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"*In-silico* Analysis and Molecular Modeling of Tropomycin Receptor Kinase Inhibitors as an Anticancer agents"

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ABSTRACT

The aim of present study is to design a series of indazole-based derivatives using structure-based drug design and evaluated through molecular docking (Autodock Vina) and *in-silico* analysis via Swiss ADME and pharmacokinetics studies. Absorption, Distribution, Metabolism, Excretion, and Toxicity, which are key pharmacokinetic and safety properties evaluated during the drug discovery and development process. Eighteen compounds were designed by incorporating oxazole, thiazole, and imidazole rings. Among them, compound 9 (oxazole) demonstrated the highest binding affinity (–9.1 kcal/mol) towards the Tropomyosin receptor kinase A receptor. Halogen substitutions (Cl, Br) on the phenyl ring enhanced hydrophobic interactions with residues like PRO 600 and PHE 521. Both electron-donating (methyl) and electron-withdrawing (nitro) groups improved binding by altering electronic distribution. Oxygen atoms contributed significantly to hydrogen bonding with HIS 492 and HIS 493. The indazole core played a key role, forming stable interactions with ASP 668 and GLU 560. Oxazole and thiazole heterocycles further enhanced binding, with compound 18 (thiazole) showing strong affinity (–8.7 kcal/mol). Overall, these findings offer a solid foundation for developing potent, selective Tropomyosin receptor kinase A inhibitors based on the indazole scaffold.

Keywords: Tyrosine receptor kinases, Tyrosine Kinase Inhibitors, Docking, Binding affinity, SWISSADME.

INTRODUCTION

Over the past twenty years, cancer has remained one of the most devastating diseases globally. The urgent need for novel anticancer agents with high efficacy and minimal side effects continues to grow. Tumor cells acquire distinct functional abilities during carcinogenesis, which are defined by eight well-established hallmarks[1] sustained cell proliferation, evasion of growth suppressors, resistance to cell death, replicative immortality, activation of invasion and metastasis, immune system evasion, and altered energy metabolism[2]. Recently, additional characteristics such as epigenetic modifications have also been recognized[3].

A major challenge in developing effective anticancer drugs is the complexity of cancer, which involves multiple pathways and diverse molecular targets. This makes it difficult for a single drug to act on all relevant targets simultaneously[4]. One of the significant obstacles in cancer treatment is chemoresistance, which limits therapeutic success. To overcome this, combination therapies that act on different signaling pathways have been explored, as they may reduce resistance and enhance treatment effectiveness.

There are numerous molecular targets for anticancer therapies, including vascular-targeting agents, cyclin-dependent kinases, tyrosine kinases, and agents that stabilize or destabilize microtubules. In the pursuit of multifunctional and effective anticancer compounds, indazole has gained attention for its promising therapeutic potential[5].

Tyrosine Kinases

Tyrosine kinases (TKs) are essential enzymes involved in regulating cancer cell growth and survival. They function by catalyzing the transfer of phosphate groups from ATP to tyrosine residues on target proteins. TKs are classified into approximately 30 distinct families, which include key receptors such as EGFR, VEGFR, and NGF. In the human genome, there are 90 tyrosine kinase genes and 43 tyrosine kinase-like genes, broadly categorized into receptor tyrosine kinases and non-receptor tyrosine kinases[8].

Receptor tyrosine kinases (RTKs), also referred to as TRKs, play a pivotal role in cellular signaling pathways that govern various biological processes. The TRK family consists of three primary isoforms-TrkA, TrkB, and TrkC-also known as NTRK1, NTRK2, and NTRK3, respectively. These proteins are transmembrane receptors involved in transmitting extracellular signals to the cell's interior. Specifically, TrkA is encoded by the NTRK1 gene, which is located on chromosome 1q21–q22[9].

TRKA and its role

Tropomyosin receptor kinase A is a receptor tyrosine kinase encoded by the NTRK1 gene.

Binds to nerve growth factor (NGF) to trigger intracellular signaling cascades. In Table 1 role and importance of TRKA is describes.

Table 1: Role and Importance of TRKA

Function/Pathway	Role of TRKA
Neuronal development	Promotes survival, differentiation, and growth of neurons.
Pain signalling	NGF-TRKA interaction plays a critical role in nociception.
Cancer	TRKA gene fusions or overexpression led to oncogenic signaling, driving tumor growth.
Neurodegenerative diseases	Loss of TRKA function is implicated in Alzheimer's disease and sensory neuropathies.

The TRKA receptor, encoded by the NTRK1 gene and belonging to the neurotrophin receptor family, is fundamental in mediating the biological actions of nerve growth factor (NGF). When NGF binds to TRKA, it induces receptor autophosphorylation, which subsequently initiates multiple downstream signaling pathways that are vital for neuronal growth and maintenance. Among these, the PI3K/AKT pathway plays a central role in enhancing cell survival by suppressing programmed cell death and promoting metabolic functions. The MAPK/ERK signaling cascade is also activated, facilitating neuronal differentiation, proliferation, and the extension of neurites. Furthermore, stimulation of the PLCγpathway increases intracellular calcium levels, which are crucial for synaptic function and plasticity. These interconnected signaling mechanisms underscore the essential contribution of TRKA to nervous system health, while its aberrant activation or expression has been associated with disorders such as cancer, chronic pain, and neurodegenerative diseases. In Fig. 1 the chemical structures of several FDA-approved molecule anticancer agents are given.

Future Perspectives

In future designed molecules will be synthesized and characterized by IR, Mass spectroscopy, proton NMR, 13 CNMR. Experimental validation *in vitro* and *in vivo* (e.g., kinase assays, cell lines, animal models) designed molecules will perform. In addition, the development of TRKA-selective inhibitors with minimal off-target effects. Furthermore, potential use in personalized medicine, especially for cancers with TRKA fusions will develop for e.g., NTRK gene fusions in lung, colon, and thyroid cancers.

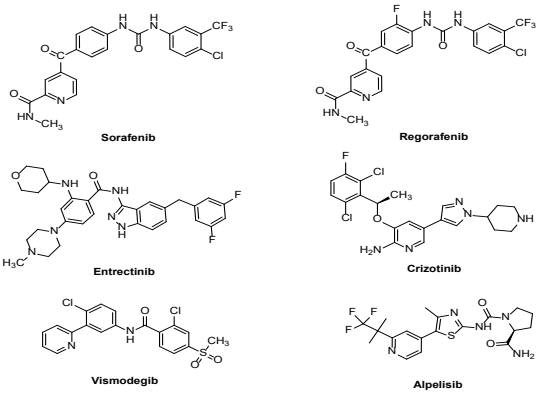

Fig. 1. FDA-approved small molecules as anti-cancer agents

MATERIALS AND METHODS

Materials

Computer System and Software

Computer system (HP), with the following specification properties, Intel® Core i3-6100U, 12 Gigabyte RAM was used throughout the present study. The software downloads and installed include Autodock 2 software, Discovery Studio Visualizer v16.1.0.15350, Chem draw Ultra software V. 12.0.2, and Swiss ADME online software. In-silico analysis was performed with the help of SWISSADME software.

Methods

Design strategy

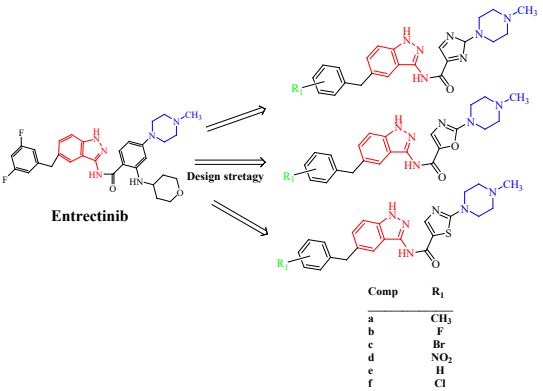

Fig. 2. Design strategy of indazole derivatives

Designing of indazole based derivatives was performed by replacement of phenyl ring of Entrectinib with thiazole, imidazole and oxazole heterocycles. Herein, we have designed molecules by application of structure-based drug designing. Furthermore, several substitutions were taken like CH_3, F, Br, NO_2, H, and Cl on phenyl ring.

In-silico analysis and ADME/Pharmacokinetics Prediction

The three-dimensional structure of the target protein (PDB ID: 5JFX) was obtained from the RCSB Protein Data Bank and employed for molecular docking studies[10]. All 18 designed compounds were docked using AutoDock Vina, which employs a stochastic gradient-based optimization method to estimate binding affinities between ligands and the receptor. The docking outcomes were further examined using Discovery Studio Visualizer to identify key amino acid residues involved in strong ligand–receptor interactions. Additionally, the SMILES (Simplified Molecular Input Line Entry System) notations of the compounds were submitted to the SwissADME tool, developed by the Swiss Institute of Bioinformatics, to assess their drug-likeness and predict essential ADME properties, including absorption, distribution, metabolism, and excretion.

Ligand preparation

We can choose that structure if the ligand molecule is present in the software database. The mol 2 file (also known as Tripos MOL2 file) is a molecular structure file format used in computational chemistry, molecular modeling, and docking studies. For novel ligand molecules, structures can either be drawn manually or submitted in .mol2 format. The docking procedure is carried out using the AutoDock Vina algorithm, which is integrated into the software platform. Prior to docking, AutoDock Tools are employed to preprocess the structures automatically-this includes the addition of hydrogen atoms (if absent), assignment of Gasteiger charges, merging of charges, and elimination of non-standard residues, non-polar hydrogens, lone pairs, and water molecules to prepare the system for accurate docking simulations.

Preparation of protein structure

The crystal structure of the TrkA protein (PDB ID: 5JFX) was chosen for this study. However, the original structure file obtained from the Protein Data Bank was not immediately suitable for molecular docking experiments. A typical PDB file contains not only heavy atoms but also co-crystallized ligands, water molecules, metal ions, and cofactors, which may interfere with the docking process. To address this, the protein structure was processed using the Protein Preparation Wizard in AutoDock Vina v1.2.0. This involved a series of preprocessing steps, including structure optimization and energy minimization, to ensure the protein was appropriately prepared for the docking analysis.

Docking

Molecular docking techniques can be used to predict the binding affinities of various ligands. The objective of this study is to explore the potential correlation between the docking scores of the inhibitors and their interactions with the target protein. All docking simulations were conducted using the default parameters to ensure the reliability and consistency of the results.

RESULT AND DISCUSSION

Results

The docking was performed through AutoDock Vina is v.1.2.0 and results were displayed after docking. The binding affinities of the indazole derivatives are provided in Table 2.1, along with the binding interactions with amino acid residues. Lipinski's Rule of Five and Veber's Rule of designed Indazole-based derivatives (1-18) are describing in Table 2.2. In Fig. 3 the binding orientation of compounds with crystal structure of TrkA (PDB Id: 5JFX) is mentioned. Fig. 4 describes the predicted SAR studies of indazole based derivatives. In Table 2.3 Pharmacokinetics properties of designed compounds 1-18 is mentioned.

Table 2.1: Binding Interaction with amino acids residues

Compound code	Interaction with amino acid residue	Binding affinity (Kcal/mol)
1	HIS 493, HIS 492, MET 489, ASP 668	-8.7
2	HIS 648, HIS 490, ASP 668, HIS 492	-7.7
3	HIS 493, HIS 492, MET 489, HIS 648, HIS 492	-7.8
4	ARG 649, HIS 492, HIS 491, HIS 490, GLU 560	-8.3
5	GLU 560, HIS 490, HIS 492, ASP 669, ASP 668	-7.8
6	HIS 491, HIS 492, LEU 689, GLU 560, ARG 649	-7.8
7	LEU 689, ARG 649, ASP 668, ASP 668	-7.7
8	HIS 492, MET 489, PRO 690, HIS 492	-7.6
9	MET 489, HIS 492, ASP 668, GLU 560, HIS 493	-9.1
10	PRO 690, MET 489, HIS 490, HIS 491, PHE 704	-8.4
11	HIS 492, ARG 649, ASP 668, PHE 704, HIS 648	-7.3
12	HIS 492, ARG 649, LEU 689, ASP 668	-7.3
13	PHE 704, PHE 646, HIS 493, ARG 649, PRO 690	-8.1
14	ARG 649, ASP 650, GLU 650, HIS 492, HIS 490	-8.7
15	ALA 520, HIS 490, HIS 492, ARG 649, ASP 668	-8.4
16	LEU 689, HIS 492, HIS 490, ARG 649	-7.9
17	MET 489, HIS 493, ARG 649, PRO 690	-7.6
18	PRO 690, GLU 560, HIS 490, MET 489, HIS 492	-8.7
19	Doxorubicin	-9.0

Table 2.2: Lipinski's Rule of Five and Veber's Rule of designed Indazole-based derivatives (1-18)

Compound code	Lipinski Rule of Five						Veber Rule		
	MW	HBA	HBD	iLogP	$n_{violations}$	DL	nRB	TPSA	DL
Rule	≤ 500	≤ 10	≤ 5	≤ 4.15	≤ 1	yes	≤ 10	≤ 140	yes
1	429.5	6	2	2.09	0	yes	6	88.98	yes
2	433.5	7	2	1.93	0	yes	6	88.98	yes
3	494.4	6	2	2.00	0	yes	6	88.98	yes
4	461.5	8	3	1.85	0	yes	7	138.64	yes
5	415.5	6	2	1.77	0	yes	6	88.98	yes
6	449.4	6	2	2.19	0	yes	6	88.98	yes
7	430.5	5	2	2.98	0	yes	6	90.29	yes
8	434.47	6	2	2.80	0	yes	6	90.29	yes
9	495.37	5	2	2.84	0	yes	6	90.29	yes
10	461.47	7	2	2.09	1	yes	7	136.11	yes
11	416.48	5	2	2.45	0	yes	6	90.29	yes
12	450.92	5	2	2.79	0	yes	6	90.29	yes
13	446.57	4	2	2.52	0	yes	6	105.39	yes
14	450.53	5	2	2.66	0	yes	6	105.39	yes
15	511.44	4	2	2.74	1	yes	6	105.39	yes
16	477.54	6	2	2.37	0	yes	7	151.21	yes
17	432.54	4	2	2.53	0	yes	6	105.39	yes
18	466.99	4	2	2.70	0	yes	6	105.39	yes

Note: MW–Molecular weight (g/mol), HBA–No. of H-bond acceptor, HBD–No. of H-bond donor, nRB–No. of rotatable bonds, TPSA–Topological Polar Surface Area (Å2), DL–Drug-likeliness

Table 2.3: Pharmacokinetics properties of 1-18.
Pharmacokinetic parameters of designed compounds 1-18.

Compound code	Pharmacokinetics					Drug-likeness
	GI	BBB	Log Kp[a]	CYP2C9inhibitor	CYP3A4inhibitor	Bioavailability score
1	High	yes	-6.82	yes	yes	0.55
2	High	No	-7.03	yes	yes	0.55
3	High	No	-6.98	yes	yes	0.55
4	High	No	-7.72	No	No	0.55
5	High	No	-6.99	yes	yes	0.55
6	High	yes	-6.75	yes	yes	0.55
7	High	yes	-6.07	yes	yes	0.55
8	High	No	-6.28	yes	yes	0.55
9	High	No	-6.23	yes	yes	0.55
10	High	No	-6.64	yes	yes	0.55
11	High	No	-6.24	yes	yes	0.55
12	High	yes	-6.00	yes	yes	0.55
13	High	No	-5.73	yes	yes	0.55
14	High	No	-6.28	yes	yes	0.55
15	High	No	-5.89	yes	yes	0.55
16	Low	No	-6.30	yes	yes	0.55
17	High	No	-5.90	yes	yes	0.55
18	High	No	-5.67	yes	yes	0.55

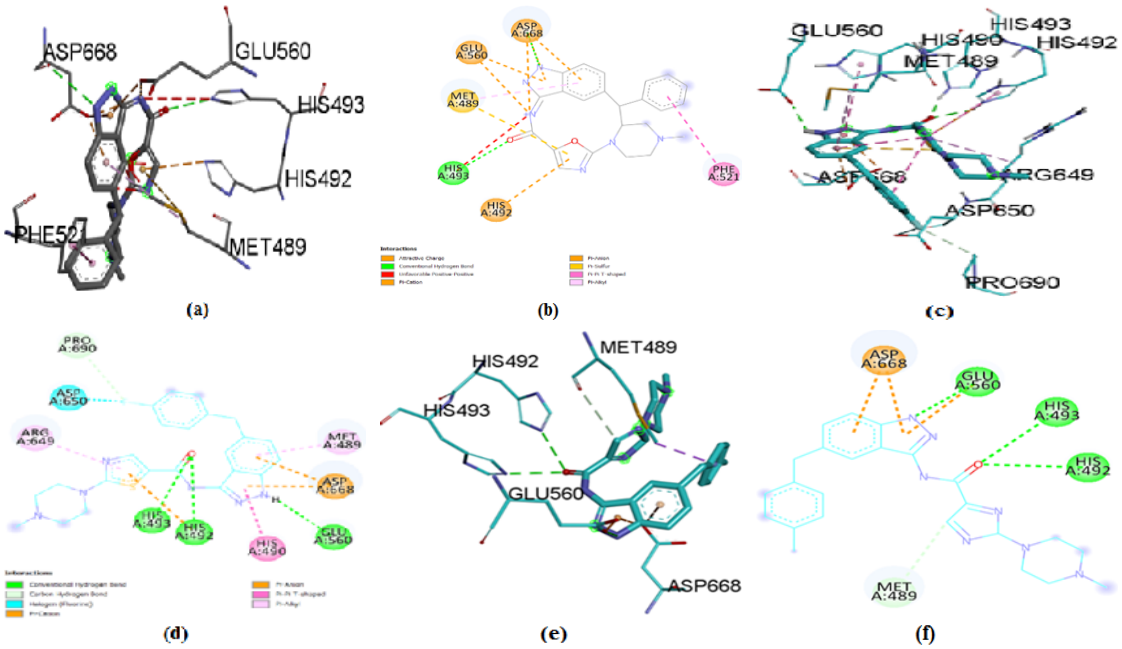

Fig. 3. Describes the binding orientation of compounds with Crystal structure of TrkA (PDB Id: 5JFX). a and b binding interaction of compound 9 and its interaction of with MET489 (golden), HIS492, ASP668, GLU560 (golden), HIS493 amino acids are describes. In addition to that c and d describes the compound 14 with its interaction towards amino acids like ARG649, ASP650, GLU650, HIS492 (light green), HIS490 (light green). Furthermore, amino acids HIS493 (light green), HIS492 (light green), MET489, ASP668 (golden) are showing interaction with compound 1(e, f)

DISCUSSIONS

Molecular Docking and Virtual Screening

The molecular docking study established that the synthesized indazole-based derivatives exhibit notable interactions with key amino acid residues within the active site of the board protein, contributing to their favorable required affinities and potential biological action. The binding affinity ranged from -7.3 to -9.1 kcal/mol, indicating moderate to strong binding potential.

Across the compound series, several amino acid residues consistently participated in hydrogen bonding, π–π stacking, and electrostatic interactions[11] Notably, HIS 492 was a recurrent interacting residue across almost all 18 compounds, likely forming hydrogen bonds or π–stacking interactions that support stable binding. MET 489 was normally intricate in hydrophobic contacts, while negatively charged residues such as ASP 668 and ASP 669 frequently engaged in hydrogen bonding and salt bridge formation. Additionally, GLU 560 and ARG 649 were involved in strong ionic connections with polar or charged moieties of the ligands.

Hydrophobic amino acids like PRO 690, PHE 704, and LEU 689 contributed to van der Waals interactions, further stabilizing the ligand-protein complex[12]. Among the tested compounds, N-(5-(4-bromobenzyl)-1H-indazol-3-yl)-2-(4-methylpiperazin-1-yl)oxazole-5-carboxamide (9) emerged as the most hopeful candidate, exhibiting the highest docking score of -9.1 kcal/mol. It interacted strongly with residues such as MET 489, HIS 492, ASP 668, GLU 560, and HIS 493, and showed vigorous electrostatic and hydrophobic contacts particularly involving the oxazole ring.

In addition to compounds 1, 14, and 18 also displayed strong binding affinities with docking scores around -8.7 kcal/mol. These molecules formed multiple significant interactions with charged and aromatic residues, including HIS, ASP, and ARG. The recurring involvement of HIS 492 and ASP 668 across various compounds suggests these residues are critical anchoring points within the active site. Moreover, the observed binding interactions align with physicochemical parameters like TPSA and log P, which influence both binding behavior and potential bioavailability[13]. The consistent, auspicious binding to catalytically important residues supports the design strategy of the indazole scaffold, and highlights compounds 9, 1, and 14 as strong candidates for further *in vitro* and *in vivo* evaluation.

***In-silico* ADME/Pharmacokinetic Predictions**

Table 2.2 assesses the drug-likeness of 18 indazole-based derivatives based on Lipinski's Rule of Five (Ro5) and Veber's Rule, both widely accepted for forecasting oral bioavailability.

According to Ro5, drug-like compounds typically have a molecular weight (MW) ≤ 500, hydrogen bond acceptors (HBA) ≤ 10, hydrogen bond donors (HBD) ≤ 5, and an iLogP ≤ 4.15, with a maximum of one allowable violation[14]. All 18 derivatives meet these criteria, with no compound exceedingly more than one parameter. Only compound 10 slightly surpasses the iLogP limit, while compound 15 marginally exceeds the MW threshold. This indicates that all compounds possess suitable physicochemical properties and are likely to be orally bioavailable.

Veber's Rule, which evaluates molecular flexibility and polarity, was also satisfied across the series with respect to the number of rotatable bonds (nRB)[15]. However, compound 16 slightly exceeds the Veber TPSA threshold (151.21 Å²), which might negatively affect its membrane penetrability. Despite this, 17 out of 18 compounds conform to Veber's guidelines, suggesting favorable prospects for oral route. Overall, the majority of compounds meet both Lipinski's and Veber's requirements. Detected variations in TPSA and iLogP across the indazole series offer valuable insights for fine-tuning permeability and solubility in future optimization steps.

Table 2.3 outlines key pharmacokinetic properties for the series (compounds 1–18), including gastrointestinal (GI) absorption, blood-brain barrier (BBB) penetration, skin permeability (Log Kp), cytochrome P450 enzyme inhibition, and overall drug-likeness[16]. All compounds except 16 exhibit high GI engagement, making them promising candidates for oral administration. The low absorption of compound 16 may be attributed to its elevated TPSA, which can hinder passive diffusion. Compounds 1, 6, 7, and 12 display the ability to penetrate the BBB, indicating potential central nervous system (CNS) activity or associated side effects. The remaining compounds do not cross the BBB, which is advantageous for drugs targeting peripheral tissues, minimizing central nervous system related hazards.

Skin permeability, expressed as Log Kp, falls between –7.72 and –5.67 across the series, reflecting moderate to low skin absorption. More negative values, such as –7.72 for compound 4, suggest lower transdermal exposure, which is beneficial for oral formulations.

Most derivatives are predicted to inhibit cytochrome P450 enzymes CYP2C9 and CYP3A4, which may lead to drug-drug interface concerns. Notably, compound 4 is non-inhibitory to both enzymes, marking it as a potentially safer choice in terms of metabolic interactions. All compounds show a consistent bioavailability score of 0.55, considered moderate, supporting their potential for further development as orally active drugs.

Structure activity relationship

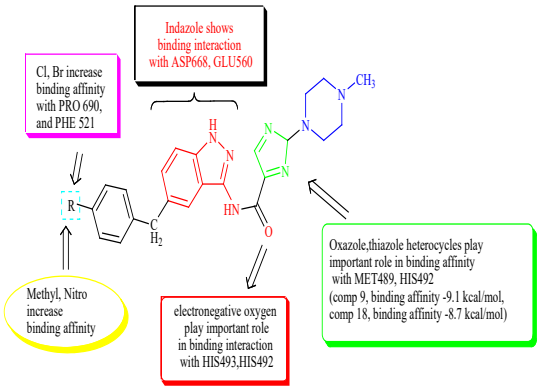

Fig. 4. Describes the predicted SAR studies of indazole based derivatives

SAR studies predict that Halogen Substitution (Cl, Br) at the phenyl ring enhances binding affinity. These groups promote interactions with hydrophobic residues like PRO 600 and PHE 521[16]. Methyl (electron-donating) and Nitro (electron-withdrawing) groups at certain positions increase binding affinity, possibly by influencing electronic density and molecular orientation in the binding pocket. Oxygen atoms (e.g., in carbonyl or nitro groups) contribute significantly to interactions with residues such as HIS 493 and HIS 492, likely through hydrogen bonding or electrostatic interactions[17]. The indazole ring is crucial for core binding and shows consistent interaction with ASP 668 and GLU 560, two negatively charged residues, indicating the importance of this scaffold in stabilizing the ligand-protein complex. Oxazole/Thiazole heterocyclic rings enhance binding through interactions with MET 489 and HIS 492. For instance, oxazole in compound 9 contributes to strong binding affinity (–9.1 kcal/mol), while thiazole in compound 18 also supports stable interactions (–8.7 kcal/mol).

CONCLUSION

The comprehensive molecular docking and *in silico* pharmacokinetic evaluation of 18 synthesized indazole-based derivatives revealed promising drug-like characteristics. Most compounds demonstrated favorable binding affinities (–7.3 to –9.1 kcal/mol) through strong interactions with key active-site residues such as HIS 492, MET 489, and ASP 668, highlighting their potential biological activity. Compound 9 emerged as the lead candidate due to its highest docking score and robust interaction profile. ADME predictions further confirmed the compounds' suitability for oral administration, with all but one showing high GI absorption andacceptable physicochemical properties under Lipinski's and Veber's rules. Although most compounds may inhibit major CYP enzymes, compound 4 showed a favorable metabolic profile, posing minimal risk for drug-drug interactions. Overall, these findings support the continued development of these indazole derivatives, particularly compounds 9, 1, and 14, as strong candidates for further *in vitro* and *in vivo* studies.

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Conflict of interest

The authors declare no conflict of interest, financial or otherwise.

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