OX1 receptor antagonist | BI-5121

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Summary

BI-5121 is highly potent and selective orexin receptor type 1 (OX1) antagonist with *in vivo* activity in rodent models. A structurally very close analogue, BI-6199, is available as a negative control.

Chemical Structure

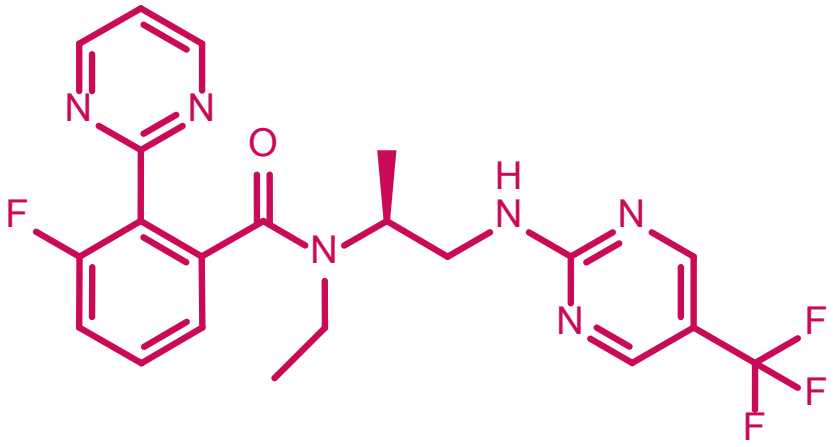


Figure 1: 2D structure of BI-5121

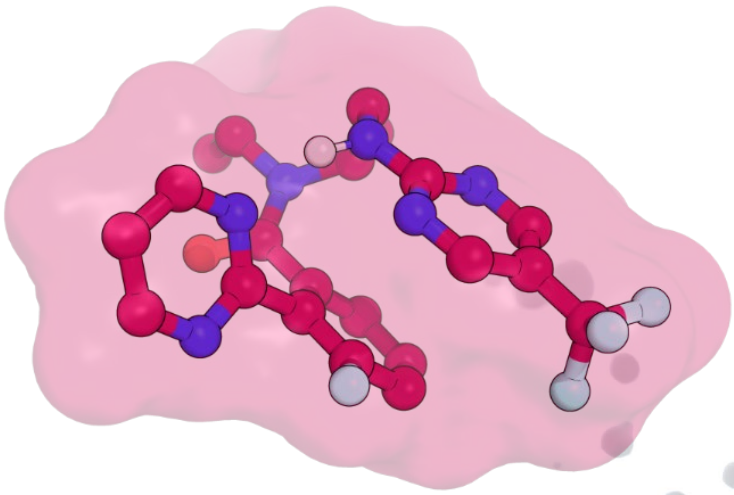


Figure 2: 3D structure of BI-5121, assumed bioactive conformation as observed in a model of the complex with Ox1

Highlights

Orexins (also known as hypocretins) are potent neuropeptides interacting with two G protein-coupled receptors, the orexin receptors type 1 (OX1) and 2 (OX2) (also known as HCRTR1, HCRTR2). Dual OX1/2 antagonism has been well described in the context of insomnia. Selective inhibitors may allow exploration of other neurological indications. BI-5121 is a selective antagonist against OX1 that has been efficacious *in vivo* in the behavioral 5-choice serial reaction time task in Lister Hooded rats[1].

Target information

Orexins (OX-A and OX-B) are neuropeptides, also known as hypocretin-1 and hypocretin-2, which are composed of 33 and 28 amino acids respectively. They bind to G protein-coupled receptors, orexin receptor type 1 (OX1) and orexin receptor type 2 (OX2). Orexinergic neurons are located in many brain regions, including the amygdala, hypothalamus, lateral hypothalamic area, and ventral tegmental area of the midbrain[2]. Dual antagonism of OX1 and OX2 by small molecules has been clinically tested and shown to be efficacious in the treatment of insomnia. As one example, the dual antagonist daridorexant has been granted market approval in both the US and the European Union for the treatment of sleeplessness. However, the involvement of the two orexin receptors in neuronal pathways appears to be partly overlapping and partly distinct. While the arousal-promoting function of orexins seems to be mainly mediated by OX2, other physiological states such as emotion and reward, cognition, impulse control, regulation of autonomic and neuroendocrine functions, arousal, and vigilance are rather linked to OX1[2-4].

Figure 3: Model of the binding mode of BI-5121 in the orthosteric pocket of orexin receptor type 1 (OX1). The model is based on an Xray structure of OX1 with a related ligand (PDB code 4ZJC)[5].

X-ray mediated structure-based analysis of the complex of orexin-1 and suvorexant, another dual OX1/2 receptor antagonist has been the starting point towards the identification of a selective orexin-1 receptor antagonist, BI-5121[1] that we now make available on opnMe.com.

In vitro activity

BI-5121 displays an IC_{50} of 1.6 nM in a human Orexin-1 IPOne HTRF (Homogeneous Time Resolved Fluorescence) assay and an IC_{50} of 62.6 nM in a human Orexin-2 IPOne HTRF assay.

PROBE NAME / NEGATIVE CONTROL	BI-5121	BI-6199
MW [Da]	448.42	437.39
Ox1 ANTA IP1 (nM)[a]	1.6	1,128.3
Ox2 ANTA IP1 (nM)[b]	62.6	8,262.9

[a,b] Activation of the orexin receptors expressed in cell lines results in an increase in intracellular IP3 concentration. IP1, a downstream metabolite of IP3, accumulates in cells following receptor activation and is stable in the presence of LiCl. Using Cisbio™`s HTRF technology with Lumi4TM-Tb cryptate and a suited fluorescence plate reader, this functional response is detectable and quantifiable. This technique was used to characterize pharmacological modification of the orexin receptors.[1]

In vitro DMPK and CMC parameters

PROBE NAME / NEGATIVE CONTROL	BI-5121	BI-6199
logP @ph 11	2.1	-
Solubility @ pH 6.8 [µg/ml]	80 (solid solubility)	50
CACO permeability @ pH 7.4 [*10^{-6} cm/s]	42	72

CACO efflux ratio	0.9	0.7
Microsomal stability (human/mouse/rat) [% Q_H]	<23 / <23 / <22	>89 / >88 / 85
Hepatocyte stability, 5% serum (human/mouse/rat) [% Q_H]	11 / 43 / 45	-
Plasma protein binding (human/mouse/rat) [%]	78.6 / 76.1 / 53.4	-
hERG (IC_{50}) [µM]	>10	-
CYP 3A4 (IC_{50}) [µM]	>50	14
CYP 2C8 (IC_{50}) [µM]	>50	>50
CYP 2C9 (IC_{50}) [µM]	>50	>50
CYP 2C19 (IC_{50}) [µM]	>50	2.4
CYP 2D6 (IC_{50}) [µM]	>50	>50

In vivo DMPK parameters

The data support oral administration of BI-5121 in rodent *in vivo* models.

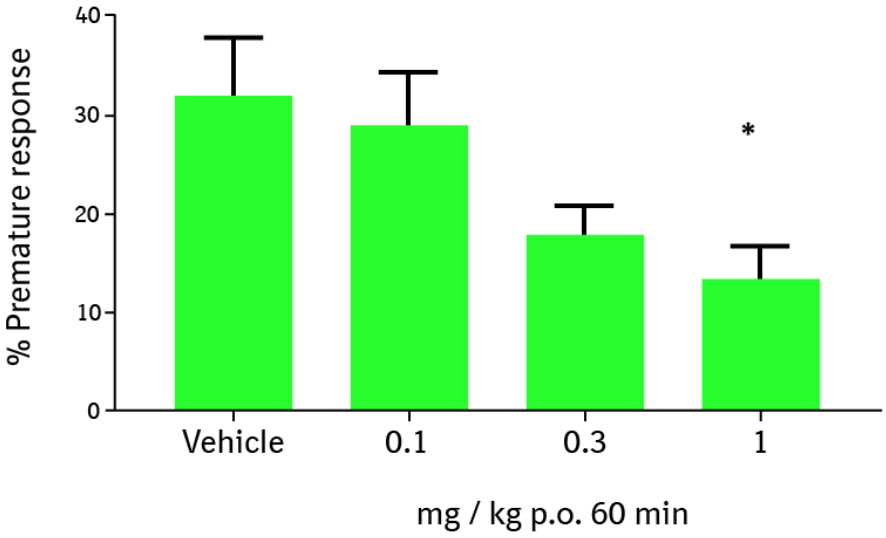
BI-5121	MOUSE	RAT
Clearance [% Q_H][b]	37.8	23.6
V_{ss} [l/kg]	1	1.6
Mean residence time after iv dose [h]	0.5	1.7
C_{max} [nM][b]	3,100	3,697

t_{max} [h][b]	0.7	0.25
AUC_{0-24} [nM*h][b]	5,010	5,238
F [%]	66	~50

[b]dose [10µg/kg]

In vivo pharmacology

Efficacy of BI-5121 has been demonstrated in the 5-choice serial reaction time impulsivity task (5CSRTT). Oral administration of the compound at 0.1, 0.3 and 1mg/kg dose-dependently, reduced premature responses in the 5CSRTT in Lister Hooded rats (associated calculated free brain exposures were 8, 18 and 181nM). Rats were trained to perform the task and on the day of the experiment were tested at 1 hour post drug treatment.



Mean±SEM. N=10 - 12.
Anova one-way p< 0.05
* p<0.05 Dunnett's multiple comparison test

Negative control

BI-6199, a structurally very close analogue, is available as a negative control.

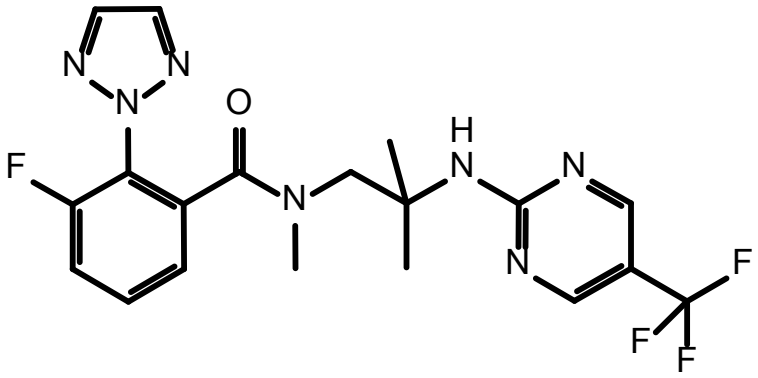


Figure 4: BI-6199 which serves as a negative control

Selectivity

All targets measured for BI-5121 in the SafetyScreen44™ are below 50% inhibition. The negative control BI-6199 inhibits KAPPA(KOP)_HU with 56% @10µM. All other targets measured in the SafetyScreen44 are below 50% inhibition. Compounds are considered selective, if they do not hit any of the measured targets in the SafetyScreen44 > 50%; panel measured at 10 µM.

SELECTIVITY DATA AVAILABLE	BI-5121	BI-6199
SafetyScreen44™ with kind support of eurofins	Yes	Yes
Invitrogen®	No	No
DiscoverX®	No	No
Dundee	No	No

Co-crystal structure of the Boehringer Ingelheim probe compound and the target protein.

The Xray crystal structure of the target in complex with a related molecule is available (PDB code: 4ZJC)[4].

Reference molecule(s)

Other available tool compounds: JNJ-61393215

Supplementary data

Selectivity data can be downloaded free of charge from opnMe.

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