

Adenosine Receptors

Key References

- Baraldi, P.G. et al. "Synthesis of new pyrazolo[4,3-e]1,2,4-triazolo[1,5-c]pyrimidine and 1,2,3-triazolo[4,5-e]1,2,4-triazolo[1,5-c]pyrimidine displaying potent and selective activity as A_{2A} adenosine receptor antagonists." *Bioorg. Med. Chem. Lett.* **4**, 2539-2544 (1994).
- Fredholm, B.B. et al. "Adenosine receptors." in: *The IUPHAR Compendium of Receptor Characterization and Classification, 2nd edition*, pp. 78-87, IUPHAR Media, London, UK (2000).
- Jacobson, K.A. et al. "8-(3-Chloro-styryl)caffeine is a selective A₂-adenosine antagonist *in vitro* and *in vivo*." *FEBS Lett.* **323**, 141-144 (1993).
- Jacobson, K.A. et al. "Adenosine receptors: Pharmacology, structure-activity relationships, and therapeutic potential." *J. Med. Chem.* **35**, 407-422 (1992).
- Kim, H.O. et al. "Selective ligands for rat A₃ adenosine receptors: Structure-activity relationships of 1,3-dialkylxanthine 7-ribose derivatives." *J. Med. Chem.* **37**, 4020-4030 (1994).
- Klotz, K.N. "Adenosine receptors and their ligands." *Naunyn Schmiedeberg's Arch. Pharmacol.* **362**, 382-391 (2000).
- Linden, J. et al. "Adenosine receptors." In: *Handbook of Receptors and Channels. G Protein-Coupled Receptors*, Vol. 1, Ed. S.J. Peroutka, pp. 29-44 CRC Press, Boca Raton, FL (1994).
- Linden, J. "Cloned adenosine A₃ receptors: Pharmacological properties, species differences and receptor functions." *Trends Pharmacol. Sci.* **15**, 298-306 (1994).
- Muller, C.E. "Adenosine receptor ligands – recent developments. Part 1. Agonists." *Curr. Med. Chem.* **7**, 1269-12688 (2000).
- Salvatore, C.A. et al. "Molecular cloning and characterization of the human A₃ adenosine receptor." *Proc. Natl. Acad. Sci. USA* **90**, 10365-10369 (1993).
- Shimada, J. "(E)-1,3-Dialkyl-7-methyl-8-(3,4,5-trimethoxystyryl) xanthines: Potent and selective adenosine A₂ antagonists." *J. Med. Chem.* **35**, 2342-2345 (1992).
- Zhou, Q.Y. et al. "Molecular cloning and characterization of an adenosine receptor: The A₃ adenosine receptor." *Proc. Natl. Acad. Sci. USA* **89**, 7432-7436 (1992).

Overview

Modulation of adenosine receptors by selective agonists and antagonists has potential for the treatment of various cardiovascular, inflammatory and neurological diseases. For example, adenosine is released in large amounts during myocardial ischemia and is capable of exerting potent cardioprotective effects in the heart. A synthetic adenosine receptor agonist might therefore be beneficial to the survival of the ischemic heart. In the asthmatic lung, however, adenosine acts as an irritant and bronchoconstrictor, such that a synthetic adenosine receptor antagonist would be desirable.

There are four known subtypes of adenosine receptors, referred to as A₁, A_{2A}, A_{2B} and A₃. All are members of the superfamily of G protein-coupled receptors and each bears the characteristic motif of seven trans-membrane spanning domains. Selectivity for A₁ receptors is typically accomplished through modification of the N⁶-position that gives rise to compounds such as CPA, CHA, R-PIA. The 2-chloro analog CCPA displays slightly greater A₁ receptor selectivity than the parent CPA. The affinities of these N⁶-substituted derivatives at A₃ receptors are often intermediate between their respective A₁ and A_{2A} affinities. Although most N⁶-substituted adenosine agonists are A₁-selective, the agonist DPMA is 30-fold selective for the A_{2A} receptor.

Small alkyl amide substitution at the 5'-position, as in NECA, provides increased potency at A_{2A} receptors. NECA is also among the most potent agonists at all four subtypes of adenosine receptors and is therefore non-selective. CGS21680 is a truly A_{2A}-selective adenosine agonist, possessing a 140-fold selectivity for A_{2A} versus A₁ receptors. Aryl amines related to CGS21680

(e.g. PAPA-APEC) and a 5-hydroxyl derivative (APE) can be radioiodinated to provide A_{2A} receptor-selective radioligands.

The most recently discovered member of the adenosine receptor family, the A₃ receptor, has a unique pharmacological profile, tissue distribution and effector coupling. In recent years, selective A₃ adenosine receptor agonists and antagonists have been described. Previously, APNEA had been used as an agent to activate A₃ receptors in the presence of non-A₃ antagonists, although APNEA is actually 8-fold selective for A₁ receptors. IB-MECA is 50-fold selective for A₃ versus either A₁ or A_{2A} receptors *in vitro* and appears to be highly A₃ selective *in vivo*. The related 4-amino derivative may be radioiodinated giving rise to [¹²⁵I]-I-AB-MECA which is widely used as a high affinity radioligand for A₃ receptors. 2-Chloro substitution, in combination with modifications at N⁶ and 5'-positions, e.g. in CI-IB-MECA (selective for rat A₃ vs A₁ and A_{2A} receptors by 2500- and 1400-fold, respectively), further enhances A₃ selectivity.

Adenosine receptor antagonists, of which xanthines and numerous classes of fused heterocyclic compounds are representative, have been under development as anti-asthmatic, anti-arrhythmic, renal-protective, anti-Parkinson's and cognition enhancing drugs. A₃ receptor antagonists have potential in treating inflammatory disorders.

The classical xanthines, theophylline (1,3-dimethylxanthine) and caffeine (1,3,7-trimethylxanthine) are non-selective adenosine receptor antagonists possessing low micromolar affinity. Selective

antagonists for A₁ receptors include many 8-aryl and 8-cycloalkyl xanthine derivatives, such as CPX which is ~500-fold selective for A₁ versus A_{2A} receptors. Certain non-xanthine antagonists, such as N-0841, are A₁ selective, whereas SCH-58261 is a highly potent and selective A_{2A} receptor antagonist. CSC, and other 8-styryl-xanthines such as KW 6002, are selective for A_{2A} receptors versus both A₁ and A_{2B} receptors. However, in dilute solution, these compounds suffer from sensitivity to photoisomerization.

At A₃ receptors, the dihydropyridine derivative MRS 1191 (not active at L-type calcium channels) and the triazolo-quinazoline MRS 1220 (not selective in rat) are both relatively potent A₃ receptor antagonists, possessing K_i values of 31 and 0.65 nM, respectively, at the human subtype. MRS 1523 is a selective A₃ adenosine receptor antagonist in the rat.

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CURRENTLY ACCEPTED NAME	A ₁	A _{2A}	A _{2B}	A ₃
ALTERNATE NAMES	R _i	A _{2a} , R _a	A _{2b}	
STRUCTURAL INFORMATION	326 aa (human)	412 aa (human)	332 aa (human)	318 aa (human)
RECEPTOR SELECTIVE AGONISTS	Adenosine amine congener (A-111) CPA (C 8031) CHA (C 9901) CCPA (C-142 , C 7938)	CGS21680 (C-141) DPMA (D-130) HE-NECA (H 8034) ^a	NECA (E 2387) ^b	IB-MECA (I-146) CI-IB-MECA (C-277)
RECEPTOR SELECTIVE ANTAGONISTS	CPX (C-101) CPT (C-102) N-0840 (N-154) WRC-0571	KW 6002 8-(3-Chlorostyryl)caffeine (C-197) SCH-58261	XAC (X-103) ^b Alloxazine (A-242) MRS 1754	I-ABOPX ^c MRS 1191 (M-227) MRS 1220 (M-228) MRS 1523 (M 1809) VUF 5574 (V 5888)
SIGNAL TRANSDUCTION MECHANISMS	G _i (cAMP modulation) G _{q/11} (increase IP ₃ /DAG) ↑K ⁺ , ↓Ca ²⁺	G _s (increase cAMP)	G _s (increase cAMP)	G _i (cAMP modulation) G _{q/11} (increase IP ₃ /DAG)
RADIOLIGANDS OF CHOICE	[³ H]-CHA [³ H]-CPX [³ H]-R-PIA	[³ H]-CGS21680 [¹²⁵ I]-PAPA-APEC [¹²⁵ I]-APE	[³ H]-MRS 1754 [³ H]-CPX	[¹²⁵ I]-APNEA [¹²⁵ I]-AB-MECA

ABBREVIATIONS

AB-MECA: N⁶-(4-Aminobenzyl)-9-[5-(methylcarbamoyl)-β-D-ribofuranosyl]adenine

APE: 2-[2-(4-Amino-3-[¹²⁵I]iodophenyl)ethylamino]adenosine

APNEA: N⁶-[2-(4-Aminophenyl)ethyl]adenosine

CCPA: 2-Chloro CPA

CGS21680: 2-p-(2-Carboxyethyl)phenethylamino-5'-N-ethylcarboxamidoadenosine

CHA: N⁶-Cyclohexyladenosine

CI-IB-MECA: 2-Chloro-N⁶-(3-Iodobenzyl)-9-[5-(methylcarbamoyl)-β-D-ribofuranosyl]adenine

CPA: N⁶-Cyclopentyladenosine

CPT: 8-Cyclopentyl-1,3-dimethylxanthine

CPX: 8-Cyclopentyl-1,3-dipropylxanthine

DBXRM: 1,3-Dibutylxanthine 7-ribose 5'-N-methylcarboxamide

DPMA: N⁶-[2-(3,5-Dimethoxyphenyl)-2-(methylphenyl)ethyl]adenosine

HE-NECA: 2-Hexynyl-adenosine-5'-N-ethyluronamide

I-ABOPX: 3-(3-Iodo-4-aminobenzyl)-8-(4-oxyacetate)-phenyl-1-propyl xanthine

IB-MECA: N⁶-(3-Iodobenzyl)-9-[5-(methylcarbamoyl)-β-D-ribofuranosyl]adenine

KW 6002: (E)-1,3-diethyl-8-(3,4-dimethoxyphenylethyl)-7-methyl-3,7-dihydro-1H-purine-2,6-dione

MRS 1191: 3-Ethyl 5-benzyl 2-methyl-6-phenyl-4-phenylethynyl-1,4-(±)-dihydropyridine-3,5-dicarboxylate

MRS 1523: 2,3-Diethyl-4,5-dipropyl-6-phenylpyridine-3-thiocarboxylate-5-carboxylate

MRS 1220: 9-Chloro-2-(2-furyl)-5-phenylacetylamino[1,2,4]-triazolo[1,5-c]quinazoline

MRS 1754: 8-[4-[[[(4-cyano)phenylcarbamoylmethyl]oxy]phenyl]-1,3-di-(n-propyl)xanthine

N-0840: N⁶-Cyclopentyl-9-methyladenine

NECA: N-Ethylcarboxamidoadenosine

PAPA-APEC: 1-[6-Amino-2-[[2-[4-[3-[[2-[[[(4-aminophenyl)acetyl]amino]ethyl]amino]-3-oxopropyl]phenyl]ethyl]amino]-9H-purin-9-yl]-1-deoxy-N-ethyl-b-D-ribofuranuronamide

PIA: R(-)-N⁶-(2-Phenylisopropyl)adenosine

SCH-58261: 5-Amino-7-(β-phenylethyl)-2-(8-furyl)pyrazolo(4,3-e)-1,2,4-triazolo(1,5-c)pyrimidine

VUF 5574: N-(2-Methoxyphenyl)-N'-(2-(3-pyridyl)quinazolin-4-yl)urea

WRC-0571: 8-(N-Methylisopropyl)amino-N-(5'-endohydroxy-endonorbornyl)-9-methyladenine

XAC: 8-[4-[[[(2-Aminoethyl)amino]carbonyl]methyl]oxy]phenyl]-1,3-dipropylxanthine; Xanthine amine congener

FOOTNOTES

a HE-NECA is also a potent agonist at A₃ receptors.

b NECA and XAC are among the most potent agents at this adenosine receptor subtype. However, these compounds are not subtype selective.

c Rat A₃ receptor is insensitive to xanthine blockade.