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In silico evaluation of natural nothoapiol derivatives for antioxidant activity

Rachida Mansouri [1,*], Abdeslem Bouzina [2], Nadjet Frissou [1], and Youssouf Driouche [1]

[1] Environmental Research Center (CRE), Annaba 23000, Algeria;
[2] Laboratory of Applied Organic Chemistry, Bioorganic Chemistry Group, Chemistry Department, Sciences Faculty, Badji Mokhtar Annaba University, Box 12, Annaba 23000, Algeria.

* Corresponding author: r.mansouri@cre.dz

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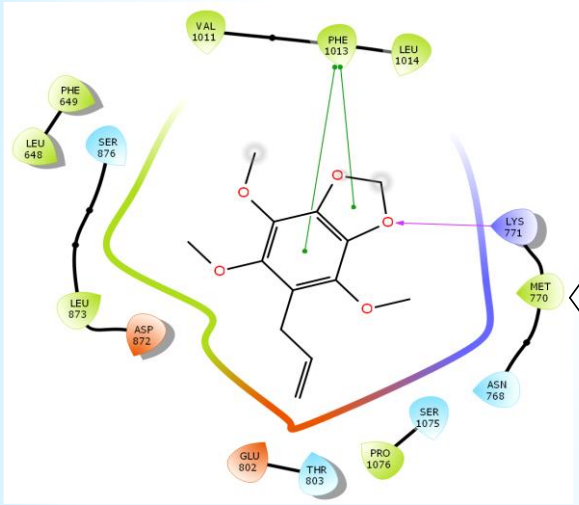
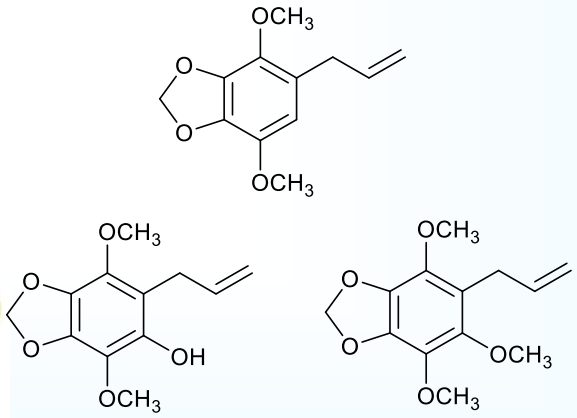
In silico evaluation of natural nothoapiol derivatives for antioxidant activity

Graphical Abstract

Molecular docking





XO target

ADMET study

pKCSM | Swiss ADME | Molsoft

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Abstract:

Medicinal plants are an important source of bioactive secondary metabolites, such as alkaloids, and phenolic compounds, which often serve as lead molecules in drug discovery. Among their many pharmacological properties, plant-derived compounds have demonstrated strong potential as inhibitors of xanthine oxidase (XO), XO a key enzyme in purine metabolism that catalyzes the oxidation of hypoxanthine to uric acid. Overproduction or impaired elimination of uric acid can lead to hyperuricemia, which is associated with various pathological conditions such as gout and cardiovascular diseases.

In this study, three nothoapiol derivatives derived from essential oils were extracted from the *Petroselinum sativum*. These compounds exhibited excellent *in vitro* antioxidant activity. To further elucidate their mechanism of inhibition and evaluate their potential as XO inhibitors, a molecular docking study was performed. Docking simulations were carried out with Glide employing the extra-precision (XP) docking protocol.
The docking results revealed that the nothoapiol derivatives exhibited strong binding affinities, with docking scores comparable to that of quercetin, a well-known standard XO inhibitor. Interaction analysis demonstrated the formation of hydrogen bonds, hydrophobic interactions, and π–π stacking with key active site residues such as Ser876, Lys771, Phe1013, and Glu802, which are critical for XO catalytic activity. In addition, ADMET analysis indicated favorable pharmacokinetic properties, particularly with respect to oral bioavailability.

Keywords: *Molecular docking; Nothoapiol; Xanthine oxidase; ADMET.*

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Introduction

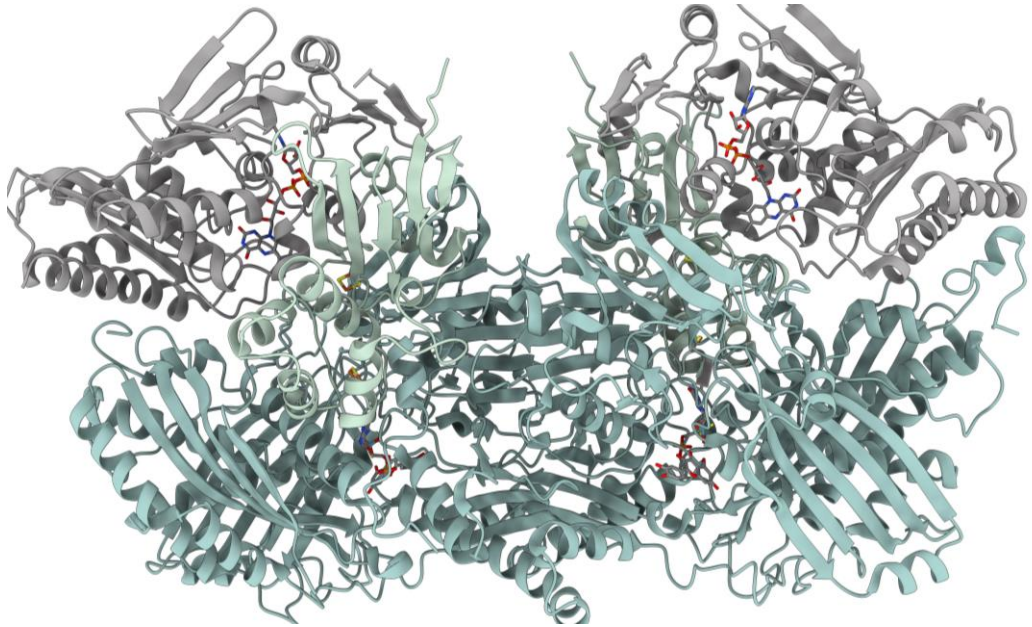
Medicinal plants have long been recognized as valuable sources of natural compounds with significant therapeutic potential. They contain a wide variety of bioactive secondary metabolites, such as alkaloids and phenolic compounds, many of which serve as lead molecules in modern drug discovery. Owing to their structural diversity and broad spectrum of biological activities, these natural products represent an essential resource for developing novel drugs with enhanced efficacy and reduced side effects.

Chaachouay, N., & Zidane, L. (**2024**). Plant-derived natural products: a source for drug discovery and development. *Drugs and Drug Candidates*, 3(1), 184-207.

Introduction

In particular, numerous plant-derived compounds have demonstrated promising inhibitory effects against key enzymes, including xanthine oxidase (XO). XO is a key enzyme in purine metabolism, responsible for catalyzing the sequential oxidation of hypoxanthine to xanthine and subsequently xanthine to uric acid. This enzyme belongs to the molybdenum-containing oxidoreductase family and plays a vital role in maintaining the balance of purine degradation in biological systems. However, excessive XO activity can lead to overproduction of uric acid, resulting in conditions such as hyperuricemia and gout, as well as contributing to oxidative stress through the generation of reactive oxygen species (ROS) during catalysis. Because of these implications, XO has become an important therapeutic target for the treatment of gout and related oxidative stress–mediated disorders.

Xanthine oxidase enzyme



Bortolotti, M., Polito, L., Battelli, M. G., & Bolognesi, A. (**2021**). Xanthine oxidoreductase: One enzyme for multiple physiological tasks. *Redox Biol*, 41, 101882.

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Introduction

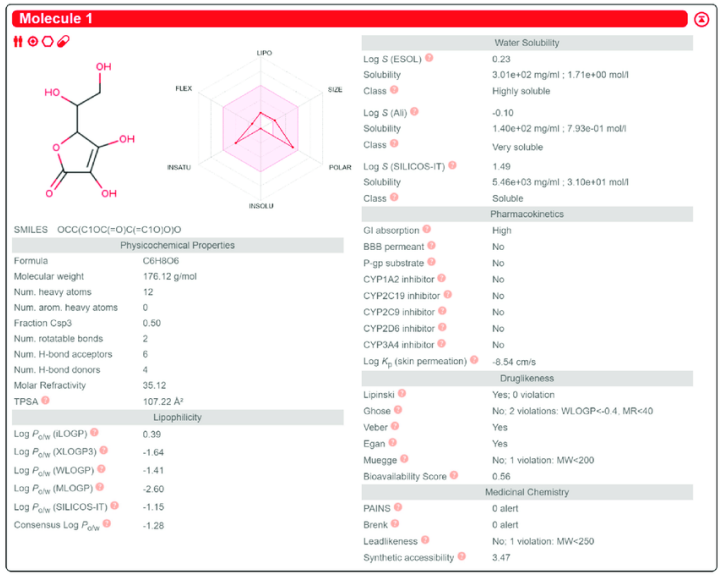
In the search for novel xanthine oxidase (XO) inhibitors derived from medicinal plants, we focused on small-molecule derivatives of nothoapiol, a compound extracted from the essential oils of the medicinal plant *Petroselinum sativum* as reported by V. Samet et *al*.

In silico methods

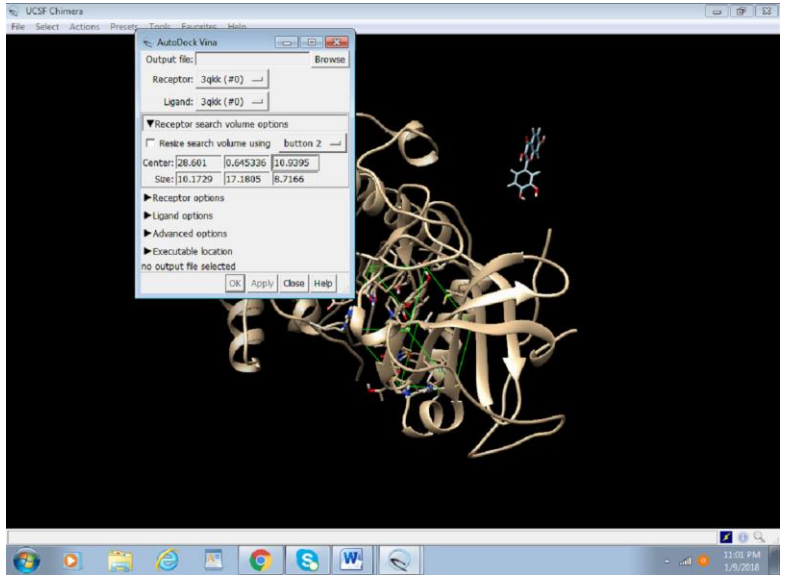
Samet, A. V., Shevchenko, O. G., Rusak, V. V., Semenov, V. V. (**2019**). *J. Nat. Prod*, 82(6), 1451-1458.

The use of computer-aided drug design based on the structure comprising molecular docking simulation and pharmacokinetics and toxicity predictive tools showed a rising interest in conceiving new drug candidates.

ADMET prediction



Molecular docking



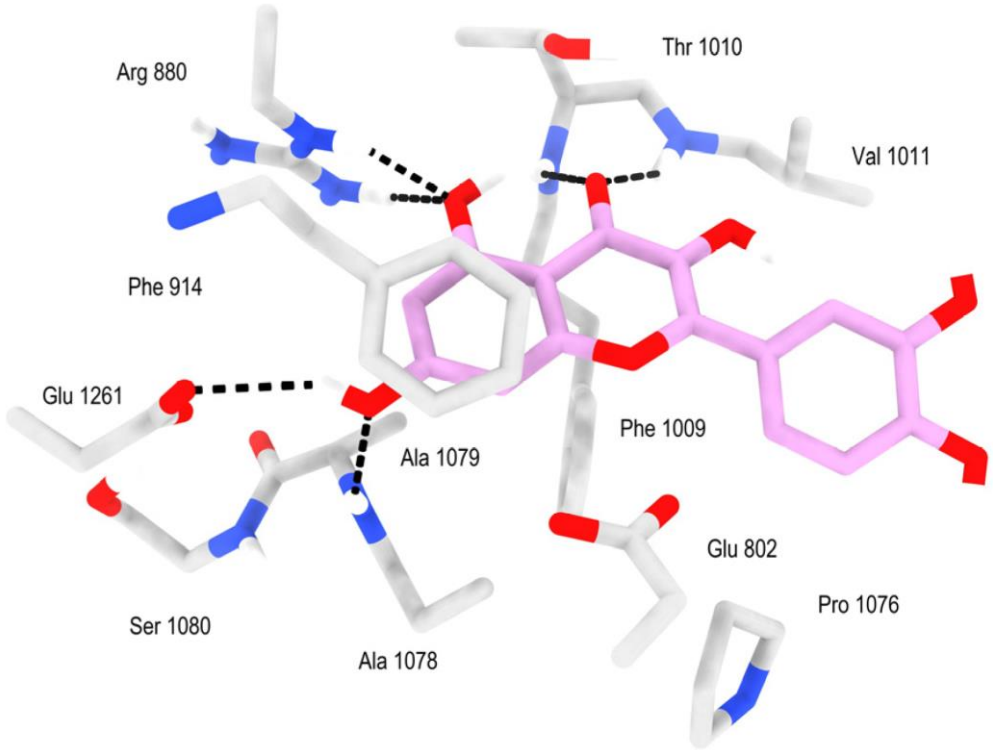
Results and discussion

Molecular docking

The molecular docking protocol was validated by re-docking quercetin into the active site of the enzyme **XO**, where the docked quercetin nearly overlapped with the crystallized form (**RMSD = 0.24 Å**).

Docking simulations were performed with Glide (extra-precision, XP) in the **Schrödinger Suite 2023-1**, and the docked complexes were analyzed using **ChimeraX** and **Maestro 12.9**.

PDB: 3NVY



3D binding interaction of quercetin in the active site of XO.

Cao, H., Pauff, J. M., & Hille, R. (**2014**). X-ray crystal structure of a xanthine oxidase complex with the flavonoid inhibitor quercetin. *J. Nat. Prod*, 77(7), 1693-1699.

Results and discussion

Molecular docking

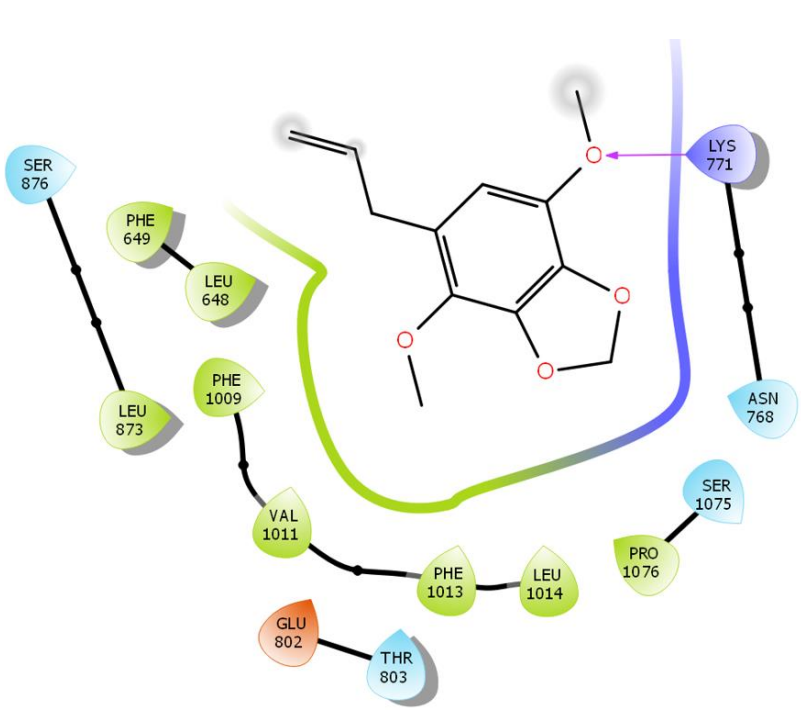
Nothoapiol and its derivatives were docked into the active site of xanthine oxidase (XO), demonstrating acceptable stability within the binding cavity, as indicated by glide scores comparable to that of the reference ligand. Among the tested compounds, hydroxyapiol exhibited the best docking score (**-6.12** kcal/mol), suggesting that this derivative maintained a stable conformation within the XO active pocket. However, all three derivatives showed lower docking scores than quercetin (**-8.20** kcal/mol), indicating that while they possess moderate binding affinities, their interaction strength remains below that of the reference antioxidant compound.

Docking score of studied nothoapiol derivatives

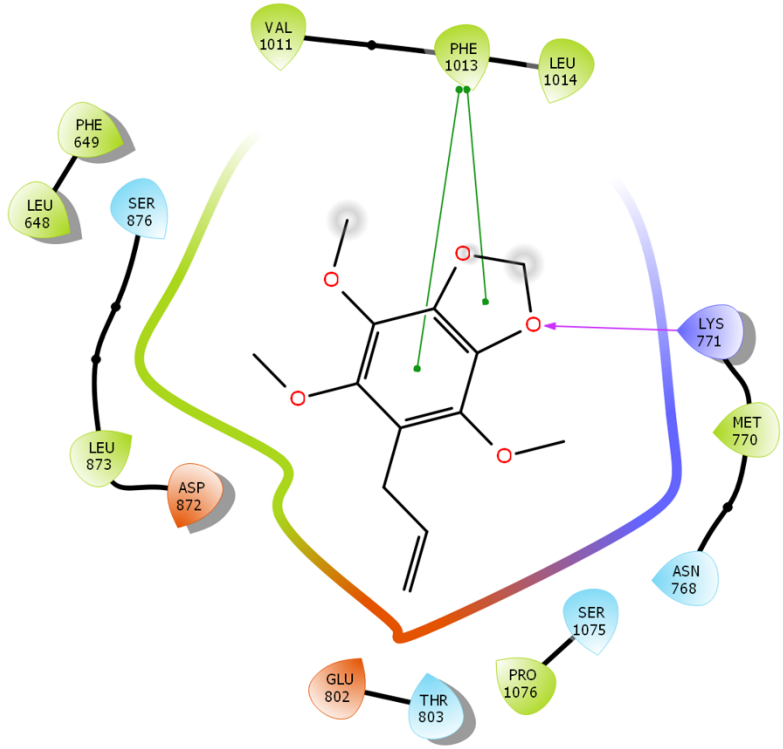
Ligands	Docking score (kcal/mol)
Apiol	-5,68
Hydroxyapiol	-6,12
Nothoapiol	-6,02
quercetin	-8,20

Results and discussion

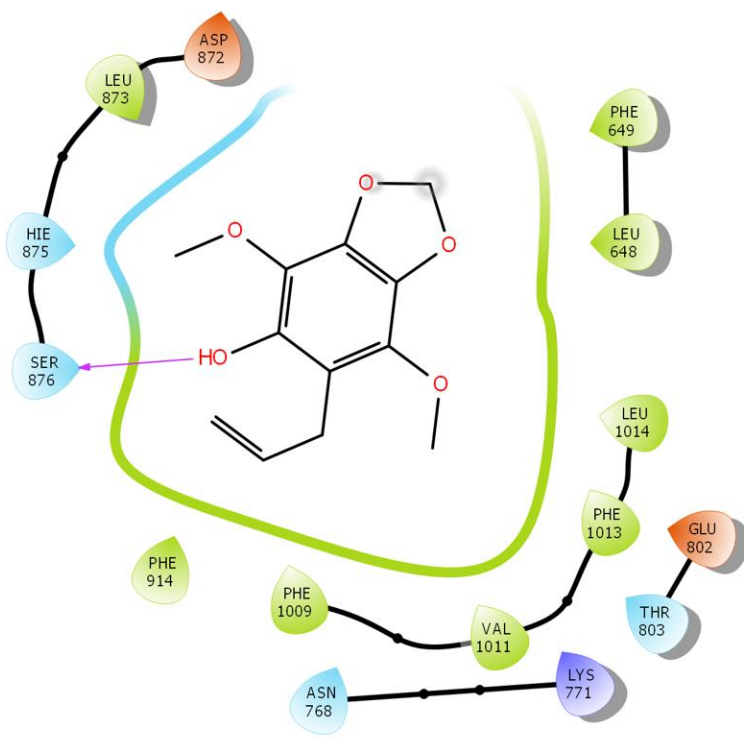
Molecular docking



Apiol-XO



Nothoapiol-XO



Hydroxyapiol-XO

*2D binding disposition of **Apiol**, **Nothoapiol** and **Hydroxyapiol** in the active site of XO.*

Results and discussion

Molecular docking

Binding mode analysis

Analysis of the molecular docking results revealed that the interactions within the active site of XO were primarily governed by hydrogen bonding, hydrophobic contacts, and electrostatic attraction forces. The apiol and nothoapiol ligands formed hydrogen bond with the Lys771 residue, thereby enhancing their stability within the active pocket through additional interactions with residues Phe649, Leu648, Phe1009, Phe1013, Leu104, and Pro1076. Nothoapiol further stabilized its binding by engaging both its aromatic and non-aromatic rings in π–π stacking interactions with the aromatic ring of Phe1013 residue. The hydroxyapiol derivative, which exhibited the best inhibitory potential, formed a hydrogen bond with Ser876 via its hydroxyl group and established additional hydrophobic interactions with key residues in the active site, contributing to its overall strong binding affinity and stability within the XO enzyme cavity.

Results and discussion

ADMET study

Pharmacokinetic properties were predicted using *in silico* tool **SwissADME** (https://www.swissadme.ch/)

Lipinski's Rule of Five
MW ≤ 500 g/mol
Log P ≤ 5
nHD ≤ 5
nHA ≤ 10
TPSA ≤ 140

Proprety	Apiol	Hydroxyapiol	Nothoapiol
MW (g/mol)	222.24	238.24	252.26
nHA	4	5	5
nHD	0	1	0
n_{rot}	4	4	5
TPSA (Å²)	36.92	57.15	46.15
Log $P_{o/w}$ (iLOGP)	2.85	2.74	3.17
n_{viol}	0	0	0
Bioavailability Score	0.55	0.55	0.55

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Results and discussion

In silico **ADMET** properties were predicted using the **pkCSM** online tool : https://biosig.lab.uq.edu.au/pkcsm

In silico ADMET prediction studies of compounds validated their oral bioavailability.

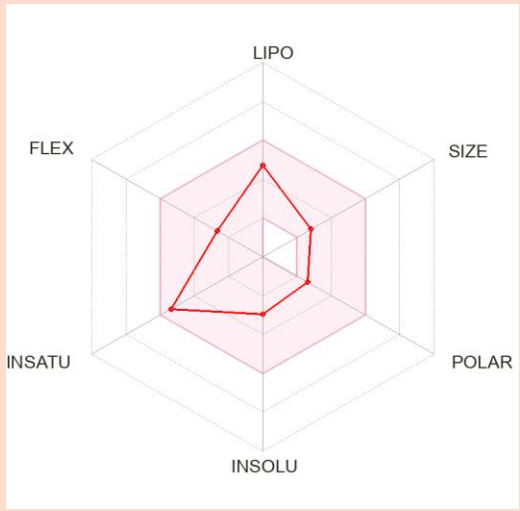
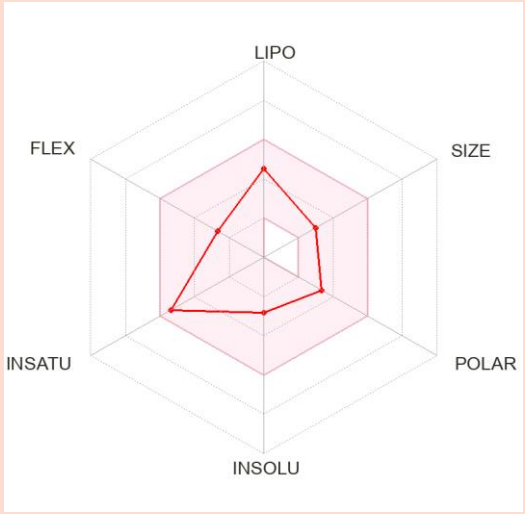
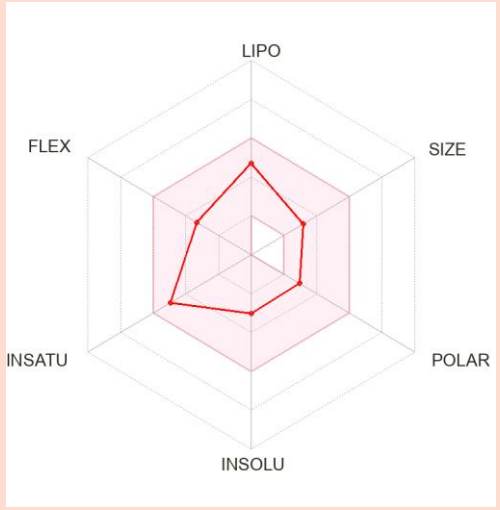
ADMET study

	Apiol	Hydroxyapiol	Nothoapiol
Absorption			
HIA (%)	98.965	96.004	98.558
Distribution			
BBB	Yes	Yes	Yes
Metabolisme			
Inhibitor of CYP1A2	Yes	Yes	Yes
Inhibitor of CYP2C19	No	No	No
Inhibitor of CYP2C9	No	No	No
Inhibitor of CYP2D6	No	No	No
Inhibitor of CYP3A4	No	No	No
Excretion			
Total clearance	0.269	0?233	0.307
Toxicity			
AMES toxicity	No	No	Yes

Results and discussion

ADMET study

All compounds are in the optimal range of flexibility, lipophilicity, solubility, polarity, and size.

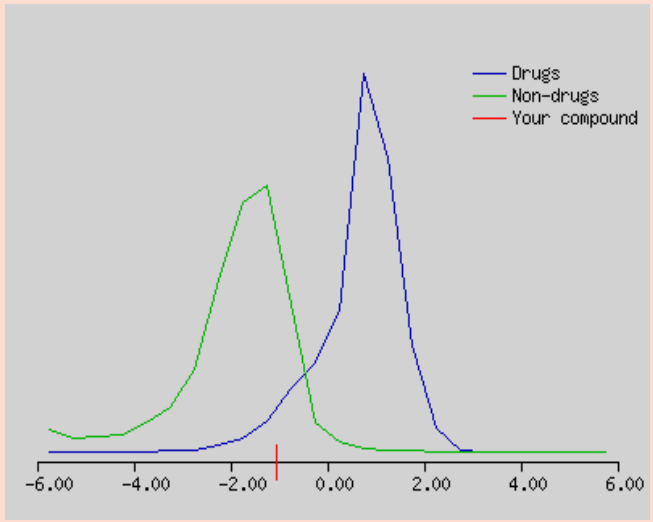
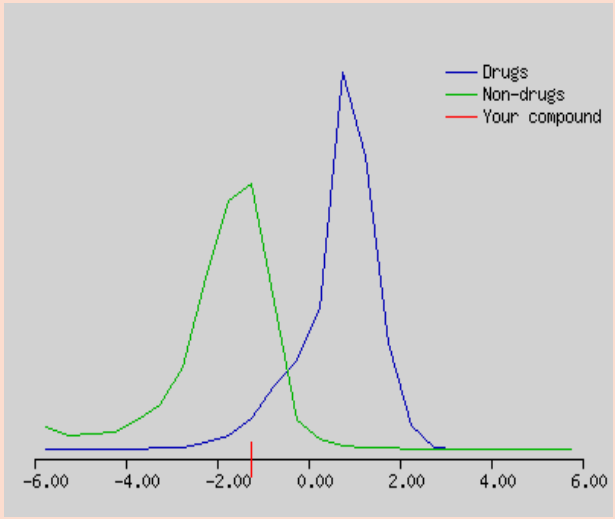
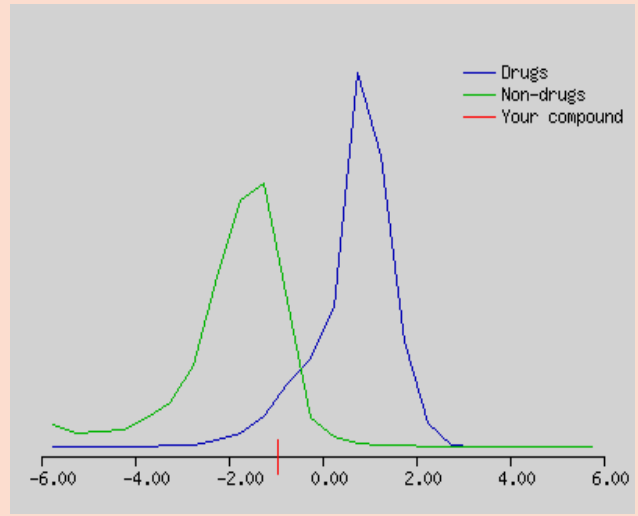
Compound	Apiol	Hydroxyapiol	Nothoapiol
Bioavailability radar			

The pink region represents the optimal physicochemical space for orally administered drugs.

Results and discussion

ADMET study

The Drug Likeness Score (DLS) results were determined using the Molsoft web tool *via* the link: https://www.molsoft.com.

Compound	Hydroxyapiol	Nothoapiol	Apiol
Drug likeness			
DLS	**-1.05**	**-1.25**	**-0.97**

Conclusions

Overall, the results of this molecular docking study demonstrate that several nothoapiol derivatives exhibit good binding affinities, with docking scores comparable to the standard drug quercetin. The three potential compounds formed hydrogen bonds, hydrophobic interactions, and π–π stacking with key residues such as Ser876, Lys771, Phe1013and Glu802, which are critical for XO activity. these findings suggest that the structural features of nothoapiol derivatives, particularly the presence of hydroxyl and methoxy groups, play a crucial role in enhancing binding stability and specificity. In addition, ADMET analysis indicated favorable pharmacokinetic properties, particularly with respect to oral bioavailability. Taken together, these results provide a strong foundation for considering nothoapiol derivatives as lead compounds for further optimization and drug development against XO-related disorders.

Acknowledgments

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