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PHARMACOLOGICAL AND TOXICOLOGICAL ASSESSMENT OF TWO MEDICINALLY POTENT COMPOUNDS (PROLYLLEUCINE AND UROCANIC ACID) ISOLATED FROM MAIZE KERNELS CULTIVATED IN KALIACHAK, MALDA (W. BENGAL), INDIA

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ABSTRACT

Pairing target-receptor molecular docking with early-stage ADMET screening offers a robust framework for filtering out weak drug candidates before expensive clinical development begins. This study used the SwissADME and ProTox 3.0 platforms to run a detailed computational evaluation of the pharmacokinetic properties, structural drug-likeness, and toxicological profiles of two distinct bioactives: urocanic acid (138.12 g/mol) and a protected prolylleucine derivative (362.40 g/mol). Computational modeling via the BOILED-EGG diagram mapped both metabolites securely within the high passive intestinal absorption zone, indicating high oral bioavailability alongside a minimal risk of central nervous system exposure due to their inability to cross the blood-brain barrier. However, clear differences emerged regarding active transport and molecular architecture. While urocanic acid behaves as a P-glycoprotein non-substrate (PGP-), prolylleucine acts as a P-gp substrate (PGP+), leaving it vulnerable to cellular efflux. Furthermore, the bioavailability radar flagged the prolylleucine compound for excessive molecular flexibility. This conformational freedom introduces an entropic penalty during target binding, even though the compound complies with Lipinski's Rule of Five. Safety analysis via ProTox 3.0 revealed pronounced liabilities for the prolylleucine scaffold, most notably a striking near-100% probability of interacting with Cytochrome P450 2E1 (CYP2E1), signaling a high risk of metabolic bioactivation and subsequent hepatotoxicity. Moreover, the compound showed high binding affinity toward endocrine hubs, including aromatase, estrogen receptor alpha, and the androgen receptor ligand-binding domain. Ultimately, while both metabolites show strong oral absorption trends, future structural modifications must focus on rigidifying the prolylleucine chain and removing the specific groups driving CYP2E1 and endocrine cross-reactivity.

KEYWORDS: Prolylleucine, Urocanic acid, Pharmacokinetics, SwissADME, Maize, Malda.

INTRODUCTION

Maize (*Zea mays* L.) is important cereal crops which is widely cultivated in the world along with India due to its multipurpose uses in different fields such as staple food, livestock feed, industrial raw material(Erenstein et al., 2022). Beyond all of these recently its uses as bio fuel production increases significantly and it also attracted scientific attention because of presence of some bioactive compounds which have potential pharmacological importance.Maize kernels (grains) contain variety of compounds like peptides, amino acid derivatives, secondary metabolites etc. which have anti-inflammatory, antimicrobial, antioxidant properties. This study is aimed to explore that maize have potential source for nutraceuticals as well as pharmaceutical agents.

Malda district is known as gateway of North Bengal, its physiogeography is consist with mainly alluvial soil due to Ganga River and tributaries following through beside Kaliachak blocks(Gazetteers of W.B, Malda, 1969). Maize cultivated intensively in region of Kaliachak because of favorableagro-climatic conditions. Metabolic profile of maize grains influenced by some environmental factors like soil fertility, composition of soil, irrigation water quality and nutrients availability etc. There is distinct gap in profiling of pharmacokinetic metabolites of maize kernels cultivated from this region remain.

Currently advancements in techniques it is so easy to identifying and characterizing bioactive compounds present in plant materials. Liquid Chromatography- Mass Spectrometry (LCMS) is one of the advance analytical techniques which used to separate, identify, quantify the known and unknown compounds present in sample; as well as chemical properties, structure of molecules also elucidated (Mukherjee, 2019). In this study HR-LCMS (High Resolution LCMS) performed for analysis of maize kernel extracts; there are so many compounds present which have medicinal importance like – Prolylleucine, Sitagliptin, 4-Methoxycinnamic Acid, Urocanic Acid, 8-Hydroxyquinolineetc.

Prolylleucine (Pro-Leu) is a bioactive dipeptide; composed of proline and leucine amino acids (ChEBI). Bioactive peptides which are protein fragments can be useful for health (Moller, Scholz-Ahrens, Roos, & Schrezenmeir, 2008). Bioactive peptides may show many biological activities, such as antioxidant, antihypertensive, antimicrobial, and immunomodulatory effects. Proline rich peptides have unique structure; it is associated with protection of cell as well as it contributes to therapeutic drug formation. Similarly, leucine is a branched chain amino acid which helps in protein synthesis, metabolism, and muscle health. The combined structure of both the Proline and Leucine amino acid residue forms Prolylleucine; which may exhibit some important biological activities such as – inhibition of Tyrosinase enzyme, peptide-based drug development and anti-microbial. Recently it has also used in therapeutic drug formation to skin whitening.

Urocanic Acid (UCA) is trans isoform of Histidine which derivate to form cis form UCA with exposure of UV-B radiation (McLoon et al; 2005). It basically formed in the stratum corneum and contains 0.7% of dry weight of epidermis (Hart & Norval; 2021). UCA plays some biological activities like photoprotection, immune-modulation, ocular health, disease biomarker and anti-inflammatory drug design. Due to these pharmacological activities of these compounds have grown substantial interest in biomedical as well as pharmaceutical research. It is as such as important that identification of any phytocompounds going through some processes like drug likeliness, pharmacokinetic behavior and medicinal appropriateness before considering therapeutic applications. Recently, preliminary screening of bioactive compounds are accelerated via computational pharmacology and in-silico tools.

SwissADME is commonly recognized online platform, where assesses compound's Physico-chemical properties, absorption, distribution, metabolism, excretion, pharmacokinetics, drug likeness and friendliness of medicinal properties ((Daina et al., 2017). This web tool helps to determined that isolated compounds are possess some characteristics which are equally important for pharmaceutical development.Therefore, this study is focused on bioactive compounds from kernel of maize cultivated in Kaliachak, Malda through use of LCMS analysis and medicinal potential & pharmacokinetic properties by the analysis of SwissADME. The study also contributes for developing maize-based nutraceuticals as well as provide subsequent evidence in therapeutic importance.

MATERIALS AND METHODS

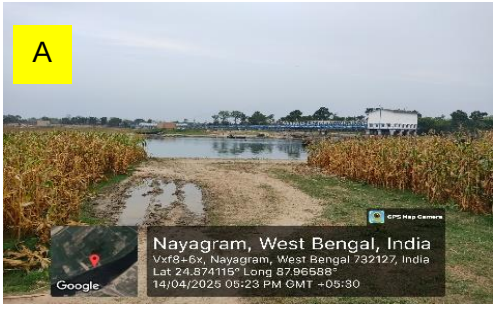
Selection of study area

The study was conducted in region of three blocks of Kaliachak, Malda district; which mostly characterized by alluvial soil of Ganga river and its tributaries.

Fig. 1: Map of sampling sites of different blocks of Kaliachak, Malda district (W. Bengal).

Sampling and biochemical assessment

- Mature flag leaf of maize plants were collected at the time of harvesting from time to time from distinct region of Kaliachak-I, II and III blocks of Malda district in India.
- After harvesting leaves were cleaned and surface sterilised with 5% detergent thereafter shade-dried and ground to powder. 5g powder of maize leaves were extracted with 50 mL 80% hydromethanolic solution; centrifuged at 5000 rpm at room temperature thrice and filtered five times.
- Then 2 mL of supernatant were taken for HR-LCMS analysis.



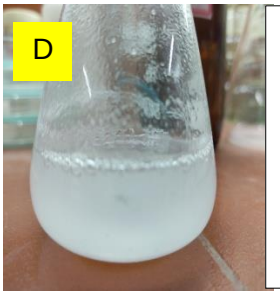


Fig. 2 A, B, C, D anticlock-wise represent Maize field (inland), Maize field (river bank), farmer & 80 percent hydromethanolic leaf extract

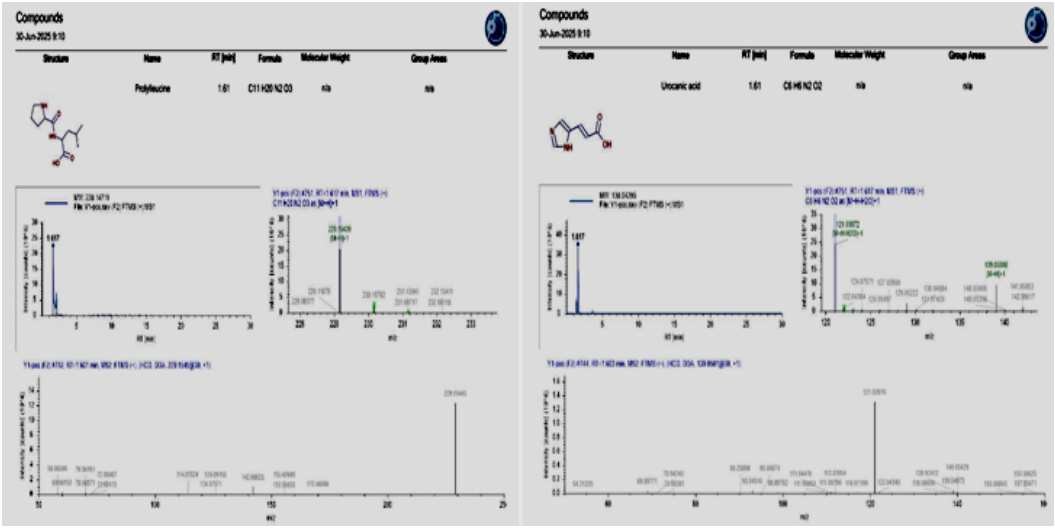
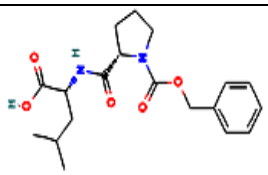
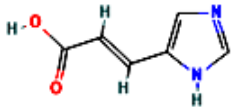


Fig. 3: LCMS chromatogram of leaf extract showing presence of two compounds, whose molecular details represented in Table-1.

Table 1: Selected bioactive compounds with molecular details.

Name of Compound	Molecular Structure	Molecular Weight	Canonical Smile
Prolylleucine		362.4 g/mol	CC(C)C[C@H](C(=O)O)NC(=O)[C@@H]1CCCN1C(=O)OCC2=CC=CC=C2
Urocanic Acid		138.12 g/mol	C1=C(NC=N1)/C=C/C(=O)O

Pharmacological assessment followed by Molecular docking

Pharmacological properties were assessed *in silico* using SwissADME software platform and toxicity parameters were investigated through *in silico* work flow on Protox version 3.0 software platform. Molecular docking of the two selected metabolites onto receptor. Molecular docking is a computational technique used to predict the preferred orientation and binding affinity of a small molecule (ligand) when bound to a target protein (receptor). The overall procedure involves the following steps: Receptor Preparation: Retreiving 3D coordinates from databases like the PDB, removing water molecules/non-essential ions, adding missing hydrogens, and assigning partial charges. Ligand Preparation: Generating 3D coordinates, minimizing energy using structural force fields, and establishing physiological protonation states. Grid Generation: Defining a 3D bounding box over the receptor's active site to restrict the

conformational search area. Conformational Search: Utilizing optimization algorithms (e.g., genetic algorithms, Monte Carlo methods) to explore structural poses of the ligand. Scoring Evaluation: Scoring mathematical functions calculate electrostatic, van der Waals, and hydrophobic interactions to rank the most thermodynamically stable poses.

RESULTS AND DISCUSSION

Pharmacokinetics and Drug-likeliness assessment

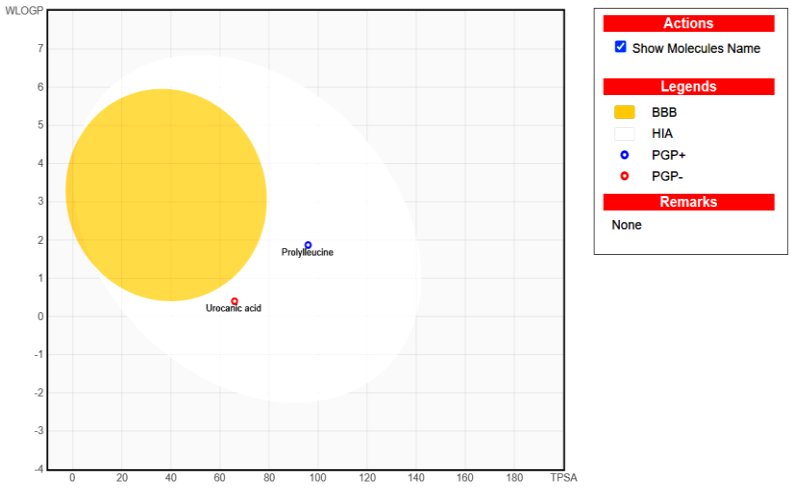


Fig. 4: Boiled egg diagram showing pharmacological assessment with reference to efficacy of the two selected metabolites for histological permeability.

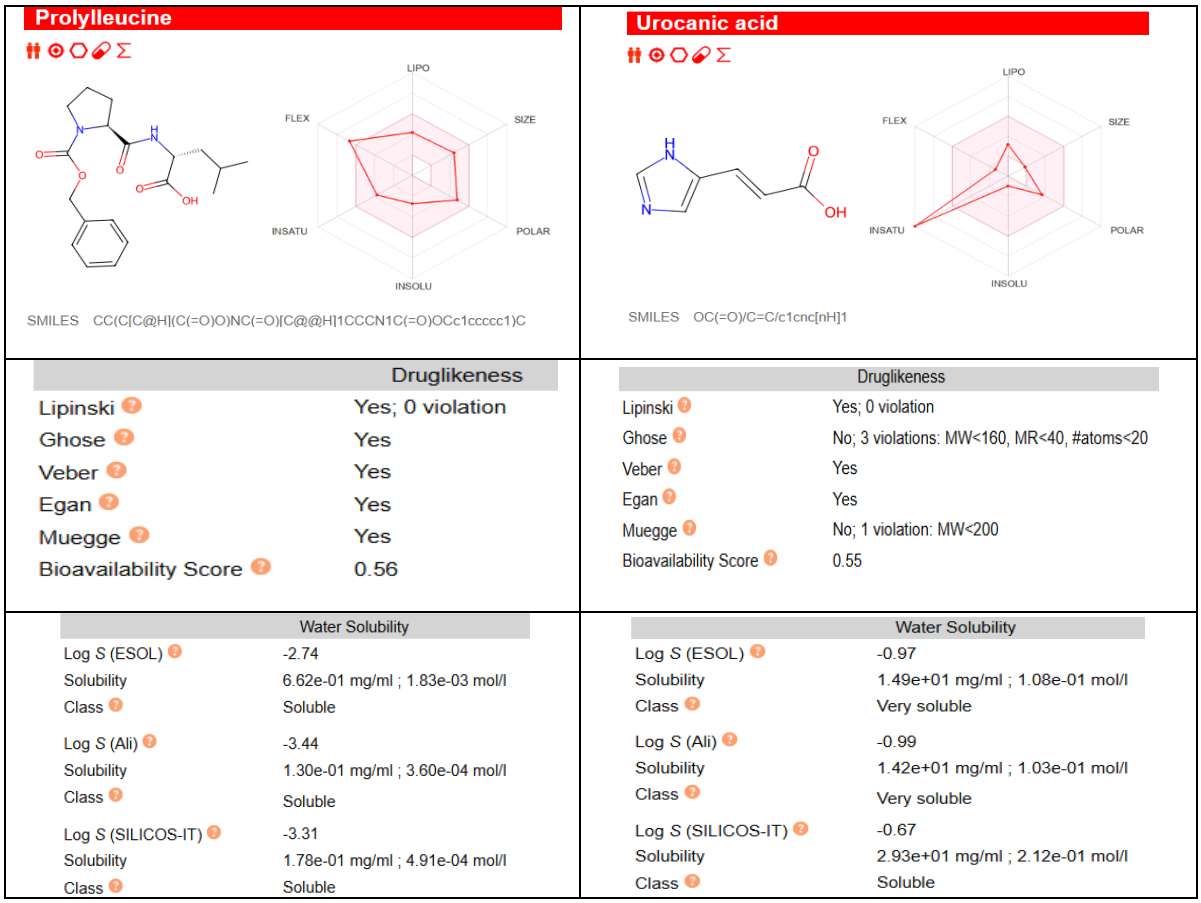
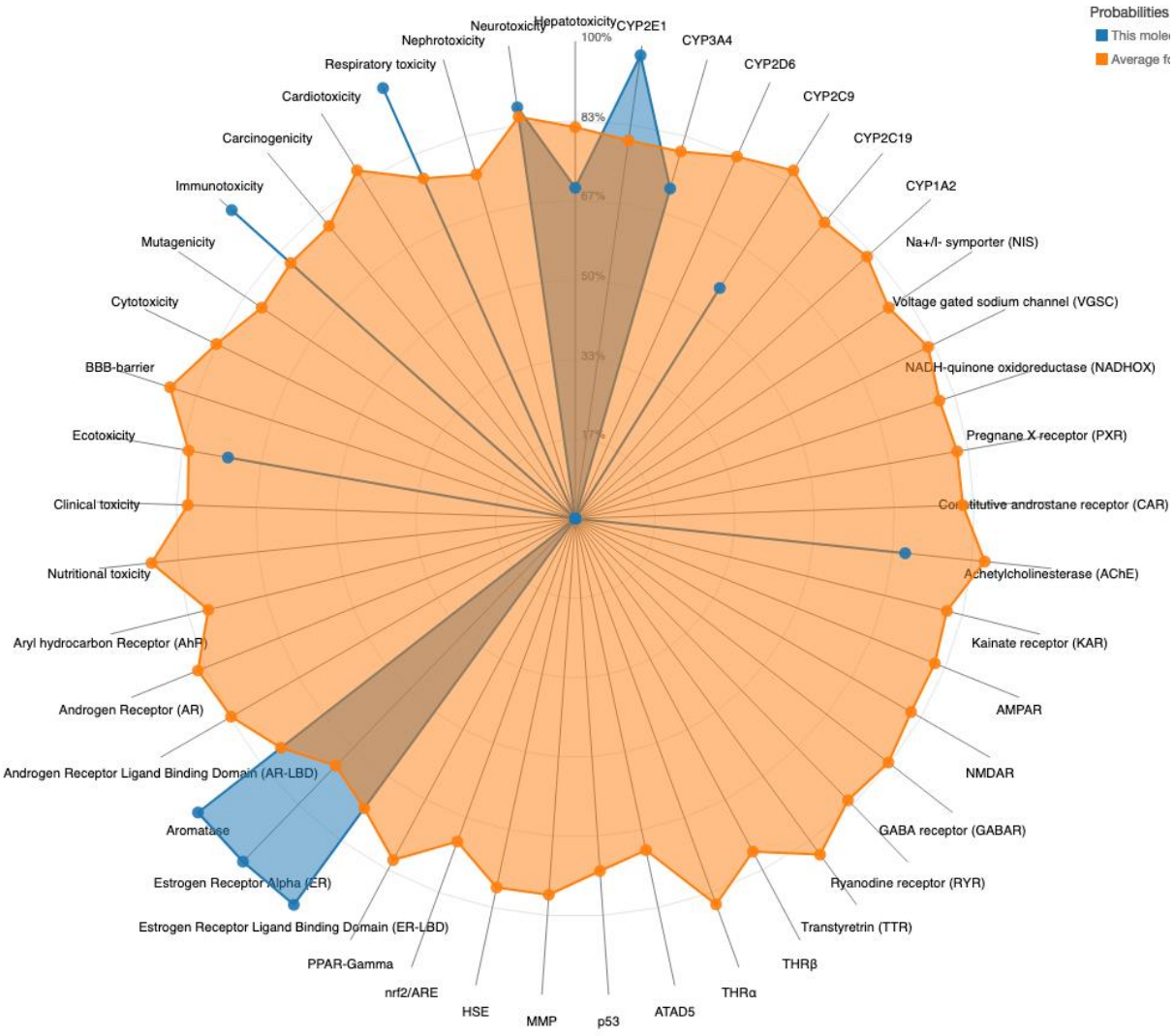


Fig. 5: Infographics-assisted output of SwissADME software showing pharmacological assessment in terms of 'Bioavailability radar', 'Drug-likeliness' and 'Water solubility' of the two selected metabolites.

Toxicity assessment



The SwissADME BOILED-EGG model evaluates gastrointestinal absorption (HIA) and blood-brain barrier (BBB) permeation simultaneously by mapping each molecule's lipophilicity (WLOGP) against polarity (TPSA). Both urocanic acid and prolylleucine fall securely within the white elliptical area of the plot, which defines the optimal physicochemical space for high passive gastrointestinal absorption. This positioning indicates that both compounds possess a favorable balance between polarity and lipophilicity, translating into promising oral bioavailability. Conversely, neither compound is located inside the yellow inner ellipse (the yolk), which marks the threshold for passive central nervous system entry. Consequently, both molecules are predicted to be BBB non-permeant, minimizing the likelihood of CNS-targeted therapeutic effects or central neurotoxicities. Their interaction with active transport systems, however, highlights key differences in cellular retention. Urocanic acid (represented by the red dot) is classified as a non-substrate for P-glycoprotein (PGP-). Free from active P-gp efflux, it is expected to maintain steady intracellular concentrations and predictable exposure profiles. In contrast, prolylleucine (the blue dot) is identified as a P-glycoprotein substrate (PGP+). While its structural properties favor strong passive oral absorption, its

net systemic availability and intracellular accumulation could be compromised in tissues where P-gp expression is highly elevated due to active efflux (Trott & Olson, 2010).

The physicochemical profile and oral drug-likeness of the prolylleucine derivative were evaluated using the SwissADME bioavailability radar. This radar plot visually assesses six core properties essential for oral bioavailability: lipophilicity (LIPO), molecular size (SIZE), polarity (POLAR), solubility (INSOLU), saturation (INSATU), and flexibility (FLEX). The pink-shaded area defines the optimal range for each parameter required for a molecule to be considered drug-like. Analysis of the radar plot reveals that the compound exhibits favorable properties across five of the six parameters. Its molecular weight, lipophilicity, and topological polar surface area (TPSA) fall entirely within the optimal pink boundaries, indicating balanced aqueous solubility and membrane permeability. Furthermore, the molecule demonstrates a satisfactory fraction of sp3-hybridized carbons (INSATU), ensuring a sufficient three-dimensional complexity that is beneficial for specific target binding while avoiding flatness. However, a significant deviation is observed along the flexibility (FLEX) axis, where the compound's red line extends past the optimal threshold. This violation is structurally driven by the presence of multiple rotatable bonds, particularly within the flexible leucine side chain and the benzyloxycarbonyl-like protecting group attached to the pyrrolidine core. According to Veber's rules, excessive molecular flexibility (typically defined as more than 10 rotatable bonds) can negatively impact oral bioavailability by increasing the entropic penalty associated with target binding and potentially hindering passive membrane permeation. Despite this flexibility violation, the compound satisfies major drug-likeness filters, such as Lipinski's Rule of Five, due to its compliant molecular weight, hydrogen bond donor/acceptor counts, and partition coefficient. In conclusion, while the compound possesses highly favorable polarity and solubility metrics for oral administration, structural optimization aimed at rigidifying the flexible chains could enhance its overall pharmacokinetic performance and binding affinity (Veber *et.al*., 2010).

The most prominent metabolic risk is directed toward the cytochrome P450 pathway, specifically showcasing a sharp peak approaching 100% probability for CYP2E1 interaction. Because CYP2E1 plays a critical role in the oxidation of low-molecular-weight xenobiotics, high binding affinity or inhibition at this isoform represents a significant liability. This metabolic channeling often correlates with the generation of reactive oxygen species (ROS) and downstream hepatotoxicity, making it a critical focal point for structural optimization. Furthermore, the compound exhibits an extensive off-target signature in the endocrine-disrupting quadrant (lower-left region). The blue shaded polygon demonstrates high-probability interactions with Aromatase, the Androgen Receptor Ligand Binding Domain (AR-LBD), and Estrogen Receptor Alpha (ER). This strong multi-receptor cross-reactivity indicates a high potential for endocrine disruption, which could interfere with steroidogenesis or reproductive hormone signaling pathways. Beyond these major pathways, the molecule displays moderate, above-average toxicological risks in several physiological domains, marked by distinct blue indicators at Cardiotoxicity, Ecotoxicity, and Acetylcholinesterase (AChE) inhibition. The predicted interaction with AChE suggests mild neurotoxic risks via acetylcholine accumulation, while the cardiotoxicity marker warrants future AChERG channel validation.The compounds avoids many acute endpoints like mutagenicity or cytotoxicity, its severe CYP2E1 metabolic focus and strong endocrine receptor binding outline its primary safety liabilities (Morris & Lim-Wilby, 2008).

In modern computer-aided drug design, combining target-receptor docking simulations with predictive ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiling is a critical strategy for filtering out

compounds with high clinical failure rates (Pinzi & Rastelli, 2019). While standard docking protocols focus on identifying energetically favorable conformations and high-affinity binding poses, downstream pharmacokinetic profiling evaluates whether these molecules can safely and effectively navigate systemic biological barriers (Daina et al., 2017). This study evaluates the pharmacokinetic profiles and toxicological footprints of two structurally unique compounds—urocanic acid and a prolylleucine derivative—using the SwissADME and ProTox platforms to clarify their therapeutic potential. A primary requirement for any oral drug candidate is its capacity to cross intestinal membranes via passive diffusion. When evaluated using the SwissADME BOILED-EGG model, which balances lipophilicity (WLOGP) against topological polar surface area (TPSA), both urocanic acid and the prolylleucine derivative map inside the white ellipse. This specific distribution indicates favorable amphiphilic properties that support strong passive gastrointestinal absorption (Daina et al., 2016). Crucially, neither molecule enters the yellow inner ellipse (the yolk), which predicts they cannot cross the blood-brain barrier. This lack of central nervous system penetration is highly beneficial for minimizing potential neurotoxic side effects (Daina et al., 2017). However, analyzing the six-axial Bioavailability Radar for the prolylleucine derivative reveals an architectural limitation.

Although the molecule complies with the optimal thresholds for molecular size, lipophilicity, polarity, solubility, and saturation, it significantly exceeds the flexibility boundary. This structural property stems from the high number of rotatable single bonds in its protected peptide scaffold. According to Veber's structural guidelines, excessive conformational freedom can reduce oral bioavailability by imposing a heavy entropic penalty during target binding or hindering effective passive transit through membranes (Veber et al., 2002). Beyond passive absorption, active cellular transport and metabolic degradation heavily influence a drug's systemic lifespan. The BOILED-EGG model identifies urocanic acid as a P-glycoprotein non-substrate (PGP-), whereas the prolylleucine derivative is flagged as a substrate (PGP+). Being a target for P-gp efflux introduces a noticeable risk of reduced tissue accumulation, as active transporter pumps can actively expel the drug from target cells—a well-documented mechanism of systemic drug resistance.

Broader physiological safety profiling via multi-axial toxicological analysis flags specific off-target risks for the prolylleucine compound. The most prominent metabolic vulnerability is a near-100% probability peak for interactions with Cytochrome P450 2E1 (CYP2E1). Because CYP2E1 actively oxidizes low-molecular-weight xenobiotics, high affinity for this isoform frequently triggers bioactivation pathways that generate reactive intermediates, which can lead to cellular hepatotoxicity or oxidative stress (Banerjee et al., 2018). Furthermore, the compound displays an extensive endocrine-disrupting signature, showing strong binding probabilities with Aromatase, the Androgen Receptor Ligand Binding Domain (AR-LBD), and Estrogen Receptor Alpha (ER). This multi-receptor cross-reactivity indicates a risk for endocrine disruption through competitive steroid pathway interference (Banerjee et al., 2018). Coupled with minor indicators for cardiotoxicity and acetylcholinesterase inhibition, these findings suggest that future optimization of this scaffold should focus on removing structural features that drive CYP2E1 and endocrine receptor interactions. Thus both molecules exhibit excellent oral absorption potential and avoid central nervous system liabilities, structural optimization remains necessary. Future development must focus on restricting the flexibility of the prolylleucine scaffold to minimize target-binding penalties, while simultaneously eliminating specific structural motifs that trigger CYP2E1 metabolism and endocrine receptor cross-reactivity.

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