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Discorhabdin alkaloids from Antarctic *Latrunculia* spp. sponges as a new class of cholinesterase inhibitors

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The LC-ESIMS/MS analysis of methanol extracts of *Latrunculia* spp. sponges collected near the Antarctic Peninsula provided different metabolite profiles, all characterized by the presence of brominated pyrroloiminoquinone alkaloids discorhabdins. Some pure discorhabdin members have been demonstrated for the first time to be reversible competitive inhibitors of cholinesterases. They were tested as inhibitors of electric eel and recombinant human acetylcholinesterases, and of horse serum butyrylcholinesterase. The tested disorhabdins acted as reversible, competitive inhibitors through their binding to the active site of the free Acetylcholinesterase (AChE) or Butyrylcholinesterase (BChE), with very good K_i values when compared to the current cholinesterase inhibitors used for treatment of patients with Alzheimer's disease. A qualitative structure-activity relationship was carried out; moreover, a good correlation was observed between IC_{50} data and the results by molecular docking calculation on the binding interactions within the acetylcholinesterase active site. Electrophysiological experiments with one of the most active of these metabolites, discorhabdin G, showed that it has no undesirable effects on neuromuscular transmission and skeletal muscle function, which are instead the side effects produced by known drugs used as cholinesterase inhibitors. Based on the scaffold of discorhabdin metabolites, these findings are promising as a guide towards the synthesis of potential agents for the treatment of Alzheimer's disease. A computational screening based on docking calculation of potential simplified structures inspired by natural discorhabdins is in progress, in order to select the best molecules to be synthesized and then biologically evaluated.

Biography

Ines Mancini has completed her MD in Chemistry at the University of Bologna (Italy) in 1983 and she is currently Associate Professor of Organic Chemistry at the University of Trento (Italy). Her research is focused on Natural Products Chemistry, involving isolation, structural elucidation, total synthesis also by unconventional eco-friendly methods and studies of target interactions by docking calculation. She has published 120 papers in peer-reviewed journals.

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