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Neuronal 5-HT Receptors and SERT

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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

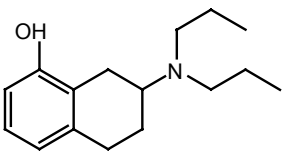
This family consists of five separate gene products: 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1D}$, 5-ht$_{1e}$, and 5-HT$_{1F}$ receptors.

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.

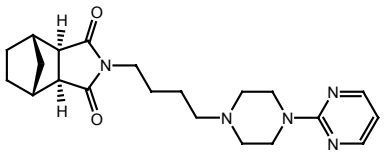
5-HT$_{1A}$ Receptors

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.

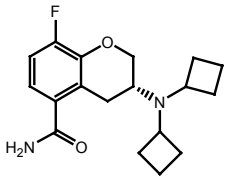
Figure 1A | 5-HT$_{1A}$ subtype-selective compounds



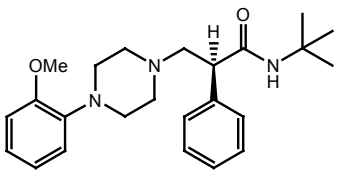
8-Hydroxy-DPAT (0529)
5-HT$_{1A}$ agonist



Tandospirone (2854)
5-HT$_{1A}$ partial agonist



NAD 299 (3282)
5-HT$_{1A}$ antagonist



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

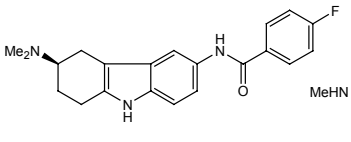
5-HT$_{1B}$ Receptors

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.

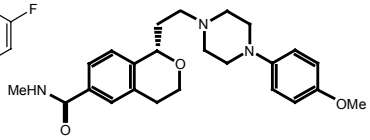
5-HT$_{1D}$ Receptors

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.

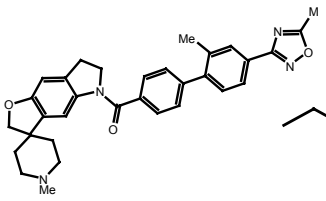
Figure 1B | 5-HT$_1$ subtype-selective compounds



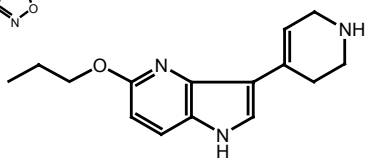
LY 344864 (2451)
5-HT$_{1F}$ agonist



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.

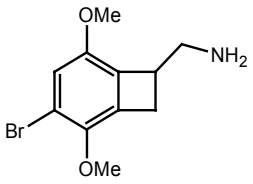
The 5-HT$_2$ Receptor Family

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 A2. The relative efficiency of coupling to these effectors varies depending on the cell type being examined.

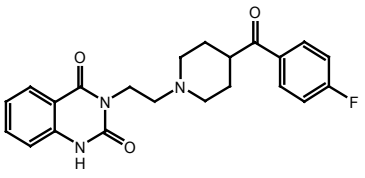
5-HT$_{2A}$ Receptors

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

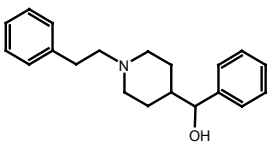
Figure 2A | 5-HT$_{2A}$ subtype-selective compounds



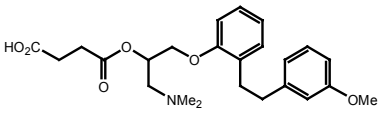
TCB-2 (2592)
5-HT$_{2A}$ agonist



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



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



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

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 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.

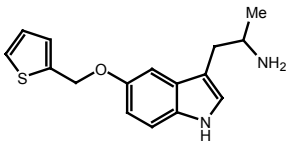
5-HT$_{2C}$ Receptors

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]

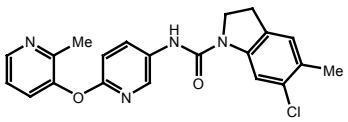
Table 1 | Summary of the structure, pharmacology and function of mammalian 5-HT$_1$ receptors

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 L 694247	–	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

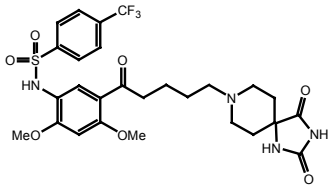
Figure 2B | 5-HT$_{2B}$ subtype-selective compounds



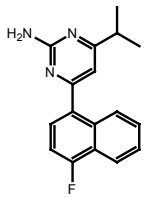
BW 723C86 (1059)
5-HT$_{2B}$ agonist



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-HT$_3$A-E, although at present only the 5-HT$_3$A and 5-HT$_3$B 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-HT$_3$A subunit alone in recombinant systems produces a functional receptor that displays many characteristics of native receptors. The caveat is that homomeric 5-HT$_3$A receptors do not generate a relatively high single channel conductance receptor, something that is evident in some populations of native neuronal receptors. Most significantly, coexpression of the 5-HT$_3$A and 5-HT$_3$B 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$_3$AB 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$_3$A receptors from heteromeric 5-HT$_3$AB receptors. The binding sites of the former would arise from A-A interfaces, whereas this structural interface was absent in heteromeric 5-HT$_3$AB 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$_3$A versus heteromeric mouse 5-HT$_3$AB 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.

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 ondansetron, 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]

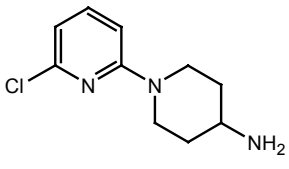
A further therapeutic utility of 5-HT$_3$ receptor ligands concerns the symptomatic relief from IBS. IBS is a recognized heterogeneous condition, which, although not life-threatening, presents a considerable health and economic burden. The potent and selective 5-HT$_3$ receptor antagonist, alosetron, 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.

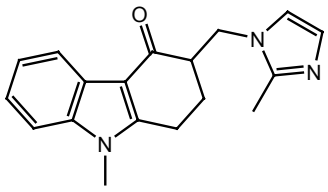
Significantly, patient pressure assisted the reinstatement of alosetron, albeit with limited availability. In Japan, however, regulatory approval exists for the use of a very low dose of the selective 5-HT_3 receptor antagonist, ramosetron with a maximum daily dose of 10 μg. This very low dose presumably 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).

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.

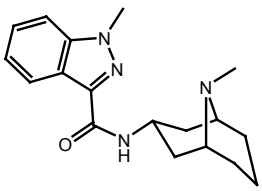
Figure 3 | 5-HT_3 selective compounds



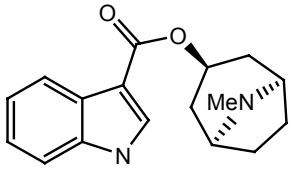
SR 57227 (1205)
5-HT_3 agonist



Ondansetron (2891)
5-HT_3 antagonist



Granisetron (2903)
5-HT_3 antagonist



Tropisetron (2459)
5-HT_3 antagonist

The 5-HT_4 Receptor

Consistent with other GPCRs, a functional 5-HT_4 receptor protein arises from a single gene. Arising mRNA, however, 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_4(d) 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.

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

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.

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.

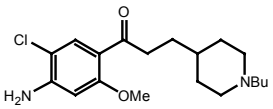
Of the two subtypes, the 5-ht_{5a} receptor has received more attention, since the human 5-ht_{5b} receptor gene sequence is likely to be a pseudogene as it contains stop codons within its open reading frame. If the resulting truncated protein were expressed it is likely that it would lack functionality.[46] 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]

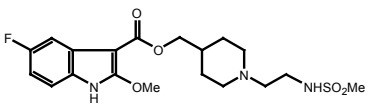
The 5-ht_{5a} receptor has also been implicated in the regulation of rodent circadian rhythm, although limited pharmacological tools to probe this receptor complicates interpretation.[53]

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 = 6.3), which further limits the utility of this compound to investigate 5-ht_{5a} receptor function through the common rodent paradigms.

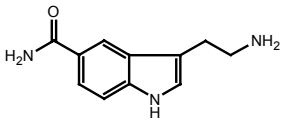
Figure 4 | 5-HT$_4$ and 5-HT$_5$ compounds



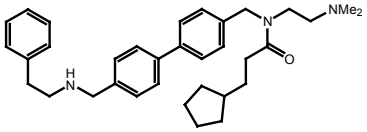
RS 67333 (0989)
5-HT$_4$ partial agonist



GR 125487 (1658)
5-HT$_4$ antagonist



5-CT (0458)
5-ht$_{5a}$ agonist



SB 699551 (3188)
5-ht$_{5a}$ antagonist

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 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 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

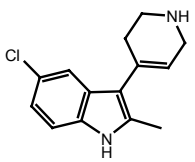
5-HT$_7$ receptors also couple to G$_s$ (activating adenylyl cyclase) and are widely distributed in the brain.[58] Several splice variants with different patterns of distribution within the CNS have been identified,[59] although they do not show meaningful pharmacological distinctions in human isoforms.[60] 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)

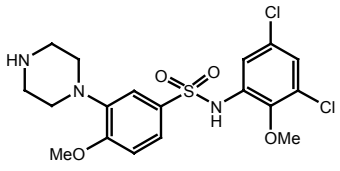
The 5-HT transporter (SERT or 5-HTT) is a Na^+/Cl^- dependent biogenic amine transporter whose family includes the dopamine (DAT) and noradrenaline (NET) transporters.[61] SERT is critical to the functioning of the 5-HT system, limiting 5-HT neurotransmission by removing synaptic neurotransmitter through 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

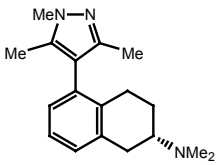
Figure 5 | 5-HT$_6$ and $_7$ selective compounds



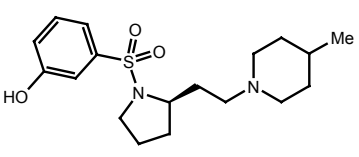
EMD 386088 (2382)
5-HT$_6$ agonist



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



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



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

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

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-$HT_{1,2,4-7}$) 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

Catalog No.	Product Name	Primary Function
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-DPA 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 D2-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	α1 antagonist. Also 5-HT$_{1A}$ receptor agonist
2491	Xaliproden hydrochloride	Orally active, high affinity 5-HT$_{1A}$ agonist
5-HT$_{1A}$ Antagonists		
2806	Alprenolol hydrochloride	Selective 5-HT$_{1A}$ agonist
3346	ATC 0175 hydrochloride	MCH1 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	5HT$_{1A/1B}$ 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
5-HT$_{1B}$ Antagonists		
0993	Cyanopindolol hemifumerate	5-HT1$_{A/1B}$ 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

Catalog No.	Product Name	Primary Function
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
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
5-HT$_{1D}$ 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$_{1E}$ Antagonists		
1129	BRL-54443	Potent 5-ht$_{1e}$/5-HT$_{1F}$ agonist
5-HT$_{1F}$ Antagonists		
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
5-HT$_{2A}$ 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$_{2A/D2}$ 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$_{2A/D2}$ antagonist; atypical antipsychotic
3996	Zotepine	5-HT$_{2A/D2}$ antagonist; atypical antipsychotic

Catalog No.	Product Name	Primary Function
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
5-HT$_{2B}$ 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	Mixed 5-HT$_{2A/2C}$ agonist
2399	Indorenate hydrochloride	5-HT$_{1}$ receptor agonist/partial 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
5-HT$_{2C}$ Antagonists		
0444	Clozapine	5-HT$_{2A/2C}$ antagonist. Also dopamine agonist with some D$_4$
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-HT2$_{C/2B}$ 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

Catalog No.	Product Name	Primary Function
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
5-HT$_3$ 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
5-HT$_4$ 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	RS 39604 hydrochloride
0785	SB 203186 hydrochloride	5-HT$_4$ antagonist
2037	SDZ 205-557 hydrochloride	5-HT$_4$/5-HT$_3$ receptor antagonist 5-ht$_5$
5-ht$_5$ Agonists		
0458	5-Carboxamidotryptamine maleate	5-HT$_1$ agonist. Also has high affinity for 5-ht$_{5A}$ and 5-HT$_7$
5-ht$_5$ Antagonists		
3188	SB 699551	Selective 5-ht$_{5A}$ antagonist
5-HT$_6$ Agonists		
2382	EMD 386088 hydrochloride	Potent 5-HT$_6$ agonist
5-HT$_6$ 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	Selective 5-HT$_6$ antagonist 5-HT$_7$
3189	SB 399885 hydrochloride	Potent and selective 5-HT$_6$ antagonist
3688	SGS 518 oxalate	Selective 5-HT$_6$ antagonist

Catalog No.	Product Name	Primary Function
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
5-HT$_7$ 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	5-HT re-uptake inhibitor
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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