Nav1.2 channel blocker | BIII 890CL (crobenetine)

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Summary

BIII 890CL (crobenetine) is a highly potent and selective Nav1.2 sodium channel blocker that can be used as tool compound to test biological hypotheses *in vitro* and *in vivo*.

Chemical Structure

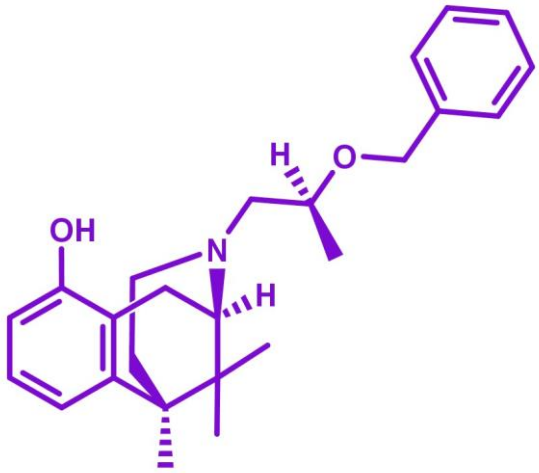

Figure 1: 2-D structure of BIII 890CL (crobenetine)

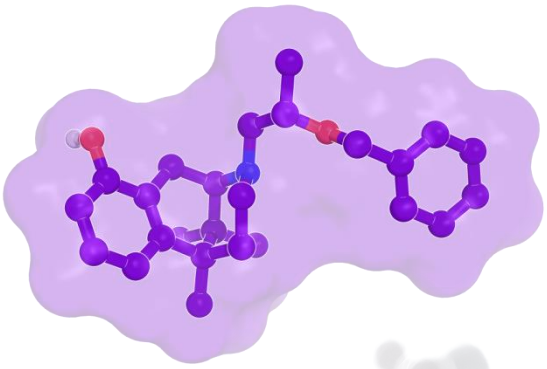

Figure 2: BIII 890CL (crobenetine), 3D conformation

Highlights

BIII 890CL is a highly potent, selective, use- and voltage-dependent sodium channel blocker. The compound has a high selectivity for site 2 of the sodium channel and preferentially binds to the inactivated state of the channel with an IC_{50} of 77 nM based on patch clamp evaluations. In contrast,

the binding at the resting state is only 18 µM. This exceptional selectivity of more than 230 fold for the different states of the sodium channel makes this compound unique compared with other sodium channel blockers.[1-4] Therefore, BIII890Cl is able to discriminate between highly (over)activated, depolarized neurons and neurons with physiological membrane potentials.
In animal studies such as the maximum electrical shock model it could be demonstrated that the compound supresses tonic seizures at doses which do not interfere with physiological functions of the sodium channel.
With BI-55CL we also offer a structurally close analogue with more than 1000 fold lower potency for site 2 of the sodium channel (K_i ~ 10 µM; [^{3}H]-BTX). Although the selectivity between the two states of the sodium channel has not been fully determined, the compound can be used as a comparator compound in *in vitro* studies.[1-4]

Target information

The voltage-gated sodium (Nav) channels are responsible for the rapid rising phase of an action potential, and thus play an essential role in membrane excitability and electrical signalling. Three distinct functional states are known: resting, active, and inactivated and all play a key role in neuronal activation. They are highly selective for the transport of sodium ions across cell membranes and become activated by a change in transmembrane voltage which is initially negatively charged. The activation results in a sodium influx and further depolarization of the neuron as the cause for an action potential. At the peak of the action potential, the sodium channels inactivate themselves by closing their inactivation gate. The neuron has to repolarize to its resting potential to bring the sodium channel back into the resting state.[1,2,4]

Sodium channels play a major role in signal propagation within the PNS and CNS but also in cardiac myocytes. Mutations that interfere with Na+ channel inactivation can contribute to cardiovascular diseases or epileptic seizures by over-excitation of muscle or nerve cells.[1,2,4]

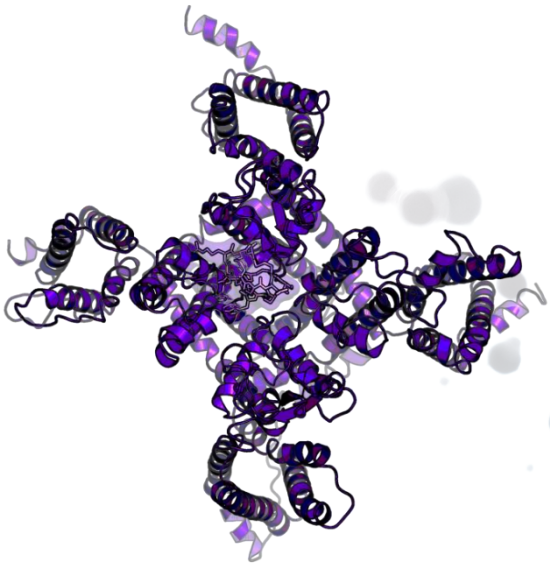

Figure 3: Cryo-EM structure of Nav1.2 in complex with cynotoxin KIIIA (X. Pan *et al*.).[5]

In vitro activity

PROBE NAME / NEGATIVE CONTROL	BIII 890CL	BI-55CL
MW [Da]	416.0 (HCl salt)	339.9 (HCl salt)
Displacement of [^{3}H]BTX K_i [nM] BTX: batrachotoxin[a]	43	>10.000
Inhibition of veratridine induced glutamate release in rat brain slices IC_{50} [nM][a]	322	n.d.

[a]for detailed assay conditions see reference 3

In vitro DMPK and CMC parameters

PROBE NAME / NEGATIVE CONTROL	BIII 890CL	BI-55CL
Melting point (°C)	258	n.d.
logP (pH 10)	3.3	n.d.
Solubility @ pH 4 / pH 6 / pH 7 [µg/ml]	2560 / 1040 / 8	n.d.
CACO permeability @ pH 7.4 [*10^{-6} cm/s]	n.d.	tbd
CACO efflux ratio	n.d.	tbd
Microsomal stability (human) [% Q_H]	87	n.d.
Hepatocyte stability (human / mouse / rat) [% Q_H]	n.d.	n.d.

Plasma protein binding (rat) [%]	99.2	n.d.
hERG [inh. % @ 1 µM]	54	n.d.
CYP 3A4 (IC_{50}) [µM]	11.4	n.d.
CYP 1A2 (IC_{50}) [µM]	25.5	n.d.
CYP 2C9 (IC_{50}) [µM]	6.9	n.d.
CYP 2C19 (IC_{50}) [µM]	2.3	n.d.
CYP 2D6 (IC_{50}) [µM]	0.03	n.d.

In vivo DMPK parameters

BIII 890CL	RAT
t_{max} [h][a]	2.83
C_{max} [nM][a]	1.51
AUC [nM][a]	24

[a] Oral dose: 3 mg/kg

In vivo pharmacology

Maximum electroshock (MES) test in mice ID_{50} = 6.1 mg/kg.[3]

Negative control

With BI-55CL we offer a structurally close analogue with more than 1000 fold lower potency for site 2 of the sodium channel (K_i ~ 10 µM; [^{3}H]-BTX).

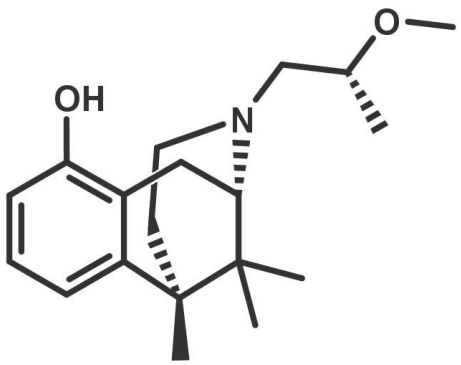

Figure 4: BI-55CL which serves as a negative control

Selectivity

BIII 890CL	SELECTIVITY DATA AVAILABLE
Cerep®	No
Panlabs®	Yes
Invitrogen®	No
DiscoverX®	No
Dundee	No

Reference molecule(s)

For a review on voltage-gated sodium channel blockers please see reference 6.

Summary

BIII 890CL is a highly potent, selective and use-dependent voltage-dependent sodium channel blocker suitable for *in vitro* and *in vivo* biological experiments. The compound has a high selectivity for site 2 of the sodium channel and preferentially binds to the inactivated state of the channel with an IC_{50} of 77 nM based on patch clamp evaluations. In contrast, the binding at the resting state is only 18 µM. This exceptional selectivity of more than 230 fold for the different states of the sodium channel makes this compound unique compared with other sodium channel blockers.[1-3] Therefore, BIII890CL is able to discriminate between highly (over)activated, depolarized neurons and neurons with physiological membrane potentials.
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Supplementary data

Selectivity data can be downloaded free of charge from opnMe.

References

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3. Matthias Grauert, Wolf. D. Bechtel, Thomas Weiser, Werner Stransky, Herbert Nar, Adrian J. Carter Synthesis and structure-activity relationships of 6,7-benzomorphan derivatives as use-dependent sodium channel blockers for the treatment of stroke *J. Med. Chem.* **2002**, *45*, 3755-3764. https://pubs.acs.org/doi/10.1021/jm020875j, PubMed.
4. Adrian J. Carter The importance of voltage-dependent sodium channels in cerebral ischaemia *Amino Acids*, **1998**, *14*, 159-169. DOI: https://doi.org/10.1007/BF01345257, PubMed
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6. John N. Wood, James Boorman Voltage-Gated Sodium Channel Blockers; Target Validation and Therapeutic Potential *Current Topics in Medicinal Chemistry*, **2005**, *5*, 529-537. DOI : 10.2174/1568026054367584, PubMed.