CHAPTER-1

INTRODUCTION TO G-PROTEIN COUPLED RECEPTORS
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INTRODUCTION TO G-PROTEIN COUPLED RECEPTORS

1.1 Introduction, aim and scope of the research:

G-protein-coupled receptors (GPCRs) provide a diverse inter cell communication in the human body. These are present on the cell surface and can bind almost all the known hormones and neurotransmitters that are secreted into the circulatory system or released synaptically [1]. The GPCR and ligand binding initiates a variety of events inside the cell that includes, changes in ionic conductance, changes in levels of second messengers and other signaling events that consequently alters cellular activities. Although, GPCRs are responsible for normal physiology in the body, their dysfunction may cause numerous disorders and diseases. Thus, GPCRs play an important role in treating various medical indications. It is estimated that [2], over forty percent of available drugs target GPCRs [2]. When one considers that the human genome expresses genes for between 800-1000 different GPCRs [3] and marketed drugs target less than 50 GPCRs, it is evident that the area of GPCR drug research will definitely grow in the years to come.

In present work, a few novel chemical series were explored as 5-Hydroxy tryptamine\(_6\) (5-HT\(_6\)) receptor ligands. The work carried out resulted in compounds showing potential drug like properties, especially for Alzheimer’s disease [4]. While synthesizing the compounds, the basic
aim was to achieve active and selective 5-HT₆ receptor ligands along with acceptable drug like properties viz. pharmacokinetic properties, adequate oral exposure [5], ADME properties [6], metabolic stability [7] & brain penetration [8]. Lastly the aim was also to screen and identify the compounds with pharmacological activity in animal models of cognition so as to project them for Alzheimer’s disease.

1.2 A brief introduction to 5-HT₆ receptor:

The 5-HT₆ receptor is one of the most recent additions to the family of mammalian 5-HT receptors [9]. It was first identified around year 1990 with the help of molecular biology [10-11]. It is positively coupled to adenylate cyclase [11, 12] and belongs to a group of 5-HT receptors. The informations regarding its functional roles and distribution are given in several reviews [13-14]. Since 5-HT₆ receptor is exclusively present in CNS, it is believed that it will cause very less peripheral side effects.

1.3 A brief introduction to neurotransmitters:

The human brain contains many neurotransmitters [15] that act as communication agents between different brain cells. These neurotransmitters are responsible for various human activities like heart rate, anxiety, mood, sleep, temperature, fear, appetite, aggression and many other psychological occurrences.
The major neurotransmitters are acetylcholine (I), norepinephrine (II) and epinephrine (III), dopamine (IV), 5-HT (serotonin) (V), γ-aminobutyric acid (VI) and glutamic acid (VII).

1.4 Agonist, antagonist and partial agonists:

The binding of a drug to a receptor either inhibits the action of the receptor or stimulates the receptor to give the physiological responses that are characteristic of the action of the drug. Drugs that bind to a receptor and give a similar response to that of the endogenous ligand are...
known as agonists [16], whereas drugs that bind to a receptor but do not cause a response are termed as antagonists [16].

Partial agonists are compounds that act as both agonists and antagonists [16]. They are believed to act as antagonists by preventing the endogenous ligand binding to the receptor but at the same time weakly activating the receptor.

1.5. G-Protein coupled receptors:

G-protein coupled receptor family is the largest family of cell surface receptors that contains seven trans-membrane protein loops [1, 17]. When a chemical messenger binds to these proteins it can initiate a sequence of events [18]. The change in shape of the trans-membrane protein allows a G-protein from within the cell to bind to part of the trans-membrane protein within the cell [18-19]. The G-protein releases a guanine diphosphate and picks up a guanine triphosphate, hence the name G-protein [20]. This change then causes the G-protein to dissociate into three sub-units (α, β and γ). The α sub-units bring about various changes that depend on their structure [21-23]. One sub-unit initiates the formation of cAMP (VIII) from adenosine triphosphate, ATP (IX). Cyclic AMP behaves as a second messenger activating protein kinase A and hence a further sequence of enzymatic reactions. Another α sub-unit from a different G-protein activates the enzyme phospholipase C. This enzyme system hydrolyses phosphatidyl inositol diphosphate (X) to inositol triphosphate (XI) and diacylglycerol (XII). The inositol
triphosphate mobilizes calcium ions, which in turn affect muscle contraction and cardiac activity. The diacylglycerol activates protein kinase C, which in turn phosphorylates various enzymes.

Fig: 1.1 Schematic diagram of a G-protein-coupled (linked) receptor

The individual ligands bind to different pockets in these G-proteins coupled trans-membrane proteins. Many of the adrenergic receptors that respond to noradrenalin (norepinephrine) (II) and adrenalin (epinephrine) (III) and dopaminergic receptors belong to this family. Most of the serotonin receptors (5-HT) belong to this family.
1.5.1 **Subtypes of G protein-coupled receptors:**

The subtypes of G protein-coupled receptors are as below:

- Adrenoreceptors
- GABA receptors
- Dopamine receptors
- Muscarinic receptors
- Nicotinic acid receptors
- Histamine receptors
- Serotonin receptors

Since the present research is related to 5-HT$_6$ receptors, a brief discussion is given on serotonin receptors as follows:

1.6 **5-HT (serotonin) receptors:**

Serotonin is unique in the monoamines family [24]. There are seven different classes (5-HT$_1$ to 5-HT$_7$, where 5-HT$_3$ is ligand gated ion channel) [24-25]. 5-HT research is 50 years old and has resulted in numerous therapeutic agents; some of them have major contribution in disease management.

1.7. **Classification of 5-HT (serotonin) receptors:**

There are seven families of 5-HT receptors which are briefly discussed below:
1.7.1. 5-HT<sub>1</sub> Receptors:

It comprises five receptor subtypes (5-HT<sub>1A</sub>, 5-HT<sub>1B</sub>, 5-HT<sub>1D</sub>, 5-HT<sub>1E</sub> and 5-HT<sub>1F</sub>). It is believed that, it inhibits cAMP (VIII) production inside the cell.

1.7.1.1 5-HT<sub>1A</sub> receptors

They are largely distributed in the CNS [24]. 5-HT<sub>1A</sub> acts as auto receptors to inhibit cell firing. It is present in limbic structures, particularly hippocampus. It mediates neuronal hyperpolarisation via G-protein coupled potassium channels. The representative example of agonist (8-OH DPAT, XIII) and antagonist (WAY-100135, XIV) is given in Table: 1.1.

1.7.1.2 5-HT<sub>1B</sub> receptors

5-HT<sub>1B</sub> receptors [24] are present in CNS particularly in the frontal cortex, cerebral arteries, vascular tissues and striatum. They are believed to serve as terminal autoreceptors.

1.7.1.3 5-HT<sub>1D</sub> Receptors:

These serotonin receptors are located primarily in hippocampus cortex, spinal cord and basal ganglia [24]. They are thought to be involved in depression, anxiety and other neuropsychiatric disorders. The agonist (L-694247, XV) and antagonist (BRL-15572, XVI) for 5-HT<sub>1D</sub> receptor is given in Table: 1.1.
1.7.2 5-HT₂ Receptors:

5-HT₂ receptor is other major subfamily of 5-HT receptors [24]. The three subtypes are 5-HT₂A, 5-HT₂B and 5-HT₂C.

5-HT₂A receptors are located primarily in the olfactory tubercle neocortex, nucleus accumbens and hippocampus. They also play a role in sleep, appetite control, and thermoregulation. The other type 5-HT₂B is located primarily in stomach fundus, GI smooth muscle and uterus. Whereas, 5-HT₂C receptors are located in limbic system, choroid plexus and basal ganglia. 5-HT₂C receptors play a role in thermoregulation, CSF volume regulation and anxiety. The structures of 5-HT₂A agonist (Sumatriptan, XVII) and antagonist (Ketanserin, XVIII) are given in Table: 1.1.

1.7.3 5-HT₃ Receptor:

5-HT₃ receptors are unique and they are nonselective K⁺/Na⁺ ion channel receptors [24]. They are found in CNS and in the periphery, with structural and functional similarity to nicotinic acetylcholnergic receptors. So far five human 5-HT₃ receptor subtypes have been identified (5-HT₃A to 5-HT₃E). The nonselective 5-HT₃ receptor agonist (m-chlorophenylbiguanide, XIX) and antagonist (Ondensetron, XX) is given in Table: 1.1.
1.7.4 5-HT_4 Receptor:

5-HT_4 receptors play a role in anxiety [26], memory and learning [27], smooth muscle relaxation and visual perception. The representative example of 5-HT_4 receptor agonist (cisapride, XXI) and antagonist (GR-113808, XXII) is given in Table: 1.1.

1.7.5 5-HT_5 receptor:

Pharmacological functions are still unknown for these receptors but, it is speculated that they may be involved in anxiety, learning motor control, depression, memory consolidation and brain development [28]. The representative example of 5-HT_5A receptor agonist (5-carboxamido tryptamine, XXIII) and antagonist (SB-699551, XXIV) is given in Table: 1.1.

1.7.6 5-HT_6 Receptor:

5-HT_6 receptor is G-protein coupled serotonergic receptor that is localized exclusively in the CNS and was cloned from rat brain [10, 29]. The human 5-HT_6 receptor has its distribution, gene structure and pharmacology very similar to that of rat receptor. The representative example of 5-HT_6 receptor agonist (WAY-181187/SAX-187, XXV) and antagonists (XXVII to XXXIV) is given in Table: 1.1.

1.7.7 5-HT_7 Receptor:

These are located primarily in the hippocampus, thalamus and hypothalamus. The function of these receptors includes the regulation of
smooth muscle relaxation, learning and memory [30-31]. The examples of agonist (**XXXV**) and antagonist (**XXXVI**) are given in Table: 1.1.

Table: 1.1 Representative examples of agonists and antagonists for 5-HT receptor subtypes.

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Agonist</th>
<th>Antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT\textsubscript{1A}</td>
<td><img src="XIII" alt="image" /></td>
<td><img src="XIV" alt="image" /></td>
</tr>
<tr>
<td>5-HT\textsubscript{1D}</td>
<td><img src="XV" alt="image" /></td>
<td><img src="XVI" alt="image" /></td>
</tr>
<tr>
<td>5-HT\textsubscript{2A}</td>
<td><img src="XVII" alt="image" /></td>
<td><img src="XVIII" alt="image" /></td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;3&lt;/sub&gt;</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td><img src="image2" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>-----------------</td>
<td>--------------------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;4&lt;/sub&gt;</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td><img src="image4" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;5A&lt;/sub&gt;</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td><img src="image6" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;5B&lt;/sub&gt;</td>
<td>No selective agonists are available</td>
<td>No selective antagonists are available</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;6&lt;/sub&gt;</td>
<td><img src="image7" alt="Chemical Structure" /></td>
<td><img src="image8" alt="Chemical Structure" /></td>
</tr>
</tbody>
</table>

No selective agonists are available.
1.8. The 5-HT₆ receptor

1.8.1 Biology

The 5-HT₆ receptor was cloned in 1993 and was found to be coupled with adenylate cyclase [11]. This receptor is located exclusively in the CNS, with the highest levels in limbic, striatum and in cortical regions.

The 5-HT₆ receptor antagonists have been implicated in the modulation of cognitive function, while the 5-HT₆ receptor agonists are also reported with positive pre-clinical data [32]. Based on strong pre-clinical in-vivo data, two 5-HT₆ antagonists, GSK-742457 (LIII) and Lu-AE58054 (LII) (See, Table 1.4), have entered phase II clinical trials for the enhancement of cognitive function in the treatment of Alzheimer’s disease or schizophrenia.

Several selective 5-HT₆ receptor antagonists have been shown to suppress food intake in food-deprived animals [13, 33]. Few reports suggest that chronic treatment with a selective 5-HT₆ receptor partial agonist decreased food consumption and body weight in a model of diet-induced obese rats [32]. It has been suggested that 5-HT₆ receptor
ligands, either block or desensitize the serotonergic receptors resulting in a reduction of GABA and a subsequent increase in α-melanocyte stimulating hormone release, thereby suppressing food intake. Two 5-HT$_6$ compounds BVT-74316 and PRX-07034 (XLIX, see table 1.4) have entered phase I clinical trial for the treatment of obesity.

### 1.8.2 Medicinal chemistry of 5-HT$_6$ receptors:

The research on 5-HT$_6$ receptors is well documented in several publications and reviews [12-14, 34-35]. It is observed in several compounds that, both the agonist and antagonist show similar favourable effects in in-vivo pharmacology and pre-clinical models of both cognitive function and body weight control.

### 1.8.3 History of agonists for 5-HT$_6$ receptor

The first reported 5-HT$_6$ receptor agonist was the tryptamine analog XXXVII (5-HT$_6$ pKi = 7.3 nM, Table: 1.2) [36]. This molecule was active towards 5-HT$_6$ receptor but also showed moderate affinity for other receptors like 5-HT$_1$ and 5-HT$_7$. The high throughput screening afforded compounds such as XXVI (Table: 1.1) with pIC50 for 5-HT$_6$ = 8.1 nM, In this compound the 2-aminoethyl side chain was replaced with a tetrahydropyridine [37].

It is observed that a common structural feature of 5-HT$_6$ receptor ligands is the presence of an N$_1$-arylsulfonyl group. This was initially used as N$_1$-protecting group, but latter found to be involved in showing 5-HT$_6$ activity. This discovery gave a series of 5-HT$_6$ receptor ligands [38].
Various other N₁-sulfonyl-indoles were reported as full 5-HT₆ receptor agonists [39-40], that includes N₁-arylsulfonylindole WAY-181187/SAX-187 (XXV, 5-HT₆ pKi = 8.7 nM, Table: 1.1).

Table: 1.2 Agonists of the 5-HT₆ receptor.

<table>
<thead>
<tr>
<th>Comp.</th>
<th>Structure</th>
<th>Compound</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>XXXVII</td>
<td><img src="image1" alt="Structure" /></td>
<td>XLI</td>
<td><img src="image2" alt="Structure" /></td>
</tr>
<tr>
<td>XXXVIII</td>
<td><img src="image3" alt="Structure" /></td>
<td>XLII</td>
<td><img src="image4" alt="Structure" /></td>
</tr>
<tr>
<td>XXXIX</td>
<td><img src="image5" alt="Structure" /></td>
<td>XLIII</td>
<td><img src="image6" alt="Structure" /></td>
</tr>
<tr>
<td>XL</td>
<td><img src="image7" alt="Structure" /></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The research on the modification on point of attachment of the arylsulfonyl on the central indole core gave 5-arylsulfonamidindoindoles E-
6801 (XXXVIII, 5-HT\textsubscript{6} pKi = 8.5 nM, Table: 1.2) and E-6837 (XXXIX, 5-HT\textsubscript{6} pKi = 9.1 nM, Table: 1.2). These were reported to be partial agonists [41-42].

Modifications to the arylsulfonyltryptamine template include reversing the phenylsulfonyl and aminoethyl fragments resulting in the partial agonist XL (5-HT\textsubscript{6} pKi = 7.9 nM, Table: 1.2) [43]. Conformational constraint of the aminoethyl side chain of the N\textsubscript{1}-arylsulfonylindoles and 5-arylsulfonamidoindoles afforded agonists, XLI (5-HT\textsubscript{6} pKi = 8.7, Table: 1.2) [44] and XLII (5-HT\textsubscript{6} pKi = 8.7, Table: 1.2) [45]. A further modification was the replacement of the indole nucleus with a pyrrolopyridine to give XLIII (5-HT\textsubscript{6} pKi = 8.4, Table: 1.2) [46]. As observed previously, the reversal of the arylsulfonyl and aminoethyl component provided compounds exhibiting both antagonism and partial agonism.

1.8.4 Antagonists of the 5-HT\textsubscript{6} receptor:

Soon after the identification of the human 5-HT\textsubscript{6} receptor, the discovery efforts for identifying 5-HT\textsubscript{6} receptor antagonists were started, that included structures like pyrimidinesulfonamide Ro 04-6790 (XLV, 5-HT\textsubscript{6} pKi = 7.3, Table: 1.3), pyridinesulfonamide Ro 63-0563 (XLIV, 5-HT\textsubscript{6} pKi = 7.9, Table: 1.3), [47] and the piperazinylbenzenesulfonamide SB-271046 (XLVI, 5-HT\textsubscript{6} pKi = 8.9, Table: 1.3) [48]. Modification of the endogenous ligand provided antagonist MS-245 (XLVII, 5-HT\textsubscript{6} pKi = 8.6, Table: 1.3). This discovery resulted in identification of range of diverse
compounds that led to the development of pharmacophore based models [49-52]. These models in combination with 5-HT6 receptor homology models [53-55] have given a range of structures which may be classified into five major groups. These are given below along with representative examples.

(a) Indoles – e.g. LY-483518 (XXVII, 5-HT6 pKi = 8.9, Table: 1.1) [56]; (b) Indole like structures – e.g. BVT-74376 (XLVIII, 5-HT6 pKi = 8.9, Table: 1.3) [57]; (c) Monocyclic arylpiperazines – e.g. PRX-07034 (XLIX, 5-HT6 pKi = 8.4, Table: 1.3) [58]; (d) Bicyclic/tricyclic arylpiperazines – e.g. (L, 5-HT6 pKi = 8.4, Table: 1.3) [59] and (e) arylsulfonyl moiety as in Ro 66-0074 (LI, pKi = 9.0, Table: 1.3) [60].

1.9 5-HT6 receptor antagonists in cognitive disorders and Obesity:

5-HT6 receptors antagonists are promising targets for the symptomatic treatment of cognitive disorders such as Alzheimer’s disease [61], due to their exclusive location in the CNS. Apart from cognition, there are several reviews available on the potential use of 5-HT6 receptor antagonists in the treatment of obesity and metabolic disorders [32].
Table: 1.3 Antagonists of the 5-HT₆ receptor.

<table>
<thead>
<tr>
<th>Comp.</th>
<th>Structure</th>
<th>Comp.</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>XLIV</td>
<td><img src="image1" alt="Structure" /></td>
<td>XLVIII</td>
<td><img src="image2" alt="Structure" /></td>
</tr>
<tr>
<td>XLV</td>
<td><img src="image3" alt="Structure" /></td>
<td>XLIX</td>
<td><img src="image4" alt="Structure" /></td>
</tr>
<tr>
<td>XLVI</td>
<td><img src="image5" alt="Structure" /></td>
<td>L</td>
<td><img src="image6" alt="Structure" /></td>
</tr>
<tr>
<td>XLVII</td>
<td><img src="image7" alt="Structure" /></td>
<td>LI</td>
<td><img src="image8" alt="Structure" /></td>
</tr>
</tbody>
</table>

Interest in this target in the context of cognition was started from the discovery of SB-271046 (XLVI, Table: 1.3). This compound showed beneficial effect on animal models of cognition like Morris Water Maze and object recognition paradigms for memory consolidation. These results concluded the role of 5-HT₆ receptor antagonists in the treatment of memory and learning disorders. The oral dosing of SB-271046 (XLVI)
in rats showed increased levels of excitatory neurotransmitters that includes, extracellular glutamate, dopamine and norepinephrine when tested in \textit{in-vivo} microdialysis in the rat [62-63]. This data pointed that 5-HT\textsubscript{6} receptors are certainly involved in modulation of several neurotransmitter systems and hence given a wide scope for research in this area.

The 5-HT\textsubscript{6} receptor antagonists that are currently in clinical trials [64-67] are listed in Table: 1.4.

Table: 1.4 5-HT\textsubscript{6} Antagonists in Clinical Development

<table>
<thead>
<tr>
<th>Comp.</th>
<th>Structure</th>
<th>Name of company</th>
<th>Indication / current status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lu-AE58054 (LII)</td>
<td><img src="image1" alt="Structure" /></td>
<td>Lundbeck</td>
<td>Cognitive impairment in schizophrenia / Phase-2</td>
</tr>
<tr>
<td>GSK-742457 (LIII)</td>
<td><img src="image2" alt="Structure" /></td>
<td>Glaxo SmithKline</td>
<td>Cognitive impairment in Alzheimer’s disease and Schizophrenia / phase-2</td>
</tr>
<tr>
<td>SAM-531 (LIV)</td>
<td><img src="image3" alt="Structure" /></td>
<td>Wyeth</td>
<td>Cognitive impairment in Alzheimer’s disease / Phase-2</td>
</tr>
<tr>
<td>SUVN-502</td>
<td>Structure not disclosed</td>
<td>Suven Life Sciences Ltd</td>
<td>Alzheimer’s disease / Completed Phase-1 successfully</td>
</tr>
</tbody>
</table>
1.10 **Summary and future perspectives for 5-HT\textsubscript{6} receptors:**

In past decade, noteworthy progress has been made in elucidating 5-HT\textsubscript{6} receptor function using modern biology techniques to demonstrate the pharmacologic potential of potent and selective 5-HT\textsubscript{6} receptor ligands identified in many laboratories. Many 5-HT\textsubscript{6} receptor antagonists have advanced to clinical development and at least three of them have reached phase-2 clinical trials. Most of these clinical candidates are for cognitive enhancement in Alzheimer’s disease and schizophrenia. Alzheimer’s disease represents one of the greatest human health challenges and current palliative treatments exert their activity via the cholinergic or glutamatergic nervous systems. Neurobiology and \textit{in-vivo} pharmacology studies in rodents have shown that 5-HT\textsubscript{6} antagonists improve memory and cognition through involvement in multiple neurotransmission systems including both cholinergic and glutamatergic systems and, therefore, may potentially provide a mechanistically distinct palliative treatment for Alzheimer’s disease that works through both of these neuronal systems. The potential for this approach for cognitive enhancement, in particular, will be validated by the ongoing clinical trials with the various 5-HT\textsubscript{6} receptor antagonists in development. All the scientific communities working in the field of 5-HT\textsubscript{6} receptor are waiting for the results of clinical trials at different phases and potential utility of these various classes of molecules in cognition and other neurodegenerative disorders.
1.11 Present work:

It is understood from the above discussion that there is increase in therapeutic importance of the 5-HT₆ receptor antagonists for cognitive disorders. Hence, the present research work was carried out in an attempt to identify the novel compounds for addressing the growing demands in the area of cognitive disorders.

1.12. Design of ligands:

1.12.1 SERIES-A: Piperidinyl aminoarylsulfonamides as 5-HT₆ receptor ligands:

Since Glennon’s publication on the first SAR of 5-HT-like structures in 1999 [68] and 2003 [29], significant contributions to the understanding of the receptor pharmacophore have been made by receptor-based and ligand-based modeling.

The structural requirements for a potent 5-HT₆ receptor ligand were postulated first in 2005 by the research group of Esteve [69] and a simplified, qualitative pharmacophore-framework model was established based on medicinal chemistry guided analysis of reference compounds. The main components for the construction of a 5-HT₆ receptor ligand are presence of two hydrophobic areas (area ‘A’ and area ‘D’), with the core area ‘D’ generally an indole, indole-like or a monocyclic/bicyclic aryl functionality. The other area ‘B’, which can accommodate diverse
hydrophobic structural elements, is dominated by the commercial availability of sulfonyl chlorides. (Fig: 1.3).

For understanding the design of present series, we shall consider the two most potent 5-HT₆ receptor ligands **XXVIII** & **XXVII** with diverse structures that are reported in the literature (Fig: 1.4). These compounds contain the piperazinyl and piperidinyl substitutions respectively.

![5-HT₆ receptor pharmacophoric model](image)

**Fig: 1.3 5-HT₆ receptor pharmacophoric model**

Based upon the pharmacophoric model and structural features of **XXVIII** and **XXVII**, we proposed that the 4-amino-piperidine group could allow the appropriate spacing of the basic amine and the distal aryl group for binding to 5-HT₆ receptor, while imparting novelty for the proposed series. It was hypothesized that the N-R⁴ group attached to ring **B** will impart the appropriate orientation for binding and the terminal nitrogen is expected to bind to the receptor.
Fig: 1.4 Designing of piperidinyl aminoarylsulfonamides.

The requirement of terminal nitrogen, which acts as a proton donor and one of the essential requirements for the construction of 5-HT₆ receptor ligand was fulfilled by piperidinyl nitrogen. The two aromatic nuclei can maintain the requirement of hydrophobic areas. The double bond acceptor could be sulfonamide group which separated two hydrophobic areas.

The literature search revealed that the designed series (Fig: 1.4) was novel and hence gave us a wide scope for research in this area.

1.12.2 SERIES B: N¹-substituted-3-aminoalkoxyindoles and their tetracyclic derivatives as 5-HT₆ receptor ligands:

Glennon first discovered the importance of a sulfonamide motif in the indole-type structures for efficient binding and antagonism of 5-HT₆ receptors. This was introduced originally as an N-protective group and is
still the main common structural motif within 5-HT\textsubscript{6} receptor ligands. His efforts have led to the discovery of one of the most potent 5-HT\textsubscript{6} antagonist MS-245 (XLVII). Soon after the Glennon’s discovery of MS-245, various efforts by different scientific groups led to diverse types of compounds while maintaining the essential sulfonamide pharmacophore. Amongst these modifications, few compounds were made with structural constraint in flexible tryptamine side chain while maintaining the sulfonamide group. These efforts were carried out to understand the effect of structural rigidizations on overall binding to 5-HT\textsubscript{6} receptor.

It was hypothesized that the structural constraints can minimize the possible unwanted conformations in molecules and hence it can improve the binding affinities towards 5-HT\textsubscript{6} receptor with limiting interactions with other binding sites.

Wyeth discovered a novel class of azepinoindole type compounds [70], where the focus was mainly on tryptamine side chain. The rigidization of the tryptamine side chain was carried out through C-2 position of indole (XXXIV, Fig: 1.5). The attempt was successful and gave very potent series of compounds with very high binding affinities towards 5-HT\textsubscript{6} receptor (5-HT\textsubscript{6} Ki = 12 nM). There was another attempt of structural rigidization, where the side chain of MS-245 was cyclized to form pyrrolidine ring (XLI, 5-HT\textsubscript{6} pKi = 8.7 nM).
Fig: 1.5 Design of 3-aminoalkoxyindole and their tetracyclic derivatives

**Suven Life Sciences Ltd.**

**XXXII**

*Ki = 11.2 nM*

**MS-245**

*Ki = 2.2 nM*

---

**XXXI**

*Suven Life Sciences Ltd.*

*Ki = 88 nM*

**XXXIV**

*Wyeth*  

*Ki = 12 nM*

**XXX**

*Wyeth*  

*pKi = 8.7 nM*

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**Series-I**

---

**Series-II**

*X = SO₂, CO, CH₂*
The other type of conformational constraints was reported by Suven life sciences Ltd [71-72], where the structural rigidization was attempted on MS-245 through arylsulfonyl moiety and C-2 of indole (XXXII). The resulted tetracyclic structure was well tolerated and gave compounds with good binding affinities towards 5-HT₆ receptor (XXXII, 5-HT₆ Ki = 11.2 nM). Few of these tetracyclic compounds were actively pursued in preclinical studies. In light of research work carried out by Wyeth, an attempt was made at Suven towards conformational restrictions in compound XXXII, where the side chain was rigidized to form pyrrolidinyl ring (XXXI) [73]. The resulted series of compounds were most rigidized with minimum possible conformational orientations. The compounds were found to be less potent (5-HT₆ Ki > 50 nM) than their relatively more flexible counterparts (XXXII), indicating that certain degree of conformational flexibility is essential to maintain the affinity towards 5-HT₆ receptor.

In this designed series, an attempt was made to replace the dimethylamino ethyl side chain with dimethylaminoalkoxy side chain (insertion of hetero atom in the side chain). The N¹-protection was either kept sulfonyl or replaced with other protections like substituted-benzoyl and benzyl (series-I). These Series-I compounds were further structurally rigidized through C-2 position of indole to obtain their tetracyclic analogues (Series-II). All these series-I and series-II compounds were tested for their 5-HT₆ receptor binding affinities, few of them were
extensively studied in *in-vivo* assays. These designed and synthesized compounds are novel and have potential drug like properties. A brief summary about subsequent chemistry and biology chapters is given in abstract on page no ix.