SYNTHESIS OF NOVEL RING STRUCTURES AS GABA\textsubscript{A} RECEPTOR LIGANDS WITH FUNCTIONAL SELECTIVITY

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The GABA\textsubscript{A} receptors are pentameric channel proteins with an high subunit diversity. So far 19 subunits were identified: six α subunit, three β, three γ, one δ, one ε, one θ, one π and three ρ subunits. The different subunits can be combined in different ways to for the pentamer, but the most accepted structure presents two α-, two β- and one γ- subunits.\textsuperscript{[1]}

Upon the binding of two molecules of GABA to the receptor, the pore opens and allows the influx of chloride ions. While the benzodiazepines act as positive allosteric modulator via a binding site located at the α+γ-interface in the extracellular domain of GABA\textsubscript{A} receptors, the 2 GABA binding sites are located at the two β+α-.\textsuperscript{[2]}

The GABA\textsubscript{A} receptor is the target of many clinically relevant drugs such as benzodiazepine, barbiturates and steroids for the treatment of anxiety, depression and epilepsy. Even though, benzodiazepines are excellent anxiolytic drugs, they show sedative side effects and due to their addictive properties they cannot be used in long term treatment. For this reason and in order to develop tools for further studies of the GABA\textsubscript{A} receptor new compounds need to be investigated.

Pyrazoloquinolinones were found to act as positive modulators at the α+β-interface, maintaining a high affinity for the benzodiazepine binding site of the receptor.

In order to gain selectivity for the binding site at the α+β-interface some modifications of this scaffold are required. Therefore, a more stretched structure needs to be synthesized which may interact better with the β subunit of the receptor, giving as a result a loss in affinity for the binding site at the α+γ-interface.\textsuperscript{[3]}

For this purpose a series of indole derivatives was synthesized (Figure 3). These compounds might maintain the same binding mode at the desired interface due to the analogy with the closed structure. Some preliminary results showed that compounds like these have low affinity for the benzodiazepine binding site, maintaining the modulation of the GABA induced current in receptor containing α and β subunits. Due to their interesting properties these compounds will be further investigated.

\textsuperscript{[3]} K.A. Wafford, B. Ebert, Curr. Opin. Pharm., 2006, 6, 30.