Development of innovative $GABA_A$ receptor ligands using a bioisosteric approach

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γ-aminobutyric acid (GABA) exerts the main inhibitory function in the central nervous system (CNS) by activating the $GABA_A$ receptors ($GABA_ARs$) and $GABA_B$ receptors. $GABA_ARs$ are ligand-gated ion channels composed by five subunits assembled around the chloride ion conducting pore (Figure 1, left).
Several subunits (e.g. α_{1-6}, β_{1-3}, γ_{1-3}, δ, ρ_{1-3}) assemble together building at least 26 native and mainly heteromeric $GABA_AR$ subtypes.[1] Different regional distribution and functional properties of the individual subtypes suggest involvement in a wide range of functions throughout the CNS.[2] Taking this knowledge, it would be important to disclose the function of each $GABA_AR$ subtypes and investigate the possibility of using orthosteric ligands as therapeutic agents.
The overall aim of this project is the development of new GABA analogues targeting $GABA_ARs$ subtypes. For this purpose, a bioisosteric approach at the carboxylic acid and amino moieties of GABA was evaluated using a diverse series of five membered heterocycles (Figure 1, right).
The synthesis, the pharmacological and physicochemical characterization of novel heterocycles in the $GABA_AR$ area were developed. Dihydroimidazole and 2-amino analogues of dihydrothiazole and dihydroimidazole were chosen and shown to translate into valid novel amino bioisosteres in the $GABA_AR$ area. On the other hand, hydroxy-1,2,5-thiadiazole and 4-hydroxytriazole were developed as carboxylic acid bioisostere for the $GABA_ARs$.
These novel heterocycles were successfully applied as bioisosteres in the $GABA_AR$ area and showed interesting and distinctive pharmacological properties for the $GABA_ARs$.

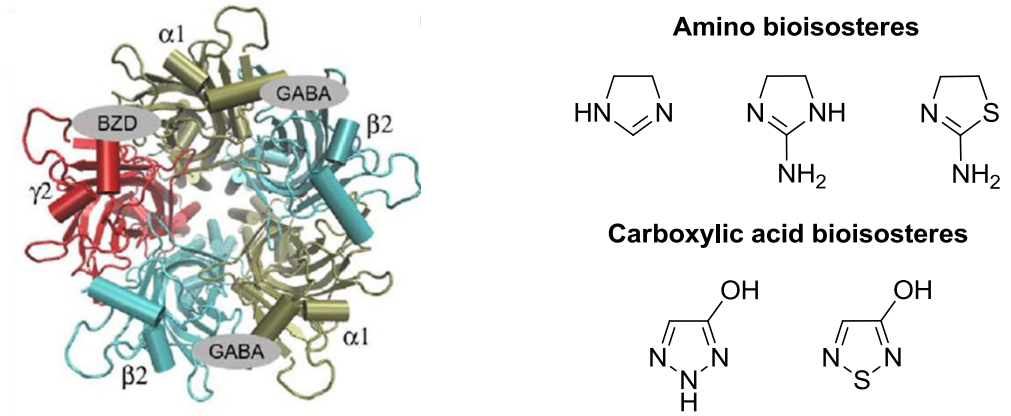

Figure 1. *Left: schematic top view of $GABA_AR$. Right: structures of novel amino and carboxylic acid bioisosteres in the $GABA_AR$ setting.*

References

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[2] Petersen, J. G.; Bergmann, R.; Krogsgaard-Larsen, P.; Balle, T.; Frolund, B., Probing the Orthosteric Binding Site of GABAA Receptors with Heterocyclic GABA Carboxylic Acid Bioisosteres. Neurochem. Res. **2014**, 39, 1005-1015.