B1 receptor antagonist | BI 113823

Table of contents

Summary

BI 113823 is a potent and selective Bradykinin 1 (B1) receptor antagonist. It shows an analgesic effect in chronic nociceptive pain conditions in preclinical animal models. The compound has shown very good solubility in aqueous media and an overall favorable pharmacokinetic profile. BI-5832 is available as a negative control.

Chemical Structure

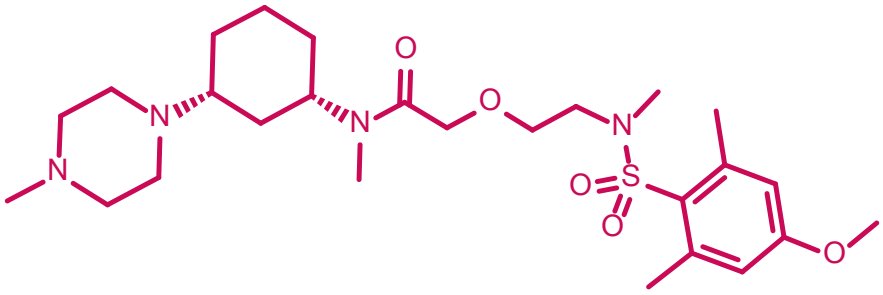

Figure 1: 2-D structure of BI 113823, a potent B1 receptor antagonist

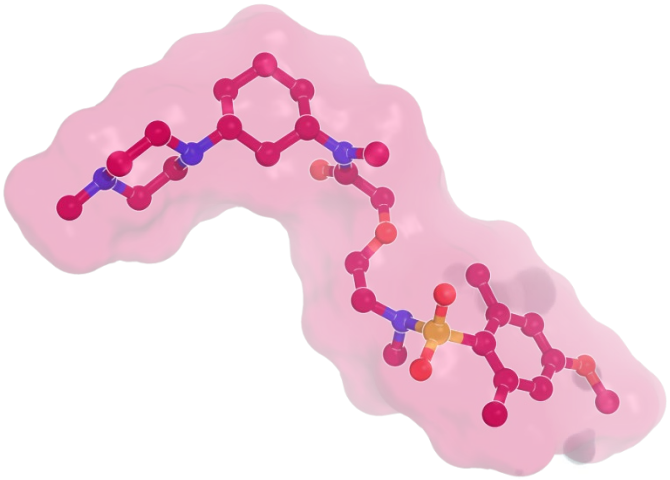

Figure 2: Low energy 3D structure of BI 113823

Highlights

BI 113823 is a selective, potent Bradykinin 1 receptor antagonist[1]. It is highly soluble and presents a favorable PK profile, making it suitable for *in vivo* experiments. Its binding affinity for Bradykinin 2 receptor is from very weak to none, being selective versus a large panel of off-targets. The structurally similar BI-5832 can be used as a negative control.

Target information

Bradykinin B1 Receptor (B1R) is a GPCR that has low expression in healthy tissues, however upon injury as well as in inflammatory conditions, higher expression is triggered. Particularly, chronic inflammation is linked with the protein expression. By binding to endogenous kinins, the signaling pathway activates phospholipase C that leads to increased intracellular calcium ion concentration leading to inflammatory responses.

Research has linked kinin B1 receptors to diverse pathological processes such as inflammation, platelet activation, smooth muscle contraction, increased vascular permeability, edema, pain, cytokine and chemokine release, cell proliferation, and tissue remodeling. The homolog, kinin B2 receptor, is expressed constitutively and play an important role in blood pressure regulation.

BI 113823 was seen to alleviate the pain-like behavior in preclinical settings. Dose dependent biological response was confirmed in rodent animal models.

Furthermore, BI 113823 shows efficacy in an experimental model of endotoxin-induced direct lung injury[2] and was shown to reduce allergen-induced airway inflammation and mucus secretion in mice[3].

Figure 3: Structure of the complex of the human Bradykinin-1 (B1) receptor (magenta) with [des-Arg10] -kallidin (white), the carboxy-terminal des-Arg metabolite of kallidin (PDB code 7EIB)[4]

In vitro activity

BI 113823 displays high affinity for the human B1 receptor determined by radioligand binding studies. Kallidin is displaced from human B1 with a K_i of 5.3 nM. K_i values of 13.3, 15.3 nM were measured for rat and rabbit, respectively. Thereby showing only little species differences – however no measurable affinity was observed for the pig B1R (K_i > 10 µM).
The compound does not exhibit any measurable binding for the human B2 receptor (K_i > 10 µM).
In addition, BI 113823 displays an IC_{50} value of 6.97 nM in a cellular assay. This is factor of 100 more potent than structurally similar negative control compound BI-5832. Finally, BI 113823 does not bind to B2 receptor.

PROBE NAME / NEGATIVE CONTROL	BI 113823	BI-5832
MW [Da]	524.72	520.73
hB1R (IC_{50}) [nM][a]	6.97	699
hB2R (IC_{50}) [K_i]	> 10 µM	n.a.

[a] CHO-K1 cell line expressing the human recombinant Bradykinin B1 receptor. Measured is inhibition of Lys-Des-Arg9-Bradykinin binding.

In vitro DMPK and CMC parameters

Both the B1 receptor antagonist BI 113823 and the negative control BI-5832 are highly soluble compounds, metabolically stable and do not inhibit CYP proteins.

PROBE NAME / NEGATIVE CONTROL	BI 113823	BI-5832
logD @ pH 11	2.5	3.22
Solubility @ pH 6.8 [µg/ml]	>10,000.0	111
CACO permeability @ pH 7.4 [*10^{-6} cm/s]	1.4	< 1.7
CACO efflux ratio	35.1	n.a.
MDCK permeability P_{app}a-b/b-a @ 10µM [10^{-6} cm/s]	6.3	0.6

MDCK efflux ratio	5.6	2
Microsomal stability (human/rat/mouse) [% Q_H]	42 / 44 / 39	53 / >88 / n.a.
Hepatocyte stability (human/rat/mouse) [% Q_H]	38 / 51 / 42	n.a.
Plasma protein binding (human) [%]	92%	n.a.
hERG [inh. % @ 10 µM]	6.9	n.a.
CYP 3A4 (IC_{50}) [µM]	> 50	> 50
CYP 2C8 (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

The pharmacokinetic profile of BI 113823 was obtained for rodent animals and is presented below.

BI 113823	MOUSE[A]	RAT[B]
$AUC_{0\text{-}inf}$ [(nmol·h) / L]	7240	2390
t_{max} [h]	0.25	0.5
C_{max} [nmol / L]	3100	1230
F [%]	39.9	37.3
Clearance [% Q_H]	73[c]	137[c]
V_{ss} [l / kg]	7.36[c]	9.43[c]

[A] Oral administration, 40 mg/kg, fed male

[B] Oral administration, 10 mg/kg, fasted male

[c] Intravenous administration, Dose: 10 mg/kg

In vivo pharmacology

B1 receptor antagonist BI 113823 has been tested in different experimental conditions where signaling via B1 receptor is known to play a role. Results of experiments include:

- Reducing endotoxin-induced direct lung injury and sepsis-induced lung inflammatory response, as well as improved survival following severe polymicrobial sepsis[2]
- Reversing pre-existing severe experimental pulmonary hypertension in rat models[5]
- Preventing the increase of retinal vascular permeability in diabetic macular edema (DME) in rat models[6]
- Reducing systemic and tissue inflammatory responses, prevented hemodynamic derangement, attenuated multiorgan injury, and improved overall survival in rats[7]
- Reduction of mechanical hyperalgesia induced by complete Freund's adjuvant mediated via antagonism of peripheral as well as spinal bradykinin B1 receptors[8]
- Reduction of postinfarction cardiac remodeling and heart failure[9]
- Improving post myocardial infarction cardiac function in rats[10]

Negative control

BI-5832 is available as a negative control. The compound is structurally similar to BI 113823. The two compounds have comparable physicochemical and pharmacokinetic profile.

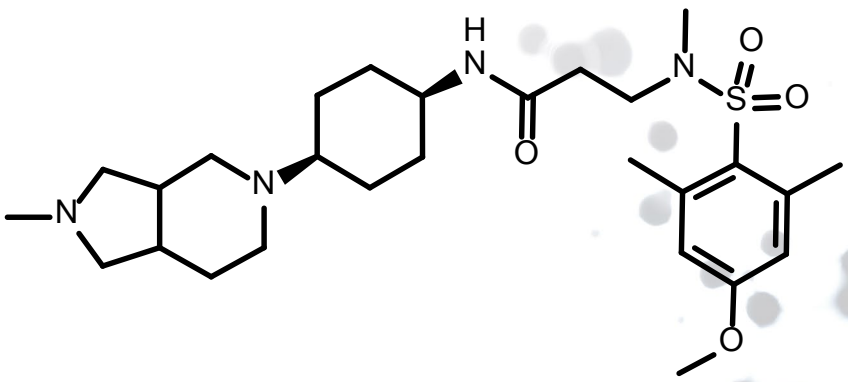

Figure 4: BI-5832, which serves as a negative control

Selectivity

BI 113823 was tested at the high concentration of 10µM on 69 targets in a selectivity panel and showed ≥1,000-fold selectivity for 67 targets (≤ 50% inhibition). In two assays (Sigma2/R, Sigma1/HU) the compound showed inhibition between 55 and 70%.
The negative control BI-5832 showed in 1 out of 44 targets inhibition with more than 50% @10 µM. It showed binding in kappa-opioid (KOP) assay with an inhibition of 58% @10µM.

SELECTIVITY DATA AVAILABLE	BI 113823	BI-5832
SafetyScreen44™ with kind support of eurofins	Yes	Yes
Invitrogen®	No	No
DiscoverX®	No	No
Dundee	No	No

Reference molecule(s)

B1-Agonist [des-Arg10]-kallidin.

Supplementary data

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

References

1. Huang H., Player M. R. Bradykinin B1 Receptor Antagonists as Potential Therapeutic Agents for Pain *J. Med. Chem.* **2010**, 53, 15, 5383–5399. DOI: 10.1021/jm1000776, PubMed.
2. Nasseri S., Gurusamy M., Jung B., Lee D., Khang G., Doods H., Wu D. Kinin B1 Receptor Antagonist BI 113823 Reduces Acute Lung Injury *Crit Care Med.* **2015**, 43, 11, 499-507. DOI: 10.1097/CCM.0000000000001268, PubMed.
3. Gurusamy M., Nasseri S., Lee H., Jung B., Lee D., Khang G., Abraham W. M., Doods H., Wu D. Kinin B1 receptor antagonist BI 113823 reduces allergen-induced airway inflammation and mucus secretion in mice *Pharmacol Res.* **2016**, 104, 132-9. DOI: 10.1016/j.phrs.2015.12.017, PubMed.

4. Yin Y.-L., Ye C., Zhou F., Wang J., Yang D., Yin W., Wang M.-W., Xu H. E., Jiang Y. Molecular basis for kinin selectivity and activation of the human bradykinin receptors *Nat Struct Mol Biol.* **2021**, 28, 9, 755-761. DOI: 10.1038/s41594-021-00645-y, PubMed.

5. Rampa D. R., Murugesan P., Chao H., Feng H., Dai W., Lee D., Pekcec A., Doods H., Wu D. Reversal of pulmonary arterial hypertension and neointimal formation by kinin B1 receptor blockade *Respir Res.* **2021**, 22, 1, 281. DOI: 10.1186/s12931-021-01875-w, PubMed.

6. Lang G. E., Tadayoni R., Tang W., Barth C., Weiss-Haljiti C., Chong V., BI 1026706 Study Group Bradykinin 1 Receptor Antagonist BI1026706 Does Not Reduce Central Retinal Thickness in Center-Involved Diabetic Macular Edema *Transl Vis Sci Technol.* **2020**, 9, 4, 25. DOI: 10.1167/tvst.9.4.25, PubMed.

7. Murugesan P., Jung B., Lee D., Khang G., Doods H., Wu D. Kinin B1 Receptor Inhibition with BI 113823 Reduces Inflammatory Response, Mitigates Organ Injury, and Improves Survival Among Rats with Severe Sepsis *J. Infect Dis.* **2016**, 213, 4, 532-40. DOI: 10.1093/infdis/jiv426, PubMed.

8. Schuelert N., Just S., Corradini L., Kuelzer R., Bernloehr C., Doods H. The bradykinin B1 receptor antagonist BI 113823 reverses inflammatory hyperalgesia by desensitization of peripheral and spinal neurons *Eur J Pain.* **2015**, 19, 1, 132-42. DOI: 10.1002/ejp.573, PubMed.

9. Lin X., Bernloehr C., Hildebrandt T., Stadler F. J., Doods H., Wu D. Kinin B1 receptor blockade and ACE inhibition attenuate cardiac postinfarction remodeling and heart failure in rats *Toxicol Appl Pharmacol.* **2016**, 305, 153-160. DOI: 10.1016/j.taap.2016.06.005, PubMed.

10. Wu D., Lin X., Bernloehr C., Hildebrandt T., Doods H. Effects of a Novel Bradykinin B1 Receptor Antagonist and Angiotensin II Receptor Blockade on Experimental Myocardial Infarction in Rats *PLoS One,* **2012**, 7, 12, e51151. DOI: 10.1371/journal.pone.0051151, PubMed.