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MEETING ABSTRACT

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$GABA_A$ receptor subtype-selective loreclezole analogues targeting an α6-specific site

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Background: γ-Aminobutyric acid type A ($GABA_A$) receptors are pentameric GABA-gated chloride channels that are, in mammalians, drawn from a repertoire of 19 different subunits. The existence of this wide variety of subunits as well as their diverse assembly into different subunit compositions result in miscellaneous receptor subtypes. In combination with the large number of known and putative allosteric binding sites, this leads to a highly complex pharmacology. Putative binding sites for loreclezole, an experimental anticonvulsant, were described to exist in the transmembrane domain (TMD) of some $GABA_A$ receptor subtypes. During the past years, the α6 subunit raised interest thanks to its highly specific expression pattern in the central and peripheral nervous system and its possible involvement in sensorimotor gating, trigeminal nociception and depression. One of our aims is therefore the generation of α6-specific positive allosteric modulators. The second aim is to discover the binding site of such ligands.

Methods: The methods used comprise computational compound design, chemical synthesis, pharmacological and mutational analysis with two-electrode voltage clamp in *Xenopus laevis* oocytes.

Results: Four loreclezole analogues synthesized by our group showed a clear α6-over-α1 preference in αβγ-containing receptors. Given that the alpha isoforms differ in only one amino acid at the alpha minus side of the candidate pocket, we hypothesize that this amino acid may be responsible for the observed subtype preference. Additionally, the shape similarities between the α6-selective compounds are significantly higher than the similarities of compounds that activate α1- and α6-containing receptors unspecifically.

Discussion: The binding site with which loreclezole interacts with the $GABA_A$ receptor has never been utilized to develop ligands with selectivity for any alpha isoform. We found candidate compounds that could provide tool compounds for the detection of α6-containing receptor subtypes and the investigation of their abundance and distribution. Molecular shape might play a crucial role for subunit selectivity and needs to be considered for a successful design of α6-selective compounds. On the long term, these molecules might be suited to treat some neuropsychiatric conditions.

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Keywords: $GABA_A$ receptor – loreclezole –; α6 subunits – allosteric modulator – drug design

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