Serotonin Receptors and Drugs Affecting Serotonergic Neurotransmission

Richard A. Glennon and Malgorzata Dukat

Drugs Covered in This Chapter*

**Antiemetic drugs (5-HT₃ receptor antagonists)**
- Alosetron
- Dolasetron
- Granisetron
- Ondansetron
- Palonosetron
- Tropisetron

**Drug for the treatment of irritable bowel syndrome (5-HT₄ agonists)**
- Rizatriptan
- Sumatriptan
- Zolmitriptan

**Drugs for the treatment of migraine (5-HT₁D/1F receptor agonists)**
- Almotriptan
- Eletriptan
- Frovatriptan
- Naratriptan
- Zolmitriptan

**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, 1-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, monoamine oxidase
- MAOI, monoamine oxidase inhibitor
- nM, nanomoles/L
- NET, norepinephrine reuptake transporter
- PMDT, 2-phenyl-5-methoxy-N,N-dimethyltryptamine
- RICHARD A. GLENNON AND MALGORZATA DUKAT

*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) and (+)-Lysergic acid diethylamide (LSD)](image)

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 and

<table>
<thead>
<tr>
<th>TABLE 11.1 Some Indications and Treatment Claims for Novel Serotonergic Agents in the Patent Literature</th>
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<td>Drug abuse</td>
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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 substance 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-monoxygenase) 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-acetylsertotonin, which undergoes O-methylation by 5-hydroxyindole-O-methyltransferase to melatonin.
Distinct types of melatonin receptors (MTRs; MTR1/MTR2) 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 (MAOIs) 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.

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-HT1 through 5-HT7, 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-HT1 and 5-HT2 receptors than about 5-HT6 and 5-HT7 receptors. Factors contributing to our current lack of understanding about
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*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-HT₁ₐ or 5-HT₁₇ receptors) is the absence of agonists and/or antagonists with selectivity for these receptors.

**History**

Tritiated LSD ([³H]LSD), the first radioligand used to identify a brain 5-HT binding site, suggested it could be a “hallucinogen receptor.” Tritiated 5-HT ([³H]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 [³H]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](image)

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 antagonists tended to display higher affinity for [³H]5-HT–labeled sites, whereas 5-HT antagonists displayed higher affinity for [³H]spiperone-labeled sites, led to the conclusion that [³H]5-HT and [³H]spiperone label two distinct populations (not conformations) of sites, termed 5-HT₁ and 5-HT₂ receptors, respectively (6). Soon thereafter, 5-HT receptors were found to consist of 5-HT₁, 5-HT₂, 5-HT₃, 5-HT₄, 5-HT₅, and 5-HT₆ 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-E (because phenoxbenzamine 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-HT₁ receptors, and 5-HT-M receptors were eventually renamed 5-HT₁ receptors. By the early 1980s, 5-HT₁, 5-HT₂, 5-HT₃, 5-HT₄, and 5-HT₅ 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 homology 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-HT₁ Receptor Family

5-HT₁ receptors were one of the first two populations of 5-HT receptors to be identified (6), and 5-HT₁ₐ, 5-HT₁₇, 5-HT₁₉, 5-HT₁ₖ, 5-HT₁₇, and 5-HT₁₉ receptor subpopulations have since been defined. 5-HT₁₉ receptors were initially described, but subsequent classification (employing the previously mentioned criteria) resulted in their being moved to the 5-HT₂ receptor family and being renamed 5-HT₆ receptors. With the exception of 5-HT₁₉ receptors, all 5-HT₁ receptors exhibit high affinity for 5-carboxamidotryptamine (5-CT).

5-HT₁α Receptors and Agents

5-HT₁α receptors are, as are all 5-HT receptors except for 5-HT₁α receptors, G protein–coupled receptors that consist of seven transmembrane-spanning helices connected...
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 second messenger system, and the 5-HT1A receptors located in the raphe nuclei correspond to somatodendritic autoreceptors (Fig. 11.4). 5-HT1A 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-HT1A receptors with high affinity (see below). Cloned 5-HT1A receptors and 5-HT1A receptor ligands have been reviewed (9,10–18).

**Structure–Activity Relationship of 5-HT1A Receptor Agonists**

![8-OH DPA T superimposed on Serotonin](image)

Numerous 5-HT–related tryptamines bind with high affinity at 5-HT1A receptors, but most are notoriously nonselective. One of the most selective 5-HT1A 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-HT1A 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-HT1A receptor action. Although numerous 8-OH DPAT

![FIGURE 11.3](image)  
**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.

![FIGURE 11.4](image)  
**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.
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 phenyl or some other aryl or heteroaryl substituent (14).

**Structure–activity Relationships of 5-HT\(_{1A}\) Receptor Antagonists**

Many 5-HT\(_{1A}\) receptor antagonists possess a 2-methoxy-phenyl 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...
new classes of $5\text{-HT}_{1A}$ receptor antagonists, termed “silent antagonists,” because they are “seemingly” without any $5\text{-HT}_{1A}$ agonist action. The alkylpiperidine spiperone is a $5\text{-HT}_{1A}$ antagonist, but spiperone displays high affinity for $\alpha_2$-dopamine receptors and $5\text{-HT}_{1A}$ receptors.

Molecular graphics studies suggest that 5-HT and $5\text{-HT}_{1A}$ receptor agonists interact with amino acid residues associated with helices 4, 5, and 6 (Site 1), whereas $5\text{-HT}_{1A}$ 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-H\text{-HT}_{1A} Receptor Agonists: Clinical Significance**

In preclinical studies, $5\text{-HT}_{1A}$ receptor agonists have demonstrated antianxiety, antidepressant, antiaggressive, and perhaps, anticonvulsant, antiinflammatory, and neuroprotective properties (15,17). Evidence also exists indicating that $5\text{-HT}_{1A}$ 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 $5\text{-HT}_{1A}$ 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). $5\text{-HT}_{1A}$ receptor agonists 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 $5\text{-HT}_{1A}$ receptor (partial) agonists could involve, primarily, presynaptic somatodendritic $5\text{-HT}_{1A}$ receptors, whereas the antidepressant actions of $5\text{-HT}_{1A}$ receptor agents could primarily involve postsynaptic $5\text{-HT}_{1A}$ receptors (17). Gepirone produced marked improvement in depressed patients, and buspirone was effective in the treatment of mixed anxious-depressive patients. 5-HT, and, possibly, $5\text{-HT}_{1A}$ receptors have been implicated in obsessive-compulsive disorders.

**5-H\text{-HT}_{1A} Receptor Antagonists: Clinical Significance**

A new direction in $5\text{-HT}_{1A}$ receptor research targets the development of $5\text{-HT}_{1A}$ receptor antagonists (15,23). Agents such as the acknowledged dopaminergic antagonist spiperone and the $\beta$-adrenoceptor antagonist propranolol were among the first to see application as $5\text{-HT}_{1A}$ receptor antagonists. These agents are, obviously, nonselective; they bind at other populations of neurotransmitter receptors with comparable or higher affinities than they display at $5\text{-HT}_{1A}$ receptors. The next generation of $5\text{-HT}_{1A}$ 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 (-)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 (-)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 $\beta$-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-H\text{-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 (25). Like 5-HT$_{1A}$ receptors, they are negatively coupled to adenylyl cyclase. (See 5-HT$_{1D}$ Receptors for further related discussion.)

**5-H\text{-HT}_{1D} Receptors: Clinical Significance**

Rodent 5-HT$_{1D}$ 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).
human subpopulations of 5-HT_{1D} receptors, 5-HT_{1Da} and 5-HT_{1Db} 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_{1Da} receptors have been renamed h5-HT_{1D}. Most agents that bind at 5-HT_{1B} receptors bind at 5-HT_{1D} receptors.

Curious exceptions have been noted with certain aryloxyalkylamines, however, such as the β-blockers, propranolol and pindolol, which exhibit very low affinity (Kᵢ ~ 5,000 nM) for human (h) 5-HT_{1D} receptors (94,35). 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.

**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 sumatriptan. 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 [³H]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_{1E}-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<sub>1A</sub> Agonists (the Triptans)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Sumatriptan</th>
<th>Zolmitriptan</th>
<th>Naratriptan</th>
<th>Rizatriptan</th>
<th>Almotriptan</th>
<th>Frovatriptan</th>
<th>Eletriptan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade name</td>
<td>Imitrex</td>
<td>Zomig</td>
<td>Maxalt1</td>
<td>Axert</td>
<td>Frova</td>
<td>Relpax</td>
<td></td>
</tr>
<tr>
<td>LogP (calc)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.7 ± 0.6</td>
<td>1.6 ± 0.4</td>
<td>1.4 ± 0.6</td>
<td>0.9 ± 0.6</td>
<td>1.9 ± 0.6</td>
<td>0.9 ± 0.4</td>
<td>3.1 ± 0.6</td>
</tr>
<tr>
<td>LogD (pH 7) (calc)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-1.7</td>
<td>-0.8</td>
<td>-1.2</td>
<td>-1.4</td>
<td>-0.5</td>
<td>-2.1</td>
<td>0.18</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral (PO)</td>
<td>14–15</td>
<td>40–50</td>
<td>70</td>
<td>40–50</td>
<td>70–80</td>
<td>20–30</td>
<td>90&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nasal</td>
<td>17</td>
<td>102</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcutaneous (SC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein binding (%)</td>
<td>97</td>
<td>25</td>
<td>28–30</td>
<td>14</td>
<td>35</td>
<td>15</td>
<td>85</td>
</tr>
<tr>
<td>Volume of distribution (L/kg)</td>
<td>PO: 90</td>
<td>PO: 7</td>
<td>PO: 110–140</td>
<td>PO: 180–200</td>
<td>PO: 3–4</td>
<td>PO: 138</td>
<td></td>
</tr>
<tr>
<td>Elimination half-life (h)</td>
<td>PO: 2.5</td>
<td>PO: 2–3</td>
<td>PO: 5–6</td>
<td>PO: 2–3</td>
<td>PO: 3–4</td>
<td>PO: 25</td>
<td>PO: 4–5</td>
</tr>
<tr>
<td>Major metabolites (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indoleacetic acid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucuronides</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Metabolizing enzymes</td>
<td>MAO-A</td>
<td>CYP3A4</td>
<td>MAO-A</td>
<td>CYP3A4/CYP2D6: 12%</td>
<td>CYP1A2</td>
<td>CYP3A4</td>
<td></td>
</tr>
<tr>
<td>Excretion (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine metabolite</td>
<td>-60</td>
<td>-30</td>
<td>-40</td>
<td>-15</td>
<td>-12</td>
<td>-10</td>
<td>-10</td>
</tr>
<tr>
<td>Feces metabolite</td>
<td>-40</td>
<td>-30</td>
<td>-15</td>
<td>-12</td>
<td>-10</td>
<td>-10</td>
<td>-10</td>
</tr>
<tr>
<td>Unchanged</td>
<td>-22</td>
<td>-50</td>
<td>-14</td>
<td>-24</td>
<td>-24</td>
<td>-24</td>
<td>-24</td>
</tr>
<tr>
<td>Time to peak concentration (min)</td>
<td>SC: 12&lt;sup&gt;e&lt;/sup&gt;</td>
<td>PO: 120–240</td>
<td>PO: 60–90</td>
<td>PO: 60–240</td>
<td>PO: 120–240</td>
<td>PO: 60–90</td>
<td></td>
</tr>
<tr>
<td>Onset (min)</td>
<td>SC: &lt;10</td>
<td>PO: 60</td>
<td>PO: 60–120</td>
<td>PO: 60–120</td>
<td>PO: 60–120</td>
<td>PO: 60–120</td>
<td></td>
</tr>
<tr>
<td>Duration (mg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral (PO)</td>
<td>PO: 1.25–5.0</td>
<td>PO: 1.0–2.5</td>
<td>PO: 5–10</td>
<td>PO: 6.25–12.5</td>
<td>PO: 2.5–5.0</td>
<td>PO: 20–40</td>
<td></td>
</tr>
<tr>
<td>Nasal</td>
<td>Max PO: 10/24 h</td>
<td>Max PO: 5/24 h</td>
<td>Max PO: 25/24 h</td>
<td>Max PO: 25/24 h</td>
<td>Max PO: 75/24 h</td>
<td>Max PO: 80/24 h</td>
<td></td>
</tr>
<tr>
<td>Onset (min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PO: 25–100</td>
<td>Duration PO: &lt;24 h</td>
<td>Duration PO: 14–16 h</td>
<td>Duration PO: &lt;24 h</td>
<td>Duration PO: 14–16 h</td>
<td>Duration PO: &lt;24 h</td>
<td>Duration PO: 18 h</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Chemical Abstracts, American Chemical Society, calculated using Advanced Chemistry Development (ACD/Labs) Software V8.14 for Solaris (1994-2006 ACD/Labs).

<sup>b</sup> First-pass metabolism.

<sup>c</sup> Delayed by food.

<sup>d</sup> Slower onset during migraine attack.

<sup*e*<sup>a</sup> act= active metabolite.
receptors. No tryptamine analogs bind 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 standing 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 agents (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_{1F} receptors typically bind as well at 5-HT_{1E} receptors; however, not all 5-HT_{1E} receptor ligands bind at 5-HT_{1F} receptors (see below).

### 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_{1F} 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_{1E/1D} receptors, are likely to display reduced coronary vasoconstrictor action associated with the triptans.

### 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_{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_{1D}) 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\textsubscript{2} antagonist with no affinity for 5-HT\textsubscript{1} receptors, and \[^{[3]}H\]ketanserin was introduced as a radioligand to label 5-HT\textsubscript{2} receptors. \(^{1-2}\,2,5\text{-Dimethoxy-4-phenyl-2-aminopropane, where X = -Br and -I (DOB and DOI, respectively), was introduced as a 5-HT\textsubscript{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\textsubscript{2} selective, including standard antagonists such as ketanserin and the agonists DOB and DOI, were later shown to bind nonselectively both to 5-HT\textsubscript{2A} and 5-HT\textsubscript{2} receptors. Consequently, pharmacologic actions originally thought to be 5-HT\textsubscript{2} mediated could actually involve 5-HT\textsubscript{2A} receptors, 5-HT\textsubscript{2} receptors, or a combination of 5-HT\textsubscript{2A} and 5-HT\textsubscript{2} receptors. The structures of the three 5-HT\textsubscript{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\textsubscript{2A} Receptors**

5-HT\textsubscript{2A} receptors, formerly termed 5-HT\textsubscript{2} receptors, have been extensively reviewed (47–51). 5-HT\textsubscript{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\textsubscript{2A} receptors and 5-HT\textsubscript{2} receptors; this could explain the observed similarities in the binding of various ligands at the two receptor subpopulations. Evidence was provided that 5-HT\textsubscript{2A} receptors exist in a high-affinity state and a low-affinity state (sometimes referred to as 5-HT\textsubscript{2A}\textsubscript{H} and 5-HT\textsubscript{2A}\textsubscript{L} 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\textsubscript{2A} Agonists**

The SAFIRs for 5-HT\textsubscript{2A} receptor binding have been reviewed (47,51). Most indolealkylamines are nonselective 5-HT\textsubscript{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\textsubscript{2A} receptors (52). Phenylalkylamines, such as DOB and DOI, act as 5-HT\textsubscript{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\textsubscript{2A} sites, but they do not differentiate between 5-HT\textsubscript{2A} 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\textsubscript{2A/2C} agonist (54). The structurally related INBMeO has been introduced as a radioligand to label 5-HT\textsubscript{2A/2C} receptors (55). Another 5-HT\textsubscript{2A/2C} agonist with DOB-like effects is the 1R,2\text{2R}-isomer of β-hydroxy DOB (β-OH DOB) (56,57).

![Chemical Structures](image)

**5-HT\textsubscript{2A} Antagonists**

One of the largest and more selective classes of 5-HT\textsubscript{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\textsubscript{2A} receptor antagonists, although fairly selective for 5-HT\textsubscript{2A/2C} receptors versus other populations of 5-HT\textsubscript{2} 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\textsubscript{2A} receptors. Spiperone (Fig. 11.7) has been employed as a 5-HT\textsubscript{2A} receptor antagonist with 1,000-fold selectivity for 5-HT\textsubscript{2A} versus 5-HT\textsubscript{2} receptors, but spiperone is also a potent dopamine receptor antagonist, a 5-HT\textsubscript{1A} receptor antagonist, and a 5-HT\textsubscript{2} receptor antagonist. Spiperone, volinanserin (MDL 100,907 or M100907), and AMI-193 were the first 5-HT\textsubscript{2A} versus 5-HT\textsubscript{2A/2C}–selective antagonists available (58,59) (Fig. 11.10). The binding selectivity of various antagonists (and agonists) at 5-HT\textsubscript{2A}, 5-HT\textsubscript{2B}, and 5-HT\textsubscript{2C} receptors has been compared (60). Spiperone and AMI-193 bind at 5-HT\textsubscript{2A} receptors with 1,000- to 3,000-fold selectivity relative to 5-HT\textsubscript{2A} receptors but display high affinity for 5-HT\textsubscript{2C} and D\textsubscript{2} dopamine receptors. A newer member of this series, KML-010, is a spiperone-related derivative that lacks affinity for 5-HT\textsubscript{2A} and 5-HT\textsubscript{2A} receptors and binds with low affinity at D\textsubscript{2}-dopamine receptors (59).
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-HT2A versus 5-HT2C receptors; one of the most selective antagonists is pruvanserin (EMD-281,014) with about 4,000-fold selectivity (Fig. 11.10).

**5-HT2A RECEPTORS: CLINICAL IMPLICATIONS** The potential therapeutic roles of 5-HT2A ligands and the possible involvement of 5-HT2A receptors in modulating normal physiologic functions and various pathologic and psychopathologic conditions have been extensively reviewed (3, 11, 20). 5-HT2A 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-HT2A receptors could actually involve 5-HT2C receptors or a combination of 5-HT2A and 5-HT2C 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-HT2A (and/or 5-HT2C) 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.
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, 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 of schizophrenia could actually be more responsive to psychotic activity, it has been suggested that certain types of 5-HT$_{2A}$ receptors can have a more prominent role than 5-HT$_{2A}$ 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 1,2,5-triazole compound LY-295893, a 5-HT$_{2A}$ receptor antagonist (15,63). 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$_{2A}$ agonists are now being examined in this regard (57).

5-HT$_{2A}$ 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$_{2A}$ receptors) to the 5-HT$_{2A}$ family of receptors were answered once they were cloned (70). The 5-HT$_{2A}$ receptors exhibit approximately 70% homology to 5-HT$_{2B}$ and 5-HT$_{2C}$ receptors, and like 5-HT$_{2A}$ receptors, they appear to couple functionally to phosphoinositide hydrolysis. Nevertheless, rat and human 5-HT$_{2A}$ receptors display more than 90% transmembrane sequence homology. Therefore, most agents that bind at 5-HT$_{2A}$ receptors also bind with similar affinity at human 5-HT$_{2A}$ 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 5-HT$_{2B}$ receptors, like human 5-HT$_{2A}$ receptors, also exist in high-affinity and low-affinity states (71). 5-HT$_{2A}$ receptors are found on cardiovascular tissue. Activation of such receptors by agents with a 5-HT$_{2A}$ 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$_{2A}$ agonist character (73). A series of 1-substituted β-carbolines (e.g., LY-23728, LY-287375, and LY-256697) have been reported to be the first 5-HT$_{2A}$-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

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$_{2A}$-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).
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 phosphoinositide 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 2B 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 2A 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. 1R,3S(-)-trans-1-Phenyl-3-dimethylamino-1,2,3,4-tetrahydroacenaphthylene, or 1R,3S(-)-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-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 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 MT1/MT2 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 2C 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), 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 \textsubscript{3} receptors in brain are located presynaptically (87). Evidence indicates that 5-HT \textsubscript{3} receptors modulate release of other neurotransmitters, including dopamine, acetylcholine, GABA, and 5-HT (88).

Five 5-HT \textsubscript{3} subunits have been cloned. 5-HT \textsubscript{3A}, 5-HT \textsubscript{3B}, 5-HT \textsubscript{3C}, and 5-HT \textsubscript{3E} subunits are similar in their topology, whereas the 5-HT \textsubscript{3D} subunit lacks most of the N-terminus including the Cys-loop. The 5-HT \textsubscript{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 \textsubscript{3A} subunit (87). This could be explained by lack of a tryptophan residue in the N-terminus of all four subunits (5-HT \textsubscript{3B}, 5-HT \textsubscript{3C}, 5-HT \textsubscript{3D}, and 5-HT \textsubscript{3E}) shown to be essential for binding. Conversely, the latest reports indicate that subunits 5-HT \textsubscript{3A}, 5-HT \textsubscript{3C}, and 5-HT \textsubscript{3E} could be present on the cell surface when expressed alone in CHO cells (89). 5-HT \textsubscript{3A} and 5-HT \textsubscript{3B} receptors are the most studied to date. 5-HT \textsubscript{3AB} receptors differ from 5-HT \textsubscript{3A} in that they have higher single-channel conductance, a lower Ca\textsuperscript{2+} permeability, faster activation and deactivation, and a lower potency for 5-HT. The subunit composition of recombinant 5-HT \textsubscript{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 \textsubscript{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 \textsubscript{3} receptors. To fully activate the ion channel of homomeric 5-HT \textsubscript{3A} receptors, three molecules of agonist are necessary, whereas in the case of heteromeric 5-HT \textsubscript{3AB} receptors, with presumed stoichiometry of 5-HT \textsubscript{3A/2B/1E}, only two agonist molecules are necessary (87).

**Structure–Activity Relationships of 5-HT \textsubscript{3} Agonists**

Only a few 5-HT \textsubscript{3} receptor agonists have been identified (Fig 12.13), and the topic has been comprehensively reviewed (90). Many tryptamine analogs bind at 5-HT \textsubscript{3} receptors in a nonselective manner. Simple \(N\)-methylation of 5-HT significantly decreases its affinity for 5-HT \textsubscript{3} receptors. Ergolines either do not bind or bind only with very low affinity. 5-HT is a nonselective 5-HT\textsubscript{3} receptor agonist that binds only with moderate affinity (\(K \sim 500\) to 1,000 nM). Its 2-methyl analog, 2-methyl 5-HT (\(K = 1,200\) 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\textsubscript{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\textsubscript{3} 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 \textsubscript{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 (\(K \sim 1,000\) nM) 5-HT\textsubscript{3} agonist is phenylbiguanide. \(m\)-Chlorophenylbiguanide (\(m\)CPG), which binds in the low nanomolar range (\(K \sim 20\) to 50 nM) and retains agonist character, has largely replaced phenylbiguanide. Because of its polar nature, \(m\)CPG does not readily penetrate the blood–brain barrier. \(m\)-Chlorophenylbiguanide (MD-354; \(m\)CPG) shows that the entire biguanide moiety is not required for serotoninergic activity. Adding multiple chloro groups to \(m\)CPG or \(m\)CPG increases their lipophilicity and affinity (90).

Simple arylpiperazines were among the first serotoninergic agents investigated at 5-HT\textsubscript{3} receptors (Fig 12.13). Many are nonselective 5-HT\textsubscript{3} ligands (see previous discussion of 5-HT\textsubscript{3} receptors). Depending on the particular substitution pattern, they can behave as 5-HT\textsubscript{3} agonists, partial agonists, or antagonists (90). This nonselectivity probably accounts for the initial lack of interest in arylpiperazines as 5-HT\textsubscript{3} ligands, but today, there is renewed interest in these.
types of agents. Quipazine was the first arylpiperazine shown to bind at 5-HT₃ receptors, even though it is also a 5-HT₂A agonist. It binds with much higher affinity than 5-HT at 5-HT₃ receptors ($K_i \sim 1 \text{nM}$) 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-HT₃ antagonists known at that time. Early structure–affinity studies showed that its fused pyridine ring attached to N₄-piperazine nitrogen distance ($\sim 5.5 \text{ Å}$) was similar to that of 5-HT. Other findings indicated that 1) the N₄-piperazine nitrogen atom, but not the N₁-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) N₄-methylation (N-methylquipazine) enhances 5-HT₃ 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).

A related group of antagonists that possess an imidazole or related heterocyclic terminal amine include ondansetron (Zofran), alosetron (Lotronex), fabepron, and ramosetron (Fig. 11.16). Many others have been described (93,94). The SARs of 5-HT₃ antagonists have been reviewed in detail (93–95).

Studies have identified pharmacophoric features (Fig. 11.17) that are common to many 5-HT₃ receptor antagonists.

**Structure–Activity Relationship of 5-HT₃ Antagonists**

Bemesetron (MDL-72222) was the first selective 5-HT₃ 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-HT₃ antagonist. Since then, many hundreds of 5-HT₃ 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-HT₃ 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 zatostron. It should be noted that some of these keto compounds also bind at 5-HT₄ receptors.

**Figure 11.13** 5-HT₃ receptor agonists or partial agonists.
5-HT₃ Receptors: Clinical Implications

One of the most noteworthy clinical success stories in 5-HT research relates to the antiemetic properties of 5-HT₃ receptor antagonists. Ondansetron was introduced as an antiemetic in the 1990s, and 5-HT₃ 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-HT₃ receptor antagonists are ondansetron, granisetron, dolasetron and, in Europe, tropisetron; a newer 5-HT₃ antagonist in clinical use in the United States is palonosetron (98). The various 5-HT₃ 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-HT₃ antagonist, whereas granisetron and tropisetron (and, perhaps, palonosetron) produce an insurmountable antagonism (98,99). Selection of a particular 5-HT₃ 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-HT₃ receptor antagonists could potentially be of benefit for the treatment of alcohol and substance abuse, anxiety, autism, bipolar disorder, cognitive impairment,
depression, eating disorders, gastrointestinal disorders, pain, and schizophrenia (87).

Very little is known about the potential therapeutic utility of 5-HT3 receptor agonists (90).

5-HT4 Receptors and Agents
A novel population of serotonergic receptors, originally identified in primary cell cultures of mouse embryo colliculi neurons and later termed 5-HT4 receptors, have broad tissue distribution and are positively coupled to adenylate cyclase (100). In the brain, 5-HT4 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-HT4 receptors have been cloned and display low transmembrane sequence homology (<50%) with other 5-HT receptors. In fact, two 5-HT4 isoforms have been isolated, a long form (5-HT4L) and a short form (5-HT4S). These isoforms are splice variants and differ only in their C-terminus ends, with identical transmembrane regions

### Table 11.4 Pharmacokinetics of the 5-HT3 Antagonists (Setrons)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Ondansetron</th>
<th>Dolasetron</th>
<th>Granisetron</th>
<th>Alosetron</th>
<th>Palonosetron</th>
<th>Tropisetron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade name</td>
<td>Zofran</td>
<td>Anzemet</td>
<td>Kytril</td>
<td>Lotronex</td>
<td>Aloxi</td>
<td>Navoban</td>
</tr>
<tr>
<td>CLogP (calc)a</td>
<td>2.1 ± 0.5</td>
<td>2.8 ± 0.5</td>
<td>1.5 ± 0.5</td>
<td>0.88 ± 0.8</td>
<td>2.6 ± 0.5</td>
<td>3.6 ± 0.3</td>
</tr>
<tr>
<td>LogD (pH 7) (calc)b</td>
<td>1.5</td>
<td>2.8</td>
<td>-1.5</td>
<td>0.4</td>
<td>0.01</td>
<td>0.8</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td>56–70(^c)</td>
<td>Hydrodolasetron: 60–80</td>
<td>60(^d)</td>
<td>50–60(^c)</td>
<td>IV</td>
<td>60 (60–100)</td>
</tr>
<tr>
<td>Protein binding (%)</td>
<td>70–76</td>
<td>Hydrodolasetron: 70–80</td>
<td>65</td>
<td>82</td>
<td>62</td>
<td>71</td>
</tr>
<tr>
<td>Volume of distribution (L/kg)</td>
<td>PO: 2.2–2.5</td>
<td>PO: 3.9</td>
<td>PO: 70 (65–95)</td>
<td>IV: 6.8–12.5</td>
<td>IV: 500</td>
<td></td>
</tr>
<tr>
<td>Elimination half-life (h)</td>
<td>PO: 3–6</td>
<td>PO: &lt;10 min</td>
<td>IV: 4–5</td>
<td>PO: 1.5–2.0</td>
<td>PO: 30–40</td>
<td>EM: PO: 6–8</td>
</tr>
<tr>
<td>Elderly: PO: 11</td>
<td>Hydrodolasetron: PO: 4–9</td>
<td>PO: &lt;6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major metabolites (%)</td>
<td>Hydroxylation</td>
<td>Hydrodolasetron</td>
<td>N-Demethyl</td>
<td>6-Hydroxylation</td>
<td>N-oxide</td>
<td>Hydrolyzation</td>
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<tr>
<td>Glucuronidation</td>
<td>Hydroxylation</td>
<td>Hydrodolasetron</td>
<td>Hepatic</td>
<td>N-Demethyl</td>
<td>6-Hydroxy</td>
<td>Glucuronides</td>
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<tr>
<td>Metabolizing enzyme (%)</td>
<td>CYP3A4</td>
<td>Carbonyl reductase</td>
<td>CYP3A4: 30</td>
<td>CYP2C9: 30</td>
<td>CYP2D6: 30</td>
<td>CYP3D6</td>
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<tr>
<td></td>
<td>CYP2D6</td>
<td>CYP2D6</td>
<td>CYP3A4: 20</td>
<td>CYP3A4: 20</td>
<td>CYP2D6</td>
<td>CYP3D6</td>
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<tr>
<td>Time to peak plasma concentration (h)</td>
<td>PO: 1–2</td>
<td>Hydrodolasetron IV: &lt;0.5</td>
<td>PO: 2–3</td>
<td>PO: 0.5–2</td>
<td>IV: 30</td>
<td>EM: PO: 3</td>
</tr>
<tr>
<td>Excretion (%)</td>
<td>Urine metab: 40–60</td>
<td>Urine metab: 48</td>
<td>Urine metab: 70</td>
<td>Urine metab: 80</td>
<td>Urine metab: ~70</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Feces metab: 25</td>
<td>Feces metab: 30</td>
<td>Feces metab: 38</td>
<td>Feces metab: 25</td>
<td>Feces metab: ~15</td>
<td></td>
</tr>
<tr>
<td>Unchanged: &lt;10</td>
<td>Unchanged hydrodolasetron: 60</td>
<td>Unchanged: &lt;10</td>
<td>Unchanged: &lt;10</td>
<td>Unchanged: 40</td>
<td>Unchanged: &lt;10</td>
<td></td>
</tr>
<tr>
<td>Duration (h)</td>
<td>———</td>
<td>———</td>
<td>8–24</td>
<td>1–10</td>
<td>&gt;24</td>
<td>———</td>
</tr>
</tbody>
</table>

IM, intramuscular; IV, intravenous; PO, oral.
\(^b\) First-pass metabolism.
\(^c\) Food delays absorption and peak plasma concentrations.
\(^d\) Food increase extent of absorption.
(101). In general, the potency of agonists to stimulate cyclic adenosine monophosphate (cAMP) was greater for the 5-HT₄ receptor than for the 5-HT₃ receptor. A mouse 5-HT₄ receptor has been cloned, and a human pseudogene has been identified that codes for a 5-HT₄-like receptor. Indeed, several new human 5-HT₄ receptor isoforms have been cloned and expressed (102). The new 5-HT₄ receptors have been termed 5-HT₄₂, 5-HT₄₃, and 5-HT₄₄; the stimulatory pattern of cAMP formation in response to the 5-HT₄ 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).

Cisapride is available as a prokinetic drug that enhances gastrointestinal activity. With respect to their central effects, it has been suggested that 5-HT₄ agonists can restore deficits in cognitive function and that 5-HT₄ antagonists could be useful as anxiolytics or in the treatment of dopamine-related disorders. It is further speculated that 5-HT₄ receptors may be involved in memory and learning, and it has been noted that 5-HT₄ receptors appear to correspond to the rodent 5-HT₄S isoform. It has been proposed that the cardiac effects of 5-HT are mediated by this short splice variant, whereas 5-HT₄L determines the neuronal effects of 5-HT (102).

Although 5-HT₄ receptors are ion channel receptors and 5-HT₃ receptors represent G protein–coupled receptors (Table 11.2), a number of 5-HT₃ receptor ligands are active at 5-HT₄ receptors. Even more interesting is that a number of 5-HT₄, antagonists, or what were considered at one time to be 5-HT₃-selective antagonists (e.g., renzapride and zacopride), actually exhibited 5-HT₄ agonist activity. Even today, there is considerable structural similarity among various 5-HT₃ and 5-HT₄ receptor ligands. In addition to their lack of selectivity for 5-HT₄ versus other 5-HT receptors, many early 5-HT₄ 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-HT₄ Agonists

In general terms, 5-HT₄ 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., RS 56532), benzoates (ML-10302), and ketones (e.g., RS 67333).

Structure–Activity Relationships of 5-HT₄ Antagonists

The 5-HT₄ antagonist tropisetron was the first agent to see application as a 5-HT₄ antagonist, and its low affinity for 5-HT₄ receptors prompted a search for higher affinity agents. Various agents have been identified (94,104,105), and 5-HT₄ antagonists are derived from structural classes similar to those from which the 5-HT₃ 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-HT₄ antagonists. Structure–activity details for different receptor preparations have been reviewed (94,104,105). It is worth noting that apart from 5-HT₃ receptors, 5-HT₄ receptors are the only other population of serotonergic sites that seem to accommodate quaternary amines.

5-HT₄ Receptors: Clinical Implications

Selective 5-HT₄ 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-HT₄ agonists can restore deficits in cognitive function and that 5-HT₄ antagonists could be useful as anxiolytics or in the treatment of dopamine-related disorders. It is further speculated that 5-HT₄ receptors may be involved in memory and learning, and it has been noted that 5-HT₄ receptors...
are markedly decreased in patients with Alzheimer disease (106, 107). A high density of 5-HT₄ 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-HT₄ receptors to activation (108). It would appear that therapeutic roles exist for both 5-HT₄ antagonists and 5-HT₄ agonists. However, it has been cautioned that the use of highly potent and selective 5-HT₄ agonists could result in cardiovascular side effects (107). If different 5-HT₄ receptor isoforms can be shown to mediate the various effects for which 5-HT₄ receptors have been implicated, the potential exists for the development of selective agents. Another problem associated with 5-HT₄ 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-HT₃ receptors (111)—that is, a population of 5-HT receptors found only in the gut. 5-HT₃ 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-HT₃ antagonists reduce colonic transit and improve fluid absorption (110). The 5-HT₃ antagonists tend to be constipating (111). The 5-HT₄ receptors mediate both excitatory and inhibitory effects on gut function (110).

**FIGURE 11.19** 5-HT₄ receptor antagonists.

Alosetron (Fig. 11.16), a 5-HT₃ antagonist, and tegaserod (Zelnorm), a 5-HT₄ 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 α₁-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 (3-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<sub>5</sub> Receptors and Agents

Two 5-HT<sub>5</sub> receptors, expressed primarily in the mouse CNS, have been identified as 5-HT<sub>5A</sub> and 5-HT<sub>5B</sub> receptors (112). The two 5-HT<sub>5</sub> receptors exhibit 77% amino acid sequence homology but less than 50% homology with other cloned serotonergic receptors. To some extent, 5-HT<sub>5</sub> receptors appear to resemble 5-HT<sub>1</sub> receptors (e.g., high affinity for 5-HT and 5-CT); however, their low homology with other 5-HT<sub>5</sub> receptors suggests that they represent a distinct family of receptors. Only 5-HT<sub>5A</sub> receptors have been identified in humans (112). Human 5-HT<sub>5A</sub> receptors are G protein–coupled receptors with a complex second messenger system (113).

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

5-HT<sub>6</sub> Receptors: Clinical Implications

Pharmacologic functions of 5-HT<sub>6</sub> 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<sub>6</sub> 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<sub>6</sub> receptor could be involved in schizophrenia (115) and that spinal 5-HT<sub>6</sub> receptors could have a role in nociception and control of pelvic floor musculature (116).

5-HT<sub>6</sub> 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<sub>6</sub>. This receptor exhibits only 40% transmembrane homology with 5-HT<sub>1A</sub>, 5-HT<sub>1B</sub>, 5-HT<sub>1D</sub>, 5-HT<sub>1E</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub>, and 5-HT<sub>3</sub> receptors. Both LSD and 5-HT display modest affinity for 5-HT<sub>6</sub> receptors (K<sub>i</sub> ~ 50 to 150 nM). Of interest is that a number of typical and atypical antipsychotic agents and tricyclic antidepressants bind with K<sub>i</sub> values in the nanomolar range.

The human 5-HT<sub>6</sub> 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<sub>6</sub> receptors with moderate affinity (K<sub>i</sub> = 65 nM), and one of the highest affinity, albeit nonselective, agents is the antipsychotic methiothepin (K<sub>i</sub> = 0.4 nM). Agents that bind at human 5-HT<sub>6</sub> receptors with K<sub>i</sub> less than 50 nM include 5-methoxytryptamine, bromocriptine, octocloethepin, the atypical antipsychotic agents clozapine and olanzapine, and the typical antipsychotics chlorpromazine, loxapine, and fluphenazine (118). Agents with K<sub>i</sub> 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<sub>6</sub> Agonists and Antagonists

2-Ethyl-5-methoxy-N,N-dimethyltryptamine (EMDT) represented the first reasonably selective 5-HT<sub>6</sub> agonist (119), and Ro 04-6790 and Ro 63-0563 represented the first 5-HT<sub>6</sub>-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<sub>6</sub> antagonists contained a 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<sub>6</sub> receptors and, depending on the nature of their pendent substituents, act as 5-HT<sub>6</sub> agonists, partial agonists, or antagonists (125,126). A comprehensive review of 5-HT<sub>6</sub>-related agents and their SARs has been published (127).
5-HT<sub>6</sub> Receptors: Clinical Implications

The exact clinical significance of 5-HT<sub>6</sub> 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<sub>6</sub> receptors and certain psychiatric disorders (128). The different binding profiles of atypical antipsychotics are responsible for their atypical nature (e.g., D<sub>2</sub>:5-HT<sub>2a</sub> 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<sub>6</sub> than at D<sub>2</sub> receptors. However, antipsychotics that produce the fewest extrapyramidal side effects in humans (e.g., clozapine, olanzapine, and fluparlapine) also possess high affinity for 5-HT<sub>6</sub> receptors (118). The atypical antipsychotic agent risperidone, which produces some extrapyramidal symptoms, binds with 1,000-fold higher affinity for 5-HT<sub>6</sub> than at 5-HT<sub>2</sub> receptors; thus, affinity of agents for 5-HT<sub>6</sub> receptors can contribute to the difference between typical and certain atypical antipsychotics (118). Furthermore, preclinical studies indicate that combinations of a 5-HT<sub>6</sub> antagonist and a 5-HT<sub>2a</sub> antagonist were effective in models of psychosis and cognition (129). PMDT differs from most other 5-HT<sub>6</sub> antagonists in that it combines both types of antagonist action in the same molecule (114). In 5-HT<sub>6</sub> knockout mice, a behavioral syndrome is produced that seems to involve an increase in cholinergic function. Blocking the receptors in rats with 5-HT<sub>6</sub> antagonists produces a similar effect. This has led to speculation that one of the roles of 5-HT<sub>6</sub> receptors may be to control cholinergic neurotransmission and that 5-HT<sub>6</sub>-selective antagonists could be useful in the treatment of anxiety and memory deficits. Other studies have shown that although 5-HT<sub>6</sub> 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<sub>6</sub> receptors have a role in neuronal plasticity (132) and can influence the actions of dopaminergic agents. Evidence also suggests that 5-HT<sub>6</sub> 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<sub>6</sub> agonists and antagonists, interest in the therapeutic potential of such agents is on the upswing.

5-HT<sub>7</sub> Receptors and Agents

Like 5-HT<sub>6</sub> receptors, 5-HT<sub>7</sub> receptors were once considered to be orphan receptors. Rat, mouse, guinea pig, and human 5-HT<sub>7</sub> receptors have now been cloned and are expressed mainly in the CNS (114,133). Structural analysis of the 5-HT<sub>7</sub> 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<sub>7</sub> receptor isoforms that vary with respect to the length of their C-terminus chains (114,134). In rat, the isoforms are named 5-HT<sub>7a</sub>, 5-HT<sub>7b</sub>, and 5-HT<sub>7c</sub>. Two of the isoforms are homologous in rat and human (5-HT<sub>7a</sub> and 5-HT<sub>7c</sub>). The third human isoform is named 5-HT<sub>7d</sub>. 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<sub>7</sub> receptors are constitutively active and that the degree of constitutive activity could vary among the isoforms. Nonselective agents with <i>K<sub>i</sub></i> values at 5-HT<sub>7</sub> receptors of 10 nM or less include 5-HT<sub>6</sub>- and 5-hydroxytryptamine, LSD, methiothepin, and mesulergine; those with <i>K<sub>i</sub></i> values in the range of 10 to 100 nM include 8-OH...
DPAT (long considered a 5-HT$_{1A}$-selective agonist!), siperone, 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, siperone (a 5-HT$_{1A}$, 2-HT$_{1A}$, 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 receptors with nanomolar or subnanomolar affinity ($K_i \leq 10$ nM), including fluphenazine, acetophenazine, chlorprothixene, zotepine, clozapine, fluperlapine, pimozide, tiospirone, and risperidone.

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 (Sisomor, $K_i = 1.3$ 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 (Sisomor, $K_i = 2$ 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 tetrahydroisoquinolinsulfonamides (139). Actually, the latter two types of compounds have been demonstrated to act as inverse agonists (139).

5-HT$_7$ Agonists

$N$-Arylaminooimidazolines (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 $\alpha$-adrenoceptors. Several new 5-HT$_7$ agonists have been recently reported, including the piperazinylhexanones (141) and 2-amino tetralins (142) (Fig. 11.22); the latter can function either as agonists (e.g., $R = nPr$) 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$_7$ 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.](image-url)
CHAPTER 11 / SEROTONIN RECEPTORS AND DRUGS AFFECTING SEROTONERGIC NEUROTRANSMISSION

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. 11.25). 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 11.22 5-HT₇ receptor agonists.

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$_{3C}$ 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$_3$ antagonist (155). The 5-HT$_{3C}$ agonist m-chlorophenylpiperazine (mCPP) 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$_{3C}$ subpopulation. The 5-HT$_{2A}$ 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 mCPP and that, in some instances, trazodone possesses 5-HT$_{2A}$ 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 antidepressanes (e.g., 5-HT$_1$, 5-HT$_2$, 5-HT$_3$, and 5-HT$_4$), 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, “It almost appears that 5-HT is involved in everything” (1).

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**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**

Both of the triptans associated with this scenario are indoleethylamines (tryptamines) that abort migraine headaches through their agonist action at 5-HT$_{1D}$ 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 sumatriptan (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-HT$_{1D}$ selectivity than the methylsulfonamide moiety of sumatriptan.
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.

**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.


References


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