The work presented in this thesis explores novel chemical series as GPCR ligands, especially as 5-HT₆ receptor ligands. The embodied work is an attempt to address the challenging medical requirements in the field of central nervous system (CNS) disorders, especially Alzheimer's disease. These presented chemical series were achieved through understanding of basic pharmacophoric requirements to get 5-HT₆ receptor activity in combination with structure-based designing. The modifications were carried out on the basis of in-vitro and in-vivo results. The basic criteria for molecules designed in the presented series were that, the molecules should have reasonable binding affinity towards 5-HT₆ receptor with high selectivity (no interaction with other closely related receptors), it should have acceptable cytochrome P450 liabilities, good metabolic stability and brain penetrative capabilities along with adequate systemic exposure. The other important criterion was that, the compound should also have activity in animal models of cognition like Morris Water Maze or Novel Object Recognition Task (NORT). The thesis is divided into six chapters and brief details are presented below.

**CHAPTER-1:** This chapter deals with introduction to G-protein coupled receptors (GPCR), their classification, neurotransmitters, receptor types and their mode of action.
Also this chapter highlights about different serotonin receptors and their physiological importance (5-HT₁ to 5-HT₇). Since the presented work is more focused on 5-HT₆ receptors, the medicinal chemistry of past and recent 5-HT₆ compounds with diverse types of antagonists and agonists which are presently in clinical studies is discussed in this chapter. This also covers the present status of research on 5-HT₆ receptor ligands. Finally, the chapter gives a brief summary about the design of targeted series as 5-HT₆ receptor ligands.

**CHAPTER-2:** This chapter deals with the preparation of 4-substituted-3-aminoarylsulfonamide using chlorosulfonation & sulfonylation reactions. The different synthetic routes adopted for the preparation of these sulfonamide compounds along with their spectral and analytical data is reported. The general structure is given below.

![Chemical Structure](image)

**CHAPTER-3:** This chapter deals with the synthesis of novel piperidinyl aminoarylsulfonamides using reductive amination and reductive alkylation methods. The various synthetic routes adopted for the preparation of these novel compounds along with their characterization data is reported. The general structure is given below.
CHAPTER-4: This chapter deals with the synthesis of substituted-N¹-acetylidolone-3-one. The various synthetic routes adopted for the preparation along with their characterization data is reported. The general structure is given below.

![Chemical structure of N¹-acetylidolone-3-one](image)

- \(R^1 = \text{Et, Me, H, OMe}\)
- \(R^2 = \text{Substituted phenyls}\)
- \(R^3 = \text{H, Me}\)
- \(R^4 = \text{H, Me}\)

CHAPTER-5: This chapter deals with the synthesis of novel N¹-substituted-3-aminoalkoxyindoles & their tetracyclic derivatives. The synthesis was carried out using O-alkylation, sulfonylation, benzoylation, benzylolation and intramolecular Heck reaction. The various synthetic routes adopted for the preparation of these novel compounds along with their characterization data is reported. The general structures are given below.

![Chemical structure of N¹-substituted-3-aminoalkoxyindoles](image)

- \(R^1 = \text{H, 5-Cl, 5-Br, 4-F, 6-Cl}\)
- \(5-\text{OMe, 5,6-DiF, 5-ET}\)
- \(5-\text{OiPr}\)
CHAPTER-6: This chapter deals with structure activity relationships, pharmacokinetic and pharmacological evaluation of substituted-aminoarylsulfonamide derivatives (discussed under Chapter-2 & 3), N1-substituted-3-aminoalkoxyindoles & their tetracyclic derivatives (discussed under Chapter-4 & 5) as potential 5-HT6 receptor ligands.