5-HT (5-Hydroxytryptamine)

5-HT (5-Hydroxytryptamine) receptors [nomenclature as agreed by NC-IUPHAR Subcommittee on 5-HT receptors (Hoyer *et al.*, 1994) and subsequently revised (Hartig *et al.*, 1996)] are, with the exception of the ionotropic 5-HT_3 class, 7TM receptors where the endogenous agonist is 5-HT. The diversity of metabotropic 5-HT receptors is increased by alternative splicing that produces isoforms of the 5-HT_{2A} (non-functional), 5-HT_{2C} (non-functional), 5-HT_4, 5-HT_6 (non-functional) and 5-HT_7 receptors. Unique to the 7TM receptors, RNA editing produces 5-HT_{2C} receptor isoforms that differ in function, such as efficiency and specificity of coupling to $G_{q/11}$ and also pharmacology (reviewed by Bockaert *et al.*, 2006; Werry *et al.*, 2008).

Nomenclature	5-HT_{1A}	5-HT_{1B}	5-HT_{1D}	5-ht_{1E}
Other names	–	5-HT1Dβ	$5\text{-HT}_{1D\alpha}$	–
Ensembl ID	ENSG00000178394	ENSG00000135321	ENSG00000179546	ENSG00000168830
Principal transduction	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$
Selective agonists (pK_i)	8-OH-DPAT (8.4–9.4), U92016A (9.7)	L694247 (9.2), CP94253 (8.7)	PNU109291 (9.0 – gorilla, Ennis *et al.*, 1998), sumatriptan (8.0–8.7), eletriptan (8.9), L694247 (9.0, Wurch *et al.*, 1998)	–
Selective antagonists (pK_i)	(±)WAY100635 (7.9–9.2), (*S*)-UH301 (7.9–8.6), NAD299 (robalzotan, 9.2)	SB236057 (8.2, inverse agonist, Middlemiss *et al.*, 1999), SB224289 (inverse agonist, 8.2–8.6), GR55562 (pK_B 7.4, Hoyer *et al.*, 2002)	SB714786 (9.1) BRL15572 (7.9)	–
Probes (K_D)	[^{3}H]WAY100635 (0.3 nM, Khawaja *et al.*, 1997), [^{3}H]NAD299 (0.16 nM), [^{3}H]8-OH-DPAT (0.4 nM), [^{11}C]WAY100635 (PET ligand), p-[^{18}F]MPPF (PET ligand)	[^{3}H]Alniditan (2.0–2.4 nM), [^{3}H]eletriptan (3 nM), [^{3}H]sumatriptan (11 nM) [^{125}I]GTI, [^{3}H]GR125743 (2.6 nM, Xie *et al.*, 1999), [*N*-methyl-$^3H_3$]AZ10419369 (PET ligand)	[^{3}H]Alniditan (1.2–1.4 nM), [^{3}H]eletriptan (0.9 nM), [^{3}H]sumatriptan (7 nM), [^{125}I]GTI, [^{3}H]GR125743 (2.8 nM, Xie *et al.*, 1999)	[^{3}H]5-HT (6 nM)

Nomenclature	5-HT_{1F}	5-HT_{2A}	5-HT_{2B}	5-HT_{2C}
Other names	$5\text{-HT}_{1E\beta}$, 5-HT_6	D, 5-HT_2	5-HT_{2F}	5-HT_{1C}
Ensembl ID	ENSG00000179097	ENSG00000102468	ENSG00000135914	ENSG00000147246
Principal transduction	$G_{i/o}$	$G_{q/11}$	$G_{q/11}$	$G_{q/11}$
Selective agonists (pK_i)	LY344864 (8.2, Phebus et al *et al.*, 1997) LY334370 (8.7)	DOI (7.4–9.2)	DOI (7.6–7.7), Ro600175 (8.3), BW723C86 (7.3–8.6)	DOI (7.2–8.6), Ro600175 (7.7–8.2), WAY163909 (8.0, Dunlop *et al.*, 2005), Locaserine (7.8, Thomsen *et al.*, 2008)
Selective antagonists (pK_i)	–	ketanserin (8.1–9.7), MDL100907 (9.4)	RS127445 (9.0), EGIS-7625 (9.0)	SB242084 (8.2–9.0), RS102221 (8.3–8.4), FR260010 (8.9, Harada *et al.*, 2006)
Probes (K_D)	[^{3}H]LY334370 (0.5 nM), [^{125}I]LSD	[^{3}H]ketanserin (0.2–1.3 nM), [^{3}H]RP62203 (fananserin, 0.13 nM – rat, Malgouris *et al.*, 1993), [^{11}C]M100907 (PET ligand), [^{18}F]altanserin (PET ligand)	[^{3}H]5-HT (8 nM – rat)	[^{3}H]mesulergine (0.5–2.2 nM), [^{3}H]LSD

Nomenclature	5-HT_4	5-ht_{5A}	5-ht_{5B}	5-HT_6
Other names	–	5-$HT_{5\alpha}$	–	–
Ensembl ID	ENSG00000164270	ENSG00000157219	ENSMUSG00000050534	ENSG00000158748
Principal transduction	G_s	G_i/G_o?	None identified	G_s
Selective agonists (pK_i)	BIMU8 (7.3), ML10302 (7.9–9.0), RS67506 (8.8 – guinea-pig, Eglen *et al.*, 1995)	–	–	WAY-181187 (8.7, Schechter *et al.*, 2008)E-6801 (partial agonist, 8.7, Holenz *et al.*, 2005)
Selective antagonists (pK_i)	GR113808 (9.3–10.3), SB204070 (9.8–10.4), RS100235 (8.7–12.2)	SB699551 (8.2)	–	SB399886 (9.4, Hirst *et al.*, 2006)SB271046 (8.9), SB357134 (8.5, Bromidge *et al.*, 2001), Ro630563 (7.9–8.4)
Probes (K_D)	[^{3}H]GR113808 (50–200 pM), [^{125}I]SB207710 (86 pM – piglet, Brown *et al.*, 1993), [^{3}H]RS57639 (0.25 nM – guinea-pig, Bonhaus *et al.*, 1997)[^{11}C] SB207145 (PET ligand)	[^{3}H]5-CT (2.5 nM), [^{125}I]LSD (0.2 nM)	[^{3}H]5-CT, [^{125}I]LSD	[^{125}I]SB258585 (1.0 nM, Hirst *et al.*, 2000), [^{3}H]Ro630563 (5 nM, Boess *et al.*, 1998), [^{3}H]5-CT, [^{125}I]LSD (2 nM)

Nomenclature	5-HT_7
Other names	5-HT_X, 5-HT_1-like
Ensembl ID	ENSG00000148680
Principal transduction	G_s
Selective agonists	–
Selective antagonists (pK_i)	SB656104 (8.7, Forbes *et al.*, 2002), SB269970 (8.6–8.9 Thomas *et al.*, 2000), SB258719 (7.5)
Radioligands (K_D)	[^{3}H]SB269970 (1.2 nM, Thomas *et al.*, 2000), [^{3}H]5-CT (0.4 nM, Thomas *et al.*, 2000) [^{3}H]LSD (3 nM), [^{3}H]5-HT (1–8 nM)

Tabulated pK_i and K_D values refer to binding to human 5-HT receptors unless indicated otherwise. Unreferenced values are extracted from the NC-IUPHAR database (http://www.iuphar-db.org). The nomenclature of 5-HT_{1B}/5-HT_{1D} receptors has been revised (Hartig *et al*., 1996). Only the non-rodent form of the receptor was previously called 5-$HT_{1D\beta}$: the human 5-HT_{1B} receptor (tabulated) displays a different pharmacology to the rodent forms of the receptor due to Thr335 of the human sequence being replaced by Asn in rodent receptors. NAS181 is a selective antagonist of the rodent 5-HT_{1B} receptor. Fananserin and ketanserin bind with high affinity to dopamine D4 and histamine H_1 receptors respectively, in addition to 5-HT_{2A} receptors. The human 5-ht_{5A} receptor has been claimed to couple to several signal transduction pathways when stably expressed in C6 glioma cells (Noda *et al*., 2003). The human orthologue of the mouse 5-ht_{5B} receptor is non-functional due to interruption of the gene by stop codons. In addition to the receptors listed in the table, an 'orphan' receptor, unofficially termed 5-HT_{1P}, has been described (Gershon, 1999).

Abbreviations: 5-CT, 5-carboxamidotryptamine; **8-OH-DPAT**, 8-hydroxy-2-(di-*n*-propylamino)tetralin; [***N*-methyl-$^3H_3$]AZ10419369**, 5-methyl-8-(4-methyl-piperazin-1-yl)-4-oxo-4*H*-chromene-2-carboxylicacid (4-morpholin-4-yl-phenyl)-amide; **BIMU8**, (endo-*N*-8-methyl-8-azabicyclo [3.2.1]oct-3-yl)-2,3-dihydro-3-isopropyl-2-oxo-1*H*-benzimidazol-1-carboxamide hydrochloride; **BRL15572**, 3-[4-(3-chlorophenyl) piperazin-1-yl]-1,1,-diphenyl-2-propanol; **BW723C86**, 1-[5(2-thienylmethoxy)-1*H*-3-indolyl]propan-2-amine hydrochloride; **CP94253**: 3- (1,2,5, 6-tetrahydro-4-pyridyl)-5-propoxypyrrolo[3, 2-b] pyridine; **E-6801**, 6-chloro-*N*-(3-(2-dimethylamino)ethyl)-1*H*-indol-5-yl)imidazo[2,1-*b*]thiazole-5-sulfonamide; **EGIS-7625**, 1-benzyl-4-[(2-nitro-4-methyl-5-amino)-phenyl]-piperazine; **FR260010**, (*N*-[3-(4-methyl-1*H*-imidazol-1-yl)phenyl]-5,6-dihydrobenzo[h]quinazolin-4-amine; **GR55562**, 3-[3-(dimethylamino)propyl]-4-hydroxy-*N*-[4-(4-pyridinyl)phenyl]benzamide; **GR113808**, [1-2[(methylsuphonyl)amino]ethyl]-4-piperidinyl]methyl-1-methyl-1*H*-indole-3-carboxylate; **GR125743**, *n*-[4-methoxy-3-(4-methyl-1-piperizinyl)phenyl]-3-methyl-4-(4-pyrindinyl)benzamide; **GTI**, 5-hydroxytryptamine-5-*O*-carboxymethylglycyltyrosinamide; **L694247**, 2-[5-[3-(4-methylsulphonylamino)benzyl-1,2,4-oxadiazol-5-yl]-1*H*-indol-3yl] ethanamine; **LY334370**, 5-(4-flurobenzoyl)amino-3-(1-methylpiperidin-4-yl)-1*H*-indole fumarate; **LY344864**, *N*-[(6*R*)-6-dimethylamino-6,7,8,9-tetrahydro-5*H*-carbazo-3-yl]-4-fluorobenzamide; **MDL100907**, (+/-)2,3-dimethoxyphenyl-1-[2-(4-piperidine)-methanol]; **NAD299**, (*R*)-3-*N*,*N*-dicyclobutylamino-8-fluoro-[6-3H]-3,4-dihydro-2H-1-benzo pyran-5-carboxamide; **NAS181**, (*R*)-(+)-2-[[[3-(morpholinomethyl)-2*H*-chromen-8-yl]oxy]methyl] morpholine methane sulfonate; **p-[^{18}F]MPPF** 4-(2′-methoxyphenyl)-1-[2′-(*N*-2″-pyridinyl)-p-fluorobenzamido]-ethyl piperazine; **PNU109291**, (*S*)-3, 4-dihydro-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-methyl-1*H*-2-benzopyran-6-caboximide; **Ro600175**, (S)-2-(6-chloro-5-fluroindol-1-yl)-1-methyethylamine; **Ro630563**, 4-amino-*N*-[2,6-bis(methylamino)pyridin-4-yl]benzenesulphonamide; **RP62203**, 2-[3-(4-(4-fluorophenyl)-piperazinyl)propyl]naphto[1,8- ca]isothiazole-1,1-dioxide; **RS57639**, 4-amino-5-chloro-2-methoxy benzoic acid 1-(3-[2,3-dihydrobenzo [1,4]dioxin-6yl)-propyl]-piperidin-4yl methyl ester; **RS67506**, 1-(4-amino-5-chloro-2-methoxyphenyl)-3-[1-(2-methyl sulphonylamino)ethyl-4-piperidinyl]-1-propanone hydrochloride; **RS100235**, 1-(8-amino-7-chloro-1,4-benzodioxan-5-yl)-5-((3-(3,4-dimethoxyphenyl)prop-1-yl) piperidin-4-yl)propan-1-one; **RS102221**, 8-[5-(5-amino 2,4-dimethoxyphenyl) 5-oxopentyl]-1,3,8-triazaspiro[4,5]decane-2,4-dione; **RS127445**, (2-amino-4-(4-fluoronaphthyl-1-yl)-6-isopropylpyrimidine); **SB204070**, 1-butyl-4-piperidinylmethyl-8-amino-7-chloro-1-4-benzoioxan-5-carboxylate; **SB207710**, 1-butyl-4-piperidinylmethyl-8-amino-7-iodo-1,4-benzodioxan-5-carboxylate; **SB224289**,1′-methyl-5[[2′-methyl-4′-) 5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]carbonyl-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4′-piperidine]oxalate; **SB236057**,1′-ethyl-5-(2′-methyl-4′-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-f]indol3-3,4′-piperidine; **SB242084**, 6-chloro-5-methyl-1-[2-(2-methylpyridyl-3-oxy)-pyrid-5-yl carbamoyl] indoline; **SB258585**, 4-iodo-*N*-[4-methoxy-3-(4-methyl-piperazin-1-yl)-phenyl]-benzenesulphonamide; **SB258719**, (R)-3,*N*-dimethyl-*N*-[1-methyl-3-(4-methylpiperidin-1-yl)propyl]benzene sulphonamide; **SB269970**, (*R*)-3-(2-(2-(4-methylpiperidin-1-yl)ethyl)pyrrolidine-1-sulphonyl)phenol; **SB271046**, 5-chloro-*N*-(4-methoxy-3-piperazin-1-yl-phenyl)-3-

methyl-2-benzothiophenesulphonamide; **SB357134**, *N*-(2,5-dibromo-3-flurophenyl)-4-methoxy-3-piperazin-1-ylbenzenesulphonamide; **SB-399885**, *N*-[3,5-dichloro-2-(methoxy)phenyl]-4-(methoxy)-3-(1-piperazinyl)benzenesulfonamide; **SB656104**, 6-((*R*)-2-[2-[4-(4-Chlorophenoxy)-piperidin-1-yl]-ethyl]-pyrrolidine-1-sulphonyl)-1*H*-indole hydrochloride; **SB699551**, 3-cyclopentyl-*N*-[2-(dimethylamino) ethyl]-*N*-[(4′-{[(2-phenylethyl)amino]methyl}-4-biphenylyl)methyl]propanamide dihydrochloride; **SB714786**, 2-methyl-5-({2-[4-(8-quinolinylmethyl)-1-piperazinyl]ethyl}oxy)quinoline; **U92016A**, (+)-R)-2-cyano-*N*,*N*-dipropyl-8-amino-6,7,8,9-tetrahydro-3*H*-benz[e]indole; **UH301**, 5-fluoro-8-hydroxy-2-(dipropylamino) tetralin; **WAY100635**, *N*-(2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-*N*-(2-pyridyl)-cyclohexanecarboxamide trichloride, **WAY163909**, (7b*R*, 10a*R*)-1,2,3,4,8,9,10,10a-octahydro-7b*H*-cyclopenta-[b][1,4]diazepino[6,7,1hi]indole; **WAY-181187**, 2-[1-(6-chloroimidazo[2,1-b]thiazol-5-ylsulfonyl)-1*H*-indol-3-yl]ethylamine

Further Reading

Barnes NM, Sharp T (1999). A review of central 5-HT receptors and their function. *Neuropharmacology* **38**: 1083–1152.

Bockaert J, Claeysen S, Becamel C, Dumuis A, Marin P (2006). Neuronal 5-HT metabotropic receptors: fine-tuning of their structure, signaling, and roles in synaptic modulation. *Cell Tissue Res* **326**: 553–572.

Bockaert J, Claeysen S, Compan V, Dumuis A (2008). 5-HT_4 receptors: history, molecular pharmacology and brain functions. *Neuropharmacology* **55**: 922–931.

Bojarski AJ (2006). Pharmacophore models for metabotropic 5-HT receptor ligands. *Curr Top Med Chem* 6:2005–2026.

Bonasera SJ, Tecott LH (2000). Mouse models of serotonin receptor function: toward a genetic dissection of serotonin systems. *Pharmacol Ther* **88**: 133–142.

Caliendo G, Santagada V, Perissutti E, Fiorino F. (2005). Derivatives as $5HT_{1A}$ receptor ligands – past and present. *Curr Med Chem* **12**: 1721–1753.

Fink KB, Göthert M (2007). 5-HT receptor regulation of neurotransmitter release. *Pharmacol Rev* **59**: 360–417.

Gershon MD (1999). Review article: roles played by 5-hydroxytryptamine in the physiology of the bowel. *Aliment Pharmacol Ther* 13 (Suppl. 2): 15–30.

Glennon RA (2003). Higher-end serotonin receptors: 5-HT_5, 5-HT_6, and 5-HT_7. *J Med Chem* **46**: 2795–812.

Hartig PR, Hoyer D, Humphrey PP, Martin GR (1996). Alignment of receptor nomenclature with the human genome: classification of 5-HT_{1B} and 5-HT_{1D} receptor subtypes. *Trends Pharmacol Sci* **17**: 103–105.

Heal DJ, Smith SL, Fisas A, Codony X, Buschmann H (2008). Selective 5-HT_6 receptor ligands: progress in the development of a novel pharmacological approach to the treatment of obesity and related metabolic disorders. *Pharmacol Ther* **117**: 207–231.

Hoyer D, Martin G (1997). 5-HT receptor classification and nomenclature: towards a harmonization with the human genome *Neuropharmacology* **36**: 419–428.

Hoyer D, Clarke DE, Fozard JR, Hartig PR, Martin GR, Mylecharane EJ *et al*. (1994). International Union of Pharmacology classification of receptors for 5-hydroxytryptamine (serotonin). *Pharmacol Rev* **46**: 157–203.

Hoyer D, Hannon JP, Martin GR (2002). Molecular, pharmacological and functional diversity of 5-HT receptors. *Pharmacol Biochem Behav* **71**: 533–554.

King MV, Marsden CA, Fone KC (2008). A role for the 5-HT_{1A}, 5-HT_4 and 5-HT_6 receptors in learning and memory. *Trends Pharmacol Sci* **29**: 482–492.

Kitson SL (2007). 5-hydroxytryptamine (5-HT) receptor ligands. *Curr Pharm Des* **13**: 2621–2637.

Lanfumey L, Hamon M (2004). 5-HT_1 receptors. *Curr Drug Targets CNS Neurol Disord* **3**: 1–10.

Leysen JE (2004). 5-HT_2 receptors. *Curr Drug Targets CNS Neurol Disord* **3**: 11–26.

Nelson DL (2004). 5-HT_5 receptors. *Curr Drug Targets CNS Neurol Disord* **3**: 53–58.

Pauwels PJ (2000). Diverse signalling by 5-hydroxytryptamine (5-HT) receptors. *Biochem Pharmacol* **60**: 1743–1750.

Ramage AG, Villalón CM (2008). 5-Hydroxytryptamine and cardiovascular regulation. *Trends Pharmacol Sci* **29**: 472–481

Sanger GJ (2008). 5-hydroxytryptamine and the gastrointestinal tract: where next? *Trends Pharmacol Sci* **29**: 465–471.

Thomas DR (2006). 5-ht_{5A} receptors as a therapeutic target. *Pharmacol Ther* **111**: 707–714.

Thomas DR, Hagan JJ (2004). 5-HT_7 receptors. *Curr Drug Targets CNS Neurol Disord* **3**: 81–90.

Villalón CM, Centurión D (2007). Cardiovascular responses produced by 5-hydroxytryptamine: a pharmacological update on the receptors/mechanisms involved and therapeutic implications. *Naunyn Schmiedebergs Arch Pharmacol* **376**: 45–63.

Werry TD, Loiacono R, Sexton PM, Christopoulos A (2008). RNA editing of the serotonin $5HT_{2C}$ receptor and its effects on cell signalling, pharmacology and brain function. *Pharmacol Ther* **119**: 7–23.

Woolley ML, Marsden CA, Fone KC (2004). 5-ht_6 receptors. *Curr Drug Targets CNS Neurol Disord* **3**: 59–79.

References

Boess FG *et al*. (1998). *Mol Pharmacol* **54**: 577–583.

Bonhaus DW *et al*. (1997). *Neuropharmacology* **36**: 671–679.

Bromidge SM *et al*. (2001). *Bioorg Med Chem Lett* **11**: 55–58.

Brown AM *et al*. (1993). *Br J Pharmacol* **110**: 10P.

Dunlop J *et al*. (2005). *J Pharmacol Exp Ther* **313**: 862–869.

Eglen RM *et al*. (1995). *Br J Pharmacol* **115**: 1387–1392.

Ennis MD *et al*. (1998). *J Med Chem* **41**: 2180–2183.

Forbes IT *et al*. (2002). *Bioorg Med Chem Lett* **12**: 3341–3344.

Harada K *et al*. (2006). *Eur J Pharmacol* **553**: 171–184.

Hirst WD *et al*. (2000). *Br J Pharmacol* **130**: 1597–1605.

Hirst WD *et al*. (2006). *Eur J Pharmacol* **553**: 109–119.

Holenz J *et al*. (2005). *J Med Chem* **48**: 1781–1795.

Khawaja X *et al*. (1997). *Life Sci* **60**: 653–665.

Malgouris C *et al*. (1993). *Eur J Pharmacol* **233**: 37–45.

Middlemiss DN *et al*. (1999). *Eur J Pharmacol* **375**: 359–365.

Noda M *et al*. (2003). *J Neurochem* **84**: 222–232.

Phebus LA *et al*. (1997). *Life Sci* **61**: 2117–2126.

Schechter LE *et al*. (2008). *Neuropsychopharmacology* **33**: 1323–1335.

Thomas DR *et al*. (2000). *Br J Pharmacol* **130**: 409–417.

Thomsen WJ *et al*. (2008). *J Pharmacol Exp Ther* **325**: 577–587.

Wurch T *et al*. (1998). *Mol Pharmacol* **54**: 1088–1096.

Xie Z *et al*. (1999). *FEBS Lett* **456**: 63–67.