Acetylcholine (muscarinic)

Overview: Muscarinic acetylcholine receptors (nomenclature as agreed by NC-IUPHAR Subcommittee 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, its structural analogues AC-260584 and 77-LH-28-1, desmethylclozapine and TBPB have been described as selective agonists of the M_1 receptor subtype via binding in a mode distinct from that utilized by non-selective agonists (Spalding *et al.*, 2002; 2006; Sur *et al.*, 2003; Langmead *et al.*, 2006; 2008; May *et al.*, 2007; Jones *et al.*, 2008). 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, KT5720, VU0090157 and VU0029767 at M_1 receptors, PG135 at M_2 receptors, N-chloromethylbrucine and WIN62,577 at M_3 receptors, thiochrome, LY2033298, VU0152099 and VU0152100 at M_4 receptors and VU0238429 at M_5 receptors (Birdsall and Lazareno, 2005; Brady *et al.*, 2008; Chan *et al.*, 2008; Shirey *et al.*, 2008; Bridges *et al.*, 2009; Marlo *et al.*, 2009). LY2033298 has also been suggested to activate the M_4 receptor directly via an allosteric site (Nawaratne *et al.*, 2008). The allosteric site for gallamine and strychnine on M_2 receptors can be labelled by [^{3}H]dimethyl-W84 (Tränkle *et al.*, 2003). McN-A-343 is a functionally selective partial agonist that appears to interact in a bitopic mode with both the orthosteric and an allosteric site on the M_2 muscarinic receptor (Valant *et al.*, 2008). THRX160209, hybrid 1 and hybrid 2, are multivalent ligands that also achieve selectivity for M_2 receptors by binding both to the orthosteric and a nearby allosteric site (Steinfeld *et al.*, 2007; Antony *et al.*, 2009). VU0255035 is a recently described competitive antagonist with selectivity for the M_1 receptor (Sheffler *et al.*, 2009).

Nomenclature	M_1	M_2	M_3
Ensembl ID	ENSG00000168539	ENSG00000181072	ENSG00000133019
Principal transduction	$G_{q/11}$	$G_{i/o}$	$G_{q/11}$
Antagonists (pK_i)	MT7 (10.9–11.0), 4-DAMP (9.2), tripitramine (8.8), darifenacin (8.3), pirenzepine (6.3–8.3), VU0255035 (7.8), guanylpirenzepine (7.7), AFDX384 (7.3–7.5), MT3 (6.5–7.1), himbacine (6.7–7.1), AFDX116 (6.2)	tripitramine (9.6), AFDX384 (8.0–9.0), 4-DAMP (8.3), himbacine (7.9–8.4), darifenacin (7.3–7.6), AFDX116 (6.7–7.3), VU0255035 (6.2), pirenzepine (4.9–6.4), MT3 (<6), guanylpirenzepine (5.6), MT7 (<5)	4-DAMP (9.3), darifenacin (9.1), AFDX384 (7.2–7.8), tripitramine (7.1–7.4), himbacine (6.9–7.2), pirenzepine (5.6–6.7), guanylpirenzepine (6.5), VU0255035 (6.1), AFDX116 (6.1), MT3 (<6), MT7 (<5)
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 (p*Ki*)	4-DAMP (8.9), MT3 (8.7), AFDX384 (8.0–8.7), AFDX116 (7–8.7), himbacine (7.9–8.2), tripitramine (7.8–8.2), darifenacin (8.1), pirenzepine (5.9–7.6), guanylpirenzepine (6.5), VU0255035 (5.9), MT7 (<5)	4-DAMP (9.0), darifenacin (8.6), tripitramine (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), VU0255035 (5.6), MT3 (<6), MT7 (<5)
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 Potter *et al.*, 2004; Servent and Fruchart-Gaillard, 2009).

Abbreviations: **77-LH-28-1**, 1-[3-(4-butyl-1-piperidinyl)propyl]-3,4-dihydro-2(1*H*)-quinolinone; **4-DAMP**, 4-diphenylacetoxy-N-methylpiperidine methiodide; **AC-42**, 4-*n*-butyl-1-[4-(2-methylphenyl)-4-oxo-1-butyl]-piperidine hydrogen chloride; **AC-260584**, 4-[3-(4-butylpiperidin-1-yl)-propyl]-7-fluoro-4*H*-benzo[1,4]oxazin-3-one; **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-2H-isoindol-2-yl)propyl]-N,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; **Hybrid 1M**, 2-{3-[1-(6-{1,1-dimethyl-1-[4-(isoxazol-3-yloxy) but-2-ynyl]-ammonium}hexyl)-1,1 dimethylammonio]propyl}isoindoline-1,3-dione dibromide; **Hybrid 2**, 2-{3-[1-(6-{1,1-dimethyl-1-[4-(isoxazol-3-yloxy)but-2-ynyl]-ammonium}hexyl)-1,1-dimethylammonio]-2,2-dimethylpropyl}-benzo[*de*]isoquinoline-1,3-dione dibromide; **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-*i*][1,6] benzodiazocine-10-carboxylic acid hexyl ester; **LY2033298**, 3-amino-5-chloro-6-methoxy-4-methyl-thieno(2,3-b)pyridine-2-carboxylic acid cyclopropylamide; **McN-A-343**, 4-(3-chlorophenyl) carbamoyloxy)-2-butynyltrimethyl ammonium chloride; NMS, N-methylscopolamine; **PG135**, (3a*S*,12*R*,12a*S*,12b*R*)-2-amino-2,3,3a,4,11,12a,12b-octahydro-10-hydroxyisoquino[2,1,8-*lma*]carbazol-5(1*H*)-one hydrochloride; QNB,

3-quinuclidinylbenzilate; **TBPB**, 1-(1′-2-methylbenzyl)-1,4′-bipiperidin-4-yl)-1*H*-benzo[d]imidazol-2(3*H*)-one; **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; **VU0029767**, (*E*)-2-(4-ethoxyphenylamino)-*N*′-((2-hydroxynaphthalen-1-yl)methylene)acetohydrazide; **VU0090157**, cyclopentyl 1,6-dimethyl-4-(6-nitrobenzo [d][1,3]-dioxol-5-yl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate; **VU0152099**, 3-amino-*N*-(benzo[d][1,3]dioxol-5-ylmethyl)-4,6-dimethylthieno[2,3-*b*]pyridine carboxamide; **VU0152100**, 3-amino-*N*-(4-methoxybenzyl)-4,6-dimethylthieno[2,3-*b*]pyridine carboxamide; **VU0238429**, structure not available; **VU0255035**, *N*-(3-oxo-3-(4-(pyridine-4-yl)piperazin-1-yl)propyl)-benzo[c][1,2,5]thiadiazole-4 sulfonamide; **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-Δ^4-androstano[3,2-*b*]pyrimido[1,2-*a*]benzimidazole

Further Reading

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