73. Selective Modulators for Migraine and Other disorders

(National Tsing Hua University)

5TH KDDF GLOBAL C&D TECH FAIR

Asset Overview

Product Type	Small Molecule
Disease Area	Others
Indication	Migraine Disorders
Current Stage	Lead Optimization
Target	α6β3γ2 receptor
MoA	α6β2/3γ2 $GABA_AR$ selective ligands
Brief Description	• Based on 3 functionally α6β2/3γ2 $GABA_AR$ selective pyrazoloquinolinones, 42 novel analogs were synthesized and their in vitro metabolic stability and cytotoxicity as well as their in vivo pharmacokinetics, basic behavioral pharmacology, and effects on locomotion was investigated. • Incorporation of deuterium into the methoxy substituents of the ligands increased their duration of action via improved metabolic stability and bioavailability, while their selectivity for the $GABA_AR$ α6 subtype was retained. • 8b was identified as the lead compound with a substantially improved pharmacokinetic profile. The ligands allosterically modulated diazepam insensitive α6β2/3γ2 $GABA_ARs$ and were functionally silent at diazepam sensitive α1β2/3γ2 $GABA_ARs$, thus no sedation was detected. • These analogs were not cytotoxic, which render them interesting candidates for treatment of CNS disorders mediated by $GABA_AR$ α6β2/3γ2 subtypes.
Intellectual Property	US10865203B2, US11427582B2
Publication	• α6-Containing $GABA_A$ Receptors: Functional Roles and Therapeutic Potentials. Pharmacol Rev. (2022) • Design and Synthesis of Novel Deuterated Ligands Functionally Selective for the γ-Aminobutyric Acid Type A Receptor ($GABA_AR$) α6 Subtype with Improved Metabolic Stability and Enhanced Bioavailability, J Med Chem. (2018)
Inventors	James Cook, Daniel Knutson, Marko Mihovilovic, Laurin Wimmer

Highlights

- α6$GABA_AR$: α6 subunit-containing $GABA_A$ receptor
  - PAM: Positive allosteric modulator
- α6$GABA_AR$-selective PAMs
  - Different site of action as benzodiazepines
  - Limited distribution of α6$GABA_ARs$
  - CNS (Cerebellum)
  - Periphery (Trigeminal ganglion)
  - Effective in Migraine and other neuropsychiatric disorders

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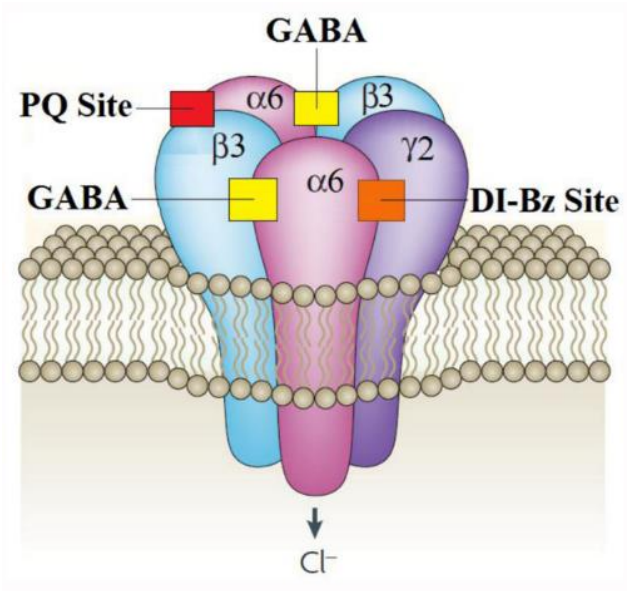
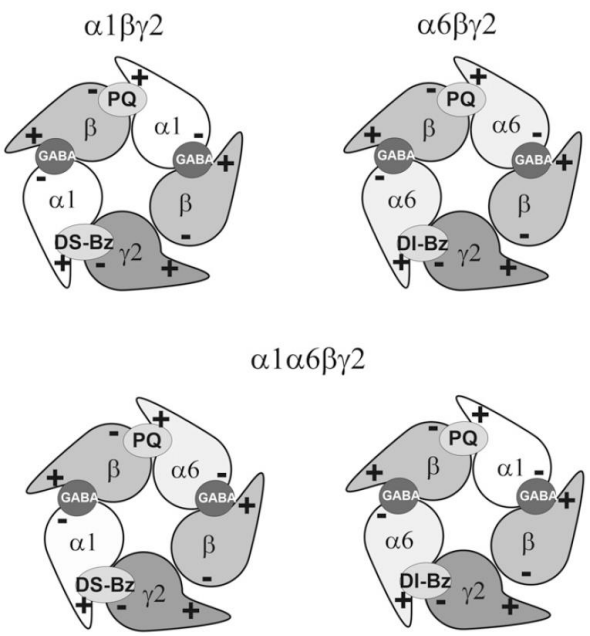
Key Data

The $GABA_AR$ α6β3γ2 Subtype[a]



- The $GABA_AR$ α6β3γ2 subtype is a pentameric ligand-gated chloride channel comprised of two α6, two β3 and one γ2 subunits. PQs, like 8b, mediate their effects at the α6+β3- interface (PQ Site) as positive allosteric modulators and act at the DI-Bz site (α6+γ2- interface) as null modulators.
- The PQ site, the DI-Bz binding site and the endogenous ligand (GABA) binding sites at the β3+α6- interfaces are displayed.

$GABA_AR$ subunit composition and arrangement



The majority of $GABA_ARs$ is composed of two a subunits, two b subunits, and one c subunit that form a central anion channel with the indicated subunit arrangement when viewed from above. The two a and b subunits can be identical or different. The upper left image depicts the experimentally verified subunit arrangement for the major GABAAR subtype composed of a1bc2 subunits, and the other three panels depict a6-containing arrangements that have been shown to exist in cerebellar granule cells (Scholze et al., 2020). Each subunit has a principal (1) and a complementary () side. The 1 side contains the large loop C in the extracellular domain that is part of the pharmacological binding sites formed by the interfaces of two subunits. This loop C is schematically depicted as the pointed end of each subunit. The two GABA binding sites are formed by the two b1/a- interfaces. The benzodiazepine binding site (Bz) is formed by the a1/c2- interface. Receptors containing a1, a2, a3, or a5 subunits form diazepam-sensitive benzodiazepine sites (DS-Bz). Receptors containing a4 or a6 subunits form diazepam-insensitive benzodiazepine binding sites (DI-Bz). Pyrazoloquinolinones (PQs) bind to two distinctive interfaces: to the benzodiazepine binding sites of all abc2 receptors with high affinity as silent binders (antagonists, similar to flumazenil) and to the PQ sites of these receptors formed by the a1/b- interfaces as modulators. a6GABAAR-selective pyrazoloquinolinones, such as Compound 6 (PZ-II-029), exert their positive modulatory action via the PQ site at the a61/b- interface. The d-containing a6bd and a1a6bd receptors presumably have a similar stoichiometry and subunit arrangement as the respective c2-containing receptors, but this is still a matter of controversy.

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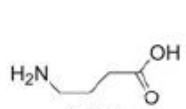
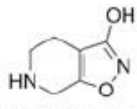
Chemical structure of $GABA_AR$ ligands. BZ, benzodiazepine

GABA site ligands

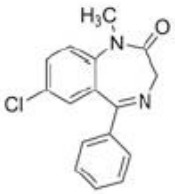


GABA

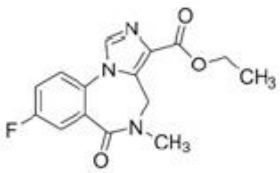


THIP (Gaboxadol)

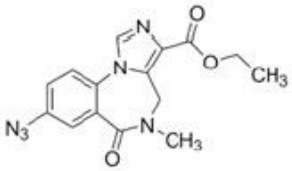
BZ site ligands



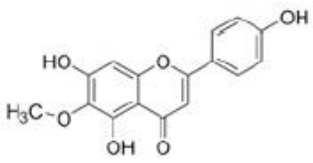
Diazepam



Ro 15-1788 (Flumazenil)

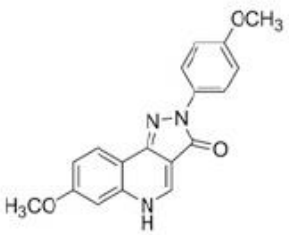


Ro 15-4513

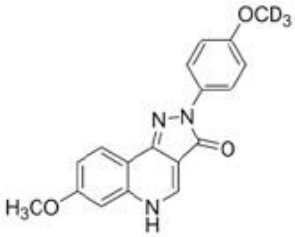


Hispidulin

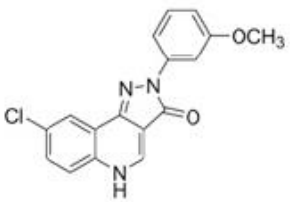
α6$GABA_AR$-selective PAMs (BZ + PQ site ligands)



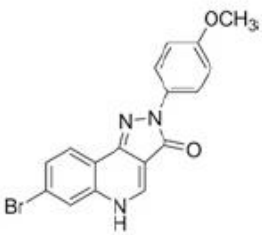
PZ-II-029 (Compound 6)



DK-I-56-1

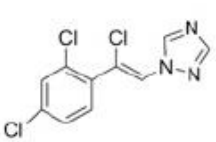


LAU 159

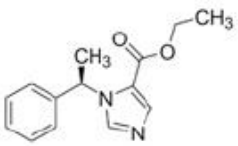


LAU 463

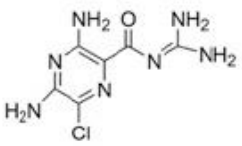
Ligands at transmembrane sites



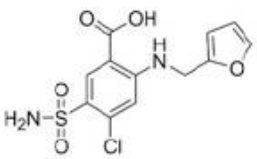
Loreclezole



Etomidate



Amiloride



Furosemide

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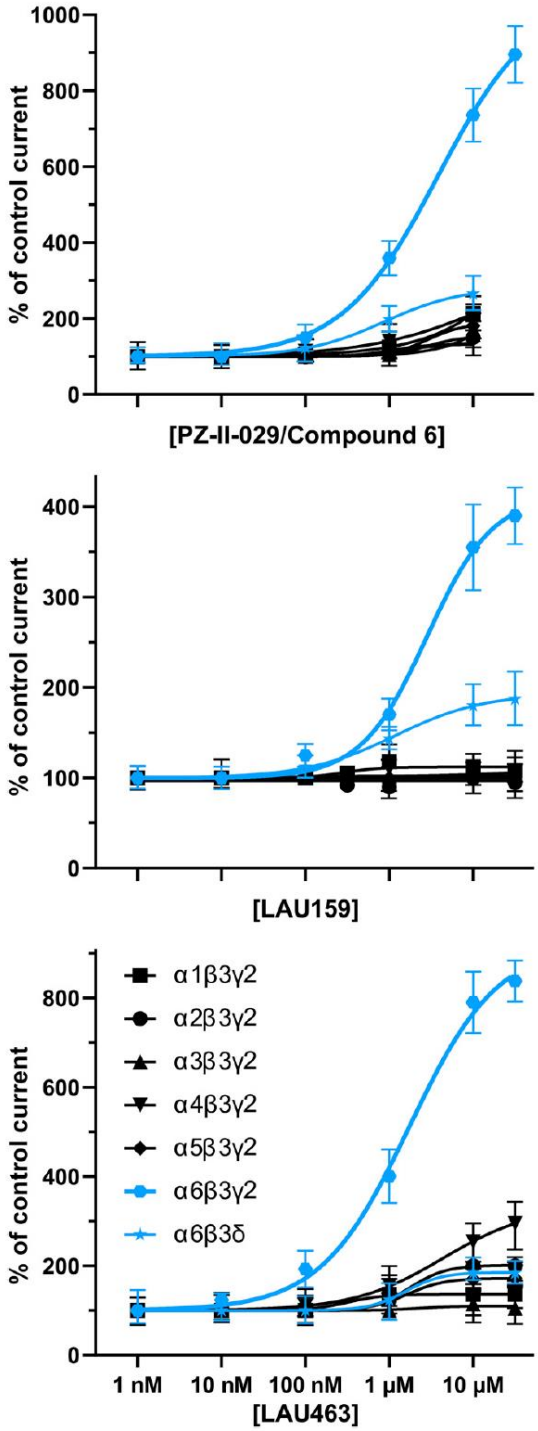
Concentration-response curves of $GABA_AR$ ligands.



Curves are reproduced based on published (Varagic et al., 2013; Chiou et al., 2018; Knutson et al., 2018; Treven et al., 2018), (PCT/US2016/035761) and unpublished data for PZ-II-029/Compound 6 (top), 8-chloro-2-(3-methoxyphenyl)-2H-pyrazolo[4,3-c]quinolin-3(5H)-one (LAU159) (middle), and 7-bromo-2-(4-methoxyphenyl)-2,5-dihydro-3H-pyrazolo[4,3-c]-quinolin-3-one) (LAU463) (bottom). Data for a6b3c2 and a6b3d are presented in blue. At 100% of control current, the response equals that of the GABA-evoked current in the absence of compounds.
All measurements were performed with GABA concentrations eliciting 3%–5% and 10%–20% of maximum GABA-elicited current for c2- and d-containing receptors, respectively. Modulation of a6-containing receptors by the indicated compounds at 100 nM was already stronger than that of receptors containing other a subunits. Deuterated derivatives, such as DK-I-56-1, behave like the respective parent compounds in concentration-response investigations at different receptor subtypes (Knutson et al., 2018).