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Pharmacology of mammalian P2X- and P2Y-receptors

Ivar von Kügelgen • *Department of Pharmacology, University of Bonn, Reuterstrasse 2b, D-53113 Bonn, Germany, Tel. +49 228 735445, Fax. +49 228 735443, e-mail: kugelgen@uni-bonn.de*

Introduction

P2-receptors are membrane-bound receptors for extracellular nucleotides such as ATP and UTP[1-5]. There are two distinct families of P2-receptors: P2X-receptors, which are ligand-gated ion channels for cations, and P2Y-receptors, which are G-protein-coupled receptors (GPCRs) with seven transmembrane regions[3-9]. Seven mammalian P2X-receptor subtypes exist ($P2X_{1-7}$)[4,10,11]. At the level of the cell membrane they form trimers[10,12] with homomeric or heteromeric receptor assemblies[4,10,11] (see Table 1). Eight mammalian P2Y-receptor subtypes have yet been cloned and functionally defined as P2-receptors ($P2Y_{1,2,4,6,11,12,13,14}$)[3,5,9,13-15]. However, the group of GPCRs mediating effects of extracellular nucleotides is even larger as shown by the fact that extracellular UDP acts in addition on some receptors for cysteinyl leukotrienes[16-18]. In addition to P2-receptors for adenine and uracil nucleotides, there are four GPCRs for the nucleoside adenosine (P1-receptors[1]: A_1, A_{2a}, A_{2b} and A_3 adenosine receptors[19]). And, finally, there exist a recently identified group of GPCRs for the nucleobase adenine[20-22] (tentatively named P0-receptors[23]).

Drug targets

P2-receptors are expressed on the surface of almost all cells. This fact underlines the physiological significance of these receptors. The receptors are activated by nucleotides that are released as extracellular signalling molecules either from neurons by vesicular transmitter release[24-26] or from many other cells by mechanisms including the opening of connexin hemichannels[27-29]. Several excellent reviews have summarised the knowledge about the distribution and the physiological roles of native P2-receptors[3,10,23,30-42]. Targets, which are important for pharmacotherapy, include $P2Y_1$- and $P2Y_{12}$-receptors involved in the aggregation of blood platelets[43,44]. In fact, the thienopyridine compound clopidogrel was the world's second highest selling pharmaceutical in 2007. Clopidogrel is used for the prevention of vascular ischemic events as well as for the therapy of patients with an acute coronary syndrome or myocardial infarction. The active metabolite of clopidogrel irreversibly blocks the platelet $P2Y_{12}$-receptor[45]. Antagonists blocking $P2X_3$-, $P2X_4$- and $P2X_7$-receptors are under development for the treatment of chronic and neuropathic pain[41,46-49]. Agonists acting on $P2Y_2$-receptors mediating an increase in ion fluxes are used for the treatment of the dry eye disease[50]. The present article now summarises the pharmacology of P2-receptor subtypes in order to facilitate the pharmacological characterization of native P2-receptors (and, thereby, the identification of new drug targets).

Agonists acting on P2X-receptors

All known assemblies of P2X-receptor subtypes are activated by ATP, which is the most potent physiological nucleoside triphosphate agonist at these receptors (Table 1 and Figure 1). With very few exceptions described below, ADP and AMP are not active. There are some nucleotide analogues with a restricted selectivity for P2X-receptor subtypes – in most cases, however, it will be difficult to characterize a P2X-subtype only by the use of different agonists.

Table 1. Principle agonists acting at functionally defined mammalian P2X-receptor homomers and heteromers (EC_{50} concentrations in µM).

Type	*Principle agonists*	*Selected references*
$P2X_1$	ATP(0.1-1 µM)= 2-methylthio-ATP(0.1-1 µM)≥ αβ-meATP(1-3 µM)> BzATP(3-30 µM)	4, 10, 36, 51-55
$P2X_2$	ATP(1-30 µM)= 2-methylthio-ATP(3-10 µM)> BzATP(30 µM)>> αβ-meATP(>300 µM)	4, 10, 36, 52-56
$P2X_3$	2-methylthio-ATP(0.3 µM)≥ ATP(1 µM)= αβ-meATP(1 µM)	4, 10, 36, 47, 53, 57, 58
$P2X_{2/3}$	2-methylthio-ATP(1 µM)> ATP(2 µM)>αβ-meATP(3 µM)	4, 10, 36, 47, 53, 58
$P2X_4$	ATP(10 µM)≥ 2-methylthio-ATP(1-100 µM)>> αβ-meATP(>300 µM)≥ BzATP(>500 µM)	4, 10, 36, 59-61
$P2X_5$	ATP(10 µM)= 2-methylthio-ATP(10 µM)>> αβ-meATP(>300 µM)≥ BzATP(>500 µM)	4, 10, 36, 62, 63
$P2X_{1/5}$	ATP(0.7 µM)> 2-methylthio-ATP(1.3 µM)> αβ-meATP(3.1 µM)	4, 10, 36, 64, 65
$P2X_6$	2-methylthio-ATP(9 µM)≥ ATP(12 µM)>> αβ-meATP(>100 µM)	4, 10, 36, 62
$P2X_{4/6}$	ATP(6.3 µM) ≥ 2-methylthio-ATP(7.7 µM)> αβ-meATP(12 µM)	4, 10, 36, 66
$P2X_7$	BzATP(3 µM)> 2-methylthio-ATP(10 µM)> ATP(100 µM)> αβ-meATP(>300 µM)	4, 10, 36, 67

αβ-meATP, α,β-methylene-ATP; BzATP, benzoyl-benzoyl-ATP.

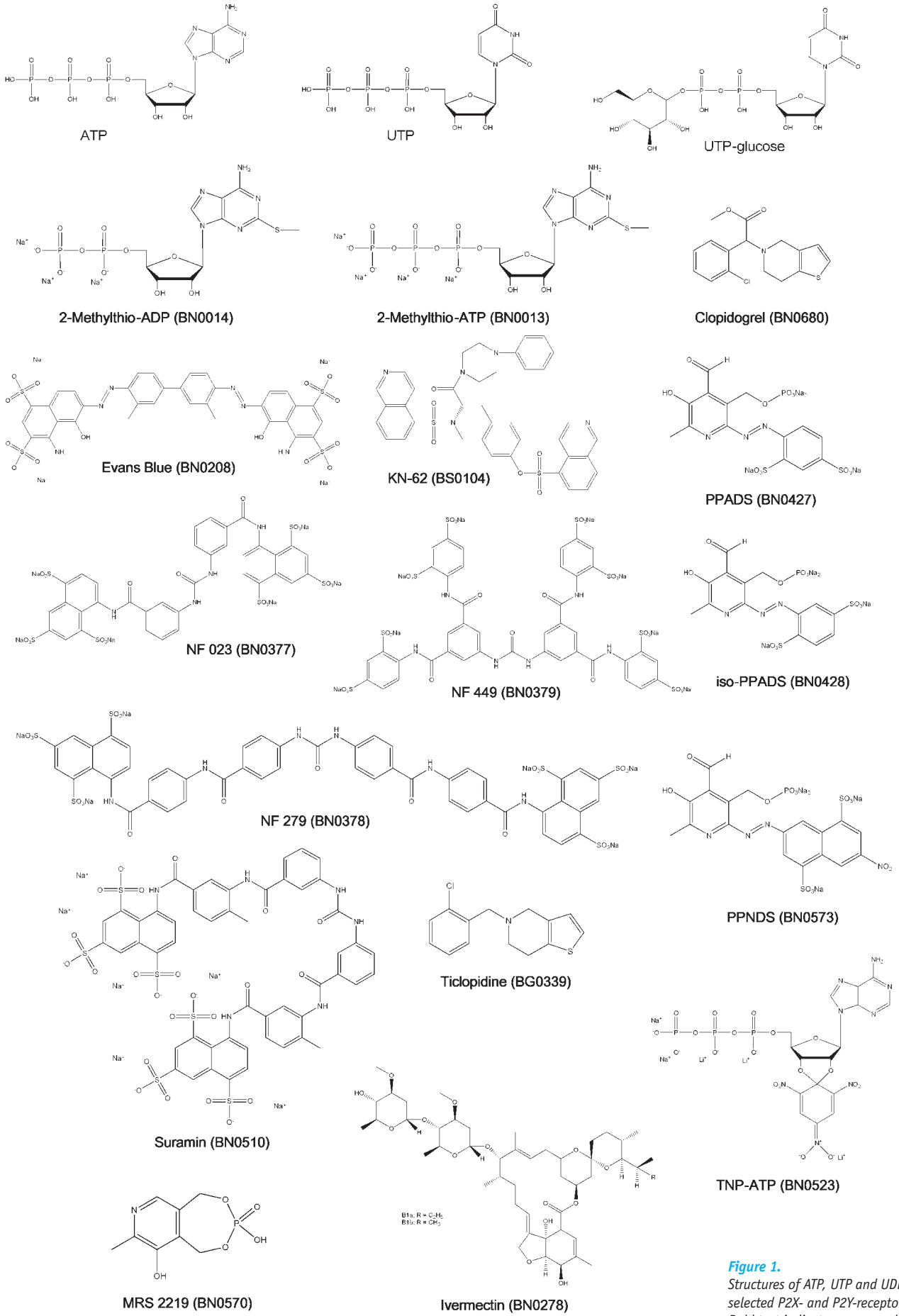

Figure 1.
Structures of ATP, UTP and UDP-glucose and selected P2X- and P2Y-receptor compounds. Bold text indicates compounds available from BIOTREND (with catalogue numbers).

$P2X_1$: $P2X_1$-receptors are abundantly expressed in smooth muscle tissues, where they mediate constriction (see ref. 3 and Table 1). ATP and the analogues 2-methylthio-ATP and ATPγS are potent agonists. The receptor is sensitive to activation and desensitation by α,β-methylene-ATP (Table 1). The naturally-occurring diadenosine polyphosphates and closely-related nucleotides (e.g. Ap_5A and Ap_5G) also act as agonists at the $P2X_1$-receptor. BzATP (benzoyl-benzoyl-ATP, Table 1) and CTP only activate the receptor when used at higher concentrations. As an exception, homomeric assemblies of a $P2X_1$-receptor splice variant (lacking 17 amino acids of exon 6) are activated by ADP, but not by ATP[68] (but see discussion[69] of the physiological relevance).

$P2X_2$: The receptor is found in many neuronal tissues in the peripheral and central nervous system (see ref. 3 and Table 1). Compared with the $P2X_1$-receptor, higher concentrations of ATP and 2-methylthio-ATP have to be used for receptor activation (Table 1). The receptor is almost insensitive to α,β-methylene-ATP (Table 1).

$P2X_3$ and $P2X_{2/3}$: $P2X_3$-homomeric as well as $P2X_{2/3}$-heteromeric assemblies play important roles in sensory neurones (see references in Table 1). The properties of $P2X_{2/3}$-heteromeric assemblies are similar to those of the $P2X_3$-homomers[4,10]. 2-Methylthio-ATP is more potent than ATP (Table 1 and Figure 1). The assemblies are sensitive to α,β-methylene-ATP (Table 1). Ap_5A and Ap_5G are also active.

$P2X_4$ and $P2X_5$: Both receptors are expressed in the CNS and are activated by higher concentrations of ATP and 2-methylthio-ATP (Table 1). Ap_4A is a partial agonist at the $P2X_4$-receptor and CTP as well as GTP activate the $P2X_5$-receptor when used at higher concentrations (see references in Table 1). The properties of $P2X_{1/5}$-heteromers are similar to those of the $P2X_1$-receptor (Table 1).

$P2X_6$ and $P2X_{4/6}$: Homomeric $P2X_6$-receptors are not readily expressed in most cells studied so far[4]. $P2X_6$-receptors as well as $P2X_{4/6}$-heteromeric assemblies respond to activation by ATP and 2-methylthio-ATP (Table 1).

$P2X_7$: The $P2X_7$-receptor operates in immunocytes and microglia cells. It is involved in pore formation of macrophages in response to stimulation by ATP (see references in Table 1). In comparison to the other P2X-receptors, there are distinguishing features of the $P2X_7$-receptor. Activation of the receptor requires high concentrations of ATP; BzATP (benzoyl-benzoyl-ATP) is a much more potent agonist than ATP itself (Table 1). For that reason, BzATP is often used in studies analysing the $P2X_7$-receptor. However, it should be noted that BzATP is not selective for the $P2X_7$-receptor (see $P2X_1$ in Table 1 and $P2Y_{11}$ in Table 3). ADP and AMP are weak agonists at the $P2X_7$-receptor; their action is potentiated after a pre-exposure of the receptors to ATP[70].

P2X-receptor antagonists

Reactive blue-2[71], suramin[72,73] and PPADS (pyridoxal-5'-phosphate-6-azophenyl-2,4-disulfonate)[74] have been used for several years to antagonize P2X- and P2Y-receptors[54,75-77]. However, suramin and PPADS block a number of P2X- and P2Y-subtypes (Tables 2 and 4). In order to facilitate the pharmacological characterization of the subtypes, several subtype-selective antagonists have been developed in the last years. These compounds include analogues of suramin and PPADS. Most of the new derivatives have fewer effects on other targets such as ectonucleotidases[91] or G-proteins.

Table 2. Potencies of selected antagonists and potentiators at recombinant P2X-receptors (IC_{50}/EC_{50} concentrations in µM)

Compound	*$P2X_1$*	*$P2X_2$*	*$P2X_3$*	*$P2X_{2/3}$*	*$P2X_4$*	*$P2X_5$*	*$P2X_6$*	*$P2X_7$*	*Selected references*
Antagonists:									
Suramin	1	8-10	3		>500	4	>100	78-500	**4, 10, 36, 55**
PPADS	1	1	1	↓80% (10 µM)	>500	3	>100	50	**4, 10, 36**
NF023	0.2	>10	8.5		>100				**4**
TNP-ATP	0.006	1	0.001	0.003	15			>30	**4, 10**
MRS2159	0.01		0.1						**78**
NF279	0.02	0.8	1.6		>300			2.8	**79-81**
NF449	0.0003	47	1.8	0.3	>300			40	**82, 83**
NF110	0.08	4.1	0.04		>300				**84**
A-317491	10	>10	0.02	0.1	>10				**85**
BB-G	>5	1.4	>10		3-10			0.01-0.3	**4**
KN-62								0.02 (human)	**86**
A-438079								0.1	**87, 88**
Potentiators:									
MRS2219	5.9								**89**
Ivermectin					0.2				**90**

The table summarizes studies analyzing potencies of P2X-receptor antagonists and potentiators at recombinant P2X-receptors. PPADS, pyridoxal-5´-phosphate-6-azophenyl-2´,4´-disulfonate; NF023, 8'-[carbonylbis(imino-3,1-phenylenecarbonylimino)]bis-1,3,5-naphthalene-trisulphonic acid; TNP-ATP, 2',3'-O-(2,4,6-trinitrophenyl)-ATP; MRS2159, pyridoxal-a5-phosphate-6-phenylazo-4'-carboxylic acid; NF279, 8,8'-(carbonylbis(imino-4, 1 -phenylenecarbonyl-imino-4,1-phenylenecarbonylimino)) bis(1,3, 5-naphthalenetrisulfonic acid); NF449, 4,4',4'',4'''-[carbonylbis(imino-5,1,3-benzenetriyl-bis (carbonylimino))]tetrakis-1,3-benzenedisulfonic acid; NF110, 4,4',4'',4'''-[carbonylbis[imino-5,1,3-benzenetriylbis(carbonylimino)]]tetrakisbenzenesulfonic acid; BB-G, brilliant blue G; KN-62, 1-[N,O-bis(5-Isoquinolinesulfonyl)-N-methyl-L-tyrosyl]-4-phenylpiperazine (also acts at an inhibitors of calcium calmodulin kinase II); A438079, 3-[[5-(2,3-Dichlorophenyl)-1H-tetrazol-1-yl]methyl] pyridine; MRS2219, 1,5-dihydro-3-hydroxy-8-methyl[1,3,2]dioxaphosphepino[5 ,6-c]pyridin-9-ol-3-oxide.

P2X$_1$: Micromolar concentrations of PPADS, suramin and NF023, an analogue of suramin, block the P2X$_1$-receptor (Table 2 and Figure 1). However, these antagonists are not subtype-selective (Table 2; for an action of NF023 on recombinant P2Y$_1$-receptors see ref. 92). The P2X$_1$-receptor is potently blocked by the nucleotide Ip$_5$I[93,94]. A further nucleotide antagonist, TNP-ATP (2',3'-O-(2,4,6-trinitrophenyl)-ATP), blocks P2X$_1$-, P2X$_3$- and P2X$_{2/3}$-assemblies, but not P2X$_2$-, P2X$_4$- and P2X$_7$-receptors when used in nanomolar concentrations (Table 2). Several non-nucleotide antagonists including NF110 (an analogue of suramin) and MRS2159 (an analogue of PPADS) have been found to exert potent effects on both P2X$_3$- and P2X$_1$-receptors (Table 2). And, recently, the suramin analogues NF279 and NF449 have been shown to act as highly potent and selective antagonists at the P2X$_1$-receptor. These antagonists clearly discriminate P2X$_1$-receptors from P2X$_3$-receptors (Table 2 and Figure 1). When tested on isolated cells, NF279 and NF449 act in nanomolar concentrations (Table 2). Possibly due to a complex kinetic of diffusion of the antagonists, one often has to use higher concentrations or a prolonged pre-incubation period in studies on organ tissues[81,95]. MRS2219[89] increased responses to activation of the P2X$_1$-receptor.

P2X$_2$: There are no subtype-selective antagonists available. The P2X$_2$-receptor is blocked by suramin, PPADS, TNP-ATP, NF279, NF110 and brilliant blue G, when these antagonists are used in micromolar concentrations (Table 2).

P2X$_3$ and P2X$_{2/3}$: Suramin and PPADS block P2X$_3$-receptors (Table 2). TNP-ATP is a very potent antagonist at P2X$_3$-homomeric as well as P2X$_{2/3}$-heteromeric assemblies (and at P2X$_1$-receptors; see Table 2). In addition, NF110 has been shown to be a non-nucleotide P2X$_3$-antagonist that can be used in studies analysing neuronal P2X$_3$-receptors[84]. However, NF110 also blocks P2X$_1$-receptors (Table 2). A further, recently developed non-nucleotide antagonist is A-317491, which potently blocks P2X$_3$-homomeric as well as P2X$_{2/3}$-heteromeric assemblies without major effects on P2X$_1$-, P2X$_2$- and P2X$_4$-receptors (Table 2).

P2X$_4$: Responses to activation of the P2X$_4$-receptor are increased by addition of ivermectin (Table 2).

P2X$_5$: The P2X$_5$-receptor is blocked by suramin and PPADS (Table 2).

P2X$_6$: There are no antagonists known.

P2X$_7$: The P2X$_7$-receptor is potentially blocked by brilliant blue G and A-438079 (Table 2). The isoquinoline compound KN-62 is a potent blocker of the human P2X$_7$-receptor (Table 2), but it is inactive at the rat P2X$_7$-receptor. KN-62 also blocks the calcium sensitive calmodulin-dependent protein kinase II.

Agonists acting on P2Y-receptors

Some P2Y-receptors are selectively activated by adenine nucleotides; the other P2Y-receptors respond to uracil nucleotides or UDP-glucose (Table 3).

Adenine-nucleotide selective P2Y-receptors

P2Y$_1$: The cloned P2Y$_1$-receptor accounts for the functionally defined P$_{2Y}$-purinoceptor[3]. It operates in a variety of tissues including smooth muscle, endothelium and neuronal tissues as well as in blood platelets. As shown in Table 3, the P2Y$_1$-receptor is selective for adenine nucleotides. ADP is the most potent physiological agonist. Its analogue 2-methylthio-ADP has a ten times higher affinity at the human P2Y$_1$-receptor than ADP[105]. The analogue N-methanocarba-2-methylthio-ADP (MRS2365)[104] displays selectivity for the P2Y$_1$-receptor over the P2Y$_{12}$- and P2Y$_{13}$-receptor. 2-Methylthio-ATP and ATPγS act as agonists at the P2Y$_1$-receptor with potencies similar to that of ADP. ATP itself is a partial agonist[105].

There is evidence for the operation of a heteromeric assembly of adenosine A$_1$ and P2Y$_1$-receptors with distinct pharmacological properties[154]; the heteromer is activated by adenine nucleotides and blocked by the adenosine A$_1$ antagonist cyclopentyl-dipropyl-xanthine (DPCPX) [154].

Table 3. Principle agonists acting at functionally defined mammalian P2Y-receptor subtypes.

Type	*Principle agonists*	*Selected references*
P2Y$_1$	**MRS2365>2-MeSADP>ADP=ADPβS**	**96-105**
P2Y$_2$	**UTP≥ATP>INS37217>Ap4A>ATPγS**	**106-115**
P2Y$_4$	**UTP>UTPγS (human)** **UTP=ATP (rat, mouse)**	**111, 114, 116-123**
P2Y$_6$	**UDP=5Br-UDP>>UTP**	**111, 124-128**
P2Y$_{11}$	**ATPγS=BzATP=ARC67085>ATP (human)** **ADPβS=2-MeSADP>ATP (canine)**	**129-135**
P2Y$_{12}$	**2-methylthio-ADP>ADP>ATP**	**104, 136-142**
P2Y$_{13}$	**2-methylthio-ADP>(=)ADP>ADPβS**	**143-146**
P2Y$_{14}$	**2-thio-UDP-glucose>UDP-glucose>UDP-galactose**	**147-150**

Not listed are non-mammalian receptors: e.g., the P2Y$_3$-receptor[151,152] representing an avian orthologue of the mammalian P2Y$_6$-receptor and the tp2y-receptor[152,153], an avian receptor similar to the mammalian P2Y$_2$- and P2Y$_4$-receptors. ARC67085, 2-propylthio-β,γ-difluoromethylene-D-ATP; Ap4A, diadenosine-tetraphosphate; ATPγS, adenosine-(0-3-thiotriphosphate); 5-Br-UDP, 5-bromo-UDP; BzATP, benzoyl-benzoyl-ATP; INS37217, P^1-(uridine 5´)-P^4-(2´-deoxycytidine-5´)tetraphosphate; 2-MeSADP, 2-methylthio-ADP; MRS2365 (N)-methanocarba-2-methylthio-ADP; 2-MeSATP, 2-methylthio-ATP; UTPγS, uridine-(0-3-thiotriphosphate).

P2Y$_{11}$: The P2Y$_{11}$-receptor is highly expressed in immunocytes[129]. The human P2Y$_{11}$-receptor is activated by ATP, NAD$^+$ [155] and, very potently, by the analogue 2-propylthio-β,γ -dichloromethylene-D-ATP (ARC67085) (Table 3). In contrast to the human receptor, ADP-analogues act as agonists at the canine P2Y$_{11}$-receptor (Table 3). There are no rodent orthologues of this receptor.

P2Y$_{12}$: The P2Y$_{12}$-receptor is expressed in platelets, microglia and neuronal tissues[5]. It plays a very important role in platelet aggregation[43]. The receptor is activated by adenine diphosphate derivatives with 2-methylthio-ADP being much more potent than ADP (Table 3).

P2Y$_{13}$: The P2Y$_{13}$-receptor is expressed in cells of haemopoietic origin as well as in neuronal cells. The P2Y$_{13}$-receptor responds to adenine diphosphate analogues, similarly as the P2Y$_{12}$-receptor (Table 3). ATP and 2-methylthio-ATP appear to be partial agonists with weak potencies at the P2Y$_{13}$-receptor[145].

P2Y-receptors activated by uracil nucleotides or UDP-sugar derivatives

P2Y$_2$: P2Y$_2$-receptors are expressed in many tissues including lung, heart, skeletal muscle, spleen, kidney, liver and epithelia[5].
The receptors play an important role in regulating ion transport in epithelial cells[38]. Most functionally defined P$_{2U}$-receptors[3] are likely to be in fact P2Y$_2$-receptors. Triphosphate nucleotides including UTP, ATP, UTP$_\gamma$S and ATP$_\gamma$S act as full agonists at this receptor (Table 3). In addition to the triphosphate nucleotides, the receptor responds to diadenosine-tetraphosphate (Ap4A)[156] as well as to Up4U (diquafosol, INS365)[157], which is used for the treatment for the dry eye disease[50]. The analogue P^1-(uridine 5´)-P^4-(2´-deoxycytidine-5´) tetraphosphate (INS37217) is a potent agonist at the P2Y$_2$-receptor with some effects at the P2Y$_4$-receptor (Table 3).

P2Y$_4$: P2Y$_4$-receptors are expressed in the placenta and at lower levels in lung and vascular smooth muscle[158]. In contrast to the rodent orthologues, the human P2Y$_4$-receptor is highly selective for uracil triphosphate derivatives (Table 3). UDP and ADP are inactive[111].

P2Y$_6$: P2Y$_6$-receptors are widely expressed[5]. The P2Y$_6$-receptor is a nucleoside diphosphate preferring receptor with UDP being much more potent than UTP[111]. Adenine nucleotides are almost inactive (Table 3).

P2Y$_{14}$: The receptor has a widespread distribution with highest expression in man in the placenta, adipose tissue, stomach and intestine[148]. UDP-glucose and its analogue 2-thio-uridine-diphosphate-glucose (2-thio-UDP-glucose) [150] are potent agonists (Table 3).

CysLT1 and CysLT2: The receptors are activated by the cysteinyl leukotrienes LTC4, LTD4, and LTE4 and, in addition, by UDP, but not by UTP or ATP[16,17].

P2Y-receptor antagonists

Reactive blue-2[71], suramin[72,73] and PPADS[74] block a number of P2X- and P2Y-receptor subtypes (Tables 2, 4 and Figure 1). More recently, subtype-selective P2Y-receptor antagonists have been developed.

P2Y$_1$: The human P2Y$_1$-receptor is blocked by suramin, PPADS, reactive blue-2 (Table 4) and, in addition, by NF023 (8'-[carbonyl-bis(imino-3,1-phenylenecarbonylimino)]bis-1,3,5-naphthalene-trisulphonic acid; an analogue of suramin) and MRS2210 (6-(2'-chloro-azophenyl)-pyridoxal-α5-phosphate; an analogue of PPADS)[92]. Bisphosphate analogues with higher affinity and selectivity for the P2Y$_1$-receptor have been developed. 2´-Deoxy-N^6-methyladenosine-3´,5´-bisphosphate (MRS2179; Table 4) acts as a competitive antagonist at the turkey P2Y$_1$-receptor with a pA$_2$-value of about 7[164]. The affinity constant of MRS2179 at the human P2Y1-receptor also amounts to about 100 nM (Table 4). It should be noted that MRS2179 has some antagonistic activity at the P2X$_1$-receptor[77] and may be broken down by ectoenzymes when used in tissues. The analogues MRS2279 (2-chloro-N^6-methyl-(N)-methanocarba-2´-deoxyadenosine 3´,5´-bisphosphate) and MRS2500 (2-iodo-N^6-methyl-(N)-methanocarba-2´-deoxyadenosine 3´,5´-bisphosphate) even have higher potencies at the P2Y$_1$-receptor (affinity constants of about 4 and 2 nM, respectively). These bisphosphate analogues show no interaction with other P2Y-receptors (Table 4).

P2Y$_2$: Suramin blocks the P2Y$_2$-receptor with an affinity about 20 times lower when compared to that determined at the P2Y$_1$-receptor (Table 4).

P2Y$_4$: Suramin does not block the P2Y$_4$-receptor even when used at high concentrations (Table 4). PPADS reduced maximal responses at functionally expressed human P2Y$_4$-receptors, but was without any effect at rat P2Y$_4$-receptors[114]. Reactive blue-2 caused a modest reduction of agonist-induced responses at the human P2Y$_4$-receptor and abolished the responses at the rat P2Y$_4$-receptor[114,119].

P2Y$_6$: The P2Y$_6$-receptor is blocked by reactive blue-2, PPADS and suramin (Table 4). 4,4'-Diisothiocyanatostilbene-2,2'-disulfonate (DIDS)[178] and its analogue MRS2578 (N,N''-1,4-butanediylbis[N'-(3-isothiocyanatophenyl)thiourea)[171] act as irreversible or slowly reversible antagonists at human and rat P2Y$_6$-receptors. MRS2578 is highly potent at the P2Y$_6$-receptor and shows no interaction with P2Y$_1$-, P2Y$_2$-, P2Y$_4$- and P2Y$_{11}$-receptors[171].

P2Y$_{11}$: Suramin is an antagonist at the human P2Y$_{11}$-receptor with a pA$_2$-value of 6.1 (Table 4). Its analogue NF157 also acts as an antagonist at the P2Y$_{11}$-receptor (Table 4). In addition, NF157 blocks P2X$_1$-receptors[155,172]. The bisphosphate derivative adenosine-3´-phosphate-5´-phosphosulfate had been shown to be a partial agonist/antagonist at the P2Y$_{11}$-receptor[130].

P2Y$_{12}$: The receptor is blocked by suramin and, with a relatively high potency, by reactive blue-2 (Table 4). 2-Methylthio-AMP and ATP are low-affinity antagonists[136,179]. In contrast, some triphosphate analogues including cangrelor (AR-C69931MX, N^6-(2-methylthioethyl)-2-(3,3,3-trifluoropropylthio)-β,γ -dichloromethylene-ATP; Table 4) and AR-C67085 (2-propylthio-β,γ -dichloromethylene-D-ATP) act as very potent and competitive P2Y$_{12}$-antagonists[180].

The pA_2-value of cangrelor (AR-C69931MX) at the recombinant human $P2Y_{12}$-receptor amounted to 9.1[174]. For AR-C67085 a pA_2-value of 8.2 has been reported[173]. However, it should be noted that these compounds are not selective for the $P2Y_{12}$-subtype. AR-C67085 acts as an agonist at the human $P2Y_{11}$-receptor (see above) and both AR-C67085 and cangrelor also block human and rat $P2Y_{13}$-receptors (see below). In contrast, the active metabolites of thienopyridine compounds appear to act as $P2Y_{12}$-selective antagonists. The thienopyridine compounds ticlopidine[181], clopidogrel[182] and prasugrel (CS-747)[183] are known to be powerful inhibitors of the ADP-induced platelet aggregation. The compounds act only in vivo; they have to be metabolized. Their active metabolites interact in a covalent manner with the receptor proteins (for clopidogrel see ref. 45). The active metabolite of prasugrel affected only human $P2Y_{12}$-, but not human $P2Y_1$-receptors[184]. The acyclic analogue of adenosine bisphosphate, MRS2395, inhibited the ADP-induced aggregation of human platelets without any effects on the $P2Y_1$-receptor mediated acceleration of phospholipase C activity[185]. And finally, an uncharged carbocyclic nucleoside analogue (AZD6140) has been developed as an orally active $P2Y_{12}$-receptor antagonist[186].

$P2Y_{13}$: The human $P2Y_{13}$-receptor is blocked by suramin, reactive blue-2 and high concentrations of PPADS (Table 4). The 2-chloro-5-nitro analogue of PPADS (MRS2211) has recently been shown to act as a competitive antagonist at the human $P2Y_{13}$-receptor with a pA_2-value of 6.3 (Table 3). Moreover, cangrelor also block the human $P2Y_{13}$-receptor with a non-competitive mode of interaction[145]. A non-competitive mode of interaction has also been shown for the blockade of the rat $P2Y_{13}$-receptor by cangrelor[146,187].

$P2Y_{14}$: A recent study demonstrated that UDP acts as an antagonist at the $P2Y_{14}$-receptor with a pK_B-value of 7.3[177].

CysLT1: Responses to UDP were blocked by the antagonist MK571 which showed no interaction with recombinant $P2Y_4$- and $P2Y_6$-receptors[16,17].

Table 4. Affinities (K_B in µM) of selected antagonists at recombinant human P2Y-receptors

Compound	*$P2Y_1$*	*$P2Y_2$*	*$P2Y_4$*	*$P2Y_6$*	*$P2Y_{11}$*	*$P2Y_{12}$*	*$P2Y_{13}$*	*$P2Y_{14}$*	*Selected references*
Suramin	3	50	- (300µM)	↓27% (100µM)	0.8	3	↓80% (10µM)		130, 138, 145, 159-161
PPADS	4-12	- (30µM)	↓30% (100µM)	↓69% (100µM)	- (100µM)	- (100µM)	↓50% (10µM)		117, 130, 132, 137, 145, 159-162
RB-2	0.8		↓33% (100µM)	1	↓80% (100µM)	0.025	↓80% (10µM)		92, 117, 130, 137, 145, 162, 163
MRS2179	0.15	- (30µM)	- (30µM)	- (30µM)		- (10µM)	- (100µM)		103, 138, 145, 164-166
MRS2279	0.004	- (30µM)	- (30µM)	- (30µM)	- (30µM)				167, 168
MRS2500	0.002					- (100µM)			169, 170
MRS2578	- (10µM)	- (10µM)	- (10µM)	0.04	- (10µM)				171
NF157					0.5				155, 172
Cangrelor						0.0008	↓80% (0.01µM)		137, 145, 173, 174
Clopidogrel m.						0.1&	- (2µM)		145, 175
MRS2211	>10					- (10 µM)	0.5		176
UDP								0.05 (human)	177

The table summarizes studies analyzing the potencies (affinity constant in µM) of P2-receptor antagonists at recombinant human P2Y-receptors or inhibitory effects mediated by these antagonists on responses to receptor stimulation. PPADS, pyridoxal-5´-phosphate-6-azophenyl-2´,4´-disulfonate; RB-2, reactive blue 2; MRS2179, 2´-deoxy-N^6-methyladenosine-3´,5´-bisphosphate; MRS2279, 2-chloro-N^6-methyl-(*N*)-methanocarba-2´-deoxyadenosine 3´,5´-bisphosphate; MRS2500, 2-iodo-N^6-methyl-(N)-methanocarba-2´-deoxyadenosine 3´,5´-bisphosphate; MRS2578, N,N''-1,4-butanediylbis[N'-(3-isothiocyanatophenyl)thio urea; NF157, 8,8'-[carbonylbis[imino-3,1-phenylenecarbonylimino(4-fluoro-3,1-phenylene)carbonylimino]]bis-1,3,5-naphthalene trisulfonic acid; cangrelor=ARC69931MX, N^6-(2-methylthioethyl)-2-(3,3,3-trifluoropropylthio)-β,γ-dichloromethylene-ATP; Clopidogrel m., active metabolites of clopidogrel; MRS2211, 2-[(2-chloro-5-nitrophenyl)azo]-5-hydroxy-6-me- thyl-3-[(phosphonooxy)methyl]-4-pyridinecarboxaldehyde. &, estimated from published data. -(30µM), no antagonistic effect at concentrations up to 30 µM; ↓30%(100µM), decrease by 30 % at the concentration of 100 µM.

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P2X- and P2Y-receptor compounds

Cat. No.	Product	Category
BN0014	2-Methylthio-ADP trisodium salt	Potent $P2Y_{1,12,13}$ agonist
BN0013	2-Methylthio-ATP tetrasodium salt	P2 purinergic agonist
BN0680	Clopidogrel hydrogensulfate	$P2Y_{12}$ purinergic antagonist, prodrug
BN0208	Evans Blue tetrasodium salt	Selective P2X purinergic antagonist
BS0104	KN-62	Non-competitive $P2X_7$ antagonist, CaM kinase II inhibitor
BN0377	NF 023	Selective $P2X_1$ antagonist, $G_{O/i\alpha}$-subunit inhibitor
BN0378	NF 279	Potent, selective $P2X_1$ antagonist
BN0379	NF 449	Potent, selective $P2X_1$ antagonist
BN0427	PPADS tetrasodium salt	Non-selective P2 purinergic antagonist
BN0428	iso-PPADS	P2X purinergic antagonist
BN0573	PPNDS	Potent, selective $P2X_1$ antagonist
BP0363	Spinorphin	Potent $P2X_3$ receptor antagonist
BN0510	Suramin hexasodium salt	Non-selective P2 purinergic antagonist, $S1P_3$ antagonist
BG0339	Ticlopidine hydrochloride	$P2Y_{12}$ purinergic antagonist, prodrug
BN0523	TNP-ATP	Potent, selective P2X antagonist

Other

Cat. No.	Product	Category
BN0278	Ivermectin	$P2X_4$ receptor positive allosteric modulator
BN0570	MRS 2219	$P2X_1$ receptor potentiator

Related Radioligands

Cat. No.	Product	Category
ART-0338	[^{3}H]-Adenosine 5'-monophosphate	P2 endogenous ligand
ART-1256	[^{3}H]-Suramin hexasodium salt	Non-selective P2 purinergic antagonist, $S1P_3$ antagonist

P2Y-Receptor Cell Lines

Receptor	Sub-type	Species	Stable Cell Lines	*EZ Cells
Purinergic	$P2Y_1$	human	A676	A476
	$P2Y_6$	human	A677	A477
	$P2Y_{11}$	human	A679	A486

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BIOTREND Chemicals AG
Unterdorfstrasse 21b
CH-8602 Wangen
Tel. +41 44 805 76 76
Fax. +41 44 805 76 77
info@biotrend.ch
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BIOTREND Chemicals LLC
136 S. Holiday Road, app. C.
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Fax. +1 850 650 - 4383
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BIOTREND Chemikalien GmbH
Im Technologiezentrum Köln
Eupener Str. 157
D-50933 Köln
Tel. +49 221 949 83 20
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Unterdorfstrasse 21b
CH-8602 Wangen
Tel. +41 44 805 76 81
Fax. +41 44 805 76 75
hassler@anawa.ch
www.anawa.ch