opnMe by Boehringer Ingelheim

GPR88 agonist

BI-9508

Boehringer Ingelheim

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Summary

BI-9508 is a potent agonist of the G-protein-coupled receptor 88 (GPR88). Its selectivity profile and good brain penetration properties compared to earlier agonists, render it suitable for *in vitro* and in *vivo* studies.

Chemical Structure

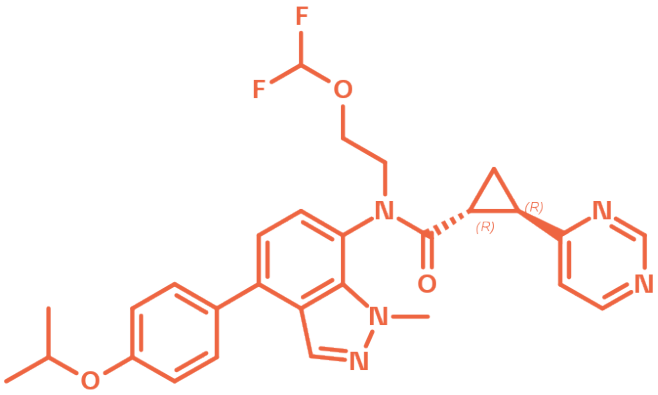

Figure 1: 2D structure of BI-9508, a GPR88 agonist.

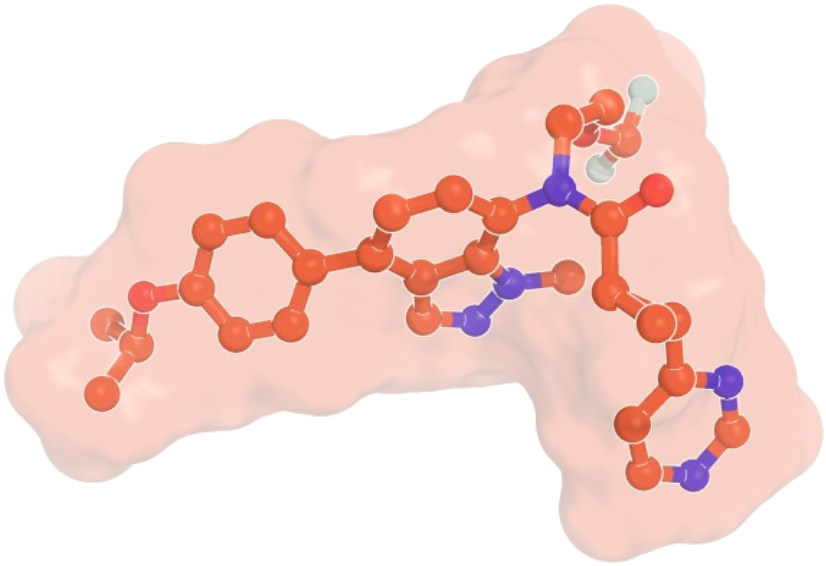

Figure 2: BI-9508, 3D conformation, as observed in a model of the complex with GPR88.

Highlights

BI-9508 is a potent and selective agonist of the orphan central nervous system (CNS) receptor GPR88. Lacking the primary amine associated with high P-glycoprotein (PGP) efflux of other GPR88 agonists reported to date, it displays good brain permeability properties, rendering it suitable for *in vitro* and *in vivo* studies. The closely related compound BI-0823 is available as a negative control.

Target information

GPR88 is an orphan G protein-coupled receptor (GPCR) primarily expressed and widely distributed in the GABAergic medium spiny neurons of the striatum[1]. Its presence has also been confirmed in other brain regions such as the cerebral cortex, amygdala, and hypothalamus[2]. The striatum itself is composed of the dorsal caudate putamen and the ventral nucleus accumbens. The former controls motor responses and is also involved in the compulsive behaviors associated with drug abuse, whereas the latter is the main center for reward and motivation behaviors, including drug and food reward[3].

GPR88 knockout mice demonstrate altered motor coordination, increased sensitivity to rewarding stimuli, and increased anxiety-like behavior[4]. Additionally, GPR88 gene expression can be modulated by anti-depressant pharmacological interventions, as well as by physiological neurotransmitters such as glutamate and dopamine[5].Overall, the research to date suggests that GPR88 may contribute to processes like locomotion, learning, emotional reactions, and social interactions, and may play a pivotal role in neurological operations[3,6].

As the endogenous ligand of GPR88 is unknown, upregulation of its function requires the use of either agonists or positive allosteric modulators (PAMs)[7,8]. BI-9508 is a brain-penetrant molecule lacking the primary amine associated with high P-glycoprotein (PGP) efflux of other GPR88 agonists reported to date. The *in vivo* PK properties of BI-9508 render it a useful tool compound to elucidate the intracellular signaling mechanisms and physiological functions of GPR88.

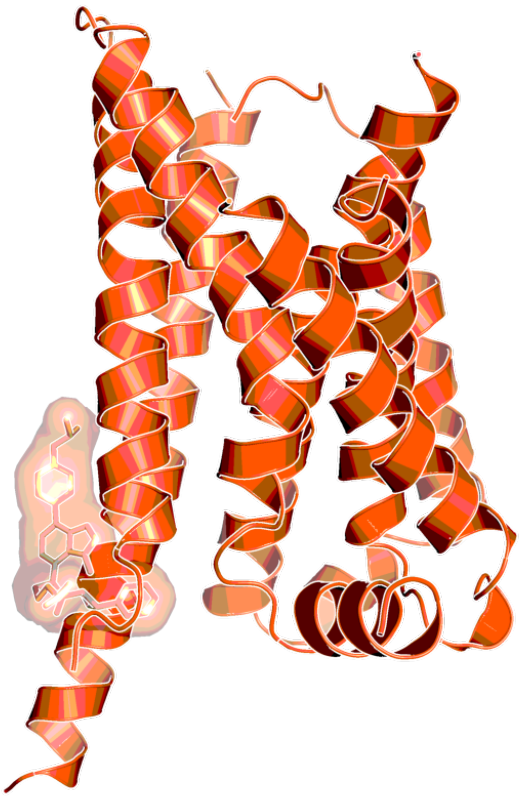

Figure 3: Model of the complex of GPR88 with BI-9509, based on 7EJX.pdb[9]

In vitro activity

BI-9508 displays an EC_{50} of 47 nM in a Gi1 BRET assay with human GPR88 (hGPR88) over-expressing HEK293 cells.

PROBE NAME / NEGATIVE CONTROL	BI-9508	BI-0823
MW [Da, free base][a]	521.6	374.3
hGPR88 Gi1 BRET assay (EC_{50}) [nM][b]	47	>99,999

[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: hGPR88 Gi1 BRET assay

The hGPR88 Gi1 BRET assay is based on transiently transfected HEK293 cells with unmodified human GPR88 receptor and a biosensor consisting of the sub-domain of the Gi/o protein-effector protein Rap1GAP fused to Renilla luciferase (RlucII) and co-expressed with alpha subunit of Gi1 protein[10]. Upon receptor activation, the energy effector translocates to the plasma membrane to bind activated Gα protein. This interaction brings RlucII in close proximity to the energy acceptor, Renilla green

fluorescent protein (rGFP), targeted to the plasma membrane through a CAAX motif (rGFP-CAAX), thus leading to an increase in BRET signal. Compounds were tested in a dose responsive manner using 20 concentrations, ranging from 100 µM to 0.003 µM, in 384 well micro titer plates. 2-PCCA had been used as positive control for receptor activation[11]

In vitro DMPK and CMC parameters

BI-9508 shows good *in vitro* MDCK permeability and low efflux. Its metabolic stability is acceptable for acute rodent studies.

PROBE NAME / NEGATIVE CONTROL	BI-9508	BI-0823
logD @ pH 2 / 11	4.3 / 4.4	1.6 / 1.8
Solubility @ pH 6.8 [µg/mL]	< 1	>75
MDCK permeability P_{appAP}@ 1µM [10^{-6} cm/s]	31	n.d.
MDCK efflux ratio	1.1	n.d.
Microsomal stability (human/mouse/rat) [% Q_H]	45 / 40 / 69	77 / >88 / 85
Hepatocyte stability (human/mouse/rat) [% Q_H]	50 / 60 / n.d.	n.d.
Plasma Protein Binding (human/mouse/rat) [%]	98.6 / 99.1 / 98.5	n.d.
hERG (IC_{50}) [µM]	5.1	n.d.
CYP 3A4 (IC_{50}) [µM]	>50	4
CYP 2C8 (IC_{50}) [µM]	>50	18
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-9508 shows an acceptable *in vivo* profile for acute rodent studies.

BI-9508	MOUSE
Clearance [% Q_H][a]	34.6
Mean residence time after *i.v.* dose [h][a]	2.9
t_{max} [h][b,c]	0.42 / 0.19
C_{max} [nM][b,c]	140.0 / 388.3
F [%][b,c]	26 /35
V_{ss} [L/kg][a]	5.4

[a] *i.v.* dose: 0.5mg/kg
[b] *p.o.* dose: 5 mg/kg
[c] *i-periton* dose: 1 mg/kg

Negative control

BI-0823 is similar in structure to BI-9508 as it contains the OCF_2, cyclopropyl amide, and aryl substitution patterns. Due to the lack of an additional aryl group that is essential for agonist activity on GPR88, BI-0823 serves as a good negative control.

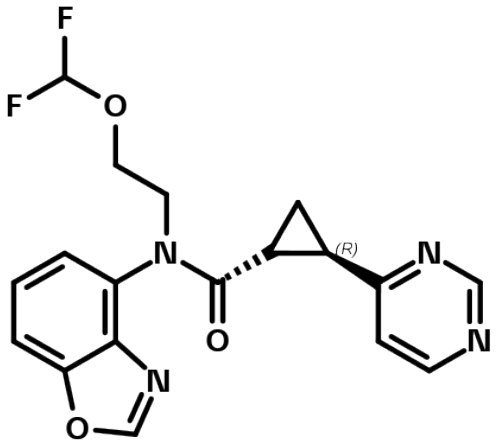

Figure 4: BI-0823 which serves as a negative control

Selectivity

BI-9508 and negative control BI-0823 hit no targets in SafetyScreen44™.

SELECTIVITY DATA AVAILABLE	BI-9508	BI-0823
SafetyScreen44™ with kind support of eurofins	Yes	Yes

Supplementary data

Selectivity data can be downloaded free of charge from opnMe.

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