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In Silico ADMET studies of Val-Trp dipeptide

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Abstract

In this study, the ADMET (absorption, distribution, metabolism, excretion and toxicity) properties of the antihypertensive Val–Trp dipeptide were investigated to assess its potential as a drug candidate. Early prediction of pharmacokinetic and toxicological parameters in the drug discovery process is of great importance in terms of reducing the risk of clinical failure. The ADMET parameters of Val–Trp dipeptide were evaluated using the SwissADME and ADMET-AI platforms. The results showed that the molecule fully complies with the Lipinski's rules and has favorable physicochemical parameters. High human intestinal absorption and oral bioavailability indicators indicate that Val–Trp dipeptide is promising for oral administration. Metabolic analysis showed minimal CYP450 inhibition and low risk of drug-drug interactions. The calculated excretion parameters confirmed the compound's rapid clearance and a minimal risk of accumulation in the body. Although the compound has low cardiotoxicity, mutagenicity and carcinogenicity risks according to toxicity predictions, a moderate risk of liver toxicity was identified. Overall, the results obtained indicate that the Val–Trp dipeptide is a promising bioactive compound and warrants its involvement in further experimental studies, especially in the antihypertensive direction.

Keywords: Val-Trp dipeptide; ADMET; pharmacokinetics; antihypertensive potential; oral drug
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1. Introduction

The modern pharmaceutical Research and Development (R&D) process is characterized by a complex system that includes disease definition, target identification, discovery and optimization of “lead” compounds, as well as preclinical and clinical testing. The best “lead” compounds should have “pharmacokinetic” properties. Pharmacokinetics is a qualitative concept that describes the extent to which a substance has drug properties in terms of factors such as bioavailability. This property is assessed based on the molecular structure of the substance before it undergoes synthesis and experimental testing. A druglike molecule must be soluble in both water and fat; because an orally administered drug substance must first cross the intestinal epithelium, be transported in the water environment of the blood, and penetrate the lipid-based cell membrane to reach its intracellular target [1]. Although millions of bioactive compounds have now been identified, the number of effective new drugs approved has not increased dramatically in recent years [2]. One of the main reasons for this is the shortcomings in terms of efficacy and safety, which is mainly associated with ADME properties and various toxicity indicators.

Protein–protein interactions (PPIs) also represent a largely unexplored source of potential targets for therapeutic interventions [3-4]. Modulation of protein–protein interactions by low molecular weight chemical compounds, especially those with oral bioavailability, may be important for the treatment of many diseases.

ADME studies cover pharmacokinetic issues and determine whether a drug molecule will reach its target protein in the body and how long it will remain in the bloodstream [5]. ADMET predictions involve the assessment of the toxicological properties of compounds in addition to the pharmacokinetic properties using computational methods [6]. The term ADMET refers to the concepts of absorption, distribution, metabolism, excretion, and toxicity. These predictions are of great importance in terms of assessing the drug similarity of molecules and their potential as therapeutic agents. In addition, predicting the absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties of key compounds using AI at the early stage of drug discovery also allows saving time and financial resources. Thus, parallel and comprehensive ADMET evaluation of the efficacy and biopharmaceutical properties of drug candidates at an early stage serves to reduce the failure rate by preventing failures in clinical trials that are mainly caused by ADMET problems and result in high costs [7-8]. Favorable absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiles are critical for drug candidates to be effective, reach their target site, and provide therapeutic benefit without causing unacceptable toxic effects.

Currently, there are a number of free and commercial computational tools for predicting ADMET properties. The ones used in this work are the SwissADME and

ADMET-AI platforms [9-10]. These modules are presented in a user-friendly, freely accessible web interface and are recommended as valuable tools for medicinal chemists in the drug discovery process.

In this work, the structure of the Val-Trp dipeptide docked against drug targets successfully passed the ADMET screening. These data may provide prospects for the future development of effective drugs against hypertensive diseases. Consequently, further studies are necessary to evaluate the mechanisms of action, toxicity and potential use of the proposed compound in the treatment of hypertension.

2. Calculation methods

In the development of natural medicines, existing AI databases and experimental results can be used to screen potential active compounds and predict disease-related drug targets [6].

The SwissADME and ADMET-AI platforms were used to evaluate the ADMET properties of the Val-Trp dipeptide [9-10]. These tools reliably predicted the pharmacokinetic and toxic properties of the dipeptide and analyzed quantitative structure-activity relationships (QSAR/QSPR). Lipinski rules were used to assess the potential of this molecular system to be used as oral drug [11].

3. Results and discussion

Data obtained from the SwissADME server reveal that Val-Trp dipeptide fully complies with Lipinski rules. Figure 1 illustrates the clinical toxicity–absorption relationship for the Val-Trp molecule, while Figure 2 summarizes its ADMET profile. The results of the ADMET calculations are reviewed in Tables 1-6.

The characteristics given in Table 1 allow us to evaluate the potential of the Val–Trp molecule as a drug candidate, its lipophilicity, hydrophilic-lipophilic balance and bioavailability. Molecules with favorable gastrointestinal absorption should not have a very large molecular mass and should have limited polarity [12]. The data given in Table 1 for the Val–Trp dipeptide indicate that this compound has high gastrointestinal absorption. The molecular weight of this compound is 303.36 Da, which places it in the 41.72 percentile in DrugBank and demonstrates that it is well absorbed through biological membranes, meeting the requirements for a favorable oral bioavailability threshold (<500 Da) [13]. The LogP value of the molecule (1.26, 35.60 percentile in DrugBank) indicates that it has moderate lipophilicity, i.e., membrane permeability potential, and balanced water solubility [14]. The Val–Trp dipeptide has 3 hydrogen bond acceptors (1.26, 31.17th percentile in DrugBank) and 4 hydrogen bond donors (1.26, 86.02nd percentile in DrugBank). This indicates a strong molecular interaction potential, supporting the interaction of the molecule with target proteins. The satisfaction of Lipinski's rules is an indicator of the suita-

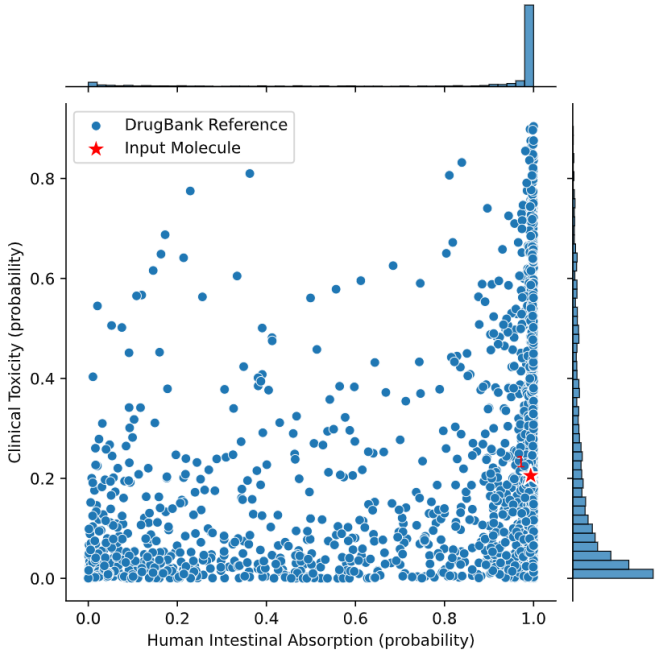

Fig. 1. Relationship between clinical toxicity and human intestinal absorption

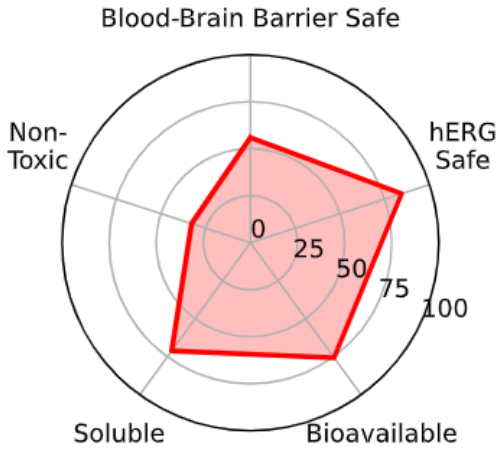

Fig. 2. Graphical representation of the ADMET properties of the Val-Trp molecule (%)

bility of the molecule as an oral drug candidate. The quantitative drug-likeness index (QED) of 0.64 for Val–Trp dipeptide is an indicator of the compliance of the molecule with the drug-likeness criteria. The dipeptide has 2 stereocenters (68.86th percentile in DrugBank), which proves that the molecule is favorable in terms of synthesis and optimization. These parameters are also confirmed by the topological

polar surface area (TPSA) value of 108.21 Å². The calculation of PSA allows predicting the extent to which the molecule can be absorbed in the intestine [15]. Thus, the topological polar surface area value is within the accepted limit for intracellular uptake (~140 Å²) [15, 16]. However, the compound may have limited relevance for the central nervous system (CNS) targets due to its relatively high TPSA value.

Table 1. Physicochemical profile of the Val-Trp dipeptide

Property	Value	DrugBank Percentile	Units
Molecular Weight	303.36	41.72%	Dalton
LogP	1.26	35.60%	log-ratio
Hydrogen Bond Acceptors	3.00	31.17%	#
Hydrogen Bond Donors	4.00	86.02%	#
Lipinski Rule of 5	4.00	63.80%	# of 4
Quantitative Estimate of Druglikeness (QED)	0.64	66.15%	-
Stereo Centers	2.00	68.86%	#
Topological Polar Surface Area (TPSA)	108.21	72.28%	$Å^2$

Table 2 shows the absorption characteristics of Val–Trp dipeptide. Using these parameters, it is possible to estimate the absorption potential, membrane permeability, and bioavailability of Val–Trp dipeptide after oral administration.

Table 2. Absorption properties of Val-Trp dipeptide

Property	Prediction	DrugBank Percentile	Units
Human Intestinal Absorption	0.99	45.75%	-
Oral Bioavailability	0.91	75.57%	-
Aqueous Solubility	-1.88	71.11%	log(mol/L)
Lipophilicity	-1.76	6.51%	log-ratio
Hydration Free Energy	-15.44	8.18%	kcal/mol
Cell Effective Permeability	-5.85	14.73%	log (10^{-6} cm/s)
PAMPA Permeability	0.16	17.45%	-
P-glycoprotein Inhibition	2.87e-03	10.35%	-

The value of 0.99 (45.75th percentile in DrugBank) for absorption from the human intestine proves that the dipeptide has a very high potential for absorption from the intestinal epithelium [17]. The percentile level in DrugBank indicates that the absorption of this molecule is satisfactory compared to the compounds in the DrugBank library. In addition, the high oral bioavailability (0.91, 75.57th percentile) confirms that the dipeptide can enter the systemic circulation well after oral administration. The solubility parameter of the molecular compound in aqueous me-

dium is considered satisfactory for molecules of peptide nature (-1.88 log mol/L, 71.11th percentile) and reveals that it has good solubility. High solubility creates favorable conditions for effective dissociation and absorption in the gastrointestinal tract and is one of the main factors supporting oral bioavailability. Lipophilicity is an important parameter in drug discovery, as it contributes to the solubility, membrane permeability, selectivity, and propensity for nonspecific action of a compound [18]. The low lipophilicity of the dipeptide (-1.76, 6.51st percentile in DrugBank) indicates that it is more hydrophilic in nature. Although this characteristic increases the solubility of the compound in water, it limits its passive membrane permeability. The hydration energy of the molecule (-15.44 kcal/mol, 8.18th percentile in DrugBank) confirms its strong propensity for hydration, explaining the stability of the molecule in water environment. The values obtained for the effective cell permeability (-5.85 log(10^{-6} cm/s), 14.73rd percentile in DrugBank) and PAMPA permeability of 0.16 (17.45th percentile in DrugBank) are also consistent with the low lipophilicity of the dipeptide, indicating that it has low membrane permeability. The low risk of efflux is evidenced by the very low degree of P-glycoprotein inhibition [19].

In order to characterize the behavior of the Val-Trp dipeptide in the bloodstream, its passage into tissues and its interaction with proteins, the distribution parameters of the dipeptide are given in Table 3. Based on the table, we can say that Val–Trp dipeptide is a compound with limited tissue distribution, blood-brain barrier penetration and moderate plasma protein binding. While this compound is more suitable for peripheral targets, as we have already mentioned (due to its high TPSA and hydrophilic nature), it has limited potential for central nervous system-targeted drugs. Thus, the molecule:

Table 3. Distribution characteristics of the Val-Trp dipeptide

Property	Prediction	DrugBank Percentile	Units
Blood-Brain Barrier Penetration	0.67	44.13%	-
Plasma Protein Binding Rate	70.74	44.63%	%
Volume of Distribution at Steady State	0.19	38.31%	L/kg

1. Blood-brain barrier penetration prediction (0.67, percentile 44.13% on DrugBank) indicates that the molecule, although limited, is able to cross the blood-brain barrier to some extent.

2. Plasma protein binding rate (70.74)– indicates that it has a relatively high level of binding. After administration of the drug, a part of it remains bound to plasma proteins (mainly albumin). Although this prolongs the half-life, it reduces the free fraction (the pharmacologically active portion of the drug in plasma that is not bound to proteins).

3. The low volume of distribution (Vd – 0.19) is explained by the fact that the

substance is mainly limited to blood plasma and extracellular fluid (its poor penetration into tissue and intracellular space). This is also consistent with the hydrophilic nature of the dipeptide.

Metabolic stability is one of the most important ADME properties of drug candidates. The metabolism characteristics of Val-Trp dipeptide, especially the interaction parameters with CYP450 enzymes, are presented in Table 4. Cytochrome P450 (CYP450) inhibition is considered one of the important parameters in ADMET studies. According to the results of the study, Val-Trp dipeptide did not show an inhibitory effect on CYP3A4, a member of the cytochrome P450 enzyme family involved in drug metabolism. As is known from the literature [20], ACE inhibitors have weak interactions with the cytochrome P450 enzyme system. At the same time, the rapid degradation and limited systemic distribution properties of dipeptides also reduce their long-term contact with CYP enzymes.

As can be seen from the table, Val-Trp dipeptide does not inhibit CYP enzymes as a whole, i.e. the risk of drug-drug interactions is low, but there is a possibility of being metabolized as a substrate. Val-Trp dipeptide is mainly metabolized by CYP2C9. This suggests that the compound under study has the potential to affect the metabolism and pharmacokinetics of CYP2C9 inhibitors [21]. The minimal CYP2D6 inhibition is explained by the low probability of Val-Trp dipeptide causing clinically significant interactions with drugs metabolized by CYP2D6. CYP2D6 substrates are usually highly lipophilic molecules, but as shown in Table 2, Val-Trp dipeptide has low lipophilicity. Therefore, the probability of Val–Trp dipeptide binding to the active site of CYP2D6 is low. Thus, the results obtained indicate that the dipeptide is close to a safe profile as a biologically active substance.

Table 4. Metabolic properties of Val-Trp dipeptide

Property	Prediction	DrugBank Percentile	Units
CYP1A2 Inhibition	0.02	40.13%	-
CYP2C19 Inhibition	0.07	44.28%	-
CYP2C9 Inhibition	0.03	48.31%	-
CYP2D6 Inhibition	0.01	28.85%	-
CYP3A4 Inhibition	0.03	40.29%	-
CYP2C9 Substrate	0.49	92.94%	-
CYP2D6 Substrate	0.09	45.41%	-
CYP3A4 Substrate	0.41	43.00%	-

The excretion characteristics of Val-Trp dipeptide indicate that it is a biologically active compound with low risk of chronic accumulation (Table 5). The half-life of 0.00 (21.52nd percentile in DrugBank) indicates that the substance is rapidly excreted without remaining in the body for a long time, which is a characteristic fea-

ture of peptide compounds. This feature can be interpreted as the rapid hydrolysis of peptides by peptidases in plasma and tissues. The very low percentile value of drug clearance in hepatocytes and microsomes indicates that CYP-dependent clearance in liver cells is poor and that metabolism may occur mainly by non-microsomal or extrahepatic pathways. The low hepatocyte clearance obtained for the dipeptide (0.00 µL/min/10^6 cells, 7.02nd percentile in DrugBank) is related to its hydrophilic nature, poor permeability across the hepatocyte membrane, and poor substrate for CYP enzymes. It should be noted that hepatocyte clearance is the rate at which a substance is effectively removed from the blood by hepatocytes through metabolic or transport mechanisms [22]. Microsomal clearance is a pharmacokinetic parameter that expresses the rate at which a substance is metabolized by enzymes located in liver microsomes (mainly the cytochrome P450 system) [22]. The very low microsomal clearance (0.00 µL/min/mg, 7.64th percentile in DrugBank) indicates that the Val-Trp dipeptide plays a minimal role in metabolism by CYP450 enzymes. These results are also consistent with the weak CYP inhibitory properties of the dipeptide given in Table 4.

Table 6 presents the toxicity characteristics of Val-Trp dipeptide. This analysis is performed to assess the safety of the substance at the cellular, organ, and organism levels. Based on the data presented in the table, Val-Trp dipeptide is a compound with a low toxicity profile.

Table 5. Excretion characteristics of Val-Trp dipeptide

Property	Prediction	DrugBank Percentile	Units
Half Life	0.00	21.52%	hr
Drug Clearance (Hepatocyte)	0.00	7.02%	uL/min/10^6 cells
Drug Clearance (Microsome)	0.00	7.64%	uL/min/mg

hERG blocking is associated with potassium channels that regulate the heart rate [8, 23]. Identification of hERG current inhibitory properties for candidate drugs is mainly done by focusing on binding sites located in the channel pore. In [24], it has been noted that biological agents are unlikely to inhibit hERG current because their poor diffusion through the plasma membrane prevents them from reaching the binding site in the channel pore. The minimal hERG channel blockade (0.02, 15.63rd percentile in DrugBank) suggests that the Val-Trp dipeptide has a low cardiotoxic potential and is a favorable compound from a clinical safety perspective. The low mutagenicity index (0.07) indicates that the compound has a low potential for adverse effects. Despite the medium percentile for carcinogenicity (51.14th percentile in DrugBank), the low predictive value suggests that it has limited carcinogenic risk. The predictions for androgen, estrogen receptors, aromatase and PPAR-γ are

Table 6. Toxicity properties of Val-Trp dipeptide

Property	Prediction	DrugBank Percentile	Units
hERG Blocking	0.02	15.63%	-
Clinical Toxicity	0.21	67.16%	-
Mutagenicity	0.07	26.87%	-
Drug Induced Liver Injury	0.54	55.87%	-
Carcinogenicity	0.16	51.14%	-
Acute Toxicity LD50	2.54	51.26%	log(1/(mol/kg))
Skin Reaction	0.23	24.66%	-
Androgen Receptor (Full Length)	0.01	34.35%	-
Androgen Receptor (Ligand Binding Domain)	0.01	35.17%	-
Aryl Hydrocarbon Receptor	0.29	86.47%	-
Aromatase	0.01	34.82%	-
Estrogen Receptor (Full Length)	0.04	20.86%	-
Estrogen Receptor (Ligand Binding Domain)	0.01	37.88%	-
Peroxisome Proliferator-Activated Receptor Gamma	0.01	64.91%	-
Nuclear Factor (Erythroid-Derived 2)-Like 2/Antioxidant Responsive Element	0.02	17.80%	-
ATPase Family AAA Domain	0.01	46.14%	-
Heat Shock Factor Response Element	0.01	43.78%	-
Mitochondrial Membrane Potential	1.94e-03	18.07%	-
Tumor Protein p53	4.70e-03	27.57%	-

in the range of 0.01–0.04. This is related to the lack of strong interactions of this dipeptide with the endocrine system. Acute toxicity is the acute toxicity dose of the molecules [25]. The prediction of 2.54 for the Val-Trp dipeptide (51.26th percentile in DrugBank) reflects that this molecule has a fairly low acute toxicity potential. Although the liver toxicity (0.54) is relatively high compared to the other parameters, the moderate DrugBank percentile value (55.87th percentile) suggests that it is not an acute hepatotoxic substance. However, the liver risk for Val-Trp dipeptide needs experimental confirmation, as the molecule is not potent, but the risk to the liver is assumed. This dipeptide is unlikely to cause allergic or irritant skin reactions (0.23, 24.66th percentile in DrugBank). Nuclear factor (erythroid-derived 2) 2-like/antioxidant responsive element (DrugBank 17.80th percentile), AAA domain-containing ATPase family protein-5 (DrugBank 46.14th percentile), heat shock factor response element (DrugBank 43.78th percentile), mitochondrial membrane po-

tential (DrugBank 18.07th percentile), and tumor suppressor protein p53 (DrugBank 27.57th percentile) indicators demonstrate that Val-Trp dipeptide does not impair mitochondrial function, does not cause DNA damage, and has a low risk of cell cycle disruption. Aromatic hydrocarbon receptor - regulates the body's response to foreign harmful substances (xenobiotics). The prediction of the aryl hydrocarbon receptor (0.29) is relatively higher than other indicators (86.47th percentile on DrugBank).

4. Conclusions

The in silico ADMET analysis showed that the Val–Trp dipeptide has favorable pharmacokinetic properties as drug. The molecule complies with Lipinski's rules and exhibits high gastrointestinal absorption and oral bioavailability due to its balanced lipophilicity–hydrophilicity properties. Although its relatively high polarity and hydrophilic nature indicate limited relevance for the central nervous system, it is more suitable for peripheral therapeutic targets. Metabolic analyses demonstrated weak inhibition of cytochrome P450 enzymes and low risk of drug–drug interactions. Toxicological parameters generally demonstrated a low risk profile, with minimal cardiotoxicity and mutagenicity. The potential for liver toxicity requires further experimental confirmation. Thus, the computational results suggest that the Val–Trp dipeptide is a promising candidate in terms of safety and pharmacokinetics. However, in vitro and in vivo studies are essential to confirm the predictions made.

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