

SELECTIVITY OF PYRAZOLOQUINOLINONE DERIVATIVES TOWARDS THE ALPHA1+/BETA1- INTERFACE OF THE GABA_A RECEPTOR

Blanca A. Vega-Alanis^a, David C.B. Siebert^a, Xenia Simeone^b, Konstantina Bampali^b, Laurin Wimmer^a, Margot Ernst^b, Marko D. Mihovilovic^{a,*}

^a TU Wien, Vienna, Austria

^b Medical University of Vienna, Vienna, Austria

GABA_A receptors are the major inhibitory neurotransmitter receptors in the central nervous system. These GABA-gated chloride channels are composed of five subunits that can belong to different subunit classes. Several pyrazoloquinolinone ligands have already been described as high affinity ligands of the benzodiazepine (Bz) binding site but also, they exert a positive modulatory effect at the $\alpha+\beta-$ interfaces.^{1,2} Previously, it was shown that some pyrazoloquinolinone derivatives showed preference towards $\beta 1$ containing receptors in terms of potency. Further studies in homology models and mutant receptors confirm that the amino acid located in position 41 of segment G in the $\beta 1$ and $\beta 3$ subunits strongly influences the potency and efficacy of the tested ligands.³ In the present study, further pyrazoloquinolinone derivatives were studied and results showed that they possess improved functional selectivity. The results of this study are herein presented and the properties of these compounds will be further investigated.

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[2] Varagic, Z. *et al.* (2013) Identification of novel positive allosteric modulators and null modulators at the GABAA receptor alpha+beta- interface. British journal of pharmacology 169, 371-383.

[3] Simeone X., Siebert DCB., *et al.* (2018). Molecular tools for GABAA receptors: High affinity ligands for $\beta 1$ -containing subtypes. Scientific Reports, 7(5674).