opnMe by Boehringer Ingelheim

PDE9 inhibitor BI 409306

BI 409306 (osoresnontrine)

Boehringer Ingelheim

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Summary

Inhibition of PDE9 is expected to restore physiological cGMP levels in neurons, thereby enhancing NMDA receptor signaling and synaptic plasticity. BI 409306 (osoresnontrine) is a highly selective oral PDE9 inhibitor and BI-8777 an inactive analog which serves as a negative control.

Chemical Structure

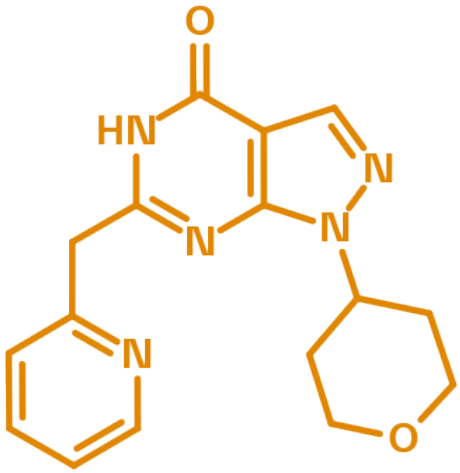

Figure 1: 2D structure of BI 409306 (osoresnontrine), a PDE9 inhibitor

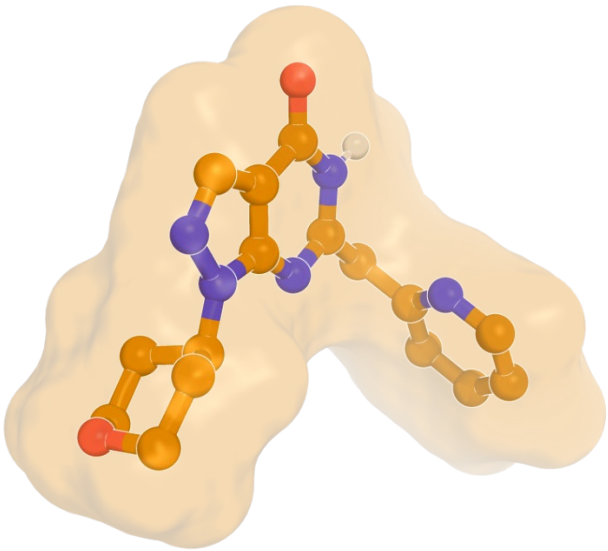

Figure 2: Bound conformation of BI 409306, based on the model of the complex with PDE9

Highlights

BI 409306 (osoresnontrine) is an oral, highly selective phosphodiesterase-9 (PDE9) inhibitor[1,2,3]. Inhibition of PDE9 is expected to restore physiological cGMP levels in neurons to improve NMDA receptor signaling and thus strengthening synaptic plasticity. Additionally, PDE9 inhibition may also impact cGMP-dependent processes in other cell types expressing PDE9, e.g. to improve cardiovascular function. BI-8777 is a structural close analog of BI 409306 and can be used as negative control.

Target information

Phosphodiesterase-9 (PDE9) is an enzyme that specifically hydrolyzes cyclic guanosine monophosphate (cGMP), a critical second messenger involved in various physiological processes, including neuronal signaling, vascular function, and cell survival. By breaking down cGMP, PDE9 regulates its intracellular levels and, consequently, the signaling pathways dependent on this molecule. Highly selective PDE9 inhibitors work by blocking the activity of PDE9, leading to an increase in cGMP levels[1,2].

Selective PDE9 inhibitors were/are being investigated for their potential in treating a variety of diseases, particularly those involving the central nervous system (CNS)[3]. In neurological and psychiatry disorders, they aimed to address cognitive deficits in schizophrenia[5] and Alzheimer's disease[6] by enhancing synaptic plasticity and neuronal communication. Beyond CNS applications, PDE9 inhibitors were/are being explored for cardiovascular diseases[7,8], where they could improve vascular function and reduce cardiac stress, as well as for other indications beyond neurological disorders and cardiovascular diseases[9].
While highly selective PDE9 inhibitors represent a promising class of drugs with potential applications in neurological, psychiatric, and cardiovascular diseases, further research is needed to fully understand their therapeutic potential and address the challenges associated[10].

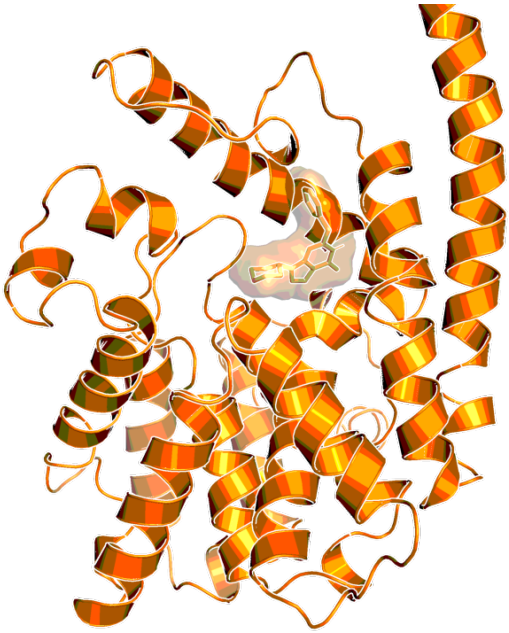

Figure 3: Model of the complex of PDE9 with BI409306, based on the crystal structure with a highly related inhibitor

In vitro activity

BI 409306 (osoresnontrine) is a potent and selective PDE9 inhibitor[2].

Probe name / Negative control	BI409306 (osoresnontrine)	BI-8777
MW [Da][a]	311.3	339.4
PDE9A (IC_{50}) [nM]	65	2,541
PDE1A (IC_{50}) [nM]	1,278	n.a.
PDE1C (IC_{50}) [nM]	1,300	3,552
PDE2A (IC_{50}) [nM]	>10,000	n.a.
PDE3A (IC50) [nM]	>10,000	n.a.
PDE4B (DC_{50}) [nM]	>10,000	n.a.
PDE5A (IC_{50}) [nM]	>10,000	n.a.
PDE6AB (IC_{50}) [nM]	>10,000	n.a.
PDE7A (IC_{50}) [nM]	>10,000	n.a.
PDE10A (IC_{50}) [nM]	>10,000	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

In vitro DMPK and CMC parameters

BI 409306 exhibits good solubility, excellent fraction unbound and low *in-vitro* efflux ratio, which makes it especially suited for brain penetrance and CNS indications & research.

Probe name / Negative control	BI 409306 (osoresnontrine)	BI-8777
logD @ pH 2, 7, 11	- / 1.7/ -	-0.34 / n.a. / 0.05
Solubility @ pH 7 [µg/ml]	500	tbd
Caco-2 permeability AB @ pH 7.4 [*10^{-6} cm/s]	58.5	53
Caco-2 efflux ratio	1.2	0.8
MDCK permeability P_{appAB} @ 1µM [10^{-6} cm/s]	24	42
MDCK efflux ratio	1.5	1.4
Microsomal stability (human/mouse/rat) [% Q_H]	<23 / <30 / <9	<23 / <23 / <23
Hepatocyte stability (human/mouse/rat) [% Q_H]	9 / 46 / 9	14 / 81 / 51
Plasma Protein Binding (human/mouse/rat) [%]	24 / 33.8 / 42	46.7 / 46.9 / 28.6
hERG (IC_{50}) [nM]	>100	tbd
CYP 3A4 (IC_{50}) [µM]	>50	tbd
CYP 1A2 (IC_{50}) [µM]	>50	>50
CYP 2C9 (IC_{50}) [µM]	>50	>50
CYP 2C19 (IC_{50}) [µM]	>50	>50
CYP 2D6 (IC_{50}) [µM]	>50	>50

In vivo DMPK parameters

BI 409306 (osoresnontrine) shows excellent brain penetrance, free brain exposure and high oral availability in rodents.

BI 409306 (osoresnontrine)	Mouse[a]	Rat[b]
Clearance [% Q_H]	30	30
Brain / Plasma ratio	0.2	0.2
CSF / Plasma ratio	0.3	0.2
Mean residence time after *i.v.* dose [h][a]	0.4	0.5

t_{max} [h]	0.5	0.5
C_{max} [nM]	2681	465
F [%]	>100%	57
V_{ss} [L/kg]	0.5	0.7

a i.v. dose: 3.1 mg/kg, p.o. dose: 1.6 mg/kg
b i.v. dose: 3.1 mg/kg, p.o. dose: 1.6 mg/kg

Ex-vivo/in vivo pharmacology

As also published previously[1,2,3], BI 409306 (osoresnontrine) has been tested in various animal test demonstrating:

- proof-of-mechanism regarding synaptic plasticity by enhancement of hippocampal LTP
- indirect target engagement by increasing cGMP in brain, microdialysis and CSF
- pro-cognitive efficacy in two mouse tasks addressing spatial working memory and episodic/ recognition memory
- efficacy in a neurodevelopmental model mouse related to schizophrenia

The effect of PDE9 inhibition on synaptic plasticity has been investigated by determination of long-term potentiation (LTP) in rat hippocampal brain slices. During the procedure, the compound was applied specifically during the stimulation period and subsequently washed out. PDE9 inhibition was found to induce a long-lasting enhancement of LTP (Fig. 4), highlighting its potential to strengthen synaptic plasticity, which serves as the molecular and cellular basis to improve memory-related processes.

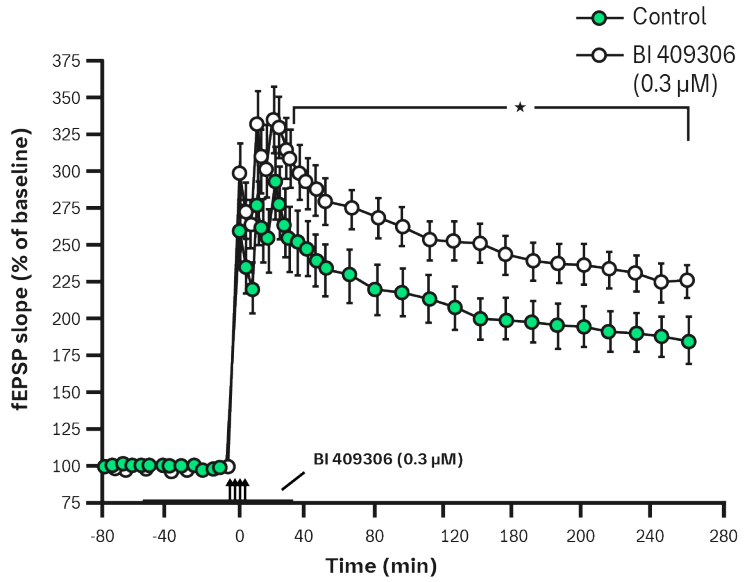

Figure 4: Inhibition of PDE9 by BI 409306 led to a significant enhancement LTP in rat hippocampal brain slice

To demonstrate the increase of cGMP after PDE9 inhibition in vivo, extracellular cGMP was measured via microdialysis after systemic administration (*i.p.*) of BI 409306. Here, BI 409306 showed a dose-dependent increase of cGMP in the prefrontal cortex (Fig. 5a). Furthermore, in order to evaluate cGMP increase in CSF as indirect target engagement, BI 409306 was administered orally to rats and the cGMP increase in CSF was determined. In this study, BI 409306 showed a dose-dependent increase of cGMP in rat CSF from 0.3 - 10 mg/kg *p.o.* up to 2.5-fold (Fig. 5b).

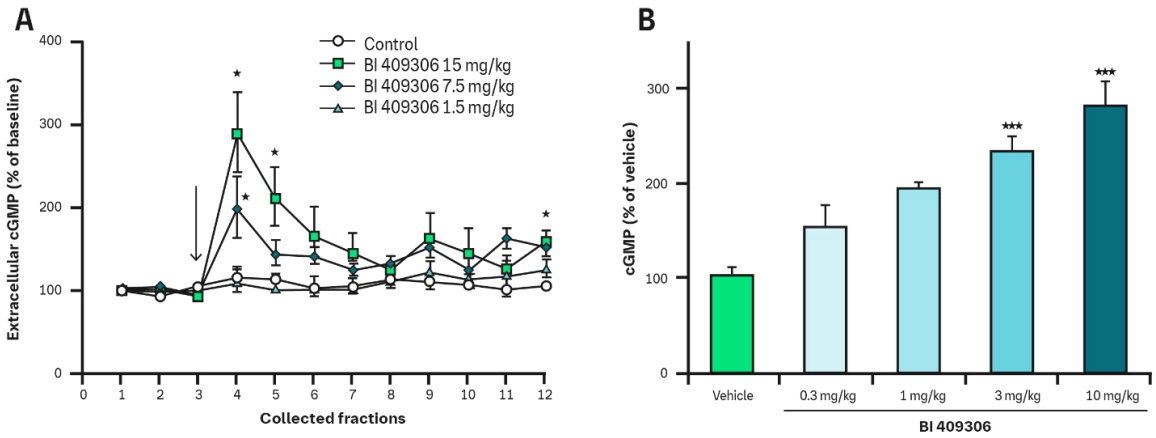

Figure 5: The effect of BI 409306 on increase of cGMP levels in (A) rat prefrontal cortex by microdialysis and (B) by collection of CSF samples after systemic administration of compound

BI 409306 was profiled in two different cognition tests in mice, i.e. T-maze spontaneous alternation test (T-maze) and novel object recognition test (NOR). In both tasks, BI 409306 showed significant improvement of cognitive performance and memory function (Fig. 6a and 6b, respectively).

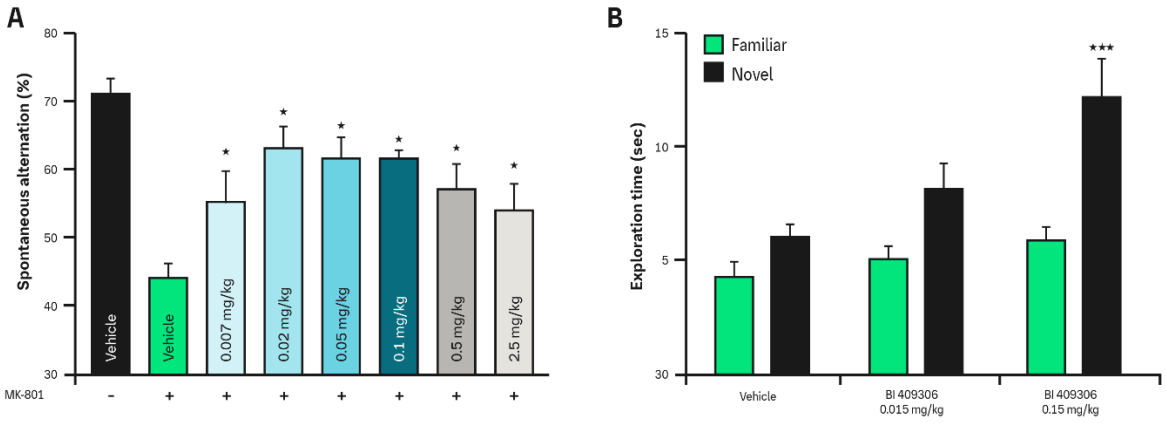

Figure 6: Efficacy of BI 409306 on (A) working memory in the T-maze spontaneous alternation task (reversal of MK-801 induced impairment) determined by spontaneous alternation behaviour and (B) on episodic memory in the object recognition task in mice determined

Furthermore, BI 409306 was tested in a neurodevelopmental mouse model, which is based on a maternal immune activation (MIA) of pregnant mice by a single injection of polyI:C (double stranded RNA), leading to a phenotype in the offspring related to schizophrenia. In this mouse model, BI 409306 significantly mitigated MIA induced social interaction deficits and amphetamine-induced hyperlocomotion, but not prepulse inhibition impairments, in a dose-dependent manner. In addition, in a second study BI 409306 treatment restricted to adolescence prevented adult deficits of the offspring in social interaction (Fig. 7).

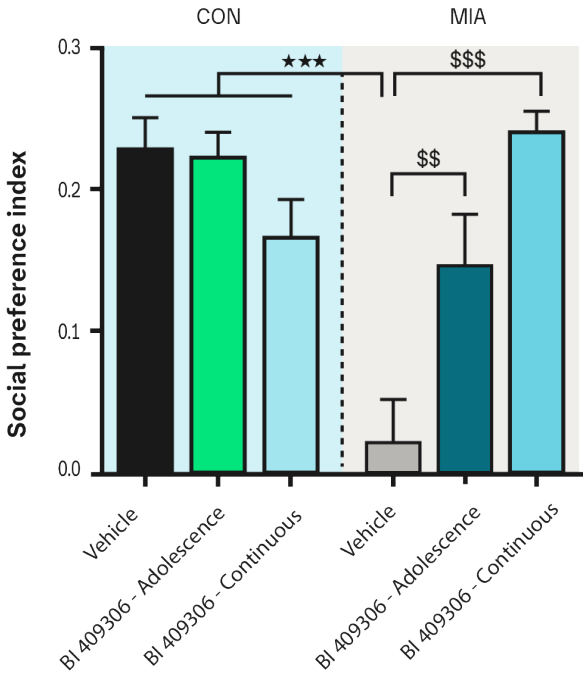

Figure 7: Effects of early chronic or preventive treatment with BI 409306 in adolescent CON or MIA offspring. Effects of vehicle or drug exposure on social interaction, as indexed by the social preference index, shows efficacy of BI 409306 on preventing social interaction deficits in adult offsprings

Negative control

BI-8777 is a structurally close analog and can be used as negative control.

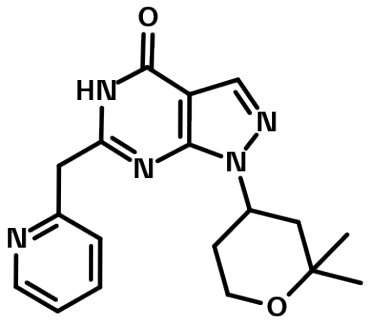

Figure 8: BI-8777 which serves as a negative control

Selectivity

BI 409306 (osoresnontrine) inhibited none out of 97 tested targets in an extended SafetyScreen44™ by greater than 50% @ 10µM.

Selectivity data available	BI 409306 (osoresnontrine)	BI-8777
SafetyScreen44™ with kind support of eurofins	Yes	No

Reference molecule(s)

Possible PDE9 tool compounds are Bay73-6691[11] and PF-4447943[12].

Supplementary data

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

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