Brazilian Amaryllidaceae: a source of acetylcholinesterase inhibitory alkaloids

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Introduction

Nine Brazilian Amaryllidaceae species were studied for their alkaloid composition and acetylcholinesterase (AChE) inhibitory activity via GC-MS and a modified Ellman assay, respectively. A total of thirty-six alkaloids were identified in these plants, of which *Hippeastrum papilio* and *H. glaucescens* exhibited the highest galanthamine content and the best IC_{50} values against AChE. Furthermore, *H. vittatum* and *Rhodophiala bifida* also showed notable AChE inhibitory effects. X-ray crystallographic data for four galanthamine-type compounds revealed significant differences in the orientation of the *N*-methyl group, which are shown to be related to AChE inhibition.

Results and Discussion

Thirty-six well-known Amaryllidaceae alkaloids were identified by GC-MS. *H. papilio* and *H. glaucescens* showed highest levels of galanthamine. Bulbs and leaves of *H. papilio* exhibited values of 0.51% (± 0.012) and 0.33% (± 0.007), respectively (mg GAL/100mg DW). Both species presented the lowest IC_{50} values for AChE inhibitory activity along with *H. vittatum* and *R. bifida*, in which elevated levels of montanine were detected.

AChE inhibitory activity was also carried out for galanthamine-type derivatives. Galanthamine and sanguinine were the most active AChE inhibitory alkaloids (IC_{50} 0.35 and 0.06 μM, respectively). Narwedine and 11*β*-hydroxygalanthamine showed IC_{50} values of 9.38 and 3.49 μM, respectively. Docking studies were inconclusive concerning the effects of the *N*-methyl group orientation into the AChE site gorge[1]. The X-ray data for galanthamine and narwedine were in agreement with those of previously reported[1] and crystallographic data for sanguinine and 11*β*-hydroxygalanthamine are reported here for the first time. Interestingly, narwedine and 11*β*-hydroxygalanthamine showed an axial orientation for the NMe group, opposite to that seen for galanthamine. Sanguinine (the most potent AChE), exhibited both orientations for the NMe group (Figure 1).

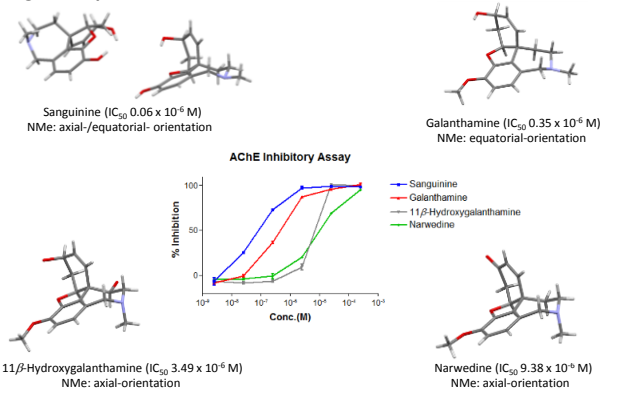

Figura 1. Acetylcholinesterase inhibition curve and X-ray structures of sanguinine, galanthamine, 11*β*-hydroxygalanthamine and narwedine showing the *N*-methyl orientation.

Conclusions

Some indigenous Brazilian species are shown to produce high quantities of the AChE inhibitors galanthamine and montanine. Galanthamine levels in leaves and bulbs of *H. papilio* were higher than those found in *Leucojum*, *Galanthus* and *Narcissus*, species traditionally recognizable for commercial exploitation[2,3]. It is known that *N*-methyl conformers interchange rapidly in the naturally bound ligand, thereby restricting *N*-methyl orientation to a secondary role in new drug design. Nevertheless, further protein-ligand crystallography and protein-ligand docking studies should clarify the exact role of *N*-methyl orientation in galanthamine-type alkaloids.

Aknowledgments

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