Chapter 11

Serotonin Receptors and Drugs Affecting Serotonergic Neurotransmission

Richard A. Glennon and Małgorzata Dukat

Drugs Covered in This Chapter*

Antiemetic drugs (5-HT_3 receptor antagonists)

- Alosetron
- Dolasetron
- Granisetron
- Ondansetron
- Palonosetron
- *Tropisetron*

Drugs for the treatment of migraine ($5\text{-HT}_{1D/1F}$ receptor agonists)

- Almotriptan
- Eletriptan
- Frovatriptan
- Naratriptan
- Rizatriptan
- Sumatriptan
- Zolmitriptan

Drug for the treatment of irritable bowel syndrome (5-HT_4 agonists)

- Tegaserod

Drugs for the treatment of neuropsychiatric disorders

- Buspirone
- Citalopram
- Clozapine
- Desipramine
- Fluoxetine
- Imipramine
- Olanzapine
- Propranolol
- Quetiapine
- Risperidone
- Tranylcypromine
- Trazodone
- Ziprasidone
- *Zotepine*

Hallucinogenic agents

- Lysergic acid diethylamide
- 2,5-dimethyl-4-bromoamphetamine
- 2,5-dimethoxy-4-iodoamphetamine

Abbreviations

cAMP, cyclic adenosine monophosphate
CNS, central nervous system
5-CT, 5-carboxamidotryptamine
DOB, 2,5-dimethyl-4-bromoamphetamine
DOI, 2,5-dimethoxy-4-iodoamphetamine
EMDT, 2-ethyl-5-methoxy-*N*,*N*-dimethyltryptamine
GABA, γ-aminobutyric acid
5-HT, serotonin
5-HTP, 5-hydroxytryptophan
IBS, irritable bowel syndrome
IBS-C, irritable bowel syndrome with constipation
IBS-D, irritable bowel syndrome with diarrhea
LCAP, long-chain arylpiperazine
L-DOPA, L-dihydroxyphenylalanine
LSD, lysergic acid diethylamide
MAO, monomaine oxidase
MAOI, monoamine oxidase inhibitor
***m*CPBG,** *m*-chlorophenylbiguanide
***m*CPG,** *m*-chlorophenylguanidine
***m*CPP,** *m*-chlorophenylpiperazine
nM, nanomoles/L
MT, melatonin
MTR, melatonin receptor
NET, norepinephrine reuptake transporter
8-OH DPAT, 8-hydroxy-2-(di-n-propylamino)tetralin
PMDT, 2-phenyl-5-methoxy-*N*,*N*-dimethyltryptamine
SAFIR, structure–affinity relationship
SAR, structure–activity relationship
SERT, serotonin transporter
SSRI, selective serotonin reuptake inhibitor

*Drugs available outside the U.S. are shown in italics.

SCENARIO

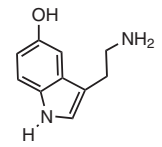
Jill T. Johnson, PharmD, BCPS

MB is a 34-year-old woman with migraines. She experiences photophobia and severe headaches with nausea and vision changes about twice per month. Recently she was prescribed sumatriptan to take as abortive therapy once she begins to feel the migraine aura. After using sumatriptan for several months, taking it routinely up to 300 mg per day for 15 days of the month, she realized it was not working as well as it had been.

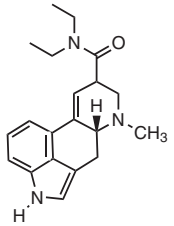
SEROTONIN

Serotonin could be considered the "baby boomer" of neurotransmitters: It was first identified in the late 1940s, its adolescent years were troubled, it made the drug scene in the 1960s, and it nearly died of an overdose in the early 1970s. It could be considered the original "sex, drugs, and rock-and-roll" receptor (as will be described below [see also Chapter 19], serotonin receptors have been implicated in sexual behavior, drug abuse [especially that involving classical hallucinogens], and the perception of sound)—but, it does much more.

At one time, it was remarked that "serotonin doesn't do anything" (1). On reaching its middle years, serotonin matured and became an important topic of study, a household name, and more complicated than ever. Serotonin has been associated with, among other things, anxiety, depression, schizophrenia, drug abuse, sleep, dreaming, hallucinogenic activity, headache, cardiovascular disorders, sexual behavior, and appetite control. Television ads now routinely refer to serotonin and serotonin receptor antagonists. This, subsequently, prompted the comment that "it almost appears that serotonin is involved in everything" (1). A review of the current patent literature provides an indication of some of the claims being made for serotonergic agents (Table 11.1). Tens of thousands of papers have been published on serotonin. Much is known—but an incredible amount remains to be learned.



Serotonin (5-HT)



(+)-Lysergic acid diethylamide (LSD)

A hormonal substance was independently identified in the late 1940s by two groups of investigators, one in the United States and the other in Italy. In the United States, the substance was called serotonin, whereas in Italy, it was termed enteramine. Its total synthesis in the early 1950s confirmed that both substances were the same structure: 5-hydroxytryptamine (5-HT). Serotonin (5-HT) was later detected in numerous plant and animal species, and in the mid-1950s, it was identified in the central nervous system (CNS) of animals. A neurotransmitter role was proposed. 5-HT was implicated in a variety of central and peripheral physiologic actions. It seemed to be involved in vasoconstriction and vasodilation, regulation of body temperature, sleep, and hormonal regulation, and early evidence suggested that it could be involved in depression. The structural similarity between 5-HT

TABLE 11.1 Some Indications and Treatment Claims for Novel Serotonergic Agents in the Patent Literature

Aggression disorders	Esophagitis	Obsessive-compulsive
Alcoholism	Gastric motility	Pain
Alzheimer's disease	Head injury	Panic disorders
Amnesia	Headache	Parkinson's disease
Anorexia	Hypertension	Psychosis
Bulimia	Impotence	Raynaud's disease
Cardiac failure syndrome	Irritable bowel	Schizophrenia
Cardiovascular disorders	Ischemia	Sedation
Cerebrovascular disorders	Migraine	Sexual dysfunction
Cognition disorders	Movement	Sleep disorders
Depression	Nausea	Substance abuse
Drug abuse	Neurodegenerative disease	Substance dependence
Emesis	Obesity	Thromboembolism

CLINICAL SIGNIFICANCE

Discovery of the different types of serotonin receptors during the past few years has created the potential to target these receptors. Altering the chemical structures may improve tolerability, reduce the risk of side effects, improve efficacy, enhance compliance, or simply provide an alternative drug should another in the class fail to provide relief for a given patient.

The clinical effects of serotonin receptors are multifaceted. At this time, only a few of the identified receptors have drugs that are currently marketed for use in humans. Buspirone stimulates the 5-HT1A receptor to cause antianxiety effects. The 5-HT1D agonists, or the "triptans," vary by side chains on essentially the same core structure to create compounds with different affinities for the 5-HT1D receptors and, likely, for other serotonin receptors as well. The varying affinities of each triptan for receptors change the profiles of their effectiveness and adverse or complimentary effects. As a rule, the triptans work to treat migraine headaches by causing vasoconstriction.

Unfortunately, they also may cause coronary vasoconstriction, making them contraindicated in patients with underlying coronary artery disease. Antagonists of the 5-HT3 receptor, ondansetron, and granisetron, work to lessen emesis in chemotherapy-induced and radiation-associated emesis as well as postoperative nausea and vomiting. A variety of drugs work to inhibit selective serotonin reuptake without acting on any specific serotonin receptor. Drugs such as fluoxetine, paroxetine, sertraline, and fluvoxamine have been effective in the treatment of depression, obsessive-compulsive disorder, and panic disorder with varying degrees of side effects like weight gain, weight loss, and drowsiness.

Jill T. Johnson, Pharm.D., BCPS
Associate Professor
Department of Pharmacy Practice
College of Pharmacy
University of Arkansas for Medical Science
Little Rock, AR

and the then recently discovered hallucinogenic agent (+)-lysergic acid diethylamide (LSD) intrigued investigators. The observation led to speculation that 5-HT could be involved in the mechanism of action of this psychoactive substances and could also have a role in certain mental disorders. LSD was shown to behave as a potent 5-HT receptor agonist in certain peripheral receptor assays and as a potent antagonist in others. The late 1960s and early 1970s, however, witnessed a decline in 5-HT research as the result of three factors: 1) sophisticated experimental techniques were still lacking for the investigation of the central actions of 5-HT; 2) apart from ergolines (LSD-related agents), only a few potent 5-HT agonists or antagonists had been developed; and 3) it was becoming increasingly difficult to understand how a single putative neurotransmitter substance could be involved in so many different central and peripheral actions. As a consequence, research interest in 5-HT entered the "doldrums." Subsequent development of histochemical fluorescence techniques and 5-HT radioligand binding methodology led to the mapping of serotonergic pathways, identifying binding sites in the brain, and measuring the affinity (i.e., K_i values) of serotonergic agents for 5-HT receptors. This rekindled interest in 5-HT receptors—big time. Much of the early work on serotonin receptors and their ligands has been reviewed (2–4); as a result, a substantial amount of the older literature is not cited here, and the interested readers are urged to consult these reviews for references to the primary literature.

Serotonin Biosynthesis, Catabolism, and Function as Targets for Drug Manipulation

5-HT is biosynthesized from its dietary precursor L-tryptophan (5) (Fig. 11.1). Serotonergic neurons contain tryptophan hydroxylase (L-tryptophan-5-monooxygenase) that converts tryptophan to 5-hydroxytryptophan (5-HTP), in what is the rate-limiting step in 5-HT biosynthesis, and aromatic L-amino acid decarboxylase (a nonselective decarboxylase previously called 5-HTP decarboxylase) that decarboxylates 5-HTP to 5-HT. This latter enzyme is also responsible for the conversion of L-dihydroxyphenylalanine (L-DOPA) to dopamine (see Chapter 13). The major route of metabolism of 5-HT is oxidative deamination by monoamine oxidase (MAO; specifically, by MAO-A) to the unstable 5-hydroxyindole-3-acetaldehyde, which is either reduced to 5-hydroxytryptophol (~15%) or to the oxidized product 5-hydroxyindole-3-acetic acid (~85%) under normal physiologic conditions. In the pineal gland, 5-HT is acetylated by 5-HT *N*-acetyltransferase to *N*-acetylserotonin, which undergoes *O*-methylation by 5-hydroxyindole-*O*-methyltransferase to melatonin.

RADIOLIGANDS

Radioligand binding techniques measure the affinity of agonists and antagonists for their respective receptors (i.e., K_i values). Radioligands are receptor agonists or antagonists to which a radioactive atom (label) is covalently attached.

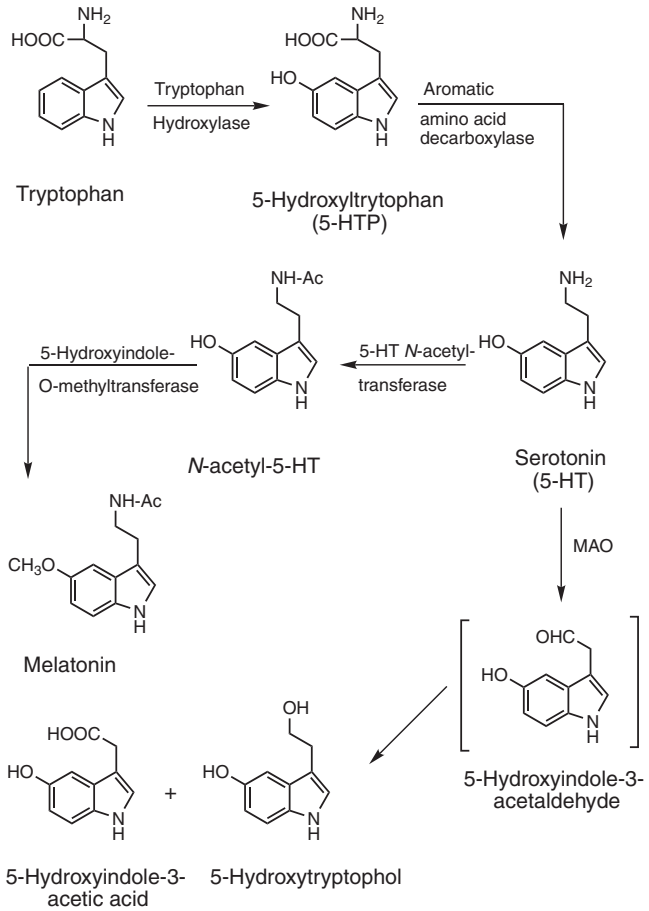


FIGURE 11.1 Biosynthesis and catabolism of serotonin. In the pineal, serotonin is converted to melatonin. Melatonin is an agonist at melatonin (MT), not 5-HT, receptors. Ac, acetyl.

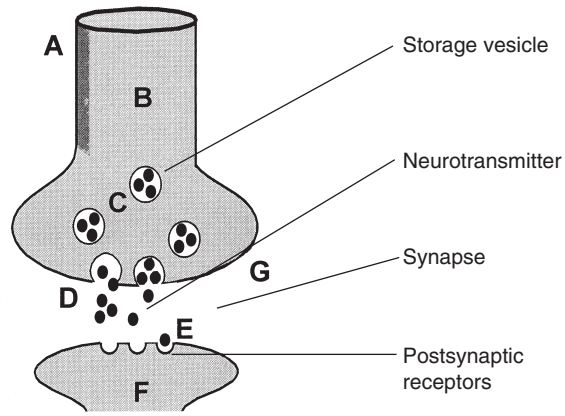
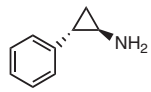


FIGURE 11.2 Steps involved in serotonergic neurotransmission. The serotonin precursor tryptophan is taken up into the neuron (A) and converted to 5-HT (B). Synthesized 5-HT is stored in synaptic vesicles (C). Under the appropriate conditions, the synaptic vesicles migrate to and fuse with the cell membrane, releasing their store of 5-HT (D). Released neurotransmitter interacts with postsynaptic receptors (E) and, in the case of G protein–coupled receptors, activates second messenger systems (F). The action of 5-HT is terminated (G) either by diffusion of 5-HT away from the synapse, with subsequent metabolism, or by the 5-HT being taken back up by 5-HT transporters into the presynaptic neuron (i.e., reuptake), where it can be re-stored in synaptic vesicles or is metabolized (by MAO).

Distinct types of melatonin receptors (MTRs; MTR_1/MTR_2) have been identified.

Each step in 5-HT biosynthesis, metabolism, and function is a hypothetical target for drug manipulation (Fig. 11.2). Tryptophan depletion, by reducing or restricting dietary tryptophan consumption, results in decreased 5-HT biosynthesis; conversely, tryptophan "loading," by increasing dietary tryptophan, results in the overproduction of 5-HT. The latter effect also can occur in nonserotonergic neurons, such as in dopaminergic neurons, because of the nonselective nature of aromatic amino acid decarboxylase. Inhibitors of tryptophan hydroxylase, such as *para*-chlorophenylalanine, are used as pharmacologic tools; they are not used therapeutically.

Therapeutically exploited serotonergic targets include presynaptic receptors, postsynaptic receptors, the reuptake mechanism (i.e., the serotonin transporter [SERT]), second messenger systems, and 5-HT metabolism. MAO inhibitors (MAOI) effectively interfere with the oxidative deamination of 5-HT to increase synaptic concentrations of 5-HT. The MAOI tranylcypromine, for example, has been employed since the 1960s as an antidepressant agent.



Tranylcypromine

A problem associated with many MAOIs is that they are notoriously nonselective and can interfere with the metabolism of other neurotransmitters, amines found in certain foods, and exogenously administered amine-containing therapeutic agents. Serotonin receptors and SERT are discussed below.

SEROTONIN RECEPTORS

Initially, 5-HT was thought to interact with what were termed 5-HT receptors. Today, seven distinct families or populations of serotonergic receptors have been identified, 5-HT_1 through 5-HT_7, and several are divided into subpopulations (Table 11.2). The discovery of the individual populations and subpopulations of 5-HT receptors follows the approximate order of their numbering and, as a consequence, more is known about 5-HT_1 and 5-HT_2 receptors than about 5-HT_6 and 5-HT_7 receptors. Factors contributing to our current lack of understanding about

TABLE 11.2 Classification and Nomenclature for the Various Populations of 5-HT Receptors

Populations and Subpopulations	Second Messenger System[a]	Currently Accepted Name[b]	Comments
5-HT_1			
5-HT_{1A}	AC(–)	5-HT_{1A}	Cloned and pharmacologic 5-HT_{1A} receptors
5-HT_{1B}	AC(–)	5-HT_{1B}	Rodent homolog of 5-HT_{1B} receptors
$5\text{-HT}_{1B\beta}$			A mouse homolog of $h5\text{-HT}_{1B}$ receptors
5-HT_{1D}			Sites identified in binding studies using human and calf brain homogenates
$5\text{-HT}_{1D\alpha}$	AC(–)	$h5\text{-HT}_{1D}$	A cloned human 5-HT_{1D} subpopulation
$5\text{-HT}_{1D\beta}$	AC(–)	$h5\text{-HT}_{1B}$	A second cloned human 5-HT_{1D} subpopulation; human counterpart of rat 5-HT_{1B}
5-HT_{1E}	AC(–)	5-HT_{1E}	Sites identified in binding studies using brain homogenates and cloned receptors
$5\text{-HT}_{1E\alpha}$			An alternate name that has been used for cloned human 5-HT_{1E} receptors
$5\text{-HT}_{1E\beta}$	AC(–)	5-ht_{1F}	A cloned mouse homolog of 5-HT_{1F} receptors
5-HT_{1F}			A cloned human 5-HT_1 receptor population
5-HT_2			
5-HT_2	PI	5-HT_{2A}	Original "5-HT_2" (sometimes called $5\text{-HT}_{2\alpha}$) receptors
5-HT_{2F}	PI	5-HT_{2B}	5-HT_2-like receptors originally found in rat fundus
5-HT_{1C}	PI	5-HT_{2C}	Originally described as 5-HT_{1C} ($5\text{-HT}_{2\beta}$) receptors
5-HT_3			
5-HT_3	Ion channel	5-HT_3	An ion channel receptor
5-HT_4	AC(+)	5-HT_4	5-HT_4 population originally described in functional studies
5-HT_{4S}			Short form of cloned 5-HT_4 receptors
5-HT_{4L}			Long form of cloned 5-HT_4 receptors
$5\text{-HT}_{4(b)\text{–}4(d)}$			Recently identified human 5-HT_4 receptor isoforms
5-HT_5			
5-HT_{5A}	?	5-HT_{5A}	Cloned mouse, rat, and human 5-HT_5 receptors
5-HT_{5B}	?	5-HT_{5A}	Cloned mouse and rat 5-HT_{5A}–like receptor
5-HT_6			
5-HT_6	AC(+)	5-HT_6	Cloned rat and human 5-HT receptor
5-HT_7			
5-HT_7	AC(+)	5-HT_7	Cloned rat, mouse, guinea pig, and human 5-HT receptors

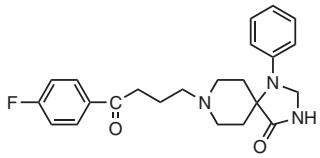
[a] AC = adenylate cyclase; (–) = negatively coupled; (+) = positively coupled; PI = phospholipase coupled.

[b] Currently accepted names are taken from Hoyer et al. (9).

the function of certain 5-HT receptor populations (e.g., 5-HT_{1E} or 5-HT_5 receptors) is the absence of agonists and/or antagonists with selectivity for these receptors.

History

Tritiated LSD ([^{3}H]LSD), the first radioligand used to identify a brain 5-HT binding site, suggested it could be a "hallucinogen receptor." Tritiated 5-HT ([^{3}H]5-HT)–labeled serotonergic sites displayed high affinity for LSD. Thus, not only did 5-HT and LSD share structural similarity, there was now evidence that these agents could be acting via a common receptor type. According to the *interconvertible receptor conformation hypothesis* that was popular at the time, 5-HT (known to be an agonist) interacted with the agonist conformation of the receptor, whereas [^{3}H]LSD (LSD being known to be a partial agonist) labeled both the agonist and antagonist conformations. A search was initiated for 5-HT receptor antagonists that could serve to label the antagonist conformation of 5-HT receptors. After the serendipitous discovery that a tritiated version of the dopamine antagonist spiperone not only labeled dopaminergic receptors but also labeled nondopaminergic receptors in other brain regions, it was shown that 5-HT displayed modest affinity for some of these sites, indicating they could represent 5-HT receptors.



Spiperone

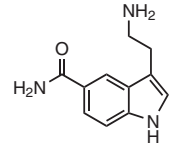
Spiperone was also shown to antagonize some of the pharmacologic effects of 5-HT in functional assays. These data, coupled with the additional observation that 5-HT receptor agonists tended to display higher affinity for [^{3}H]5-HT–labeled sites, whereas 5-HT antagonists displayed higher affinity for [^{3}H]spiperone-labeled sites, led to the conclusion that [^{3}H]5-HT and [^{3}H]spiperone label two distinct populations (not conformations) of sites, termed 5-HT_1 and 5-HT_2 receptors, respectively (6). Soon thereafter, 5-HT_1 receptors were found to consist of 5-HT_{1A} and 5-HT_{1B} subpopulations. Earlier, during the 1950s, Gaddum and Picarelli had demonstrated the existence of two populations of serotonergic receptors in isolated guinea pig ileum and termed these receptors 5-HT-D (because phenoxybenzamine or dibenzyline blocked the actions of 5-HT at this receptor) and 5-HT-M (because morphine and cocaine blocked the actions of 5-HT at the second population). Later, 5-HT-D receptors were found to be similar to 5-HT_2 receptors, and 5-HT-M receptors were eventually renamed 5-HT_3 receptors. By the early 1980s, 5-HT_{1A}, 5-HT_{1B}, 5-HT_2, and 5-HT_3 receptors had been identified, and interest in 5-HT research exploded. Molecular biology intervened in the late 1980s and early 1990s; new populations of serotonergic receptors were cloned and expressed. Perhaps the multitude of actions of 5-HT, previously thought impossible to understand, are mediated by multiple subtypes of 5-HT receptors. This led to attempts to develop selective agonists and antagonists for each subpopulation (2,7).

Table 11.2 lists the receptor classification and nomenclatures that have been employed for serotonergic receptors. Care should be used when reading the older primary literature because 5-HT receptor nomenclature has changed so dramatically and, often, can be confusing and very frustrating to comprehend.

All of the seven serotonergic receptor populations (and subpopulations) have been cloned and, together with the cloning of other neurotransmitter receptors, has led to generalizations regarding amino acid sequence homology (8). Any two receptors with amino acid sequences that are approximately 70% to 80% identical in their transmembrane-spanning segments are called the *intermediate-homology group*. This group of receptors could be members of the same subfamily and have highly similar to nearly indistinguishable pharmacologic profiles or second messenger systems. A *low-homology group* (~35% to 55% transmembrane homology) consists of distantly related receptor subtypes from the same neurotransmitter family, and a *high-homology group* (~95% to 99% transmembrane homology) consists of species homologs from the same gene in different species (8). Species homologs of the same gene reveal high sequence conservation in regions outside the transmembrane domains, whereas intraspecies receptor subtypes usually are quite different (8). Current 5-HT receptor classification and nomenclature require that several criteria be met before a receptor population can be adequately characterized. Receptor populations must be identified on the basis of drug binding characteristics (*operational* or *recognitory criteria*), receptor–effector coupling (*transductional criteria*), and gene and receptor structure sequences for the nucleotide and amino acid components, respectively (*structural criteria*) (7–9).

5-HT_1 Receptor Family

5-HT_1 receptors were one of the first two populations of 5-HT receptors to be identified (6), and 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, and 5-HT_{1F} receptor subpopulations have since been defined. 5-HT_{1C} receptors were initially described, but subsequent classification (employing the previously mentioned criteria) resulted in their being moved to the 5-HT_2 receptor family and being renamed 5-HT_{2C} receptors. With the exception of 5-HT_{1E} receptors, all 5-HT_1 receptors exhibit high affinity for 5-carboxamidotryptamine (5-CT).



5-CT

5-HT_{1A} Receptors and Agents

5-HT_{1A} receptors are, as are all 5-HT receptors except for 5-HT_3 receptors, G protein–coupled receptors that consist of seven transmembrane-spanning helices connected

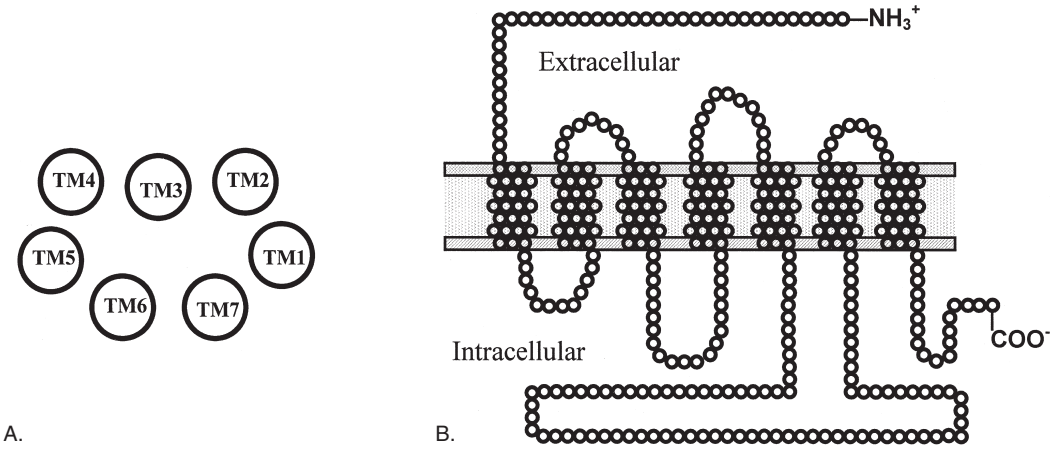
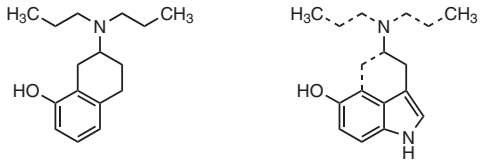


FIGURE 11.3 Top (A) and side (B) views of a schematic representation of a typical G protein–coupled receptor (GPCR). In B, the transmembrane-spanning helical portions are numbered, from left to right, as TM1 to TM7. The seven helices are connected by extracellular and intracellular loops. The large intracellular loop between TM5 and TM6 is believed to be associated with coupling to a second messenger system. The helices are arranged in such a manner that TM1 is adjacent to TM7, as shown in A. Molecular graphics studies suggest that agonists could bind in a manner that utilizes an aspartate residue in TM3 (common to all G protein–coupled 5-HT receptors) and residues in the TM4, TM5, and TM6 regions, whereas antagonists likely utilize the aspartate moiety but residues in the TM6, TM7, and TM1 regions.

by intracellular and extracellular loops (see Fig. 11.3 for a schematic representation of a generalized G protein receptor structure). The receptors are negatively coupled to an adenylate cyclase[*1] second messenger system, and the 5-HT_{1A} receptors located in the raphe nuclei correspond to somatodendritic autoreceptors (Fig. 11.4). 5-HT_{1A} receptors differ significantly in structure from most other 5-HT receptors and exhibit a substantial similarity to adrenergic receptors, which likely explains why a number of adrenoceptor agents bind at 5-HT_{1A} receptors with high affinity (see below). Cloned 5-HT_{1A} receptors and 5-HT_{1A} receptor ligands have been reviewed (9,10–18).

Structure–Activity Relationship of 5-HT_{1A} Receptor Agonists



8-OH DPAT 8-OH DPAT superimposed on Serotonin

Numerous 5-HT–related tryptamines bind with high affinity at 5-HT_{1A} receptors, but most are notoriously nonselective. One of the most selective 5-HT_{1A} receptor agonists is the aminotetralin derivative 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH DPAT), and its early discovery was significant in advancing understanding of 5-HT_{1A} receptors. Furthermore, because the structure of 8-OH DPAT is similar to that of 5-HT (see 8-OH DPAT/5-HT superimposition), its activity indicated that an intact indole nucleus was not required for 5-HT_{1A} receptor action. Although numerous 8-OH DPAT

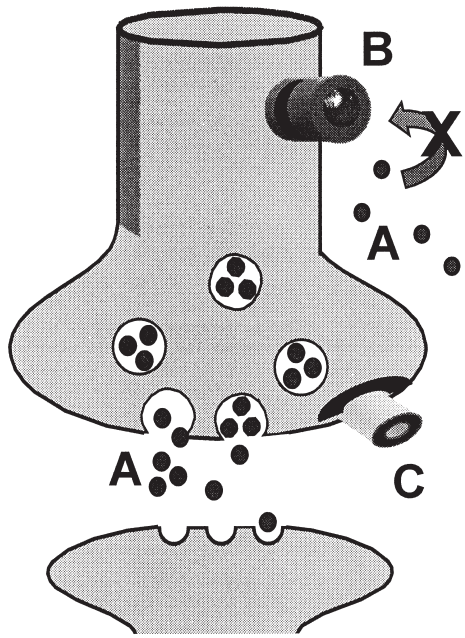


FIGURE 11.4 Typical nerve ending showing the cell body (i.e., somatodendritic) autoreceptors (B) and the terminal autoreceptors (C). Neurotransmitter molecules are also shown (A). 5-HT can interact with cell body autoreceptors (B) to regulate synthesis, and with terminal autoreceptors (C) to regulate release. Shown above is a drug molecule blocking the cell body autoreceptor and preventing an interaction with the neurotransmitter.

[*]This enzyme is known by two names, *adenylate cyclase (EC 4.6.1.1)*, its official name from the International Union of Biochemistry and Molecular Biology Nomenclature Committee, or its alternative name, adenylyl cyclase.

derivatives have been reported, none is used therapeutically because of low oral bioavailability. This has led to efforts to develop novel aminotetralins with greater oral bioavailability.

Long-Chain Arylpiperazines Simple arylpiperazines (i.e., those bearing no N_4-substituent or only a small N_4-substituent), such as 1-(phenyl)piperazine (Fig. 11.5), bind with modest to reasonably high affinity at multiple receptor types and are considered nonselective agents. Long-chain arylpiperazines (LCAPs) are piperazines possessing a long-chain N_4 substituent and represent the largest class of 5-HT_{1A} receptor ligands. Buspirone (Fig. 11.5), the first arylpiperazine approved for clinical use as an anxiolytic agent, and the structurally related gepirone and ipsapirone bind at 5-HT_{1A} receptors and behave as agonists or partial agonists. Structure–activity relationships (SARs) and structure–affinity relationships (SAFIRs) have been formulated, and this has led to LCAPs with enhanced 5-HT_{1A} receptor affinity and selectivity (12–15). With the LCAPs, there is substantial structural latitude for 5-HT_{1A} receptor binding (14,15).

The aryl portion of these agents (Fig. 11.6) typically is a phenyl, substituted phenyl, or heteroaryl group (such as 2-pyrimidinyl). The intact piperazine ring seems to be optimal for binding to 5-HT_{1A} receptors. A spacer or linker separates the N_4-nitrogen atom of the piperazine and the terminus or terminal structural moiety. There has been controversy as to whether the spacer participates in binding to the receptor or whether it acts simply as a "connector"; in any event, a chain of two to five atoms is common. The terminus typically is an amide or imide, but it has been shown that neither is required for binding. Alternatively, the terminus can be a

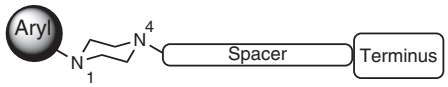


FIGURE 11.6 General structure of long-chain arylpiperazines (LCAPs).

phenyl or some other aryl or heteroaryl substituent (14). With respect to spacer length, when the spacer is -$(CH_2)_n$–, 2 to 4 methylene groups appear optimal. Chain length (n) can influence affinity and selectivity. When the terminus contains a heteroarylamide, n = 4 seems to be optimal, whereas when the terminus is an alkylamide, optimal affinity is associated with n = 2. A region of bulk tolerance is associated with the terminus, or at least a portion thereof, and very bulky groups have been introduced into this part of the molecule (12–15). Some LCAPs are nonselective and variously bind at other populations of 5-HT receptors, dopamine receptors, or adrenoceptors.

Structure–activity Relationships of 5-HT_{1A} Receptor Antagonists

Many 5-HT_{1A} receptor antagonists possess a 2-methoxyphenyl group with structural similarity to buspirone. BMY 7378 and NAN-190 were among the first agents shown to be very low-efficacy partial agonists at 5-HT_{1A} receptors and were used as antagonists for many years (Fig. 11.7). Certain aminotetralins [e.g., S(–)UH-301] and arylpiperazines (e.g., WAY 100135 and WAY 100635) represent

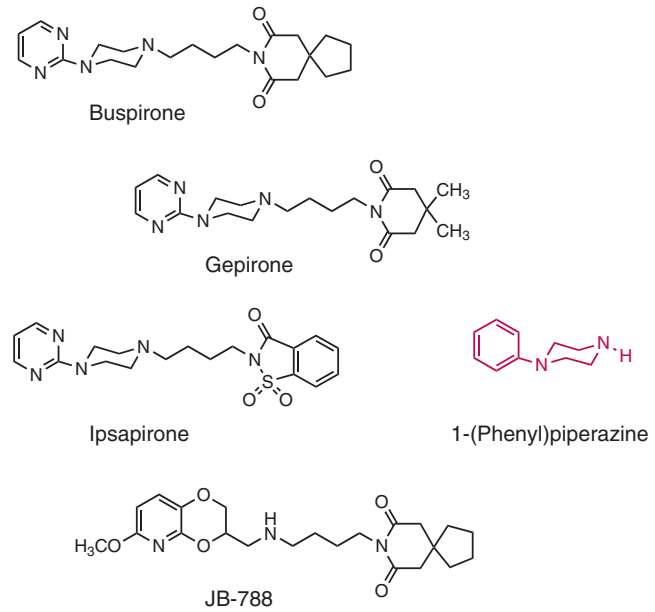


FIGURE 11.5 5-HT_{1A} receptor agonists (arylpiperazines).

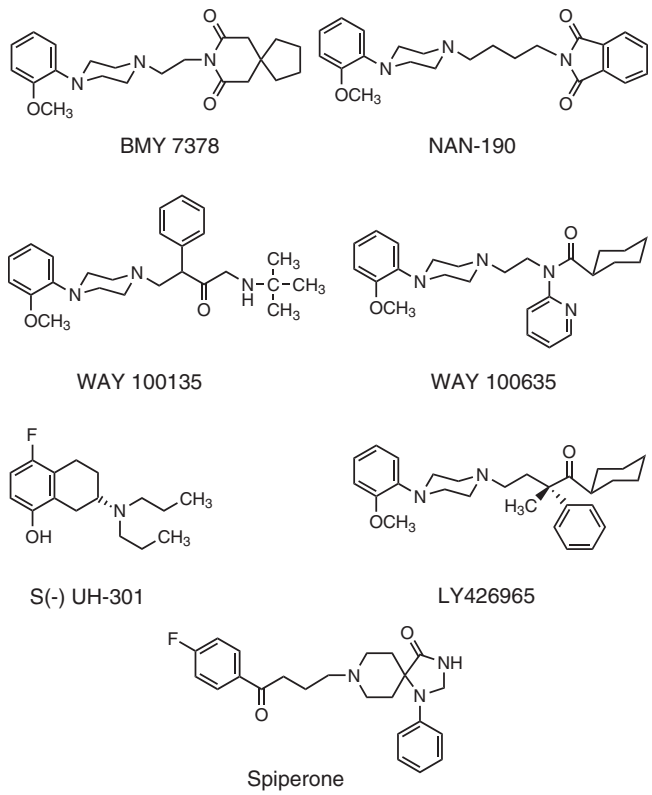


FIGURE 11.7 5-HT_{1A} receptor antagonists.

new classes of 5-HT$_{1A}$ receptor antagonists, termed "silent antagonists," because they are "seemingly" without any 5-HT$_{1A}$ agonist action. The alkylpiperidine spiperone is a 5-HT$_{1A}$ antagonist, but spiperone displays high affinity for D_2-dopamine receptors and 5-HT$_{2A}$ receptors.

Molecular graphics studies suggest that 5-HT and 5-HT$_{1A}$ receptor agonists interact with amino acid residues associated with helices 4, 5, and 6 (Site 1), whereas 5-HT$_{1A}$ receptor antagonists likely interact with amino acid residues in helices 1, 2, 7, and, perhaps, 6 (Site 2) (16). The basic amine for both types of agents is thought to bind at a common aspartate residue found in TM helix 3 (Fig. 11.3). The 5-hydroxy group of 5-HT is thought to form a hydrogen bond with the threonine residue in TM5 (16).

5-HT$_{1A}$ Receptor Agonists: Clinical Significance

In preclinical studies, 5-HT$_{1A}$ receptor agonists have demonstrated antianxiety, antidepressant, antiaggressive, and perhaps, anticraving, anticataleptic, antiemetic, and neuroprotective properties (15,17). Evidence also exists indicating that 5-HT$_{1A}$ receptors could be involved in sleep, impulsivity, alcoholism, sexual behavior, appetite control, thermoregulation, and cardiovascular function (17,19,20). The main focus of drug development for 5-HT$_{1A}$ receptors is their therapeutic potential for the treatment of anxiety and depression (15,19). Buspirone (Buspar) was the first LCAP to become clinically available as an anxiolytic agent. A number of structurally related agents hold promise as novel anxiolytics (11,12,21); one of the newest is JB-788 (22). 5-HT$_{1A}$ receptor agents could also be useful in the treatment of depression (15), and there seems to be a relationship between 5-HT metabolism, depression, and violent behavior. The antianxiety actions of 5-HT$_{1A}$ receptor (partial) agonists could involve, primarily, presynaptic somatodendritic 5-HT$_{1A}$ receptors, whereas the antidepressant actions of 5-HT$_{1A}$ receptor agents could primarily involve postsynaptic 5-HT$_{1A}$ receptors (17). Gepirone produced marked improvement in depressed patients, and buspirone was effective in the treatment of mixed anxious-depressive patients. 5-HT$_1$ and, possibly, 5-HT$_{1A}$ receptors have been implicated in obsessive-compulsive disorders.

5-HT$_{1A}$ Receptor Antagonists: Clinical Significance

A new direction in 5-HT$_{1A}$ receptor research targets the development of 5-HT$_{1A}$ receptor antagonists (15,23). Agents such as the acknowledged dopaminergic antagonist spiperone and the β-adrenoceptor antagonist propranolol were among the first to see application as 5-HT$_{1A}$ receptor antagonists. These agents are, obviously, nonselective; they bind at other populations of neurotransmitter receptors with comparable or higher affinities than they display at 5-HT$_{1A}$ receptors. The next generation of 5-HT$_{1A}$ receptor antagonists, the LCAPs BMY 7378 and NAN-190, possessed postsynaptic antagonist character but also behaved as low-efficacy partial agonists (14,23) (Fig. 11.7). A third generation of agents—"silent" 5-HT$_{1A}$ receptor antagonists—has been developed and includes WAY 100635, WAY 100135 (a structural relative of BMY 7378 and NAN-190), and S(–)UH-301 (a derivative of the 5-HT$_{1A}$ agonist 8-OH DPAT); these are both presynaptic and postsynaptic 5-HT$_{1A}$ receptor antagonists (23,24). Silent 5-HT$_{1A}$ receptor antagonists, such as WAY 100135 and S(–) UH-301, are not intrinsically inactive and can indirectly produce non–5-HT$_{1A}$ serotonin-mediated actions (25,26). These antagonists presumably block presynaptic 5-HT$_{1A}$ autoreceptors, increasing the synaptic concentration of 5-HT, which results in the activation of other 5-HT receptor populations. Human evaluation of "so-called" silent and selective 5-HT$_{1A}$ receptor antagonists should prove interesting and could open new vistas in 5-HT$_{1A}$ research and therapeutics. For example, pretreatment of patients with 5-HT$_{1A}$ receptor antagonists accelerates the effects of selective serotonin reuptake inhibitors (SSRIs) and enhance their clinical efficacy as antidepressants (27). The 5-HT$_{1A}$ receptor antagonist WAY 100635 enhances the anorectic effect of citalopram in animals (28) and, thus, may be of benefit in weight reduction. Combination therapy using an SSRI plus a 5-HT$_{1A}$ receptor antagonist, including the β-blocker pindolol, which binds at 5-HT$_{1A}$ receptors, has been reported (29). A new LCAP, LY426965, is more metabolically stable than WAY 100635 and is orally bioavailable. In combination with fluoxetine, LY426965 increase extracellular levels of 5-HT beyond that achievable by fluoxetine alone, and it is being examined for the treatment of depression and as a smoking cessation agent (30). The therapeutic potential of 5-HT$_{1A}$ receptor antagonists is quite intriguing.

5-HT$_{1B}$ Receptors and Agents

Early studies identified 5-HT$_{1B}$ receptors in rodent brain homogenates using radioligand binding techniques but failed to find them in human brain. 5-HT$_{1B}$ receptors are located both presynaptically, where they regulate the release of 5-HT (Fig. 11.4), and postsynaptically (31). Like 5-HT$_{1A}$ receptors, they are negatively coupled to adenylate cyclase. (See 5-HT$_{1D}$ Receptors for further related discussion.)

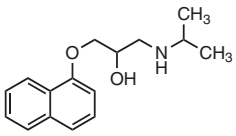
5-HT$_{1B}$ Receptors: Clinical Significance

Rodent 5-HT$_{1B}$ receptors have been implicated as having a role in thermoregulation, respiration, appetite control, sexual behavior, aggression, locomotor activity, sleep regulation, sensorimotor inhibition, and anxiety (32).

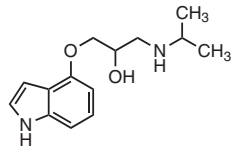
5-HT$_{1D}$ Receptors

5-HT$_{1D}$ receptors were first identified by radioligand binding techniques, and they are widely distributed throughout the CNS (33). They are G protein–linked and are coupled to inhibition of adenylate cyclase. Two

human subpopulations of 5-HT$_{1D}$ receptors, 5-HT$_{1D\alpha}$ and 5-HT$_{1D\beta}$ receptors, display approximately 77% sequence homology, and their pharmacologic properties are nearly indistinguishable. Because of the high degree of species homology with rat and mouse 5-HT$_{1B}$ receptors, human 5-HT$_{1D\beta}$ receptors have been renamed h5-HT$_{1B}$ receptors. Human 5-HT$_{1D\alpha}$ receptors have been renamed h5-HT$_{1D}$. Most agents that bind at 5-HT$_{1B}$ receptors bind at 5-HT$_{1D}$ receptors.



Propranolol

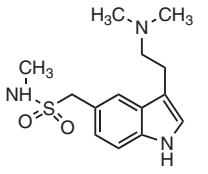


Pindolol

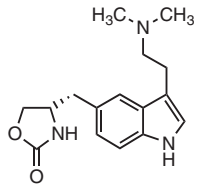
Curious exceptions have been noted with certain aryloxyalkylamines, however, such as the β-blockers, propranolol and pindolol, which exhibit very low affinity (K_i ~ 5,000 nM) for human (h) 5-HT$_{1D}$ receptors (34,35). The major functional difference between rat 5-HT$_{1B}$ receptors and h5-HT$_{1B}$ receptors has been attributed to both the presence of a threonine residue at position 355 (i.e., Thr^{355}) in TM7 of the latter and the presence of an asparagine residue at the corresponding position in 5-HT$_{1B}$ receptors; site-directed mutagenesis studies have demonstrated that conversion of Thr^{355} to an asparagine (i.e., a T355N mutant) accounts for the binding differences of certain ligands (e.g., aryloxyalkylamines such as propranolol). Combined ligand SAR, site-directed mutagenesis, and molecular modeling studies have led to the conclusion that although most typical serotonergic agonists bind in the central cavity formed by TM3, TM4, TM5, and TM6 (Site 1) (Fig. 11.3), propranolol most likely occupies the region defined by TM1, TM2, TM3, and TM7 (Site 2). The higher affinity of propranolol for T355N mutant 5-HT$_{1B}$ receptors relative to the wild-type receptors was specifically attributed to the formation of two hydrogen bonds between the receptor asparagine and the ether and hydroxyl oxygen atoms of propranolol (35).

5-HT$_{1D}$ Agonists and Antagonists

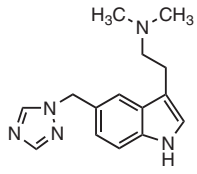
There are few 5-HT$_{1D}$–selective agonists, but one agent commonly referred to as a prototypical 5-HT$_{1D}$ receptor agonist is sumatriptan (Imitrex). Sumatriptan, however, exhibits only 2- to 20-fold greater selectivity for the 5-HT$_{1D}$ receptors than for certain other populations of 5-HT$_1$ (especially 5-HT$_{1A}$) receptors, binds at h5-HT$_{1D}$ and h5-HT$_{1B}$ receptors with nearly identical affinity and also binds at 5-HT$_{1F}$ receptors (36). SARs for 5-HT$_{1D}$ receptor agonists have been reported for many indolealkylamines or tryptamine derivatives, which bind with high affinity but with little selectivity. Newer agents displaying high affinity and reasonable selectivity for h5-HT$_{1D}$/h5-HT$_{1B}$ receptors over other populations of 5-HT receptors (37) include, for example, zolmitriptan (Zomig), naratriptan (Amerge), rizatriptan (Maxalt), and alniditan. Of these, all are tryptamine derivatives or sumatriptan-related structures except for the benzopyran alniditan. Many of these are commercially available or currently undergoing clinical trials. Other investigational agonists are shown in Figure 11.8.



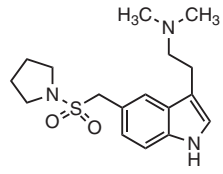
Sumatriptan



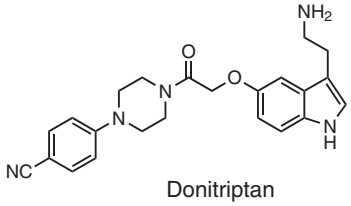
Zolmitriptan



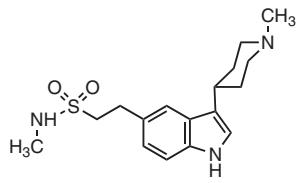
Rizatriptan



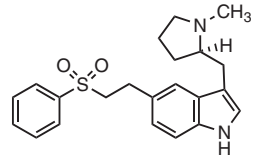
Almotriptan



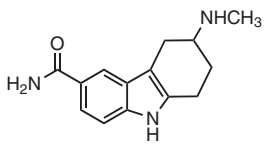
Donitriptan



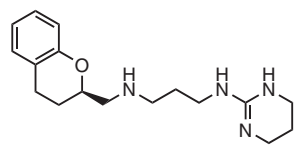
Naratriptan



Eletriptan

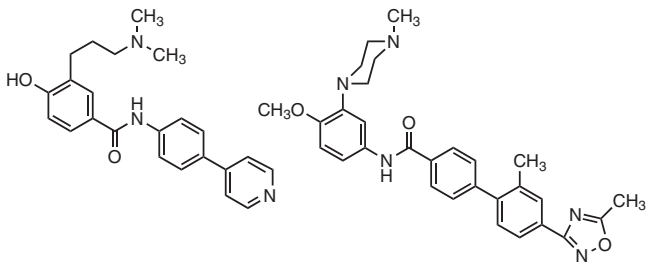


Frovatriptan



Alniditan

FIGURE 11.8 5-HT$_{1D}$ receptor agonists.



Several 5-HT$_{1D}$ receptor antagonists have been developed, including GR127935 (high affinity for h5-HT$_{1D}$/h5-HT$_{1B}$ receptors but possibly a low-efficacy partial agonist) and GR55562. Both of these agents antagonize many of the effects of sumatriptan.

5-HT$_{1D}$ Receptors: Clinical Significance

The clinical significance of 5-HT$_{1D}$ receptors remains largely unknown. These receptors are speculated to be involved in anxiety, depression, and other neuropsychiatric disorders, but this remains to be substantiated. However, recent studies show that 5-HT$_{1D}$ receptors are the dominant species in human cerebral blood vessels. Sumatriptan and several closely related agents are clinically effective in the treatment of migraine, and logical extrapolation implies a role for 5-HT$_{1D}$ receptors in this disorder. Agents with 5-HT$_{1D}$ receptor agonist activity that have found application in the treatment of migraine are, as a group, termed *triptans*, because the first agent introduced was suma*triptan*. As efficacious as the triptans may be however, it is unknown if their activity involves action only in the periphery or in the CNS as well (38). Sumatriptan is an h5-HT$_{1B}$ and h5-HT$_{1D}$ receptor agonist. It is also an agonist at 5-HT$_{1F}$ receptors. Most triptans share a similar binding profile. The vasoconstrictor properties of sumatriptan probably are mediated by its action on arterial smooth muscle. The triptans are also believed to inhibit the activation of peripheral nociceptors (38), and this could be related to the localization of 5-HT$_{1D}$ receptors on peptide nociceptors.

Relatively little sumatriptan normally penetrates the blood–brain barrier. Although it has been speculated that transient changes in blood–brain barrier permeability could occur during migraine attacks (38), agents with greater lipophilicity (and, hence, enhanced ability to penetrate the blood–brain barrier) have been introduced, including zolmitriptan and rizatriptan (Table 11.3). Their greater lipophilicity, however, does not seem to correlate with significantly improved clinical efficacy over sumatriptan (38). Other triptans (Fig. 11.8) currently being examined include eletriptan, almotriptan, donatriptan, and frovatriptan (37).

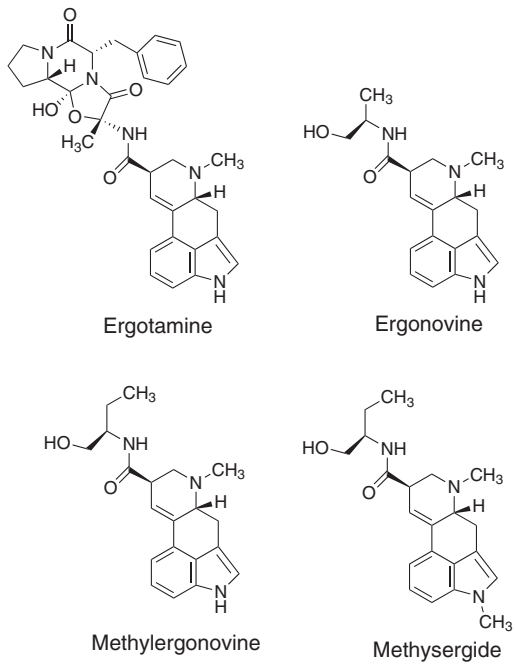
In general, the newer triptans (e.g., zolmitriptan, rizatriptan, and naratriptan) have a higher oral bioavailability and a longer plasma half-life than sumatriptan (39,40) (Table 11.3). Most triptans also bind at 5-HT$_{1F}$ receptors, and 5-HT$_{1F}$ receptor agonists have demonstrated efficacy in the treatment of migraine (41). The 5-HT receptor binding characteristics of various triptans have been compared (37).

The safety of the triptans has been established; more than 8 million patients have been treated for more than 340 million attacks with sumatriptan alone. All triptans narrow coronary arteries by 10% to 20% at clinical doses and should not be administered to patients with coronary or cerebrovascular disease. Triptans with potential for significant drug–drug interactions include sumatriptan, naratriptan, rizatriptan, almotriptan, and MAOIs; rizatriptan and propranolol; zolmitriptan and cimetidine; zolmitriptan, naratriptan, and eletriptan; CYP3A4-metabolized drugs; and P-glycoprotein pump inhibitors.

The rational employment of triptans should be governed by the use of these medications for patients with disability associated with migraine. Patients with greater than 10 days of at least 50% disability during 3 months have benefited from treatment with triptans as their first-line treatment for acute attacks. When the decision has been made to treat with a triptan, the patient should be instructed to treat early in the attack, when the pain is at a mild phase. This approach increases the likelihood of achieving a pain-free response, with fewer adverse events and with lower likelihood of the headache recurring.

5-HT$_{1E}$ Receptors and Agents

In early binding experiments using [^{3}H]5-HT as radioligand, masking of brain 5-HT$_{1A}$ and 5-HT$_{1B}$ receptors resulted in biphasic competition curves providing evidence for additional 5-HT$_1$-like receptor populations. One of these was the 5-HT$_{1D}$ receptors; the other was termed 5-HT$_{1E}$ receptors.



The low affinity of 5-CT and ergotamine for 5-HT$_{1E}$ receptors allowed their differentiation from 5-HT$_{1D}$

TABLE 11.3 Pharmacokinetics of the 5-HT$_1$ Agonists (the Triptans)

Parameters	Sumatriptan	Zolmitriptan	Naratriptan	Rizatriptan	Almotriptan	Frovatriptan	Eletriptan
Trade name	Imitrex	Zomig	Amerge	Maxalt	Axert	Frova	Relpax
LogP (calc)[a]	0.7 ± 0.6	1.6 ± 0.4	1.4 ± 0.6	0.9 ± 0.6	1.9 ± 0.6	0.9 ± 0.4	3.1 ± 0.6
LogD (pH 7) (calc)[a]	−1.7	−0.8	−1.2	−1.4	−0.5	−2.1	0.18
Bioavailability (%)							
Oral (PO)	14–15[b]	40–50[b]	70[c]	40–50[b]	70–80	20–30[b]	50[cd]
Nasal	17	102	—	—	—	—	—
Subcutaneous (SC)	97		—	—	—	—	—
Protein binding (%)	14–20	25	28–30	14	35	15	85
Volume of distribution (L/kg)	PO: 50	PO: 7	PO: 170	PO: 110–140	PO: 180–200	PO: 3–4	PO: 138
		Nasal: 9					
Elimination half-life (h)	PO: 2.5	PO: 2–3	PO: 5–6	PO: 2–3	PO: 3–4	PO: 25	PO: 4–5
	SC: 2.5	Nasal: 3–4					PO Elderly: 6
Major metabolites (%)	Indoleacetic acid	*N*-Demethyl (act)[e]: 4	Hepatic: 50%	Indolacetate	Indolacetate	*N*-Demethyl (act)	*N*-Demethyl (act)
	Glucuronides	Indoleacetate: 31		*N*-Demethyl (act)	GABA	*N*-Ac demethyl	
	Hepatic: 60%			6-OH	*N*-demethyl		
					Hepatic: 60%		
Metabolizing enzymes	MAO-A	CYP3A4	CYP3A4	MAO-A	CYP3A4/CYP2D6: 12%	CYP1A2	CYP3A4
			MAO-A	CYP3A4	MAO-A: 27%		
Excretion (%)	Urine metab: ~60	Urine metab: 60	Urine metab: 30	Urine metab: 80	Urine metab: 75	Urine metab: 10–30	Urine metab: ~90%
	Feces metab: ~40	Feces metab: 30	Feces metab: ~15	Feces metab: 12	Feces metab: 10	Feces metab: 60	Unchanged: <10
	Unchanged: 3–22	Unchanged: <10	Unchanged: 50	Unchanged: 14	Unchanged: 40–50		
Time to peak concentration (min)	SC: 12 (5–20)	PO: 120–240	PO: 60–180	PO: 60–90	PO: 60–240	PO: 120–240	PO: 60–90
	Nasal: 60–90	Nasal: 180–240			SC: <30		
	PO: 60–120						
Onset (min)	SC: <10	PO: 60	PO: 60–180	PO: 30–120	PO: 60–120	PO: 120	PO: <60
	Nasal: <15				SC: 60–120		
	PO: <30						
Dosage range (mg)	SC: 6	PO: 1.25–5.00	PO: 1.0–2.5	PO: 5–10	PO: 6.25–12.5	PO: 2.5–5.0	PO: 20–40
	Nasal: 5–20	Max PO: 10/24 h	Max PO: 5/24 h	Max PO: 25/24 h	Max PO: 25/24 h	Max PO: 7.5/24 h	Max PO: 80/24 h
	PO: 25–100		Duration PO: <24 h	Duration PO: 14–16 h		Duration PO: <24 h	Duration PO: 18 h
	Max PO: 200/24 h						
	Duration PO: 2–4 h						

[a] Chemical Abstracts, American Chemical Society, calculated using Advanced Chemistry Development (ACD/Labs) Software V8.14 for Solaris (1994-2006 ACD/Labs).
[b] First-pass metabolism.
[c] Delayed by food.
[d] Slower onset during migraine attack.
[e] act= active metabolite

receptors. No tryptamine analog binds at 5-HT$_{1E}$ receptors with substantially higher affinity than 5-HT (K_i ~ 10 nM), and even simple *O*-methylation of 5-HT reduces its affinity for this receptor by approximately 100-fold (42). Ergolines, such as ergonovine (Ergotrate), methylergonovine (Methergine), and methysergide (Sansert), bind to 5-HT$_{1E}$ receptors with K_i values in the 50 to 150 nM range (42). Studies indicate that these receptors are negatively coupled to adenylate cyclase. No 5-HT$_{1E}$–selective receptor agonists or antagonists have yet been reported (43); this has created a problem for investigating this receptor subpopulation. One problem stalling development of selective agents is the lack of 5-HT$_{1E}$ receptors in rodent (i.e., mouse, rat) brain, the animal species commonly employed in preclinical drug development; however, the recent discovery of this receptor type in guinea pig brain bodes well for future studies.

5-HT$_{1F}$ Receptors

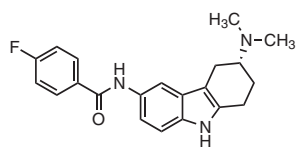
The newest 5-HT$_1$ receptor subpopulation to be cloned is the human 5-HT$_{1F}$ receptor (44), which exhibits intermediate (~50% to 70%) amino acid sequence homology with other 5-HT$_1$ receptor subpopulations. The receptors are coupled to inhibition of adenylate cyclase. Detection of these receptors in the uterus and mesentery suggests a possible role in vascular contraction. Although their distribution in the brain appears to be limited, distributional similarities with h5-HT$_{1B}$ receptors have been observed. A 4-(3-indolyl)piperidine, LY-334370, and an aminocarbazole, LY-344864, were identified as the first 5-HT$_{1F}$–selective agonists (45) with potential for the treatment of migraine. A more selective (nearly 300-fold more selective over 5-HT$_{1E}$) agent, lasmiditan, has been recently identified (46). Preliminary evidence suggests that lasmiditan, unlike most of the triptans, will not constrict the coronary artery (46). The nonselective 5-HT$_1$ receptor antagonist methiothepin has been shown to act as a 5-HT$_{1F}$ receptor antagonist. The SAFIR for the binding of tryptamines at 5-HT$_{1F}$ receptors has been reported (43). Interestingly, there is a statistically significant correlation between the affinities of several dozen tryptamine derivatives at 5-HT$_{1E}$ and 5-HT$_{1F}$ receptors (43), indicating common or similar binding requirements; interestingly, 5-HT$_{1F}$, but not 5-HT$_{1E}$ (vide supra), receptors allow substitution at the tryptamine 5-position. This opens the door for the development of additional 5-HT$_{1F}$– versus 5-HT$_{1E}$–selective agents. Many agents that bind at 5-HT$_{1E}$ receptors typically bind as well at 5-HT$_{1F}$ receptors; however, not all 5-HT$_{1F}$ receptor ligands bind at 5-HT$_{1E}$ receptors (see below).

ERGOLINES

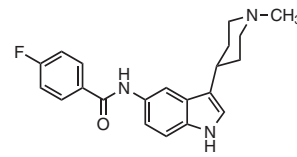
Ergolines, a large group of indole alkaloids with varied effects known for more than 2,000 years, are isolated from the ergot fungus, Claviceps purpurea, a plant parasite principally infecting rye. Eating rye grain contaminated with ergot caused a severely debilitating and painful disease during the Middle Ages called St. Anthony's Fire (ergotism), but in small doses, ergot was known to midwives for centuries for its ability to stimulate uterine contractions. Gangrene with burning pain in the extremities was one of two common presentations of ergot poisoning, which also could produce convulsions, hallucinations, severe psychosis, and death. St. Anthony was the patron saint of those who were stricken, and the Order of St. Anthony provided care for these patients. Outbreaks of "dancing mania," which occurred between the 13th and 16th centuries, sometimes have been attributed to ergotism, and one appealing—if unprovable—theory proposes that the women accused of witchcraft in the Salem trials of 1692 were suffering from ergot-induced psychosis and convulsions. The pharmacology of the various ergolines is complex, and they exhibit affinity for α-adrenergic, dopaminergic, and serotonergic receptor systems. The ergolines have been largely displaced by other more selective and effective drugs.

5-HT$_{1F}$ Receptors: Clinical Significance

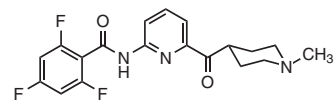
The clinical significance of 5-HT$_{1F}$ receptors is unknown at this time. The binding of sumatriptan to this receptor population suggests a relationship between 5-HT$_{1F}$ receptor binding and antimigraine activity. Other antimigraine agents, including naratriptan, rizatriptan, and zolmitriptan, also bind at 5-HT$_{1F}$ receptors (37). Studies show that 5-HT$_{1D}$ receptors are the dominant species in human cerebral blood vessels but that 5-HT$_{1F}$ receptors are also expressed both in neural and vascular tissue; however, 5-HT$_{1F}$ receptor agents could have a role in migraine as well (41). Indeed, lasmiditan could represent a prototype for a new generation of antimigraine agents that, because they do not bind at 5-HT$_{1B/1D}$ receptors, are likely to display reduced coronary vasoconstrictor action associated with the triptans.



LY-344864



LY-334370



Lasmiditan

5-HT$_2$ Receptor Family

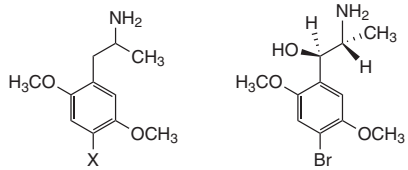
Serotonin receptors were first divided into 5-HT$_1$ and 5-HT$_2$ receptor families in 1979 (6), and the latter was subsequently divided into the subfamilies 5-HT$_{2A}$, 5-HT$_{2B}$, and 5-HT$_{2C}$ (formerly 5-HT$_{1C}$) receptors. Now, the term "5-HT$_2$" refers to a receptor family, not to an individual population of receptors. Ketanserin (Fig. 11.9) was

identified early on as a 5-HT_2 receptor antagonist with no affinity for 5-HT_1 receptors, and [^{3}H]ketanserin was introduced as a radioligand to label 5-HT_2 receptors. 1-(2,5-Dimethoxy-4X-phenyl)-2-aminopropane, where X = -Br and -I (DOB and DOI, respectively), was introduced as a 5-HT_2 receptor agonist. A significant amount of pharmacology was published, and structure–activity studies led to the development of many novel agents. Many of the original agents thought to be 5-HT_2 selective, including standard antagonists such as ketanserin and the agonists DOB and DOI, were later shown to bind nonselectively both to 5-HT_{2A} and 5-HT_{2C} receptors. Consequently, pharmacologic actions originally thought to be 5-HT_2 mediated could actually involve 5-HT_{2A} receptors, 5-HT_{2C} receptors, or a combination of 5-HT_{2A} and 5-HT_{2C} receptors. The structures of the three 5-HT_2 receptor subpopulations were found to be consistent with those of transmembrane-spanning G protein–coupled receptors, and the receptors all use a phospholipase C second messenger system. Approximately 70% to 80% sequence homology is found among the three receptor subtypes (10). Only relatively recently have novel agents with subpopulation selectivity been reported.

5-HT_{2A} Receptors

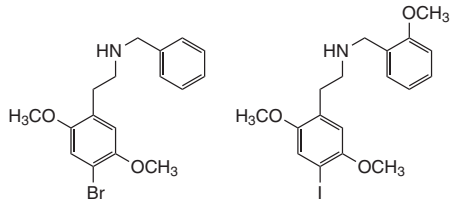
5-HT_{2A} receptors, formerly termed 5-HT_2 receptors, have been extensively reviewed (47–51). 5-HT_{2A} receptors have been cloned from various species, including human, and exhibit a high degree (>90%) of species homology. Significant (78%) amino acid sequence homology is found between the transmembrane portions of cloned 5-HT_{2A} receptors and 5-HT_{2C} receptors; this could explain the observed similarities in the binding of various ligands at the two receptor subpopulations. Evidence was provided that 5-HT_{2A} receptors exist in a high-affinity state and a low-affinity state (sometimes referred to as 5-HT_{2H} and 5-HT_{2L} states, respectively); under normal conditions, the low-affinity state predominates. The tritiated antagonist, [^{3}H]ketanserin, displays comparable affinity for both states, whereas agonists display higher affinity for the high-affinity state (e.g., when a tritiated agonist is employed as radioligand).

5-HT_{2A} Agonists The SAFIRs for 5-HT_{2A} receptor binding have been reviewed (47,51). Most indolealkylamines are nonselective 5-HT_{2A} receptor ligands, and typically bind with high affinity at the tritiated agonist-labeled high-affinity state. Investigations suggest that all indolealkylamines could not bind in the same manner at 5-HT_{2A} receptors (52). Phenylalkylamines, such as DOB and DOI, act as 5-HT_{2A} receptor agonists or high-efficacy partial agonists (see Chapter 19) and are significantly more selective than the indolealkylamines because of the low affinity of the former for non–5-HT_{2A} sites, but they do not differentiate between 5-HT_2 receptor subpopulations. [^{3}H]DOB and [^{125}I]DOI have been introduced as agonist radioligands (53). Interestingly, although *N*-alkylation of DOB-type compounds typically results in decreased affinity, it was found that *N*-benzyl-α-desmethyl DOB is a very high-affinity compound and, furthermore, that it behaves as a 5-$HT_{2A/2C}$ agonist (54). The structurally related INBMeO has been introduced as a radioligand to label 5-$HT_{2A/2C}$ receptors (55). Another 5-$HT_{2A/2C}$ agonist with DOB-like effects is the 1*R*,2*R*-isomer of β-hydroxy DOB (β-OH DOB) (56,57).



DOB X = Br
DOI X = I

1*R*,2*R*–β-OH DOB



N-Benzyl-α-desmethyl DOB

INBMeO

5-HT_{2A} Antagonists One of the largest and more selective classes of 5-HT_{2A} receptor antagonists is the *N*-alkylpiperidines. The best-known examples are ketanserin and ritanserin. Although numerous ketanserin-related derivatives have been reported, their SAR still has not been completely defined. Nevertheless, far less than the entire structure of ketanserin is required for high affinity. Some 5-HT_{2A} receptor antagonists, although fairly selective for 5-$HT_{2A/2C}$ receptors versus most other populations of 5-HT receptors, bind with modest to high affinity at dopaminergic, histaminergic, and/or adrenergic receptors. The tricyclic antipsychotics, atypical antipsychotics (risperidone, clozapine, and olanzapine) (Fig. 11.9), and tricyclic antidepressants also bind at 5-HT_{2A} receptors. Spiperone (Fig. 11.7) has been employed as a 5-HT_{2A} receptor antagonist with 1,000-fold selectivity for 5-HT_{2A} versus 5-HT_{2C} receptors, but spiperone is also a potent dopamine receptor antagonist, a 5-HT_{1A} receptor antagonist, and a 5-HT_7 receptor antagonist. Spiperone, volinanserin (MDL 100,907 or M100907), and AMI-193 were the first 5-HT_{2A}– versus 5-HT_{2C}–selective antagonists available (58,59) (Fig. 11.10). The binding selectivity of various antagonists (and agonists) at 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors has been compared (60). Spiperone and AMI-193 bind at 5-HT_{2A} receptors with 1,000- to 3,000-fold selectivity relative to 5-HT_{2C} receptors but display high affinity for 5-HT_{1A} and D_2 dopamine receptors. A newer member of this series, KML-010, is a spiperone-related derivative that lacks affinity for 5-HT_{2C} and 5-HT_{1A} receptors and binds with low affinity at D_2-dopamine receptors (59).

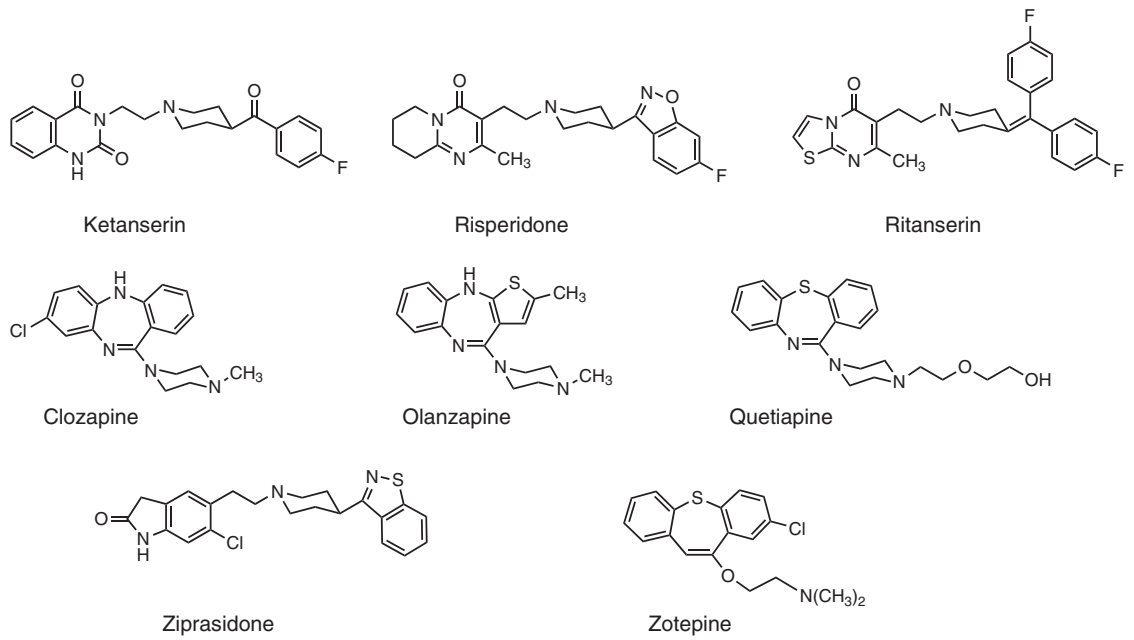


FIGURE 11.9 5-HT$_2$ receptor antagonists.

Volinanserin is a widely used pharmacologic tool with greater than 100-fold selectivity over most other receptor types (58). Pimavanserin and nelotanserin (ADP-125) display 10-fold and 250-fold selectivity, respectively, for 5-HT$_{2A}$ versus 5-HT$_{2C}$ receptors; one of the most selective antagonists is pruvanserin (EMD-281,014) with about 4,000-fold selectivity (Fig. 11.10).

5-HT$_{2A}$ Receptors: Clinical Implications The potential therapeutic roles of 5-HT$_{2A}$ ligands and the possible involvement of 5-HT$_{2A}$ receptors in modulating normal physiologic functions and various pathologic and psychopathologic conditions have been extensively reviewed (3,11,20). 5-HT$_{2A}$ receptors appear to have a role in thermoregulation and sleep, and they could be involved in appetite control, learning, and, along with various other serotonergic receptor populations, cardiovascular function and muscle contraction. Many of the clinical implications of 5-HT$_{2A}$ receptors could actually involve 5-HT$_{2C}$ receptors or a combination of 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors, due to the high homology between the two receptor populations resulting in many antagonists that bind to both with relatively little selectivity. For example, 5-HT$_{2A}$ (and/or 5-HT$_{2C}$) antagonists could be useful for the treatment of anxiety (particularly posttraumatic stress disorder) and sleep, cognitive, and mood disorders (61,62). With the recent development of subpopulation-selective agents, this is currently an important area of research. For example, nelotanserin, pimavanserin, pruvanserin, and volinanserin are being examined for their effectiveness in treating insomnia, schizophrenia, depression, and anxiety.

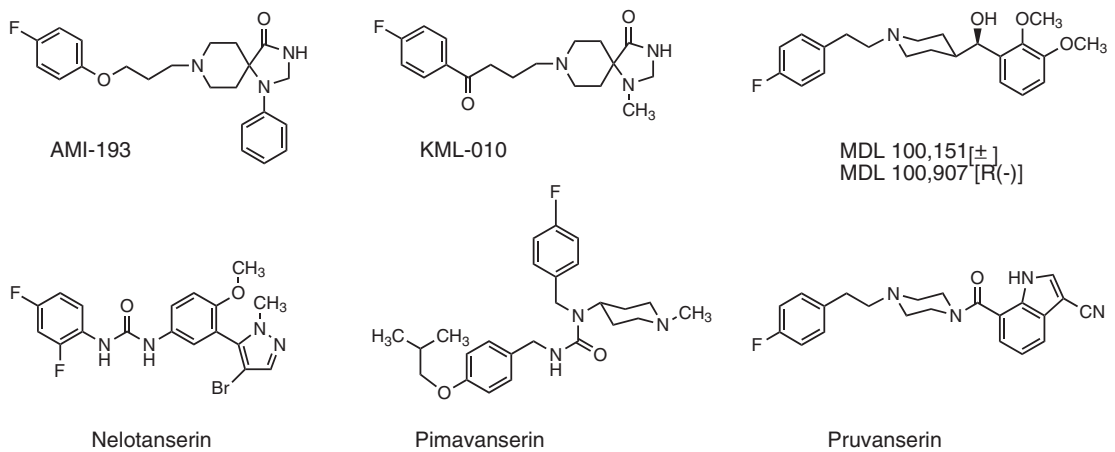


FIGURE 11.10 Examples of 5-HT$_{2A}$ subpopulation selective agents.

Antipsychotic Agents and Antidepressants Various typical and atypical antipsychotic agents (see Chapter 14) and antidepressants (see Chapter 18) bind with relatively high affinity at 5-HT_{2A} receptors as antagonists (15,63). Although no direct correlation exists between their receptor affinities and clinically effective doses, evidence suggests that these disorders involve, at least to some extent, 5-HT_{2A} receptors. For example, chronic administration of 5-HT_{2A} antagonists results in a paradoxical downregulation of 5-HT_{2A} receptors. Such a downregulation would be of benefit in the treatment of depression. Several agents with 5-HT_{2A} antagonist action possess antipsychotic activity; an example is the atypical antipsychotic risperidone. Some 5-HT_{2A} antagonists also bind at dopamine receptors. Indeed, the atypical antipsychotics clozapine, olanzapine, quetiapine, risperidone, ziprasidone, and zotepine, bind both at 5-HT_{2A} and dopamine D_2 receptors (63,64) and often at other serotonergic and nonserotonergic receptors. Although this can obfuscate the role of 5-HT_{2A} antagonism as being important for (atypical) antipsychotic activity, it has been suggested that certain types of schizophrenia could actually be more responsive to the combined effect. That is, D_2-dopaminergic antagonist antipsychotics have been claimed to be more effective for treating the positive symptoms of schizophrenia, whereas the 5-HT_{2A} antagonists could be more effective in treating the negative symptoms; this has led to the development of the serotonin–dopamine antagonists. This theory also suggests that increasing the 5-HT_{2A} component of binding could be related to a decrease in extrapyramidal side effects associated with these types of agents. However, a recent study has found that whereas certain atypical antipsychotics (e.g., clozapine, olanzapine, risperidone) are more efficacious than typical antipsychotics agents against overall positive and negative symptoms of schizophrenia, this was not true for certain others (e.g., quetiapine, ziprasidone, zotepine) (65). Nevertheless, all agents produced decreased extrapyramidal stimulation as an undesirable side effect. From preclinical studies, there are indications that certain 5-HT_{2A} receptor antagonists also possess anxiolytic properties; for example, ritanserin (Fig. 11.9) has been demonstrated to produce both antipsychotic and antianxiety effects in humans.

Classical Hallucinogens 5-HT_{2A} receptors can be involved in the actions of the classical hallucinogens (66) (see Chapter 19). Although indolealkylamine (e.g., 5-methoxy-*N*,*N*-dimethyltryptamine) and ergoline-related (e.g., LSD) classical hallucinogens are fairly nonselective agents that bind to multiple populations of serotonergic receptors, the phenylalkylamine hallucinogens (e.g., DOB, and DOI) are much more 5-HT_2–selective agonists. Furthermore, a significant correlation exists between the human hallucinogenic potencies of classical hallucinogens and their 5-HT_{2A} receptor affinities (66). Interestingly, phenylalkylamine hallucinogens also bind at 5-HT_{2B} and 5-HT_{2C} receptors, and here, too, a significant correlation is found between human potency and receptor affinity for 17 different agents (67). Recent studies suggest that 5-HT_{2A} receptors can have a more prominent role than 5-HT_{2B} or 5-HT_{2C} receptors for the behavioral actions of hallucinogens (67), and differences may exist in the manner in which hallucinogens activate the different receptor populations (68,69).

An interesting twist, with potential therapeutic ramifications, was the development of the 1*R*,2*R* isomer of β-OH DOB (56). 5-HT_{2A} receptors are found in the eye, and activation of these receptors can reduce intraocular pressure and could be of benefit for the treatment of glaucoma. However, 5-HT_{2A} agonists such as DOB are hallucinogenic. A DOB analog, β-OH DOB, was developed as a less lipid-soluble version of DOB. With its reduced lipophilicity, and because of its route of administration (ocular installation), the adverse effects of this agent should be minimized. Other 5-HT_2 agonists are now being examined in this regard (57).

5-HT_{2B} Receptors

The rat fundus preparation is a peripheral tissue assay that has been used as a functional assay for serotonergic action for more than 50 years. Long-standing questions concerning the pharmacologic similarity of serotonergic fundus receptors (now called 5-HT_{2B} receptors) to the 5-HT_2 family of receptors were answered once they were cloned (70). The 5-HT_{2B} receptors exhibit approximately 70% homology to 5-HT_{2A} and 5-HT_{2C} receptors, and like 5-HT_{2A} receptors, they appear to couple functionally to phosphoinositol hydrolysis. Nevertheless, rat and human 5-HT_{2B} receptors display more than 90% transmembrane sequence homology. Therefore, most agents that bind at rat 5-HT_{2B} receptors also bind with similar affinity at human 5-HT_{2B} receptors. There are, however, some exceptions (71). The standard 5-HT_{2A} receptor antagonist ketanserin and the 5-HT_{2A} receptor agonists DOI and DOB display higher affinity for 5-HT_{2A} and 5-HT_{2C} receptors than for 5-HT_{2B} receptors (67). Evidence suggests that human 5-HT_{2B} receptors, like human 5-HT_{2A} receptors, also exist in high-affinity and low-affinity states (71). 5-HT_{2B} receptors are found on cardiovascular tissue. Activation of such receptors by agents with a 5-HT_{2B} agonist character could result in cardiac valvulopathy; valvular heart disease associated with the anorectic agent fenfluramine could involve its metabolism to norfenfluramine—a high-affinity 5-HT_{2B} agonist (72). The designer drug 3,4-methylenedioxymethamphetamine (MDMA; Ecstasy) and its *N*-desmethyl analog MDA also show a 5-HT_{2B} agonist character (73). A series of 1-substituted β-carbolines (e.g., LY-23728, LY-287375, and LY-266097) have been reported to be the first 5-HT_{2B}–selective antagonists (74).

In the periphery, 5-HT_{2B} receptors seem to be involved in muscle contraction; however, their function in the CNS (if any) is still a matter of speculation. On the basis of some preliminary studies, and considering their central distribution in brain, 5-HT_{2B} receptors could be involved, at least in

rodents, in anxiety, cognition, food intake, neuroendocrine regulation, locomotor coordination, and balance (75).

5-HT$_{2C}$ Receptors

The 5-HT$_{2C}$ receptors, formerly called 5-HT$_{1C}$ receptors, originally were identified in various regions of the brain using autoradiographic and radioligand binding techniques. Cloned human 5-HT$_{2C}$ receptors display a high amino acid sequence homology with 5-HT$_{2A}$ receptors, and like 5-HT$_{2A}$ receptors, they are coupled to phosphoinositol hydrolysis. As previously mentioned, some pharmacologic functions once attributed to "5-HT$_2$" receptors actually could involve a 5-HT$_{2C}$ receptor mechanism. For example, the hyperthermic activity of a series of phenylisopropylamines is significantly correlated not only with 5-HT$_{2A}$ but also with their 5-HT$_{2C}$ receptor affinity. Numerous atypical antipsychotic agents bind at 5-HT$_{2C}$ receptors as well as at 5-HT$_{2A}$ receptors; however, no significant correlation exists between their atypical properties and binding affinity. 5-HT$_{2C}$ receptors can have a greater role than 5-HT$_{2A}$ receptors in migraine. Other studies suggest that 5-HT$_{2C}$ receptor modulators could be useful in the treatment of obesity, schizophrenia, depression, anxiety, drug abuse, erectile dysfunction, urinary incontinence, and Parkinson disease (76). Several selective agents are now available.

A series of isotryptamine derivatives, including Ro 60-0175 (ORG-35030), has been shown to display high selectivity for 5-HT$_{2C}$ versus 5-HT$_{2A}$ receptors and to possess 5-HT agonist activity (77); however, some of the results could not be replicated (78). Structurally related tricyclic analogs, such as Ro 60-0332 (ORG-35035), also have been examined and display more than 100-fold selectivity (79). 10-Methoxy-9-methylpyrazino[1,2-a] indole, Ro 60-0175, and Ro 60-0332 all were active in animal models predictive of therapeutic utility for obsessive-compulsive disorders, panic disorders, and depression (79). WAY-163909 (Fig. 11.11), a full agonist at 5-HT$_{2C}$ receptors with weak partial agonist action at 5-HT$_{2B}$ receptors and inactive at 5-HT$_{2A}$ receptors, was effective in animal models of obesity, psychotic-like behavior, and depression (80). Lorcaserin (APD-356) (Fig. 11.11) is a 5-HT$_{2C}$ receptor agonist developed for the treatment of obesity (81); although it has completed phase III clinical trials, it has not yet been approved by the U.S. Food and Drug Administration. 1*R*,3*S*(–) *trans*-1-Phenyl-3-dimethylamino-1,2,3,4-tetrahydronaphthalene, or 1*R*,3*S*(–) *trans*-PAT (Fig. 11.11), a full agonist at 5-HT$_{2C}$ receptors, is an inverse agonist and competitive antagonist at 5-HT$_{2A}$ and 5-HT$_{2B}$ receptors and produced anorexia in animals (82).

Interestingly, selective 5-HT$_{2C}$ receptor antagonists appear to target some of the same actions as 5-HT$_{2C}$ receptor agonists. Perhaps the first 5-HT$_{2C/2B}$–selective antagonist was SB-206553, which was identified in the 1990s; continued work with this molecule ultimately resulted in SB-243213—actually, an inverse agonist (83,84). The latter displays greater than 100-fold selectivity over the other two populations of 5-HT$_2$ receptors and is being

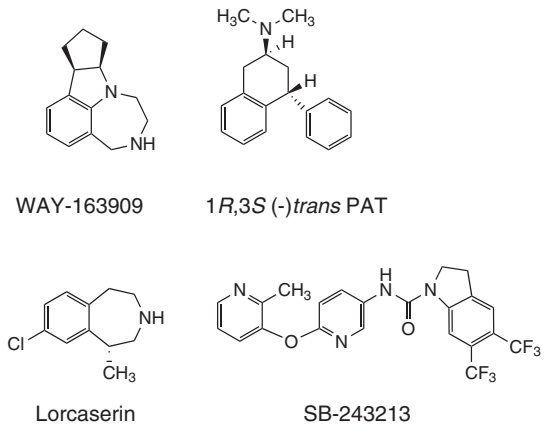
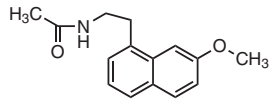


FIGURE 11.11 5-HT$_{2C}$ receptor–selective agonists and antagonists.

examined for its potential use in the treatment of anxiety, depression, and schizophrenia. SB-243213 is claimed to possess an improved anxiolytic profile relative to the benzodiazepines and could have utility in the treatment of schizophrenia and motor disorders (83). It should be noted that agomelatine (Valdoxan), although not strictly a 5-HT$_{2C}$–selective receptor antagonist, has been found more effective than fluoxetine in a randomized double-blind study in patients with severe major depressive disorder (85), and is currently in clinical trials in the United States. Initially developed as a melatonin (MT) receptor agonist, agomelatine is a nonselective MT$_1$/MT$_2$ receptor agonist with 5-HT$_{2C}$ receptor antagonist character (Chapter 18).



It is still not known with confidence specifically what pharmacologic effects are related to what 5-HT$_2$ receptor subpopulation. However, with the availability of subtype-selective agents, the problem comes closer to being solved.

5-HT$_3$ Receptor Family

Unlike with most 5-HT receptor populations, early 5-HT$_3$ pharmacologic studies relied almost exclusively on functional (i.e., peripheral tissue) assays. It was a number of years before radioligands were available to identify 5-HT$_3$ receptors in brain. 5-HT$_3$ receptors, ligand-gated ion channel receptors, are members of the Cys-loop family that includes nicotinic acetylcholine, γ-aminobutyric acid (GABA)$_A$ and glycine receptors, and a Zn^{2+}-activated cation channel (86,87). They consist of five subunits surrounding a cation-permeable (Na^+, Ca^{2+}, K^+), water-filled pore. Each subunit is composed of four transmembrane-spanning helices (TM1 to TM4)

with the TM2 domains of each forming the channel pore (Fig. 11.12). Both, a large N-terminus with a Cys-loop and a short C-terminus are located extracellularly (86,87). Approximately 70% to 80% of 5-HT_3 receptors in brain are located presynaptically (87). Evidence indicates that 5-HT_3 receptors modulate release of other neurotransmitters, including dopamine, acetylcholine, GABA, and 5-HT (88).

Five 5-HT_3 subunits have been cloned. 5-HT_{3A}, 5-HT_{3B}, 5-HT_{3C}, and 5-HT_{3E} subunits are similar in their topology, whereas the 5-HT_{3D} subunit lacks most of the N-terminus including the Cys-loop. The 5-HT_{3A} subunit is the only one that forms functional homomeric receptors when expressed in *Xenopus* oocytes. The other subunits are unable to form functional homomeric receptors in vitro, but they can assemble to functional heteromeric receptors with the 5-HT_{3A} subunit (87). This could be explained by lack of a tryptophan residue in the N-terminus of all four subunits (5-HT_{3B}, 5-HT_C, 5-HT_D, and 5-HT_E) shown to be essential for binding. Conversely, the latest reports indicate that subunits 5-HT_{3C}, 5-HT_{3D}, and 5-HT_{3E} could be present on the cell surface when expressed alone in CHO cells (89). 5-HT_{3A}- and 5-HT_{3AB} receptors are the most studied to date. 5-HT_{3AB} receptors differ from 5-HT_{3A} in that they have higher single-channel conductance, a lower Ca^{2+} permeability, faster activation and deactivation, and a lower potency for 5-HT. The subunit composition of recombinant 5-HT_{3AB} receptors in HEK293 cells has been shown to be B-B-A-B-A, but this could not be the case for native 5-HT_3 receptors (87). The orthosteric ligand binding site is believed to be located at the interface of two adjacent subunits where it is formed by three loops (A to C) of the "principal" and three loops (D to F) of the "complementary" subunit as shown for acetylcholine binding protein and adapted for 5-HT_3 receptors. To fully activate the ion channel of homomeric 5-HT_{3A} receptors, three molecules of agonist are necessary, whereas in the case of heteromeric 5-HT_{3AB} receptors, with presumed stoichiometry of 5-$HT_{3(A)2(B)3,}$ only two agonist molecules are necessary (87).

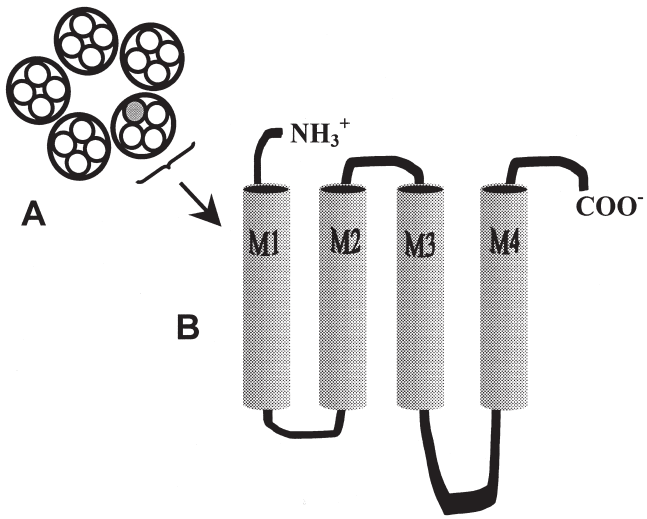


FIGURE 11.12 Top (A) and side (B) views of a schematic representation of an idealized ion channel receptor (such as the 5-HT_3 receptor). Ion channel receptors are pentameric units arranged to form a pore or ion channel. Each subunit consists of four transmembrane-spanning amino acid chains (M_1–M_4) constructed such that the M_2 chain faces the channel. The transmembrane portions are connected by extracellular and intracellular loops. In the serotonin family, only 5-HT_3 receptors have been identified as ion channel receptors.

Structure–Activity Relationships of 5-HT_3 Agonists

Only a few 5-HT_3 receptor agonists have been identified (Fig 12.13), and the topic has been comprehensively reviewed (90). Many tryptamine analogs bind at 5-HT_3 receptors in a nonselective manner. Simple *O*-methylation of 5-HT significantly decreases its affinity for 5-HT_3 receptors. Ergolines either do not bind or bind only with very low affinity. 5-HT is a nonselective 5-HT_3 receptor agonist that binds only with modest affinity (K_i ~ 500 to 1,000 nM). Its 2-methyl analog, 2-methyl 5-HT (K_i = 1,200 nM) (Fig. 11.13), is somewhat more selective but binds with slightly lower affinity than 5-HT. Although 2-methyl 5-HT may be only a partial agonist, it has found widespread application in 5-HT_3 research due to its greater selectivity over 5-HT. Recently, however, 2-methyl 5-HT was shown to bind with high affinity at 5-HT_6 receptors (see below). The *N,N,N*-trimethyl quaternary amine analog of 5-HT, 5-HTQ, binds with approximately 10-fold greater affinity and is much more selective than 5-HT; however, because of its quaternary nature, it could not readily penetrate the blood–brain barrier when administered systemically. Using cloned mouse 5-HT_3 receptors, 5-HT and 5-HTQ act as full agonists, suggesting that the quaternary nature of 5-HTQ has little effect on efficacy, whereas 2-methyl 5-HT and tryptamine act as partial agonists. Another example of a low-affinity (K_i ~ 1,000 nM) 5-HT_3 agonist is phenylbiguanide. *m*-Chlorophenylbiguanide (*m*CPBG), which binds in the low nanomolar range (K_i ~ 20 to 50 nM) and retains agonist character, has largely replaced phenylbiguanide. Because of its polar nature, *m*CPBG does not readily penetrate the blood–brain barrier. *m*-Chlorophenylguanidine (MD-354; *m*CPG) shows that the entire biguanide moiety is not required for serotonergic activity. Adding multiple chloro groups to *m*CPBG or *m*CPG increases their lipophilicity and affinity (90).

Simple arylpiperazines were among the first serotonergic agents investigated at 5-HT_3 receptors (Fig 12.13). Many are nonselective 5-HT_3 ligands (see previous discussion of 5-HT_{1A} receptors). Depending on the particular substitution pattern, they can behave as 5-HT_3 agonists, partial agonists, or antagonists (90). This nonselectivity probably accounts for the initial lack of interest in arylpiperazines as 5-HT_3 ligands, but today, there is renewed interest in these

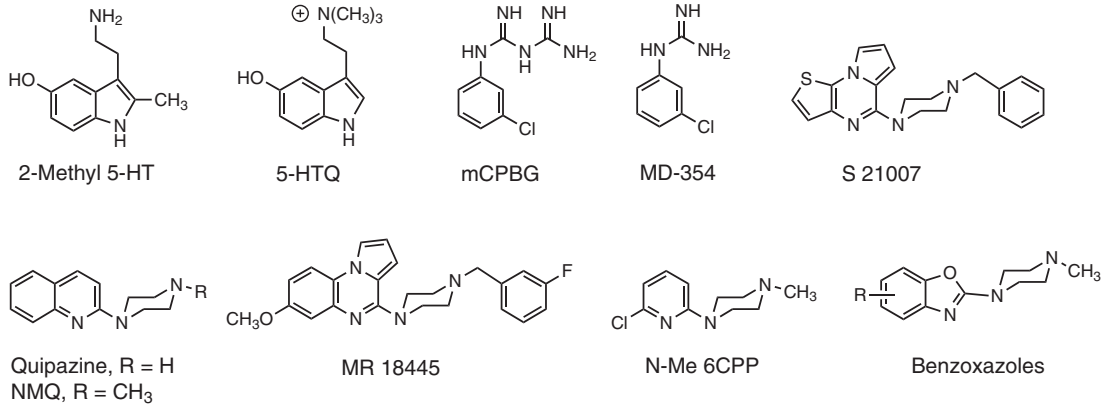


FIGURE 11.13 5-HT_3 receptor agonists or partial agonists.

types of agents. Quipazine was the first arylpiperazine shown to bind at 5-HT_3 receptors, even though it is also a 5-HT_{2A} agonist. It binds with much higher affinity than 5-HT at 5-HT_3 receptors (K_i ~ 1 nM) and was subsequently shown to act as an agonist in certain assays and as an antagonist in others. Interestingly, its structure was quite different from that of other 5-HT_3 antagonists known at that time. Early structure–affinity studies showed that its fused pyridine ring attached to N_4-piperazine nitrogen distance (~5.5 Å) was similar to that of 5-HT. Other findings indicated that 1) the N_4-piperazine nitrogen atom, but not the N_1-piperazine nitrogen atom, was important for binding; 2) the quinoline ring nitrogen atom was a major contributor to binding; 3) the benzene ring portion of the quinoline nucleus was not required for binding, but its presence was optimal for high affinity; and 4) N_4-methylation (*N*-methylquipazine) enhances 5-HT_3 receptor selectivity (Fig. 11.13) (90). With the availability of newer arylpiperazines, it has been possible to conduct more comprehensive structure–activity studies. A summary of quipazine SAR is shown in Figure 11.14; results of other SAR studies and several pharmacophoric models have been described (90). Appropriate structural modification of arylpiperazines can result in rather selective 5-HT_3 agonists (Fig. 11.13). For example, ring-fused quipazine-related analogs, such as the pyrrolo[1,2-*a*]quinoxalines, represent novel 5-HT_3 receptor agonists. Some are full agonists, whereas others (e.g., MR 18445) are partial agonists (90–93).

Structure–Activity Relationship of 5-HT_3 Antagonists

Bemesetron (MDL-72222) was the first selective 5-HT_3 receptor antagonist (Fig. 11.15). Its development stems from the structural modification of cocaine, an agent that had been previously shown to be a weak 5-HT_3 antagonist. Since then, many hundreds of 5-HT_3 antagonists have been identified as antiemetics (93,94). Many of these agents belong to the structural class of compounds broadly referred to as keto compounds and contain an amide, reverse amide, ester, reverse ester, carbamoyl, or ketone function. Typical of these 5-HT_3 antagonists is retention of the bulky tropane or tropane-like amine group. Some of the more widely used or newer antiemetic agents include dolasetron (Anzemet), granisetron (Kytril), itasetron, renzapride, ricasetron, tropisetron, WAY-100289, zacopride, and zatosetron. It should be noted that some of these keto compounds also bind at 5-HT_4 receptors.

A related group of antagonists that possess an imidazole or related heterocyclic terminal amine include ondansetron (Zofran), alosetron (Lotronex), fabesetron, and ramosetron (Fig. 11.16). Many others have been described (93,94). The SARs of 5-HT_3 antagonists have been reviewed in detail (93–95).

Studies have identified pharmacophoric features (Fig. 11.17) that are common to many 5-HT_3 receptor antagonists.

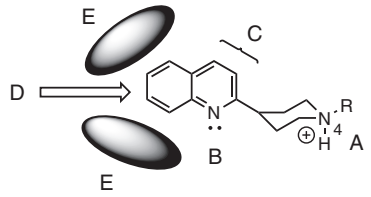


FIGURE 11.14 Structure–activity composite for quipazine analogs binding at 5-HT_3 receptors. (A) The N_4-piperazine nitrogen atom, but not the N_1-piperazine nitrogen atom, is important for binding; a 5-position-CH_3 is tolerated and results in somewhat greater 5-HT_3 selectivity. (B) The quinoline nitrogen atom is required for high affinity, and its replacement by an sp^2-hybridized carbon atom results in a more than 100-fold decrease in affinity. (C) Substituents in this region are tolerated and can influence intrinsic activity. (D) An aromatic moiety (e.g., benzene ring or isosteric structure), although not required for binding, results in optimal affinity. (E) Regions of limited bulk tolerance.

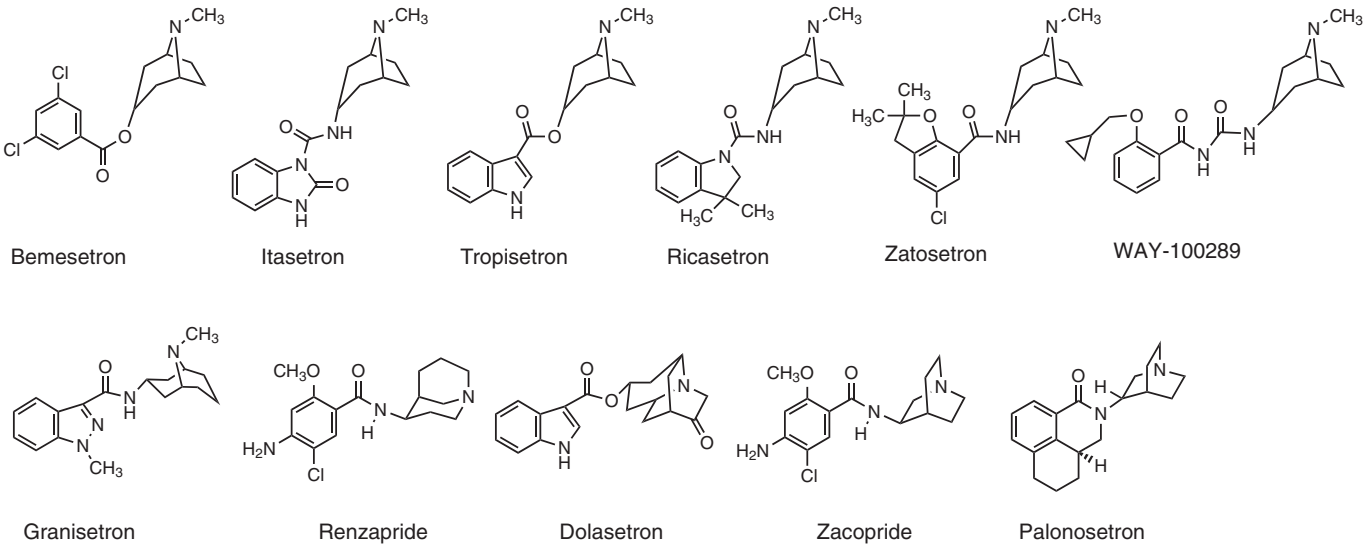


FIGURE 11.15 5-HT$_3$ receptor antagonists.

5-HT$_3$ Receptors: Clinical Implications

One of the most noteworthy clinical success stories in 5-HT research relates to the antiemetic properties of 5-HT$_3$ receptor antagonists. Ondansetron was introduced as an antiemetic in the 1990s, and 5-HT$_3$ receptor antagonists are now the "gold standard" for treatment of chemotherapy- and radiation-induced nausea and vomiting (96). Twenty or so years ago, nausea and vomiting were inevitable side effects that forced many patients to delay or avoid chemotherapy (97). With the current antiemetic therapy, nausea and vomiting can be prevented in nearly 80% of patients (97). The most commonly employed 5-HT$_3$ receptor antagonists are ondansetron, granisetron, dolasetron and, in Europe, tropisetron; a newer 5-HT$_3$ antagonist in clinical use in the United States is palonosetron (98). The various 5-HT$_3$ antagonists are commonly perceived as being of comparable efficacy and safety (99); however, they vary widely in their pharmacologic and pharmacokinetic properties (96–99) (Table 11.4). For example, their duration of action and elimination half-lives differ considerably. Ondansetron displays the shortest half-life (~4 hours), whereas the half-life of palonosetron has been reported to be up to 128 hours (99). Another difference in their pharmacology is that ondansetron is a competitive 5-HT$_3$ antagonist, whereas granisetron and tropisetron (and, perhaps, palonosetron) produce an insurmountable antagonism (98,99). Selection of a particular 5-HT$_3$ antiemetic follows specific guidelines that are related, at least in part, to such factors as the emeticity of the chemotherapeutic regimen, side effect tolerability, patient history, and financial considerations. Patients who are refractory to the effect of a particular antiemetic may benefit by switching antiemetic agents—improvement could be related to different routes of metabolism (96) (Table 11.4).

Preclinical and limited clinical studies suggest that 5-HT$_3$ receptor antagonists could potentially be of benefit for the treatment of alcohol and substance abuse, anxiety, autism, bipolar disorder, cognitive impairment,

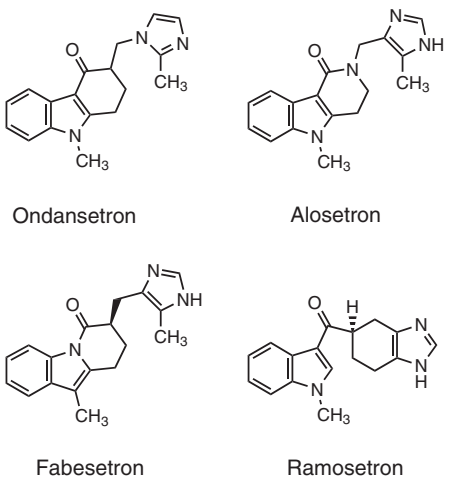


FIGURE 11.16 Imidazole-containing 5-HT$_3$ receptor antagonists.

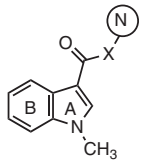


FIGURE 11.17 A composite pharmacophore model for 5-HT$_3$ receptor antagonists. An aromatic centroid (A) to oxygen (O) distance of 3.3 to 3.5 Å is thought to be optimal. Distances calculated from the terminal amine (N) to the oxygen atom (O) and from the terminal amine N to centroid A are from 5.1 to 5.2 and from 6.7 to 7.2 Å, respectively. It has been speculated that ring A is not required for binding and acts as a spacer. Ring B can be more important for binding, and associated hydrophobic binding regions have been proposed.

TABLE 11.4 Pharmacokinetics of the 5-HT3 Antagonists (Setrons)

Parameters	Ondansetron	Dolasetron	Granisetron	Alosetron	Palonosetron	Tropisetron
Trade name	Zofran	Anzemet	Kytril	Lotronex	Aloxi	Navoban
CLogP (calc)[a]	2.1 ± 0.5	2.8 ± 0.5	1.5 ± 0.5	0.88 ± 0.8	2.6 ± 0.5	3.6 ± 0.3
LogD (pH 7) (calc)[a]	1.5	2.8	−1.5	0.4	0.01	0.8
Bioavailability (%)	56–70[d]	Hydrodolasetron: 60–80	60[d]	50–60[bc]	IV	60 (60–100)
Protein binding (%)	70–76	Hydrodolasetron: 70–80	65	82	62	71
Volume of distribution (L/kg)	PO: 2.2–2.5	Hydrodolasetron: PO: 5.8–10	PO: 3.9	PO: 70 (65–95)	IV: 6.8–12.5	IV: 500
		PO: 6-7				
Elimination half-life (h)	PO: 3–6	PO: <10 min	IV: 4–5	PO: 1.5–2.0	PO: 30–40	EM: PO: 6–8
	Elderly: PO: 11	Hydrodolasetron: PO: 4–9	PO: ~6			PM: PO: 30
Major metabolites (%)	Hydroxylation	Hydrodolasetron	*N*-Demethyl	6-Hydroxylation	*N*-oxide	Hydrolyzation
	Glucuronidation	Hydroxylation	Hepatic	*N*-Demethyl	6S-Hydroxy	Glucuronides
	Hepatic	*N*-Demethyl			Hepatic: 50%	
Metabolizing enzyme (%)	CYP3A4	Carbonyl reductase	CYP3A4	CYP2C9: 30	CYP2D6	CYP2D6
	CYP2D6	CYP2D6		CYP3A4: 20	CYP3A4	
		CYP3A4 (*N*-oxide)		CYP1A2: 10	CYP1A2	
Time to peak plasma concentration (h)	PO: 1–2	Hydrodolasetron IV: <0.5	PO: 2–3	PO: 0.5–2	IV: 30 s	EM: PO: 3
		Hydrodolasetron PO: <1				PM: PO: 4
Excretion (%)	Urine metab: 40–60	Urine metab: 45	Urine metab: 48	Urine metab: 70	Urine metab: 80	Urine metab: ~70
	Feces metab: 25	Feces: 30	Feces metab: 38	Feces metab: 25		Feces metab: ~15
	Unchanged: <10	Unchanged hydrodolasetron: 60	Unchanged: <10	Unchanged: <10	Unchanged: 40	Unchanged: <10
Duration (h)	———	———	8–24	1–10	>24	———

IM, intramuscular; IV, intravenous; PO, oral.
[a] Chemical Abstracts, American Chemical Society, calculated using Advanced Chemistry Development (ACD/Labs) Software V8.14 for Solaris (1994–2006 ACD/Labs).
[b] First-pass metabolism.
[c] Food delays absorption and peak plasma concentrations.
[d] Food increase extent of absorption.

depression, eating disorders, gastrointestinal disorders, pain, and schizophrenia (87).

Very little is known about the potential therapeutic utility of 5-HT_3 receptor agonists (90).

5-HT_4 Receptors and Agents

A novel population of serotonergic receptors, originally identified in primary cell cultures of mouse embryo colliculi neurons and later termed 5-HT_4 receptors, have broad tissue distribution and are positively coupled to adenylate cyclase (100). In the brain, 5-HT_4 receptors appear to be localized on neurons and can mediate the slow excitatory responses to 5-HT. Peripherally, these receptors facilitate acetylcholine release in guinea pig ileum and can have a role in peristalsis. The uniqueness of this receptor type and its potential therapeutic utility spurred initial interest in drug development. Human 5-HT_4 receptors have been cloned and display low transmembrane sequence homology (<50%) with other 5-HT receptors. In fact, two 5-HT_4 isoforms have been isolated, a long form (5-HT_{4L}) and a short form (5-HT_{4S}). These isoforms are splice variants and differ only in their C-terminus ends, with identical transmembrane regions

(101). In general, the potency of agonists to stimulate cyclic adenosine monophosphate (cAMP) was greater for the 5-HT_{4S} receptor than for the 5-HT_{4L} receptor. A mouse 5-HT_{4L} receptor has been cloned, and a human pseudogene has been identified that codes for a 5-HT_4-like receptor. Indeed, several new human 5-HT_4 receptor isoforms have been cloned and expressed (102). The new 5-HT_4 receptors have been termed 5-$HT_{4(b)}$, 5-$HT_{4(c)}$, and 5-$HT_{4(d)}$; the stimulatory pattern of cAMP formation in response to the 5-HT_4 agonist renzapride was found to be different for the various isoforms, suggesting that the splice variants could differ in the manner by which they trigger signal transduction following receptor activation (102). In the rat gastrointestinal tract, both 5-HT_{4L} and 5-HT_{4S} receptors are expressed, whereas only 5-HT_{4S} receptors are found in the heart, with localization almost exclusively in the atrium. The 5-HT_{4a} receptors have been cloned from human atrium and appear to correspond to the rodent 5-HT_{4S} isoform. It has been proposed that the cardiac effects of 5-HT are mediated by this short splice variant, whereas 5-HT_{4L} determines the neuronal effects of 5-HT (102).

Although 5-HT_3 receptors are ion channel receptors and 5-HT_4 receptors represent G protein–coupled receptors (Table 11.2), a number of 5-HT_3 receptor ligands are active at 5-HT_4 receptors. Even more interesting is that a number of 5-HT_3 antagonists, or what were considered at one time to be 5-HT_3–selective antagonists (e.g., renzapride and zacopride), actually exhibited 5-HT_4 agonist activity. Even today, there is considerable structural similarity among various 5-HT_3 and 5-HT_4 receptor ligands. In addition to their lack of selectivity for 5-HT_4 versus other 5-HT receptors, many early 5-HT_4 receptor ligands suffered from several other disadvantages, such as their affinity for other receptor types, inability or difficulty in penetrating the blood–brain barrier, and hydrolytic instability (103).

Structure–Activity Relationships of 5-HT_4 Agonists

In general terms, 5-HT_4 agonists can be divided into several different categories (Fig. 11.18) (90): tryptamines (e.g., 5-HT and 5-CT, with 2-methyl 5-HT and 5-methoxy-*N*,*N*-dimethyltryptamine being nearly inactive), benzamides (particularly those bearing a 2-methoxy-4-amino-5-chloro substitution pattern, e.g., SC 53116, renzapride, zacopride, and cisapride), benzimidazolones (e.g., BIMU 8), quinolines (e.g., SDZ 216,908), naphthalimides (e.g., *S*-RS 56532), benzoates (ML-10302), and ketones (e.g., RS 67333).

Structure–Activity Relationships of 5-HT_4 Antagonists

The 5-HT_3 antagonist tropisetron was the first agent to see application as a 5-HT_4 antagonist, and its low affinity for 5-HT_4 receptors prompted a search for higher affinity agents. Various agents have been identified (94,104,105), and 5-HT_4 antagonists are derived from structural classes similar to those from which the 5-HT_4 agonists are derived. These include indole esters and amides (e.g., GR 113,808), benzoates (e.g., SB 204070), benzimidazolones (e.g., DAU 6285), imidazoles (e.g., SC 53606), and ketones (e.g., RS 100235) (Fig. 11.19). These are just a few representative examples of the many agents that have been examined as 5-HT_4 antagonists. Structure–activity details for several different receptor preparations have been reviewed (94,104,105). It is worth noting that apart from 5-HT_3 receptors, 5-HT_4 receptors are the only other population of serotonergic sites that seem to accommodate quaternary amines.

5-HT_4 Receptors: Clinical Implications

Selective 5-HT_4 agents have been recently developed, and studies regarding their clinical potential are still in their infancy. Peripheral actions currently being examined include irritable bowel syndrome (IBS), gastrointestinal tract motility, bladder contraction, gastroesophageal reflux, corticosteroid secretion, and atrial contractility. Cisapride is available as a prokinetic drug that enhances gastrointestinal activity. With respect to their central effects, it has been suggested that 5-HT_4 agonists can restore deficits in cognitive function and that 5-HT_4 antagonists could be useful as anxiolytics or in the treatment of dopamine-related disorders. It is further speculated that 5-HT_4 receptors may be involved in memory and learning, and it has been noted that 5-HT_4 receptors

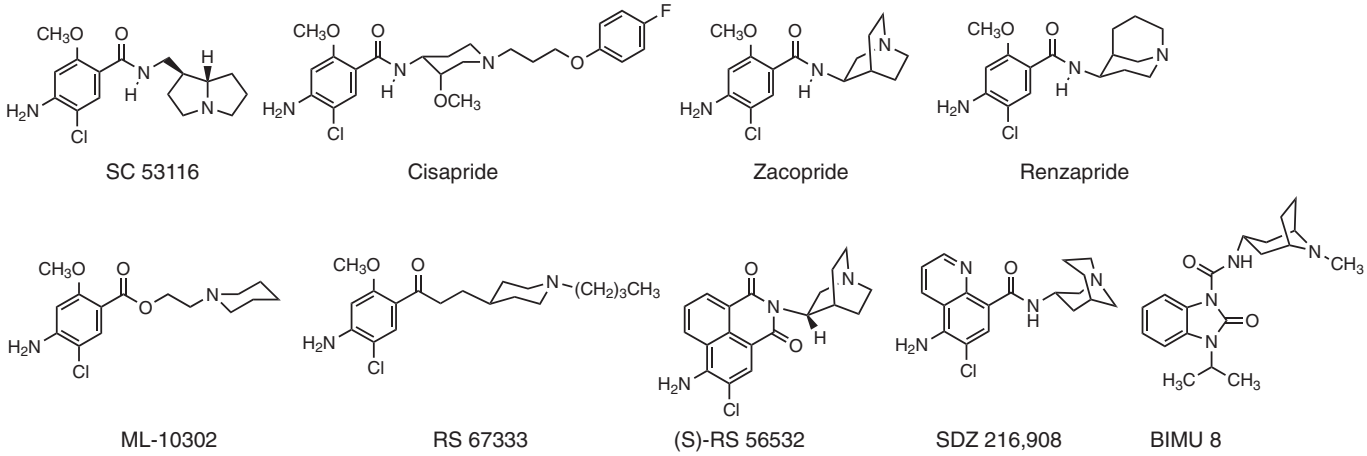


FIGURE 11.18 5-HT_4 receptor agonists.

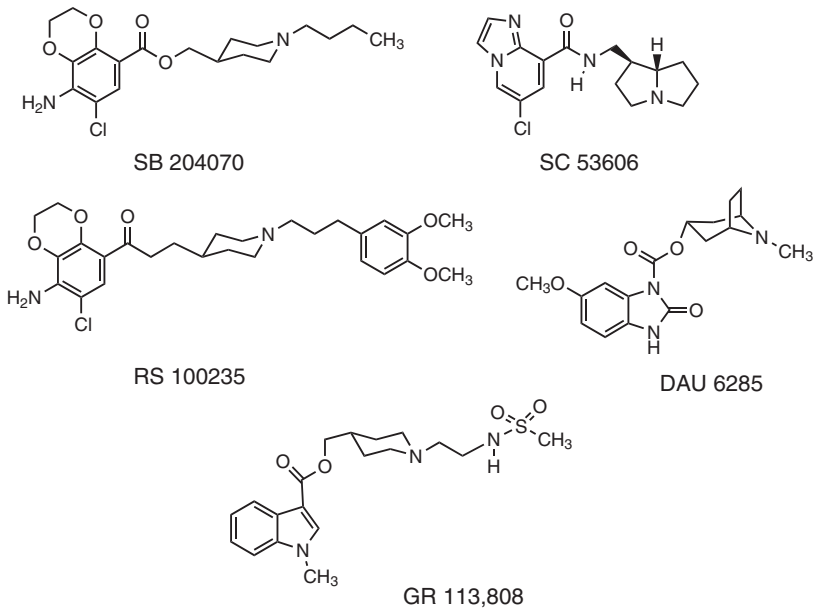
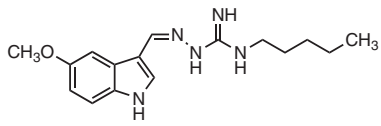


FIGURE 11.19 5-HT$_4$ receptor antagonists.

are markedly decreased in patients with Alzheimer disease (106,107). A high density of 5-HT$_4$ receptors in the nucleus accumbens has led some to speculate that these receptors may be involved in the reward system and that they could influence drug self-administration behavior. Other central roles are also beginning to emerge; for example, repeated administration of antidepressants decreases the responsiveness of central 5-HT$_4$ receptors to activation (108). It would appear that therapeutic roles exist for both 5-HT$_4$ antagonists and 5-HT$_4$ agonists. However, it has been cautioned that the use of highly potent and selective 5-HT$_4$ agonists could result in cardiovascular side effects (107). If different 5-HT$_4$ receptor isoforms can be shown to mediate the various effects for which 5-HT$_4$ receptors have been implicated, the potential exists for the development of selective agents. Another problem associated with 5-HT$_4$ agents is their lack of oral bioavailability (109).

IBS is one of the most common gastrointestinal disorders in the United States, accounting for more than 3.5 million doctor visits per year (110). IBS is characterized by abdominal discomfort or pain associated with altered bowel function (i.e., constipation [IBS-C]), diarrhea (IBS-D), or alternating constipation and diarrhea. Until recently, treatment has been limited by the poor efficacy or side effects of available agents. Agents commonly used to treat IBS include laxatives, antispasmodics and smooth muscle relaxants (e.g., dicyclomine and hyoscyamine), and tricyclic antidepressants, but only 40% of patients are satisfied with these medications (110). Because more than 95% of all 5-HT in the body is found in the gut, it would seem logical that serotonergic agents should be of benefit in the treatment of IBS.

In general, peristaltic and secretory reflexes are initiated by 5-HT acting at 5-HT$_{1P}$ receptors (111)—that is, a population of 5-HT receptors found only in the gut. 5-HT$_3$ receptors are associated with excitation of the gastrointestinal tract, resulting in increased motility, secretion, and excitation (110) as well as signaling to the CNS (111); 5-HT$_3$ antagonists reduce colonic transit and improve fluid absorption (110). The 5-HT$_3$ antagonists tend to be constipating (111). The 5-HT$_4$ receptors mediate both excitatory and inhibitory effects on gut function (110).



Tegaserod

Alosetron (Fig. 11.16), a 5-HT$_3$ antagonist, and tegaserod (Zelnorm), a 5-HT$_4$ agonist, are two of the most recent entries for the treatment of IBS. Recent clinical trials have found that both agents are more effective than placebo for the treatment of IBS-C and IBS-D (110). Tegaserod acts by accelerating small bowel and colonic transit in patients with IBS. It is rapidly absorbed following oral administration, with a bioavailability of approximately 10%, except that food reduces the bioavailability by 40% to 65%. Peak plasma concentrations are reached in approximately 1 hour. Tegaserod is approximately 98% bound to plasma proteins, primarily to α_1-acid glycoprotein. Its volume of distribution is approximately 368 L/kg. Tegaserod undergoes presystemic acid-catalyzed hydrolysis in the stomach, followed by hepatic oxidation to its principal inactive metabolite (5-methoxyindole-3-carboxylic acid), its acyl glucuronide, and three isomeric *N*-glucuronides. The terminal half-life is approximately 11 hours following intravenous administration. Approximately two-thirds of the orally administered dose of tegaserod is excreted unchanged in feces,

with the remainder excreted in urine, primarily as glucuronide. Tegaserod exhibits dose-proportional kinetics when given twice daily at therapeutic doses for 5 days, with no relevant accumulation. No dosage adjustment is required in elderly patients or those with mild to moderate hepatic or renal impairment. No clinically relevant drug–drug interactions have been identified with tegaserod. However, in 2007, tegaserod was removed from the U.S. market due increased risks of heart attack or stroke and was made available only through a restricted distribution program. As of 2008, tegaserod is available only in emergency life-threatening situations.

5-HT$_5$ Receptors and Agents

Two 5-HT$_5$ receptors, expressed primarily in the mouse CNS, have been identified as 5-HT$_{5A}$ and 5-HT$_{5B}$ receptors (112). The two 5-HT$_5$ receptors exhibit 77% amino acid sequence homology but less than 50% homology with other cloned serotonergic receptors. To some extent, 5-HT$_5$ receptors appear to resemble 5-HT$_1$ receptors (e.g., high affinity for 5-HT and 5-CT); however, their low homology with other 5-HT$_1$ receptors suggests that they represent a distinct family of receptors. Only 5-HT$_{5A}$ receptors have been identified in humans (112). Human 5-HT$_{5A}$ receptors are G protein–coupled receptors with a complex second messenger system (113).

Radiolabeled LSD binds to both 5-HT$_{5A}$ and 5-HT$_{5B}$ receptors, with 5-CT having 10-fold greater affinity for human 5-HT$_{5A}$ receptors than 5-HT, which binds with modest affinity (K_i = 100 to 250 nM). The SAR for the binding of various ligands at 5-HT$_{5A}$ receptors has been reviewed elsewhere (114). Ergotamine and methiothepin bind with high affinity at human 5-HT$_{5A}$ receptors, whereas agents such as spiperone, sumatriptan, yohimbine, ketanserin, propranolol, zacopride, and clozapine bind with much lower affinity (K_i > 1,000 nM). To date, no 5-HT$_{5A}$–selective agonists or antagonists have been reported.

5-HT$_5$ Receptors: Clinical Implications

Pharmacologic functions of 5-HT$_5$ receptors are currently unknown. It has been speculated, on the basis of their localization, that they could be involved in motor control, feeding, anxiety, depression, learning, memory consolidation, adaptive behavior, and brain development (112). 5-HT$_{5A}$ receptors also could be involved in a neuronally driven mechanism for regulating astrocyte physiology with relevance to gliosis; disruption of 5-HT neuronal–glial interactions can be involved in the development of certain CNS pathologies, including Alzheimer disease, Down syndrome, and some drug-induced developmental deficits. Recent evidence indicates that genes that encode for the human 5-HT$_{5A}$ receptor could be involved in schizophrenia (115) and that spinal 5-HT$_{5A}$ receptors could have a role in nociception and control of pelvic floor musculature (116).

5-HT$_6$ Receptors and Agents

A novel G protein–coupled serotonergic receptor that appears to be localized exclusively in the CNS was cloned from rat brain and named 5-HT$_6$. This receptor exhibits only 40% transmembrane homology with 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1D}$, 5-HT$_{1E}$, 5-HT$_{2A}$, and 5-HT$_{2C}$ receptors. Both LSD and 5-HT display modest affinity for 5-HT$_6$ receptors (K_i ~ 50 to 150 nM). Of interest is that a number of typical and atypical antipsychotic agents and tricyclic antidepressants bind with K_i values in the nanomolar range.

The human 5-HT$_6$ receptor was cloned, and its gene structure, distribution, and pharmacology were found to be similar to those of the rat receptor (117). Like the rat receptor, the human receptor is positively coupled to adenylate cyclase. 5-HT binds at human 5-HT$_6$ receptors with moderate affinity (K_i = 65 nM), and one of the highest affinity, albeit nonselective, agents is the antipsychotic methiothepin (K_i = 0.4 nM). Agents that bind at human 5-HT$_6$ receptors with K_i less than 50 nM include 5-methoxytryptamine, bromocriptine, octoclothepin, the atypical antipsychotic agents clozapine and olanzapine, and the typical antipsychotics chlorpromazine, loxapine, and fluphenazine (118). Agents with K_i greater than 500 nM include 5-CT, sumatriptan, quipazine, ketanserin, 8-OH DPAT, haloperidol, risperidone, and mesulergine (118). A number of other antipsychotic agents, both typical and atypical, as well as antidepressants bind with low nanomolar affinity (114,117,118).

5-HT$_6$ Agonists and Antagonists

2-Ethyl-5-methoxy-*N*,*N*-dimethyltryptamine (EMDT) represented the first reasonably selective 5-HT$_6$ agonist (119), and Ro 04-6790 and Ro 63-0563 represented the first 5-HT$_6$–selective antagonists (120) (Fig. 11.20). These were soon followed by the antagonists SB-271046 (121), MS-245 (119,122), and PMDT (2-phenyl-5-methoxy-*N*,*N*-dimethyltryptamine, also known as BGC20-761) (119). Since then, work has continued on related structure types, leading to agents with greater metabolic stability and bioavailability (114). It should be noted that most of the early 5-HT$_6$ antagonists contained an arylsulfonamide moiety. Interestingly, the importance of this functionality was an independent discovery from several different laboratories, and this structural feature is now commonplace among many 5-HT$_6$ agents. In some cases, the sulfonamido moiety can be replaced by a sulfone (e.g., naphthylsulfones) (Fig. 11.20). Numerous structural modifications have now been reported, and one of the interesting findings is that the basic side chain of MS-245–type compounds can be moved to the indole 4-position (Fig. 11.20) (123,124) or removed altogether (e.g., amino-BSS) (114) with retention of antagonist action. 5-Sulfonamidotryptamines also bind with high affinity at 5-HT$_6$ receptors and, depending on the nature of their pendent substituents, act as 5-HT$_6$ agonists, partial agonists, or antagonists (125,126). A comprehensive review of 5-HT$_6$–related agents and their SARs has been published (127).

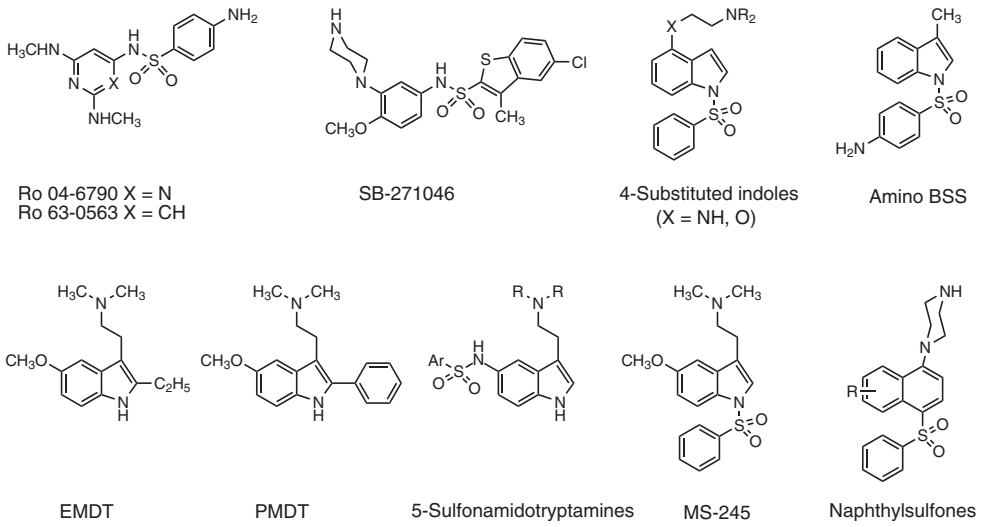


FIGURE 11.20 5-HT$_6$ receptor agonists and antagonists.

5-HT$_6$ Receptors: Clinical Implications

The exact clinical significance of 5-HT$_6$ receptors is unknown at this time. The high affinity of various antipsychotics, particularly atypical antipsychotics (see Chapter 14), and antidepressants suggests a possible connection between 5-HT$_6$ receptors and certain psychiatric disorders (128). The different binding profiles of atypical antipsychotics can be responsible for their atypical nature (e.g., D$_2$:5-HT$_{2A}$ ratio); for example, certain agents, such as clozapine, can be classified as atypical on the basis of their binding with higher affinity at 5-HT$_{2A}$ than at D$_2$ receptors. However, antipsychotics that produce the fewest extrapyramidal side effects in humans (e.g., clozapine, olanzapine, and fluperlapine) also possess high affinity for 5-HT$_6$ receptors (118). The atypical antipsychotic agent risperidone, which produces some extrapyramidal symptoms, binds with 1,000-fold higher affinity at 5-HT$_{2A}$ than at 5-HT$_6$ receptors; thus, affinity of agents for 5-HT$_6$ receptors can contribute to the difference between typical and certain atypical antipsychotics (118). Furthermore, preclinical studies indicate that combinations of a 5-HT$_6$ antagonist and a 5-HT$_{2A}$ antagonist were effective in models of psychosis and cognition (129). PMDT differs from most other 5-HT$_6$ antagonists in that it combines both types of antagonist action in the same molecule (114). In 5-HT$_6$ knockout mice, a behavioral syndrome is produced that seems to involve an increase in cholinergic function. Blocking the receptors in rats with 5-HT$_6$ antagonists produces a similar effect. This has led to speculation that one of the roles of 5-HT$_6$ receptors may be to control cholinergic neurotransmission and that 5-HT$_6$–selective antagonists could be useful in the treatment of anxiety and memory deficits. Other studies have shown that although 5-HT$_6$ antagonists could not influence basal levels of dopamine by themselves, they apparently increase amphetamine-induced increases in brain dopamine and can potentiate certain dopamine-mediated behavioral effects (130,131). The exact mechanisms underlying this process are not understood, but 5-HT$_6$ receptors have a role in neuronal plasticity (132) and can influence the actions of dopaminergic agents. Evidence also suggests that 5-HT$_6$ receptors could be involved in motor function, mood-dependent behavior, anxiety disorders, appetite control, anticonvulsant activity, and early growth processes involving 5-HT (117,119,123). With the newly identified 5-HT$_6$ agonists and antagonists, interest in the therapeutic potential of such agents is on the upswing.

5-HT$_7$ Receptors and Agents

Like 5-HT$_5$ receptors, 5-HT$_7$ receptors were once considered to be orphan receptors. Rat, mouse, guinea pig, and human 5-HT$_7$ receptors have now been cloned and are expressed mainly in the CNS (114,133). Structural analysis of the 5-HT$_7$ receptor suggests a seven transmembrane-spanning G protein–coupled receptor. These receptors are positively coupled to adenylate cyclase, and several splice variants have been identified. Alternative splicing in rat and human receptors results in four 5-HT$_7$ receptor isoforms that vary with respect to the length of their C-terminus chains (114,134). In rat, the isoforms are named 5-HT$_{7a}$, 5-HT$_{7b}$, and 5-HT$_{7c}$. Two of the isoforms are homologous in rat and human (5-HT$_{7a}$ and 5-HT$_{7b}$). The third human isoform is named 5-HT$_{7d}$. These different isoforms could have important functional consequences, such as different distribution or G protein–coupling efficiency or different susceptibility to desensitization (134,135). Apparently, the three human isoforms are pharmacologically indistinguishable and show similar affinity for various ligands. Evidence suggests that 5-HT$_7$ receptors are constitutively active and that the degree of constitutive activity could vary among the isoforms. Nonselective agents with K_i values at 5-HT$_7$ receptors of 10 nM or less include 5-HT, 5-methoxytryptamine, LSD, methiothepin, and mesulergine; those with K_i values in the range of 10 to 100 nM include 8-OH

DPAT (long considered a 5-HT_{1A}–selective agonist!), spiperone, ritanserin, metergoline, mianserin, and chlorpromazine; those with K_i values in the range of 100 to 1,000 nM include NAN-190, sumatriptan, and haloperidol; and those with K_i values of greater than 1,000 nM include 2-methyl 5-HT, tropisetron, pindolol, and ketanserin. Reportedly, 5-HT, 5-CT, and 8-OH DPAT act as agonists, whereas methiothepin, mianserin, mesulergine, ritanserin, spiperone (a 5-HT_{1A}, 2-HT_{2A}, and D_2 antagonist), NAN-190 (a 5-HT_{1A} antagonist), and clozapine act as antagonists. Numerous antidepressants and antipsychotic agents bind at 5-HT_7 receptors with nanomolar or subnanomolar affinity ($K_i \leq 10$ nM), including fluphenazine, acetophenazine, chlorprothixene, zotepine, clorotepine, clozapine, fluperlapine, pimozide, tiospirone, and risperidone (114,135).

5-HT_7 Antagonists

Several reasonably selective 5-HT_7 agents have been identified. The first reported 5-HT_7 antagonist was SB-258719 ($K_i \sim 30$ nM) (136), and attempts to optimize binding affinity and selectivity led to SB-269970 (*S*-isomer, K_i = 1.3 nM) (Fig. 11.21). Both compounds displayed some inverse agonist action. The high in vivo blood clearance of SB-269970 resulted in further structural modification, leading to compounds such as SB-656104 (*S*-isomer, K_i = 2 nM) (114). Another early series of 5-HT_7 antagonists was the DR compounds: DR4004 was the first of these to show activity as a competitive antagonist; structural modification resulted in others, including DR4365 ($K_i = 4$ nM) (137). Other antagonists Fig. 11 include phenylpyrrole-containing LCAPs (Fig. 11.21), which because of their structural similarity to other 5-HT_{1A} ligands could have been expected to—and do—bind at 5-HT_{1A} receptors (138); arylpiperazinosulfonamides; and tetrahydroisoquinolinylsulfonamides (139). Actually, the latter two types of compounds have been demonstrated to act as inverse agonists (139).

5-HT_7 Agonists

N-Arylaminoimidazolines (Fig. 11.22) were identified as the first 5-HT_7 agonists (140); however, they have not been pursued because of their profound effects on blood pressure and heart rate, which are probably a consequence of their affinity for α-adrenoceptors. Several new 5-HT_7 agonists have been recently reported, including the piperazinylhexanones (141) and 2-aminotetralins (142) (Fig. 11.22); the latter can function either as agonists (e.g., R = *n*Pr) or antagonists (e.g., R = Me), depending on the nature of the R group. Pharmacophore models have been proposed for 5-HT_7 agonists (143), antagonists (144), and inverse agonists (139).

5-HT_7 Receptors: Clinical Implications

Because of the previous unavailability of 5-HT_7–selective agents, the pharmacology of the 5-HT_7 system is still relatively unexplored. Nevertheless, studies with nonselective agents, 5-HT_7 receptor knockout animals, and some of the first few selective agents that were identified have provided some tantalizing clues (114,135,145–147). The 5-HT_7 receptors could be involved in mood and learning as well as in neuroendocrine and vegetative behaviors. The 5-HT_2 ligand ritanserin, certain tricyclic antidepressants (e.g., amitriptyline), classical antipsychotic agents (e.g., chlorpromazine), and nonclassical antipsychotic agents (e.g., clozapine) bind with K_i values of less than 100 nM (128). On this basis, it has been speculated that 5-HT_7 receptors may have a role in certain neuropsychiatric disorders. Consistent with these suggestions, 5-HT_7 receptors are sensitive to antidepressant treatment (148). The 5-HT_7 receptors have been implicated in serotonergic regulation of circadian rhythm, leading to suggestions that 5-HT_7–selective agents could be effective in the treatment of jet lag or sleep disorders of a circadian nature (149). 5-HT_7 receptors could also be involved in sleep disorders, anxiety, memory and cognition, epilepsy, pain, migraine, and thermoregulation. In the periphery, 5-HT produces both contraction and relaxation of coronary artery from various species (150). It has been proposed that relaxation of coronary artery may be mediated by 5-HT_7 receptors. Agents active at 5-HT_7 receptors could thus be effective in the treatment of coronary heart disease. Now that newer, more selective agents are finally available, many of these hypotheses can be further tested.

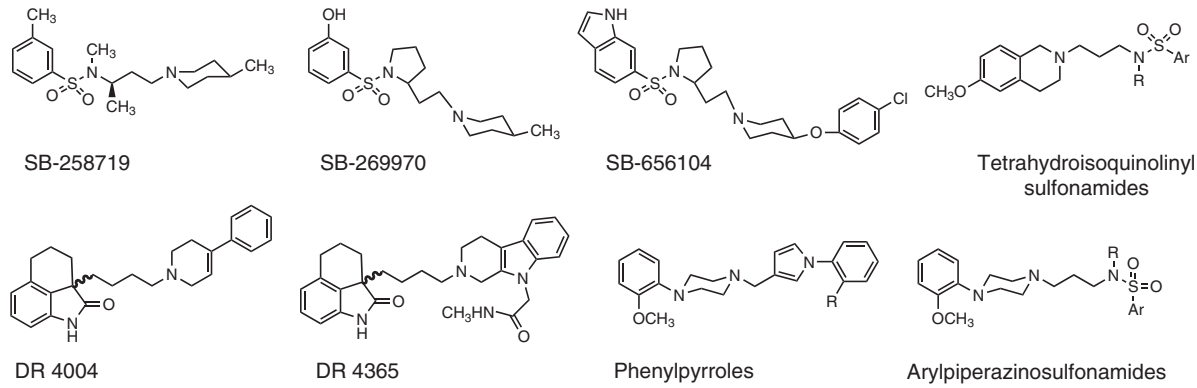


FIGURE 11.21 5-HT_7 receptor antagonists.

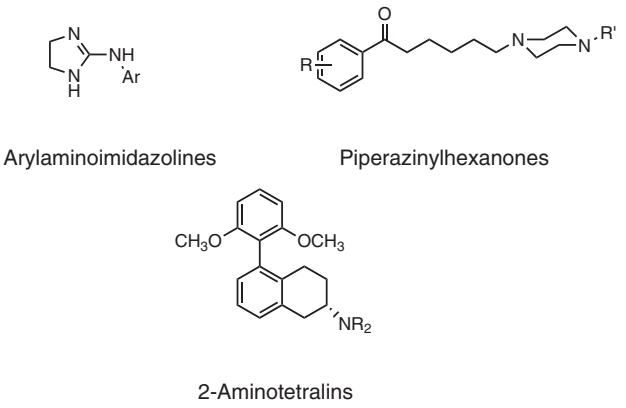
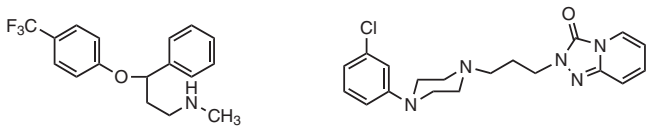


FIGURE 11.22 5-HT$_7$ receptor agonists.

THE SEROTONIN TRANSPORTER

The actions of 5-HT are terminated by its diffusion away from the synapse, by enzymatic degradation, and by reuptake into the presynaptic terminal (see Chapter 18 for further discussion). After reuptake, once 5-HT is inside the neuron, it can be re-stored in storage vesicles or metabolized. The 5-HT reuptake process involves a high-affinity transporter protein that is localized in the presynaptic terminal membrane. The 5-HT reuptake transporter (SERT) regulates the duration and magnitude of postsynaptic response to 5-HT. A different transporter is associated with different neurotransmitters (e.g., norepinephrine reuptake transporter [NET] transports norepinephrine). SERT has been cloned and expressed (138), and its putative structure is roughly similar to the general receptor structure shown in Figure 11.3 except that 1) it consists of 12 membrane-spanning helices, 2) both the amino terminus and the carboxy terminus are located on the intracellular side, and 3) it has an exaggerated extracellular loop between TM3 and TM4 (Fig. 11.23). SERT possesses approximately 50% homology with the NET and the dopamine transporter. For 5-HT transport, a ternary complex of protonated 5-HT, Na^+, and Cl^- binds to the transporter protein to form a quaternary complex; the transporter undergoes a conformational change to release 5-HT into the cytoplasm of the neuron (151).

The 5-HT transporter has been implicated as having a role in affective disorders (Chapter 18). Agents that block the transporter and, thereby, increase synaptic levels of 5-HT are useful for the treatment of depression, obsessive-compulsive behavior, and panic disorders. Tricyclic antidepressants (e.g., imipramine, desipramine) block the 5-HT transporter and the NET to varying degrees. Some display a preference for one transporter over the other, but most are nonselective (152). SSRIs display greater selectivity for SERT than for NET. The first SSRI to be used clinically was fluoxetine; several other agents have since become available. The SARs of SSRIs have been reviewed elsewhere (153); see Chapter 18 for further discussion of antidepressants and examples. Certain drugs of abuse (e.g., cocaine) also block the 5-HT transporter, although cocaine's primary mechanism of action likely involves the dopamine transporter.



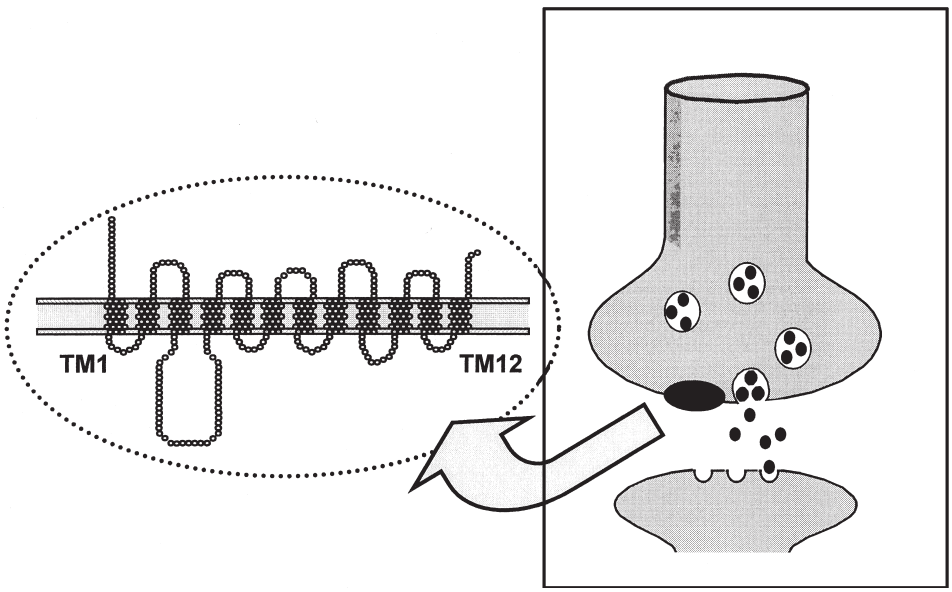


FIGURE 11.23 Schematic of a neuron showing the general location and basic structure (inset) of a serotonin transporter (SERT). Note that the transporter possesses 12 transmembrane-spanning helices (TM1–TM12). Both the amine terminus (attached to TM1) and the carboxy terminus (attached to TM12) are on the intracellular side.

Various tricyclic antidepressants and SSRIs, including fluoxetine, also bind at 5-HT_{2A} and 5-HT_{2C} receptors (154,155). The role, if any, derived from a direct interaction of these agents with 5-HT_2 receptors versus their interaction at SERT remains to be determined. 5-HT_2 antagonists typically downregulate 5-HT_2 receptors. The antidepressant trazodone, for example, is a weak SSRI but binds at 5-HT_2 receptors and is also a 5-HT_2 antagonist (155). The 5-HT_{2C} agonist *m*-chlorophenylpiperazine (*m*CPP) induces panic attacks in patients with panic disorder and increases obsessive compulsions in patients with obsessive-compulsive disorder (156), implicating a role for this specific 5-HT_{2C} subpopulation. The 5-HT_{2C} receptor antagonists could be useful targets for the development of novel agents to treat these disorders. This issue is complicated, however, by findings that trazodone is metabolized to *m*CPP and that, in some instances, trazodone possesses 5-HT_{2C} agonist properties (157). In any event, long-term treatment with tricyclic antidepressants (and MAOIs) leads to a downregulation in the number of 5-HT_2 receptors, the time course for which approximates the clinical response in depressed patients (152). Some SSRIs produce adaptive changes involving decreased responsiveness of 5-HT_2 receptors, whereas electroconvulsive therapy increases the number of 5-HT_2 receptors (152). Several 5-HT receptor populations have been implicated in the actions of antidepressants (e.g., 5-HT_1, 5-HT_2, 5-HT_6, and 5-HT_7), but SERT remains an attractive target for the development of novel psychotherapeutic agents.

SUMMARY

5-HT is a major neurotransmitter in the brain and is also involved in a number of peripheral actions. Seven families or populations of 5-HT receptors have been identified (5-HT_1 to 5-HT_7), and several are divided into distinct subpopulations (Table 11.2). Excluding splice variants, 14 different populations and subpopulations of 5-HT receptors have been cloned. Over the past 30 years, selective agonists and antagonists have been developed and identified for many of the subpopulations, but subpopulations remain for which selective agents have yet to be developed. The availability of such agents is important, because it aids functional investigations of the different 5-HT receptors. In addition to acting directly on 5-HT receptors, therapeutic agents with other mechanisms are available for influencing serotonergic transmission, including SSRIs and MAO inhibitors. Studies with 5-HT receptors have led to the introduction of agents useful for treating anxiety (e.g., buspirone), migraine (e.g., sumatriptan), irritable bowel syndrome (e.g. tegaserod), and chemotherapy-induced emesis (e.g., ondansetron); numerous other agents are currently in clinical trials for the treatment of depression, schizophrenia, and obsessive-compulsive and other disorders. Investigations also have led to a greater understanding of cardiovascular pharmacology, obesity, neurodegenerative disorders, aggression, sexual behavior, and drug abuse, just to mention a few examples. To reiterate a phrase from the introduction, "[I]t almost appears that 5-HT is involved in everything" (1).

SCENARIO: OUTCOME AND ANALYSIS

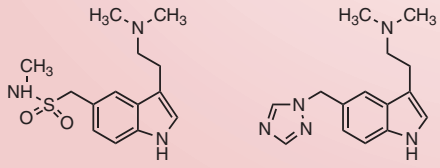
Outcome

Jill T. Johnson, PharmD, BCPS

The pharmacist referred her back to her physician to seek a different "triptan." The pharmacist also counseled the patient about using the drug for aborting migraines, not as prophylaxis. The pharmacist described medication overuse headaches that one can experience from taking triptans too often. Because the maximum dose of sumatriptan for migraines is 200 mg per day, the patient likely was experiencing overuse headaches. She was prescribed rizatriptan, which has worked to abort her migraines for many months. She takes rizatriptan only for aborting migraines and limits its use to not more than 15 mg in 24 hours. She now has fewer than 3 migraines in a month.

Chemical Analysis

Victoria Roche and S. William Zito



Sumatriptan Rizatriptan

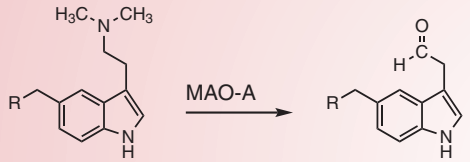
Both of the triptans associated with this scenario are indoleethylamines (tryptamines) that abort migraine headaches through their agonist action at 5-HT1D receptors. Sumatriptan was the first molecule in this class to be developed, and its selectivity for this receptor subtype, while acceptable, is not absolute. Other serotonergic receptors stimulated by sumatriptan include the 1B (formerly classified as a 1D receptor), 1A, and 1F subtypes, the latter of which also may be beneficial in treating migraines. Triptans work by constricting central vessels that dilate during migraine headaches. Overuse of vasoconstrictors results in rebound vasodilation, which could explain why MB's inappropriate (daily) use of sumatriptan gave her less relief from headache pain than expected.

The sulfonamide sidechain of sumatriptan produces a more polar triptan compared to other analogs that followed, and penetration of the blood–brain barrier under normal physiological conditions is low. Though rizatriptan's triazole substituent is certainly not the most lipophilic of rings, the drug's log P is higher than that of sumatripan (1.4 vs. 0.8). The more lipophilic structure confers a higher oral bioavailability on rizatriptan and allows a more facile penetration of the blood–brain barrier to reach central sites of action. The actual therapeutic impact of this enhanced distribution profile is, however, uncertain. The triazole ring of rizatriptan also confers a higher level of 5-HT1D selectivity than the methylsulfonamide moiety of sumatriptan.

SCENARIO: OUTCOME AND ANALYSIS *(Continued)*

As ethylamines, both sumatriptan and rizatriptan are vulnerable to oxidative deamination by MAO-A, and this is the major biotransformation route for both drugs. The *N*-dealkylated metabolite of rizatriptan (which forms before deamination) is known to be equally active with the parent structure, although it is generated to a minor (14%) extent.

Either triptan should be effective to abort MB's headaches if taken as directed, which is during the very early phase of a migraine when the pain level is low. Likewise, either triptan, if taken on a chronic basis rather than as needed, will promote rebound vasodilation and undermine therapeutic efficacy when it's needed most.



Triptan

Inactive deaminated metabolite

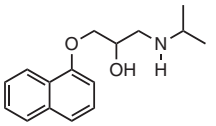
CASE STUDY

Victoria Roche and S. William Zito

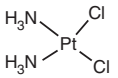
Sr. MT is a 61-year-old woman with newly diagnosed ovarian cancer, and is a member of the Sisters of St. Agnes. The mission of this order of nuns includes community outreach related to social justice and health care, and Sr. MT is beloved by all those whom she has served over the years, including members of your family. Sr. MT will soon begin cisplatin/doxorubicin chemotherapy known as the AP regimen. She has been told that these two drugs induce severe nausea and vomiting that, in addition to occurring during or shortly after therapy, can also be delayed for several days after drug administration. Sr. MT has moderate coronary artery disease, and she is currently taking rosuvastatin to lower serum lipids and is taking propranolol (β-blocker)/hydrochlorothiazide (diuretic) antihypertensive therapy. Though she believes the propranolol in her blood pressure medication is helping her feel less anxious about the discomforting side effects of her chemotherapy, she also wants to minimize the disabling nausea and vomiting so she can continue serving her community for as long as possible.

Recognizing the value of serotonergic receptor antagonists in the treatment of chemotherapy-induced nausea, you recall the structures of three serotonin-related agents you studied in Medicinal Chemistry class, and contemplate their value in easing your friend's way in the days ahead.

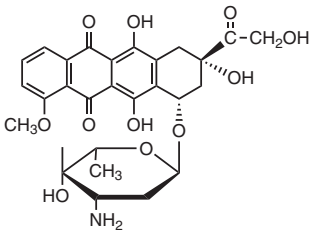
1. Conduct a thorough and mechanistic SAR analysis of the three therapeutic options in the case.
2. Apply the chemical understanding gained from the SAR analysis to this patient's specific needs to make a therapeutic recommendation.



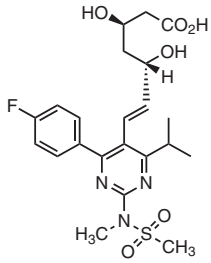
Propranolol



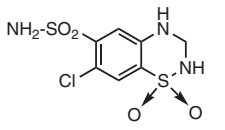
Cisplatin



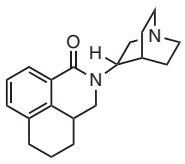
Doxorubicin



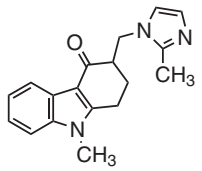
Rosuvastatin



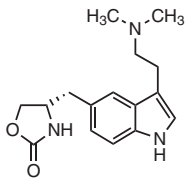
Hydrochlorothiazide



1



2



3

References

1. Rapport MR. The discovery of serotonin. Perspect Biol Med 1997;40:260–273.
2. Glennon RA, Dukat M. Serotonin receptors and drugs affecting serotonergic neurotransmission. In: Lemke TL, Williams DA, Roche VF, et al., eds. Foye's Principles of Medicinal Chemistry, 6th Ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2008:415–443.
3. Roth BL, ed. The Serotonin Receptors: From Molecular Pharmacology to Human Therapeutics. Totowa, NJ: Humana Press, 2006.
4. Nichols DE, Nichols CD. Serotonin receptors. Chem Rev 2008;108:1614–1641.
5. Frazer A, Hensler JG. Serotonin. In: Siegel GJ, Agranoff BW, Albers RW, et al., eds. Basic Neurochemistry. New York: Raven Press, 1993:283–308.
6. Peroutka SJ, Snyder SH. Multiple serotonin receptors: differential binding of [^{3}H]5-hydroxytryptamine, [^{3}H]lysergic acid diethylamide and [^{3}H]spiroperidol. Mol Pharmacol 1979;16:687–699.
7. Hoyer D, Hannon JP, Martin GR. Molecular, pharmacological, and functional diversity of 5-HT receptors. Pharmacol Biochem Behav 2002;71:533–534.
8. Hartig PR, Branchek TA, Weinshank RL. A subfamily of 5-HT$_{1D}$ receptor genes. Trends Pharmacol Sci 1992;3:152–159.
9. Hoyer D, Clarke DE, Fozard JR, et al. International Union of Pharmacology Nomenclature and Classification of receptors for 5-hydroxytryptamine (serotonin). Pharmacol Rev 1994;46:157–203.
10. Westkaemper RB, Roth BL. Structure and function reveal insights into the pharmacology of 5-HT receptors. In: Roth BL, ed. The Serotonin Receptors: From Molecular Pharmacology to Human Therapeutics. Totowa, NJ: Humana Press, 2006:39–58.
11. van Wijngaarden I, Soudijn W, Tulp MTM. 5-HT$_{1A}$ receptor ligands. In: Olivier B, van Wijngaarden I, Soudin W, eds. Serotonin Receptors and Their Ligands. Amsterdam: Elsevier, 1997:17–43.
12. Glennon RA, Dukat M. 5-HT$_1$ receptor ligands: update 1997. Invest Drugs Res Alerts 1997;2:351–372.
13. Glennon RA. Strategies for the development of selective serotonergic agents. In: Roth BL, ed. The Serotonin Receptors: From Molecular Pharmacology to Human Therapeutics. Totowa, NJ: Humana Press, 2006.
14. Glennon RA. Concepts for the design of 5-HT$_{1A}$ serotonin agonists and antagonists. Drug Dev Res 1992;6:251–274.
15. Glennon RA, Iversen L. Antidepressants. In: Abraham DJ, Rotella DP, eds. Burger's Medicinal Chemistry and Drug Discovery, 7th Ed, Vol 8, CNS Disorders. New York: Wiley, 2010:219–264.
16. Kuipers W. Structural characteristics of 5-HT$_{1A}$ receptors and their ligands. In: Olivier B, van Wijngaarden I, Soudin W, eds. Serotonin Receptors and Their Ligands. Amsterdam: Elsevier, 1997:45–64.
17. De Vry J. 5-HT$_{1A}$ receptor agonists: recent developments and controversial issues. Psychopharmacology 1995;121:1–26.
18. Caliendo G, Santagada V, Perissutti E, et al. Derivatives as 5-HT$_{1A}$ receptor ligands—past and present. Curr Med Chem 2005;12:1721–1753.
19. File SE. Recent developments in anxiety, stress, and depression. Pharmacol Biochem Behav 1996;54:3–12.
20. Jones BJ, Blackburn TP. The medical benefit of 5-HT research. Pharmacol Biochem Behav 2002;71:555–568.
21. Chessick CA, Allen MH, Thase M, et al. Azapirones for generalized anxiety disorder. Cochrane Database Syst Rev 2006;3:CD006115.
22. Picard M, Morisset S, Cloix JF, et al. Pharmacological, neurochemical, and behavioral profile of JB-788, a new 5-HT$_{1A}$ agonist. Neuroscience 2010;169:1337–1347.
23. Fletcher A, Cliffe I, Dourish CT. Silent 5-HT$_{1A}$ receptor antagonists: utility as research tools and therapeutic agents. Trends Pharmacol Sci 1993;14:441–448.
24. Assie M-B, Koek W. Effects of 5-HT$_{1A}$ receptor antagonists on hippocampal 5-hydroxytryptamine levels: (S)-WAY100135, but not WAY100635, has partial agonist properties. Eur J Pharmacol 1996;304:15–21.
25. Darmani NA, Reeves SL. The mechanism by which the selective 5-HT$_{1A}$ receptor antagonist S-(–)-UH-301 produces head-twitches in mice. Pharmacol Biochem Behav 1996;55:1–10.
26. Mundey MK, Fletcher A, Marsden CA. Effects of 8-OH DPAT and 5-HT$_{1A}$ antagonists WAY 100135 and WAY 100635 on guinea pig behavior and dorsal raphe 5-HT neuron firing. Br J Pharmacol 1996;117:750–756.
27. Arborelius L, Nomikos GG, Hertel P, et al. The 5-HT$_{1A}$ receptor antagonist (S)-UH-301 augments the increase in extracellular concentrations of 5-HT in the frontal cortex produced by both acute and chronic treatment with citalopram. Naunyn-Schmiedeberg Arch Pharmacol 1996;353:630–640.
28. Grignaschi G, Invernizzi RW, Fanelli E, et al. Citalopram-induced hypophagia is enhanced by blockade of 5-HT$_{1A}$ receptors: role of 5-HT$_{2C}$ receptors. Br J Pharmacol 1998;124:1781–1787.
29. Segrave R, Nathan PJ. Pindolol augmentation of selective serotonin reuptake inhibitors: accounting for the variability of results of placebo-controlled double-blind studies in patients with major depression. Human Psychopharmacol 2005;20:163–174.
30. Rasmussen K, Calligaro DO, Czachura JF, et al. The novel 5-hydroxytryptamine$_{1A}$ antagonist LY426965: effects on nicotine withdrawal and interactions with fluoxetine. J Pharmacol Exp Ther 2000;294:688–700.
31. Schoeffter P, Hoyer D. Interaction of arylpiperazines with 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1C}$, and 5-HT$_{1D}$ receptors. Do discriminatory 5-HT$_{1B}$ receptor ligands exist? Naunyn-Schmiedeberg Arch Pharmacol 1989;339:675–683.
32. Glennon RA, Westkaemper RB. 5-HT$_{1D}$ receptors: a serotonin receptor population for the 1990s. Drug News Perspect 1993;6:390–405.
33. Middlemiss DN, Beer MS, Matassa VG. 5-HT1D receptors. In: Olivier B, van Wijngaarden I, Soudin W, eds. Serotonin Receptors and Their Ligands. Amsterdam: Elsevier, 1997:101–138.
34. Adham N, Tamm JA, Salon JA, et al. A single point mutation increases the affinity of serotonin 5-HT$_{1D\alpha}$, 5-HT$_{1D\beta}$, 5-HT$_{1E}$, and 5-HT$_{1F}$ receptors for β-adrenergic antagonists. Neuropharmacology 1994;33:387–391.
35. Glennon RA, Dukat M, Westkaemper RB, et al. The binding of propranolol at 5-hydroxytryptamine$_{1D\beta}$ T355N mutant receptors may involve formation of two hydrogen bonds to asparagine. Mol Pharmacol 1996;49:198–206.
36. Hamel E. 5-HT$_{1D}$ receptors: pharmacology and therapeutic potential. Serotonin 1996;1:19–29.
37. Saxena PR, Tfelt-Hansen P. Success and failure of triptans. J Headache Pain 2001;2:3–11.
38. Ahn AH, Basbaum AI. Where do triptans act in the treatment of migraine? Pain 2005;115:1–4.
39. Villalon CM, Centurion D, Valdivia IF, et al. Migraine: pathophysiology, pharmacology treatment, and future trends. Curr Vasc Pharmacol 2003;1:71–84.
40. Mathew NT, Loder EW. Evaluating the triptans. Am J Med 2005;118(Suppl 1):28S–35S.
41. Ramadan NM, Skljarevski V, Phebus LA, et al. 5-HT$_{1F}$ receptor agonists in acute migraine treatment: a hypothesis. Cephalgia 2003;23:778–785.
42. Dukat M, Smith C, Herrick-Davis K, et al. Binding of tryptamine analogs at h5-HT$_{1E}$ receptors: a structure–affinity investigation. Bioorg Med Chem 2004;12:2545–2552.
43. Klein MT, Dukat M, Glennon RA, et al. Toward selective drug development for the human 5-HT$_{1E}$ receptor: a comparison of 5-HT$_{1E}$ and 5-HT$_{1F}$ receptor structure-affinity relationships. J Pharmacol Exp Ther 2011;337:860–867.
44. McAllister G, Castro JL. 5-HT$_{1E}$ and 5-HT$_{1F}$ receptors. In: Olivier B, van Wijngaarden I, Soudin W, eds. Serotonin Receptors and Their Ligands. Amsterdam: Elsevier, 1997:141–157.
45. Phebus LA, Johnson KW, Zgombick JM, et al. Characterization of LY344864 as a pharmacological tool to study 5-HT$_{1F}$ receptors: binding affinities, brain penetration, and activity in the neurogenic dural inflammation model of migraine. Life Sci 1997;61:2117–2126.
46. Nelson DL, Phebus LA, Johnson KW, et al. Preclinical pharmacological profile of the selective 5-HT$_{1F}$ receptor agonist lasmiditan. Cephalalgia 2010;30:1159–1169.
47. Sanders-Bush E, Fentress H, Hazelwood L. Serotonin 5-HT$_2$ receptors: molecular and genomic diversity. Mol Interventions 2003;3:319–330.
48. Leysen JE. 5-HT$_2$ receptors. Curr Drug Targets CNS Neurol Disord 2004;3:11–26.
49. Gavarini S, Becamel C, Chanrion B, et al. Molecular and functional characterization of proteins interacting with the C-terminal domains of 5-HT$_2$ receptors: emergence of 5-HT$_2$ "receptorsomes." Biol Cell 2004;96:373–381.
50. Roth B, Willins DL, Kristiansen K, et al. 5-hydroxytryptamine2-family receptors (5-hydroxytryptamine$_{2A}$, 5-hydroxytryptamine$_{2B}$, 5-hydroxytryptamine$_{2C}$): where structure meets function. Pharmacol Ther 1998;79:231–257.
51. van Wijngaarden I, Soudijn W. 5-HT$_{2A}$, 5-HT$_{2B}$, and 5-HT$_{2C}$ receptor ligands. In: Olivier B, van Wijngaarden I, Soudin W, eds. Serotonin Receptors and Their Ligands. Amsterdam: Elsevier, 1997:161–197.
52. Johnson MP, Wainscott DB, Lucaites VL, et al. Mutations of transmembrane IV and V serines indicate that all tryptamines do not bind to rat 5-HT$_{2A}$ receptors in the same manner. Mol Brain Res 1997;49:1–6.
53. Glennon RA, Seggel MR, Soine WH, et al. [^{125}I]-1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropane: an iodinated radioligand that specifically labels the agonist high-affinity state of 5-HT$_2$ serotonin receptors. J Med Chem 1988;31:5–7.
54. Glennon RA, Dukat M, El-Bermawy M, et al. Influence of amine substituents on 5-HT$_{2A}$ versus 5-HT$_{2C}$ binding of phenylalkyl- and indolylalkylamines. J Med Chem 1994;37:1929–1935.
55. Nichols DE, Frescas SP, Chemel BR, et al. High specific activity tritium-labeled N-(2-methoxybenzyl)-2,5-dimethoxy-4-iodophenethylamine (INBMeO): a high-affinity 5-HT$_{2A}$ receptor-selective agonist radioligand. Bioorg Med Chem 2008;16:6116–6123.
56. Glennon RA, Bondarev ML, Khorana N, et al. β-Oxygenated analogues of the 5-HT$_{2A}$ serotonin agonist 1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane. J Med Chem 2004;47:6034–6041.
57. Sharif NA. Serotonin-2 receptor agonists as novel ocular hypotensive agents and their cellular and molecular mechanisms of action. Curr Drug Targets 2010;11:978–993.
58. Kehne JH, Baron BM, Carr AA, et al. Preclinical characterization of the potential of the putative atypical antipsychotic MDL 100,907 as a potent 5-HT$_{2A}$ antagonist with a favorable CNS safety profile. J Pharmacol Exp Ther 1996;277:968–981.
59. Metwally KA, Dukat M, Egan CT, et al. Spiperone: influence of spiro ring substituents on 5-HT$_{2A}$ serotonin receptor binding. J Med Chem 1998;41:5084–5093.
60. Knight AR, Misra A, Quirk K, et al. Pharmacological characterisation of the agonist radioligand binding site of 5-HT$_{2A}$, 5-HT$_{2B}$ and 5-HT$_{2C}$ receptors. Naunyn Schmiedeberg Arch Pharmacol 2004;370:114–123.
61. Monti JM. Serotonin 5-HT$_{2A}$ receptor antagonists in the treatment of insomnia: present status and future prospects. Drugs Today 2010;46:183–193.

62. Landolt HP, Wehrle R. Antagonism of serotonergic 5-$HT_{2A/2C}$ receptors: mutual improvement of sleep, cognition and mood? Eur J Neurosci 2009;29:1795–1809.
63. Meltzer HY, Li Z, Kaneda Y, et al. Serotonin receptors: their key role in drugs to treat schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2003;27:1159–1172.
64. Reynolds GP. Receptor mechanisms in the treatment of schizophrenia. J Psychopharmacol 2004;18:340–345.
65. Leucht S, Corves C, Arbter D, et al. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet 2009;373:31–41.
66. Glennon RA. Do hallucinogens act as 5-HT_2 agonists or antagonists? Neuropsychopharmacology 1990;56:509–517.
67. Nelson DL, Lucaites VL, Wainscott DB, et al. Comparison of hallucinogenic phenylisopropylamine binding affinities at cloned human 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors. Naunyn-Schmiedeberg Arch Pharmacol 1999;359:1–6.
68. Smith RL, Canton H, Barrett RJ, et al. Agonist properties of N,N-dimethyltryptamine at serotonin 5-HT_{2A} and 5-HT_{2C} receptors. Pharmacol Biochem Behav 1998;61:323–330.
69. Newton RA, Phipps SL, Flanigan TP, et al. Characterisation of human 5-hydroxytryptamine$_{2A}$ and 5-hydroxytryptamine$_{2C}$ receptors expressed in the human neuroblastoma cell line SH-SY5Y: comparative stimulation by hallucinogenic drugs. J Neurochem 1996;67:2521–2531.
70. Nelson DL. The serotonin2 (5-HT_2) subfamily of receptors: pharmacological challenges. Med Chem Res 1993;3:306–316.
71. Wainscott DB, Sasso DA, Kursar JD, et al. [^{3}H]Rauwolscine: an antagonist radioligand for the cloned human 5-hydroxytryptamine$_{2B}$ (5-HT_{2B}) receptor. Naunyn-Schmeideberg Arch Pharmacol 1998;375:17–24.
72. Rothman RB, Baumann MH, Savage JE, et al. Evidence for possible involvement of 5-HT_{2B} receptors in the cardiac valvulopathy associated with fenfluramine and other serotonergic medications. Circulation 2000;102:2836–2841.
73. SetolaV,HufeisenSJ,Grande-AllenKJ,etal.3,4-Methylenedioxymethamphetamine (MDMA, "Ecstasy") induces fenfluramine-like proliferative actions on human cardiac valvular interstitial cells in vitro. Mol Pharmacol 2003;63:1223–1229.
74. Auclair AL, Cathala A, Sarrazin F, et al. The central serotonin 2B receptor: a new pharmacological target to modulate the mesoaccumbens dopaminergic pathway activity. J Neurochem 2010;114:1323–1332.
75. Duxon MS, Flanigan TP, Reavley AC, et al. Evidence for expression of the 5-hydroxytryptamine-2B receptor system in the rat central nervous system. Neuroscience 1997;76:323–329.
76. Lee J, Jung ME, Lee J. 5-HT_{2C} receptor modulators: a patent survey. Expert Opin Ther Pat 2010;20:1429–1455.
77. Bös M, Jenck F, Martin JR, et al. Novel agonists of 5-HT_{2C} receptors. Synthesis and biological evaluation of 2-(indol-1-yl)-1-methylethylamines and 2-(indeno[1,2-b]pyrrol-1-yl)-1-methylethylamines. Improved therapeutics for obsessive compulsive disorder. J Med Chem 1997;40:2762–2769.
78. Chang-Fong J, Addo J, Dukat M, et al. Evaluation of isotryptamine derivatives at 5-HT_2 serotonin receptors. Bioorg Med Chem Lett 2002;12:155–158.
79. Martin JR, Bos M, Jenck F, et al. 5-HT_{2C} receptor agonists: pharmacological characteristics and therapeutic potential. J Pharmacol Exp Ther 1998;286:913–924.
80. Dunlop J, Marquis KL, Lim HK, et al. Pharmacological profile of the 5-HT2C receptor agonist WAY-163909; therapeutic potential in multiple indications. CNS Drug Rev 2006;12:167–177.
81. Smith BM, Smith JM, Tsai JH, et al. Discovery and structure-activity relationship of (1*R*)-8-chloro-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (lorcaserin), a selective 5-HT_{2C} receptor agonist for the treatment of obesity. J Med Chem 2008;51:305–313.
82. Booth RG, Fang L, Huang Y, et al. (1*R*,3*S*)-(-)-*trans*-PAT: a novel full-efficacy serotonin 5-HT_{2C} receptor agonist with 5-HT_{2A} and 5-HT_{2B} receptor inverse agonist/antagonist activity. Eur J Pharmacol 2009;61:1–9.
83. Wood MD, Reavill C, Trail B, et al. SB-243213; a selective 5-HT_{2C} receptor inverse agonist with improved anxiolytic profile: lack of tolerance and withdrawal anxiety. Neuropharmacology 2001;41:186–199.
84. Bromidge SM, Dabbs S, Davies DT, et al. Biarylcarbamoylindolines are novel and selective 5-HT_{2C} receptor inverse agonists: identification of 5-methyl-1-[[2-[(2-methyl-3-pyridyl)oxy]-5-pyridyl]carbamoyl]-6-trifluoromethylindoline (SB-243213) as a potential antidepressant/ anxiolytic agent. J Med Chem 2000;43:1123–1134.
85. Hale A, Corral RM, Mencacci C, et al. Superior antidepressant efficacy results of agomelatine versus fluoxetine in severe MDD patients: a randomized, double-blind study. Int Clin Psychopharmacol 2010;25:305–314.
86. Lummis SC. The transmembrane domain of the 5-HT_3 receptors: its role in selectivity and gating. Biochem Soc Trans 2004;32(Part 3):535–539.
87. Walstab J, Rappold G, Niesler B. 5-HT_3 receptors: role in disease and target of drugs. Pharmacol Ther 2010;128:146–169.
88. Farber L, Haus U, Spath M, et al. Physiology and pathophysiology of the 5-HT_3 receptor. Scand J Rheumatol Suppl 2004;119:2–8.
89. Holbrook JD, Gill CH, Zebda N, et al. Characterisation of 5-HT_{3C}, 5-HT_{3D} and 5-HT_{3E} receptor subunits: evolution, distribution and function. J Neurochem 2009;108:384–396.
90. Dukat M. 5-HT_3 serotonin receptor agonists: a pharmacophoric journey. Curr Med Chem 2004;4:77–94.
91. Campiani G, Cappelli A, Nacci V, et al. Novel and highly potent 5-HT_3 receptor agonists based on a pyrroloquinozaline structure. J Med Chem 1997;40:3670–3678.
92. Katounina T, Besret L, Dhilly M, et al. Synthesis and biological investigations of [^{18}F]MR 18445, a 5-HT_3 receptor partial agonist. Bioorg Med Chem 1998;6:789–795.
93. Gozlan H. 5-HT_3 receptors. In: Olivier B, van Wijngaarden I, Soudin W, eds. Serotonin Receptors and Their Ligands. Amsterdam: Elsevier, 1997:221–258.
94. Gaster LM, King FD. Serotonin 5-HT_3 and 5-HT_4 receptor antagonists. Med Res Rev 1997;17:163–214.
95. Heidempergher F, Pillan A, Pinciroli V, et al. Phenylimidazolidin-2-one derivatives as selective 5-HT_3 receptor antagonists and refinement of the pharmacophore model for 5-HT_3 receptor binding. J Med Chem 1997;40:3369–3380.
96. De Wit R, Aapro M, Blower PR. Is there a pharmacological basis for differences in 5-HT_3-receptor antagonist efficacy in refractory patients? Cancer Chemother Pharmacol 2005;56:231–238.
97. Jordin K, Kasper C, Schmoll H-J. Chemotherapy-induced nausea and vomiting: current and new standards in antiemetic prophylaxis and treatment. Eur J Cancer 2005;41:199–205.
98. Aapro M, Blower P. 5-Hydroxytryptamine type-3 antagonists for chemotherapy-induced and radiotherapy-induced nausea and vomiting. Cancer 2005;104:1–13.
99. Aapro M. Optimizing antiemetic therapy: what are the problems and how can they be overcome? Curr Med Res Opin 2005;21:885–897.
100. Bockaert J, Claeysen S, Compau V, et al. 5-HT_4 receptors. Curr Drug Targets CNS Neurol Disord 2004;3:39–51.
101. Gerald C, Adham N, Kao H-T, et al. The 5-HT_4 receptor: molecular cloning and pharmacological classification of two splice variants. EMBO J 1995;14:2806–2815.
102. Blondel O, Gastineau M, Dahmoune Y, et al. Cloning, expression, and pharmacology of four human 5-hydroxytryptamine$_4$ receptor isoforms produced by alternative splicing in the carboxyl terminus. J Neurochem 1998;70:2252–2261.
103. Eglen RM, Bonhaus DW, Clark RD, et al. (R) and (S) RS 56532: mixed 5-HT_3 and 5-HT_4 receptor ligands with opposing enantiomeric selectivity. Neuropharmacology 1994;33:515–526.
104. Langlois M, Fischmeister R. 5-HT_4 receptor ligands: applications and new prospects. J Med Chem 2003;30:319–344.
105. Lopez-Rodriguez ML, Benhamu B, Morcillo MJ, et al. 5-HT_4 receptor antagonists: structure–affinity relationships and ligand receptor interactions. Curr Top Med Chem 2002;2:625–641.
106. Maillet M, Robert SJ, Lezoualch F. New insights into serotonin 5-HT_4 receptors: a novel therapeutic target for Alzheimer's disease? Curr Alzheimer Res 2004;1:79–85.
107. Eglen RM, Wong EHF, Dumuis A, et al. Central 5-HT_4 receptors. Trends Pharmacol Sci 1995;16:391–398.
108. Bijak M, Tokarski K, Maj J. Repeated treatment with antidepressant drugs induces subsensitivity to the excitatory effect of 5-HT_4 receptor activation in the rat hippocampus. Naunyn-Schmeideberg Arch Pharmacol 1997;355:14–19.
109. Schaus JM, Thompson DC, Bloomquist WE, et al. Synthesis and structure–activity relationships of potent and orally active 5-HT_4 receptor antagonists: indazole and benzimidazolone derivatives. J Med Chem 1998;41:1943–1955.
110. Johanson JF. Options for patients with irritable bowel syndrome: contrasting traditional; and novel serotonergic therapies. Neurogastroenterol Motil 2004;16:701–711.
111. Gershon MD. Review article: serotonin receptors and transporters—roles in normal and abnormal gastrointestinal motility. Aliment Pharmacol Ther 2004;20(Suppl 7):3–14.
112. Nelson DL. 5-HT_5 receptors. Curr Drug Targets CNS Neurol Disord 2004;3:53–58.
113. Raymond JR, Turner JH, Gelasca AK, et al. 5-HT receptor signal transduction pathways. In: Roth BL, ed. The Serotonin Receptors: From Molecular Pharmacology to Human Therapeutics. Totowa, NJ: Humana Press, 2006:143–206.
114. Glennon RA. Higher-end serotonin receptors: 5-HT_5, 5-HT_6, and 5-HT_7. J Med Chem 2003;46:2795–2812.
115. Dubertret C, Hanoun N, Ades J, et al. Family-based association studies between 5-HT_{5A} receptor gene and schizophrenia. J Psychiat Res 2004;38:371–376.
116. Doly S, Fischer J, Brisorgueh M-J, et al. 5-HT_{5A} receptor localization in the rat spinal cord suggests a role in nociception and control of pelvic floor musculature. J Comp Neurol 2004;476:316–329.
117. Woolley ML, Marsden CA, Fone KC. 5-HT_6 receptors. Curr Drug Targets CNS Neurol Disord 2004;3:59–79.
118. Kohen R, Metcalf MA, Khan N, et al. Cloning, characterization, and chromosomal localization of a human 5-HT6 serotonin receptor. J Neurochem 1996;66:47–56.

119. Glennon RA, Lee M, Rangisetty JB, et al. 2-Substituted tryptamines: agents with selectivity for 5-HT_6 serotonin receptors. J Med Chem 2000;43:1011–1018.
120. Sleight AJ, Boess FG, Bos M, et al. Characterization of Ro 04-6790 and Ro 63-0563; potent and selective antagonists at human and rat 5-HT_6 receptors. Br J Pharmacol 1998;124:556–562.
121. Bromidge SM, Brown AM, Clarke SE, et al. 5-Chloro-*N*-(4-methoxy-3-piperazin-1-yl-phenyl)-3-methyl-2-benzothiophenesulfonamide (SB-271046): a potent, selective, and orally bioavailable 5-HT_6 receptor antagonist. J Med Chem 1999;42:202–205.
122. Tsai Y, Dukat M, Slassi A, et al. *N*1-(Benzenesulfonyl)tryptamines as novel 5-HT_6 antagonists. Bioorg Med Chem Lett 2000;10:2295–2299.
123. Russell MGN, Baker RJ, Barden L, et al. *N*-Arylsulfonylindole derivatives as serotonin 5-HT_6 receptor ligands. J Med Chem 2001;44:3881–3895.
124. Zhou P, Yan Y, Bernotas R, et al. 4-(2-Aminoethoxy)-*N*-(phenylsulfonyl) indoles as novel 5-HT_6 receptor ligands. Bioorg Med Chem Lett 2005;15:1393–1396.
125. Holenz J, Merce R, Diaz JL, et al. Medicinal chemistry driven approaches toward novel and selective 5-HT_6 receptor ligands. J Med Chem 2005;48:1781–1795.
126. Cole DC, Lennox WJ, Lombardi S, et al. Discovery of 5-arylsulfonamido-3-(pyrrolidin-2-ylmethyl)-1*H*-indole derivatives as potent, selective 5-HT_6 receptor agonists and antagonists. J Med Chem 2005;48:353–356.
127. Glennon RA, Siripurapu U, Roth BL, et al. The medicinal chemistry of 5-HT_6 receptor ligands with a focus on arylsulfonyltryptamines. Curr Topics Med Chem 2010;10:579–595.
128. Roth BL, Craigo SC, Choudhary MS, et al. Binding of typical and atypical antipsychotic agents to 5-hydroxytryptamine-6 and 5-hydroxytryptamine-7 receptors. J Pharmacol Exp Ther 1994;268:1403–1410.
129. Hedley L, Kamphuis S, Secchi R, et al. The combined effects of the 5-HT_{2A} antagonist MDL 100,907 and the selective 5-HT_6 receptor antagonist Ro 4368554 in rat models of psychosis and cognition. Behav Pharmacol 2005;16(Suppl 1):S23.
130. Frantz KJ, Hannson KJ, Stouffer DG, et al. 5-HT_6 receptor antagonism potentiates the behavioral and neurochemical effects of amphetamine but not cocaine. Neuropharmacology 2002;42:170–180.
131. Dawson LA, Nguyen HQ, Li P. Potentiation of amphetamine-induced changes in dopamine and 5-HT by a 5-HT_6 receptor antagonist. Brain Res Bull 2003;59:513–521.
132. Svenningsson P, Tzavara ET, Liu F, et al. DARPP-32 mediates serotonergic neurotransmission in the forebrain. Proc Nat Acad Sci USA 2002;99:3188–3193.
133. Eglen RM, Jasper JR, Chang DJ, et al. The 5-HT_7 receptor: orphan found. Trends Pharmacol Sci 1997;18:104–107.
134. Heidmann DE, Metcalf MA, Kohen R, et al. Four 5-hydroxytryptamine$_7$ (5-HT_7) receptor isoforms in human and rat produced by alternative splicing. Species differences due to altered intron–exon organization. J Neurochem 1997;68:1372–1381.
135. Vanhoenacker P, Haegeman G, Leysen JE. 5-HT_7 receptors: current knowledge and future prospects. Trends Pharmacol Sci 2000;21:70–77.
136. Forbes IT, Dabbs S, Duckworth DM, et al. *R*-3,*N*-Dimethyl-*N*-[1-methyl-3-(4-methylpiperidin-1-yl)propyl]benzenesulfonamide: the first selective 5-HT_7 receptor antagonist. J Med Chem 1998;41:655–657.
137. Kikuchi C, Ando T, Watanabe T, et al. 2α-[4-(Tetrahydropyrodoindol-2-yl) butyl]tetrahydrobenzindole derivatives: new, selective, antagonists of the 5-hydroxytryptamine$_7$ receptor. J Med Chem 2002;45:2197–2206.
138. Paillet-Loilier M, Fabis F, Lepailleur A, et al. Phenylpyrroles, a new chemolibrary virtual screening class of 5-HT_7 receptor ligands. Bioorg Med Chem Lett 2005;15:3753–3757.
139. Vermeulen ES, van Smeden M, Schmidt AW, et al. Novel 5-HT7 receptor inverse agonists. Synthesis and molecular modeling of arylpiperazine- and 1,2,3,4-tetrahydroisoquinolin-based arylsulfonamides. J Med Chem 2004;47:5451–5466.
140. Parikh V, Welch WM, Schmidt AW. Discovery of a series of (4,5-dihydroimidazol-2-yl)biphenylamine 5-HT_7 agonists. Bioorg Med Chem Lett 2003;13:269–271.
141. Perrone R, Berardi F, Colabufo NA, et al. Synthesis and structure–affinity relationships of 1-[ω-(4-aryl-1-piperazinyl)alkyl]-1-aryl ketones as 5-HT_7 receptor ligands. J Med Chem 2003;46:646–649.
142. Holmberg P, Sohn D, Leideborg R, et al. Novel 2-aminotetralin and 3-aminochroman derivatives as selective serotonin 5-HT_7 receptor agonists and antagonists. J Med Chem 2004;47:3927–3930.
143. Vermeulen ES, Schmidt AW, Sprouse JS, et al. Characterization of the 5-HT_7 receptor. Determination of the pharmacophore for 5-HT_7 receptor agonism and CoMFA-based modeling of the agonist binding site. J Med Chem 2003;46:5365–5374.
144. Lopez-Rodriguez ML, Porras E, Morcillo MJ, et al. Optimization of the pharmacophore model for 5-HT_7R antagonism. Design and synthesis of new naphtholoactam and naphthosultam derivatives. J Med Chem 2003;46:5638–5650.
145. Pouzet B. SB-258741: a 5-HT_7 receptor antagonist of potential clinical interest. CNS Drug Rev 2002;8:90–100.
146. Thomas DR, Hagan JJ. 5-HT_7 receptors. Curr Drug Targets CNS Neurol Disord 2004;3:81–90.
147. Hedlund PB, Sutcliffe JG. Functional, molecular and pharmacological advances in 5-HT_7 receptor research. Trends Pharmacol Sci 2004;25: 481–486.
148. Sleight AJ, Carolo C, Petit N, et al. Identification of 5-hydroxytryptamine$_7$ receptor binding sites in rat hypothalamus: sensitivity to chronic antidepressant treatment. Mol Pharmacol 1995;47:99–103.
149. Lovenberg TW, Baron BM, de Lecea L, et al. A novel adenylyl cyclase–activating serotonin receptor (5-HT_7) implicated in the regulation of mammalian circadian rhythms. Neuron 1993;11:449–458.
150. Cushing DJ, Zgombick JM, Nelson DL, et al. LY215840, a high-affinity 5-HT_7 receptor ligand blocks serotonin-induced relaxation in canine coronary artery. J Pharmacol Exp Ther 1996;277:1560–1566.
151. Barker EL, Blakely RD. Norepinephrine and serotonin transporters. In: Bloom FE, Kupfer DJ, eds. Psychopharmacology: The Fourth Generation of Progress. New York: Raven Press, 1995:321–333.
152. Maes M, Meltzer HY. The serotonin hypothesis of major depression. In: Bloom FE, Kupfer DJ, eds. Psychopharmacology: The Fourth Generation of Progress. New York: Raven Press, 1995:933–944.
153. Soudjin W, van Wijngaarden I. 5-HT transporter. In: Olivier B, van Wijngaarden I, Soudin W, eds. Serotonin Receptors and Their Ligands. Amsterdam: Elsevier, 1997:327–361.
154. Stanford SC. Prozac: panacea or puzzle? Trends Pharmacol Sci 1996;17:150–154.
155. Jenck F, Moreau JL, Mutel V, et al. Brain 5-HT_{1C} receptors and antidepressants. Prog Neuropsychopharmacol Biol Psychiatry 1994;18:563–574.
156. Broekkamp CLE, Leysen D, Peeters BWMM, et al. Prospects for improved antidepressants. J Med Chem 1995;38:4615–4633.
157. Marcoli M, Maura G, Tortarolo M, et al. Trazodone is a potent agonist at 5-HT_{2C} receptors mediating inhibition of the *N*-methyl-D-aspartate/nitric oxide/cyclic GMP pathway in rat cerebellum. J Pharmacol Exp Ther 1998;285:983–986.