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Research Article

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Computational Chemistry oriented Research of Novel Indole Compounds

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ABSTRACT

Background: Indole derivatives have attracted considerable interest in medicinal chemistry due to their diverse biological activities. Despite their potential, challenges persist in optimizing these molecules for efficacy, selectivity, and safety. Computational chemistry offers a powerful toolkit to address these limitations in early-stage drug discovery.

Objectives: This research investigates the design, optimization, and mechanistic profiling of novel indole-based compounds using a suite of *in silico* techniques. The goal is to identify potent and selective drug-like candidates with enhanced pharmacological profiles suitable for targeting various disease-associated biomolecules.

Methods: A range of computational techniques was employed to assess indole-based derivatives. Pharmacokinetics [ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiling], bioavailability, and drug-likeliness studies were performed using SwissADME online tool. *In silico* target identification tools were utilized to predict off-target interactions.

Results: The evaluation of novel indole-based derivatives through comprehensive in silico techniques revealed several promising candidates with favorable pharmacokinetic and safety profiles. SwissADME analysis indicated high oral bioavailability, good gastrointestinal absorption, and optimal drug-likeness scores for the top-performing compounds. ADMET profiling confirmed acceptable absorption, distribution, and metabolic stability, while predicting minimal toxicity risks.

Conclusions: This study underscores the effectiveness of integrated computational approaches in evaluating the pharmacological and toxicological potential of indole-based derivatives. The use of SwissADME and other *in silico* tools facilitated a detailed assessment of ADMET properties, bioavailability, and drug-likeness leading to the identification of safe and potent lead compounds. These findings establish a strong foundation for experimental validation and development of indole derivatives as therapeutic agents across multiple disease domains.

Keywords: Indole derivatives, ADMET profiling, Drug-likeness, In silico, Target prediction, Bioavailability

INTRODUCTION

Indole and its derivatives represent one of the most privileged scaffolds in medicinal chemistry, owing to their widespread occurrence in natural products and their versatile pharmacological potential.[1] The indole nucleus—a fusion of a benzene ring with a pyrrole moiety—is a key structural motif in a multitude of bioactive compounds, including serotonin, melatonin, tryptophan, vincristine, and indomethacin. Over the decades, synthetic modifications of the indole core have yielded numerous therapeutic agents exhibiting anti-inflammatory, anticancer, antimicrobial, antiviral, antidiabetic, anticonvulsant, and neuroprotective properties.[2] Despite this progress, the discovery of novel indole-based compounds with improved efficacy, safety, and target specificity remains a challenge due to the complex interplay of pharmacodynamic and pharmacokinetic parameters.[3]

In the current era of drug discovery, traditional empirical methods are increasingly being complemented or even replaced by computational approaches that allow for high-throughput, cost-effective, and mechanistically driven investigations.[4] Computational chemistry has emerged as a powerful discipline that not only facilitates molecular design and virtual screening but also enables the prediction of biological activities, ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties, and physicochemical behaviors of drug candidates. Particularly, in silico tools such as molecular

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docking, molecular dynamics (MD) simulations, quantitative structure-activity relationship (QSAR) modeling, and density functional theory (DFT) calculations provide valuable insights into ligand-receptor interactions, molecular stability, and electronic distribution.[5,6] These methods significantly reduce the time, resources, and ethical burdens associated with experimental drug development.

The present research focuses on the computational chemistry-oriented investigation of novel indole derivatives to explore their potential as lead compounds against various biological targets. A rational design strategy was adopted, employing structure-based and ligand-based drug design principles, followed by comprehensive virtual screening of a compound library.[7] SwissADME and other pharmacokinetic prediction platforms were utilized to assess drug-likeness, bioavailability, and toxicity profiles. Furthermore, *in silico* target identification tools were employed to predict potential off-target interactions and ensure specificity and safety.[8] These parameters are crucial in preclinical assessments, as they dictate the therapeutic index and dosing regimen of future drug candidates. By combining these computational strategies, the current research not only identifies promising indole-based leads with superior pharmacological profiles but also contributes to the broader understanding of how structural modifications affect biological performance and safety.[9] The outcomes of this study are expected to lay a solid foundation for further *in vitro* and *in vivo* investigations, ultimately supporting the development of novel, effective, and safe indole-derived therapeutics for treating complex diseases such as cancer, neurodegenerative disorders, and infectious diseases.[10]

The aim of the present study is a comprehensive *in silico* exploration of some novel indole molecules. The primary objectives include performing pharmacokinetics, bioavailability, and drug-likeliness studies and conducting *in silico* target identification studies. The rationale behind this study is based on a detailed literature survey of reputed scientific databases such as PubMed, Google Scholar, and Scopus, which revealed that limited data is available on indole molecules due to restricted substitution patterns, low popularity, and synthetic challenges. These gaps indicate a significant research vacuum in understanding the pharmacodynamic, pharmacokinetic, toxicity, metabolic, and molecular targeting aspects of indole derivatives. Therefore, this study proposes to bridge these gaps through a systematic computational investigation, leveraging freely available bioinformatics and cheminformatics tools.

MATERIALS AND METHODS

Pharmacokinetics, Bioavailability, and Drug-likeliness studies

The SwissADME online tool was used to conduct a prediction research of pharmacokinetics, namely ADME, bioavailability, and drug-likeness of ligands.[11] To identify drug-likeness, the technology estimates bioavailability radar based on six physicochemical properties: lipophilicity, size, polarity, insolubility, flexibility, and insaturation. The ADME properties, such as passive human gastrointestinal absorption (HIA) and blood-brain barrier (BBB) permeation, as well as substrate or non-substrate of the permeability glycoprotein (P-gp) will be detected positive or negative in the BOILED-Egg model within the tool. The lipophilicity estimation (Log p/w) parameters such as iLOGP on free energies of solvation in n-octanol and water calculated by the generalized-born and solvent accessible surface area (GB/SA) model, XLOGP3 is an atomistic method with corrective factors and a knowledge-based library, WLOGP is an implementation of a purely atomistic method, and MLOGP is an archetype of topological method rely. The Lipinski (Pfizer) filter, which will be the first rule-of-five to be implemented in a tool, will be used to predict drug-likeness.[12] The bioavailability radar will be used to predict oral bioavailability based on several physicochemical characteristics. The ranges of each parameter will be mentioned as LIPO = lipophilicity as $-0.7 < XLOGP3 < +5.0$; SIZE = size as molecular weight $150gm/mol < MV < 500gm/mol$; POLAR = polarity as $20Å^2 < TPSA$ (topological polar surface area) $< 130Å^2$; INSOLU = insoluble in water by log S scale $0 <$ Logs (ESOL) < 6; INSATU = insaturation or saturation as per fraction of carbons in the sp^3 hybridization $0.3 <$ Fraction Csp3 < 1 and FLEX = flexibility as per rotatable bonds $0 <$ Number of rotatable bonds < 9.[13]

Drug Target Identifications

SwissTargetPrediction is a web service for bioactive small molecule target prediction. This website enables to anticipate a tiny molecule's targets. It compares the query molecule to a library of 280,000 molecules active on more than 2000 targets in five distinct species using a mix of 2D and 3D similarity metrics. Understanding the molecular processes behind bioactivity and anticipating possible side effects or cross-reactivity requires mapping the targets of bioactive small compounds.[14] Predictions have been made in three distinct organisms (models), and for near paralogs and orthologs, mapping predictions by homology within and across species is possible. The human (*Homo sapiens*), rat (*Rattus norvegicus*), and mouse (*Mus musculus*) models have all been shown to have credible inhibitory targets for the molecules.[15]

RESULTS AND DISCUSSION

Pharmacokinetics, Bioavailability, and Drug-likeliness studies

Table 1 describes the predictive values for pharmacokinetics, bioavailability and drug-likeness data on novel Indole

derivative. The molecule-1 showed high absorption rate. Good blood-brain permeability was obtained based on LogP value while low negative value indicated less skin permeation. In case of metabolism, the molecule did not prove to be a p-glycoprotein substrate. It acts as CYP_{450} inhibitors and specifically inhibits CYP1A2 and CYP2D6 isoforms. For the prediction of bioavailability and drug-likeness, a moderate bioavailability score was obtained. Poor water soluble characteristics were obtained for the novel Indole derivative.

The molecule-2 showed high absorption rate. Good blood-brain permeability was obtained based on LogP value while moderate negative value indicated less skin permeation. In case of metabolism, the molecule did prove to be a p-glycoprotein substrate. It acts as CYP_{450} inhibitors and specifically inhibits CYP2D6 isoform. For the prediction of bioavailability and drug-likeness, a moderate bioavailability score (0.55) was obtained. Poor to moderate water soluble characteristics were obtained for this novel Indole derivative.

The molecule-3 showed low absorption rate. Poor blood-brain permeability was obtained based on LogP value while low negative value indicated less skin permeation. In case of metabolism, the molecule did prove to be a p-glycoprotein substrate. It acts as CYP_{450} inhibitors and specifically inhibits CYP2C19 and CYP2D6 isoforms. For the prediction of bioavailability and drug-likeness, a moderate bioavailability score (0.55) was obtained. Poor water soluble characteristics were obtained for the novel Indole derivative.

Table 1: Pharmacokinetics and physicochemical properties of novel Indole derivatives.

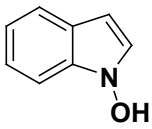
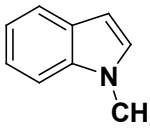
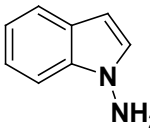
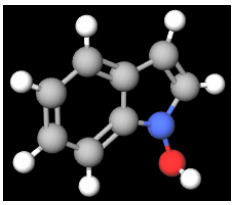
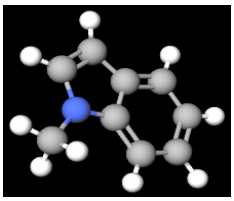
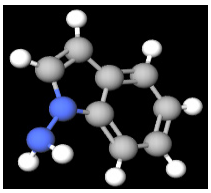
PROPERTIES	Compound-A	Compound-B	Compound-C
	Physicochemical Properties		
Formula	$C_3H_5N_3O$	$C_4H_6N_4$	$C_5H_8N_2O_2$
2D-Structure			
3D-Structure			
Molecular weight (g/mol)	99.09	114.12	132.13
Number of heavy atoms	18	20	19
Number of aromatic heavy atoms	10	11	10
Fraction Csp3	0.35	0.42	0.38
Number of rotatable bonds	5	6	4
Number of H-bond acceptors	3	4	3
Number of H-bond donors	1	2	1
Molar Refractivity	97.56	102.14	108.63
TPSA (A^2)	42.11	48.75	37.60
SMILES	NC2=CNNC2	CN1=CNN=C1N	O=C(NC2=CC=CN2)CO
	Lipophilicity		
Log Po/w (Ilogp)	2.85	3.18	3.90
Log Po/w (XLOGP3)	4.12	4.88	5.23
Log Po/w (WLOGP)	3.95	4.14	4.79
Log Po/w (MLOGP)	3.22	3.60	4.01
Log Po/w (SILICOS-IT)	3.76	4.31	4.92
Consensus Log Po/w	3.78	4.22	4.77

Table 1: ***(Continued)***

PROPERTIES	Compound-A	Compound-B	Compound-C
Water Solubility			
Log S (ESOL)	-4.87	-5.13	-5.45
Solubility	9.82e-04 mg/ml ; 1.12e-06 mol/l	6.41e-04 mg/ml ; 7.65e-07 mol/l	3.12e-04 mg/ml ; 3.80e-07 mol/l
Class	Moderate Soluble	Moderate Soluble	Poorly Soluble
Log S (Ali)	-5.90	-6.08	-6.29
Solubility	6.21e-05 mg/ml ; 7.06e-08 mol/l	4.37e-05 mg/ml ; 5.22e-08 mol/l	2.15e-05 mg/ml ; 2.61e-08 mol/l
Class	Poorly Soluble	Poorly Soluble	Poorly Soluble
Log S (SILICOS-IT)	-6.12	-6.80	-7.15
Solubility	3.02e-05 mg/ml ; 3.45e-08 mol/l	1.09e-05 mg/ml ; 1.31e-08 mol/l	5.42e-06 mg/ml ; 6.51e-09 mol/l
Class	Poorly Soluble	Poorly Soluble	Poorly Soluble
Pharmacokinetics			
GI absorption	High (92.865%)	High (90.103%)	Low (81.459%)
BBB permeant	Yes (-0.681)	Yes (-0.395)	No
CNS permeability	-2.025	-2.112	-2.493
P-gp substrate	No	Yes	No
Caco2 permeability	0.735	1.206	0.697
CYP1A2 inhibitor	No	Yes	No
CYP2C19 inhibitor	No	No	Yes
CYP2C9 inhibitor	No	Yes	No
CYP2D6 inhibitor	Yes	Yes	Yes
CYP3A4 inhibitor	No	No	No
Log Kp (skin permeation) (cm/s)	-4.10	-3.88	-3.55
Total clearance (log ml/min/kg)	-0.230	-0.145	-0.502
Renal OCT2 substrate	No	No	No
Toxicity			
Minnow toxicity (log mM)	-1.403	-1.180	-0.945
T. pyriformis toxicity (log µg/L)	0.411	1.015	1.198
Oral Rat Acute Toxicity (LD_{50}) (mol/kg)	2.142	2.603	2.785
Oral Rat Chronic Toxicity (LOAEL) (log mg/kg_bw/day)	1.208	1.331	1.417
Max. tolerated dose (human) (log mg/kg/day)	0.411	0.602	0.449
Hepatotoxicity	No	No	No
Skin Sensitisation	No	No	No
AMES toxicity	No	No	No
Drug-likeness			
Lipinski	Yes; 0 violation	Yes; 1 violation: MLOGP>4.15	Yes; 1 violation: MLOGP>4.15
Ghose	Yes	No; 1 violation: WLOGP>5.6	No; 1 violation: WLOGP>5.6
Veber	Yes	Yes	Yes
Egan	Yes	Yes	No; 1 violation: WLOGP>5.88

Table 1: ***(Continued)***

PROPERTIES	Compound-A	Compound-B	Compound-C
Muegge	No; 1 violation: XLOGP3>5	No; 1 violation: XLOGP3>5	No; 1 violation: XLOGP3>5
Bioavailability Score	0.55	0.55	0.55
Medicinal Chemistry			
PAINS	0 alert	0 alert	0 alert
Brenk	0 alert	0 alert	0 alert
Lead-likeness	No; 2 violations: MW>350, XLOGP3>3.5	No; 2 violations: MW>350, Rotors>7	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	3.10	3.25	3.35

Bioavailability Radar Plot

The bioavailability radar for oral bioavailability prediction showed desired INSATU = insaturation as per Csp^3 as 0.48, FLEX as per number of rotable bond 7, INSOLU Logs (ESOL) as -5.68 (insoluble), SIZE as molecular weight (g/mol) of 329.04, POLAR as TPSA (Å²) 35.05, and LIPO as XLOGP3 value of 5.99 (**Figure 1A**). The bioavailability radar for oral bioavailability prediction showed desired INSATU = insaturation as per Csp^3 as 0.50, FLEX as per number of rotable bond 8, INSOLU Logs (ESOL) as -5.90 (insoluble), SIZE as molecular weight (g/mol) of 366.54, POLAR as TPSA (Å²) 24.50, and LIPO as XLOGP3 value of 6.32 (**Figure 1B**). The bioavailability radar for oral bioavailability prediction showed desired INSATU = insaturation as per Csp^3 as 0.50, FLEX as per number of rotable bond 7, INSOLU Logs (ESOL) as -6.12 (insoluble), SIZE as molecular weight (g/mol) of 350.54, POLAR as TPSA (Å²) 15.27, and LIPO as XLOGP3 value of 6.71 (**Figure 1C**).

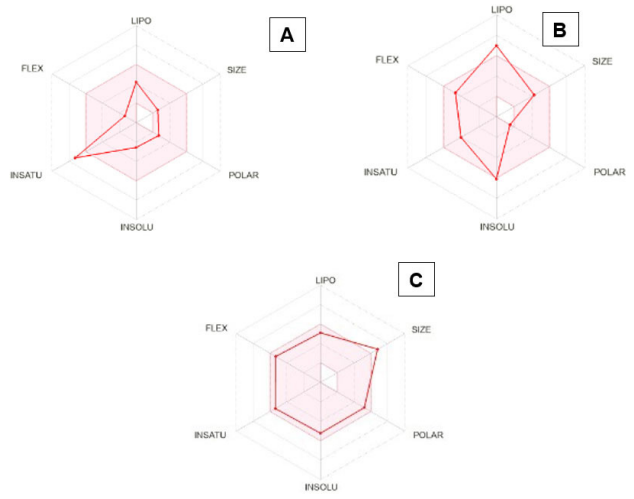


Figure 1: Bioavailability Radar Plot (A) Compound-1, (B) Compound-2, and (C) Compound-3.

Boiled Egg Plot

In case of BOILED-Egg model (**Figure 2**), the Brain OrIntestinaLEstimateD permeation method (BOILED-Egg) has already been proposed as an accurate predictive model, which helps by computational prediction of the lipophilicity and polarity of small molecules. In overall predictive results, novel Indole derivative can be suitable drug candidate as per bioavailability radar and BOILED-Egg representation. It was observed in the predictions that compound-1 (**Figure 2A**) was a PGP positive non-substrate. PGP positive non-substrate molecules are compounds that interact with P-glycoprotein but are not themselves transported by it. These molecules can influence PGP activity in several ways, such as inhibiting or activating its transport function, altering its expression levels, or modulating its conformation. Unlike substrates that are actively pumped out of cells by PGP, non-substrate molecules bind to PGP and affect its function without being expelled. It was obtained that novel Indole derivative, compound-2 (**Figure 2B**) has limited capability of blood-brain barrier penetration as well as it also showed low gastrointestinal absorption. The molecule was found to be PGP positive as non-substrate in predictive model. PGP positive non-substrate behaviour was observed in the predictions for compound-3 (**Figure 2C**). PGP positive non-substrate molecules represent a significant area of interest in pharmacology and drug development. By modulating the function and expression of P-glycoprotein, these molecules offer potential strategies for overcoming multidrug resistance, optimizing drug pharmacokinetics, and enhancing therapeutic efficacy. Ongoing research continues to explore and develop new PGP inhibitors and modulators, aiming to address the challenges posed by drug resistance and improve patient outcomes across various medical conditions.

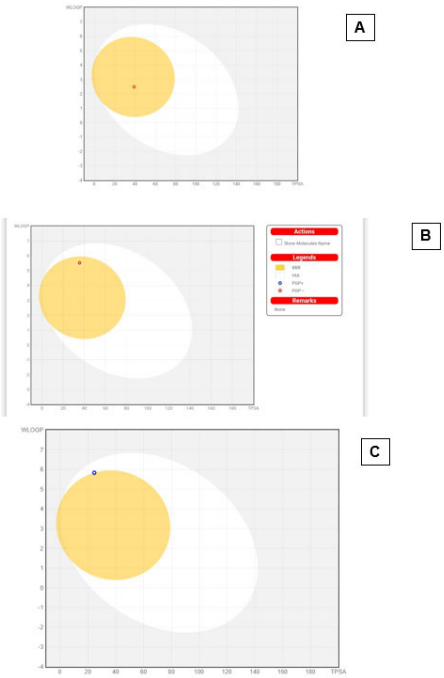


Figure 2: Boiled Egg Plot (A) Compound-1, (B) Compound-2, and (C) Compound-3.

Drug Target Identifications

As the study is focused on drug repurposing, it remains crucial to determine the plausible therapeutic targets against which Compound-1 can inhibit them with micromolar concentrations, ideally. The human (*Homo sapiens*), rat (*Rattus norvegicus*), and mouse (*Mus musculus*) models revealed the inhibitory perspectives of compound-1 against several targets like hydrolase, enzyme, oxidoreductase, Family A G protein-coupled receptor, transferase, voltage-gated ion channel, primary active transporter, ligand-gated ion channel, etc. The predicted results strongly supported the basis of semi-synthesized natural product for possible applications against inflammation by revealing the possibilities of drug interactions with multiple targets.

As the study is focused on determining the interacting profile of Compound-2 against therapeutic targets that have immense pharmacological perspectives, it remains crucial to exactly quantify the plausible therapeutic targets against which Compound-2 can inhibit them with micromolar concentrations, ideally. The human (*Homo sapiens*) model revealed the inhibitory perspectives of Compound-2 against the targets such as Family A G protein-coupled receptor (33.3%), Kinase (26.7%), Electrochemical transporter (13.3%), Protease (20%), and Hydrolase (6.7%). The mouse (*Mus musculus*) model revealed the inhibitory perspectives of Compound-2 against the targets such as Family A G protein-coupled receptor (53.3%), Kinase (6.7%), Electrochemical transporter (6.7%), Unclassified protein (6.7%), Protease (20%), and Enzymes (6.7%). The rat (*Rattus norvegicus*) model revealed the inhibitory perspectives of Compound-2 against the targets such as Family A G protein-coupled receptor (33.3%), Ligand-gated ion channel (20%), Voltage-gated ion channel (6.7%), Electrochemical transporter (6.7%), Enzyme (6.7%), Kinase (6.7%), and Hydrolase (6.7%). The procured predicted results strongly supported the basis of interaction of this small molecule for possible applications against colorectal cancer by revealing the possibilities of interactions with multiple targets (majorly with Family A G protein-coupled receptor).

As the study is focused on determining the interacting profile of Compound-3 against therapeutic targets that have immense pharmacological perspectives, it remains crucial to exactly quantify the plausible therapeutic targets against which Compound-3 can inhibit them with micromolar concentrations, ideally. The human (*Homo sapiens*) model revealed the inhibitory perspectives of Compound-3 against the targets such as Family A G protein-coupled receptor (40%), secreted proteins (20%), other cytosolic protein (20%), enzymes (13.3%), and kinase (6.7%). The mouse (*Mus musculus*) model revealed the inhibitory perspectives of Compound-3 against the targets such as Family A G protein-coupled receptor (40%), kinase (6.7%), enzymes (6.7%), nuclear receptor (6.7%), transcription factor (6.7%), unclassified protein (6.7%), electrochemical transporter (6.7%), and other cytosolic protein (6.7%). The rat (*Rattus norvegicus*) model revealed the inhibitory perspectives of Compound-3 against the targets such as Family A G protein-coupled receptor (40%), enzymes (13.3%), voltage-gated ion channel (6.7%), ligand-gated ion channel (6.7%), kinase (6.7%), nuclear receptor (6.7%), and unclassified protein (6.7%). The procured predicted results strongly supported the basis of interaction of this small molecule for possible applications against inflammatory targets by revealing the possibilities of interactions with multiple targets (majorly with Family A G protein-coupled receptor).

CONCLUSION

The present study provides comprehensive insights into the pharmacological viability and toxicological safety of novel indole-based derivatives through the application of advanced *in silico* methodologies. SwissADME proved to be instrumental in accurately predicting pharmacokinetic behaviors such as gastrointestinal absorption, metabolic stability, and blood-brain barrier permeability, as well as determining drug-likeness and bioavailability. Moreover, off-target prediction tools added significant value by identifying possible unintended interactions, thus allowing early-stage refinement of lead molecules. Organ-specific toxicity predictions, including those for hepatotoxicity, nephrotoxicity, and neurotoxicity, further strengthened the risk-benefit evaluation of the proposed compounds. Overall,

this work highlights the indispensable role of computational chemistry in rational drug design and screening. The findings not only support the potential of indole derivatives as multifunctional therapeutic agents but also pave the way for further *in vitro* and *in vivo* studies. By minimizing the cost and time associated with traditional drug discovery processes, this integrative computational strategy offers a robust starting point for the clinical development of safer, more effective indole-based pharmaceuticals targeting a wide range of diseases including cancer, microbial infections, and neurodegenerative disorders.

CONFLICT OF INTEREST

None declared.

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