opnMe by Boehringer Ingelheim

mGluR1

Positive Allosteric Modulators

BI02982816 and its chemically optimized reiteration BI-1752

Boehringer Ingelheim

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Summary

BI02982816 and its chemically optimized reiteration BI-1752 are positive allosteric modulators of metabotropic glutamate receptors that play a role in the regulation of neurotransmission and synaptic plasticity. BI-4066 is available as negative control.

Chemical Structure

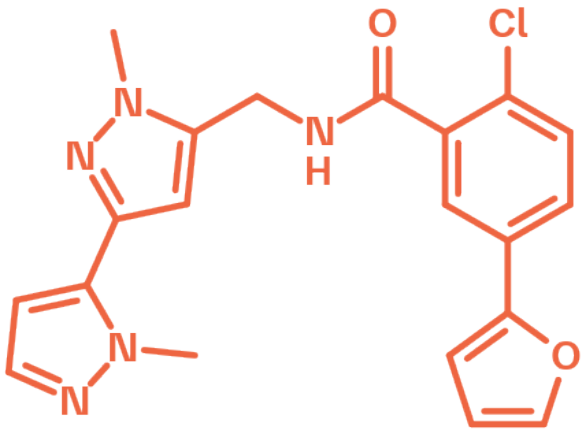

Figure 1: 2D structure of BI02982816

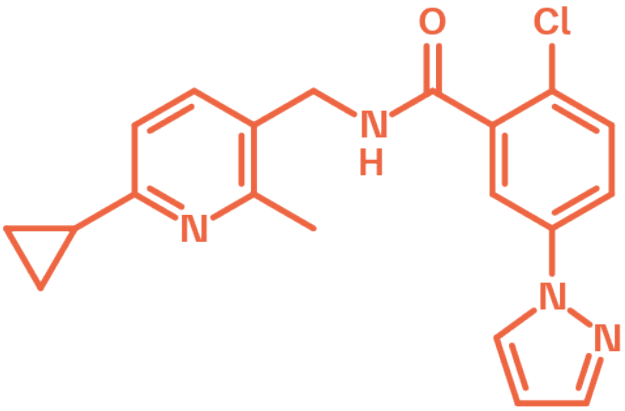

Figure 2: 2D structure of BI-1752

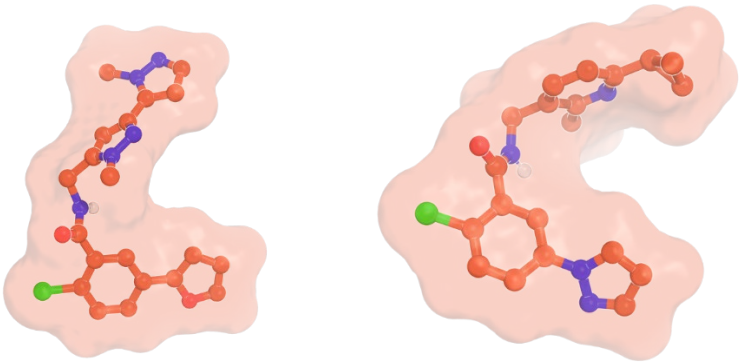

Figure 3: BI02982816 and BI-1752 3D conformations

Highlights

BI02982816 and BI-1752 are positive allosteric modulators of the metabotropic glutamate receptor subtype 1 (mGluR1), suitable for *in vivo* studies. BI-1752, the chemically optimized reiteration of BI02982816, features improved drug metabolism and pharmacokinetic properties while maintaining efficacy preclinically. The molecules emerged from a collaboration with the Warren Center for Neuroscience Drug Discovery at Vanderbilt University.

Target information

mGluR1 receptors are Gq/11-coupled metabotropic glutamate receptors predominantly expressed in the central nervous system, particularly within the cortico-striatal and thalamo-striatal circuits. Activation of mGluR1 enhances intracellular calcium signaling and promotes endocannabinoid (eCB) release, which in turn inhibits dopamine (DA) release via CB2 receptor activation on presynaptic terminals[1]. This mechanism is especially relevant in the dorsolateral striatum, a region implicated in the pathophysiology of schizophrenia[1].
Positive allosteric modulators of mGluR1 potentiate this signaling cascade, leading to normalization of hyperdopaminergic states in preclinical models without directly inhibiting D1 receptor signaling. Preclinical evidence indicates that this may preserve motivational and cognitive functions[1-4].

In addition, mGluR1 PAMs have demonstrated antipsychotic-like efficacy in preclinical models, including reversal of amphetamine-induced hyperlocomotion and MK-801-induced cognitive deficits [1,5,6,7]. Genetic studies have linked GRM1 mutations to schizophrenia, and mGluR1 PAMs have shown the ability to restore function in mutant receptors[8]. Together, these findings suggest a potential role of mGluR1 PAMs in impacting positive and cognitive symptoms of schizophrenia through modulation of glutamatergic and dopaminergic signaling in disease-relevant brain circuits[1-9].

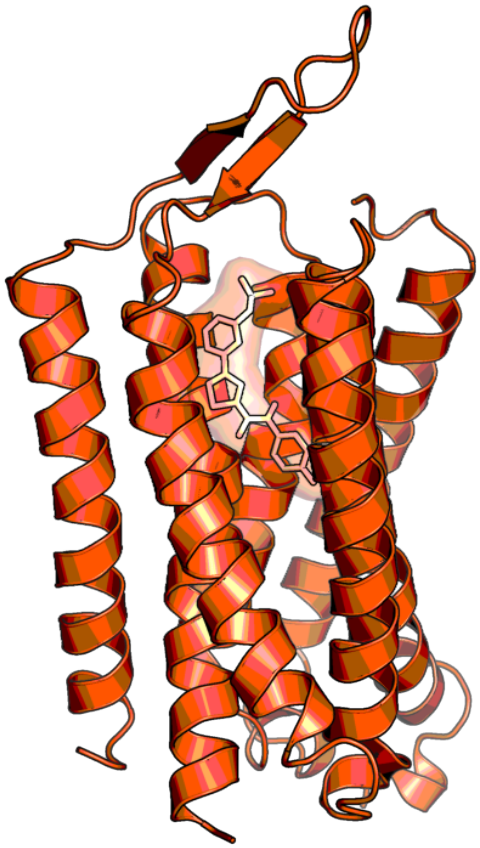

Figure 4: Transmembrane domain of mGluR1 in complex with a negative allosteric modulator, indicating the location of the allosteric binding site, as observed by X-ray crystallography (PDB code: 4or2.pdb)[10].

In vitro activity

The potency of mGluR1 PAMs was determined using calcium flux measurements, as described in previous studies[7,11]. From a weak high-throughput screening hit (EC_{50} >10 µM, 71% Glu_{max}), optimization efforts improved functional potency over 350-fold to deliver the selective (inactive on mGlu2-5,7,8) and CNS penetrant (rat K_p = 0.99, $K_{p,uu}$ = 0.82; MDCK-MDR1 ER = 1.7, P_{app} = 73 x 10-6 cm/s) $mGluR_1$ PAM (BI02982816, EC_{50} = 54 nM, 83% Glu_{max}).

Probe names / Negative control	BI02982816	BI-1752	BI-4066
MW [Da][a]	396	367	426
Human mGluR1 (EC_{50}) [nM][b]/Emax [%][b]	54 / 83	39 / 65	> 10,000 / 42
Rat mGluR1 (EC_{50}) [nM][b]/Emax [%]	46 / 124	107 / 94	n.a.

[a] *For the salt form you will get, please refer to the label on the vial and for the molecular weight of the salt, please refer to the FAQs*

[b] assay conditions – Calcium mobilization assay, see reference 8

In vitro DMPK and CMC parameters

BI02982816 has an acceptable fraction unbound in plasma while predicted hepatic clearance is moderate across species. BI02982816 is not a human P-gp substrate, but has an acceptable CYP450 profile, and shows no 3A4 mechanism-based inhibition.
BI-1752 has an advanced *in vitro* DMPK profile with acceptable hepatic clearance across species and good fraction unbound in plasma. Compared to BI02982816, this compound has an improved CYP450 profile and is predicted to be highly CNS penetrant in humans and is found to be highly CNS penetrant in rats, respectively.
Finally, the negative control BI-4066 shows moderate predicted brain efflux and stability across species, while demonstrating an excellent CYP450 profile.

Probe names / Negative control	BI02982816	BI-1752	BI-4066
logD @ pH 11/2	2.7 / 2.6	3.3	1.6 / 0.2
Solubility @ pH 7 [µg/mL]	< 0.001	< 1	>103
MDCK permeability P_{appAB} @ 1µM [10^{-6} cm/s]	35.0	41.0	34
MDCK efflux ratio	0.7	0.9	2.5
Microsomal stability (human/mouse/rat) [% Q_H]	81 / 82 / 51	29 / n.a. / 42	52 / 62 / 31
Hepatocyte stability 50% (human/mouse/rat) [% Q_H]	29 / 96 / 11	13 / 80 / 32	n.a.
Plasma Protein Binding (human/mouse/rat) [%]	98.8 / 98 / 98	95.7 / 96 / 94	n.a.
hERG (IC_{50}) [µM]	> 10.0	3.5	n.a.
CYP 3A4 (IC_{50}) [µM] (MDZ)	50.0	50.0	>50
CYP 2C8 (IC_{50}) [µM]	3.9	45.6	43.5
CYP 2C9 (IC_{50}) [µM]	21.4	50.0	>50
CYP 2C19 (IC_{50}) [µM]	25.6	26.8	>50
CYP 2D6 (IC_{50}) [µM]	50.0	50.0	>50
CYP 1A2 (IC_{50}) [µM]	43.5	48.0	>50
CYP 2B6 (IC_{50}) [µM]	20.7	50.0	>50

In vivo DMPK parameters

BI-1752, the chemically optimized iteration of BI02982816, features improved drug metabolism and pharmacokinetic properties while maintaining efficacy in preclinical *in vivo* models. Both BI02982816 and BI-1752 demonstrate good brain exposure at their respective minimum effective oral doses in rats: 3 mg/kg for BI02982816 yielding a free brain concentration of 32 nM (~0.6× EC_{50}), and 10 mg/kg for BI-1752 yielding 80 nM (~0.74× EC_{50}). Dose escalation to 10 mg/kg for BI02982816 increased exposure to 67 nM (~1.2× EC_{50}) without adverse effects, while 30 mg/kg of BI-1752 raised free brain levels to ~579 nM (~5.2× EC_{50}) but was associated with adverse events, limiting further dose escalation.

Probe name / Negative control	BI02982816	BI-1752
Clearance (rat/mouse) [% Q_H][a]	11.9 / n.a.	65.5 / 102
Mean residence time after *i.v.* dose (rat/mouse) [h][a]	3.5 / n.a.	1.2 / 0.3
t_{max} [h][b]	2 h	0.5
C_{max} [nM][b]	10,500	2,400
F [%][b]	100	42.8
V_{ss} (rat/mouse) [L/kg][a]	1.8 / n.a.	3.3 / 1.8

[a] *i.v.* dose: rat= 0.58 mg/kg, mouse= 0.58 mg/kg
[b] *p.o.* dose: rat= 3.0 mg/kg, mouse= 5.8mg/kg

In vivo pharmacology

BI02982816 was active in amphetamine-induced hyperlocomotion (minimum effective dose (MED) = 3 mg/kg, *p.o.*) and MK-801 (antagonist of the NMDA receptor) induced disruptions of novel object recognition (MED = 10 mg/kg *p.o.*). Similarly, BI-1752 showed activity in both models. It reduced amphetamine-induced hyperlocomotion (MED = 3 mg/kg *p.o.*) and improved novel object recognition (NOR) disrupted by MK-801 (MED = 10 mg/kg *p.o.*). Furthermore, BI-1752 exhibited a clear pharmacokinetic–pharmacodynamic (PK/PD) relationship.

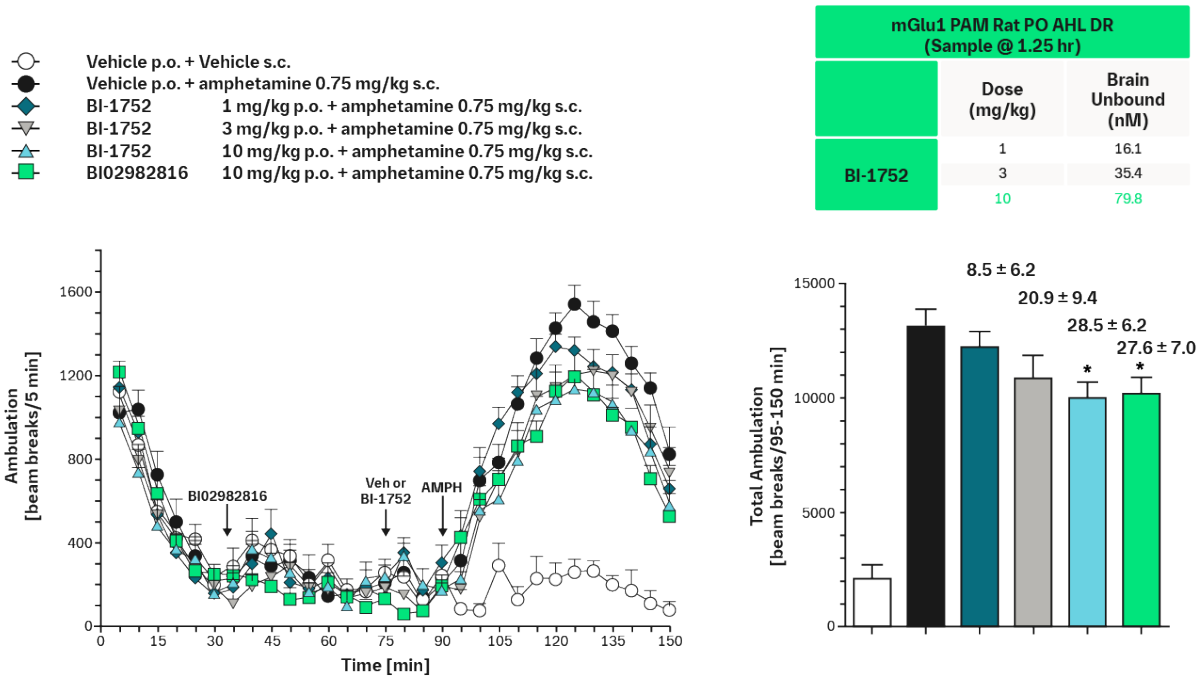

Figure 5: Rat amphetamine-induced hyperlocomotion and reversal by mGluR1 PAMs. Amphetamine (0.75 mg/kg *s.c.*) induced robust hyperlocomotion, which was dose-dependently reversed by oral administration (0.5% Natrasol/0.015% Tween 80) of BI-1752. A clear PK/PD relationship with efficacy was noted at ~0.7-fold the *in vitro* rat mGluR1 EC_{50} in unbound brain, in agreement with BI02982816[11].

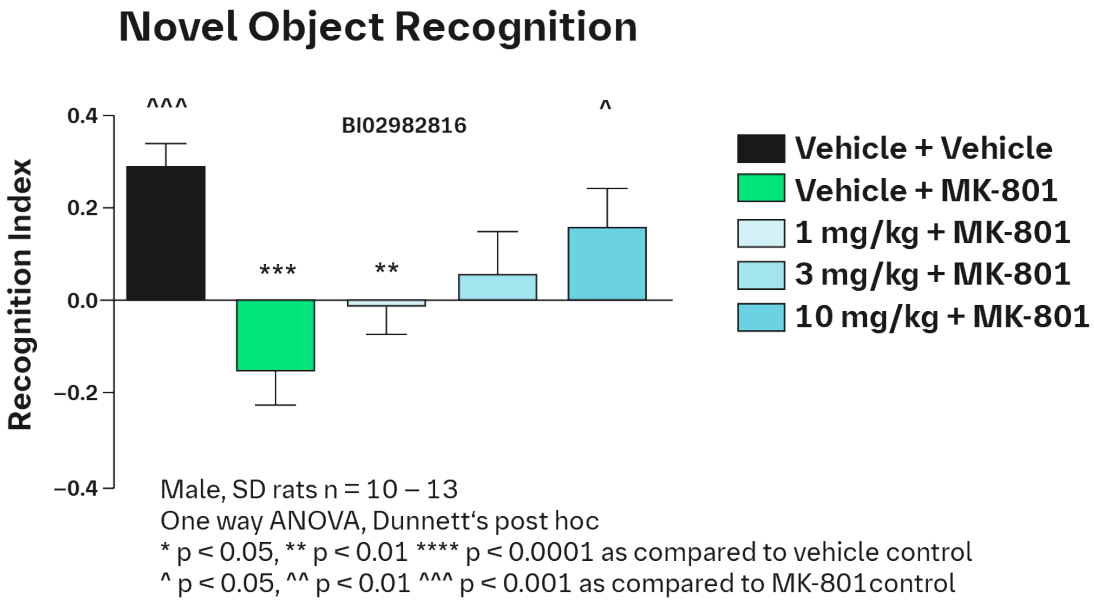

Figure 6: Rat MK-801 (NMDA receptor antagonist) induced disruption of novel object recognition (NOR) and reversal by BI02982816. MK-801 (0.5 mg/kg *i.p.*) induced a robust

disruption of NOR, which was dose-dependently reversed by oral administration (10% tween 80) of BI02982816[7].

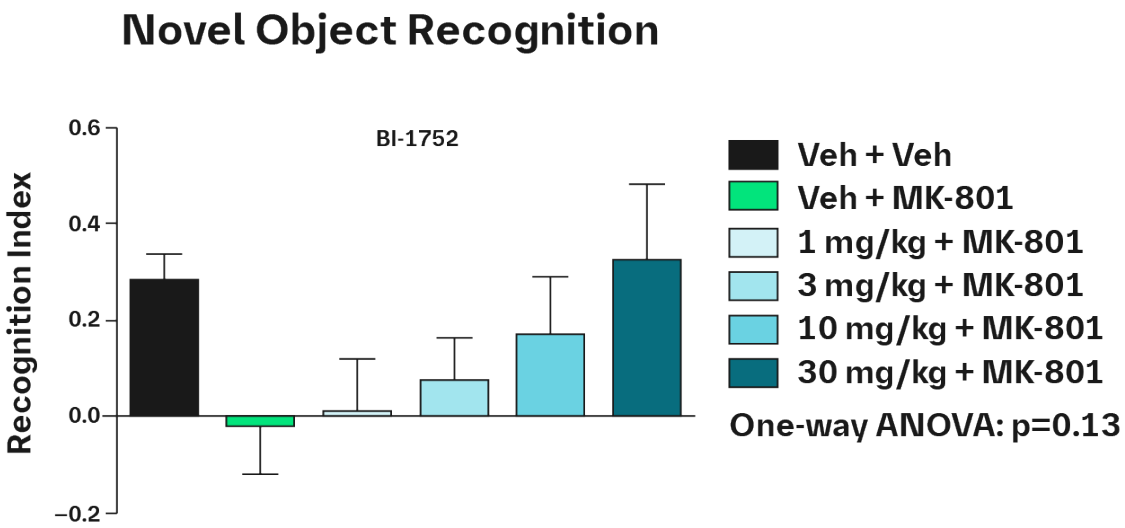

Figure 7: Rat MK-801-induced disruption of novel object recognition and reversal by BI-1752. MK-801 (0.075 mg/kg SC) induced a robust disruption of NOR, which was dose-dependently reversed by oral administration (0.5% Natrasol/0.015% Tween 80 in water). N = 12–15/group of male Sprague–Dawley rats. One-way ANOVA: p = 0.13[11].

Negative control

BI-4066, a structurally close analog of BI-1752, can be used as negative control.

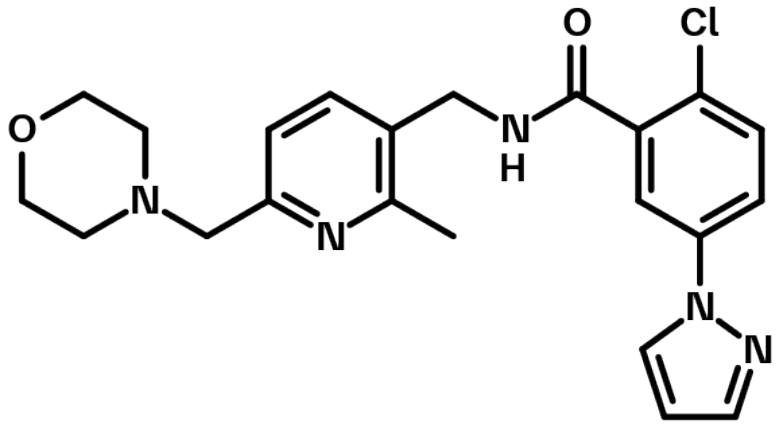

Figure 8: BI-4066 which serves as a negative control

Selectivity

Both BI02982816 and BI-1752 are highly selective versus mGluR2-8 as well as against a broad panel of GPCRs, ion channels, and transporters. BI02982816 inhibited 5HT2B/H with 70% inhibition at 10µM. BI-1752 and also the negative control BI-4066 inhibited none of the targets with > 50% at a 10µM in the SafetyScreen44™.

Selectivity data available	BI02982816	BI-1752	BI-4066
SafetyScreen44™ with kind support of eurofins	Yes	Yes	Yes

Reference molecule(s)

Ro 07-11401 and VU6004909 are tool compounds for *in vivo* target validation studies[1].

Supplementary data

2D structure files can be downloaded free of charge from opnMe.

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