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 Pisar, Mazura [c]; Mohd Hashim, Siti Nur Aisyah [c]; Hamzah, Nurasyikin [a, b, e]; +1 author

[a] Department of Chemistry, Kulliyyah of Science, International Islamic University Malaysia (IIUM), Pahang, Kuantan, 25200, Malaysia

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 μg/mL) markedly lower than XNT (1) (IC_{50} = 203.56 μg/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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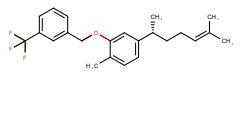
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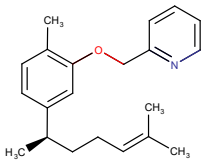
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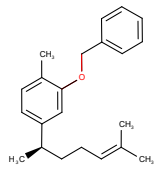
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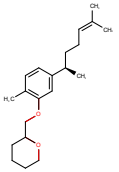
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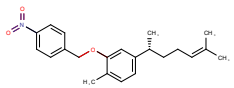
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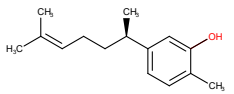
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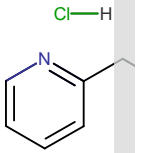
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Corresponding authors