$GABA_A$ α5 | BI-1030

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Summary

GABA type A receptors are chloride ion channels that drive inhibitory neurotransmission in the mammalian central nervous system upon binding of GABA, the primary inhibitory neurotransmitter in the central nervous system. BI-1030 is a potent and functionally selective $GABA_A$ α5 receptor negative allosteric modulator (NAM), suitable for *in vitro* as well as *in vivo* use.

Chemical Structure

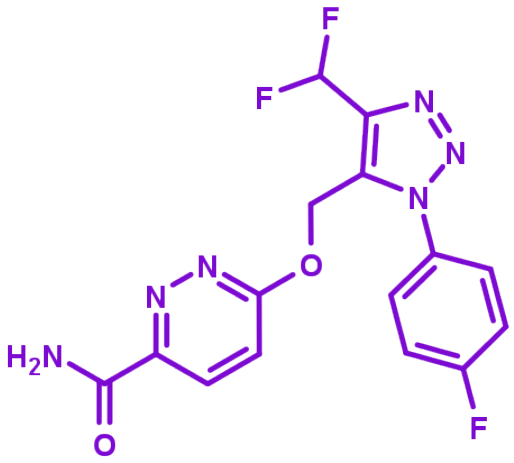


Figure 1: 2-D structure of BI-1030

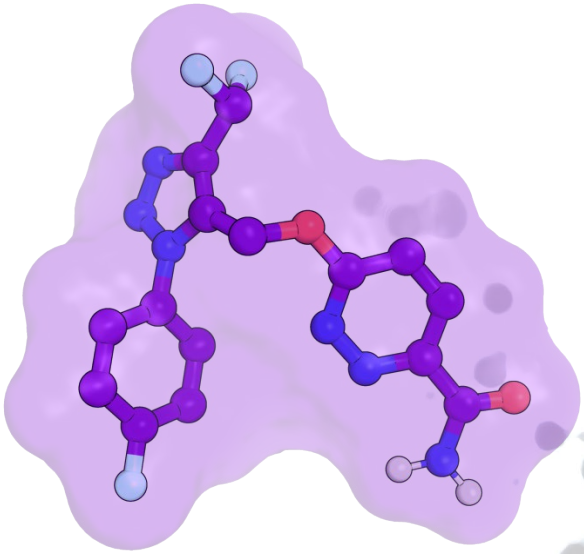


Figure 2: BI-1030, 3D conformation, as observed in a model of the complex forming the interface of the α5 and γ2 $GABA_A$ receptor subunits

Highlights

GABA type A receptor subtypes containing α5 subunits are of particular research interest due to their specific brain distribution, unusual surface localization and key roles in synaptic plasticity, cognition and memory. Only a few molecules in the literature are showing subtype selectivity for $GABA_A$ α5 receptors and Boehringer Ingelheim in collaboration with Saniona A/S, have designed a very potent, selective, and *in vivo* ready $GABA_A$ α5 functionally selective negative allosteric modulator (NAM), BI-1030.

Target information

The γ-aminobutyric acid (GABA) type A receptors ($GABA_A$Rs) are heteropentameric ligand-gated chloride ion (Cl^-) channels typically composed of two α (α1–6), two β (β1–3), and one γ (γ1–3) or δ subunits[1]. Binding of the neurotransmitter GABA opens an intrinsic ion channel that permits the passage of chloride ions and drives inhibitory neurotransmission in the mammalian central nervous system. $GABA_A$Rs play critical roles in the central nervous system (CNS) implying neuronal plasticity, and drugs targeting $GABA_A$Rs show diverse central pharmacology[2]. α5-containing $GABA_A$Rs in particular, are highly expressed in both the hippocampus and olfactory bulb. Characteristically, α5 $GABA_A$Rs comprise close to 25% of all hippocampal $GABA_A$Rs, and over a third of the neurons in the internal granule cell layer of the olfactory bulb[1].

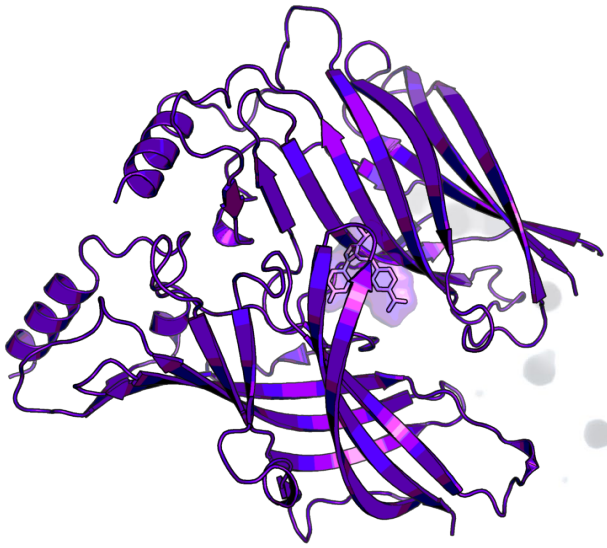


Figure 3: Model of the complex of BI-1030 bound to the interface of the α_5 and the γ_2 $GABA_A$ receptor subunits (only extracellular domains shown).

In vitro activity

BI-1030 displays a K_i of 57 nM on the $GABA_A$ α5 receptor, and it is functionally selective for the $GABA_A$ receptor subtypes α1, α2, and α3.

PROBE NAME / NEGATIVE CONTROL	BI-1030
MW [Da]	364
$GABA_A$ α5 Bdg (K_i) [nM][a]	57.1
$GABA_A$ α5 EPHys (EC_{50}) [nM][b]	114.4
$GABA_A$ α5 EPHys (Emax) [nM] [b]	-28.5
$GABA_A$ α1 EPHys (EC_{50}) [nM] [b]	-
$GABA_A$ α1 EPHys (Emax) [nM] [b]	-2.8
$GABA_A$ α2 EPHys (EC_{50}) [nM] [b]	-
$GABA_A$ α2 EPHys (Emax) [nM] [b]	-4.3
$GABA_A$ α3 EPHys (EC_{50}) [nM] [b]	-
$GABA_A$ α3 EPHys (Emax) [nM] [b]	0.8
$GABA_A$ α1 Bdg (K_i) [nM] [a]	1,100
$GABA_A$ α4 Bdg (K_i) [nM] [a]	14,000
$GABA_A$ α6 Bdg (K_i) [nM] [a]	>14,000

[a] *In vitro* inhibition of 3H-flumazenil binding HEK cells expressing the human $GABA_A$ α5β3γ2. Details of the experiment can be found in reference 3.

[b] Modulatory efficacy on $GABA_A$ subtypes is determined by electrophysiological recordings in oocytes using the two-electrode voltage clamp (TEVC) technique. Oocytes are injected with cRNA for human $GABA_A$ receptor subunits. Details of the experiment can be found in references 3 and 4.

In vitro DMPK and CMC parameters

BI-1030 presents good in vitro DMPK and CMC properties, being soluble and metabolically stable.

PROBE NAME / NEGATIVE CONTROL	BI-1030
logP/logD (@pH 2.0/11.0)	1.4/ (-/-)
Solubility @ pH 6.8 [µg/ml]	0.01
MDCK permeability P_{app}a-b/b-a @ 1µM [10^{-6} cm/s]	45
MDCK efflux ratio	1.1
Microsomal stability (human/mouse/rat/dog/MP) [% Q_H]	<23 / <23 / <22 / <20 / <23
Hepatocyte stability (human/mouse/rat/dog) [% Q_H]	10/ 21 / 6 / 34
Plasma protein binding (human/mouse/rat/dog/MP) [%]	65 / 59 / 52 / 55 / 67
hERG KI [µM]	>10
CYP 3A4 (IC_{50}) [µM]	>25
CYP 2C8 (IC_{50}) [µM]	>50
CYP 2C9 (IC_{50}) [µM]	>25
CYP 2C19 (IC_{50}) [µM]	>25

CYP 2D6 (IC_{50}) [µM]	>25

In vivo DMPK parameters

BI-1030 is stable in different species, with an excellent bioavailability allowing its use *in vivo*.

BI-1030	MOUSE[a]	RAT[b]	DOG[c]
Clearance [% Q_H]	6.6	5.7	25
Mean residence time after iv dose [h]	2.6	3.3	2.7
t_{max} [h]	0.7	4	1.3
C_{max} [nM]	495	354	225
F [%]	100	65	64
V_{ss} [l/kg]	0.9	0.8	1.3

[a] 0.4 mg/kg *iv* and 1.8 mg/kg *po*

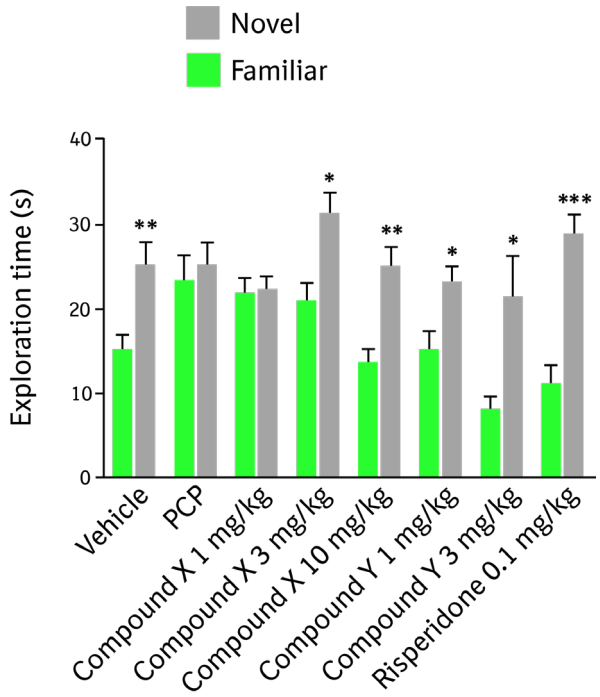
[b] 0.4 mg/kg *iv* dose [mg/kg] 3.6 mg/kg *po*

[c] 0.4 mg/kg *iv* dose [mg/kg] 3.6 mg/kg *po*

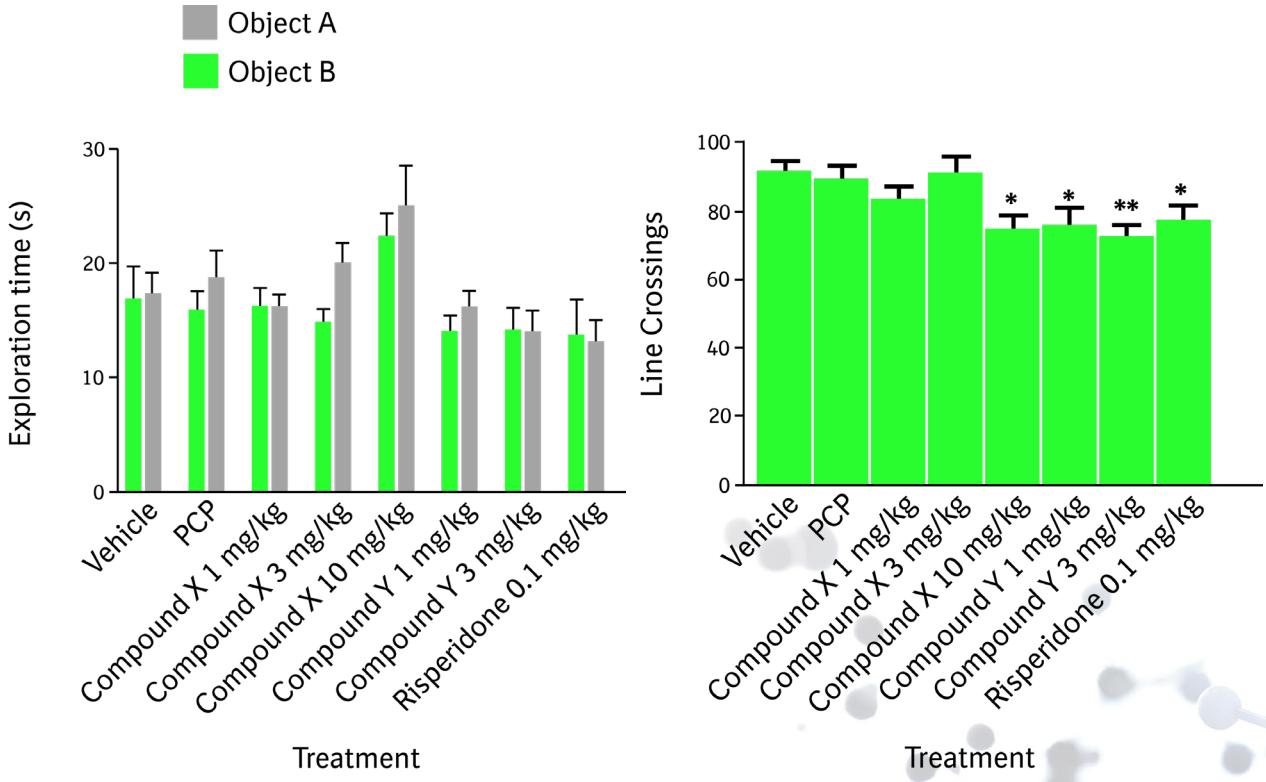
In vivo pharmacology

BI-1030 shows a very favorable *in vivo* profile in different CNS *in vivo* models showing that the $GABA_A$ α5 NAM is a reliable mode of action to potentially address complex central disease mechanisms.

BI-1030 attenuates sub-chronic phencyclidine (PCP)-induced impairment in novel object recognition tasks in rats, indicating potential beneficial effects on episodic memory.



X: BI-1030: 1, 3, 10 mg/kg, po, t= -60 minutes
Y: RO4938581: 1, 3 mg/kg, po, t= -60 minutes
PCP: 2 mg/kg, *i.p. BID* 7 days on/7 days off prior to behavioral testing
Rats: female Lister hooded rats



Data produced by Grayson B. and Neill J., b-neuro, Faculty of Biology, Medicine & Health, The University of Manchester, Manchester, UK, 2016.

Selectivity

BI-1030 displays a $K_{i\alpha}$ of 57 nM on the $GABA_A$ α5 receptor, and it is functionally selective for subtypes α1, α2, and α3. Otherwise, it is also clean in the SafetyScreen profile from Eurofins.

SELECTIVITY DATA AVAILABLE	BI-1030
SafetyScreen44™ with kind of support of eurofins	Yes
Invitrogen®	No
DiscoverX®	No
Dundee	No

Supplementary data

Selectivity data can be downloaded free of charge from opnMe.

Reference molecule

Basmisanil (RG1662, Cas No.:1159600-41-5)5, a highly selective GABAA-α5 negative allosteric modulator.

References

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