

# **IPR19: a prolyl oligopeptidase inhibitor for the treatment of cognitive impairment associated with schizophrenia**

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## **ABSTRACT**

Prolyl oligopeptidase (POP) is an 81-kDa monomeric serine protease expressed in brain tissue. Recent advances suggest that this enzyme participates in protein-protein interactions that control brain functions and cognition processes. POP inhibition produces neuroprotective, anti-amnesic and cognition-enhancing effects in some rodent models. However, to achieve this, POP inhibitors must cross the blood-brain barrier (BBB), a formidable physical and enzymatic barrier that tightly controls the passage of molecules from the blood to the brain.

Here we present IPR19, a potent and selective peptidomimetic POP inhibitor for the treatment of the cognitive symptoms of schizophrenia—an unmet clinical need. The structure of this compound has been optimized to cross the BBB by passive diffusion. During this process, the following five key parameters have been taken into account in order to obtain a suitable compound for *in vivo* use: potency, selectivity, stability, toxicity, and relationship with BBB efflux pumps. IPR19 shows a good balance between these parameters, thus having the capacity to cross the BBB and inhibit brain POP in mice. The efficacy of the compound for the treatment of the cognitive symptoms of schizophrenia has been tested in three schizophrenia-like mouse models using a battery of behavioral paradigms, obtaining positive results. Overall, our data show that IPR19 crosses the BBB efficiently and enhances cognitive performance in animal models of schizophrenia. In particular, the new POP inhibitor IPR19 is a promising candidate as a cognition enhancer in schizophrenia treatment regimes. We are currently starting the regulatory preclinical phase for this product.