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Molecular Docking and ADME pharmacokinetic prediction studies of some indole-triazole hydrazone hybrids as anticancer potential via TDO2 inhibition

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ABSTRACT

One of the crucial enzymes in the tryptophan metabolic pathway, tryptophan 2,3-dioxygenase (TDO2), is also a major target for the development of anticancer medications, as it enhances tumor immune evasion mechanisms. Computational studies (in silico) are useful tools for assessing ligand-protein interactions and forecasting binding affinity. To examine the binding pattern of previously described drugs with the TDO2 enzyme's active site, molecular docking was carried out in this work utilizing the PyRx program. Using this technique, the binding energy was predicted, and the important interactions between the ligands and the vital amino acid residues in the active site of the enzyme were examined. The docking results showed that compound 5b has the highest predicted binding affinity toward the target protein, with a binding energy of −8.8 kcal/mol. In addition, an ADME pharmacokinetic property analysis was conducted using SwissADME to predict the pharmacological properties of the studied compounds. According to the findings, most compounds exhibit appropriate physicochemical properties and comply with the Lipinski Rule of Five, indicating potential for oral bioavailability. Overall, the findings of ADME analysis and molecular docking studies suggest that the investigated compounds would be good candidates for additional experimental testing and might aid in the creation of potent TDO2 enzyme inhibitors.

Keywords: Molecular docking; TDO2; Binding affinity; ADME .

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1. Introduction

Despite medical advancements, cancer remains a major global health issue and is considered one of the most common causes of death in the world, after cardiovascular diseases. Recent epidemiological data indicate millions of newly diagnosed cases annually, with a significant increase in mortality rates expected over the coming decades [1]. This disease consists of a heterogeneous group of disorders characterized by uncontrolled cellular proliferation due to a malfunction in the natural cell cycle mechanisms. Both genetic predisposition and environmental influences significantly contribute to the initiation and progression of cancer [2]. Reprogramming of metabolism is recognized as a hallmark of cancer, and the kynurenine pathway in tryptophan metabolism has garnered significant scientific interest in this context. Approximately 95% of systemic tryptophan is metabolized through this pathway [3][4], generating kynurenine and several bioactive metabolites downstream [5]. Accumulating evidence suggests that these metabolites contribute to tumor immune tolerance by suppressing the activity of cytotoxic T lymphocytes while promoting the expansion of regulatory T cells [6][7]. These immunosuppressive conditions aid in tumor survival and progression. Additionally, kynurenine acts as a ligand that activates the aryl hydrocarbon receptor (AhR), a transcription factor involved in gene expression and in promoting tumor cell proliferation, migration, and invasiveness [8-11]. Typtophan 2,3-dioxygenase (TDO) is a tetrameric enzyme containing a heme cofactor that initiates the degradation of tryptophan by catalyzing the rate-limiting step in the kynurenine metabolic pathway. producing N-formylkynurenine [12]. Elevated expression of TDO has been documented in various malignancies and has been linked to inflammation [13][14], immune escape, and tumor progression [15][16]. By accelerating tryptophan depletion and increasing kynurenine production, TDO contributes to impaired antitumor immune responses within the tumor microenvironment. Consequently, targeting TDO has emerged as a promising strategy in anticancer drugs [17] (Figure 1).

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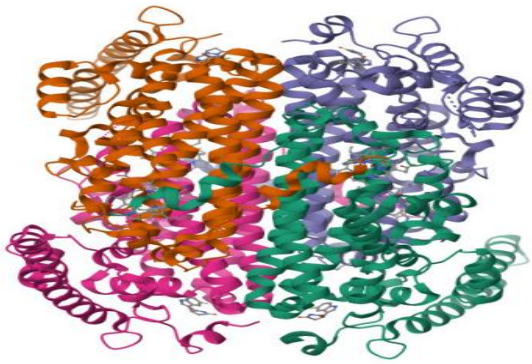

Figure 1. Crystal Structure of human Tryptophan 2,3-dioxygenase

Molecular docking represents a fundamental approach in computer-aided drug design (CADD) used to estimate the binding affinity and determine the most favorable orientation of a ligand within the active site of a biological target, such as an enzyme or receptor. This method plays a significant role in structure-based drug design (SBDD), as it facilitates the identification of promising lead compounds. In addition, docking analysis provides valuable insights into structure–activity relationships (SAR) by ligand–protein interactions and scoring function[18-20] Additionally, in-silico analysis of molecular physicochemical features, including polarity, lipophilicity, solubility, molecular dimensions, structural flexibility, and saturation, plays a significant role in evaluating potential drug candidates, offering essential information regarding the drug-likeness and developmental potential of candidate molecules during early stages of drug discovery [21][22]. Various studies have explored indole-based molecules as TDO2 inhibitors, revealing that changes in their chemical structure can strongly affect enzyme binding and biological activity [23]. These insights have guided the development of derivatives with improved potency and oral bioavailability. Furthermore, research has examined compounds capable of dual inhibition of TDO2 and indoleamine 2,3-dioxygenase 1 (IDO1), broadening the range of bioactive scaffolds for modulating immune responses [24][25]. Reviews and patent analyses underscore the ongoing interest in small molecules that selectively target TDO2 for therapeutic applications [26]. Building on these findings, the present investigation aims to perform molecular docking of eleven (11) indole-bearing triazole-3-thione hydrazone compounds (5a-5k) using molecular docking against TDO2 as the target. The objective was to identify a promising candidate that could serve as a structural template for designing new

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derivatives with enhanced binding affinity and improved interaction patterns within the receptor active site. Furthermore, the pharmacokinetic behavior of the synthesized compounds was assessed through computational evaluation of pharmacokinetic parameters, including absorption, distribution, metabolism, and excretion (ADME). parameters to further determine their potential suitability as drug candidates.

2. Experimental Methods

2.1 Computational Tools and Software

All computational studies were conducted using an HP computer equipped with an Intel® Core i5-8365U processor operating at 1.60 GHz and 8 GB of RAM. Several software packages were utilized during this study, including PyRx virtual screening software (version 0.8), Discovery Studio Visualizer (version 25.1.0.24284), Chem3D (version 23.1.1.3), PyMOL (version 3.1.6.1), and the SwissADME online platform for ADME prediction.

2.2 In-Silico Docking And ADME/Pharmacokinetics

Prediction Molecular docking studies were performed using PyRx software (version 0.8), which utilizes AutoDock Vina as the docking engine. The 3D crystal Structure of human Tryptophan 2,3-dioxygenase was retrieved from the Protein Data Bank (PDB) (6YPP) with R-Value Work of 0.191, R-Value Free of 0.237, and resolution of 2.40 A, https://doi.org/10.2210/pdb6PYY/pdb. The protein structure was prepared using PyMOL by removing water molecules and the co-crystallized ligand 3-(5-fluoro-1H-indol-3-yl)pyrrolidine-2,5-dione. The compounds were used in this study (Figure 2), and their chemical structures were drawn using Chem3D software. (version 23.1.1.3). Following energy minimization, these ligands and protein were converted to PDBQT format within PyRx. Docking was carried out using a grid box encompassing the active site of the protein with dimensions of [x = 25.0, y = 25.0, z = 25.0 Å, and exhaustiveness = 8]. Binding affinities were expressed in kcal/mol, and the most favourable docking poses were selected based on the lowest binding energy values. Protein–ligand interactions were further visualized and analysed using Discovery Studio Visualizer (version 25.1.0.24284) and PyMOL software (version 3.1.6.1) [27]. Figure 1 shows the 3D of TDO2. Furthermore, the Simplified Molecular Input Line Entry System (SMILES) format of the molecules was pasted on the

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swissADME webserver (Swiss Institute of Bioinformatics, Switzerland) to generate their ADME/pharmacokinetic profile and drug-likeness parameters.

3. Results and Discussions

3.1. Molecular Docking and Virtual Screening

The molecular docking results revealed that all compounds (5a–5k) exhibited notable binding affinities toward the target protein (Table 2), with docking scores ranging from -7.9 to -8.8 kcal/mol, in comparison with the co-crystallized ligand 3-(5-fluoro-1H-indol-3-yl)pyrrolidine-2,5-dione which showed a binding affinity of -8.4 kcal/mol, forming stable hydrogen bonds with key active-site residues such as Glu80, Ala150, Ser151, and HEM401. Among the designed compounds, 5b demonstrated the highest binding affinity (-8.8 kcal/mol), indicating stronger predicted interactions than the reference ligand 3-(5-fluoro-1H-indol-3-yl)pyrrolidine-2,5-dione. This compound formed multiple hydrogen bonds with crucial residues (Glu80, Ala150, Ser151) at short distances (2.1–2.9 Å), suggesting a stable and compact ligand–protein complex. Similarly, 5a, 5f, and 5i also exhibited superior docking scores (-8.6 kcal/mol each), maintaining strong interactions with the same residues within the active pocket. On the other hand, 5c, 5g, and 5k displayed comparatively lower binding affinities (-7.9 kcal/mol) and longer hydrogen-bond distances, reflecting weaker stabilization within the binding site. 5j showed a score (-8.3 kcal/mol) close to that of the reference ligand, confirming its good binding potential. Overall, these findings indicate that several of the newly synthesized derivatives, particularly 5b, could exhibit stronger binding efficiency than the native ligand. Their favourable binding energies and interaction patterns highlight them as promising candidates for further biological and pharmacological evaluation.

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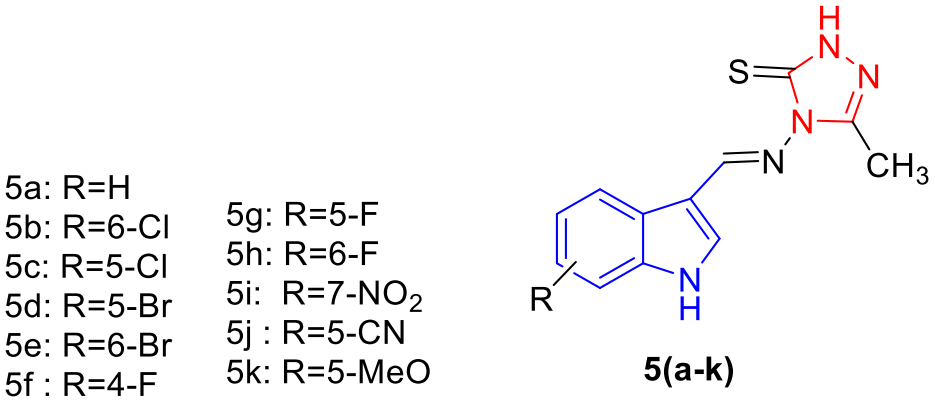

Figure 2. General structure of compounds (5a–5k), where the substituents (R) are defined in (Table 1)

Table 1. Definition of variable substituents (R) in compounds 5a-5k

compound	R(substituent)	Description
5a	H	Hydrogen
5b	Cl	Chloro at position 6
5c	Cl	Chloro at position 5
5d	Br	Bromo at position 5
5e	Br	Bromo at position 6
5f	F	Floro at position 4
5g	F	Floro at position 5
5h	F	Floro at position 6
5i	NO_2	Nitro group at position 7

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5j	CN	Cyano group at position 5
5k	MeO	Methoxy group at position 5

Table 2. Molecular docking results of compounds 5a-5k

Compound	Binding affinity kcal/mol	Interaction (Distance A°)		
		H-bonds	Pi-Pi	PI-Alkyl
5a	-8.6	NH(indole)-Ala150 (2.9A°)	Indole-HEM401 (5.8A°) Indole-Phe72 (6.2 A°)	Indole-Leu147 (6.2A°)
5b	-8.8	NH(triazole)-Glu80 (2.1A °) NH(indole)-Ala150 (2.9 A°)	Indole-HEM40 (5.9A°) Indole-Phe72 (6.2 A°) triazole-His76 (4.6 A°)	Indole-Leu147 (3.6A°)
5c	-7.9	———	Indole-HEM401 (6.5A°) Indole -Phe72 (4.8 A°) Indole-His76 (4.9 A°)	Indole_Leu147 (4.9A°) Triazole-Ile73 (4.4A°)
5d	-8.1	NH(indole)-Glu80(2A°) NH(triazole)_Ala150 (2.9A°)	Indole -HEM 401 (3.5A°)	Indole -Ile73 (4.2A°)
5e	-8.2	NH(indole)-Glu80 (2.2 A°) NH(triazole)-Ala150 (2.9 A°)	———	Indole-Ile73 (4.20A°)
5f	-8.6	NH(triazole) -Glu80 (2.2 A°) NH(indole)-Ala150 (3A°) Florine-His67(2.4 A°)	Indole -Phe72 (4.8 A°)	Indole-Leu147 (3.6A°) Florine-HEM401 (3.9 A°)
5g	-7.9	NH(indole) -Glu80 (2 A°) thione-Gly152 (2.7 A°)	———	Triazole-Ala150 (4.4A°) Indole-Leu147 (4.4A°)
5h	-8	NH(indole) -Glu80 (2.2A°) NH(triazole)-Ala150 (2.9 A°)	Indole-HEM 401 (3.6A°) Indole -Phe72 (4.7 A°)	Indole-Leu147 (5.6A°)
		NH(triazole) -Glu80 (2A°) NH(indole)-Ala150 (2.9 A°)	Indole-HEM401 (3.7A°) Indole-His76 (4.2 A°)	Indole-Leu147 (3.9A°)

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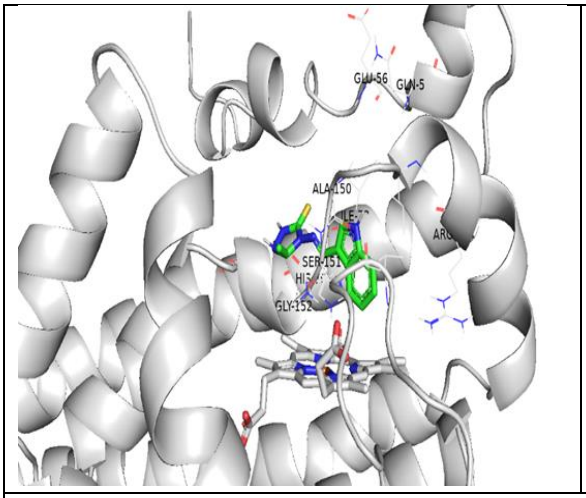
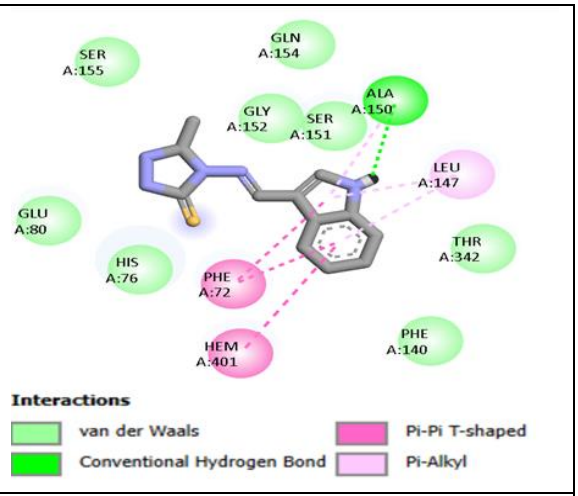
5i	-8.6	Nitro-The342 (2 A°)	Indole -Phe72 (4.6A°)	
5j	-8.3	NH(indole) -Glu80 (2.1A°) NH(triazole)-Ala150 (2.9 A°)	_____	Indole-Leu147 (5.7A°)
5k	-7.9	NH(indole) -Glu80 (2A°) NH(triazole)-Ala150 (2.9 A°)	_____	Indole-Leu147 (5.7A°) Indole-Ile73 (4.5 A°)
3-(5-fluoro-1H-indol-3-yl)pyrrolidine-2,5-dione	-8.4	Florine-Thr342 (3.2 A°)	Indole-HEM401 (4.8A°) Indole-Phe72 (4.6A°)	_____

Table 3. Docking Poses 2D and 3D





Compound 5a

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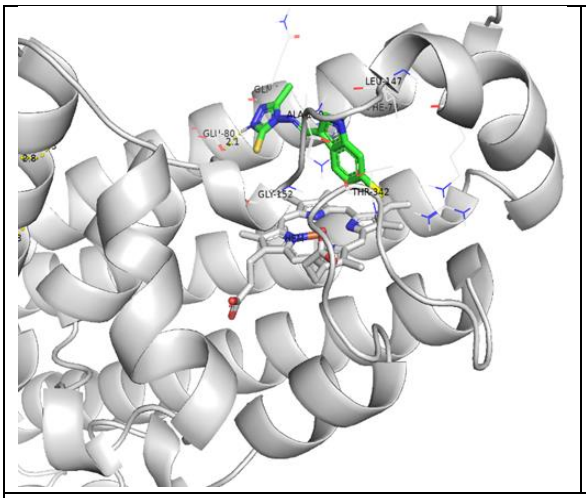
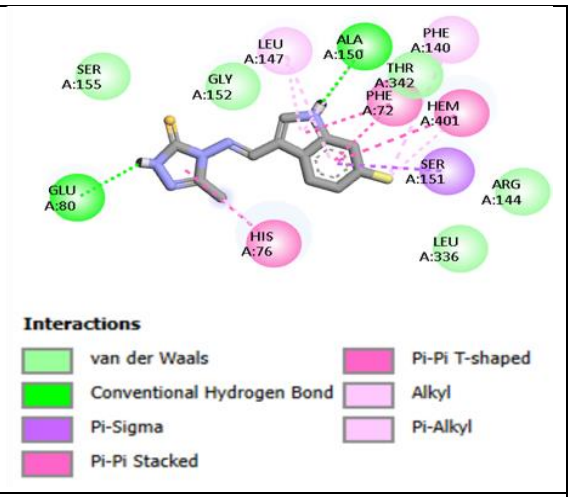
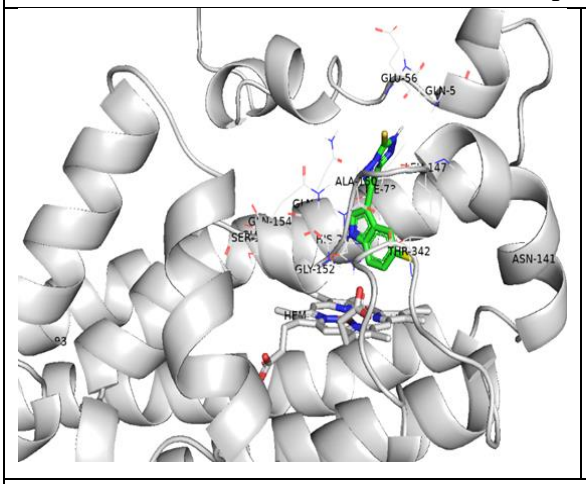
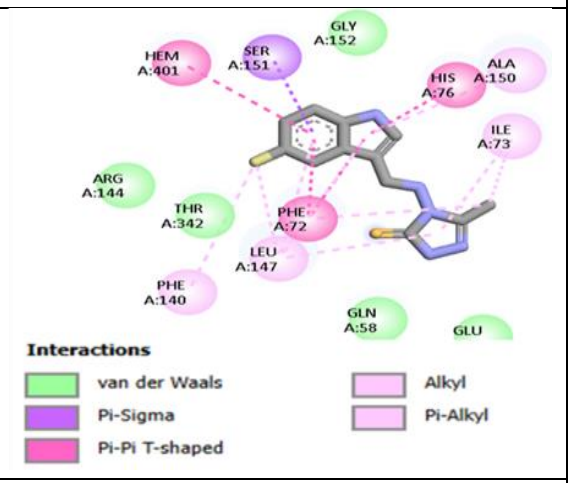


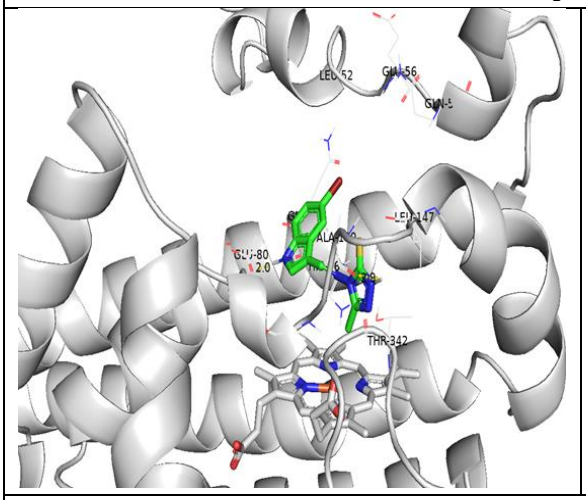


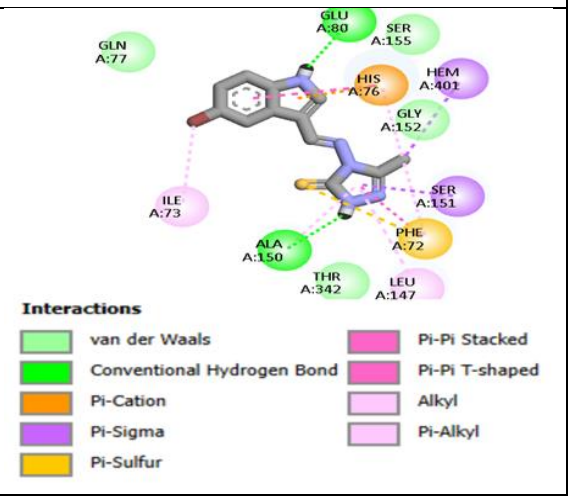
Compound 5b





Compound 5c





Compound 5d

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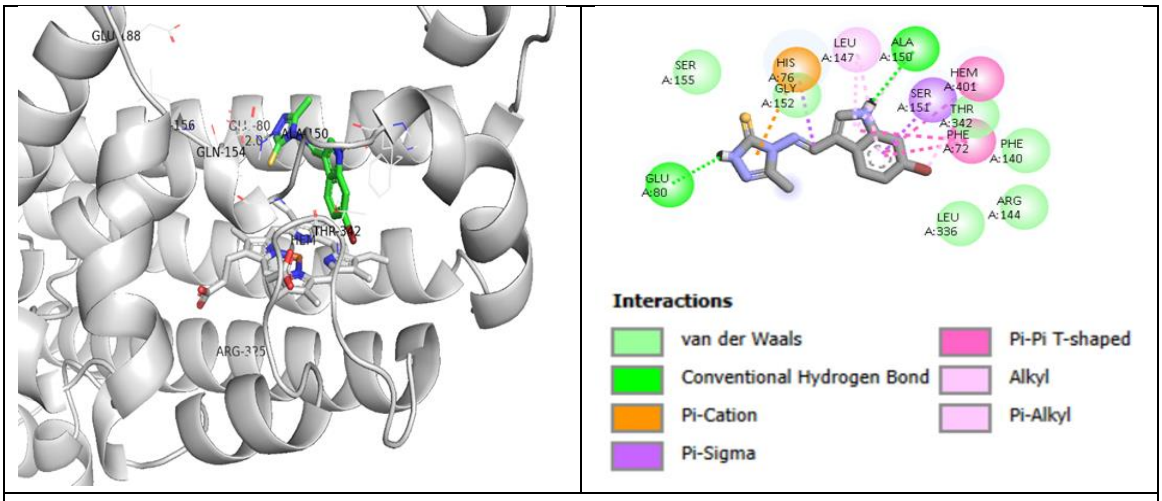
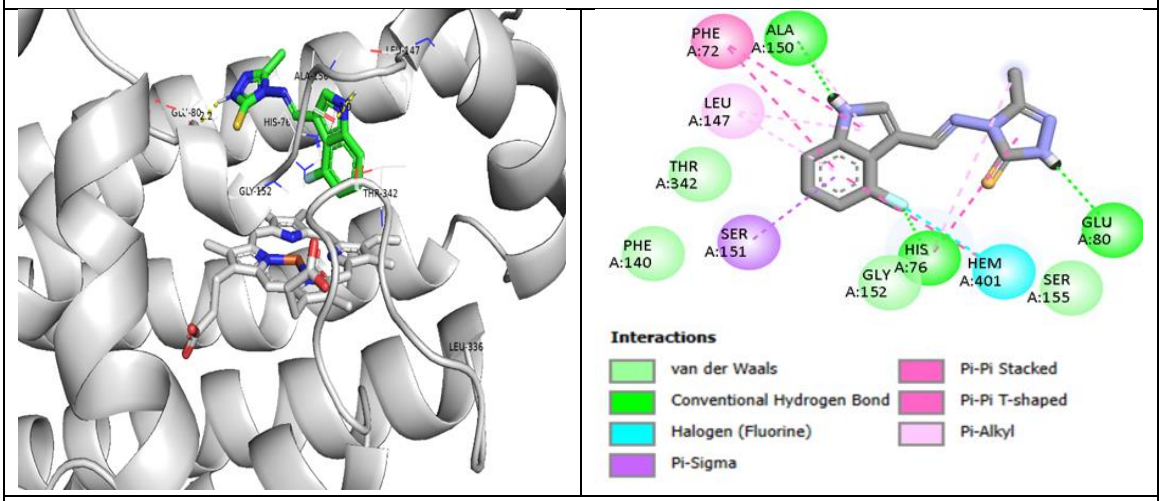


Compound 5e



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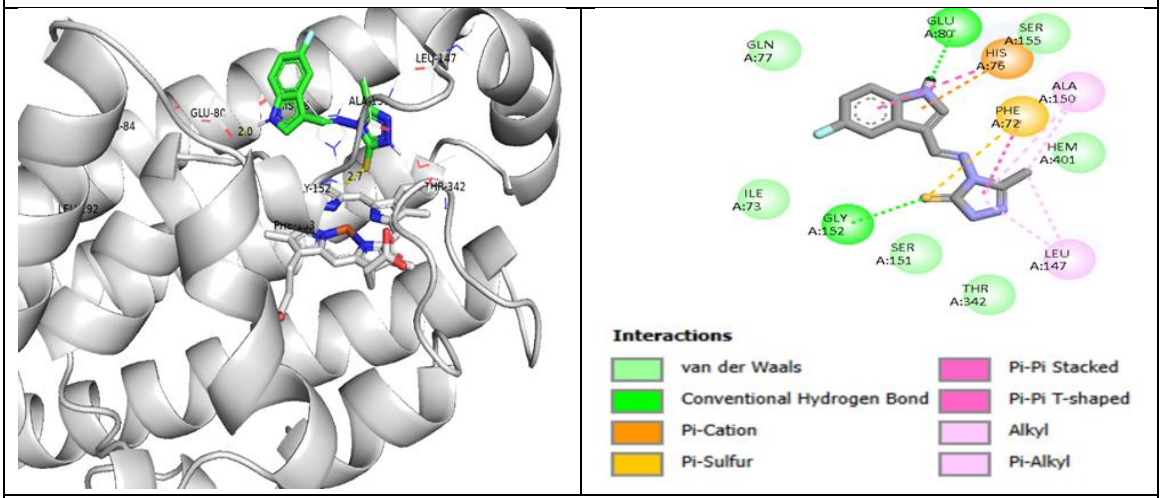

Compound 5g

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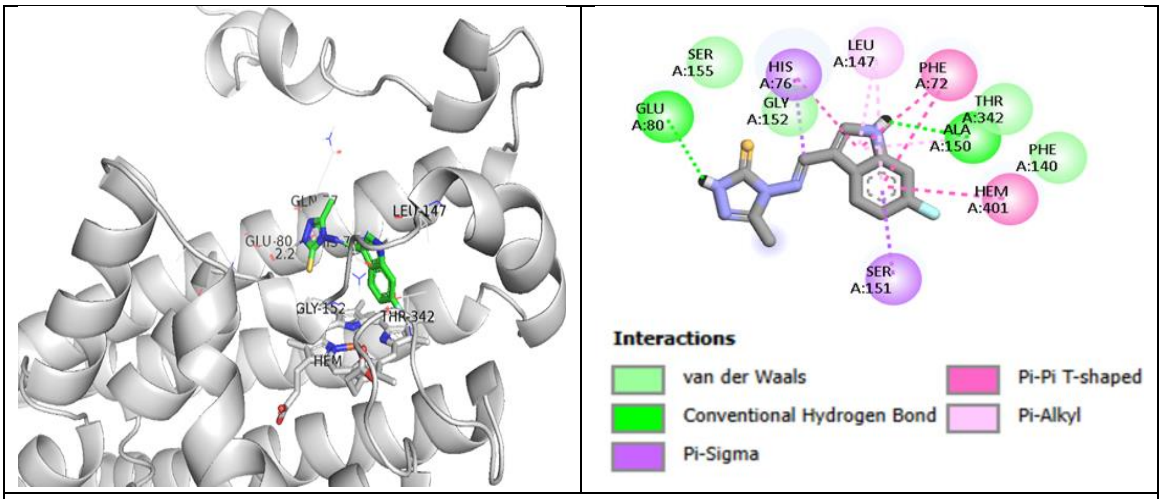
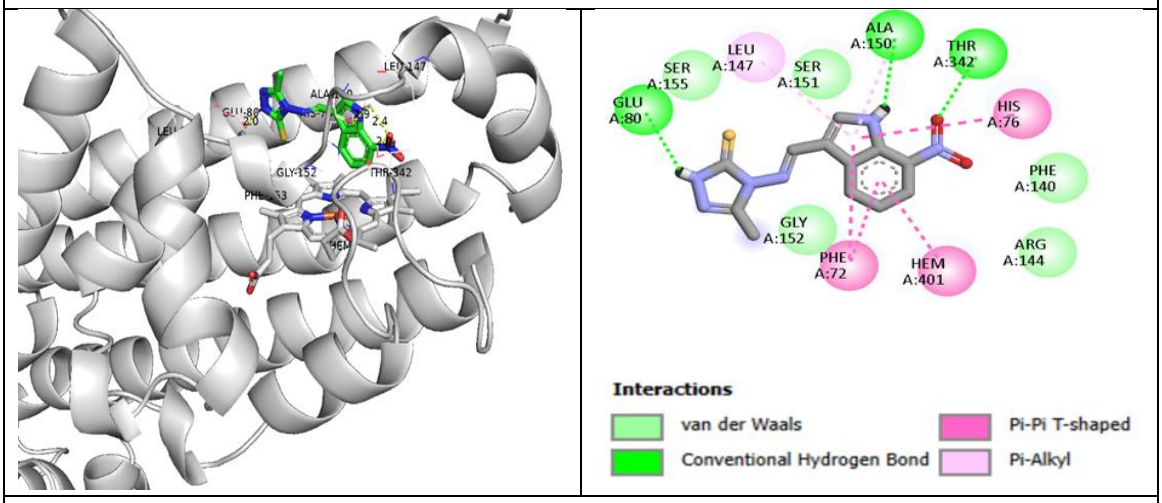
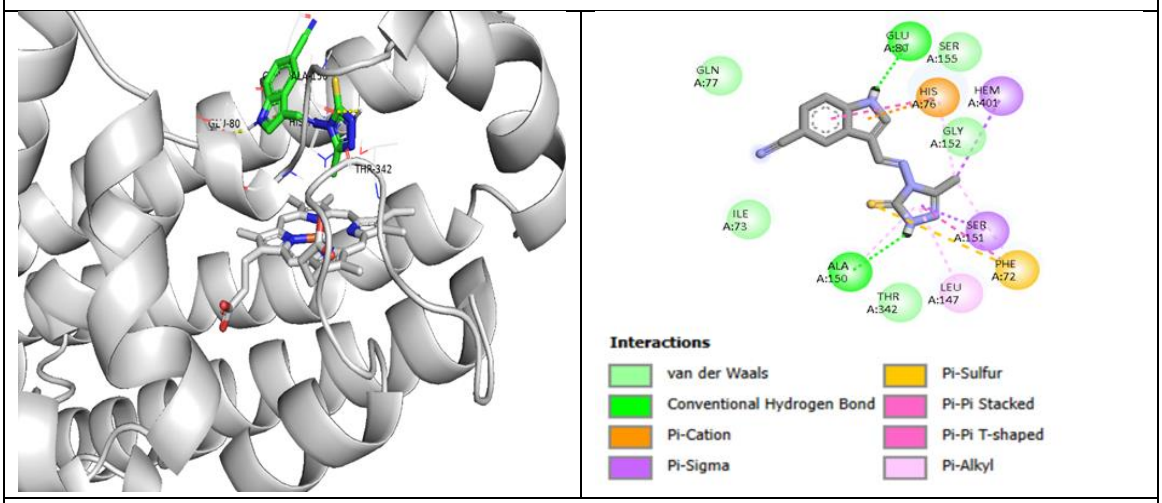


Compound 5h



Compound i



Compound 5j

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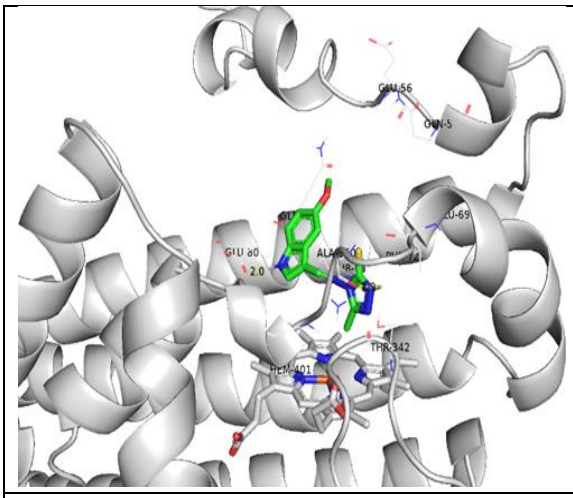
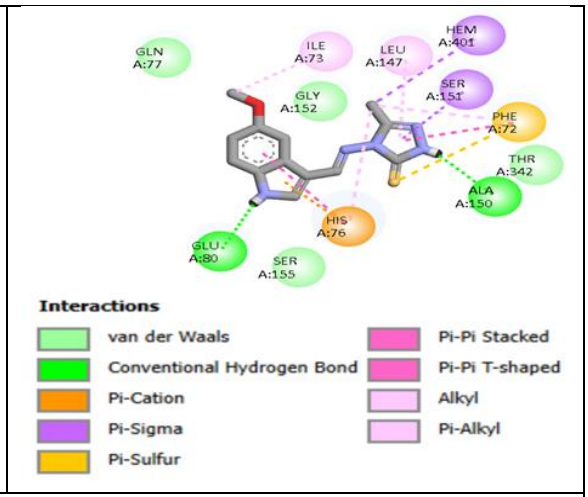
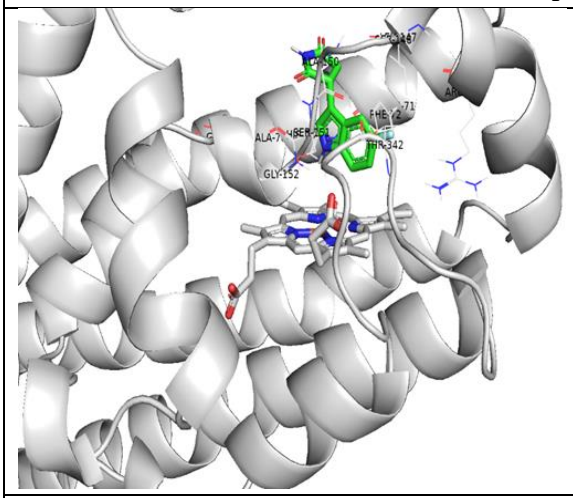
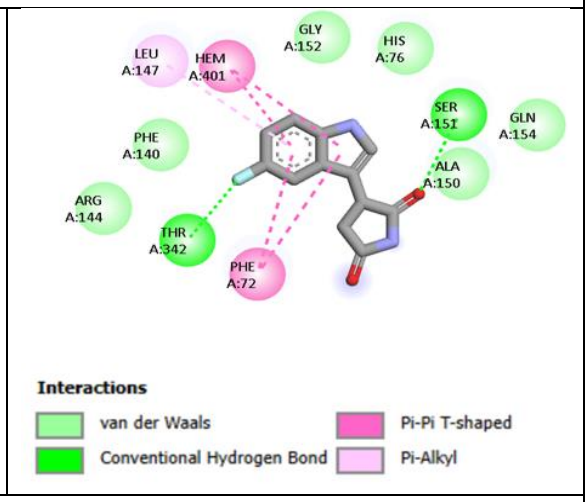




Compound 5k





Compound 3-(5-fluoro-1H-indol-3-yl)pyrrolidine-2,5-dione

3.2 In-silico ADME/Pharmacokinetic Assessment

The inhibitory activity of a compound toward an enzyme or receptor does not necessarily guarantee its suitability as a therapeutic agent [28]. Consequently, evaluating ADME parameters (absorption, distribution, metabolism, and excretion) alongside drug-likeness criteria is a crucial step in the drug discovery process [22]. These assessments support informed decisions regarding whether a compound can be effectively administered in biological systems. Compounds exhibiting poor ADME characteristics or elevated toxicity are frequently responsible for failure during advanced stages of drug development. Introduced in 1997 by Christopher A. Lipinski, the rule of five (Ro5) is a widely used criterion for predicting the drug-like properties of chemical compounds, estimating oral drug-likeness, and predicting whether a compound is likely to be

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orally active in humans [28]. According to this rule, poor absorption is more probable when a molecule violates two or more of the following criteria: molecular weight between 150-500 g/mol, octanol/water partition coefficient (iLOGP) ≤ 5, hydrogen bond acceptors (nHBA) ≤ 10, hydrogen bond donors (nHBD) ≤ 5, and topological polar surface area (TPSA) < 140 Å2. Based on the ADME and drug-likeness data summarized in Table 3, compounds 5a-5k showed zero violations of Lipinski's rule, and all compounds have a molecular weight below 500 g/ mol. The examined drug-likeness properties reflect essential pharmacokinetic features, including solubility in water and permeability through the intestinal barrier, which largely determine a compound's oral bioavailability. [29]. The predicted pharmacokinetic profile indicated favorable properties, with all compounds demonstrating high gastrointestinal absorption. Table 4 summarizes the physicochemical and pharmacokinetic properties of compounds 5a–5k. All compounds comply with Lipinski's Rule of Five, with molecular weights below 500 g/mol and favorable LogP and TPSA values, indicating good oral bioavailability. Most compounds have TPSA well below 140 $Å^2$, the identical TPSA values observed for compounds 5b–5h are attributed to the presence of the same number and type of polar functional groups, while differences in the type and position of halogen substituents (Cl, F, Br) do not significantly influence TPSA. In contrast, compounds 5i–5k exhibit different TPSA values due to the presence of additional polar groups such as nitro (NO_2), methoxy (OCH_3), and cyano (CN), which increase molecular polarity. corresponding to high predicted gastrointestinal absorption (HIA). (5i) has a TPSA of 139.67 $Å^2$, close to the threshold, resulting in slightly lower predicted HIA. Overall, the data indicate that all compounds exhibit favorable drug-likeness and pharmacokinetic properties suitable for oral administration.

Table 4. ADME and drug likeness parameters of compounds

Molecule	SA	BS	Pgp	BBB	GI	iLOGP	TPSA $Å^2$	nHBD	nHBA	MW g/mol
5a	2.59	0.55	No	No	High	1.88	93.85	2	2	257.31
5b	2.58	0.55	No	No	High	2.33	93.85	2	2	291.76
5c	2.61	0.55	No	No	High	2.33	93.85	2	2	291.76
5d	2.62	0.55	No	No	High	2.46	93.85	2	2	336.21
5e	2.63	0.55	No	No	High	2.44	93.85	2	2	336.21
5f	2.73	0.55	No	No	High	2.16	93.85	2	3	275.3

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5g	2.63	0.55	No	No	High	2.18	93.85	2	3	275.3
5h	2.67	0.55	No	No	High	2.18	93.85	2	3	275.3
5i	2.69	0.55	No	No	Low	2.04	139.67	2	4	302.31
5j	2.73	0.55	No	No	High	1.82	117.64	2	3	282.32
5k	2.66	0.55	No	No	High	2.24	103.08	2	3	287.34

A: Synthetic accessibility; BS: Bioavailability score; P-gp: P-glycoprotein substrate; BBB: Blood–brain barrier permeant; GI: Gastrointestinal absorption; iLOGP: Octanol/water partition coefficient; TPSA: Topological polar surface area; nHBD: Number of hydrogen bond donors; nHBA: Number of hydrogen bond acceptors; MW: Molecular weight; nLV: Number of Lipinski rule violations.

The BOILED-Egg model, also referred to as the Egan egg graph (Figure 3) for the 11 compounds, was generated using the SwissADME web tool https://www.swissadme.ch/. This graphical model visually predicts the likelihood of intestinal absorption and blood–brain barrier permeability [22]. The BOILED-Egg model predicted that most compounds are located within the white region, indicating high intestinal absorption. None of the compounds fall within the yolk, suggesting that they are unlikely to cross the BBB, which is advantageous for non-CNS drugs. The compound (5i) with TPSA = 139.67 Å² lies just outside the white region, consistent with its slightly reduced predicted intestinal permeability. These results visually confirm the ADME predictions summarized in Table 4.

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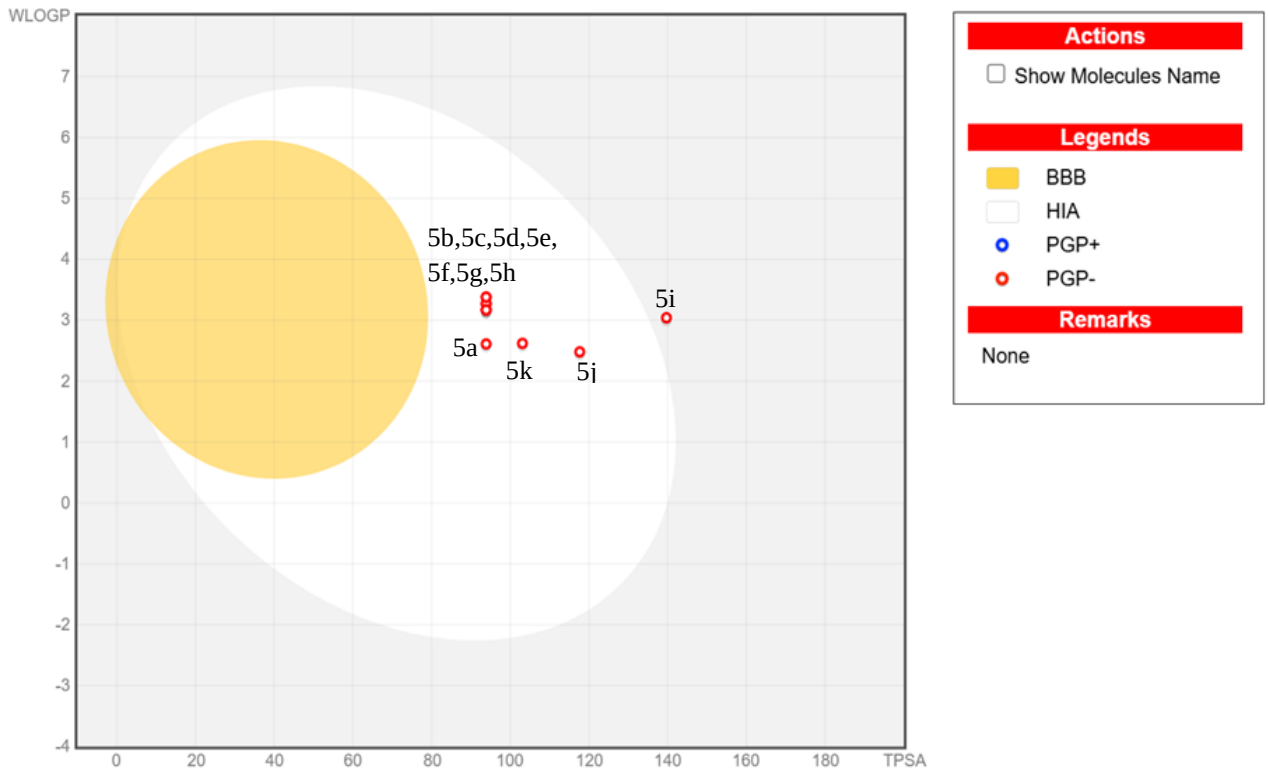

Figure 3. BOILED-Egg graph of the 5a-5k molecules

Source: Generated using SwissADME

4. Conclusion

Molecular docking simulation of molecules of indole bearing triazole-3-thione with theoretical binding interactions with TDO2 were assessed through molecular docking studies, and the compounds' structures were carefully drawn using ChemDraw, followed by docking simulations conducted through the PyRx virtual screening tool. Among the designed compounds, 5b demonstrated the highest binding affinity (-8.8 kcal/mol), indicating stronger predicted interactions than the co-crystallized ligand 3-(5-fluoro-1H-indol-3-yl)pyrrolidine-2,5-dione. This compound formed multiple hydrogen bonds with crucial residues (Glu80, Ala150, Ser151) at short distances (2.1–2.9 Å), suggesting a stable and compact ligand–protein complex. Similarly, 5a and 5f also exhibited docking scores (-8.6 kcal/mol each), maintaining strong interactions with the same residues within the active pocket. computational ADME and drug-likeness analyses indicated that the compounds exhibit favorable pharmacokinetic properties, including high gastrointestinal absorption and good oral bioavailability, except 5i, which was found outside

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the BOILED-Egg region, suggesting limited intestinal absorption, possibly due to its high topological polar surface area (TPSA) 139.67Å2, which may support medicinal chemists in creating more effective pharmaceutical compounds

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