NMDA receptor antagonist | BIII 277CL

Table of contents

Summary

BIII 277CL is a highly potent and selective antagonist of the NMDA receptor (K_i 4.5 nM) that can be used to test biological hypotheses.

Chemical Structure

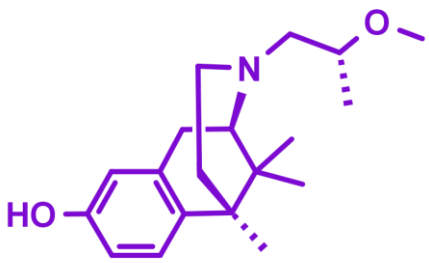

Figure 1: 2-D structure of BIII 277CL

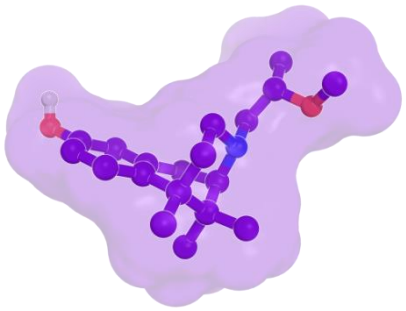

Figure 2: 3-D structure of BIII 277CL

Highlights

BIII 277CL is a high affinity blocker of the NMDA receptor ion channel (K_i = 4.5 nM; [^{3}H]MK-801 displacement assay in rat brain synaptosomal membrane) with specificity over other binding sites of the NMDA receptor–channel complex (glycine and NMDA binding sites). In addition, BIII 277CL did not exhibit significant affinities for other central neurotransmitter receptors.

BIII 277CL also antagonized NMDA-induced [^{3}H]noradrenaline release and NMDA-induced inhibition of protein synthesis in rat hippocampal slices.

In mice, the title compound prevented NMDA-induced lethality and caused disturbances in motor coordination (ID_{50} = 0.54 mg/kg *s.c.* and ED_{50} = 0.47 mg/kg *s.c.*, respectively). Furthermore, intraperitoneal or subcutaneous application of BIII 277CL to mice dose-dependently reduced the cortical infarct area from focal cerebral ischemia by unilateral occlusion of the middle cerebral artery.

Target information

The NMDA receptor is a subtype of excitatory amino acid receptor found in nerve cells, which allows cationic influx upon activation by glutamate and glycine.

Structurally, the NMDA receptor–channel complex consists of a voltage-dependent Na^{+}/Ca^{2+} channel and at least 3 different regulatory domains: neurotransmitter recognition site (glutamate, aspartate, or NMDA binding site), strychnine-insensitive glycine site, and ion channel itself (can be blocked by Mg^{2+} or other blockers).

During ischemia, large amounts of glutamate and aspartate (excitatory neurotransmitters) are released into the extracellular space, which can lead to neuronal deaths. This implicates the NMDA receptor–channel complex with pathophysiology of numerous neurological disorders, such as stroke, epilepsy, Alzheimer's disease, ALS, and others.

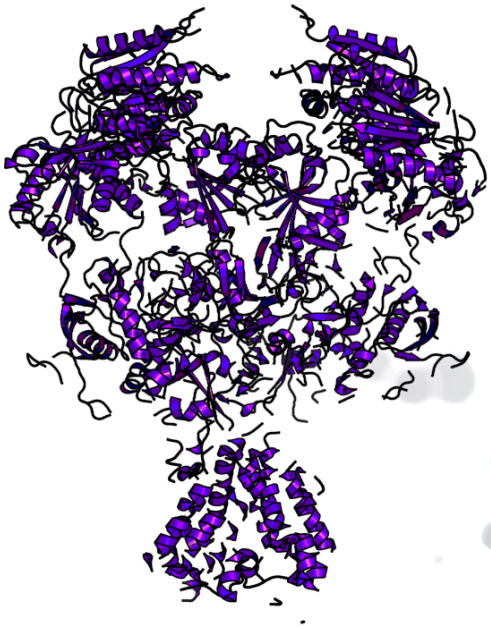

Figure 3: Structure of the NMDA receptor from Xenopus laevis (4TLM.pdb; Lee et. al., Nature 511 (2014), p.191-197)

In vitro activity

PROBE NAME / NEGATIVE CONTROL	BIII 277CL	BI-25CL
MW [Da]	339.1 (HCl Salt)	339.1 (HCl Salt)
Displacement of [^{3}H]MK-801 K_i [nM]a MK-801: dizocilpine	4.5	>50,000

[a] Assay conditions see reference 1

In vitro DMPK and CMC parameters

PROBE NAME / NEGATIVE CONTROL	BIII 277CL	BI-25CL
Solubility @ pH 7 [µg/ml]	>38	>74
Solubility @ pH 4 [µg/ml]	>38	>77
CACO permeability @ pH 7.4 [*10^{-6} cm/s]	ongoing	ongoing
CACO efflux ratio	ongoing	ongoing
MDCK permeability P_{app}a-b/b-a @ 1µM [10^{-6} cm/s]	ongoing	ongoing
MDCK efflux ratio	ongoing	ongoing
Microsomal stability (human) [% Q_H]	49	ongoing
Hepatocyte stability (human/mouse/rat) [% Q_H]	ongoing	ongoing

Plasma protein binding (human/mouse/rat) [%]	ongoing	ongoing
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	18.5
CYP 2D6 (IC_{50}) [µM]	14.7	>50

In vivo DMPK parameters

BIII 277CL	RAT
Clearance [% Q_H][b]	ongoing
Mean residence time after iv dose [l/kg]	ongoing
t_{max} [h]	ongoing
C_{max} [nM]	ongoing
F [%]	ongoing
V_{ss} [l/kg]	ongoing

[b]dose [mg/kg]

In vivo pharmacology

In mice, BIII 277CL showed significant neuroprotective effects. The title compound prevented NMDA-induced lethality and caused disturbances in motor coordination (ID_{50} = 0.54 mg/kg *s.c.* and ED_{50} = 0.47 mg/kg *s.c.*, respectively).

Furthermore, intraperitoneal or subcutaneous application of BIII 277CL to mice dose-dependently reduced the cortical infarct area from focal cerebral ischemia by unilateral occlusion of the middle cerebral artery.

Negative control

In addition, we offer a structurally closely related BI-25CL, which showed no marked affinity at the NMDA receptor ion channel (K_i = 50 μM; [^{3}H] MK-801 displacement assay in rat brain synaptosomal membrane) to be used as a control compound in *in vitro* studies.

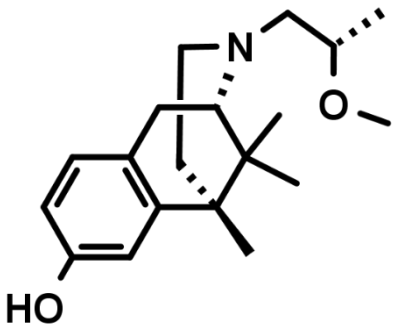

Figure 4: BI-25CL which serves as a negative control

Selectivity

BIII 277CL displayed only weak affinities for σ- and μ-opiate binding sites ([^{3}H]DTG, [^{3}H]dihydromorphine, [^{3}H]naloxone displacement assays in rat brain synaptosomal membrane) and 200-fold selectivity toward the channel site of the NMDA receptor–channel complex with no marked affinities up to 10 μM for the glycine site and the NMDA binding site of the NMDA receptor–channel complex.
Additionally, BIII 277CL did not exhibit affinities up to 100 μM for the dopamine D_1 and D_2 receptors ([^{3}H]SCH 23390 and [^{3}H]spiroperidol displacement assay).

BIII 277CL	SELECTIVITY DATA AVAILABLE
Cerep®	ongoing
Panlabs®	No
Invitrogen®	No
DiscoverX®	No
Dundee	No

Reference molecule(s)

For an overview of NMDA receptor antagonists please refer to the corresponding Wikipedia article and references therein.

Summary

BIII 277CL is a selective high affinity blocker of the NMDA receptor ion channel (K_i = 4.5 nM), which displayed beneficial effects in reducing the cortical infarct area in mice with focal cerebral ischemia. We offer BIII 277CL to test biological hypotheses *in vitro* and *in vivo*.

Supplementary data

Selectivity data can be downloaded free of charge from opnMe.

References

1. Matthias Grauert, Wolf D. Bechtel, Helmut A. Ensinger, Herbert Merz, and Adrian J. Carter, Synthesis and Structure-Activity Relationships of 6,7-Benzomorphan Derivatives as Antagonists of the NMDA Receptor–Channel Complex. *J. Med. Chem.* **1997**, *40*, 2922-2930. DOI: 10.1021/jm970131j, PubMed.

2. Adrian J. Carter, Wolf D. Bechtel, Matthias Grauert, Paul Harrison, Herbert Merz and Werner Stransky, BIII 277 CL Is a Potent and Specific Ion-channel Blocker of the NMDA Receptor–Channel Complex. *J. Pharmacol. Exp. Ther.* **1995**, *275*, 1382-1389. http://jpet.aspetjournals.org/content/275/3/1382.long, PubMed.

3. Matthias Grauert, Jong M. Rho, Swaminathan Subramaniam, and Michael A. Rogawski, N-Methyl-D-Aspartate Receptor Channel Block by the Enantiomeric 6,7-Benzomorphans BIII 277 CL and BIII 281 CL *J. Pharmacol. Exp. Ther.* **1998**, 285, 767-776. http://jpet.aspetjournals.org/content/285/2/767.long, PubMed.

4. Uwe Pschorn and Adrian J. Carter, The Influence of Repeated Doses, Route and Time of Administration on the Neuroprotective Effects of BIII 277 CL in a Rat Model of Focal Cerebral Ischemia, *J. Stroke Cerebrovasc. Dis.* **1996**, *6*, 93-99. https://linkinghub.elsevier.com/retrieve/pii/S1052-3057(96)80010-3, PubMed.

5. 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.