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We Need 2C but Not 2B: Developing Serotonin 2C (5-HT_{2C}) Receptor Agonists for the Treatment of CNS Disorders

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Abstract

The serotonin 2C (5-HT_{2C}) receptor has been identified as a potential drug target for the treatment of a variety of central nervous system (CNS) disorders, such as obesity, substance abuse, and schizophrenia. In this Viewpoint article, recent progress in developing selective 5-HT_{2C} agonists for use in treating these disorders is summarized, including the work of our group. Challenges in this field and the possible future directions are described. Homology modeling as a method to predict the binding modes of 5-HT_{2C} ligands to the receptor is also discussed. Compared to known ligands, the improved pharmacological profiles of the 2-phenylcyclopropylmethylamine-based 5-HT_{2C} agonists make them preferred candidates for further studies.

Keywords

drug discovery; medicinal chemistry; receptors; schizophrenia; serotonin

Introduction

We have worked for a number of years to identify the best possible 5-HT_{2C} receptor agonists for use in the treatment of a host of central nervous system (CNS) disorders. Herein, we provide a short overview of our efforts in this area of science together with our thoughts as to how these compounds might be used therapeutically.

The 5-HT_{2C} Receptor as a Drug Target for CNS Disorders

The serotonin 2C (5-HT_{2C}) receptor is a member of the super-family of G-protein-coupled receptors (GPCRs). First identified in 1984 from radioligand binding studies in the pig choroid plexus,[1] 5-HT_{2C} belongs to the subfamily of serotonin receptors, of which 14 different members (5-$HT_{1–7}$, some of these with further subclassifications) have been identified.[2] The 5-HT_{2C} receptor was originally designated as 5-HT_{1C}, but subsequent signal transduction pathway studies and amino sequence analysis revealed its close sequence

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homology with 5-HT_{2A} and 5-HT_{2B}; thus it was renamed as 5-HT_{2C}.[3] It exhibits 46–50% overall sequence identity with 5-HT_{2A} and 5-HT_{2B}, and all of these subtypes couple preferentially to $G_{q/11}$ to increase the hydrolysis of inositol phosphates and elevate cytosolic calcium concentrations. The 5-HT_{2C} receptor is the only known GPCR that has been found to undergo RNA editing, which affects its cell signaling, pharmacology, and brain function.[4]

Each subtype of serotonin receptors has a distinct distribution pattern. For the three 5-HT_2 subtypes,[5] 5-HT_{2A} is found in both central nervous system (CNS) and peripheral tissues such as gastrointestinal tissues and blood vessels. 5-HT_{2B} receptors are localized mainly in vascular and cardiac tissues. The expression of 5-HT_{2C} receptors, however, has been found to be restricted to the CNS, with negligible distribution in cardiac and vascular tissues. This feature of the 5-HT_{2C} receptor makes it an ideal target for the treatment of CNS disorders, as drugs targeting it would have limited peripheral side effects. 5-HT_{2C} has been found to play roles in a variety of CNS functions and pathological conditions, and 5-HT_{2C} agonists have been proposed to be potential therapeutics for many CNS disorders, such as obesity, schizophrenia, and substance abuse.[6]

One significant challenge for developing 5-HT_{2C} agonists as drug candidates is their selectivity against 5-HT_{2A} and 5-HT_{2B}, as the molecular determinants involved in ligand recognition by these receptors are highly conserved. More importantly, the activation of 5-HT_{2A} and 5-HT_{2B} receptors has been found to be related to hallucinogenic effects and cardiac valvulopathy, respectively.[7] Thus, the discovery of ligands possessing exquisite selectivity against 5-HT_{2A} and 5-HT_{2B} receptors is a key criterion for the advancement of 5-HT_{2C} agonists.

Selective 5-HT_{2C} receptor agonists

A number of selective 5-HT_{2C} agonists have been discovered in the past two decades,[8] and representative structures are shown in Figure 1, along with the endogenous ligand serotonin (5-HT, **1**). Pharmacological profiles of these compounds at the 5-HT_{2C}, 5-HT_{2A}, and 5-HT_{2B} receptors are summarized in Table 1.

As can be seen from Figure 1, all of these 5-HT_{2C} agonists have an amino group as a mimic of the primary amine in 5-HT. This group can be protonated at physiological pH and then engage in a charge–charge interaction with the receptor. The linker between the aromatic ring and the ammonium “head” contains between two and three C or N atoms. Compound RO 60-01752 (**2**) shares a similar backbone with 5-HT, and the α-methyl group was incorporated to suppress metabolic side chain deamination and to increase the lipophilicity of the compound. Of its enantiomers, the (*S*)-isomer showed better potency and selectivity.[9] RO 60-01752 displayed a moderate potency at 5-HT_{2C} receptors (EC_{50}=52 nM) and an eightfold selectivity over 5-HT_{2A}, but no selectivity against 5-HT_{2B} (Table 1).[10] YM-348 (**3**) is an orally active 5-HT_{2C} receptor agonist that was under investigation by Yamanouchi (now Astellas) for the potential treatment of obesity. It has a similar scaffold as RO 60-01752, into which a fused furan ring was incorporated. YM-348 showed excellent potency at 5-HT_{2C} receptors and good selectivity over 5-HT_{2A}, but little selectivity against 5-HT_{2B}.[10]

meta-Chlorophenylpiperazine (*mCPP*, **4**) was one of the earliest tool compounds used in pharmacological studies of the 5-HT_{2C} receptor.[11] Although it is a nonspecific serotonergic agent, *m*CPP showed moderate potency at 5-HT_{2C} and good "functional" selectivity over 5-HT_{2A} and 5-HT_{2B}, as the intrinsic efficacy of this compound is low at the latter two targets (Table 1). *m*CPP was one of the earliest compounds that was shown to induce satiety thereby reducing food intake in humans,[12] thus encouraging the development of 5-HT_{2C} agonists for the treatment of obesity. Compound CP-809101 (**5**), which shares an arylpiperazine core structure with *m*CPP, is the most potent 5-HT_{2C} agonist reported to date, showing an EC_{50} of 0.11 nM and good selectivity against both 5-HT_{2A} and 5-HT_{2B} receptors.[13] However, CP-809101 is relatively potent at 5-HT_{2B} receptors (EC_{50}=65.3 nM, E_{max}=57%), and its development has been discontinued due to the observation of genotoxicity in preclinical studies.[14]

Another series of 5-HT_{2C} agonists bear the benz[d]azepine or benzodiazepine scaffold, exemplified by the compounds lorcaserin (**6**), vabicaserin (**7**), and WAY-163909 (**8**). Lorcaserin was developed by Arena Pharmaceuticals,[18] and it showed a good pharmacological profile, with an EC_{50} of 9 nM at 5-HT_{2C} and good selectivity against the other two receptors.[15] It was approved by the US Food and Drug Administration (FDA) in 2012 for the treatment of obesity under the tradename Belviq. The homologues vabicaserin and WAY-163909 were developed by Wyeth (now Pfizer), both of which displayed good potency at the 5-HT_{2C} receptor. Vabicaserin is an antagonist of the 5-HT_{2A} receptor, while its functional efficacy at 5-HT_{2B} depends on the receptor density: it showed no activity at low receptor density but greater potency when tested at higher receptor density.[16] Vabicaserin has been studied in clinical trials for the treatment of acute schizophrenia.[19] It was well tolerated with no significant safety issues emerging, and it caused no weight gain. A proof of concept was achieved as 200 $mgkg^{-1}$ vabicaserin demonstrated therapeutic effects on both the positive and negative symptoms of the patients. However, vabicaserin failed to meet its primary endpoints in this trial (ClinicalTrials.gov Identifier: NCT00563706.). WAY-163909 was studied in various preclinical animal models of psychosis, but no clinical trial has been initiated.[17,20]

Developing 2-phenylcyclopropylmethylamines as selective serotonin 2C (5-HT_{2C}) receptor agonists

We initiated our research in this field by the high-throughput screening (HTS) of a chemical library of 800 compounds (Figure 2). Using this approach, the reversible monoamine oxidase (MAO) inhibitor tranylcypromine (**9**) was identified as a lead compound.[21] The first round of structure–activity relationship (SAR) studies identified its homolog **10** as a potent 5-HT_{2C} agonist (EC_{50}=13 nM), with good selectivity over 5-HT_{2A} and moderate selectivity over 5-HT_{2B}, respectively (Table 2). The introduction of a methyl group at position 5 gave compound **11**, with enhanced 5-HT_{2C} potency (EC_{50}=4.8 nM) as well as good selectivity against 5-HT_{2B}. Compounds with a *trans* configuration of the cyclopropane ring were found to show better potency than the *cis* isomers, and the (1*S*, 2*S*) absolute configuration is favored for compound **10**.[21]

In the second round of SAR studies, we discovered that the introduction of an alkoxy group into the *ortho*-position relative to the cyclopropylmethylamine moiety on the benzene ring led to significant improvements in terms of ligand efficacy and selectivity. Cyclopropylmethyl ethers provided the best selectivity profiles, exemplified by compounds **13-15** (Table 2). Compound **13** showed an EC_{50} of 21 nM at 5-HT_{2C}, while it is functionally selective against 5-HT_{2A} and 5-HT_{2B}, at which it showed E_{max} values below 30%. Compound **14** displayed a better profile, with an EC_{50}<10 nM and no activity at 5-HT_{2B}. Both compounds **13** and **14** were shown to normalize the phencyclidine (PCP)-disrupted prepulse inhibition (PPI) of startle in mice.[22] Removal of the 5-substituent led to compound **15**, which showed no activity at 5-HT_{2B} or 5-HT_{2A} and acted as a moderately potent 5-HT_{2C} partial agonist (EC_{50}=55 nM, E_{max} =61%).[23]

In the third round of SAR work, a multiparameter optimization process involving ligand efficacy and selectivity, pharmacokinetic (PK) properties, brain penetration profile, as well as toxicity potentials led to the discovery of compounds **16** and **17** as the best two agonists from this series of compounds.[24] Both compounds showed EC_{50} values below 5 nM at 5-HT_{2C} receptors, no activity at 5-HT_{2B}, and around 100-fold selectivity versus 5-HT_{2A} (Table 2). Their excellent pharmacological profiles position these two compounds as the best 5-HT_{2C} agonists reported to date. Both compounds showed efficacy in the amphetamine-induced hyperactivity model in mice,[24] and results from other schizophrenia-like animal behavioral tests (data not published) strongly support their advancement as therapeutic candidates for treating schizophrenia.

Homology modeling and putative binding preference of 2-phenylcyclopropylmethyl-amine-based 5-HT_{2C} agonists

Around 30 different GPCR crystal structures have been solved from among the >800 GPCRs present in the human genome (http://gpcr.usc.edu/index.html). However, the 3D structure of the 5-HT_{2C} receptor has yet to be disclosed. GPCR homology modeling is a commonly used approach for structure-based drug discovery (SBDD) and optimization when the structure of the target is unknown.[25] A β_2-adrenergic receptor based homology model has been generated and used to predict the possible binding modes of putative 5-HT_{2C} ligands to this receptor.[26] In our study, we used the β_2-AR structure in its inactive mode for generating a homology model of 5-HT_{2C} in its inactive mode, while the active mode model was generated by combining the resolved structure of the 5-HT_{2B} and the β_2-AR in its fully active state.[24] The binding modes of one of our best 5-HT_{2c} ligands, namely compound **16**, to the receptors were predicted by docking simulations, and the ligand was found to fit nicely into the active conformation of the 5-HT_{2C} homology model. The binding is stabilized by the ion pair between the ligand's ammonium group and Asp134 on TM3 along with various π–π and hydrophobic interactions.[24]

In the subfamily of serotonin receptors, the crystal structures of both the 5-HT_{1B} and 5-HT_{2B} receptors have been solved recently, both in their inactive conformations.[27] The homology model of the 5-HT_{2C} receptor described above displays considerable similarity to the reported crystal structure of the 5-HT_{2B} receptor. Interestingly, compound **16** shows nearly equivalent binding to both the 5-HT_{2B} and 5-HT_{2C} receptors (K_i=46 nM and 37 nM,

respectively).[24] However, the intrinsic activity of this compound is different at these two receptors, as it is a full agonist for 5-HT_{2C} while showing no agonism at 5-HT_{2B}. Thus, we anticipate that compound **16** shows a preference for the active conformation of the 5-HT_{2C} receptor and for the inactive conformation of 5-HT_{2B} (Figure 3). A more precise delineation of the structural basis for these results will require the determination of the X-ray structures of the 5-HT_{2C} receptor in both its active and inactive conformations, as well as of the 5-HT_{2B} receptor in its active conformation. Such information would greatly facilitate the rational design of selective 5-HT_{2C} agonists devoid of 5-HT_{2B} agonism in the future.

Summary and Outlook

The discovery of selective 5-HT_{2C} agonists has enabled the development of drugs or drug candidates that take advantage of the many roles this receptor plays in the CNS. To date, obesity is the only clinical indication for which a 5-HT_{2C} agonist, the marketed drug lorcaserin, has been approved by the FDA. However, certain restrictions apply to the use of lorcaserin for obesity, including its use in patients with a body mass index (BMI) of over 30, or a BMI over 27 who have at least one weight-related health condition, such as high blood pressure, type 2 diabetes, or high cholesterol. Furthermore, the moderate 5-HT_{2B} activity of lorcaserin has also been a concern as it might induce cardiac valvulopathy.[28] Due to the lack of availa bility of effective and safe anti-obesity drugs with other mechanisms of action in the marketplace,[29] the development of 5-HT_{2C} agonists with better selectivity profiles for this worldwide disease would be of great value.

It is also well known that behavioral and neurobiological commonalities coexist between obesity and drug addiction,[30] and that the use of 5-HT_{2C} agonists can be extended to the treatment of substance abuse.[6d] Lorcaserin attenuates self-stimulation and blocks the reward-enhancing effects of nicotine.[31] A clinical study of lorcaserin to evaluate its effect on smoking cessation has been completed; however, the results are yet to be disclosed (ClinicalTrials.gov Identifier: NCT02044874.). Considering the large number of tobacco smokers worldwide and the detrimental effects of this behavior on human health, as well as the limitations of existing therapies (e.g. varenicline and bupropion), including concerns about their safety,[32] the development of 5-HT_{2C} agonists for smoking cessation or drug abuse is a new field that warrants further exploration.

As mentioned above, 5-HT_{2C} agonists have been shown to function as potential therapeutics for the treatment of schizophrenia.[6b] The 5-HT_{2C} receptor is an advantageous target for treating schizophrenia as the activation of it specifically decreases mesolimbic dopamine release without affecting nigrostriatal dopamine.[20] Thus it is predicted to have antipsychotic efficacy while causing few extrapyramidal side effects (EPS). Also, the fact that 5-HT_{2C} agonists can induce weight loss means that such drugs would likely be devoid of the undesired side effect of weight gain and related metabolic disorders, which have been associated with most currently used antipsychotic drugs.[33] Although vabicaserin failed to meet its primary clinical endpoints in human trials, a proof of concept was achieved as some reduction in the positive symptoms of schizophrenia were observed. It should also be kept in mind that the high drop-out rates that were observed in this study may have contributed to the poor results.[19] We have evaluated our compounds in various schizophrenia-like animal

behavioral models, such as amphetamine-induced hyperactivity and amphetamine/PCP-disrupted PPI.[22,24] Results of our reported studies together with unpublished data strongly support these agents for further advancement as therapeutic candidates for the treatment of schizophrenia.

In summary, the development of selective 5-HT_{2C} agonists for the treatment of related CNS disorders such as obesity, substance abuse, and schizophrenia is a new and active direction. As stated above, selectivity is one of the most important criteria for the development of 5-HT_{2C} agonists. Compared with other reported compounds, the improved pharmacological profiles of 2-phenylcyclopropylmethylamine derivatives make them preferred candidates for further studies.

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Ernsberger P, Jayathilake K, Meltzer HY, Roth BL. Neuropsychopharmacology. 2003; 28:519–526. [PubMed: 12629531]

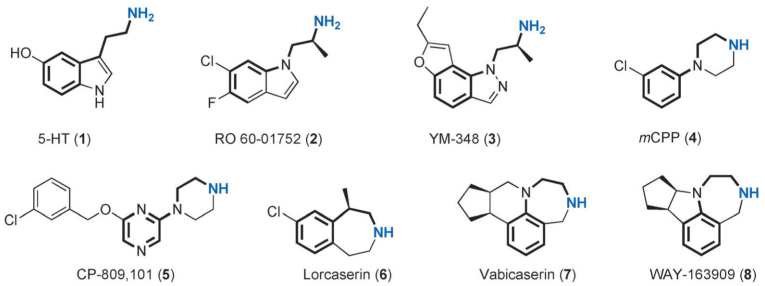

Figure 1.
Structures of 5-HT and representative 5-HT_{2C} selective agonists.

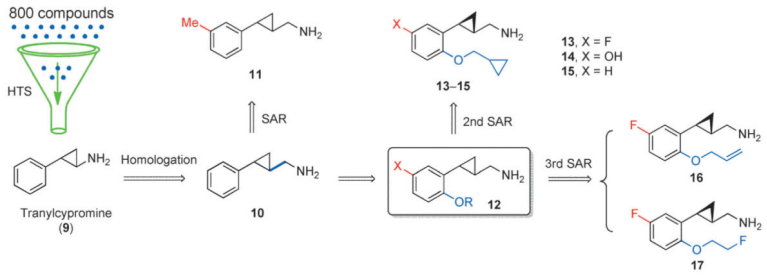

Figure 2.

Development of 2-phenylcyclopropylmethylamines as selective 5-HT_{2C} receptor agonists.

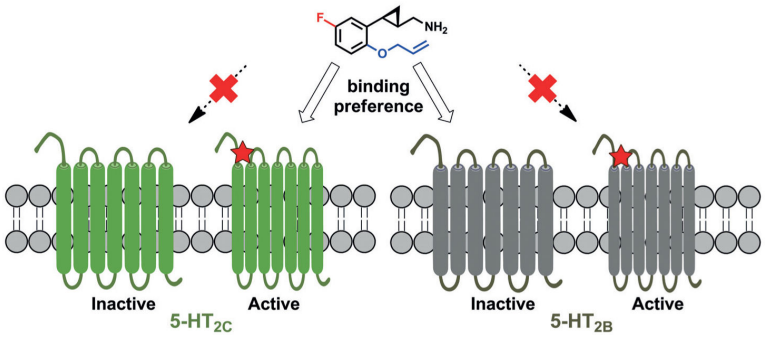

Figure 3.
Putative binding preference of 2-phenylcyclopropylmethylamine-based 5-HT_{2C} agonists.

Table 1

Pharmacological profiles of representative 5-HT_{2C} agonists.

Compound	5-HT_{2C}		5-HT_{2A}		5-HT_{2B}		Ref.
	EC_{50} [nM]	E_{max} [%]	EC_{50} [nM]	E_{max} [%]	EC_{50} [nM]	E_{max} [%]	
RO 60-01752	52±3	88±20	400±20	91±5	2.4±1	130±30	[10]
YM-348	1.0±0.2	76±1	93±10	97±2	3.2±3	110±10	[10]
*m*CPP	120±10	63±3	150±20	18±2	93±50	21±9	[10]
CP-809101	0.11	93	153	67	65.3	57	[13]
Lorcaserin	9±0.5	100	168±11	75	943±90	100	[15]
Vabicaserin	8	100	1650	–[a]	1.5[b] >10000[c]	80 –	[16]
WAY-163909	8±3	90±6	NE	NE	185±105	40±3	[17]

[a]Antagonist;

[b]Receptor density at 5000 fmolmg^{-1};

[c]Receptor density at 500 or 1500 fmolmg^{-1}. Values with errors represent the mean±SD; NE: no effect; – not applicable.

Table 2

Pharmacological profiles of 2-phenylcyclopropylmethylamine-based compounds.

Compound	5-HT$_{2C}$		5-HT$_{2A}$		5-HT$_{2B}$		Ref.
	EC$_{50}$ [nM]	E_{max} [%]	EC$_{50}$ [nM]	E_{max} [%]	EC$_{50}$ [nM]	E_{max} [%]	
9	2697	109	NA	–	>5000	29	[21]
(±)-10	13	96	1399	74	85	93	[21]
(+)-10 (1*S*, 2*S*)	5.2	108	1396	79	37	111	[21]
11	4.8	95	585	86	65	93	[21]
13 (X=F)	21	71	894	28	289	21	[22]
14 (X=OH)	9.3	70	372	18	NA	–	[22]
15 (X=H)	55	61	NA	–	NA	–	[23]
16	4.2	87	374	56	NA	–	[24]
17	3.4	89	359	76	NA	–	[24]

NA: no activity at 10 μM; – not applicable.