1. INTRODUCTION

Serotonin (5-hydroxytryptamin, 5-HT), an ancient biochemical has been manipulated by nature through evolution for being utilized extensively in animal and plant kingdom.[1, 2] It is a combination of neurotransmitter and modulator system that controls the functioning of gastrointestinal tract,[3] platelets[4] and central nervous system (CNS).[5] Around 80 % of 5-HT is synthesized in the enterochromaffin cells which are located in the gastrointestinal tract along with serotonergic neurons present in the CNS.[1, 6] Various membrane-bound receptors that emanate in the central and peripheral nervous system[7] (CNS/PNS) along with several neuronal tissues in the gut, cardiovascular system and blood are responsive to 5-HT.[8, 9] 5-HT regulates feeding and energy balance, vomiting, aggression, mood, sex, perception, modulation of temperature, pain and such other physiological processes. Down regulation in serotonergic neurotransmission has been proposed to be involved in a variety of disorders, including schizophrenia, depression, and anxiety. [10]

Based on their structure, function and transduction-coupling properties, 5-HT receptors have been classified. It is a ubiquitous neurotransmitter which mediates its action *via* fourteen different membrane bound receptor subtypes[9, 11] which have been broadly classified into seven major families i.e. 5-HT_{1-7} **(Figure 1)**. All 5-HT receptors belong to the family of G-protein coupled receptors except for 5-HT_3 receptor which belongs to the family of ligand gated ion channel receptor. [12]

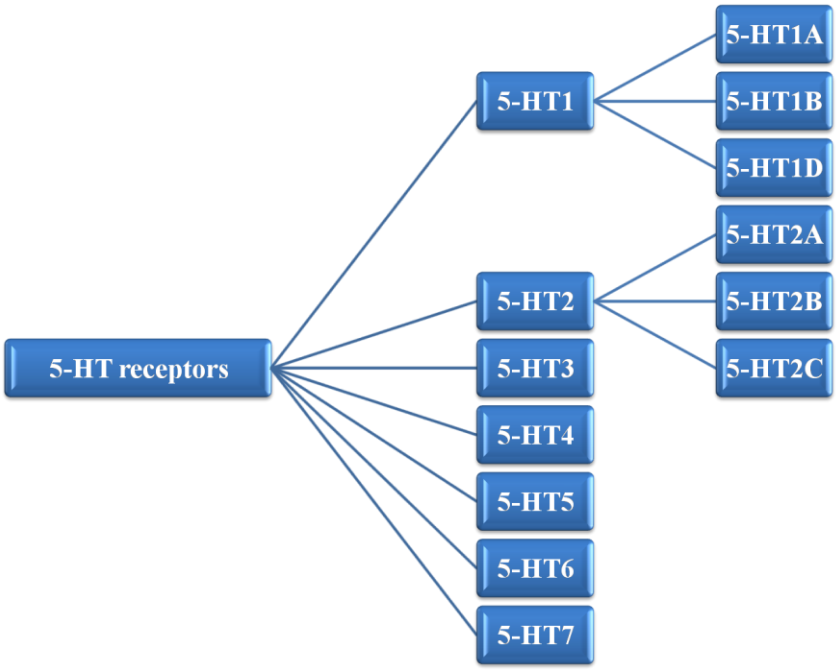


Figure 1. Types of 5-HT receptors

Based on their signal transduction and pharmacological effects the 5-HT receptors have been classified further. Classification of 5-HT receptors with their agonists and antagonists is represented in (**Table 1.1** and **Figure 1**).

Table 1.1: The main 5-HT receptor sub-types[13]

Sr.No	Receptor	Location	Main effect	Agonist	Antagonist
1	5-HT_{1A}	CNS	Neuronal inhibition Behavioural effects: sleep, feeding, thermoregulation, anxiety	5-CT 8-OH-DPAT Buspirone (partial agonist)	Spiperone Methiothepin Ergotamine (partial antagonist)
2	5-HT_{1B}	CNS, Vascular smooth muscle	Presynaptic inhibition Behavioural effects Pulmonary vasoconstriction	5-CT Ergotamine (partial agonist)	Methiothepin
3	5-HT_{1D}	CNS, Blood vessels	Cerebral vasoconstriction Behavioural effects: locomotion	5-CT Sumatriptan	Methiothepin Ergotamine (PA)
4	5-HT_{2A}	CNS, PNS, Smooth muscle Platelets	Neuronal excitation Behavioural effects Smooth muscle contraction (gut, bronchi, etc.) Platelet aggregation Vasoconstriction or Vasodilatation	α-Me-5-HT, LSD (CNS) LSD (periphery)	Ketanserin Cyproheptadine Pizotifen (non-selective) Methysergide
5	5-HT_{2B}	Gastric fundus	Contraction	α-Me-5-HT	-
6	5-HT_{2C}	CNS, Choroid plexus	Cerebrospinal fluid Secretion	α-Me-5-HT, LSD	Methysergide
7	5-HT_3	PNS, CNS	Neuronal excitation (autonomic, nociceptive neurons) Emesis Behavioural effects: anxiety	2-Me-5-HT, Chlorophenyl-biguanide	Ondansetron, Tropisetron, Granisetron,
8	5-HT_4	PNS (GI tract) CNS	Neuronal excitation GI motility	5-Methoxy-tryptamine Metoclopramide Tegaserod	Various experimental compounds (e.g. GR113808, SB207266)
9	5-HT_5	CNS	Not known	Not known	Not known
10	5-HT_6	CNS	Not known	Not known	Not known
11	5-HT_7	CNS, GI tract Blood vessels	Not known	5-CT LSD No selective agonists	Various 5-HT_2 antagonists No selective antagonists

1.1 5-HT$_1$ receptor family

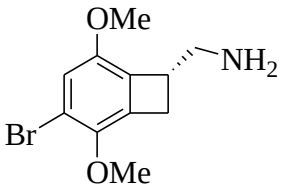
The 5-HT$_1$ receptor family is constituted of five other major subtype receptors i.e; 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1D}$, 5-HT$_{1E}$, and 5-HT$_{1F}$ receptors. The role of two receptors 5-HT$_{1E}$, and 5-HT$_{1F}$ has not been recognized, the remaining three 5-HT$_{1A}$, 5-HT$_{1B}$ and 5-HT$_{1D}$ are known to act as auto-receptors on 5-HT nerve terminals and/or on cell bodies.[14] All of these receptors couple to Heterotrimeric G protein ($G_{i/o}$) to inhibit adenyl cyclase and reduce cAMP levels.

1.2 5-HT$_2$ receptor family

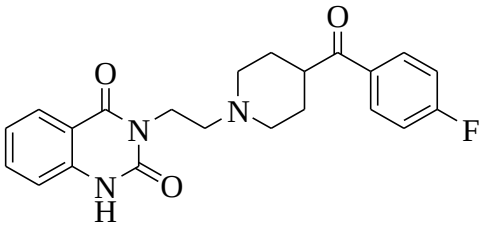
The 5-HT$_2$ receptors comprise of three members 5-HT$_{2A}$, 5-HT$_{2B}$ and 5-HT$_{2C,}$ belonging to the super family of G-protein-coupled receptors.[2, 15] After activation these receptors stimulate a second messenger (phospholipase C) causing hydrolysis of phosphoinositide, which leads to increase in intracellular calcium levels.[16] Apart from phospholipase C pathway, activation of phospholipase A_2 by these sub-receptors leading to release of arachidonic acid has also been proposed.[17] The effect of 5-HT$_2$ receptors present in CNS and peripheral sites (specifically blood vessels, platelets, ANS), neuronal and smooth muscles is excitatory. Lysergic acid diethylamide (LSD: agonist in CNS, antagonist in periphery) is a specific agonist while ketanserine, methysergide and cyproheptadine are specific antagonists.

1.2.1 5-HT$_{2A}$ receptor

5-HT$_{2A}$ receptor is profusely found in the forebrain, mostly in cortex, and is expressed in both interneuron and pyramidal neurons.[16] Several ligands have shown complex pharmacological patterns of activity at 5-HT$_{2A}$ receptor, from full to partial agonism. However their degree of intrinsic activity for the activation of different second messenger systems by the same population of 5-HT$_{2A}$ receptor varies from neutral antagonism to inverse agonistic behaviour.[16, 18] The affinity of 5-HT is relatively low for the 5-HT$_{2A}$ receptor although the high affinity active conformational state has roughly ten-fold higher affinity for 5-HT$_{2A}$.[18] Agonists such as 2,5-dimethoxy-4-iodoamphetamine (DOI) and LSD have high affinity for 5-HT$_{2A}$ receptor. While others like TCB-2 **(I),** which is conformationally restricted derivatives of the phenethylamine 2C-B as demonstrate selective potency and are non selective.[18] Antagonists such as ketanserin **(II)** display high selectivity for 5-HT$_{2A}$ receptor. [13]



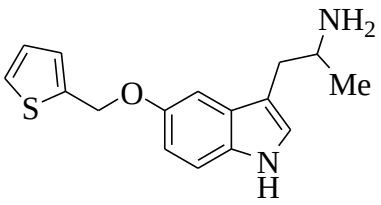
TCB-2 **(I)**



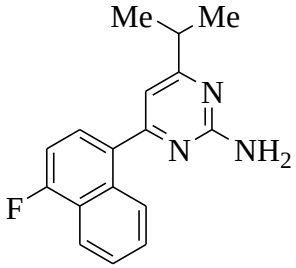
Ketanserine **(II)**

1.2.2 5-HT$_{2B}$ receptor

The 5-HT$_{2B}$ receptor is profoundly expressed in liver, kidney, heart and the fundus of the stomach, but is expressed low in CNS. [16] On the other hand, 5-HT$_{2B}$ pattern of expression differs from 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors, which are expressed comparatively at higher levels in the CNS.[16] The 5-HT$_{2B}$ receptors' physiological role is still not known, but they have been associated with cardiac function, morphogenesis, and anxiety.[19] Signal transduction coupling of 5-HT$_{2B}$ is similar to other 5-HT$_2$ receptors *in vitro*, but there is less evidence for endogenous receptors. Compound **(III)** is agonist to the 5-HT$_{2B}$ receptor and compound **(IV)** is antagonist to the 5-HT$_{2B}$ receptor. [16]



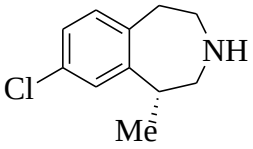
BW 732C86 **(III)**



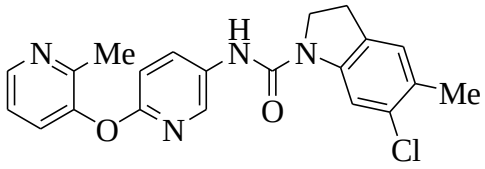
RS 127445 **(IV)**

1.2.3 5-HT$_{2C}$ receptor

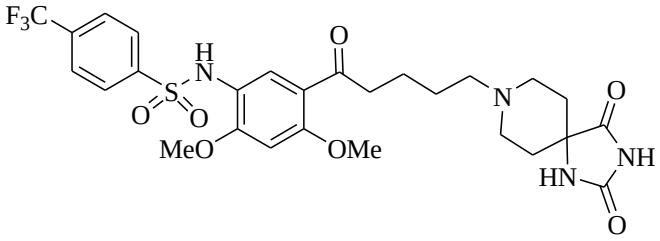
5-HT$_{2C}$ receptor is widely expressed throughout the CNS, sparsely expressed outside the brain and is a unique 5-HT sub-receptor as its mRNA transcript can be edited, leading to subtle changes in coding sequence.[19] 5-HT$_{2C}$ receptors are responsible for mid-life obesity, glucose intolerance and seizures.[20]



Lorcaserine **(V)**



SB 242084 **(VI)**



RS 102221 **(VII)**

There is a similarity between the pharmacology of 5-HT_{2C} receptor and other 5-HT_2 receptors and it shows complex interactions with signal transducing mechanisms. Evidence from animal models indicates that 5-HT_{2C} receptor may result in anxiety, appetite, addiction, and antipsychotic drug actions. Lorcaserin **(V)** displays some selectivity for the 5-HT_{2C} receptor.[16, 21] SB 242084 **(VI)** and RS 102221 **(VII)** are 5-HT_{2C} antagonists.

1.3 5-HT_3 receptor family

The 5-HT_3 receptor belongs to ligand-gated ion channel (LGIC) family [22] having a pentameric receptor complex consistent with other LGIC family members.[23] The combination of five subunits, named 5-HT_{3a-e}, forms the pentameric receptor complex. The 5-HT_3 receptor complex is a non-selective cation channel, (most permeable to $Ca2^+$, Na^+ and K^+ ions) mediates fast synaptic depolarizing neurotransmission in the brain and is prone to rapid desensitization.[9, 24] 5-HT_3 receptors are highly expressed in the areas related to brainstem nuclei around the chemoreceptor trigger zone,[25] but are also expressed in human's hippocampus, amygdala and caudate-putamen.[26] Ondansetron, granisetron and tropisetron were approved as selective antagonists to reduce emesis.[27] 5-HT_3 receptors have low affinity for second generation compounds like alosetron and palonosetron but they have been approved as medicines. Activation of the 5-HT_3 receptor causes release of dopamine, GABA and 5-HT. [28, 29]

1.4 5-HT$_4$ receptor family

A functional 5-HT$_4$ receptor protein emerges from a single gene.[9, 30] Splicing of mRNA arising from single gene produces ten isoforms 5-HT$_{4(a-g)}$, 5-HT$_{4(hb)}$, 5-HT$_{4(i)}$ and 5-HT$_{4(n)}$. All the 5-HT$_4$ receptor isoform transcripts are expressed in the brain, except for the 5-HT$_{4D}$ receptor isoform.[31] The highest expression of 5-HT$_4$ receptor is in the basal ganglia, which includes substantia nigra, globus pallidus, caudate nucleus, putamen, nucleus accumbens, hippocampus (CA1 and subiculum) and cortex. [31] When stimulated, 5-HT$_4$ receptor increases the discharge of a number of neurotransmitters that includes cortical acetylcholine, nigral-striatal dopamine and hippocampus 5-HT. The 5-HT$_4$ receptor is believed to have a role in learning, memory and anxiety. [16]

1.5 5-HT$_5$ receptor family

The 5-HT$_{5A}$ and 5-HT$_{5B}$ are two gene products and part of the subfamily of 5-HT$_5$ receptor.[16, 32] 5-HT$_{5A}$ receptor in heterologous expression systems may inhibit adenyl cyclase activity, may be due to Gi, however some other reports do not support such response.[16, 33] Other transduction processes impacted by this receptor may include an increase in intracellular Ca^{2+} mobilization or coupling to an inwardly rectifying potassium channel.[16, 33]

1.6 5-HT$_6$ receptor family

The 5-HT$_6$ receptor is prominently expressed in CNS and has particularly intense expression in striatum and hippocampus.[16, 34] Being coupled with heterotrimeric stimulatory G proteins (Gs) it activates adenyl cyclase showing affinity towards serotonin. The 5-HT$_6$ receptor has been found in animal models to offer promise as a target for cognitive enhancement and possibly weight loss. [16, 34]

1.7 5-HT$_7$ receptor family

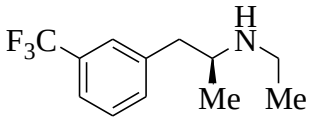
5-HT$_7$ receptor is distributed in the brain and it couples with heterotrimeric stimulatory G protein (Gs) (activating adenyl cyclase).[35] Within the CNS various splice variants with different patterns of distribution have been identified [36] though, 5-HT$_7$ receptors have not exhibited meaningful pharmacological distinctions in human isoforms.[37] Some of traditionally related ligands of other 5-HT receptors such as 5-HT$_{1A}$, 5-HT$_{2A}$ and 5-HT$_6$ also bind to 5-HT$_7$ receptor. 8-OH-DPAT, a full agonist, has about ten-fold higher affinity for 5-HT$_{1A}$ than for 5-HT$_7$ receptor. [37]

1.8 Therapeutic potential of 5-HT_{2C} receptor modulators

1.8.1 Obesity

Increase in the number of obesity cases has been associated with economic burden.[38] Obesity is associated with many diseased conditions like stroke, Type 2 diabetes, osteoarthritis, hypertension, ischemia, and also several forms of cancer including kidney and colon.[39]

A number of 5-HT_{2C} agonists have been approved by USFDA for the treatment of obesity.[40] Dexfenfluramine **(VIII)** was the first anti-obesity drug to be approved for duration of usage in excess of 3 months in the INDEX study and it produced 10% reduction in body weight. [41]



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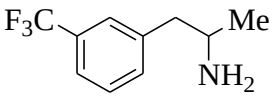


(IX)

Dexfenfluramine **(VIII)** reduces the body weight, and also causes improvement in glycemic control, lipid parameter and blood pressure.[41, 42] The active metabolite of dexfenfluramine is nordexfenfluramine **(IX)**, which is also a potent full 5-HT_{2C} receptor agonist and has similar efficacy as dexfenfluramine. Results suggest that dexfenfluramine's efficacy results from 5-HT_{2C} receptor activation by nordexfenfluramine **(IX)** [41, 42]. Both of the drugs have been withdrawn from the market because of side effect like heart valve abnormality which could be due to non-selectivity towards the peripheral $5HT_{2B}$ psychotropic effect.[9]

1.8.2 Anxiety

5-HT_{2C} receptor has been related to mood and anxiety disorders and it is a target for development of novel anxiolytic drugs.[43] 5-HT_{2C} receptor antagonists reduce anxiety-like behaviour at least in an acute fashion.[43] Results of various studies suggest that 5-HT_{2C} receptor activation is an important component of anxiogenesis and 5-HT_{2C} antagonists may be effective anxiolytic agents devoid of many usual side effects associated with benzodiazepines like tolerance and dependence, and SSRIs related side effects mainly insomnia, agitation and sexual dysfunction. [9]

1.8.3 Depression

An outsized body of evidence suggests that the serotonergic system is hypofunctional in depressed patients. [43] In harmony with this data, treatments that enhance serotonergic function such as selective serotonin reuptake inhibitors (SSRIs), are clinically effective treatments of depression. 5-HT_{2C} receptors located in a number of corticolimbic areas are thought to be involved in the mediation or treatment of depressive states. [43]

1.8.4 Schizophrenia

5-HT_{2A} receptor has gained lot of attention in schizophrenia. Evidence suggested involvement of 5-HT_{2C} receptor in schizophrenia and $5HT_{2A}$ and $5HT_{2C}$ are homologically closer. [43, 44] Schizophrenia is a chronic mental illness in nearly 1% of the population. Its causes are unknown but epidemiological approaches are associated with both genetic and environmental factors.[9] Schizophrenia drugs generally show antagonism of dopaminergic D_2 receptors in the mesolimbic and mesocortical regions of the brain.[43, 44] Some researchers suggest that 5-HT_{2C} receptor activation inhibits dopaminergic neuronal activity and dopamine release. The opposite effects occur with 5-HT_{2C} antagonists, such as increased dopaminergic neurotransmission and thus reduced risk of extrapyramidal side effect.

1.8.5 Epilepsy, Alzheimer's disease and Parkinson's disease

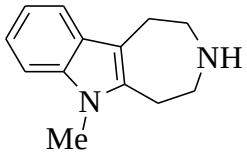
Currently several drugs are used to inhibit seizures and the most common ones are the drugs affecting voltage gated sodium or calcium ion channels while some other drugs affect neurotransmitter GABA.[45] Serotonergic neurotransmission modulates experimentally induced seizures in some animal models of epilepsy and, more specifically, recent findings indicate that 5-HT_{2C} receptor agonists have an anticonvulsant effect.[45] It has been proposed that 5-HT_{2C} receptor-null mutant mice displayed an epilepsy phenotype characterized by higher spontaneous seizures, lower seizure threshold, and enhanced seizure propagation and sound-induced seizure susceptibility.

1.8.6 Penile erection

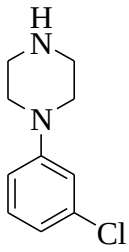
There are various reports[46 9 47 48] which suggested that induction of penil erection in rat is associated with 5-HT pathways in the brain.

1.9 5-HT_{2C} Receptor and satiety

In the current era of innovative medication, 5-HT_{2C} receptor has drawn much more attention due to its association with regulating body weight for both humans and rats. Clinical studies suggested that 5-HT_{2C} knockout mice were obese and defective in food intake; however 5-HT_{2C} receptor agonists reduced the appetite and body weight. A high concentration of 5-HT_{2C} receptors is present in manily the central nervous system (CNS).[49] A number of 5-HT_{2C} agonists have been developed and have shown weight loss in humans by inhibiting food intake. For example, PNU-22394A **(X)** and *m*-CPP **(XI),**[50] non-selective 5-HT_{2C} agonists, have caused considerable weight loss in clinical trials. [51]



PNU-22394A **(X)**



m-CPP **(XI)**

Brief introduction of this receptor has been given previously but it is not sufficient to understand the whole mechanism of satiety. The 5-HT_{2C} receptor has been found only in the CNS. [51] Short mechanism of action of a 5-HT_{2C} agonist is given in **(Figure 2)**

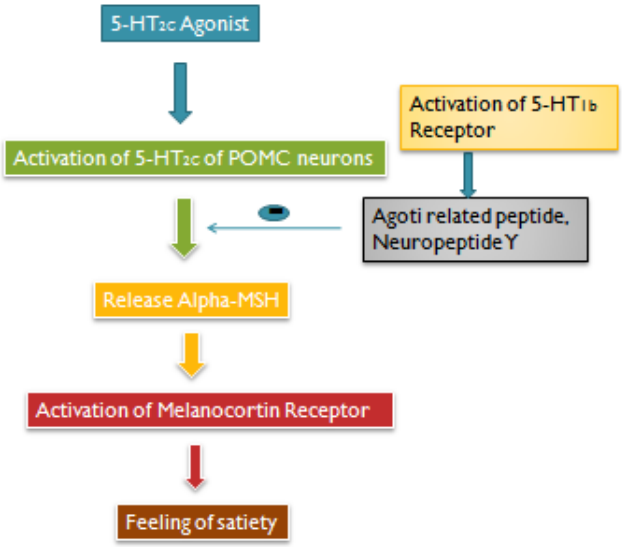


Figure 2. Mechanism showing the feeling of satiety, POMC: Preopiomelanocortin, MSH: melanosite stimulating hormone

As the *m*-CPP **(XI)** induced anxiety seems to be mediated via the 5-HT_{2C} receptor, it has been hypothesized that 5-HT_{2C} antagonists could prove to be potential drugs for the treatment of anxiety.[16, 52] Evidence for the involvement of the 5-HT_{2C} receptor in the regulation of feeding and satiety has been the subject of matter in a number of reviews.[16, 53] 5-HT_{2C} receptor is the only known GPCR subject to form of a post transcriptional modification known as RNA editing, a process in which specific adenosine residues are converted to inosine resulting in functional recoding of mRNA.[36] Editing of 5-HT_{2C} receptor transcripts alters the functional signalling characteristics of the receptor, thus modulating the role of the receptor that it plays in various neural processes.[38]

5-HT_{2C} receptors are activated by agonists in the neurons of the preopiomelanocortins which release the alpha-melanosite stimulating hormone that ultimately activates the melanocortin receptor, generating the satiety feeling. Mechanism behind the satiety is given in (**Figure 3**) which explains the relation of 5-HT_{2C} receptor with other metabolic functions.

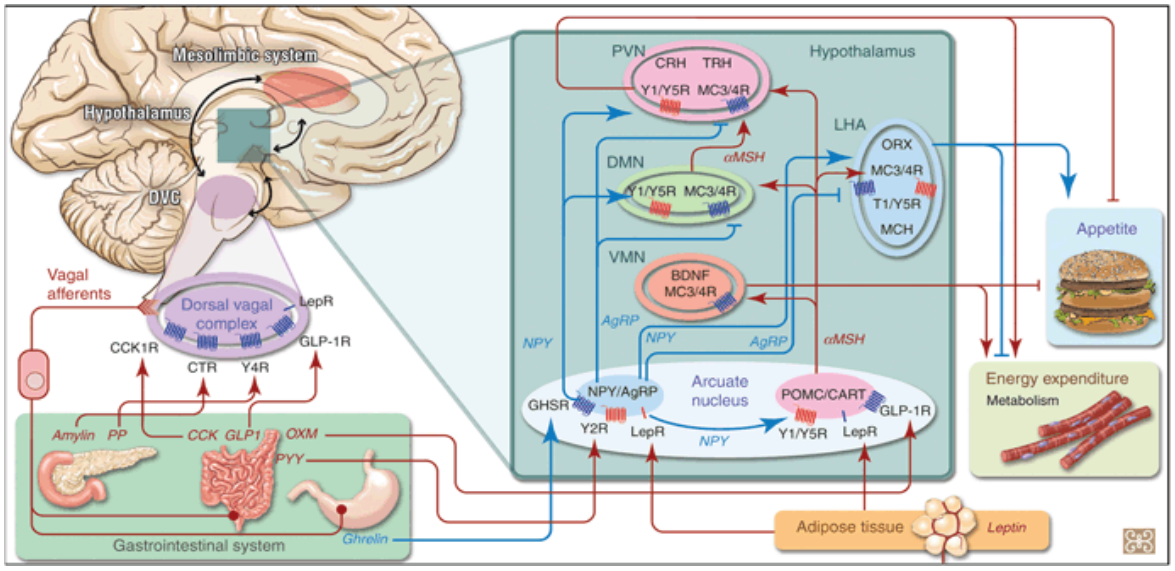


Figure 3. Central regulation of appetite and energy homoeostasis:[54] Peraventriculer nucleus (PVN), neuropeptide Y (NPY), agouti-related peptide (AgRP), anorexigenic pro-opiomelanocortin (POMC),cocaine-and amphetamine-regulated transcript (CART), dorsomedial nucleus (DMN), ventromedial nucleus (VMN), and lateral hypothalamic area (LHA), corticotropin-releasing hormone (CRH), thyrotropin-releasing hormone (TRH), and brain-derived neurotrophic factor (BDNF), orexin (ORX) and melanin-concentrating hormone (MCH), glucagon-like peptide 1 receptor(GLP-1R), ventromedial nucleus (VMN).

(Symbols: blue receptor, activating; red receptor, inhibiting; blue arrow, appetite-stimulating pathway; red arrow, appetite-suppressing pathway. GLP-1R, glucagon-like peptide 1 receptor).

Hypothalamus is the major site of integration of anorexigenic and orexigenic signaling.[55-57] Peripheral satiety hormones, such as ghrelin from the stomach and leptin from adipose tissue, primarily bind and activate their cognate receptors directly in the

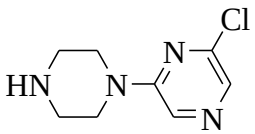
hypothalamus, particularly in the arcuate nucleus, or in the dorsal vagal complex in the medulla, which communicates with the hypothalamus (**Figure 3**). Among the neurons in the arcuate nucleus, there exist two populations of neurons: those expressing the orexigenic NPY or AgRP and those expressing the anorexigenic POMC and CART.[58, 59] Several satiety hormones induce their anorectic effects by either inhibiting the activity of NPY/AgRP neurons or activating POMC/CART neurons (**Figure 3**). These neurons in the arcuate nucleus project to second-order neurons in other hypothalamic nuclei, including the PVN, DMN, VMN and LHA. These second-order hypothalamic neurons express anorexigenic neuropeptides (CRH, TRH, and BDNF) and orexigenic neuropeptides (ORX, MCH) which modulate appetite and energy homeostasis.

2. REVIEW OF LITERATURE

2.1 5-HT_{2c} agonists: recently reported ligands

Although the SAR of the 5-HT_{2C} receptor agonists is of great interest, many of the early molecular tools available to probe the consequences of 5-HT_{2C} receptor activation lacked selectivity versus the other 5-HT_2 subtypes. Worldwide, various research groups like Hoffman-La Roche, Vernalis, Biovitrum, Dupont, Lilly, Pfizer, Pharmacia and Upjohn, Organon, Yamanouchi, Bayer, American Home Products, Arena Pharmaceutical and Daya Drug Discovery have all been active in claiming novel compounds that are 5-HT_{2C} agonists.

Number of series related to MK-212 **(XII)** and m-CPP **(XI)** are older arylpiperazines whose anorectic effects were discovered decades ago and are now known to be 5-HT_{2C} agonists but not selective for 5-HT_{2C} receptor.[60, 61] Discovery of the fenfluramine **(VIII)** and nordexfenfluramine **(IX)** has become history in the research area of the 5-HT_{2C} agonists.[60] 5-HT agonist *m*-CPP **(XI)** is mainly used as a probe in clinical studies to test brain 5-HT functions in humans.[62]

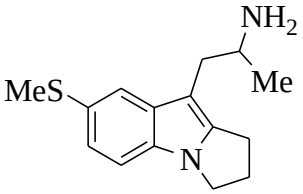


(XII)

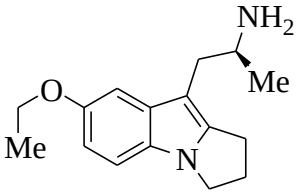
Vernalis has reported a patent application on indoles related to serotonin with an alkyl linker connecting the indole nitrogen atom to the C-2 carbon to form a tricyclic system, for example the racemic compound **(XIII)**.[63] The ethylamine side chain contains a methyl group on the alpha position to amine as this group is important for 5-HT_{2C} agonists. Some of

literature reports suggest that the 2-aminopropyl group is more important over 2-aminoethyl group due to its improved selectivity over 5-HT_1 receptors.[64, 65] Vernalis collabrating with Hoffmann La Roche filed a patent for the compounds very similar to compound **(XIII)**, such as compound **(XIV)**.[66] Compound **(XV)** (indazole with the 2-aminopropyl chain attached to postion-3) was also synthesized by Vernalis which is covered under the patent application.[67]

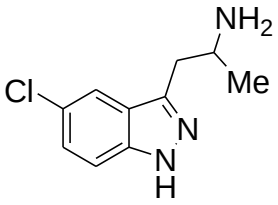
Compound **(XIII)** has excellent selectivity for 5-HT_{2C} over 5-HT_{2A} (h5-HT_{2C}: EC_{50}=8 nM) [80% of the 5-HT response]. Compound **(XIV)** was reported to reduce food intake in food deprived rats after an oral dose of 30 mg/kg and to reduce weight gain in diet induced obese rats.



(XIII)

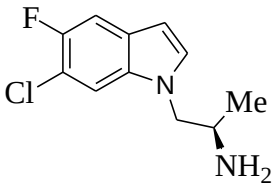


(XIV)

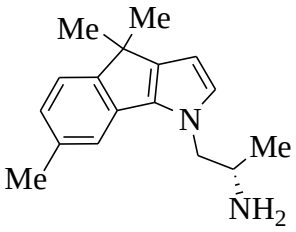


(XV)

Hoffmann-La Roche group filed a patent application on indoles and related rings to discover compounds such as Ro 60-0175 (**XVI)** and Ro 60-0332 **(XVII).**[68, 69] Both the compounds regularly used as pharmacological tools to establish 5-HT_{2C} mechanism of action, are agonists at 5-HT_{2C} but lack selectivity over 5-HT_{2B} receptor. [70] In the literature these compounds reported to be effective in rat penil erection model have been claimed for use in sexual dysfunction also. Both compounds have also been found effective in reducing food intake in rat.[70, 71]

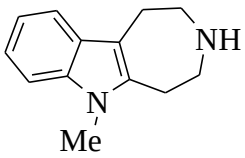


(XVI)

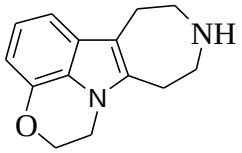


(XVII)

Upjohn Company (Pfizer) filed a patent application on azepinoindole compound **(XVIII)** (PNU-22394A) for schizophrenia but described it recently as an anorectic agent. [72, 73] Compound **(XVIII)** has been described as a potent 5-HT_{2A}/5-HT_{2C} agonist (5-HT_{2A}: *K*i = 19 nM [64% functional response of 5-HT]; 5-HT_{2B}: *K*i = 28.5 nM [13%]; 5-HT_{2C}: *K*i = 18.8 nM [83%])



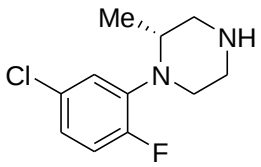
(XVIII)



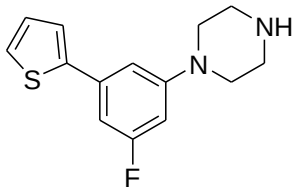
(XIX)

Pharmacia and Upjohn have also described closely related tetracyclic azepinoindoles, such as compound **(XIX).**[74] The patent application contained brief data with compound **(XIX)** reported to be a potent 5-HT_{2C} agonist (h5-HT_{2C}: *K*i = 4.3 nM) with no selectivity over 5-HT_{2A} and demonstrated its activity in some animal models that were predictive of its anxiolytic efficacy. [75]

Arena Pharmaceuticals published a PCT application regarding lorcaserin **(V)** as a 5-HT_{2C} receptor modulator.[76] Benzazepine, as a constrained 7-membered azepine ring fused to benzene, was selected for this purpose. Out of multiple synthesized compounds lorcaserin **(V)** was identified as a potent and selective (*in vitro* pEC_{50} values in functional assays measuring [^{3}H] phosphoinositol turnover: 5-HT_{2C} = 8.1; 5-HT_{2A} = 6.8; 5-HT_{2B} = 6.1) and was also found to be potent in acute *in vivo* rat food intake model on oral administration (ED_{50} at 6 h = 18 mg/kg). Pharmacokinetic study on lorcaserin was performed in a single-dose study in rat ($t_{1/2}$ = 3.7 h; F = 86%) and a 28-day model of weight gain in growing Sprague-Dawley rat (8.5% decrease in weight gain observed at 36 mg/kg twice a day).[77] Arena has developed a number of benzazepine derivatives in search of a selective 5-HT_{2C} agonist.



(XX)

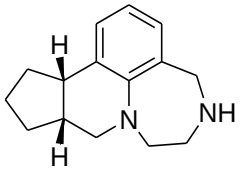


(XXI)

Arena has also highlighted a series of arylpiperazine derivatives which are structurally related to *m*-CPP **(XI)**, as 5-HT_{2C} receptor agonists in a series of publications involving *N*-phenylpiperazine derivatives like compound **(XX)**.[78] Compound **(XX)** showed good selectivity for 5-HT_{2C} over 5-HT_{2A}, 5-HT_{2B} (IP accumulation assay: 5-HT_{2C}: EC_{50} = 8.0 nM; 5-HT_{2A}: EC_{50} = 529 nM; 5-HT_{2B} = inactive). This compound also reduced food intake in normal rats in acute model after oral administration. Arena also reported N-biaryl and *N*-

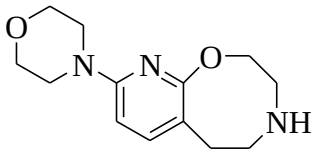
arylheteroaryl piperazine derivatives as modulators of $5HT_{2C}$ receptor.[79] For instance, thiophenylphenylpiperazine **(XXI)** displayed EC_{50} values of 7 nM for 5-HT_{2C} and > 10 μM for 5-HT_{2A} receptors, respectively, while it was claimed to be essentially inactive at the 5-HT_{2B} receptor.

Wyeth (now Pfizer) published [1,4]diazepino[6,7,1-*ij*]quinoline derivatives. Vabicaserin **(XXII**) was a representative molecule of the series developed as antipsychotic and anti-obesity agents.[80] Currently, vabicaserin **(XXII)** is in Phase II clinical trials for both bipolar disorder and schizophrenia. Previously, Wyeth also attempted to develop vabicaserin **(XXII)** for the potential treatment of depression. Vabicaserin demonstrated full agonist activity for 5-HT_{2C} coupled calcium mobilization (EC_{50} = 8 nM, E_{max} = 100%),

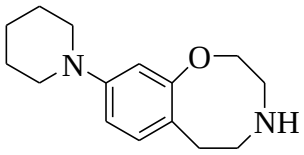


(XXII)

Takeda Pharmaceutical reported a group of fused heterocyclic compounds containg tetrahydropyridooxazocine.[81] Multiple compounds are reported but one such compound **(XXIII)** has shown agonistic activity at 5-HT_{2C} (83% at 1 μM). Takeda also filed patent on benzoxazocine derivatives. One of these compounds **(XXIV)** demonstrated agonistic activity at 5-HT_{2C} (94.3% at 1 μM).



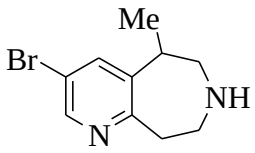
(XXIII)



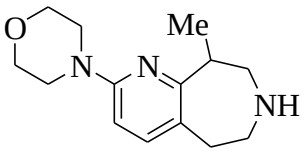
(XXIV)

Forest Laboratories filed a patent application on a series of pyridoazepine derivatives as exemplified by compound **(XV)** as 5-HT_{2C} agonist for the treatment of obesity.[82] Also the researchers from NPS Allelix Corp. reported pyridoazepine analogs as 5-HT_{2C} agonists for the treatment of a number of CNS disorders. One such representative compound **(XVI)** is reported to be the most potent (5-HT_{2C} EC_{50} = 2.1 nM) one.[83] Researchers from Cascade Therapeutics have also claimed pyridoazepine derivatives as 5-HT_{2C} agonists for the treatment of a variety of CNS disorders.[84] One of them, compound **(XXVII)** showed a good

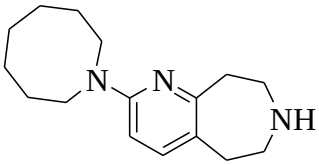
potency and selectivity for 5-HT_{2C} receptor with respect to 5-HT_{2A} and 5-HT_{2B} receptors (for 5-HT_{2C}, EC_{50} = 30 nM and relative efficacy is 86%; for 5-HT_{2A}, EC_{50} = 290 nM and relative efficacy is 77%; for 5-HT_{2B}, EC_{50} = 3992 nM and relative efficacy is 12%) when evaluated for its ability to mobilize intracellular calcium.



(XXV)



(XXVI)



(XXVII)