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MEETING ABSTRACT

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Valerenic acid serves as a scaffold for novel $GABA_A$ receptor-modulating anticonvulsants derived from a ligand-based pharmacophore model

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Background: Valerenic acid (VA) is a sesquiterpenoid from the common valerian, a prevalently used herbal medicinal plant and displays β2/3 subunit-selective $GABA_A$ receptor-modulating properties. VA exerts anxiolytic and anticonvulsive effects without concomitant sedation combined with a promising pharmacokinetic profile, thus making this compound an interesting drug candidate. Despite recent progress in the total synthesis of VA, alternative compounds are of high interest as they provide a straightforward access towards development of novel drugs. This study focuses on the synthesis of simplified molecules maintaining subunit-selective properties based on the VA scaffold and their *in vitro* and *in vivo* characterization.

Methods: A small-focused library of novel, simplified VA analogues was suggested by a pharmacophore model based on the known β2/3 subunit-selective $GABA_A$ modulators VA and loreclezole. Their effect on GABA-induced chloride currents (I_{GABA}) through $GABA_A$ receptors composed of α1β1-3γ2S subunits expressed in *Xenopus laevis* oocytes was analysed by means of the two-microelectrode voltage clamp technique. Anticonvulsant activity was assessed by means of the pentylenetetrazole test (PTZ) conducted in C57BL/6N mice.

Results: Efficacy of I_{GABA} enhancement by derivatives AR-013, AR-016, SM-226-1 and SM-408-1a was comparable to that of VA, while a slightly reduced potency was observed. Compound SM-408-1b displayed significantly increased potency and efficacy compared to VA on α1β3γ2S receptors while activity on α1β1γ2S receptors was dramatically decreased similar to VA. PTZ-induced seizure threshold was shifted by SM-408-1b at concentrations of 0.1 mg/kg body weight indicating more potent anticonvulsant activity compared to VA. The other studied compounds were either less efficacious or did not display significant potentiation of I_{GABA} at concentrations ≥30 µM.

Discussion: By using a ligand-based pharmacophore model, novel, simplified structures with β2/3 selectivity comparable to that of VA were identified. One compound, SM-408-1b, maintained subunit selective properties of VA and may therefore serve as a starting point for the development of novel, selective $GABA_A$ receptor-modulating anticonvulsants.

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