**Thesis Title: STRUCTURAL AND FUNCTIONAL STUDIES ON $GABA_A$ RECEPTOR SUBTYPES: A COMPUTATIONAL PATHWAY FOR DESIGNING NOVEL NON-SEDATIVE MODULATORS**

## Abstract

In this stressful era, maintaining the proper balance of neuronal excitation and inhibition remains the central demand of human brain. To harmonize the optimal brain functioning, γ-Amino Butyric Acid type A Receptors ($GABA_A$-Rs) play a vital role by mediating the fast inhibitory neurotransmissions. These GABA-gated chloride ion channels maintain the delicate balance between neuronal excitation and inhibition. The formation of $GABA_A$-R uses repertoire of 19 different subunit subtypes $\alpha_{1-6}$, $\beta_{1-3}$, $\gamma_{1-3}$, δ, ε, π, θ and $\rho_{1-3}$, out of which two $\alpha_1$, two $\beta_2$ and one $\gamma_2$ form the most abundant native $GABA_A$-R structure. In the absence of heteropentameric human $GABA_A$-R structure the structural biology remains yet to be fully explored. Manipulation of GABAergic transmission is aimed to provide the benefits in the treatment of a host of neurological and psychiatric disorders. We utilised the existing experimental data and carried out a computational study to obtain the structural details of different $GABA_A$-Rs. This computational pathway sequentially proceeds for : i) obtaining the different $GABA_A$-R states and subtypes; ii) understanding the logic of their existence and correlating structure-function details for each of them; iii) unravelling the complete journey of molecular events that fine tune the state dependent channel transitions in normal conditions including ligand unoccupied closed, open, uncapped receptive states and GABA occupied singly and doubly bound states; iv) understanding the nature of cross-talk between two orthosteric sites and third allosteric BZD-site when we brought it into consideration; v) identifying a set of governing rules/markers forming the structural basis of selective modulation for BZD-site agonists at $\alpha_1$- and $\alpha_2$-$GABA_A$-R subtypes.

Accordingly, to fulfil the deliberate demand of clinically efficacious $\alpha_2$-selective non-sedative modulator/s the underlying logic is systematically demarcated under single platform. The crux from the early stage modulatory pathways of subtype selective actions provides newer avenues to guide the designing of novel modulator/s having desired pharmacological endpoints in diseased states.

Overall, this channelled study is bound to track the structure-function-novel drug designing, based on the understanding of $GABA_A$-R modulatory pathways.

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