Xanthines as Adenosine Receptor Antagonists

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Abstract

The natural plant alkaloids caffeine and theophylline were the first adenosine receptor (AR) antagonists described in the literature. They exhibit micromolar affinities and are non-selective. A large number of derivatives and analogs have subsequently been synthesized and evaluated as AR antagonists. Very potent antagonists have thus been developed with selectivity for each of the four AR subtypes.

Keywords

adenosine receptors; A_1 receptor antagonists; A_{2A} receptor antagonists; A_{2B} receptor antagonists; A_3 receptor antagonists; caffeine; deazaxanthines; molecular probes; paraxanthine; theobromine; theophylline; tricyclic xanthine derivatives; xanthines

1. Caffeine and theophylline - historical aspects and early structural modification

1.1. Naturally occuring xanthines

The earliest adenosine receptor (AR) antagonists identified were the naturally-occurring alkylxanthines, most notably among these being caffeine (1,3,7-trimethylxanthine, **1**) and theophylline (1,3-dimethylxanthine, **2**) (see Fig. 1) (Daly 1982; Fredholm 1999; Stefanovich 1989). Another simple natural xanthine, theobromine (**3**) was shown to have only weak activity as AR antagonist (Müller et al. 1993a). The major caffeine metabolites in humans, paraxanthine (**4**) and 1-methylxanthine (**5**) (Krämer and Testa 2008), the latter being also the major metabolite of theophylline, are similarly potent as caffeine and theophylline and may contribute their activity (Daly et al. 1986a; Müller et al. 1993b). These simple alkylxanthines are of micromolar affinity, at best, at the ARs, and variation of affinity between species has been documented (see table 1). This affinity range was later shown to apply generally to all human AR subtypes, A_1, A_{2A}, A_{2B} and A_3, but only to three of the AR subtypes of the rat (A_1, A_{2A}, and A_{2B}). At the rat A_3AR, the simple alkylxanthines were shown to have much higher K_i values of ~ 10^{-4} M or higher (Fredholm et al. 1994; van Galen et al. 1994).

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1.1. Early modification of 8-unsubstituted xanthine derivatives

The first xanthine analogues with enhanced affinity at the ARs were modified from caffeine and theophylline (Daly 2000; Dlay 2007; Müller et al. 1993a; Fredholm et al. 2009). In the early 1980s, one particular type of modification of the xanthine structure proved to be especially useful in enhancing affinity: the elongation of the 1,3-dimethyl groups to propyl or larger alkyl groups (Bruns 1981; Ukena et al. 1986b). For example, substitution of the 1,3-dimethyl groups with 1,3-dipropyl groups in **16** increased affinity at the rat A_1AR by ~ 20-fold (table 1). Substitutions at the 1-, 3-, or 7-positions, particularly small hydrophobic groups, were generally much better tolerated in AR binding than substitution at the 9-position (Daly 1982; Müller et al. 1993a). Evaluation of a series of mono-substituted xanthines (**5–14**) showed that substitution at N1 was most important for all AR subtypes (Müller et al., 1993b). While a 1-propyl residue was best for A_{2B} and A_3 receptors, a 1-benzyl residue was optimal for the A_1 and A_{2A} AR subtypes (see table 1). 1-Propylxanthine (**6**) shows the highest affinity of the small, simple xanthine derivatives for the human A_{2B} receptor (K_i 360 nM) along with some selectivity (at least 7-fold vs. the other subtypes) (Kim et al. 2002), while 3-propylxanthine (enprofylline, **10**) is less potent (K_i human A_{2B} 4,730 nM), but even more selective (at least 14-fold).

3,7-Dimethyl-1-propargylxanthine (DMPX, **20**) was the first A_2-selective AR antagonist described in the literature (Ukena et al. 1986b; Seale et al. 1988). It is similarly potent at A_{2A} and A_{2B} receptors, but the degree of selectivity versus A_1 receptors is low (Jacobson et al. 1992a). A comparison with the 7-unmethylated derivative 3-methyl-1-propargylxanthine (**18**) indicated that a 7-methyl group led to a large decrease in A_1 affinity and thus increased selectivity for A_{2A} or A_{2B} (Müller et al. 1993b; Kim et al. 2002). The theophylline derivative doxofylline **15** bearing a 1,3-dioxolan-2-ylmethyl residue in the 7-position is virtually inactive at A_1 and A_{2A}AR and is believed to exert its antiasthmatic activity via inhibition of phosphodiesterases (Cirillo et al. 1988; Shukla et al. 2009).

The branched analogue IBMX **17** shows potency as a phosphodiesterase (PDE) inhibitor in the same concentration range as is required to block ARs (Ukena et al. 1993).

1,3-Dibutylxanthine-7-ribosides (**21**,**22**) were found to bind effectively at A_3 receptors indicating that the ribose group – as in adenosine – can act as a secondary anchor or recognition moiety in the receptor binding site (van Galen et al. 1994; Kim et al. 1994b; Park et al. 1998). This series of xanthine-7-ribosides also provided an early indication of modes of ligand binding at ARs, i.e. the overlay of receptor-bound positions of xanthine and adenine moieties. The 5′-uronamide modification of the CH_2OH group of the ribose moiety greatly enhanced A_3AR affinity as was shown for adenosine agonists, such that DBXRM was 143-fold selective (Kim et al. 1994b). DBXRM (**22**) was found to be a full agonist at the A_3AR, unlike other xanthine derivatives. It is proposed that the ribose moiety contains the essential structure and required flexibility to effect the conformational change of the receptor needed for activation (Gao et al. 2002).

1.2. Progression to xanthines with subtype selectivity

In addition to substitution of the 1,3-dimethyl groups with larger 1,3-dialkyl groups, a means of increasing affinity at the rat A_1AR was found to be the introduction of 8-aryl substituents (fig. 2 and table 2) (Bruns 1981; Daly et al. 1986b; Jacobson et al. 1988; Jacobson et al. 1992a; Müller et al. 1996). For example, placement of a phenyl group at the 8-position, generally increased A_1AR affinity by at least an order of magnitude (table 2). The first analogue having both 1,3-dialkyl and 8-phenyl modifications to be studied in detail was 1,3-diethyl-8-phenylxanthine (DPX, **25**), which diplayed a K_i value of 44 nM at the rat A_1AR and was beginning to show selectivity for that subtype (Bruns et al. 1987a). [^{3}H]DPX was

demonstrated as the first AR antagonist radioligand, but its hydrophobicity limited its use (Bruns et al. 1980). Homologation to the 1,3-propyl groups in the 8-aryl analogue **26** provided a desired boost in affinity, however, the unintended consequence of rapidly diminishing aqueous solubility made this series unable to be used in typical pharmacological studies (Ukena et al. 1986b; Bruns and Fergus 1989). The 8-*p*-hydroxyphenyl-substituted derivative **33** (NPC-205) was slightly more potent than **26** (Shamim et al. 1988). The low aqueous solubility, which is both a function of lipophilic groups present on the xanthine and the tendency of 8-arylxanthine derivatives to form highly stable crystal lattices, resulted in low bioavailability of **26** and similar compounds (Müller et al. 1996; Frédérick et al. 2005).

Several approaches were taken to increase the water solubility. A sulfonate group was introduced at the *p*-position of the 8-phenyl ring, which greatly increased solubility (Daly et al. 1985; Shamim et al. 1989). However, this modification tended to decrease both affinity and selectivity, in comparison to the uncharged 8-phenyl analogues. Thus, SPT (**27**) and DPSPX (**28**), the latter of which is somewhat more potent, were both useful in pharmacological experiments where a blockade of all AR subtypes is required. It has to be kept in mind that these compounds do not block rat A_3 receptors but are active at other species like human and sheep (table 2). SPT (**27**) was shown not to penetrate into the brain due to its high polarity (Baumgold et al. 1992).

2. Adenosine A_1 receptor antagonists

2.1. 8-Aryl- and 8-arylalkyl-substituted xanthines

An alternative approach to the introduction of charged groups for increasing water solubility resulted in the synthesis of the 8-aryl derivatives in which the charged group was separated from the phenyl ring by a spacer group. Various substitutions of an 8-phenyl ring indicated that an electron-donating group provided a favorable AR affinity (Jacobson et al. 1985b; Shamim et al. 1988). Thus, a methoxy substituent was elaborated into a carboxymethyloxy group resulting in carboxylic congener XCC **36** and amine congener 8-[4-[[[[(2-aminoethyl)amino]carbonyl]methyl]oxy]phenyl]-l,3-dipropylxanthine (XAC, **30**) (fig. 2 and table 2) (Jacobson et al. 1985b; Jacobson et al. 1999). By placing the charged group at a distance from the 8-aryl ring, it was possible to maintain and even enhance the high affinity seen with neutral, but poorly soluble analogues. Thus, XAC was found to have a K_i value of 1.2 nM at the rat A_1AR and ~50-fold selectivity in comparison to the rat A_2AR. The initial measure of A_2AR affinity used in Jacobson et al. (1985b) was the inhibition of cyclic AMP accumulation in rat brain slices, which corresponds more closely to the A_{2B}AR, rather than the A_{2A}AR. However, subsequent tests at the rat A_{2A}AR confirmed that there was still a margin of selectivity of XAC in binding to the A_1AR in rat (Ukena et al, 1986c). The substitution of the 1,3-dipropyl groups of XAC with 1,3-diethyl increased affinity at the A_{2A}AR while decreasing it at the A_1AR (Jacobson et al. 1987a). The aqueous solubility of XAC was found to be 25 μM, which was an improvement over the uncharged 8-aryl derivatives. Therefore, XAC was suitable for use in pharmacological experiments as a general AR antagonist and was the first such antagonist to display moderate A_1AR selectivity at least in rat.

Given the promise of a relatively water-soluble and somewhat selective xanthine derivative, this amine-functionalized derivative of 1,3-dipropyl-8-phenylxanthine was specifically radiolabeled on the 1,3-dipropyl groups by catalytic reduction of a 1,3-diallyl precursor. The resulting [^{3}H]XAC was useful as a radiotracer in binding experiments at rat cerebral cortical A_1ARs with a K_D value of ~ 1 nM, and was thus the first generally useful antagonist radioligand for study of this receptor (Jacobson et al. 1986a). [^{3}H]XCC **36** was also introduced as a high affinity radioligand for the A_1AR (Jarvis et al. 1987).

Another rationale for the design of XAC with a primary amino group was the "functionalized congener approach" to drug design (Jacobson et al. 1986b; Jacobson 2009). By this approach, a chemically functionalized chain is incorporated at an insensitive site on the xanthine pharmacophore and can be extended to enable a conjugation strategy. Such high affinity conjugates are useful for AR characterization and can be coupled to radioactive or spectroscopic reporter groups without losing the ability to bind to the receptor (Jacobson et al. 1987b). XAC was also used as an immobilized high-affinity ligand for the purpose of affinity chromatography leading to the isolation of both A_1 and A_{2A} receptors and their purification to homogeneity (Olah et al. 1989; Weiss and Grisshammer 2002). While in XAC the polar, basic residue was connected to the 8-phenyl ring via ether and amide linkages, in another series sulphonamide-linked derivatives were investigated (**31**,**32**, fig. 2). Compound **31** and its congeners were potent A_1 antagonists, but showed only a moderate degree of selectivity (table 2) (Bruns et al. 1986; Bruns et al. 1987a).

Besides 8-phenylxanthine derivatives 8-benzyl- (**62**) and 8-phenylethyl-substituted xanthines (**59–61**) have also been investigated and optimized with respect to A_1 affinity (Peet et al. 1993). Among 8-(arylalkyl)-xanthine derivatives, 3-[2-(4-aminophenyl)ethyl]-8-benzyl-7-{2-ethyl(2-hydroxyethyl)amino]ethyl}-1-propyl-3,7-dihydropurine-2,6-dione (L-97-1, **62**) is weaker in binding than typical 8-arylxanthine probes, but is a water soluble A_1 AR antagonist bearing a basic substituent at N7 that has been proposed for the treatment of asthma (Obiefuna et al., 2005). 1,3-Dipropyl-8-phenylethyl-xanthine derivatives with a methyl (**59–60**) or ethyl (**61**) substituent at the α-carbon atom adjacent to the xanthine C8-position showed particularly high affinity and selectivity for A_1AR with a configurational preference for the (*R*)- over the (*S*)-enantiomer (Peet et al. 1993).

2.2. 8-Cycloalkylxanthines

The introduction of 8-cycloalkyl groups instead of 8-aryl groups proved to be beneficial for affinity at the A_1AR, and also allowed sufficient aqueous solubility for broad pharmacological application (fig. 3 and table 3). The 8-cycloalkylxanthine derivative that is most widely used as a pharmacological tool is DPCPX (**65**, also known as CPX), which is ~500-fold selective for rat A_1AR in comparison to the A_{2A}AR (Bruns et al. 1987a). Among the human ARs, the A_1AR selectivity is less than in the rat (table 3). The corresponding cyclohexyl analogue is similar in its pharmacological profile (Shamim et al. 1989). Curiously, DPCPX was in clinical trials for the treatment of cystic fibrosis through a non-AR related mechanism. It was found to act on the CFTR (cystic fibrosis-related chloride transporter) to enhance chloride in cells systems, an action that is unrelated to its AR antagonism (Cohen et al. 1997; Sorbera et al. 2000).

More bulky cycloalkyl substituents in the xanthine 8-position, such as 3-noradamantyl (e.g. rolofylline (KW3902, **69**) and **77**), (substituted) norbornyl (naxifylline (BG-9719, CVT124, **80**), and the lactone **81**), dicyclopropylmethyl (MPDX, **83**, and KF15372, **84**) and bicyclo[2.2.2]octyl (toponafylline (BG-9928, **82**)) yielded very potent and selective A_1 antagonists (fig. 3 and table 3).

The 2-thio analog of DPCPX (**65**), 2-thio-DPCPX (**66**) was similarly potent and selective as **65** showing that in the 2-position a hydrogen bond acceptor (like a keto group) was not required (Jacobson et al. 1989b)). Replacement of the 3-propyl residue in DPCPX by a phenyl (**73**), benzyl (**72**), or a chiral methylbenzyl residue (**70**,**71**) was well tolerated (Weyler et al. 2006). However, the affinity for the human A_3AR was increased by the lipophilic, aromatic residues, and the compounds lost A_1-selectivity vs. A_3. The introduction of polar hydroxy groups in the 3-position was well tolerated by the A_1, but not by the A_3AR leading to very potent and highly selective A_1 antagonists (**74**,**75**,**77–79**) (Weyler et al.

2006; Massip et al. 2006). In fact, 1-butyl-3-(3-hydroxypropyl)8-(3-noradamantyl)xanthine (PSB-36, **77**) is one of the most potent A_1 antagonists described to date showing K_i values of 0.124 nM (rat), and 700 nM (human), respectively. The hydroxylated DPCPX derivative **74** (PSB-16) was converted to its phosphoric acid ester disodium salt, yielding a highly water-soluble A_1 antagonist prodrug suitable for parenteral application without the need for detergents and organic solvents (Weyler et al. 2006).

Several other polar derivatives and analogs of DPCPX were developed in order to further improve water-solubility and bioavailability. Apaxifylline (**67**) with a keto group at C3 of the cyclopentyl ring was clinically evaluated as a memory-enhancing drug for the treatment of dementias (Schingnitz et al. 1991). An amino-substituted DPCPX derivative, midaxifylline (**68**) has also been investigated (Ceccarelli et al. 1995). A promising second-generation compound currently undergoing clinical trials for the treatment of chronic heart failure is toponafylline (**82**), which contains a carboxylate function (Doggrell, 2005). Rolofylline (**69**), an A_1 antagonist of the first generation, had shown promising results in a pilot phase III study in patients with acute heart failure, but in a recently published larger phase III study (PROTECT) it did not exhibit significant improvement over placebo (Slawsky et al. 2009). Further potential applications for A_1AR antagonists include hypertension and renal diseases due to their diuretic and kidney-protective effects. The feasibility of designing kidney-selective prodrugs of an A_1AR antagonist has been demonstrated (Barone et al. 1989). Yet other applications are cardiac arrhythmia, asthma and other respiratory disorders, and the prevention of organ damage, e.g. resulting from transplantation (Jacobson et al. 1992a; Müller et al. 1996; Müller 1997; Jacobson et al. 2006; Moro et al. 2006; Givertz 2009).

2.3. Species differences

Among the human ARs, the A_1AR affinity and selectivity (vs. A_{2A} and A_{2B}AR) of 8-cycloalkyl and 8-aryl derivatives is typically less than in the rat (see table 2 and 3). Several groups have studied the species dependence of the AR affinity of xanthine derivatives (see Ukena et al. 1986b; Klotz et al. 1991; Müller et al. 1993; Müller 1997; Kull et al. 1999; Fozard et al. 2003; Auchampach 2009). An early conclusion was that the affinity of typical 8-substituted analogues (both aryl and cycloalkyl) was greatest at the bovine A_1AR, intermediate at the rat A_1AR, and lowest at the porcine A_1AR. Later, it was found that the human A_1AR most closely resembled the porcine A_1AR, in that respect. At the A_{2A} and the A_{2B}AR the opposite is true although differences are moderate: 8-substituted xanthines, such as XAC and DPCPX, are more potent at the human receptor than at the rat ortholog. The largest species differences are observed for the A_3 receptor: 8-phenyl- and 8-cyclopentylxanthines are typically much more potent at the human than at the rat A_3 receptor (Linden 1994; Ji et al 1994; Jacobson 1998; Müller 2001; Müller 2003).

2.4. Deaza- and azaxanthines

Analogs of xanthine derivatives, such as caffeine, theophylline, and 1,3-dialkyl-8-phenylxanthine have been synthesized which are lacking either the N7 (“7-deazaxanthines”) or the N9 nitrogen atom (“9-deazaxanthines”) in the imidazole partial structure (compounds **109–116**, fig. 5 and table 5). It was found that the nitrogen atom in the 9-position was not required for high receptor affinity, the 9-deazaxanthines being even slightly more potent at A_1AR in comparison with the corresponding xanthine derivatives (Grahner et al., 1994). To the contrary, 7-deazaxanthines were much less potent proving that the xanthines will bind as 7*H*-rather than 9*H*-tautomers to the receptors (Grahner et al., 1994). The addition of another nitrogen atom into the 8-position of xanthines was less successful: 8-azaxanthines (**123–126**, fig. 5 and table 5) showed only moderate affinity for the receptors (Franchetti et al. 1994)

which can be explained by the lacking of the N7-*H* atom that is required as a hydrogen bond donor for high-affinity binding.

2.5. Tricyclic xanthine derivatives

Several different types of tricyclic xanthine derivatives have been prepared and investigated (fig. 6 and table 6). Cycloalkyl-substituted dihydro-imidazo[2,1-*i*]purinones (**127**,**128**) showed high A_1 affinity and selectivity combined with improved water-solubility due to the presence of a basic nitrogen atom that can be protonated (Suzuki et al. 1992; Vu et al. 2006). A new class of heterotricyclic xanthine derivatives in which the 3-alkyl-substituent is tethered to the N9 atom – pyrimido[1,2,3-*cd*]purinediones (**151–153**) - was synthesized and investigated (fig. 6) (Weyler et al. 2006). Interestingly, the cyclopentyl-substituted derivative **151**, an analog of DPCPX, was only weakly active probably due to the lacking of the N7-H atom. In contrast, the 3-noradamantyl-substituted analogs (**152**,**153**) showed relatively high A_1 affinity. While propyl derivative **152** (PSB-63) was very selective versus the other AR subtypes, butyl derivative **153** was also quite potent at human A_3AR (table 6). Another novel tricyclic analog of DPCPX, the oxazolo[3,2-*a*]purinone derivative **154**, showed only weak affinity for AR (table 6) (Müller 1994). In a series of tricyclic pyrimido[2,1-*f*]purinediones the N,N-dipropyl-substituted derivative **139** (fig. 6) bearing a *m*-chlorobenzyl residue attached to the additional ring was a relatively potent A_1 antagonist with some selectivity (table 6) (Drabczynska et al. 2007a).

3. Adenosine A_{2A} receptor antagonists

A_{2A}AR selective antagonists of both xanthine and nonxanthine classes have been developed and some have entered clinical trials for Parkinson's disease, based on the opposing action of adenosine and dopamine in the striatal pathways in the brain (Richardson et al. 1997; Schapira et al 2006; Schwarzschild et al. 2006; Müller et al. 2007; Baraldi et al. 2008). The cellular mechanisms of the motor and neuroprotective effects of A_{2A}AR antagonists have been explored (Yu et al. 2008). Recently, ameliorating effects of A_{2A} antagonists including xanthine derivatives on animal models of Alzheimer's disease and cognitive dysfunction have been reported (Dall'Igna et al. 2007; Cunha et al. 2008; Takahashi et al. 2008). Since the early 1990s, there has been a major medicinal chemical effort to increase the A_{2A}AR selectivity of simple xanthines by structural modification.

Prior to the synthesis of truly A_{2A}AR selective antagonists, certain high affinity xanthines were used in a nonselective fashion as probes of the A_{2A}AR. For example, [^{3}H]XAC (**30**) was useful as a radiotracer in binding experiments at the A_{2A}AR in human platelets and was therefore the first antagonist radioligand with high affinity at the A_{2A}AR (Ukena et al. 1986a). PD115,199 **32** was prepared in tritiated form and shown to bind with high affinity to the rat A_{2A}AR (Bruns et al. 1987b).

The first "selective" A_{2A} receptor antagonist described in the literature was the caffeine analog 3,7-dimethyl-1-propargylxanthine (DMPX, **20**, fig. 1 and table 1) (Ukena et al. 1986b). Like caffeine, the compound possesses low A_{2A} receptor affinity and moderate selectivity versus A_1 receptors. Nevertheless, this compound has been widely used in *in vivo* studies because of its good water solubility and bioavailability (Seale et al. 1988; Thorsell et al. 2007). Later on it was found that DMPX is equally potent at A_{2B} as at A_{2A} receptors. The species dependence of affinity at the A_{2A} receptor of 1,3,7- and 1,3,8-trisubstituted xanthines has been reported (Stone et al. 1988).

An early example of a caffeine analogue that displayed selectivity for the A_{2A} receptor was 8-trifluoromethylcaffeine, but the affinity was still low with at K_i value in binding at the rat A_{2A}AR of 29 μM (Jacobson et al. 1993b). This effect of the 8-trifluoromethyl group was not

observed in the corresponding (inactive) theophylline derivative. A 8-(*trans*-2-carboxyvinyl) derivative of caffeine also proved to be similarly selective for the A_{2A} receptor.

3.1. 8-Styrylxanthines

The observation that N7-methylation in 8-substituted xanthine derivatives was better tolerated by the A_{2A} than the A_1 receptor (Shamim et al. 1989), and that the 8-substituent had to be coplanar for achieving high A_{2A} receptor affinity (Erickson et al. 1991) led to the first highly potent and selective A_{2A} receptor antagonists: the 1,3,7-alkyl-substituted 8-styrylxanthine derivatives **87–95** and **99** (table 4).

A small alkyl group at N1 (methyl, ethyl, propyl, propargyl) proved to be optimal for high A_1 affinity and selectivity, while methylation is required in the 7-position (Jacobson et al. 1993a; Nonaka et al. 1994a; Shimada et al. 1997; Müller et al. 1998a; Müller et al. 2000; Kase 2003). The 8-styryl residue has to be (*E*)-configured, and *meta*-chloro or –methoxy substitution improved affinity and selectivity. The *m*-position of the 8-styryl ring can be substituted with elongated chains with retention of A_{2A} receptor selectivity and enhancement of water solubility (Jacobson et al. 1993a). The phenyl ring in the 8-styryl residue can be substituted by heterocyclic rings, such as a 3-thienyl ring (**102**) (Del Giudice et al. 1996).

The most common substitutents at N3 in A_{2A} receptor-selective xanthine derivatives have been small alkyl residues, such as methyl, propyl, and 3-hydroxypropyl (reviewed Müller 2000; Cacciari et al. 2003; Vu 2005; Yuzlenko et al. 2006; Müller et al. 2007; Cristalli et al. 2007; Cristalli et al. 2009). Recently, the develoment of a new synthetic approach allowed the preparation of a series of xanthine derivatives with more variations in the 3-position (Massip et al. 2006). It was found that the A_{2A} receptor tolerated bulky, functionalized substituents in the 3-position. For instance, N3-phenoxypropyl-substituted 8-(methoxystyryl)xanthine derivatives (e.g. **103**) are potent and selective A_{2A} antagonists (Massip et al. 2006).

Some of the best A_{2A} antagonists were istradefylline (KW6002, **87**), *m*-chlorostyrylcaffeine (CSC, **89**), *m*-bromostyryl-DMPX (**93**), and MSX-2 (**99**). (*E*)-8-(3-chlorostyryl)caffeine (**89**) is not only a potent A_{2A} antagonist (K_i rA_{2A} 54 nM), but in addition, it has been reported to be a potent inhibitor of monoamineoxidase B (baboon MAO-B, K_i 80.6 nM), an enzyme which metabolizes dopamine (van den Berg et al. 2007; Petzer et al. 2009). This activity may contribute to the potency of CSC in in vivo studies, e.g. in animal models of Parkinson's disease. All other styrylxanthine derivatives investigated so far, including 8-styrylcaffeine (**88**) and istradefylline (**87**), are considerably less potent as MAO-B inhibitors than CSC. Recently, a chain-extended homolog of CSC, 8-(*m*-chlorophenylbutadienyl)caffeine (**108**) has been described to show similar dual activity as A_{2A} antagonist and MAO-B inhibitor (Pretorius et al. 2008).

Istradefylline (KW-6002, **87**) has been intensively studied in vitro and in a number of animal models. Until recently (Fernandez et al. 2010), it was in Phase IIIb clinical trials for Parkinson's disease. In phase II clinical trials istradefylline reduced motoric dysfunction without producing dyskinesias (reviewed by Knutsen et al. 2001). An ^{11}C-labelled version of istradefylline has been prepared and used for positron emission tomography (PET) studies in healthy human brain (Hirani et al. 2001).

A major drawback of styrylxanthine derivatives, however, is their high lipophilicity and low water-solubility. Introduction of a polar sulfonate group into 8-styryl-DMPX resulting in compound **98** led to an almost 10-fold reduction in A_{2A} affinity, but increased water-solubility (Müller et al. 1998b). A more successful approach has been the preparation of

water-soluble prodrugs, particulary of the 3-(3-hydroxypropyl)-substituted 1-propargyl-8-styrylxanthine derivative MSX-2 (**99**) (Müller 2009). MSX-3 (**100**) is a water-soluble phosphate prodrug of MSX-2, which is cleaved in vivo by ubiquitous phosphatases to release the A_{2A} receptor antagonist MSX-2 (Sauer et al. 2000). MSX-3 has proven useful for animal studies and is widely used for studying the in vivo effects of A_{2A} antagonists (Hauber et al. 1998; Strömberg et al. 2000; Hauber et al. 2001; Ferré et al. 2001; Nagel et al. 2003; Blum et al. 2003; Schindler et al. 2004; Schindler et al. 2005; Antoniou et al. 2005; Karcz-Kubich et al. 2003a; Karcz-Kubicha et al. 2003b; Filip et al. 2006; Fuxe et al. 2007; Ishiwari et al. 2007; Farrar et al. 2007; Carriba et al. 2007; Salamone et al. 2008; Marcellino et al. 2008; Ferré et al. 2008; Mott et al. 2009; Worden et al. 2009). Due to its very high water-solubility at physiologic pH of 7.4 (9 mg/mL) it can be directly injected into specific brain areas, but is also an effective A_{2A} antagonist after systemic application. Recently, an amino acid ester prodrug of MSX-2, MSX-4 (**101**) has been synthesized, which was found to be well soluble in water, highly stable in artificial gastric fluid, but readily cleaved by esterases and may be a suitable prodrug for peroral administration (Vollmann et al. 2008).

Care has to be taken when using the (*E*)-configurated styrylxanthines since they easily undergo light-induced isomerization in dilute solutions yielding mixtures of (*E*)- and (*Z*)-isomers, the (*Z*)-isomers being only weakly active or inactive (Nonaka et al. 1993; Müller et al. 1998b). This isomerisation does not occur in concentrated solution, e.g. during synthesis of the compounds, or when the compounds are applied as solid dosage forms. However, styrylxanthines can also undergo light-induced dimerization ([2+2]-cycloaddition reaction) in the solid state, and therefore have to be rigorously stored under exclusion of light (Hockemeyer et al. 2004).

3.2. Configurationally stable analogs of 8-styrylxanthines

To overcome the problem of the photoisomerization, the styryl moiety has been replaced with different more stable bioisosteric groups (*e.g.* replacement of the double bond for a cyclopropyl ring in **104**, a 2-naphthyl residue in **105**, a triple bond in **107**) (Müller et al. 1997c), or a tricyclic constrained structure (**133–143**) (Kiec-Kononowicz et al. 2001; Drabczynska et al. 2003; Fhid et al. 2003; Drabczynska et al. 2004; Drabczynska et al. 2006; Drabczynska et al. 2007). In most cases a significant loss of affinity was observed by such modifications. The most promising compounds were the pyrimido[2,1-*f*]purinedione derivative **141** (K_i hA_{2A} 630 nM, rA_{2A} 230 nM) and 8-phenylethynyl-DMPX (**107**, K_i A_{2A} 314 nM, rA_{2A} 300 nM), both endowed with high selectivity. The latter class of compounds has been optimized towards increased A_{2A} affinity and the obtained highly potent and selective A_{2A} antagonists have been described in a recent patent (Müller et al. 2008). Furthermore, a substitution of the ethenyl group with a diazo structure has been performed. The obtained compounds retained selectivity but showed only moderate affinity (Müller et al. 1997b).

3.3. A_{2A}-selective radiolabelled xanthine derivatives

The tritiated derivative of the 8-styrylxanthine KF17837S (the equilibrium mixture of (*E*)- and (*Z*)- KF17837 isomers) was shown to bind to rat striatal membranes in a saturable and reversible way, with K_D values at low nanomolar concentration (Nonaka et al. 1994b). Another A_{2A} antagonist radioligand was prepared, [^{3}H]3-(3-hydroxypropyl)-7-methyl-8-(*m*-methoxystyryl)-1-propargylxanthine ([^{3}H]MSX-2). This molecule showed high affinity (K_D =8.0 nM) for rat and human A_{2A} AR, with saturable and reversible binding, and also a selectivity of at least two orders of magnitude versus all other AR subtypes (Müller et al. 2000).

3.4. Heterocyclic compounds related to xanthines

A tricyclic styryl-substituted imidazo[2,1-*i*]purin-5-one derivative (**132**, fig. 6 and table 6) showed enhanced water-solubility but reduced A_{2A}R affinity and moderate selectivity (Müller et al. 2002a).

4. Adenosine A_{2B} receptor antagonists

4.1. Aryl-substituted 1,3-dialkylxanthines

From the initial studies of Daly and coworkers using cAMP studies in the brain slice, it was recognized that 1,3,7- and 1,3,8-trisubstituted xanthines have considerable affinity at the A_{2B}AR. Also, the simple xanthine enprofylline **10** was discovered to have slight selectivity for the A_{2B}AR, which was proposed to be responsible for its antiasthmatic action in the clinic (Stefanovich 1989; Daly 2000; Daly 2007). Screening efforts by Bruns (1981) followed by more detailed studies by Müller, Daly and Jacobson showed that 1-monosubstituted xanthine derivatives, such as 1-propylxanthine (**6**) and 1-butylxanthine (**7**) were about 10-fold more potent than enprofylline at A_{2B}AR and equally selective (Müller et al. 1993b; Kim et al. 2002).

In fact, the unintended interaction at the A_{2B}AR of widely used xanthine antagonists of the ARs has proven to be a complication in pharmacological studies.

Many known xanthines were screened at the A_{2B}AR to identify leads for the design of novel A_{2B}AR antagonists. The first successful efforts to enhance the activity of 1,3,8-trisubstituted xanthines at the A_{2B}AR by Jacobson and colleagues resulted in one compound of intermediate selectivity at the human, but not rat A_{2B}AR, MRS1595 (**41**), which is a hydrazide derivative of XCC (fig. 2 and table 2) (Kim et al. 2000). Then, further probing of SAR culminated in the introduction of MRS1754 (**37**), which was the first selective A_{2B}AR antagonist with nanomolar affinity at the human receptor (Kim et al. 2000). The degree of selectivity for the human A_{2B}AR was >120 fold, but selectivity for the rat A_{2B}AR was considerably less (fig. 2 and table 2). Thus, it remained a challenge to design a rat A_{2B}AR-selective xanthine antagonist. Another drawback in the series of anilide derivatives of XCC is the low aqueous solubility, which is partly remedied in related antagonists such as MRS1706 (**38**). Nevertheless, [^{3}H]MRS1754 has found application as a useful radioligand of the A_{2B}AR (Ji et al. 2001). Structurally related 8-phenylxanthine derivatives include CVT-5440 (**40**), in which additional aromatic rings were attached by an ether linkage, and **42** with a modified 3-substituent (3-methoxypropyl), have been developed as potent and selective A_{2B} antagonists (Kim et al. 2000; Nieto et al. 2009). Newer derivatives in this series, which have two pyridine rings linked by an amide group, include the highly selective A_{2B}AR antagonists ATL-802 (**57**) and ATL-852 (**58**). [^{3}H]ATL-852 has been reported as a high affinity radioligand at this receptor (Cagnina et al. 2009).

8-Pyrazolyl-substituted xanthines that have been developed as selective human A_{2B}AR antagonists include MRE-2029-F20 (**56**), which was also reported as a high affinity radioligand (Baraldi et al. 2004). A different series of isomeric 8-pyrazolyl-xanthines yielded the highly potent A_{2B} antagonists **53–55** (CVT-6694, CVT-7124 and CVT-6883) (Kalla et al. 2008; Elzein et al. 2008; Kalla et al. 2009). High selectivity at human receptors has been reported for all of these pyrazolylxanthines, but no data for rodent receptors has been reported. CVT-6883 (**55**) is a promising candidate for the treatment of diabetes or asthma and has entered phase I clinical trials. Pain treatment is another potential area under consideration for A_{2B}AR antagonists (Abo-Salem et al. 2004; Akkari et al. 2006; Bilkei-Gorzo et al. 2008; Michael et al. 2010).

4.2. 1,8-Disubstituted xanthines

The observation that 1-monosubstituted and 1,8-disubstituted xanthine derivatives showed high affinity and increased selectivity for A_{2B}AR led to the development of a series of 1-alkyl-8-phenylxanthine derivatives (**43–52**) (Hayallah et al. 2002; Yan et al. 2004; Yan et al. 2006; Borrmann et al. 2009). These compounds also appeared to show reduced affinity at the rat A_1 receptor and therefore increased A_{2B} selectivity in rat. 1-Propyl-8-p-sulfophenylxanthine (PSB-1115, **43**) was developed as a water-soluble A_{2B} antagonist, useful as a pharmacological tool for in vivo studies (Müller et al. 1993b; Kirfel et al. 1997; Abo-Salem et al. 2004; Bilkei-Gorzo et al. 2008). 1-Butyl-8-(p-carboxyphenyl)xanthine (PSB-53, **45**) showed similar affinity and selectivity. The 1-propargyl-8-*p*-bromophenylxanthine (PSB-50, **44**) was more potent, but somewhat less selective and much less water-soluble. The 8-phenylxanthine derivatives PSB-55 (**46**), a benzylpiperazine derivative, and PSB-298 (**47**), a hydroxyethylamide, were synthesized to obtain more polar compounds with high A_{2B} affinity. PSB-298 was obtained in tritiated form and was found to have a low degree of non-specific binding (Bertarelli et al. 2006). However, its affinity and selectivity was not satisfactory.

Starting from the sulfonate PSB-1115 (**43**), sulfonic acid esters (e.g. **48**) and sulphonamides (e.g. **49–52**) were obtained (Yan et al. 2004; Yan et al. 2006). Compound **48** can be envisaged as a lipophilic prodrug of the highly polar sulfonate **43**, which may show peroral bioavailability and release of **43** after absorption (Yan et al. 2004). However, **48** has high A_{2B} affinity itself and is therefore a co-drug rather than a prodrug, although without selectivity versus A_1AR (fig. 2 and table 2). The most potent and selective A_{2B} antagonists described to date are the sulphonamide derivatives **50–52**, whose development was based on PSB-601 (**49**) an already very potent and selective A_{2B} antagonist (K_i 3.6 nM). Compounds **50–52** show subnanomolar affinity for A_{2B} receptors and very high selectivity in humans and in rodents. [^{3}H]PSB-603 was prepared as a selective, high-affinity A_{2B} antagonist radioligand with K_d values of 0.403 nM at human and 0.351 nM at mouse A_{2B}AR (Borrmann et al. 2009).

4.3. 9-Deazaxanthines

Several series of 9-deazaxanthine derivatives (**115**, **117–121**) were developed as A_{2B} antagonists, which were structurally related to the 8-phenylxanthine derivatives described above (fig. 5 and table 5). A number of compounds with low nanomolar affinity were obtained, and some were selective for the human A_{2B} receptor (Carotti et al. 2006; Esteve et al. 2006; Stefanachi et al. 2008).

4.4. 8-Furylmethyl-substituted xanthines

8-(2-Furyl)methyl-substituted xanthined derivatives, e.g. **63**, have been developed as A_{2B} antagonists (fig. 2 and table 2). Some of them showed high A_{2B} affinity but only moderate selectivity (Balo et al. 2009).

5. Adenosine A_3 receptor antagonists

In the search for A_3AR antagonists, alkylxanthines were initially rejected as a suitable lead in favor of nonxanthine chemically diverse heterocycles, because of the exceptionally low affinity of alkylxanthines at the rat A_3AR. For example, the classical adenosine antagonists caffeine and theophylline have K_i values of >100 μM at the rat A_3AR (table 1). Initial SAR studies at the rat A_3AR were conducted using multiply substituted xanthines, many of which retained selectivity for the A_3AR (van Galen et al. 1994). Only slight A_3AR selectivity was observed for analogues containing 8-alkyl and 2-thio substitutions (Kim et al. 1994b). However, when other species orthologues of the A_3AR were cloned and studied

pharmacologically, such as sheep, and human A_3AR, many xanthines were found to display good affinity for those A_3 receptors (Linden 1994). Thus, attention returned to the xanthines as a source for A_3AR antagonist leads.

One of the earliest approaches to enhancing the affinity of xanthines at the A_3AR was to attach a ribose group at the 7-position (**21**,**22**). The 5′-uronamide derivative *N*-methyl-1,3-dibutylxanthine-7-β-D-ribofuronamide (DBXRM, **22**) is 140-fold selective for the A_3AR, but the presence of the uronamide function increases the efficacy such that it is an agonist at this receptor (van Galen et al. 1994; Kim et al. 1994b; Bridson et al. 1998).

5.1. 8-Aryl-substituted xanthine derivatives

8-Phenylxanthine derivatives bearing a carboxylate group attached to the phenyl ring via an ethylene (**35**) or an oxymethylene spacer (**34**) were initially found to be potent antagonists at the human A_3AR, but both compounds are also very potent A_1 and A_{2B} antagonists (fig. 2 and table 2). [^{125}I]I-ABOPX (BW-A522, **34**) has been used as a radioligand for labelling the A_1AR as well as human A_3 and human A_{2B}ARs (Patel et al. 1988; Salvatore et al. 1993; Linden et al. 1999). The corresponding *p*-azido derivative was previously used for photoaffinity labeling of the A_1AR. The xanthine derivative **34** is characterized by a *p*-amino-*m*-iodobenzyl residue at N3 of the xanthine core (fig. 2) and is therefore quite lipophilic. As observed for other xanthine antagonists, **34** is much less potent (65-fold) at rat as compared to human A_3 receptors.

5.2. Tricyclic xanthine and deazaxanthine derivatives

Cyclized derivatives of xanthines, such as (8*R*)-8-ethyl-4-methyl-2-phenyl-4,5,7,8-tetrahydro-1*H*-imidazo[2.1-*i*]purin-5-one (PSB-11, **130**), its trichloro-phenyl-substituted derivative PSB-10 (**129**), and the 8-unsubstituted 8-bromophenyl derivative **131** are very potent A_3-selective antagonists (fig. 6 and table 6) (Müller et al. 2002a; Saki et al. 2002; Ozola et al. 2003). PSB-11 (K_D 4.9 nM) was prepared as a radioligand by catalytic hydrogenation from the polychlorinated precursor PSB-10 (Müller et al. 2002b; Burbiel et al. 2003). Due to its increased polarity and solubility in comparison to xanthines [^{3}H]PSB-11 shows only low non-specific binding. Further tricyclic xanthine derivatives, in which an additional ring was attached to the imidazole rather than the pyrimidine ring of the xanthine core structure (pyrido-, imidazo-, pyrrolo- and triazolo-purinediones, **144–150**), were developed as A_3-selective antagonists (Priego et al. 2002; Baraldi et al. 2005; Pastorin et al. 2005; Priego et al. 2008). An aromatic residue (mostly benzyl) attached to the N3 (xanthine numbering) increases A_3 affinity in xanthine derivatives including the tricyclic ones.

Besides tricyclic xanthine derivatives, tricyclic deazaxanthines have also been obtained (Ishiyama et al. 2009). Compound **122** (fig. 5 and table 5) was one of the most potent and selective compounds in this series.

6. Xanthine derivatives used as molecular probes

6.1. Irreversible ligand probes

The amine congener XAC (**30**) was coupled to a variety of bifunctional crosslinking reagents to form products containing a single chemically reactive group (fig. 7 and table 7). For example, 1,3- and 1,4-phenylene diisothiocyanates were conjugated to XAC to form the A_1 AR-selective antagonists *m*-DITC-XAC **164** and *p*-DITC-XAC **165**, which were demonstrated to bind irreversibly at submicromolar concentrations to the A_1AR to act as covalent affinity labels. Similarly, prosthetic reagents designed for radiolabeling and photoaffinity labeling could be coupled to XAC and similar amine congeners (Stiles et al.

1988; Jacobson et al. 1989a). The conjugate with the *p*-aminophenylacetyl moiety was readily iodinated to form the radioligand **172**, which could then be converted to the photoactivatable *p*-azide (Stiles and Jacobson 1987). This azide then served to crosslink a radiolabeled AR antagonist suitable to the A_1AR protein, which could be visualized by gel electrophoresis. The sulfonyl fluoride group present in **158** was also means of crosslinking a xanthine derivative to the A_1AR (Scammels et al. 1994; van Muijlswijk-Koezen et al. 2001).

6.2. Spectroscopic probes: spin labeled and fluorescent probes

Other types of reporter groups could be similarly incorporated into xanthine functionalized congeners with retention of moderate AR affinity, for example, chelating groups capable of complexing radioactive metal ions; spin labels for electron spin resonance (ESR) spectroscopy, e.g., **167**; a perfluorinated acyl prosthetic group, as in **170**, intended for use in fluorine-NMR spectroscopy, and fluorescent dyes, e.g., **173** and **174** (Jacobson et al. 1987b). The fluorescent conjugate **174** of XAC and BODIPY (6-(((4,4-difluoro-5-(2-thienyl)-4-bora-3a,4a-diaza-s-indacene-3-yl)styryloxy)acetic acid), with an intermediate ε-aminocaproyl spacer, has proven useful in fluorescence correlation spectroscopy to characterize ligand complexes of the A_1AR (Briddon et al. 2004).

Spin-labeled probes that retained high A_1 affinity were obtained by inserting the spin-label into the molecule as part of the pharmacophore. The most potent and A_1-selective compounds were the DPCPX analogs **155** (replacement of the 3-substituent by a spin label) and **156** (substitution of the cyclopentyl ring by a structurally related spin label). Both compounds showed affinity for A_1AR in the low nanomolar range combined with high selectivity versus the other receptor subtypes (Ilas et al. 2005). The 1-propyl-8-phenyl derivative **157**, in which the spin label was integrated into the 8-substituent, showed good affinity for A_1 as well as A_{2B} receptors (fig. 7 and table 7).

6.3. Specialized radioligand probes based on conjugation

Trifunctional probes derived from XAC were synthesized for the purpose of crosslinking to both a reporter group and the receptor (Boring et al. 1991). By this means, the xanthine would deliver a radioactive or spectroscopic prosthetic group to the receptor, to which it would react irreversibly by virtue of an electrophilic group such as an isothiocyante. This approach was illustrated with a series of analogues of *m*-DITC-XAC containing a third substituent in the phenyl isothiocyanate ring. For example, in **166** the third substituent contained a 3-(4-hydroxy-phenyl)propionate moiety for radioiodination (Jacobson et al 1992b). This antagonist derivative effectively radiolabeled the bovine A_1 AR in a covalent manner. Similar trifunctional xanthine probes for covalent labeling of ARs that furthermore contained a cleavable disulfide linkage within the chain linked to the xanthine moiety were reported (Jacobson et al. 1995). The intended strategy was to be able to remove the label after isolation of the modified receptor in order to regenerate the binding ability of the receptor.

6.4. Xanthine radioligand probes for positron emission tomography

There is a need for the development of imaging agents based on high affinity ligands for ARs. For example, ligands for *in vivo* positron emission tomographic (PET) imaging of A_1, A_{2A}, and A_3 ARs have been developed. The high affinity A_1AR antagonist DPCPX gave rise to the high affinity analogue in which a terminal hydrogen of the 3-propyl group has been substitued with radiofluorine: [^{18}F]CPFPX (8-cyclopentyl-1-propyl-3-(3-fluoropropyl)-xanthine, **159**), similar in structure to DPCPX). This tracer is being developed for PET imaging of the A_1AR in the brain (Holschbach et al. 2002; Bauer et al. 2009).

PET ligands for the A_{2A} AR in the 8-styrylxanthine series that are structurally related to KW6002, have been developed: for example, [7-methyl-^{11}C]-(E)-8-(3,4,5-trimethoxystyryl)-1,3,7-trimethylxanthine ([^{11}C]TMSX) (Ishiwata et al. 2000a). This compound was alternately named [^{11}C]KF18446 ([7-methyl-^{11}C]-(*E*)-8-(3,4,5-trimethoxystyryl)-1,3,7-trimethylxanthine, (Ishiwata et al. 2000b; Ishiwata et al. 2002; Ishiwata et al. 2003a; Ishiwata et al. 2003b). Ex vivo autoradiography for this molecule showed a high striatal uptake and a high uptake ratio of the striatum in comparison to other brain regions; [^{11}C]KF18446 was therefore proposed as a suitable radioligand for mapping A_{2A}AR of the brain by PET (Mishina et al. 2007). In 2001 the synthesis and the testing of the 8-styrylxanthine derivative [^{11}C]KW-6002 as a PET ligand was reported. This molecule showed high retention in the striatum but it bound also to extra-striatal regions, so its potential as a PET ligand appeared to require further investigation (Hirani et al. 2001; Brooks et al. 2008).

In an earlier study, ^{11}C-labeled (*E*)-KF17837 was synthesised and tested, and it was proposed as a potential positron emission tomography (PET) radioligand for mapping the A_{2A}AR in the heart and the brain (Ishiwata et al. 1996; Ishiwata et al. 1997). Further studies on radiolabeled xanthine derivatives as A_{2A}AR radioligands were carried out by preparing and testing an ^{11}C-labeled selective antagonist, (*E*)-8-(3-chlorostyryl)-1,3-dimethyl-7-[^{11}C]methylxanthine [^{11}C]CSC). This molecule was shown to accumulate in the striatum, and PET studies on rabbits showed a fast brain uptake of [^{11}C]CSC, reaching a maximum in less than 2 min (Marian et al. 1999). Few years later, iodinated and brominated styrylxanthine derivatives labeled with ^{11}C were tested as *in vivo* probes (Ishiwata et al. 2000c). [7-Methyl-^{11}C]-(*E*)-3,7-dimethyl-8-(3-iodostyryl)-1-propargylxanthine ([^{11}C]IS-DMPX) and [7-methyl-^{11}C]-(*E*)-8-(3-bromostyryl)-3,7-dimethyl-1-propargylxanthine ([^{11}C]BS-DMPX) showed K_i affinities of 8.9 and 7.7 nM respectively, and high A_{2A}/A_1 selectivity values. Unfortunately, biological studies proved that the two ligands were only slightly concentrated in the striatum, and that they were not suitable as in vivo ligands because of low selectivity for the striatal A_{2A} receptors and a high nonspecific binding (Ishiwata et al. 2000c).

6.5. Conjugated ligand probes and bivalent ligands

Three biotin conjugates **161–163** of 1,3-dipropyl-8-phenylxanthine (fig 7) were reported as being able to bind competitively to the rat A_1 AR, but in the case of **161** and **162** only in the absence of avidin. This was in contrast to similar conjugates of functionalized nucleoside agonists, which more readily bound simultaneously to both avidin and the A_1 AR. Results were interpreted in terms of the possible reorientation of the ligands at the receptor binding site (Jacobson et al. 1985a; Jacobson 1990).

Two different pharmacophores, one being a xanthine AR antagonist, have been tethered with the intention to create a dual selectivity in a single functional unit. For example, XAC was coupled covalently through an L-Lys linker to a segment derived from the neurotransmitter peptide substance P (SP) to form a binary drug **169** (Jacobson et al. 1987c). The Lys linker served to increase aqueous solubility and to preserve A_1 AR by virtue of a free amino group in the spacer chain. Thus, conjugate **169** bound to the rat A_1 receptor with a K_i value of 35 nM and to the NK1 (neurokinin type 1) receptor with a K_i value of 300 nM. Similarly, XAC was coupled to functionalized agonist ligands for opioid receptors, e.g., **175**, and for D2 dopamine receptors, e.g., **176** (fig. 7 and table 7) (Jacobson 2009; Soriano et al. 2009). Each of these conjugates bound effectively to both relevant receptors.

7. Conclusions

The pharmacological activity of the natural xanthines currently used in therapy, namely theophylline (as an antiasthmatic) and caffeine (as CNS stimulant, for the treatment of apnoea in newborn babies, and as analgesic in combination therapy e.g. for the treatment of headaches) is mainly mediated by a (non-selective) inhibition of AR subtypes. AR subtype-selective xanthine derivatives with high potency have been developed and are evaluated in animal models and clinical trials.

Abbreviations

AR(s)	Adenosine receptor(s)
c	calf or cow
d	dog
CHO	Chinese hamster ovary
gp	guinea pig
h	human
m	mouse
MAO	monoaminoxidase
MAO-B	monoaminoxidase type B
mk	monkey
nd	not determined
p	pig
r	rat
rb	rabbit
s	sheep
X	xanthine(s)

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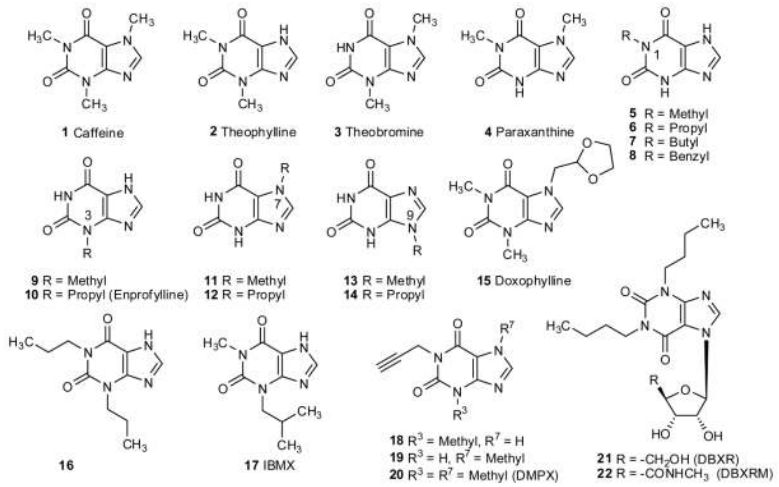

Fig. 1.
8-Unsubstituted xanthine derivatives

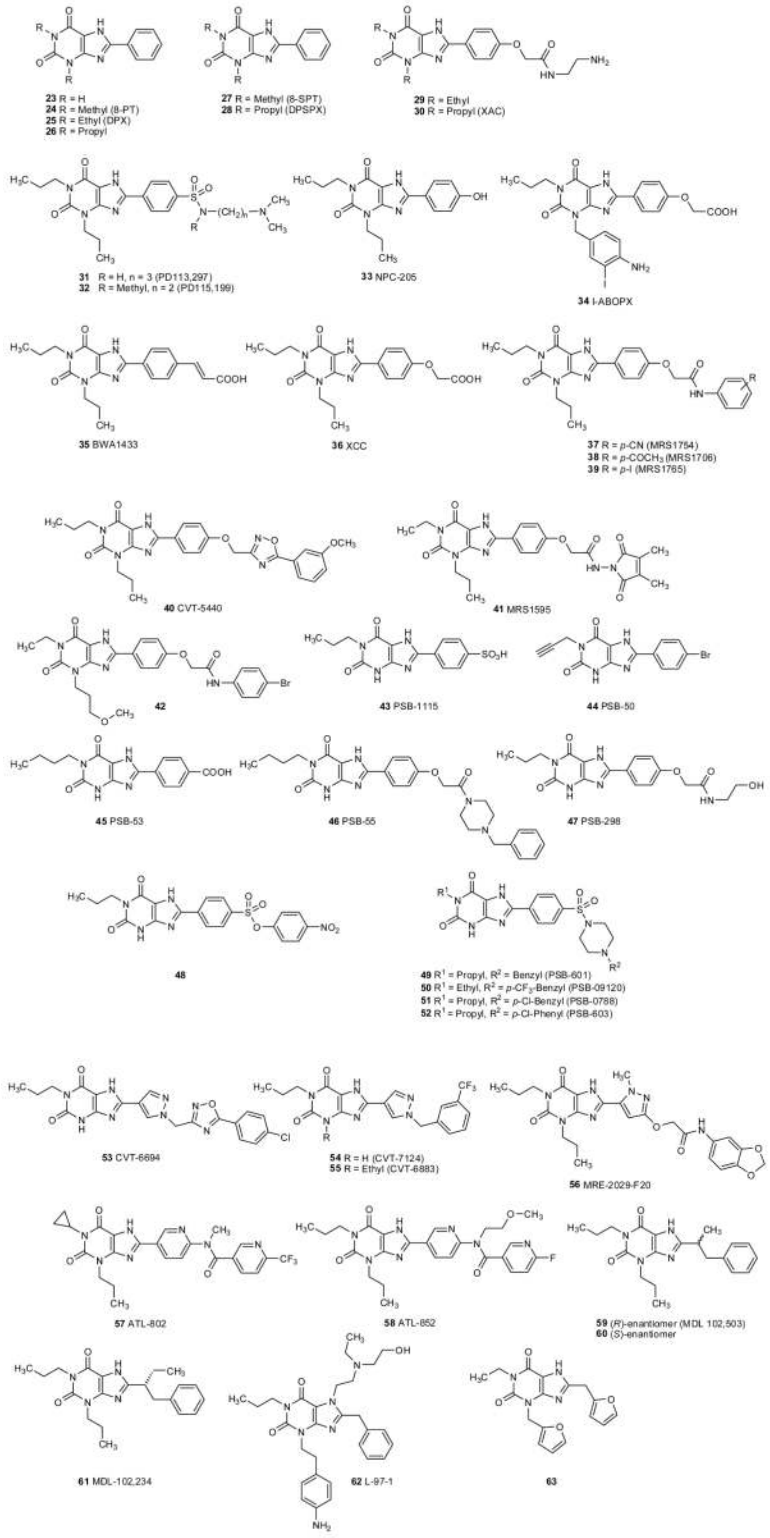

Fig. 2.

8-Phenyl- and 8-phenylalkyl-substituted xanthines and heteroaromatically substituted derivatives

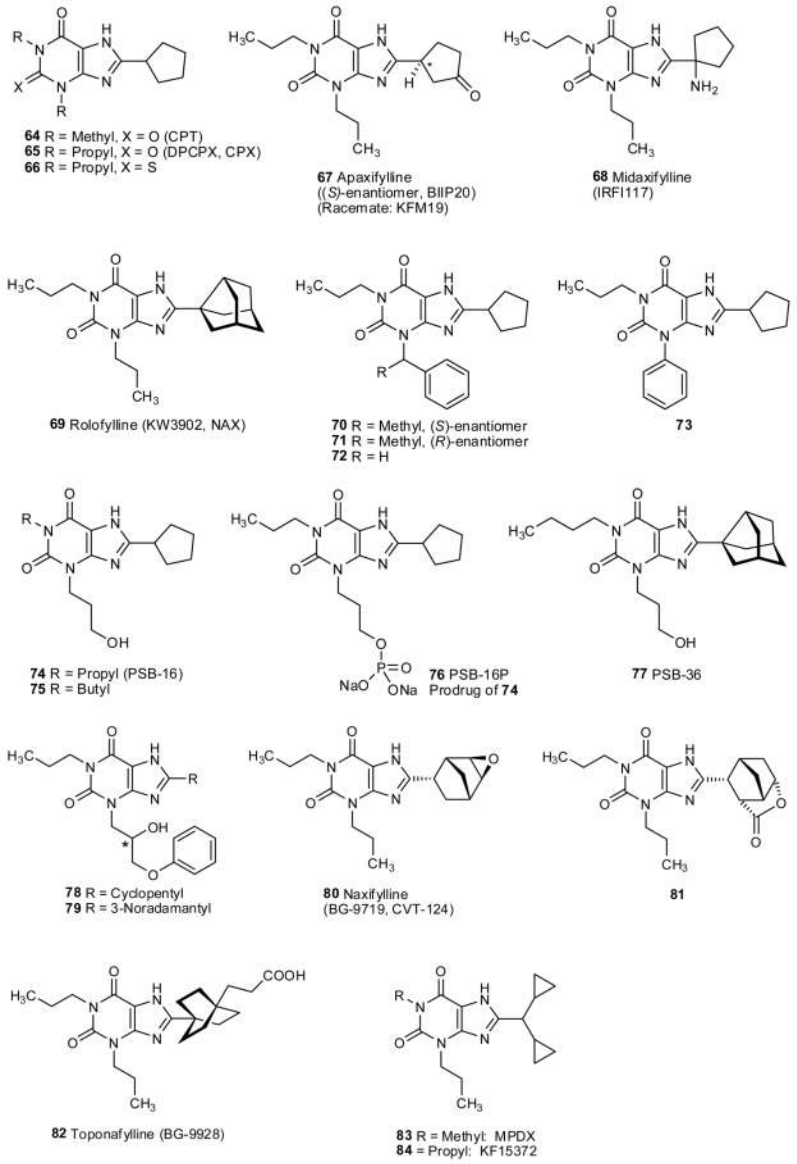

Fig. 3.
8-Cycloalkylxanthines

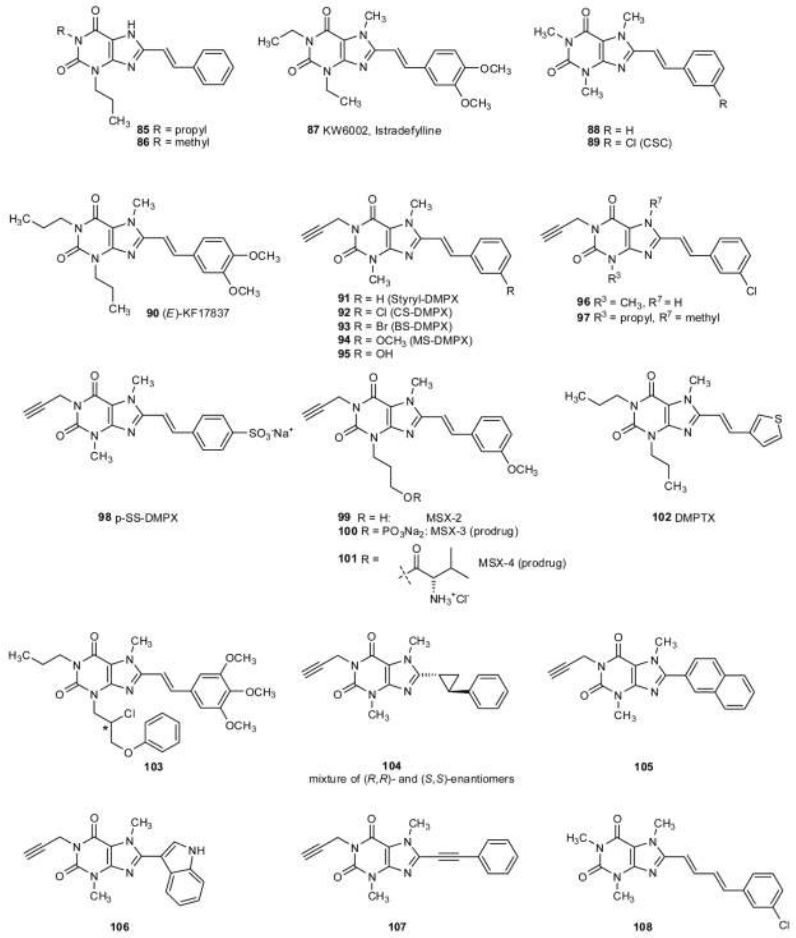

Fig. 4.
8-Styrylxanthines and configurationally stable analogs

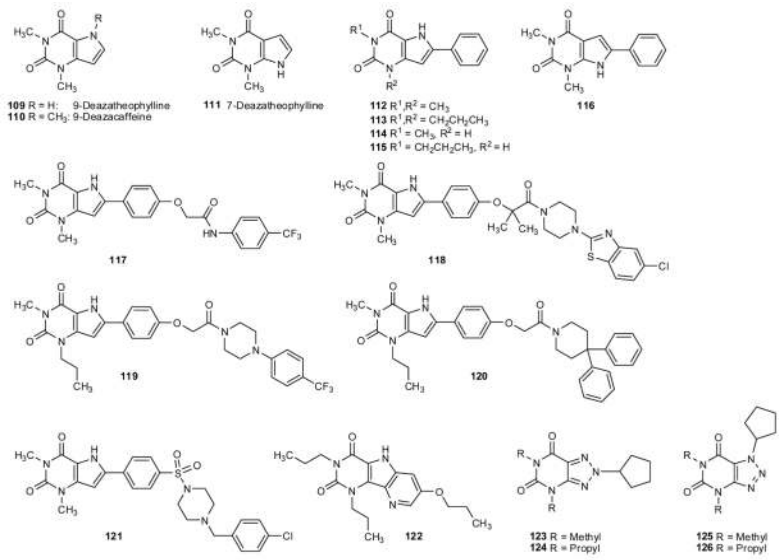

Fig. 5.
Deazaxanthines and azaxanthines

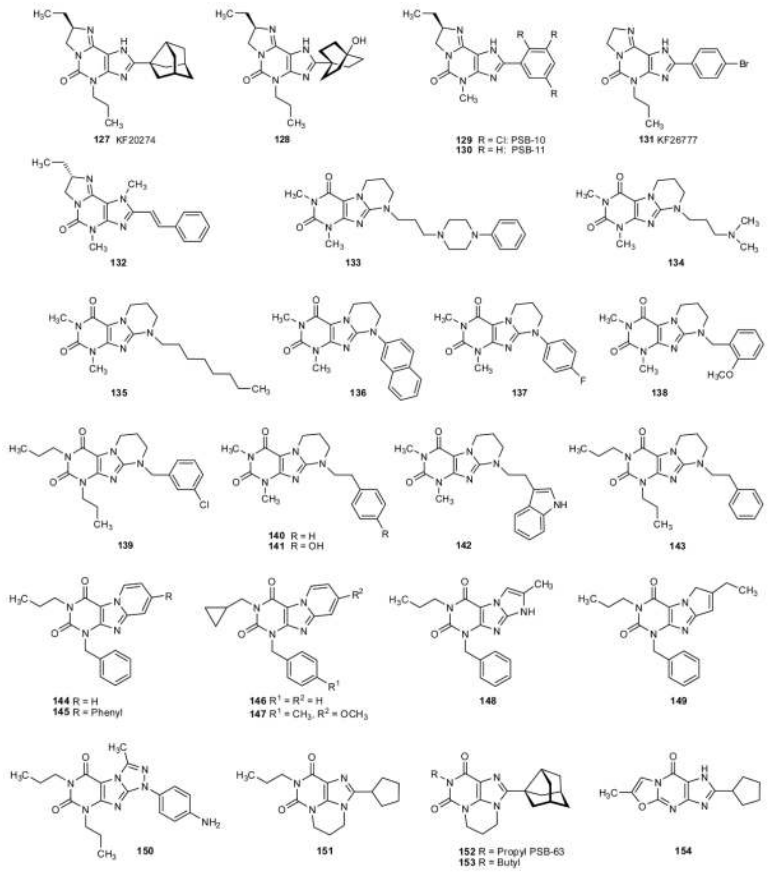

Fig. 6.
Tricyclic xanthine derivatives

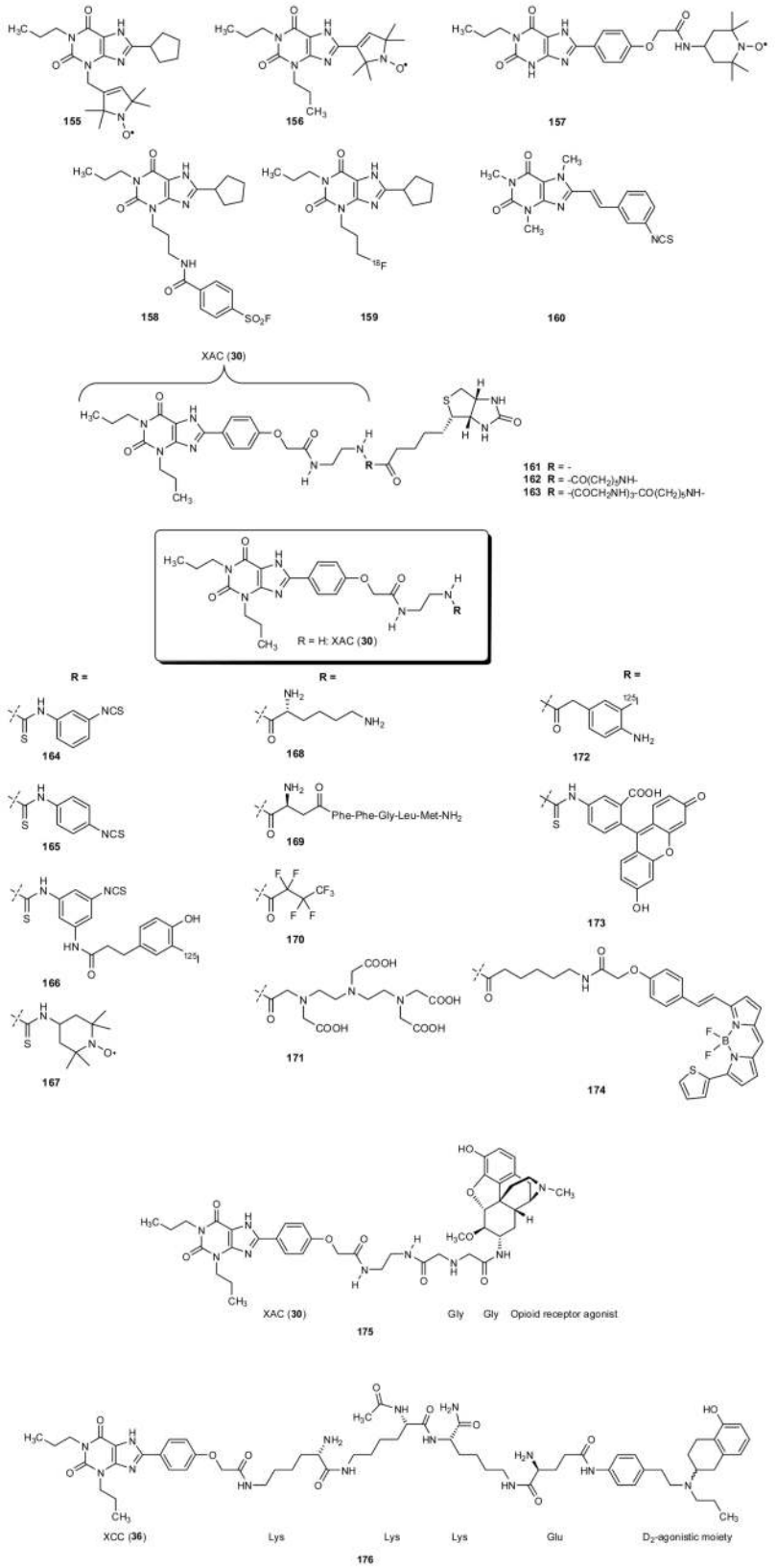

Fig. 7.
Functionalized xanthines as molecular probes

Table 1

Adenosine receptor affinities of 8-unsubstituted xanthine derivatives

		K_i (nM)[a]			
		A_1	A_{2A}	A_{2B}	A_3
Natural xanthine (X) derivatives					
1	Caffeine (1,3,7-TrimethylX)	10,700 (h)[1] 44,900 (h)[2] 41,000 (r)[3] 44,000 (r)[4] 47,000 (gp)[5] 44,000 (c)[5]	23,400 (h)[2] 9,560 (h)[1] 45,000 (r)[4] 32,500 (r)[6] 48,000 (r)[1]	33,800 (h)[7] 10,400 (h)[8] 20,500 (h)[9] 30,000 (r)[10] 13,000 (m)[10]	13,300 (h)[1] >100,000 (r)[11]
2	Theophylline (1,3-DimethylX)	6,770 (h)[12] 14,000 (r)[13] 8,740 (r)[1] 7,060 (gp)[14] 4,710 (rb)[14] 9,050 (s)[14] 6,330 (c)[14]	1,710 (h)[12] 6,700 (h)[1] 22,000 (r)[13] 25,300 (r)[1]	9,070 (h)[8] 74,000 (h)[9] 15,100 (r)[8] 5,630 (m)[15] 11,000 (gp)[16] 17,700 (rb)[15] 38,700 (d)[15]	22,300 (h)[1] 86,400 (h)[12] >100,000 (r)[11] 85,000 (r)[17] >100,000 (d)[18]
3	Theobromine (3,7-DimethylX)	105,000 (r)[13] 83,400 (r)[19]	>250,000 (r)[13] 187,000 (r)[19]	130,000 (h)[19]	>100,000 (r)[11]
4	Paraxanthine (1,7-DimethylX)	21,000 (r)[13]	32,000 (r)[13]	4,500 (h)[20]	>100,000 (r)[11]
Mono-substituted xanthine derivatives					
5	1-MethylX	36,000 (r)[13] 11,400 (r)[19]	47,000 (r) [13] 36,200 (r)[19]	6,600 (h)[19]	>100,000 (r)[11]
6	1-PropylX	13,000 (r) [13]	33,000 (r) [13]	360 (h)[8] 1,880 (r)[8]	2,370 (h)[8]
7	1-ButylX	9,000 (r) [13]	61,000 (r) [13]	421 (h)[8]	4,610 (h)[8]
8	1-BenzylX	2,800 (r) [13]	22,000 (r) [13]	nd	nd
9	3-MethylX	>100,000 (r) [13] 35,000 (r) [21]	59,000 (r) [13]	87,000 (h)[20]	>100,000 (r)[11]
10	Enprofylline (3-PropylX)	156,000 (h)[22] 42,000 (h)[1] 32,000 (r)[13]	32,000 (h)[22] 81,300 (h)[1] 137,000 (r)[13]	7,000 (h)[22] 4,730 (h)[8] 19,800 (h)[23]	92,600 (h)[1] 65,000 (h)[22] 93,000 (r)[1]

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		K_i (nM)[a]			
		A_1	**A_{2A}**	**A_{2B}**	**A_3**
		29,100 (r)[19] >100,000 (d)[18]	103,000 (r)[19]	26,000 (r)[24] 5,630 (m)[15] 5,840 (rb)[15] 6,960 (d)[15]	>100,000 (d)[18]
11	7-MethylX	33,000 (r) [13]	59,000 (r) [13]	97,000 (h)[20]	>100,000 (r)[11]
12	7-PropylX	18,000 (r) [13]	>200,000 (r) [13]	nd	nd
13	9-MethylX	>250,000 (r) [13]	>250,000 (r) [13]	>1,000,000 (h)[20]	>100,000 (r)[11]
14	9-PropylX	>250,000 (r) [13]	>250,000 (r) [13]	nd	nd
Di- and trisubstituted xanthine derivatives					
15	Doxofylline	ca. 100,000[25]	ca. 100,000[25]	nd	nd
16	1,3-DipropylX	700 (r)[13] 450 (r)[19] 1,310 (gp)[5] 340 (c)[5]	6,600 (r)[13] 5,160 (r)[19]	1,110 (h)[8] 680 (h)[20]	1,940 (h)[1]
17 IBMX	3-Isobutyl-1-methylX	7,000 (r)[13] 2,460 (r)[19] 8,600 (gp)[5] 4,400 (c)[5]	16,000 (r)[13] 13,800 (r)[19]	3,500 (h)[19]	nd
18	3-Methyl-1-propargylX	820 (r) [13] 5,830 (r)[8]	4,800 (r) [13] 33,600 (r)[8]	511 (h)[8] 2,150 (r)[8]	10,900 (h)[8]
19	7-Methyl-1-propargylX	22,000 (r) [13]	16,000 (r) [13]	nd	nd
20 DMPX	3,7-Dimethyl-1-propargylX	45,000 (r)[4] 11,000 (r)[5] 25,800 (gp)[5] 16,400 (c)[5]	16,000 (r)[4] 5,600 (r)[6]	4,130 (h)[8]	>10,000 (r)[26]
21	DBXR	4,190 (r)[11]	19,500(r)[11]	nd	6,030 (r)[11,b]
22	DBXRM	37,300 (r)[27]	>100,000 (r)[27]	nd	229 (r)[27,c]

[a] h = human; c = cow; d = dog; gp = guinea pig; m= mouse; r = rat; rb = rabbit; a few A_{2B} data are from functional (cAMP) studies; nd = no data available

[b] partial agonist;

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[c] full agonist

[1] Jacobson et al., 1999

[2] Abo-Salem et al., 2004

[3] Grahner et al., 1994

[4] Daly et al., 1991

[5] Ukena et al., 1986b

[6] Müller et al., 2000

[7] Borrmann et al., 2009

[8] Kim et al., 2002

[9] Bertarelli et al., 2006

[10] Brackett and Daly, 1994

[11] van Galen et al., 1994

[12] Klotz et al., 1998

[13] Müller et al., 1993b

[14] Klotz et al., 1991

[15] Auchampach et al., 2009

[16] Fozard et al., 2003

[17] Jacobson et al., 1995

[18] Auchampach et al., 1997

[19] Bruns et al., 1986

[20] Bruns, 1981

[21] Shamim et al., 1989

[22] Robeva et al., 1996

[23] Ji et al., 2001

[24] Alexander et al., 1996

[25] Cirillo et al., 1988

[26] Müller et al., 2007

[27] Kim et al., 1994b

Table 2

Adenosine receptor affinities of 8-phenyl- and 8-phenylalkyl-substituted xanthines and heteroaromatically substituted derivatives

		K_i (nM)[a]			
		A_1	A_{2A}	A_{2B}	A_3
First-generation 8-phenylxanthine derivatives					
23	8-PhenylX	2,500 (r)[1]	21,000 (r)[1]	810 (h)[2]	nd
24	8-Phenyl-theophylline (8-PT)	1,340 (h)[3] 115 (h)[4] 86 (r)[5] 76 (r)[6] 1,540 (gp)[6] 7.6 (c)[6]	454 (h)[3] 850 (r)[5]	415 (h)[7] 436 (m)[8] 249 (rb)[8] 371 (d)[8]	1,250 (h)[3] >100,000 (r)[9]
25	1,3-Diethyl-8-phenylX (DPX)	44 (r)[10]	860 (r)[10] 190 (h)[11]	62.0 (h)[7]	nd
26	1,3-Dipropyl-8-phenylX	10 (r)[6] 0.22 (c)[6] 20.9 (gp)[6]	180 (r)[12] 2100 (h)[13]	18.9 (h)[7]	nd
27	SPT	1,000 (h)[3] 4,500 (r)[5] 1,000 (r)[6] 10,100 (gp)[6] 6,460 (d)[14] 300 (c)[6]	7,050 (h)[3] 14,000 (r)[5]	1,330 (h)[7] 1,590 (r)[15] 4,990 (m)[8] 2,190 (gp)[15] 2,370 (rb)[8] 7,240 (d)[8] 224 (d)[15]	5,890 (h)[16] 11,000 (h)[17] ≫10,000 (r)[16] 25,300 (d)[14]
28	DPSPX	210 (r)[5] 140 (r)[9]	1,400 (r)[5] 790 (r)[9]	568 (m)[8] 200 (rb)[8] 721 (d)[8]	183 (s)[18] >100,000 (r)[9] 22,500 (rb)[19]
29		12 (r)[20]	83 (r)[20]	nd	nd
30	XAC	6.8 (h)[21] 29.1 (h)[22] 1.2 (r)[23] 0.49 (r)[19] 5.49 (gp)[19] 0.45 (rb)[19] 0.09 (s)[19]	18 (h)[21] 1.00 (h)[22] 63 (r)[23]	7.8 (h)[23] 16.0 (h)[7] 42.7 (r)[15] 4.51 (m)[8] 17.8 (gp)[15] 4.47 (rb)[8] 29.8 (d)[8]	91.9 (h)[22] 26 (h)[21] 71 (h)[14] 29,000 (r)[14] 106 (rb)[14] 180 (s)[18,24] 138 (d)[14]

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		K_i (nM)[a]			
		A_1	A_{2A}	A_{2B}	A_3
41	MRS1595	3,030 (h)[21] 11.1 (r)[21]	1,970 (h)[21] 126 (r)[21]	26.6 (h)[21]	670 (h)[21]
42		100 (r)[33]	97.7 (h)[33]	2.88 (h)[33]	1,290 (h)[33]
43	PSB-1115	>10,000 (h)[2] 2,200 (r)[1]	24,000 (r)[1]	53.4 (h)[2]	>10,000 (h)[2]
44	PSB-50	60 (r)[2]	199 (r)[2]	6.8 (h)[2]	477 (h)[2]
45	PSB-53	1,181 (h)[2] 481 (r)[2]	ca. 10,000 (h)[2] 3,800 (r)[2]	24 (h)[2]	4,622 (h)[2]
46	PSB-55	122 (h)[2] 37 (r)[2]	ca. 10,000 (r)[2] 550 (r)[2]	1.3 (h)[2]	475 (h)[2]
47	PSB-298	68 (h)[2] 35 (r)[2]	2,139 (r)[2]	1.2 (h)[2] 60 (h)[34]	422 (h)[2]
48		3.6 (r)[35]	74 (r)[35]	5.4 (h)[35]	≥10,000 (h)[35]
49	PSB-601	2,067 (h)[36] 260 (r)[36]	484 (h)[36] 93.7 (r)[36]	3.6 (h)[36]	>1,000 (h)[36]
50	PSB-09120	>10,000 (h)[37] >1,000 (r)[37]	22.7 (h)[37] 122 (r)[37]	0.157 (h)[37]	>10,000 (h)[37]
51	PSB-0788	2,240 (h)[37] 386 (r)[37]	333 (h)[37] 1,730 (r)[37]	0.393 (h)[37]	>1,000 (h)[37]
52	PSB-603	>10,000 (h)[37] >10,000 (r)[37]	>10,000 (h)[37] >10,000 (r)[37]	0.553 (h)[37] K_D 0.403 (h)[37] K_D 0.351 (m)[37]	>10,000 (h)[37]
53	CVT-6694	>6,000 (h)[38]	>5,000 (h)[38]	7 (h)[38]	>9,000 (h)[38]
54	CVT-7124	>6,000 (h)[38]	>5,000 (h)[38]	6 (h)[38]	>9,000 (h)[38]
55	CVT-6883	1,940 (h)[39]	3,280 (h)[39]	22 (h)[39]	1,070 (h)[39]
56	MRE-2029-F20	200 (h)[40]	>1,000 (h)[40]	5.5 (h)[40]	>1,000 (h)[40]
57	ATL 802	369 (h)[41] 9,583 (m)[41]	654 (h)[41] 8,393 (m)[41]	2.36 (h)[41] 8.58 (m)[41]	>1,000 (h)[41] >10,000 (m)[41]

		K_i (nM)[a]			
		A_1	A_{2A}	A_{2B}	A_3
58	ATL 852	nd	nd	28.5 (h)[c]	nd
8-Phenylalkyl-substituted xanthines					
59	MDL 102,503	6.9 (r)[42]	157 (r)[42]	nd	nd
60		60.7 (r)[42]	848 (r)[42]	nd	nd
61	MDL 102,234	23.2 (r)[42]	3,510 (r)[42]	nd	nd
62	L-97-1	580 (h)[43]	>100,000 (h)[43]	>100,000 (h)[43]	nd
63		102 (r)[44]	83.2 (h)[44]	7.41 (h)[44]	10,000 (h)[44]

[a] h = human; c = cow; d = dog; gp = guinea pig; m= mouse; r = rat; rb = rabbit; a few A_{2B} data are from functional (cAMP) studies; nd = no data available;

[c] personal communication (J. Linden), also see [41]

[1] Müller et al., 1993b

[2] Hayallah et al., 2002

[3] Kim et al., 1999

[4] Ferkany et al., 1986

[5] Daly, 1991

[6] Ukena et al., 1986b

[7] Kim et al., 2002

[8] Auchampach et al., 2009

[9] van Galen et al., 1994

[10] Bruns et al., 1987

[11] Ukena et al., 1986a

[12] Bruns et al., 1986

[13] Shamim et al., 1989

[14] Auchampach et al., 1997

[15] Fozard et al., 2003
[16] Abo-Salem et al., 2004
[17] Martin et al., 1996
[18] Linden et al., 1993
[19] Klotz et al., 1991
[20] Jacobson et al., 1988
[21] Kim et al., 2000
[22] Klotz et al., 1998
[23] Jacobson et al., 1999
[24] Salvatore et al., 1993
[25] Bruns et al., 1987a
[26] Ji et al., 1991
[27] Brackett and Daly, 1994
[28] Shamim et al., 1988
[29] Daly et al., 1986b
[30] Linden, 1994
[31] Kim et al., 1994a
[32] Zablocki et al., 2005
[33] Nieto et al., 2009
[34] Bertarelli et al., 2006
[35] Yan et al., 2004
[36] Yan et al., 2006
[37] Borrmann et al., 2009
[38] Kalla et al., 2008
[39] Elzein et al., 2008

[40] Baraldi et al., 2004

[41] Cagnina et al., 2009

[42] Peet et al., 1993

[43] Obiefuna et al., 2005

[44] Balo et al., 2009

[45] Linden et al., 1999

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Table 3

Adenosine receptor affinities of 8-cycloalkylxanthines

		K_i (nM)[a]			
		A_1	A_{2A}	A_{2B}	A_3
64	8-Cyclopentyl-theophylline	24 (r)[1] 6.3 (r)[3] 26.1 (gp)[3] 6.4 (rb)[3] 2.9 (s)[3] 1.4 (c)[3]	1,400 (r)[1] 3,170 (r)[27]	710 (h)[2] 902 (h)[27]	~100,000 (h)[1] >10,000 (r)[27]
65	DPCPX (CPX)	3.0 (h)[4] 0.50 (r)[4] 1.0 (r)[5] 0.18 (r)[3] 1.06 (gp)[3] 3.9 (gp)[6] 0.21 (rb)[3] 0.10 (s)[3] 0.05 (c)[3] 0.29 (c)[6] 11.4 (d)[7]	129 (h)[8] 60 (h)[9] 157 (r) [10] 500 (r)[5]	51 (h)[4] 63.8 (h)[5] 186 (r)[5] 200 (r)[11] 86.2 (m)[12] 145 (gp)[11] 96.0 (rb)[12] 147 (d)[12] 132 (d)[11]	795 (h)[13] 243 (h)[4] 509 (h)[7] 3,960 (h)[8] >10,000 (r)[9] 43,000 (r)[7] 708 (rb)[7] 115 (d)[7]
66	2-Thio-CPX	0.655 (r)[14]	314 (r)[14]	2800 (h)[15]	nd
67 KFM19 (rac.) BIIP-20 (*S*-(−))	Apaxifylline (*S*-(−)-configurated enantiomer)	10.5 (mk)[16,b] 3 (r)[17]	1,512 (mk)[16,b] 2,640 (r)[17]	nd	nd
68 IRFI117	Midaxifylline (8-(1-Aminocyclo-pentyl)-1,3-dipropylX	26[18]	54,600[18]	nd	nd
69 KW3902 (NAX)	Rolofylline 1,3-Dipropyl-8-(3-noradamantyl)X	0.72 (h)[19] 8.0 (h)[20] 0.19 (r)[21] 12.6 (r)[19]	108 (h)[19] 673 (h)[20] 380 (r)[21] 510 (r)[19]	296 (h)[20]	4,390 (h)[20]
70	1-Propyl-3-(*S*)-1-methylbenzyl-8-cyclopentylX	10.1 (r)[9]	3,500 (r)[9]	8,000 (h)[9]	85 (h)[9] >10,000 (r)[9]
71	1-Propyl-3-(*R*)-1-methylbenzyl-8-cyclopentylX	23.8 (r)[9]	2,400 (r)[9]	2,960 (h)[9]	370 (h)[9]
72	1-Propyl-3-benzyl-8-cyclopentylX	24.3 (h)[9] 8.70 (r)[9]	511 (r)[9]	8,000 (h)[9]	54.6 (h)[9]

		K_i (nM)[a]			
		A_1	A_{2A}	A_{2B}	A_3
73	1-Propyl-3-phenyl-8-cyclopentylX	7.1 (h)[9] 1.01 (r)[9]	1,200 (h)[9] 492 (r)[9]	625 (h)[9]	395 (h)[9]
74 PSB-16	1-Propyl-3-(3-hydroxypropyl)-8-cyclopentylX	5.74 (h)[9] 0.57 (r)[9]	664 (r)[9]	194 (h)[9]	3,100 (h)[9]
75	1-Butyl-3-(3-hydroxypropyl)-8-cyclopentyl X	0.45 (r)[9]	582 (r)[9]	nd	1,190 (h)[9]
77 PSB-36	1-Butyl-3-(3-hydroxypropyl)-8- (3-noradamantyl)X	0.7 (h)[9] 0.124 (r)[9]	980 (h)[9] 552 (r)[9]	187 (h)[9]	2,300 (h)[9] 6,500 (r)[9]
78		49 (h)[22] 55 (r)[22]	>10,000 (h)[22] >10,000 (r)[22]	nd	3,550 (h)[22]
79		29 (h)[22] 21 (r)[22]	>10,000 (h)[22] >10,000 (r)[22]	nd	>10,000 (h)[22]
80 BG-9719 (CVT-124)	Naxifylline	0.45 (h)[19] 12 (h)[21] 0.67 (r)[19]	1,100 (h)[19] 1,660 (h)[21] 1,250 (r)[19]	611 (h)[21] 1,010 (m)[12] 470 (rb)[12] 742 (d)[12]	4,810 (h)[21]
81		18 (h)[21] 3.0 (r)[21]	657 (h)[21] 264 (r)[21]	802 (h)[21]	>1,000 (h)[21]
82 BG-9928	Toponafylline	7.4 (h)[20] 3.9 (mk)[23] 1.3 (r)[20] 29 (d)[23]	6,410 (h)[20] 943 (mk)[23] 2,440 (r)[20] 4307 (d)[23]	90 (h)[20]	>10,000 (h)[20]
83	MPDX (1-Methyl analog of KF 15372)	4.2 (r)[24]	>100 (r)[24]	nd	nd
84	KF 15372	0.99 (r) [25] 3.0 (r)[26] 3.0 (gp)[25]	430 (r) [25]	nd	nd

[a] h = human; c = cow; d = dog; gp = guinea pig; m= mouse; mk = monkey; r = rat; rb = rabbit; a few data are from functional (cAMP) studies; nd = no data available A_{2B}

[b] data for the racemate (KFM-19)

[1] van Galen et al., 1994

[2] Bruns et al., 1986

[3] Klotz et al., 1991

[4] Bulicz et al., 2006

[5] Kim et al., 2002

[6] Ukena et al., 1986b

[7] Auchampach et al., 1997

[8] Klotz et al., 1998

[9] Weyler et al., 2006

[10] Müller et al., 2000

[11] Fozard et al., 2003

[12] Auchampach et al., 2009

[13] Hayallah et al., 2002

[14] Jacobson et al., 1989b

[15] Jacobson et al., 1999

[16] Schingnitz et al., 1991

[17] Müller, 1997

[18] Ceccarelli et al., 1995

[19] Pfister et al., 1997

[20] Kiesman et al., 2006b

[21] Kiesman et al., 2006a

[22] Massip et al., 2006

[23] Doggrell, 2005

[24] Noguchi et al., 1997

[25] Suzuki et al., 1992a

[26] Shimada et al., 1992a

Table 4

Adenosine receptor affinities of 8-styrylxanthines and configurationally stable analogs

		K_i (nM)[a]			
		A_1	A_{2A}	A_{2B}	A_3
Styrylxanthines[b]					
85	1,3-Dipropyl-8-stryrylX	22.2 (r)[1]	85.1 (r)[1]	nd	nd
86	1-Methyl-3-propyl-8-styrylX	31.1 (r)[1]	46.5 (r)[1]	nd	nd
87	Istradefylline (KW-6002) (K_i MAO-B = 28,000 nM)[2]	841 (h)[c] 230 (r)[c]	12 (h)[3] 91.2 (h)[c] 2.2 (r)[4] 4.46 (r)[5]	>10,000 (h)[c]	4,470 (h)[c]
88	8-Styrylcaffeine (K_i MAO-B = 2,864 nM)[6]	3890 (r)[7]	94 (r)[7]	nd	nd
89	CSC (K_i MAO-B = 80.6 nM MAO-B)[5]	28,000 (r)[7]	54 (r)[7]	8,200[8]	>10,000 (r)[9]
90	KF17837	390 (r)[10]	7.9 (r)[10] (*E*/*Z*) 1.0 (r)[10] (*E*)	1,500 (h)[10]	nd
91	Styryl-DMPX	1,100 (r)[11]	27 (r)[11]	nd	nd
92	CS-DMPX	1,300 (r)[11]	13 (r)[11]	nd	nd
93	BS-DMPX	1,200 (r)[11]	8.2 (r)[11] 10 (r)[12]	>10,000 (h)[13]	>10,000 (h)[13]
94	*m*-Methoxystyryl-DMPX	1,280 (r)[13]	12 (r)[13]	nd	nd
95	*m*-Hydroxystyryl-DMPX	940 (r)[13]	21 (r)[13]	nd	nd
96	7-unsubst. analog of CS-DMPX	250 (r)[11]	410 (r)[11]	nd	nd
97	3-Propyl analog of CS-DMPX	102 (r)[11]	5.1 (r)[11]	nd	nd
98	*p*-SS-DMPX	4,900 (r)[12]	240 (r)[12]	nd	nd
99	MSX-2	900 (r)[14] 2,500 (h)[14]	8.04 (r)[13,14] 5.38 (h)[14,d] 14.5 (h) [14,e]	>10,000 (h)[14] 2,900 (h)[15]	>10,000 (h)[14]
102	DMPTX (8-(3-thienylethenyl)-1,3-dipropylX)	561 (r)[16]	19 (r)[16]	nd	nd

		K_i (nM)[a]			
		A_1	A_{2A}	A_{2B}	A_3
103		44 (r)[17]	>10,000 (r)[17]	nd	nd
Analogs of Styrylxanthines					
104	Phenylcyclopropyl-DMPX (*trans, rac.*)	4,600 (r)[18]	1,700 (r)[18]	nd	nd
105	β-Naphthyl-DMPX	980 (r)[18]	380 (r)[18]	nd	nd
106	3-Indolyl-DMPX	1,000 (r)[18]	300 (r)[18]	nd	nd
107	Phenylethynyl-DMPX	>3,000 (r)[18]	314 (h)[c] 300 (r)[18]	nd	5,000 (h)[c]
108	PhenylbutadienylX (K_i MAO-B = 42.1 nM)[5]	nd	104 (r)[18]	nd	nd

[a] h = human; c = cow; d = dog; gp = guinea pig; m= mouse; mk = monkey; r = rat; rb = rabbit; a few A_{2B} data are from functional (cAMP) studies; nd = no data available

[b] most data probably represent data from mixture of *E*/*Z* isomers since in dilute solutions light-induced isomerization occurs very fast and is difficult to avoid under standard testing conditions

[c] Müller et al., unpublished data

[d] recombinant receptors expressed in CHO cells

[e] native receptors (post-mortem human brain cortex)

[1] Erickson et al., 1991

[2] Petzer et al. 2003

[3] Kase, 2003

[4] Shimada et al. 1997

[5] Pretorius et al. 2008

[6] Vlok et al. 2006

[7] Jacobson et al., 1993a

[8] Daly et al., 1995

[9] van Galen et al., 1994

[10] Nonaka et al., 1994a

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[11] Müller et al., 1997a

[12] Müller et al. 1998b

[13] Müller et al., 2000

[14] Sauer et al. 2000

[15] Solinas et al., 2005

[16] Del Giudice et al., 1996

[17] Massip et al., 2006

[18] Müller et al., 1997a

Table 5

Adenosine receptor affinitities of deazaxanthines and azaxanthines

		K_i (nM)[a]			
		A_1	A_{2A}	A_{2B}	A_3
Deazaxanthines					
109	9-Deaza-theophylline	5,400 (r)[1]	12,000 (r)[1]	nd	nd
110	9-Deazacaffeine	32,000 (r)[1]	72,000 (r)[1]	nd	nd
111	7-Deaza-theophylline	43,000 (r)[1]	>250,000 (r)[1]	nd	nd
112	1,3-Dimethyl-8-phenyl-9-deazaX	47 (r)[1]	510 (r)[1]	nd	nd
113	1,3-Dipropyl-8-phenyl-9-daX	13 (r)[1]	450 (r)[1]	nd	nd
114	1-Methyl-8-phenyl-9-deazaX	97 (r)[1]	2000 (r)[1]	520 (h)[2]	2098 (h)[2]
115	1-Propyl-8-phenyl-9-daX	45 (h)[2] 39 (r)[1]	>10,000 (h)[2] 1,200 (r)[1]	42 (h)[2]	380 (h)[2]
116	1,3-Dimethyl-8-phenyl-7-deazaX	3,100[1]	12,000[1]	nd	nd
117		14.8 (h)[3]	64.6 (h)[3]	3.02 (h)[3]	>1,000 (h)[3]
118		>1,000 (h)[4]	10,000 (h)[4]	11.0 (h)[4]	>1,000 (h)[4]
119		89.1 (h)[4]	324 (h)[4]	2.04 (h)[4]	2,240 (h)[4]
120		676 (h)[4]	3,550 (h)[4]	5.26 (h)[4]	>1,000 (h)[4]
121		183 (h)[5]	nd	1 (h)[5]	12,260 (h)[5]
122	Tricyclic 9-DeazaX	346 (h)[6]	164 (h)[6]	nd	3.82 (h)[6]
8-Azaxanthines					
123	1,3-Dimethyl-8-cyclopentyl-8-azaX	110,000 (c)[7]	58,000 (c)[7]	nd	nd
124	1,3-Dipropyl-8-cyclopentyl-8-azaX	1,300 (c)[7]	13,000 (c)[7]	nd	nd
125	1,3-Dimethyl-7-cyclopentyl-8-azaX	11,000 (c)[7]	292,000 (c)[7]	nd	nd
126	1,3-Dipropyl-7-cyclopentyl-8-azaX	340 (c)[7]	10,000 (c)[7]	nd	nd

[a] h = human; c = cow; r = rat; a few A_{2B} data may be from functional (cAMP) studies; nd = no data available

Handb Exp Pharmacol. Author manuscript; available in PMC 2014 January 07.

[1] Grahner et al., 1994

[2] Hayallah et al., 2002

[3] Carotti et al., 2006

[4] Stefanachi et al., 2008

[5] Esteve et al., 2006

[6] Ishiyama et al., 2009

[7] Francheti et al., 1994

Table 6

Adenosine receptor affinities of tricyclic xanthine derivatives

		K_i (nM)[a]			
		A_1	A_{2A}	A_{2B}	A_3
Imidazo[2,1-*i*]purin-5-ones					
127	KF20274	2.7 (r)[1]	290 (r)[1]	nd	nd
128		22 (h)[2] 6 (r)[2]	4,400 (h)[2] 2,700 (r)[2]	580 (h)[2]	>10,000 (h)[2]
129	PSB-10	1,700 (h)[3] 805 (r)[4]	2,700 (h)[3] 6,040 (r)[4]	nd	0.441 (h)[4]
130	PSB-11	1,640 (h)[3] 440 (r)[3]	1,280 (h)[3] 2,100 (r)[3]	2,100 (m)[4]	2.34 (h)[3] K_D 4.9 (h)[5]
131	KF26777	1,800 (h)[6]	470 (h)[6]	620 (h)[6]	0.20 (h)[6]
132		14,900 (r)[4]	424 (r)[4]	3,700 (m)[4]	30,600 (h)[4]
Pyrimido[2,1-*f*]purinediones					
133		15,000 (r)[7]	16,000 (r)[7]	nd	nd
134		20,000 (r)[7]	>250,000 (r)[7]	nd	nd
135		>25,000 (r)[8]	998 (r)[8]	5,200 (h)[8]	12,300 (h)[8]
136		26,800 (h)[9] ≥25,000 (r)[9]	2,870 (h)[9] 219 (r)[9]	ca. 10,000 (h)[9]	>10,000 (h)[9]
137		16,700 (h)[9] >25,000 (r)[9]	1,880 (h)[9] 147 (r)[9]	ca. 10,000 (h)[9]	>10,000 (h)[9]
138		>25,000 (r)[10]	11,300 (h)[10] 699 (r)[10]	nd	nd
139		89 (r)[10]	478 (r)[10]	nd	1,290 (h)[10]
140		>10,000 (h)[11] >25,000 (r)[11]	2,890 (h)[11] 320 (r)[11]	ca. 10,000 (h)[11]	>10,000 (h)[11]
141		>25,000 (h)[11] ca. 25,000 (r)[11]	630 (h)[11] 230 (r)[11]	7,200 (h)[11]	>10,000 (h)[11]

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		K_i (nM)[a]			
		A_1	A_{2A}	A_{2B}	A_3
142		>25,000 (h)[11] ca. 25,000 (r)[11]	4,560 (h)[11] 330 (r)[11]	ca. 10,000 (h)[11]	>10,000 (h)[11]
143		620(r)[11]	860(r)[11]	590 (h)[11]	3,660 (h)[11]
Pyrido[2,1-*f*]purinediones					
144		50 (h)[12]	119 (h)[12]	nd	4.0 (h)[12]
145		>10,000 (h)[12]	>10,000 (h)[12]	nd	35 (h)[12]
146		>1,000 (h)[13]	242 (h)[13]	nd	4.2 (h)[13]
147		>1,000 (h)[13]	>1,000 (h)[13]	>1,000 (h)[13]	2.24 (h)[13]
Imidazo-, Pyrrolo- and Triazolopurinediones					
148		>1,000 (h)[14]	>1,000 (h)[14]	>1,000 (h)[14]	0.8 (h)[14]
149		>1,000 (h)[14]	>1,000 (h)[14]	>1,000 (h)[14]	3.5 (h)[14]
150		>10,000 (h)[15]	2,050 (h)[15]	>100,000 (h)[15]	1,330 (h)[15]
4,5-Dihydro-6*H*,8*H*-pyrimido[1,2,3-*cd*]purine-8,10-diones					
151		1,440 (r)[16]	12,400 (r)[16]	42,600 (h)[16]	nd
152	**PSB-63**	16.9 (r)[16] 90.6 (h)[16]	22,000 (r)[16] 34,500 (h)[16]	3,190 (h)[16]	>10,000 (h)[16]
153		40.6 (r)[16] 13.8 (h)[16]	23,400 (r)[16] ca. 25,000 (h)[16]	22,300 (h)[16]	188 (h)[16]
Oxazolo[3,2-*a*]purinone					
154		770 (r)[17]	20,600 (r)[17]	nd	nd

[a] h = human; m = mouse; r = rat; a few A_{2B} data may be from functional (cAMP) studies; nd = no data available

[1] Suzuki et al., 1992b

[2] Vu et al., 2006

[3] Ozola et al., 2003

[4] Müller et al., 2002a

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[5] Müller et al., 2002b

[6] Saki et al., 2002

[7] Geis et al. 1995

[8] Drabczynska et al., 2004

[9] Drabczynska et al., 2006

[10] Drabczynska et al., 2007a

[11] Drabczynska et al., 2007b

[12] Priego et al., 2002

[13] Priego et al., 2008

[14] Baraldi et al., 2005

[15] Pastorin et al., 2005

[16] Weyler et al., 2006

[17] Müller, 1994

Table 7

Adenosine receptor affinities of functionalized xanthines as molecular probes

		K_i (nM)[a]			
		A_1	A_{2A}	A_{2B}	A_3
Spin-labeled probes					
155		5.47 (r)[1]	8,780 (r)[1]	>1,000 (h)[1]	1,700 (h)[1]
156		8.23 (r)[1]	3,800 (r)[1]	3,100 (h)[1]	ca. 10,000 (h)[1]
157		15.7 (r)[1]	1,270 (r)[1]	48 (h)[1]	350 (h)[1]
167	TEMPO-XAC	4.9 (r)[2] 0.30 (c)[2]	nd	nd	nd
Irreversible ligands					
158	FSCPX[3,4]	10 (r)[3]	nd	nd	nd
160	ISC	42,600 (r)[5] 51,400 (gp)[5] 89,500 (rb)[5] 63,400 (c)[5]	146 (r)[5] 160 (gp)[5] 413 (rb)[5] 516 (c)[5]	nd	nd
164	m-DITC-XAC	2.39 (r)[6] 52 (r)[7]	nd	nd	nd
165	p-DITC-XAC	6.60 (r)[6] 27 (r)[7]	nd	nd	nd
Radioligands					
159	[^{18}F]CPFPX	1.26 (h)[8] 0.63 (r)[8] 1.37(p)[8] 0.18 (c)[8]	940 (h)[8] 812 (r)[8]	nd	nd
166		40 [IC_{50}] (c) [9]	nd	nd	nd
172	[^{125}I]PAPA-XAC	0.1 (c)[10]	nd	nd	nd
Biotin conjugates					
161		54 (r)[11,12]	nd	nd	nd
162		50 (r)[11,12]	nd	nd	nd

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		K_i (nM)[a]			
		A_1	A_{2A}	A_{2B}	A_3
163		60 (r)[12]	nd	nd	nd
Various conjugates					
168	D-Lys-XAC	1.74 [IC_{50}] (r) [13]	159 [IC_{50}] (r)[13]	nd	nd
169		35 (r)[12]	nd	nd	nd
170		8.1 (r)[2] 0.8 (c)[2]	nd	nd	nd
171	DTPA-XAC	59.5 (r)[2] 3.25 (c)[2]	nd	nd	nd
Fluorescent ligands					
173	FITC-XAC	125 (r)[2] 9.3 (c)[2]	nd	nd	nd
174	XAC-BY630	151 (h)[14]	nd	nd	nd
Bivalent ligand conjugates					
175[11,15]		31 (r)	nd	nd	nd
176	A_{2A} antagonist/D_2 agonist for A_{2A}/D_2 receptor heteromers K_i D_2 (s) = 1.0 nM)[16]	nd	55 (s)[16]	nd	nd

[a] h = human; c = cow; d = dog; gp = guinea pig; p = pig; r = rat; rb = rabbit; s = sheep

[1] Ilas et al., 2005

[2] Jacobson et al., 1987b

[3] Scammels et al., 1994

[4] Muijlwijk-Koezen et al., 2001

[5] Ji et al., 1993

[6] Jacobson et al., 1989a

[7] Stiles and Jacobson, 1988

[8] Holschbach et al., 2002

[9] Jacobson et al., 1992b

[10] Stiles and Jacobson, 1987

[11] Jacobson, 2009

[12] Jacobson et al., 1987c

[13] Jacobson et al., 1986b

[14] Briddon et al. 2004

[15] Jacobson et al., unpublished

[16] Soriano et al., 2009