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Predictive *In Silico* Studies of Human 5-hydroxytryptamine Receptor Subtype 2B (5-HT_{2B}) and Valvular Heart Disease

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Abstract

Serotonin (5-HT) receptors are neuromodulator neurotransmitter receptors which when activated generate a signal transduction pathway within cells resulting in cell-cell communication. 5-hydroxytryptamine (serotonin) receptor 2B (5-HT_{2B}) is a subtype of the seven members of 5-hydroxytryptamine (5-HT) family of receptors which is the largest member of the super family of 7-transmembrane G-protein coupled receptors (GPCRs). Not only do 5-HT receptors play physiological roles in the cardiovascular system, gastrointestinal and endocrine function and the central nervous, but they also play a role in behavioral functions. In particular 5-HT_{2B} receptor is wide spread with regards to its distribution throughout bodily tissues and is expressed at high levels in the lungs, peripheral tissues, liver, kidney and prostate just to name a few. Hence 5-HT_{2B} participates in multiple biological functions including CNS regulation, regulation of gastrointestinal motility, cardiovascular regulation and 5-HT transport system regulation. While 5-HT_{2B} is a viable drug target and has therapeutic indications for treating obesity, psychotherapy, Parkinson's disease etc. there is a growing concern regarding adverse drug reactions, specifically valvulopathy associated with 5-HT_{2B} agonists. Due to the sequence homology experienced by 5-HT₂ subtypes there is also a concern regarding the off target effects of 5-HT_{2A} and 5-HT_{2C} agonists. The concept of subtype selectivity is of paramount importance and can be tackled with the aid of *in silico* studies, specifically cheminformatics, to develop models to predict valvulopathy associated toxicity of drug candidates prior to clinical trials. This review has highlighted three *in silico* approaches thus far that have been successful in either predicting 5-HT_{2B} toxicity of molecules or identifying important interactions between 5-HT_{2B} and drug molecules that bring about valvulopathy related toxicities.

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

Keywords

5-hydroxytryptamine (serotonin) receptor 2B; valvular heart disease; G protein-coupled receptors; in silico; cheminformatics; quantitative structure–activity relationship; homology modeling; molecular docking; molecular dynamics; virtual screening

1. INTRODUCTION

5-hydroxytryptamine (serotonin) receptor 2B (5-HT_{2B}), a subtype of the seven members of 5-hydroxytryptamine (5-HT) family of receptors with the exception of 5-HT₃ receptor which is a part of the ligand-gated ion channel associated receptors, is the largest member of the super family of 7-transmembrane G-protein coupled receptors (GPCRs). GPCRs are one of the most exploited drug targets accounting for over 40% of the blockbuster drugs currently on the market.^{1,2} The large diversity of 5-HT receptor is as a consequence of evolutionary growth over a long period of time, which adds to the pharmacological complexity of these receptors. To date seven 5-HT families, 5-HT₁ through 5-HT₇, have been identified with a total of nineteen known subfamilies (Table 1).^{3,4}

Serotonin (5-HT) receptors are neuromodulator neurotransmitter receptors which when activated generate a signal transduction pathway within cells resulting in cell-cell communication. In mammals, serotonin plays a variety of physiological roles in the cardiovascular system, gastrointestinal and endocrine function and the central nervous. Not only do 5-HT receptors have physiological functions they also regulate behavioral functions such as maintenance of aggression and mood, appetite control, control of sleep-wake cycles, sex and memory.⁵ These receptors are neither excitatory nor inhibitory rather they mediate the actions of serotonin neurotransmitters to which they bind.

2. 5-HT_{2B} RECEPTOR

5-HT_{2B}, a member of the 5-HT₂ group of receptors, is widely distributed body tissues. The receptor is expressed at high levels in the liver, kidney, alimentary canal, fundus of the stomach and intestines, which partially makes up the gastrointestinal tract where 95% of total body serotonin is synthesized. To a lesser extent 5-HT_{2B} is also expressed in the lungs, cardiovascular tissues and central nervous system (CNS) of mammals.⁶⁻⁹ However, more recent studies are reporting the expression of several 5-HT receptors in the human heart.¹⁰ 5-HT_{2B} receptors are known to participate in multiple biological functions, three of the more infamous roles being;

A. CNS regulation - The mechanism by which 5-HT_{2B} functions in the brain is unknown but we do know that 5-HT_{2B} is associated with behavioral disorders such as reduced grooming, non-rapid eye movement sleep regulation etc.¹¹

B. Regulation of gastrointestinal motility – In mice, of the 5-HT receptors, 5-HT_{2B} mRNA was the only found in the interstitial cells of cajal (ICC). In mice, 5-HT is found to regulate ICC proliferation through 5-HT_{2B}.¹² ICC regulation is necessary for the proper function of the gastrointestinal (GI) system as it generates slow wave electrical activity, that causes

phasic contraction of the GI tract. The GI system is able to process and transport food via the control of the motor patterns of smooth muscles which is ultimately in part controlled by the ICC.^{2,13} Thus 5-HT_{2B} is known to play key roles in intestinal disorders like irritable bowel syndrome (IBS). It has also been proposed the effects of 5-HT in the human colon are mediated by 5-HT_{2B} receptor.¹⁴

C. Cardiovascular regulation – 5-HT_{2B} plays a vital role in the regulation of cardiovascular functions and development both at the embryonic stage and adulthood. Thus irregular levels of 5-HT_{2B} receptor concentration may lead to vascular pathologies which will be discussed further in the later section of this review.¹⁵

D. 5-HT transport system regulation – Plasma serotonin level are controlled by 5-HT_{2B} receptors. Studies of serotonin plasma level in mice that had acute agonist and antagonist stimulation revealed serotonin levels increased with agonist stimulation and decreased with antagonist stimulation.¹⁶

There is a large phenogenetic similarity between members of the 5-HT₂ family due to the presence of highly conserved motifs within the seven transmembrane regions.⁵ The human 5-HT_{2B} receptor shows 58% homology to 5-HT_{2A} and 51% homology to 5-HT_{2C} in overall sequence identity, however in the transmembrane regions homology ranges between 68-79%.^{2,17} Although the homology among the subtypes are relatively close and the binding properties are similar, binding of the 5-HT_{2B} is distinctly different. This was observed in a study by Chan and Eglen et.al where SB 204741, a 5-HT_{2B} antagonist, had a 20 fold selectivity to human 5-HT_{2B} compared to 5-HT_{2C}. Similarly 5-HT_{2B} receptor had a low affinity for ritanserin and higher affinity for yohimbine than 5-HT_{2C} and 5-HT_{2A}.^{6,18} This trend in affinity is observed by many 5-HT₂ ligands and supports the conclusion above.¹⁹

Hence, subtype selectivity becomes an important consideration in the design of drugs to target 5-HT₂ receptors. A lack of selectivity will result in residual affinities for undesirable targets causing off-target effects. Additionally, the metabolites of drugs should be devoid of any agonist effect, simply put, drug metabolites cannot bind to other targets causing or triggering a response. Such was the case with the drug flenfluramine (trade name Pondimin) and 3, 4-methylenedioxymethamphetamine (MDMA, “Ecstasy”).

2.1 Valvular Heart Disease

Valvular heart disease (VHD) , a cardiovascular disease (CVD), which refers to disorders or defects of the heart valves, is a major health concern in the United States and worldwide. According to the 2011 report from the American Heart Association, in 2007 alone 2200 Americans die from CVD per day resulting in 150,000 deaths that year. Of the 150,000 Americans who died from CVD, 23,313 died as a result of VHD.²⁰ Valvulopathy is the main cause of human mortality worldwide with costly and invasive surgery as the treatment option. VHD is an iatrogenic induced cardiopathy associated with pharmaceutical agents like Ergot alkaloids, amphetamines/hallucinogens, anorexigens and dopamine agonists acting through a serotonergic pathways involving the activation of 5-HT_{2B}. Evidence of this has emerged from a variety of studies including, experimental, clinical and observational

studies. As a result, many drugs for treatment of obesity, depression, psychotherapy, pain etc. have been removed from the market.

Flenfluramine is a serotonin agonist approved by the U.S. Food and Drug Administration (FDA) in 1973 for the treatment of obesity. After reports of VHD and pulmonary hypertension the drug was withdrawn from the market in 1997.²¹⁻²³ Rothman et al. in 2009 provided evidence supporting the hypothesis that VHD is as a result of the activation of various serotonin receptors, specifically and most importantly 5-HT_{2B} receptor by amphetamine derivative, norfenfluramine, the metabolite of fenfluramine, eliciting an agonist activity.^{22,24} Receptorome screening by Setola et al. 2003 has also revealed the affinity for the popular amphetamine derivative, 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy"), to preferentially bind to and activate 5-HT_{2B} receptors inducing mitogenesis in human heart valve resulting in VHD.²⁵ Reports of other VHD-associated drugs include ergot derivatives like pergolide, methysergide and ergotamine which are used in the treatment of Parkinson's disease, restless leg syndrome and migraines respectively. Due to the structural similarity of these ergot derivatives to serotonin (Figure 1), it is thought that iatrogenic induced VHD is associated with the accumulation of excess serotonin.^{10,26,27}

Subsequently other drugs of various classes that have a serotonergic mechanism that can activate 5-HT_{2B} receptor may elicit VHD and should be avoided. Thus preclinical screening of the valvulopathogenic actions of drugs is a leading topic of research focus. This review focuses on human 5-HT_{2B} receptor, its role in cardiovascular disease, explicitly valvular heart disease and recent efforts in *in silico* predictions of drug toxicity prior to clinical trials.

3. MECHANISM OF ACTION

In order to develop a method to predict cardiopathic toxicities, specifically induced-VHD, of drug candidates, we must clearly understand the mechanism of action of 5-HT_{2B} activation by valvulopathic agents. Due to a 300 fold higher concentration of 5-HT_{2B} receptor transcripts in the human heart valves and pulmonary arteries, 5-HT_{2B} is the likely candidate contributing to VHD.²⁸

The following classes of drugs, ergot alkaloids, amphetamines/hallucinogens, anorexigens and dopamine agonists, exert an agonist effect when bound to 5-HT_{2B} receptors. Drugs that target transporter proteins such as serotonin receptor's/transporters (SERTs) are categorized into two types based on their mechanism of action; (1) reuptake inhibitors and (2) substrate-type releasers. Reuptake inhibitors inhibit the transporter-mediated reuptake of neurotransmitters from synapse thereby leading to an increase in the extracellular transmitter concentration. While substrate-type releasers bind to transporter proteins and are transported into the cell cytoplasm.²⁹

There are three proposed mitogenic pathways by which 5-HT_{2B} receptors are activated resulting in VHD^{10,24,30};

1. The drug molecules first bind to and activate 5-HT_{2B} receptor in the cell membrane which leads to the dissociation of the G-protein releasing G_q subunits. G_q subunit in turn activates phospholipase C- β (PLC- β) causing the activation of protein kinase C (PKC).

2. In addition to the activation of PLC- β , G α_q is also thought to activate Src-P which upregulates the activity of transforming growth factor- β 1 (TFG- β 1).³¹
3. Finally the mitogenesis involving the phosphorylation of retinoblastoma protein via activation of 5-HT_{2B} receptors causing excess cell division and proliferation resulting in valvulopathy.

4. SELECTIVE AGONISTS AND ANTAGONISTS OF 5-HT_{2B} RECEPTOR

So far little information regarding selective binders of 5-HT_{2B} receptor has been reported, while the number of non-selective agonist and antagonists appears to be large (Table 2). Recently there have been reports of a few molecular scaffolds considered as selective agonists of 5-HT_{2B} receptor. These scaffolds include; (1) arylureas, (2) arylpiperazines, (3) indolonaphthyridines, (4) pyrimidines and tetrahydro- β -carboline (Figure 3).³² Arylureas have a high affinity for 5-HT_{2B} > 5-HT_{2C} which seems to be caused by the conformational restrictions of the ring system that lowers the affinity for 5-HT_{2C}. On the other hand pyrimidines and some tetrahydro- β -carboline exhibit a 100 fold selectivity for 5-HT_{2B} compared to 5-HT_{2A/C}.

The ergot alkaloid derivatives can be considered privileged structures as their molecular scaffolds (Figure 1) bind to multiple targets thus displaying diverse biological activity.³³ Ergot alkaloids such as, Carbergoline³⁴, Methylergonovine and Pergolide³⁵, exhibit interactions with serotonergic, dopaminergic, and adrenergic receptors (Table 2). Not only do these privileged structures act as agonists, they also can act as partial agonists and antagonists as seen with Methylergonovine and Methysergide. As mentioned in section 2.1, there is structural similarity between the ergot derivatives and serotonin. A close analysis of the ergot scaffold reveals a constrained serotonin structure embedded inside.

Hallucinogens are agents that produce hallucinogenic effect and bind to 5-HT₂ receptors. There are various classes of classical hallucinogens such as: (1) ergoline, (2) indolealkylamine and (3) phenylalkylamine classes.³⁶ MDMA is a drug of the amphetamine class which are a part of the phenylalkylamine class of hallucinogens, while LSD is a part of the ergoline class (Figure 3).

Nelson et.al and colleagues have studied the structure activity relationship of a large number of phenyl-isopropylamines (Figure 3, 4) and their binding affinities to all three subtypes of 5-HT₂ class of receptors. Their findings revealed significant correlations among binding data targeting 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C}. This information correlates with a study conducted by Porter et. al which ranked the potency of phenyl-isopropylamines at 5-HT₂ receptor site to be 5-HT_{2A} > 5-HT_{2B} > 5-HT_{2C}.³⁷ Nelson et. al also reported substitutions of hydrophobic groups at R₁ displayed selectivity for 5-HT_{2A/2C} receptors but there was no significant difference in binding affinities for 5-HT_{2B}.³⁸ These findings indicate there are structural differences at the active sites of 5-HT₂ receptors that should be taken into account in the development of selective agents for 5-HT_{2B} receptors so as to eliminate the ADRs-like VHD.

Rothman et. al., Porter et. al. and Fitzgerald et. al. have all reported norfenfluramines display a significantly higher binding affinity to 5-HT_{2B} receptor when compared to fenfluramines which exhibit a low affinity to all 5-HT₂ receptors.^{28,37,39} The only structural difference between fenfluramines and norfenfluramines is the presence of a secondary amine as opposed to a primary amine respectively (Figure 5).

From the studies mentioned in section 4, it is quite obvious that; (1) even though there is close structural homology between 5-HT₂ receptor subtypes there is however structural differences at the active sites of each subtype, and (2) small changes of substituent groups can cause significant differences in selectivity to each subtype.

5. CURRENT IN SILICO STUDIES TO PREDICT DRUG TOXICITY

Increasing evidence suggests that activation of 5-HT_{2B} is the primary cause of drug induced-VHD. It has led to increasing interest in developing analytical methods for determining whether a drug candidate or drug is 5-HT_{2B} active. Stahura et.al proposed the use of high through put (HTS) screening of molecules against biological targets. The disadvantages of this method being: (1) it is expensive and (2) it is time consuming.⁴⁰ Therefore, fast, simple and efficient new methods to predict adverse drug reactions (ADRs) prior to clinical trials have been under intense research. One option to explore is *in silico* research which is less expensive to conduct and will ultimately improve the safety and cost of drug development. Thus far and to the best of our knowledge, there have been two *in silico* studies reported in literature that have proposed methods of predicting 5-HT_{2B} toxicity of investigational drugs as well as drugs currently on the market which we will discuss in detail below.⁴¹

5.1. Cheminformatics Studies on 5-HT_{2B} Receptor Ligands

A promising cost effective and efficient method of preselecting 5-HT_{2B} active molecules is with the aid of *in silico* techniques for conducting virtual screening (VS).

5.1.1. 2D Classification QSAR Studies and Screening—Tropsha et. al. has successfully employed cheminformatic models to accurately identify (with a 90% hit rate) compounds with a high affinity toward 5-HT_{2B} receptor.⁴² A dataset of 800 compounds obtained from the Psychoactive Drug Screening Program (PDSP), which consist of 2200 compounds, was the basis for the model generation. Upon completion of the data curation process the data was randomly split into a modeling set (used for model generation) and a validation set (used for validating the model accuracy). An additional independent external validation was conducted on the remaining 1400 compounds from PDSP. QSAR methods for model development included the use of *k*-Nearest Neighbor algorithm (*k*-NN), classification based on association (CBA) and distance weighted discrimination (DWD). To ensure the validity and robustness of the models generated Y-randomization tests were included. If y-randomized models resulted in a high correct correlation rate (CCR) it indicates the employed QSAR method is unable generate an acceptable classification model. The most statistically predictive and robust models based on the results of both internal and external datasets were employed for virtual screening of the world drug index (WDI) database, which led to the identification of 122 hit molecules targeting 5-HT_{2B} actives. Of the 122 possible 5-HT_{2B} hits, 10 structurally diverse compounds were chosen for

experimental validation of which 9 were experimentally confirmed to be 5-HT_{2B} active. This study suggests the use of cheminformatics as a possible tool to quickly and efficiently proactively screen drug candidates for potential valvulopathy toxicity.

5.1.2. 3D Classification QSAR Studies—Within the same realm of cheminformatics is the use of shape signatures for toxicology modeling.^{43,44} Welsh et. al. proposed a novel method which utilizes shape-dependent signatures to generate 3-D descriptors which are used to classify molecules with respect to their biological activity. The premise of shape signature is to generate a detailed 3-D representation of the shape of molecules, with the aid of smooth molecular surface triangular algorithm (SMART) and ray tracing algorithm to derive probability distributions that characterize the ray trace and then use the information as compact descriptors of the shape (1D signatures). This approach also includes the use of molecular electrostatic potential (MEP) to define the 2D signature. Thus the 3D molecular features are a composition of the overall molecular shape and distribution of charges of a molecule. Welsh has extended the use of shape signatures 3D molecular descriptors to generate 5-HT_{2B} toxicity models utilizing classification techniques such as *k*-Nearest Neighbor algorithm (*k*-NN), Support Vector Machine (SVM) and Kohonen self-organizing maps (SOM). The results of this study exhibited an overall prediction accuracy of the test set ranging from 70-84%. There are advantages of using shape signature approach as opposed to the traditional descriptor-based QSAR methods (Cheminformatics) such as:

1. Shape signature will work for all types of compounds example, organics, inorganics, organometallics, ions etc. Whereas adequate descriptors have not been developed for inorganics and organometallics, thus these molecules are not included in any cheminformatic modelling.⁴⁵
2. Models generated by shape signatures are much less sensitive to the chemical structures in the training set compared to cheminformatic models. Applicability domain becomes a major concern when accessing QSAR model validity and is one of the six basic principles implemented when using QSARs for regulatory purposes.^{46,47}
3. Models generated from shape signatures once created do not have to be refitted to accommodate for new task.
4. Preprocessing/Data curation is necessary when generating the traditional QSAR model, and it is a time consuming process. No preprocessing of data is necessary for shape signature methods.

5.2. Structure-based Studies on 5-HT_{2B} Receptor and Its Ligands

Some *in silico* studies are not designed to develop predictive toxicity models for 5-HT_{2B}, instead they are designed to understand 5-HT_{2B} selectivity. As a result of the high homology (~ 80%) experienced between 5-HT₂ receptors, there is concern regarding similar affinities for receptor antagonists, specifically between 5-HT_{2B} and 5-HT_{2C}. A good understanding of the subtype selectivity of 5-HT₂ receptor subtypes will aid in the design of more selective drug molecules for 5-HT₂ subtypes thereby greatly reducing the risk of toxicity by reducing the risk of off-target effects. To attempt to do so without a crystal structure of 5-HT_{2B}

receptor is difficult. Kim et. al and colleagues were able to not only predict the structure of 5-HT_{2B} receptor but also the structure of 5-HT_{2C} receptor using MembEnsemb technique.^{48,49} They have also predicted the binding site, known agonists/antagonists and identified the key residues in the active site that determine the selectivity of 5-HT_{2B} ligands using a GenMSCDock technique. The homology modeling approach employed by Kim et.al involved the use of MembEnsemb Program v.4. The first step was to predict the seven transmembrane (TM) regions of 5-HT_{2B} receptor by analyzing sequence alignments and conducting a hydropathicity analysis. The next step was to then decipher the hydrophobic centers which are integral to maintaining the structural integrity of the TMs. Upon predicting the hydrophobic centers they were then able to attempt to generate a PDB template of 5-HT_{2B} receptor from frog rhodopsin (fRho).⁵⁰ Structures of known GPCRs exhibit α -helical extensions above the surface membranes which Kim et.al has predicted for the 5-HT₂ receptors using a secondary standard structure prediction sever (PSIPRED), located at the N-terminus of TM6 which includes a (D/E)RY motif.⁵¹ Further studies were conducted to decipher the role of the ionic locks in the (D/E)RY motif of the TM6 extensions, followed by a helix scan to determine the best packing structure of 5-HT_{2B}. MembEnsemb in combination with BiHelix methods were employed to attain this feat. The loops were generated by CCB LOOP builder. Upon complete elucidation of the 5-HT_{2B} receptor, 5-HT_{2C} receptor was mutated from the predicted 5-HT_{2B} receptor. From docking studies using GenMSDock, which utilized known agonists and antagonists of 5-HT_{2B} receptor, Kim et.al and colleagues were able to identify the binding sites as well as key interaction that determined 5-HT_{2B}/5-HT_{2C} selectivity. It was concluded that, antagonist selectivity of 5-HT_{2B} receptor involved key interactions with two valine (V103, V190) residues, two leucine (L132, L347) residues and an alanine (A225) residue in the active site. Finally, molecular dynamic simulation of the predicted agonist-5-HT_{2B} and antagonist- 5-HT_{2B} revealed that the state of the (D/E)RY motif was crucial for antagonist or agonist behavior of molecules. The salt bridges in the (D/E)RY motif was maintained for antagonists dynamics and destroyed in agonist dynamics.

More recently Wacker et. al. elucidated the complete crystal structures of 5-HT_{2B} in complex ERG and 5-HT_{1B}/ERG in an effort to investigate the differences in the protein structures that can account for the biased signaling and potential selectivity.⁵² Three major differences between 5-HT_{2B} and 5-HT_{1B} structures outlined by Wacker et. al. are:

1. At the cytoplasmic end of the receptor subtypes, 5-HT_{1B} helix rotates clockwise towards the active-site while this effect is absent in 5-HT_{2B}.
2. An important motif of 5-HT receptors is D(E)/RY which makes a salt bridge between D(E) and R. While the salt bridge is maintained by 5-HT_{2B} receptor it broken in the 5-HT_{1B} receptor structure.
3. Also structural differences in the extracellular loop region of both subtypes can explain their selectivity. An observed kink in the 5-HT_{2B} loop that is stabilized by a water molecule via hydrogen bonding causes additional conformational changes within the protein.

6. CONCLUSIONS

There has been a great concern regarding ADRs, specifically occurrence of drug induced valvulopathy, associated with 5-HT_{2B} agonists. This is a legitimate and important concern for pharmaceutical industry as drugs designed to target 5-HT receptors for the treatment pain, psychotherapy and obesity etc. are blockbuster drugs. With the relatively new discovery of the role that 5-HT_{2B} receptors play in bringing about various cardiopathies, development of cost effective and efficacious methods for preclinical screening of the valvulopathogenic actions of drugs is a topic of research focus currently. An area of considerable interest in drug discovery research is *in silico* methods of modeling toxicity-related proteins like 5-HT_{2B} to identify ADRs early in the drug discovery process. This review has highlighted three *in silico* approaches thus far that have been successful in either predicting 5-HT_{2B} toxicity of molecules or identifying important interactions between 5-HT_{2B} and drug molecules that bring about toxicities. We hope this review will bring awareness to the current issues of predicting drug induced cardiotoxicities and highlight the fact that limited research is being conducted in this area.

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Fig. 1.
The chemical structure of Ergot (Left) and Serotonin (Right).

Arylurea scaffold

Arylpiperazine scaffold

Indolonaphthyridine

Pyrimidine scaffold

Tetrahydro- β -carboline scaffold

Fig. 2.
The chemical scaffolds of selective 5-HT_{2B} binders.

Fig. 3. Amphetamine (phenyl-isopropylamine) scaffold and examples of amphetamine-derived hallucinogens (MDMA, LSD).

Fig. 4.
The chemical structure of Phenyl-isopropylamine derivatives.

Fig. 5.
The chemical structure of Fenfluramine derivatives

Table 1

List of human serotonin receptor family and subtypes.

Receptor Family	5-HT ₁	5-HT ₂	5-HT ₃	5-HT ₄	5-HT ₅	5-HT ₆	5-HT ₇
Subtypes	5-HT _{1A}	5-HT _{2A}	5-HT _{3A}	5-HT _{4A}	5-HT _{5A}		
	5-HT _{1B}	5-HT _{2B}	5-HT _{3B}	5-HT _{4B}			
	5-HT _{1D}	5-HT _{2C}		5-HT _{4C}			
	5-HT _{1E}			5-HT _{4D}			
	5-HT _{1F}			5-HT _{4E}			
				5-HT _{4F}			
				5-HT _{4G}			
				5-HT _{4H}			

Table 2List of some human 5-HT_{2B} receptor agonists and antagonists and their therapeutic indications.

5-HT _{2B} Agents	Name	Structure	Mechanism of action	Therapeutic Indication
	Fenfluramine ²²		Increases Serotonin levels	Controls food intake or suppresses Obesity
	Norfenfluramine ²²		Metabolite of Fenfluramine. Increases Serotonin levels	Controls food intake or suppresses Obesity
	3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") ²⁵		Increases Serotonin levels	Posttraumatic stress disorder, Psychotherapy
	Alpha-methyl-5-HT ³		Increases Serotonin levels	Its prodrug alpha-methyltryptophan is used for treatment of disorders where serotonin is deficient
AGONISTS	Lysergic acid diethylamide (LSD) ³		5-HT receptor agonist	Psychotherapy, Pain, Alcoholism etc.
	Carbergoline ⁴²		Dopamine agonist	hyperprolactinemia, Parkinson's disease etc.
	Dihydroergotamine ⁴²		Serotonin receptor agonist	Migraine treatment

5-HT _{2B} Agents	Name	Structure	Mechanism of action	Therapeutic Indication
	Methylergonovine ⁴²		Partial agonist/antagonist on serotonergic, dopaminergic and alpha- adrenergic receptors	Control of postpartum hemorrhage & Migraines
	Pergolide ⁴²		Dopamine agonist	Parkinson's Disease and Hyperprolactinemic Disorders
	Agomelatine ³		MT ₁ and MT ₂ agonist as well as 5-HT _{2C} antagonist	Antidepressant
ANTAGONISTS	Asenapine ³			Schizophrenia and mania associated with bipolar disorder
	Ketanserin ³		alpha-1 adrenergic receptor antagonist	Antihypertensive
	Methysergide ³		5-HT _{2B} receptor agonist	Treatment of Migraines
	Ritanserin ³		5HT _{2A/2C} antagonist	Treatment of schizophrenia

5-HT _{2B} Agents	Name	Structure	Mechanism of action	Therapeutic Indication
	Tegaserod ³		5-HT ₄ agonist	Management of irritable bowel syndrome and constipation
	Yohimbine ³		Alpha-2 adrenergic receptor antagonist	Treatment of impotence or erectile dysfunction