EUROPEAN SYNCHROTRON RADIATION FACILITY
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ESRF

Experiment Report Form

ESRF	**Experiment title:** Solution confirmation of the binding of the bivalent potential drug against glutaminergic excitotoxicity diseases, targeted at PDZ-domains	**Experiment number:** MX- 1190
Beamline:	**Date of experiment:** from: Dec 9 2010 to: Dec 10 2010	**Date of report:**
Shifts: 3	**Local contact(s):** Adam Round	*Received at ESRF:*

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Report:

Abstract

Inhibition of the ternary protein complex of the synaptic scaffolding protein postsynaptic density protein-95 (PSD-95), neuronal nitric oxide synthase (nNOS), and the N-methyl-d-aspartate (NMDA) receptor is a potential strategy for treating ischemic brain damage, but high-affinity inhibitors are lacking. Here we report the design and synthesis of a novel dimeric inhibitor, Tat-NPEG4(IETDV)(2) (Tat-N-dimer), which binds the tandem PDZ1-2 domain of PSD-95 with an unprecedented high affinity of 4.6 nM, and displays extensive protease-resistance as evaluated in vitro by stability-measurements in human blood plasma. X-ray crystallography, NMR, and small-angle X-ray scattering (SAXS) deduced a true bivalent interaction between dimeric inhibitor and PDZ1-2, and also provided a dynamic model of the conformational changes of PDZ1-2 induced by the dimeric inhibitor. A single intravenous injection of Tat-N-dimer (3 nmol/g) to mice subjected to focal cerebral ischemia reduces infarct volume with 40% and restores motor functions. Thus, Tat-N-dimer is a highly efficacious neuroprotective agent with therapeutic potential in stroke.

Full reference:

Bach, A; Clausen B. H.; Møller, M.; Vestergaard, B.; Chi, C.N.; Round, A.; Sørensen, P.L.; Nissen, K.B.; Kastrup, J.S.; Gajhede, M.; Jemth, P.; Kristensen, A.S.; Lundström, P.; Lambertsen, K.L. & Strømgaade, K. (2012) A high-affinity, dimeric inhibitor of PSD-95 bivalently interacts with PDZ1-2 and protects against ischemic brain damage. Proc. Natl. Acad. Sci. U S A.109: 3317-22.