© 2025 Journal of Pharmacy & Pharmacognosy Research, 13 (3), 757-773, 2025
ISSN 0719-4250
https://jppres.com

DOI: https://doi.org/10.56499/jppres24.2064_13.3.757

Original Article

In vitro and *in silico* cholinesterase inhibitory activities of aaptamine and derivatives from *Aaptos suberitoides*

[Actividades inhibidoras de la colinesterasa *in vitro* e *in silico* de la aaptamina y derivados de *Aaptos suberitoides*]

Suciati Suciati[1,2*], Hanifa Rahma Putri[3], Kishneth Palaniveloo[4,5], Ong Kuan Hung[4], Mohammed Rizman-Idid[4], Aty Widyawaruyanti[1,2], Nitra Nuengchamnong[6], Nungruthai Suphrom[7], Rhesi Kristiana[8], I Wayan Mudianta[9], Mary George[10], Edwin Setiawan[11]

[1]Department of Pharmaceutical Sciences, Faculty of Pharmacy, Universitas Airlangga, Surabaya, 60115, East Java, Indonesia.
[2]Center for Natural Product Medicine Research and Development, Institute of Tropical Diseases, Universitas Airlangga, Surabaya, 60115, East Java, Indonesia.
[3]Master Program in Pharmaceutical Science, Faculty of Pharmacy, Universitas Airlangga, Surabaya, 60115, East Java, Indonesia.
[4]Institute of Ocean and Earth Sciences, Advanced Studies Complex, Universiti Malaya, 50603 Wilayah Persekutuan Kuala Lumpur, Malaysia.
[5]Center for Natural Products Research and Drug Discovery (CENAR), Level 3, Research Management & Innovation Complex, Universiti Malaya, 50603 Wilayah Persekutuan Kuala Lumpur, Malaysia.
[6]Science Laboratory Center, Faculty of Science, Naresuan University, Phitsanulok 65000, Thailand.
[7]Department of Chemistry, Faculty of Science and Center of Excellence for Innovation in Chemistry, Naresuan University, Phitsanulok 65000, Thailand.
[8]Indonesian Marine Education & Research Organisation (MERO) Foundation, Desa Tulamben, Karangasem 80853, Bali, Indonesia.
[9]Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Pendidikan Ganesha, Singaraja 81116, Bali, Indonesia.
[10]Faculty of Law, Universiti Malaya, 50603 Wilayah Persekutuan Kuala Lumpur, Malaysia.
[11]Department of Biology, Faculty of Science and Data Analytics, Institut Teknologi Sepuluh November, Surabaya 60111, East Java, Indonesia.
*E-mail: suciati@ff.unair.ac.id

Abstract

Context: Marine sponges from the genus *Aaptos* produce compounds, often alkaloids, with a wide range of bioactivities. *Aaptos suberitoides* exhibits anticancer, antioxidant, antibacterial proteasome inhibitory, and receptor activator of NF-kappaB ligand (RANKL) inhibitory activities. Alkaloids from marine sponges have shown potency as cholinesterase inhibitors, one of the targets in Alzheimer's disease treatment.

Aims: To isolate, identify, and investigate the potency of alkaloids from the water fraction of marine sponge *A. suberitoides* as cholinesterase inhibitors.

Methods: Bioassay-guided isolation was employed to obtain active alkaloids. The cholinesterase inhibitory assay was conducted based on Ellman's method with slight modification. Identification of isolated compounds was carried out based on NMR and MS data. The identified compounds were also subjected to molecular docking analysis as well as an ADMET study.

Results: Bioassay-guided isolation of water fraction yielded aaptamine (**1**) and a mixture containing five benzo[de][1,6]-naphthyridine derivatives, identified based on NMR and LC-MS/MS spectroscopy. Aaptamine **(1)** inhibited both acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) with IC_{50} values of 0.23 and 1.38 µg/mL, respectively. Likewise, the benzo[de][1,6]-naphthyridine mixture of N-demethylaaptanone (**2**), aaptanone (**3**), demethylaaptamine (**4**), aaptosine (**5**) and 8,9,9-trimethoxy-9H-benzo[de][1,6]-naphthyridine (**6**) recorded IC_{50} values of 0.39 and 1.61 µg/mL, respectively. Computational molecular docking analysis calculated the S-score and RMSD values of aaptamine (**1**) to be the best compared to galantamine for both AChE (PBD: 4EY6) and BChE (PDB: 4BDS) with values of -6.65 kcal/mol, 0.57 Å and -5.98 kcal/mol, 1.05 Å, respectively.

Conclusions: These findings suggest that benzo[de][1,6]-naphthyridine alkaloids from *A. suberitoides* can be good candidates as cholinesterase inhibitors.

Keywords: *Aaptos suberitoides;* Alzheimer's disease; benzo[de][1,6]-naphthyridine alkaloids; cholinesterase inhibitor; marine sponge.

Resumen

Contexto: Las esponjas marinas del género *Aaptos* producen compuestos con una amplia gama de bioactividades. *Aaptos suberitoides* exhibe actividades anticancerígenas, antioxidantes, antibacterianas, inhibidoras del proteasoma y del activador del receptor del ligando NF-kappaB (RANKL). Los alcaloides de las esponjas marinas han demostrado potencia como inhibidores de la colinesterasa, uno de los objetivos en el tratamiento de la enfermedad de Alzheimer.

Objetivos: Aislar, identificar e investigar la potencia de los alcaloides de la fracción acuosa de la esponja marina *A. suberitoides* como inhibidores de la colinesterasa (iChE).

Métodos: Se empleó un aislamiento guiado por bioensayo para obtener alcaloides activos. El ensayo inhibidor de la colinesterasa se realizó según el método de Ellman con una ligera modificación. La identificación de los compuestos aislados se llevó a cabo según los datos de RMN y MS. Los compuestos identificados también se sometieron a un análisis de acoplamiento molecular, así como a un estudio ADMET.

Resultados: El aislamiento de la fracción acuosa mediante bioensayo permitió obtener aaptamina **(1)** y una mezcla que contenía cinco derivados de benzo[de][1,6]-naftiridina, identificados mediante espectroscopia RMN y LC-MS/MS. La aaptamina **(1)** inhibió tanto la acetilcolinesterasa (AChE) como la butirilcolinesterasa (BChE) con valores de CI_{50} de 0,23 y 1,38 µg/mL, respectivamente. Asimismo, la mezcla de benzo[de][1,6]-naftiridina de N-desmetilaaptanona **(2)**, aaptanona **(3)**, desmetilaaptamina **(4)**, aaptosina **(5)** y 8,9,9-trimetoxi-9H-benzo[de][1,6]-naftiridina **(6)** registró valores de CI_{50} de 0,39 y 1,61 µg/mL, respectivamente. El análisis computacional de acoplamiento molecular calculó que los valores de S-score y RMSD de aaptamina **(1)** eran los mejores en comparación con galantamina tanto para AChE (PBD: 4EY6) como para BChE (PDB: 4BDS) con valores de -6,65 kcal/mol, 0,57 Å y -5,98 kcal/mol, 1,05 Å, respectivamente.

Conclusiones: Estos hallazgos sugieren que los alcaloides benzo[de][1,6]-naftiridina de *A. suberitoides* pueden ser buenos candidatos como iChE.

Palabras Clave: *Aaptos suberitoides*; alcaloides benzo[de][1,6]-naftiridina; enfermedad de Alzheimer; esponja marina; inhibidor de la colinesterasa.

ARTICLE INFO
Received: April 26, 2024.
Accepted: November 22, 2024.
Available Online: December 17, 2024.

AUTHOR INFO
ORCID: 0000-0003-2436-4119 (SS) 0000-0002-2231-2502 (MRI) 0000-0002-6152-4305 (RK)
0000-0001-6016-8479 (HRP) 0000-0003-4639-1599 (AW) 0000-0002-0388-3828 (IWM)
0000-0003-0466-2602 (KP) 0000-0001-5659-9786 (NN) 0000-0003-1233-0835 (MG)
0000-0002-3108-7570 (OKH) 0000-0003-3767-8387 (NS) 0000-0003-3947-3334 (ES)