5-HT Receptors and their Ligands

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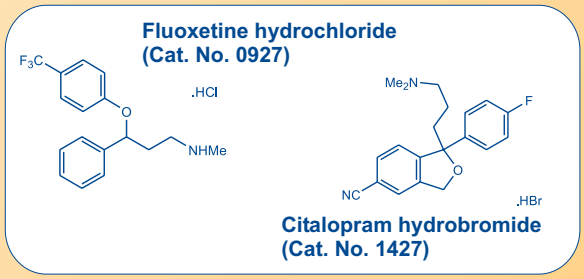
Introduction

Serotonin (5-hydroxytryptamine, 5-HT) produces its effects through a variety of membrane-bound receptors. 5-HT and its receptors are found both in the central and peripheral nervous system (CNS/PNS), as well as in a number of non-neuronal tissues in the gut, cardiovascular system and blood. 5-HT has been implicated in the aetiology of numerous disease states, including depression, anxiety, social phobia, schizophrenia, obsessive-compulsive and panic disorders; in addition to migraine, hypertension, pulmonary hypertension, eating disorders, vomiting and irritable bowel syndrome. Except for the 5-HT_3 receptor, which is a ligand-gated ion channel, 5-HT receptors belong to the G protein-coupled receptor (GPCR) superfamily and, with at least fourteen distinct members, represent one of the most complex families of neurotransmitter receptors (Tables 1, 2). Splice variants (5-HT_3, 5-HT_4, 5-ht_6, 5-HT_7) and RNA edited isoforms (5-HT_{2C}) have been described, whilst there is evidence that amongst the heptahelical 5-HT receptors, homo- and heterodimerisation (5-$HT_{1B,1D}$) can occur. It should also be noted that there is emerging evidence that 5-HT receptor subtypes have naturally occurring polymorphic variants, and these could be an additional source of biological variation within the 5-HT system.

Figure 1. Structures of some 5-HT uptake inhibitors



(Bold text denotes compounds available from Tocris)

Current efforts pursue the identification of either efficacious or silent ligands with high selectivity for the different receptor subtypes. The issue of ligand efficacy is both complex and difficult to improve as we know today that ligands may display a wide spectrum of activities: efficacious to partial agonism, silent neutral antagonism, partial to efficacious inverse agonism (Table 3), or in some cases protean agonism.[1] Although it is well established that different agonists do not necessarily elicit the same magnitude of response, it is less clear whether these agonists also differentiate between various possible signal transduction pathways.[1,2] Such differential signalling *via* a single receptor subtype is an intriguing issue in molecular pharmacology and emphasizes that a single receptor target could be activated in different ways. Consequently, it would be possible to obtain agonists with properties that are both *quantitatively* and *qualitatively* distinct. It is anticipated that both efficacious and selective receptor probes will provide tools to advance definition of functional effects *in situ*, be it *in vitro* or *in vivo*, and, in addition, lead to more efficacious drug treatments with fewer side effects for a variety of disorders. Molecular genetic approaches offer a

Table 1. Different 5-HT receptor subtypes

	5-HT_1	5-HT_2	5-HT_3	5-HT_4	5-ht_5	5-ht_6	5-HT_7
Subtypes	5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-ht_{1E}, 5-ht_{1F}	5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}	5-HT_{3A}, 5-HT_{3B}		5-ht_{5A}, 5-ht_{5B}		
Major signalling pathway	cAMP↓	IP_3↑	Ion channel	cAMP↑	cAMP?	cAMP↑	cAMP↑

Table 2. Summary of changes in 5-HT receptor nomenclature

Old nomenclature		New nomenclature
Receptor	**Species**	
5-HT_{1B}	Rat	
5-HT_{1D}	Human, guinea pig	5-HT_{1B}[a]
5-$HT_{1D\beta}$	All species	
5-$HT_{1D\alpha}$	All species	5-HT_{1D}
5-HT_2	All species	5-HT_{2A}
5-HT_D		
5-HT_{2F}	All species	5-HT_{2B}
5-HT_{1C}	All species	5-HT_{2C}

[a]Species equivalent, e.g. r5-HT_{1B} for rodents and h5-HT_{1B} for humans. Taken from Barnes and Sharp (1999) Neuropharmacology ***38*** 1083.[3]

complementary strategy for studying distinct 5-HT receptor subtypes *via* the generation of gene-targeted and transgenic lines of mice with altered expression of 5-HT receptor genes. 5-HT is also a substrate for the 5-HT transporter, itself a target in the treatment of depression and social phobia. The 5-HT transporter is the target for selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, paroxetine and citalopram (Figure 1), an important class of drugs that emerged during the 20th century. 5-HT receptors are divided, according to the NC-IUPHAR subcommittee on 5-HT receptors, into seven distinct classes (5-HT_1 to 5-HT_7), largely on the basis of their structural and operational characteristics. The reader is referred to the following reviews on 5-HT receptors (Pauwels, 2000; Barnes and Sharp, 1999; Hoyer *et al*, 2002)[2,3,4] for further reading and details. The present paper focuses on the 5-HT receptor ligands that are available as tools for experimental research.

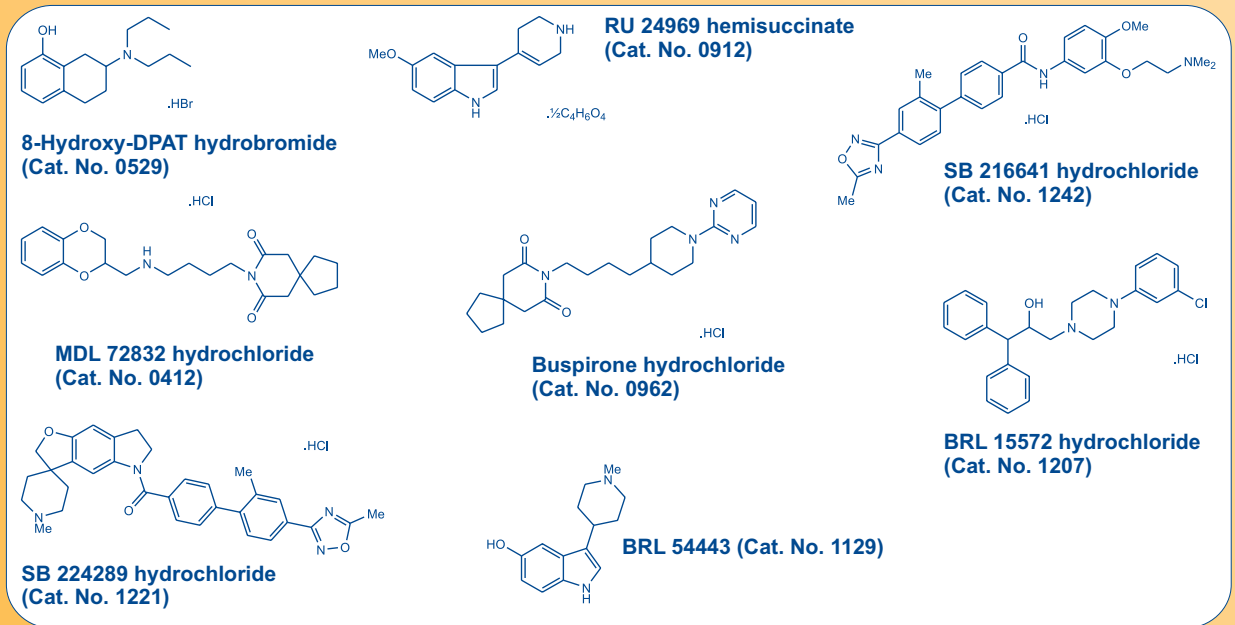
The 5-HT_1 receptor class

The 5-HT_1 receptor class is comprised of five receptor subtypes (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-ht_{1E} and 5-ht_{1F}), which, in humans, share 40-63% overall sequence identity and couple preferentially, although not exclusively, to $G_{i/o}$ proteins to inhibit cAMP formation. The 5-ht_{1E} and 5-ht_{1F} receptors are given a lower case appellation to denote that endogenous receptors with a physiological role have not yet been found. In contrast, 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptors have been demonstrated functionally in a variety of tissues from various species.

5-HT_{1A} receptors

5-HT_{1A} receptors are distributed largely throughout the CNS. In the raphé nuclei, they are somatodendritic and act as autoreceptors to inhibit cell firing; postsynaptic 5-HT_{1A} receptors are present in a number of limbic structures, particularly the hippocampus. Activation of 5-HT_{1A} receptors causes neuronal hyper-polarisation.[5] Furthermore, in the gastro-intestinal tract, 5-HT_{1A} receptors were identified on the guinea pig myenteric plexus where they function as inhibitory modulators of fast excitatory postsynaptic potentials. 5-HT_{1A} receptors have been implicated in the neuroendocrine regulation of adrenocortico-trophic hormone (ACTH), but not prolactin secretion.[6] It has been established that activation of postsynaptic 5-HT_{1A} receptors induces a behavioural syndrome, characterized by flat body posture, reciprocal forepaw treading and head weaving. The spontaneous tail-flick response has also been attributed to postsynaptic 5-HT_{1A} receptor activation;[7,8,9] whereas evidence for a presynaptic 5-HT_{1A} (auto)receptor in the hyperphagia response appears convincing.[10] A decrease in blood pressure and heart rate and increased locomotor responses can be induced by central 5-HT_{1A} receptor activation, whilst fluoxetine-induced penile erections can be markedly

Figure 2. Structures of some 5-HT_1 receptor ligands



(Bold text denotes compounds available from Tocris)

Table 3. Examples of 5-HT ligands, previously characterised as antagonists, behaving as either a partial agonist, a neutral antagonist or an inverse agonist at 5-HT receptors

Receptor subtype	Partial agonist	Neutral antagonist	Partial inverse agonist	Inverse agonist	References
Wild-type h5-HT_{1A}		WAY 100635		**Spiperone, methiothepin**	155, 156, 157
Wild-type h5-HT_{1B}	GR 125743, **GR 127935**, 1-naphthylpiperazine			**GR 55562**, **SB 224289**, **methiothepin**	148, 158, 159
r5-HT_{2A} $Cys^{322}Lys$				Chlorpromazine, **clozapine**, **haloperidol**, loxapine, risperidone	160
Wild-type r5-HT_{2C}				**Mianserin**, **spiperone**, mesulergine, **ketanserin**, **clozapine**, **cyproheptadine**	161, 162
r5-HT_{2C} $Ser^{312}Lys$				**Mianserin**, mesulergine	163
Wild-type h5-HT_{4C}				ML 10375	109
Wild-type h5-HT_{7long}			SB 258719, mesulergine	Risperidone, **methiothepin**, olanzapine, **clozapine**	164

(Bold text denotes compounds available from Tocris)

Taken from Pauwels (2000) Biochem.Pharmacol. ***60*** 1743.[2]

potentiated by combined 5-$HT_{1A/1B}$ receptor blockade.[11-14]

The proposed role of 5-HT_{1A} receptors in modulating anxiety-related behaviours is supported by recent studies utilising 5-HT_{1A} receptor knockout (KO) mice. These animals demonstrated increased anxiety in a number of experimental paradigms. The KO animals spent less time in the open arms of the elevated plus maze, the elevated zero maze and the centre of an open field, and less time exploring a novel object. Moreover, these animals demonstrated decreased baseline immobility in the forced swimming and tail suspension tests.[15,16]

5-HT_{1A} receptor agonists, such as buspirone (Figure 2) or gepirone, are being used or developed for the treatment of anxiety and depression.[17,18] The 5-HT_{1A} receptor antagonist and β-adrenoceptor blocker, pindolol, was reported to enhance the therapeutic efficacy and shorten the onset of action of SSRIs when co-administered in depressed patients. However, both positive and negative findings have been reported.[19] Flesinoxan, a 5-HT_{1A} receptor partial agonist, was initially developed as an antihypertensive agent. This approach has been abandoned.

Several agonists show selectivity for the 5-HT_{1A} receptor, particularly 8-hydroxy-di-*n*-propylamino tetralin (8-OH-DPAT, Figure 2), which may act as a full agonist in experimental systems, whilst the anxiolytics buspirone and gepirone and other ligands, such as MDL 72832 (Figure 2), are definitely partial agonists. The only selective high-affinity silent antagonist at this receptor is WAY 100635.[20,21] Additional ligands include the agonists U-92016A and (+)-UH 301, and the putative antagonists (-)-UH 301 and NAD 299.[22,23,24,25] Recent compounds (F 13714 and F 13640) have been used to examine further the hypothesis that the magnitude of the intrinsic activity of agonists at 5-HT_{1A} receptors determines the magnitude of their psychotropic activity. F 13714 displayed maximal effects in the forced swimming test, effects which were significantly larger than any of the other 5-HT compounds examined because of its higher intrinsic activity at 5-HT_{1A} receptors.[26] Large-amplitude 5-HT_{1A} receptor activation with F 13640 has been observed and constitutes a novel mechanism of profound, central analgesia.[27]

5-HT_{1B} receptors

5-HT_{1B} receptors are expressed in the CNS, concentrated in the basal ganglia, striatum and frontal cortex and are thought to serve as terminal autoreceptors. In addition, the receptor may also act as a terminal heteroreceptor, controlling the release of other neuro-transmitters, such as acetylcholine, glutamate, dopamine, noradrenaline and γ-aminobutyric acid.[28] The receptors are also found on cerebral arteries and other vascular tissues. Peripheral effects have been described, such as inhibition of noradrenaline release in the vena cava and inhibition of plasma extravasation produced by trigeminal ganglion stimulation in guinea pigs and rats. 5-HT_{1B} receptors mediate contraction of rat caudal arteries. In non-rodents, they exhibit the 5-HT_{1D} "pharmacology".

Interest in 5-HT_{1B} receptor agonists has been enhanced by the antimigraine properties of sumatriptan, a non-selective 5-$HT_{1D/1B}$ receptor agonist; thus other agonists [dihydroergotamine (DHE), zolmitriptan (BW 311C90), naratriptan, rizatriptan (MK 462), elitriptan, almotriptan, and donitriptan] have been, and are being, developed for this indication.[29,30] Donitriptan, despite its mixed activity at both 5-HT_{1D} and 5-HT_{1B} receptors, displays uniquely high selectivity towards cranial *versus* peripheral tissues, thereby leading to drug candidates with fewer cardiovascular side effects.[31] Donitriptan has completed phase I clinical trial for migraine and is currently being evaluated in phase II clinical trials. Besides the antimigraine activity of the 5-$HT_{1B/1D}$ agonists in clinical evaluation or already on the market, other potential therapeutic uses of these drugs, such as for gastric motor effect, bipolar disorder, autism and

anti-aggressive effects are being investigated.[32] The putative 5-HT_{1B} receptor agonist, anpirtoline, has analgesic and antidepressant-like properties in rodents. 5-HT_{1B} receptor KO mice were reported to be both highly aggressive and have an increased preference for alcohol.[33,34,35] However, recent findings have diminished the perceived utility of 5-HT_{1B} receptor KO mice as a model of alcoholism, as attempts to replicate such abnormalities in ethanol consumption were unsuccessful.[36,37] The 5-HT_{1B} receptor KO animals display decreases in measures of anxiety in the elevated plus maze, open field and tail suspension test, in addition to an increase in aggression in the resident intruder paradigm.[33,38,39] An attempt was made to develop 5-HT_{1B} agonist "serenics", such a eltoprazine; however, the expected antiaggressive effects were not observed in patients.[40]

RU 24969 (Figure 2) was the first reported full agonist at the 5-HT_{1B} receptor and earlier studies utilised the strong locomotor response to this ligand, as a model of postsynaptic receptor function.[13,41] Additional effects tentatively attributed to central 5-HT_{1B} receptor activation in rats include hypophagia, hypothermia and penile erection.[14,42]

Other characterized 5-HT_{1B} agonists (in rodents) include SKF 99101H, GR 46611 and CP 93129. In addition, some 5-HT_{1B} agonists, e.g. sumatriptan, naratriptan, zolmitriptan, eletriptan and rizatriptan[44] have significant affinity at 5-ht_{1F} receptors. Some of these molecules recognise 5-HT_{1B} and 5-HT_{1D} receptors almost equally; e.g. L-694,247 in addition to 5-HT_{1A} receptors.[45] However, SB 216641 (h5-HT_{1B}) and BRL 15572 (h5-HT_{1D}) (Figure 2) have permitted discrimination of the effects mediated by one or the other of these receptor subtypes, in appropriate species, at the level of presynaptic auto- and heteroreceptors.[46-49]

With respect to antagonists, there are few with selectivity for the 5-HT_{1B} receptor. The most commonly used (in rodents), pindolol, cyanopindolol and SDZ 21009, are equipotent at 5-HT_{1A} receptors, where they have antagonist or partial agonist properties and are more potent as β-adrenoceptor antagonists. SB 216641, SB 272183 and GR 55562 demonstrate a certain degree of 5-HT_{1B} selectivity, whilst others demonstrate inverse agonism (e.g. SB 224289 and SB 236057) (Figure 2), thus allowing the characterisation of 5-HT_{1B} receptor tone.[50] Moreover, the use of these new compounds, displaying different levels of intrinsic activity at these receptors, demonstrates that terminal 5-HT autoreceptors are of the 5-HT_{1B} type.[46-55]

5-HT_{1D} receptors

The 5-HT_{1D} receptor possesses 63% overall structural homology with the 5-HT_{1B} receptor. Its level of expression is very low compared with 5-HT_{1B} receptors. The use of 5-HT_{1B} receptor compounds has suggested the presence of a 5-HT_{1D} autoreceptor in the dorsal raphé nuclei.[48,49,51,56,57] 5-HT_{1D} receptors have also been found in the human heart, where they modulate 5-HT release.

The currently available antimigraine drugs do not distinguish between 5-HT_{1B} and 5-HT_{1D} receptors. It has been proposed that neurogenic inflammation and nociceptive activity within trigeminovascular afferents may be 5-HT_{1D} receptor-mediated due to the presence of 5-HT_{1D}, but not 5-HT_{1B} receptor mRNA in the trigeminal ganglia, but this has not been confirmed. The selective 5-HT_{1D} receptor agonist PNU 109291 has been shown to play a significant role in the supression of meningeal neurogenic inflammation and trigeminal nociception in guinea pig models, suggesting that the 5-HT_{1D} receptor subtype may represent a useful therapeutic target for migraine and related headaches.[58] PNU 109291, however, did not show a significant effect in clinical studies. Another clinical candidate from this series, PNU 142633, has been stopped in development.[32]

5-ht_{1E} receptors

The putative 5-ht_{1E} receptor was first identified in binding studies in homogenates of human frontal cortex, but it was not possible to readily determine its overall distribution and pharmacology. It is a 365-amino acid protein, negatively linked to adenylyl cyclase in recombinant cell systems. The 5-ht_{1E} receptor's function is presently unknown, and selective ligands are largely unavailable. The 5-ht_{1E} receptor (like the 5-ht_{1F} receptor) is characterized by its high affinity for 5-HT and lower affinity for 5-CT. A relative low affinity for sumatriptan sets it apart from the 5-ht_{1F} binding site.[3]

5-ht_{1F} receptors

The 5-ht_{1F} receptor consists of a 366-amino acid protein, negatively linked to adenylyl cyclase in recombinant cell systems. This receptor is most closely related to the 5-ht_{1E} receptor with >70% sequence homology across the seven transmembrane domains. Little is known about the distribution and function of the 5-ht_{1F} receptor; mRNA for the human receptor protein has been identified in the brain, mesentery and uterus, but not in kidney, liver, spleen, heart, pancreas or testis. Its distribution suggests that it may possess a role as a 5-HT autoreceptor. Interestingly, the antimigraine 5-$HT_{1B/1D}$ agonists sumatriptan and eletriptan label 5-ht_{1F} sites with high affinity. Moreover, naratriptan has higher affinity for 5-ht_{1F} receptors, whereas zolmitriptan and rizatriptan display less affinity. In contrast, alniditan and donitriptan are virtually free of binding affinity for 5-ht_{1F} sites.[44] It has been hypothesised that the 5-ht_{1F} receptor might be a target for drugs with antimigraine properties as 5-ht_{1F} receptor mRNA has been detected in the trigeminal ganglia, stimulation of which leads to plasma extravasation in the dura, a component of neurogenic inflammation thought to be a possible cause of migraine.[59] LY 334370, a putative selective 5-ht_{1F} receptor agonist, which also has affinity for 5-HT_{1A} receptors,[60] inhibits trigeminal stimulation-induced early activated

gene (Fos protein) expression in nociceptive neurones in the rat brainstem.[61] Further selective ligands are currently in development, i.e. LY 344864 and BRL 54443 (Figure 2). However, these also have affinity for 5-ht_{1E} receptors.[62,63]

The 5-HT_2 receptor class

The 5-HT_2 receptor class is comprised of the 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptor subtypes, which exhibit 46-50% overall sequence identity and couple preferentially to $G_{q/11}$ to increase the hydrolysis of inositol phosphates and elevate cytosolic Ca^{2+}. The binding affinity of various 5-HT ligands at 5-HT_2 receptor subtypes is summarised in Table 4.

5-HT_{2A} receptors

The 5-HT_{2A} receptor contains 471 amino acids in rats, mice and humans and is widely distributed in peripheral and central tissues. 5-HT_{2A} receptors mediate contractile responses in a series of vascular smooth muscle preparations. In addition, platelet aggregation and increased capillary permeability following exposure to 5-HT have been attributed to 5-HT_{2A} receptor-mediated functions. Centrally, these receptors are principally located in the cortex, claustrum and basal ganglia. Activation of 5-HT_{2A} receptors stimulates hormone secretion, e.g. ACTH, corticosterone, oxytocin, renin and prolactin.[64] 5-HT_{2A} receptor agonists mediate certain behavioural syndromes *in vivo*. Head twitching in mice, and wetdog shakes and back muscle contractions in rats, can be inhibited with 5-HT_2 receptor antagonists with a potency correlating with their affinity for 5-HT_{2A} receptor binding sites. In confirmation, such head twitching has been demonstrated to be inhibited by the selective 5-HT_{2A} receptor antagonist MDL 100907.[65-67] The production of drug discriminative stimulus properties of 5-HT_2 receptor agonists, e.g. (-)-2,5,-dimethoxy-4-methamphetamine (DOM) can be blocked by 5-HT_2 receptor antagonists, such as ketanserin (Figure 3), suggesting that the discriminative cue is 5-HT_{2A} receptor-mediated.[68,69]

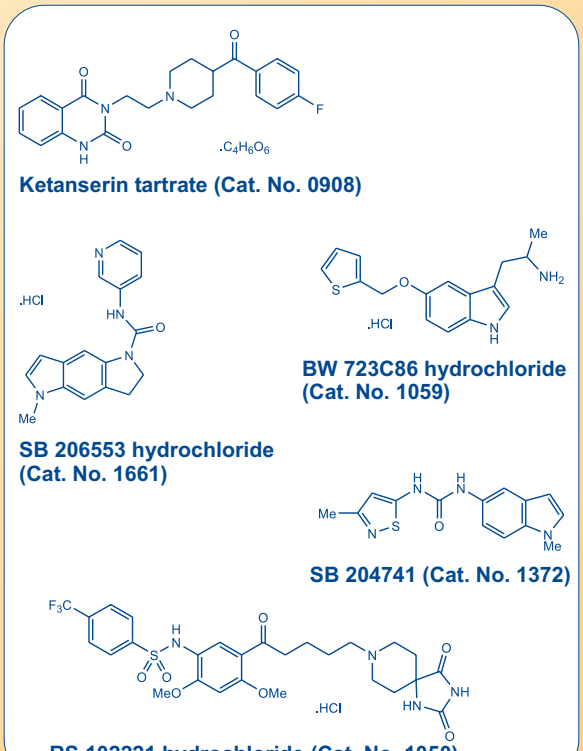
Table 4. Affinity (pK_i) of various ligands for 5-HT_2 receptor subtypes

	5-HT_{2A}	5-HT_{2B}	5-HT_{2C}
5-HT_{2A} receptor			
Spiperone	8.8	5.5	5.9
MDL 100907	9.4	nd	6.9
Ketanserin	8.9	5.4	7.0
5-HT_{2B} receptor			
5-MeOT	7.4[a]	8.8[a]	6.2[a]
α-Methyl-5-HT	6.1[a]	8.4[a]	7.3[a]
SB 204741	< 5.3	7.8	< 6.0
BW 723C86	< 5.4[a]	7.9[a]	< 6.9
5-HT_{2C} receptor			
SB 242084	6.8	7.0	9.0
RS 102221	6.0	6.1	8.4
Ro 60-0175	6.0	5.8	8.8
5-$HT_{2B/2C}$ receptors			
SB 200646A	5.2	7.5	6.9
mCPP	6.7	7.4[a]	7.8
SB 206553	5.8	8.9	7.9
Non-selective			
LY 53857	7.3	8.2	8.1
ICI 170809	9.1	nd	8.3
Ritanserin	8.8	8.3	8.9
Mianserin	8.1	7.3	8.0
DOI	7.3[a]	7.4[a]	7.8[a]

(Bold text denotes compounds available from Tocris)

[a]pEC_{50} value for agonist; nd = not determined.
Taken from **Barnes and Sharp** (1999) Neuropharmacology ***30*** 1104.[165]

Figure 3. Structures of some 5-HT_2 receptor ligands



(Bold text denotes compounds available from Tocris)

The most selective agents, in terms of 5-HT_{2A} receptor affinity, are ketanserin and MDL 100907. The former agent was developed for the treatment of hypertension, but it remains to be established whether 5-HT_{2A} receptor antagonism is a valid antihypertensive principle, since ketanserin is also an α_1-adrenoceptor antagonist. 5-HT_{2A} receptor antagonists, such as risperidone, ritanserin, seroquel, olanzapine and MDL 100907, demonstrate divergent selectivity and have been indicated/developed for the treatment of schizophrenia. Inverse agonist activity for most of these compounds has been found at both 5-HT_{2A} and 5-HT_{2C} receptors. Therefore, this receptor-mediated inverse agonist activity seems to be a common feature for antipsychotic drugs.[70] However, it is not clear at the present time what the benefit would be of a silent neutral antagonist instead of an inverse agonist at these receptor subtypes. In any case, it appears that truly silent, neutral antagonists are much more uncommon than we would have previously speculated.[2] Development of MDL 100907 for acute schizophrenia was terminated, apparently due to insufficient efficacy; although other similar molecules are still in the pipeline. Selective

5-HT_{2A} receptor agonists have not been described, as αMe-5-HT, DOI and DOB also recognise other receptors of the 5-HT_2 receptor class.

5-HT_{2B} receptors

Activation of the 5-HT_{2B} receptor subtype leads to fundic smooth muscle contraction. It has proven difficult to pharmacologically characterize this receptor subtype due to operational characteristics similar to those of other members of the 5-HT_2 family.[71] The situation was clarified with the cloning of the rat, mouse and human "fundic" receptors.[72] Selective agonists (BW 723C86[73] (Figure 3)) and antagonists (RS 127445[74]) will undoubtedly facilitate the classification of 5-HT_{2B} receptor-mediated effects. 5-HT_{2B} receptor-like immunoreactivity has been reported, restricted to a few brain regions particularly cerebellum, lateral septum, hypothalamus and medial amygdala.[75] Interestingly, direct injection of BW 723C86 into the medial amygdala was reported to have anxiolytic properties in the rat social interaction test.[76] 5-HT_{2B} receptor activation has also been implicated in mediating hyperphagia and causing a reduction in grooming frequency.[73] 5-HT_{2B} receptors mediate endothelium-dependent relaxation in isolated rat jugular vein and contraction of longitudinal muscle in human small intestine. In addition, when stably expressed in a mouse fibroblast cell line, 5-HT_{2B} receptors have been reported to cause mitogenesis, *via* MAP kinase activation, linked to tumour-transforming activity.
SB 200646 and SB 206553 (Figure 3) have been reported as selective 5-$HT_{2C/2B}$ receptor antagonists, with low affinity for 5-HT_{2A} and other binding sites.[77,78] SB 204741 (Figure 3) has been reported as the first selective 5-HT_{2B} receptor antagonist, whilst LY 53857 has high affinity at recombinant human 5-HT_{2B} receptors[4]. Agonists with some selectivity are αMe-5-HT and 5-MeOT, which act as high affinity full agonists for the 5-HT_{2B} site.[79] BW 723C86 has been reported to have selectivity for the rat 5-HT_{2B} receptor, although such selectivity was less pronounced at human recombinant receptors. 5-HT_{2B} receptor antagonists, such as SB 200646, are relatively new and may be indicated for the treatment of migraine prophylaxis. It also appears that this receptor, expressed in cardiac valves, is responsible for the valvulopathies reported from dex-fenfluramine containing preparations utilised as appetite suppressant agents.[80,81]

5-HT_{2C} receptors

Due to the lack of selective 5-HT_{2C} receptor ligands, current knowledge concerning a functional role of this receptor is rather limited. Its distribution has been limited to the CNS and choroid plexus. Although it has been demonstrated that 5-HT_{2C} receptors in the choroid plexus couple to PLC activity, additional functional correlates remain to be established. Fourteen functional isoforms of the 5-HT_{2C} receptor have been identified; they are produced by adenine deaminase editing of receptor mRNA.[82,83] These 5-HT_{2C} receptor isoforms display varying degrees of constitutive activity.[70,84]

MK 212 and Ro 600175 represent moderately selective agonists whilst, amongst the antagonists, LY 53857, ZM 170809, ritanserin, mianserin and mesulergine have been utilized, but they are essentially nonselective.[85] It has been suggested that the anxiogenic component of mCPP is mediated by 5-HT_{2C} receptor activation, and selective 5-HT_{2C} receptor antagonists, such as SB 242084, display anxiolytic properties in animal models.[86] Following treatment with agents such as mCPP and Ro 600175, additional characteristic behavioural responses, attributed to central 5-HT_{2C} receptor activation, include hypoactivity, hypophagia, increased penile grooming/erections and oral dyskinesia.[43,77,87-90] 5-HT_{2C} receptor activation has been shown to exert a tonic, inhibitory influence upon frontocortical dopaminergic and adrenergic, but not serotonergic transmission and, in part, to play a role in neuroendocrine function.[91-93] Consistent with its action as a 5-HT_{2C} receptor antagonist, RS 102221 (Figure 3) increased food intake and weight gain in rats, yet, it failed to reverse the hypolocomotion induced by mCPP, possibly due to restricted brain penetration.[94] The 5-HT_{2C} receptor, therefore, is an attractive target for the discovery of novel treatments for feeding disorders.[95]

The 5-HT_3 receptor class: an intrinsic ligand-gated channel

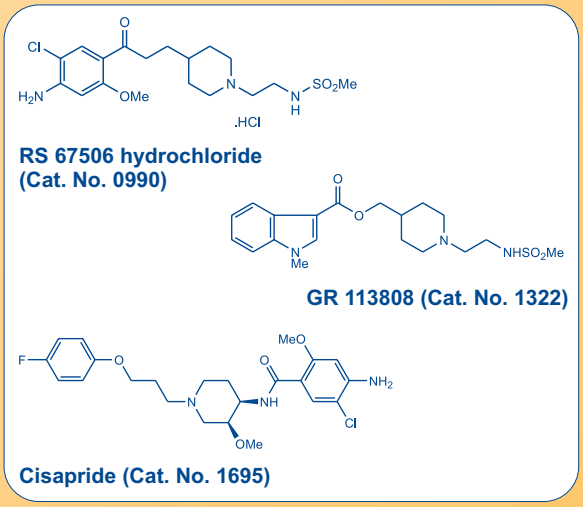
5-HT_3 receptors are found on neurones, of both central and peripheral origin, where they trigger rapid depolarisation due to a transient inward current, subsequent to the opening of nonselective cation channels (Na^+, Ca^{2+} influx, K^+ efflux). The response desensitises and resensitises rapidly. Heteromeric combination of 5-HT_{3A} and 5-HT_{3B} subunits is necessary to provide the functional features of the 5-HT_3 receptor.[96,97] Two splice variants of the 5-HT_{3A} receptor have been described in neuroblastoma-glioma (NCB-20, NG 108-15) cells and rat native tissues. These variants appear to possess similar distribution, pharmacological profiles and electro-physiological characteristics when expressed as homomers.[4] In addition, Bruss *et al* (2000)[98] reported on four different splice variants of the 5-HT_{3A} receptor. 5-HT_3 receptors are involved in chemotherapy- and radiotherapy-induced nausea and vomiting, which can be treated with ondansetron, granisetron and tropisetron (ICS 205-930). Since 5-HT_3 receptor activation in the brain leads to dopamine release and 5-HT_3 receptor antagonists produce central effects comparable to those of antipsychotics and anxiolytics, 5-HT_3 receptor involvement in schizophrenia and anxiety was considered. 5-HT_3 receptor antagonists have also been reported to induce cognition enhancing effects in rats, suggesting their potential use as memory-enhancing agents. However, to date, there are no clinical data to substantiate such activities.

Similarly, the hypothesis that 5-HT_3 antagonists may prove useful in the treatment of migraine did not materialize in clinical studies. More recently, alosetron was developed for the treatment of women suffering from irritable bowel syndrome with diarrhoea, but it had to be withdrawn due to safety reasons.[99]

5-HT_4 receptors

Multiple human 5-HT_4 receptor isoforms have been described. Seven C-terminal splice variants of the receptor have been identified (5-HT_{4A-H}).[100-106] Moreover, a splice variant, 5-HT_{4HB}, with a 14-amino acid insertion in the second extracellular loop has been reported.[107] These receptor variants couple positively to adenylyl cyclase and available data show that the pharmacology of the variants is apparently similar. However, one important feature of the 5-HT_4 receptor is the level of its constitutive (agonist-independent) activity, which is expressed at rather low receptor levels. This feature may well explain differences that have been observed with respect to variable intrinsic activity for a number of 5-HT ligands. Indeed, a putative antagonist may display either silent or inverse agonist properties, depending on the level of constitutive receptor activity. This scenario may be even too simple. Recently, a few non-5-HT compounds (in particular weak partial agonists) have been reported to behave as protean agonists.[1,108] They may illustrate either partial agonism or partial inverse agonism depending on the magnitude of basal receptor activity. Tissue distribution studies demonstrate specificity in the expression pattern of the human 5-HT_4 receptor isoforms. Moreover, the h5-HT_{4D} receptor isoform appears to be unique because, in contrast to the other isoforms, it has not been described in any other species yet.[106] Its expression appears to be restricted to the gut,[109] whereas the other isoforms are expressed in cardiac atria and brain.[101,105] In addition to adenylyl cyclase stimulation, direct coupling to potassium channels and voltage-sensitive calcium channels have been proposed as postreceptor events.

Figure 4. Structures of some 5-HT_4 receptor ligands



(Bold text denotes compounds available from Tocris)

5-HT_4 receptor activation triggers acetylcholine release in the guinea pig ileum and contracts the oesophagus and colon. In addition to its modulator function on gastrointestinal motility, the 5-HT_4 receptor is also involved in mediating secretory responses to 5-HT in intestinal mucosa. Electrogenic ion transport is stimulated through 5-HT_4 receptors in the small intestine whilst, in the piglet heart, the receptors mediate tachycardia (right atria) and positive inotropic effects (left atria). Similarly, isolated (human atria) appendages respond with increased contractile force to 5-HT_4 receptor agonists. 5-HT_4 receptors in the CNS appear to modulate neurotransmitter (acetylcholine, dopamine, serotonin and GABA) release and enhance synaptic transmission, and they may also play a role in memory enhancement; however, positive clinical studies are still eagerly awaited.[110]

The potent 5-HT_3 receptor antagonist tropisetron (ICS 205-930) was described as the first competitive 5-HT_4 receptor antagonist. Several potent and selective 5-HT_4 receptor ligands are now available, such as the agonists BIMU 8, RS 67506 (Figure 4) and ML 10302[111] and the antagonists GR 113808 (Figure 4), SB 204070, SB 203186, RS 23597-190 and RS 39604[112,113] which should allow definition of the (patho) physiological roles of this receptor. Cisapride (Figure 4), a gastroprokinetic agent, acts as an agonist at the 5-HT_4 receptor, whilst a new generation 5-HT_4 receptor partial agonist, tegaserod (HTF-919), is currently prescribed for constipation-predominant irritable bowel syndrome.[114,115] Selective 5-HT_4 receptor ligands have been proposed to possess putative therapeutic utility in a number of disorders, including cardiac arrhythmia,[116,117] neuro-degenerative diseases[118,119] and urinary incontinence.[120,121]

5-ht_5 receptors

No evidence has been obtained to confirm that the recombinant 5-ht_5 receptor is expressed in an endogenous setting. Two subtypes of the 5-ht_5 receptor (5-ht_{5A} and 5-ht_{5B}), sharing 70% overall sequence identity, have been found in rodents.[122] There have been no published reports concerning a physiological functional response, and specific binding to a 5-ht_5 recognition site has not been described.

5-ht_6 Receptors

Two 5-ht_6 receptor splice variants have been described.[123] One is the full-length 5-ht_6 receptor (440 amino acids), highly expressed in limbic and extrapyramidal brain areas. The other splice variant corresponds to a deletion of 289 base pairs generating a truncated receptor, expressed in the caudate and substantia nigra. Selective ligands are becoming available for the 5-ht_6 receptor. The site can be labelled with [^{125}I]SB 258585.[124] Moreover, Bromidge *et al* (1999)[125] reported SB 271046 as a potent, selective and bioavailable 5-ht_6 receptor antagonist[126-128] whilst Glennon *et al* (2000)[129]

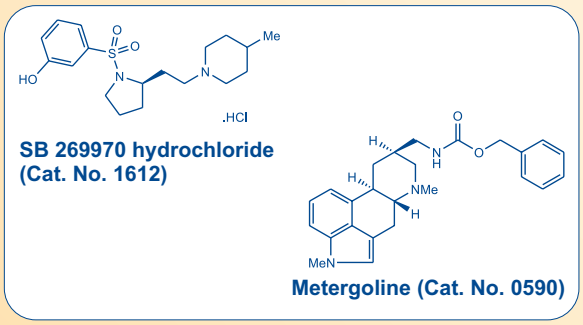
have described the identification of EMDT, a selective 5-ht$_6$ receptor agonist. The selective 5-ht$_6$ receptor antagonist Ro 04-6790 produces a behavioural syndrome involving an increase in acetylcholine neurotransmission.[130] Enhanced retention of spatial learning has been reported.[131,132] Ro 04-6790, Ro 63-0563 and SB 271046 have poor to modest brain penetration. More lipophilic analogues of Ro 04-6790 appear to penetrate the brain more readily. Reversing the sulfonamide linkage of SB 271046 led to a new series of compounds being developed, such as SB 357134, which also has increased CNS penetration.[133] In pharmacological studies, several antipsychotic agents (notably clozapine, olanzapine, fluperlapine and seroquel) and antidepressants (clomipramine, amitryptyline, doxepin and nortryptyline) have high affinity and act as antagonists at 5-ht$_6$ receptors. This attribute tempted speculation of a potential involvement of the 5-ht$_6$ receptor in the pathogenesis of psychiatric disorders.

5-HT$_7$ receptors

The 5-HT$_7$ human receptor has 445 amino acids and was shown to positively modulate cAMP formation *via* G$_s$.[134-136] The receptor also activates the mitogen-activated protein kinase, ERK, in primary neuronal cultures.[137] Alternate splicing has been reported to generate four 5-HT$_7$ receptor isoforms (5-HT$_{7A-D}$), which differ in their C-termini.[138] However, these isoforms, to date, have not been shown to differ in their respective pharmacology, signal transduction or tissue distribution.[139,140] Conversely, the pharmacological profile of the receptor is characterized by a high affinity for the prototypical 5-HT$_1$ agonists 5-CT, 5-MeOT and 8-OH-DPAT, the 5-HT$_2$ receptor ligand LSD and the antagonists ritanserin, metergoline (Figure 5), methysergide and mesulergine. Operational studies have confirmed that the 5-HT$_7$ receptor has an extensive vascular distribution and is responsible for the prominent, persistent vasodilator response to 5-HT in anaesthetised animals.[141] The receptors are also expressed in nonvascular smooth muscle[142,143] and the CNS.

Atypical antipsychotics, e.g. clozapine, risperidone and antidepressants, have high affinity for the 5-HT$_7$ receptor.[144] Furthermore, a down-regulation of 5-HT$_7$ receptors occurs after chronic antidepressant treatment,[145,146] whilst acute, but not chronic, stress has been demonstrated to regulate 5-HT$_7$ receptor mRNA expression.[147]

Figure 5. Structures of some 5-HT$_7$ receptor ligands



SB 269970 hydrochloride (Cat. No. 1612)

Metergoline (Cat. No. 0590)

(Bold text denotes compounds available from Tocris)

Relatively recently, a number of ligands have been reported, which will allow further characterization of these receptors in native tissues and *in vivo*, in particular, the selective antagonists SB 258719, SB 258741 and SB 269970[148-153] (Table 5). A role for the 5-HT$_7$ receptor has been proposed in the regulation of 5-CT-induced hypothermia in guinea pigs, as the response was blocked by both SB 269970 (Figure 5) and the nonselective 5-HT$_7$ receptor antagonist metergoline. Moreover, when administered at the start of the sleep period, SB 269970 significantly reduced time spent in paradoxical sleep (analogous to REM sleep in humans) during the first 3 h of EEG recording in conscious rats.[149] This effect mimics those seen with SSRIs in the clinic and provides preliminary evidence that 5-HT$_7$ receptor antagonists may be of interest in further investigations into sleep disorders and depression.

Conclusions

The 5-HT receptor family has grown very fast from a few members to a complex family of fourteen distinct members. This complexity illustrates that 5-HT has many ways to exert its multiple effects. The observed splice variants, RNA edited forms and naturally occurring polymorphic variants give an extra-dimension to the complexity of this receptor family. Berg *et al* (1998)[154] suggested some 5-HT compounds preferentially activate one signaling pathway *versus* another one *via* a single 5-HT$_{2A}$ receptor subtype. This implies that pharmacological diversity may not only occur between different

Table 5. Receptor binding profiles and selectivity of the 5-HT$_7$ receptor antagonists

Ligands	5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{1D}$	5-ht$_{1E}$	5-ht$_{1F}$	5-HT$_{2A}$	5-HT$_{2B}$	5-HT$_{2C}$	5-HT$_4$	5-ht$_{5A}$	5-ht$_6$	5-HT$_7$	α_{1b}	D$_2$	D$_3$	Selectivity
SB 258719	< 5.1	< 5.3	5.5	< 4.8	< 5.2	< 4.8	< 5.3	< 4.8	< 5.0	nd	< 4.8	7.5	< 4.8	5.4	5.4	100
SB 258741	6.0	5.8	5.5	< 5.0	< 5.0	< 5.3	< 5.6	< 5.3	< 5.0	nd	nd	8.5	< 5.5	5.8	5.9	300
SB 269970	< 5.0	6.0	5.8	< 5.2	< 5.5	< 5.0	5.0	< 5.0	5.9	7.2	5.2	8.9	< 5.0	6.5	5.6	100

(Bold text denotes compounds available from Tocris)

pK$_i$ values. Taken from **Pouzet** (2002) CNS Drug Reviews ***8*** 90.[153]; nd = no data

receptor subtypes, but also within one single 5-HT receptor subtype. Therefore, 5-HT pharmacology was “apparently” easier in the old days. Nonetheless, the design of bioavailable selective 5-HT ligands that can be safely administered to man remains today the key-issue to ameliorate disease-states with dysregulations of the 5-HT system. The recent progress in receptor signal transduction pathways should truly help us to make more efficacious ligands. The issue of constitutive 5-HT receptor activity also opens the possibility to differentiate between silent neutral antagonists and inverse agonists. We may expect a different therapeutic potential for each of these latter ligands. 5-HT is important and a lot needs still to be resolved to better understand this neurotransmitter. Molecular biology provided a lot in the early nineties. We should now equilibrate our research efforts, in particular by giving sufficient attention to integrated 5-HT pharmacology.

Ligand abbreviations used in this review

αMe-5-HT: α-methyl-5-hydroxytryptamine
5-CT: 5-carboxamidotryptamine
5-HT: 5-hydroxytryptamine, serotonin
5-MeOT: 5-methoxytryptamine
8-OH-DPAT: (±)-8-hydroxy-2-dipropylaminotetralin
ACTH: adrenocorticotrophic hormone
DHE: dihydroergotamine
DOB: 2,5-dimethoxy-4-bromoamphetamine
DOI: 2,5-dimethoxy-4-iodoamphetamine
DOM: 2,5-dimethoxy-4-methamphetamine
EMDT: 2-ethyl-5-methoxy-*NN*-dimethyltryptamine
LSD: lysergic acid diethylamide
mCPP: 2-(2-methyl-4-chlorophenoxy)propanoic acid

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Serotonin Receptor Compounds available from Tocris

5-HT$_1$ Receptor Selective

Agonists

0703	Anpirtoline	Highly potent 5-HT$_{1B}$ agonist. Also 5-HT$_3$ antagonist
1006	BMY 7378	5-HT$_{1A}$ partial agonist
0556	BP-554	Selective 5-HT$_{1A}$ agonist
1129	BRL 54443	Selective 5-ht$_{1E/F}$ agonist
0962	Buspirone	5-HT$_{1A}$ partial agonist
0458	5-Carboxamido-tryptamine	5-HT$_1$ agonist. Also has high affinity for 5-ht$_{5A}$ and 5-HT$_7$
0638	CGS 12066B	5-HT$_{1B}$ agonist
1032	CP 93129	5-HT$_{1B}$ agonist
1317	CP 94253	Potent, selective 5-HT$_{1B}$ agonist
0864	GR 46611	5-HT$_{1D}$ agonist
0529	8-Hydroxy-DPAT	Selective 5-HT$_{1A}$ agonist. Also has moderate affinity for 5-HT$_7$
1080	(*R*)-(+)-8-Hydroxy DPAT	More active enantiomer
0797	8-Hydroxy-PIPAT	High affinity 5-HT$_{1A}$ agonist
0781	L-694,247	5-HT$_{1D}$ agonist
0411	MDL 73005EF	Potent and selective 5-HT$_{1A}$ partial agonist
0901	5-Nonyloxytryptamine	Selective 5-HT$_{1B}$ agonist
0912	RU 24969	5-HT$_{1B/1A}$ agonist
1771	S 14506	Highly potent 5-HT$_{1A}$ agonist; displays unique binding mechanism
0968	TFMPP	5-HT$_{1B}$ partial agonist
1772	Urapidil	5-HT$_{1A}$ agonist. Also α_1-adrenoceptor antagonist

Antagonists

1207	BRL 15572	Selective h5-HT$_{1D}$ antagonist
0993	Cyanopindolol	5-HT$_{1A/1B}$ antagonist. Also β-adrenergic antagonist
1054	GR 55562	5-HT$_{1B}$ antagonist
1477	GR 127935	Potent, selective 5-HT$_{1B/1D}$ antagonist
0992	Isamoltane	5-HT$_{1B}$ antagonist
0933	MM 77	5-HT$_{1A}$ (postsynaptic) antagonist
0553	NAN-190	5-HT$_{1A}$ antagonist
1413	NAS-181	Selective r5-HT$_{1B}$ antagonist. Active *in vivo*
0994	Pindolol	5-HT$_{1A/1B}$ antagonist. Also β-adrenergic antagonist
1060	(*S*)-(-)-Pindolol	More active enantiomer
1242	SB 216641	Selective h5-HT$_{1B}$ antagonist
1221	SB 224289	Selective 5-HT$_{1B}$ antagonist
0631	Spiroxatrine	5-HT$_{1A}$ antagonist
1253	(*S*)-WAY 100135	Potent, selective 5-HT$_{1A}$ antagonist

Other

0412	MDL 72832	Potent 5-HT$_{1A}$ ligand
0580	3-[2-[4-(2-Methoxyphenyl) piperazin-1-yl]ethyl]-1,5-dimethylpyrimido[5,4-b] indole-2,4-dione	5-HT$_{1A}$ ligand
0581	3-[2-[4-(2-Methoxyphenyl) piperazin-1-yl]-ethyl] pyrimido[5,4-b]indole-2,4-dione	5-HT$_{1A}$ ligand

5-HT$_2$ Receptor Selective

Agonists

1059	BW 723C86	5-HT$_{2B}$ agonist
0875	*m*-CPP	5-HT$_{2B/2C}$ receptor agonist
0557	α-Methyl-5-hydroxytryptamine	5-HT$_2$ agonist
0941	MK 212	5-HT$_{2C}$ agonist
1801	WAY 161503	Potent, selective 5-HT$_{2C}$ agonist

Antagonists

0524	AMI-193	Selective 5-HT$_2$ antagonist
0460	Cinanserin	Selective 5-HT$_2$ antagonist
0996	Cyproheptadine	5-HT$_2$ antagonist
1007	*N*-Desmethylclozapine	5-HT$_{2C}$ antagonist
0523	4F 4PP	Selective 5-HT$_2$ antagonist
0908	Ketanserin	Selective 5-HT$_{2A/2C}$ antagonist. Also antagonist at 5-HT$_{1D}$
0870	MDL 11,939	5-HT$_2$ antagonist
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	5-HT$_2$/5-HT$_1$ antagonist. Has moderate affinity for 5-ht$_6$
1050	RS 102221	Selective 5-HT$_{2C}$ antagonist
1371	SB 200646	5-HT$_{2C/2B}$ antagonist
1372	SB 204741	Potent, selective 5-HT$_{2B}$ antagonist
1661	SB 206553	Potent, selective 5-HT$_{2C}$/5-HT$_{2B}$ antagonist. Orally active
1379	SB 221284	Potent, selective 5-HT$_{2C/2B}$ antagonist
1255	SDZ SER 082	Selective 5-HT$_{2B/2C}$ antagonist
0995	Spiperone	5-HT$_{2A}$ antagonist. Also D$_2$ antagonist

Other

0755	*N*-(4-Bromobenzyl)-5-methoxytryptamine	5-HT$_{2A}$ ligand

5-HT$_3$ Receptor Selective

Agonists

0440	*m*-Chlorophenyl-biguanide	Potent and specific 5-HT$_3$ agonist
0558	2-Methyl-5-hydroxytryptamine	5-HT$_3$ agonist/potent 5-ht$_6$ ligand
0566	*N*-Methylquipazine	5-HT$_3$ agonist
0969	1-Phenylbiguanide	5-HT$_3$ agonist
0629	Quipazine	5-HT$_3$ agonist
0988	RS 56812	5-HT$_3$ partial agonist
1205	SR 57227	Potent, selective 5-HT$_3$ agonist

Antagonists

0666	3-(4-Allylpiperazin-1-yl)-2-quinoxalinecarbonitrile	5-HT$_3$ antagonist
0640	MDL 72222	5-HT$_3$ antagonist
0641	Tropanyl 3,5-dimethylbenzoate	5-HT$_3$ antagonist
0380	Y-25130	Potent, selective 5-HT$_3$ antagonist
1795	Zacopride	Highly potent 5-HT$_3$ receptor antagonist. Also 5-HT$_4$ agonist

Other

1015	RS 16566	5-HT$_3$ ligand. Also shows affinity for zacopride binding site

5-HT$_4$ Receptor Selective

Agonists

1695	Cisapride	5-HT$_4$ agonist; stimulates intestinal ACh release
0736	2-[1-(4-Piperonyl) piperazinyl] benzothiazole	5-HT$_4$ agonist. Also 5-HT$_3$ antagonist
0989	RS 67333	5-HT$_4$ partial agonist
0990	RS 67506	5-HT$_4$ partial agonist
1795	Zacopride	5-HT$_4$ agonist. Also highly potent 5-HT$_3$ antagonist

Antagonists

1322	GR 113808	Potent, selective 5-HT$_4$ antagonist
1658	GR 125487	Potent, selective 5-HT$_4$ antagonist. Active *in vivo*
0728	RS 23597-190	5-HT$_4$ antagonist
0991	RS 39604	5-HT$_4$ antagonist
0785	SB 203186	5-HT$_4$ antagonist

5-ht$_5$, 5-ht$_6$, and 5-HT$_7$ Receptors

0458	5-Carboxamido-tryptamine	Has high affinity for 5-ht$_{5A}$ and 5-HT$_7$. Also 5-HT$_1$ agonist
0529	8-Hydroxy-DPAT	Has moderate affinity for 5-HT$_7$. Also 5-HT$_{1A}$ agonist
0590	Metergoline	Has moderate affinity for 5-ht$_6$ and high affinity for 5-HT$_7$. Also 5-HT$_1$ agonist and 5-HT$_2$ antagonist
0558	2-Methyl-5-hydroxytryptamine	5-HT$_3$ agonist/potent 5-ht$_6$ ligand
0997	Mianserin	Has moderate affinity for 5-ht$_6$. Also 5-HT$_2$ antagonist
0937	Pimozide	High affinity for 5-HT$_7$. Also D$_2$ antagonist
1612	SB 269970	Potent, selective 5-HT$_7$ antagonist. Brain penetrant

5-HT Uptake Inhibitors

R1315	[^{3}H]-β-CIT ☢	Potent radioligand for 5-HT and dopamine transporters
1427	Citalopram	Highly potent and selective 5-HT uptake inhibitor
0457	Clomipramine	5-HT re-uptake inhibitor
0927	Fluoxetine	5-HT re-uptake inhibitor
1033	Fluvoxamine	5-HT re-uptake inhibitor
1588	Indatraline	Potent 5-HT uptake inhibitor. Also inhibits dopamine and noradrenaline uptake
0596	6-Nitroquipazine	Potent 5-HT re-uptake inhibitor

Other Serotonergic Related Compounds

0357	*N*-Acetyltryptamine	Serotonin *N*-acetyl transferase substrate
0767	Bifemelane	MAO-A and MAO-B inhibitor
0938	*p*-Chlorophenylalanine	Tryptophan hydroxylase inhibitor
0444	Clozapine	5-HT$_{2A/2C}$ antagonist. Has moderate affinity for 5-ht$_6$ and 5-HT$_7$. Also muscarinic and dopamine antagonist
1095	(*R*)-(-)-Deprenyl	MAO-B inhibitor
0474	Dihydroergocristine	5-HT antagonist. Also partial agonist at adrenergic and dopaminergic receptors
0475	Dihydroergotamine	5-HT antagonist. Also partial agonist at adrenergic and dopaminergic D$_2$ receptors
0582	Methiothepin	Has moderate affinity for 5-ht$_5$ and high affinity for 5-ht$_6$ and 5-HT$_7$. Also antagonist at 5-HT$_1$ and 5-HT$_2$
0549	Methylergometrine	Active metabolite of methysergide
1064	Methysergide	5-HT$_1$/5-HT$_2$ antagonist
0878	Oleamide	Potentiator at 5-HT$_{2A/2C}$ receptors
0610	Parthenolide	5-HT release inhibitor
0724	Pirlindole	MAO-A inhibitor
0376	Ro 16-6491	MAO-B inhibitor
1559	Roxindole	5-HT uptake inhibitor with affinity for 5-HT$_{1A}$ receptors. Also D$_2$ dopamine agonist
0723	Tetrindole	MAO-A inhibitor
0968	TFMPP	Active at 5-HT$_{1B/1A/2C}$ receptors

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