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Structure-activity Relationship of Protoberberine Derivatives: Comparative Evaluation of Their Protective Role Against Misfolded Protein Oligomers in Alzheimer's Disease

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Numerous neurodegenerative diseases are linked with the self-assembly of proteins into amyloid deposits. Natural compounds like berberine (Brb), a quaternary ammonium alkaloid, offer potential for multi-target drug development. Brb has shown promise in Alzheimer's disease (AD) by reducing Aβ generation, slowing down amyloid fibril formation, and improving cognitive function in animal models. Its ability to cross the blood-brain barrier strengthens its therapeutic potential, though its precise mechanism of action remains unclear. The availability of several natural protoberberine derivatives enabled a structure-activity relationship study that provides deeper insight. Fluorescence quenching and anisotropy assays showed that protoberberine derivatives bind to liposomes membrane with different affinities, causing its stiffening. Some of them also inhibit the binding of misfolded oligomers to the membrane, without significantly modifying their structure. In human neuroblastoma cells, Brb and most derivatives bind to the cell membrane, cross it and penetrate the cytosol. Moreover, they reduce the calcium influx induced by misfolded oligomers to different extents. This study shows how specific structural elements of protoberberine derivatives influence their ability to interact with biological membranes and their biological activity, aiding drug design for neurodegenerative diseases.