Neuronal 5-HT Receptors and SERT

TOCRIS bioscience

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Contents

Introduction

5-hydroxytryptamine (5-HT, serotonin) is an ancient biochemical manipulated through evolution to be utilized extensively throughout the animal and plant kingdoms. Mammals employ 5-HT as a neurotransmitter within the central and peripheral nervous systems, and also as a local hormone in numerous other tissues, including the gastrointestinal tract, the cardiovascular system and immune cells. This multiplicity of function implicates 5-HT in a vast array of physiological and pathological processes. This plethora of roles has consequently encouraged the development of many compounds of therapeutic value, including various antidepressant, antipsychotic and antiemetic drugs.

Part of the ability of 5-HT to mediate a wide range of actions arises from the imposing number of 5-HT receptors.[1] Numerous 5-HT receptor families and subtypes have evolved. Currently, 18 genes are recognized as being responsible for 14 distinct mammalian 5-HT receptor subtypes, which are divided into 7 families, all but one of which are members of the G-protein coupled receptor (GPCR) superfamily. The exception is the 5-HT$_3$ receptor, a Cys-loop ligand-gated ion channel (LGIC) that in evolutionary terms arose independent of the GPCR 5-HT receptors along with other members of this superfamily (e.g. the nicotinic acetylcholine receptor, GABA$_A$ receptor, glycine receptor and the Zn^{2+}-activated receptor). Further receptor heterogeneity is generated through alternative splicing (e.g. 5-HT$_3$, 5-HT$_4$ and 5-HT$_7$ receptors), RNA editing (the 5-HT$_{2C}$ receptor), and the putative formation of homo- and heterodimers (5-HT$_4$ and the β_2 adrenoceptor).[2]

The 5-HT$_1$ Receptor Family

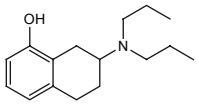
This family consists of five separate gene products: 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1D}$, 5-ht$_{1e}$, and 5-HT$_{1F}$ receptors.

Previously, some of these were thought to be species-specific homologs (e.g. 5-HT_{1B} receptor in rats and 5-HT_{1D} receptor in humans), but the genes for each of these receptors are now known to be present in every mammalian species examined so far. Each is encoded by a single, intron-less reading frame and they share considerable sequence homology. All of these receptors couple to $G_{i/o}$ to inhibit adenylyl cyclase and reduce cAMP levels, but additional signal transduction mechanisms have also been described. While their gene structure and molecular properties are similar, important cellular differences and distinct patterns of regional expression in the body underlie divergent physiological features. Several of these receptors are well known as autoreceptors that regulate the excitability of serotonin neurons and the release of serotonin,[3] but also they are expressed in nonserotonergic neurons, where they can have analogous effects on other neurotransmitters.

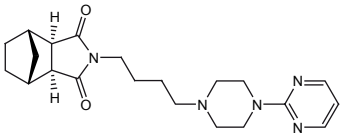
5-HT_{1A} Receptors

5-HT_{1A} receptors are distributed broadly in the CNS, found in the soma, dendrites and in some cases the axon hillock of neurons, and the cell body and processes of astrocytes. This receptor is expressed by all serotonin neurons (as autoreceptors) and by many nonserotonergic neurons (as heteroreceptors). The electrophysiological effect of 5-HT_{1A} receptor activation on neurons is generally inhibitory and acts by reducing neuronal firing rate. A number of highly selective ligands have been developed, and they range from full agonists to partial agonists, antagonists, and inverse agonists. 5-HT_{1A} receptors are thought to be therapeutic targets for several neuropsychiatric disorders including anxiety, depression, and schizophrenia. Clinically used ligands include some of the atypical antipsychotics, which have partial agonist or neutral antagonist activity and buspirone, a partial agonist that is used for generalized anxiety disorder. 5-HT_{1A} receptor partial agonists are clinically useful anxiolytic drugs and may act on the autoreceptors to reduce serotonergic activity, whereas 5-HT_{1A} receptors in the hippocampus have been implicated in the mechanism of antidepressant action (by facilitating neurogenesis) and in regulating the hypothalamic-pituitary-adrenal axis. Other physiological effects of CNS 5-HT_{1A} receptor activation include hypothermia, hyperphagia, and serotonin syndrome.[1] 5-HT_{1A} receptor knockout mice have heightened anxiety and may exhibit diminished depression-like features.[4,5] As with the other serotonin receptors this may involve receptor actions during early brain development as well as during processing of emotional experience in the adult. A number of highly selective ligands for 5-HT_{1A} receptors have been developed, although it should also be noted that some of these share affinity for 5-HT_7 receptors (e.g. 8-OH-DPAT) and others for other 5-HT_1 or 5-HT_2 receptors. WAY 100635 has often been used as a highly selective 5-HT_{1A} receptor neutral antagonist. Xaliproden and S-14506 are selective agonists.

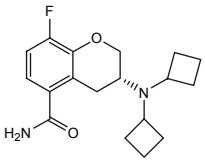
Figure 1A | 5-HT_{1A} subtype-selective compounds



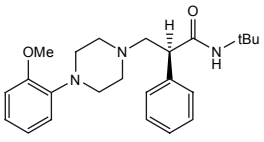
8-Hydroxy-DPAT (0529)
5-HT_{1A} agonist



Tandospirone (2854)
5-HT_{1A} partial agonist



NAD 299 (3282)
5-HT_{1A} antagonist



(S)-WAY 100135 (1253)
5-HT_{1A} antagonist

5-HT_{1B} Receptors

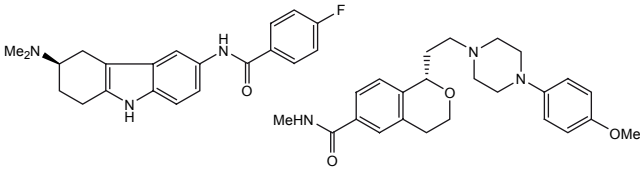
5-HT_{1B} receptors are also distributed broadly in the CNS in serotonergic and nonserotonergic neurons; these receptors are predominantly translocated to axon terminals, so there is an anatomical mismatch between the localization of mRNA and mature 5-HT_{1B} receptor protein. Historically the 5-HT_{1B} receptor was thought to be the rat analog of 5-HT_{1D} receptors, but it is now clear that both receptors are present in all mammalian species examined and their regional distributions differ.[6] β-adrenergic antagonists have high affinity for 5-HT_{1B} receptors in some but not all species. 5-HT_{1B} autoreceptors have been found to reduce 5-HT synthesis and release and enhance reuptake via the serotonin transporter. 5-HT_{1B} heteroreceptors inhibit the release of a range of different neurotransmitters, depending on the neuron types that express them. Systemic administration of 5-HT_{1B} receptor agonists have several behavioral effects including increased locomotion, changes in brain reward mechanisms, and decreased aggression, whereas selective antagonists may have some procognitive potential.[7,8] The expression of these receptors in diverse and potentially competing sets of neurons may impact their utility as a clinical target, although several 5-$HT_{1B/D}$ receptor agonists are effective as antimigraine treatments. 5-HT_{1B} receptor knockout mice have been tested extensively and have a distinct phenotype characterized by increased aggression and, in most cases, predisposition for addiction-like behaviors. Their phenotype may

however depend on compensatory changes in the dopamine system during development rather than being due to decreased 5-HT$_{1B}$ receptor signaling in adults. Several moderately selective agonists have been developed, including CP 93129 and the more brain-penetrant CP 94253, and antagonists such as SB 224289 are used commonly to identify 5-HT$_{1B}$ receptor-mediated responses.

5-HT$_{1D}$ Receptors

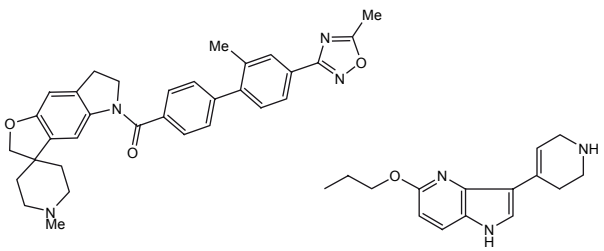
5-HT$_{1D}$ receptors are expressed at more modest levels than 5-HT$_{1B}$ receptors in the brain, but the largest extent of expression seems to be in the raphe nuclei. Similarly, 5-HT$_{1D}$ receptor binding sites are present at a lower level than 5-HT$_{1B}$ receptor binding sites in most brain areas.[9] Most evidence, using 5-HT$_{1B}$ receptor knockout mice as controls, indicates that terminal serotonin autoreceptor activity in the forebrain is of the 5-HT$_{1B}$ receptor type,[10] but there may be somatodendritic 5-HT$_{1D}$ autoreceptors that regulate serotonin release within the raphe nuclei.[11] The dilemma for most putative selective 5-HT$_{1D}$ receptor ligands is that they have high affinity for more than one receptor, usually either the 5-HT$_{1B}$ or 5-HT$_{1A}$ receptors, but often not both, allowing combinations of drugs to achieve conditions that are reasonably selective for activation or inhibition of 5-HT$_{1D}$ receptors. Interestingly, ketanserin has ~100-fold higher affinity for human 5-HT$_{1D}$ than 5-HT$_{1B}$ receptors, but it has the highest affinity for 5-HT$_{2A}$ receptors.

Figure 1B | 5-HT$_1$ subtype-selective compounds



LY 344864 (2451)
5-HT$_{1F}$ agonist

PNU 109291 (2556)
5-HT$_{1D}$ agonist



SB 224289 (1221)
5-HT$_{1B}$ antagonist

CP 94253 (1317)
5-HT$_{1B}$ agonist

5-ht$_{1e}$ Receptors

The lower case letters denote that this receptor has not been confirmed to have meaningful physiological functions *in vivo*. The existence of this receptor was originally postulated based on radioligand binding studies using brain homogenates, indicating that a 5-HT$_1$-like receptor with low affinity for 5-carboxamidotryptamine could be demonstrated. It is now clear that several binding sites might have contributed to this observation. The gene sequence for the 5-ht$_{1e}$ receptor has been cloned from a human placental library and guinea pig brain genomic DNA but was undetectable in rat and mouse.[12] There have been few pharmacological studies of this receptor in rodents or in human tissue, but it was detected by RT-PCR in various brain regions of guinea pig and in the human and monkey brain by *in situ* hybridization.[6] Furthermore, no highly selective ligands have been developed, although a number of typical 5-HT$_1$ receptor agonists and antagonists display modest affinity at these receptors in heterologous expression systems. A recent method for labeling 5-ht$_{1e}$ binding sites in guinea pig was recently described and may be a useful strategy for modeling human 5-ht$_{1e}$ receptors.[13] The physiological significance of this receptor therefore remains uncertain.

5-HT$_{1F}$ Receptors

The 5-HT$_{1F}$ receptor has been detected in multiple species and has been cloned from human, rat, guinea pig, and mouse genomes. Like other members of the 5-HT$_1$ receptor family, this receptor inhibits adenylyl cyclase via a G_i-dependent mechanism. It is expressed at modest levels in the CNS in both serotonergic and nonserotonergic cell bodies where it acts as both an autoreceptor and heteroreceptor, respectively. Like 5-HT$_{1B}$ receptors, 5-HT$_{1F}$ is expressed in trigeminal ganglion and vestibular nuclei neurons and has a high affinity for triptan drugs that are useful for the treatment of migraine headache. The relative contribution of each of these two receptors to pain relief in migraine has not been resolved. It is possible that less selective agonists that can potentially activate multiple 5-HT$_1$ receptors (e.g. 5-HT$_{1B/D/F}$ subtypes, such as the 'triptans') may relieve migraine headaches via multiple mechanisms; therefore, more selective drugs may have distinct clinical efficacy and side effect profiles. For example, the relatively selective 5-HT$_{1F}$ receptor agonist LY 334370, which has ~100-fold higher affinity for 5-HT$_{1F}$ over 5-HT$_{1B}$ receptors, is active in animal models of anti-migraine activity but seems to act on the trigeminal nucleus rather than through a vascular mechanism.[14] To date, no selective 5-HT$_{1F}$ antagonists have been identified.

Table 1 | Summary of the structure, pharmacology and function of mammalian 5-HT$_1$ receptors

Receptor	5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{1D}$	5-ht$_{1e}$	5-HT$_{1F}$
Human Gene	5q11.2–q13	6q13	1p34.3–36.3	6q14–q15	3q11
Structure	GPCR	GPCR	GPCR	GPCR	GPCR
Transduction System	↓cAMP G-protein coupled- K^+ current	↓cAMP	↓cAMP	↓cAMP	↓cAMP
Agonists	8-OH-DPAT (*R*)-UH301 U 92016A	Sumatriptan L 694247	Sumatriptan PNU 109291 L694247	-	LY 344864 LY 334370
Antagonists	WAY 100 635 (*S*)-UH301 NAD 299 (Robalzotan)	GR 55562 SB 224289 SB 236057	BRL 15572 SB 714786	-	-
Effect on Neurotransmission	↑Acetylcholine ↑Noradrenaline ↑Dopamine	↓5-HT ↓Acetylcholine ↓Glutamate ↓Dopamine	↓Glutamate	-	-
Therapeutic Target	Depression Anxiety/stress Panic Aggression Cognition	Depression Anxiety Aggression Migraine Drug addiction	Migraine	-	Migraine

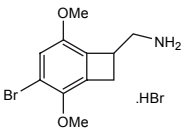
The 5-HT$_2$ Receptor Family

The 5-HT$_2$ family has three members, 5-HT$_{2A}$, 5-HT$_{2B}$ and 5-HT$_{2C}$ receptors. Their pharmacological significance is substantial due to both the clinical importance and complex pharmacological features of these receptors. 5-HT$_2$ receptors were originally posited based on an important study by Gaddum and Picarelli in 1957.[15] Using a guinea pig ileum contraction bioassay, they observed two classes of 'tryptamine' receptors (namely 'M' and 'D') that correspond to 5-HT$_3$ and 5-HT$_2$ receptors in current nomenclature. Constituents of the 5-HT$_2$ receptor family share similar sequence homology, structural motifs, and overlapping pharmacology, although considerable ligand development has occurred and highly selective ligands are available.[16] Some of the notable features of these receptors include the prominence of inverse agonists, multiple signal transduction pathways, agonist-directed signaling and important clinical roles in neuropsychiatric conditions. Like 5-HT$_1$ receptors, 5-HT$_2$ receptors have a seven-transmembrane domain motif but couple to phospholipases C and A$_2$. The relative efficiency of coupling to these effectors varies depending on the cell type being examined.

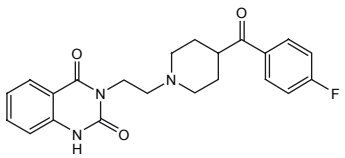
5-HT$_{2A}$ Receptors

5-HT$_{2A}$ receptors are densely expressed in the forebrain, especially the cortex, and are expressed in both interneurons and pyramidal neurons. Various ligands display complex pharmacological patterns of activity at 5-HT$_{2A}$ receptors, ranging from full to partial agonism, and from neutral antagonism to inverse agonistic behavior. These different activities are thought to reflect ligand stabilization of multiple structural conformations which have been resolved by X-ray crystallography in some cases. Structure-activity models have also been tested using site directed mutagenesis. A great deal of biophysical information has been generated using molecular strategies and heterologous expression of 5-HT$_{2A}$ receptors. Furthermore, simultaneous analysis of multiple signal transduction mechanisms in cell culture systems has shown that the same ligand may have differing degrees of intrinsic activity for the activation of different second messenger systems by the same population of 5-HT$_{2A}$ receptors.[17] This

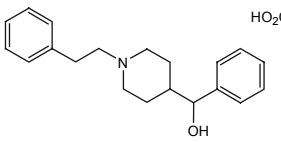
Figure 2A | 5-HT$_{2A}$ subtype-selective compounds



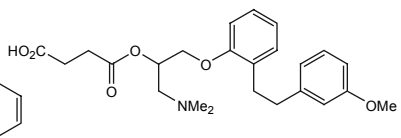
TCB-2 (2592)
5-HT$_{2A}$ agonist



Ketanserin (0908)
5-HT$_{2A}$ antagonist



MDL 11,939 (0870)
5-HT$_{2A}$ antagonist



Sarpogrelate (3739)
5-HT$_{2A}$ antagonist

further supports the notion of complex and dynamic structure-activity relationships for 5-HT_{2A} and 5-HT_{2C} receptors.

5-HT has relatively low affinity for the 5-HT_{2A} receptor compared to other 5-HT receptors, with a K_d in the low micromolar range. It can be argued however that the high affinity, active conformational state has roughly ten-fold higher affinity for 5-HT_{2A}. Several agonists, such as DOI and LSD, have high affinity for 5-HT_{2A} receptors and others demonstrate selective potency for stimulating one signal transduction pathway over another (e.g. TCB-2). These, however are not particularly selective as they also bind to other 5-HT_2 receptors. Several well-characterized antagonists display high selectivity for 5-HT_{2A} receptors, including ketanserin and MDL 100907. A number of others have high affinity but their specificity is not fully described. Some 5-HT_{2A} receptor agonists produce psychotomimetic effects (most famously LSD), and therefore several antipsychotic medications are high affinity 5-HT_{2A} receptor antagonists.

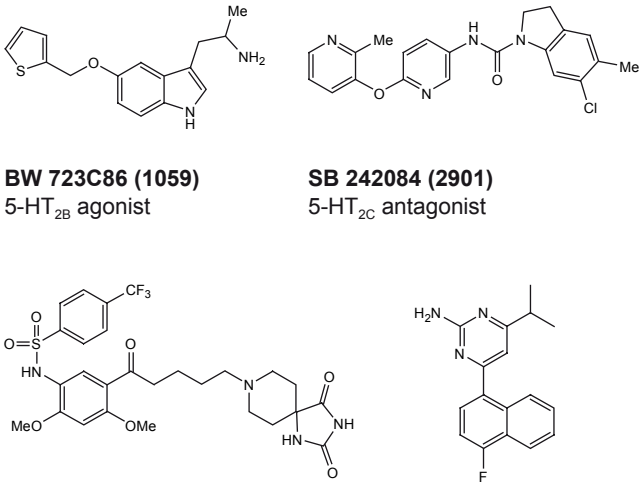
5-HT_{2B} Receptors

5-HT_{2B} receptors are sparsely expressed in discrete subregions of CNS, but are heavily expressed in liver, kidney, heart and the fundus of the stomach. This pattern of expression differs from 5-HT_{2A} and 5-HT_{2C} receptors, which are expressed at relatively higher levels in the CNS. They share affinity for many of the same drugs, but a few highly selective 5-HT_{2B} receptor antagonists have been described, including RS 127445. The physiological role of 5-HT_{2B} receptors is still unclear, but they have been implicated in cardiac function, morphogenesis, and anxiety. 5-HT_{2B} receptors have similar signal transduction coupling to other 5-HT_2 receptors *in vitro*, but less evidence has accumulated for endogenous receptors.

5-HT_{2C} Receptors

5-HT_{2C} receptors are strongly expressed throughout the CNS but are expressed at lower levels outside the brain. They are unique among the 5-HT receptors because the mRNA transcript can be edited, leading to subtle changes in coding sequence that can have functionally relevant impacts on the mature receptor protein.[18] 5-HT_{2C} receptor knockout mice have been generated which interestingly develop mid-life obesity, glucose intolerance and seizures.[19] The pharmacology of 5-HT_{2C} receptors is similar to the other 5-HT_2 receptors; they display complex interactions with signal transducing mechanisms, agonist directed signaling and inverse agonism by some atypical antipsychotics. Evidence from animal models indicates that 5-HT_{2C} receptors may impact anxiety, appetite, addiction, and antipsychotic drug actions. SB 242084 is a fairly selective 5-HT_{2C} receptor antagonist with anxiolytic activity. There are no highly selective 5-HT_{2C} agonists developed to date as those described also have affinity for other 5-HT_2 receptors. Lorcaserin displays some selectivity for the 5-HT_{2C} receptor, although there are no readily available sources for this molecule outside of custom synthesis.[20]

Figure 2B | 5-HT_{2B} subtype-selective compounds



BW 723C86 (1059)
5-HT_{2B} agonist

SB 242084 (2901)
5-HT_{2C} antagonist

RS 102221 (1050)
5-HT_{2C} antagonist

RS 127445 (2993)
5-HT_{2B} antagonist

The 5-HT_3 Receptor

The 5-HT_3 receptor is the only 5-HT receptor that is a member of the Cys-loop ligand-gated ion channel family.[21] The receptor complex is thought to be pentameric which is consistent with other Cys-loop LGIC family members.[22] This complex may be formed by a combination of up to 5 different subunits, named 5-HT3A-E, although at present only the 5-HT3A and 5-HT3B subunits have been studied in detail. The 5-HT_3 receptor complex is a non-selective cation channel (most permeable to Ca^{2+}, Na^+ and K^+ ions) that mediates fast synaptic depolarizing neurotransmission in the brain and is prone to rapid desensitization. Recent attention has focused on the combination of subunits forming the functional channel in native tissue. Expression of the 5-HT3A subunit alone in recombinant systems produces a functional receptor that displays many characteristics of native receptors. The caveat is that homomeric 5-HT_3A receptors do not generate a relatively high single channel conductance receptor, something that is evident in some populations of native neuronal receptors. Most significantly, co-expression of the 5-HT3A and 5-HT3B subunits results in a heteromeric receptor that mimics the high single channel conductance of some populations of native receptors more faithfully.[23,24] In addition to 5-HT, 5-HT_3 receptor action is modulated allosterically by volatile anesthetics and alcohols.[25,26,27] The actions

of these compounds may, however, depend on the subunit composition of the receptor.[28]

Within the brain, the highest densities of 5-HT_3 receptors are associated with the brainstem nuclei encompassing the chemoreceptor trigger zone; namely the dorsal motor nucleus of the vagus nerve, area postrema and nucleus tractus solitarius.[29] The 5-HT_3 receptor is also expressed in human forebrain regions including the hippocampus, amygdala and caudate-putamen.[30] Of note, expression within the extrapyramidal system (caudate-putamen [striatum] and substantia nigra) is not readily detectable in other species (such as rodents and/or non-human primates).

The 5-HT binding site within the 5-HT_3 receptor complex is constructed by two adjacent N-termini from neighboring subunits in the pentameric complex. Structural analysis has identified that three peptide loops (designated A, B and C) contribute from the 'principal' subunit and a further three peptide loops from the 'complementary' subunit (D, E and F) participate in ligand binding. Hence, the initial report concerning the stoichiometry of the heteromeric 5-HT_3AB receptor (with a subunit composition B-A-B-B-A) generated much debate concerning the potential to identify pharmacological compounds that would discriminate homomeric 5-HT_3A receptors from heteromeric 5-HT_3AB receptors. The binding sites of the former would arise from A-A interfaces, whereas this structural interface was absent in heteromeric 5-HT_3AB receptors. Recently, however, the B-A-B-B-A stoichiometry has been questioned.[31]

The majority of compounds investigated so far appear unable to discriminate between molecular isoforms of the 5-HT_3 receptor. A notable exception is picrotoxin, which displays weak (micromolar) affinity but good selectivity (approx. 100 -fold for homomeric mouse 5-HT_3A versus heteromeric mouse 5-HT_3AB receptors).[32] This has been demonstrated in functional recordings and the molecular interaction is likely to be a channel blockade of the 5-HT_3 receptor rather than competition at the 5-HT binding site.

Whilst the search continues for the identification of compounds that discriminate readily between 5-HT_3 receptor molecular isoforms, a large number of ligands exist that display high selectivity for the 5-HT_3 receptor versus other neurotransmitter receptors. Initial examples of selective antagonists with nanomolar affinity arose in the 1980s with compounds such as ondansetron, granisetron and tropisetron (although the latter also has micromolar affinity for the 5-HT_4 receptor). All three of these compounds were subsequently approved as drugs to reduce emesis (nausea and vomiting). Subsequently second generation compounds have been developed such as alosetron and palonosetron. These have very high affinity for the 5-HT_3 receptor and have also gained regulatory approval as medicines; the former for irritable bowel syndrome (IBS), whilst the latter appears to display particularly long-lasting anti-emetic actions. Indeed this long duration of action of palonosetron would appear to be considerably more than would be predicted from its metabolic half-life and some evidence suggests that this antagonist induces internalization of 5-HT_3 receptors.[33]

Table 2 | Summary of the structure, pharmacology and function of mammalian 5-HT_{2-3} receptors

Receptor	5-HT_{2A}	5-HT_{2B}	5-HT_{2C}	5-HT_3
Human Gene	13q14–q21	2q36.3–2q37.1	Xq24	11q23.1-23.2 (A) 11q23.1 (B) 3q27 (C/D/E)
Structure	GPCR	GPCR	GPCR	LGIC
Transduction System	↑PLC	↑PLC	↑PLC	Ion conductance (K^+, Na^+, Ca^{2+})
Agonists	DOI	DOI BW 723C86 Ro 600175	DOI Ro 600175 Lorcaserin	2-methyl 5-HT SR 57227 *m*-chlorophenyl-biguanide
Antagonists	Ketanserin MDL 100907	RS 127445 SB 200646 SB 204741	SB 242084 RS 102221	Granisetron Ondansetron Tropisetron
Effect on Neurotransmission	↑Glutamate ↑Dopamine		?↓Dopamine	↑5-HT ↑Dopamine ↓Acetylcholine
Therapeutic Target	Depression Anxiety Schizophrenia Cognition Eating Disorders Sleep Disorder	Depression Anxiety Sleep Disorder Migraine	Anxiety Obesity Cognition	Emesis Anxiety Cognition Drug Addiction Analgesia Chronic Fatigue Syndrome

In addition to antagonists, there are also high affinity and selective agonists for the 5-HT_3 receptor, although these tend to be partial agonists similar to the non-selective exogenous agonist, 2-methyl-5-HT. Some examples of partial agonists are pumosetrag (DDP733), PBG and mCPBG; SR 57227A is a good example of an exogenous near full agonist.

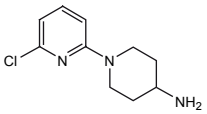
Activation of the 5-HT_3 receptor modulates release of various neurotransmitters, including a facilitation of dopamine, GABA and 5-HT release, although the receptor is not thought to be expressed by 5-HT neurons.[34,35] Conversely, the 5-HT_3 receptor has an inhibitory effect on acetylcholine release in the cortex.[36,37] This is likely to be mediated via GABAergic interneurons.[37,38]

A number of 5-HT_3 receptor ligands – including odansetron, granisetron, tropisetron and palonosetron – have now been exploited for therapeutic benefit from their ability to alleviate the nausea and vomiting resulting from anticancer chemo- and radiotherapy and also post-operative emesis particularly evident following procedures involving the abdomen.[39]

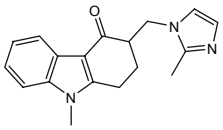
A further therapeutic utility of 5-HT_3 receptor ligands concerns the symptomatic relief from IBS. IBS is a recognized heterogeneous condition, which, although not life-threatening, presents a considerable health and economic burden. The potent and selective 5-HT_3 receptor antagonist, alosetron, displays clear efficacy in reducing the symptoms of IBS-d (IBS presenting with diarrhea). Marketing approval for this medication was withdrawn due to rare occurrences of potentially fatal ischemic colitis. This side-effect was also noted – again at a relatively low incidence – in the aborted trials of another 5-HT_3 receptor antagonist, cilansetron, suggesting this side-effect is not an 'off-target' phenomenon. The relatively high number of patients that have received 5-HT_3 receptor antagonists to control emesis – without a single report of ischemic colitis - suggests this side effect results from the combination of 5-HT_3 receptor antagonism and the IBS condition.

Significantly, patient pressure assisted the reinstatement of alosetron, albeit with limited availability. In Japan, however, regulatory approval exists for the use of a very low dose of the selective 5-HT_3 receptor antagonist, ramosetron with a maximum daily dose of 10 μg. This very low dose presumably reduces the occurrence of ischemic colitis by limiting the degree of blockade of the 5-HT_3 receptor, although the levels of efficacy achieved by these low doses are open to question. An alternative pharmacological strategy targeting the 5-HT_3 receptor has also been evaluated for IBS-c (IBS presenting with constipation). Here the predicted prokinetic action of a 5-HT_3 receptor partial agonist, DDP733, was assessed; unfortunately the compound displayed relatively high levels of agonist activity (intrinsic activity) such that the compound caused emesis in some patients (predictable for 5-HT_3 receptor agonists with high intrinsic activity).

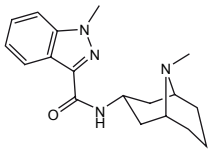
Figure 3 | 5-HT_3 selective compounds



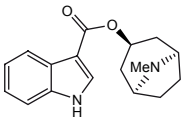
SR 57227 (1205)
5-HT_3 agonist



Ondansetron (2891)
5-HT_3 antagonist



Granisetron (2903)
5-HT_3 antagonist



Tropisetron (2459)
5-HT_3 antagonist

The potential efficacy of 5-HT_3 receptor antagonists to reduce behaviors likely to be mediated via the forebrain (for example anxiety, cognitive dysfunction, and alcohol-induced reward) is not fully understood. Indeed the initial potential of antagonists as therapies for these effects failed to translate in consistent clinical findings. A potential explanation for this is the considerable differences apparent in the cellular and regional expression of the 5-HT_3 receptor when comparing laboratory animals (rodents and New World primates) with humans. Interestingly, some effects of 5-HT_3 receptor antagonists have been identified in humans without prior identification in animal models including fibromyalgia and chronic fatigue syndrome.

The 5-HT_4 Receptor

Consistent with other GPCRs, a functional 5-HT_4 receptor protein arises from a single gene. Arising mRNA, however, can can be alternatively spliced within the region corresponding to the extracellular link between the fourth and fifth transmembrane domain and the region corresponding to the C-terminus. This produces ten isoforms – 5-$HT_{4(a-g)}$, 5-$HT_{4(hb)}$, 5-$HT_{4(i)}$ and 5-$HT_{4(n)}$ – although it is possible that even more will become apparent. With the exception of the 5-HT_{4d} receptor isoform, 5-HT_4 receptor transcripts are expressed in the brain. With the role of the C-terminus to facilitate subcellular

localization and to communicate receptor activation rather than impact pharmacology of the orthosteric site, it is not surprising that 5-HT_4 receptor isoforms do not tend to differ pharmacologically, although functional differences are apparent.

Expression of the 5-HT_4 receptor is evident in the brain, gut and cardiovascular tissues. Within the brain, protein and mRNA tend to colocalize indicating a post-synaptic location. Maximal levels of expression are in the basal ganglia, including the substantia nigra, globus pallidus, caudate nucleus, putamen, nucleus accumbens, hippocampus (CA1 and subiculum) and cortex.[40]

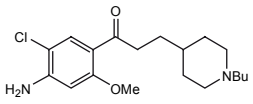
The 5-HT_4 receptor is positively coupled to adenylyl cyclase via G_s, with receptor activation resulting in neuronal excitability, although coupling to ion channels is also evident. Excitatory 5-HT_4 receptors enhance the release of a number of neurotransmitters including cortical acetylcholine, nigral-striatal dopamine and hippocampal 5-HT.

The 5-HT_4 receptor is believed to have a role in learning and memory. Many studies have shown that 5-HT_4 receptor activation improves performance in various behavioral paradigms of cognitive function.[41] The beneficial effects of 5-HT_4 receptor activation may be mediated by facilitation of acetylcholine release in the cerebral cortex. An alternative relevant process attributed to the 5-HT_4 receptor relates to amyloid precursor protein (APP) metabolism. 5-HT_4 receptors promote secretion of sAPPα, a neuroprotective peptide that facilitates neuronal growth and enhances memory functions in behavioral paradigms and also ablates the cellular toxicity associated with excessive glutamatergic transmission that can result in cognitive impairment.[42] In addition, the 5-HT_4 receptor may also enhance cognitive performance through depolarization of pyramidal cells within the CA1 field of the hippocampus and hence promote the induction of hippocampal long-term potentiation (LTP), a cellular phenomenon regarded as a neurophysiological basis of memory.[43]

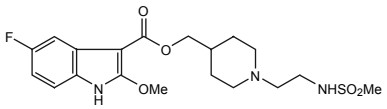
The 5-HT_4 receptor may also have a role in the generation of anxiety. 5-HT_4 receptor antagonists have been shown to exhibit anxiolytic properties, whilst the 5-HT_4 receptor knockout mouse exhibited abnormal responses to stress, whereby stress-induced hypophagia was attenuated in the knockout mouse compared with the wild-type strain.[44,45] Consistent with the dogma associating excessive 5-HT function with anxiety, 5-HT_4 receptor antagonists decrease hippocampal 5-HT release.

A number of drug tools are available to either antagonize or activate 5-HT_4 receptors. Selective high affinity antagonists include GR 113808, SB 204070 and RS 100235, whereas non-tryptamine selective agonists include RS 67506, ML 10302 and BIMU8. The tryptamine derivative agonist, 5-methoxytryptamine is also a potent, but non-selective agonist of the 5-HT_4 receptor. Some benzamide derivatives, such as cisapride, display agonist actions. Cisapride was marketed as a gastro-prokinetic before it was withdrawn due to cardiovascular side-effects, consistent with the expression of 5-HT_4 receptors in atria. A further 5-HT_4 receptor agonist, tegaserod, developed for IBS-c was withdrawn for similar reasons.

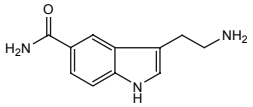
Figure 4 | 5-HT_4 and 5-ht_5 compounds



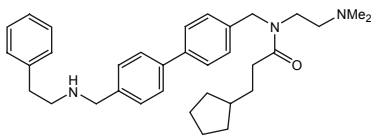
RS 67333 (0989)
5-HT_4 partial agonist



GR 125487 (1658)
5-HT_4 antagonist



5-CT (0458)
5-ht_{5a} agonist



SB 699551 (3188)
5-ht_{5a} antagonist

The 5-ht_5 Receptors

The 5-ht_5 receptor subfamily contains two gene products; the 5-ht_{5a} and 5-ht_{5b} receptors. Despite being discovered nearly 20 years ago, they remain the most poorly understood 5-HT receptor subtypes. There is no conclusive evidence as to how they elicit second messenger responses in native tissue, despite their structural classification as GPCRs. The lack of clear physiological roles for these receptor subtypes has necessitated lower-case appellation to emphasize their current status as merely gene products, contrasting with the upper-case notation of a receptor with known cellular functions in native cells or tissues.

Of the two subtypes, the 5-ht_{5a} receptor has received more attention, since the human 5-ht_{5b} receptor gene sequence is likely to be a pseudogene as it contains stop codons within its open reading frame. If the resulting truncated protein were expressed it

is likely that it would lack functionality.[46] The rodent 5-ht$_{5b}$ receptor, however, would appear capable of functional expression although little evidence has been generated. 5-ht$_{5b}$ receptor mRNA in the rat brain is evident in the hippocampus, habenula, entorhinal and piriform cortices, and the olfactory bulb.[47]

Within heterologous expression systems, the 5-ht$_{5a}$ receptor may inhibit adenylyl cyclase activity, presumably via G_i,[48,49] although other reports have detected no such response.[50] Alternative transduction processes impacted by this receptor may include an increase in intracellular Ca^{2+} mobilization[51] or coupling to an inwardly rectifying potassium channel.[50]

The lack of suitable selective ligands has hampered autoradiographic study of the 5-ht$_{5a}$ receptor. 5-ht$_{5a}$ receptor protein expression in the rat brain is associated with neurons, and is evident in the hypothalamus, raphe nuclei, locus coeruleus, horizontal nucleus of the diagonal band and amygdala, with more moderate immunoreactivity in the cerebral cortex (particularly entorhinal cortex), hippocampus, lateral habenula, substantia nigra, ventral tegmental area, pons and cerebellum. *In situ* hybridization using human brain tissue has demonstrated 5-ht$_{5a}$ receptor transcripts in the cortex, hippocampus, amygdala and cerebellum.[52]

Although no definitive role for native 5-ht$_{5a}$ receptors has been identified, a few studies have suggested putative functions. For instance, 5-ht$_{5a}$ receptor knockout mice display enhanced exploratory behavior in response to a novel environment.[46]

The 5-ht$_{5a}$ receptor has also been implicated in the regulation of rodent circadian rhythm, although limited pharmacological tools to probe this receptor complicates interpretation.[53] The most promising compound, SB 699551-A,[54] displays a 30-fold selectivity for the human 5-ht$_{5a}$ receptor over other 5-HT receptor subtypes and other neuronal targets, aside from the serotonin transporter, which it impacts at only 10-fold higher concentrations.[54] Unfortunately, SB 699551-A displays inter-species variation in affinity for the 5-ht$_{5a}$ receptor and displays relatively low affinity for rodent 5-ht$_{5a}$ receptors (pK_i = 6.3), which further limits the utility of this compound to investigate 5-ht$_{5a}$ receptor function through the common rodent paradigms.

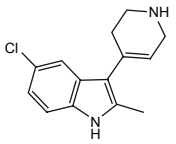
5-HT$_6$ Receptors

The 5-HT$_6$ receptor is coupled to G_s to activate adenylyl cyclase and shows moderate affinity for serotonin. It is strongly and selectively expressed in CNS but has species-specific patterns of expression with rat and human showing intense expression in striatum and hippocampus but about 1/10 of the expression level in mice and litter regional variation in different areas of the mouse brain.[55] A 5-HT$_6$ receptor knockout mouse has been developed but the phenotypic relevance is unclear given the low levels of 5-HT$_6$ receptor expression in wild-type mice as compared to rat or human.[56] The rat and human 5-HT$_6$ receptor are more similar pharmacologically to each other than to the mouse receptor. The 5-HT$_6$ receptor has been found in animal models to offer promise as a target for cognitive enhancement and

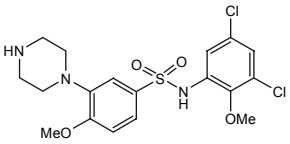
Table 3 | Summary of the structure, pharmacology and function of mammalian 5-HT$_{4-7}$ receptors

Receptor	5-HT$_4$	5-ht$_{5a}$	5-ht$_{5b}$	5-HT$_6$	5-HT$_7$
Human Gene	5q31–q33	7q36	2q11–13 (Non-functional)	1p35–36	10q21–q24
Structure	GPCR	GPCR	GPCR	GPCR	GPCR
Transduction System	↑cAMP	?↓cAMP ?Ca^{2+} mobilization ?K^+ current	Not Known	↑cAMP	↑cAMP
Agonists	BIMU 8 RS 67506 ML 10302	5-CT	5-CT	-	8-OH-DPAT
Antagonists	GR 113808 SB 204070 RS 100235	SB 699551-A	-	Ro 630563 SB 271046 SB 357134	SB 258719 SB 269970 SB 656104
Effect on Neurotransmission	↑Acetylcholine ↑Dopamine ↑5-HT	Not Known	Not Known	↓Acetylcholine ↓Dopamine ↓Glutamate	?↑↓5-HT
Therapeutic Target	Cognition Anxiety	Not Known	Not Known	Cognition Schizophrenia Depression Anxiety/Stress Epilepsy Obesity	Depression Schizophrenia Sleep Disorder Epilepsy Cognition

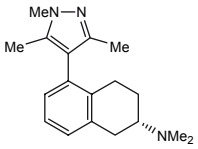
Figure 4 | 5-HT$_6$ and $_7$ selective compounds



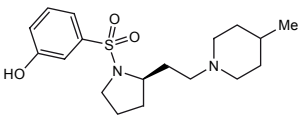
EMD 386088 (2382)
5-HT$_6$ agonist



SB 399885 (3189)
5-HT$_6$ antagonist



AS 19 (1968)
5-HT$_7$ agonist



SB 269970 (1612)
5-HT$_7$ antagonist

possibly weight loss.[57] EMDT, EMD 386088, and WAY 181,187 are relatively selective 5-HT$_6$ receptor agonists, and a number of selective antagonists have also been developed including SB 399885, SB 258585 and Ro 4368554. The less selective ligands tend to also have high affinity for 5-HT$_{2A}$ and D$_2$ receptors. A number of clinically important antipsychotic and antidepressant drugs also share high affinity for this receptor along with their other targets.

The 5-HT$_7$ Receptor

5-HT$_7$ receptors also couple to G$_s$ (activating adenylyl cyclase) and are widely distributed in the brain.[58] Several splice variants with different patterns of distribution within the CNS have been identified,[59] although they do not show meaningful pharmacological distinctions in human isoforms.[60] Several atypical antipsychotic and antidepressant drugs have sufficient affinity for this receptor and will occupy it at commonly used dosages. Some ligands traditionally associated with other 5-HT receptors also bind to 5-HT$_7$ receptors, especially those associated with 5-HT$_{1A}$, 5-HT$_{2A}$, and 5-HT$_6$ receptors. A particular compound to note is the agonist, 8-OH-DPAT, a full agonist that has only about ten-fold higher affinity for 5-HT$_{1A}$ than 5-HT$_7$ receptors. 5-HT$_7$ receptors have been implicated in a variety of behavioral and physiological processes, including affective behavior, circadian rhythmicity and vasodilation. 5-HT$_7$ receptor knockout mice have reduced immobility in the forced swim test consistent with the pharmacological data suggesting that blockade of this receptor can produce antidepressant effects. Several moderately selective agonists have been reported, including AS 19 and LP 12; SB 258719 and SB 269970 are very selective antagonists at 5-HT$_7$ receptors.

The 5-HT transporter (SERT)

The 5-HT transporter (SERT or 5-HTT) is a Na^+/Cl^- dependent biogenic amine transporter whose family includes the dopamine (DAT) and noradrenaline (NET) transporters.[61] SERT is critical to the functioning of the 5-HT system, limiting 5-HT neurotransmission by removing synaptic neurotransmitter through transport across the presynaptic membrane.[62] Following the original sequencing of rat SERT,[63] subsequent studies have indicated that the functional complex may exist as an oligomer.[64,65]

Within the brain SERT is located throughout 5-HT neurons, and hence displays a distribution at the protein level that closely matches the regions receiving 5-HT neuron innervation. Indeed, the protein offers a phenotypic marker for 5-HT neurons.[66] Consistently, *in situ* hybridization studies demonstrate that SERT transcript expression is associated with the cell bodies of 5-HT neurons.[67] In the developing mouse brain however, expression of the transporter occurs transiently in glutamatergic thalamocortical afferents that lack the ability to synthesize 5-HT.[68,69] These neurons may therefore sequester 5-HT, enabling the afferents to mediate serotonergic transmission during brain development.

More than one form of SERT protein appears to be present *in vivo*. Shigematsu and colleagues conducted immunohistochemical studies on the mouse brain with two selective antibodies, raised against different epitopes within the C- and N-terminus.[70] They observed that immunoreactivity with the N-terminal antibody was absent in the CA3 field of the hippocampus, whereas the C-terminal antibody indicated SERT expression. This implies that SERT may contain variable N-terminal domains, potentially though alternative splicing of exon 1. Further molecular diversity appears to be apparent in human immune cells, where SERT may function to deliver 5-HT to other immune cells across the immunological synapse.[71]

The efficacy of a range of antidepressant drugs, in particular the selective serotonin reuptake inhibitors (SSRIs), has encouraged elucidation of the physiological roles of SERT in the brain. It is indisputable that the transporter has an effect upon depression, though its precise function is still debated. Further evidence comes from the genetic variation that occurs upstream of the SERT coding sequence, the so-called 5-HTT gene-linked polymorphic region (5-HTTLPR). A series of repeated units incorporated within this sequence forms a promoter region regulating SERT expression.[72,73] One common polymorphism within this region is a 44 base pair deletion, denoted as a short form (S) for the gene, along with two variations of a long form (LG and

LA). The short form allele reduces SERT expression and function relative to the long forms.[72,74] It has been reported however, that LG may result in SERT expression comparable with the short form variant[75] and the short allele may not be associated with reduced SERT levels in the adult brain,[76] complicating the research area. Individuals carrying at least one short form allele appear predisposed to depressive episodes. In further support from *in vivo* imaging, SERT expression is reduced within the brainstem,[77] amygdala and midbrain[78] in patients presenting with depression.

A number of reports correlate SERT expression with the brains of suicide victims although this area remains controversial.[79] SERT knockout mice do however display behavioral abnormalities related to depression and anxiety.[80,81]

In contrast to SERT being a molecular therapeutic target, it is also a target for various drugs of abuse, including MDMA ('ecstasy') and cocaine. MDMA, for example, blocks 5-HT reuptake and enhances 5-HT release.[82,83] Whilst cocaine is predominantly considered to act upon DAT, SERT interaction appears to contribute to the rewarding actions of cocaine.[84]

Conclusion

From the initial discovery of serotonin in the mid-twentieth century, the 5-HT receptor research field continues to expand both scientifically and commercially. Over the last sixty years, considerable physiological and pharmacological processes involving 5-HT receptors and the 5-HT transporter have been identified. The consecutive discovery of the 6 classes of G-protein coupled 5-HT receptors ($5\text{-HT}_{1,2,4\text{-}7}$) and their subclasses along with the ligand-gated ion channel 5-HT_3 has provided an exciting research platform that holds promise for future drug discovery. Both 5-ht_5 and 5-ht_{1e} receptors are relatively uncharacterized and the generation of selective ligands for these receptors may well aid our understanding of their functions *in vivo*. One of the most significant problems in this field has been the absence of sufficiently selective ligands to identify the relative contribution of multiple serotonin receptors to complex behavioral and physiological phenomena mediated by serotonin. As new molecular and pharmacological tools become available, targeting specific 5-HT receptors should lead to the development of many compounds of therapeutic value that will reduce the potential for undesired side effects. The future holds the promise for a new generation of serotonergic drugs that may be useful as antidepressant, antipsychotic, procognitive, and antiemetic treatments. It can be anticipated that 5-HT receptor research will continue to progress and yield exciting results in the years to come.

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5-HT Receptor Compounds Available from Tocris

5-HT$_1$ Receptors

5-HT$_{1A}$

Agonists

0556 **BP-554 maleate**
Selective 5-HT$_{1A}$ agonist

1006 **BMY 7378 dihydrochloride**
5-HT$_{1A}$ partial agonist

0962 **Buspirone hydrochloride**
5-HT$_{1A}$ partial agonist

0529 **8-Hydroxy-DPAT hydrobromide**
Selective 5-HT$_{1A}$ agonist. Also has moderate affinity for 5-HT$_7$

1080 **(*R*)-(+)-8-Hydroxy-DPAT hydrobromide**
Selective 5-HT$_{1A}$ agonist. More active enantiomer of 8-Hydroxy-DPAT hydrobromide (Cat. No. 0529)

0797 **8-Hydroxy-PIPAT oxalate**
High affinity 5-HT$_{1A}$ agonist

2399 **Indorenate hydrochloride**
5-HT$_{1A}$, 5-HT$_{1B}$ and 5-HT$_{2C}$ agonist

1869 **Ipsapirone**
Selective 5-HT$_{1A}$ agonist

0411 **MDL 73005EF hydrochloride**
Potent and selective 5-HT$_{1A}$ partial agonist

1746 **Nemonapride**
Highly potent D$_2$-like antagonist. Also 5-HT$_{1A}$ agonist

0912 **RU 24969 hemisuccinate**
5-HT$_{1B/1A}$ agonist

1771 **S 14506 hydrochloride**
Highly potent 5-HT$_{1A}$ agonist; displays unique binding mechanism

2854 **Tandospirone hydrochloride**
Selective 5-HT$_{1A}$ partial agonist

2739 **U 92016A**
Selective 5-HT$_{1A}$ agonist

1772 **Urapidil hydrochloride**
α$_1$ antagonist. Also 5-HT$_{1A}$ receptor agonist

2491 **Xaliproden hydrochloride**
Orally active, high affinity 5-HT$_{1A}$ agonist

Antagonists

2806 **Alprenolol hydrochloride**
5-HT$_{1A}$ antagonist

3346 **ATC 0175 hydrochloride**
MCH$_1$ antagonist; also 5-HT$_{2B}$ antagonist and partial antagonist of 5-HT$_{1A}$

0993 **Cyanopindolol hemifumerate**
5-HT$_{1A/1B}$ antagonist. Also β-adrenergic antagonist

0933 **MM 77 dihydrochloride**
5-HT$_{1A}$ (postsynaptic) antagonist

3282 **NAD 299**
Selective, high affinity 5-HT$_{1A}$ receptor antagonist

0553 **NAN-190 hydrobromide**
5-HT$_{1A}$ antagonist

0994 **Pindolol**
5-HT$_{1A/1B}$ antagonist. Also β-adrenergic antagonist

1060 **(*S*)-(-)-Pindolol**
5-HT$_{1A/1B}$ antagonist. Also β-adrenergic antagonist. More active enantiomer of pindolol (Cat. No. 0994)

1516 **SDZ 21009**
β-adrenoceptor antagonist. Also 5-HT$_{1A/1B}$ antagonist

0631 **Spiroxatrine**
5-HT$_{1A}$ antagonist

1253 **(*S*)-WAY 100135 dihydrochloride**
Potent, selective 5-HT$_{1A}$ antagonist

5-HT$_{1B}$

Agonists

0703 **Anpirtoline hydrochloride**
Highly potent 5-HT$_{1B}$ agonist. Also 5-HT$_3$ antagonist

0638 **CGS 12066B dimaleate**
5-HT$_{1B}$ agonist

1032 **CP 93129 dihydrochloride**
5-HT$_{1B}$ agonist

1317 **CP 94253 hydrochloride**
Potent, selective 5-HT$_{1B}$ agonist

3665 **Donitriptan hydrochloride**
5-HT$_{1B/1D}$ agonist

3862 **Eletriptan hydrochloride**
Orally active, selective 5-HT$_{1B/1D}$ agonist

1860 **Eltoprazine hydrochloride**
5-HT$_1$ receptor agonist/partial agonist

2399 **Indorenate hydrochloride**
5-HT$_{1A}$, 5-HT$_{1B}$ and 5-HT$_{2C}$ agonist

0901 **5-Nonloxytryptamine oxalate**
Selective 5-HT$_{1B}$ agonist

0912 **RU 24969 hemisuccinate**
5-HT$_{1B/1A}$ agonist

Antagonists

0993 **Cyanopindolol hemifumerate**
5-HT$_{1A/1B}$ antagonist. Also β-adrenergic antagonist

1054 **GR 55562 dihydrochloride**
5-HT$_{1B}$ antagonist

1477 **GR 127935 hydrochloride**
Potent, selective 5-HT$_{1B/1D}$ antagonist

0992 **Isamoltane hemifumarate**
5-HT$_{1B}$ antagonist

3350 **LY 393558**
Dual 5-HT$_{1B/1D}$ antagonist and 5-HT re-uptake inhibitor

1413 **NAS-181**
Selective rat 5-HT_{1B} antagonist. Active *in vivo*
0994 **Pindolol**
5-$HT_{1A/1B}$ antagonist. Also β-adrenergic antagonist
1060 **(*S*)-(-)-Pindolol**
5-$HT_{1A/1B}$ antagonist. Also β-adrenergic antagonist. More active enantiomer of pindolol (Cat. No. 0994)
1242 **SB 216641 hydrochloride**
Selective human 5-HT_{1B} antagonist
1221 **SB 224289 hydrochloride**
Selective 5-HT_{1B} antagonist
1516 **SDZ 21009**
β-adrenoceptor antagonist. Also 5-$HT_{1A/1B}$ antagonist

5-HT_{1D}

Agonists

3783 **CP-135807**
Selective 5-HT_{1D} agonist
3665 **Donitriptan hydrochloride**
5-$HT_{1B/1D}$ agonist
3862 **Eletriptan hydrobromide**
Orally active, selective 5-$HT_{1B/1D}$ agonist
0864 **GR 46611**
5-HT_{1D} agonist
0781 **L-694,247**
5-HT_{1D} agonist
2640 **L-703,664 succinate**
Selective 5-HT_{1D} receptor agonist
2556 **PNU 109291**
Potent and selective 5-HT_{1D} agonist
1985 **PNU 142633**
Highly selective 5-HT_{1D} agonist

Antagonists

1207 **BRL 15572 hydrochloride**
Selective human 5-HT_{1D} antagonist
1477 **GR 127935 hydrochloride**
Potent, selective 5-$HT_{1B/1D}$ antagonist
3078 **LY 310762 hydrochloride**
5-HT_{1D}-preferring antagonist
3350 **LY 393558**
Dual 5-$HT_{1B/1D}$ antagonist and 5-HT re-uptake inhibitor

5-ht_{1e}

1129 **BRL-54443**
Potent 5-ht_{1e}/5-HT_{1F} agonist

5-HT_{1F}

1129 **BRL-54443**
Potent 5-ht_{1e}/5-HT_{1F} agonist
3079 **LY 334370 hydrochloride**
Selective 5-HT_{1F} agonist
2451 **LY 344864 hydrochloride**
Potent, selective 5-HT_{1F} agonist

5-HT_1

General

0458 **5-Carboxamidotryptamine maleate**
5-HT_1 agonist. Also has high affinity for 5-ht_{5A} and 5-HT_7
3586 **Sumatriptan**
5-HT_1 receptor agonist

5-HT_2 Receptors

5-HT_{2A}

Agonists

2643 **DOI hydrochloride**
Mixed 5-$HT_{2A/2C}$ agonist
2201 **PNU 22394 hydrochloride**
5-HT_{2C} agonist and 5-$HT_{2A/2B}$ partial agonist
2592 **TCB-2**
Potent, high affinity 5-HT_{2A} agonist

Antagonists

1809 **Altanserin hydrochloride**
5-HT_{2A} receptor antagonist
0444 **Clozapine**
Dopamine antagonist with some D_4 selectivity. Also 5-$HT_{2A/2C}$ antagonist
2645 **Fananserin**
5-HT_{2A} antagonist. Also D_4 antagonist
0523 **4F 4PP oxalate**
Selective 5-HT_{2A} antagonist
0908 **Ketanserin tartrate**
Selective 5-HT_{2A} antagonist. Also antagonist at 5-HT_{1D}
0870 **MDL 11,939**
5-HT_{2A} antagonist
2495 **Melperone hydrochloride**
5-HT_{2A}/D_2 receptor antagonist; neuroleptic
1644 **Mesulergine hydrochloride**
5-HT_{2A} and 5-HT_{2C} antagonist. Also dopamine receptor partial agonist
2777 **Nefazodone hydrochloride**
5-HT_{2A} antagonist and 5-HT uptake inhibitor. Antidepressant
2735 **PNU 06415E**
D_4 and 5-HT_{2A} antagonist; antipsychotic
1742 **R-96544 hydrochloride**
Potent, selective 5-HT_{2A} antagonist
2865 **Risperidone**
5-HT_{2A} antagonist
3739 **Sarpogrelate hydrochloride**
Selective 5-HT_{2A} antagonist
0995 **Spiperone hydrochloride**
5-HT_{2A} antagonist. Also D_2-like antagonist
3085 **Ziprasidone hydrochloride**
5-HT_{2A}/D_2 antagonist; atypical antipsychotic
3996 **Zotepine**
5-HT_{2A}/D_2 antagonist; atypical antipsychotic

5-HT_{2B}

Agonists

1059 **BW 723C86 hydrochloride**
5-HT_{2B} agonist
0875 ***m*-CPP hydrochloride**
5-$HT_{2B/2C}$ receptor agonist
0557 **α-Methyl-5-hydroxytryptamine maleate**
5-HT_{2B} agonist

Antagonists

3346 **ATC 0175 hydrochloride**
MCH1 antagonist; also 5-HT_{2B} antagonist and partial antagonist of 5-HT_{1A}
3077 **LY 272015 hydrochloride**
High affinity 5-HT_{2B} antagonist, orally active
2993 **RS 127445 hydrochloride**
Selective, high affinity 5-HT_{2B} antagonist
1371 **SB 200646 hydrochloride**
5-$HT_{2C/2B}$ antagonist
1372 **SB 204741**
Potent, selective 5-HT_{2B} antagonist
1661 **SB 206553 hydrochloride**
Potent, selective 5-HT_{2C}/5-HT_{2B} antagonist. Orally active
1379 **SB 221284**
Potent, selective 5-$HT_{2C/2B}$ antagonist
1375 **SB 228357**
5-$HT_{2C/2B}$ antagonist/inverse agonist
1255 **SDZ SER 082 fumarate**
Selective 5-$HT_{2B/2C}$ antagonist

5-HT_{2C}

Agonists

3041 **CP 809101 hydrochloride**
Potent and selective 5-HT_{2C} agonist
0875 ***m*-CPP hydrochloride**
5-$HT_{2B/2C}$ receptor agonist
2643 **DOI hydrochloride**
Mixed 5-$HT_{2A/2C}$ agonist
1860 **Eltoprazine hydrochloride**
5-HT_1 receptor agonist/partial agonist
2399 **Indorenate hydrochloride**
5-HT_{1A}, 5-HT_{1B} and 5-HT_{2C} agonist
3017 **1-Methylpsilocin**
Potent and selective 5-HT_{2C} agonist
0941 **MK 212 hydrochloride**
5-HT_{2C} agonist
3585 **Org 12962 hydrochloride**
Selective 5-HT_{2C} agonist
2201 **PNU 22394 hydrochloride**
5-HT_{2C} agonist and 5-$HT_{2A/2B}$ partial agonist
1854 **Ro 60-0175 fumarate**
Potent, selective 5-HT_{2C} agonist
0925 **SCH 23390 hydrochloride**
Standard selective D_1-like antagonist. Also 5-HT_{2C} agonist
2173 **WAY-629 hydrochloride**
Selective 5-HT_{2C} agonist
1801 **WAY 16503 hydrochloride**
Potent, selective 5-HT_{2C} agonist

Antagonists

0444 **Clozapine**
5-$HT_{2A/2C}$ antagonist. Also dopamine agonist with some D_4 selectivity
1007 ***N*-Desmethylclozapine**
5-HT_{2C} antagonist
1644 **Mesulergine hydrochloride**
5-HT_{2A} and 5-HT_{2C} antagonist. Also dopamine receptor partial agonist
1050 **RS 102221 hydrochloride**
Selective 5-HT_{2C} antagonist
1371 **SB 200646 hydrochloride**
5-$HT_{2C/2B}$ antagonist
1661 **SB 206553 hydrochloride**
Potent, selective 5-HT_{2C}/5-HT_{2B} antagonist. Orally active
1379 **SB 221284**
Potent, selective 5-$HT_{2C/2B}$ antagonist
1375 **SB 228357**
5-$HT_{2C/2B}$ antagonist/inverse agonist
2901 **SB 242084**
Selective 5-HT_{2C} antagonist; brain penetrant
1255 **SDZ SER 082 fumarate**
Selective 5-$HT_{2B/2C}$ antagonist

5-HT_2

General

0524 **AMI-193**
Selective 5-HT_2 antagonist
2746 **Amperozide hydrochloride**
Atypical antipsychotic; high affinity 5-HT_2 ligand
0460 **Cinanserin hydrochloride**
Selective 5-HT_2 antagonist
2863 **DOB hydrochloride**
Selective 5-HT_2 agonist
0590 **Metergoline**
5-HT_2 antagonist. Also 5-HT_1 antagonist and 5-HT_{1D} ligand. Has moderate affinity for 5-HT_6 and high affinity for 5-HT_7
0997 **Mianserin hydrochloride**
5-HT_2 antagonist. Has moderate affinity for 5-ht_6
2018 **Mirtazepine**
Potent 5-HT_2 antagonist. Also 5-HT_3, H_1 and α_2-antagonist. Antidepressant
1955 **Ritanserin**
Potent 5-HT_2 antagonist

5-HT_{3-7} Receptors

5-HT_3

Agonists

0440 ***m*-Chlorophenylbiguanide hydrochloride**
Potent and specific 5-HT_3 agonist
0558 **2-Methyl-5-hydroxytryptamine hydrochloride**
5-HT_3 agonist/potent 5-HT_6 ligand
0566 ***N*-Methylquipazine dimaleate**
5-HT_3 agonist
0969 **1-Phenylbiguanide hydrochloride**
5-HT_3 agonist
0629 **Quipazine dimaleate**
5-HT_3 agonist
0988 **RS 56812 hydrochloride**
5-HT_3 partial agonist
1205 **SR 57227A hydrochloride**
Potent, selective 5-HT_3 agonist

Antagonists

0666 **3-AQC**
5-HT_3 antagonist
2759 **B-HT 920**
D_2 receptor agonist. Also α_2 agonist and 5-HT_3 antagonist
2903 **Granisetron hydrochloride**
5-HT_3 antagonist
0640 **MDL 72222**
5-HT_3 antagonist
2018 **Mirtazepine**
Potent 5-HT_2 antagonist. Also 5-HT_3, H_1 and α_2-antagonist. Antidepressant
2844 **Mosapride citrate**
5-HT_4 agonist and 5-HT_3 antagonist
2891 **Ondansetron hydrochloride**
Selective 5-HT_3 antagonist
2037 **SDZ 205-557 hydrochloride**
5-HT_4/5-HT_3 receptor antagonist
0641 **Tropanyl 3,5-dimethylbenzoate**
5-HT_3 antagonist
2459 **Tropisetron hydrochloride**
Potent 5-HT_3 receptor antagonist; orally active
0380 **Y-25130 hydrochloride**
Potent, selective 5-HT_3 antagonist
1795 **Zacopride hydrochloride**
Highly potent 5-HT_3 receptor antagonist. Also 5-HT_4 agonist

5-HT_4

Agonists

1695 **Cisapride**
5-HT_4 agonist; stimulates intestinal ACh release
3089 **CJ 033466**
Selective 5-HT_4 partial agonist
3499 **ML 10302 hydrochloride**
Potent and selective 5-HT_4 partial agonist
2844 **Mosapride citrate**
5-HT_4 agonist and 5-HT_3 antagonist
0736 **2-[1-(4-Piperonyl)piperazinyl]benzothiazole**
5-HT_4 agonist. Also 5-HT_3 antagonist
0989 **RS 67333 hydrochloride**
5-HT_4 partial agonist
0990 **RS 67506 hydrochloride**
5-HT_4 partial agonist
1795 **Zacopride hydrochloride**
Highly potent 5-HT_3 receptor antagonist. Also 5-HT_4 agonist

Antagonists

1322 **GR 113808**
Potent, selective 5-HT_4 antagonist
1658 **GR 125487 sulfamate**
Potent, selective 5-HT_4 antagonist. Active *in vivo*
0728 **RS 23597-190 hydrochloride**
5-HT_4 antagonist
0991 **RS 39604 hydrochloride**
5-HT_4 antagonist
0785 **SB 203186 hydrochloride**
5-HT_4 antagonist
2037 **SDZ 205-557 hydrochloride**
5-HT_4/5-HT_3 receptor antagonist

5-ht_5

Agonists

0458 **5-Carboxamidotryptamine maleate**
5-HT_1 agonist. Also has high affinity for 5-ht_{5A} and 5-HT_7

Antagonists

3188 **SB 699551**
Selective 5-ht_{5A} antagonist

5-HT_6

Agonists

2382 **EMD 386088 hydrochloride**
Potent 5-HT_6 agonist

Antagonists

3326 **BGC 20-761**
High affinity 5-HT_6 antagonist
3904 **WAY 208466**
Selective, high affinity 5-HT_6 agonist
2911 **Ro 04-6790**
Potent and selective 5-HT_6 antagonist
3885 **Ro 630563**
Selective, high affinity 5-HT_6 antagonist
1961 **SB 258585 hydrochloride**
Potent, selective 5-HT_6 antagonist
3368 **SB 271046 hydrochloride**
Orally active, selective 5-HT_6 antagonist
3189 **SB 399885 hydrochloride**
Potent and selective 5-HT_6 antagonist
3688 **SGS 518 oxalate**
Selective 5-HT_6 antagonist

5-HT_7

Agonists

1968 **AS-19**
Reported potent 5-HT_7 agonist
2925 **LP 12 hydrochloride**
5-HT_7 agonist
2534 **LP 44**
High affinity 5-HT_7 agonist

Antagonists

1523 **LY 215840**
5-HT_2/5-HT_7 antagonist

2726 **SB 258719 hydrochloride**
Selective 5-HT_7 antagonist
1612 **SB 269970 hydrochloride**
Potent selective 5-HT_7 antagonist. Brain penetrant

5-HT Transporters

2341 **A 80426 mesylate**
High affinity α_2 antagonist. Also 5-HT uptake inhibitor
2322 **BTS 54-505 hydrochloride**
Potent SNRI; active metabolite of sibutramine (Cat. No. 2290)
1427 **Citalopram hydrobromide**
Highly potent and selective 5-HT uptake inhibitor
0457 **Clomipramine hydrochloride**
5-HT re-uptake inhibitor
2833 **Cocaine hydrochloride**
Inhibitor of monoamine transporters
2695 **Dexfenfluramine hydrochloride**
5-HT re-uptake inhibitor. Also stimulates 5-HT release
3428 **DMT**
Endogenous σ_1 ligand. Also 5-HT_{2A} agonist
0927 **Fluoxetine hydrochloride**
5-HT re-uptake inhibitor
1033 **Fluvoxamine maleate**
5-HT re-uptake inhibitor
1588 **Indatraline hydrochloride**
Potent 5-HT uptake inhibitor. Also inhibits dopamine and noradrenalin uptake
2545 **Lofepramine**
5-HT and noradrenalin re-uptake inhibitor (SNRI)
3350 **LY 393558**
Dual 5-$HT_{1B/1D}$ antagonist and 5-HT re-uptake inhibitor
2148 **(±)-McN 5652**
Potent, orally active 5-HT uptake inhibitor. Also inhibits noradrenalin and dopamine uptake *in vitro*
3027 **MDMA hydrochloride**
Inhibitor of 5-HT and dopamine uptake; hallucinogenic
3286 **Milnacipran hydrochloride**
5-HT and noradrenalin re-uptake inhibitor (SNRI)
2777 **Nefazodone hydrochloride**
5-HT_{2A} antagonist and 5-HT uptake inhibitor. Antidepressant
2141 **Paroxetine maleate**
Highly potent and selective 5-HT uptake inhibitor
2742 **Reserpine**
Inhibitor of vesicular monoamine transport
2395 **Sertraline hydrochloride**
5-HT re-uptake inhibitor
2290 **Sibutramine hydrochloride**
5-HT and noradrenalin re-uptake inhibitor (SNRI)
2175 **Tetrabenazine**
Potent inhibitor of vesicular monoamine transport; depletes dopamine stores
2917 **Venlafaxine hydrochloride**
Dual serotonin/noradrenalin re-uptake inhibitor
1767 **Zimelidene hydrochloride**
Selective 5-HT uptake inhibitor

5-HT

General

3991 **NPEC-caged-serotonin**
Caged serotonin
3547 **Serotonin hydrochloride**
Endogenous 5-HT receptor agonist

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