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Azoloazines as A_{2a} receptor antagonists. Structure–activity relationship

Konstantin V. Savateev,[a] Evgeny N. Ulomsky,[a] Ilya I. Butorin,[a] Valery N. Charushin,[a, b] Vladimir L. Rusinov,[a, b] Oleg N. Chupakhin[a, b]

[a] *Ural Federal University named after the First President of Russia B.N.Yeltsin ul. Mira 19, 620002 Ekaterinburg, Russian Federation*
[b] *Postovsky Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences ul. S.Kovalevskoi/Akademicheskaya 22/20, 620137 Ekaterinburg, Russian Federation*

Non-xanthine inhibitors of the adenosine A_{2a} receptor of the azoloazine series are good candidates for use as drugs for the treatment of neurodegenerative diseases and sepsis. This review systematizes and summarizes the structure–activity relationships in the series of triazoloazines, including annulated pyrimidines, pyrazines and triazines, as well as their tricyclic fused analogues. The above relationships for such systems are analyzed. The structures of the most efficient functional moieties from the point of view of affinity for the A_{2a} receptor and selectivity for other types of adenosine receptors (A_1, A_{2b}, A_3) are presented.
The bibliography includes 71 references.

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1. Introduction

Purines and purine nucleosides are of great importance for living organisms as DNA and RNA fragments; however, this function is not the only one for them. A special place is held by adenosine contained in adenosine triphosphate (ATP) and coenzymes, such as nicotinamide adenine dinucleotide (NAD), flavin adenine dinucleotide (FAD), *S*-adenosylmethionine, *etc*. In addition, adenosine plays an essential regulatory role in the body as an adenosine receptor (AR) agonist.[1] A variety of physiological and pathological processes are triggered by the stimulation of A_1, A_{2a}, A_{2b} and A_3 adenosine receptors. In particular, the blocking of the A_1 receptor reduces the inflammation of the respiratory passages and alleviates bronchial obstruction.[2–5] The effect of the A_{2a} receptor on inflammatory processes in the tissues and neurodegenerative disorders, including Parkinson's disease, has been revealed.[6–8]

However, in order to treat these pathologies, the effect of adenosine per se is often insufficient, and there is a need

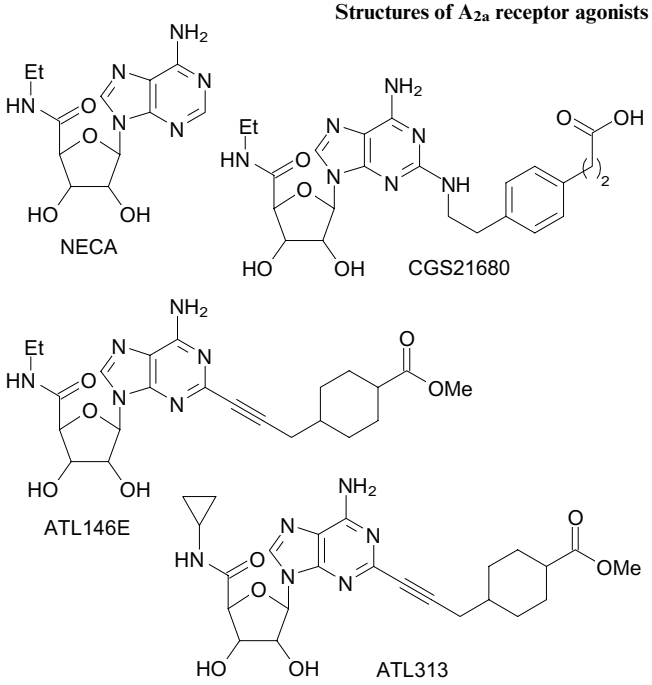
K.V.Savateev. PhD in Chemistry, Junior Researcher at the UrFU. E-mail: i-krafttt@yandex.ru
E.N.Ulomsky. Doctor of Chemical Sciences, Professor of the same University. E-mail: ulomsky@yandex.ru
I.I.Butorin. Student at the same University. E-mail: butilig@gmail.com
Current research interests of the authors: anomalous nucleosides, chemical modification of antibiotics and antiviral drugs, synthesis of azaheterocyclic compounds, structure–activity relationships.
V.N.Charushin. Academician, Doctor of Chemical Sciences, Director of the IOS UB RAS, Professor of the UrFU.
Telephone: +7(343)369–3058, e-mail: charushin@ios.uran.ru
Current research interests: heterocyclic chemistry, fluorinated compounds, medicinal chemistry.
V.L.Rusinov. Corresponding Member of the RAS, Doctor of Chemical Sciences, Director of the Institute of Chemistry and Technology at the UrFU, Leading Researcher at the IOS UB RAS.
Telephone: +7(343)374–0458, e-mail: v.l.rusinov@urfu.ru
Current research interests: anomalous nucleosides, chemical modification of antibiotics and antiviral drugs, synthesis of azaheterocyclic compounds, structure–activity relationships.
O.N.Chupakhin. Academician, Doctor of Chemical Sciences, Scientific Supervisor of the IOS UB RAS, Professor of the UrFU.
Telephone: +7(343)374–1189, e-mail: chupakhin@ios.uran.ru
Current research interests: synthetic organic chemistry, heterocyclic and organofluorine chemistry, supramolecular chemistry, medicinal chemistry.

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for compounds that have a higher affinity for the target. Equally important is the selectivity of the drug, since various receptors from the adenosine family are similar in structure;[9] for the therapeutic effect to be manifested, a targeted impact on a specific receptor is often necessary. In some cases, it is most efficient to use not only agonists but also antagonists of ARs to treat the disease. Thus, a challenging task is to search for compounds possessing the properties of AR effectors (agonists or antagonists) and a higher affinity for them as compared with adenosine.

Structures of A_{2a} receptor agonists



The basic approach to the search for highly selective AR agonists was initially to synthesize adenosine derivatives.[10] Various modifications of xanthines, such as caffeine and theophylline, were considered as antagonists. Among A_{2a} receptor agonists and antagonists (see reviews[9–12]), the nonselective agonist NECA, as well as selective agonists CGS21680, ATL146E and ATL313 are the most popular compounds.[12]

As candidates for creating effectors with a higher affinity and selectivity for ARs, compounds isosteric to adenosine, guanosine and hypoxanthine are of interest azolopyrimidines and azolo-1,2,4-triazines with a bridging nitrogen atom.[13–16]

Previously, we have reported the synthesis and *in vivo* antiseptic activity of 6-nitrotriazolo[1,5-*a*]pyrimidines.[17,18] It can be assumed that these nitroazolopyrimidines are A_{2a} receptor antagonists, since currently such a target is believed to be responsible for the development and arrest of septic states.[19–21] This hypothesis is supported by the revealed specific features of the molecular structure of known and most promising adenosine receptor antagonists. It turned out that such compounds are regarded to some extent as structural analogues of purines and, hence, are classified with a large family of azoloazines and their derivatives containing at least two fused heterocyclic moieties.

For example, one of the strongest A_{2a} receptor inhibitors, ZM-241385 (4-{2-[7-amino-2-(2-furyl)-1,2,4-triazolo[1,5-*a*][1,3,5]triazin-5-ylamino]ethyl}phenol),[22,23] contains, as a key structure, the 1,2,4-triazolo[1,5-*a*][1,3,5]triazine ring system.

A significant impetus to study A_{2a} receptor antagonists and agonists was provided by X-ray crystallographic data on complexes with this receptor of some key effectors, both natural and artificial. The interactions of natural ligands — adenosine, caffeine and XAC (xanthine amine congener) —

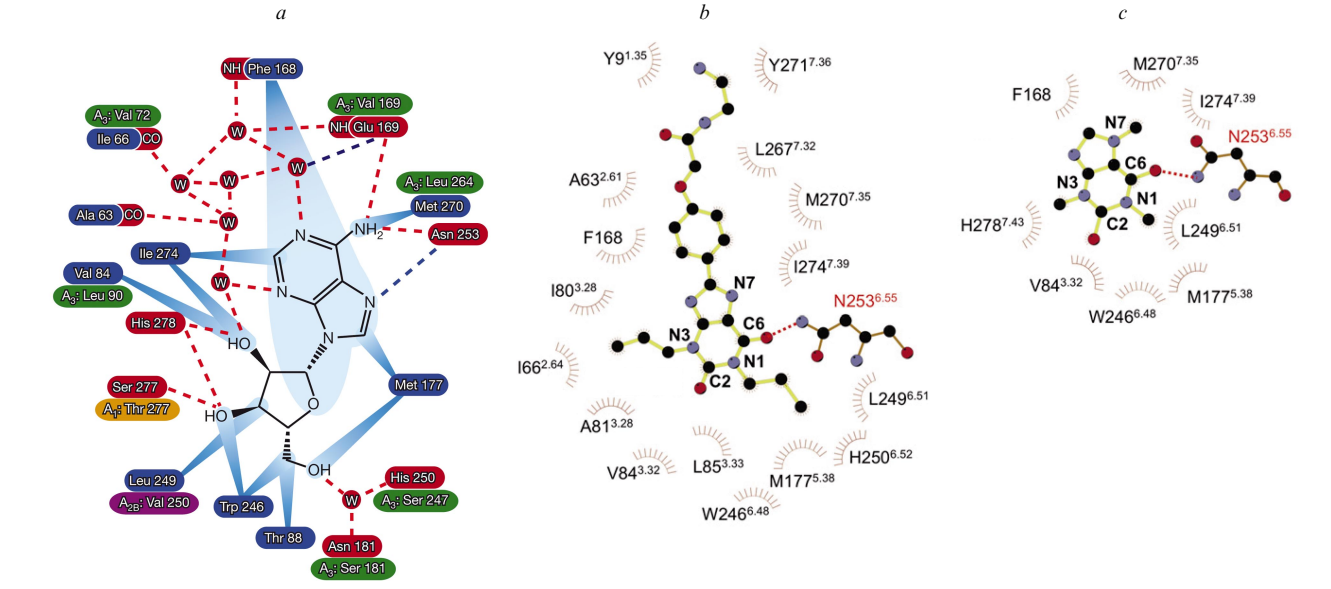
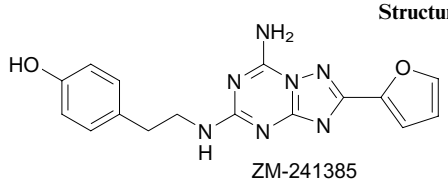


Figure 1. Schematic representation of key interactions of adenosine (*a*), XAC (*b*) and caffeine (*c*) with the binding site of the A_{2a} receptor.[24,25]
(*a*) Receptor moieties that form van der Waals interactions and hydrogen bonds are shown in blue and red, respectively.

Structure of ZM-241385



with the binding site of the A_{2a} receptor have been studied.[24,25] It has been demonstrated that the key role in the binding of adenosine and its analogues to the receptor is played by π–π interactions between one of the phenylalanine residues and the heterocyclic core of the effector molecule, as well as the formation of hydrogen bonds involving the asparagine moiety of the receptor binding site and amino or oxo groups of the azine ring. In addition to these interactions, the formation of hydrogen bonds involving hydroxy groups of the riboside residue and serine and histidine receptor residues plays an important role in adenosine binding (Fig. 1).

An important contribution to the development of directed synthesis of new efficient antagonists has been made by X-ray crystallographic data on the binding of the ZM-241385 effector with the A_{2a} receptor.[26] It has been noted that the high affinity of this antagonist is primarily determined by the π–π interactions of the triazolotriazine ring system with the phenylalanine moiety of the receptor binding site, as well as by hydrogen bonds of glutamic acid and asparagine residues with the primary amino group of ZM-241385 and with a furyl moiety. The furan ring plays an important role in binding, as it is also responsible for the

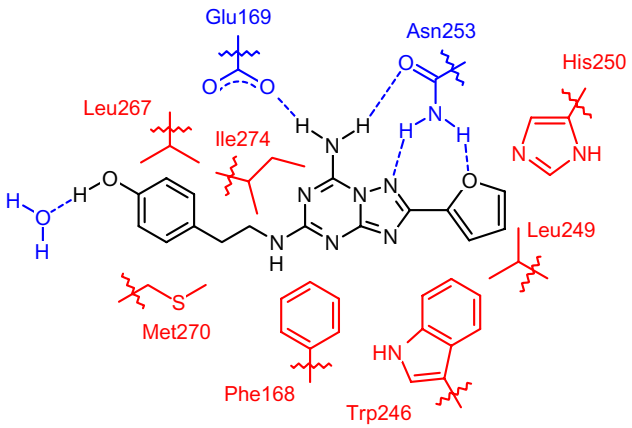


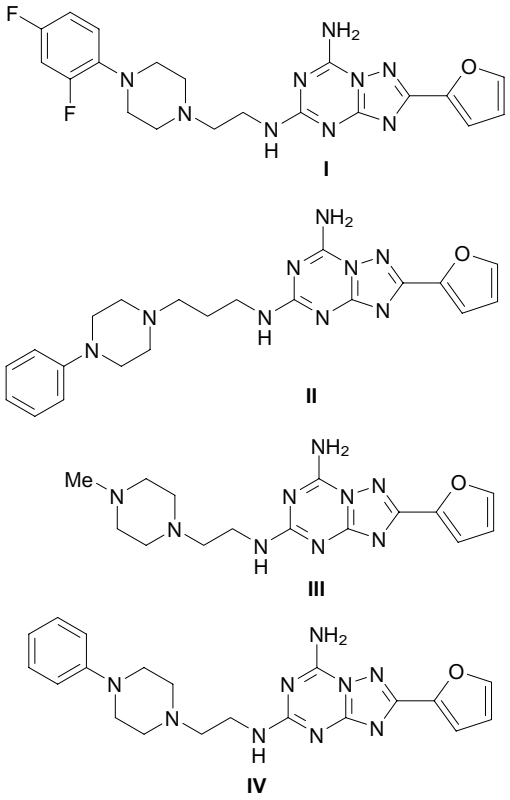
Figure 2. Schematic representation of key interactions of compound ZM-241385 with the binding site of the A_{2a} receptor.[26] Moieties forming hydrogen bonds and van der Waals interactions are shown in blue and red, respectively.

hydrophobic interaction with the tryptophan residue and for π–π stacking with the histidine moiety (Fig. 2).

X-Ray crystallographic data on A_{2a} receptor–antagonist complexes have also been reported for triazolotriazine structural analogues of ZM-241385 — compounds **I**–**IV**.[27]

The type of binding of ligands **I**–**IV** to the A_{2a} receptor is the same as that for ZM-241385, while key differences pertain to the interaction of the linker group with histamine and glutamic acid residues (Fig. 3).[27]

Structures I–IV



The growing interest in this subject is manifested primarily as the increase in the number of publications dealing with the directed synthesis of effectors and X-ray diffraction analysis of the complexes studied. A number of reviews

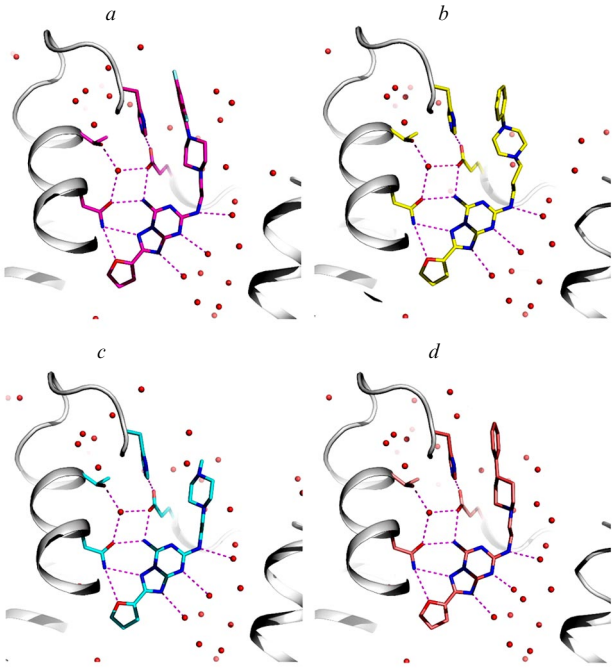


Figure 3. Schematic representation of key interactions of heterocycles **I** (*a*), **II** (*b*), **III** (*c*), **IV** (*d*) with the binding site of the A_{2a} receptor.[27]

have recently been published,[26, 28–40] but only some have addressed the most therapeutically promising A_{2a} receptor. The authors of these publications, as a rule, consider a wide range of xanthine and non-xanthine effectors, but the former often demonstrate low affinity and selectivity, being inferior in this respect to azoloazines with a bridging nitrogen atom.

This review addresses non-xanthine azoloazines containing a bridging nitrogen atom as a common molecular fragment, which are the most promising structures with high affinity for the A_{2a} receptor and high selectivity, as well as structure–activity relationships in this series of heterocycles.

2. Bicyclic nitrogen-containing heterocyclic systems

2.1. Triazolopyrimidines and triazolopyrazines

Triazolo[1,5-*c*]- and triazolo[1,5-*a*]pyrimidines are believed to be promising AR antagonists. Several works have recently been published[41–45] dealing with the synthesis and modification of triazolopyrimidine systems aimed at searching for structures with a high affinity and selectivity for these receptors [$K_i(A_1)$, $K_i(A_{2a})$ are inhibitory constants towards the A_1 and A_{2a} receptors, respectively].

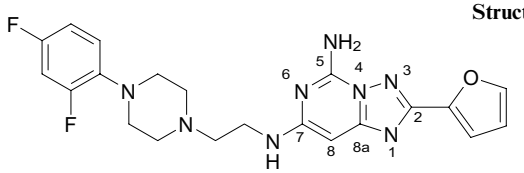
In particular, piperazine analogues **1**–**4** of the well-known AR antagonist ZM-241385 have been synthesized on the basis of the triazolo[1,5-*c*]pyrimidine skeleton.[41] It turned out that methylation of the secondary amino group attached to the triazoloazine system leads to an increase in the affinity for the receptor up to the activity that manifests itself in a low nanomolar concentration range in the case of compound **3**.

The same research team[42] synthesized series of triazolo[1,5-*a*]- and triazolo[1,5-*c*]pyrimidines **5**–**12**, which demonstrated inhibitory constants for the A_{2a} receptor in the range from 10 to 660 nmol litre^{-1}, and no advantage of one of the annulation types was observed (Table 1).

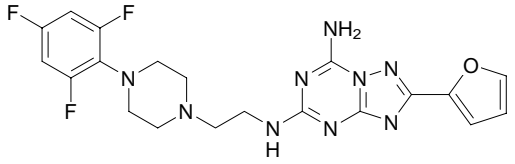
By contrast, it has been shown[43] that triazolo[1,5-*a*]pyrimidines **13**–**19** exhibit lower inhibitory constants for the A_{2a} receptor than triazolo[1,5-*c*]pyrimidines **20**–**26** with the same substituents in the heterocyclic moiety (Table 2).

Nevertheless, one of triazolo[1,5-*a*]pyrimidine compounds **27**–**29** has a high affinity toward the receptor at a rather high selectivity [$K_i(A_{2a}) = 45$, 830 and 80 nmol litre^{-1}, respectively; for all derivatives $K_i(A_1) > 500$ nmol litre^{-1}].

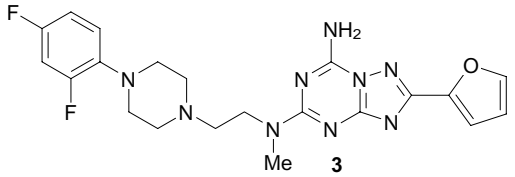
Structures 1–4



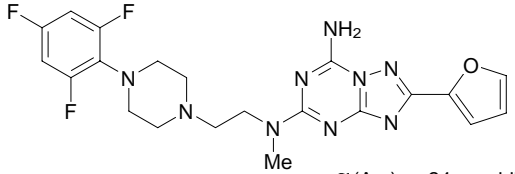
1 $K_i(A_{2a}) = 55$ nmol litre^{-1}; $K_i(A_1) = 2600$ nmol litre^{-1}



2 $K_i(A_{2a}) = 92$ nmol litre^{-1}; $K_i(A_1) > 500$ nmol litre^{-1}

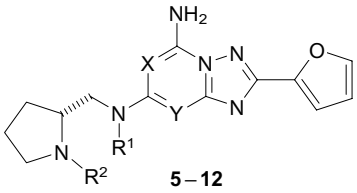


3 $K_i(A_{2a}) = 6.5$ nmol litre^{-1}; $K_i(A_1) = 750$ nmol litre^{-1}



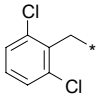
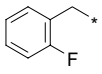
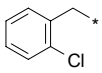
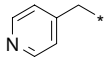
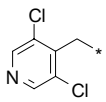
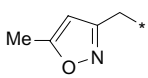
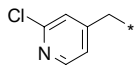
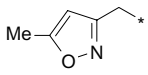
4 $K_i(A_{2a}) = 24$ nmol litre^{-1}; $K_i(A_1) = 790$ nmol litre^{-1}

Structures 5–12



5–12

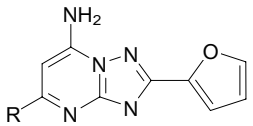
Table 1. Structure–activity relationship for triazolo[1,5-*a*]- and triazolo[1,5-*c*]pyrimidines **5**–**12**.[42]

Compound	R^1	R^2	$K_i(A_{2a})$/nmol litre^{-1}	
			X = N, Y = CH	X = CH, Y = N
5	H		312	659
6	H		127	187
7	H		192	148
8	H		100	112
9	H		366	397
10[a]	H		57	44
11[a]	H		10	79
12[a]	Me		19	11

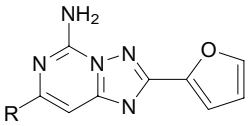
Note. Here and hereafter, a binding site is labelled with '*'.

[a] $K_i(A_1) > 250$ nmol litre^{-1}; for the other compounds, K_i were not determined.

Structure 13 – 26



13 – 19

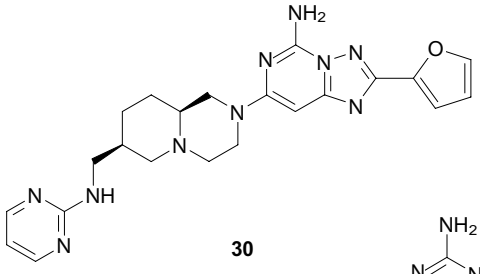


20 – 26

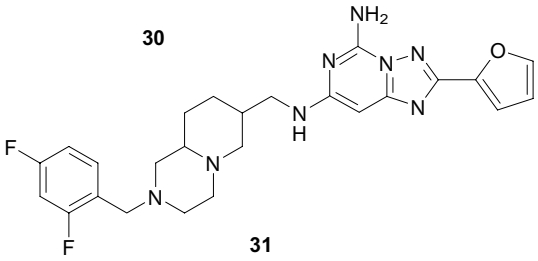
In the series of triazolo[1,5-*c*]pyrimidines, derivatives **30** and **31** were also found to be the leading compounds with inhibitory constant for the A_{2a} receptor of 47 and 49 nmol litre^{-1}, respectively, at the selectivity, *i.e.*, the ratio of inhibitory constants for the A_1 and A_{2a} receptors [$K_i(A_1)$/$K_i(A_{2a})$], ranging from 10 to 20.

In another series of triazolo[1,5-*c*]pyrimidines (heterocycles **32 – 54**), compounds with the affinity for the receptor in the nanomolar concentration range but unsatisfactory

Structures 30, 31

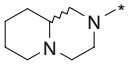
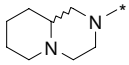
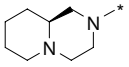
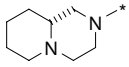
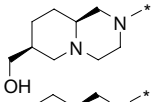
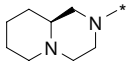
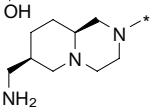
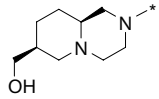
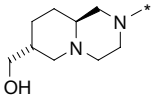
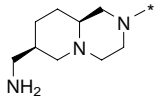
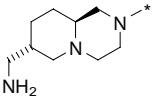
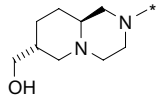
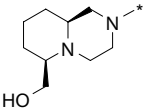
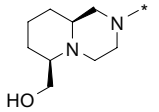


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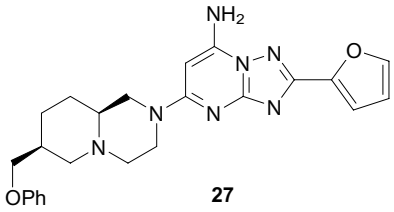


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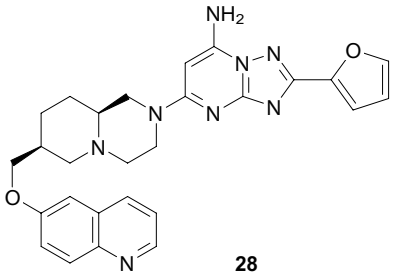
Table 2. Structure – activity relationship for triazolo[1,5-*a*]- (**13 – 19**) and triazolo[1,5-*c*]pyrimidines (**20 – 26**).[43]

Compound	R	K_i /nmol litre^{-1}		Compound	R	K_i /nmol litre^{-1}	
		A_{2a}	A_1			A_{2a}	A_1
13		38	> 500	**20**		140	> 500
14		170	> 500	**21**		63	1100
15		230	> 500	**22**		110	> 500
16		110	> 500	**23**		96	> 500
17		860	> 1000	**24**		56	> 500
18		370	> 500	**25**		240	> 1000
19		610	> 500	**26**		110	> 500

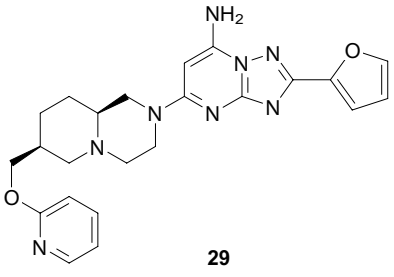
Structures 27 – 29



27



28



29

Structures 32 – 67

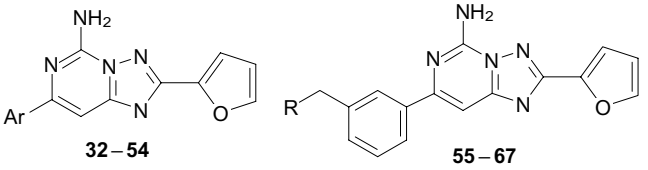


Table 3. Structure – activity relationship for triazolo[1,5-*c*]pyrimidines **32 – 54**.[44]

Compound	Ar	K_i /nmol litre^{-1}	
		A_{2a}	A_1
32	Ph	7.0	21.0
33	2-MeC_6H_4	22.0	264.0
34	3-MeC_6H_4	3.7	48.1
35	4-MeC_6H_4	8.4	159.6
36	2-$MeOC_6H_4$	4.3	116.1
37	3-$MeOC_6H_4$	5.0	100.0
38	4-$MeOC_6H_4$	7.3	751.9
39	2,4-$(MeO)_2C_6H_3$	2.9	284.2
40	3,4-$(MeO)_2C_6H_3$	7.3	467.2
41	2,5-$(MeO)_2C_6H_3$	4.5	292.5
42	2,6-$(MeO)_2C_6H_3$	1700.0	1700.0
43	2,3-$(MeO)_2C_6H_3$	21.7	585.9
44	3,4,5-$(MeO)_3C_6H_2$	4.5	310.5
45	2,3,4-$(MeO)_3C_6H_2$	4.5	76.5
46	2-Th	4.4	66.0
47	4-Py	1.9	125.4
48	3-Py	6.6	429.0
49	2-Py	1.4	47.6
50	3-$Pr^iC_6H_4$	4.7	145.7
51	3-PhC_6H_4	5.5	451.0
52	3-$H_2NC_6H_4$	5.0	55.0
53	3-NCC_6H_4	5.4	75.6
54	3-$HOCH_2C_6H_4$	2.8	378.0

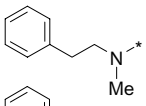
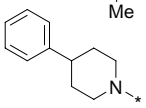
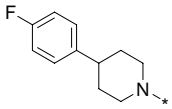
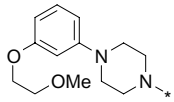
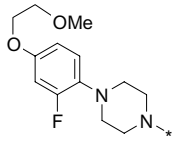
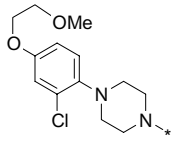
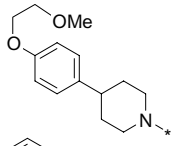
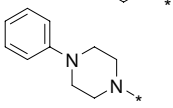
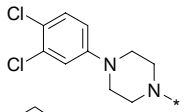
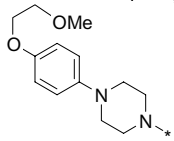
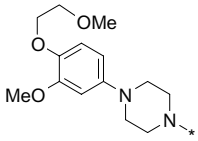
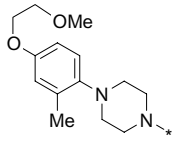
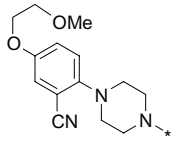
Note. Th is thienyl, Py is pyridyl.

selectivity have been found.[44] Structure optimization for the compounds of this series made it possible to increase the selectivity by introducing oxygen-containing substituents into the phenyl moiety (compounds **38**, **54**) (Table 3).

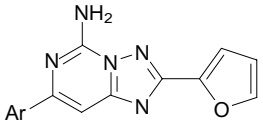
Further modification of the side chain of the aryl substituent by introducing nitrogen-containing functional groups (compounds **55 – 67**) led to several derivatives with a high affinity for the receptor and good selectivity. In particular, compound **61**, in which the side chain has an oxygen-containing moiety in the *para*-position of the *N*-phenylpiperazine substituent, had the inhibitory constant of 2.8 nmol litre^{-1} at the selectivity $K_i(A_1)/K_i(A_{2a}) = 601$. The additional introduction of a fluorine atom into this phenyl moiety led to a decrease in inhibitory constant $K_i(A_{2a})$ to 2.7 nmol litre^{-1} and selectivity $K_i(A_1)/K_i(A_{2a})$ to 642 for compound **63** (Table 4).

The influence of the aromatic substituent on the affinity for the receptor has been studied for the series of triazolo[1,5-*c*]-pyrimidines **68 – 93**.[45] Among the synthesized structures, the lowest inhibitory constants have been found for *meta*-substituted heterocycles, while for the *para*-substituted systems the affinity for the A_{2a} receptor was reduced (Table 5).

Table 4. Structure – activity relationship for triazolo[1,5-*c*]pyrimidines **55 – 67**.[44]

Compound	R	K_i /nmol litre^{-1}	
		A_{2a}	A_1
55		3.6	486.0
56		4.6	317.4
57		7.4	851.0
58		8.9	1797.8
59		4.6	317.4
60		10.5	31.5
61		2.8	1682.8
62		4.0	460.0
63		2.7	1733.4
64		2.9	591.6
65		3.3	442.2
66		2.7	194.4
67		3.6	306.0

Structures 68–93



68–93

Table 5. Structure–activity relationship for triazolo[1,5-*c*]pyrimidines **68–93**.[45]

Compound	Ar	$K_i(A_{2a})$ /nmol litre^{-1}
68	3-Pr^{i}C$_6$H$_4$	680
69	3-H$_2$NC$_6$H$_4$	630
70	4-H$_2$NC$_6$H$_4$	> 1000
71	3-AcNHC$_6$H$_4$	160
72	3-AcC$_6$H$_4$	75
73	3-O$_2$NC$_6$H$_4$	460
74	4-O$_2$NC$_6$H$_4$	> 1000
75	3-Me$_2$NC$_6$H$_4$	140
76	4-Me$_2$NC$_6$H$_4$	> 1000
77	3-EtO$_2$CC$_6$H$_4$	370
78	4-EtO$_2$C$_6$H$_4$	> 1000
79	3-NCC$_6$H$_4$	160
80	4-NCC$_6$H$_4$	> 1000
81	3-F$_3$CC$_6$H$_4$	220
82	4-F$_3$CC$_6$H$_4$	> 1000
83	3-HOCH$_2$C$_6$H$_4$	470
84	4-HOCH$_2$C$_6$H$_4$	> 1000
85	3-MeOC$_6$H$_4$	270
86	3-MeSO$_2$C$_6$H$_4$	110
87	3-H$_2$NC(O)C$_6$H$_4$	110
88	3-HO$_2$CC$_6$H$_4$	> 1000
89	3-Py	460
90	2-Fu	400
91	1-Naph	420
92	Quinolin-8-yl	250
93	Pyrimidin-5-yl	360

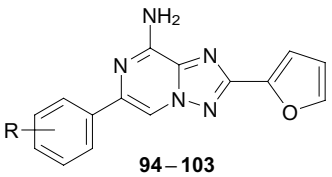
Note. Fu is furyl, Naph is naphthyl.

In addition, it has been shown[45] that, among triazolo[1,5-*a*]pyrazines **94–103**, disubstituted amides have a higher affinity for the receptor as compared with monosubstituted amide **94**, but a lower selectivity (Table 6).

Among triazolopyrazines **104–111**, compound **107**, containing the tyramine residue, which is also present in the ZM-241385 structure, is worthy of special note. Heterocycle **107** showed a high affinity for the receptor and good selectivity [$K_i(A_{2a})$ = 1 nmol litre^{-1}, $K_i(A_1)/K_i(A_{2a})$ = 320].

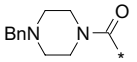
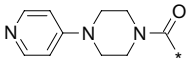
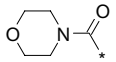
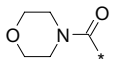
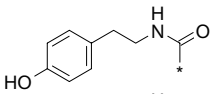
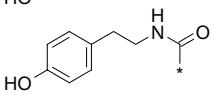
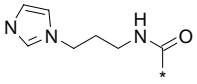
All triazolo[5,1-*b*]quinazolines **112–136** showed moderate affinity for the A_{2a} receptor (K_i = 10 μmol litre^{-1}),[46]

Structures 94–103



94–103

Table 6. Structure–activity relationship for triazolo[1,5-*a*]pyrazines **94–103**.[45]

Compound	R	Isomer	K_i /nmol litre^{-1}	
			A_{2a}	A_1
94	Pr^{i}NHC(O)	*meta*	140	290
95	Me$_2$NC(O)	*meta*	70	120
96	Et$_2$NC(O)	*meta*	1	41
97		*meta*	680	> 250
98		*meta*	730	3
99		*meta*	240	> 250
100		*para*	19	1800
101		*meta*	180	> 250
102		*para*	830	36
103		*papa*	330	> 250

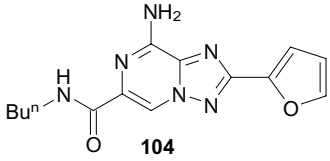
being significantly inferior in inhibitory constants to the known AR antagonists (Table 7).

Virtual screening of a commercial vendor library[47] made it possible to select compounds **137–141** of triazolopyrimidine, triazoloquinazoline and thiadiazolopyrimidine structures exhibiting high inhibitory constants, which means low affinities for the A_{2a} receptor (the inhibitory constant can also be expressed in percentage of inhibition at the definite concentration of a compound).

Triazolo[1,5-*a*]pyrimidine **142** showed the affinity for the A_{2a} receptor in the micromolar concentrations range at low selectivity [$K_i(A_1) = 6.8 \pm 0.4$ nmol litre^{-1}, $K_i(A_{2a}) = 1.2 \pm 0.3$ nmol litre^{-1}].[48] Attempts of the authors to improve the affinity for the receptor and selectivity by modifying the triazolopyrimidine core were unsuccessful: none of derivatives **143–148** surpassed starting compound **142** (Table 8).

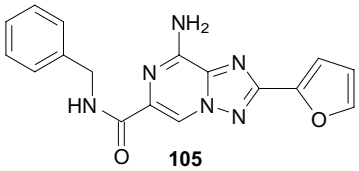
Testing results for a wide range of triazolo[1,5-*c*]pyrimidines **149–210** have been reported[49] (Table 9). It has been noted that the presence of a nitrogen-containing substituent in 5-position of the heterocyclic system is essential to manifest affinity for the receptor, since compound **149** bearing the methylsulfanyl group at C(5) does not exhibit a significant activity towards all types of ARs. The lowest inhibitory constants against the A_{2a} receptor were shown by compounds containing a free amino group (**154–156**) or a phenylurea moiety (**157**, **163**). Derivatives **157**, **163** showed also higher selectivity to other ARs than compounds with a free amino group. In addition, the introduction of heterocyclic amines into the 5-position significantly decreased the affinity of compounds **186**, **187**, **190** for all AR types. The

Structures 104 – 111



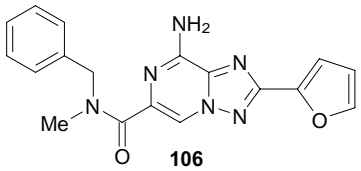
104

$K_i(A_{2a})$ = 1 nmol litre^{-1};
$K_i(A_1)$ = 120 nmol litre^{-1}



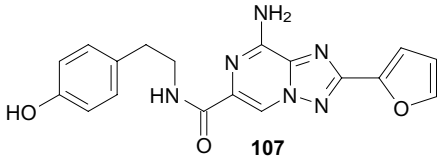
105

$K_i(A_{2a})$ = 2 nmol litre^{-1};
$K_i(A_1)$ = 14 nmol litre^{-1}



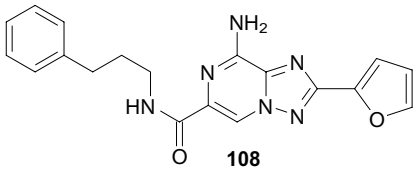
106

$K_i(A_{2a})$ = 27 nmol litre^{-1};
$K_i(A_1)$ = 160 nmol litre^{-1}



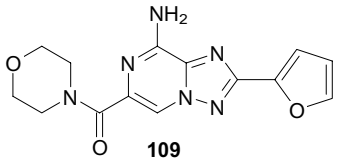
107

$K_i(A_{2a})$ = 1 nmol litre^{-1};
$K_i(A_1)$ = 320 nmol litre^{-1}



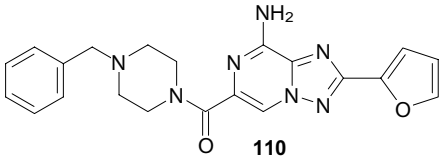
108

$K_i(A_{2a})$ = 28 nmol litre^{-1};
$K_i(A_1)$ = 240 nmol litre^{-1}



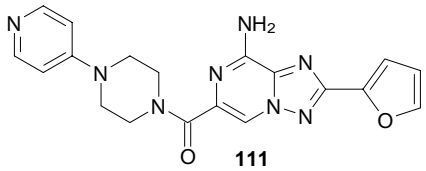
109

$K_i(A_{2a})$ > 250 nmol litre^{-1};
$K_i(A_1)$ > 250 nmol litre^{-1}



110

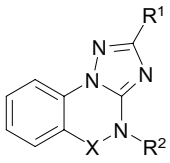
$K_i(A_{2a})$ > 250 nmol litre^{-1};
$K_i(A_1)$ > 250 nmol litre^{-1}



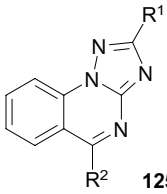
111

$K_i(A_{2a})$ > 250 nmol litre^{-1};
$K_i(A_1)$ > 250 nmol litre^{-1}

Structure 112 – 136

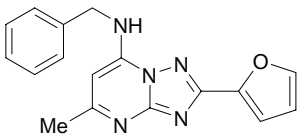


112 – 124



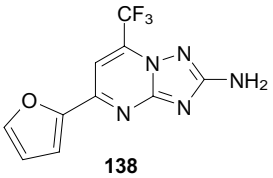
125 – 136

Structure 137 – 139



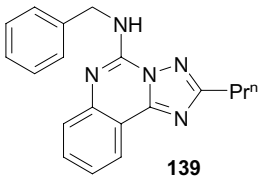
137

$K_i(A_1)$ = 5.97 ± 1.91 nmol litre^{-1};
$K_i(A_{2a})$ = 0.77 ± 0.12 nmol litre^{-1};
$K_i(A_{2b})$ = 0%;[a]
$K_i(A_3)$ = 1.12 ± 0.18 nmol litre^{-1}



138

$K_i(A_1)$ = 11%;[a]
$K_i(A_{2a})$ = 32%;[a]
$K_i(A_{2b})$ = 2%;[a]
$K_i(A_3)$ = 0%[a]



139

$K_i(A_1)$ = 3.80 ± 0.57 nmol litre^{-1};
$K_i(A_{2a})$ = 42%;[a] $K_i(A_{2b})$ = 2%;[a]
$K_i(A_3)$ = 5.62 ± 2.26 nmol litre^{-1}

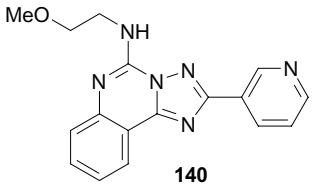
[a] At a concentration of 10 μmol litre^{-1}.

Table 7. Structure – activity relationship for triazolo[5,1-*b*]quinazolines **112 – 136**.[46]

Compound	R^1	R^2	X	K_i /μmol litre^{-1} (see [a])	
				A_1	A_{2a}
112	BnO	H	C(O)	4.25	> 10
113	EtO	H	C(O)	2.4	–
114	MeO	H	C(O)	5	–
115	$Ph(CH_2)_2O$	H	C(O)	6.8	–
116	EtO	$CH_2{=}CHCH_2$	C(O)	2.2	> 10
117	EtO	$HC{\equiv}CCH_2$	C(O)	1.1	2.5
118	EtO	4-$FC_6H_4CH_2$	C(O)	15.1	3
119	EtO	H	CH_2	6	–
120	EtO	H	CH_2	6	> 10
121	$Ph(CH_2)_2O$	H	CH_2	> 10	–
122	$Ph(CH_2)_2O$	H	C(S)	4.4	> 10
123	MeO	H	C(S)	> 10	–
124	BnO	H	C(S)	5	> 10
125	MeO	$CH_2{=}CHCH_2S$	–	3.4	> 10
126	MeO	BnS	–	5.1	> 10
127	BnO	C(O)	–	4	> 10
128	EtO	C(O)	–	3.1	> 10
129	$Ph(CH_2)_2O$	C(O)	–	6.8	> 10
130	BnO	EtO	–	0.154	> 10
131	EtO	BnO	–	0.068	> 10
132	EtO	MeO	–	7.5	–
133	BnO	NH_2NH	–	> 10	–
134	$Ph(CH_2)_2O$	NH_2NH	–	> 10	–
135	EtO	EtO_2CNHNH	–	> 10	–
136	EtO	BnO_2CNHNH	–	–	–

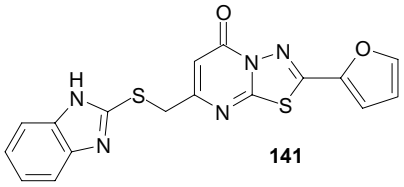
[a] A dash in the K_i columns means that the constant was not determined.

Structures 140 – 142

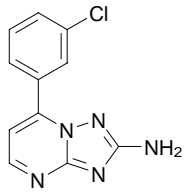


140

$K_i(A_1) = 3.09 \pm 0.30$ nmol litre^{-1};
$K_i(A_{2a}) = 41\%$;[a] $K_i(A_{2b}) = 13\%$;[a]
$K_i(A_3) = 0.23 \pm 0.07$ nmol litre^{-1}



141



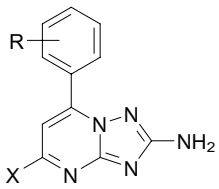
142

$K_i(A_1) = 32\%$;[a] $K_i(A_{2a}) = 33\%$;[a]
$K_i(A_{2b}) = 0\%$;[a] $K_i(A_3) = 0\%$ [a]

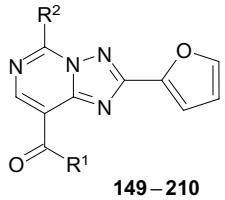
[a] At a concentration of 10 μmol litre^{-1}.

presence of the ethoxycarbonyl group at C(8) is more preferable for the manifestation of high affinity for ARs than the presence of a free carboxyl function in this position: compounds **195 – 210** did not exhibit a noticeable affinity for the A_{2a} receptor.

Structures 143 – 210



143 – 148



149 – 210

Table 8. Structure – activity relationship for triazolo[1,5-*a*]pyrimidines **143 – 148**.[48]

Compound	X	R	K_i /μmol litre^{-1} (% of substitution at 10 μmol litre^{-1})	
			A_1	A_{2a}
143	H	H	(2)	101 ± 6
144	H	4-Cl	(17)	99 ± 5
145	Me	H	3.5 ± 0.3	2.1 ± 0.2
146	Me	4-OMe	2.8 ± 0.2	8.7 ± 0.1
147	Me	4-Me	2.4 ± 0.3	3.4 ± 0.4
148	Me	4-Cl	2.5 ± 0.2	9.1 ± 0.2

Table 9. Structure – activity relationship for triazolo[1,5-*c*]pyrimidines **149 – 210**.[49]

Compound	R^1	R^2	K_i /nmol litre^{-1}			
			A_1	A_{2a}	A_{2b}	A_3
149	EtO	MeS	5720	9500	> 30 000	2640
150	EtO	3,4-$(MeO)_2C_6H_3CH_2NH$	315	116	13 300	38.7
151	HO	3,4-$(MeO)_2C_6H_3CH_2NH$	958	5320	> 30 000	159
152	MeNH	3,4-$(MeO)_2C_6H_3CH_2NH$	428	25.8	2490	282
153	$BnCH_2NH$	3,4-$(MeO)_2C_6H_3CH_2NH$	385	65.2	> 30 000	87.7
154	MeNH	H_2N	135	15.0	2030	609
155	$BnCH_2NH$	H_2N	57.1	11.1	5320	140
156	EtO	H_2N	185	3.32	1110	238
157	MeNH	PhNHC(O)NH	126	5.76	1180	730
158	MeNH	cyclo-$C_6H_{11}NHC(O)NH$	8990	1520	> 30 000	18 700
159	MeNH	BnC(O)NH	296	12.4	4840	1190
160	$BnCH_2NH$	PhNHC(O)NH	365	51.4	> 30 000	1350
161	$BnCH_2NH$	cyclo-$C_6H_{11}NHC(O)NH$	> 100 000	773	> 30 000	4220
162	$BnCH_2NH$	BnC(O)NH	317	28.1	> 30 000	553
163	EtO	PhNHC(O)NH	322	4.82	1900	357
164	EtO	cyclo-$C_6H_{11}NHC(O)NH$	12700	183	> 30 000	2510
165	EtO	BnC(O)NH	> 100 000	42 700	> 30 000	2590
166	HO	cyclo-$C_6H_{11}NHC(O)NH$	> 100 000	24 700	> 30 000	59 400
167	EtO	MeNH	978	104	2450	4.14
168	EtO	EtNH	162	50.3	3060	3.30
169	EtO	n-$C_5H_{11}NH$	613	50.1	> 10 000	11.3
170	EtO	Pr^iNH	40.0	103	~ 10 000	9.46
171	EtO	$Pr^iCH(Et)CH_2NH$	1150	215	> 10 000	39.3
172	EtO	cyclo-C_3H_5NH	60.7	37.4	2260	9.52
173	EtO	cyclo-C_5H_9NH	34.4	43.4	4620	35
174	EtO	cyclo-$C_6H_{11}CH_2NH$	432	121	> 10 000	41.2
175	EtO	BnNH	940	32.0	2510	10.0
176	EtO	4-$MeC_6H_4CH_2NH$	1340	122	~ 10 000	56.1
177	EtO	4-$MeOC_6H_4CH_2NH$	1250	142	4810	57.6
178	EtO	4-$FC_6H_4CH_2NH$	932	39.3	1970	46.3
179	EtO	4-$ClC_6H_4CH_2NH$	866	73.2	1630	56.8
180	EtO	4-$F_3CC_6H_4CH_2NH$	1590	209	2040	323
181	EtO	4-$PhC_6H_4CH_2NH$	890	187	> 30 000	875
182	EtO	Ph_2CHNH	943	385	> 30 000	336

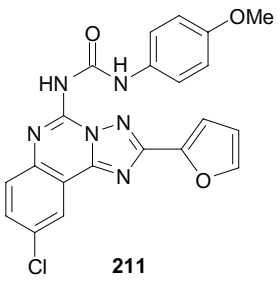
Table 9 (continued).

Compound	R^1	R^2	K_i/nmol litre^{-1}			
			A_1	A_{2a}	A_{2b}	A_3
183	EtO	cyclo-C_4H_7NH	75.2	28.9	> 3000	11.7
184	EtO	cyclo-$C_7H_{13}NH$	231	235	> 10 000	321
185	EtO	cyclo-$C_8H_{15}NH$	176	351	> 10 000	517
186	EtO	Pyrrolidino	15 600	10 200	> 10 000	836
187	EtO	Piperidino	8860	8180	> 10 000	1770
188	EtO	$MeO(CH_2)_2NH$	2270	292	> 10 000	105
189	EtO	Me_2N	13 400	6480	> 10 000	275
190	EtO	Morpholino	> 100 000	17 600	> 10 000	8700
191	EtO	cyclo-$C_6H_{11}NH$	141	58.9	> 10 000	131
192	EtO	Morpholinoamino	> 100 000	> 100 000	> 10 000	> 30 000
193	EtO	Bu^iNH	45.6	44.4	7150	24.4
194	EtO	MeONH	6510	210	> 10 000	1190
195	HO	MeNH	> 100 000	> 100 000	> 10 000	15 900
196	HO	EtNH	11 900	3680	> 10 000	480
197	HO	n-$C_5H_{11}NH$	10 400	26 900	> 10 000	26 300
198	HO	Pr^iNH	4490	7660	> 10 000	17 500
199	HO	$Bu^nCH(Et)CH_2NH$	1780	33 800	> 10 000	16 400
200	HO	cyclo-C_3H_5NH	1110	596	> 10 000	165
201	HO	cyclo-C_5H_9NH	3790	37 300	> 10 000	17 700
202	HO	cyclo-$C_6H_{11}CH_2NH$	2740	33 900	> 10 000	15 800
203	HO	BnNH	5090	3660	> 10 000	2230
204	HO	4-$MeC_6H_4CH_2NH$	2730	1190	> 10 000	751
205	HO	4-$MeOC_6H_4CH_2NH$	5760	12 400	> 10 000	5520
206	HO	4-$FC_6H_4CH_2NH$	> 100 000	6390	> 10 000	14 000
207	HO	4-$ClC_6H_4CH_2NH$	> 100 000	> 100 000	> 10 000	11 600
208	HO	4-$F_3CC_6H_4CH_2NH$	> 100 000	18 000	> 10 000	15 900
209	HO	4-$PhC_6H_4CH_2NH$	30 100	> 100 000	> 10 000	28 300
210	HO	Ph_2CHNH	2450	> 100 000	> 10 000	2070

Two triazoloquinazolines (**211**, **212**)[50] turned out to be one order of magnitude more active towards the A_3 receptor than towards A_{2a}.

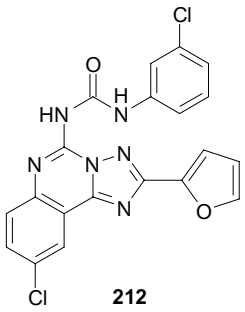
Data on a considerably wider spectrum of triazoloquinoxalines **213**–**247**[51] were published simultaneously with the above paper (Table 10). The parent compound **213** exhibited a higher affinity for the A_1 receptor than for A_{2a} and was used for further modifications. The introduction of alkyl substituents and halogen atoms into the benzene ring did not enhance the affinity of the compounds for the A_{2a} receptor, except derivative **214**, which was more active [$K_i(A_{2a})$ = 14.6 nmol litre^{-1}] than initial compound **213**, while the selectivity was absent. In addition to modification of the phenyl moiety, attempts were made to enhance the affinity for the A_{2a} receptor by introducing substituents to the amino group; however, such structural changes did not lead to a low inhibitory constant. In addition, compounds with a substituted amino group but without substituents in the phenyl moiety turned out to be completely inactive to the A_{2a} receptor. The same pertains also to compounds **236**–**247**, containing a carbonyl function instead of the amino group.

Structures 211, 212



211

$K_i(A_1)$ = 7.6 nmol litre^{-1};
$K_i(A_{2a})$ = 9.4 nmol litre^{-1};
$K_i(A_{2b})$ = 22 nmol litre^{-1};
$K_i(A_3)$ = 0.14 nmol litre^{-1}



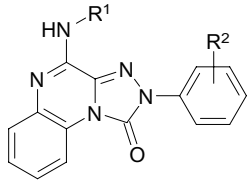
212

$K_i(A_1)$ = 8.1 nmol litre^{-1};
$K_i(A_{2a})$ = 9.5 nmol litre^{-1};
$K_i(A_{2b})$ = 30 nmol litre^{-1};
$K_i(A_3)$ = 0.19 nmol litre^{-1}

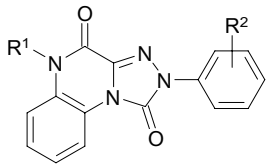
In the later study,[52] the same research team has shown that the presence of hetarylalkylamino substituent at C(6) in the triazoloquinoxaline ring system of compounds **248**–**268** enhances the affinity for the A_{2a} receptor at a rather good selectivity towards the A_1 and A_3 receptors (Table 11). However, the most favourable substituent from the viewpoint of the affinity for the A_{2a} receptor was the C(6)-benzylamino group: compound **248** showed the inhibitory constant of 6.5 nmol litre^{-1} and high selectivity. On the other hand, it was noted that the presence of the 8-benzylamino- (derivative **267**) or 8-dibenzylamino group (**268**) considerably reduces the affinity for the A_{2a} receptor.

Synthesis of triazolo[1,5-*a*]pyrazine derivatives **269**–**286**, containing a propargyl alcohol moiety, and their testing results for the A_{2a} and A_1 receptors have been described.[53] It has been stated that the presence of the alkyl or aryl group at the triple bond is essential for the manifestation of affinity for the A_{2a} receptor. In addition,

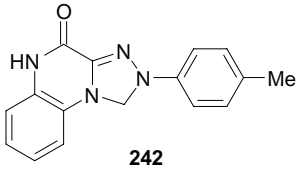
Structures 213 – 268



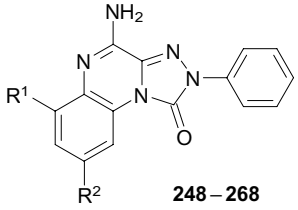
213 – 235



236 – 241, 243 – 247



242



248 – 268

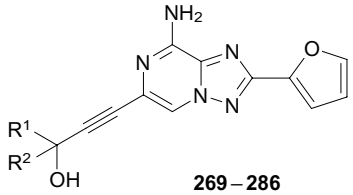
Table 10. Structure – activity relationship for triazoloquinoxalines **213** – **247**.[51]

Compound	R^1	R^2	K_i /nmol litre^{-1} (% of substitution at 20 μmol litre^{-1})		
			A_1	A_{2a}	A_3
213	H	H	11.0 ± 0.9	49.0 ± 3.7	(36)
214	H	3-Me	20.0 ± 1.8	14.6 ± 1.2	28.5 ± 1.9
215	H	4-Me	19.5 ± 1.6	85.8 ± 7.4	48.3 ± 3.6
216	H	3-F	28.5 ± 2.2	72.0 ± 6.1	157 ± 11
217	H	4-OMe	312 ± 27	376 ± 30	45.3 ± 3.8
218	H	4-Cl	426 ± 38	(37)	329 ± 28
219	cyclo-C_6H_{11}	H	1.43 ± 0.1	1370 ± 118	506 ± 43
220	cyclo-C_6H_{11}	3-Me	4.2 ± 0.23	(41)	548 ± 43
221	cyclo-C_6H_{11}	3-F	4.9 ± 0.31	66.0 ± 5.2	44.2 ± 3.5
222	cyclo-C_6H_{11}	4-Cl	80.1 ± 7.1	(0)	56.1 ± 4.2
223	cyclo-C_5H_9	H	0.42 ± 0.03	986 ± 82	55.4 ± 4.2
224	cyclo-C_5H_9	3-Me	1.21 ± 0.10	1400 ± 125	27.5 ± 1.9
225	cyclo-C_5H_9	3-F	1.1 ± 0.09	148 ± 13.1	173 ± 14
226	Bn	H	55.0 ± 4.3	(59)	1700 ± 138
227	$Ph(CH_2)_2$	H	4.8 ± 0.30	(59)	201 ± 14
228	$Ph(CH_2)_3$	H	17.9 ± 1.4	(61)	40.9 ± 3.3
229	Ph_2CHCH_2	H	(54)	(50)	1020 ± 99
230	Ac	H	4.3 ± 0.38	(70)	2.0 ± 0.13
231	EtC(O)	H	9.3 ± 0.79	2818 ± 199	15.8 ± 1.2
232	Bz	H	89.6 ± 7.2	(53)	1.47 ± 0.11
233	BnC(O)	H	6.3 ± 0.48	(62)	3.75 ± 0.20
234	PhNHC(O)	H	50.8 ± 4.2	2300 ± 219	276 ± 21
235	4-$MeOC_6H_4NHC(O)$	H	2600 ± 229	2800 ± 240	960 ± 86
236	H	H	515 ± 43	(64)	80.0 ± 6.3
237	H	3-Me	436 ± 36	(5)	91.0 ± 7.8
238	H	4-Me	155 ± 11	(0)	25.0 ± 1.6
239	H	3-F	200 ± 17	(20)	63.0 ± 4.5
240	H	4-OMe	934 ± 85	(0)	16 ± 1.2
241	H	4-Cl	1015 ± 97	(5.5)	114 ± 9.7
242			(48)	(18)	197 ± 14.2
243	Me	H	309 ± 2.5	(53)	36.6 ± 2.5
244	Me	4-Me	(22)	(0)	504 ± 43
245	Me	4-Cl	(29)	(8)	137 ± 11.8
246	Pr^n	H	406 ± 36	(44)	1246 ± 110
247	$CH{\equiv}CCH_2$	H	2200 ± 140	(0)	479 ± 34

the presence of the second substituent, especially the methyl group, in the side chain also enhances this effect (compound **269**). However, the activity decreases if the trifluoromethyl rather than methyl group is present (compound **275**). Aromatic derivatives **282**, **283** were shown to be completely devoid of activity towards the A_{2a} receptor (Table 12).

In addition, it has been noted that propargyl alcohols **284** – **286** with cycloalkyl substituents exhibit activity comparable with that of acyclic derivatives (Table 12). At the same time, tests of compounds **287** – **294** without hydroxy group in the side chain (Table 13) have shown that the

Structures 269 – 286

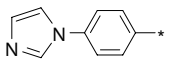
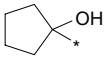
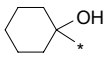
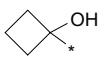


269 – 286

Table 11. Structure – activity relationship for triazoloquinoxalines **248** – **268**.[52]

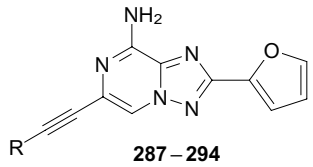
Compound	R^1	R^2	K_i/nmol litre^{-1} (% of substitution at 20 μmol litre^{-1})		
			A_1	A_{2a}	A_3
248	BnNH	H	730 ± 75.1	6.5 ± 0.7	(30)
249	2-$FC_6H_4CH_2NH$	H	93.9 ± 8.8	152 ± 16.4	(31)
250	4-$FC_6H_4CH_2NH$	H	37 ± 3.9	74 ± 6.9	750 ± 76.8
251	2-$MeOC_6H_4CH_2NH$	H	365 ± 39.2	42.5 ± 3.9	830 ± 81.1
252	2-$HOC_6H_4CH_2NH$	H	650 ± 55.4	49.7 ± 5.2	(23.9)
253	4-$ClC_6H_4CH_2NH$	H	(74)	229 ± 23.5	(44)
254	3-$HO_2CC_6H_4CH_2NH$	H	92 ± 7.8	15.2 ± 1.6	817 ± 79.6
255	4-$MeO_2CC_6H_4CH_2NH$	H	627 ± 59.4	74 ± 6.6	(52)
256	4-$HO_2CC_6H_4CH_2NH$	H	94 ± 8.3	22 ± 1.9	(41)
257	2-$FuCH_2NH$	H	189.4 ± 22.4	8.66 ± 0.9	(6)
258	2-(5-Methylfuryl)CH_2NH	H	281 ± 27.2	22 ± 2.4	(50)
259	3-$FuCH_2NH$	H	90 ± 8.5	15 ± 1.4	327 ± 29.4
260	2-$ThCH_2NH$	H	171 ± 15.9	18.6 ± 1.7	(37)
261	3-$ThCH_2NH$	H	259 ± 16.2	10 ± 1.9	(31.5)
262	3-$PyCH_2NH$	H	124 ± 10.5	26 ± 1.9	(40.8)
263	4-$PyCH_2NH$	H	3260 ± 343	65.2 ± 7.2	(38.7)
264	1-Oxo-2-benzofuran-3-ylamino	H	16 ± 1.5	31.5 ± 2.9	25 ± 2.2
265	$Ph(CH_2)_2NH$	H	116 ± 10.5	151 ± 13.9	(36)
266	4-$MeOC_6H_4(CH_2)_2NH$	H	204 ± 19.6	42.3 ± 5.1	(0)
267	H	$Ph(CH_2)_2NH$	9.4 ± 0.8	549 ± 48.6	62 ± 5.9
268	H	Bn_2N	56 ± 4.8	2086 ± 199	120 ± 11.4

Table 12. Structure – activity relationship for triazolo[1,5-*a*]pyrazines **269** – **286**.[53]

Compound	R^1	R^2	K_i/nmol litre^{-1}	
			A_{2a}	A_1
269	iso-C_5H_{11}	Me	3.79	24
270	Pr^i	Pr^i	7	8
271	Et	Et	9	33
272	H	H	> 500	> 500
273	Ph	Me	12	41
274	Ph	H	340	2400
275	Ph	F_3C	74	2200
276	4-$PyCH_2$	Me	1.1	100
277	4-Py	Me	25	170
278		Me	33	110
279	1-Benzothiophen-3-yl	Me	33	340
280	1-Benzothiophen-3-yl	H	260	73
281	4-HOC_6H_4	Me	42	66
282	4-$Me_2NC_6H_4$	F_3C	1100	–
283	2-F-3-$F_3CC_6H_3$	Me	1600	–
284		H	30	72
285		H	7.3	11
286		H	12	2.5

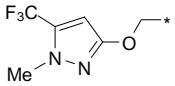
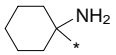
presence of oxygen atom (as an ether moiety) is crucial for the affinity for the A_{2a} receptor: compounds **293**, **294** demonstrated a considerable increase in the inhibitory constant against this type of AR.

Structures 287 – 294



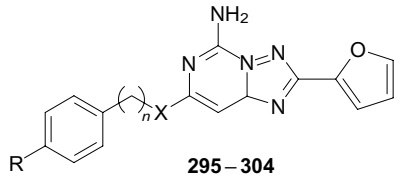
287 – 294

Table 13. Structure – activity relationship for triazolo[1,5-*a*]pyrazines **287** – **294**.[53]

Compound	R	K_i/nmol litre^{-1}	
		$A_{2б}$	A_1
287	$PhOCH_2$	390	530
288	3-Cl-4-$FC_6H_3OCH_2$	310	4300
289	3-$PyOCH_2$	92	110
290		89	1800
291	$Bu^tOCH(Me)$	37	96
292		210	35
293	2,4-$F_2C_6H_3$	> 1000	–
294	cyclo-$C_6H_{11}CH_2$	280	680

It has been demonstrated[54] that the activity of triazolo[1,5-*c*]pyrimidine analogues of ZM-241385 with various linkers **295** – **304** decreases with shortening of the alkyl chain of the linker (compound **300**) and increases with its elongation (**297**). In addition, the replacement of the

Structures 295–304



295–304

Table 14. Structure–activity relationship for triazolo[1,5-*c*]pyrimidines **295–304**.[54]

Compound	X	*n*	R	K_i/nmol litre^{-1}	
				A_{2a}	A_1
295	O	2	MeO	2.8	58
296	HN	2	MeO	5.8	20
297	MeN	2	MeO	1.8	473
298	S	2	MeO	1.6	58
299	H_2C	2	MeO	11.5	31
300	MeN	1	MeO	46.0	40
301	MeN	3	MeO	5.7	76
302	MeN	2	F	2.0	248
303	EtN	2	F	3.0	525
304	$MeO(CH_2)_2N$	2	F	1.0	566

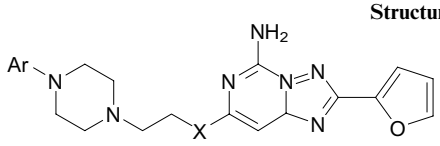
methoxy group (**295–301**) in the phenyl moiety by the fluorine atom (**302–304**) improves both the affinity for ARs and the selectivity (Table 14).

Compounds **305–318**, containing the piperazine moiety instead of the phenyl moiety in the side chain exhibit the inhibitory constant in the low nanomolar range and excellent selectivity, being in some cases up to three orders of magnitude (see derivatives **311**, **315**) (Table 15).

Another modification of piperazine derivatives was the substitution of various aromatic fragments for the furan ring at the C(2) atom of the heterocyclic system. In particular, the introduction of the 5-chlorofuran moiety into this position (compound **319**) led to a decrease in the affinity for the receptor as well as in the case of the unsubstituted benzene ring (**320**). However, in the case of substituted phenyl moieties (**321**, **322**) and other hetaryl derivatives (**323**, **324**), the resulting heterocycles exhibited activity in the low nanomolar concentration range and excellent selectivity (Table 16).

Attempts were made to enhance the affinity for the A_{2a} receptor and improve the selectivity as compared with initial compound **325**.[55] However, for none of derivatives

Structures 305–318



305–318

Table 15. Structure–activity relationship for triazolo[1,5-*c*]pyrimidines **305–318**.[54]

Compound	X	Ar	K_i/nmol litre^{-1}	
			A_{2a}	A_1
305	O	2,4-$F_2C_6H_3$	6.0	1650.0
306	O	4-$MeO(CH_2)_2OC_6H_4$	2.8	1134.0
307	S	2,4-$F_2C_6H_3$	1.4	511.0
308	S	4-$MeO(CH_2)_2OC_6H_4$	1.5	1447.5
309	HN	2,4-$F_2C_6H_3$	1.5	393.0
310	HN	4-$MeO(CH_2)_2OC_6H_4$	9.5	1377.5
311	MeN	2,4-$F_2C_6H_3$	1.0	1580.0
312	MeN	4-$MeO(CH_2)_2OC_6H_4$	2.5	1735.0
313	EtN	2,4-$F_2C_6H_3$	0.9	280.8
314	EtN	4-$MeO(CH_2)_2OC_6H_4$	1.5	153.0
315	$MeO(CH_2)_2N$	2,4-$F_2C_6H_3$	0.5	529.5
316	$MeO(CH_2)_2N$	4-$MeO(CH_2)_2OC_6H_4$	0.7	236.6
317	cyclo-$C_3H_5CH_2N$	2,4-$F_2C_6H_3$	0.3	249.3
318	cyclo-$C_3H_5CH_2N$	4-$MeO(CH_2)_2OC_6H_4$	0.8	187.2

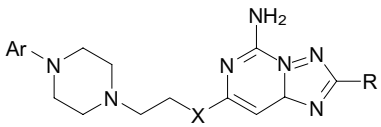
326–330, even for the most promising structure **330**, these characteristics significantly increased.

Virtual screening[56] made it possible to select compounds that do not contain undesirable units, such as a readily metabolized furyl moiety. For example, tetrahydrotriazolo-[1,5-*a*]pyrimidine **331** exhibited only insignificant activity against the A_{2a} receptor [$pK_i(A_{2a}) = 5.7$].

Thus, for triazolopyrimidines and their derivatives, the following trends in structure–activity relationships can be outlined:

— generally, triazolo[1,5-*c*]pyrimidines are slightly more active against the A_{2a} receptor than triazolo[1,5-*a*]pyrimidines and triazoloquinazolines;

Structures 319–324

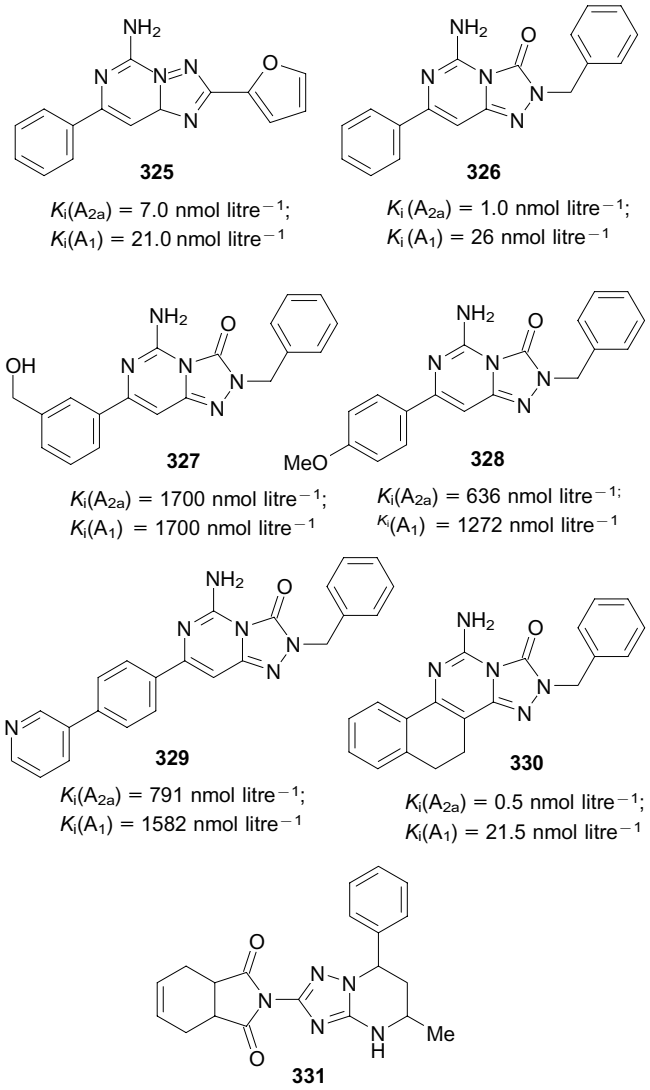


319–324

Table 16. Structure–activity relationship for triazolo[1,5-*c*]pyrimidines **319–324**.[54]

Compound	X	Ar	R	K_i/nmol litre^{-1}	
				A_{2a}	A_1
319	O	4-$MeO(CH_2)_2OC_6H_4$	5-Chlorofuran-2-yl	40	1600
320	MeN	4-$MeO(CH_2)_2OC_6H_4$	Ph	25	1400
321	MeN	2,4-$F_2C_6H_3$	2-NCC_6H_4	1.8	1116
322	MeN	4-$MeO(CH_2)_2OC_6H_4$	2-NCC_6H_4	0.7	749.7
323	MeN	2,4-$F_2C_6H_3$	Oxazol-2-yl	0.3	2100
324	MeN	2,4-$F_2C_6H_3$	3-Methylpyrazin-2-yl	0.3	2210

Structures 325 – 331



— 2-furyl substituent in triazolo[1,5-*a*]- and triazolo[1,5-*c*]pyrimidines plays a key role for the manifestation of high affinity for the receptor: series of compounds without furyl moiety (**112** – **136**, **143** – **148**) exhibited considerably higher inhibitory constants against the A_{2a}-receptor;

— by contrast, in the triazoloquinazoline series, the furyl moiety can be replaced by an aromatic residue without the decrease in affinity for the receptor; in particular, compound **248** exhibited activity in a low nanomolar concentration range with excellent selectivity;

— the presence of the amino group in the 5-position of the heterocyclic core has also a significant effect on the affinity for the receptor: compounds **236** – **247** with the carbonyl group in this position do not interact with the A_{2a} receptor;

— compounds with free amino group in the 5-position, as a rule, exhibit higher selectivity than the structures with the 5-acylamino moiety;

— the most promising linker group in triazolopyrimidines is 2-(4-arylpiperazino)ethyl moiety bound to the hetero atom (X). In particular, compounds **322** – **324** have affinity for the A_{2a} receptor in a low nanomolar concentration range at a selectivity of 3 – 4 orders of magnitude.

2.2. Triazolotriazines

As mentioned above, one of the most promising AR antagonists is triazolotriazine ZM-241385, which shows high affinity for the A_{2a} receptor (K_i = 0.95 nmol litre^{-1}) and good selectivity: 1000 for the A_1 receptor, 91 for A_{2b}, 500 000 for A_3. One of the key disadvantages of this candidate for use as a drug is low biological activity at oral administration. In addition, α-unsubstituted furyl moiety can be metabolically oxidized to highly reactive aldehydes, which is undoubtedly responsible for the increase in toxicity of the drug. On this basis, many research teams have attempted to modify the triazolotriazine structure, retaining a high affinity for the receptor and selectivity, but at the same time eliminating the inherent disadvantages of ZM-241385.

In one of the early studies,[41] the authors replaced the phenyl moiety in the ZM-241385 structure with the piperazine one, varying the methylene chain length and aromatic substituents at the nitrogen atom in the piperazine ring (compounds **332** – **339**). It has been shown that a two-carbon chain is more preferable than a three-carbon one for the inhibitory activity against the A_{2a} receptor. In addition, the presence of the 2,4-disubstituted phenyl moiety leads to a higher affinity for this receptor and better selectivity than those of the corresponding 2,4,6-trisubstituted analogues. At the same time, methylation of the secondary amino group associated with the triazolotriazine system results in a two-fold decrease in the inhibitory constant and an increase in the selectivity for the A_1 receptor by 2 – 3 times (compounds **338**, **339**) (Table 17).

It has been demonstrated[35] that compounds **340** – **347** with the N-substituted pyrrole moiety exhibit moderate activity towards the A_{2a} receptor, but low selectivity (Table 18).

It was postulated in 2000[43] that the key stage in the metabolic cleavage of ZM-241385 and similar structures is N-dealkylation, which also affects the low biological activity at oral administration of compounds **348**, **349**.

Structures 332 – 339

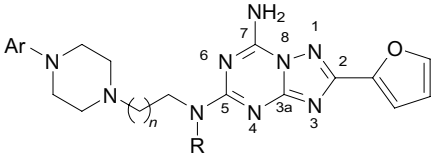
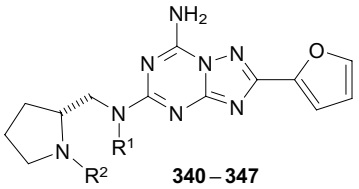


Table 17. Structure – activity relationship for ZM-241385 analogues — compounds **332** – **339**.[41]

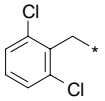
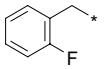
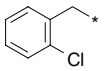
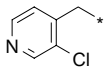
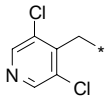
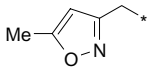
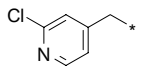
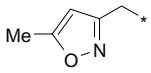
Compound	Ar	*n*	R	K_i/nmol litre^{-1}	
				A_{2a}	A_1
332	Ph	1	H	22	> 500
333	Ph	2	H	190	> 500
334	2,4,6-$F_3C_6H_2$	1	H	24	> 500
335	2,4,6-$F_3C_6H_2$	2	H	100	> 500
336	2,4-$F_2C_6H_3$	1	H	7.1	1100
337	2,4-$F_2C_6H_3$	2	H	93	> 500
338	Ph	1	Me	11	1500
339	2,4-$F_2C_6H_3$	1	Me	4.0	820

Structures 340–347



340–347

Table 18. Structure–activity relationship for ZM-241385 analogues — compounds **340**–**347**.[35]

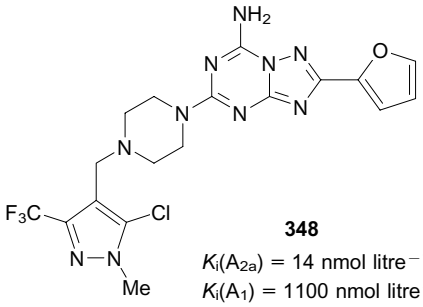
Compound	R^1	R^2	K_i/nmol litre^{-1}	
			A_{2a}	A_1
340	H		18	> 250
341	H		6	> 250
342	H		39	> 250
343	H		37	> 250
344	H		60	> 250
345	H		25	> 250
346	H		4	> 250
347	Me		12	> 250

To eliminate this drawback, a number of systems with an unsubstituted piperazine ring (**350**) and bicyclic piperazine moieties were synthesized. Compounds **351**–**359**, in addition to the absence of possibility of dealkylation, should retain their spatial configuration, which, according to the authors,[43] often correlates with increased activity at oral administration (Table 19).

Based on the data obtained, the researchers noted that the spatial structure of the piperazine substituent affects the affinity for the receptor and selectivity, since the difference in these parameters for *cis* and *trans* isomers is obvious (see Table 19). Developing this assumption, the authors noticed that, in the series of heterocycles **360**–**362**, the 7-*cis* derivatives were more selective and had a higher affinity for the receptor than the 7-*trans* and 6-*cis* isomers. In addition, fluorinated phenyl moieties R proved to be more preferable than their analogues containing the methoxy group.

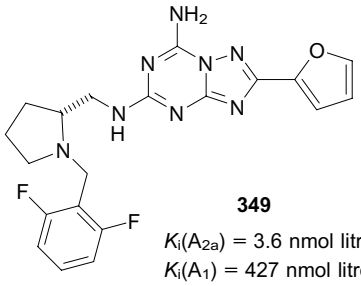
Among compounds **363**, monosubstituted amines (R^1 or R^2 = H) are superior to disubstituted amines (R^1, $R^2 \neq$ H) in the A_{2a} receptor affinity. In the case of disubstituted amines, the inhibitory constant was reduced by introducing polar fragments, such as pyrazole or furfuryl, to this nitrogen atom.

Structures 348–359



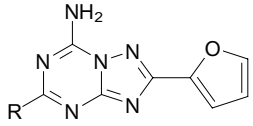
348

$K_i(A_{2a})$ = 14 nmol litre^{-1};
$K_i(A_1)$ = 1100 nmol litre^{-1}



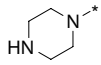
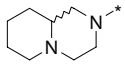
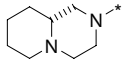
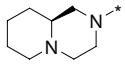
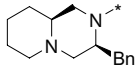
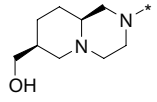
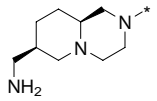
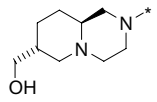
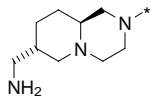
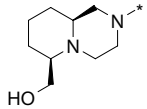
349

$K_i(A_{2a})$ = 3.6 nmol litre^{-1};
$K_i(A_1)$ = 427 nmol litre^{-1}

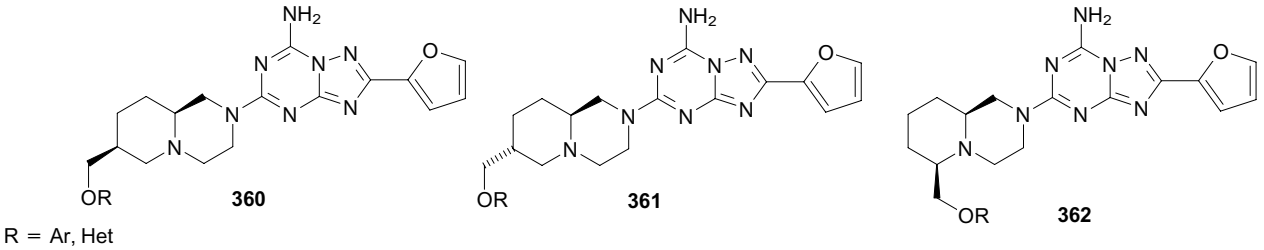


350–359

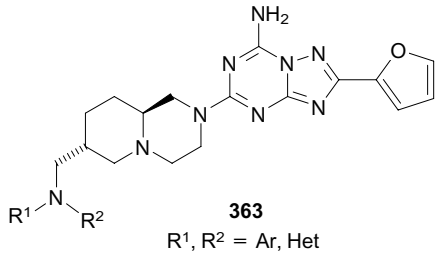
Table 19. Structure–activity relationship for ZM-241385 analogues — compounds **350**–**359**.[43]

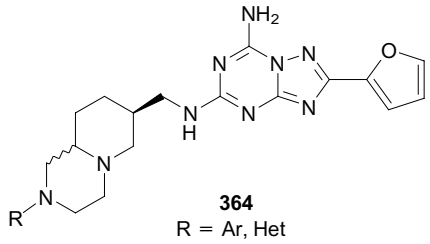
Compound	R	K_i/nmol litre^{-1}	
		A_{2a}	A_1
350		> 5000	–
351		12	860
352		30	1200
353		46	> 500
354		490	> 1000
355		45	660
356		16	> 500
357		71	6100
358		2	3500
359		3	1300

Structures 360 – 362



Structures 363, 364

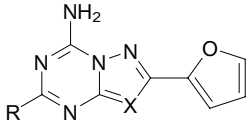




Among structures **364**, the *cis*-piperazines were also superior to the *trans* isomers in inhibitory constants for the A_{2a} receptor.[43] In addition, it was noted that the 3,5-difluorophenyl derivative is more preferable that the 2,4-disubstituted analogue for the manifestation of the A_{2a} receptor affinity.

An alternative series of ZM-241385 analogues (compounds **365** – **382**) have been synthesized and bioassayed (Table 20).[57]

Structures 365 – 382



365 – 382

In particular, heterocycle **368**, in which there is no hydroxy function, showed a 40-fold increase in affinity for the A_1 receptor compared to ZM-241385, while the affinity for the A_{2a} receptor remained nearly the same. From this fact it can be concluded that the selectivity of ZM-241385 is based precisely on the presence of phenol hydroxy group in the molecule. Among benzyl derivatives, the best result was shown by the 3-chloro derivative **373** with an inhibitory constant against the A_{2a} receptor of 5.5 nmol litre^{-1}; however, this compound was devoid of selectivity. At the same time, for heterocyclic compound **380** with the tertiary amino group, a reduced affinity for all types of ARs was observed. In addition, the pyrazolotriazine structure **366** demonstrated a decrease in A_{2a} affinity and an increase in activity

Table 20. Structure – activity relationship for ZM-241385 analogues — compounds **365** – **382**.[57]

Compound	R	X	K_i/nmol litre^{-1} (% of inhibition at 1 μmol litre^{-1})			
			A_1	A_{2a}	A_{2b}	A_3
365	4-$HOC_6H_4(CH_2)_2NH$	N	257 ± 88	1.78 ± 0.52	16.5 ± 2.9	3090 ± 1170
366	4-$HOC_6H_4(CH_2)_2NH$	CH	56.4 ± 7.7	9.3 ± 2.7	31 ± 13	464 ± 168
367	MeS	N	266 ± 26	99 ± 26	65 ± 8	(21)
368	$Ph(CH_2)_2NH$	N	7.1 ± 2.9	5.4 ± 1.2	9.9 ± 4.4	1450 ± 580
369	BnNH	N	13 ± 5	13 ± 5	7.6 ± 2.7	207 ± 13
370	PhNH	N	23 ± 8	3.0 ± 0.5	33 ± 6	376 ± 56
371	$Ph(CH_2)_3NH$	N	36 ± 12	37.3 ± 12	284 ± 89	(42)
372	4-$ClC_6H_4CH_2NH$	N	31.6 ± 5.7	34 ± 14	159 ± 60	500 ± 24
373	3-$ClC_6H_4CH_2NH$	N	5.9 ± 0.3	5.5 ± 1.3	23.6 ± 11	131 ± 18
374	3,4-$Cl_2C_6H_3CH_2NH$	N	25.1 ± 7.6	15.7 ± 3.4	326 ± 146	272 ± 23
375	4-$MeOC_6H_4CH_2NH$	N	78.7 ± 15	78.5 ± 9.5	197 ± 23	(41)
376	4-$MeC_6H_4CH_2NH$	N	37.0 ± 10.2	25.5 ± 5.0	169 ± 81	327 ± 110
377	(*R*)-PhCHMeNH	N	40.3 ± 4.1	133 ± 41	1881 ± 101	59.2 ± 14.7
378	(*S*)- PhCHMeNH	N	50.8 ± 12	50.1 ± 10.6	182 ± 3	816 ± 92
379	Ph_2CHNH	N	3.6 ± 0.9	35.9 ± 11.5	> 10000	22.3 ± 7.4
380	BnNMe	N	83.8 ± 9.4	47.5 ± 13.4	118 ± 44	457 ± 41
381	PhNHNH	N	40 ± 18	7.7 ± 0.9	7.6 ± 46	(38)
382	cyclo-$C_6H_{11}CH_2NH$	N	2.8 ± 1.1	6.0 ± 0.7	35.5 ± 12	783 ± 214

for the A_1 receptor, indicating an important contribution of one of the triazole nitrogen atoms to the binding to the A_{2a} receptor.

ZM-241385 analogues with the piperazine moiety as the linker group — compounds **383**–**398** — have been synthesized and studied (Table 21).[22]

It has been noted that the increase in the electron-withdrawing properties of substituents in the phenyl ring is favourable for the enhancement of affinity for the A_{2a} receptor. In particular, trifluorobenzyl derivative **398** turned out to be more active than trichlorobenzyl analogue **393**, which was superior to monochlorinated derivative **391** in affinity for the A_{2a} receptor.

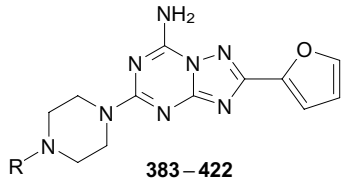
Derivatives **399**–**422** with unsaturated heterocyclic moieties in the side chain inhibited the A_{2a} receptor in the nanomolar concentration range at satisfactory selectivity (Table 22).[22]

A wide spectrum of structures **423**–**440**, which contained the triazolotriazine ring and the oxazole moiety linked by various diamino bridges, have been studied (Table 23).[58]

According to testing results, compound **437**, bearing the pyrrolidine moiety, proved to be the most promising one.

Optimization of a series of ZM-241385 analogues with N-substituted pyrrolidine rings in the side chain led to derivatives **441**–**472**, which had the inhibitory constant for ARs in a low nanomolar concentration range (Table 24). The increase in the electron-withdrawing ability of substituents in the benzyl moiety bonded to the pyrrolidine ring enhanced the affinity for the A_{2a} receptor. The replacement of the aromatic ring by a heteroaromatic ring was also

Structures 383–422

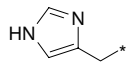
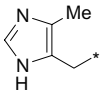
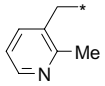
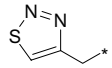
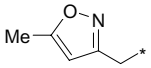
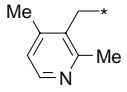
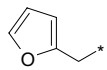
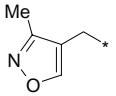
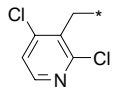
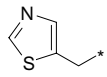
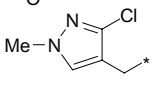
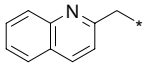
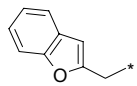
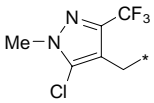
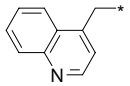
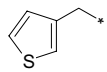
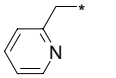
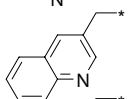
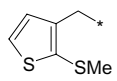
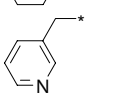
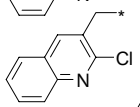
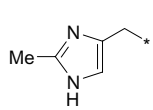
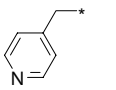
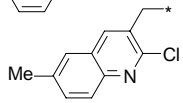


383–422

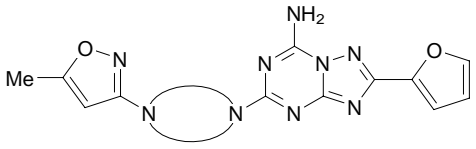
Table 21. Structure–activity for ZM-241385 analogues — **383**–**398**.[22]

Compound	R	K_i /nmol litre^{-1}	
		A_{2a}	A_1
383	H	> 5000	–
384	Ph	190	> 500
385	Bn	140	> 500
386	$Ph(CH_2)_2$	1500	> 500
387	$Ph(CH_2)_3$	1300	> 500
388	2-$MeOC_6H_4CH_2$	360	> 500
389	2-$ClC_6H_4CH_2$	180	> 500
390	3-$ClC_6H_4CH_2$	1200	> 500
391	4-$ClC_6H_4CH_2$	1100	> 500
392	2,6-$Cl_2C_6H_3CH_2$	114	4500
393	2,5,6-$Cl_3C_6H_2CH_2$	18	840
394	2,6-$F_2C_6H_3CH_2$	16	> 500
395	2,5,6-$F_3C_6H_2CH_2$	10	1500
396	2,6-F_2-5-$ClC_6H_2CH_2$	30	1300
397	2-Cl-5,6-$F_2C_6H_2CH_2$	5	500
398	2,4,6-$F_3C_6H_2CH_2$	3	1300

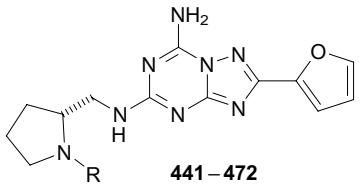
Table 22. Structure–activity relationship for ZM-241385 analogues — compounds **399**–**422**.[22]

Compound	R	K_i /nmol litre^{-1}		Compound	R	K_i /nmol litre^{-1}		Compound	R	K_i /nmol litre^{-1}	
		A_{2a}	A_1			A_{2a}	A_1			A_{2a}	A_1
399		320	> 500	**407**		130	> 500	**415**		48	> 500
400		96	> 500	**408**		180	> 500	**416**		36	> 500
401		47	> 500	**409**		18	2900	**417**		2	670
402		54	720	**410**		58	420	**418**		73	> 500
403		74	650	**411**		14	1100	**419**		85	7400
404		75	–	**412**		110	2700	**420**		57	670
405		35	–	**413**		290	> 500	**421**		5	250
406		220	> 500	**414**		140	> 500	**422**		12	360

Structures 423–472



423–440



441–472

possible since derivatives **461–472** exhibited the inhibitory constant in the same range.

Studying the effect of substituents in the 5-position of the triazolotriazine system and the nature of substituents in the amino group on the affinity for all four types of ARs among structural analogues of ZM-241385 — compounds **473–493** — demonstrated that derivatives with a free amino group had higher affinity for the A_{2a} receptor than acylated analogues, except heterocycle **486**, which had the inhibitory constant of 38.9 nmol litre^{-1} at good selectivity for the other types of ARs.[59] The presence of the methylsulfanyl or phenoxy group at the C(5) was found to enhance the A_{2a} affinity at good selectivity, while the dimethylamino group in this position reduced the inhibitory properties against all four types of ARs (Table 25).

Later, the same research team[60] extended the range of derivatives (Table 26). All compounds **494–530** appeared to be inactive against the A_3 receptor, except two derivatives with inhibitory constants ~1 μmol litre^{-1}. An analogous situation was also observed for the A_{2b} receptor. At the same time, the affinity for the A_{2a} receptor was satisfactory

Table 23. Structure–activity relationship for ZM-241385 analogues — compounds **423–440**.[58]

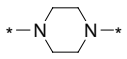
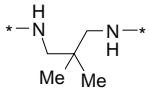
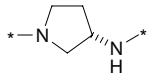
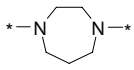
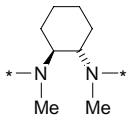
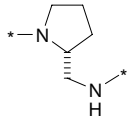
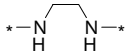
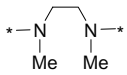
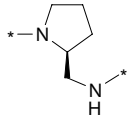
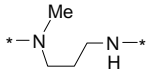
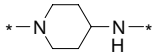
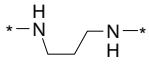
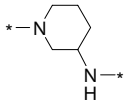
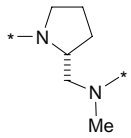
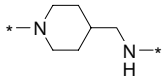
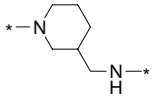
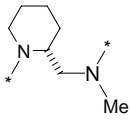
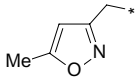
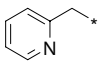
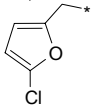
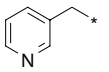
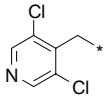
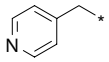
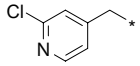
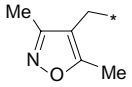
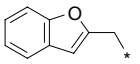
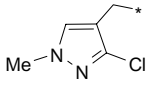
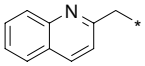
Compound	N⊃N	$K_i(A_{2a})$ /nmol litre^{-1}	Compound	N⊃N	$K_i(A_{2a})$ /nmol litre^{-1}	Compound	N⊃N	$K_i(A_{2a})$ /nmol litre^{-1}
423		180	**430**		>1000	**436**		>500
424		52	**431**		>1000	**437**		25
425		200						
426		130	**432**		>1000	**438**		64
427		79	**433**		270			
428		>1000	**434**		680	**439**		12
429		560	**435**		150	**440**		14

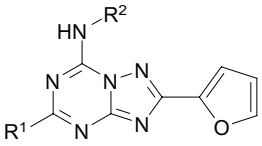
Table 24. Structure–activity relationship for ZM-241385 analogues — compounds **441–472**.[58]

Compound	R	K_i /nmol litre^{-1}		Compound	R	K_i /nmol litre^{-1}	
		A_{2a}	A_1			A_{2a}	A_1
441	2-$ClC_6H_4CH_2$	39	>250	**451**	2,3-$F_2C_6H_3CH_2$	5	>250
442	3-$ClC_6H_4CH_2$	14	>250	**452**	2-F-3-$ClC_6H_3CH_2$	7	>250
443	4-$ClC_6H_4CH_2$	39	>25	**453**	2,6-$F_2C_6H_3CH_2$	4	430
444	3,5-$Cl_2C_6H_3CH_2$	57	>250	**454**	2,4,5- $F_3C_6H_2CH_2$	8	>250
445	2,4-$Cl_2C_6H_3CH_2$	11	1700	**455**	2,3,6-$F_3C_6H_2CH_2$	4	>250
446	3-$MeC_6H_4CH_2$	30	>250	**456**	2,4,6-$F_3C_6H_2CH_2$	2	800
447	3-$FC_6H_4CH_2$	25	>250	**457**	2-F-5-$F_3CC_6H_3CH_2$	4	>250
448	3,5-$F_2C_6H_3CH_2$	36	>250	**458**	2-F-4-$F_3CC_6H_3CH_2$	5	>250
449	2,5-$F_2C_6H_3CH_2$	30	>250	**459**	2-Cl-3,6-$F_2C_6H_2CH_2$	4	>250
450	2,4-$F_2C_6H_3CH_2$	14	1000	**460**	2-F_3C-5-Cl-6-$FC_6H_2CH_2$	8	>250

Table 24 (continued).

Compound	R	K_i /nmol litre^{-1}		Compound	R	K_i /nmol litre^{-1}	
		A_{2a}	A_1			A_{2a}	A_1
461		25	> 250	**467**		18	> 250
462		15	> 250	**468**		3	> 250
463		7	> 250	**469**		22	> 250
464		37	> 250	**470**		4	> 250
465		516	> 250	**471**		12	> 250
466		7	> 250	**472**		17	> 250

Structures 473–530



473–530

with different selectivities for the A_1 receptor. In particular, the introduction of the amino or mono-Boc-diamino group (Boc is *tert*-butoxycarbonyl) into the 5-position of the heterocycle led to compounds with inhibitory constants for the A_{2a} receptor in the range of 18–70 nmol litre^{-1} and different selectivies for the A_1 receptor. In particular, compound **495** with the pyrrolidine ring at the C(5) atom exhibited a satisfactory affinity for the A_{2a} receptor (K_i = 59.1 nmol litre^{-1}), but low selectivity (by a factor of 33) for

Table 25. Structure–activity relationship for ZM-241385 analogues — compounds **473**–**493**.[59]

Compound	R^1	R^2	K_i /nmol litre^{-1} (% of inhibition at 10 μmol litre^{-1})			$EC_{50}(A_{2b})$ (see [a])
			A_1	A_{2a}	A_3	
473	PhO	H	2720 ± 680	18.3 ± 3.4	489 ± 63	3420 ± 200
474	MeS	H	1730 ± 360	96.5 ± 36.1	2580 ± 780	14 900 ± 1700
475	Me_2N	H	31 400 ± 8000	3800 ± 1230	7270 ± 2230	33 700 ± 1800
476	MeS	$Ph_2CHC(O)$	557 ± 205	> 10 000	170 ± 45	> 100 000
477	MeS	BnC(O)	1420 ± 260	429 ± 38	4200 ± 950	> 100 000
478	MeS	4-$MeOC_6H_4CH_2C(O)$	5000 ± 1170	1570 ± 660	2100 ± 400	42 400 ± 9900
479	MeS	n-$C_5H_{11}C(O)$	1520 ± 170	427 ± 96	(24 ± 3)	> 100 000
480	MeS	PhNHC(O)	10 000 ± 2900	1660 ± 1120	414 ± 29	17 100 ± 2700
481	MeS	4-$MeC_6H_4NHC(O)$	3440 ± 690	742 ± 194	2200 ± 54	16 800 ± 3100
482	PhO	$Ph_2CHC(O)$	(< 10)	1880 ± 310	4400 ± 1150	> 100 000
483	PhO	BnC(O)	7260 ± 2820	136 ± 48	1020 ± 173	> 100 000
484	PhO	4-$MeOC_6H_4CH_2C(O)$	(12 ± 2)	892 ± 252	5200 ± 1300	> 100 000
485	PhO	n-$C_5H_{11}C(O)$	2900 ± 710	189 ± 26	2200 ± 470	> 100 000
486	PhO	PhNHC(O)	(17 ± 5)	38.9 ± 3.5	633 ± 37	8870 ± 1680
487	PhO	4-$MeC_6H_4NHC(O)$	(35 ± 5)	214 ± 72	750 ± 130	20 000 ± 3600
488	Me_2N	$Ph_2CHC(O)$	951 ± 88	4090 ± 1360	473 ± 85	> 100 000
489	Me_2N	BnC(O)	6080 ± 1040	6700 ± 3200	1050 ± 466	> 100 000
490	Me_2N	4-$MeOC_6H_4CH_2C(O)$	8740 ± 590	10300 ± 1300	2700 ± 345	> 100 000
491	Me_2N	n-$C_5H_{11}C(O)$	1570 ± 380	> 100 000	2200 ± 370	> 100 000
492	Me_2N	PhNHC(O)	3150 ± 550	580 ±100	311 ± 122	> 100 000
493	Me_2N	4-$MeC_6H_4NHC(O)$	2720 ± 830	2720 ± 2090	9600 ± 1200	> 100 000

[a] Half maximal inhibitory concentration is given /nmol litre^{-1}.

Table 26. Structure–activity relationship for ZM-241385 analogues — compounds **494**–**530**.[60]

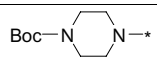
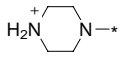
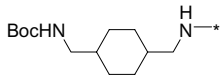
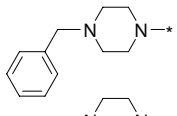
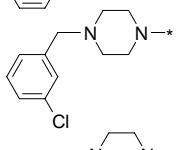
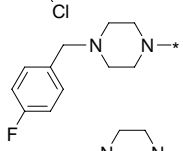
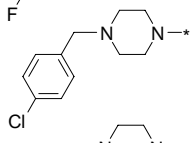
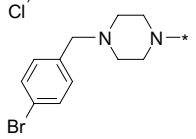
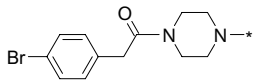
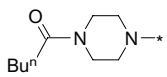
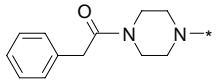
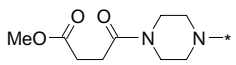
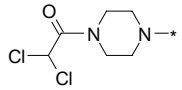
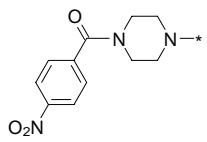
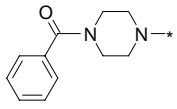
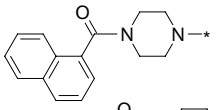
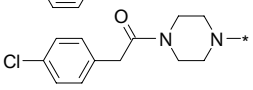
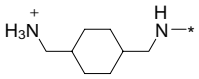
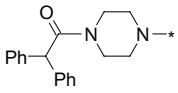
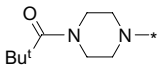
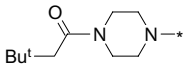
Compound	R^1	R^2	K_i/nmol litre^{-1} (% of substitution at 10 μmol litre^{-1})			$IC_{50}(A_{2b})$ (see [a])
			A_1	A_{2a}	A_3	
494		H	5400 ± 500	21 ± 4.5	(56.6 ± 1.3)	> 10 000
495	Pyrrolidino	H	1940 ± 70	59.1 ± 13.7	(75.0 ± 4.7)	> 30 000
496		H	(28.6 ± 6.0)	153 ± 32	29.9 ± 0.4	> 30 000
497	$BocNH(CH_2)_2NH$	$BocNH(CH_2)_2$	7.4 ± 4.5%	4360 ± 1670	8490 ± 4810	> 30 000
498	$BocNH(CH_2)_2NH$	H	3730 ± 740	40.9 ± 5.7	1490 ± 480	> 100 000
499		H	3890 ± 560	69.7 ± 12.7	75.5 ± 0.3	> 10 000
500	$BocNH(CH_2)_3NH$	H	344 ± 16	38.6 ± 11.5	(77.3 ± 0.3)	7140 ± 2960
501	$BocNH(CH_2)_5NH$	H	963 ± 139	44.7 ± 9.9	(68.6 ± 0.9)	20 600 ± 1100
502	$BocNH(CH_2)_2(CH_2CH_2O)_2NH$	H	1580 ± 100	17.8 ± 6.7	(74.0 ± 0.8)	> 10 000
503		H	978±146	20.6±14.5	(71.9 ± 0.7)	> 10 000
504		H	1510 ± 500	51.8 ± 23.0	(52.7 ± 1.2)	> 30 000
505		H	655±100	52.3±32.3	(71.3 ± 1.9)	> 30 000
506		H	220 ± 88	102 ± 108	(66.8 ± 6.0)	> 10 000
507		H	86.7 ± 22.6	27.3 ± 18.0	(49.8 ± 0.8)	> 30 000
508	$^+NH_3(CH_2)_2(CH_2CH_2O)_2NH$	H	769 ± 308	11.5 ± 2.2	(59.2 ± 2.6)	> 10 000
509		H	1010 ± 150	86.2 ± 41.4	3100 ± 1100	> 10 000
510		H	10.8 ± 5.3%	124 ± 50	(56.2 ± 8.1)	> 30 000
511		H	3510 ± 220	94.8 ± 40.7	(64.5 ± 1.8)	> 100 000
512		H	19.4 ± 2.5	66.2 ± 10.4	(37.2 ± 6.6)	> 100 000
513		H	34.6 ± 1.5	282 ± 164	(33.6 ± 0.7)	> 100 000
514		H	(35.5 ± 7.4)	212 ± 49	(50.9 ± 6.9)	> 100 000
515		H	(27.7 ± 3.3)	348 ± 76	(22.6 ± 1.7)	> 100 000

Table 26 (continued).

Compound	R^1	R^2	K_i/nmol litre^{-1} (% of substitution at 10 μmol litre^{-1})			$IC_{50}(A_{2b})$ (see [a])
			A_1	A_{2a}	A_3	
516		H	(4.9 ± 0.8)	7680 ± 2190	(31.1 ± 8.4)	> 100 000
517		H	991 ± 226	39.1 ± 13.9	1260 ± 490	> 100 000
518	$^+NH_3(CH_2)_2NH$	$^+NH_3(CH_2)_2$	(10.7 ± 1.5)	38 200 ± 14 600	(17.7 ± 3.6)	> 100 000
519	$^+NH_3(CH_2)_2NH$	H	(35.8 ± 4.9)	567 ± 43	(30.8 ± 3.7)	> 100 000
520		H	1350 ± 70	16.9 ± 2.3	(72.8 ± 0.4)	10 700 ± 3700
521	$^+NH_3(CH_2)_3NH$	H	(44.3 ± 1.6)	270 ± 9	(40.5 ± 0.2)	> 30 000
522	$^+NH_3(CH_2)_5NH$	H	2950 ± 260	90.1 ± 15.9	(49.9 ± 3.5)	> 10 000
523		H	7470 ± 6820	92.9 ± 24.7	(40.6 ± 22.2)	> 100 000
524		H	38.7 ± 4.8	58.4 ± 18.9	(32.3 ± 3.37)	> 100 000
525		H	(53.1 ± 4.7)	11.1 ± 6.3	(41.9 ± 8.3)	> 100 000
526	PhO	Bz	(26.2 ± 5.5)	1000 ± 110	(32.3 ± 9.7)	> 10 000
527	HO	H	3110 ± 970	201 ± 61	(43.9 ± 6.0)	> 10 000
528	H_2N	H	1410 ± 80	160 ± 42	(36.4 ± 0.2)	11 100 ± 3900
529	HO	Bz	(34.4 ± 9.2)	1750 ± 390	(75.9 ± 1.2)	> 100 000
530	H_2N	Bz	1800 ± 150	44.1 ± 13.6	(67.2 ± 3.3)	7060 ± 2935

[a] Half maximal inhibitory concentration is given /nmol litre^{-1}.

the A_1 receptor. At the same time, the introduction of the Boc-piperidine (**494**) or Boc-ethylenediamine moiety (**498**) enhanced both the affinity for the A_{2a} receptor (two-fold) and selectivity (by an order of magnitude).

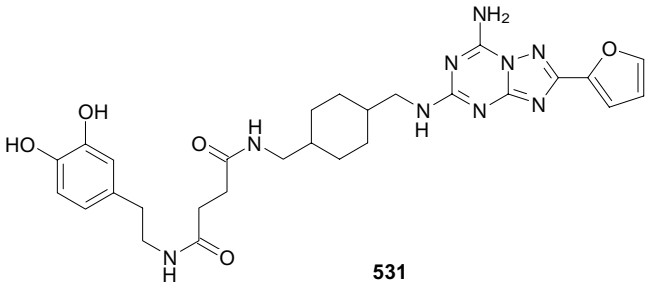
It should be noted that elongation of the side alkyl chain led to derivatives **500**, **501** with a high affinity for the A_{2a} receptor but low selectivity for the A_1 receptor. In addition, it turned out that trifluoroacetate salts **519**, **521**, **522**, were, as a rule, less active than the corresponding *tert*-butoxycarbonyl derivatives. The introduction of symmetric diamino moieties into the 5- and 7-positions of the heterocycle led to compounds completely inactive against all types of ARs, both in the protected form (**497**) and in the salt form (**518**).

A somewhat different situation is observed for derivatives with a piperazine moiety: in N-benzyl-substituted compounds **503**–**507**, the affinity for the A_{2a} receptor remained at a satisfactory level, while the affinity for the A_1 receptor increased, which points to a decrease in selectivity. At the same time, the introduction of the acyl group (compounds **509**–**517**) led to a considerable decrease in the A_{2a} affinity (K_i = 212–328 nmol litre^{-1}) and in selectivity [$K_i(A_1)/K_i(A_{2a})$ = 35–49]. The acylation of the piperazine moiety with 3,3-dimethylbutanoyl group made it possible to improve the affinity and selectivity: compound **525** showed excellent affinity for this receptor (K_i = 11.1 nmol litre^{-1}) and high selectivity [$K_i(A_1)/K_i(A_{2a})$ = 900]. At the same time, derivatives **526**–**530** with small substituents in the 5- and 7-positions exhibited weak affinity for the A_{2a} receptor and low selectivity.

Heterocyclic derivative **531** combines the key elements of the ZM-241385 structure and dopamine. This compound showed A_{2a} affinity in a low nanomolar concentration range (K_i = 2.07 ± 0.23 nmol litre^{-1}).[61]

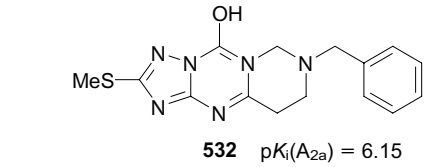
Previously,[55] virtual screening of a commercial vendor library discarded molecules with undesirable structural units (for example, furan ring). As a result, one structure

Structure 531

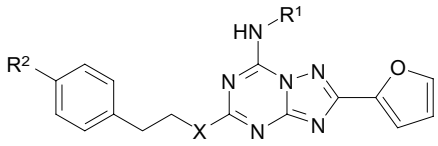


531

Structures 532–540

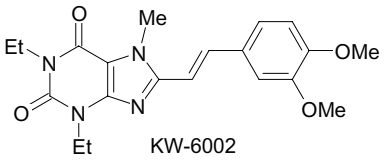


532 $pK_i(A_{2a}) = 6.15$



533–540

Structure KW-6002



KW-6002

of the triazolotriazine series (**532**) was selected with the inhibitory constant $K_i = 6$ μmol litre^{-1}.

Modification of the side amino moiety in ZM-241385, which is responsible for the activity of the compound in the extracellular space but should not deteriorate the receptor affinity, was studied, and the activity of the resulting compounds was compared with that of azolopyrimidine KW-6002 (Table 27).[62]

Table 27. Structure–activity relationship for compounds KW-6002 and **533–540**.[62]

Compound	X	R^1	R^2	$IC_{50}(A_{2a})$ /nmol litre^{-1}
KW-6002	—	—	—	5250
533	HN	H	Br	182
534	O	H	H	41
535	HN	H	$EtO_2C(CH_2)_3O$	50
536	HN	$EtO_2C(CH_2)_3$	HO	> 10 000
537	HN	$EtO_2C(CH_2)_3$	$EtO_2C(CH_2)_3O$	> 100 000
538	HN	H	AcO	39
539	HN	H	Pr^nCO_2	30
540	HN	H	n-$C_9H_{19}CO_2$	182

In the series of synthesized compounds **533–540**, the replacement of the phenol hydroxy group by a bromine atom (compound **533**) leads to the four-fold decrease in activity, presumably because of the large size of the bromine atom, while the replacement of a secondary amino group by an oxygen bridge gives compound **534** with a similar affinity for the A_{2a} receptor. It has been stated [62] that the protection of the phenol oxygen atom is a good option for placing the linker, since compounds **535**, **538**, **539** showed an activity comparable to that for ZM-241385 [$IC_{50}(A_{2a}) = 42$ nmol litre^{-1}], while N(7)-alkylated compounds **536**, **537** were inactive against this receptor. In addition, it was noted that the length of the methylene chain of the linker has little effect on the affinity for the receptor.

On the basis of the information presented in this Section, the following conclusions about the structure–activity relationship in the triazolotriazine series can be drawn:

— the presence of a furyl moiety attached to the triazole ring is essential for affinity for the A_{2a} receptor for triazolotriazines; for example, compound **532**, containing the methylsulfanyl group in the 2-position, exhibited the inhibitory constant exceeding that for the furyl analogues by three orders of magnitude;

— the presence of free 5-amino group also causes high activity against the A_{2a} receptor since for heterocycles **476–493** with protected amino group, the inhibitory constant increased;

— the most efficient structure of the linker group is a combination of the diamino and aromatic moieties.

3. Tricyclic nitrogen-containing heterocyclic systems

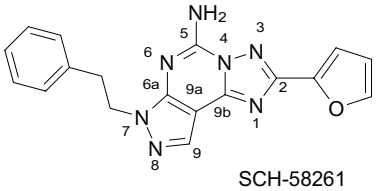
Currently, one of the most promising A_{2a} receptor inhibitors is 5-amino-7-(2-phenylethyl)-2-(2-furyl)pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine (SCH-58261), which has the inhibitory constant of 1.3 nmol litre^{-1} and high selectivity towards the other types of ARs [$K_i(A_1)/K_i(A_{2a}) = 323$, $K_i(A_{2b})/K_i(A_{2a}) = 53$, $K_i(A_3)/K_i(A_{2a}) = 100$]. The key feature of this structure responsible for the efficient binding to the receptor is a heterocyclic core and a furyl substituent in the triazole moiety.

In order to increase the affinity for the receptor and selectivity and improve other pharmacological characteristics of compound SCH-58261, a rather wide range of pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidines and similar structures was obtained.

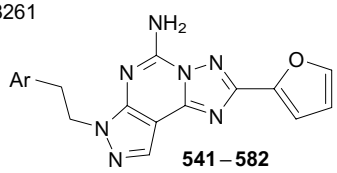
In particular, a series of SCH-58261 derivatives containing different nitrogen-containing heterocycles instead of the phenyl moiety have been synthesized and the affinity of compounds **541–565** for the A_{2a} receptor and selectivity $K_i(A_1)/K_i(A_{2a})$ have been evaluated (Table 28).[63] The inhibitory constant for the A_{2a} receptor in this series of compounds is in the nanomolar range at good selectivity. Nevertheless, none of these compounds was superior to the initial compound SCH-58261 in the combination of affinity–selectivity properties.

A series of SCH-58261 analogues containing biphenyl moieties and their aza analogues as well as quinolines **566–582** have been described (Table 29).[64] Some of these derivatives (**568**, **578**, **580**, **581**) exhibited considerably

Structures SCH-58261, 541–582

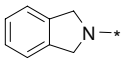
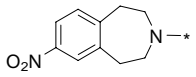
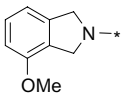
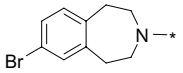
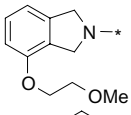
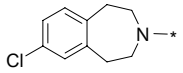
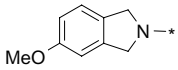
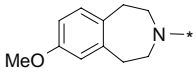
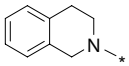
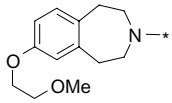
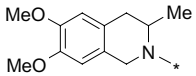
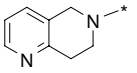
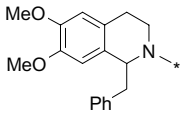
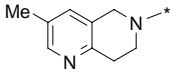
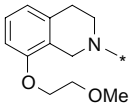
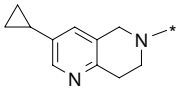
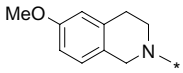
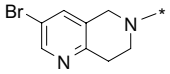
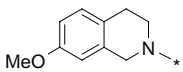
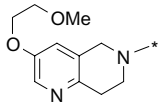
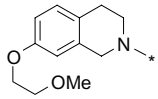
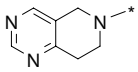
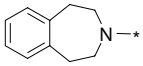
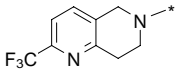
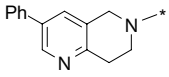


SCH-58261



541–582

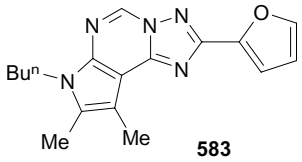
Table 28. Structure–activity relationship for SCH-58261 analogues — compounds **541**–**565**.[63]

Compound	Ar	K_i/nmol litre^{-1}		Compound	Ar	K_i/nmol litre^{-1}	
		A_{2a}	A_1			A_{2a}	A_1
541		14.7	1705.2	**553**		0.7	49.7
542		6.0	630.0	**554**		1.1	68.2
543		7.1	745.5	**555**		3.3	108.9
544		5.4	680.4	**556**		1.9	879.7
545		4.1	385.4	**557**		2.0	612.0
546		1.9	283.1	**558**		4.8	307.2
547		2.3	335.8	**559**		2.0	358.0
548		1.5	469.5	**560**		1.9	100.7
549		2.5	170.0	**561**		1.6	97.6
550		3.2	192.0	**562**		3.1	254.2
551		5.1	285.6	**563**		6.2	142.6
552		2.0	430.0	**564**		5.0	100.0
				565		17.9	483.3

better selectivity as compared to SCH-58261, while the inhibitory constant for the A_{2a} receptor remained in a low nanomolar concentration range.

Virtual screening of a commercial vendor library[47] was used to select several classes of compounds of similar structure, and lead compounds were selected among the compounds of each class. Heterocycle **583**, pyrrolo[3,2-*e*]-triazolo[1,5-*c*]pyrimidine, turned out to be the closest analogue of SCH-58261. However, this compound has a significantly lower affinity for the receptor (by a factor of more than 1000 as compared with SCH-58261) and selectivity for the A_1 receptor. It is likely that the π-electron system of the pyrazole ring and phenyl substituent play a significant role in these characteristics, and the replacement of the pyrazole moiety by the pyrrole one and the replacement of the phenyl residue by methyl in compound **583** leads to a decrease in affinity for ARs and selectivity.

Structure 583

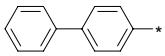
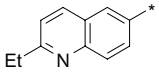
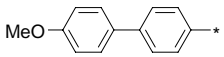
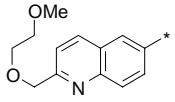
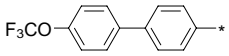
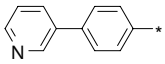
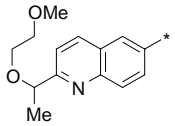
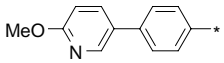
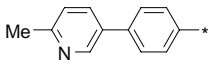
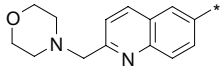
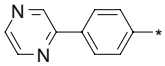
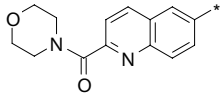
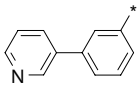
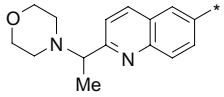
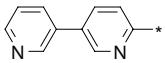
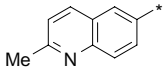
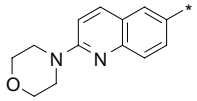


583

$K_i(A_1) = 3.18 \pm 0.36$ μmol litre^{-1};
$K_i(A_{2a}) = 1.24 \pm 0.28$ μmol litre^{-1};
$K_i(A_{2b}) = 15\%$ (at 10 μmol litre^{-1});
$K_i(A_3) = 40\%$ (at 10 μmol litre^{-1})

A series of studies dealing with different adenosine receptor antagonists have been published; in one of them,[50] N(8)-alkylated pyrazolotriazolopyrimidines **584**–**621** have been synthesized. It has been stated that the presence of a free amino group in the 5-position is essential

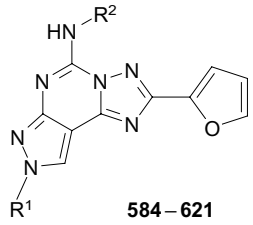
Table 29. Structure – activity relationship for SCH-58261 analogues — heterocycles **566** – **582**.[64]

Compound	Ar	K_i/nmol litre^{-1}		Compound	Ar	K_i/nmol litre^{-1}	
		A_{2a}	A_1			A_{2a}	A_1
566		1.1	119.9	**576**		2.7	653.4
567		0.5	1062	**577**		2.8	1221
568		7.8	780.0				
569		1.5	382.5	**578**		1.5	1980
570		1.9	537.7				
571		0.6	154.2	**579**		2.3	837.2
572		0.9	334.8	**580**		1.6	801.6
573		5.5	363.0	**581**		1.3	1661
574		11.4	342.0				
575		2.4	405.6	**582**		1.8	3850

for the manifestation of affinity for the A_{2a} receptor since N-alkylated derivatives, as a rule, exhibit the inhibitory constant higher by two orders of magnitude than that of the compound with free amino group. However, all synthesized compounds did not show the necessary selectivity, thus indicating the importance of the alkylation position in the pyrazole ring (Table 30).

Testing results for a series of N(7)-alkylated compounds **622** – **642**, in which the alkyl chain length and functional groups in the aromatic substituent were varied (Table 31), demonstrated that derivative **626** with the nitrile group

Structures 584 – 621



584 – 621

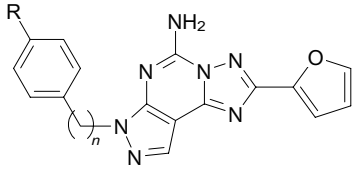
Table 30. Structure – activity relationship for pyrazolotriazolopyrimidine derivatives **584** – **621**.[50]

Compound	R^1	R^2	K_i/nmol litre^{-1}			
			A_1	A_{2a}	A_{2b}	A_3
584	H	H	140	20	51	348
585	H	4-$MeOC_6H_4NHC(O)$	448	520	350	0.14
586	H	3-$ClC_6H_4NHC(O)$	238	248	70	0.50
587	Me	H	101	2.80	90	300
588	Me	4-$MeOC_6H_4NHC(O)$	1097	1390	261	0.20
589	Me	3-$ClC_6H_4NHC(O)$	350	1195	205	0.40
590	Et	H	5.00	1.95	65	331
591	Et	4-$MeOC_6H_4NHC(O)$	1026	1040	245	0.60
592	Et	3-$ClC_6H_4NHC(O)$	249	180	150	1.60
593	Pr^n	H	10	2.51	39	408
594	Pr^n	4-$MeOC_6H_4NHC(O)$	1197	140	2056	0.80

Table 30 (continued).

Compound	R^1	R^2	K_i /nmol litre^{-1}			
			A_1	A_{2a}	A_{2b}	A_3
595	Pr^n	3-$ClC_6H_4NHC(O)$	30	1220	57	0.91
596	All	H	–	–	–	–
597	All	4-$MeOC_6H_4NHC(O)$	1531	176	2030	0.48
598	Bu^n	H	14	1.60	53	600
599	Bu^n	4-$MeOC_6H_4NHC(O)$	296	80	303	0.32
600	Bu^n	3-$ClC_6H_4NHC(O)$	245	95	70	0.60
601	Bu^t	H	175	45	400	1149
602	Bu^t	4-$MeOC_6H_4NHC(O)$	796	545	1715	0.80
603	Bu^t	3-$ClC_6H_4NHC(O)$	1015	796	450	2.78
604	iso-C_5H_{11}	H	2.00	0.78	9.1	700
605	iso-C_5H_{11}	4-$MeOC_6H_4NHC(O)$	175	65	54	30
606	iso-C_5H_{11}	3-$ClC_6H_4NHC(O)$	100	115	61	40
607	$Me_2C{=}CHCH_2$	H	5.42	0.80	12	811
608	$Me_2C{=}CHCH_2$	4-$MeOC_6H_4NHC(O)$	300	1025	58	40
609	$Me_2C{=}CHCH_2$	3-$ClC_6H_4NHC(O)$	352	110	81	55
610	$Ph(CH_2)_2$	H	1.00	0.34	5.1	280
611	$Ph(CH_2)_2$	4-$MeOC_6H_4NHC(O)$	201	120	81	0.98
612	$Ph(CH_2)_2$	3-$ClC_6H_4NHC(O)$	251	105	90	8.0
613	$Ph(CH_2)_3$	H	3.00	0.16	49	430
614	$Ph(CH_2)_3$	4-$MeOC_6H_4NHC(O)$	251	1010	802	40
615	$Ph(CH_2)_3$	3-$ClC_6H_4NHC(O)$	1500	200	226	60
616	2,4,5-$Br_3C_6H_2(CH_2)_2$	H	247	348	1113	4481
617	2,4,5-$Br_3C_6H_2(CH_2)_2$	4-$MeOC_6H_4NHC(O)$	255	2030	> 10000	25
618	2,4,5-$Br_3C_6H_2(CH_2)_2$	3-$ClC_6H_4NHC(O)$	389	3600	1816	71
619	1-$Naph(CH_2)_2$	H	348	896	4294	3416
620	1-$Naph(CH_2)_2$	4-$MeOC_6H_4NHC(O)$	2466	3260	> 10000	16
621	1-$Naph(CH_2)_2$	3-$ClC_6H_4NHC(O)$	3164	> 10000	> 10000	51

Structures 622–642



622–642

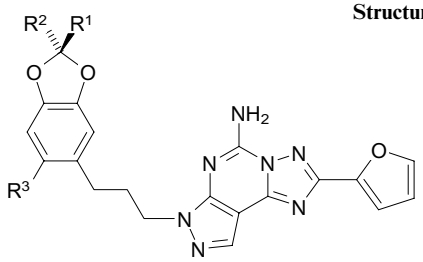
exhibited a reduced affinity for the receptor.[65] However, amino analogues **629**, **630**, **632** synthesized on its basis had the inhibitory constant for the A_{2a} receptor in a low nanomolar concentration range with a selectivity of several orders of magnitude for the A_1 receptor.

Testing results show that pyrazolotriazolopyrimidines **643–648** are inactive against the A_{2b} and A_3 receptors. Upon the introduction of the SO_3H group in compound **643**, the inhibitory constant for the A_{2a} receptor considerably increased as compared to derivative **644**, containing the ethoxycarbonyl group. Conversely, the addition of the

Table 31. Structure–activity relationship for pyrazolotriazolopyrimidines **622–642**.[65]

Compound	*n*	R	K_i /nmol litre^{-1}		Compound	*n*	R	K_i /nmol litre^{-1}	
			A_1	A_{2a}				A_1	A_{2a}
622	3	O_2N	1026	1.00	**633**	3	$HN{=}CNH_2$	75	55
623	2	AcNH	419	4.8	**634**	3	HO_2C	4965	4.4
624	3	$(HOCH_2CH_2)_2N$	558	1.1	**635**	2	HO_2CCH_2O	4927	4.63
625	2	$(HOCH_2CH_2)_2N$	123	0.12	**636**	2	HO_3S	190	100
626	3	NC	6469	86	**637**	2	$H_2NS(O_2)$	2630	1.31
627	3	EtO_2C	4494	4.0	**638**	2	$(HOCH_2CH_2)_2NS(O_2)$	2495	0.80
628	2	EtO_2CCH_2O	4197	0.43	**639**	2	$O_2S[N(CH_2CH_2)_2N]$-cyclo	369	3.8
629	3	H_2N	2160	0.22	**640**	2	$(ClCH_2CH_2)_2NS(O_2)$	5297	0.59
630	3	$HON{=}CNH_2$	179	0.18	**641**	2	$HO_2CCH_2NHS(O_2)$	9330	50.0
631	3	NH_2CH_2	60	6.0	**642**	3	HO_3S	139	140
632	2	H_2N	576	0.13					

Structures 643 – 648



643 – 648

Table 32. Structure – activity relationship for pyrazolotriazolopyrimidines **643 – 648**.[65]

Compound	R^1	R^2	R^3	K_i /nmol litre^{-1}	
				A_1	A_{2a}
643	H	H	HO_3S	6392	75
644	EtO_2C	H	H	1793	5.48
645	$HOCH_2$	$HOCH_2$	H	432	0.19
646	HO_2C	HO_2C	H	9399	120
647	HO_2C	H	H	3599	59
648	NaO_2C	NaO_2C	H	9533	120

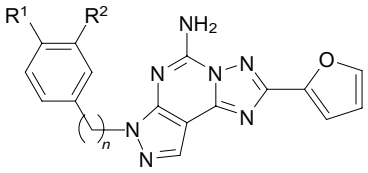
second carboxy group to the heterocyclic skeleton (compound **646**) led to the decrease in activity by several orders of magnitude (Table 32).

Studying a wider series of similar compounds[66] has demonstrated that the most promising compound among **649 – 657** is phenol derivative **651** bearing the trimethylene side chain, which exhibits activity in a low nanomolar concentration range and selectivity of three orders of magnitude [$K_i(A_1)/K_i(A_{2a})$ = 788] (Table 33).

In addition, the authors[66] continued studying a series of N(8)-alkylated heterocycles **658 – 668** (see Table 34). However, attempts to improve the selectivity in this group of compounds as compared with the above derivatives **584 – 621** failed.

Another attempt to enhance the selectivity of N(8)-alkylated derivatives was made through the protection of the amino group in the 5-position by various acyl groups,[66] but such modification led to compounds **669 – 687** with

Structures 649 – 657



649 – 657

Table 33. Structure – activity relationship for pyrazolotriazolopyrimidines **649 – 657**.[66]

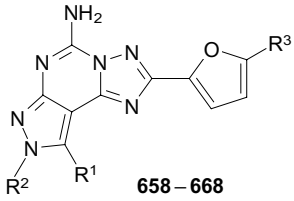
Compound	n	R^1	R^2	K_i /nmol litre^{-1} (see [a])	
				A_1	A_{2a}
649	3	OCH_2O		1841	3.8
650	3	MeO	MeO	2825	5.3
651	3	H	HO	741	0.94
652	1	H	BnO	9450	246
653	2	H	BnO	> 10 000	59
654	3	H	BnO	1460	45
655	1	H	HO	13400	53
656	2	H	HO	444	1.7
657	3	HO	HO	2250	49

[a] For all compounds, $K_i(A_3)$ exceeded 10 000 nmol litre^{-1}.

reduced affinity for the A_{2a} receptor at invariably low selectivity (Table 35). This fact provides evidence that free amino group is essential for achieving low inhibitory constants for the A_{2a} receptor.

The introduction of the morpholine (**688**) or piperazine (**689**) moiety into the α-position of the furan ring also led to

Structures 658 – 668



658 – 668

Table 34. Structure – activity relationship for pyrazolotriazolopyrimidines **658 – 668**.[66]

Compound	R^1	R^3	K_i /nmol litre^{-1}			
			A_1	A_{2a}	A_{2b}	A_3
658	EtNH	H	50	10	81	225
659	4-$MeOC_6H_4NH$	H	260	> 1000	> 10 000	> 1000
660	4-Methylpiperazino	H	30	156	35	> 1000
661	MeS	H	8.4	1.2	10.3	35
662	Pr^nS	H	9	2.1	69	224
663 [a]	MeS	H	175	22	31	> 1000
664	MeS	4-Methylpiperazino	> 1000	> 1000	> 10 000	> 1000
665	4-$MeOC_6H_4NH$	H	666	1100	2060	308
666	EtNH · HCl	H	41	10	36	25
667	4-Methylpiperazino [b]	H	48	135	12	> 1000
668	MeS	4-Methylpiperazino [b]	> 1000	> 1000	> 1000	> 1000

[a] $R^2 = Ph(CH_2)_3$, for the other compounds R^2 = Me; [b] for hydrochloride.

Structures 669–687

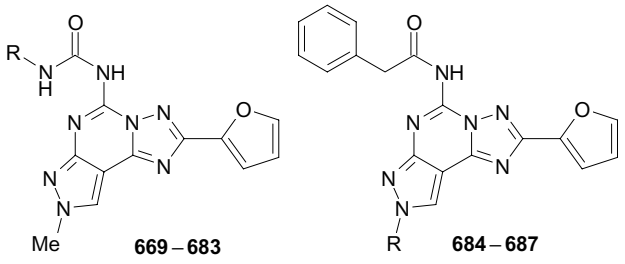


Table 35. Structure–activity relationship for pyrazolotriazolopyrimidines **669**–**687**.[66]

Compound	R	K_i/nmol litre^{-1}			
		A_1	A_{2a}	A_{2b}	A_3
669	Ph	594	381	222	0.16
670	3,4-$Cl_2C_6H_4$	392	143	116	3.4
671	3,4-$(OCH_2O)C_6H_3$	1015	680	142	0.24
672	4-$HO_3SC_6H_4$	> 10 000	594	> 10 000	25
673	4-$O_2NC_6H_4$	1115	695	180	0.43
674	4-MeC_6H_4	731	110	302	0.31
675	4-BrC_6H_4	600	100	181	0.46
676	4-FC_6H_4	700	120	226	0.34
677	4-$F_3CC_6H_4$	750	140	286	0.74
678	4-ClC_6H_4	430	180	128	0.29
679	2-ClC_6H_4	400	200	101	0.91
680	2-$MeOC_6H_4$	450	180	223	0.7
681	3-$MeOC_6H_4$	500	160	251	0.8
682	4-Py	250	60	200	0.04
683	4-Py (HCl)	350	100	250	0.01
684	Me	702	423	165	0.81
685	Et	714	335	161	1.03
686	Pr^n	351	306	143	1.01
687	Bu^n	602	400	101	1.11

a surprising result: the inhibitory constants for the A_1, A_{2a}, A_{2b} and A_3 receptors proved to be 1000 nmol litre^{-1}.[67]

Yet another modification involved the substitution of an aromatic moiety for the furan ring in pyrazolotriazolopyrimidine series **690**–**696** (Table 36) and led to complete loss of affinity for all the four types of ARs.[67]

In addition, N(8)-alkylated derivatives **697**–**714** were synthesized,[67] which showed satisfactory selectivity. In particular, compound **705** methylated at the N(8) atom and containing the methylsulfanyl residue in the 9-position exhibited the inhibitory constant of 3.1 nmol litre^{-1} for the

Structures 688–696

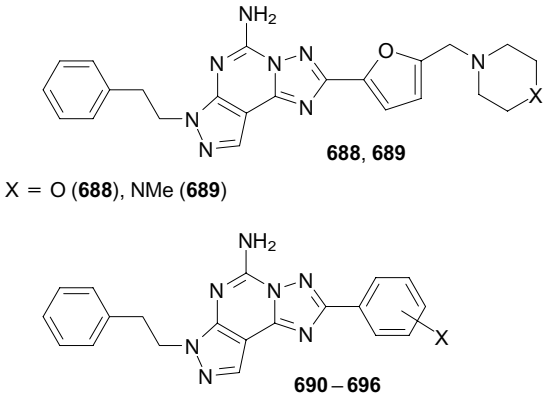


Table 36. Structure–activity relationship for pyrazolotriazolopyrimidines **690**–**696**.[67]

Compound	X	K_i/nmol litre^{-1} (see [a])	
		A_1	A_3
690	4-OH	> 1000	> 1000
691	4-Cl	> 1000	> 1000
692	2-OEt	> 1000	348
693	H	235	> 1000
694	4-OCH_2CO_2Et	> 1000	> 1000
695	4-OCH_2CO_2H	> 1000	> 1000
696	4-$OCH_2C(O)NHC_6H_4I$-4′	> 1000	> 1000

[a] For all compounds, $K_i(A_{2a})$ and $K_i(A_{2b})$ exceeded 1000 nmol litre^{-1}.

A_{2a} receptor at satisfactory selectivity; similar characteristics were also observed for compound **708** with a similar structure (Table 37). At the same time, for derivative **714** with a substituted furan ring, the inhibitory constants

Structures 697–714

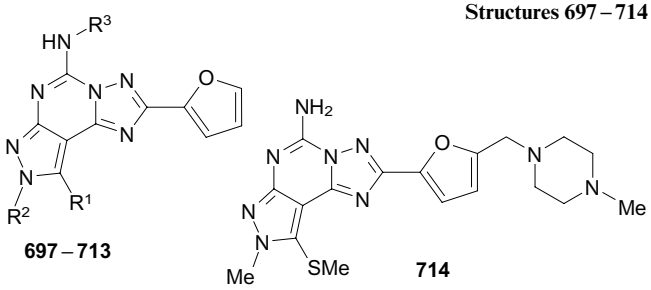


Table 37. Structure–activity relationship for pyrazolotriazolopyrimidines **697**–**714**.[67]

Compound	R^1	R^3	K_i/nmol litre^{-1}			
			A_1	A_{2a}	A_{2b}	A_3
697	EtNH	H	50	10	81	225
698	3-$MeOC_6H_4$	H	260	> 1000	> 1000	> 1000
699	4-Methylpiperazino	H	30	156	35	> 1000
700	MeS	H	8.4	1.2	10.3	35
701	Pr^nS	H	9	2.1	69	224
702 [a]	MeS	H	175	22	31	> 1000
703	EtNH	4-$MeOC_6H_4NHC(O)$	150	21	37	14
704	4-Methylpiperazino	HC(O)	316	> 1000	26	> 1000

Table 37 (continued).

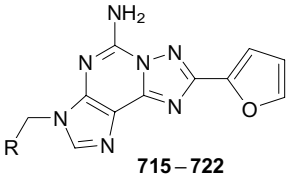
Compound	R^1	R^3	K_i/nmol litre^{-1}			
			A_1	A_{2a}	A_{2b}	A_3
705	MeS	4-$MeOC_6H_4NHC(O)$	70	3.1	24	212
706	MeS	4-$MeOC_6H_4CH_2NHC(O)$	80	15	45	> 1000
707	MeS	4-$Bu^iC_6H_4NHC(O)$	780	50	180	> 1000
708	MeS	3,4-$(MeO)_2C_6H_3NHC(O)$	70	4.1	30	110
709	EtNH	3,4-$(MeO)_2C_6H_3NHC(O)$	136	61	65	183
710	3-$MeOC_6H_4$	H	666	> 1000	> 1000	308
711	EtNH[b]	H	41	10	36	25
712	4-Methylpiperazino[c]	H	48	135	12	> 1000
713	EtNH[b]	4-$MeOC_6H_4NHC(O)$	100	16	23	9

[a] $R^2 = Ph(CH_2)_3$, for the other compounds R^2 = Me; [b] for hydrochloride; [c] for dihydrochloride.

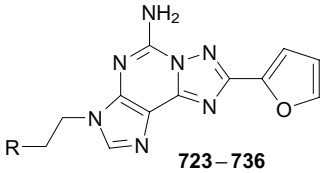
against the A_1, A_{2a}, A_{2b} and A_3 receptors exceeded 1000 nmol litre^{-1}.

A series of SCH-58261 derivatives has been synthesized by varying the aromatic moiety in the imidazo[4,5-*e*]triazolo[1,5-*c*]pyrimidine skeleton.[68] It has been demonstrated that the nature of the aromatic moiety has little effect on the inhibitory constant but a significant effect on selectivity. In particular, among derivatives **715**–**722**, good selectivity was observed only for heterocycle **718** (Table 38).

Structures 715–736



715–722



723–736

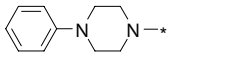
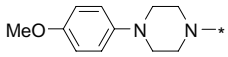
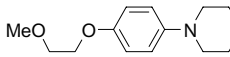
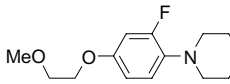
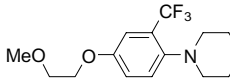
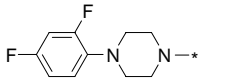
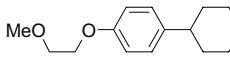
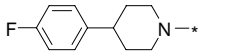
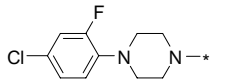
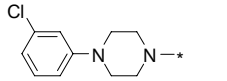
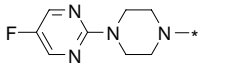
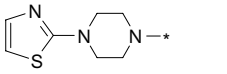
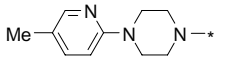
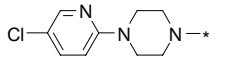
Table 38. Structure–activity relationship for imidazotriazolopyrimidines **715**–**722**.[68]

Compound	R	K_i/nmol litre^{-1}	
		A_{2a}	A_1
715	Et	5.9	295.0
716	Morpholinomethyl	6.3	233.1
717	Bn	4.1	135.3
718	4-Phenylpiperazinomethyl	1.7	309.4
719	Ph	1.5	25.5
720	2-BrC_6H_4	4.6	32.2
721	2-ClC_6H_4	1.7	15.3
722	2-$F_3CC_6H_4$	4.6	138.0

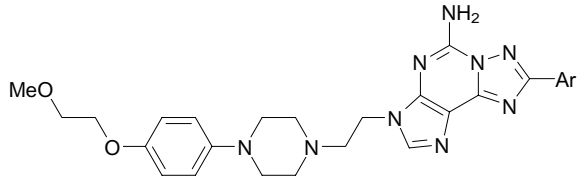
Optimization of the structure of the most promising piperazine derivative **718** made it possible to synthesize a series of compounds **723**–**736** with the increased affinity for the A_{2a} receptor and good selectivity. In particular, the introduction of methoxy group gave compound **724** with the inhibitory constant of 0.1 nmol litre^{-1} and selectivity A_1/A_{2a} being 1695 (Table 39).

Attempts to replace the furyl moiety in the optimized structure by various phenyl or pyridine moieties (compounds **737**–**744**) led to the decrease in both the affinity for the A_{2a} receptor and selectivity for the A_1 receptor (Table 40).

Table 39. Structure–activity relationship for imidazotriazolopyrimidines **723**–**736**.[68]

Compound	R	K_i/nmol litre^{-1}	
		A_{2a}	A_1
723		1.7	309.4
724		0.1	169.5
725		0.9	602.1
726		0.8	413.6
727		0.4	87.2
728		0.7	61.6
729		0.7	363.3
730		0.9	176.4
731		0.3	120.9
732		0.4	148.4
733		1.4	529.2
734		1.7	234.6
735		1.0	162.0
736		0.9	299.7

Structures 737–744

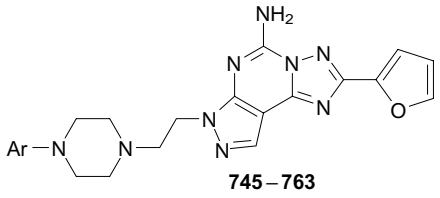


737–744

Table 40. Structure–activity relationship for imidazotriazolopyrimidines **737–744**.[68]

Compound	Ar	K_i/nmol litre^{-1}	
		A_{2a}	A_1
737	2-Fu	0.9	602.1
738	Ph	3.7	336.7
739	3-FC_6H_4	2.0	166.0
740	2-FC_6H_4	9.3	139.5
741	2-$F_3CC_6H_4$	10.0	1810
742	2-MeC_6H_4	20.5	1558
743	2-Py	12.6	1361
744	2-Py-N-oxide	89.7	1525

Structures 745–763



745–763

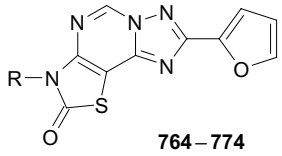
Table 41. Structure–activity relationship for pyrazolotriazolopyrimidines **745–763**.[69]

Compound	Ar	K_i/nmol litre^{-1}	
		A_{2a}	A_1
745	Ph	1.6	548.8
746	4-HOC_6H_4	1.3	241.8
747	4-$EtOC_6H_4$	1.4	1187
748	4-NCC_6H_4	2.1	1199
749	4-FC_6H_4	1.0	101.0
750	4-ClC_6H_4	0.5	674.0
751	2-FC_6H_4	0.6	536.4
752	2,4-$F_2C_6H_3$	0.6	>960
753	3,4-$F_2C_6H_3$	1.4	236.6
754	2,3,4-$F_3C_6H_2$	0.6	898.8
755	2,4,6-$F_3C_6H_2$	1.1	350.9
756	4-$(MeOCH_2CH_2O)C_6H_4$	1.1	1474
757	4-$(MeOCH_2CH_2O)$-2-FC_6H_3	0.4	694.4
758	4-$(HOCH_2CH_2O)C_6H_4$	0.6	915.0
759	4-$(MeOCHMeCH_2O)C_6H_4$	1.6	862.4
760	4-$AcCH_2OC_6H_4$	0.8	341.6
761	4-$MeS(O)CH_2OC_6H_4$	2.2	1151
762	4-$(MeO(CH_2)_3O)C_6H_4$	0.6	694.8
763	4-(cyclo-$C_3H_5OCH_2CH_2O)C_6H_4$	0.6	558.0

Piperazine derivatives **745–763** with different substituents in the phenyl moiety have been reported (Table 41).[69] All compounds of this series exhibited high affinity for the receptor in the range K_i = 0.4–2.2 nmol litre^{-1} and excellent selectivity, which was as high as 3–4 orders of magnitude.

Several studies have been devoted to modifications of the heterocyclic skeleton of AR antagonists. In particular, the thiazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine system was used instead of the pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]-pyrimidine core and derivatives of this series were synthesized.[70] The resulting compounds **764–774** (Table 42) exhibited high affinity for the A_{2a} receptor but different selectivity: for example, heterocycles **764**, **770–772** demonstrated a higher affinity for the A_1 receptor. However, the elongation of the N(3)-alkyl chain (compound **766**) led to the increase in selectivity while the inhibitory constant remained unaltered. In addition, upon the replacement of the alkyl substituent by the phenyl group, the affinity for the A_{2a} receptor for compounds **768–774** remained high, but selectivity decreased.

Structures 764–774



764–774

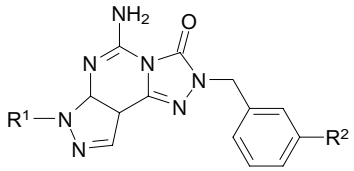
Table 42. Structure–activity for thiazolotriazolopyrimidines **764–774**.[70]

Compound	R	K_i/nmol litre^{-1}	
		A_{2a}	A_1
764	Et	3.56	0.3
765	Pr^n	0.38	86.8
766	Bu^n	0.12	17.7
767	All	0.016	0.3
768	Ph	1.1	52.8
769	4-FC_6H_4	2.02	6.5
770	4-ClC_6H_4	0.152	0.0046
771	3-ClC_6H_4	0.038	0.0072
772	2-IC_6H_4	0.70	0.2800
773	4-IC_6H_4	0.57	3.4941
774	3-IC_6H_4	0.0082	0.0215

Pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*a*]pyrimidines **775–794** without a furan ring have been synthesized.[56] The most promising compound was **775**, which had the inhibitory constant of 0.3 nmol litre^{-1} for the A_{2a} receptor and a selectivity for the A_1 receptor of three orders of magnitude. It should be noted that the introduction of the chlorine atom into the *meta* position of the benzyl moiety (compound **776**) led to the three-fold decrease in selectivity (Table 43).

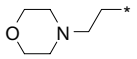
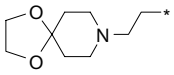
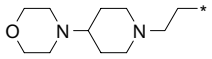
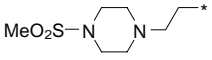
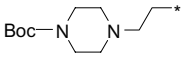
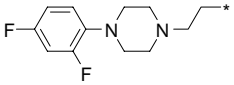
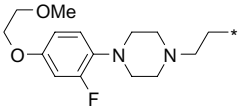
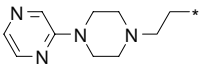
The replacement of the benzyl moiety in structure **775** by the cyclopropylmethyl one in derivatives **795–797** led to a considerable decrease in both the affinity for the A_{2a} receptor and the selectivity.

Structures 775–794



775–794

Table 43. Structure–activity relationship for pyrazolotriazolopyrimidines **775–794**.[56]

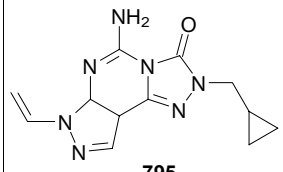
R^1	Compound	R^2	K_i/nmol litre^{-1}	
			A_{2a}	A_1
$CH_2{=}CH$	**775**	H	0.3	334.5
	776	Cl	0.4	142.4
$Me_2NCH_2CH_2$	**777**	H	>1500	–
	778	Cl	5.2	1399
	**779**	H	9.0	1404
	780	Cl	14.2	1406
	**781**	H	8.7	1409
	782	Cl	11.0	1397
	**783**	H	28.4	1505
	784	Cl	6.7	1501
	**785**	H	8.9	1397
	786	Cl	10.5	1397
	**787**	H	>1300	–
	788	Cl	556	1112
	**789**	H	>1300	–
	790	Cl	23.4	1404
	**791**	H	>1300	–
	792	Cl	15.6	1404
	**793**	H	12.7	1397
	794	Cl	12.9	1406

Pyrrolo- and pyrazolo[3,4-*e*]-1,2,4-triazolo[5,1-*c*]pyrimidines **798–826** have been synthesized and tested for activity against ARs by Baraldi's team.[71] The authors have stated that compounds **798–801** with a free amino group in the 5-position of the pyrrolotriazolopyrimidine system exhibit the inhibitory constant for the A_{2a} receptor in the nanomolar range, but they have no selectivity for the other types of ARs. The introduction of the phenylcarbamoyl moiety did not lead to the increase in selectivity: conversely, heterocycles **802–805** exhibited a higher affinity for the A_3 receptor (Table 44).

As an alternative to the pyrrole moiety, the pyrazole ring was suggested (heterocycles **807–822**) (Table 45).

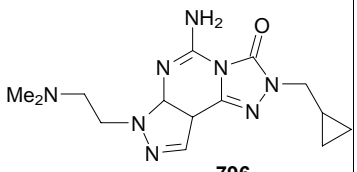
Among pyrazolo[3,4-*e*]-1,2,4-triazolo[5,1-*c*]pyrimidines **807–822**, the lowest inhibitory constant for the A_{2a} receptor was demonstrated by heterocycles **807–810**, **815–818** with a free amino group at the C(5) atom, while any modifications of this substituent led to compounds **811–814**, **819–826** with lower activity against all types of

Structures 795–797



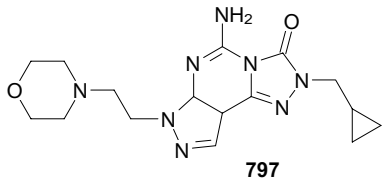
795

$K_i(A_{2a})$ = 27.4 nmol litre^{-1};
$K_i(A_1)$ = 1507 nmol litre^{-1}



796

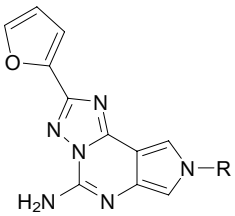
$K_i(A_{2a})$ > 1500 nmol litre^{-1}



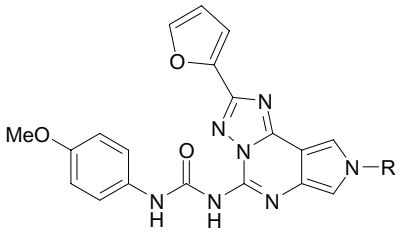
797

$K_i(A_{2a})$ = 381 nmol litre^{-1};
$K_i(A_1)$ = 1524 nmol litre^{-1}

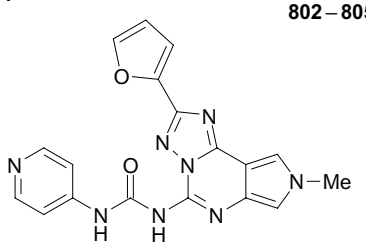
Structures 798–806



798–801



802–805



806

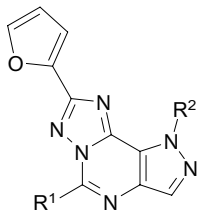
Table 44. Structure–activity relationship for pyrrolotriazolopyrimidines **798–806**.[71]

Compound	R	K_i/nmol litre^{-1}			$IC_{50}(A_{2b})$/nmol litre^{-1}
		A_1	A_{2a}	A_3	
798	Me	100	20	50	42
799	Pr^n	35	30	55	90
800	$Ph(CH_2)_2$	4.3	3.9	124	46
801	$Ph(CH_2)_3$	18	50	241	251
802	Me	800	500	15	838
803	Pr^n	743	200	10	906
804	$Ph(CH_2)_2$	178	148	12	740
805	$Ph(CH_2)_3$	210	130	13	>1000
806		355	>1000	111	>1000

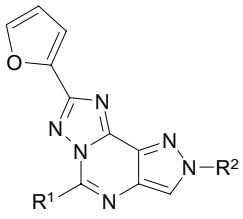
Table 45. Structure–activity relationship for tricyclic derivatives **807**–**826**.[71]

Compound	R^1	R^2	K_i/nmol litre^{-1}			$IC_{50}(A_{2b})$/nmol litre^{-1}
			A_1	A_{2a}	A_3	
807	H_2N	Me	10	3.6	749	31
808	H_2N	Pr^n	14	12	83	40
809	H_2N	$Ph(CH_2)_2$	33	42	603	31
810	H_2N	$Ph(CH_2)_3$	85	122	802	595
811	4-$MeOC_6H_4NHC(O)NH$	Me	129	68	61	122
812	4-$MeOC_6H_4NHC(O)NH$	Pr^n	61	20	161	32
813	4-$MeOC_6H_4NHC(O)NH$	$Ph(CH_2)_2$	524	626	208	772
814	4-$MeOC_6H_4NHC(O)NH$	$Ph(CH_2)_3$	> 1000	> 1000	> 1000	> 1000
815	H_2N	Me	30	8.1	125	33
816	H_2N	Pr^n	22	17	432	45
817	H_2N	$Ph(CH_2)_2$	4.9	9.2	315	27
818	H_2N	$Ph(CH_2)_3$	7.1	11	526	32
819	4-$MeOC_6H_4NHC(O)NH$	Me	923	222	110	580
820	4-$MeOC_6H_4NHC(O)NH$	Pr^n	240	208	50	863
821	4-$MeOC_6H_4NHC(O)NH$	$Ph(CH_2)_2$	753	672	314	548
822	4-$MeOC_6H_4NHC(O)NH$	$Ph(CH_2)_3$	> 1000	> 1000	815	> 1000
823	cyclo-$C_6H_{11}NH$	Me	12	119	507	915
824	Morpholino	Me	> 1000	> 1000	> 1000	> 1000
825	4-Methylpiperazino	Me	> 1000	> 1000	> 1000	> 1000
826	4-Phenylpiperazino	Me	> 1000	> 1000	> 1000	> 1000

Structures 807–826



807–814, 823–826



815–822

ARs. This provides evidence that the presence of free amino group in this position is essential for the binding to the receptor.

It is worth noting that the shift of the alkyl substituent from the N(9) atom to the neighbouring N(8) atom leads to a decrease in affinity for the A_{2a} receptor, except heterocycles **809**, **810**, **817**, **818**. Hence, the introduction of bulky substituents to the N(9) atom decreases the affinity of the corresponding molecules. By affinity and selectivity for the A_{2a} receptor, heterocycles **807**–**826** are comparable to pyrrole derivatives **798**–**806**.

In general, the following trends in structure–activity relationship in a series of tricyclic systems can be noted:

— comparison of the triazolotriazine and pyrazolotriazolopyrimidine series shows that triazolotriazines exhibit lower affinity for the A_{2a} receptor than tricyclic fused systems; however, they win in selectivity;

— the presence of pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]-pyrimidine skeleton is essential for the manifestation of the affinity for the receptor; however, modifications of the heterocyclic system to form pyrrolo-1,2,4-triazolo[1,5-*c*]pyrimidine **583**, imidazo-1,2,4-triazolo-[1,5-*c*]pyrimidines **715**–**744** and thiazolo-1,2,4-triazolo[1,5-*c*]-pyrimidines **764**–**774** are also possible, since such compounds also showed high values of these characteristics;

— the introduction of substituents into the α-position of the furan ring (compounds **664**, **668**, **688**, **689**, **714**) like the replacement of this ring by the phenyl moiety (**690**–**696**) leads to inactive compounds against the A_{2a} receptor;

— the free amino group at the C(5) atom of the heterocyclic system is favourable for the decrease in the inhibitory constant for the A_{2a} receptor, while its acylation (**669**–**687**) reduces the affinity for this receptor;

— in the general case, N(7)-alkylated pyrazolo[4,3-*e*]-1,2,4-triazolo [1,5-*c*] pyrimidine are more active and selective than their N(8)-alkylated isomers;

— the optimal length of the methylene chain of the linker group is 2–3 carbon atoms, since compounds **652**, **655** with a methylene bridge showed a decrease in affinity for the A_{2a} receptor;

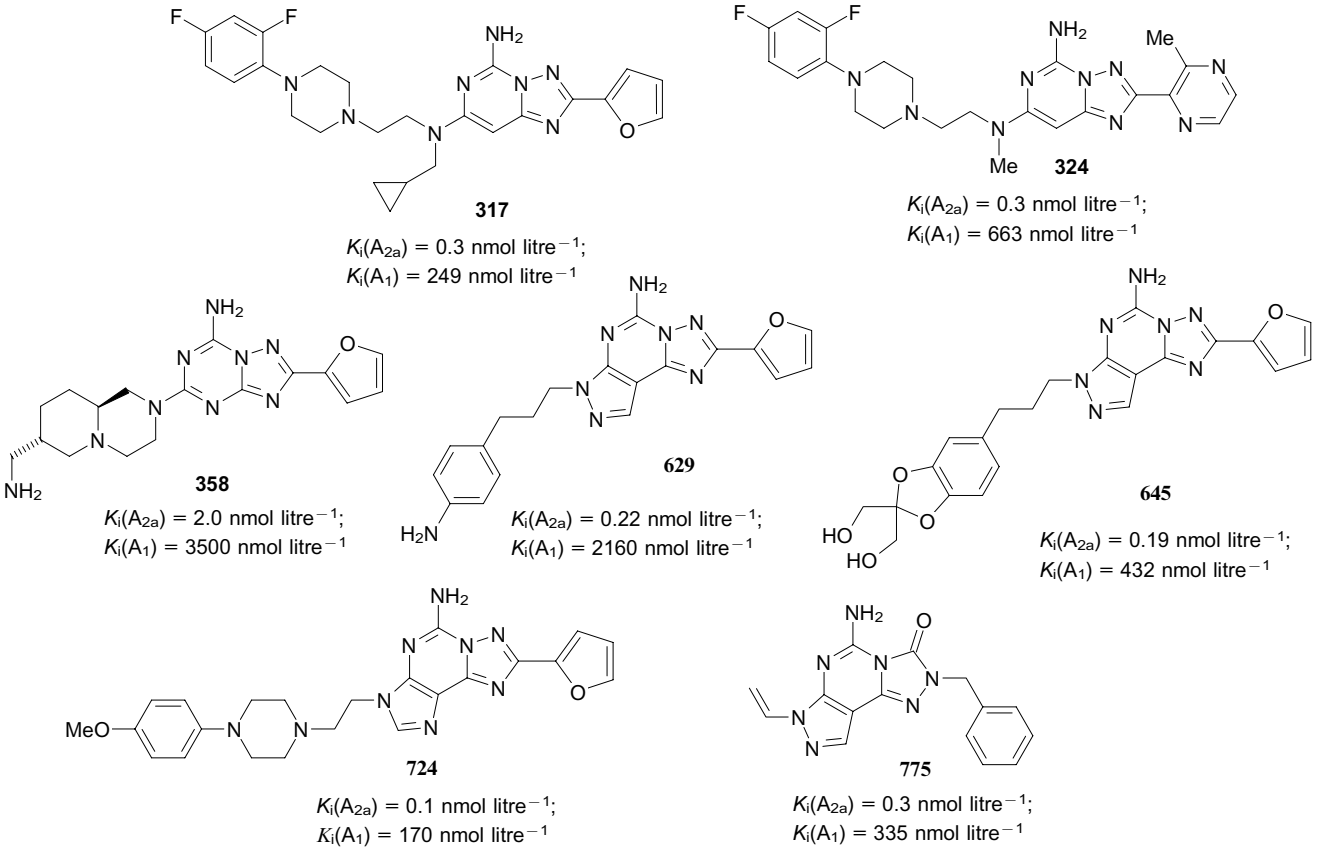
— the presence of an aromatic moiety in the linker group is important primarily for the selectivity of the compound, and the most potent and selective A_{2a} receptor antagonists (**556**, **567**, **625**, **645**, **651**) have in the aromatic ring an oxygen-containing group, which is presumably involved in the formation of hydrogen bonds with the receptor.

4. Conclusion

The literature data available to date show that bi- and tricyclic azoloazines containing a bridging nitrogen atom are active effectors of the adenosine A_{2a} receptor. Such systems can be considered as good candidates for synthesis and study of biological activity for a variety of pathological states in order to search for new drugs.

Despite the most frequent mention of effectors, such as ZM-241385 and SCH-58261, modern publications present heterocycles that have a higher affinity for the A_{2a} receptor and selectivity for the other types of ARs. In particular, among triazolopyrimidines, heterocyclic compound **324** should be noted, which is superior to ZM-241385 both in

Structures 317, 324, 358, 629, 645, 724, 775



affinity for the A_{2a} receptor and selectivity for A_1. An important feature of this compound is the absence of a metabolically unstable furan ring, which, together with the value of its inhibitory constant and selectivity, indicates the possibility of an alternative to this moiety in the directed synthesis of AR antagonists. Compound **317** containing the furan ring exhibits lower selectivity than derivative **324**; however, its inhibitory constant for the A_{2a} receptor remains at the same level. Triazolotriazine analogue **358** exhibits the affinity for the A_{2a} receptor twice as low as that of ZM-241385, while its selectivity for the A_1 receptor is twice as high.

It should be noted that all promising molecules **317**, **324**, **358** contain a free amino group and a tertiary amine moiety bound to the azine ring. Probably, the dealkylation reaction in the metabolic cleavage of the molecule occurs with difficulty, which allows one to expect higher pharmacokinetic characteristics of such effectors.[39]

In the series of tricyclic nitrogen-containing heterocycles, several promising structures have also been found which are superior to the known SCH-58261 agent in affinity for ARs and selectivity.

In particular, three furan derivatives **629**, **645**, **724** exhibit affinity for the A_{2a} receptor in a low nanomolar concentration range at a selectivity of 3–4 orders of magnitude. The key difference of the structure of these heterocycles from SCH-58261 is a longer linker group as an aryl-containing moiety bonded to the pyrazole or imidazole rings. At the same time, derivative **775**, which contains neither a furyl substituent nor a linker, can be considered a promising alternative. This compound exhibits an inhibitory constant of 0.3 nmol litre^{-1} for the A_{2a} receptor and a selectivity of three orders of magnitude for the A_1 receptor.

Thus, based on analysis of structural units, main features of molecules most promising as AR effectors at high selectivity can be formulated:

1) π-electron system of triazoloazine with a bridgehead nitrogen atom;

2) the presence of an aryl or hetaryl substituent in the triazole moiety;

3) the presence of a free amino group at the azine ring as the hydrogen bond donor;

4) the presence of the linker group containing an aryl or hetaryl terminal moiety and bound to the heterocyclic core through the tertiary nitrogen atom.

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