REVIEW

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Adenosine A_{2A} receptor antagonists as novel anti-Parkinsonian agents: a review of structure-activity relationships

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The adenosine A_{2A} receptor ($AA_{2A}R$) has emerged as an attractive target for the treatment of Parkinson's disease. Evidence suggests that antagonists of the $AA_{2A}R$ may be neuroprotective and may help to alleviate the symptoms of Parkinson's disease. During last decade, many efforts have been accomplished searching potent and selective $AA_{2A}R$ antagonists. In this field, various xanthines and non-xanthine heterocyclic compounds of monocyclic, bicyclic and tricyclic nucleus possessing very good affinity with a broad range of selectivity have been proposed. The aim of this article is to summarize available data on different chemical classes of $AA_{2A}R$ antagonists including those in clinical development, and briefly present an overview of the structure–activity relationships found for these compounds.

1. Parkinson's disease and its treatment

Parkinson's disease (PD) is caused by degeneration of dopaminergic neurons in the substantia nigra that innervate the striatum. The subsequent decreased levels of dopamine in the striatum lead to a disturbed regulation of motor behavior causing the symptoms typically observed in PD (Abou-Sleiman et al. 2006). Currently, the therapy of PD is largely focused on dopamine replacement strategies with the dopamine precursor levodopa and dopamine agonist drugs (Allain et al. 2008; Cavalli et al. 2008). Although these strategies are highly effective in controlling the early stages of the disease, long-term treatment is associated with drug-related complications such as a loss of drug efficacy, the onset of dyskinesias and the occurrence of psychosis and depression (Schwarzschild et al. 2006; Dauer and Przedborski 2003; Jenner 2000). The inadequacies of dopamine replacement therapy have prompted the search for alternative drug targets (Azam 2009; Azam et al. 2009a,b).

2. Adenosine A_{2A} receptor antagonists

Adenosine is considered to be one of the human body's most important neuromodulators, in both the central and peripheral nervous systems (Nomoto 2000). The effects of this purine nucleoside are modulated via four receptor subtypes: A_1, A_{2A}, A_{2B} and A_3 (Fredholm et al. 2001). These four adenosine receptor subtypes belong to the family of seven trans-membrane G-protein coupled receptors (Ralevic and Burnstock 1998; Moreau and Huber 1999). Among adenosine receptors, A_{2A} receptors appear to play the most important role in the control of motor behaviour and in the modulation of dopamine-mediated responses (Durcan and Morgan 1989; Ferre et al. 1992; Morelli et al. 1994). Adenosine A_{2A} receptors ($AA_{2A}R$) are highly distributed in the central nervous system and are found in abundance in the basal ganglia, a region of the brain associated with motor function (Nonaka and Ichimura 2000; Svenningsson et al. 1999). The colocalization of $AA_{2A}R$ and dopamine D_2 receptors in the striatopallidal neurons provides the anatomical basis for the existence of a functional antagonistic interaction between these receptors (Pinna et al. 2005b). Stimulation of the dopamine D_2 receptors with dopamine or other dopamine D_2 receptor agonists enhances motor activity whereas stimulation of $AA_{2A}Rs$ reduces this effect (Fuxe et al. 1998; Salamone et al. 2009). Results from different studies showed that $AA_{2A}Rs$ exert an excitatory influence on striatopallidal neurons, and antagonism of these receptors is responsible for the motor stimulant effects (Kase 2000). Likewise, a number of $AA_{2A}R$ antagonists have been shown to improve motor disabilities in animal models of PD (Kanda and Jenner 2000; Galluzzo et al. 2008; Tronci et al. 2007; Pinna et al. 2005a) and are being considered as promising agents for the symptomatic treatment of PD (Xu et al. 2005; Schapira et al. 2006). In addition, evidence suggests that $AA_{2A}R$ antagonists may slow the course of the PD by protecting against the underlying neurodegenerative processes (Kachroo et al. 2005; Mojsilovic-Petrovic et al. 2006; Petzer et al. 2009) and may prevent the development of dyskinesias that are normally associated with levodopa treatment (Bibbiani et al. 2003; Schapira et al. 2006). Furthermore, $AA_{2A}R$ antagonists were found not only to diminish the symptoms of PD but also to potentiate the effect of levodopa (Wardas et al. 2001; Rose et al. 2006), so, it may be possible to reduce the dose of the dopaminergic drugs and therefore the occurrence of side effects (Schwarzschild et al. 2006; Bara-Jimenez et al. 2003). $AA_{2A}R$ antagonists are therefore a promising adjunctive to dopamine replacement therapy, and several companies have now advanced selective antagonists

of this receptor into clinical development (Neustadt et al. 2007).

Over the past decade, a number of xanthine and non-xanthine heterocyclic derivatives possessing very good affinity in nM range and with a broad range of selectivity, have been proposed as antagonists of the $AA_{2A}Rs$ (IJzerman et al. 1994; Song et al. 2001). To this end, the present review summarizes the available data and provides an overview of the structure–activity relationships (SAR) found for $AA_{2A}R$ antagonists. Care has been taken to cover the most relevant and recent references.

3. SAR of Adenosine A_{2A} receptor antagonists

3.1. Xanthine derivatives

3.1.1. Bicyclic xanthine derivatives

The xanthine core structure has served as the basis for numerous selective antagonists for adenosine receptors (Dong et al. 2008). SARs for xanthines as antagonists for adenosine receptors have been studied extensively in efforts to develop both potent and selective agents. Caffeine [Fig. 2 (**1**)] and theophylline [Fig. 2 (**2**)], which are naturally occurring antagonists for adenosine receptors, have represented the starting point in the search for potent and selective antagonists for the four different adenosine receptor subtypes. In particular, an optimization of substitutions at the 1-, 3-, and 8-positions led to the discovery of potent and selective antagonists for the various adenosine receptor subtypes (Pastorin et al. 2005). The main structural requirements for receptor interaction of xanthine derivatives are presented in Fig. 1.

3.1.1.1. Position 1. Substitution at the 1-position of the xanthine heterocycle is most important for high A_1 and A_{2A} receptor affinity (Shimada and Suzuki 2000). Bulk tolerance at this position is more limited for the $AA_{2A}R$ compared to the adenosine A_1 receptors (AA_1R). Small substituents, such as methyl, allyl, propargyl and cyclopentyl appear to fit well into the 1-substituent-binding pocket of the $AA_{2A}Rs$. Larger substituents, such as benzyl, butyl (Sakai et al. 1992) and 3-butenyl (Miyamoto et al. 1993) increase AA_1R affinity to a large extent but not $AA_{2A}R$ affinity. The propyl substituent increases affinity at both receptors, but more at the AA_1R leading to A_1-selective compounds (Kiesman et al. 2006; Strappaghetti et al. 2001). Replacement of 1-methyl of caffeine with 1-propargyl group resulted in 3,7-dimethyl-1-propargylxanthine [DMPX, Fig. 2 (**3**)], the first "selective" $AA_{2A}R$ antagonist described in the literature (Seale et al. 1988; Daly et al. 1996).

Alkyl substitution at the 1-position of 8-styrylxanthine is a critical determinant of affinity for the $AA_{2A}R$ (Muller et al. 1997a). Introduction of a propargyl moiety at the 1-position of styrylxanthine led to the development of 3-(3-hydroxypropyl)-8-(*m*-methoxystyryl)-1-propargylxanthine [MSX-2, Fig. 3 (**4**)] which showed high affinity for $AA_{2A}R$, and remarkable selectivity over AA_1R. Poor water-solubility of MSX-2 was overcome by making its disodium phosphate prodrug [MSX-3, Fig. 3 (**5**)], which is cleaved *in vivo* by ubiquitous phosphatases to release the $AA_{2A}R$ 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 $AA_{2A}R$ antagonists (Quarta et al. 2004; Karcz-Kubicha et al. 2003; Agnati et al. 2004; Blum et al. 2003; Hauber et al. 2001). Allyl substitution decreased $AA_{2A}R$ affinity about 4-fold compared to propargyl, while 1,3-dipropyl or 1,3-diethyl substitution enhanced $AA_{2A}R$ affinity (Pretorius et al. 2008). Diethyl substitution at the 1- and 3-position

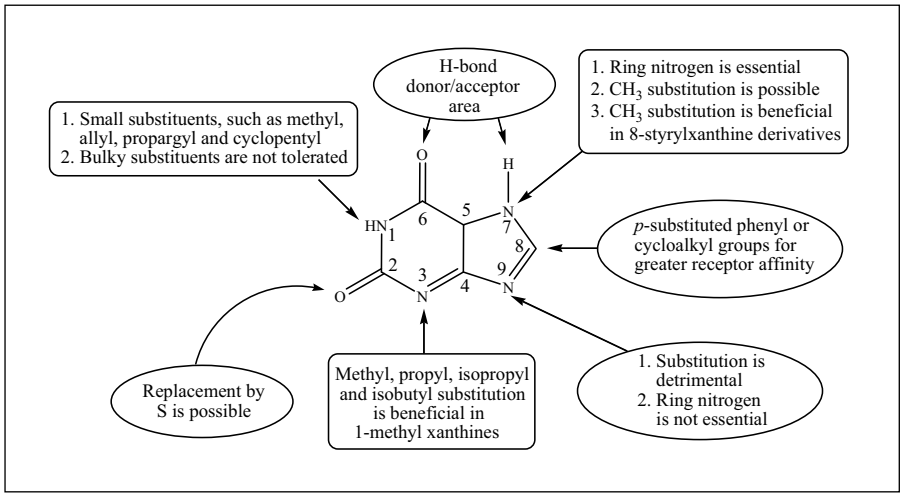


Fig. 1: The main structural requirements for receptor interaction of xanthine derivatives

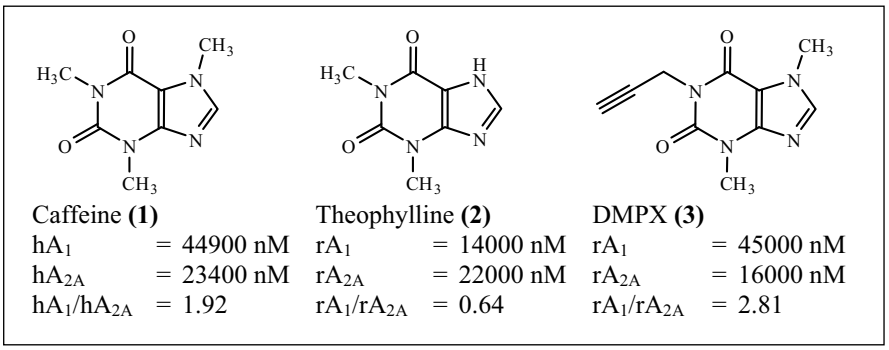
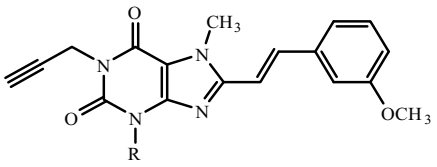


Fig. 2: Naturally occurring xanthines and their derivative. Data represent *K*i values (h = human, r = rat) and are taken from references indicated in the text



MSX-2 **(4)**
R= $(CH_2)_3OH$
hA_1 = 0.9 nM
hA_{2A} = 0.008 nM
hA_1/hA_{2A} = 113

MSX-3 **(5)**
R = $(CH_2)_3OPO(ONa)_2$
(Prodrug of MSX-2)

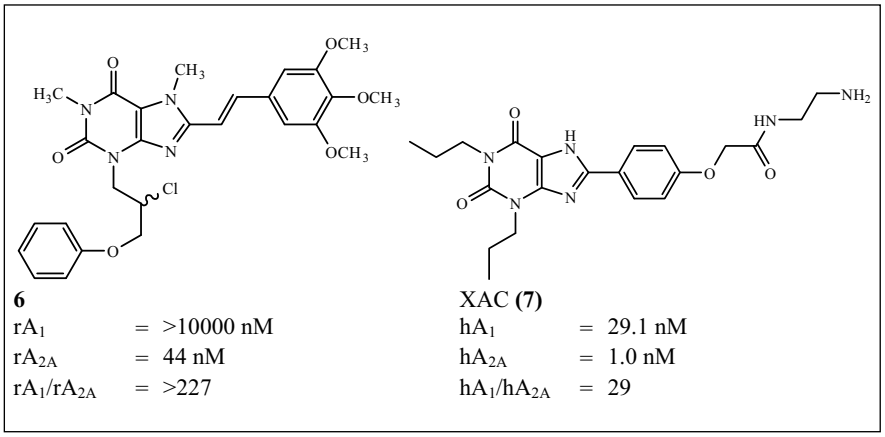
Fig. 3: Styrylxanthine derivative and its prodrug. Data represent *K*i values (h = human) and are taken from reference indicated in the text

dramatically potentiated the activity without exception presumably due to increased oral bioavailability (Shimada et al. 1997). 1,3-Dimethyl or 1,3-diallyl substitution at the 1- and 3-positions reduced affinity for the AA_1R, resulting in higher $AA_{2A}R$ selectivity (Muller et al. 1997b).

3.1.1.2. Position 3. At N3 of xanthine derivatives, small alkyl residues such as methyl, propyl, and 3-hydroxypropyl have been the most common substitutents in $AA_{2A}R$-selective antagonists (Cacciari et al. 2003; Muller 2000; Muller and Ferre 2007; Muller et al. 1993). Recently, a series of xanthine derivatives with more variations in the 3-position were developed. It was found that the $AA_{2A}R$ tolerated bulky, functionalized substituents in the 3-position. For instance, N3-phenoxypropyl-substituted 8-(methoxystyryl)xanthine derivatives [Fig. 4 (**6**)] are potent and selective $AA_{2A}R$ antagonists (Massip et al. 2006). The introduction of a substituent in the 3-position of 1-substituted xanthines leads to theophylline analogs. Methyl, propyl, isopropyl and isobutyl substituents increase $AA_{2A}R$ affinity of 1-methylxanthine slightly, but AA_1R affinity to a larger extent (Jacobson et al. 1986; Muller et al. 1997a). The hydrophilic β-hydroxyethyl-substituent in the 3-position is not well tolerated by both receptors. 3-Propyl-substitution of 1-propylxanthine gave a dramatic increment on both AA_1R and $AA_{2A}R$ affinity. The introduction of a 3-benzyl or 3-allyl into 1-benzyl or 1-allylxanthine, respectively, has virtually no effect on adenosine receptor affinity of the compounds (Muller and Scior 1993). Exchange of methyl for propyl in the 3-position of xanthines increases $AA_{2A}R$ affinity, but at the same time decreases selectivity over AA_1Rs (Muller et al. 1997a). Introduction of benzyl at 3-position decreases both AA_1R and $AA_{2A}R$ affinity (Muller et al. 1997a).

3.1.1.3. Position 7. 7-Monosubstituted xanthines are rather potent adenosine receptor antagonists. Generally, 7-methyl substitution shifts the affinity of caffeine and paraxanthine analogs towards $AA_{2A}R$-selectivity. The introduction of 7-methyl group or 7-propargyl group into 1-substituted xanthines increases $AA_{2A}R$ affinity [Fig. 2 (**3**)]. 7-Alkylation of 1,3-dimethylxanthine slightly reduces $AA_{2A}R$ affinity (7-methyl, 7-allyl and 7-propyl) or does not alter $AA_{2A}R$ affinity (7-propargyl, 7-phenyl) (Muller and Scior 1993). 2-chloroethyl moiety is often associated with increased affinity of $AA_{2A}R$ (Kim et al. 2002).
It is interesting that 7-methylation of 8-substituted xanthines generally resulted in a reduced affinity for both AA_1R and $AA_{2A}R$. 7-Methylation of 8-substituted xanthines was found to reduce AA_1R affinity to a larger extent than $AA_{2A}R$ affinity leading to $AA_{2A}R$-selective antagonists (Shamim et al. 1989). However, if the 8-substituent was a styryl residue, the effect of 7-methylation differed. AA_1R affinity was still reduced, but $AA_{2A}R$ affinity was unchanged or increased in 8-styrylxanthine derivatives. The reduced AA_1R affinity can be explained by the importance of having a hydrogen bond donor at the 7-position of the xanthine nuclei for the binding to adenosine AA_1R receptors (Dooley et al. 1996). In contrast, the enhanced $AA_{2A}R$ affinity of 8-styrylxanthines by 7-methylation may be explained by steric factors. The methyl group may sterically interact with the styryl group to force the latter into a favorable conformation for interaction with the adenosine $AA_{2A}R$. Similar to 8-styrylxanthines, 7-methyl substitution does not alter the affinity for $AA_{2A}Rs$ in 8-(2-phenylethyl) and (*E*)-cinnamyl xanthines. In contrast to this observation, introduction of a methyl group into the 7-position of 8-(2-cyclopentylethyl)- or 8-cyclopentyl-substituted xanthine results in decreased affinity for the $AA_{2A}R$. Consequently, the electrostatic effects of the 2-phenylethyl or cinnamyl group appear to be more favorable for an interaction with the $AA_{2A}R$ than those of a cyclopentyl group (Muller et al. 1997a). Hydrophilic substituents in the 7-position, such as hydroxyethyl, aminoethyl, 2-oxopropyl and 2,3-dihydroxypropyl are unfavourable for both AA_1R and $AA_{2A}R$ affinity (Muller and Scior 1993).

3.1.1.4. Position 8. The substitution of xanthines with a phenyl ring or other substituents in the 8-position was an important step towards highly potent and selective adenosine receptor antagonists (Bruns et al. 1983; Hamilton et al. 1985; Martinson et al. 1987; Jacobson et al. 1988, 1993a,b,c; Shamim et al. 1988; Katsushima et al. 1990; Nieto et al. 2009). Most 8-phenylxanthines are selective for the AA_1R (Shimada et al. 1991). The introduction of a distal amide function in the



6
rA_1 = >10000 nM
rA_{2A} = 44 nM
rA_1/rA_{2A} = >227

XAC **(7)**
hA_1 = 29.1 nM
hA_{2A} = 1.0 nM
hA_1/hA_{2A} = 29

Fig. 4: Xanthine derivatives with variation at 1-, 3- and 8-positions. Data represent *K*i values (h = human, r = rat) and are taken from references indicated in the text

para-position of an 8-phenyl- or 8-cyclohexyl ring enhances $AA_{2A}R$ affinity (Bruns et al. 1987), as in xanthine amine congener [XAC, Fig. 4 (**7**), Jacobson et al. 1988]. It has been observed that substitution pattern on 8-phenyl group greatly affects the affinity and selectivity at adenosine receptors, with $AA_{2A}R$ tolerating bulkier substituents than did AA_1Rs (Bansal et al. 2009). In addition, 8-cycloalkyl substituents (cyclopentyl and cyclohexyl) increase the affinity of caffeine and 1,3-dipropyl-7-methylxanthine for the $AA_{2A}R$ (Shamim et al. 1989). The substitution of the 8 position with a variety of groups, has led the medicinal chemists to discover that the introduction of the styryl group in this position was critical in achieving compounds endowed with selective $AA_{2A}R$ antagonistic properties (Baraldi et al. 1995; Shimada et al. 1992b; Muller et al. 1996b; Jacobson et al. 1993b). The result of this effort was the discovery of KF 17837 [Fig. 5 (**8**)], istradefylline [KW 6002, Fig. 5 (**9**)], and (*E*)-8-3-chlorostyryl)caffeine [CSC, Fig. 5 (**10**)], the pharmacological characteristics of which have been studied extensively (Behan and Stone 2002; Correa et al. 2004; Jenner 2003; Bove et al. 2006; Coccurello et al. 2004). One of the major problems with 8-styrylxanthines is their photosensitivity. They rapidly isomerize when exposed to normal daylight in dilute solution. The potency of the *E*- and *Z*-isomers of KF17837 [Fig. 5 (**8**)] in radioligand binding assays revealed that *E*-isomer possess high affinity and selectivity for $AA_{2A}Rs$ (Nonaka et al. 1994; Shimada et al. 1997); different ratios of (*E*)/(*Z*) mixtures have been observed, but usually the (*Z*) isomer was predominant (Cacciari et al. 2003). In addition, incorporation of a methyl group into the vinylene group caused reduction in affinity for both AA_1R and $AA_{2A}Rs$. Thus, the vinylene group between the xanthine and the phenyl group appears to play an important role for the receptor interactions.

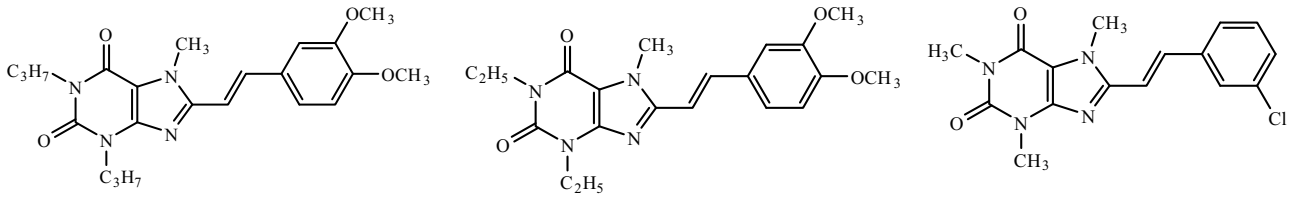
Introduction of methoxy substituents into the phenyl group of (*E*)-l,3-dipropyl-7-methyl-8-styrylxanthine enhanced the $AA_{2A}R$ selectivity in general (Petzer et al. 2003; Shimada et al. 1992a; Muller et al. 1997a). Furthermore, the $AA_{2A}R$ selectivity of the compounds could also be enhanced by monosubstitution of the phenyl ring with a halogen atom, preferably in the *meta* position (Jacobson et al. 1993a). Replacement of the styryl phenyl group by heterocycles, such as thienyl, furyl, pyridyl and pyrazolyl also led to adenosine $AA_{2A}R$ antagonists, but these compounds were inferior to the styryl-substituted xanthines with regard to selectivity and/or potency (Giudice et al. 1996; Muller et al. 1997a; Kalla et al. 2008). Aza-analogues of 8-styrylxanthine, in which the ethenyl bridge is replaced by an imine, amide, or azo function, show relatively high $AA_{2A}R$ affinity (Muller et al. 1997b). Moreover, based on DMPX, Muller et al. (1997a) have developed a series of 3,7-dimethyl-1-propargyl-8-styrylxanthine derivatives as $AA_{2A}R$-selective antagonists, among which 8-(m-bromostyryl)-3,7-dimethyl-1-propargylxanthine [BS-DMPX, Fig. 6 (**11**)] and 8-(m-methoxystyryl)-3,7-dimethyl-1-propargylxanthine [MS-DMPX, Fig. 6 (**12**)] were found to exhibit high affinity and selectivity for $AA_{2A}Rs$.

Daly et al. (1985) have synthesized 8-*p*-sulfophenylxanthines to enhance the water solubility of the compounds. The adenosine receptor affinity was reduced by the polar substituents. Nevertheless, the compounds have proven useful research tools due to their high water solubility. In addition, several other hydrophilic functions were introduced into the 8-substituent of xanthines to increase water solubility of the compounds (Martinson et al. 1987; Shamim et al. 1988; Katsushima et al. 1990).

In 8-substituted xanthines the SARs for substituents at the 1-, 3- and 7-position appear to be similar to the SARs in 8-unsubstituted xanthenes (Erickson et al. 1991). The 1-substituent is most important for high AA_1R and $AA_{2A}R$ affinity. Again, the bulk tolerance in the 1-position is more limited at the $AA_{2A}R$ than at the AA_1R. A propargyl function in the 1-position appears to be optimal for $AA_{2A}R$ affinity, while propyl or benzyl is favourable for high AA_1R affinity. Larger substituents, such as isobutyl and benzyl at the 3-position (Linden et al. 1988; Patel et al. 1988; Ali et al. 1991) are tolerated by both receptors.

3.1.1.5. Position 9. Data for 9-substituted xanthines as adenosine receptor antagonists is very limited. 9-Substitution appears to be detrimental to $AA_{2A}R$ and AA_1R affinity of xanthines. The AA_1R tolerates 9-substituents somewhat better than the $AA_{2A}Rs$ (Muller and Scior 1993).

3.1.1.6. Deaza-xanthines. A series of xanthines where either the N9 or the N7 nitrogen is exchanged by CH_2 were synthesized and evaluated in AA_1R and $AA_{2A}R$-binding assays (Daly et al. 1988; Hess et al. 2000; Muller et al. 1990, 1996a). 9- Deazaxanthines and 7-deazaxanthines are generally equipotent or somewhat more potent than the corresponding xanthines at both $AA_{2A}R$ and AA_1R subtypes (Castelhano et al. 2003). These results indicate that xanthines bind to adenosine receptors in the N7-H tautomeric form while N9 of xanthines is not necessary as a hydrogen bond acceptor for high adenosine receptor affinity as had been hypothesized before (Van Galen et al. 1990). In fact, various 1-, 3- and 8-substituted-9-deazaxanthine derivatives (Stefanachi et al. 2008a), 1,3-dialkyl/aryl-8-substituted-9-deazaxanthine derivatives (Carotti et al. 2004) and 1,3-dialkyl-8-(hetero)aryl-9-hydroxy-9-deazaxanthine (Stefanachi et al. 2008b) derivatives have excellent affinity for adenosine A_{2B} receptors.



KF17837 **(8)**		KW6002 **(9)**		CSC **(10)**	
rA_1	= 62 nM	rA_1	= 150 nM	rA_1	= 28,000 nM
rA_{2A}	= 1.0 nM	rA_{2A}	= 2.2 nM	rA_{2A}	= 54 nM
rA_1/rA_{2A}	= 62	rA_1/rA_{2A}	= 68	rA_1/rA_{2A}	= 518

Fig. 5: Examples of $AA_{2A}R$ antagonists in clinical development. Data represent *K*i values (r = rat) and are taken from references indicated in the text

3.1.1.7. Thioxanthines. In a series of 8-substituted xanthines, 2-thio derivatives were equally potent compared to their oxygen analogs at AA_1R and $AA_{2A}Rs$ with one striking exception: 8-phenyl-2-thiotheophylline showed high AA_1R affinity but a complete loss of $AA_{2A}R$ affinity. In the 1,3-dipropyl series and the 8-cyclopentyl series, however, a 2-thio function had only very slight effects on AA_1R and $AA_{2A}R$ binding affinity (Jacobson et al. 1989). This result could indicate that different binding modes for xanthines exist depending on the substitution patterns at the 1,3-positions (dimethyl versus dipropyl) and the 8-position (phenyl versus cyclopentyl). 6-Thioxanthines were generally less potent than their oxygen counterparts at AA_1R and $AA_{2A}Rs$.

3.1.2. Tricyclic xanthine derivatives

Several tricyclic xanthine derivatives were shown to be moderately potent adenosine receptor antagonists exhibiting selectivity for $AA_{2A}Rs$ (Drabczynska et al. 2003; Weyler et al. 2006; Muller 2003). Different tricyclic xanthine derivatives reported to be adenosine receptor antagonists are presented in Fig. 7.

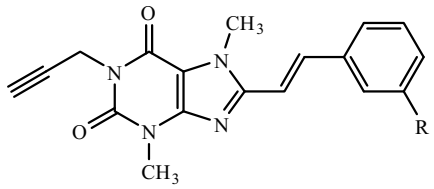
3.1.2.1. Imidazo[2,1-*i*]purin-5-ones and imidazo[2,1-*i*]purin-2,4-diones. Recently, fused ring-enlarged analogs, imidazo[2,1-*i*]purin-5-ones derived from xanthine derivatives have been synthesized. In comparison with xanthines, the tricyclic compounds exhibit increased water solubility due to a basic nitrogen atom, which can be protonated under physiological conditions. The most potent compound at $AA_{2A}R$ in this series was enantiomerically pure (*S*)-1,4-dimethyl-8-ethyl-2-styryl-imidazo[2,1-*i*]purinone [Fig. 7 (**13**)] possessing enhanced water solubility in comparison with corresponding xanthine derivatives (Muller et al. 2002). Imidazo[2,1-*i*]purin-2,4-dione derivatives showed decreased affinity for both AA_1R and $AA_{2A}Rs$ (Baraldi et al. 2005).

3.1.2.2. Oxazolo[2,3-*f*]purinediones. Examining tricyclic oxazolo[2,3-*f*]purinediones, it was suggested that the most preferable substituent for $AA_{2A}R$ selective binding was a long alkyl chain at 6-position of oxazole ring [Fig. 7 (**14**)]. Substituents containing phenyl ring appeared to be less active (Drabczynska et al. 2004).

3.1.2.3. Pyrimido[2,1-*f*]purindiones. A number of dimethyl (un)substituted arylalkyl pyrimido[2,1-*f*]purindione derivatives have been identified as selective $AA_{2A}R$ antagonists. Varying the N10-substituents it was observed that the larger spacer between aryl substituent and tricyclic system was advantageous for $AA_{2A}R$ selectivity [Fig. 7 (**15**)], while introduction of heteroatom into the spacer led to adenosine AA_1R antagonists (Yuzlenko and Kononowicz 2006). Replacement of the N-methyl groups in the pyrimidinedione ring by propyl residues increased AA_1R affinity yielding non-selective compounds, e.g. compound **15** (Fig. 7, Drabczynska et al. 2003; Muller and Ferre 2007).

3.2. Non-xanthine analogues

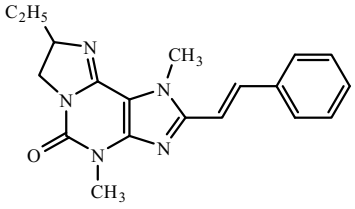
A major problem of xanthine $AA_{2A}R$ antagonists was their low-selectivity and low-water solubility (Sauer et al. 2000; Muller et al. 1997a; Muller et al. 1998; Nonaka et al. 1993). As a



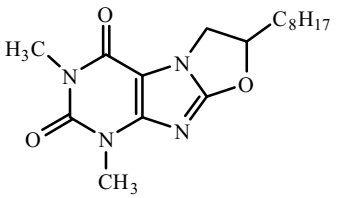
BS-DMPX **(11)**
R= Br
rA_1 = 1200 nM
rA_{2A} = 8.2 nM
rA_1/rA_{2A} = 146

MS-DMPX **(12)**
R = OCH_3
rA_1 = 1280 nM
rA_{2A} = 12 nM
rA_1/rA_{2A} = 106

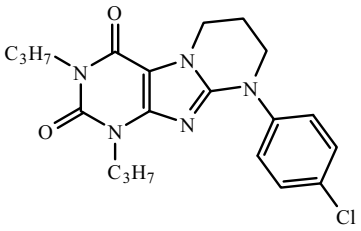
Fig. 6: Bromo and methoxy derivatives of DMPX. Data represent *K*i values (r = rat) and are taken from references indicated in the text



13
hA_1 = 14900 nM
hA_{2A} = 420 nM
hA_1/hA_{2A} = 35



14
hA_1 = >25000 nM
hA_{2A} = 998 nM
hA_1/hA_{2A} = >25



15
hA_1 = 360 nM
hA_{2A} = 380 nM
hA_1/hA_{2A} = 0.95

Fig. 7: Xanthine derivatives bearing tricyclic nucleus. Data represent *K*i values (h = human) and are taken from references indicated in the text

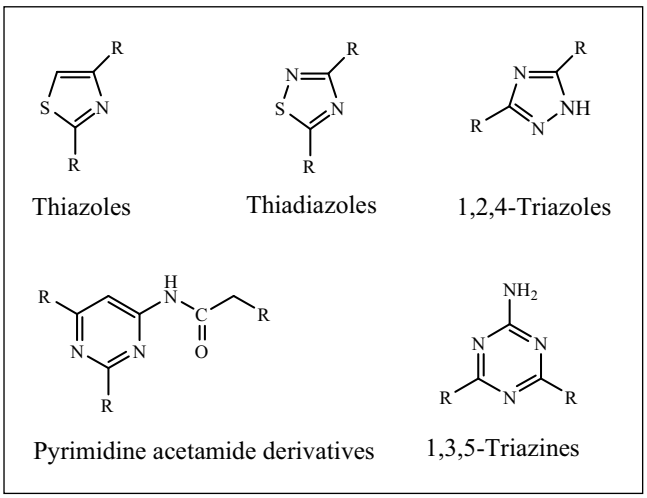


Fig. 8: Monocyclic templates of adenosine receptor antagonists

result, non-xanthine type heterocyclic $AA_{2A}R$ antagonists have been developed, and three main classes of monocyclic, bicyclic and tricyclic derivatives show interesting properties over xanthine derivatives (Slee et al. 2008a; Baraldi et al. 2002b; Matasi et al. 2005b; Vu et al. 2004b,c). Non-xanthine antagonists of the $AA_{2A}R$ receptor often take the form of nitrogen-containing monocyclic and fused bicyclic or tricyclic systems that lack the agonism-conferring ribose moiety of adenosine but feature hydrophobic substituents that impart selectivity (Cacciari et al. 2003).

3.2.1. Monocyclic non-xanthine analogues

A number of monocyclic templates such as 1,2,4-triazoles (Alanine et al. 2004), thiazole derivatives (van Tilburg et al. 2001), thiadiazole derivatives (Jung et al. 2004; Borghini et al. 2005; van Muijlwijk-Koezen et al. 2001) and triazine derivatives (Richardson et al. 2006) are currently being examined as the central structural motif of potential $AA_{2A}R$ antagonists and some of these are illustrated in Fig. 8. In particular, pyrimidine acetamide derivatives display high affinity and selectivity for $AA_{2A}Rs$ which has been strongly investigated from the point of view of SARs and are being described in detail. However, other class of monocyclic derivatives depicted in Fig. 8 have shown their affinity towards other adenosine receptor subclass.

3.2.1.1. Pyrimidine acetamide derivatives. The analysis of SARs of pyrimidine acetamide derivatives, the major group of monocyclic $AA_{2A}R$ antagonists, revealed the main requirements for their activity which are presented in Fig. 9. There are a number of reports where pyrimidin-4-amine derivatives were synthesized as $AA_{2A}R$ antagonists to be useful in the treatment or prevention of PD and other diseases known to be susceptible to improvement by treatment with an $AA_{2A}R$ antagonist (Crespo et al. 2008).

3.2.1.1.1. Position 2. In most cases, substitution of 2-furyl moiety at position 2 is favoured for high $AA_{2A}R$ affinity and selectivity over AA_1R (Fig. 10). Unfortunately, the furan ring causes toxicities that are attributed to reactive intermediates derived from metabolism of the furan moiety (Dalvie et al. 2002; Evans et al. 2004; Kalgutkar et al. 2005). The furan ring can be replaced with alternative heterocycles such as 1-pyrazolyl, 2-thiazolyl or 2-pyridyl and substituted furyl moieties but with reduced risk of producing chemically reactive metabolites. Simply adding a methyl group to the furan ring halts its metabolism imparting a large negative effect on $AA_{2A}R$ affinity. Interestingly, the addition of methyl groups to the pyrazole at position 6 counteracts this effect and restores the potency [e.g. compounds **18**–**20** (Fig. 11) and **21** (Fig. 12), Moorjani et al. 2008b; Slee et al. 2008a; Zhang et al. 2008a].

3.2.1.1.2. Position 4. SAR studies of position 4 revealed that the primary amine [Fig. 10 (**16**)] can be converted to an acetamide moiety [Fig. 10 (**17**)] for better $AA_{2A}R$ affinity (Slee et al. 2008d). Various substituted phenyl, substituted benzyl, substituted phenoxy and substituted heterocycles were appended to the acetyl group to explore SAR (Moorjani et al. 2008a; Moorjani et al. 2008b; Zhang et al. 2008b). In addition, alkyl, alkoxy or alkylamino substituted piperazinyl and pyrrolidinyl moiety are also associated with an improved affinity at $AA_{2A}R$ site (Slee et al. 2008c). Substitution of basic amine to the phenol ring [Fig. 11 (**18**)] leads to a group of antagonists with improved solubility and retained potency/selectivity. A further increment of potency as well as selectivity was observed when methoxy group was placed at phenol ring in addition to amine functionality [Fig. 11 (**19**), Zhang et al. 2008a]. The study of Moorjani et al. (2008b) showed that compounds substituted with 3,5-dimethoxyphenyl at α-carbon of acetamide moiety in the position 4 had higher affinity for $AA_{2A}Rs$ than both the unsubstituted phenyl and monomethoxyphenyl groups [Fig. 12 (**21**)].

3.2.1.1.3. Position 5. Generally, position-5 is unsubstituted for $AA_{2A}R$ binding (Moorjani et al. 2008a; Slee et al.

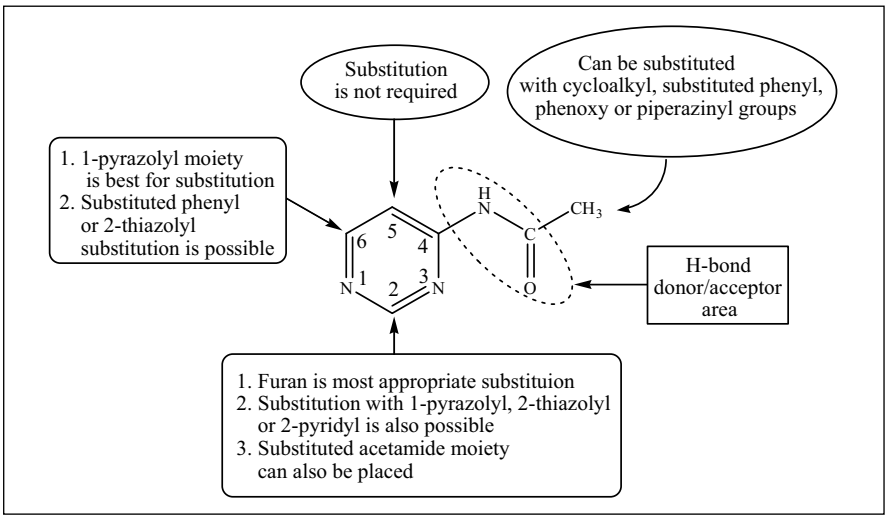
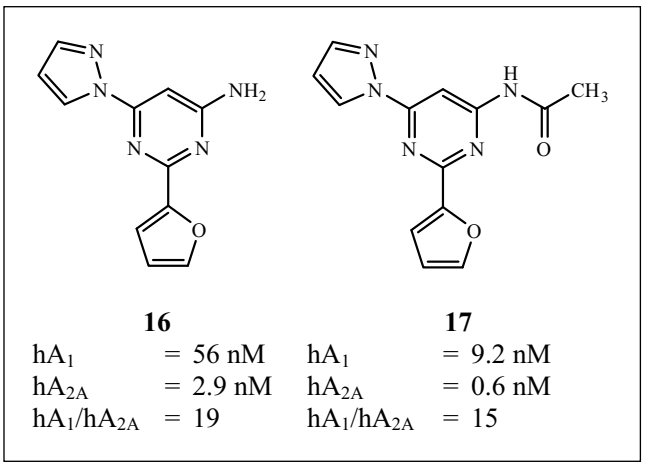


Fig. 9: Main structural requirements for $AA_{2A}R$ interaction of pyrimidineacetamide derivatives



16		**17**	
hA_1	= 56 nM	hA_1	= 9.2 nM
hA_{2A}	= 2.9 nM	hA_{2A}	= 0.6 nM
hA_1/hA_{2A}	= 19	hA_1/hA_{2A}	= 15

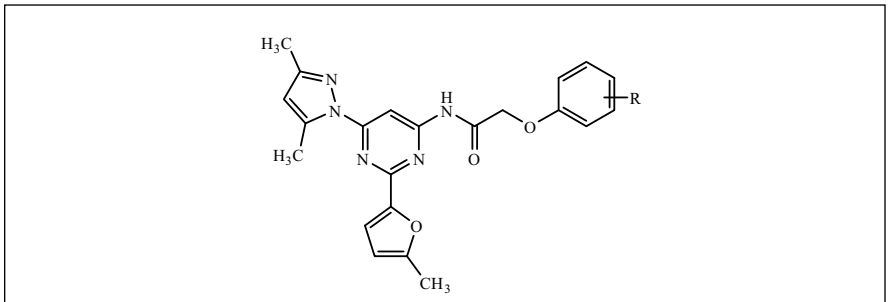
Fig. 10: Examples of $AA_{2A}R$ antagonists bearing a pyrimidine nucleus. Data represent *K*i values (h = human) and are taken from references indicated in the text

2008c; Zhang et al. 2008b); however, van Veldhoven et al. (2008) synthesized various di-and tri-substituted aminopyrimidine derivatives where introduction of a cyano group at this position afforded compounds with moderate $AA_{2A}R$ affinity.

3.2.1.1.4. Position 6. Substitution with 1-pyrazolyl ring is favourable at position 6 for $AA_{2A}R$ affinity. However, both $AA_{2A}R$ potency and selectivity over AA_1R improves significantly when pyrazole is replaced with dimethylpyrazole at this position [eg. compounds **18**–**20** (Fig. 11) and **21** (Fig. 12), Moorjani et al. 2008a,b]. When the 1-pyrazolyl moiety was substituted with 2-thiazolyl moiety at this position [Fig. 12 (**22**)], better $AA_{2A}R$ affinity and remarkable selectivity over AA_1R were observed (Slee et al. 2008a,d). The methylfuran and dimethylpyrazole combination at position 2 and position 6 respectively [Fig. 11 (**20**)] provided the best selectivity (Zhang et al. 2008b). Replacement of pyrazole with the oxazole ring resulted in poor $AA_{2A}R$ antagonists, indicating that the presence of an oxygen atom at the position 6 was not tolerated (Slee et al. 2008a,b).

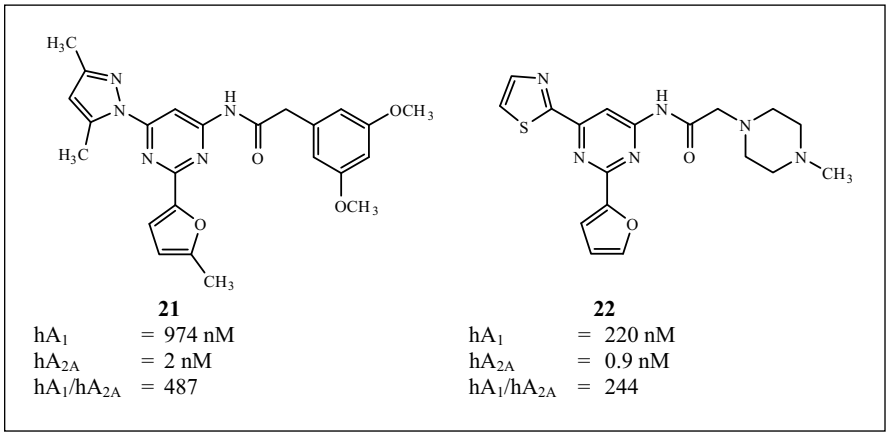
Placement of the simple phenyl group at position-6 showed modest $AA_{2A}R$ activity but poor selectivity over the AA_1R. By the addition of a methoxy group, potency and selectivity were greatly increased. In particular, substitution in the *ortho* or *meta* positions of the phenyl ring gave very potent compounds [e.g. compound **23** (Fig. 13)], which not only showed an increase in potency but the selectivity over AA_1R was also sound. From this survey, it can be concluded that incorporation of a hydrogen bond acceptor, preferably in *meta* position of the phenyl ring is preferred for $AA_{2A}R$ binding (Moorjani et al. 2008a; Zhang et al. 2008b). Furthermore, placement of pyrrolidines substituted with simple alkyl and alkoxy side chains resulted in moderate $AA_{2A}R$ affinity, selectivity, and solubility (Lanier et al. 2009).

3.2.1.2. 1,2,4-Triazoles. Alanine et al. synthesized a series of monocyclic 1,2,4-triazole derivatives as $AA_{2A}R$ antagonists [Fig. 13 (**24**, **25**)]. The initial SAR showed that the *m*-methoxyphenyl moiety is important and very little variation is permitted. The benzyl moiety afforded more scope for variation



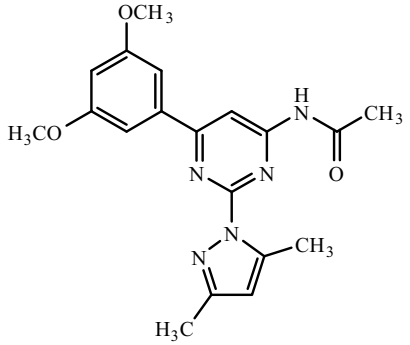
18		**19**		**20**	
R= 3-[$(CH_2)N(Me)(Et)$]		R= 2-OCH_3; 4-$(CH_2)N(Me)_2$		R= 3-F	
hA_1	= 68 nM	hA_1	= 100 nM	hA_1	= 9700 nM
hA_{2A}	= 0.3 nM	hA_{2A}	= 0.2 nM	hA_{2A}	= 3.7 nM
hA_1/hA_{2A}	= 227	hA_1/hA_{2A}	= 500	hA_1/hA_{2A}	= 2622

Fig. 11: *N*-Pyrimidinyl-2-phenoxyacetamides. Data represent *K*i values (h = human) and are taken from references indicated in the text



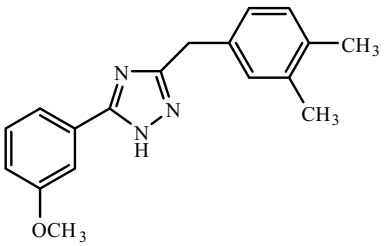
21		**22**	
hA_1	= 974 nM	hA_1	= 220 nM
hA_{2A}	= 2 nM	hA_{2A}	= 0.9 nM
hA_1/hA_{2A}	= 487	hA_1/hA_{2A}	= 244

Fig. 12: Pyrimidineacetamide derivatives. Data represent *K*i values (h = human) and are taken from references indicated in the text



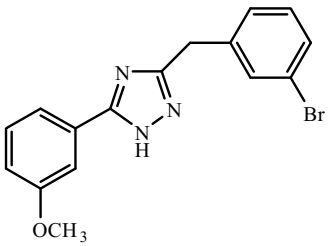
23

hA_1 = 22.2 nM
hA_{2A} = 0.2 nM
hA_1/hA_{2A} = 111



24

hA_1 = 1380 nM
hA_{2A} = 20 nM
hA_1/hA_{2A} = 69



25

hA_1 = 70 nM
hA_{2A} = 10 nM
hA_1/hA_{2A} = 7

Fig. 13: Examples of pyrimidineacetamide derivative and 1,2,4-triazoles. Data represent *K*i values (h = human) and are taken from references indicated in the text

provided substituents are hydrophobic in nature but introduction of a polar group (e.g. methylpiperidine) dramatically abolished binding activity. The compounds showed satisfactory aqueous solubility and compound **24** (Fig. 13) exhibited good permeability tested with artificial membranes (Alanine et al. 2004).

3.2.1.3. 1,3,5-Triazine derivatives. Among the recently synthesized 1,3,5-triazine derivatives (Richardson et al. 2006), the 4-(ethylthio)-6-phenyl-1,3,5-triazin-2-amine has shown interesting profile with high affinity for AA_{2A}Rs [Fig. 14 (**26**)]. A slight decrease in potency and an increase in selectivity toward AA_1R were observed when 6-methoxypyridin-3-yl moiety [Fig. 14 (**27**)] was substituted at 3 position of the phenyl ring of compound **26** (Fig. 14).

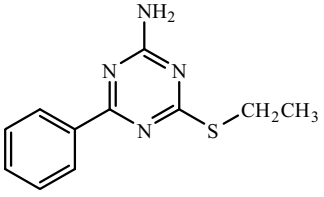
3.2.2. Bicyclic non-xanthine derivatives

The bicyclic moiety is associated with reduced molecular flexibility, which often correlates with good oral bioavailability (Veber et al. 2002) and central nervous system penetration (Crivori et al. 2000). The development of selective antagonists for the AA_{2A}R has relied on chemically rather diverse structural leads. [1,2,4]Triazolo[1,5-*a*][1,3,5]triazine (Vu et al. 2005; Vu et al. 2004b; Peng et al. 2007), [1,2,4]triazolo[1,5-*c*]pyrimidine (Neustadt and Liu 2006; Matasi et al. 2006; Vu et al. 2007), [1,2,4]triazolo[1,5-*a*]pyridine (Neustadt and Liu 2003a; Guba et al. 2004), [1,2,3]triazolo[4,5-*d*]pyrimidine derivatives (Gillespie et al. 2008d) and [1,2,4]triazolo[1,5-*a*]pyrazine (Andrews et al. 2009; Dowling et al. 2007) have all been identified as bicyclic nonxanthine derivatives of AA_{2A}R antagonists through the screening of chemical libraries. Numerous substituents have now been installed onto each of these core heterocyclic templates to explore potent and selective AA_{2A}R antagonists. Fig. 15 illustrates some bicyclic nonxanthine core as AA_{2A} R antagonists.

3.2.2.1. [1,2,4]Triazolo[1,5-*a*]pyrazine derivatives. The general structural requirements for AA_{2A}R affinity of [1,2,4]triazolo[1,5-*a*]pyrazine derivatives are presented in Fig. 16. Compounds containing *m*-substituted phenyl rings at position-6 exhibited the better AA_{2A}R antagonistic activity whereas bi- and heterocyclic derivatives exhibited comparable potency.

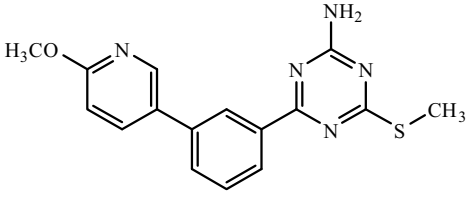
Substitution with *N,N*-diethylamide [Fig. 17 (**28**)], could enhance the AA_{2A}R affinity but concomitantly conferred significant potency toward the AA_1R also. Compound **29** (Fig. 17), which incorporates the amino-ethylphenol unit exhibited high AA_{2A}R affinity and impressive selectivity (300-fold) against the AA_1R (Dowling et al. 2005).

A SAR study was presented by Yao et al. (2005) for a series of alkyne derivatives of triazolopyrazine as AA_{2A}R antagonists.



26

hA_1 = 67 nM
hA_{2A} = 5 nM
hA_1/hA_{2A} = 13



27

hA_1 = 840 nM
hA_{2A} = 23 nM
hA_1/hA_{2A} = 36

Fig. 14: 1,3,5-Triazine derivatives. Data represent *K*i values (h = human) and are taken from references indicated in the text

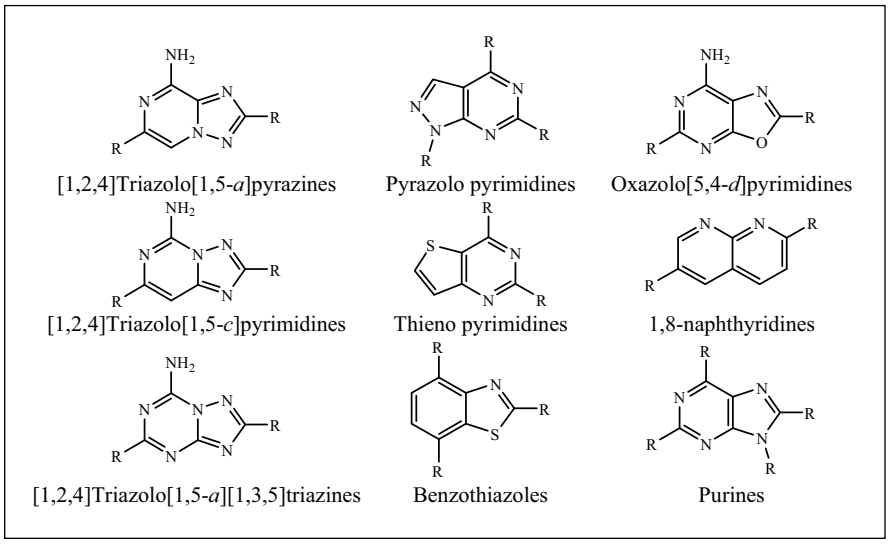


Fig. 15: Bicyclic nonxanthine core

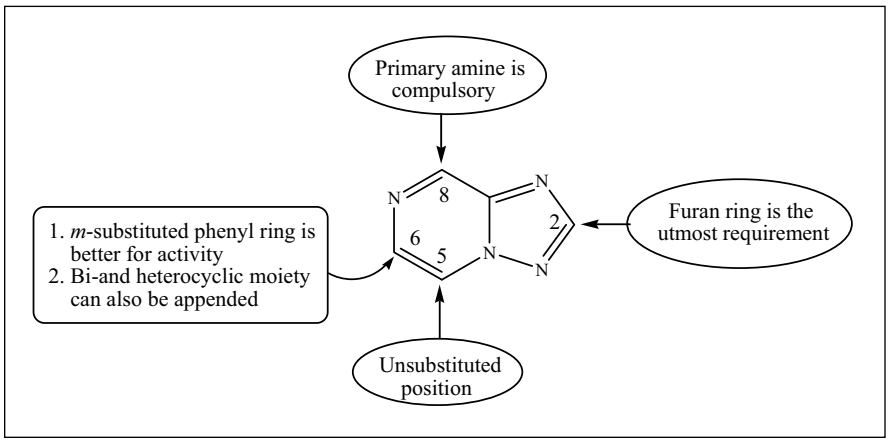


Fig. 16: The general structural requirements for $AA_{2A}R$ affinity of [1,2,4]triazolo[1,5-*a*]pyrazine derivatives

The summarized results were: (a) the presence of alkyl or aryl groups on the terminus of the acetylene side chain is clearly beneficial for the adenosine $AA_{2A}R$ affinity, with compound **30** (Fig. 18) being most potent ($AA_{2A}R$, 1.1 nM) and selective ($AA_1R/AA_{2A}R = 91$). Propargyl alcohol gives only an inactive compound; (b) the presence of a second substituent on the terminus of the acetylene can also be beneficial, but the selectivity over AA_1R is poor [Fig. 18 (**31**)]. However, the activity decreases dramatically when the methyl group is replaced with either hydrogen or CF_3 group; (c) the activity is totally lost when *p*-(dimethylamino)phenyl, a basic group, or the bulkier 2-fluoro-3-(trifluoromethyl)phenyl groups are present at the terminus of the acetylene side chain. However, a phenol is well tolerated.

3.2.2.2. [1,2,4]Triazolo[1,5-*c*]pyrimidine derivatives. An extensive SAR study revealed that furan ring and free amino function at position 2 and 5 respectively are essential for $AA_{2A}R$ antagonistic activity (Matasi et al. 2005b; Neustadt et al. 2009). Chief structural features of [1,2,4]triazolo[1,5-*c*]pyrimidine derivatives for $AA_{2A}R$ interaction are illustrated in Fig. 19.

A variety of aromatic and heteroaromatic substituents were placed at C-7 and the results were summarized as: (a) The tolyl analogs retained the affinity for $AA_{2A}R$ but failed to improve desired selectivity; (b) the methoxy phenyl analogs provided compounds with high affinity for $AA_{2A}R$ [Fig. 20 (**32**)] with moderate to good selectivity over AA_1R except compound **33**

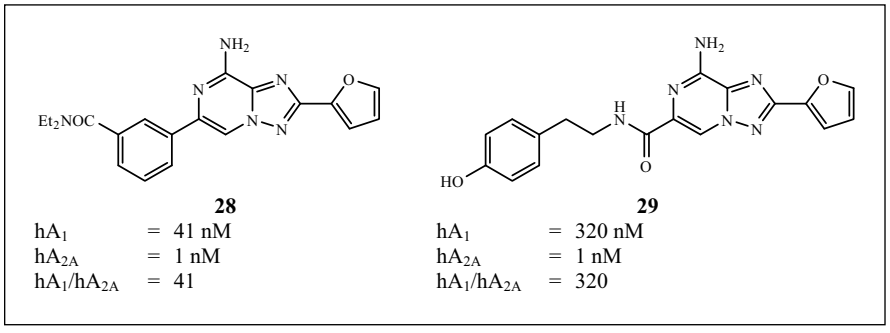


Fig. 17: [1,2,4]Triazolo[1,5-*a*]pyrazine derivatives. Data represent *K*i values (h = human) and are taken from references indicated in the text

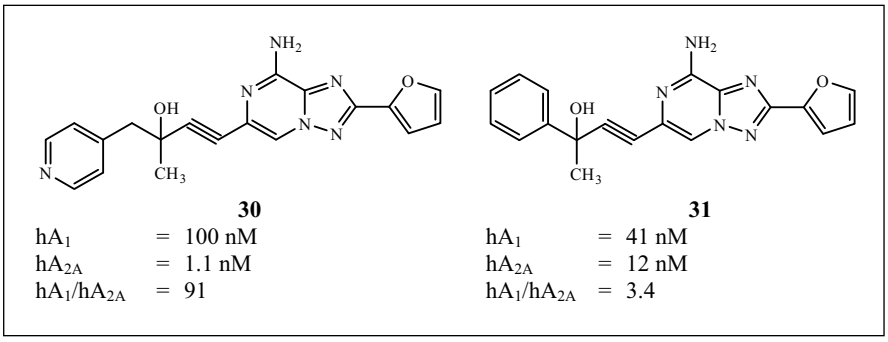


Fig. 18: Alkyne derivatives of [1,2,4]triazolo[1,5-*a*]pyrazine. Data represent *K*i values (h = human) and are taken from references indicated in the text

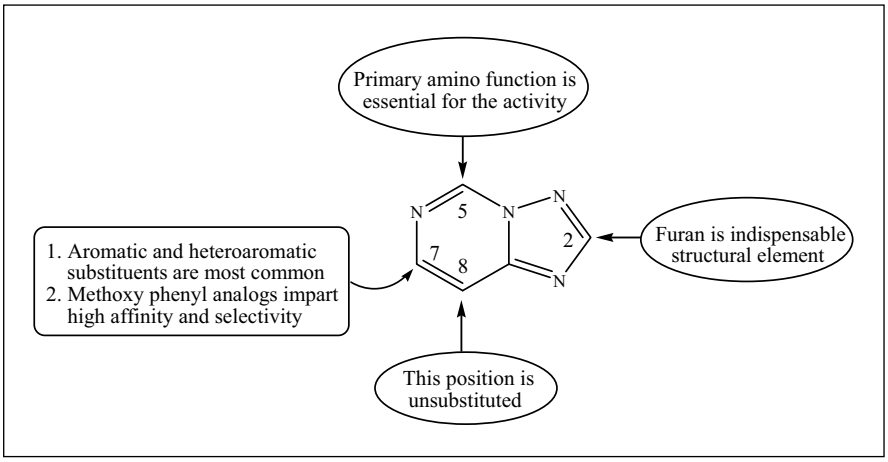


Fig. 19: SAR of [1,2,4]triazolo[1,5-*c*]pyrimidine derivatives

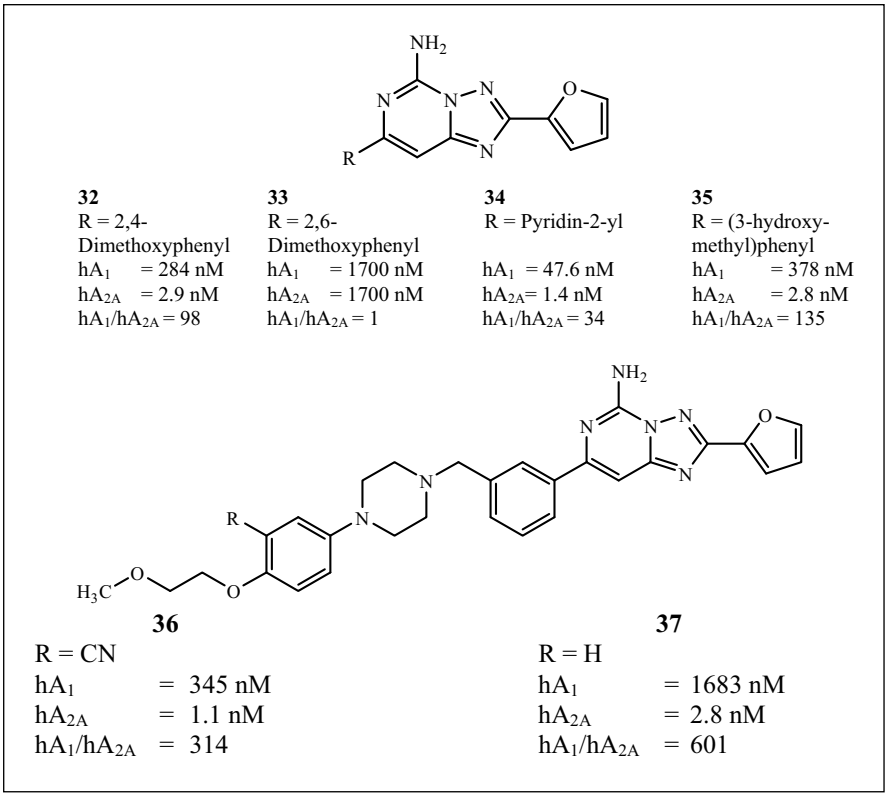


Fig. 20: [1,2,4]Triazolo[1,5-*c*]pyrimidine derivatives. Data represent *K*i values (h = human) and are taken from references indicated in the text

(Fig. 20) which had very poor affinity for $AA_{2A}R$, suggesting that orthogonality between the arene and the triazolopyrimidine ring system was not tolerated; (c) heteroaromatic analogs also retained single-digit nanomolar potency for $AA_{2A}R$ with no improvement in selectivity over the AA_1R [Fig. 20 (**34**)]; (d) *meta*-substituted compounds retained single digit nanomolar

$AA_{2A}R$ affinity and acceptable selectivity over AA_1R; particularly compound **35** (Fig. 20), which was 135-fold selective; (e) Substitution of the *meta*-position of the phenyl with either 4-(phenyl)-piperidine or 4-(phenyl)-piperazine derivatives was well tolerated, e.g. compound **36** (Fig. 20); (f) the incorporation of the methoxethoxy substituent, as in **37** (Fig. 20), seemed particularly beneficial in terms of selectivity over AA_1R. Fig. 21.

3.2.2.3. [1,2,4]Triazolo[1,5-*a*][1,3,5]triazine. The [1,2,4]triazolo[1,5-*a*][1,3,5]triazine derivative ZM-241385 [Fig. 22 (**38**)] is among the potent $AA_{2A}R$ antagonists used as tools in pharmacological studies exhibited protection against neuronal death produced by ischaemia or excitotoxicity (Ongini et al. 1999; Stone et al. 2001). Based on ZM-241385, a variety of compounds bearing ethanamine, ethylenediamine, pyrrolidine, piperazine and (*S*)-octahydro-1*H*-pyrido[1,2-*a*]pyrazine in the side chain have been synthesized.

Peng et al. (2004) have incorporated (*S*)-octahydro-1*H*-pyrido[1,2-*a*]pyrazine moiety between the triazolotriazine nucleus and aromatic system leading to the successful development of a series of highly potent and selective $AA_{2A}R$ antagonists, e.g. compounds **39**–**43** (Fig. 22). The SAR studies revealed that substituted aryl fluorides [Fig. 22 (**39**)] are better $AA_{2A}R$ antagonists (Vu et al. 2004b, 2005). In particular, 3-fluorophenyl [Fig. 22 (**40**)] rendered the most potent $AA_{2A}R$ binder, with greater than 16500-fold selectivity over the AA_1R (Peng et al. 2004). Furthermore, 6-quinolinyl moiety afforded potent $AA_{2A}R$ binding [Fig. 22 (**41**)] with 5833-fold selectivity over AA_1R, presumably due in part to the electron-withdrawing effect of the nitrogen atom in the 6-quinolinyl group, suggesting that the bulky groups are well-accommodated at the 7-*cis* position. In contrast, similar substitutions with the 6-*cis* configuration led to substantial loss of potency. Similarly, 3-pyridyl group at the 7-*cis* position [Fig. 22 (**42**)] exhibited better $AA_{2A}R$ potency and 4666-fold selectivity over AA_1R. Among the compounds directly capped with five-membered heterocycles through a nitrogen atom, imidazole [Fig. 22 (**43**)] showed higher affinity than the triazole and the tetrazole (Peng et al. 2004).

A number of [1,2,4]triazolo[1,5-*a*][1,3,5]triazine derivatives have been synthesized by Vu et al. (2005) as potent and selective $AA_{2A}R$ antagonists incorporating a variety of diamines at C5. When piperazine at C-5 was replaced with homopiperazine, a slight gain of $AA_{2A}R$ binding affinity was observed while a modest loss in $AA_{2A}R$ binding affinity was shown by the ethylenediamine linker. Methylating the amino group did result in a slight increase in $AA_{2A}R$ binding affinity as well as increased oral bioavailability. Replacing the ethylenediamine linker with a longer chain resulted in a substantial loss of $AA_{2A}R$ binding affinity. A loss in $AA_{2A}R$ antagonistic activity was also observed when the piperazino group was replaced with 4-aminopiperidine, 3-aminopiperidine, 4-(aminomethyl) piperidine, or 3-aminopyrrolidine moieties. However, when (*R*)-2-(aminomethyl)-pyrrolidine was used, a fairly significant

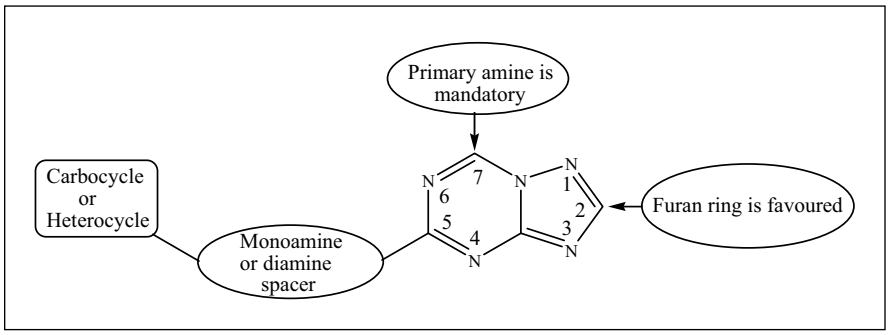


Fig. 21: SAR of [1,2,4]triazolo[1,5-*a*][1,3,5]triazine template

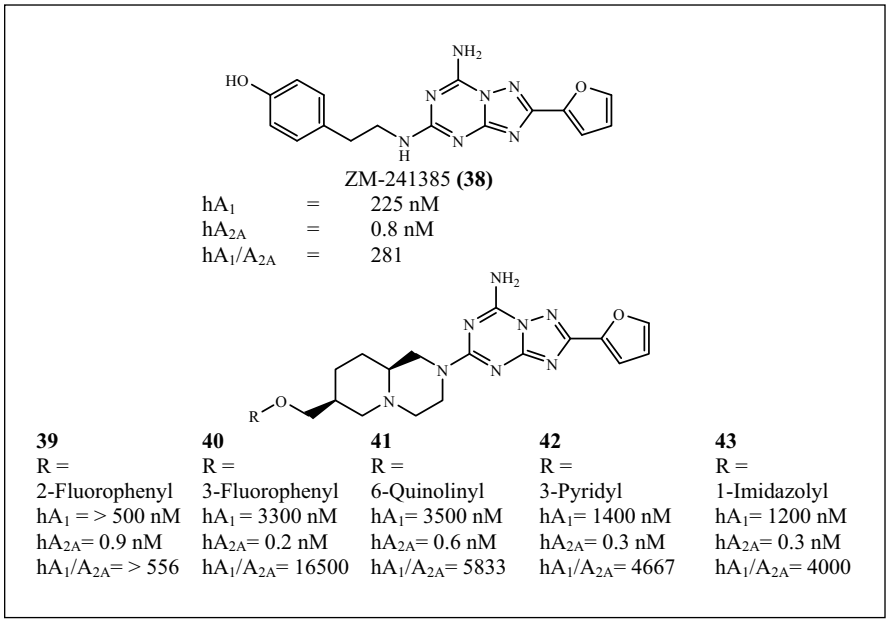


Fig. 22: Highly potent and selective $AA_{2A}R$ antagonists belonging to class [1,2,4]triazolo[1,5-*a*][1,3,5]triazine. Data represent *K*i values (h = human) and are taken from references indicated in the text

increase in $AA_{2A}R$ binding affinity was observed. Interestingly, the (*S*)-isomer of 2-(aminomethy)pyrrolidine was not as active as the (*R*)-isomer. Moreover, analogues prepared using the (*R*)-2-(aminomethy)pyrrolidine were more active against $AA_{2A}R$ than those prepared using piperazine as the diamine component (Baraldi et al. 1995). Also, antagonists with the 7-*cis* configuration were more potent and selective for $AA_{2A}R$ than their 7-*trans* or 6-*cis* counterparts (Peng et al. 2004).

A series of piperazine derivatives of [1,2,4]triazolo[1,5-*a*][1,3,5]triazine were synthesized as potent and selective $AA_{2A}R$ antagonists by Vu et al. (2004b) and SAR were presented as follows: (a) Some form of capping group on piperazine nitrogen is needed for $AA_{2A}R$ antagonistic activity; when a phenyl or heterocyclic group was installed as a capping group, the $AA_{2A}R$ affinity was improved; (b) the electron-withdrawing groups such as chloro and fluoro were more favorable than electron-donating groups such as OMe as substituents on the phenyl ring; (c) with chlorine as the aromatic substituent, *ortho*-substitution was clearly superior to either *meta* or *para* substitution; with two chlorine atoms, the binding affinity toward $AA_{2A}R$ improved somewhat while a more dramatic improvement in $AA_{2A}R$ binding affinity was observed with three chlorine atoms; (d) when [(3,5-dichloropyridin-4-yl)methyl] substituent was attached with piperazine nitrogen, a potent and selective $AA_{2A}R$ antagonist was obtained [Fig. 23 (**44**)]; (e) substituting fluoro for chloro was better for $AA_{2A}R$ activity, and again, trisubstitution on the phenyl ring with the *o,o,p*-substitution pattern, a very potent and selective $AA_{2A}R$ antagonist was obtained [Fig. 23 (**45**)]. Similarly, trisubstitution on the phenyl ring of compound **46** (Fig. 23) proved to be beneficial for $AA_{2A}R$ affinity (Vu et al. 2005).

In a comparative study of three heterocyclic nuclei (Fig. 15), it was found that the [1,2,4]triazolo[1,5-*a*][1,3,5]triazines are generally more potent $AA_{2A}R$ antagonists than their triazolo[1,5-*c*]pyrimidine and triazolo[1,5-*a*]pyrimidine counterparts (Peng et al. 2004; Vu et al. 2004a, c).

3.2.2.4. Pyrazolo pyrimidine derivatives.

3.2.2.4.1. Position 1. Regarding the substitutions at the 1 position, it has been clearly demonstrated that an aromatic ring attached to the nitrogen is essential for both affinity and selectivity at the $AA_{2A}R$s (Fig. 24, Chebib et al. 2000; Gillespie et al. 2008c). In particular, the introduction of benzyl group led to **47** (Fig. 25), which proved to be a quite potent and selective $AA_{2A}R$ antagonist with retained *in vivo* activity. Saturation of the phenyl ring of **47** (Fig. 25) or incorporation of heteroatoms was tolerated, but did not improve affinity significantly.

Extension of the linker between the phenyl ring and pyrazole by one methylene group was detrimental to $AA_{2A}R$ potency, but further extension regained $AA_{2A}R$ potency at the expense of AA_1R selectivity [Fig. 25 (**48**)]. *m*-Substitution of the phenyl ring with a range of electron-rich and deficient substituents was tolerated, with the 3-chlorobenzyl analogue showing increased $AA_{2A}R$ potency and selectivity over AA_1R [Fig. 25 (**49**)]. *Ortho* and *para* substitution was largely detrimental to the desired biological profile, although 2-fluoro substitution can be tolerated (Gillespie et al. 2008c).

3.2.2.4.2. Position 2. Replacement of N-2 with CH (pyrrolo[2,3-*d*]pyrimidine analogues) resulted in a significant drop in potency at $AA_{2A}R$, along with a smaller drop in selectivity over AA_1R (Gillespie et. al 2008c).

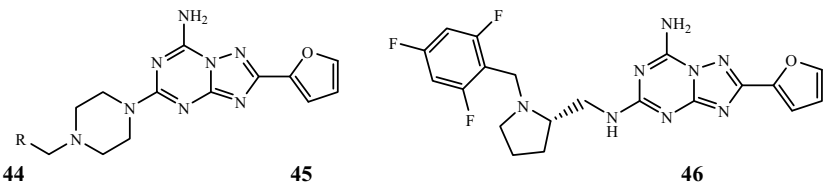
3.2.2.4.3. Position 4. Generally, compounds substituted with an amino group in the C4 position had higher affinity for both AA_1R and $AA_{2A}R$s than both the thiol and thiomethyl substituents. The thiomethyl compounds had greater affinity than the thiol compounds (Chebib et al. 2000).

3.2.2.4.4. Position 6. It was observed that for high affinity at both AA_1R and $AA_{2A}R$s the distal amide should be separated from the C6 thiol by only one carbon. Introduction of the *N*-ethyl group in thioamide moiety at C6 gave increased affinity at AA_1Rs. As the *N*-alkyl group increased from an ethyl to a propyl group, the AA_1R and the $AA_{2A}R$ affinity decreased. The AA_1R affinity was further decreased with the butyl compounds, but the $AA_{2A}R$ affinity remained relatively unchanged. This suggests that there is a tolerance for larger *N*-alkyl substituents at the C6 position for the $AA_{2A}R$ than the AA_1R. With *N*,*N*-dialkyl substituents, there was a loss in affinity for both the AA_1R and $AA_{2A}R$, suggesting possible hydrogen bonding of the amide group to the receptor (Poulsen and Quinn 1996). Replacement of the amino substituent with a 2-aminoethanol or 2-dimethylamino substituent reduced $AA_{2A}R$ potency (Gillespie et al. 2008c).

3.2.2.5. Thieno pyrimidine derivatives. A reasonable affinity for $AA_{2A}R$s was exhibited by thieno[3,2-*d*]pyrimidine derivatives with small alkyl and alkylamino substituents at C-2 (Gillespie et al. 2001, 2004, 2008a). Furthermore, it is apparent from SAR investigation of thienopyrimidines that, a 2-thiazolyl group offers a significant advantage over other heteroaryl groups in the 4-position and affords a number of highly potent and selective analogues. Moreover, with a 2-thiazolyl substituent in place at the C-4 position, a wide range of C-2 substituents are tolerated and provide a series of highly potent and selective $AA_{2A}R$ antagonists. $AA_{2A}R$ affinity and selectivity over AA_1R is particularly noteworthy when the C-2 substituent is a small lipophilic group such as alkyl or dialkylamino as in compounds **50**-**53** (Fig. 26, Gillespie et al. 2008b).

3.2.2.6. Purine derivatives. The SAR of adenine derivatives as adenosine receptor antagonists is summarized in Fig. 27 (Camaioni et al. 1998; Klotz et al. 2003; Beauglehole et al. 2005).

3.2.2.6.1. Position 2. Analyzing the different substituents, a phenethoxy group in 2-position gave the highest $AA_{2A}R$



44
R = 3,5-Dichloropyridin-4-yl
rA_1 = 670 nM
rA_{2A} = 2 nM
rA_1/rA_{2A} = 335

45
R = 2,4,6-Trifluorophenyl
rA_1 = 1300 nM
rA_{2A} = 3 nM
rA_1/rA_{2A} = 433

46
rA_1 = 800 nM
rA_{2A} = 2 nM
rA_1/rA_{2A} = 400

Fig. 23: Piperazine and pyrrolidine derivatives of [1,2,4]triazolo[1,5-*a*][1,3,5]triazine. Data represent *K*i values (r = rat) and are taken from references indicated in the text

versus $AA_{2B}R$ selectivity (near 400-fold) but the selectivity over AA_1R was poor [Fig. 28 (**54**)], whereas a phenethylamino group in 2- and 6-position improved the affinity at $AA_{2B}Rs$ (Camaioni et al. 1998). Among 2-alkynyl-substituted adenine derivatives, **55** (Fig. 28) emerged as the most potent $AA_{2A}R$ antagonist exhibiting high $AA_{2A}R$ affinity, but moderate selectivity, especially versus the AA_1R.

3.2.2.6.2. Position 3. The N3 nitrogen atom appeared not to be important since 3-deaza-adenine derivatives were about as potent as the corresponding purines (Minetti et al. 2005). Most of the described purine derivatives that were potent at $AA_{2A}Rs$ exhibited only moderate selectivity especially versus the AA_1R subtype.

3.2.2.6.3. Position 6. Replacing the 6-amino by alkoxy or alkynyl groups greatly diminished affinity at the adenosine receptor subtypes, suggesting that a N-H group is required to provide a H-bond donor for a good interaction with all the adenosine receptors (Camaioni et al. 1998).

3.2.2.6.4. Position 7. The nitrogen atom in the 7-position is not required for high $AA_{2A}R$ affinity. Corresponding pyrrolo[2,3-*d*]pyrimidines [Fig. 28 (**56**)], Gillespie and Lerpinier 2002] and pyrazolo [3,4-*d*]pyrimidines [e.g. com-

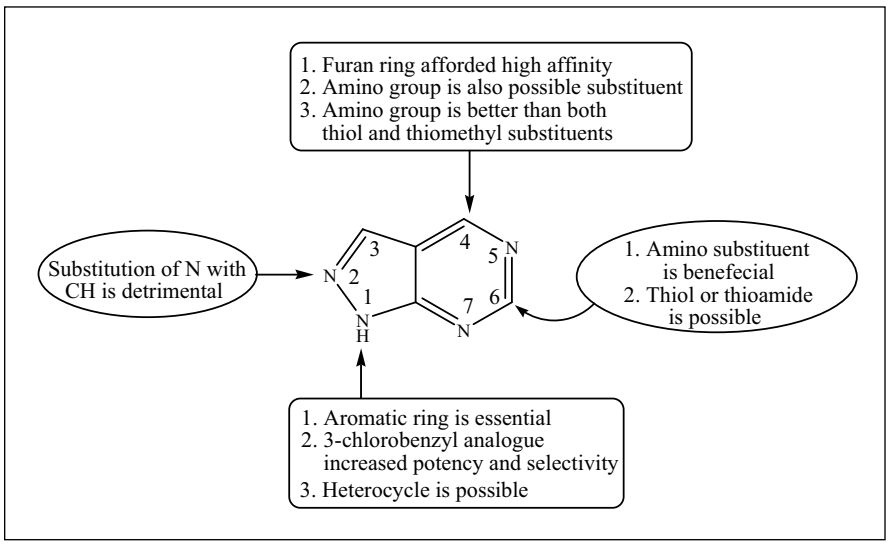


Fig. 24: SAR of pyrazolo pyrimidines

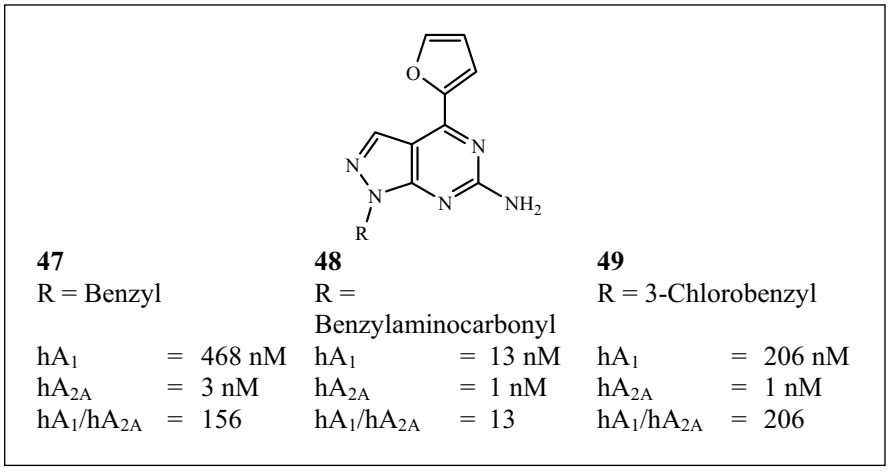


Fig. 25: Pyrazolo pyrimidine derivatives. Data represent *K*i values (h = human) and are taken from references indicated in the text

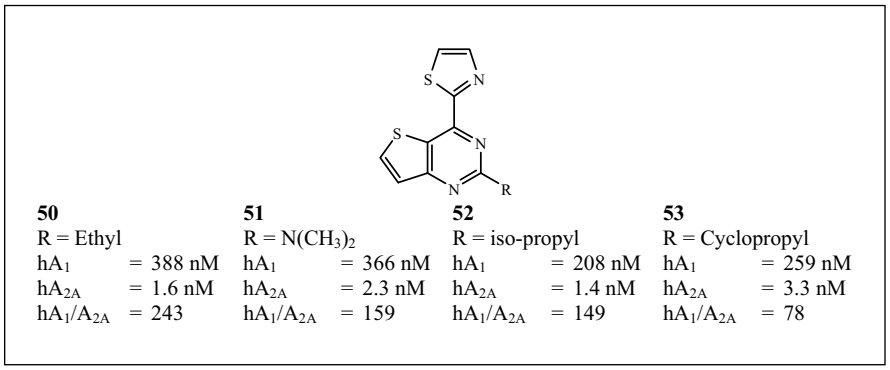


Fig. 26: Examples of thieno pyrimidine derivatives. Data represent *K*i values (h = human) and are taken from references indicated in the text

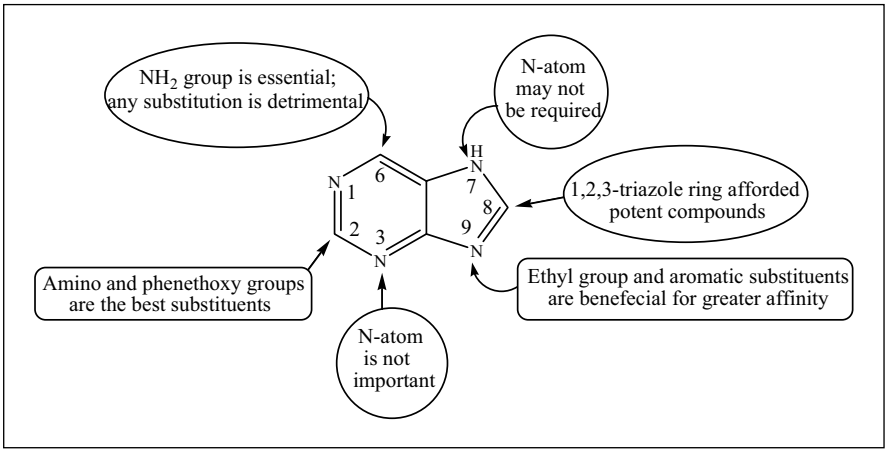


Fig. 27: Structural requirements for purine derivatives

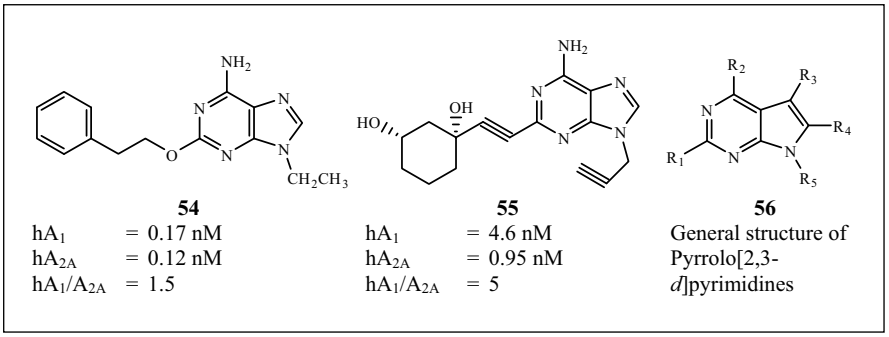


Fig. 28: Purine derivatives and general structure of pyrrolo[2,3-*d*]pyrimidines. Data represent *K*i values (h = human) and are taken from references indicated in the text

pounds **47**–**49** (Fig. 25)] were also highly potent (Gillespie et al. 2008c, 2006).

3.2.2.6.5. Position 8. Purine derivatives substituted in the 8-position by a 1,2,3-triazole ring were developed as potent $AA_{2A}R$ antagonists (Minetti et al. 2005). One of the most potent compound among the series was 9-methyl-2-phenethyl-8-[1,2,3]triazol-2-yl-adenine [Fig. 29 (**57**)]. The corresponding 2-butyl and 2-pentyl derivatives were similarly potent.

3.2.2.6.6. Position 9. A propargyl substitutent at N9-replacing the ribose moiety present in the agonistic adenosine derivatives appears to be favourable for high $AA_{2A}R$ affinity. In a series of substituted 9-alkylpurines, 8-bromo-9-ethyladenine [Fig. 29 (**58**)] showed higher affinity for AA_1R and $AA_{2A}Rs$ (Lambertucci et al. 2009). Presence of ethyl group at position-9 is important for greater affinity at both AA_1R and $AA_{2A}R$ subtypes. Some low molecular weight compounds, e.g. 8-ethoxy-9-ethyladenine [Fig. 29 (**59**)], were found to exhibit good $AA_{2A}R$ affinity and selectivity. In addition, ANR-94 reversed haloperidol-induced catalepsy, potentiated levodopa effects on turning behaviour in unilaterally 6-hydroxydopamine-lesioned rats, and induced contralateral turning behaviour in rats sensitized to levodopa (Pinna et al. 2005a).

In a series of 6-(2-furyl)-substituted 2-aminoadenine derivatives, e.g. compounds **60**–**62** (Fig. 30) bearing an aromatic, e.g. (substituted) benzyl residue at N9, were found to be potent $AA_{2A}R$ antagonists (Kiselgof et al. 2005; Weiss et al. 2003). Compound **62** (Fig. 30) was shown to reverse haloperidol-induced catalepsy in mice in a dose-dependent manner (Weiss et al. 2003).

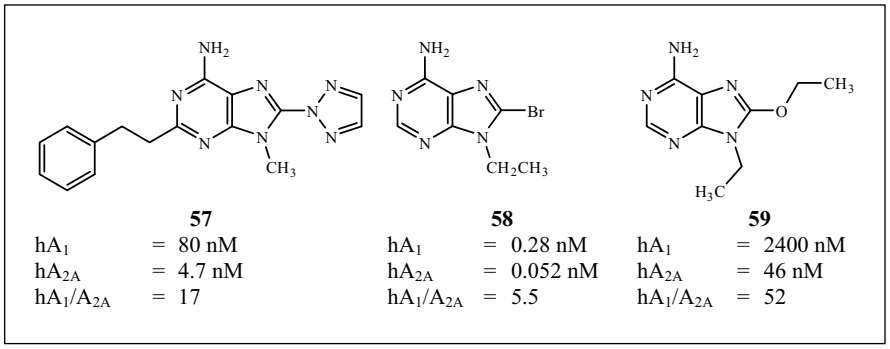
3.2.2.7. Oxazolo[5,4-*d*]pyrimidines. Holschbach et al. (2006) synthesized a series of oxazolo[5,4-*d*]pyrimidines where compounds **63** and **64** (Fig. 31) were observed as the most $AA_{2A}R$-selective derivatives of the series. Isomers bearing a 3-furyl instead of a 2-furyl residue were less selective versus AA_1Rs. Compound **63** (Fig. 31) was obtained in [^{3}H]-labeled form. Radioligand binding studies showed a high degree of non-specific binding rendering the compound unsuitable as a potential ligand for positron emission tomography after labelling with a neutron-deficient nuclide.

3.2.2.8. Benzothiazole derivatives. Alanine et al developed a novel series of 4-methoxy-substituted benzothiazole derivatives [Fig. 32 (**65**, **66**)] as potent and selective $AA_{2A}R$ antagonists (Alanine et al. 2001, 2006).

3.2.2.9. 1,8-Naphthyridines. The binding results of Ferrarini et al. (2000, 2004) showed that a large part of the new 1,8-naphthyridine derivatives proved to be bovine AA_1R selective, with a high affinity in the low nanomolar range. As regards the affinity for the bovine $AA_{2A}R$, 1,8-naphthyridine derivatives generally possess a moderate affinity, and this remained approximately the same as for the native human $AA_{2A}R$. However, compound **67** (Fig. 32) synthesized by Manera et al. (2005) was found to possess high $AA_{2A}R$ affinity and selectivity over AA_1R.

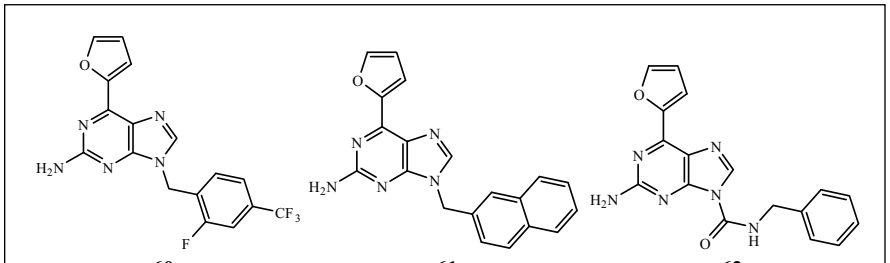
3.2.3. Tricyclic non-xanthine analogues

Among the non-xanthine heterocycles bearing tricyclic nucleus, several classes of compounds have been emerged as $AA_{2A}R$ antagonists (Fig. 33). Initially, triazolo[1,5-*c*]quinazolines (Kim et al. 1998), triazolo[4,3-*a*]quinoxalines (Sarges et al. 1990), triazolo[4,3-*a*]quinoxalin-1-ones (Holschbach et al. 2005; Colotta et al. 2003a, b), triazolo[1,5-*a*]quinoxalines (Martinez et al. 2008; Catarzi et al. 2004, 2005), 1,2,4-triazolo[5,1-*i*]purine derivatives (Okamura et al. 2002), pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines (Neustadt et al. 2003b,



57		58		59	
hA_1	= 80 nM	hA_1	= 0.28 nM	hA_1	= 2400 nM
hA_{2A}	= 4.7 nM	hA_{2A}	= 0.052 nM	hA_{2A}	= 46 nM
hA_1/A_{2A}	= 17	hA_1/A_{2A}	= 5.5	hA_1/A_{2A}	= 52

Fig. 29: Adenine derivatives. Data represent *K*i values (h = human) and are taken from references indicated in the text

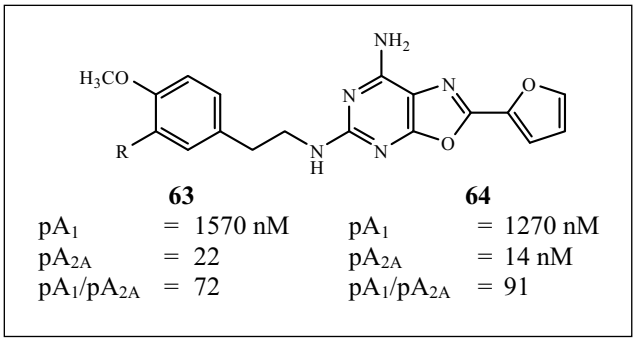


60		61		62	
hA_1	= 418 nM	hA_1	= 466 nM	hA_1	= 17 nM
hA_{2A}	= 2.8 nM	hA_{2A}	= 1.4 nM	hA_{2A}	= 1.1 nM
hA_1/A_{2A}	= 149	hA_1/A_{2A}	= 333	hA_1/A_{2A}	= 16

Fig. 30: 6-(2-Furyl)-substituted 2-aminoadenine derivatives. Data represent *K*i values (h = human) and are taken from references indicated in the text

2005), pyrrolo[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines (Moorman 2008a, b) and indeno[1,2-*d*]pyrimidines (Matasi et al. 2005a) have shown interesting properties, however they also interacted with other adenosine receptors (Ongini et al. 1999). Recent developments in non-xanthine groups of $AA_{2A}R$-selective antagonists with fused tricyclic moiety include mainly pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidines (Baraldi et al. 2000; Shah et al. 2008a, b; Cacciari et al. 2007).

3.2.3.1. [1,2,4]Triazolo[1,5-*c*]quinazolines. SAR investigation of a series of triazoloquinazolines showed that the 5-amino-9-chloro-2(2-furyl)-l,2,4-triazolo[1,5-*c*]-quinazoline [CGS 15943, Fig. 34 (**68**)], is the most potent and selective $AA_{2A}R$ antagonist (Francis et al. 1988), in which replacement of either the amino or the 2-furyl group caused a severe loss of activity (Balo et al. 2007). Substitution of the chlorophenyl group of the quinazoline with the fluorobenzylpyrazole led to the development of 8-(4-fluorobenzyl)-2-(furan-2-yl)-8*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5-amine [8FB-PTP, Fig. 34 (**69**)], the first compound with pyrazolo-triazolo-pyrimidine nucleus as adenosine receptor antagonist, which displayed potent binding to $AA_{2A}Rs$ but the selectivity over AA_1Rs was not pleasing (Gatta et al. 1993; Dionisotti et al. 1994).



63		64	
pA_1	= 1570 nM	pA_1	= 1270 nM
pA_{2A}	= 22	pA_{2A}	= 14 nM
pA_1/pA_{2A}	= 72	pA_1/pA_{2A}	= 91

Fig. 31: Oxazolo[5,4-*d*]pyrimidines. Data represent *K*i values (p = pig) and are taken from references indicated in the text

3.2.3.2. 1,2,4-Triazolo[4,3-*a*]quinoxalin-1-one derivatives. In the triazolo-quinoxalin-1-one series, compound **70** (Fig. 35) showed an interesting binding profile versus $AA_{2A}R$ subtype. Amino group seems to be very sensible at any kind of modification. In fact, any modification (e.g. alkylation of amino group, replacement of amino group with carbonyl function) produced a dramatic reduction of the affinity at $AA_{2A}Rs$ (Cacciari et al. 2003). However, introduction of 6-aralkylamino moiety on the 4-amino-1,2,4-triazoloquinoxalin-1-one core afforded potent compound [Fig. 35 (**71**)]. On the contrary, the presence of the 8-benzylamino group and the 8-dibenzylamino substituent significantly reduced the $AA_{2A}R$ affinity while it is profitable for anchoring to the AA_1R (Colotta et al. 2003b).
Fig. 36.

3.2.3.3. Pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine. Beginning in 1994, pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidines have been the subject of most structural and medicinal studies because of their indispensable potential as adenosine receptor antagonists with fine potency and selectivity at $AA_{2A}R$ (Baraldi et al. 1994, 1998, 2003, 1996).

3.2.3.3.1. Position 2. In general, it was observed that substitution of the furanyl moiety with a (substituted)aromatic function or a phenyl ring causes a complete loss of affinity at the $AA_{2A}R$ subtype probably due to an increased steric hindrance by the (substituted)aromatic rings introduced (Francis et al. 1988; Gatta et al. 1993; Baraldi et al. 1999; Bolcato et al. 2008). This provides supportive evidence that the furanyl ring at the 2-position of the tricyclic structure [Fig. 37 (**72**)] is a necessary element to guarantee the activity of the molecule, probably because in this heterocycle is present an oxygen atom that produces a favourable electronic condition for the

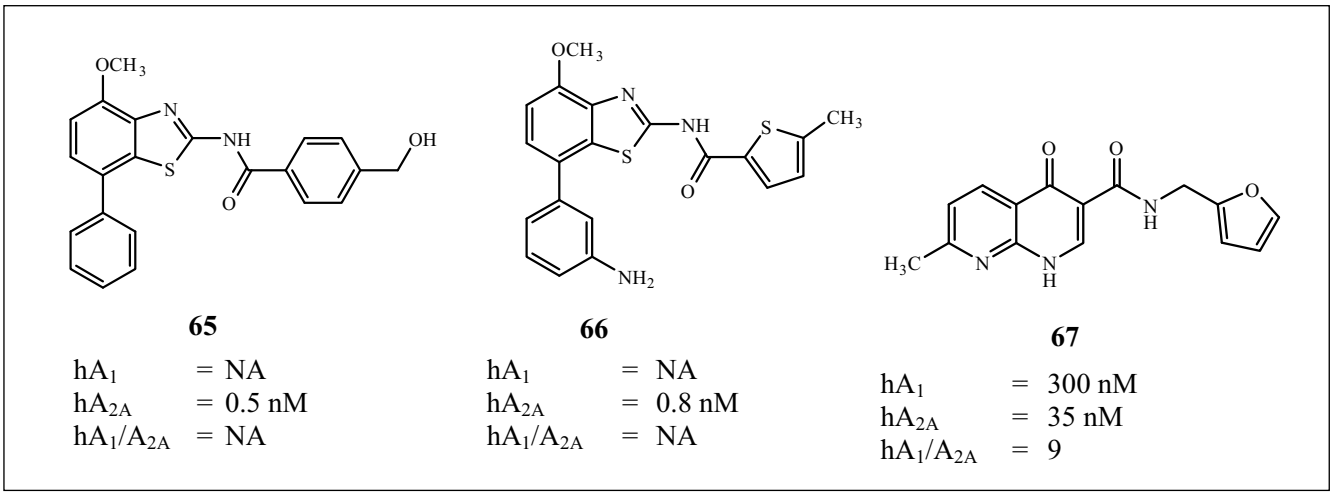


Fig. 32: Benzothiazole and 1,8-naphthyridine derivatives. Data represent *K*i values (h = human) and are taken from references indicated in the text. (NA = Not available)

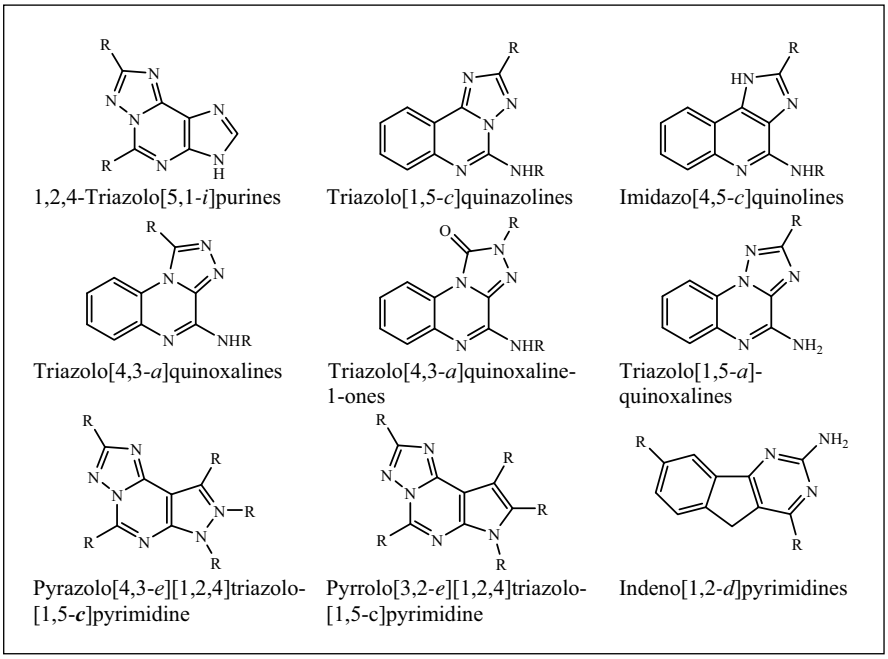


Fig. 33: General structures of some representative tricyclic adenosine antagonists

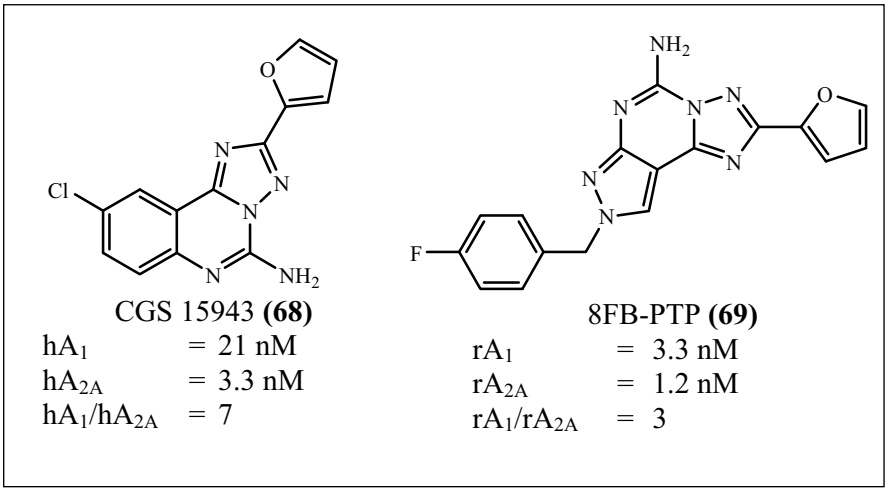
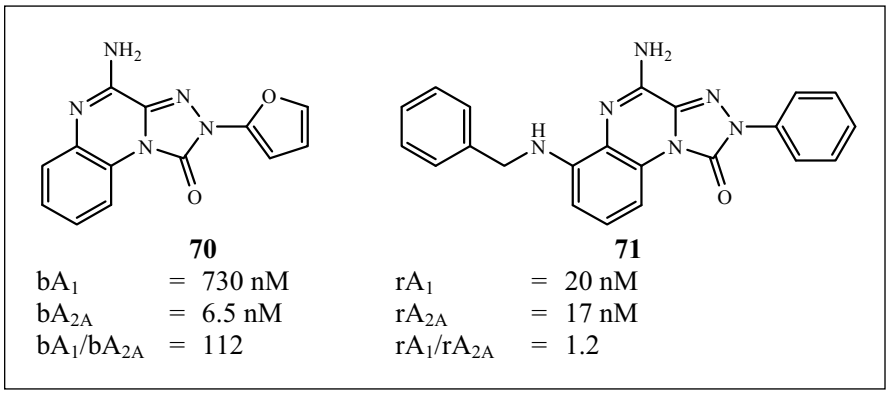


Fig. 34: [1,2,4]Triazolo[1,5-*c*]quinazolines. Data represent *K*i values (h = human, r = rat) and are taken from references indicated in the text



70		**71**	
bA_1	= 730 nM	rA_1	= 20 nM
bA_{2A}	= 6.5 nM	rA_{2A}	= 17 nM
bA_1/bA_{2A}	= 112	rA_1/rA_{2A}	= 1.2

Fig. 35: 1,2,4-Triazolo[4,3-*a*]quinoxalin-1-one derivatives. Data represent *K*i values (b = bovine, r = rat) and are taken from references indicated in the text

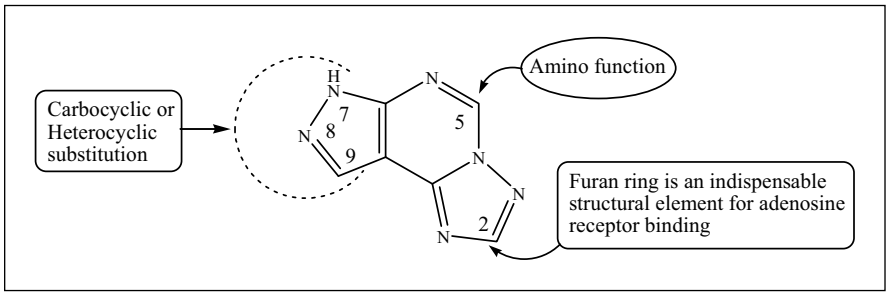
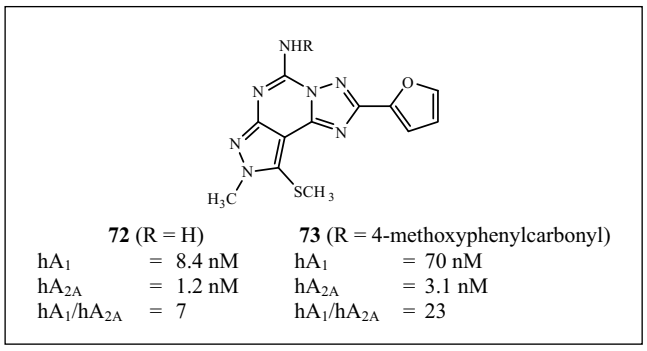


Fig. 36: SAR of pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines

interaction with the adenosine receptor. The introduction of an ethoxy group at the *ortho*-position of the aromatic ring, to imitate the oxygen of the furan, proved unsuccessful for $AA_{2A}R$ interaction. The introduction of an ester, acid, or amide function in the *p*-position, introduced to promote the formation of a hydrogen bond between the molecule and the adenosine receptor surface, also proved fruitless (Baraldi et al. 2003).

3.2.3.3.2. Position 5. A number of reports have described that the amino group is a necessary element for receptor interaction and that slight modifications are allowed (Baraldi et al. 2003; Francis et al. 1988; Gatta et al. 1993; Ongini et al. 2001). Compound **72** (Fig. 37), which has a free amino group at the 5-position, shows good affinity for the $AA_{2A}R$ but, unfortunately, low selectivity. Transformation of the amino group into urea [Fig. 37 (**73**)] or amide functions preserves $AA_{2A}R$ affinity (Baraldi et al. 2002a).

3.2.3.3.3. Position 7. From earlier studies, the effect of the substituent on the pyrazole ring seems to be fundamental for both high affinity and selectivity for the $AA_{2A}R$ subtype. The pyrazole nitrogens play a fundamental role in receptor recognition and discrimination; any substitutions on the pyrazolotriazolopyrimidine nucleus modulate affinity and selectivity vs. adenosine receptor subtypes (Baraldi et al. 2002b, 2000). In a comprehensive exploration on the effect of the chain at the N7 position, it was clearly demonstrated that, for having both potency and selectivity at the $AA_{2A}Rs$, the presence of an aralkyl chain seems to be essential (Baraldi et al. 1998, 1996). However, the length for the alkyl chain is limited to 2-3 methylene groups for better potency and selectivity of $AA_{2A}R$, as evidenced by the potent compounds SCH 58261 [Fig. 38 (**74**)] and SCH 63390 [Fig. 38 (**75**)]. Unfortunately, the major problem of this class of compounds is related to their low water solubility and the consequent poor bioavailability. For this reason, many efforts were done to increase the hydrophilicity of these compounds by the introduction of polar moieties on the phenyl ring of the side chain on the pyrazole nucleus. In particular, the introduction of a hydroxyl function at the *p*-position on the phenyl ring of compounds **74** and **75** (Fig. 38), led to the discovery of compounds **76** and **77** (Fig. 38), which not only showed a better hydrophilic character, but also a significant increase of both affinity and selectivity (Baraldi et al. 1998). Moreover, the introduction of *p*-methoxy group [Fig. 39 (**78**)] on the phenyl ring afforded a highly potent and selective $AA_{2A}R$ antagonist (Todde et al. 2000).



72 (R = H)		**73** (R = 4-methoxyphenylcarbonyl)	
hA_1	= 8.4 nM	hA_1	= 70 nM
hA_{2A}	= 1.2 nM	hA_{2A}	= 3.1 nM
hA_1/hA_{2A}	= 7	hA_1/hA_{2A}	= 23

Fig. 37: Examples of pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines. Data represent *K*i values (h = human) and are taken from references indicated in the text

However, the introduction of oxygenated groups on the phenyl ring at the side chain was not enough to confer the necessary water solubility and the introduction of other functions resulted an impelling need. To this purpose, carboxylic and sulfonic moieties were introduced which contributed highly to the water solubility [Fig. 39 (**79**, **80**)], in particular the sulfonic moiety, but there was also a great loss of affinity with respect to reference compounds [Fig. 38 (**76**–**77**), Fig. 39 (**78**)] for the $AA_{2A}Rs$. Interestingly, when free SO_3H moiety of compound **80** (Fig. 39) was converted to SO_2NH_2 [Fig. 39 (**81**)], $SO_2N(CH_2CH_2OH)_2$ [Fig. 39 (**82**)] and $SO_2N(CH_2CH_2Cl)_2$ [Fig. 39 (**83**)], there was a remarkable gain in $AA_{2A}R$ affinity. On the basis of the thermodynamic studies, these data contributed to hypothesize the presence of a lipophilic pocket where the side chain could fit and the substituent on the aromatic ring can form a hydrogen bond.

This could mean that the presumed pocket can have mainly a lipophilic character and carboxylic or sulfonic groups, partially present in their ionic form at physiological pH, cannot fit in it (Baraldi et al. 1998, 2002b).

The cyano derivative [Fig. 39 (**84**)] showed a poor affinity for the $AA_{2A}R$ subtype, but it was a useful key-intermediate for obtaining the N-hydroxyamidine [Fig. 40 (**85**)], which showed a restored affinity for this receptor subtype. The introduction of amino group at *p*-position of the phenyl ring in the side chain [Fig. 40 (**86**, **87**)] gave the better results in terms of affinity and selectivity for $AA_{2A}R$ subtype, but the water solubility was not optimal for a possible therapeutic use (Baraldi et al. 2002b).

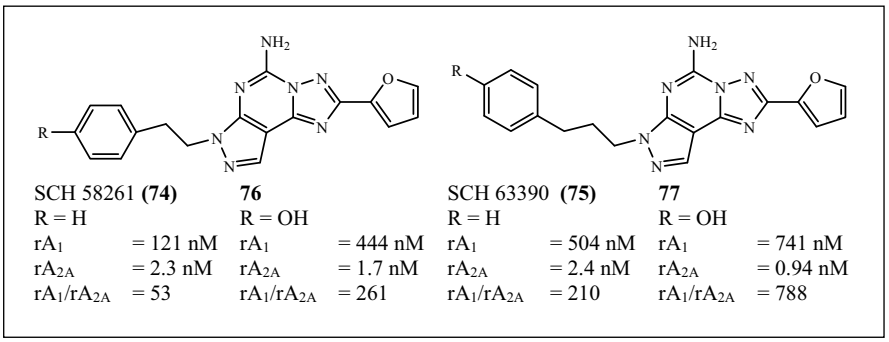


Fig. 38: Examples of $AA_{2A}R$ antagonists in clinical development. Data represent *K*i values (r = rat) and are taken from references indicated in the text

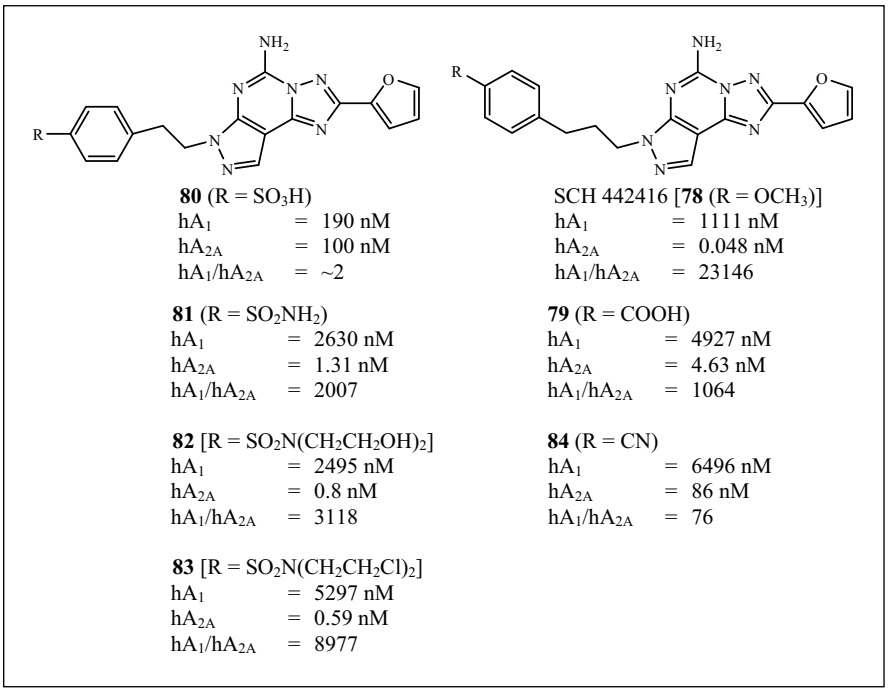


Fig. 39: Pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine derivatives with hydrophilic moieties in the phenyl ring. Data represent *K*i values (h = human) and are taken from references indicated in the text

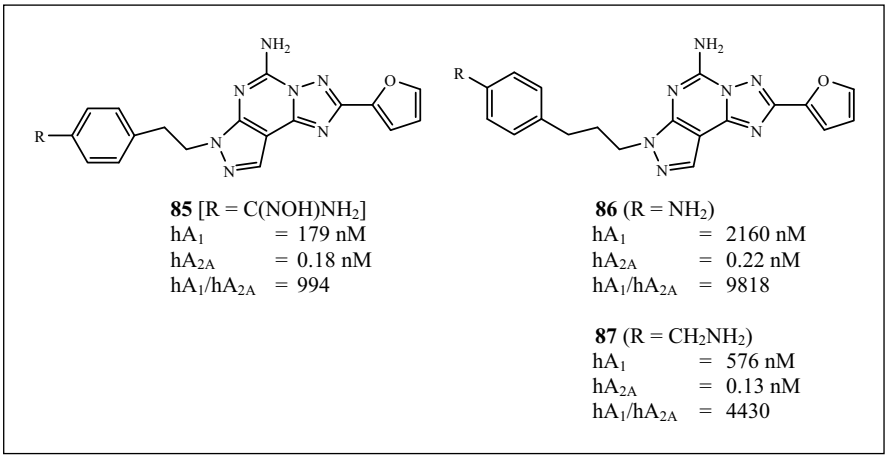
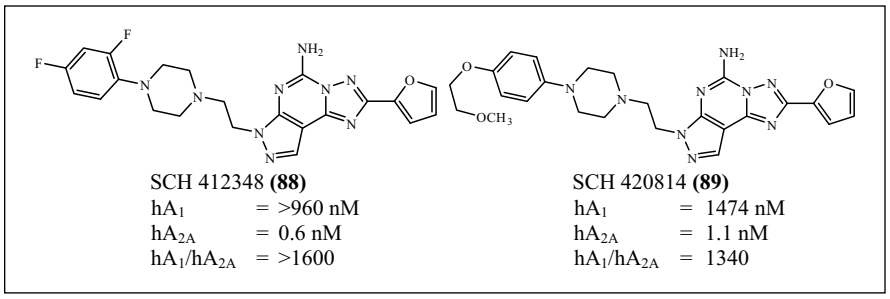


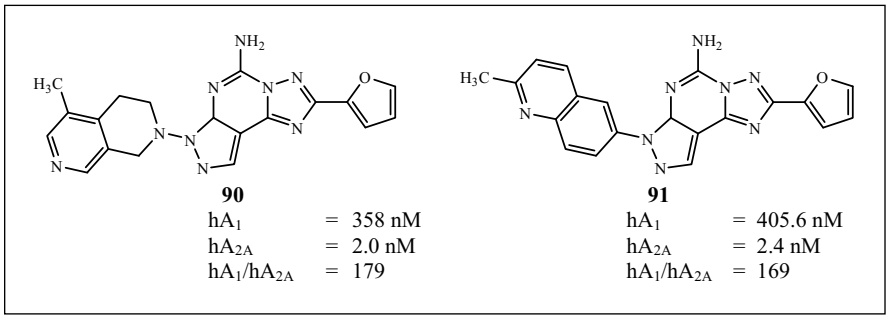
Fig. 40: Pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine derivatives with amino functions in the phenyl ring. Data represent *K*i values (h = human) and are taken from references indicated in the text



SCH 412348 **(88)**
hA_1 = >960 nM
hA_{2A} = 0.6 nM
hA_1/hA_{2A} = >1600

SCH 420814 **(89)**
hA_1 = 1474 nM
hA_{2A} = 1.1 nM
hA_1/hA_{2A} = 1340

Fig. 41: Examples of $AA_{2A}R$ antagonists in clinical development. Data represent *K*i values (h = human) and are taken from references indicated in the text



90
hA_1 = 358 nM
hA_{2A} = 2.0 nM
hA_1/hA_{2A} = 179

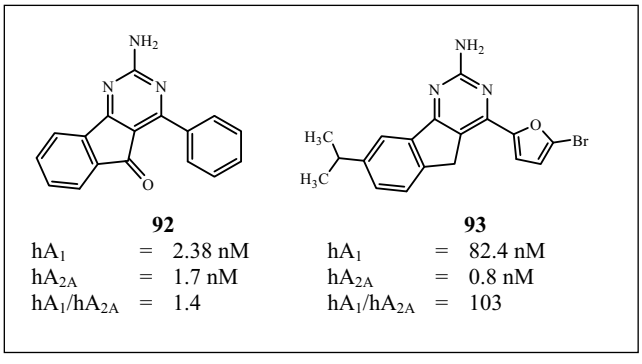
91
hA_1 = 405.6 nM
hA_{2A} = 2.4 nM
hA_1/hA_{2A} = 169

Fig. 42: Heteroaryl derivatives of SCH 58261. Data represent *K*i values (h = human) and are taken from references indicated in the text

Replacement of the phenyl group of SCH 58261 [Fig. 38 (**74**)] with an *N*-arylpiperazine moiety can produce potent and selective $AA_{2A}R$ antagonists (Silverman et al. 2007; Neustadt et al. 2007). In particular, SCH 412348 [Fig. 41 (**88**)] and SCH 420814 [Fig. 41 (**89**)] were emerged as effectual and selective $AA_{2A}R$ antagonists with potent oral anti-cataleptic activity and favorable pharmacokinetic properties when 1-(2,4-difluorophenyl)piperazinyl and 1-[4-(2-methoxyethoxy)phenyl]piperazinyl groups respectively were substituted.

Additionally, by incorporating polar heterocyclic moieties, improved aqueous solubility can be achieved (Shah et al. 2008a, b). In this regard, tetrahydronaphthyridine analog [Fig. 42 (**90**), Shah et al. 2008b] and methylquinoline analog [Fig. 42 (**91**), Shah et al. 2008a] proved to be a superior $AA_{2A}R$ antagonist over SCH 58261 [Fig. 38 (**74**)] in terms of binding affinity, selectivity over AA_1R, pharmacokinetics and oral activity in the catalepsy assay.

3.2.3.3.4. Position 8. N8 substitution always induces an increase in the affinity associated with the concomitant decrease in the $AA_{2A}R$ versus AA_1R selectivity (Baraldi et al. 1994). A small substitution group like methyl at N8-position is better tolerated than a phenylpropyl substituent by $AA_{2A}R$ subtype. Introduction of a phenylpropyl group at N8-position, instead of a methyl group, leads to a decrease of $AA_{2A}R$ interaction (Baraldi et al. 2003).



92
hA_1 = 2.38 nM
hA_{2A} = 1.7 nM
hA_1/hA_{2A} = 1.4

93
hA_1 = 82.4 nM
hA_{2A} = 0.8 nM
hA_1/hA_{2A} = 103

Fig. 43: Indeno[1,2-*d*]pyrimidine derivatives. Data represent *K*i values (h = human) and are taken from references indicated in the text

3.2.3.3.5. Position 9. The introduction of a substituent at the 9-position instead of a hydrogen leads to a loss of selectivity, but the receptor affinity is maintained. In general the methylthio group at the 9-position is the best tolerated [Fig. 37 (**72**)]. However, modifications at the 9-position maintain antagonistic activity, particularly with small groups introduced, like methylthio or ethylamino, but lead to a significant loss of selectivity. Functionalization of the amino group into a *p*-methoxyphenylurea causes a decrease of $AA_{2A}R$ affinity. The introduction of hindered amino functions at 9-position, such as *p*-methoxyphenylamino, *N*-methylpiperazine, or *p*-hydroxyphenylamino, was ineffectual for $AA_{2A}R$-interaction (Baraldi et al. 2003).

3.2.3.4. Indeno[1,2-*d*]pyrimidine derivatives. A SAR study was presented by Matasi et al. (2005a) for a series of indeno[1,2-*d*]pyrimidine derivatives as $AA_{2A}R$ antagonists. In general, it has been observed that the amino functionality is essential for $AA_{2A}R$ affinity, since either alkylation or acylation produced compounds with significantly reduced affinity for the $AA_{2A}R$. It was also realized that, the position-5 is best for carbonyl group [Fig. 43 (**92**)], as reduction of the ketone to a methylene or its replacement with the ether linkage produced compounds with reduced $AA_{2A}R$ affinity and selectivity over AA_1R.

Introduction of a substituent on the C4 position (e.g. furyl or substituted furyl) led to retention of the $AA_{2A}R$ affinity and improvement in selectivity over AA_1R. Indeed, introduction of substituents at the C8-position is well tolerated by the $AA_{2A}R$ and can be substituted with a variety of susbtituents. In particular, isopropyl group at this position afforded a potent $AA_{2A}R$ antagonist [Fig. 43 (**93**)] with almost 129-fold selectivity over the AA_1R (Matasi et al. 2005a).

4. Conclusion

In conclusion, this review provides useful information about the structural requirements necessary for $AA_{2A}R$ antagonists. In view of the great efforts made for searching $AA_{2A}R$ antagonists among nonxanthine heterocycles, it is necessary to highlight that if the problem of affinity and selectivity has been completely solved, more effort is necessary for trying to obtain water soluble

derivatives, hydrophobicity being the major problem of this class of compounds.

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