5-Hydroxytryptamine 2C (5-HT_{2C}) Receptor Agonists as Potential Antiobesity Agents

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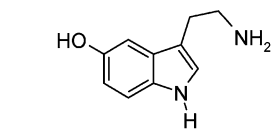
Received June 16, 2005

Introduction

Currently, only two drugs are approved for the long-term treatment of obesity: the dual serotonin (5-hydroxytryptamine, 5-HT, **1**) and noradrenaline reuptake inhibitor sibutramine (**2**); the lipase inhibitor orlistat (**3**). Sibutramine and orlistat were approved by the U.S. Food and Drug Administration (FDA) in November 1997 and April 1999, respectively. Since these agents have been reported to have drawbacks in terms of limited clinical efficacy and potential side effects,[1] there is room for improvements concerning upcoming antiobesity therapies. In addition to well-known side effects associated with these two antiobesity drugs, some new ones have recently been reported: hypermenorrhea with sibutramine and forgetfulness (amnesia) with both orlistat and sibutramine.[2,3] Additionally, it appears that sibutramine should be used with caution in patients with concomitant glaucoma because there is some evidence that it may slightly increase intraocular pressure (IOP).[4] Because elevated IOP is considered a major risk factor for glaucoma, this finding may have clinical relevance in light of a reported association between elevated IOP and obesity.[5] With respect to potential novel pharmacotherapies for the treatment of obesity, the cannabinoid-1 (CB_1) receptor antagonist rimonabant (**4**) may represent a promising approach.[6] This drug is currently under review for marketing approval by the FDA.[7]



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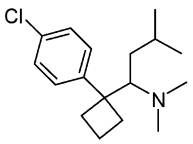

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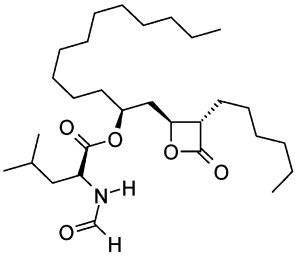

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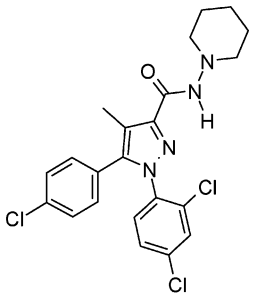

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The limited therapies available, a need for more effective and better tolerated medications, and recent advances in the study of mechanisms involved in body weight regulation linked with the elucidation of new transmitter systems have led to a rapid expansion of research on antiobesity drugs. Given the compelling evidence for the involvement of the 5-HT_{2C} receptor in the serotonergic control of food intake and body weight, which is discussed in greater detail below, it is not surprising that one of the most promising targets for the development of novel antiobesity treatments at present appears to be the 5-HT_{2C} receptor. Consequently, the area of 5-HT_{2C} receptor agonists has been reviewed in a number of articles.[8−16] Apart from a summary of preclinical and clinical evidence validating the 5-HT_{2C} receptor as a potential target for antiobesity therapy, the present review provides an update on recently reported 5-HT_{2C} receptor agonists.

5-HT_{2C} Receptor: Characteristics, Distribution, and Biological Role

Serotonin mediates its effects through at least 14 different receptor subtypes that are classified into seven major families, 5-HT_1 to 5-HT_7, based on pharmacological, structural, and signal transductional properties. The 5-HT_2 family of receptors has three members, 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}, which belong to the superfamily of G-protein-coupled receptors. Upon activation, the 5-HT_2 receptor subtypes stimulate the phospholipase C second messenger pathway, resulting in phosphoinositide hydrolysis and a subsequent transient increase in intracellular calcium.[17−19] However, besides the conventional phospholipase C pathway, subsequent studies have revealed that the 5-HT_2 receptor subtypes can also activate other transduction pathways, such as phospholipase A_2 leading to release of arachidonic acid.[18,19]

The 5-HT_{2C} receptor was identified in 1984 from radioligand binding studies in the pig choroid plexus and was originally designated 5-HT_{1C} because of the high affinity labeling by [^{3}H]-5-HT, and ligands reported as selective for 5-HT_{1A}, 5-HT_{1B}, or 5-HT_{2A} (formerly designated 5-HT_2) receptor subtypes show low affinity for this tissue.[20] However, once the signal transduction pathway and receptor amino acid sequence data became available, the receptor was renamed as 5-HT_{2C}.[21] The human 5-HT_{2C} receptor was cloned in 1991.[22] Unlike the 5-HT_{2A} and 5-HT_{2B} receptors, the expression of 5-HT_{2C} receptors appears to be restricted to the central nervous system (CNS) where it demonstrates a wide distribution. For example, in the choroid plexus of the brain ventricles, the 5-HT_{2C} receptor is the only 5-HT receptor subtype identified and is expressed at densities which are 10-times higher than those found elsewhere in the CNS. Within the choroid plexus, a role in the regulation of cerebrospinal fluid formation, as well as in the synthesis and secretion of the iron carrier protein transferrin, has been suggested for the 5-HT_{2C} receptor.[23] Curiously, given the link between transferrin and the 5-HT_{2C} receptor, it would be of interest to study whether other transport proteins synthesized in the choroid plexus, in particular transthyretin (formerly called prealbumin), also are modulated by 5-HT_{2C} receptors. While speculative, this may be relevant for research on Alzheimer's disease (AD) because independent studies have indicated that both 5-HT_{2C} receptor agonism and transthyretin may reduce the amyloidogenic cleavage of the amyloid precursor protein (APP),

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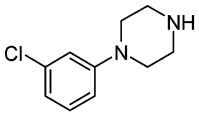
10.1021/jm058240i CCC: $33.50
Published on Web 06/17/2006

a cleavage that produces neurotoxic β-amyloid protein, the principal proteinaceous component of brain amyloid plaques characteristic of AD.[24,25]

The presence of 5-HT_{2C} receptors in multiple hypothalamic regions of the brain is believed to play a key role in the serotonergic control of appetite regulation. For example, a local perfusion study with the preferential 5-HT_{2C} receptor agonist *m*-chlorophenylpiperazine (*m*-CPP, **5**) administered into different brain regions in the rat and a 5-HT_{2C} receptor mRNA expression study in diet-induced obese (DIO) mice indicate that 5-HT_{2C} receptors in the ventromedial hypothalamic nucleus (VMH) play an important role in the regulation of food intake.[26,27] Another study has shown that hypophagia could be produced when nordexfenfluramine (**6**), which has direct agonist action at the 5-HT_{2C} receptor (vide infra),[28] was infused into the paraventricular nucleus (PVN) of the hypothalamus in the rat.[29] Furthermore, a recent report has linked 5-HT_{2C} receptor-mediated hypophagia to the activation of 5-HT_{2C} receptors expressed on pro-opiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus.[30]



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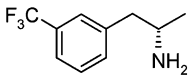

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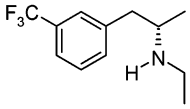

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However, 5-HT_{2C} receptors expressed at extrahypothalmic sites may also play a role in the serotonergic regulation of ingestive behavior. For example, 5-HT_{2C} receptors in the caudal brainstem have been implicated in the anorectic actions of *m*-CPP and dexfenfluramine (**7**).[31] Additionally, 5-HT_{2C} receptors might also be involved in modulation of the rewarding properties of food, which is linked to increased mesolimbic dopamine levels in the nucleus accumbens of the brain in response to food ingestion. A number of studies have suggested that food and drug rewards may share some common neural substrates, specifically the nucleus accumbens.[32] Given that 5-HT_{2C} receptor agonists may decrease dopamine levels in the nucleus accumbens and that reward-related behaviors (e.g., cocaine or nicotine self-administration in rats) may be reduced by 5-HT_{2C} receptor activation, the possibility that 5-HT_{2C} receptor agonists may reduce the rewarding properties of food should also be considered.[33]

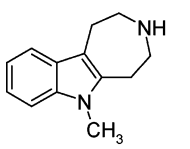
Validation, Proof of Concept Studies, and Safety Aspects

In 1995, it was reported that knockout mice lacking the 5-HT_{2C} receptor develop hyperphagia and become gradually overweight and obese.[34] The body weights and adiposity levels of the 5-HT_{2C} receptor mutants did not diverge significantly from wild-type levels until 5−6 months of age. A recent study has shown that total oxygen consumption is decreased in older (9−10 months of age) obese 5-HT_{2C} receptor mutant mice relative to age-matched wild-type controls, despite elevated locomotor activity levels in the mutants and the fact that no changes in resting metabolic rates were observed.[35] This finding may, at least in part, be related to a secondary age-dependent decrease in β_3-adrenergic receptor gene expression found in white adipose tissue of the 5-HT_{2C} receptor mutant mice.[36] Moreover, hyperphagic young (∼3 months of age) 5-HT_{2C} receptor mutant mice have normal plasma leptin levels and show normal responsiveness to the anorectic effect of exogenous leptin administration. This indicates that 5-HT_{2C} receptors are not required for leptin action and that hyperphagia is not likely to result from perturbed leptin signaling in these mice.[37] However, old 5-HT_{2C} receptor mutant mice have higher plasma leptin levels and are partially resistant to the anorectic effect of exogenous leptin, findings that are suggested to be secondary consequences of enhanced adiposity.[37]

The 5-HT_{2C} receptor mutant mice, in contrast to the corresponding wild-type mice, are resistant to the anorectic effect mediated by the prototypical 5-HT_{2C} receptor agonist *m*-CPP, confirming the specific role of the 5-HT_{2C} receptor in the regulation of food intake.[34] The hypophagic effect of *m*-CPP in wild-type rodents has been demonstrated in numerous studies. Moreover, behavioral satiety sequence studies in rodents, which allow satiating responses to be discriminated from nonspecific effects such as nausea and sedation, suggest that 5-HT_{2C} receptor agonists, such as *m*-CPP, exert their hypophagic effect by inducing satiety.[38,39]

The potential for the development of tolerance to 5-HT_{2C} receptor agonist-induced hypophagia and body weight loss following repeated administration has been a subject of considerable investigation. The observation that continuous subcutaneous infusion of 5-HT_{2C} receptor agonists, for example, *m*-CPP, via osmotic minipumps to lean rats for 14 days did not affect 5-HT_{2C} receptor mRNA levels in the hypothalamus suggests that hypothalamic 5-HT_{2C} receptors do not down-regulate under these conditions.[40] Interestingly, when lean rats were treated with *m*-CPP (10 mg/kg, po, b.i.d.) for 28 days, tolerance to the effects on food intake and body weight did not develop because *m*-CPP decreased food intake and body weight gain for the duration of treatment.[41] Similarly, *m*-CPP given to humans was found to produce a sustained body weight loss (0.75 kg) in 15 out of 18 obese subjects after 2 weeks of oral treatment.[42]

Also, early retrospective clinical data, along with current knowledge about 5-HT_{2C} receptor function, have recently provided additional support to the concept. In a clinical trial with the azepinoindole **8** (PNU-22394A) from The Upjohn Company (now Pfizer) for schizophrenia in 1967, which did not find evidence of antipsychotic efficacy, it was found that **8** caused a sustained body weight loss (3.5 kg) in 11 out of 12 patients following 9 weeks of treatment, an effect that is now interpreted as resulting from 5-HT_{2C} receptor agonism.[43,44] Recently, it was revealed that **8** behaves as a nonselective 5-HT_{2C} receptor agonist with similar affinities for all human 5-HT_2 receptor subtypes (5-HT_{2C} K_i = 18 nM; 5-HT_{2A} K_i = 18 nM; 5-HT_{2B} K_i = 66 nM) in receptor binding studies.[44] It displays greater relative efficacy at the human 5-HT_{2C} receptor (87%) than at the human 5-HT_{2A} and 5-HT_{2B} receptors, where it exhibits relative efficacies of 65% and <15%, respectively, as determined by measurements of calcium release. Furthermore, the hypophagic effect of **8** in rats could be blocked by pretreatment with the selective 5-HT_{2C} receptor antagonist **9** (SB-242084, GlaxoSmithKline),[45] supporting the central role of 5-HT_{2C} receptors in mediating this response.[44]



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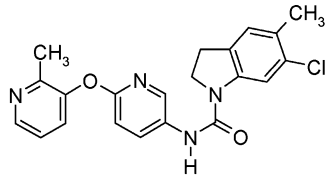

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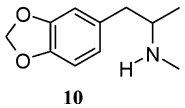

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Dexfenfluramine (**7**), a 5-HT releaser/reuptake inhibitor without CNS stimulant properties, was approved by the FDA in April 1996 for the treatment of obesity but was withdrawn from the marketplace in September 1997 because of its association with heart valve damage and pulmonary hypertension.[46,47] It appears that the anorectic effect of dexfenfluramine is mainly attributed to the 5-HT_{2C} receptor; 5-HT_{2C} receptor knockout mice show a reduced hypophagic response to dexfenfluramine, and dexfenfluramine-induced hypophagia in the rat is dose-dependently inhibited by pretreatment with the selective 5-HT_{2C} receptor antagonist **9** but not with a selective 5-HT_{2A} or 5-HT_{2B} receptor antagonist.[48] It has also been suggested that part of the anorectic properties of dexfenfluramine may be due to direct agonist activity at 5-HT_{2C} receptors of its major metabolite nordexfenfluramine (**6**), which, in contrast to the parent compound, has appreciable affinity and agonist efficacy at the human 5-HT_{2C} receptor ($pK_i = 7.29$, $pEC_{50} = 6.77$, relative efficacy of 77% in a calcium release assay).[28,49] In this regard, it may be worth noting that nordexfenfluramine has a significantly longer plasma half-life than the parent drug in humans (32 vs 17 h).[50] Overall, there is ample support to suggest that continuous activation of 5-HT_{2C} receptors may result in a sustained body weight reduction in man, and further supporting evidence is given in the compound review sections below.

Since 5-HT_{2C} receptors are apparently absent in peripheral tissues, it is unlikely that activation of 5-HT_{2C} receptors is responsible for the cardiopulmonary toxicity associated with dexfenfluramine. The cause of toxicity has not been defined, but the 5-HT_{2B} receptor, which is notably expressed in heart valves and pulmonary arteries, has been implicated.[51−55] Nordexfenfluramine, but not the parent molecule dexfenfluramine, displays high agonist potency at the human 5-HT_{2B} receptor along with high receptor affinity ($pEC_{50} = 8.06$, relative efficacy of 66% in a calcium release assay, and $K_i = 11.2$ nM for nordexfenfluramine).[28,51] Also, other drugs reported to stimulate 5-HT_{2B} receptors, such as the ergot-derived dopamine receptor agonists pergolide and cabergoline, which are used in the treatment of Parkinson's disease, have recently been associated with cardiac valvular fibrosis.[56,57] Similarly, the recreational drug 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy", **10**), a 5-HT and noradrenaline releaser that originally was described as an appetite suppressant, has recently been suspected to be valvulopathogenic because of its 5-HT_{2B} receptor agonist properties.[58,59] It may be worth noting that other reports on the cardiopulmonary toxicity linked to dexfenfluramine treatment have raised the possibility that activation of the 5-HT_{2A} receptor also may play a role.[60]

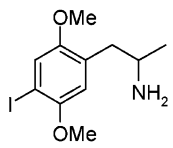
Further, 5-HT_{2A} receptor agonism has also been reported to be associated with hallucinogenic actions, blood platelet aggregation, and vasoconstriction.[61,62] For example, various lines of evidence indicate that the hallucinogenic actions induced by drugs such as LSD (lysergic acid diethylamide) and mescaline are attributed to their 5-HT_{2A} receptor agonist properties.[61] Thus, taken together, it is likely that functional subtype-selective 5-HT_{2C} receptor agonists will be important for identifying a safe treatment option for obesity.

Functional Characterization of Agonists at the 5-HT_2 Receptor Subtypes

For functional characterization of newly identified 5-HT_{2C} receptor agonists, functional data are nowadays generally based on measurements of a defined second messenger response, such as phosphoinositide hydrolysis or increase in intracellular calcium, at the human 5-HT_{2C}, 5-HT_{2A}, and 5-HT_{2B} receptors expressed in the same parental cell line, for example in CHO-K1 (Chinese hamster ovary K1) cells.[28,63] However, several other diverse functional models have been described in the literature for the pharmacological characterization of the 5-HT_2 receptor subtypes, that is, in vitro models (biochemical assays or tissue preparations) such as phosphoinositide hydrolysis in rat or pig choroid plexus (5-HT_{2C}),[64−66] phosphoinositide hydrolysis in rat cortex (5-HT_{2A}),[64] effect on human platelet aggregation (5-HT_{2A}),[67] contraction of rat jugular vein (5-HT_{2A}),[68] contraction of the isolated rat tail artery (5-HT_{2A}),[69] and contraction of isolated rat stomach fundus muscle strips (5-HT_{2B}),[70,71] as well as in vivo models such as head-twitch response in rodents (5-HT_{2A})[72] and penile erections in rats (5-HT_{2C}).[73]

However, comparisons of agonist potency and relative efficacy between studies may prove to be difficult; the data do not always reflect the literature in terms of absolute potency and relative efficacy. Apart from possible species differences, it should be kept in mind that functional data often are dependent on the in vitro or in vivo test system used. For example, the potency and efficacy of agonists in functional assays are highly dependent on receptor expression levels.[74] Both receptor−effector coupling and receptor reserve can show large variations from one system and/or tissue to the other. Additionally, the signal transduction characteristics of transfected receptors may be dependent on the identity of the host cell line.[28,63,75] Yet another complicating factor is the finding that the 5-HT_{2C} receptor undergoes post-transcriptional mRNA editing.[76] Such editing is associated with different G-protein-coupling efficiencies of the isoforms. It has been shown that 5-HT is less potent in stimulating phosphatidylinositol hydrolysis at edited versions of the 5-HT_{2C} receptor than at the nonedited 5-HT_{2C} receptor isoform INI.[76,77] Thus, several factors combine to make comparisons of functional data for the 5-HT_2 receptor subtypes reported across different laboratories a difficult task. For example, *m*-CPP has been shown to act as a partial agonist at the 5-HT_{2B} receptor in the rat stomach fundus ($pEC_{50} = 7.68$, relative efficacy of 38%).[71] However, at the human 5-HT_{2B} receptor expressed in HEK-293 (human embryonic kidney) cells, *m*-CPP has been reported to act as an antagonist ($pK_B = 7.5$)[78] whereas it acts as a partial agonist at the same receptor when expressed in CHO cells ($pEC_{50} = 6.98$, relative efficacy of 37.9%).[63]

Moreover, predicting in vivo responses from in vitro data may also prove to be difficult, which is illustrated by a recent study by Vickers et al.; administration of the preferential 5-HT_{2A} receptor agonist 2,5-dimethoxy-4-iodoamphetamine (DOI, **11**: $pEC_{50} = 8.86$, relative efficacy of 67% at the rat 5-HT_{2A} receptor as determined by measurements of calcium release) to rats resulted in a characteristic head-twitch response that could be blocked by a selective 5-HT_{2A} receptor antagonist.[79] In contrast, **12** (Ro-60-0175, vide infra) did not induce head-twitches in rats when given alone, although it behaves as an agonist at the rat 5-HT_{2A} receptor in vitro ($pEC_{50} = 6.78$, relative efficacy of 80% in a calcium release assay). It was suggested that the concurrent 5-HT_{2C} receptor agonist action of **12** ($pEC_{50} = 7.92$, relative efficacy of 90% at the rat 5-HT_{2C} receptor by measuring calcium release) might inhibit the 5-HT_{2A} receptor agonist-mediated head-twitch response. In fact, in rats pretreated with the selective 5-HT_{2C} receptor antagonist **9**, compound **12** induced a head-twitch response that could be blocked by a selective 5-HT_{2A} receptor antagonist.[79]



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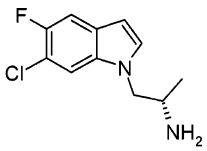

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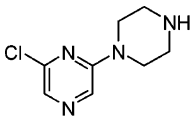
Overview of 5-HT$_{2C}$ Receptor Agonists: Prototypical or "Classical" Ligands

Arylpiperazine derivatives lacking a piperazine N4 substituent were among the first non-tryptamine-based 5-HT$_{2C}$ receptor agonists to be identified. These early agents are commonly used as pharmacological tools to probe 5-HT$_{2C}$ receptor function. The anorectic effects of arylpiperazines such as **5** (*m*-CPP) and **13** (MK-212) were known prior to the identification of the 5-HT$_{2C}$ receptor and its association with feeding regulation. *m*-CPP was patented by American Cyanamid in the 1960s as an appetite suppressant.[80] The pyrazine isoster of *m*-CPP (i.e., **13**) was patented by Merck & Co. for its anorectic effect in the 1970s[81] but was advanced into clinical trials for depression. However, it was dropped for this indication because of unconvincing results regarding therapeutic efficacy.[9] The involvement of the 5-HT$_{2C}$ receptor in the anorectic effect of *m*-CPP and its structurally related analogue 1-(*m*-trifluoromethylphenyl)piperazine (TFMPP, **14**) was originally implicated in 1988.[82,83] Yet another classic arylpiperazine known to induce hypophagia in rats is quipazine (**15**).[84] Like *m*-CPP, **13**, and TFMPP, quipazine has later been shown to have 5-HT$_{2C}$ receptor agonist properties.[85] Additional simple arylpiperzines structurally related to *m*-CPP and TFMPP, such as **16** and **17**, have been patented as anorectic agents in the early 1970s.[86,87] However, whether these agents actually exhibit 5-HT$_{2C}$ receptor agonist properties does not appear to have been published. A common feature of the early 5-HT$_{2C}$ receptor agonists is that these agents only show little binding selectivity, if any, toward the 5-HT$_{2C}$ receptor over 5-HT$_{2A}$ and 5-HT$_{2B}$ receptors as well as over 5-HT$_{1B}$ and 5-HT$_3$ receptors.[9,49,66,88] However, some agents show some degree of functional selectivity for the 5-HT$_{2C}$ receptor; *m*-CPP and TFMPP show lower relative efficacy at 5-HT$_{2A}$ and 5-HT$_{2B}$ receptors than at the 5-HT$_{2C}$ receptor. For example, *m*-CPP shows a relative efficacy of 65% at human 5-HT$_{2C}$ receptors, whereas it has relative efficacies of 22% and 24% at human 5-HT$_{2A}$ and 5-HT$_{2B}$ receptors, respectively, as determined by measurements of calcium release.[28]



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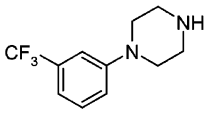

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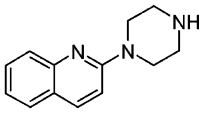

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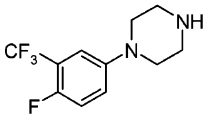

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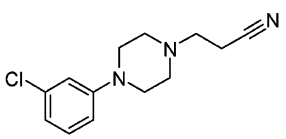

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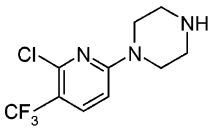
Recently Developed Ligands

In light of the extensive data supporting the therapeutic potential of 5-HT$_{2C}$ receptor agonists for the treatment of obesity, numerous reports on the development of 5-HT$_{2C}$ receptor agonist compounds have appeared in the literature in recent years. Research efforts at several pharmaceutical companies have resulted in the identification of potent and subtype-selective 5-HT$_{2C}$ receptor agonists with promising properties as potential antiobesity agents.

Organon (a business unit of Akzo Nobel) has developed the arylpiperazine **18** (ORG-12962), a compound that originally was patented as a preferential 5-HT$_{1B}$ receptor agonist having pK_i values of 7.0 and 5.6 for 5-HT$_{1B}$ and 5-HT$_{1A}$ receptors, respectively, in receptor binding studies.[89] However, it is now known that **18** also behaves as a partial agonist at human 5-HT$_{2C}$ receptors with low binding selectivity relative to human 5-HT$_{2A}$ receptors (K_i = 12 and 65 nM, respectively).[90] In functional in vitro assays measuring calcium release, this compound displays pEC$_{50}$ values of 7.01, 6.38, and 6.28, along with relative efficacies of 62%, 54%, and 41%, at the human 5-HT$_{2C}$, 5-HT$_{2A}$, and 5-HT$_{2B}$ receptors, respectively.[28] Although no study details were provided, **18** has been reported to be effective in an acute rat feeding model (minimum effective dose 3 mg/kg, po).[9] This compound has also been evaluated in phase II clinical trials for the potential treatment of depression.[91]

Another 5-HT$_{2C}$ receptor agonist from Organon is **19** (ORG-37684), which was developed by optimizing **18** for potency and selectivity. Although **19** exhibits improved affinity and selectivity for the human 5-HT$_{2C}$ receptor (K_i = 5 nM) over the human 5-HT$_{2A}$ receptor (K_i = 320 nM) compared to **18**, it displays poor functional selectivity, showing pEC$_{50}$ values of 8.17, 7.11, and 7.96, along with relative efficacies of 55%, 45%, and 34%, for the human 5-HT$_{2C}$, 5-HT$_{2A}$, and 5-HT$_{2B}$ receptors, respectively.[28,90] Compound **19** was originally considered for progression to phase I clinical studies as a potential antidepressant, while subsequent studies have demonstrated that this compound possesses anorectic properties by virtue of its action at 5-HT$_{2C}$ receptors.[92] The corresponding azetidine homologue **20** (ORG-36262) has a 5-HT$_2$ receptor binding profile similar to that of **19** (**20**: 5-HT$_{2C}$ K_i = 15 nM; 5-HT$_{2A}$ K_i = 500 nM).[90] Further, the bridged benzocycloocteenamine **21** (ORG-8484), with an absolute configuration determined as 5*S*,8*R*,9*S*, has only briefly been described by Organon. It was reported to exhibit 270-fold binding selectivity for the 5-HT$_{2C}$ (K_i = 6 nM) versus the 5-HT$_{2A}$ receptor (K_i = 1600 nM).[90] However, no data on its affinity for 5-HT$_{2B}$ receptors have been disclosed and no further development information about this compound appears to be available.



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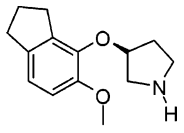

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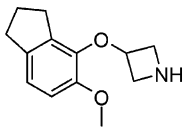

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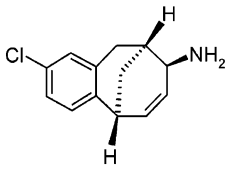
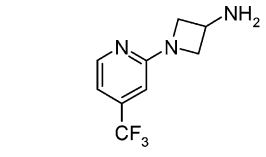


21

In an attempt to find suitable bioisosteres for the piperazine ring, researchers at Organon prepared and tested the 3-aminoazetidine analogue **22**. While the corresponding piperazine-based analogue **23** had appreciable affinity for the 5-HT$_{2C}$ receptor (K_i = 40 nM), it was evident that the 3-aminoazetidine moiety was not a promising bioisosteric replacement for the piperazine ring regarding 5-HT$_{2C}$ receptor activity because **22** was essentially inactive (K_i > 20 μM). Although being somewhat less

active than their piperazine counterpart (TFMPP, **14**), the "reversed" aminoazetidine (**24**) and oxyazetidine (**25**) analogues partially retained the affinity for the 5-HT_{2C} receptor; the observed K_i values were 60, 200, and 300 nM for **14**, **24**, and **25**, respectively.[90] Next, replacement of the piperazine ring in **14** by a 2-morpholinyl group produced 2-(3-trifluoromethylphenyl)morpholine (**26**).[9] The (+)-enantiomer of this compound showed increased affinity for the 5-HT_{2C} receptor (K_i = 25 nM) compared to **14** and was 40-fold selective over the 5-HT_{2A} receptor in receptor binding studies.[90] Curiously, the racemic version (i.e., **26**), also known as 1841 CERM, was originally reported to possess analgetic properties while no association with 5-HT_{2C} receptor activity was mentioned.[93]



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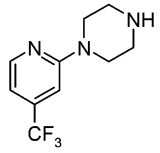

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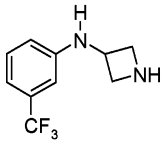

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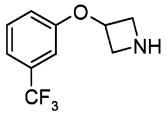

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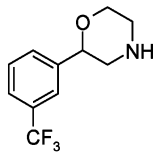


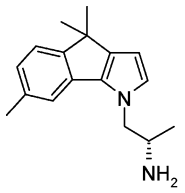
26

Hoffmann-La Roche in collaboration with Organon has developed the isotryptamine-based 5-HT_{2C} receptor agonist **12**. This compound has been reported to exhibit 32-fold binding selectivity for the human 5-HT_{2C} over the human 5-HT_{2A} receptor (pK_i values of 9.0 and 7.5, respectively) and >100-fold selectivity over other 5-HT receptors with the exception of the 5-HT_{2B} receptor at which it has high potency and efficacy (isolated rat fundus assay: pD_2 = 7.9, relative efficacy of 70%).[94] Moreover, according to a recent study, **12** also shows high binding affinity and agonist potency at the human 5-HT_{2B} receptor (pK_i = 9.26; pEC_{50} = 9.23, relative efficacy of 90%).[63]

The 1,4-dihydroindeno[1,2-*b*]pyrrole derivative **27** (Ro-60-0332) is another 5-HT_{2C} receptor agonist from the collaborative research effort between Hoffmann-La Roche and Organon. This compound displays binding affinities toward the human 5-HT_{2C} and 5-HT_{2A} receptors (pK_i values of 8.5 and 7.0, respectively) similar to those observed for **12**, while it displays lower agonist potency in the 5-HT_{2B} rat fundus assay (pD_2 = 6.1 vs 7.9).[94] At the human 5-HT_{2B} receptor, **27** has about 100-fold lower potency (pEC_{50} = 7.26, relative efficacy of 91%) than **12**.[63]

Interestingly, the *gem*-dimethyl groups present in the indeno substructure of **27** appear to protect from genotoxicity in the Ames test. This is because the corresponding analogue lacking the gem-dimethyl groups is positive in the Ames test. It has been suggested that dimethyl substitution of the indeno substructure reduces the DNA intercalating ability, resulting in loss of mutagenic activity.[95]

Both **12** and **27** have been reported to decrease food intake in rats after acute oral administration.[94] The hypophagic action of **12** in rats could be substantially reduced by pretreatment with **9**, suggesting that the effect depends on activation of 5-HT_{2C} receptors.[96] Compound **12** has also been observed to maintain a reduced body weight in lean rats following continuous subcutaneous infusion for 14 days.[40]



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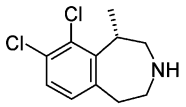

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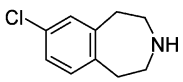
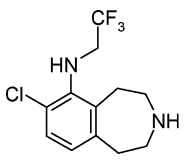


29

Arena has recently reported on a series of 3-benzazepines as 5-HT_{2C} receptor agonists.[97] From the biological data disclosed, it appears that the most interesting compound in terms of functional potency and selectivity is the 8,9-dichloro substituted benzazepine **28**. This compound, which has *S* configuration at the chiral center, displays EC_{50} values of 3 and 135 nM at the human 5-HT_{2C} and 5-HT_{2A} receptors, respectively. The corresponding relative efficacy values were estimated to be 90% (5-HT_{2C}) and 35% (5-HT_{2A}) as determined by measurements of [^{3}H]phosphoinositol turnover in HEK-293 cells. At the human 5-HT_{2B} receptor, **28** showed only 25% response relative to 5-HT at the highest concentration tested (10 μM). Although little information on in vivo activity is available, **28** has been stated to be active in an acute feeding model in rats following oral administration (decreased food intake with an ED_{50} value in the range 10−40 mg/kg over a 6-h period).[97] Curiously, the structurally related 7-chloro substituted benzazepine **29** has been claimed in a patent by Ciba-Geigy in the 1970s to possess anorectic activity and to be useful for the treatment of obesity. As seen from the description of the invention, **29** decreased food intake in rats after oral administration (10 mg/kg).[98] However, no implications regarding the mechanism of in vivo efficacy were disclosed in the patent. Interestingly, as seen from data on human 5-HT_2 receptors in the publication by Arena, **29** behaves as a 5-HT_{2C} receptor agonist with high functional selectivity over 5-HT_{2B} receptors whereas it retains moderate-to-high potency at the 5-HT_{2A} receptor (for 5-HT_{2C}, EC_{50} = 12 nM and relative efficacy is 85%; for 5-HT_{2A}, EC_{50} = 90 nM and relative efficacy is 100%; for 5-HT_{2B}, EC_{50} = 1000 nM and relative efficacy is 100%).[97]

Yamanouchi and, more recently, Eli Lilly have disclosed benzazepine analogues as 5-HT_{2C} receptor agonists that are structurally related to those developed by Arena.[99−101] For example, Eli Lilly's compound **30** has EC_{50} values of 12, 696, and 119 nM, along with relative efficacies of 106%, 71%, and 34%, at the human 5-HT_{2C}, 5-HT_{2A}, and 5-HT_{2B} receptors, respectively, in functional assays measuring [^{35}S]GTPγS binding.[100] Although no detailed in vivo data have been disclosed, **30** is reported to be active in rat feeding assays. For example, it decreased body weight gain in DIO rats in a dose-dependent manner after oral administration over 14 days.[100]



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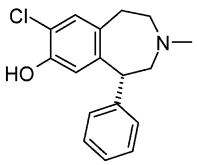

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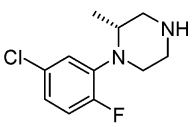


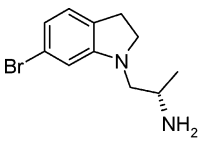
33

The benzazepine-based 5-HT_{2C} receptor agonists reported by Arena, Yamanouchi, and Eli Lilly bear some structural similarity to the well-known dopamine D_1 receptor antagonist **31** (SCH-23390) developed by Schering-Plough.[102] It may be worth noting that this compound also behaves as a potent and high-efficacy agonist at human 5-HT_{2C} receptors (EC_{50} = 2.6 nM, 92% efficacy versus 5-HT as seen from phosphoinositide hydroly-

sis).[103] However, another study reports lower relative efficacy for **31** at human 5-HT_{2C} receptors (32% in an assay measuring calcium release).[28]

From the series of 3-benzazepines, Arena has advanced the 5-HT_{2C} receptor agonist **32**[104] (APD-356) into clinical trials. The chemical structure of **32** has not yet been disclosed, but the compound is covered by a recently issued U.S. patent[105,106] (see Note Added in Proof). In a phase IIa clinical study involving 352 obese subjects, **32** caused a statistically significant average weight loss of 1.3 kg in obese patients taking the highest dose (15 mg/kg, po), compared to 0.4 kg for those on placebo, after once-daily administration for 28 days.[107,108] More recently, Arena has announced additional positive data from a subsequent phase IIb clinical trial with **32** in 469 obese patients; the drug produced a statistically significant average weight loss of 1.8, 2.6, and 3.6 kg at oral doses of 10 and 15 mg once daily and 10 mg twice daily, respectively, compared to 0.3 kg for the placebo group, after a 12-week treatment period.[109] Moreover, echocardiograms taken in patients at baseline and at the end of the study revealed no adverse effect of **32** on heart valves or pulmonary artery pressure.[109] Some preclinical data have also been reported for **32**. In terms of functional selectivity for the 5-HT_{2C} receptor it shows 22- and 171-fold selectivity versus 5-HT_{2A} and 5-HT_{2B} receptors with estimated EC_{50} values of 4.8, 105, and 823 nM for the human 5-HT_{2C}, 5-HT_{2A}, and 5-HT_{2B} receptors, respectively, as determined by measurements of phosphoinositide hydrolysis. Following a 14-day study in diet-induced obese Levin rats with **32**, weight loss at the highest dose (18 mg/kg, po, b.i.d.) was comparable to that observed with 6 mg/kg/day sibutramine. Furthermore, the in vivo experiment showed that **32** selectively reduced fat mass in the obese rats without affecting lean body mass. In this study, **32** (18 mg/kg b.i.d.) also improved metabolic parameters because it reduced plasma levels of leptin, insulin, glucose, triglycerides, and total cholesterol compared to vehicle-treated animals.[110]

Arena has also disclosed a series of arylpiperazine derivatives, structurally related to *m*-CPP, as 5-HT_{2C} receptor agonists in a recently published patent application.[111] Biological data were provided for two compounds. One of these, compound **33**, displayed EC_{50} values of 8 and 529 nM at the 5-HT_{2C} and 5-HT_{2A} receptors, respectively, while it was claimed to be essentially functionally inactive at the 5-HT_{2B} receptor, as determined by measurements of phosphoinositide hydrolysis. Compound **33** also reduced food intake in normal rats in an acute model after oral administration.[111]



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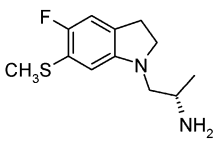

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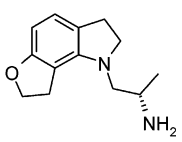
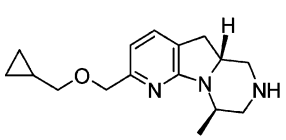


36

Vernalis in collaboration with Hoffmann-La Roche has published several promising 5-HT_{2C} receptor agonists. Some of these agents have been summarized in recent review articles.[112] More recently, indoline-based analogues typified by **34** (VER-3323), **35** (VER-5593), and **36** (VER-5384) were published.[113] Compound **34** displayed EC_{50} values of 44, 719, and 11 nM at the human 5-HT_{2C}, 5-HT_{2A}, and 5-HT_{2B} receptors, respectively. The corresponding relative efficacy values were 88%, 54%, and 78%, as determined by measurements of calcium release. Although **35** exhibited higher functional potency at the 5-HT_{2C} receptor (EC_{50} = 6.7 nM, relative efficacy of 97%) compared to **34**, it did not show functional selectivity over 5-HT_{2B} receptors (EC_{50} = 4.1 nM, relative efficacy of 72%). However, **35** still displayed some (11-fold) selectivity for the 5-HT_{2C} receptor over the 5-HT_{2A} receptor (EC_{50} = 76 nM, relative efficacy of 87%). Compound **36** (for 5-HT_{2C}, EC_{50} = 4.5 nM and relative efficacy is 98%; for 5-HT_{2A}, EC_{50} = 62 nM and relative efficacy is 81%; for 5-HT_{2B}, EC_{50} = 3 nM and relative efficacy is 74%) displayed a functional activity profile similar to that of **35**. When tested for their ability to decrease food intake in food-deprived rats, **34**−**36** significantly reduced feeding in a dose-dependent manner over 23 h following subcutaneous or oral administration. The minimal efficacious doses of these compounds following oral dosing were 30, 3, and 1 mg/kg, respectively.[113] Additionally, the hypophagic effect of **34** could be blocked by pretreatment with **9**.[12] The azaindoline derivative **37** with the *R*,*R* configuration has been identified in a subsequent study by the Vernalis/Hoffmann-La Roche collaborative team, displaying EC_{50} values of 15 and 23 nM, along with relative efficacies of 90% and 31% (calcium mobilization assay), at the human 5-HT_{2C} and 5-HT_{2B} receptors, respectively. At the human 5-HT_{2A} receptor, **37** behaved as an antagonist of 5-HT-induced calcium release (pK_B = 6.7). In vivo, **37** was found to produce a dose-dependent reduction in food intake in rats after acute oral administration, an effect that could be antagonized by **9**.[114]



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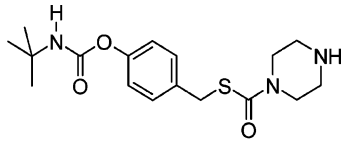

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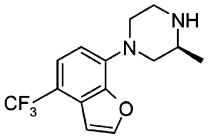


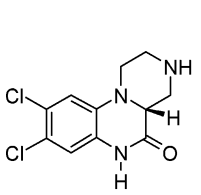
39

Perhaps an even more promising 5-HT_{2C} receptor agonist from Vernalis/Hoffmann-La Roche is the recently reported *S*-(4-*tert*-butylcarbamoyloxybenzyl) ester of piperazine 1-carbothioic acid (**38**, VER-8775). This compound has been described as a partial agonist at 5-HT_{2C} receptors (EC_{50} = 6 nM, relative efficacy of 69%) with 15- and 476-fold selectivity for 5-HT_{2C} over 5-HT_{2A} and 5-HT_{2B} receptors, respectively. Furthermore, **38** exhibited only low relative efficacy at 5-HT_{2A} and 5-HT_{2B} receptors (20% and 11%, respectively). In vivo, it was shown that **38** could reverse weight gain in DIO mice after oral dosing.[115]

Compound **39** (LY-448100) is an arylpiperazine-based 5-HT_{2C} receptor agonist from Eli Lilly that displays high binding affinity for 5-HT_{2C} receptors (K_i = 9 nM) and is claimed to be at least 15-fold selective over other 5-HT receptors. Functionally, it behaves as an agonist with high potency and efficacy at the 5-HT_{2C} receptor (EC_{50} = 8 nM, relative efficacy of 110%). Furthermore, **39** produced weight loss in DIO rats due to fat loss, while maintaining lean body mass, following 2 weeks of oral treatment.[14,116]

The "quinoxalinone" **40** (WAY-161503), which has the *R* configuration at the chiral center, is a 5-HT_{2C} receptor agonist developed by American Home Product (now Wyeth). As seen from receptor binding data, it has only 5- and 18-fold selectivity for the 5-HT_{2C} (K_i = 3.3 nM) versus the 5-HT_{2A} (K_i = 18 nM) and 5-HT_{2B} (K_i = 60 nM) receptors. In functional in vitro studies, using inositol monophosphate (IP1) formation as readout

in CHO cell lines expressing each of the human 5-HT_2 receptor subtypes, **40** displayed about 95-fold selectivity for 5-HT_{2C} (EC_{50} = 8.5 nM, full agonism) over 5-HT_{2A} receptors (EC_{50} = 802 nM, partial agonism) but no selectivity over 5-HT_{2B} receptors (EC_{50} = 6.9 nM, full agonism).[117,118] Compound **40** has also been shown to produce a sustained decrease in food intake and body weight in obese Zucker rats when administered ip over 15 days.[117]



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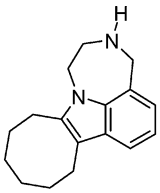

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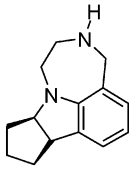
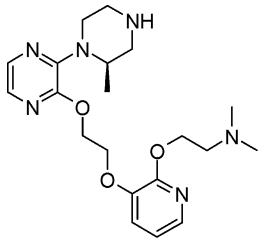


42

More recently, Wyeth has reported on a series of diazepinoindoles as 5-HT_{2C} receptor agonists. A representative compound is the cyclooctyldiazepinoindole analogue **41** (WAY-470), which showed K_i values of 13, 36, and >5000 nM for the human 5-HT_{2C}, 5-HT_{2A}, and 5-HT_{2B} receptors, respectively, in binding studies. As seen from the in vitro functional data (stimulation of IP1 production), **41** displayed relative efficacies of 102% and 80% at the 5-HT_{2C} and 5-HT_{2A} receptors, respectively. However, with respect to functional potency, only the EC_{50} value at the 5-HT_{2A} receptor (64 μM) was disclosed.[119]

Yet another recent 5-HT_{2C} receptor agonist from Wyeth is the diazepinoindoline derivative **42** (WAY-163909) having *R*,*R* configuration at the chiral centers. This compound is reported to be a potent and selective 5-HT_{2C} receptor agonist, displaying EC_{50} values of 8 nM, >10 μM, and 185 nM at the human 5-HT_{2C}, 5-HT_{2A}, and 5-HT_{2B} receptors, respectively.[120] With respect to efficacy, it acts as a nearly full agonist at the 5-HT_{2C} receptor (relative efficacy of 90%) and as a partial agonist at the 5-HT_{2B} receptor (relative efficacy of 40%) as determined by measurements of calcium release. Compound **42** reduced food intake in a number of animal models. For example, it produced a dose-dependent decrease in food intake over a 2-h test period in DIO mice after ip administration as well as in normal rats after both ip and oral administration. The anorectic effect of **42** in normal rats could be inhibited by pretreatment with the 5-HT_{2C} receptor antagonist **9**. Moreover, following a 10-day study in normal rats, once daily dosing with **42** (30 mg/kg, po) produced a statistically significant reduction in body weight gain from day 4 and onward, along with an observed 40% reduction in triglyceride levels at the end of the study.[120]

BVT.933 (**43**, structure undisclosed) is a 5-HT_{2C} receptor agonist developed at Biovitrum AB (formerly part of Pharmacia & Upjohn).[13] This compound has recently been reported to be effective in reducing food intake in ob/ob mice with a mechanism indicating increased satiety as revealed by meal pattern analysis (prolongation of the intermeal interval without affecting the size of individual meals). Moreover, continuous subcutaneous infusion of **43** via osmotic minipumps in DIO rats over 14 days produced a dose-dependent reduction of food intake and body weight throughout the study duration.[121] Interestingly, the preclinical finding regarding body weight is consistent with a study in humans. Although no clinical data on **43** have been published in peer-reviewed journals, it has been announced that the compound showed efficacy in a phase IIa clinical trial because it induced a statistically significant and clinically relevant reduction in body weight compared with placebo.[122] However, according to company press releases, Biovitrum and its development partner since 2002, GlaxoSmithKline, are now focused on developing other 5-HT_{2C} receptor agonists for obesity that possess greater 5-HT_{2C} receptor selectivity. A recent patent application from Biovitrum discloses a series of 5-HT_{2C} receptor agonists with excellent selectivity in receptor binding and functional assays. For example, the arylpiperazine **44**, a representative compound in this series, shows binding affinities with K_i values of 12, >1000, and >1000 nM at the human 5-HT_{2C}, 5-HT_{2A}, and 5-HT_{2B} receptors, respectively. This compound also exhibits a notable selectivity for the 5-HT_{2C} receptor in functional in vitro studies, showing EC_{50} values of 4.2, 1200, and 1940 nM, along with relative efficacies of 117%, 14%, and 16%, at the human 5-HT_{2C}, 5-HT_{2A}, and 5-HT_{2B} receptors, respectively, when evaluated for its ability to mobilize intracellular calcium.[123]



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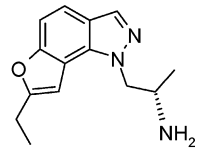
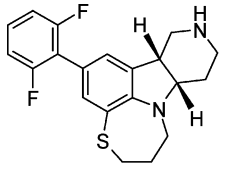


45

The indazole derivative **45** (YM-348) is a 5-HT_{2C} receptor agonist reported by Yamanouchi. Although it shows functional selectivity for the 5-HT_{2C} (EC_{50} = 1 nM, relative efficacy of 76%) over the 5-HT_{2A} receptor (EC_{50} = 93 nM, relative efficacy of 97%), it displays poor functional selectivity over the 5-HT_{2B} receptor (EC_{50} = 3.2 nM, relative efficacy of 110%) as determined by measurements of phosphoinositide hydrolysis in cell lines transfected with the human 5-HT_2 receptor subtypes.[124] An in vivo study showed that hypophagia induced by acute oral administration of **45** to Zucker rats could be inhibited by pretreatment with **9**.[125] It has also been reported that **45** may increase energy expenditure after oral administration to Wistar rats, an effect that could be significantly attenuated by predosing with **9**.[126] Moreover, a significant decrease in body weight gain was observed throughout the study period after subcutaneous infusion of **45** (3 and 30 mg/kg/day) in obese Zucker rats over 14 days. It was suggested that the maintenance of thermogenesis contributed to the observed weight loss. Additionally, plasma triglycerides and epididymal fat pad weight were significantly decreased at the 30 mg/kg/day dosage.[125]



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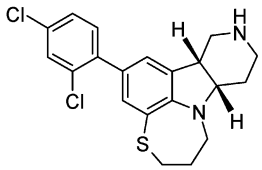

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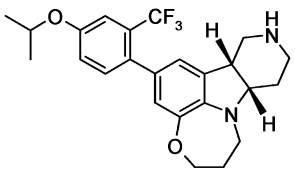
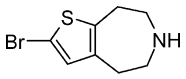


48

The 5-HT_{2C} receptor agonists **46** (IL-639) and **47** (IK-264) have been developed at DuPont Pharmaceuticals (now part of

Bristol-Myers Squibb (BMS)).[127] Compound **46** displays excellent affinity for the 5-HT_{2C} receptor (K_i = 5.2 nM, relative efficacy of 57%) and has about 250-fold selectivity over 5-HT_{2A} (K_i = 1440 nM) and 5-HT_{2B} (K_i = 1510 nM) receptors. The closely related analogue **47** binds with slightly lower affinity at the 5-HT_{2C} receptor (K_i = 10.5 nM, relative efficacy of 46%) and exhibits lower selectivity over 5-HT_{2A} (K_i = 406 nM) and 5-HT_{2B} (K_i = 209 nM) receptors. Both compounds were shown to be orally available and efficacious in a chronic model of feeding in male rats.[11,127] More recently, BMS reported some preclinical data on the partial 5-HT_{2C} receptor agonist **48** (A-37215), which is structurally related to **46** and **47**. Compound **48** binds at 5-HT_{2C} receptors with high affinity (K_i = 3.1 nM) and displays 294- and 108-fold selectivity over 5-HT_{2A} and 5-HT_{2B} receptors, respectively.[128,129] However, no information whether any of compounds **46**−**48** have advanced into clinical trials appears to have been published.



49

Yet another company investigating 5-HT_{2C} receptor agonists for obesity is Athersys. Two recently published patent applications from Athersys cover heteroaryl fused azepine and tricyclic indenopyrrole derivatives as 5-HT_{2C} receptor agonists.[130,131] For example, the thienoazepine derivative **49** was reported to have an EC_{50} value of <10 nM for ligand-induced calcium release in HEK-293 cells expressing human 5-HT_{2C} receptors.[130] According to recent meeting reports, Athersys has identified two lead compounds, ATH-88651 and ATHX-105 (structures undisclosed), that reduce food intake and body weight gain in preclinical models of obesity.[132,133]

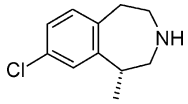
5-HT_{2C} Receptor Agonists in the Treatment of Obesity: Challenges and Clinical Outlook

As summarized above, there is substantial evidence supporting the concept that a selective 5-HT_{2C} receptor agonist should provide benefit in the treatment of obesity. Additional potential clinical opportunities for 5-HT_{2C} receptor agonists beyond obesity exist and have been summarized in previous reports.[8−10,13,14] Research efforts have identified several promising 5-HT_{2C} receptor agonists that display high functional selectivity over 5-HT_{2A} and 5-HT_{2B} receptors and also high selectivity over unrelated targets. The most advanced 5-HT_{2C} receptor agonist for the obesity indication appears to be **32** from Arena, which has recently undergone phase IIb clinical trials.[109]

Apart from long-term efficacy regarding weight loss, a 5-HT_{2C} receptor agonist will improve obesity-related comorbidities and risk factors, such as diabetes, dyslipidemia, and hypertension, to become a therapeutically useful antiobesity drug. Thus, 5-HT_{2C} receptor agonists will hopefully expand the choices of antiobesity agents provided that they can overcome the challenges of past and existing drugs with regard to safety, tolerability, and long-term efficacy. However, because of multiple pathways and compensatory mechanisms involved in the regulation of body weight, it will perhaps be necessary to use a combination of drugs (e.g., combinations of centrally acting agents with different mechanisms of action or of a centrally and a peripherally acting agent) to achieve long-lasting therapeutic efficacy.[134]

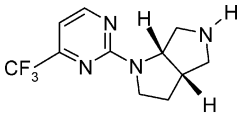
Note Added In Proof

During the editorial processing of this paper, the United States Adopted Names (USAN) Council has approved the nonproprietary name lorcaserin hydrochloride for Arena's developmental compound **32**.[135] The announced chemical structure of **32**, which has the *R* configuration of the chiral center, is as follows:[136]



32

Interestingly, researchers at Athersys have very recently identified 2,7-diazabicyclo[3.3.0]octane as a suitable isostere for piperazine in a series of 2-(2,7-diazabicyclo[3.3.0]octan-2-yl)pyrimidines as 5-HT_{2C} receptor agonists. Compound **50**, a prototypical compound from this series having *S*,*S* configuration at the chiral centers, showed decent functional potency at 5-HT_{2C} receptors (EC_{50} = 23 nM) but had only modest selectivity over 5-HT_{2A} (EC_{50} = 116 nM) and 5-HT_{2B} (EC_{50} = 62 nM) receptors, as determined by measurements of intracellular calcium release.[137]



50

Moreover, a further review on 5-HT_{2C} receptor agonists has recently been published.[138]

Acknowledgment. The author thanks Dr. Jan Svartengren for comments on the manuscript.

Biography

Björn M. Nilsson received his Ph.D. in medicinal chemistry in 1992 from Uppsala University (Sweden) under the direction of Prof. Uli Hacksell. In 1992, he joined the Glaucoma Research group at Pharmacia AB, Uppsala, focusing on the synthesis of prostaglandin derivatives as potential antiglaucoma agents. During the period 1997−2002, he was responsible for the medicinal chemistry activities in the 5-HT_{2C} receptor agonist project at Biovitrum AB (Pharmacia AB and Pharmacia & Upjohn prior to August 2001). He acted as Project Team Leader for the 5-HT_{2C} receptor agonist backup project in 2000.

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JM058240I