

Acetylcholine (muscarinic)

Overview: Muscarinic acetylcholine receptors (nomenclature as agreed by NC-IUPHAR sub-committee on Muscarinic Acetylcholine Receptors, Caulfield and Birdsall, 1998) are 7TM receptors of the rhodopsin-like family where the endogenous agonist is acetylcholine. In addition to the agents listed in the table, AC-42 and desmethylclozapine have been described as selective agonists of the M₁ receptor subtype *via* binding to a site distinct to that recognised by non-selective agonists (Spalding *et al.*, 2002; Sur *et al.*, 2003). There are two allosteric sites on muscarinic receptors, one defined by it binding gallamine, strychnine and brucine and the other binds KT5720, WIN62,577, WIN51,708 and staurosporine (Lazareno *et al.*, 2000, 2002). There are selective enhancers of acetylcholine binding and action; brucine and KT5720 at M₁ receptors, PG135 at M₂ receptors, N-chloromethylbrucine and WIN62,577 at M₃ receptors and thiochrome at M₄ receptors (Birdsall and Lazareno, 2005). The allosteric site for gallamine and strychnine on M₂ receptors can be labelled by [³H]dimethyl-W84 (Tränkle *et al.*, 2003). THRX-160209 is a multivalent ligand that may achieve its selectivity for M₂ receptors by binding both to the orthosteric and a nearby allosteric site (Steinfeld *et al.*, 2007).

Nomenclature	M ₁	M ₂	M ₃
Ensembl ID	ENSG00000168539	ENSG00000181072	ENSG00000133019
Principal transduction	G _{q/11}	G _{i/o}	G _{q/11}
Antagonists	MT7 (11.0), 4-DAMP (9.2), triptiramine (8.8), darifenacin (8.3), pirenzepine (6.3–8.3), guanylpirenzepine (7.7), AFDX384 (7.3–7.5), MT3 (7.1), himbacine (6.7–7.1), AFDX116 (6.2)	triptiramine (9.6), AFDX384 (8.0–9.0), 4-DAMP (8.4), himbacine (7.9–8.4), darifenacin (7.3–7.6), AFDX116 (6.7–7.3), pirenzepine (4.9–6.4), MT7 (<6), MT3 (<6), guanylpirenzepine (5.6)	4-DAMP (9.3), darifenacin (9.1), AFDX384 (7.2–7.8), triptiramine (7.1–7.4), himbacine (6.9–7.2), pirenzepine (5.6–6.7), guanylpirenzepine (6.5), AFDX116 (6.1), MT3 (<6), MT7 (<6)
Probes (K _D)	[³ H]NMS (80–150 pM), [³ H]QNB (15–60 pM), [³ H]pirenzepine (3–15 nM), (R,R)-quinuclidinyl-4-[¹⁸ F]-fluoromethyl-benzilate (PET ligand), [¹¹ C]xanomeline (PET ligand), [¹¹ C]butylthio-TZTP (PET ligand)	[³ H]NMS (200–400 pM), [³ H]QNB (20–50 pM), [¹⁸ F]FP-TZTP (PET ligand),	[³ H]NMS (150–250 pM), [³ H]QNB (30–90 pM), [³ H]darifenacin (300 pM)

Nomenclature	M ₄	M ₅
Ensembl ID	ENSG00000180720	ENSG00000184984
Principal transduction	G _{i/o}	G _{q/11}
Antagonists	4-DAMP (8.9), MT3 (8.7), AFDX384 (8.0–8.7), AFDX116 (7–8.7), himbacine (7.9–8.2), triptiramine (7.8–8.2), darifenacin (8.1), pirenzepine (5.9–7.6), guanylpirenzepine (6.5), MT7 (<6)	4-DAMP (9.0), darifenacin (8.6), triptiramine (7.3–7.5), guanylpirenzepine (6.8), pirenzepine (6.2–6.9), himbacine (5.4–6.5), AFDX384 (6.3), AFDX116 (5.3–5.6), MT3 (<6), MT7 (<6)
Probes (K _D)	[³ H]NMS (50–100 pM), [³ H]QNB (20–80 pM)	[³ H]NMS (500–700 pM), [³ H]QNB (20–60 pM)

Antagonist data tabulated are pK_i values determined for human recombinant receptors. MT3 (m4-toxin) and MT7 (m1-toxin1) are toxins contained with the venom of the Eastern green mamba (*Dendroaspis augusticeps*) (see Bradley, 2000; Potter *et al.*, 2004).

Abbreviations: 4-DAMP, 4-diphenylacetoxy-N-methylpiperidine methiodide; AC-42, 4-*n*-butyl-1-[4-(2-methylphenyl)-4-oxo-1-butyl]-piperidine hydrogen chloride; AFDX116, (otenzepad), 1-[2-[2-(diethylaminomethyl)piperidin-1-yl]acetyl]-5*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-one; AFDX384, (±)-5,11-dihydro-11-[(2-[2-[dipropylamino)methyl]-1-piperidinyl)ethyl]amino)carbonyl]-6*H*-pyrido[2,3-*b*](1,4)benzodiazepine-6-one; Butylthio-TZTP, butylthio-thiadiazolyltetrahydro-1-methyl-pyridine; Dimethyl-W84, N,N'-bis[3-(1,3-dihydro-1,3-dioxo-4-methyl-2*H*-isoindol-2-yl)propyl]-N,N',N'-tetramethyl-1,6-hexanediaminium diiodide; FP-TZTP, [3-(3-(3-Fluoropropyl)thio)-1,2,5-thiadiazol-4-yl]1,2,5,6-tetrahydro-1-methylpyridine; KT5720, (9*S*,10*S*,12*R*)-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-9,12-epoxy-1*H*-diindolo[1,2,3-*fg*:3',2',1'-*kl*]pyrrolo[3,4-*l*][1,6]benzodiazocine-10-carboxylic acid hexyl ester; NMS, N-methylscopolamine; PG135, (3*aS*,12*R*,12*aS*,12*bR*)-2-amino-2,3,3*a*,4,11,12*a*,12*b*-octahydro-10-hydroxyisoquino[2,1,8-*lma*]carbazol-5(1*H*)-one hydrochloride; QNB, 3-quinuclidinylbenzilate; THRX160209, 4-[*N*-[7-(3-(*S*)-(1-carbamoyl-1,1-diphenylmethyl)pyrrolidin-1-yl)hept-1-yl]-*N*-(*n*-propyl)amino]-1-(2,6-dimethoxy-benzyl)piperidine; WIN51,708, 17-β-hydroxy-17-α-ethynyl-5-α-androstano[3,2-*b*]pyrimido[1,2-*a*]benzimidazole; WIN62,577, 17-β-hydroxy-17-α-ethynyl-Δ⁴-androstano[3,2-*b*]pyrimido[1,2-*a*]benzimidazole

Further Reading

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Citation Information

We recommend that any citations to information in the Guide are presented in the following format:

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