E. Müller, D. Shi, M. Manning Jr., J.W. Daly, Synthesis of paraxanthine analogs (1,7-disubstituted xanthines) and other xanthines unsubstituted at the 3-position: structure–activity relationships at adenosine receptors, J. Med. Chem. 36 (1993) 3341–3349.

[152] K.N. Klotz, H. Vogt, H. Tawfik-Schlieper, Comparison of adenosine receptors in brain from different species by radioligand binding and photoaffinity labelling, Naunyn Schmiedebergs Arch. Pharmacol. 343 (1991) 196–201.

[153] J.R. Fozard, F. Baur, C. Wolber, Antagonist pharmacology of adenosine A_{2B} receptors from rat, guinea pig and dog, Eur. J. Pharmacol. 475 (2003) 79–84.

[154] K.A. Jacobson, B. Fischer, X.D. Ji, A "cleavable trifunctional" approach to receptor affinity labeling: regeneration of binding to A_1-adenosine receptors, Bioconjug. Chem. 6 (1995) 255–263.

[155] J.A. Auchampach, X. Jin, T.C. Wan, G.H. Caughey, J. Linden, Canine mast cell adenosine receptors: cloning and expression of the A_3 receptor and evidence that degranulation is mediated by the A_{2B} receptor, Mol. Pharmacol. 52 (1997) 846–860.

[156] A.M. Hayallah, J. Sandoval-Ramírez, U. Reith, U. Schobert, B. Preiss, B. Schumacher, J.W. Daly, C.E. Müller, 1,8-Disubstituted xanthine derivatives: synthesis of potent A2B-selective adenosine receptor antagonists, J. Med. Chem. 45 (2002) 1500–1510.

[157] W.F. Kiesman, J. Zhao, P.R. Conlon, R.C. Petter, X. Jin, G. Smits, F. Lutterodt, G.W. Sullivan, J. Linden, Norbornyllactone-substituted xanthines as adenosine A_1 receptor antagonists, Bioorg. Med. Chem. 14 (2006) 3654–3661.

[158] W.F. Kiesman, J. Zhao, P.R. Conlon, J.E. Dowling, R.C. Petter, F. Lutterodt, X. Jin, G. Smits, M. Fure, A. Jayaraj, J. Kim, G. Sullivan, J. Linden, Potent and orally bioavailable 8-bicyclo[2.2.2]octylxanthines as adenosine A_1 receptor antagonists, J. Med. Chem. 49 (2006) 7119–7131.

[159] S.A. Doggrell, BG-9928 (Biogen Idec), Curr. Opin. Investig. Drugs 6 (2005) 962–968.

[160] P. Kalk, B. Eggert, K. Relle, M. Godes, S. Heiden, Y. Sharkovska, Y. Fischer, D. Ziegler, G.W. Bielenberg, B. Hocher, The adenosine A_1 receptor antagonist SLV320 reduces myocardial fibrosis in rats with 5/6 nephrectomy without affecting blood pressure, Br. J. Pharmacol. 151 (2007) 1025–1032.

[161] P.C. Obiefuna, V.K. Batra, A. Nadeem, P. Borron, C.N.H. Wilson, S.J. Mustafa, A novel A1 adenosine receptor antagonist, L-97-1 [3-[2-(4-aminophenyl)-ethyl]-8-benzyl-7-{2-ethyl-(2-hydroxy-ethyl)-amino]-ethyl}-1-propyl-3,7-dihydro-purine-2,6-dione], reduces allergic responses to house dust mite in an allergic rabbit model of asthma, J. Pharmacol. Exp. Ther. 315 (2005) 329–336.

[162] H. Kase, The adenosine A_{2A} receptor selective antagonist KW6002: research toward a novel nondopaminergic therapy for Parkinson's disease, Neurology 61 (2003) S97–S100.

[163] J. Shimada, N. Koike, H. Nonaka, S. Shiozaki, K. Yanagawa, T. Kanda, H. Kobayashi, M. Ichimura, J. Nakamura, H. Kase, F. Suzuki, Adenosine A_{2A} antagonists with potent anti-cataleptic activity, Bioorg. Med. Chem. Lett. 7 (1997) 2349–2352.

[164] J. Pretorius, S.F. Malan, N. Castagnoli Jr., J.J. Bergh, J.P. Petzer, Dual inhibition of monoamine oxidase B and antagonism of the adenosine A2A receptor by (*E*,*E*)-8-(4-phenylbutadien-1-yl)caffeine analogues, Bioorg. Med. Chem. 16 (2008) 8676–8684.

[165] K.A. Jacobson, C. Gallo-Rodriguez, N. Melman, B. Fischer, M. Maillard, A. van Bergen, P.J. van Galen, Y. Karton, Structure–activity relationships of 8-styrylxanthines as A_2-selective adenosine antagonists, J. Med. Chem. 36 (1993) 1333–1342.

[166] R.J. Gillespie, S.J. Bamford, R. Botting, M. Comer, S. Denny, S. Gaur, M. Griffin, A.M. Jordan, A.R. Knight, J. Lerpiniere, S. Leonardi, S. Lightowler, S. McAteer, A. Merrett, A. Misra, A. Padfield, M. Reece, M. Saadi, D.L. Selwood, G.C. Stratton, D. Surry, R. Todd, X. Tong, V. Ruston, R. Upton, S.M. Weiss, Antagonists of the human A2A receptor. 4. Design, synthesis, and preclinical evaluation of 7-aryltriazolo [4,5-*d*]pyrimidines, J. Med. Chem. 52 (2009) 33–47.

[167] P. Minetti, M.O. Tinti, P. Carminati, M. Castorina, M.A. Di Cesare, S. Di Serio, G. Gallo, O. Ghirardi, F. Giorgi, L. Giorgi, G. Piersanti, F. Bartoccini, G. Tarzia, 2-n-Butyl-9-methyl-8-[1,2,3]triazol-2-yl-9H-purin-6-ylamine and analogues as A2A adenosine receptor antagonists. Design, synthesis, and pharmacological characterization, J. Med. Chem. 48 (2005) 6887–6896.

[168] Y.-S. Kim, X.-d. Ji, N. Melman, J. Linden, K.A. Jacobson, Anilide derivatives of an 8-phenylxanthine carboxylic congener are highly potent and selective antagonists at human A_{2B} adenosine receptors, J. Med. Chem. 43 (2000) 1165–1172.

[169] P.G. Baraldi, M.A. Tabrizi, D. Preti, A. Bovero, R. Romagnoli, F. Fruttarolo, N.A. Zaid, A.R. Moorman, K. Varani, S. Gessi, S. Merighi, P.A. Borea, Design, synthesis, and biological evaluation of new 8-heterocyclic xanthine derivatives as highly potent and selective human A_{2B} adenosine receptor antagonists, J. Med. Chem. 47 (2004) 1434–1447.

[170] E. Elzein, R.V. Kalla, X. Li, T. Perry, A. Gimbel, D. Zeng, D. Lustig, K. Leung, J. Zablocki, Discovery of a novel A_{2B} adenosine receptor antagonist as a clinical candidate for chronic inflammatory airway diseases, J. Med. Chem. 51 (2008) 2267–2278.

[171] P. Eastwood, J. Gonzalez, S. Paredes, A. Nueda, T. Domenech, J. Alberti, B. Vidal, Discovery of N-(5,6-diarylpyridin-2-yl)amide derivatives as potent and selective A2B adenosine receptor antagonists, Bioorg. Med. Chem. Lett. 20 (2010) 1697–1700.

[172] B. Vidal, A. Nueda, C. Esteve, T. Domenech, S. Benito, R.F. Reinoso, M. Pont, M. Clabet, R. Lopez, M.I. Cadavid, M.I. Loza, A. Cardenas, N. Godessart, J. Beleta, G. Varrellow, H. Ryder, Discovery and characterization of 4′-(2-furyl)-N-pyridin-3-yl-4,5′-bipyridmidin-2′-amine (LAS38096), a potent, selective, and efficacious A2B adenosine receptor antagonist, J. Med. Chem. 50 (2007) 2732–2736.

[173] S.T. Bedford, K.R. Benwell, T. Brooks, I. Chen, M. Comer, S. Dugdale, T. Haymes, A.M. Jordan, G.A. Kennett, A.R. Knight, B. Klenke, L. LeStrat, A. Merrett, A. Misra, S. Lightowler, A. Padfield, K. Poullennec, M. Reece, H. Simmonite, M. Wong, I.A. Yule, Discovery and optimization of potent and selective functional antagonists of the human adenosine A_{2B} receptor, Bioorg. Med. Chem. Lett. 19 (2009) 5945–5949.

[174] A.W.-H. Cheung, J. Brinkman, F. Firooznia, A. Flohr, J. Grimsby, M.L. Gubler, K. Guertin, R. Hamid, N. Marcopulos, R. Norcross, L. Qi, G. Ramsey, J. Tan, Y. Wen, R. Sarabu, 4-Substituted-7-N-alkyl-N-acetyl 2-aminobenzothiazole amides: drug-like and non-xanthine based A_{2B} adenosine receptor antagonists, Bioorg. Med. Chem. Lett. 20 (2010) 4140–4146.

[175] P. Eastwood, J. Gonzales, S. Paredes, S. Fonquerna, A. Cardús, J.A. Alonso, A. Nueda, T. Domenech, R.F. Reinoso, B. Vidal, Discovery of potent and selective bicyclic A_{2B} adenosine receptor antagonists via bioisosteric amide replacement, Bioorg. Med. Chem. Lett. 20 (2010) 1634–1637.

[176] M. Stewart, A.G. Steinig, C. Ma, J.P. Song, B. McKibben, A.L. Castelhano, S.J. MacLennan, [^{3}H]OSIP339391, a selective, novel, and high affinity antagonist radioligand for adenosine A_{2B} receptors, Biochem. Pharmacol. 68 (2004) 305–312.

[177] J.R. Fozard, et al., in: Borea (Ed.), A_3 Adenosine Receptors From Cell Biology to Pharmacology, 2010., Chapter 1.

[178] S.L. Cheong, A. Dolzhenko, S. Kachler, S. Paoletta, S. Federico, B. Cacciari, A. Dolzhenko, K.-N. Klotz, S. Moro, G. Spalluto, G. Pastorin, The significance of 2-furyl ring substitution with a 2-(para-substituted) aryl group in a new series of pyrazolo-triazolo-pyrimidines as potent and highly selective hA_3 adenosine receptor antagonists: new insights into structure–affinity relationship and receptor-antagonist recognition, J. Med. Chem. 53 (2010) 3361–3375.

[179] J.E. van Muijlwijk-Koezen, H. Timmerman, H. van der Goot, W.M. Menge, J. Freijtag von Drabbe Künzel, A.P. IJzerman, Isoquinoline and quinazoline urea analogues as antagonists for the human adenosine A_3 receptor, J. Med. Chem. 43 (2000) 2227–2238.

[180] M. Saki, H. Tsumuki, H. Nonaka, J. Shimada, M. Ichimura, KF26777 (2-(4-bromophenyl)-7,8-dihydro-4-propyl-1*H*-imidazo[2,1-*i*]purin-5(4*H*)-one dihydrochloride), a new potent and selective adenosine A3 receptor antagonist, Eur. J. Pharmacol. 444 (2002) 133–141.

[181] V. Ozola, M. Thorand, M. Diekmann, R. Qurishi, B. Schumacher, K.A. Jacobson, C.E. Müller, 2-Phenylimidazo[2,1-*i*]purin-5-ones: structure–activity relationships and characterization of potent and selective inverse agonists at human A3 adenosine receptors, Bioorg. Med. Chem. 11 (2003) 347–356.

[182] C.E. Müller, M. Diekmann, M. Thorand, V. Ozola, [3H]8-Ethyl-4-methyl-2-phenyl-(8*R*)-4,5,7,8-tetrahydro-1*H*-imidazo[2,1-*i*]purin-5-one ([3H]PSB-11), a novel high-affinity antagonist radioligand for human A3 adenosine receptors, Bioorg. Med. Chem. Lett. 12 (2002) 501–503.

[183] O. Lenzi, V. Colotta, D. Catarzi, F. Varano, D. Poli, G. Filacchioni, K. Varani, F. Vicenzi, P.A. Borea, S. Paoletta, E. Morizzo, S. Moro, 2-Phenylpyrazolo[4,3-*d*] pyrimidin-7-one as a new scaffold to obtain potent and selective human A3 adenosine receptor antagonists: new insights into the receptor-antagonist recognition, J. Med. Chem. 52 (2009) 7640–7652.

[184] S. Pal, W.J. Choi, S.A. Choe, C.L. Heller, Z.G. Gao, M. Chinn, K.A. Jacobson, X. Hou, S.K. Lee, H.O. Kim, L.S. Jeong, Structure–activity relationships of truncated adenosine derivatives as highly potent and selective human A_3 adenosine receptor antagonists, Bioorg. Med. Chem. 17 (2009) 3733–3738.

[185] T. Maemoto, M. Tada, T. Mihara, N. Ueyama, H. Matsuoka, K. Harada, T. Yamaji, K. Shirakawa, S. Kuroda, A. Akahane, A. Iwashita, N. Matsuoka, S. Mutoh, Pharmacological characterization of FR194921, a new potent, selective, and orally active antagonist for central adenosine A_1 receptors, J. Pharmacol. Sci. 96 (2004) 42–52.

[186] H. Nonaka, A. Mori, M. Ichimura, T. Shindou, K. Yanagawa, J. Shimada, H. Kase, Binding of [$_3$H]KF17837S, a selective adenosine A2 receptor antagonist, to rat brain membranes, Mol. Pharmacol. 46 (1994) 817–822.

[187] C.E. Müller, J. Hipp, U. Schobert, W. Frobenius, M. Pawlowski, F. Suzuki, J. Sandoval-Ramírez, Synthesis and structure–activity relationships of 3,7-dimethyl-1-propargylxanthine derivatives, A2A-selective adenosine receptor antagonists, J. Med. Chem. 40 (1997) 4396–4405.

[188] C.E. Müller, A_{2A} Adenosine receptor antagonists — future drugs for Parkinson's disease? Drugs Fut. 25 (2000) 1043–1052.

[189] A.-H. Li, S. Moro, N. Forsyth, N. Melman, X.-D. Ji, K.A. Jacobson, Synthesis, CoMFA analysis, and receptor docking of 3,5-diacyl-2,4-dialkylpyridine derivatives as selective A3 adenosine receptor antagonists, J. Med. Chem. 42 (1999) 706–721.

[190] E. Hirani, J. Gillies, A. Karasawa, J. Shimad, H. Kase, J. Opacka-Juffry, S. Osman, S.K. Kuthra, S.P. Hume, D.J. Brooks, Evaluation of [4-O-methyl-^{11}C]KW-6002 as a potential PET ligand for mapping central adenosine A_{2A} receptors in rats, Synapse 42 (2001) 164–176.

[191] W. Al Jaroudi, A.E. Iskandrian, Regadenoson: a new myocardial stress agent, J. Am. Coll. Cardiol. 54 (2009) 1123–1130.

[192] P. Eastwood, C. Esteve, J. González, S. Fonquerna, J. Aiguadé, I. Carranco, T. Doménech, M. Aparici, M. Miralpeix, J. Albertí, M. Córdoba, R, Fernández, M. Pont, N. Godessart, N. Prats, M. I. Loza, M. I. Cadavid, A. Nueda, B. Vidal, Discovery of LAS101057: a potent, selective, and orally efficacious A_{2B} adenosine receptor antagonist. ACS Med. Chem. Lett. 1 (in press) doi:10.1021/ml100249e.