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A REVIEW ON IN SILICO ADMET PREDICTION OF ANTIHISTAMINIC DRUGS

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ABSTRACT

Antihistaminic agents remain essential in the management of allergic, gastric and neurologic disorders, yet many candidates fail during development because of poor absorption, metabolic instability or unexpected toxicity. Early evaluation of absorption, distribution, metabolism, excretion and toxicity (ADMET) is therefore a critical step in optimising safety and efficacy. Computational approaches provide rapid, cost-effective screening by predicting pharmacokinetic and toxicological behaviour from chemical structure. This article presents an overview of in-silico ADMET profiling applied to commonly used antihistamines across the H1–H4 receptor spectrum. Molecular descriptors were retrieved from freely available databases and assessed using web-based platforms such as SwissADME, pkCSM and admetSAR. Predicted properties—including lipophilicity, polar surface area, intestinal permeability, blood–brain barrier transport, cytochrome P450 interactions, clearance and potential cardiotoxicity—were compared with information reported in clinical literature. Second-generation H1 antagonists demonstrated favourable oral absorption with minimal central penetration, whereas several first-generation agents showed higher lipophilicity and a risk for hERG channel blockade, consistent with their sedative and cardiac profiles. The study highlights how software-assisted prediction can complement experimental data, support rational drug design and guide safer selection of antihistaminic candidates for further development.

KEYWORDS: ADMET profiling, antihistamine, in-silico prediction, pharmacokinetics.

INTRODUCTION

Antihistamines that act on the histamine H_1 receptor remain indispensable for managing allergic conditions such as rhinitis, urticaria, and conjunctivitis. First-generation H_1 antagonists exhibit potent therapeutic effects but readily cross the blood–brain barrier, producing sedation and psychomotor impairment that limit their clinical utility.[1,2] Although second- and third-generation compounds demonstrate improved receptor selectivity and reduced central nervous system penetration, challenges such as variable bioavailability, metabolic instability, and hERG channel inhibition continue to restrict optimal therapy.

Histamine receptors (H_1–H_4) mediate a wide range of physiological and pathological responses. Among them, H_1 receptors are expressed in smooth muscle, endothelial, and immune cells, and are chiefly responsible for vasodilation, bronchoconstriction, and pruritus observed in hypersensitivity reactions.[8,9] Therefore, rational modulation of H_1 receptor activity remains a key strategy for developing safer, non-sedative antihistamines.

In modern drug design, a compound's pharmacodynamic potency must be balanced with its pharmacokinetic and toxicological profile. The ADMET principle—Absorption, Distribution, Metabolism, Excretion, and Toxicity—governs the in-vivo fate of a drug and strongly influences its success in clinical development.[10–13] Poor ADMET properties account for a large proportion of late-stage drug failures, highlighting the need for early screening during discovery.[6,7] Coupling ADMET assessment with drug metabolism and pharmacokinetics (DMPK) evaluation provides a comprehensive understanding of bioavailability, metabolic stability, and systemic safety.

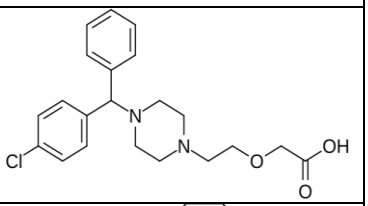
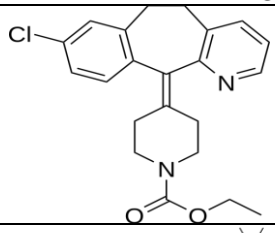
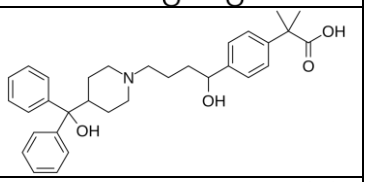
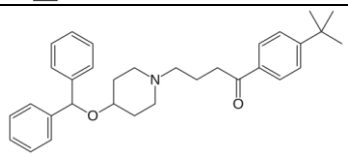
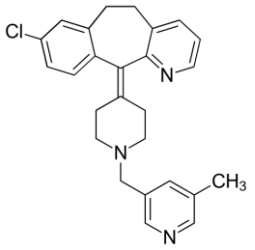
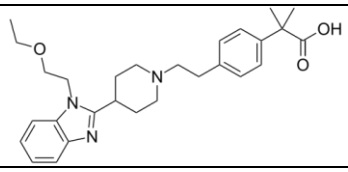
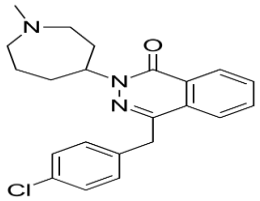
Computational and in-silico methods now offer rapid, cost-effective means to predict ADMET behavior before synthesis or biological testing. Platforms such as SwissADME[3], ADMETlab 3.0[4], and admetSAR 3.0[5] allow systematic evaluation of key pharmacokinetic parameters, including gastrointestinal absorption, blood–brain barrier permeability, CYP450 inhibition, and cardiotoxicity risk, thus reducing experimental attrition.

The objective of this review is to critically summarize and compare computational approaches employed for ADMET profiling of H_1-antihistaminic compounds. By integrating predictive outcomes with available experimental data, this work aims to support the rational design of next-generation antihistamines exhibiting enhanced pharmacokinetic performance, minimal central nervous effects, and improved overall safety.

MATERIAL AND METHODOLOGY

Selection of Drug Candidates: Candidate molecules for this study were selected from previously reported H_1 receptor antagonists[5,6,7] and publicly accessible chemical databases, including PubChem and DrugBank.

Table 1: The selected Drug compounds for this study.

DRUG NAME	IUPAC NAME	CHEMICAL FORMULA	M.W.	STRUCTURE
Cetrizine	(±)-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]acetic acid	C21H25ClN2O3	388.89 g·mol^{-1}	
Loratadine	Ethyl 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidinecarboxylate	C22H23ClN2O2	382.89 g·mol^{-1}	
Fexofenadine	(±)-4-[1-Hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-α, α-dimethyl benzeneacetic acid	C32H39NO4	501.667 g·mol−1	
Ebastine	4-(4-benzhydryloxy-1-piperidyl)-1-(4-tert-butylphenyl)butan-1-one	C32H39NO2	469.669 g·mol−1	
Rupatadine	8-Chloro-6,11-dihydro-11-[1-[(5-methyl-3-pyridinyl)methyl]-4-piperidinylidene]-5H-benzo[5,6]cyclohepta[1,2-b]pyridine fumarate	C26H26ClN3	415.97 g·mol−1	
Bilastine	2-[4-(2-{4-[1-(2-Ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl}ethyl)phenyl]-2-methylpropanoic acid	C28H37N3O3	463.622 g·mol−1	
Azelastine	(RS)-4-[(4-Chlorophenyl)methyl]-2-(1-methylazepan-4-yl)-phthalazin-1-one	C22H24ClN3O	381.90 g·mol−1	

Chemical structures of the selected compounds were retrieved in SDF or MOL format for computational analysis.

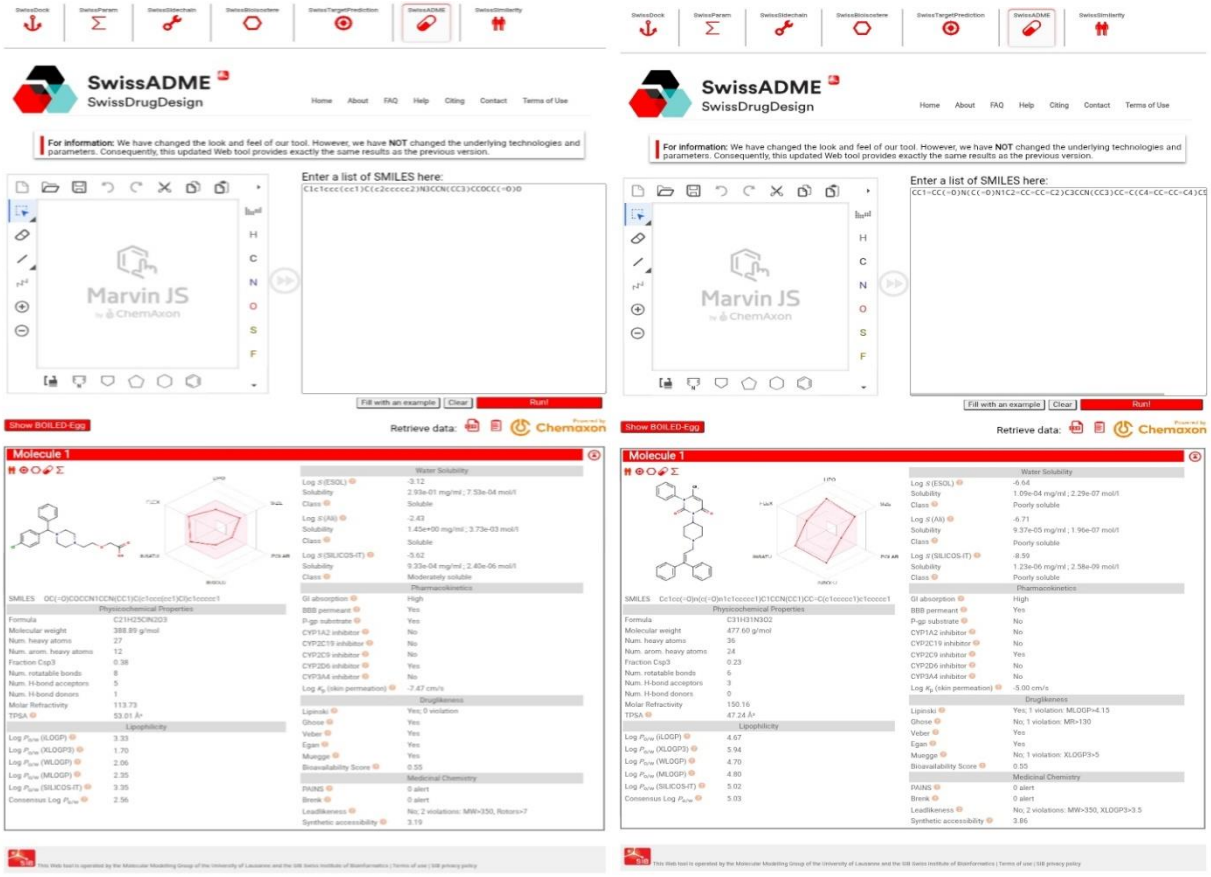
The H_1 receptor, along with other histamine receptor subtypes, plays a central role in mediating allergic responses through interactions with smooth muscle, endothelial, and immune cells.[1,2] The biological and systemic distribution of histamine receptors guided the selection of candidate molecules by highlighting pharmacologically relevant targets. A comprehensive overview of histamine receptor subtypes and their major physiological effects is presented in Table 1.

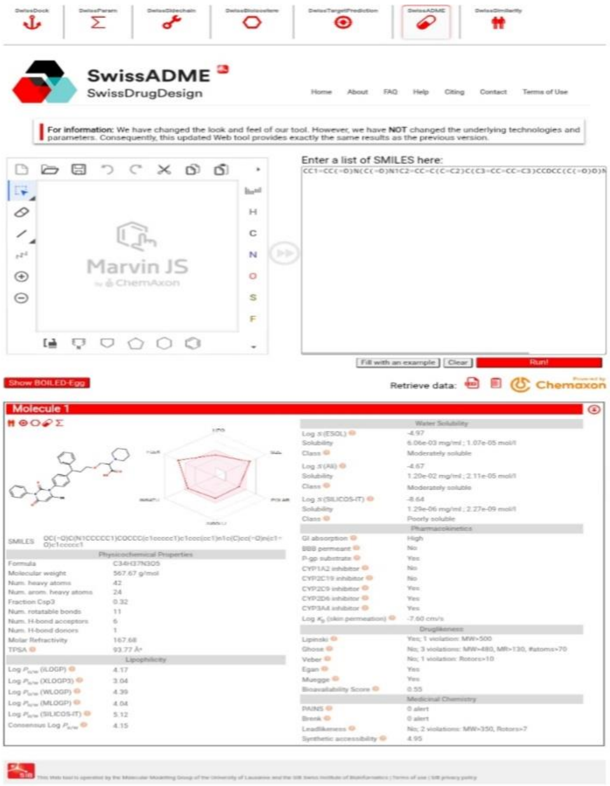
Table 2: Cellular and systemic distribution of histamine receptor subtypes and their major physiological effects.

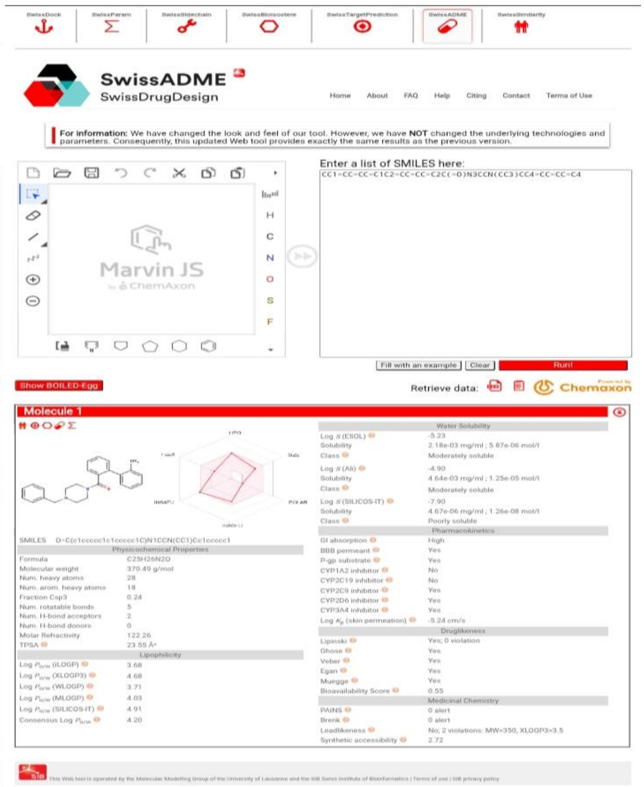
Histamine Receptor	Location by cells	Systemic Location	Major Effects
H1	Smooth muscles, Endothelial cells, Epithelial cells, Neutrophils, Eosinophil, Monocytes, Macrophage, T and B cells	Exocrine Respiratory Intestinal Skin Neuromuscular Cardiovascular	Increase mucus secretions Bronchiolar constriction decrease lung capacity Intestinal cramps Diarrhea Triple responce Itch and pain Positive Chronotropic , Ionotropism
H2	Parietal cells Smooth cells	Stomach Cardiovascular	Increased acid secretion Positive Chronotopic
H3	Histaminergic neurons	CNS	Congnitive effects pain, sleep
H4	Mast cells, Eosinophil, T and Dendritic cells	Immune system	Immune response

ADMET TOOLS

1] SwissADME




SwissADME
SwissDrugDesign
Marvin JS
Enter a list of SMILES here:
Molecule 1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SwissDrugDesign
Marvin JS
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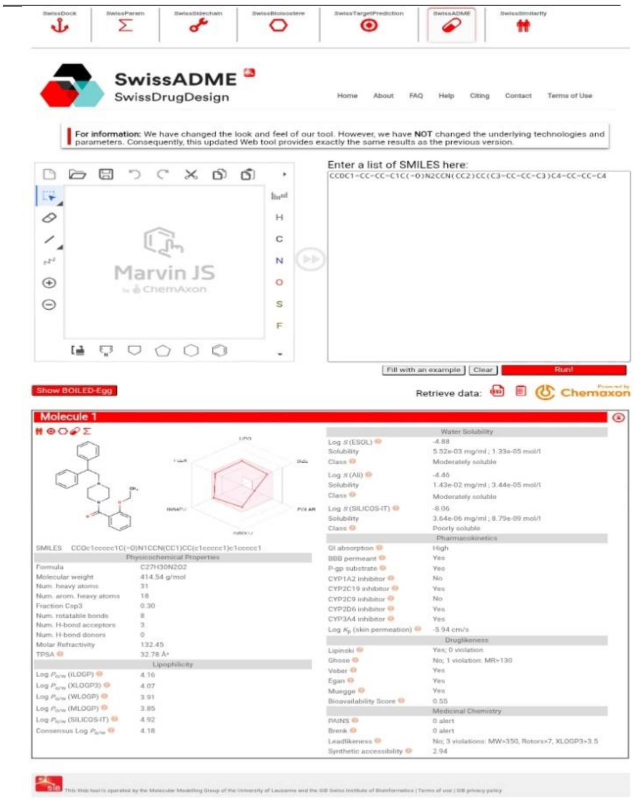
Molecule 1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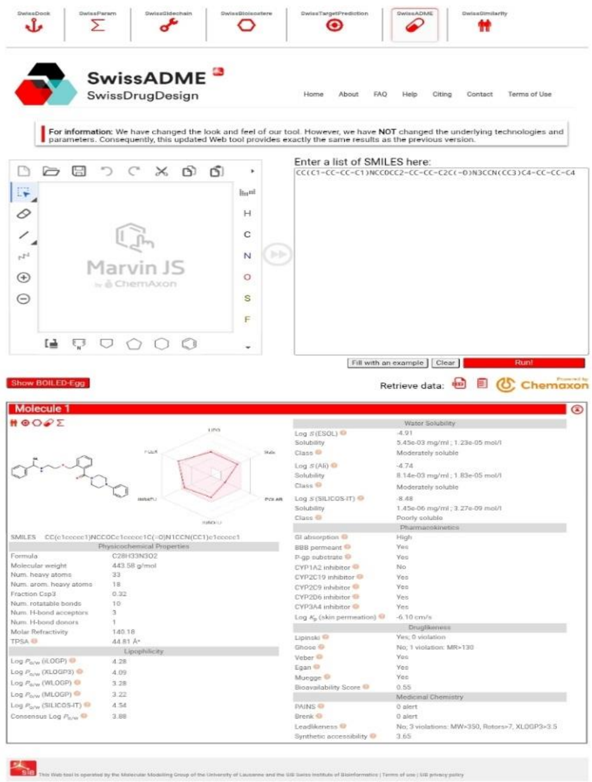
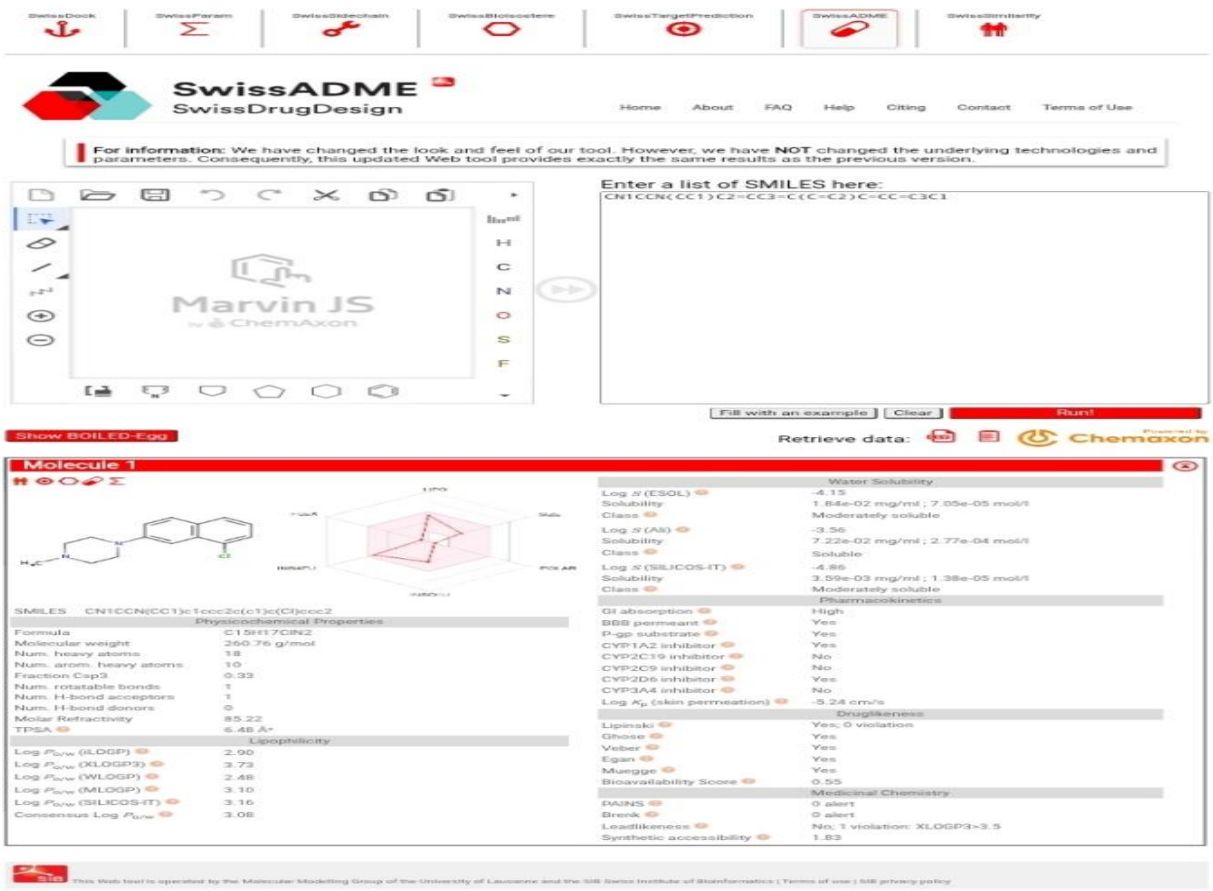
Molecule 1


SwissADME
SwissDrugDesign
Marvin JS
Enter a list of SMILES here:
Molecule 1



SwissADME is a free, web-based platform developed by the Swiss Institute of Bioinformatics that predicts pharmacokinetic, drug-likeness, and medicinal chemistry properties of small molecules.[51] It is widely used to screen and profile compounds during the early stages of drug discovery, helping to reduce attrition by highlighting ADMET issues before synthesis.[51,52]

Historical background of swissADME

The development of SwissADME was initiated by the Swiss Institute of Bioinformatics (SIB) to provide an accessible, free platform for computational prediction of physicochemical, pharmacokinetic, and drug-likeness properties of small molecules.[51] It was officially released in 2017 as an open-access web server, integrating several models previously published by its creators, such as the BOILED-Egg (for intestinal absorption and BBB penetration) and the Bioavailability Radar (for oral drug-likeness).[51,52] SwissADME was designed to address a major bottleneck in drug discovery: the high attrition rate due to poor absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiles. By providing rapid, user-friendly predictions, it has enabled researchers worldwide to assess pharmacokinetics and medicinal chemistry properties before investing in costly experimental work.[51,54] Since its launch, SwissADME has been integrated into academic research, pharmaceutical pipelines, and teaching, gaining widespread citation in medicinal chemistry and computational drug design studies.[54] Its success led to complementary tools (e.g., SwissSidechain, SwissTargetPrediction) being developed by the same group, expanding the SIB "SwissDrugDesign" platform.[51,54]

Key Features

- Physicochemical properties – molecular weight, topological polar surface area (TPSA), rotatable bonds, saturation, flexibility.[51]
- Lipophilicity – multiple algorithms (XLOGP3, WLOGP, MLOGP, SILICOS-IT) and iLOGP, with a consensus logP for robustness.[51]
- Solubility – qualitative and quantitative water solubility prediction (log S).[51]
- Pharmacokinetics – BOILED-Egg model predicts human intestinal absorption (HIA) and blood–brain barrier (BBB) permeation; identifies P-glycoprotein substrates; predicts CYP450 inhibition.[51,53]
- Drug-likeness – integrates Lipinski, Ghose, Veber, Egan, and Muegge filters, with alerts for problematic fragments.[51]
- Medicinal chemistry filters – structural alerts and synthetic accessibility (SA) score.[51]
- Graphical outputs – Bioavailability Radar and BOILED-Egg plots give a clear visualization of absorption, lipophilicity, and BBB potential.[51]

Strengths

- Combines multiple prediction models for reliability.[51]

- Fast batch processing and user-friendly interface.[51]
- Graphical outputs facilitate understanding even for non-experts.[52]

Limitations
- Models approximate reality; quantitative data may be lacking for some endpoints.[51,53]
- BOILED-Egg only accounts for passive diffusion, not active transport.[51]
- Predictions may be less accurate for molecules far outside the training set.[51]

2] pkCSM

pkCSM was introduced in 2015 by researchers at the University of Queensland using graph-based signatures to predict ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties of small molecules.[65] Since then, it has undergone updates to improve predictive accuracy, incorporate more experimental data, and refine algorithms for better reliability in in silico ADMET profiling.[66]

Architecture & Features

Graph-based signatures: Molecules are represented as graphs (atoms = nodes, bonds = edges) to capture structural information relevant to ADMET properties.[65]

Endpoints covered: Absorption (Caco-2 permeability), Distribution (BBB penetration), Metabolism (CYP450 inhibition), Excretion (renal clearance), Toxicity (mutagenicity, hepatotoxicity, cardiotoxicity).[65]

Interface

Web-based platform, accepts SMILES input, supports batch predictions, user-friendly for researchers without computational expertise.[66]

Applications
- Early-stage drug discovery for pharmacokinetic and toxicity profiling.[65]
- Chemical risk assessment for pesticides, food additives, and other chemicals.[65]
- Regulatory compliance support via in silico predictions.[65]

Strengths
- Comprehensive coverage of ADMET endpoints.[65]
- Graph-based modeling captures complex molecular features for improved predictions.[65]
- Freely accessible web server for global research use.[66]

Limitations
- Accuracy depends on chemical similarity to training data.[65]
- Some endpoints may have lower reliability if experimental data is sparse.[65]

3] ADMETLab 3.0

ADMETlab was first introduced in 2018 as a web-based platform for systematic ADMET evaluation built from a comprehensively collected dataset.[55] In 2024 the platform was substantially updated and released as ADMETlab 3.0, expanding endpoint coverage, enlarging datasets, improving model performance, and adding API access and uncertainty estimation.[56]

Data & Model Architecture

The ADMETlab 3.0 database aggregates hundreds of thousands of molecules from public sources (e.g., ChEMBL, PubChem) and literature; data preprocessing includes standardizing SMILES and removing mixtures prior to modelling.[56] Models are implemented using a multi-task Directed Message Passing Neural Network (DMPNN) combined with molecular descriptors (DMPNN-Des) to improve predictive accuracy and generalizability.[56]

Endpoint Coverage

ADMETlab 3.0 provides prediction for 119 endpoints across physicochemical, absorption, distribution, metabolism, excretion and toxicity categories. Newly added endpoints include pKa, melting/boiling point predictions, PAMPA permeability, transporter-related endpoints, and several organ-specific toxicity subendpoints.[56]

Model Validation & Performance

The platform implements both regression and classification models (many endpoints show strong performance metrics). Validation reported in the ADMETlab 3.0 publication indicates robust R^2 and AUC values for most endpoints, and the authors provide applicability/uncertainty estimates to help interpret model confidence.[56]

User Interface & API

ADMETlab 3.0 is accessible via a web interface that accepts SMILES input or batch uploads and returns tabular and graphical results. An API enables programmatic submission and retrieval of predictions, which facilitates batch screening and integration into workflows.[56]

Strengths
- Very broad endpoint coverage (119 endpoints) enabling comprehensive early-stage profiling.[56]
- Modern deep-learning architecture (DMPNN + descriptors) trained on large, diverse datasets.[56]
- Uncertainty estimates and API support increase practical usability for medicinal chemists.[56]

Limitations & Considerations: As with all in-silico platforms, predictions are approximate and may be less reliable for chemical scaffolds outside the training domain; users should consult the provided uncertainty/applicability warnings.[56] The breadth of

endpoints increases computational cost for very large batch jobs compared with lighter tools.[56]

4] preADMET

PreADMET is a web-based application developed by the Bioinformatics & Molecular Design Research Center (BMDRC), Yonsei University, South Korea. It was first released in the early 2000s, with PC-version 1.0 coming out circa 2004, and later upgraded to PreADMET 2.0 with more functionalities.[57] The motivation was to provide a rapid computational prediction platform for ADME and toxicity (ADMET) properties during early stages of drug discovery, to reduce cost/time before experimental evaluation.[58]

Architecture & Core Modules

PreADMET consists of several main components.[59,60]

1. Molecular Descriptor Calculation: Using the "TOPOMOL" module, PreADMET can compute >2,500 molecular descriptors (constitutional, topological, electrostatic, geometrical etc.) from 2D/3D chemical structures.[59]
2. Drug-likeness Prediction: Implements rule-based filters including Lipinski's "rule of five", lead-likeness, and other drug-like rules derived from databases like WDI, CMC, MDDR.[59]
3. ADME Prediction: Includes models for in vitro cell-based assays (Caco-2, MDCK), human intestinal absorption (HIA), skin permeability, blood–brain barrier (BBB) penetration, plasma protein binding. Also includes genetic algorithm / neural network (Rprop) to select relevant descriptors and develop nonlinear models.[59]
4. Toxicity Prediction: Predicts mutagenicity via Ames test (various strains), rodent carcinogenicity (mouse/rat 2-year assays), etc.[59]

Input / Output Options

- Accepts chemical structures via SMILES, Mol / SDF files.[59]
- Outputs include predicted numerical values (e.g. % HIA, permeability rates, binding %, logP etc.), classification (yes/no) for toxicity endpoints.[61]
- Interface is web-based; some versions allow batch upload.[59]

Strengths

- Broad set of molecular descriptors, which supports better selection of features for QSAR / ADME modelling.[59]
- Provides both absorption / distribution endpoints and toxicity predictions, which helps in early filtering of compounds.[60]
- Useful for academic users as it is (at least partly) freely accessible.[59]

Limitations:

- Some descriptor calculations are computationally heavy when dealing with large batches; might be slower than more streamlined tools.[59]
- Model reliability depends on chemical similarity to training data. For molecules structurally very different, prediction confidence may be lower.[59]
- Toxicity predictions are mostly classification; quantitative toxicity metrics or organ-specific toxicity may be limited.[60]

5] admetSAR 3.0

admetSAR was first introduced in 2012 as a web-based tool for predicting ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties of chemicals.[62] admetSAR 2.0 (2019) expanded the database and improved model accuracy with more data and refined algorithms.[63] admetSAR 3.0 (2023) further enhanced the platform with a broader range of endpoints, modern deep learning models, improved user interface, and molecular optimization features.[64]

Architecture & Features

- Database: >370,000 experimentally collected ADMET data for >100,000 unique compounds.[64]
- Models: Multi-task graph neural network framework (CLMGraph) combining contrastive learning and multi-task learning for accurate ADMET predictions.[64]
- Endpoint coverage: 119 endpoints including physicochemical, ADME, toxicity, environmental, and cosmetic properties.[64]
- Molecular optimization: Provides transformation rule-based and scaffold-hopping strategies to improve predicted ADMET profiles.[64]
- Interface: Web-based platform supporting SMILES input, structure drawing, and batch predictions.[64]

Applications

- Early-stage drug discovery for candidate screening.[64]
- Chemical risk assessment (pesticides, food additives, cosmetics).[64]
- Regulatory compliance support via in silico predictions.[64]

Strengths

- Broad endpoint coverage and large dataset support generalizability.[64]
- Modern deep learning improves predictive performance.[64]
- User-friendly interface and batch processing capabilities.[64]

Limitations: GI absorption Prediction ability of a compound to be absorbed in the gastrointestinal tractEnsures adequate bioavailability for orally administered drugPredictions are less reliable for molecules outside the training chemical space.[64] Batch predictions may take longer due to the complexity of multi-task models.[64]

Table 3: Common ADMET endpoints and their significance.

Blood-Brain Barrier[BBB]permeability	Measure likelihood ofcrossing the BBB importance for cns drugs	Low bbb penetration desired for non-sedative antihistamines

This review collates and analyses published work on the use of computational approaches for ADMET profiling of antihistaminic drugs. By summarising predictive outcomes and highlighting gaps between theoretical and experimental data, it aims to support the rational Tabl2. Common ADMET endpoints used in in silico profiling and their significance in drug discovery. design of next-generation, non-sedative H_1 receptor antagonists with improved safety and pharmacokinetic performance.

Data Compilation and Comparative Analysis

Table 4: Predicted Physicochemical and Pharmacokinetic Properties of Selected H_1 Antihistamines (SwissADME).

Drug Name	GI Absorption	BBB Permability	Log P	TPSA (Å²)	No. Of H-Bond Acceptors	No. Of H-Bond Donors	No. Of Rotatable Bonds	Bioavailability Score
Cetrazine	High	Yes	2.56	53.01	5	1	8	0.55
Loratadine	High	Yes	5.03	47.24	3	0	6	0.55
Fexofenadine	High	No	4.15	93.77	6	1	11	0.55
Ebastine	High	Yes	4.18	32.78	3	0	8	0.55
Rupatadine	High	Yes	4.20	23.55	2	0	5	0.55
Bilastine	High	Yes	3.88	44.81	3	1	10	0.55
Azelastine	High	Yes	3.08	6.48	0	1	1	0.55

A)FUTURE OF IN SILICO ADMET PREDICTION STUDIES

The field of in silico ADMET prediction is rapidly evolving, driven by advances in computational power, machine learning, and availability of large experimental datasets. The future of this domain focuses on improving accuracy, reliability, and integration with other drug discovery pipelines.

1. Integration with AI and Deep Learning: 2. High-Throughput Screening and Automation:3. Multi-Target and Polypharmacology Consideration: 4. Personalized and Precision Medicine Applications: 5. Regulatory Acceptance and Standardization.

B) LIMITATIONS OF CURRENT IN SILICO ADMET STUDY

While in silico ADMET prediction tools have revolutionized early-stage drug discovery, there are several limitations that researchers should consider.

1. Accuracy Depends on Training Data.
2. Predictions are heavily dependent on the chemical space of the training datasets. Unusual scaffolds or novel compounds may yield less reliable results.[70,71]
3. Incomplete Endpoint Coverage.
4. Not all tools predict every ADMET endpoint.[71,72]
5. Lack of Integration with Experimental Data.
6. In silico predictions often need validation through in vitro or in vivo experiments. Discrepancies between predicted and experimental results can occur due to biological complexity.[70,72]
7. Limited Multi-Target / Polypharmacology Analysis.
8. Most ADMET tools evaluate a compound in isolation and do not account for drug-drug interactions or systemic biological effects.[71]

Despite these limitations, in silico ADMET prediction remains a valuable tool in early drug discovery, helping reduce cost, time, and attrition rates when combined with experimental validation.

CONCLUSION

In silico ADMET prediction has become an indispensable step in modern drug discovery, providing early insight into pharmacokinetic and toxicity profiles before resource-intensive laboratory testing. For second-generation antihistamines such as cetirizine, loratadine, fexofenadine, ebastine, rupatadine, bilastine, and azelastine, platforms including SwissADME[74], pkCSM[73], ADMETlab 3.0[76], admetSAR 3.0[75], and preADMET[77] enable rapid evaluation of absorption, distribution, metabolism, excretion, and toxicity (ADMET) endpoints.

These computational methods reduce the cost and time of screening and allow prioritization of drug candidates. However, they face limitations such as incomplete endpoint coverage, dependency on the quality of training datasets, and lower predictive accuracy for novel or complex chemical scaffolds.[73,74,75,76,77]

Looking forward, advances in machine learning, integration of multi-omics data, and stronger validation standards will enhance predictive accuracy and promote regulatory acceptance.[73,74,75,76,77] When combined with experimental studies, in silico tools — including preADMET — represent a powerful strategy for the rational design and optimization of next-generation antihistamines.

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