10:00 - 10:15 Day 2 Oral 2 – Maria-Tresa Iorio

Towards functional selectivity for $GABA_A$ receptor subtypes

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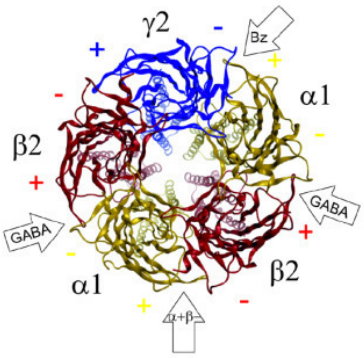
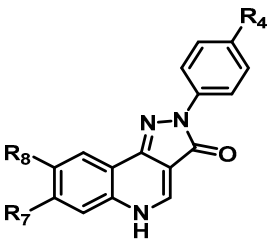


Gamma- aminobutyric acid type A receptors ($GABA_A$) are pentameric channel proteins with a high subunit diversity. In mammalian species 19 subunits were identified: six α, three β, three γ, one δ, one ε, one θ, one π and three ρ. The different subunits can be arranged in various ways to form a pentamer, and the most accepted combination is assumed to consist of two α, two β and one γ subunits [1].

$GABA_A$ receptors are targets of many clinically relevant drugs such as benzodiazepine (BZ), barbiturates and steroids for the treatment of anxiety, depression and epilepsy. While the benzodiazepines act as positive allosteric modulators *via* a binding site located at the α+/γ- interface, its natural agonist -GABA- binds at the β+/α- interfaces (Fig.1) [2].



pyrazoquinolinones

Fig. 2

The pyrazoloquinolinones (Fig.2) bind with high affinity at the BZ binding site, where they usually act as null modulators and in addition they bind with low affinity to newly described binding site at the α+/β- interfaces where they act as positive allosteric modulators (Fig.1)[3].

Here a set of Pyrazoquinolinones with a putative functional selectivity for α6 containing receptors is reported. A series of these compounds with different substituents in R7 position was synthesized and their behaviour in α6β3γ2 receptors was investigated.

[1] Sieghart, W. and G. Sperk,. *Curr Top Med Chem*, **2002**,.*2* (8); 795-816

[2] Varagic , Z. et al. *British Journal of Pharmacology*, **2013**, *169* (2), 371–383

[3] Ramerstorfer J et al., *J Neurosci*, **2011**, *31*, 870-877.