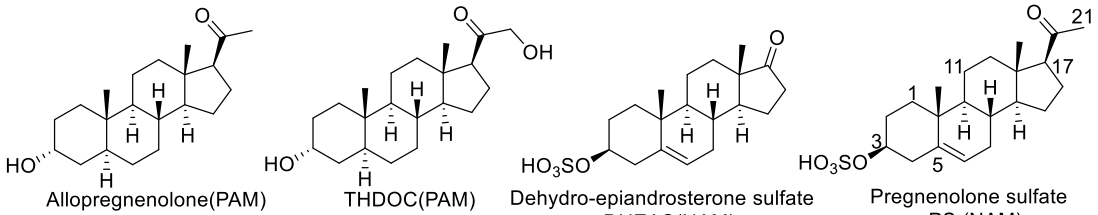
Abstract

$GABA_A$ receptors ($GABA_ARs$) are pentameric ligand-gated ion channels in the central nervous system, and are crucial for the overall balance between neuronal excitation and inhibition. Neuroactive steroids (NASs) are a series of allosteric modulators related to GABAergic neurotransmission, which can be classified into either positive allosteric modulators (PAMs) or negative allosteric modulators (NAMs). Recent studies of X-ray crystallography and cryo-electron microscopy revealed the binding sites of NASs, which provide insight into the molecular basis of allosteric modulation induced by NASs. There is tremendous therapeutic potential for the development of NASs in terms of anticonvulsant, anxiolytic, sedative, hypnotic, and anesthetic properties for its targeting at either synaptic or extrasynaptic $GABA_ARs$. However, the molecular chemical determines that mediate NASs induced modulation are not fully understood. The work presented in this thesis includes three projects aimed at elucidating the molecular basis of NAS binding sites at $GABA_ARs$ and developing novel allosteric modulators for NAS binding sites.



First, a series of pregnenolone sulfate analogues bearing C21 substituents were developed and then subjected to pharmacological characterization. The structural basis of the pharmacological result was further investigated by molecular dynamic simulations, mutagenesis studies and kinetic modelling, resulting in identification of differentiated modulation of PS analogues on either the shut or desensitized states of $GABA_ARs$.

Secondly, The NASs binding sites on physiological $GABA_ARs$ were explored by homology models. Subsequently, shape-similarity models of potentiating and inhibitory NASs were generated and validated. A screening of a commercially available compound library revealed compound hits, being pharmacological active at $GABA_ARs$.

Thirdly, a series of compounds with simplified 'rings system' compared to NASs were synthesized to explore the structure-activity relationship (SAR) of the rings NASs and to achieve the aim of scaffold hopping to nonsteroidal compounds.

In conclusion, this project provides insight into the molecular determinants for the allosteric modulation of NASs and yields a series of nonsteroidal compounds via shape-similarity based virtual screening and synthetic chemistry.