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Targeting the 5-HT_{2C} Receptor in Biological Context and the Current State of 5-HT_{2C} Receptor Ligand Development

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Abstract

Serotonin (5-HT) 5-HT_{2C} receptor (5-HT_{2C}R) is recognized as a critical mediator of disease-related pathways and behaviors based upon actions in the central nervous system (CNS). Since 5-HT_{2C}R is a class A G protein-coupled receptor (GPCR), drug discovery efforts have traditionally pursued the activation of the receptor through synthetic ligands with agonists proposed for the treatment of obesity, substance use disorders and impulse control disorders while antagonists may add value for the treatment of anxiety, depression and schizophrenia. The most significant agonist discovery to date is the FDA-approved anti-obesity medication lorcaserin. In recent years, efforts towards developing other mechanisms to enhance receptor function have resulted in the discovery of Positive Allosteric Modulators (PAMs) for the 5-HT_{2C}R, with several molecule series now reported. The biological significance and context for signaling and function of the 5-HT_{2C}R, and the current status of 5-HT_{2C}R agonists and PAMs are discussed in this review.

Keywords

5-HT_{2C} receptor; Agonists; Allosteric modulation; Positive allosteric modulators; Target selectivity; Signaling bias; Drug discovery; Ligand development; Pharmacological probes; Central nervous system disorders; Neurotherapeutics

1. INTRODUCTION TO THE 5-HT_{2C}R PROTEIN STRUCTURE AND FUNCTION

The G protein-coupled receptor (GPCR) super family, a vast group of proteins imbedded in cellular membranes, represents nearly one-third of all therapeutic targets [1]. Out of the approximately 800 different GPCRs identified in mammals, only 25% have been exploited for therapeutic development and the function of ~200 have yet to be elucidated [2]. The family of serotonin (5-HT) receptors (5-HT_XRs) are believed to be, from an evolutionary standpoint, among the oldest GPCRs [3]. There are seven classes of 5-HT_XRs: 5-HT_1R, 5-

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HT_2R, 5-HT_3R (a ligand-gated ion channel), 5-HT_4R, 5-HT_5R, 5-HT_6R, and 5-HT_7R, which are classified based on sequence homology and functional aspects. The 5-HT_{2C} receptor (5-$HT_{2C}R$), a receptor subtype in the 5-HT_2R family (5-$HT_{2A}R$, 5-$HT_{2B}R$, 5-$HT_{2C}R$) has been increasingly investigated as a therapeutic target in recent years. Like all other GPCRs, 5-$HT_{2C}R$ is characterized by seven transmembrane spanning helices (TM I – VII), three extracellular (ECL 1–3) and three intracellular loops (ICL 1–3), an intracellular carboxy-terminus, and an extracellular amino-terminus (Fig. 1) [4, 5]. Importantly, the X-ray crystal structure of the 5-$HT_{2C}R$ has recently been solved with non-selective 5-HT agonist ergotamine ("active-like" state) or the 5-HT_2R antagonist/inverse agonist ritanserin (inactive state), further allowing a critical review of the receptor's structural features and conformations for structure-based drug design (PDB: 6BQG) [5]. Reviewing the 5-$HT_{2C}R$ sequence, there is approximately 80% sequence homology in the TM region between members of the 5-HT_2R family, the region that forms the orthosteric binding site for 5-HT, while the ECL and ICL sequences are known to vary across receptor subtypes [6]. In addition to the sequence similarity of the orthosteric sites across the 5-HT_2R family that makes the selective chemotype targeting of 5-HT_2Rs difficult, there is the ubiquitous issue that 5-HT binding to all 5-HT_2R, including the 5-$HT_{2C}R$, results in activation of complex webs of intracellular signaling processes, several of which are inadequately appreciated at present.

The canonical G protein-dependent signaling through the 5-$HT_{2C}R$ is engendered by 5-HT-stimulated coupling to $G\alpha_{q/11}$ to activate the enzyme phospholipase C_β (PLC_β) mediated hydrolysis of phosphatidylinositol 4,5-biphosphate (PIP2) to generate the intracellular second messenger inositol-1,4,5-trisphosphate (IP_3), accumulation of the downstream IP3 metabolite inositol monophosphate (IP_1), and diacylglycerol (DAG) (Fig. 2). Intracellular calcium (Ca_f^{2+}) mobilization, frequently measured with calcium-binding fluorescent dyes, and IP_1 levels, assessed with [^{3}H]-inositol, are well-characterized to be elevated following the activation of the 5-$HT_{2C}R$ (for reviews) [7, 8]. In fact, the release of Ca_f^{2+} and/or IP_1 is often utilized as a readout in functional cellular assays to measure the extent to which the 5-$HT_{2C}R$ is activated [9].

5-$HT_{2C}R$ has also been shown to regulate ion channels and transport processes as well activate other downstream effectors, including Phospholipase A_2 (PLA_2), Phospholipase D (PLD), cyclic nucleotides, and extracellular signal-regulated kinases ($ERK_{1/2}$) [4, 10]. For instance, stimulation of the 5-$HT_{2C}R$ is thought to activate cytosolic PLA_2 which hydrolyzes arachidonic acid-containing phospholipids to produce free arachidonic acid and a host of its metabolites that are functionally relevant in this signaling web (for review) [11]. Agonist signaling bias can result in the activation of PLC_β over PLA_2, and vice versa, depending on the ligand that binds to the receptor [12]. Stimulation of the 5-$HT_{2C}R$ leads to the activation of protein kinase C (PKC) and downstream stimulation of the mitogen-activated protein kinase cascade resulting in the phosphorylation of $ERK_{1/2}$ [13, 14]. In fact, 5-$HT_{2C}R$ was shown to couple $ERK_{1/2}$ via a PLD-and PKC-dependent pathway possibly through $G\alpha_{12/13}$ proteins [14]. The PLD and PKC involvement in $ERK_{1/2}$ phosphorylation evoked by 5-$HT_{2C}R$ stimulation has recently been validated in a mouse hypothalamic cell line [15].

The signaling web for the 5-HT_{2C}R is influenced by the fact that this receptor is the only known GPCR that under-goes RNA editing [16]. Five closely spaced adenosines within the second intracellular loop of the 5-HT_{2C}R are subject to deamination by Adenosine Deaminases that Act on RNA (ADAR), resulting in adenosine to inosine substitution which alters the coupling efficiency between the receptor and its G protein and restricts its ability to activate intracellular cascades [17–21]. Editing allows the 5-HT_{2C}R to exist in 32 mRNA variants that encode up to 24 predicted proteoforms [22, 23]. Thus, mRNA editing is fundamentally important to normal 5-HT_{2C}R biological function [24]. In addition to the increased diversity of signaling afforded by RNA editing of the 5-HT_{2C}R, evidence is accumulating that signaling via the 5-HT_{2C}R is further diversified by the formation of oligomers, in fact the 5-HT_{2C}R appears to function as a homodimer [25]. Heterodimers are reported to form between the different isoforms of the 5-HT_{2C}R generated by RNA editing [26]. Likewise, 5-HT_{2C}R has been reported to heterodimerize with the ghrelin growth hormone secretagogue receptor 1α, the melatonin MT_2 receptor, and the N-methyl-D-aspartate-gated ion channel subunit GluN2A, and most recently with the 5-HT_{2A}R and 5-HT_{2B}R [27–32]. Intriguingly, the 5-HT_{2A}R:5-HT_{2C}R complex did not modify the $G\alpha_{q/11}$ coupling of the receptor subunits, but rather the 5-HT_{2C}R exerted dominance when in complex with the 5-HT_{2A}R, such that only the 5-HT_{2C}R coupled with the G protein to generate intracellular signaling; the 5-HT_{2A}R signaling is ‘masked’ [31]. Thus, 5-HT_{2A}R:5-HT_{2C}R protein complex appears to be a distinct molecular species, which contributes to cellular signaling, generating unique properties when co-expressed *in vitro* [31].

5-HT_{2C}R, as for other GPCRs, acts via the “receptor-some,” the composition of membrane, cytosolic and accessory proteins through which protein-protein interactions interface GPCR coupling to downstream intracellular signaling cascades to tailor cellular responsivity. For example, 5-HT_{2C}R interacts with PSD-95/disk large/zonula occludens domain-containing proteins, calmodulin, β-arrestins, and phosphatase and tensin homolog, and all of them have been shown to modulate receptor kinetics by varying mechanisms [4, 10, 33]. Of relevance, β-arrestins are known to play a key role in desensitization and resensitization processes that regulate the functional activity of 5-HT_{2C}R, and edited 5-HT_{2C}R isoforms have been shown to modify the kinetics of these processes due to divergent magnitudes of association with β-arrestin [34]. Agonist-dependent desensitization is associated with 5-HT_{2C}R phosphorylation involving G protein receptor $kinase_2$ (GRK_2), binding of β-arrestin and uncoupling of the receptor from the G protein to result in receptor internalization into endosomes; resensitization and recycling to the plasma membrane occur with dephosphorylation [17, 23]. Thus, there is a rich opportunity to regulate the biological function of the 5-HT_{2C}R.

The localization of the family of 5-HT receptors is region- and cell-specific throughout the body, and this is true for 5-HT_{2C}R, whose expression and function in the central nervous system (CNS) drives its primary, known biology. Serotonergic cell bodies project from the dorsal raphe nuclei in the midbrain to key brain regions associated with the reward pathway (*e.g.*, ventral tegmental area, VTA; nucleus accumbens, NAc) and higher executive function (*e.g.*, prefrontal cortex, PFC) [35, 36]. Postsynaptic expression of the 5-HT_{2C}R is reported in various neuronal cell types including those that employ acetylcholine, dopamine, and γ-aminobutyric acid (GABA) as neurotransmitters, with a major outcome of 5-HT_{2C}R

stimulation defined as the modulation of dopamine neuronal function (for review) [35]. For example, stimulation of the 5-HT_{2C}R in the VTA increases the firing rate of GABA interneurons, enhances basal GABA release in the VTA in a brain slice preparation, and decreases firing rates of dopaminergic neurons [37–39]. Interestingly, while 5-HT_{2C}R antagonists have been reported to increase dopaminergic neurotransmission and dopamine levels in the NAc, local activation of the NAc 5-HT_{2C}R *in vivo* suppressed potassium-stimulated GABA release [40–42]. Intriguingly, 5-HT_{2C}R has also been shown to be expressed on VTA dopamine neurons, including those that project to the NAc [43, 44]. 5-HT_{2C}R localized to VTA dopamine receptors has recently been demonstrated as a key regulator of their physiology as well as binge-like eating behavior in mice [45]. Thus, 5-HT_{2C}R controls dopamine neurotransmission within the VTA as well as its target regions in the limbic-corticostriatal circuit, including the NAc and medial prefrontal cortex (mPFC) (Fig. 3) [46, 47]. These data are but a fraction of research findings that illustrate the nature and complexity of cell- and region-specific roles of this receptor in neurobiology.

The interaction between the 5-HT_{2C}R and 5-HT_{2A}R was demonstrated in mPFC and the resulting signaling control *in vivo* is an underappreciated area of research that has recently provided clues to suggest therapeutic modalities for neuropsychiatric disorders [35, 36, 48]. A review of early work on this topic indicated a likely oppositional relationship between the 5-HT_{2A}R and 5-HT_{2C}R in the control of certain behaviors [49]. However, the relationship is now proving to be more interactive and synergistic in studies that show a combination of a selective 5-HT_{2A}R antagonist and selective 5-HT_{2C}R agonist can work in concert to suppress behaviors associated with substance use disorders (SUDs) in rodents, at doses far below the effective doses needed when administered independently [50]. This result also suggests a delicate balance of 5-HT_2R signaling in healthy individuals that necessitates reliable, selective 5-HT_{2C}R tool compounds for use in probing the mechanisms that underlie chronic psychiatric conditions. The clinical significance of selective 5-HT_{2C}R modulation alone has recently been validated by the approval of the 5-HT_{2C}R agonist lorcaserin (**14**, Fig. 5) for the treatment of obesity [51, 52]. Given the notion that 5-HT_{2C}R can exert inhibitory control over dopaminergic tone in brain regions that drive reward-related behaviors and cortical areas of the brain responsible for higher order executive functions related to acting impulsively and reacting to external cues, the development of 5-HT_{2C}R ligands is a promising approach to treating obesity, SUDs, and other neuropsychiatric conditions [53–55]. Additionally, improved and functionally diverse 5-HT_{2C}R agonists may enable beneficial combination therapies with 5-HT_{2A}R-acting medications. However, the development of selective small molecule 5-HT_{2C}R agonists remains a challenge and the chemical diversity of known synthetic 5-HT_{2C}R agonists is minimal.

2. 5-HT_{2C}R AS A THERAPEUTIC TARGET

5-HT_{2C}R has been targeted for the development of therapeutics for several chronic pathological disorders. Agonists have been suggested for the treatment of obesity, SUDs and impulse control disorders while antagonists may add value in the treatment of anxiety, depression and schizophrenia. In particular, a strong case for the use of a selective 5-HT_{2C}R agonist was made for obesity. The constitutive 5-HT_{2C}R knockout mouse exhibited hypophagia and increased body mass in the context of both insulin resistance and late-onset

obesity. Weight gain as well as a greater relative risk of metabolic dysfunction and diabetes occurs upon chronic treatment with atypical antipsychotics with 5-HT_{2C}R antagonist properties (*e.g.*, olanzapine) in humans and animals [56–59]. Selective 5-HT_{2C}R agonists have been consistently demonstrated to suppress food intake [56, 60–62], in fact, the selective 5-HT_{2C}R agonist WAY163909 dose-dependently decreased food intake in normal Sprague–Dawley rats, obese Zuker rats and mice with diet-induced obesity [63]. Investigations of 5-HT involvement in the mechanisms underlying satiety have focused predominantly on neural loci in the hypothalamus and midbrain/hindbrain circuits which synchronize energy balance and glucose homeostasis in concert with peripheral systems (for reviews) [64, 65]. Based upon these findings, lorcaserin (Belviq®) was approved by the U.S. Federal Drug Administration (FDA) as the first-in-class 5-HT_{2C}R agonist marketed for weight reduction in patients with a body-to-mass (BMI) index of >30 or with a BMI >27 comorbid with type-2 diabetes, hypertension or dyslipidemia [51, 66].

Extensive preclinical studies have also demonstrated the role of the 5-HT_{2C}R in the rewarding and incentive-salience value of cocaine, other psychostimulants, ethanol and, most recently, opioids as well as factors involved in relapse vulnerability during recovery from SUDs [35, 48, 67–69]. For example, employing the self-administration assay, the preclinical model with the best validity for human drug-taking, systemic administration of a selective 5-HT_{2C}R agonist suppressed cocaine intake and the resurgence of drug-seeking evoked by pretreatment with cocaine or exposure to cocaine-associated cues [*i.e.*, drug-taking environment, and the discrete cues associated with previous cocaine delivery (*e.g.*, lights, tones)] [70–72]. These effects of the 5-HT_{2C}R agonist are reversed by a selective 5-HT_{2C}R antagonist. Conversely, pretreatment with a selective 5-HT_{2C}R antagonist enhanced self-administration of low doses of cocaine and cocaine-evoked reinstatement of drug-seeking, while the selective 5-HT_{2C}R antagonist SB242084 is self-administered in primates [73–76]. In humans, lorcaserin improved smoking cessation rates and significantly decreased corticolimbic activation elicited by palatable food cue exposure, further supporting the role of the 5-HT_{2C}R in as a common mediator of reward and cue-associated events across abused drugs and palatable food [77, 78]. The added value of lorcaserin to suppress the rewarding effects of cocaine and other abused drugs imputes a further dimension of likely therapeutic utility [36, 48, 50], and lorcaserin is currently in clinical trials for Cocaine Use Disorder (CUD) and other SUDs (clinicaltrials.gov; accessed May 6, 2019).

Serotonin is one of the primary regulators of behavioral inhibition, a fundamental aspect of impulse control. Impulsivity, a predisposition toward rapid unplanned reactions to stimuli without regard to the negative consequences contributes to initial drug use and is perpetrated by continued use of the abused drug (for reviews) [79, 80]. Intriguingly, individuals with poor impulse control may be more vulnerable to drug-associated stimuli, and less capable of engaging processes that override heightened attentional bias for cues [81, 82]. The role of the 5-HT_{2C}R in these interlocked behavioral phenotypes has been demonstrated in that selective 5-HT_{2C}R agonists consistently reduce and the 5-HT_{2C}R antagonist SB242084 enhance motor impulsivity, while mice with a constitutive loss of the 5-HT_{2C}R exhibit elevated motor impulsivity [33, 71, 83–85]. The status of 5-HT_{2C}R function in the mPFC appears to be a contributor to the vulnerability of impulsive rats to cocaine reward and

sensitivity to cue-associated relapse vulnerability, which is interwoven with vulnerability to endogenous factors (*e.g.*, craving, stress, withdrawal), all of which can serve as immediate antecedents to relapse [48, 86]. Relapse is a major hurdle for the successful treatment of chronic SUD and a pharmacotherapy that can improve inhibitory control would represent a first-in-class drug for those sufferers [87, 88]. Thus, the 5-HT_{2C}R is a potential therapeutic target at the intersection of disinhibited behaviors that contribute to obesity and SUD. Given that obesity is at epidemic levels in the U.S. while drug overdoses and SUDs continue to drive unprecedented mortality and morbidity rates, targeting the 5-HT_{2C}R is an attractive and urgent approach towards the development of a neuropharmacotherapy to treat these intractable public health concerns.

Selective targeting of the 5-HT_{2C}R remains a challenge for medicinal chemists primarily due to the fourteen 5-HT receptor subtypes distributed throughout the body in various cell types and tissues and that each receptor accommodates 5-HT at a conserved orthosteric binding site. It is well established that, when only comparing the 5-HT_2R subtypes (5-HT_{2A}R, 5-HT_{2B}R, and 5-HT_{2C}R), receptor subtype selectivity is a major determining factor with regard to the scale of potential therapeutic utility (Fig. 4). With the understanding that 5-HT_{2A}R or 5-HT_{2B}R agonists are expected to evoke hallucinations or cardiac valvulopathy, respectively, the need for 5-HT_{2C}R orthosteric agonists that lack demonstrable efficacy at 5-HT_{2A}R and 5-HT_{2B}R sharpened [89, 90]. For example, the potent 5-HT releaser fenfluramine was approved and marketed in the U.S. as an appetite suppressant in combination with the norepinephrine releaser phentermine (Fen-Phen) in 1983. A proportion of patients treated with fenfluramine developed pulmonary hypertension and valvular heart disease, resulting in its withdrawal from the market in 1997 and subsequent legal damages exceeding $10 billion U.S. [91]. Activation of the 5-HT_{2B}R on heart values by the fenfluramine metabolite norfenfluramine is the primary pathogenic mechanism [90]. An additional example of this scale in clinical utility stems from concern over lorcaserin which has a low potential for abuse but could lead to positive subjective effects at supratherapeutic doses, based upon its action as a partial agonist at the 5-HT_{2A}R, which is responsible for hallucinogenic actions [92]. The FDA deliberations let to a Schedule IV classification for lorcaserin under the Controlled Substances Act. Thus, the therapeutic utility of lorcaserin (**14**; Fig. 5) in the general population is limited by concern of side effects [92, 93].

3. THE CURRENT STATE OF 5-HT_{2C}R AGONISTS

Targeting the 5-HT_{2C}R for therapeutic purposes has led to the discovery of many ligands that vary in activity and selectivity yet, in a general sense, come from very similar chemotypes. A brief structural survey of the most selective 5-HT_{2C}R agonists highlights the lack of chemical diversity, which in turn leads to a limited selection of tool compounds (Fig. 5). Coupled with the reality that the 5-HT_2R subtype orthosteric sites share high homology, agonists that lack diverse scaffolds are historically unlikely to overcome the subtype selectivity challenge. Virtually all compounds shown in (Fig. 5) rely on the phenethylamine moiety or a derivative thereof. More accurately, each of the indicated agonists require a general scaffold that incorporates an aromatic ring attached to an ionizable nitrogen via a two-three atom linker, usually carbon (Fig. 5). While many examples of 5-HT_{2C}R agonists from the aforementioned chemotypes are known, most do not demonstrate an acceptable

functional selectivity for the 5-HT_{2C}R over the 5-HT_{2A}R and 5-HT_{2B}R (Table 1). Though several compounds show promise, even the most selective compounds are similar to **14**, while the most selective compound listed herein, CP-809101 (**10**), has been shown to produce genotoxic effects [94]. As observed in early work on 5-HT_{2C}R agonist discovery, novel scaffolds that deviate from the traditional chemotype and can selectively target the 5-HT_{2C}R are difficult to discover and further exploration of chemical space may yield therapeutically important scaffolds.

Within the past few years, there has been renewed attention on the 5-HT_{2C}R and innovative drug discovery strategies have been employed to probe the chemical space for 5-HT_{2C}R agents and also to uncover unique functional characteristics of the 5-HT_{2C}R. Towards novel chemotype discovery, Wacker and co-workers at Bristol-Myers Squibb reported a series of analogues lacking a basic amine interaction at the active site Asp 134 residue, which is a requisite interaction for traditional 5-HT_{2C}R synthetic agonists and 5-HT [109]. Noteworthy contributions from this work included the screening of ligands in cells expressing the edited (VNV) isoform of the 5-HT_{2C}R containing a residue mutation, replacing the active site Asp 134 residue with Ala (D134A). This mutant allowed the subsequent screening of agonist hits, found via traditional compound library screening techniques, to selectively identify and optimize atypical agonists. Compound **20** was obtained after rounds of optimization to a non-basic heterocyclic amide agonist hit and was administered orally to rats, displaying a reduction in food intake that could be reversed via a 5-HT_{2C}R antagonist (Fig. 6). Additionally, Wacker and co-workers reported that the initial hit compounds were discovered during a search for 5-HT_{2C}R positive allosteric modulators (PAMs), further demonstrating the increased interest in diverse approaches for potentiating 5-HT_{2C}R signaling.

A phenomenon in GPCR signaling known as signaling bias or functional selectivity is evident under conditions in which an agonist displays divergent levels of activation through the multiple signaling pathways linked to receptor activation. Functional selectivity is well-characterized for the 5-HT_{2C}R [23, 101]. For example, compounds **7** and **8** reported by Kozikowski and colleagues display preferential activation through the $G\alpha_q$-mediated signaling pathway (Fig. 5) [101]. Significantly, incorporation of the *N*-benzyl moiety that differentiates **8** from **7** leads to a complete loss of function at the 5-HT_{2B}R, while retaining efficacy for the 5-HT_{2C}R. This compound (**8**) suppressed amphetamine-induced hyperactivity in rodents, consistent with the efficacy of other 5-HT_{2C}R agonists [101]. Additionally, a recent manuscript by Booth and coworkers provides a further investigation into 5-HT_{2C}R desensitization after agonist activation, which is understood to be mediated to some extent by the β-arrestin signaling pathway [110]. Multiple agonists were tested in a PLC_β-activation desensitization assay, including 5-HT (**1**), **14** and *m*-chlorophenylpiperazine (*m*CPP) (**9**) (Fig. 5). The magnitude of 5-HT_{2C}R-mediated PLC_β activation correlated with desensitization in their assay. Furthermore, the selection of agonists was assessed in a β-arrestin recruitment assay, where a correlation between desensitization and β-arrestin recruitment was observed. Expanded chemical space, functional selectivity, and 5-HT_{2C}R desensitization are concepts that, when incorporated into ligand discovery, will greatly aid in the development of novel 5-HT_{2C}R agonists with improved selectivity and functional

profiles. However, there continues to be a lack of subtype selective, novel chemotypes that display significant clinical potential, which is evidenced by a recent surge of interest in targeting spatially distinct, allosteric binding sites.

4. BACKGROUND AND RATIONALE FOR 5-HT$_{2C}$R ALLOSTERIC MODULATORS

Agonists and antagonists targeted to GPCRs that are traditionally designed to bind to a receptor orthosteric site, which has co-evolved with an endogenous ligand for a given receptor. However, in many cases, endogenous signaling ligands activate multiple receptors that are classified in a family. To accommodate the same signaling ligand, the orthosteric site is highly conserved among GPCR family members, which may modulate diverse physiological functions in distinct tissues. Exemplary GPCR families include the metabotropic glutamate receptors (mGluRs) and 5-HT$_X$Rs which are comprised of eight and 14 receptor subtypes respectively [67, 111]. Thus, targeting the orthosteric site of the 5-HT$_{2C}$R among closely related subtypes, 5-HT$_{2A}$R and 5-HT$_{2B}$R, has remained a challenge for medicinal chemists.

One strategy that has emerged over the past decade for the selective modulation of GPCRs is the identification and targeting of allosteric sites, which are defined as ligand binding sites that are spatially distinct from an orthosteric site [112]. In many cases, allosteric sites have proven to be less conserved than the respective receptor orthosteric sites, leading to improved ligand selectivity across subtypes [113–116]. Thus, allosteric modulation provides an opportunity to specifically target receptors that belong to a subfamily of similar GPCRs, potentially minimizing off-target effects, a significant advantage over typical agonists that at the endogenous ligand binding pocket. Additionally, most GPCR-targeted neurotherapeutic regimens result in chronic exposure of the receptor to orthosteric ligands, differing from the temporal control of endogenous ligands, which has been shown to alter 5-HT$_{2C}$R trafficking kinetics due to internalization and desensitization and resensitization processes [110, 117]. An allosteric modulator may minimize the aforementioned detrimental effects of synthetic agonists by maintaining the natural spatial and temporal signaling characteristics that are key features of neuronal circuitry [118]. Additionally, the fine-tuning of GPCR signaling may be afforded by allosteric ligand structural modifications that result in separate control of orthosteric ligand affinity or efficacy [119].

Theoretically, small molecule allosteric modulators of the 5-HT$_{2C}$R can promote a conformational change in the receptor or stabilize certain conformational populations of the receptor that produce several possible outcomes when coupled with agonist (*e.g.*, 5-HT) binding: (i) positive allosteric modulators (PAMs) increase the binding affinity and/or efficacy of orthosteric ligands, (ii) negative allosteric modulators (NAMs) decrease binding affinity and/or efficacy of the orthosteric ligand, and (iii) neutral allosteric ligands (NALs) bind to the allosteric site without actuating a change in orthosteric ligand binding or efficacy [120–122]. Another important, yet understudied aspect of 5-HT$_{2C}$R allosteric modulation is the potential leveraging of biased signaling (*i.e.*, promotion of one signaling pathway over another at the same receptor) or probe dependence (differing signaling outcomes based on

the identity of the orthosteric ligand), which may be exploited as a novel modality toward the treatment of complex neuropsychiatric disorders (Fig. 7) [123]. Importantly, from a structural biology perspective, rapid progress is being made in the analysis of structural determinants for allosteric modulator function at well-studied GPCRs and an X-ray crystal structure of the 5-HT_{2C}R is now available that is amenable to allosteric modulator docking and modelling [5, 124]. From the pharmacology and medicinal chemistry perspectives, key concepts with regard to GPCR allosteric modulator discovery and development have been extensively analyzed and reported, with a major focus on mGluR and muscarinic receptor allosteric modulators [125, 126]. These insights on how to approach the development of GPCR allosteric modulators lay the groundwork for the exploration of allosteric modulation at other GPCRs, including efforts to develop allosteric modulators for the 5-HT_{2C}R [127].

Certain distinctive challenges exist in the development of GPCR allosteric modulators, which are applicable to the 5-HT_{2C}R (see reviews) [113, 116, 128]. For instance, less-conserved allosteric sites across a subfamily of receptors (*e.g.*, 5-HT_2Rs) that are a result of decreased evolutionary pressure at these sites might lead to residue or structural differences in the allosteric site of the 5-HT_{2C}R between species. Additionally, most drug discovery initiatives in this arena ascribe pharmacological profiles to discovered compounds based upon screening in cells expressing the human unedited (INI) 5-HT_{2C}R, however, this is not the most abundant isoform localized in brain and the importance of the diversity of signaling afforded by RNA editing of the 5-HT_{2C}R is left out of the equation of developing new ligands in this chemical space. The potential of probe dependence of novel 5-HT_{2C}R allosteric modulators necessitates careful selection of orthosteric ligands for assays in which the endogenous ligand 5-HT is a preferred choice. However, efforts to selectively potentiate the FDA-approved anti-obesity medication and 5-HT_{2C}R agonist **14** at the 5-HT_{2C}R over other 5-HT_2Rs should preferentially employ **14** in cell-based screening assays. Further, allosteric modulator design may suffer from a featureless or “flat” structure-activity relationship (SAR) if only binding affinity or efficacy is considered without appreciation of other parameters such as the cooperativity between the affinity and efficacy of the allosteric and orthosteric ligands. Elegant work has been accomplished to aid in the quantification of allosteric effects through the development of the “operational model of allostery”, which may be employed to aid the analysis of SAR and appropriately define allosteric modulator mechanism [114]. Given that 5-HT_{2C}R agonists interact at the conserved orthosteric site of the receptor and, in general, 5-HT_{2C}R agonists are of similar chemotypes, PAMs targeting a topologically distinct site may be ideal for the discovery of selective small molecules with expanded clinical utility.

5. THE CURRENT STATE OF 5-HT_{2C}R POSITIVE ALLOSTERIC MODULATORS

The design of allosteric modulators for GPCRs is a relatively recent endeavor and interest in designing allosteric modulators for numerous, diverse GPCRs is increasing (see reviews) [112, 113, 129]. Very few examples of allosteric modulators of 5-HT_XRs are known. Provided with consistent evidence that activation of the 5-HT_{2C}R will afford therapeutic

benefits, it is presumed that 5-HT_{2C}R PAMs will engender therapeutic benefits alongside the intrinsic advantages of allosteric modulation.

The discovery of PNU-69176E (**21**) as the first known subtype-selective 5-HT_{2C}R PAM was the result of an early, undescribed screening of a chemical library by Pharmacia (now Pfizer) in 1999 (Fig. 8) [130]. Structurally, **21** is an analogue of the natural product antibiotic lincomycin (**23**) and a derivative of the clinically available clindamycin (**24**) (Fig. 8) [131]. As such, **21** was likely the product of an antibiotic medicinal chemistry campaign. The compound consists of three readily identifiable fragments. At the core is a piperidinyl carboxamide displaying a 2,4-*cis* geometry. A distinct Polar Head (PH) moiety comprised of an α-D-galactopyranoside and an undecyl lipophilic tail (LT) contribute to the stereochemistry- and sp^3-rich (tetrahedral) framework, a significant departure from known 5-HT_{2C}R activators and small molecule therapeutics in general [132]. The natural product-like framework can allow for a more robust exploration of the chemical space in three-dimensions versus the typical sp^2-rich (planar) carbon frameworks commonly employed in medicinal chemistry as a result of the current state of metal-mediated coupling chemistry. However, the calculated physicochemical parameters of **21** are less than ideal according to Lipinski's Rule of Five [*e.g.*, total polar surface area (TPSA) = 111.04, ClogP = 4.90, molecular weight (MW) = 537.21, hydrogen bond donors (HBD) = 5].

Our team validated 5-HT_{2C}R PAM activity for compound **21** via in-house synthesis and pharmacological characterization in a cell-based assay used to measure Ca_i^{2+} release as a result of 5-HT_{2C}R activation [132]. Compound **21** potentiated Ca_i^{2+} release evoked by 5-HT [0.3 nM, a concentration that induced ~20% of maximal Ca_i^{2+} release (EC_{20})] in cells stably expressing physiological levels of the unedited (INI), human isoform of the 5-HT_{2C}R. Subsequently, **21** or its diastereomer were added to provide titration curves used to elucidate the extent to which **21** potentiated Ca_i^{2+} release in the presence of 5-HT [132]. We found that **21** enhanced 5-HT-induced Ca_i^{2+} release over a range of concentrations. On the other hand, the diastereomer did not potentiate 5-HT_{2C}R-mediated signaling under the same conditions, indicating a stereochemical requirement for the PAM activity. Consistent with PAM activity, **21** did not display intrinsic activity as a 5-HT_{2C}R agonist. Furthermore, the **21** did not alter Ca_i^{2+} release in cells stably expressing the highly homologous human 5-HT_{2A}R, underscoring that this scaffold-type can allow for subtype selective targeting of 5-HT_2Rs.

An additional compound that was characterized in earlier work as an allosteric modulator of the 5-HT_{2C}R was oleamide (**22**), the primary amide of oleic acid (Fig. 8). Structurally, oleamide contains a primary amide and a long hydrophobic tail that contains 17 carbons and a *cis*-double bond at the 9-position. Compound **22** was discovered to exist in the cerebrospinal fluid of sleep-deprived cats and has been shown to modulate sleep in rats [127]. Evidence of its *de novo* synthesis from rat brain microsomes has been reported [133–135]. This naturally occurring compound has been reported to exhibit a complex pharmacological profile interacting with systems including cannabinoid receptors and various 5-HT_XRs [136, 137]. Initial investigations illustrated that **22** positively modulated 5-HT-induced 5-HT_{2A}R- and 5-HT_{2C}R-mediated chloride currents in *Xenopus* oocytes [138]. A follow-up study demonstrated that **22** may act as an allosteric modulator at the 5-HT_{2A}R

by increasing 5-HT-induced potentiation of phosphoinositide hydrolysis *in vitro* while no effect was observed in the absence of 5-HT. Additionally, in the same study, **22** acted as a NAM at the 5-HT_7R, leading to a decreased production of cyclic adenosine monophosphate (cAMP) in the presence of 5-HT. However, in the absence of 5-HT, **22** displayed partial agonist activity and promoted cAMP production *via* an allosteric site [139]. An analysis of **22** and related compounds was conducted to establish ligand subtype selectivity with respect to the 5-HT_{2A}R versus the 5-HT_{1A}R. Compound **22** displayed no selectivity and potentiated signaling through both receptor subtypes in the presence of 5-HT [137]. In addition to functional modulation of the 5-HT_7R, **22** induced a robust increase in 5-HT binding affinity to the 5-HT_7R orthosteric site [140]. Behavioral pharmacological studies in rodents agree with the *in vitro* observations [135, 136, 141]. Given the complex pharmacology of **22**, further investigation into the optimization of this compound as a potential therapeutic is warranted.

Recently, three groups have embarked on drug discovery campaigns to identify 5-HT_{2C}R PAMs and as a result, there are three new synthetic 5-HT_{2C}R lead PAMs that display interesting scaffold diversity (Fig. 9). In a trend seen among other GPCR allosteric modulators, these compounds are characterized as generally lipophilic, with each displaying a CLogP greater than 4, as calculated by the BioByte algorithm *via* ChemDraw Professional. While lipophilic small molecules are understood to engender an enhanced ability to pass through the hydrophobic cell phospholipid bilayer and passively diffuse into the CNS, additional pharmacodynamic obstacles are faced when compounds are highly lipophilic [142–144]. Thus, these 5-HT_{2C}R PAMs represent the beginning stages of drug discovery in this space.

López-Rodríguez and colleagues reported the first of the recent synthetic 5-HT_{2C}R PAMs, VA012 (**25**), in a manuscript published in 2017 (Fig. 9) [142]. The team from Vivia Biotech implemented a proprietary high-throughput screening method based on whole-cell flow cytometry, termed Ex-viTech, in which ~1,600 small molecules from an in-house library were screened against the 5-HT_{2C}R at 10 μM concentration in HeLa cells stably expressing physiological levels of the human 5-HT_{2C}R. In the same manner, hits from the 5-HT_{2C}R-based assay were counter-screened at the 5-HT_{2A}R and 5-HT_{2B}R. Hit compound activity was validated *via* a functional cell-based assay designed to measure IP_1 levels, a well-known component of the $G\alpha_q$ signaling cascade. The reported compounds are characterized by a common 1-benzyl-1*H*-indole scaffold with various cyclic and heterocyclic moieties substituted at the 3 position. The necessity of an aromatic moiety at the indole 1 position was probed by substituting a cyclopropane ring in this position, which resulted in the loss of PAM activity. The project yielded **25**, which was subsequently evaluated for off-target effects showing no effects in a GPCR panel and brain penetration showing a brain-plasma ratio of 3.8 after 120 min at 10 mg/kg in rodents. In an *in vitro* IP_1-based functional assay, **25** potentiated a 5-HT-induced functional response in a concentration-dependent manner at the 5-HT_{2C}R and did not display significant 5-HT binding inhibition at 10 μM, as tested in an *in vitro* competition binding assay. *In vivo*, **25** reduced food intake and body weight gain in a rodent feeding model without producing CNS-related malaise or resulting in taste

aversion to **25**. These results support the assertion that 5-HT_{2C}R PAMs may hold therapeutic potential for obesity.

Our group reported a different strategy towards identifying novel 5-Ht_{2C}R PAMs in 2019 [121]. Following on our work characterizing **21**, we sought to deconstruct this hit into a simplified pharmacophore in which a piperidine core was flanked by an undecyl carbon chain at the 4 position and a simplified alcohol connected by an amide linker at the 2 position [132]. Our primary goal was to improve the drug-likeness of **21**, which was already shown to be subtype selective, by replacing the complex α-D-galactopyranoside with a simplified fragment that retained activity to investigate the therapeutic potential of 5-HT_{2C}R PAMs *in vivo*. The resulting lead compound, CYD-1–79 (**27**), was discovered by substituting a propanediol moiety in place of the α-D-galactopyranoside, which engendered a more drug-like profile and improved synthetic scale-up feasibility. Compound **27** was confirmed to be an *in vivo* rodent model candidate following *in vitro* pharmacological evaluation, off-target panel screening, and pharmacokinetic/pharmacodynamic profiling (Fig. 9).

Specifically, **27** enhanced *in vitro* 5-HT_{2C}R functional response to 5-HT in a concentration-dependent manner and was inactive in a similar assay at the 5-HT_{2A}R. A radioligand competition binding assay was used to profile off-target interactions and resulted in no significant binding inhibition at any 5-HT_XR family member. Compound **27** was assessed in a battery of rat behavioral assays following an *in vivo* rat pharmacokinetic evaluation that showed reasonable oral bioavailability (F% = 39.1) and half-life ($T_{1/2}$ = 5.82 ± 0.37 h). We found that **27** suppressed motor activity in the presence of exogenous 5-HT_{2C}R stimulation with the selective 5-HT_{2C}R agonist **16**. In rats trained to discriminate the 5-HT_{2C}R agonist **16** from saline, compound **27** partially substituted for **16** and synergized with a low dose of **16** to substitute fully for the stimulus effects of **16**. Given that the drug discrimination assay has face validity for modeling the subjective effects of drugs that penetrate the blood-brain barrier and has been employed to establish allosteric modulator effects on the interoceptive effects of receptor-selective agonists, these data support the contention that **27** is a 5-HT_{2C}R PAM [145–147]. Lastly, in a cocaine self-administration model in rats, **27** suppressed cocaine-seeking provoked by exposure to the cocaine-taking environment and cocaine-associated cues. The sensitivity to cocaine-associated cues increases the risk of craving and relapse during abstinence, thus, these findings suggest that **27** may provide value as a therapeutic strategy to extend recovery in CUD.

The latest 5-HT_{2C}R PAM in this trio is **26** which was reported by Yadav and colleagues in 2019 (Fig. 9) [143]. This work identifies a phenyl cyclopropyl-linked *N*-heterocycle pharmacophore as producing multiple derivatives with PAM activity at the 5-HT_{2C}R and one compound (**26**) with additional NAM activity at the 5-HT_{2B}R. Robust SAR studies were reported for their scaffold of interest, however the origin of this pharmacophore and the rationale for designing *N*-heterocycle compounds as potential 5-HT_{2C}R PAMs was not fully disclosed. Interestingly, using an *in vitro* luciferase-based assay, **27** was shown to enhance a 5-HT-mediated functional response at the 5-HT_{2C}R up to 139% E_{max}, while additionally reducing 5-HT potency at the 5-HT_{2B}R with no effect on 5-HT E_{max} at the 5-HT_{2B}R. In agreement with its *in vitro* characterization as a 5-HT_{2C}R PAM, **26** decreased food intake

with approximately equivalent efficacy as lorcaserin in Sprague Dawley rats. Thus, this report provides additional *in vivo* evidence that 5-HT_{2C}R PAMs may prove to be therapeutically important molecules for obesity and additional optimization should proceed.

CONCLUSION AND FUTURE DIRECTIONS

5-HT_{2C}R is an important clinical target for obesity and several chronic pathological disorders [122], and will certainly continue to be actively pursued for therapeutic development as well as further study of the complex neurobiology that is coordinated through the 5-HT_{2C}R. One such aspect that requires further study is the signaling and trafficking mechanisms of class A GPCRs in their oligomeric forms. Specifically for the 5-HT_{2C}R, it is important to understand the functional implications of homodimerization (two 5-HT_{2C}R proteins) or heterodimerization (one 5-HT_{2C}R protein interacting with, for example, one 5-HT_{2A}R protein), which is only beginning to be unraveled by a few research groups [28, 29, 148]. As new biological information is available, medicinal chemists will be enabled to strategically design new compounds to modulate oligomerization or biased signaling, which may lead to future breakthrough therapies. The 5-HT_{2C}R PAMs reported to date share an interesting characteristic in that significant increases in 5-HT efficacy (E_{max}), but not potency, at the 5-HT_{2C}R are observed *in vitro*. Observations such as this will direct structural biology studies in the future to investigate conformational shifts responsible for efficacy increases and solving the structure of a PAM-agonist-5-HT_{2C}R co-complex will provide valuable information towards this goal. It is conceivable that a structure such as this will be available in the coming years due to recent successes in solving 5-HT_{2C}R active and inactive state crystal structures [5]. Additionally, the discovery of 5-HT_{2C}R PAMs that enhance 5-HT potency will enable the investigation of similar or contrasting *in vivo* effects compared to 5-HT_{2C}R PAMs that enhance 5-HT efficacy alone. In light of the complex modulatory role for the 5-HT_{2C}R in neurobiological processes, a diverse array of ligand modulation modalities should improve our understanding of the specific ligand profiles needed to pursue clinical endpoints.

As an important therapeutic target for diverse neurological and psychiatric disorders, medicinal chemists should pursue diverse mechanisms of receptor engagement at the 5-HT_{2C}R and groups have begun to rise to this challenging task. For agonist discovery, expansion of available pharmacophores is critically important and significant work towards this goal has recently been reported by Wacker and coworkers at Bristol-Myers Squibb utilizing an orthosteric-site mutant version of the 5-HT_{2C}R. Additionally, further investigation into the complexity of 5-HT_{2C}R signaling and oligomerization, as studied recently by Cunningham and colleagues [110] will help guide future compound design. In conclusion, there has been considerable recent progress in targeting the 5-HT_{2C}R, as shown by the FDA-approved agonist **14**, yet significant gaps in understanding 5-HT_{2C}R biology remain as do pharmacophore challenges for medicinal chemists in moving towards safer, more efficacious clinical therapies targeting the 5-HT_{2C}R.

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LIST OF ABBREVIATIONS

GPCR	G protein-Coupled Receptor
5-HT	Serotonin
5-HT$_{2A}$R	Serotonin5-HT$_{2A}$ Receptor
5-HT$_{2B}$R	Serotonin 5-HT$_{2B}$ Receptor
5-HT$_{2C}$R	Serotonin 5-HT$_{2C}$ Receptor
5-HT$_{X}$R	Serotonin Receptor Subtypes
AA	Arachidonic Acid
Ca_i^{2+}	Intracellular Calcium
CaM	Calmodulin
cAMP	Cyclic Adenosine Monophosphate
CNS	Central Nervous System
CUD	Cocaine Use Disorder
DAG	Diacylglycerol
ECL	Extracellular Loop
GABA	γ-Aminobutyric Acid
ICL	Intracellular Loop
IP$_1$	Inositol Monophosphate
IP$_3$	Inositol-1,4,5-Triphosphate
NAc	Nucleus Accumbens
NAL	Neutral Allosteric Ligand
NAM	Negative Allosteric Modulator
PAM	Positive Allosteric Modulator
PKC	Protein Kinase C
PLA$_2$	Phospholipase A$_2$
PLCβ	Phospholipase Cβ
PFC	Prefrontal Cortex

SUD	Substance Use Disorder
TM	Transmembrane Domain
VTA	Ventral Tegmental Area

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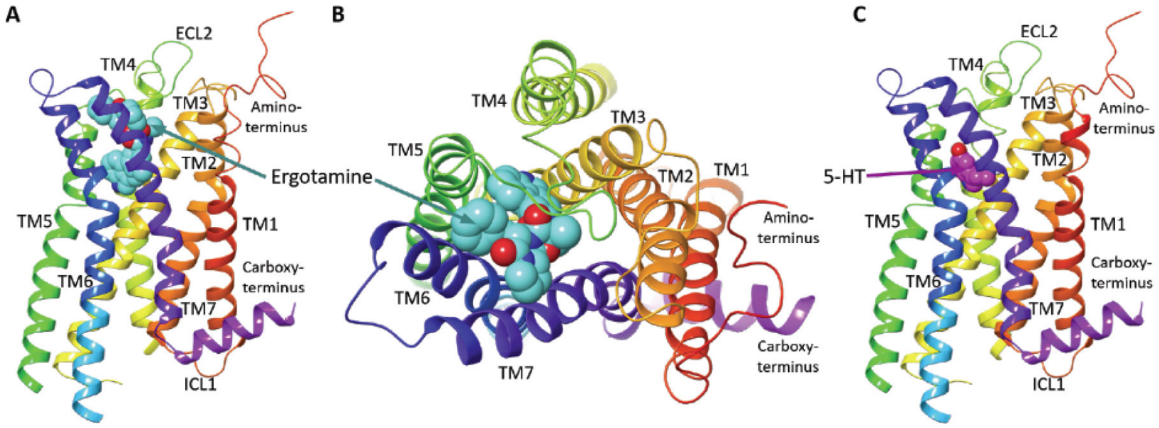


Fig. (1).

The recently solved X-ray crystal structure of the "active-like" state of the 5-HT_{2C}R bound to ergotamine (PDB code: 6BQG) and 5-HT_{2C}R model bound to 5-HT is depicted. (**A**) The side view of the ergotamine-bound 5-HT_{2C}R crystal structure with the N- and C-termini, extracellular and intracellular loops, and the transmembrane helices labeled; ECL = extracellular loop, ICL = intracellular loop, TM = transmembrane domain helix, ergotamine (cyan space fill representation) at the orthosteric site [5]. (**B**) Top/extracellular-view of the ergotamine binding site. (**C**) The side view of a 5-HT_{2C}R structure model based on the crystal structure with 5-HT docked to the orthosteric site; 5-HT (magenta space fill representation). The 5-HT-bound 5-HT_{2C}R was generated via induced fit docking protocols on 6BQG using the Schrödinger Drug Discovery Suite. All ligands shown in space filling representation and CPK coloring scheme for N and O atoms.

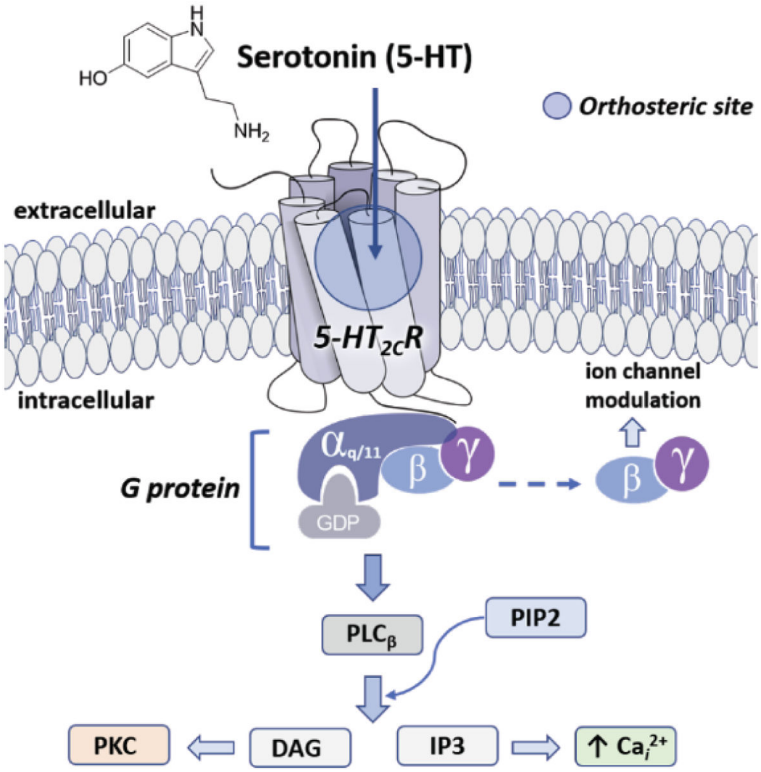


Fig. (2). A cross-section of the 5-HT$_{2C}$R signaling webs initiated by 5-HT binding to the orthosteric site is presented.

Activation of G$\alpha_{q/11}$ promotes phospholipase C$_\beta$ (PLC$_\beta$) mediated hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP2) into diacylglycerol (DAG) and inositol-1,4,5-triphosphate (IP$_3$). IP$_3$ promotes release of intracellular calcium (Ca_i^{2+}) while DAG binds to downstream effector protein kinase C (PKC).

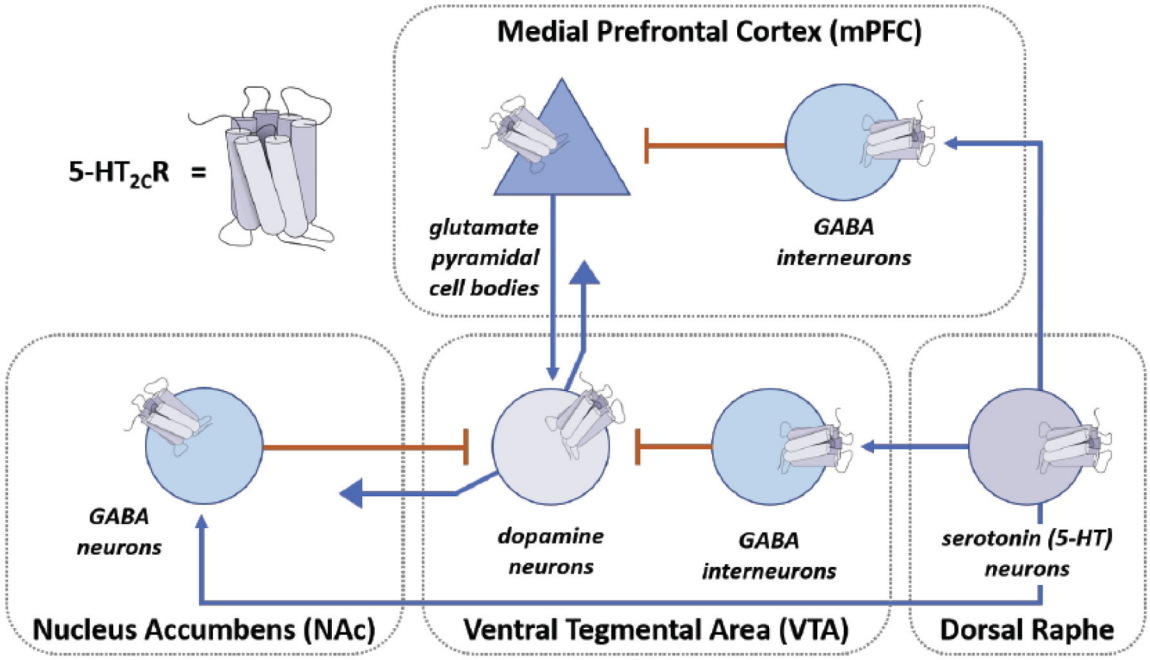


Fig. (3). A schematic presentation of the proposed 5-HT$_{2C}$R modulation of limbic-corticoaccumbens circuit is represented.

Serotonin (5-HT) neurons originating from the dorsal raphe nuclei innervate GABA interneurons in the medial prefrontal cortex (mPFC), nucleus accumbens (NAc), and the ventral tegmental area (VTA). Inhibitory GABAergic neurons facilitate decreased dopaminergic neuronal firing in the VTA both directly and indirectly. 5-HT$_{2C}$R localizes to neurons within each of the nodes in this circuitry.

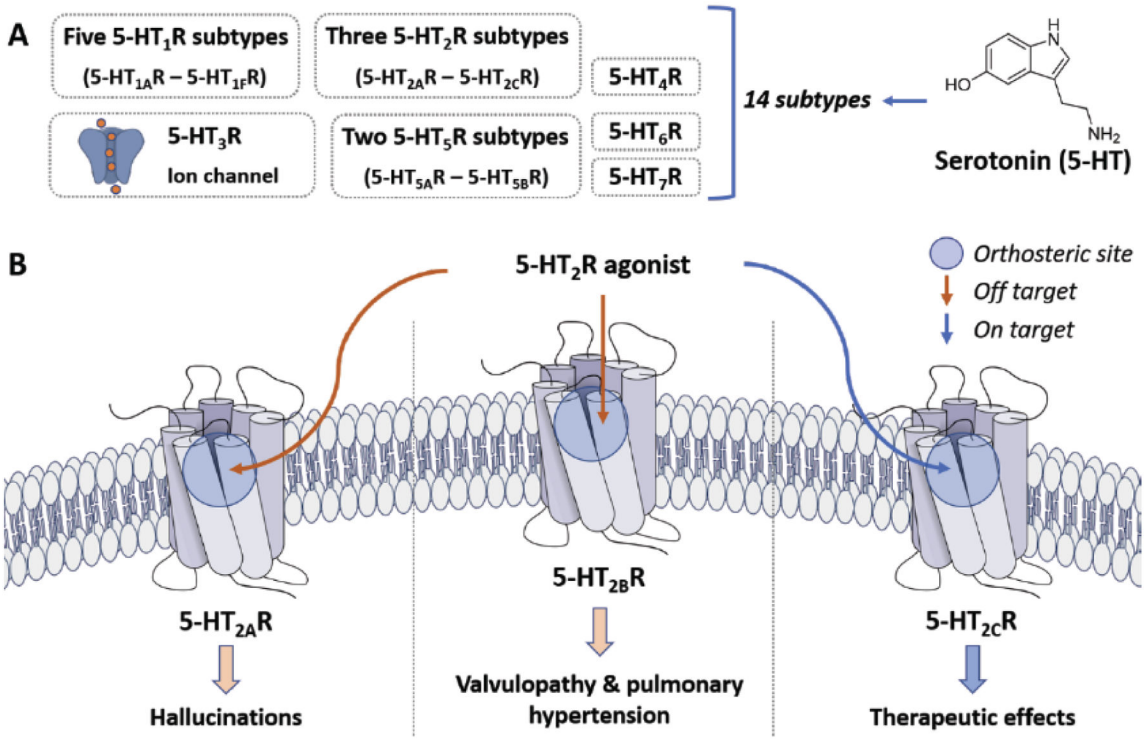


Fig. (4). Proposed outcomes mediated by activation of specific members of the 5-HT$_2$R family are depicted.

(**A**) The 5-HT receptor family is comprised of 13 GPCRs and one ligand-gated ion channel (divided into seven subtype categories). Each receptor is activated by endogenous 5-HT. Therefore, the orthosteric site is highly conserved across receptor subtypes. (**B**) Agonist-mediated activation of 5-HT$_{2A}$R accounts for the hallucinogenic actions of such abused drugs as *d*-lysergic acid diethylamide. Agonist-mediated activation of 5-HT$_{2B}$R can lead to pulmonary hypertension and valvular heart disease. Agonist-mediated activation of 5-HT$_{2C}$R represents an attractive therapeutic approach to treat obesity, substance use disorders and impulse control disorders. However, the high sequence homology at the orthosteric sites of these receptors present challenges to selectively target the 5-HT$_{2C}$R.

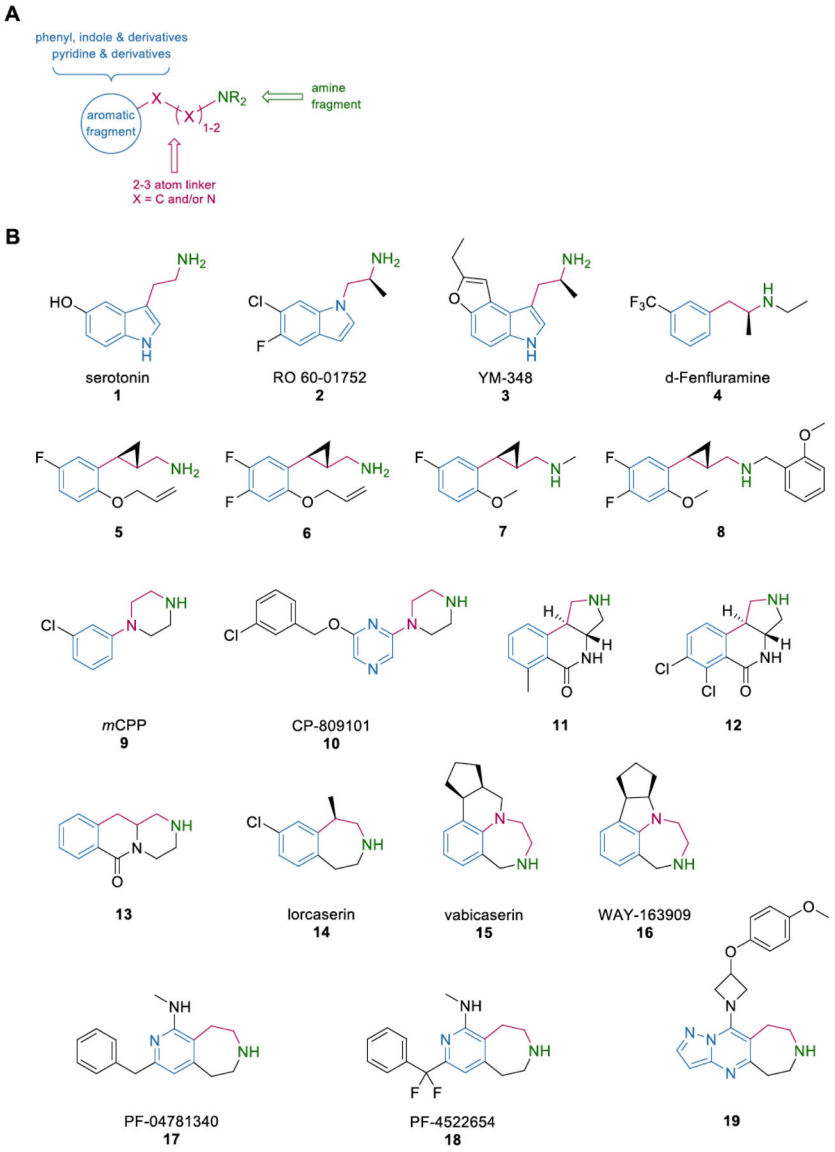
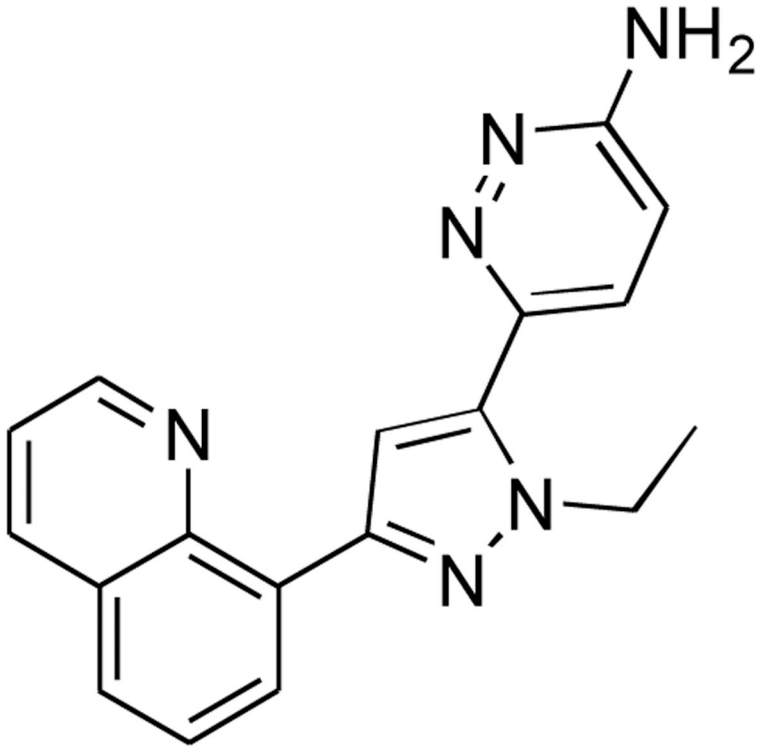


Fig. (5). Current synthetic 5-HT$_{2C}$R agonists share similarities in their pharmacophore.
(**A**) The general chemical scheme describing structural requirements for 5-HT$_{2C}$R agonists is presented. (**B**) Selected 5-HT$_{2C}$R agonists are organized based on chemotype. Blue indicates the common aromatic fragment, green indicates the requisite ionizable amine, and magenta highlights the linker.



20

Fig. (6). A novel pharmacophore for 5-HT_{2C}R agonists is described.

Compound **20** is the result of an intentional screening and optimization study which sought to discover non-traditional 5-HT_{2C}R ligands, as defined by an aromatic ring joined to an amine fragment by a short aliphatic linker [109].

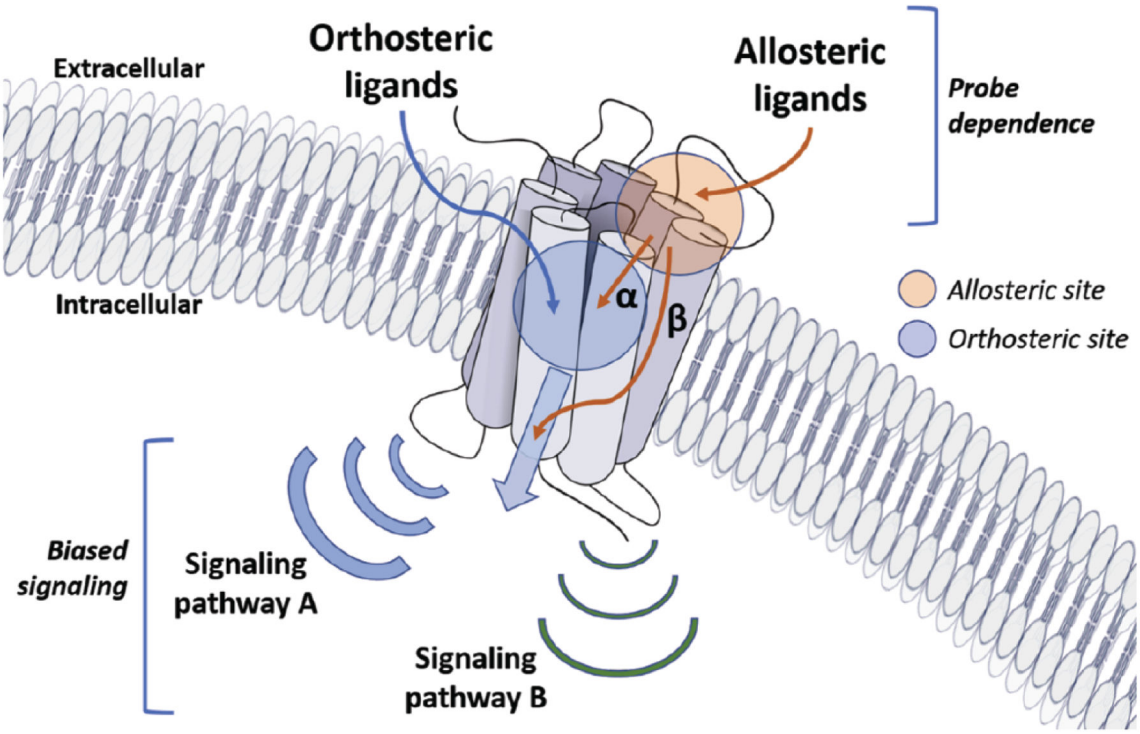


Fig. (7). A schematic presentation of potential allosteric modulation of GPCR signal transduction is depicted.

The allosteric ligand binds to a site (orange circle) that is distinctly different than the orthosteric site (blue circle) which accommodates the orthosteric ligand. Actual binding site locations are generally dictated by the specific GPCR family member. Allosteric modulators can modulate binding affinity (α) and/or efficacy (β) of orthosteric ligands in a positive (PAM) or negative manner (NAM), or may simply occupy the site as a neutral allosteric ligand (NAL). The nature of the modulation is determined by several features of signaling including the orthosteric ligand employed (*i.e.*, probe dependence) as well as the ligand-dependent selectivity for certain downstream transduction mechanisms within a given cell (*i.e.*, biased signaling).

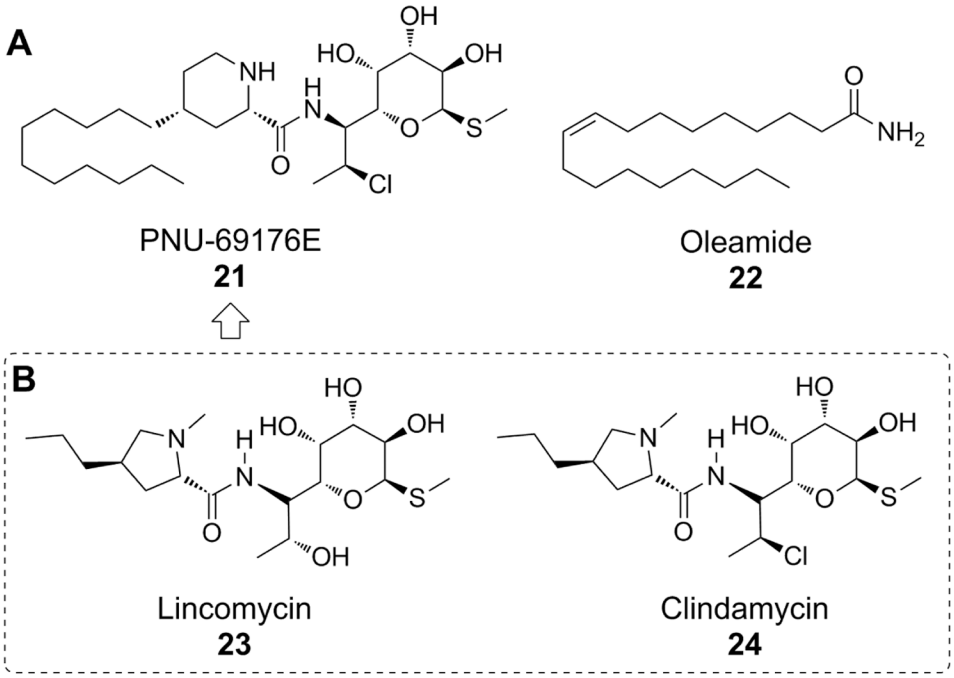


Fig. (8).

(A) The earliest reported small molecules with allosteric modulatory activity at the 5-HT_{2C}R are PNU-69176E (**21**) and oleamide (**22**). **(B)** PNU-69176E is an analogue of the natural product antibiotic lincomycin (**23**) and a derivative of the clinically available antibiotic clindamycin (**24**).

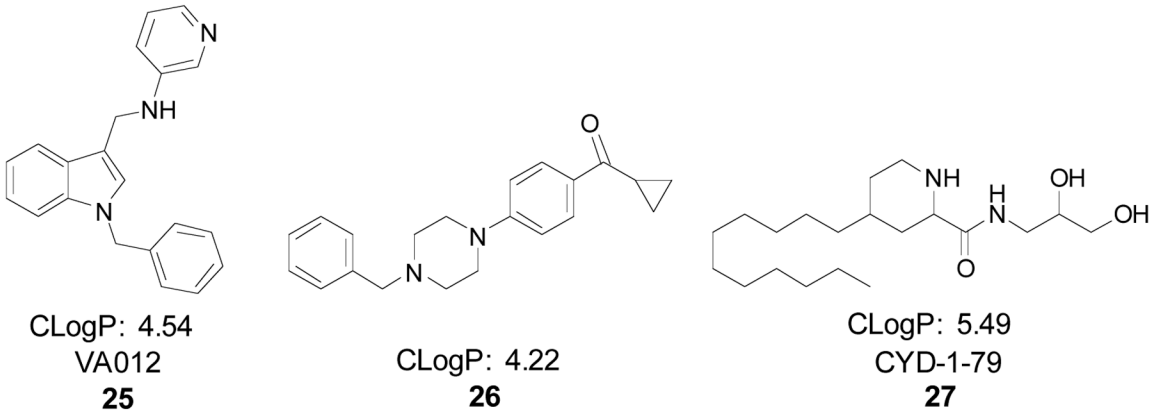


Fig. (9). A new generation of 5-HT$_{2C}$R PAMs has emerged.

The lead compounds from recent 5-HT$_{2C}$R PAM discovery projects include VA012 (**25**) [142], **26** [143], and CYD-1–79 (**27**) [121] respectively. The CLogPs are reported to demonstrate that elevated lipophilicity is common among these newly discovered 5-HT$_{2C}$R PAMs.

Table 1.

Functional profiling of numerous 5-HT_{2C}R agonists and respective profiles at the 5-HT_{2A}R and 5-HT_{2B}R to show subtype selectivity among 5-HT_2Rs.

Compound	5-HT_{2C}R		5-HT_{2A}R		5-HT_{2B}R				Refs.
	EC_{50} (nM)	E_{max} (%)	EC_{50} (nM)	E_{max} (%)	EC_{50} (nM)	E_{max} (%)	2A/2C ratio	2B/2C ratio	
5-HT (**1**)	3.48	100	14.04	100	20 ± 2.8	100	4.03	5.75	[95]
RO 60–0175 (**2**)	52 ± 3	88 ± 20	400 ± 20	91 ± 5	2.4 ± 1	130 ± 30	7.69	0.05	[96]
YM-348 (**3**)	1.0 ± 0.2	76 ± 1	93 ± 10	97 ± 2	3.2 ± 3	110 ± 10	93.0	3.2	[97]
d-fenfluramine (**4**)	300 ± 29	90 ± 9	720 ± 77	80 ± 4	23 ± 4	100 ± 10	2.4	0.08	[98]
5	4.2	87	374	56	NE	NE	89.0	-	[99]
6	8.7	97 ± 1	491	21 ± 0	1745	35 ± 7	57.1	200.6	[100]
7	7.65	71	6.57	79	7.05	54	0.86	0.92	[101]
8	7.63	92	NE	NE	6.86	63	-	0.90	[63]
*m*CPP (**9**)	120 ± 10	63 ± 3	150 ± 20	18 ± 2	93 ± 50	21 ± 9	1.25	0.78	[97]
CP-809101 (**10**)	0.11	93	153	67	65.3	57	1391	593.6	[102]
11	1.1 ± 0.4	90	127 ± 82	100	94 ± 68	50	115.5	85.5	[103]
12	3.3 ± 1.8	90	128 ± 44	100	414 ± 468	130	38.8	125.5	[103]
13	36	100	707	100	>10000	-	19.6	>277.8	[104]
lorcaserin (**14**)	9 ± 0.5	100	168 ± 11	75	943 ± 90	100	18.7	104.8	[51]
vabicaserin (**15**)	8	100	1650	-[a]	>10,000	80	206.3	0.19	[105]
WAY-163909 (**16**)	8 ± 3	90 ± 6	NE	NE	185 ± 105	40 ± 3	-	23.1	[63]
PF-04781340 (**17**)	9	99	-	-	1484	69	-	164	[106]
PF-4522654 **(18)**	16	58	NE	NE	>10000	<10	-	>625	[107]
19	95	76	2634	21	503	31	27.7	5.3	[108]
20	5 ± 3	-	635 ± 862	-	48 ± 41	-	127	9.6	[109]

[a]Functional output indicated antagonist activity; Values with error represent the mean ± SD; For 5-HT_{2A}R and 5-HT_{2B}R, large reported errors indicate inconsistent results from compounds showing no effect and intermittent positive effects; No effect (NE); Not applicable or not tested (−).