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In silico evaluation of drug-likeness and toxicity profiling of selected organic compounds

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Abstract

In silico approaches have become essential tools in modern drug discovery for the therapeutic and cost–effective evaluation of chemical compounds. This study focuses on the assessment of drug-likeness and toxicity profiles of five selected organic compounds: aspirin, caffeine, ibuprofen, metformin, and benzene. The compounds were analyzed using computational tools to evaluate their pharmacokinetic properties based on established criteria such as Lipinski's rule of five, along with toxicity prediction models. The drug likeness analysis revealed that aspirin, caffeine, ibuprofen, and metformin exhibit favorable physicochemical properties, indicating good oral bioavailability and suitability as potential drug candidates. Benzene showed significant toxicity concerns, including predicted carcinogenicity and neurotoxicity. These findings highlight that compliance with drug-likeness rules alone does not guarantee safety and underscore the importance of complementary toxicity assessment during early–stage screening. Toxicity profiling indicated that most compounds possess acceptable safety profiles, whereas benzene demonstrated higher toxicity risks, including possible carcinogenic and mutagenic effects. Overall, this study demonstrates that in silico methods are effective tools for early–stage screening of drug candidates, helping to reduce time, cost, and experimental effort in pharmaceutical research.

Keywords
In silico analysis, drug-likeness, toxicity profiling, lipinski's rule of five, pharmacokinetics.

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1 Introduction

The steps in the drug research and development pipeline are as follows: Target validation and identification, hit-to-lead molecule generation, lead molecule optimization and characterization, drug formulation and delivery, pharmacokinetics and drug disposition, preclinical drug candidate identification, bio analytical testing, and clinical trials [1].Over the past few decades, computational drug discovery has gained significant attention, primarily because it is less risky, time consuming, cost-effective, and resource-intensive than traditional experimental methods. There is always a

great need for new medications that are more effective and less hazardous, but the process of finding and developing new medications is expensive, time-consuming, and fraught with difficulties. Aside from the difficulties with hit discovery and target validation, poor pharmacokinetics, low effectiveness, and excessive toxicity frequently result in a high failure rate in clinical trials [2].

Target identification is the first step in the drug discovery process. Target validation, hit finding, lead optimization, and preclinical/clinical development come next. If a medication candidate is successful, it moves on to the development stage, where it goes through several stages of clinical trials before being submitted for clearance to go on sale [3]. Any unwanted or negative impact of a substance is measured by its toxicity. These negative effects can be quantitative (e.g., LD50: lethal dose to 50% of tested individuals) or qualitative (e.g., binary (e.g., toxic or non-toxic) or ordinary (e.g., low, moderate, or high toxicity). Some of these adverse effects are referred to as toxicity endpoints, such as carcinogenicity or genotoxicity. One kind of toxicity assessment is in silico toxicology, also known as computational toxicology, which organizes, analyzes, models, simulates, visualizes, or predicts the toxicity of chemicals using computational resources (i.e., methodologies, algorithms, software, data, etc.) [4]. In order to possibly eliminate the need for animal testing, lower the cost and duration of toxicity tests, and enhance toxicity prediction and safety evaluation, computational approaches are intended to supplement in vitro and in vivo toxicity experiments. Furthermore, the ability to assess a chemical's toxicity before it is manufactured is a special benefit of computational approaches.Drug discovery has been greatly expedited by the quick development of combinatorial synthesis and high-throughput screening (HTS). These methods make it possible to efficiently create and assess large chemical libraries against biological targets. Natural products continue to be a rich source of bioactive chemicals and aim to play a crucial role in medication development, despite the considerable potential of these approaches [5,6].

Early toxicity assessment is critical for both regulatory agencies and medication development. Confirming the hazardous potential of substances, both separately and in combination, requires experiments. In order to forecast the toxicity of potentially hazardous substances to humans, animals, plants, and the environment, in silico toxicity modeling is quickly emerging as a crucial technique. This field combines expertise from several fields, including as computer science, systems biology, toxicology, and biostatistics [7,8].

Mutagenicity, carcinogenicity, organ toxicity, signaling pathways, and metabolism are just a few of the endpoints that may be used to evaluate a chemical's toxicity. Computational biology methods such as ProTox may be used to quantify it quantitatively (LD_{50}–lethal dosage) and qualitatively (inactive or active) for assays or expression areas such as cytotoxicity, immunotoxicity, and hepatotoxicity [9]. Analyzing the structural characteristics of lead compounds with known hazardous effects is essential to the toxicity model. ProTox 3.0 predicts 45 toxicity outcomes by combining machine learning techniques with molecular similarity [10]. Both the presence of contaminants and the active components themselves can cause drug toxicity. Because of their chemical structure, many contaminants may be harmful. Toxicity may be predicted based on structure-activity relationships (SARs) utilizing computational technologies like computational chemistry and molecular docking [11,12].

One of the primary stages in the creation of drugs and chemicals is toxicity assessment. To assess the possible harmful effects of medications and substances, computational prediction models are thus in great demand. To support the green chemistry paradigm and recognize the significance of green toxicology, regulatory decision-making organizations like the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) as well as environmental health protection organizations like the U.S. Environmental Protection Agency (EPA) and the European Environment Agency (EEA) [13]. Green toxicology helps create chemicals that are safer and less harmful to the environment. Many times, there are still a lot of compounds that need to be evaluated, and testing resources and substance amounts are constrained. These restrictions need the application of computational and higher-throughput in vitro techniques. In silico modeling, high-throughput screening, and structure–activity relationship analysis are examples of intelligent testing techniques that make it possible to quickly and affordably identify any toxicity issues. Researchers may select safer options and create goods with less negative effects on the environment and human health by utilizing these prediction technologies [14].

This study presents a novel in silico approach for the evaluation of drug-likeness and toxicity profiling of selected organic compounds. Unlike previous studies that focuses on a limited number of parameters, this research integrates multiple computational tools such as SwissADME and toxicity

prediction platforms to provide a comprehensive assessment. Rather than introducing novel compounds, this study presents a comparative benchmark analysis of five structurally diverse reference compounds using SwissADME and ProTox 3.0. The work highlights how computational tools evaluate compounds with different pharmacological and toxicological characteristics and demonstrates their applicability and limitations in early- stage screening.

2 Materials and methods

Five compounds, namely aspirin, caffeine, ibuprofen, metformin, and benzene, were selected for the present study. The canonical SMILES and PubChem Compound Identification Numbers (CID) of the selected compounds were obtained from the PubChem database and input for all computational analyses, Table 1.

Table 1: PubChem CID and canonical SMILES of selected compounds

Compound	PubChem CID	Canonical SMILES
Aspirin	2244	CC(=O)OC1=CC=CC=C1C(=O)O
Caffeine	2519	CN1C=NC2=C1C(=O)N(C(=O)N2C)C
Ibuprofen	3672	CC(C)CC1=CC=C(C=C1)C(C)C(=O)O
Metformin	4091	CN(C)C(=N)N=C(N)N
Benzene	241	C1=CC=CC=C1

2.1 Pharmacokinetic properties and drug-likeness of selected organic compounds

Pharmacokinetics properties and drug–likeness parameters of the selected compounds were evaluated using the SwissADME web server (http://www.swissadme.ch/ accessed on march 20, 2026). The canonical SMILES of aspirin, caffeine, ibuprofen, metformin, and benzene were obtained from the PubChem database and used as input for analysis. The platform was used to predict physicochemical properties, lipophilicity, water solubility, pharmacokinetic parameters, drug-likeness characteristics, and BOILED-Egg profiles. All analyses were performed using the default settings of the SwissADME server [15].

2.2 *In silico* toxicity prediction

Toxicity prediction was performed using the ProTox–3.0 web server (http://tox.charite.de/protox3/ accessed on March 20, 2026). The canonical SMILES of each compound were submitted to the platform to predict LD_{50} values, toxicity classes, mutagenicity, carcinogenicity, cytotoxicity, and immunotoxicity. The toxicity classification was based on the Globally Harmonized System (GHS) for chemical classification and labeling. All predictions were carried out using the default settings of the server [16].

Table 2: Phytochemical properties of the selected organic compounds

Mol.	Name	SMILES	No. heavy atoms	No. arom. heavy atoms	Fraction Csp3	No. rotable bonds	No. H-bond acceptors	No. H-bond donors	Molar refractivity	TPSA (Å^2)
1	Aspirin	CC(=O)OC1=CC=CC=C1C(=O)O	13	6	0.11	3	4	1	44.90	63.60
2	Caffeine	CN1C=NC2=C1C(=O)N(C(=O)N2C)C	14	9	0.38	0	3	0	52.04	61.82
3	Ibuprofen	CC(C)CC1=CC=C(C=C1)C(C)C(=O)O	15	6	0.46	4	2	1	62.18	37.30
4	Metformin	CN(C)C(=N)N=C(N)N	9	0	0.50	2	2	3	36.93	91.49
5	Benzene	C1=CC=CC=C1	6	6	0.00	0	0	0	26.44	0.00

3 Results and discussion

3.1 Results

3.1.1 Physicochemical properties of the selected organic compounds

The SwissADME website was used to produce the compounds' physicochemical characteristics. Table 2 lists the overall number of heavy atoms and aromatic heavy atoms, the proportion of carbon atoms in a molecule (Csp3), the number of rotatable bonds, hydrogen bond providers and acceptors, molar refractivity, and the molecules' topological polar surface area (TPSA). The number of hydrogen donors ranged from 0 to 3, the number of hydrogen acceptors ranged from 0 to 4, the molecules' molar refractivity ranged from 26.44 to 62.18, and the TPSA ranged from 0 to 91.49.

The radar chart (Figure 1) visually compares the molecular weight (MW), lipophilicity (LogP), topological polar surface area (TPSA), hydrogen bond donors (HBD), and hydrogen bond acceptors (HBA) of aspirin, caffeine, ibuprofen, metformin and benzene. Among the selected compounds, aspirin exhibits the highest molecular weight (MW), while ibuprofen shows the highest lipophilicity (LogP), indicating its greater hydrophobic nature. Metformin has the highest TPSA and the highest number of hydrogen bond donors (HBD = 3), reflecting its highly polar and hydrophilic character. Caffeine possesses the highest number of hydrogen bond acceptors (HBA = 4), whereas benzene has the lowest TPSA ($Å^2$) and contains no hydrogen bond donors or acceptors, resulting in the smallest polar profile. Overall, the radar chart clearly demonstrates the distinct physicochemical characteristics of the five selected compounds and facilitates their visual comparison.

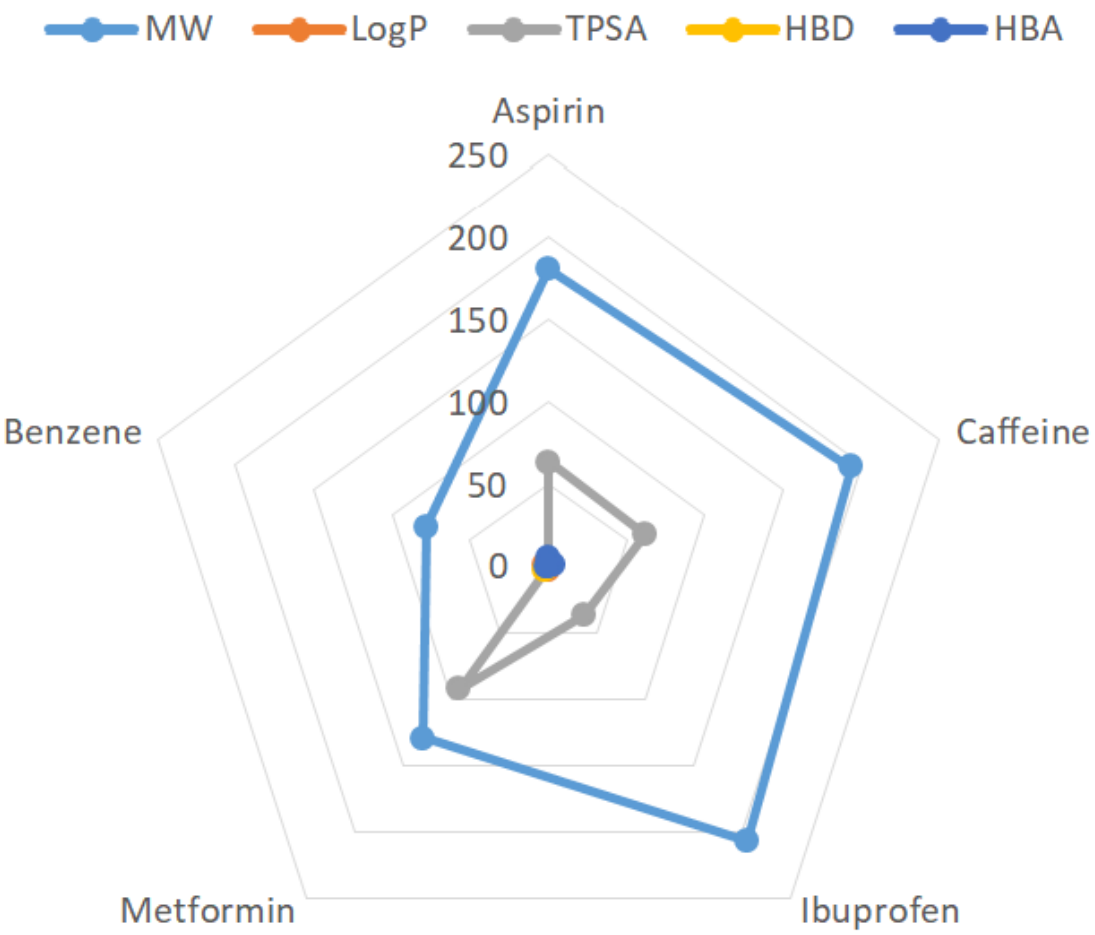

Figure 1: Radar chart comparing the physiochemical properties of aspirin, caffeine, ibuprofen, metformin, and benzene based on molecular weight (MW), lipophilicity(LogP), topological polar surface (TPSA), hydrogen bond donors (HBD), and hydrogen bond acceptors.

Table 3: Lipophilicity of the selected organic compounds

Molecule	iLOGP	XLOGP3	WLOGP	MLOGP	SILICOS-IT	Consensus Log $P_{o/w}$
1	1.30	1.19	1.31	1.51	1.10	1.28
2	1.79	-0.07	-1.03	0.22	-0.50	0.08
3	2.17	3.50	3.07	3.13	3.15	3.00
4	0.34	-1.27	-1.24	-0.56	-1.74	-0.89
5	1.58	2.13	1.69	3.17	2.12	2.14

Table 4: Water solubility of the selected organic compounds

Molecule	ESOL				Ali			
	Log S (ESOL)	Solubility (mg/mL)	Mol/L	Class	Log S (Ali)	Solubility (mg/mL)	Mol/L	Class
1	-1.85	2.54E+00	1.41E−02	Very soluble	-2.12	1.36E+00	7.56E−03	Soluble
2	-1.48	6.50E+00	3.35E−02	Very soluble	-0.78	3.25E+01	1.67E−01	Very soluble
3	-3.36	9.09E−02	4.41E−04	Soluble	-3.97	2.23E−02	1.08E−04	Soluble
4	0.29	2.53E+02	1.96E+00	Highly soluble	-0.15	9.05E+01	7.00E−01	Very soluble
5	-2.14	3.07E−01	3.92E−03	Soluble	-1.76	1.35E+00	1.73E−02	Very soluble

Table 5: Pharmacokinetic parameters of the selected organic compounds

Molecule	GI absorption	BBB permeant	P-gp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor
1	High	Yes	No	No	No	No	No
2	High	No	No	No	No	No	No
3	High	Yes	No	No	No	No	No
4	High	No	No	No	No	No	No
5	Low	No	No	Yes	No	No	No

3.1.2 Lipophilicity and solubility of the selected organic compounds

The SwissADME website was used to determine the compounds' lipophilicity and solubility. The lipophilicity of the all compounds were ranged from 0.34 to 2.17, it should be less than 5 (Table 3). Every molecule belongs to the Ali and ESOL soluble class, and every molecule belongs to the SILICOS-IT soluble class (Table 4).

3.1.3 Pharmacokinetic parameter of the selected organic compounds

Table 5 shows the pharmacokinetic characteristics of the selected organic compounds. The gastrointestinal absorption of molecules 1, 2, 3, and 4 was High, while that of 5 molecule was Low. The molecules 1 and 3 are excellent BBB permeates, but molecules 2, 4, and 5 have a detrimental effect. P-glycoprotein results were negative for all molecules. The compounds' cytochrome p40 enzyme inhibition results are shown in Table 5.

The predicted gastrointestinal absorption and blood-brain barrier permeation characteristics of the selected compounds were further evaluated using the SwissADME BOILED-Egg model (Figure 2). The yellow region indicates a high probability of gastrointestinal (GI) absorption, whereas the white region indicates a high probability of blood –brain barrier (BBB) permeation. The position of each compound within the BOILED-Egg model provides a visual representation of its predicted pharmacokinetic behavior.

3.1.4 Drug likeness properties of the selected organic compounds

All selected organic compounds follow Lipinski's rule. Table 6 lists the additional rules, such as Ghose, Egan, Veber, and Muegge findings, that were assessed for drug likeness for each of the 5 compounds. The bioavailability score of molecules 2, 4, and 5 was 0.55; the other molecules had a bioavailability score of 0.85. According to the Lipinski rule of five, molecules should have a molecular weight of less than 500 g/mol, a lipophilicity of less than five, less than five hydrogen bond providers and acceptors, a molar refractivity of less than 120, solubility, and TPSA between 0 and 140 Å.

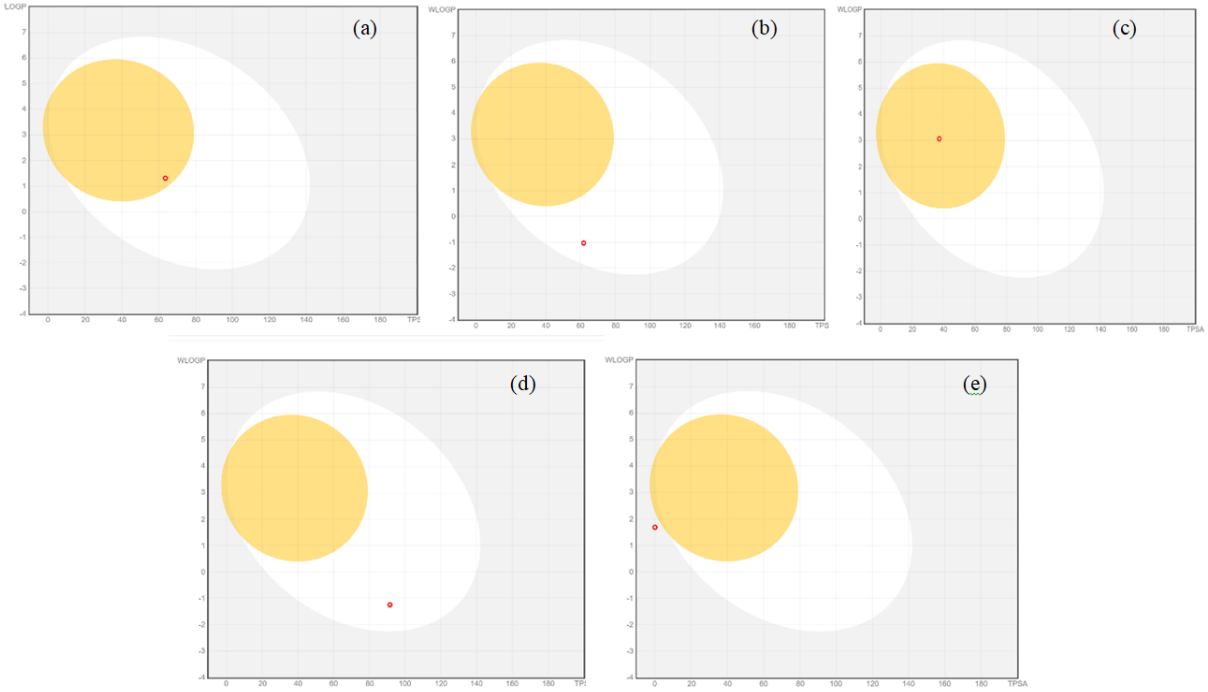

Figure 2: Comparative BOILED-Egg plots generated using SwissADME for the selected compounds: (A) Aspirin, (B) Caffeine, (C) Ibuprofen, (D) Metformin, and (E) Benzene.

Table 6: Drug-likeness properties of the selected organic compounds

Molecule	Lipinski	Ghose	Veber	Egan	Muegge	Bioavailability score
1	0, Yes	Yes	Yes	Yes	1, No	0.85
2	0, Yes	Yes	1, No	Yes	0, No	0.55
3	0, Yes	Yes	Yes	Yes	Yes	0.85
4	0, Yes	3, No	Yes	Yes	2, No	0.55
5	0, Yes	3, No	Yes	Yes	2, No	0.55

Table 7: Oral toxicity of selected organic compounds predicted by ProTox 3

Tested compound	Result of oral toxicity prediction			
	Predicted toxicity class	Predicted LD_{50} (mg/kg bw)	Average similarity (%)	Prediction accuracy (%)
1	3	250	100.00	100.00
2	3	127	100.00	100.00
3	3	299	100.00	100.00
4	4	680	49.12	54.26
5	4	930	100.00	100.00

3.1.5 In silico toxicity prediction by ProTox 3

Table 7 records the oral acute toxicity data and the associated toxicity class for each medication. Molecules 1, 2 and 3 were expected to be in the III toxicity class, molecule 4 was anticipated to be in the IV toxicity class. For molecule 1, the predicted fatal doses (LD_{50}) are 250 mg/kg body weight, 127 mg/kg body weight for molecules 2. Molecule 3, 4 and 5 have 299, 680 and 930 mg/kg body weight respectively. The projected accuracy percentage for the chosen compounds was between 54.24 to 100,

whereas the average similarity percentage varied from 49.12 to 100.

For each of the chosen compounds, the organ toxicity probability was estimated and is shown in Table 8. According to the results, all of the molecules fall into classes IV and the fatal dose was found to be between 680 and 930 mg/kg of body weight, indicating that the compounds are less harmful when taken orally. In terms of organ toxicity probability, the five chosen compounds are inactive for hepatotoxicity and cardio toxicity, and in terms of toxicity endpoint probability, they are inactive for mutagenicity. Nevertheless, molecules 2 and 5 are active for Neurotoxicity and molecule 5 carcinogenicity.

Table 8: Hepatotoxicity and toxicological endpoint predictions of the selected organic compounds estimated using the ProTox-3 web server

Molecule	Organ Toxicity				Toxicity Endpoint (Probability)			
	Hepato–toxicity	Neuro–toxicity	Respiratory toxicity	Cardio–toxicity	Carcino–toxicity	Immuno–toxicity	Mutagenicity	Cytotoxicity
1	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
2	Inactive	Active	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
3	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
4	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
5	Inactive	Active	Inactive	Inactive	Active	Inactive	Inactive	Inactive

3.2 Discussion

With the exception of compounds 8, 12, and 21, all of the compounds had numbers of hydrogen acceptors ranging from 0 to 7, which should be less than 10, numbers of hydrogen donors ranging from 0 to 2, which should be less than 5, molar refractivity ranging from 37 to 112, which should be less than 120, and TPSA ranging from 0 to 84, which should be between 0 and 140 [17]. A set of guidelines for creating drug-like chemical libraries was put forth by Ghose et al. [18], who suggested the following ranges of properties: molecular weights between 160 and 480, computed logP values between - 0.4 and 5.6, acceptable molar refractivity values between 40 and 130, and a total atom count between 20 and 70.According to Veber's rule, which is used in medication development, compounds with a polar surface area (PSA) of 140 or less and no more than 10 rotatable bonds often exhibit high oral bioavailability [19]. According to Egan criteria, compounds with good oral absorption usually have a molecular weight between 200 and 600 Daltons, a LogP between - 0.4 and 5.0, and a maximum of six hydrogen bond donors, five acceptors, and twelve hydrogen bond acceptors [20].According to Muegge rules, a compound is likely to have good oral bioavailability and effective absorption if it has a molecular weight between 200 and 600 Da, a LogP within –2 to 5, a polar surface area less than 150 $Å^2$ under seven ring structures, a reduced hydrogen bonding potential (donors < 5, acceptors < 10), and rotatable bonds (less than 15) [21]. An online program called SwissADME forecasts a drug candidate's absorption, distribution, metabolism, and excretion (ADME) characteristics. It does this by assessing factors such drug-likeness, water solubility, pharmacokinetic characteristics, lipophilicity, physicochemical descriptors, and medicinal chemistry compatibility [22]. A popular method for evaluating a compound's molecular properties and identifying those that are more likely to be effective therapeutic candidates is Lipinski's "Rule of 5." Important factors including molecular weight, the quantity of hydrogen bond donors and acceptors, lipophilicity, and molar refractivity are all examined by this rule. Metabolites in this study adhere to Lipinski's Rule of 5 as they are within the suggested bounds without going against any of the guidelines [23]. A medicinal molecule may be more flexible if it has fewer rotatable bonds. When taken orally, the drug's gastrointestinal absorption indicates that it can enter the digestive system. The blood-brain barrier (BBB), a physiological barrier that divides the brain from the circulation, is made up of a layer of micro vascular endothelial cells. The central nervous system depends on substances that can pass across the blood-brain barrier. Many pharmaceutical substances are P-glycoprotein substrates, which reduces oral bioavailability, permeability, absorption, and retention time. P-glycoproteins are more abundantly expressed in cancer cells, which makes it difficult to diagnose cancer since they encourage drug efflux and make chemotherapy less successful. Thus, ligands that are not P-glycoprotein substrates are thought to be more appropriate for the therapy of cancer. The amount of a medication that enters the circulation when taken orally is known as its bioavailability, and it is an important factor in drug design. Bioavailability is mostly determined by intestinal absorption. A medication is more likely to be efficiently digested and become accessible after oral delivery if it does not block enzymes. When assessing medications used for transdermal distribution, skin permeability is a crucial consideration. Lower skin permeability for

the chemical is indicated by a larger negative logKp value [24].

Four toxicological outcomes are predicted by ProTox-3: immunotoxicity, cytotoxicity, mutagenicity, and carcinogenicity. The capacity of some substances or cell mediators to harm or destroy living cells is known as cytotoxicity. A comparison between ProTox 3 predictions and available experimental evidence revealed both the strengths and limitations of computational toxicity assessment. Aspirin, caffeine, ibuprofen, and metformin exhibited toxicity profiles that were generally consistent with their established safety records and pharmacological applications. In contrast, ProTox 3 predicted benzene as inactive for mutagenicity, whereas extensive experimental and epidemiological studies have identified benzene as a confirmed in vivo mutagen and a Group 1 human carcinogen. This discrepancy may arise from limitations in predictive modeling, training datasets, or the complexity of benzene-induced genotoxic mechanisms. Therefore, while in silico tools provide valuable preliminary toxicity screening, their predictions should be interpreted alongside experimental evidence and authoritative toxicological that computational predictions are useful for early-stage evaluation but cannot fully replace laboratory and clinical toxicological investigations. If cytotoxic effects develop close to the site of damage, this process may impede the healing of the lesion [25]. The ability of a chemical or medication to damage DNA or chromosomes and result in mutations is known as mutagenicity; compounds that are able to do so are referred to as mutagens. Although genotoxicity refers to transient alterations in DNA or chromosomes, the terms mutagenicity and genotoxicity are sometimes used interchangeably. Not all genotoxic compounds are mutagenic, even if all mutagenic substances are genotoxic [25,26]. A substance's capacity to encourage the development of cancer is known as carcinogenicity, and it is defined by its capacity to produce aberrant cell growth in either people or animals [27].

4 Conclusion

This study successfully conducted an in silico evaluation of drug likeness and toxicity profiles of selected organic compounds, namely aspirin, caffeine, ibuprofen, metformin and benzene, The drug-likeness assessment revealed that aspirin, caffeine, ibuprofen and metformin largely comply with established criteria such as Lipinski's rule of five, indicating favorable pharmacokinetic properties and suitability as drug candidates. Benzene satisfies Lipinski's rule despite being a known carcinogen, demonstrating that drug-likeness rules alone cannot identify toxic compounds.

Toxicity profiling further highlighted significant differences among the compounds. While aspirin, caffeine, ibuprofen, and metformin demonstrated acceptable safety profiles within predicted limits, benzene exhibited highly toxicity risks, including potential carcinogenicity and mutagenicity. These findings emphasize the importance of structural features in determining both efficacy and safety of chemical compounds. Overall, this study demonstrates that in silico tools are effective, rapid, and cost efficient approaches for preliminary screening of drug-likeness and toxicity. Such computational methods can significantly reduce the need for extensive experimental studies in early stage drug discovery. The results support the continued use of computational approaches compounds while eliminating potentially hazardous substances at early stage.

Abbreviations

LogP: Lipophilicity
TPSA: Topological polar surface area
HBD: Hydrogen bond donor
HBA: Hydrogen bond acceptor
ADME: Absorption Distribution, Metabolism, and Excretion
BBB: Blood Brain Barrier
GI: Gastro intestinal
CID: Compound identification numbers

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Conflicts of interest

The authors declare that there are no conflicts of interest associated with the publication of this research paper.

Author's contribution

DRJ: Performed work, writing, review, Data analysis and original draft. SRO: Writing, review, editing, and Formal analysis. IO: Writing, review and Data analysis.

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