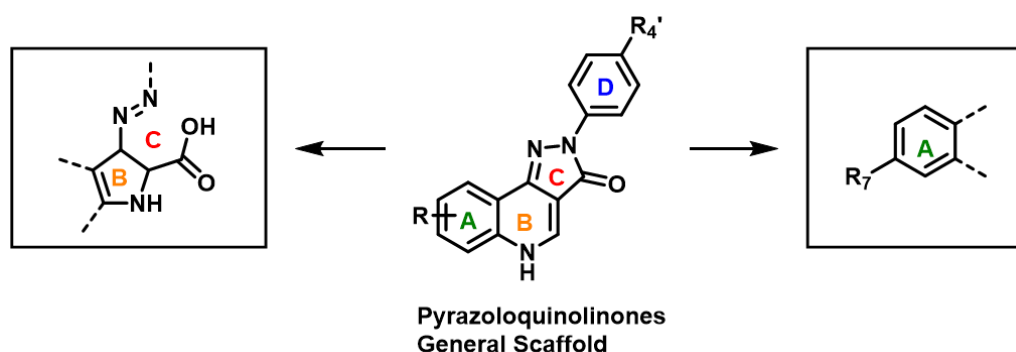


New Modifications of an Old Scaffold: Pyrazoloquinolinone Derivatives and Analogues as Active Compounds on GABA_A Receptors

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GABA_A receptors (GABA_ARs) are a class of receptors belonging to a superfamily of pentameric ligand-gated ion channels. So far, nineteen genes coding for nineteen different subunits (α 1–6, β 1–3, γ 1–3, δ , ϵ , θ , π and ρ 1–3) have been identified in mammalian, and even though heteropentameric assembly leads to a huge subtype heterogeneity, it is believed that the most common receptors are composed of two α , two β , and a γ subunit. (Olsen and Sieghart 2008; Sieghart 1995) These receptors are targets of many clinically used compounds such as i.v. and volatile anesthetics or benzodiazepines, which modulate them via an allosteric binding site at the interface between the α and the γ subunit. Among the allosteric modulators identified so far, pyrazoloquinolinones (PQs) have been extensively studied in the last decades for their interesting pharmacological properties on GABA_A receptors (Yokoyama, Ritter, and Neubert 1982). Over the years, many modifications of the general PQ scaffold have been performed in order to accomplish compounds with better properties in terms of selectivity, potency and detectability. In this work we investigated modification of ring A, B and C of the PQ scaffold. On ring A, many modifications - both in terms of position of substituents and

dimensions of the ring- have been explored; among them, the introduction of substituents in position R7 resulted in compounds with functional selectivity for $\alpha_6\beta_3\gamma_2$ receptors (Varagic et al. 2013; Knutson et al. 2018). On the contrary, modifications on rings B and C (Nilsson et al. 2011) are less investigated. Here, we further explored the impact of R7 on activity of PQ derivatives in $\alpha_6\beta_3\gamma_2$, synthesizing a library of compounds differently substituted in position 7. Furthermore, in order to gain more insight on the effect of changes at rings A and B, we used the pharmacophore of the PQ as template to design a new scaffold, in which the size of ring B is reduced and the ring C is open. Herein we describe the synthesis and the biological properties of the resulting indole-derivatives on $\alpha_1\beta_3$, $\alpha_4\beta_3\delta$ and $\alpha_6\beta_3\delta$ receptors.

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