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Isolation of *Lycopodium* alkaloids from Thai and Philippine *Huperzia squarrosa* and syntheses of Huperzine A derivatives via amidation reaction

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Statement of the Problem: *Lycopodium* alkaloids are quinolizine, pyridine and pyridone alkaloids isolated from club mosses (Lycopodiaceae). The most notable alkaloid from this group is huperzine A, which is a potent reversible Acetylcholinesterase (AChE) inhibitor. Studies on *Lycopodium* alkaloids from club mosses in Southeast Asia are deficient. This work aimed to phytochemically investigate club mosses native to Thailand and the Philippines.

Methodology: Whole plants of *H. squarrosa* collected from Thailand and the Philippines were extracted with methanol. The methanolic extracts were subjected to acid-base extraction. The obtained alkaloidal fractions were further purified through column chromatography.

Findings: *H. squarrosa* from Thailand yielded four alkaloids. Two known *Lycopodium* alkaloids were identified to be huperzine A (1) and 12-epilycodoline N-oxide (4). Squarrosine A (2) was a new fawcettimine-type *Lycopodium* alkaloid which possessed intramolecular hydrogen bonding. (R)-2-piperidineacetic acid (5) has never been reportedly isolated. This alkaloid was speculated to derive from precursors of *Lycopodium* alkaloids. From Philippine *H. squarrosa*, huperzine A (1) and pyrrolhuperzine A (3), a new lycodine-related *Lycopodium* alkaloid bearing a rare pyrrole moiety, were isolated. Semi-synthetic approaches to pyrrolhuperzine A (3) were achieved to confirm its structure elucidation, and two plausible biogenetic pathways from huperzine A (1) to pyrrolhuperzine A (3) were proposed. Furthermore, huperzine A (1) was chemically transformed into three amide derivatives (6-8). The newly isolated and semi-synthetic alkaloids were assayed for their anti-AChE activities. Huperzine A derivatives 6 and 7 exhibited strong AChE inhibition.

Conclusion & Significance: Thai and Philippine *H. squarrosa* contained high amount of Huperzine A (1) (0.014% and 0.13%, respectively). The synthesis of pyrrolyl derivative of Huperzine A has been accomplished for the first time.

Biography

Thanasan Nilsu is doing his PhD in Applied Biological Sciences at Chulabhorn Graduate Institute, Chulabhorn Royal Academy of Science, Bangkok, Thailand. He has been working on the isolation of *Lycopodium* alkaloids from Thai club mosses and derivatization of huperzine A. His research also includes pharmacological evaluation of natural and synthetic compounds in mammalian cell culture.

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