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Pharmacokinetics and Druglikeness of Amoxicillin Drug using SwissADME

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Abstract— Amoxicillin, a widely utilized semi-synthetic penicillin derivative, remains a cornerstone in treating various bacterial infections. Despite its extensive clinical application, a comprehensive *in silico* assessment of its pharmacokinetic and "druglikeness" properties using modern computational tools can provide valuable complementary insights. This study employed the SwissADME web platform to meticulously analyze the computed descriptors, physicochemical characteristics, ADME profile, druglikeness, and medicinal chemistry aspects of amoxicillin. The chemical structure of amoxicillin, represented by its SMILES string, was retrieved from the PubChem database and subsequently input into SwissADME for analysis. The results indicate that amoxicillin possesses a molecular weight of 365.40 g/mol and a hydrophilic nature, as evidenced by its consensus LogP value of -0.39 and high water solubility predictions. Its Topological Polar Surface Area (TPSA) is 158.26 Å^2, and it contains 4 hydrogen bond donors and 6 hydrogen bond acceptors. While the *in silico* prediction for gastrointestinal (GI) absorption was "Low" (likely due to the high TPSA and hydrophilicity, suggesting reliance on active transport mechanisms *in vivo*), amoxicillin fully complies with Lipinski's Rule of Five, indicating good oral bioavailability potential. Furthermore, it is predicted not to permeate the Blood-Brain Barrier (BBB) and shows no inhibitory activity against major CYP450 enzymes (CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4) or P-glycoprotein, minimizing potential drug-drug interactions. The absence of PAINS and Brenk alerts signifies a clean chemical profile regarding assay interference and toxicity flags. Although some stricter druglikeness filters were violated due to its polar nature, amoxicillin's overall *in silico* profile, combined with its established clinical efficacy, highlights the complex interplay of physicochemical properties and biological transport mechanisms. This study reaffirms amoxicillin's favorable attributes from a computational perspective, serving as a valuable reference for understanding established antibiotics and guiding future antimicrobial design.

Keywords: Amoxicillin, Pharmacokinetics, Druglikeness, SwissADME, In silico.

1. Introduction

Bacterial infections represent a significant global health issue that continues to pose serious challenges, contributing notably to illness and death rates worldwide [1]. Pathogenic bacteria can result in various diseases, ranging from respiratory infections and urinary tract infections to life-threatening systemic infections [2]. To combat these infections, antibiotics have served as a fundamental line of defense since Alexander Fleming discovered penicillin [3]. However, the widespread and sometimes uncontrolled use of antibiotics has led to antimicrobial resistance (AMR) emerging as an urgent global threat, diminishing

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the effectiveness of many previously reliable antibiotics [4].

Amoxicillin, a semi-synthetic derivative of penicillin, is a broad-spectrum beta-lactam antibiotic commonly prescribed for various infections caused by Gram-positive bacteria and some Gram-negative ones [5]. Its proven effectiveness, relatively favorable safety profile, and wide availability make it one of the most frequently prescribed antibiotics globally [6]. Nevertheless, a thorough understanding of amoxicillin's pharmacokinetics and its "druglikeness" characteristics is essential to ensure optimal therapeutic effectiveness, minimize side effects, and aid in addressing resistance strategies [7].

Pharmacokinetics is a branch of pharmacology that investigates the journey of drugs within the body, covering processes like absorption, distribution, metabolism, and elimination (ADME) [8]. Pharmacokinetic parameters such as bioavailability, half-life, distribution volume, and clearance influence the precise dosage, administration frequency, and treatment duration needed to achieve effective therapeutic concentrations at the infection site [9]. Meanwhile, "druglikeness" is a crucial concept in drug discovery and development that refers to the likelihood that a compound will exhibit favorable physicochemical properties and ADME characteristics, making it a potential successful drug candidate [10]. The attributes of druglikeness predict whether a molecule will demonstrate good absorption, adequate distribution, reasonable metabolism, proper elimination, and low toxicity [11].

With advancements in computing and bioinformatics, in silico methods have become invaluable tools for expediting drug discovery and development [12]. One widely utilized tool is SwissADME, a free web platform that provides comprehensive predictions about a molecule's ADME properties, pharmacokinetics, and druglikeness based on its chemical structure [13]. Utilizing SwissADME facilitates the rapid and efficient initial evaluation of a compound's potential as a drug, significantly reducing the need for costly and time-intensive in vitro and in vivo experiments, especially during the early stages of research [14].

Although amoxicillin has been extensively utilized over the years, a thorough analysis of its pharmacokinetic properties and druglikeness using modern in silico tools like SwissADME remains relevant and could yield additional insights [15]. This study aims to conduct an in-depth analysis of the pharmacokinetic characteristics and druglikeness of amoxicillin using the SwissADME platform [16]. The findings of this research are expected to reaffirm and enhance existing data on amoxicillin from a computational standpoint, providing a better understanding of why amoxicillin exhibits a favorable profile as an antibiotic and potentially serving as a reference for further research in optimizing antibiotics or developing new antimicrobial agents [17].

2. Method

This study adopts a computational in silico approach to evaluate the pharmacokinetic and druglikeness properties of amoxicillin by utilizing publicly accessible chemical databases and specialized bioinformatics tools. The methodology is divided into two main stages: data acquisition and computational analysis using the SwissADME platform.

The first stage involves the acquisition of chemical structure data. Specifically, the Simplified Molecular Input Line Entry System (SMILES) representation of amoxicillin was retrieved from the PubChem database, a well-established and openly accessible chemical information resource maintained by the National Center for Biotechnology Information (NCBI). PubChem provides validated and standardized data on chemical compounds, including their 2D and 3D structures, biological activities, and literature references. To obtain the canonical SMILES string, a direct search for "Amoxicillin" was performed on the

PubChem website (https://pubchem.ncbi.nlm.nih.gov), and the structure was extracted from the compound's dedicated entry. This textual format is essential as it offers a unique, machine-readable representation of the molecule, ensuring compatibility with computational tools. Figure 1 presents the two-dimensional depiction of the amoxicillin molecule, while Figure 2 displays the interactive three-dimensional model sourced from PubChem.

Once the canonical SMILES string was obtained and verified against known structural representations to ensure accuracy, the second stage—computational analysis using SwissADME—was conducted. SwissADME (https://www.swissadme.ch), developed by the Swiss Institute of Bioinformatics (SIB), is a widely recognized web-based tool for predicting various physicochemical and pharmacokinetic properties, as well as druglikeness and medicinal chemistry friendliness. Upon accessing the SwissADME platform, the SMILES string of amoxicillin was entered into the input interface. The tool then generated a comprehensive report covering multiple predictive categories.

The first analytical category includes physicochemical properties, such as molecular weight, lipophilicity (LogP), number of hydrogen bond donors (HBD), number of hydrogen bond acceptors (HBA), topological polar surface area (TPSA), and the number of rotatable bonds. These parameters provide insight into the molecule’s potential for absorption and permeability across biological membranes. The second category pertains to pharmacokinetic (ADME) properties, including gastrointestinal (GI) absorption (predicted as high or low), blood–brain barrier (BBB) permeability, P-glycoprotein (P-gp) substrate/inhibitor predictions, and the inhibitory potential against cytochrome P450 (CYP) isoenzymes—specifically CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4. These attributes are critical for evaluating oral bioavailability, brain penetration potential, and drug–drug interaction risks.

The third aspect of the analysis addresses the druglikeness of amoxicillin, assessed through several established filters including Lipinski’s Rule of Five, Ghose, Veber, Egan, and Muegge filters. These rules offer predictive criteria for evaluating oral bioavailability and membrane permeability. Any violations or deviations from these rules are noted and discussed to determine the implications for drug-likeness. Figure 3 illustrates a mind map summary of these predictive domains.

Lastly, the medicinal chemistry friendliness of the compound is evaluated, which encompasses synthetic accessibility (SA) scores—indicating the ease of chemical synthesis—and the identification of any PAINS (Pan Assay Interference Compounds) or Brenk alerts. These structural alerts highlight molecular fragments that are frequently associated with assay interference or toxicity concerns. Although amoxicillin is an established pharmaceutical agent, this additional layer of analysis provides modern insights into its structural and chemical properties from a drug discovery perspective.

All outputs generated by SwissADME were systematically recorded. Both the numerical values and qualitative predictions (e.g., "High," "Low," "Yes," "No") formed the basis for interpretation and discussion. The use of a single, standardized tool ensures consistency and comparability across all parameters, enhancing the reliability of the findings. Table 1 summarizes the key computed descriptors of amoxicillin, including its IUPAC name, InChI, InChIKey, SMILES string, and molecular formula.

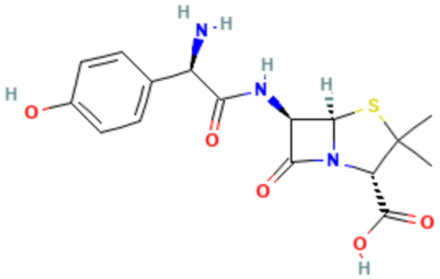


Figure 1. Chemical Structure Depiction

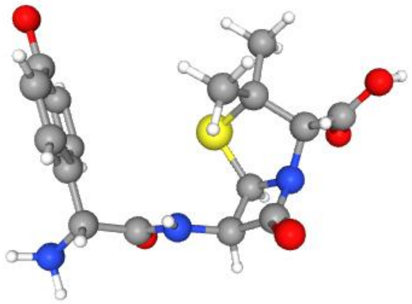


Figure 2. Interactive Chemical Structure Model

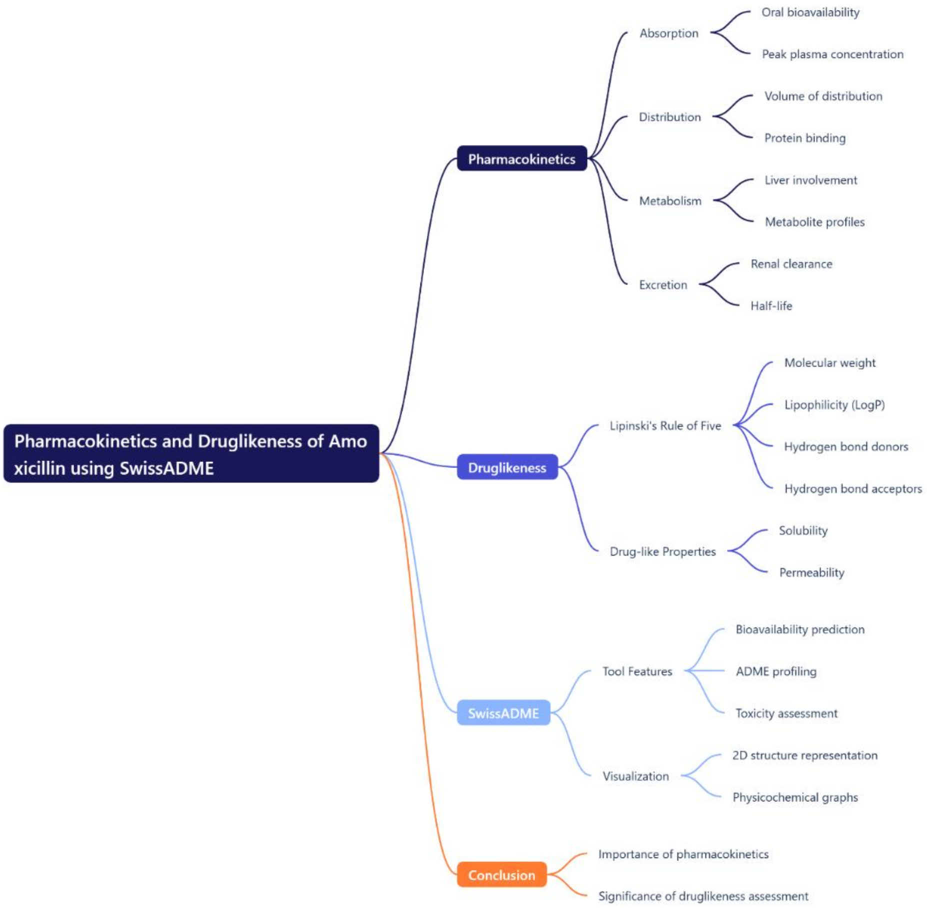


Figure 3. Mind Maps

Tabel 1. Computed Descriptors of Amoxicillin

Category	Sub-Category	Description
2.1 Computed Descriptors	2.1.1 IUPAC Name	(2S,5R,6R)-6-[[(2R)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid
	2.1.2 InChI	InChI=1S/C16H19N3O5S/c1-16(2)11(15(23)24)19-13(22)10(14(19)25-16)18-12(21)9(17)7-3-5-8(20)6-4-7/h3-6,9-11,14,20H,17H2,1-2H3,(H,18,21)(H,23,24)/t9-,10-,11+,14-/m1/s1
	2.1.3 InChIKey	LSQZJLSUYDQPKJ-NJBDSQKTSA-N
	2.1.4 SMILES	CC1(C@@HC(=O)O)C
2.2 Molecular Formula		C16H19N3O5S

3. Result and Discussion

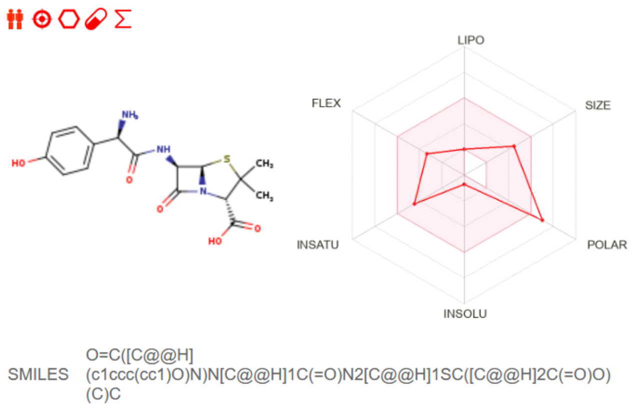
The in silico analysis of Amoxicillin using the SwissADME platform yields comprehensive insights into its physicochemical properties, pharmacokinetic profile, druglikeness, and medicinal chemistry characteristics. These computational predictions are particularly valuable in early-stage drug discovery as they provide efficient, cost-effective evaluations of a compound's potential behavior within biological systems. Given Amoxicillin's well-established role as a beta-lactam antibiotic, it serves as an ideal reference model to explore the reliability and depth of in silico assessments.

SwissADME identifies the compound under investigation as "Molecule 1," corresponding to Amoxicillin. The general chemical features of Amoxicillin are illustrated in Figure 4, which presents both its two-dimensional structural representation and associated chemical information. The molecule features a beta-lactam ring, thiazolidine core, and a side chain incorporating a phenol ring and an amino group. Its canonical SMILES string—O=C(C@HN)NC(=O)[C@H]1N2C@HC(=O)O—accurately encodes its molecular structure for computational analysis. With a molecular formula of $C_{16}H_{19}N_3O_5S$ and a molecular weight of 365.40 g/mol, Amoxicillin falls within the ideal range (<500 g/mol) for oral drug candidates. Additionally, it contains 25 heavy atoms and 6 aromatic heavy atoms. A fraction Csp^3 value of 0.44 indicates a relatively balanced degree of saturation, which may influence solubility and target interactions.

Figure 5 highlights the molecule's physicochemical properties, essential for predicting oral bioavailability. Amoxicillin has five rotatable bonds, consistent with favorable molecular flexibility for oral drugs. It possesses six hydrogen bond acceptors and four donors, parameters well-aligned with Lipinski's Rule of Five. The molar refractivity value is 94.59, suggesting a moderate potential for nonspecific interactions. Notably, its topological polar surface area (TPSA) is 158.26 Å^2—exceeding the 140 Å^2 threshold typically associated with optimal intestinal absorption. This high TPSA also suggests limited capacity to cross the blood–brain barrier.

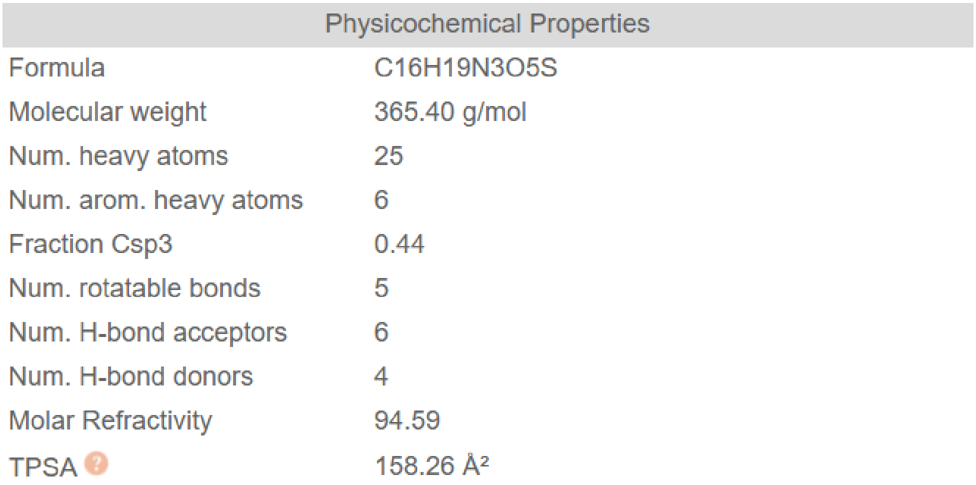
Figure 6 presents Amoxicillin's lipophilicity profile, a critical determinant of membrane permeability. Multiple LogP values were calculated using different algorithms, with the consensus Log $P_o/_x$ value of -0.39 indicating a predominantly hydrophilic nature. While such hydrophilicity supports solubility, it may hinder passive diffusion through lipid membranes. However, despite this, Amoxicillin exhibits good oral bioavailability in practice—likely due to transporter-mediated absorption, rather than passive diffusion alone.

Consistent with this interpretation, Figure 7 reports the water solubility predictions, with values such as Log S (ESOL) at -0.70, Log S (Ali) at -0.81, and Log S (SILICOS-IT) at -1.62, all classifying Amoxicillin as "very soluble" or "soluble" in water. This is a highly desirable trait for oral drugs, as it promotes rapid dissolution in gastrointestinal fluids.



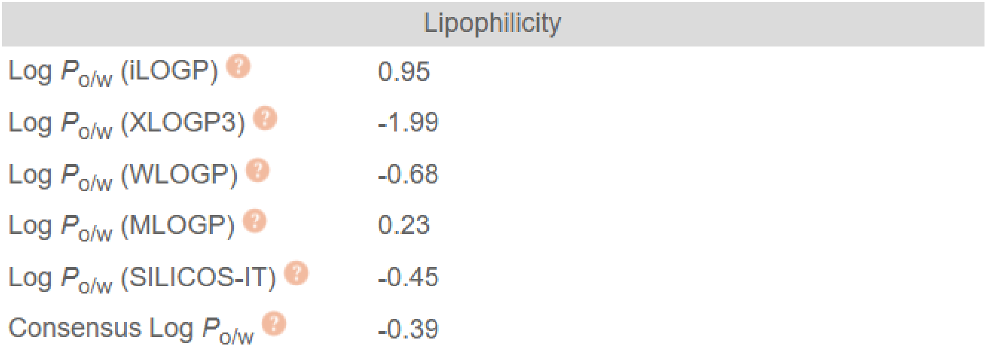
SMILES O=C([C@@H](c1ccc(cc1)O)N)N[C@@H]1C(=O)N2[C@@H]1SC([C@@H]2C(=O)O)(C)C

Figure 4. General Molecule Information and Chemical Structure



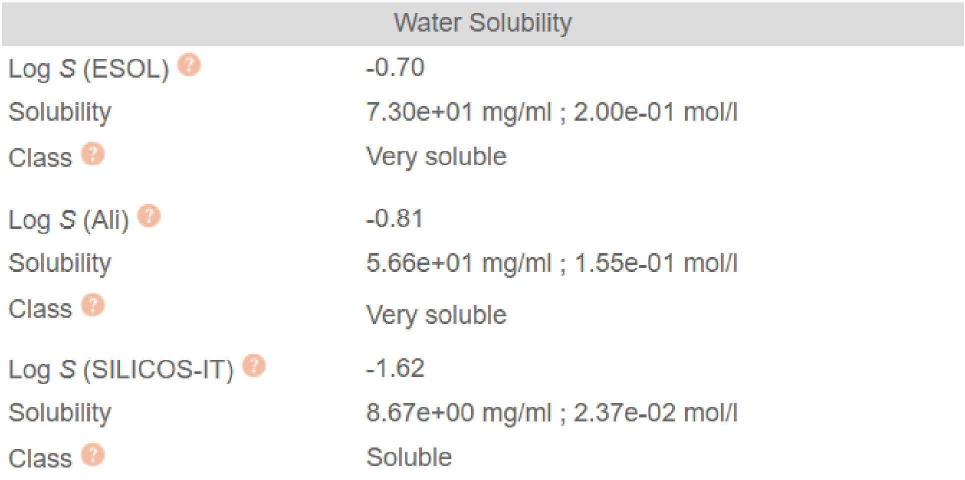
Physicochemical Properties	
Formula	C16H19N3O5S
Molecular weight	365.40 g/mol
Num. heavy atoms	25
Num. arom. heavy atoms	6
Fraction Csp3	0.44
Num. rotatable bonds	5
Num. H-bond acceptors	6
Num. H-bond donors	4
Molar Refractivity	94.59
TPSA	158.26 Å²

Figure 5. Physicochemical Properties



Lipophilicity	
Log $P_{o/w}$ (iLOGP)	0.95
Log $P_{o/w}$ (XLOGP3)	-1.99
Log $P_{o/w}$ (WLOGP)	-0.68
Log $P_{o/w}$ (MLOGP)	0.23
Log $P_{o/w}$ (SILICOS-IT)	-0.45
Consensus Log $P_{o/w}$	-0.39

Figure 6. Lipophilicity



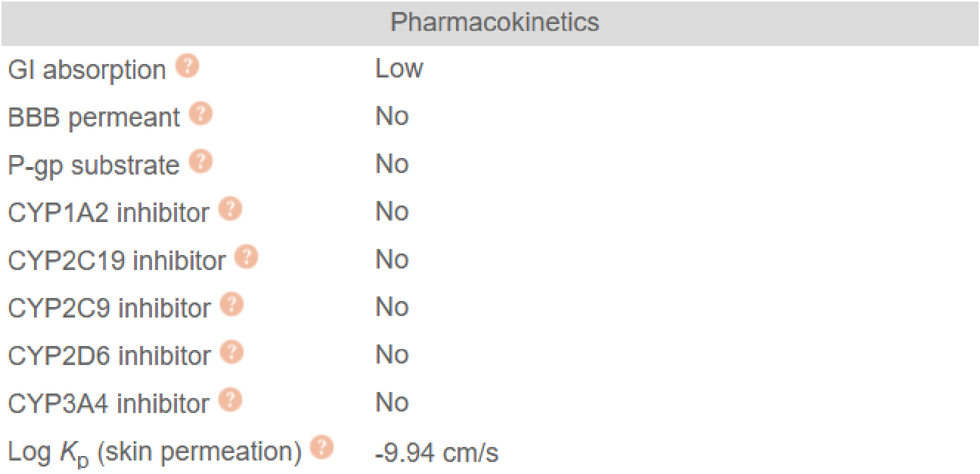
Water Solubility	
Log *S* (ESOL)	-0.70
Solubility	7.30e+01 mg/ml ; 2.00e-01 mol/l
Class	Very soluble
Log *S* (Ali)	-0.81
Solubility	5.66e+01 mg/ml ; 1.55e-01 mol/l
Class	Very soluble
Log *S* (SILICOS-IT)	-1.62
Solubility	8.67e+00 mg/ml ; 2.37e-02 mol/l
Class	Soluble

Figure 7. Water Solubility

Figure 8 outlines the pharmacokinetic predictions. Gastrointestinal (GI) absorption is predicted to be "Low," which contrasts with Amoxicillin's known oral effectiveness. This discrepancy likely stems from SwissADME's reliance on passive permeability models, whereas Amoxicillin's real-world absorption is facilitated by peptide transporters. Blood–brain barrier (BBB) permeation is predicted as "No," aligning with its high TPSA and hydrophilic profile. The molecule is neither a P-glycoprotein (P-gp) substrate nor an inhibitor, indicating low likelihood of efflux transport or transporter-mediated interactions. Furthermore, Amoxicillin is not predicted to inhibit major cytochrome P450 isoenzymes (CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4), suggesting a favorable drug–drug interaction profile. The predicted skin permeation coefficient (Log Kp) is -9.94 cm/s, confirming poor dermal absorption and reinforcing its unsuitability for transdermal delivery.

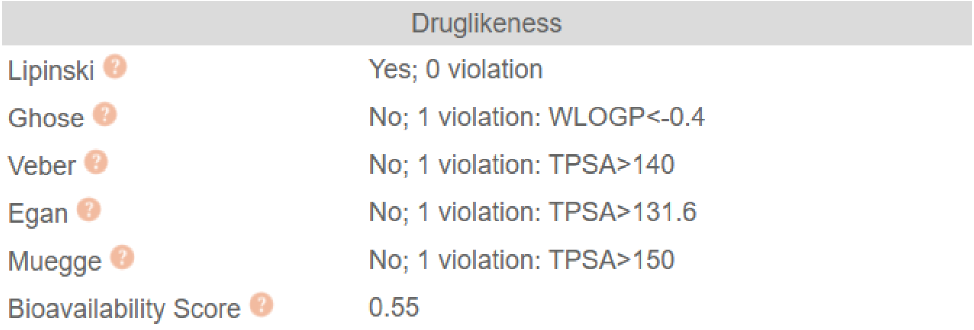
Assessment of druglikeness is shown in Figure 9. Amoxicillin fully complies with Lipinski's Rule of Five, showing no violations, which is a strong indicator of druglikeness. However, it violates one criterion each in the Ghose (WLOGP < -0.4), Veber (TPSA > 140), Egan (TPSA > 131.6), and Muegge (TPSA > 150) filters—mainly due to its high TPSA and low lipophilicity. Despite these violations, the compound's bioavailability score of 0.55 suggests moderate oral bioavailability. This result exemplifies how standard filters might not accommodate hydrophilic, actively transported drugs like beta-lactams.

The medicinal chemistry profile, illustrated in Figure 10, reveals no PAINS (Pan Assay Interference Compounds) or Brenk alerts, indicating that Amoxicillin lacks substructures associated with nonspecific activity or toxicity. While it fails the leadlikeness criterion due to its molecular weight exceeding 350 g/mol, this limitation is less relevant given that Amoxicillin is a marketed drug, not a lead compound. Its synthetic accessibility score of 4.17 denotes moderate ease of synthesis, which is favorable for large-scale production.



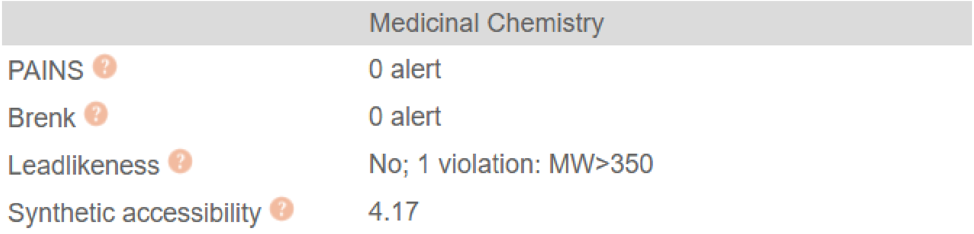
Pharmacokinetics	
GI absorption	Low
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-9.94 cm/s

Figure 8. Pharmacokinetics



Druglikeness	
Lipinski	Yes; 0 violation
Ghose	No; 1 violation: WLOGP<-0.4
Veber	No; 1 violation: TPSA>140
Egan	No; 1 violation: TPSA>131.6
Muegge	No; 1 violation: TPSA>150
Bioavailability Score	0.55

Figure 9. Druglikeness



Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 1 violation: MW>350
Synthetic accessibility	4.17

Figure 10. Medicinal Chemistry

4. Conclusion

Based on the SwissADME analysis, amoxicillin exhibits an interesting profile as an antibiotic. Its high hydrophilic nature (negative LogP, high TPSA) correlates with excellent water solubility. While the in silico GI absorption prediction is "Low" (likely due to passive models not accounting for transporters), its compliance with Lipinski's rules and a decent bioavailability score suggest that amoxicillin still possesses good oral absorption potential, likely aided by biological transporter mechanisms in vivo.

The lack of BBB permeation and the absence of CYP450 enzyme and P-gp inhibition, along with no PAINS or Brenk alerts, contribute to its favorable safety and drug interaction profile. Amoxicillin is a perfect example of a molecule that, despite violating some modern druglikeness filters (particularly concerning its high TPSA and low LogP), remains a highly effective and widely used drug. This highlights that in silico predictions are powerful tools for initial screening but must be interpreted with a comprehensive understanding of drug biology and mechanisms of action, including the role of transporters and alternative metabolic pathways. This SwissADME data strongly supports the understanding of why amoxicillin performs well as a therapeutic agent.

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