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Xanthorrhizol derivatives as hyaluronidase inhibitors: In silico fragment-based drug design, in vitro evaluation and molecular dynamics simulations

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[Tengku Nazmi, Tengku Kamilah](#)^a; [Aminudin, Nurul Iman](#)^{a, b} ; [Md Pizar, Mazura](#)^c; [Mohd Hashim, Siti Nur Aisyah](#)^c; [Hamzah, Nurasyikin](#)^{a, b, e}; [+1 author](#)

^aDepartment of Chemistry, Kulliyah of Science, International Islamic University Malaysia (IIUM), Pahang, Kuantan, 25200, Malaysia

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Abstract

In this study, the anti-inflammatory potential of xanthorrhizol (XNT), a natural compound isolated from *Curcuma xanthorrhiza*, was enhanced through structural optimisation using in silico fragment-based drug design (FBDD) and molecular docking, targeting the hyaluronidase enzyme. The design process yielded five XNT derivatives: one known compound (2) and four novel derivatives (3–6). Derivative (3) exhibited the most favourable drug-likeness property and showed the most

potent activity ($IC_{50} = 44.54 \mu\text{g/mL}$) markedly lower than XNT (1) ($IC_{50} = 203.56 \mu\text{g/mL}$). Furthermore, molecular dynamics simulation revealed that derivative (3) maintained a stable interaction within the hyaluronidase binding pocket with key amino acid residues, with a favourable binding free energy of -26.95 kcal/mol as calculated by the Molecular Mechanics/Generalized Born Surface Area (MM/GBSA) method. These findings suggest that derivative (3) holds a promise as hyaluronidase inhibitor and potentially to be further developed as anti-inflammatory agent. © 2025 Elsevier B.V.

Author keywords

ADME; Fragment-based drug design; Hyaluronidase; Molecular dynamics; Optimisation; Xanthorrhizol

Indexed keywords

Engineering controlled terms

Binding energy; Design; Drug delivery; Drug discovery; Free energy; Molecular docking; Molecular mechanics

Engineering uncontrolled terms

ADME; Anti-inflammatories; Drug Design; Dynamics simulation; Fragment-based drug design; Hyaluronidase; In-silico; In-vitro evaluation; Optimisations; Xanthorrhizol

Engineering main heading

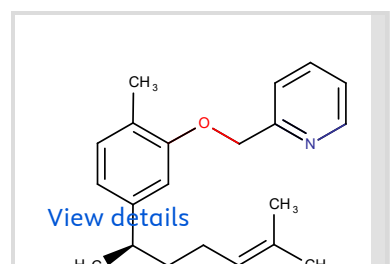
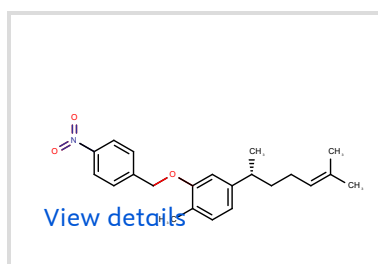
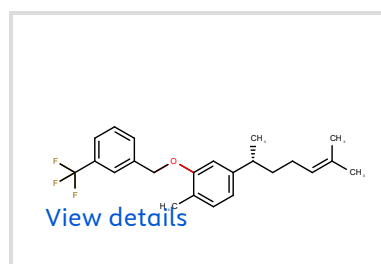
Molecular dynamics

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Corresponding authors

Corresponding author	N.I. Aminudin
Affiliation	Department of Chemistry, Kulliyah of Science, International Islamic University Malaysia (IIUM), Pahang, Kuantan, 25200, Malaysia
Email address	nuruliman@iium.edu.my