

# [The usage of prolyl oligopeptide](https://assignbuster.com/the-usage-of-prolyl-oligopeptide/)

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Prolyl oligopeptidase or prolyl endopeptidase (EC 3. 4. 21. 26) is a post-proline cleaving enzyme that belongs to the family of serine proteases. It is also abbreviated as PO, PE, PEP, POP, or PREP (herein referred as POP) (Polgar, 2002). POP is primarily expressed in the hippocampus, hypothalamus, cortex, amygdala, and striatum regions of the human brain. Earlier, POP was discovered as an oxytocin cleaving enzyme and later demonstrated to be a peptidase that cleaved short peptides at the carboxyl side of proline with a high specificity (Walter et al., 1971; Polgar and Szeltner, 2008).

It has been demonstrated that POP serves an important role in the brain function as it cleaves several neuropeptides and also in the maturation of peptide hormones as well as recognize several neuroactive peptides as its substrates including oxytocin, bradykinin, angiotensins I and II, substance P, arginine vasopressin, and thyrotropin releasing hormone (Polgar and Szeltner, 2008. In addition to its peptidase activity, POP is capable of modulating the function of several proteins such as О±-tubulin (Schulz et al., 2005), GAP-43 (Di Daniel et al., 2009), and О±-synuclein (Lambeir, 2011a) through protein-protein interactions. Furthermore, numerous inhibitors against POP were proposed that are effective in several aspects of the central nervous system, including learning, memory and mood-related behaviors (MГ¤nnistГ¶ et al., 2007; Lawandi et al., 2010; Lambeir, 2011b).

Besides its suggested role in eating and mood disorders, hypertension and cell-cycle progression, POP is related to the pathological process of neurodegeneration in Parkinson’s, Alzheimer’s, and Huntington’s disease (Hannula et al., 2013). Numerous POP inhibitors possessing anti-amnesic, cognition-enhancing and neuroprotective properties have been reported by several academic research groups (Lawandi et al., 2010; LГіpez et al., 2011; LГіpez et al., 2013). Early efforts included the development of substrate-like peptidomimetic compounds that were based on the systematic modification of the prototypical POP inhibitor N-benzyloxycarbonyl prolyl-prolinal (ZPP) (Yoshimoto et al., 1985).

Over the past 30 years, several POP inhibitors have been patented and entered the early phases of clinical trials [11]. Despite the development of potent inhibitors of POP having nanomolar activities, they failed in the clinical trials and none are currently in the market for human therapy (LГіpez et al., 2011). The most common reason for failure is their unfavorable pharmacokinetic properties and inability to cross the blood-brain barrier (BBB) (LГіpez et al., 2013).

Hence, the exploration of new scaffolds and potent inhibitors which have good pharmacokinetic, pharmacodynamic and toxic properties becomes critical. Consistent effort have been made to identify potential inhibitors against POP through in silico studies highlight the need of POP inhibitors along with the contribution of in silico research to therapeutics (Haffner et al., 2008; Lawandi et al., 2009; De Cesco et al., 2012; Mariaule et al., 2015; De Almeida et al., 2016; Kumar et al., 2017).

Therefore, computer-aided drug discovery strategies offer promising choice to the identification of new hit compounds, their optimization into potential hits with improved absorption, distribution, metabolism, excretion and toxicity profile and avoid adverse effects, cost, and time with limited resources (Kapetanovic, 2008; Macalino et al., 2015).