Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(3), 1371-1377 | ISSN:2251-6727

In silico studies and synthesis of Coumarin derivatives with Promising anticoagulant activity

Dr. Suchita G[1], Dr. Smita T[2], Suvarna P[3], Sahil M[4] , Harshada S[4], Kalpesh M[4], Anuj U[4], Shubham P[4], Sayli N[4], Jayesh N[4], Suraj S[4].

Associate Professor[1], Principal[2], Assistant Professor[3], Final Year B.Pharm Students[4]

Ideal College of Pharmacy & Research, Bhal, P.O. Dwarli, Haji Malang Road, Kalyan Dist.-Thane, Maharashtra- 421306.

(Received: 16 March 2025 Revised: 20 April 2025 Accepted: 01 May2025)

Keywords: Coumarin, Swiss ADME.

ABSTRACT:

The absorption, distribution, metabolism, and excretion (ADME) properties of coumarin derivatives play a crucial role in their pharmacokinetic profiles and therapeutic efficacy. This study aims to evaluate the ADME properties of a novel coumarin derivative using the computational tool Swiss ADME. Swiss ADME offers a reliable and comprehensive platform for predicting pharmacokinetic parameters, physicochemical properties, and drug-likeness of small molecules. The coumarin derivative was subjected to Swiss ADME analysis to predict its gastrointestinal absorption, blood-brain barrier permeability, metabolic stability, and potential for drug-drug interactions. Key parameters such as water solubility, lipophilicity, bioavailability score, and the presence of structural alerts for toxicity were assessed. Additionally, the molecule's compliance with Lipinski's Rule of Five and other drug-likeness filters were evaluated to determine its potential as an orally active drug.

Objectives: The results indicated that the coumarin derivative possesses favorable ADME properties, including high gastrointestinal absorption and moderate permeability across the blood-brain barrier. The compound demonstrated acceptable metabolic stability and a low risk of cytochrome P450-mediated drug-drug interactions. Furthermore, the molecule adhered to Lipinski's Rule of Five, suggesting good oral bioavailability.

Methods: The Swiss ADME software (available at www.swissadme.ch) developed by the Swiss Institute of Bioinformatics (http://www.sib.swiss) was utilized through a web server. This server provides a submission page that can be accessed via Google, facilitating the estimation of individual ADME behaviours of plant-derived compounds. The input area features a molecular sketcher based on Chem Axon's Marvin JS (http://www.chemaxon.com), enabling users to draw and modify 2D chemical structures. These structures are then listed on the right side of the submission page, which serves as the actual input for computations. The list is formatted to include one molecule per line, with multiple inputs defined by the simplified molecular input line entry system (SMILES). The results for each molecule are displayed in tables, graphs, and also provided in an Excel spreadsheet. The output from SwissADME consists of a panel for each molecule, offering a clear presentation and export option that includes all relevant information about the molecules.

Results Modern drug discovery involves evaluating the efficacy of dynamic molecules and their ability to reach the target site in a bioactive form. This process includes cellular, animal, and human clinical trials, which are costly and fraught with risks (Ndombera et al., 2019; Ranjith & Viswanath, 2019). Currently, computer-aided drug development facilitates the prediction of absorption, distribution, metabolism, and excretion (ADME) properties. These computational tools provide anticipatory and reliable data rapidly, complementing experimental approaches (Sliwoski et al., 2014; Ndombera et al.,

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(3), 1371-1377 | ISSN:2251-6727

2019). Early assessment of ADME properties during the discovery phase significantly reduces the incidence of pharmacokinetic-related failures during clinical trials.

In SwissADME, Lipinski's Rule of 5 plays a crucial role in assessing the drug-likeness of small molecules based on their physicochemical properties. This rule, developed by Christopher Lipinski, outlines four key criteria that predict whether a compound is likely to have good oral bioavailability and permeability.

Conclusions According to Lipinski's Rule of 5, a molecule is considered more likely to be orally bioavailable if it has a molecular weight less than 500 daltons (Da), a partition coefficient (log P) less than 5, no more than 5 hydrogen bond donors, and no more than 10 hydrogen bond acceptors. These parameters reflect the ideal characteristics for small molecules to be efficiently absorbed in the gastrointestinal tract and potentially reach systemic circulation. By applying Lipinski's Rule of 5 within SwissADME, researchers can quickly screen compounds to prioritize those with higher probabilities of being successful drug candidates, thus optimizing the early stages of drug discovery and development processes.

1. Introduction:

Swiss ADME is a comprehensive online tool designed to evaluate the pharmacokinetic properties, drug-likeness, and medicinal chemistry friendliness of small molecules. Developed by the Swiss Institute of Bioinformatics, SwissADME provides a user-friendly interface that allows researchers to input molecular structures and obtain a detailed analysis of various ADME (Absorption, Distribution, Metabolism, and Excretion) parameters. This tool is invaluable for drug discovery and development, offering insights into molecular properties such as lipophilicity, water solubility, and bioavailability, among others. By leveraging a combination of well-established predictive models and innovative algorithms, SwissADME helps scientists streamline the process of identifying promising drug candidates and optimizing their chemical properties for better therapeutic efficacy.

Coumarin, a naturally occurring aromatic organic compound found in many plants, has garnered significant interest due to its wide range of pharmacological properties, including anticoagulant, anti-inflammatory, and anticancer activities. In recent years, the synthesis of coumarin derivatives has been a focal point in medicinal chemistry, aiming to enhance its therapeutic potential and reduce side effects. To streamline the drug discovery process and optimize the pharmacokinetic The profiles of these derivatives, computational tools like Swiss ADME have become invaluable. Swiss ADME, a free web-based platform, enables the prediction of absorption, distribution, metabolism, and excretion (ADME) properties, alongside drug-likeness and medicinal chemistry friendliness of small molecules. By employing SwissADME in the early stages of drug development, researchers can efficiently identify promising coumarin-based candidates, thereby accelerating the journey from bench to bedside.

Objectives: The results indicated that the coumarin derivative possesses favorable ADME properties, including high gastrointestinal absorption and moderate permeability across the blood-brain barrier. The compound demonstrated acceptable metabolic stability and a low risk of cytochrome P450-mediated drug-drug interactions. Furthermore, the molecule adhered to Lipinski's Rule of Five, suggesting good oral bioavailability.

Methods

Swiss ADME:

The Swiss ADME software (available at www.swissadme.ch) developed by the Swiss Institute of Bioinformatics (http://www.sib.swiss) was utilized through a web server. This server provides a submission page that can be accessed via Google, facilitating the estimation of individual ADME behaviors of plant-derived compounds. The input area features a molecular sketcher based on Chem Axon's Marvin JS (http://www.chemaxon.com), enabling users to draw and modify 2D chemical structures. These structures are then listed on the right side of the submission page, which

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(3), 1371-1377 | ISSN:2251-6727

serves as the actual input for computations. The list is formatted to include one molecule per line, with multiple inputs defined by the simplified molecular input line entry system (SMILES). The results for each molecule are displayed in tables, graphs, and also provided in an Excel spreadsheet. The output from SwissADME consists of a panel for each molecule, offering a clear presentation and export option that includes all relevant information about the molecules.

2.2 Structure and bioavailability radar:

The first section displays the two-dimensional chemical structure along with the canonical SMILES notation. The bioavailability radar provides an initial evaluation of the drug-likeness of the molecules. The pink area represents the ideal physicochemical space for properties predicted to be orally bioavailable. Six physicochemical properties are considered: Lipophilicity (LIPO), Size, Polarity (POLAR), Insolubility (INSOLU), Instauration (INSATU), and Flexibility (FLEX). These properties are defined as follows: lipophilicity with XLOGP3 values between -0.7 and +5.0, size with a molecular weight (MW) between 150 and 500 g/mol, polarity with a topological polar surface area (TPSA) between 20 and 130 Å², solubility with log S not higher than 6, saturation with a fraction of carbons in sp^3 hybridization not less than 0.25, and flexibility with no more than 9 rotatable bonds.

2.3 Physicochemical properties:

This section includes detailed molecular and physicochemical characteristics such as molecular formula, molecular weight, number of heavy atoms, number of aromatic heavy atoms, fraction of sp^3 hybridized carbons (csp^3), number of rotatable bonds, number of hydrogen bond acceptors, number of hydrogen bond donors, molar refractivity, and topological polar surface area (TPSA). These values were calculated using Open Babel version 2.3.0. A novel method for calculating molecular polar surface area (PSA), called TPSA (Topological PSA), was developed. This method calculates TPSA by summing the tabulated surface contributions of polar fragments, determined through least squares fitting of fragment-based TPSA to the single conformer 3D PSA for a large set of drug-like structures. The database was refined by removing molecules with apparent valence errors, molecular weights outside the 100-800 g/mol range, and molecules lacking at least one oxygen, nitrogen, sulfur, or phosphorus atom.

2.4 Lipophilicity:

Lipophilicity is a crucial parameter in drug discovery and design because it complements the most informative and successful physicochemical property in medicinal chemistry. It is experimentally determined as partition coefficients (log P) or distribution coefficients (log D). Log P represents the partition equilibrium of an un-ionized solute between water and an immiscible organic solvent, with higher log P values indicating greater lipophilicity.

There are two primary techniques for measuring lipophilicity: the shake flask method and potentiometric titration. The potentiometric method assesses an aqueous pKa and converts it to an apparent pKa in a biphasic system (water-octanol) using difference curve analysis, resulting in the partition coefficient between n-octanol and water, denoted as log Po/w.

To evaluate a compound's lipophilicity Swiss ADME offers five freely available models: XLOGP3, WLOGP, MLOGP, SILICOS-IT, and iLOGP. XLOGP3 is an atomistic approach incorporating corrective factors and a knowledge-based library; WLOGP uses a purely atomistic method based on a fragmental system; MLOGP employs a topological method based on a linear relationship with 13 molecular descriptors; SILICOS-IT is a hybrid method relying on 27 fragments and 7 topological descriptors; and iLOGP is a physics-based method using free energies of solvation in n-octanol and water calculated by the generalized-born and solvent-accessible surface area (GB/SA) model. The consensus log Po/w is the arithmetic mean of the values predicted by these five methods.

Solubility:

The solubility of a compound significantly depends on the solvent used, ambient temperature, and pressure. Solubility is measured as the saturation concentration, where adding more solute does not increase its concentration in the solution. A drug is considered highly soluble if its highest dose strength dissolves in 250 mL or less of aqueous media across a pH range of 1 to 7.5. The 250 mL volume estimate is based on typical bioequivalence study protocols, which require administering a drug product to fasting human volunteers

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(3), 1371-1377 | ISSN:2251-6727

with a glass of water. Drugs are categorized into four classes: class I (high solubility and high permeability), class II (low solubility and high permeability), class III (high solubility and low permeability), and class IV (low solubility and low permeability).

SwissADME includes two topological approaches for predicting water solubility. The first is the ESOL model, which classifies solubility on a log S scale: Insoluble < -10, Poorly < -6, Moderately < -4, Soluble < -2, Very < 0, Highly. The second model, adapted from Ali et al., 2012, uses a similar scale: Insoluble < -10, Poorly < -6, Moderately < -4, Soluble < -2, Very < 0, Highly. Both models differ from the general solubility equation by excluding the melting point parameter but still show a strong linear correlation between predicted and experimental values (R^2 = 0.69 and 0.81, respectively). The third solubility predictor in SwissADME, developed by SILICOS-IT, also uses a log S scale: Insoluble < -10, Poorly < -6, Moderately < -4, Soluble < -2, Very < 0, Highly, with the linear coefficient corrected by molecular weight (R^2 = 0.75). All predicted values are the decimal logarithm of the molar solubility in water (log S). SwissADME also provides solubility data in mol/L and mg/mL, along with qualitative solubility classes.

Pharmacokinetics:

The delineation occurs within a region characterized by favorable properties for gastrointestinal (GI) absorption, depicted on a plot using two computed descriptors: ALOGP versus PSA. This region, predominantly populated by well-absorbed molecules, forms an elliptical shape referred to as the Egan egg. It serves to evaluate the predictive capability of models for GI passive absorption and brain permeation via passive diffusion, culminating in the BOILED-Egg (Brain or Intestinal Estimated permeation predictive model). This model provides a rapid and effective method for forecasting passive GI absorption, crucial for drug discovery and development.

The white region indicates molecules with a higher propensity for GI absorption, while the yellow region (yolk) signifies those most likely to permeate into the brain. Cytochrome P450 (CYP) isoenzymes metabolize 50-90% of therapeutic molecules through major isoforms: CYP1A2, CYP3A4, CYP2C9, CYP2C19, and CYP2D6. P-glycoprotein (P-gp), found widely in intestinal epithelium and brain capillary endothelial cells, actively transports xenobiotics back into the intestinal lumen and brain capillaries. SwissADME employs the support vector machine (SVM) algorithm for binary classification of datasets comprising known substrates/non-substrates or inhibitors/non-inhibitors. The model predicts whether a molecule is likely to be a substrate for both P-gp and CYP, providing a "Yes" or "No" response, respectively.

Various SVM models were trained and tested for inhibitors of different CYP isoforms, demonstrating high accuracy and area under the curve (AUC) values across training and external validation datasets. Transdermal distribution offers an alternative to oral and hypodermic drug delivery methods. Its advantages include avoiding gastric degradation, maintaining consistent plasma levels, bypassing first-pass metabolism, enhancing patient compliance, being cost-effective, minimally invasive, easy to administer, and reducing side effects.

The steady-state transport of molecules across biological membranes follows the solubility diffusion process. The permeability coefficient (Kp), which relates solute flux to the concentration gradient across the membrane, is expressed as $Kp = Km \times Dm / \delta$, where Km is the permeant's membrane/water partition coefficient, Dm is its diffusivity within the membrane, and δ is the diffusion path length.

2.7 Drug likeness:

Drug likeness refers to the assessment of a molecule's potential to become an oral drug based on its bioavailability. This property is typically evaluated using various filters, each designed by different pharmaceutical companies to enhance the qualityof their chemical collections.

The Lipinski filter (Pfizer), also known as the rule of five, is a pioneering set of criteria that categorizes small molecules based on physicochemical properties. These include a molecular weight (MW) less than 500, MLOGP $\leq$ 4.15, no more than 10 nitrogen or oxygen atoms, and no more than 5 nitrogen-hydrogen or oxygen-hydrogen groups acting as hydrogen bond donors. Additionally, aliphatic fluorines are considered hydrogen bond acceptors, while nitrogen atoms in aliphatic amines neither donate nor accept hydrogen bonds. The Ghose filter (Amgen) assesses small molecules based on molecular weight (160-480 Da), WLOGP (-0.4 to 5.6),

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(3), 1371-1377 | ISSN:2251-6727

molar refractivity (MR) (40-130), and total atom count (20-70 atoms). The Veber filter (GSK) identifies drug-like molecules as those with ≤ 10 rotatable bonds and a topological polar surface area (TPSA) of ≤ 140 Å², and fewer than 12 hydrogen bond donors and acceptors. The Egan filter (Pharmacia) predicts drug absorption based on membrane permeability processes, defining drug-like molecules as those with WLOGP ≤ 5.88 and TPSA ≤ 131.6. The Muegge filter (Bayer) categorizes molecules as drug-like if they fall within specific ranges for molecular weight, XLOGP, TPSA, number of rings, carbon atoms, heteroatoms, rotatable bonds, hydrogen bond acceptors, and donors.

Finally, the Abbott bioavailability score estimates the likelihood of a compound having at least 10% oral bioavailability in rats or measurable permeability in Caco-2 cells, focusing on rapid screening of chemical libraries to prioritize molecules for synthesis.

2.8 Medicinal chemistry:

The primary objective of these guidelines is to support medicinal chemists in their efforts during drug discovery. PAINS (Pan Assay Interference compounds are molecules that exhibit potent responses in various assays regardless of the specific protein targets. They are often considered as potential starting points for further exploration. Swiss ADME flags such compounds during evaluation to alert researchers. Brenk's model extends beyond Lipinski's Rule of 5, focusing on smaller, less hydrophobic compounds. It excludes molecules with potentially mutagenic or reactive groups like nitro, sulfate, phosphate, 2-halopyridines, and thiols. Criteria include ClogP/ClogD between 0 and 4, fewer than 4 hydrogen-bond donors, fewer than 7 acceptors, and a limited number of heavy atoms and rotatable bonds. Additionally, compounds should have fewer than 5 ring systems with no more than 2 fused rings. Lead likeness aims to provide compounds with high affinity in high throughput screening (HTS), facilitating subsequent lead optimization by allowing chemical modifications that decrease size and increase lipophilicity. Such leads typically have a molecular weight between 100 and 350 Da and a ClogP between 1 and 3.0, which are considered more suitable for optimization than typical drug-like compounds.

Synthetic accessibility (SA) estimation is crucial in computer-aided drug design (CADD) to select promising virtual molecules for biological assays. SA Score, based on a fingerprint-based approach, assesses how easily a molecule can be synthesized, ranging from 1 (very easy) to 10 (very difficult). This score incorporates 1024 fragmental contributions, adjusted for size and complexity penalties, and has been validated with a high degree of accuracy ($r^2 = 0.94$).

1. Results

Swiss ADME is a tool used to predict various pharmacokinetic and physicochemical properties of drugs. It provides insights into absorption, distribution, metabolism, and excretion (ADME) characteristics crucial for drug development. The properties evaluated include lipophilicity (logP), water solubility, permeability, and the likelihood of blood-brain barrier penetration. SwissADME also assesses pharmacokinetic parameters such as bioavailability and metabolism by cytochrome P450 enzymes. These predictions aid researchers in prioritizing lead compounds during the drug discovery process, enhancing the likelihood of selecting candidates with favorable pharmacological profiles and improved therapeutic potential. Modern drug discovery involves evaluating the efficacy of dynamic molecules and their ability to reach the target site in a bioactive form. This process includes cellular, animal, and human clinical trials, which are costly and fraught with risks (Ndombera et al., 2019; Ranjith & Viswanath, 2019). Currently, computer-aided drug development facilitates the prediction of absorption, distribution, metabolism, and excretion (ADME) properties. These computational tools provide anticipatory and reliable data rapidly, complementing experimental approaches. Early assessment of ADME properties during the discovery phase significantly reduces the incidence of pharmacokinetic-related failures during clinical trials.

2. Discussion

In Swiss ADME, Lipinski's Rule of 5 plays a crucial role in assessing the drug-likeness of small molecules based on their physicochemical properties. This rule, developed by Christopher Lipinski, outlines four key criteria that predict whether a compound is likely to have good oral bioavailability and permeability. According to Lipinski's Rule of 5, a molecule is considered more likely to be orally bioavailable if it has a molecular weight less than 500 daltons (Da), a partition coefficient (log P) less

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(3), 1371-1377 | ISSN:2251-6727

than 5, no more than 5 hydrogen bond donors, and no more than 10 hydrogen bond acceptors. These parameters reflect the ideal characteristics for small molecules to be efficiently absorbed in the gastrointestinal tract and potentially reach systemic circulation. By applying Lipinski's Rule of 5 within Swiss ADME, researchers can quickly screen compounds to prioritize those with higher probabilities of being successful drug candidates, thus optimizing the early stages of drug discovery and development processes.

3. **References**

1. Boopathi CA, Sivakumar R. Phytochemical Screening on leaves and stem of *Andrographis neesiana* Wight-An endemic medicinal plant from India. World Appl. Sci J. 2011; 12(3): 307-311.
2. Testa, B. & raemer, S. D. e Biochemistry of Drug Metabolism – An Introduction - Testa - 2007 - Chemistry & Biodiversity - Wiley Online Library. Chem. Biodivers (2007).
3. Hollenberg, P. F. Characteristics and common properties of inhibitors, inducers, and activators of CYP enzymes. Drug Metabev.
4. 34, 17–35 (2002)
5. Huang P, Gao L-L, Zhang Z. Synthesis and biological evaluation of novel coumarin derivatives as antiplatelet agents. Heterocycles. 2016; 92:511–20.
6. Hay M., Thomas D. W., Craighead J. L., Economides C. & Rosenthal J. Clinical development success rates for investigational drugs. Nature Biotechnol. 32, 40–51 (2014). - PubMed
7. Lipinski C. A., Lombardo F., Dominy B. W. & Feeney P. J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv. Drug. Deliv. Rev. 46, 3–26 (2001). - PubMed
8. O'Boyle N. M. et al..OpenBabel: An open chemical toolbox. J. Cheminform. 3, 33 (2011). - PMC - PubMed
9. Upadhyay SN. Immunomodulation. Narosa Publishing House, India, 1997.
10. Huang P, Gao L-L, Zhang Z. Synthesis and biological evaluation of novel coumarin derivatives as antiplatelet agents. Heterocycles. 2016;92:511–20.
11. Mitchell J. B. O. Machine learning methods in chemoinformatics. WIREs Comput. Mol. Sci. 4, 468–481 (2014). - PMC - PubMed
12. Quezada E, Delogu G, Picciau C, Santana L, Podda G, Borges F, et al. Synthesis and vasorelaxant and platelet antiaggregatory activities of a new series of 6-halo-3-phenylcoumarins. Molecules. 2010;15:270–9.
13. Gfeller D. et al..SwissTargetPrediction: a web server for target prediction of bioactive small molecules. Nucleic Acids Res. 42, W32–W38 (2014). - PMC - PubMed
14. Abutaha, N., & Almutairi, B. O. (2023). Exploring the therapeutic potential of GC–MS separated compounds from Dracaena cinnabari against dengue virus and Aedes aegypti using in silico tools. Journal of King Saud University - Science, 35(2), 102478. https://doi.org/10.1016/j.jksus.2022.102478 - DOI
15. Manolov I, Maichle-Moessmer C, Danchev N. Synthesis, structure, toxicological and pharmacological investigations of 4-hydroxycoumarin derivatives. Eur J Med Chem. 2006;41:882–90.
16. Messina, J. P., Brady, O. J., Golding, N., Kraemer, M. U. G., Wint, G. R. W., Ray, S. E., & Hay, S. I. (2019). The current and future global distribution and population at risk of dengue. Nature Microbiology, 4(9), 1508–1515. https://doi.org/10.1038/s41564-019-0476-8 - DOI - PubMed -PMC
17. Guzman, M. G., Gubler, D. J., Izquierdo, A., Martinez, E., & Halstead, S. B. (2016). Dengue infection. Nature reviews. Disease primers, 2, 16055. https://doi.org/10.1038/nrdp.2016.55 - DOI - PubMed
18. Bachman, M., Mann, S. E., and Sheppard, T. D. (2012). Rapid Synthesis of Highly Functionalised α-amino Amides and Medium Ring Lactones Using Multicomponent Reactions of Amino Alcohols and

Isocyanides. Org. Biomol. Chem. 10, 162–170. doi:10.1039/c1ob06534c

19. Biswas, B., Golder, M., Abid, M. A., Mazumder, K., & Sadhu, S. K. (2021). Terpenoids enriched ethanol extracts of aerial roots of Ceriopsdecandra (Griff.) and Ceriops tagal (Perr.) promote diuresis in mice. Heliyon, 7(7), e07580. https://doi.org/10.1016/j.heliyon.2021.e07580 - DOI -PubMed - PMC

20. Boezio, B., Audouze, K., Ducrot, P., &Taboureau, O. (2017). Network-based Approaches in Pharmacology. Molecular Informatics, 36(10), 1–10. https://doi.org/10.1002/minf.201700048 -DOI

21. Salehi B., Rescigno A., Dettori T., et al. Avocado-soybean unsaponifiables: a panoply of potentialities to be exploited. Biomolecules. 2020;10(1):p. 20. [PMC free article] [PubMed] [Google Scholar]

22. Hrubša M, Nurjamal K, Carazo A, Nayek N, Karlíčková J, Applová L, et al. Screening of synthetic heterocyclic compounds as antiplatelet drugs. Med Chem. 2022;18:536–43.

23. Bang NC, Abyshev A, Ivkin DY. Synthesis and in vivo evaluation of new coumarin conjugates as potential indirect-action anticoagulants. Pharm Chem J. 2019;53:419–22.

24. Daina A, Zoete V. A BOILED-Egg to Predict Gastrointestinal Absorption and Brain Penetration of Small Molecules. Chem Med Chem. 2016; 11:1117-1121.