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MOLECULAR DOCKING AND *IN SILICO* SCREENING OF 2-((4-AMINO-5-(THIOPHEN-2-YLMETHYL)-4H-1,2,4-TRIAZOL-3-YL)THIO)ETHANOIC ACID AS AN ANTIOXIDANT AGENT

Keywords: 1,2,4-triazole, properties, docking, ADMET profile

ABSTRACT

The targeted search for highly effective and safe antioxidants to counteract the damaging effects of oxidative stress remains a priority in modern medicinal chemistry. 1,2,4-Triazole derivatives incorporating a thiophene moiety represent promising bioactive scaffolds whose conformational flexibility and complementarity with biological targets may be effectively evaluated using computer modeling techniques.

The aim of this research was to provide a theoretical substantiation of the antioxidant potential of 2-((4-amino-5-(thiophen-2-ylmethyl)-4*H*-1,2,4-triazol-3-yl)thio)ethanoic acid via molecular docking studies with key enzymes and receptors of the redox system, alongside an integrated *in silico* evaluation of its pharmacokinetic profile.

Methods and Results. Molecular docking was performed using the DockingPie plugin within the PyMOL software package against the active sites of six redox-associated targets: peroxiredoxin (PDB ID: 3MNG), nitric oxide synthase (PDB ID: 6NGJ), NAD(P)H oxidase (PDB ID: 2CDU), tyrosinase (PDB ID: 3NM8), NMDA receptor (PDB ID: 4KFQ), and heme oxygenase (PDB ID: 1N3U). The docking protocol was validated via redocking of the native ligands. Physicochemical parameters and the ADMET profile were predicted using the SwissADME platform.

Based on the virtual screening results, binding free energy (ΔG) values were determined. The investigated compound displayed high affinity for most of the enzymes. The most prominent result was achieved obtained for tyrosinase (ΔG = -7.199 kcal/mol), where the ligand outperformed the native inhibitor (kojic acid). Complex stabilization is driven by a network of hydrogen bonds with the residues His60, His42, Asn205, and Gly216, as well as specific pi-Sulfur and pi-cation interactions with Phe197 and Arg209. SwissADME screening confirmed full compliance with Lipinski's Rule of Five, with zero violations. The consensus Log *P* value is 1.14. The compound exhibits high intestinal absorption, potential blood-brain barrier (BBB) permeability, and an acceptable toxicity profile (Toxicity Class III, LD_{50} = 2.13 mol/kg) with no predicted mutagenic or carcinogenic risks.

The findings of this integrated *in silico* study highlight the potential of 2-((4-amino-5-(thiophen-2-ylmethyl)-4*H*-1,2,4-triazol-3-yl)thio)ethanoic acid as a potential antioxidant agent and justify its further *in vitro* and *in vivo* evaluation as a promising lead scaffold for the development of novel metabolitotropic drugs.

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МОЛЕКУЛЯРНИЙ ДОКІНГ ТА *IN SILICO* СКРИНІНГ 2-((4-АМІНО-5-(ТІОФЕН-2-ІЛМЕТИЛ)-4*H*-1,2,4-ТРИАЗОЛ-3-ІЛ)ТІО)ЕТАНОВОЇ КИСЛОТИ ЯК АНТИОКСИДАНТНОГО АГЕНТА

Ключові слова: 1,2,4-триазол, властивості, докінг, ADMET-профіль.

АНОТАЦІЯ

Спрямований пошук високоефективних та безпечних антиоксидантів є одним із пріоритетних завдань сучасної фармацевтичної хімії для нівелювання наслідків окиснювального стресу. Похідні 1,2,4-триазолу, що містять тіофеновий фрагмент, є перспективними біоактивними скаффолдами, конформаційну рухливість та комплементарність яких можна ефективно оцінити за допомогою методів комп'ютерного моделювання.

Метою даної роботи було теоретичне обґрунтування антиоксидантного потенціалу 2-((4-аміно-5-(тіофен-2-ілметил)-4*H*-1,2,4-триазол-3-іл)тіо)етанової кислоти шляхом проведення молекулярного докінгу з ключовими біомішенями редокс-системи, а також інтегрована оцінка її фармакокінетичного профілю *in silico*.

Молекулярний докінг проведено з використанням плагіна DockingPie у програмному комплексі PyMOL щодо активних центрів шести редокс-асоційованих біомішеней: пероксиредоксину (PDB ID: 3MNG), нітрооксид синтази (PDB ID: 6NGJ), НАД(Ф)Н-оксидази (PDB ID: 2CDU), тирозинази (PDB ID: 3NM8), NMDA-рецептора (PDB ID: 4KFQ) та гемоксигенази (PDB ID: 1N3U). Процедуру валідовано шляхом редокінгу нативних лігандів. Прогнозування фізико-хімічних параметрів та ADMET-профілю здійснювали за допомогою платформи SwissADME.

За результатами віртуального скринінгу встановлено параметри вільної енергії зв'язування (ΔG). Досліджувана сполука виявила високу термодинамічну афінність до більшості ферментів. Найкращий результат зафіксовано щодо тирозинази (ΔG = -7,199 ккал/моль), де ліганд перевершив нативний інгібітор (коєву кислоту). Стабілізація комплексу забезпечується мережею водневих зав'язків із залишками His60, His42, Asn205, Gly216 та специфічними pi-Sulfur і pi-катіонними контактами з Phe197 та Arg209. Скринінг SwissADME підтвердив відповідність сполуки правилу Ліпінського без порушень. Консенсусний Log *P* становить 1,14. Сполука характеризується високою кишковою абсорбцією, потенційною здатністю проникати крізь гематоенцефалічний бар'єр та прийнятним профілем токсичності (III клас, LD_{50} = 2,13 моль/кг), не виявляючи мутагенних або канцерогенних властивостей.

Результати інтегрованого *in silico* дослідження свідчать про високу перспективність 2-((4-аміно-5-(тіофен-2-ілметил)-4*H*-1,2,4-триазол-3-іл)тіо)етанової кислоти як антиоксидантного агента та обґрунтовують доцільність її подальшого вивчення *in vitro* та *in vivo* як базової структури для створення нових метаболітотропних лікарських засобів.

Introduction

Oxidative stress, caused by an imbalance between the production of reactive oxygen species (ROS) and the efficiency of the endogenous antioxidant defense system, is a factor link in the pathogenesis of a number of socially significant diseases, including cardiovascular pathologies, neurodegenerative disorders, diabetes mellitus, and chronic inflammatory processes [1]. In this regard, the targeted search and design of novel highly effective antioxidant agents with low toxicity remains one of the priority tasks of modern medicinal and pharmaceutical chemistry [2, 3].

In recent years, computer modeling methodology (particularly molecular docking) has transformed from an auxiliary tool into an essential stage of rational drug design. This allows for the evaluation of the affinity and nature of intermolecular interactions between potential ligands and the active sites of target enzymes responsible for radical generation or regulation of the cellular redox status at the molecular level [4].

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In the context of novel bioactive molecules design, heterocyclic systems that combine a 1,2,4-triazole core [5–8] and a thiophene moiety in their structure attract particular attention. Due to the presence of several hydrogen bond donors and acceptors, the triazole heterocycle ensures high complementarity to druggable sites and optimizes the pharmacokinetic profile [9–11]. In turn, the introduction of a lipophilic thiophene substituent promotes better permeability through biomembranes, while the presence of a thioethane bridge provides the necessary conformational mobility for the optimal geometric positioning of the ligand within the lipophilic pockets of enzymes.

It is well known that during the experimental pharmacological evaluation of organic salts, the biological effect is formed by the joint contribution of both the cation and the anion of the compound [12, 13]. However, primary molecular recognition and binding to protein receptors are determined specifically by the structure of the active organic molecule (the anionic or cationic part, depending on the type of salt). With this in mind, free 2-((4-amino-5-(thiophen-2-ylmethyl)-4*H*-1,2,4-triazol-3-yl)thio)ethanoic acid (ASP acid) was selected as the active agent (lead structure) for the molecular docking studies. Predicting its interaction with the specified enzymes will allow for establishing the molecular mechanism of its potential antioxidant and radical-scavenging action, as well as justifying the feasibility of further *in vitro* and *in vivo* testing of salts based on it, namely sodium 2-((4-amino-5-(thiophen-2-ylmethyl)-4*H*-1,2,4-triazol-3-yl)thio)acetate (ASP). This work is part of a comprehensive study on the pharmacological activity and safety profile of ASP [14].

The **aim** of this paper was to provide a theoretical substantiation of the antioxidant potential of 2-((4-amino-5-(thiophen-2-ylmethyl)-4*H*-1,2,4-triazol-3-yl)thio)ethanoic acid via molecular docking studies with key enzymes and receptors of the redox system, alongside an integrated *in silico* evaluation of its pharmacokinetic profile.

Material and methods

Molecular Docking Studies

Virtual screening and molecular docking of 2-((4-amino-5-(thiophen-2-ylmethyl)-4*H*-1,2,4-triazol-3-yl)thio)ethanoic acid were performed to elucidate the molecular mechanisms of its potential antioxidant activity through the targeted inhibition of key enzymatic macromolecules of the cellular redox system.

Macromolecule (Protein) Preparation:

The three-dimensional structures of the target receptors and enzymes were retrieved from the international Protein Data Bank (PDB):

- peroxiredoxin (PDB ID: 3MNG),
- nitric oxide synthase (PDB ID: 6NGJ),
- NAD(P)H oxidase (PDB ID: 2CDU),
- tyrosinase (PDB ID: 3NM8),
- NMDA receptor (GluN1 subunit, PDB ID: 4KFQ),
- heme oxygenase (PDB ID: 1N3U).

The preparation of the protein crystal structures was carried out within the PyMOL software environment. Crystallographic water molecules, cofactors (unless directly involved in the active site architecture), and heteroatoms/co-crystallized ligands were removed

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from the structures. Polar hydrogen atoms were added, partial charges were assigned, and the geometry of amino acid residues was optimized using integrated macromolecule preparation tools.

Ligand Preparation:

The geometry of the investigated active agent (ASP acid) and native reference ligands was optimized using standard force fields to the minimum energy state, generating the most stable conformations at physiological pH values.

Validation of the Docking Protocol (Redocking):

To verify and confirm the reliability of the selected docking parameters, a redocking procedure was executed. Co-crystallized (native) ligands were extracted from their geometric binding sites and re-docked into the active sites of the respective enzymes. The docking protocol was considered validated based on the complementarity of the spatial orientation and intermolecular interaction geometry of the redocked ligand compared to the original crystallographic data.

Grid Box Parameters and Docking Execution:

The virtual grid space (Grid Box) generation to restrict the conformational search area was performed directly based on the structural coordinates of the native ligands embedded in the protein crystal matrix, utilizing the DockingPie plugin within the PyMOL software. The center coordinates and geometric dimensions (Grid Box size) for each biomaterial target are presented in Table 1. The evaluation of binding energy parameters and visualization of intermolecular contacts (hydrogen bonds, hydrophobic, and electrostatic interactions) were conducted for the most thermodynamically favorable conformational clusters.

Table 1

Chemotaxonomic characteristics of druggable sites, structure of native ligands, and spatial parameters of the docking zone (Grid Box)

Receptor	Ligand	Grid Box Center Coordinates	Grid Box Size
Peroxiredoxin (PDB ID: 3MNG),	(4S,5S)-1,2- dithiane-4,5-diol	7.96 x 42.45 y 32.35 z	16 x 16 y 16 z
Nitric oxide synthase (PDB ID: 6NGJ)	6-(3-fluoro-5-(3-(methylamino)prop-1-yn-1-yl) phenethyl)-4-methylpyridin-2-amine	10.92 x 2.92 y 27.24 z	22 x 22 y 26 z
NAD(P)H oxidase (PDB ID: 2CDU)	adenosine-5'-diphosphate	19.12 x -5.23 y -0.07 z	22 x 22 y 22 z
Tyrosinase (PDB ID: 3NM8)	5-hydroxy-2-(hydroxymethyl)-4H-pyran-4-one	1.68 x 9.88 y 54.96 z	30 x 14 y 32 z
NMDA receptor (PDB ID: 4KFQ)	1-sulfanyl[1,2,4]triazolo[4,3-a]quinoxalin-4(5H)-one	27.51 x 34.68 y 46.90 z	18 x 18 y 18 z
Heme oxygenase (PDB ID: 1N3U)	protoporphyrin IX	25.92 x 17.39 y -36.81 z	22 x 18 y 20 z

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Research results and discussion

Based on the virtual screening results, the thermodynamic affinity parameters (binding free energy, ΔG) of the investigated active agent, ASP acid, with the active sites of six key target enzymes of the pro- and antioxidant systems were determined. The obtained scoring function values for the most stable conformational clusters are presented in Table 2.

It is well established that a lower (more exergonic) value of the binding free energy ΔG indicates higher thermodynamic stability of the ligand–receptor complex and a superior degree of complementarity of the investigated molecule toward the hydrophobic pockets and amino acid residues of the enzyme's active site.

Table 2

Molecular docking results of ASP acid and native ligands with target biomarkers

Compound	Binding energy ΔG (kcal/mol)					
	6NGJ	4KFQ	1N3U	3NM8	3NMG	2CDU
ASP acid	-7.024	-6.874	-6.357	-7.199	-3.556	-6.779
(4S,5S)-1,2- dithiane-4,5-diol	-9.723	-	-	-	-	-
1-sulfanyl[1,2,4]triazolo[4,3-a]quinoxalin-4(5H)-one	-	-8.451	-	-	-	-
Protoporphyrin IX	-	-	-10.478	-	-	-
5-hydroxy-2-(hydroxymethyl)-4H-pyran-4-one	-	-	-	-6.959	-	-
(4S,5S)-1,2- dithiane-4,5-diol	-	-	-	-	-3.708	-
adenosine-5'-diphosphate	-	-	-	-	-	-10.364

To perform an integral evaluation of the physicochemical properties and oral bioavailability of the investigated ASP acid, a Bioavailability Radar diagram was generated using the SwissADME online platform (Fig. 1). This tool enabled the prediction of the molecule's compliance with optimal criteria based on six key descriptors: lipophilicity (LIPO), size (SIZE), polarity (POLAR), insolubility (INSOLU), insaturation (INSATU), and conformational flexibility (FLEX).

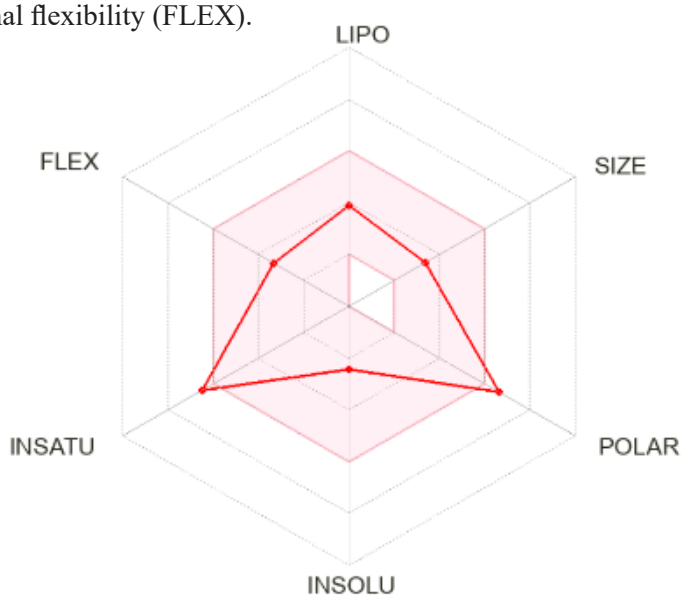


Fig. 1. **Pharmacokinetic characteristics of 2-((4-amino-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-3-yl)thio)ethanoic acid**

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Analysis of the radar chart indicates a favorable bioavailability profile for ASP acid, as it demonstrated minimal deviations from the reference zone only in terms of insaturation (INSATU) and polarity (POLAR) parameters, which is entirely acceptable for compounds of this class. The calculated consensus lipophilicity coefficient (Consensus Log *P*) for the investigated acid is 1.14, indicating an optimal balance between its hydrophilic and lipophilic properties. Furthermore, the compound fully satisfies the criteria of Lipinski's Rule of Five with zero violations, confirming its high potential for oral administration. The integral screening results of the ADMET profile for the investigated active agent are summarized in Tables 3 and 4.

Table 3

Pharmacokinetic profile of absorption, metabolism, and distribution of ASP acid

Predicted ADMET profile	Acid probability/ value	Predicted ADMET profile	Acid probability/ value	Predicted ADMET profile	Acid probability/ value
Human intestinal absorption	+/0,9279	OATP1B3 inhibitor	+/0,9393	CYP2C9 substrate	-/1,0000
CACO-2	-/0,6975	MATE1 Inhibitor	-/0,8600	CYP2D6 substrate	-/0,8877
Blood-brain barrier	+/0,8250	OCT2 Inhibitor	-/0,6428	CYP3A4 inhibition	-/0,8856
Oral bioavailability in humans	+/0,5857	BSEP Inhibitor	-/0,8250	CYP2C9 inhibition	-/0,8497
Subcellular localization (mitochondria)	+/0,6688	P-glycoprotein inhibitor	-/0,9591	CYP2C19 inhibition	-/0,8562
OATP2B1 Inhibitor	-/1,0000	P-glycoprotein substrate	-/0,9028	CYP2D6 inhibition	-/0,8760
OATP1B1 Inhibitor	+/0,9147	CYP3A4 substrate	-/0,5762	CYP1A2 inhibition	-/0,7435

Table 4

Pharmacokinetic profile of acid toxicity

Predicted ADMET profile	Acid probability/ value	Predicted ADMET profile	Acid probability/ value	Predicted ADMET profile	Acid probability/ value
Ames mutagenesis	-/0,6100	eye irritation	-/0,9871	binding to glucocorticoid receptors	+/0,8641
Hepatotoxicity	+/0,7250	acute oral toxicity	III/0,5151	hERG inhibition	-/0,3663
Skin sensitization	-/0,8539	estrogen receptor binding	+/0,5485	aquatic toxicity to fish	+/0,8034
Respiratory toxicity	+/0,8222	binding to the androgen receptor	-/0,7074	honey bee toxicity	-/0,8497
Reproductive toxicity	+/0,8667	binding to thyroid receptors	+/0,5658	biodegradation	-/0,7000
Mitochondrial toxicity	+/0,8125	carcinogenicity (binary)	-/0,8000	aquatic toxicity to crustaceans	-/0,6600
Nephrotoxicity	-/0,8185	aromatase binding	-/0,5401	LD_{50} моль/кг	2.13

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The spatial localization of the reference inhibitor, 5-hydroxy-2-(hydroxymethyl)-4H-pyran-4-one (kojic acid), within the catalytic cavity of tyrosinase is driven by its specific interaction with key amino acid residues at the entrance of the enzyme's active site: Phe197, Pro201, Asn205, and Arg209. Notably, computer modeling of the complex of the investigated acid with this biomarket reveals that the same topographic determinants of the active site participate in the molecular recognition process. The detailed architecture of the intermolecular contacts of ASP acid within the docked site of tyrosinase (PDB\ ID:\ 3NM8) is presented in Figure 2, Figure 3. The stabilization of the most thermodynamically favorable conformation of the ligand is ensured by the formation of an extended network of hydrogen bonds. Specifically, the carboxylic group of the thioethane residue forms strong H-bonds with the imidazole rings of His60 and His42 residues with interatomic distances of 3.0 Å and 3.1 Å, respectively. The nitrogen atom (N^1) of the heterocyclic 1,2,4-triazole core acts as a hydrogen bond acceptor interacting with the Asn205 residue (3.2 Å). Furthermore, the exocyclic amino group at the fourth position of the triazole system functions as a hydrogen bond donor to the carbonyl oxygen of the peptide backbone of the Gly216 residue (2.8 Å).

A significant contribution to the total binding affinity is made by specific non-covalent contacts involving heteroatoms: His208 and Phe197 residues form coordinated pi-Sulfur interactions with the aliphatic thiomethylene linker and the sulfur atom (S) of the thiophene ring, respectively. The only electrostatic contact in this binding topology is realized as a pi-cation interaction between the positively charged guanidinium moiety of Arg209 and the polarized pi-electron system of the aromatic thiophene ring. Among hydrophobic interactions, pi-alkyl contacts (with the Pro201 residue) and pi-pi T-shaped stacking (with the Phe197 residue) were detected, which additionally anchor the thiophene pharmacophore inside the lipophilic pocket of the enzyme.

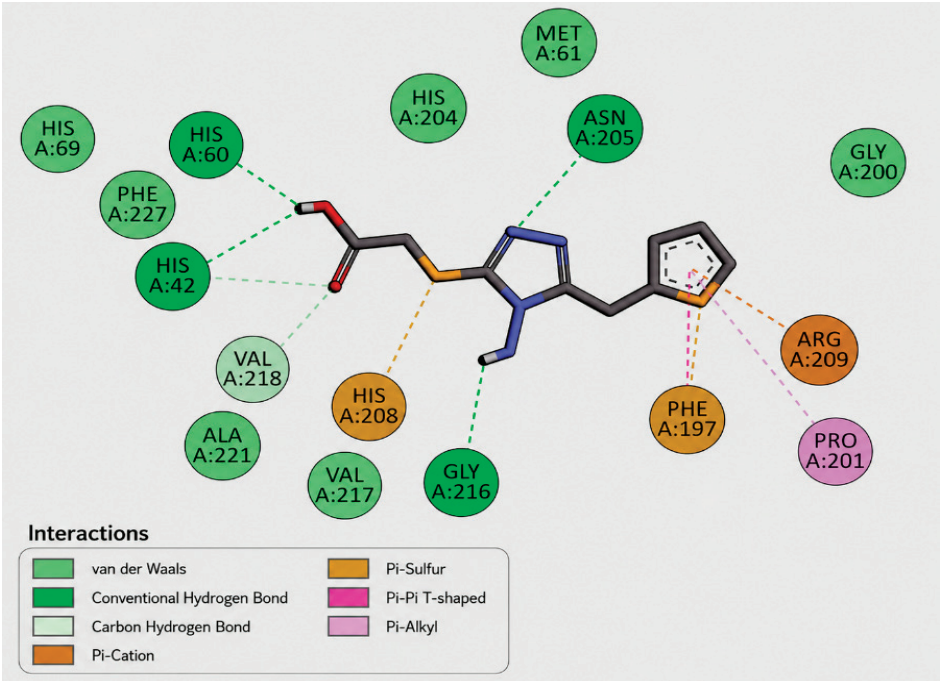


Fig. 2. **Two-dimensional (2D) topology of intermolecular acid interactions in the active site of tyrosinase (PDB\ ID:\ 3NM8) based on the results of molecular docking.**

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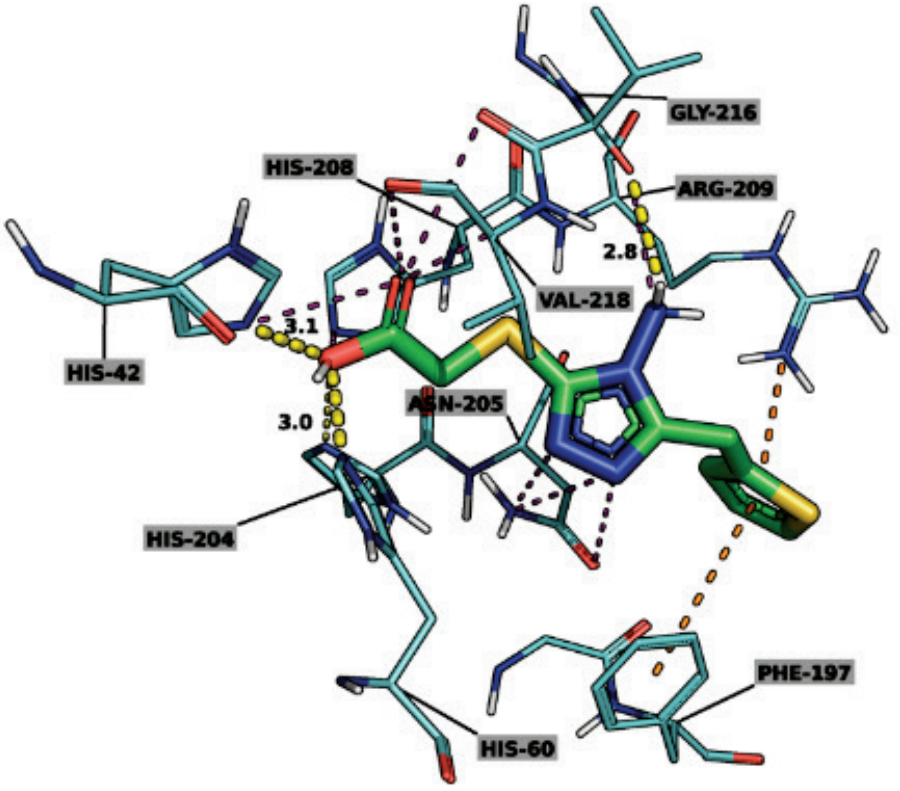


Fig. 3. **Three-dimensional (3D) topology of intermolecular acid interactions.**

According to the obtained predictive data, ASP acid is characterized by a high level of intestinal absorption and favorable oral bioavailability. The compound is capable of passive diffusion across the blood–brain barrier (BBB). Its absorption efficiency is further supported by the predicted capacity for satisfactory permeability across a Caco-2 cell monolayer. In the distribution process, the substance exhibits a potential ability to inhibit plasma transport proteins OATP1B1 and OATP1B3, which may influence its hepatic clearance. Importantly, ASP acid is not an inhibitor of key cytochrome P450 isoenzymes, specifically CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4. This indicates the absence of any risk regarding undesirable drug–drug interactions and confirms that it will not interfere with the normal biotransformation of concomitant medications metabolized by this enzyme system.

Virtual toxicity analysis revealed that ASP acid belongs to Toxicity Class III, with a calculated median lethal dose (LD_{50}) value of 2.13 mol/kg (Table 4). The investigated ligand shows no signs of carcinogenicity, nephrotoxicity, or mutagenic activity (via the Ames test). At the same types, the computer model points to a probability of hepatotoxicity, as well as reproductive and respiratory toxicity, which necessitates strict dosage control during subsequent *in vivo* trials. Evaluation of the ecotoxicological profile revealed moderate toxicity toward fish, yet low toxicity for honeybees and crustaceans. Additionally, the compound was found to be a weak inhibitor of hERG potassium channels, minimizing the risk of developing cardiotoxicity and QT interval prolongation.

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Conclusions

1. Based on the *in silico* evaluation 2-((4-amino-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-3-yl)thio)ethanoic acid may be considered a promising bioactive agent with high oral bioavailability, acceptable absorption and distribution parameters, and balanced interactions with major transporters. Its strict compliance with Lipinski's Rule of Five and optimal redox profile substantiate the feasibility of its further evaluation as a lead structure for the development of novel therapeutic agents.

2. Studied 2-((4-amino-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-3-yl)thio)ethanoic acid is a promising candidate for subsequent molecular dynamics simulations aimed at a detailed study of the ligand's conformational behavior in a dynamic system and the evaluation of the kinetic stability of the formed ligand–receptor complex.

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