NEW MODIFICATIONS OF AN OLD SCAFFOLD: PYRAZOLOQUINOLINONE DERIVATIVES AND ANALOGUES AS ACTIVE COMPOUNDS ON $GABA_A$ RECEPTORS

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$GABA_A$ receptors ($GABA_A$Rs) are a class of receptors belonging to a superfamily of pentameric ligand-gated ion channels. So far, nineteen genes coding for nineteen different subunits (α1–6, β1–3, γ1–3, 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.[1, 2] These receptors are targets of many clinically used compounds such as intravenous 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 [3]. 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 α6β3γ2 receptors[4, 5]. On the contrary, modifications on rings B and C are less investigated [6]. Here, we further explored the impact of R7 on activity of PQ derivatives in α6β3γ2, synthesizing a library of compounds differently substituted in position 7. Furthermore, in order to gain more insight on the effect of changes at rings B and C, 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 $\alpha_1\beta_3$ receptors.

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[1] Olsen, R.W. and W. Sieghart, *International Union of Pharmacology. LXX. Subtypes of γ-Aminobutyric Acid(A) Receptors: Classification on the Basis of Subunit Composition, Pharmacology, and Function. Update.* Pharmacol Rev, 2008. **60**(3): p. 243-60.

[2] Sieghart, W., *Structure and pharmacology of gamma-aminobutyric acidA receptor subtypes.* Pharmacological Reviews, 1995. **47**(2): p. 181-234.

[3] Yokoyama, N., B. Ritter, and A.D. Neubert, *2-Arylpyrazolo[4,3-c]quinolin-3-ones: a novel agonist, a partial agonist and an antagonist of benzodiazepines.* Journal of Medicinal Chemistry, 1982. **25**(4): p. 337-339.

[4] Varagic, Z., et al., *Subtype selectivity of α+β− site ligands of GABA(A) receptors: identification of the first highly specific positive modulators at α6β2/3γ2 receptors.* Br J Pharmacol, 2013. **169**(2): p. 384-99.

[5] Knutson, D.E., et al., *Design and Synthesis of Novel Deuterated Ligands Functionally Selective for the γ-Aminobutyric Acid Type A Receptor (GABAAR) α6 Subtype with Improved Metabolic Stability and Enhanced Bioavailability.* Journal of Medicinal Chemistry, 2018. **61**(6): p. 2422-2446.

[6] Nilsson, J., et al., *Triazoloquinazolinediones as novel high affinity ligands for the benzodiazepine site of GABAA receptors.* Bioorganic & Medicinal Chemistry, 2011. **19**(1): p. 111-121.