Cumhuriyet Sci. J., 45(4) (2024) 591-597
DOI: https://doi.org/10.17776/csj.1483156

Cumhuriyet Science Journal

| csj.cumhuriyet.edu.tr | Founded: 2002 ISSN: 2587-2680 e-ISSN: 2587-246X Publisher: Sivas Cumhuriyet University

Geometry Optimization, Molecular Docking and ADMET Studies of Echimidine Molecule

Bilge Bıçak [1,a,*]

[1] *Physics Department, Science Faculty, Istanbul University, 34134, Istanbul, Türkiye.*
**Corresponding author*

Research Article

History
Received: 13/05/2024
Accepted: 12/08/2024

ABSTRACT

Plants are an important food group that has been used as a source of nutrition and healing from past to present. Plants contain secondary metabolites that are still under investigation in drug development studies. Alkaloids, which are secondary metabolites, have antioxidant and antibacterial properties as well as therapeutic potential in various diseases such as Alzheimer's disease. Acetylcholinesterase (AChE) inhibitors come to the fore in the treatment strategy of Alzheimer's disease. Echimidine, a pyrrolizidine alkaloid, is an important compound known to be active in AChE inhibition. Molecular docking method has an important place in elucidating biochemical processes by examining the interactions of drugs or drug candidates with the receptors targeted for the disease. Additionally, information on the absorption, distribution, metabolism, excretion, and toxicity (ADMET) of drug candidate molecules is important in drug development studies. In this study, echimidine molecule was optimized, the molecular docking study was carried out with AChE and the interaction types, binding profile, and binding affinity of echimidine was determined. ADMET analysis of echimidine was also realized to estimate its drug potential. With this study, geometry optimization of the molecule, elucidation of its interactions with AChE, and prediction of its pharmacokinetic properties were achieved for the first time.

Keywords: Echimidine, Acetylcholinesterase, Molecular Docking, ADMET.

[a] *bbicak@istanbul.edu.tr* *https://orcid.org/0000-0003-1147-006X*

Introduction

Plants are known to contain various secondary metabolites such as alkaloids, phenols, steroids, glycosides, tannins, terpenoids and phytoalexins to survive and reproduce. Alkaloids are structures that have an important place among secondary metabolites [1]. Alkaloids are secondary metabolites that come to the fore in treatment studies that show various effects such as AChE inhibitor, butyrylcholinesterase inhibitor, muscarinic and adenosine receptor agonists [2]. Moreover, alkaloids are compounds that show antioxidant, anti-inflammatory, antibacterial effects and have therapeutic potential in various diseases such as Alzheimer's disease [3-5]. Pyrrolizidine alkaloids are secondary metabolites found in plants used for medicinal purposes but are known for their hepatotoxic, genotoxic and neurological effects [6]. It has been reported that these compounds, which are the subject of controversy due to their toxic effects, can be used temporarily, considering that the exposure will be low, when found in trace amounts in herbal medicinal products [7]. Echimidine, a pyrrolizidine alkaloid, is an important compound known to be active in AChE inhibition [8]. As it is known, Cholinesterase inhibitors are an important enzyme that stands out in studies on the treatment of diseases such as Alzheimer's disease [8, 9]. Echimidine also shows binding activity to Muscarinergic receptors and 5-HT2 [10]. Echimidine has been reported to have comprehensive pharmacological effects due to its various activations [1].

The three-dimensional structures of molecules are related to molecular interactions and affect biological processes. Considering that the three-dimensional structures of molecules are important, the optimization of these structures is also very important. With geometry optimization, information is obtained about the optimum three-dimensional arrangement of the atoms that make up the molecules. The molecular docking method is a computer-aided method that plays a key role in elucidating biochemical processes by theoretically examining the interactions of small molecules called ligands and the receptors that these ligands have the potential to interact with. ADMET analysis, a predictive tool to evaluate a molecule's drug potential, provides information regarding absorption, distribution, metabolism, excretion, and toxicity.

In this study, firstly, the optimized geometry of the echimidine molecule was obtained using the DFT/B3LYP/6-311++G(d,p) method. Then, in order to elucidate the AChE inhibitor activity of the echimidine molecule, its binding affinity and binding profile were obtained by molecular docking method. Finally, the pharmacokinetic properties and toxicity profile of the echimidine molecule were evaluated by the ADMET study.

Methods

Molecular Optimization

The three-dimensional molecular structure of echimidine was downloaded from Pubchem (https://pubchem.ncbi.nlm.nih.gov/, CID: 5281729). The optimization of echimidine was realized with DFT method, B3LYP theory level, 6-311++G(d,p) basis set using Gaussian09 software program [11].

Molecular Docking

Echimidine molecule was prepared as a ligand for molecular docking study with AutoDock Tools 1.5.6. The structure of AChE given with 2ACE PDB Code was downloaded from PDB DataBank (https://www.rcsb.org/) [12]. AChE was prepared for molecular docking study by deleting water and other ligands and adding polar hydrogens. After the ligand and receptor were prepared, the grid box was prepared and all the necessary input information for the molecular docking study was obtained. Then, molecular docking study was successfully carried out by AutoDock Vina [13]. The Echimidine-AChE complex structure and the binding profile of echimidine obtained as a result of the molecular docking study were visualized with the Discovery Studio Visualizer 2019 [14].

ADMET Analysis

ADME and toxicity properties of echimidine molecule were determined by SwissADME and pkCSM online servers [15, 16].

Results and Discussion

Optimization

Echimidine molecule was optimized using Gaussian09 package program at DFT/B3LYP/6-311++G(d,p) basis set. The optimized parameters of the molecule were listed in Table 1,2,3. The energy value of optimized molecule was calculated as -1362.4795376 a.u.

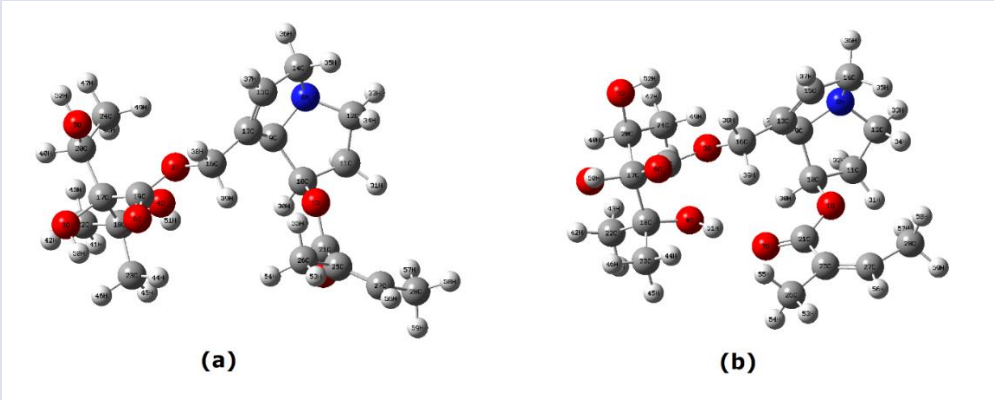

Figure 1 The input and output structures of Echimidine

Table 1. The bond lengths of optimized echimidine molecule.

Bond	Length (Å)	Bond	Length (Å)	Bond	Length (Å)
R(1,10)	1,4579	R(11,12)	1,534	R(22,41)	1,0922
R(1,21)	1,347	R(11,31)	1,0908	R(22,42)	1,0905
R(2,16)	1,4535	R(11,32)	1,0936	R(22,43)	1,0907
R(2,19)	1,3418	R(12,33)	1,0939	R(23,44)	1,093
R(3,17)	1,4237	R(12,34)	1,1022	R(23,45)	1,0925
R(3,50)	0,9676	R(13,15)	1,3332	R(23,46)	1,0897
R(4,18)	1,4296	R(13,16)	1,4953	R(24,47)	1,0936
R(4,51)	0,9684	R(14,15)	1,5031	R(24,48)	1,088
R(5,20)	1,4364	R(14,35)	1,1023	R(24,49)	1,0917
R(5,52)	0,9633	R(14,36)	1,0983	R(25,26)	1,5122
R(6,19)	1,2105	R(15,37)	1,0841	R(25,27)	1,3458
R(7,21)	1,219	R(16,38)	1,0908	R(26,53)	1,0909
R(7,51)	2,0136	R(16,39)	1,0926	R(26,54)	1,0928
R(8,9)	1,4878	R(17,18)	1,5939	R(26,55)	1,0937
R(8,12)	1,4665	R(17,19)	1,5361	R(27,28)	1,497
R(8,14)	1,4681	R(17,20)	1,5661	R(27,56)	1,0892
R(9,10)	1,5467	R(18,22)	1,5329	R(28,57)	1,0851
R(9,13)	1,5144	R(18,23)	1,5357	R(28,58)	1,0971
R(9,29)	1,0979	R(20,24)	1,5252	R(28,59)	1,0946
R(10,11)	1,5295	R(20,40)	1,0915		
R(10,30)	1,0859	R(21,25)	1,4906		

Table 2. The angle values of optimized echimidine molecule.

Angle	Degree(°)	Angle	Degree(°)	Angle	Degree(°)
A(10,1,21)	118,2036	A(8,14,35)	111,4463	A(18,22,41)	108,8119
A(16,2,19)	115,9465	A(8,14,36)	111,7616	A(18,22,42)	110,6741
A(17,3,50)	107,5038	A(15,14,35)	111,5863	A(18,22,43)	111,6055
A(18,4,51)	109,6462	A(15,14,36)	111,5232	A(41,22,42)	109,0885
A(20,5,52)	107,9582	A(35,14,36)	106,5445	A(41,22,43)	107,6632
A(9,8,12)	109,5407	A(13,15,14)	111,9899	A(42,22,43)	108,9201
A(9,8,14)	109,6123	A(13,15,37)	125,2854	A(18,23,44)	111,8142
A(12,8,14)	117,4101	A(14,15,37)	122,7219	A(18,23,45)	108,5819
A(8,9,10)	105,9679	A(2,16,13)	108,7554	A(18,23,46)	111,1434
A(8,9,13)	104,1709	A(2,16,38)	109,5147	A(44,23,45)	107,8425
A(8,9,29)	110,372	A(13,16,38)	111,4775	A(44,23,46)	108,4926
A(10,9,13)	120,9332	A(13,16,39)	112,0527	A(45,23,46)	108,8723
A(10,9,29)	105,7523	A(38,16,39)	107,7218	A(20,24,47)	108,1866
A(13,9,29)	109,4268	A(3,17,18)	106,7093	A(20,24,48)	112,3584
A(1,10,9)	112,1335	A(3,17,19)	106,8099	A(20,24,49)	111,1192
A(1,10,11)	107,4348	A(3,17,20)	105,4648	A(47,24,48)	109,1928
A(1,10,30)	108,6231	A(18,17,19)	110,6013	A(47,24,49)	108,7286
A(9,10,11)	101,9672	A(18,17,20)	115,6273	A(48,24,49)	107,1896
A(9,10,30)	112,4717	A(19,17,20)	111,0296	A(21,25,26)	113,1742
A(11,10,30)	114,058	A(4,18,17)	111,327	A(21,25,27)	125,9756
A(10,11,12)	103,5985	A(4,18,22)	106,6775	A(26,25,27)	120,8259
A(10,11,31)	112,4104	A(4,18,23)	109,6945	A(25,26,53)	110,5886
A(10,11,32)	108,4265	A(17,18,22)	109,3928	A(25,26,54)	110,9602
A(12,11,31)	113,7485	A(17,18,23)	110,25	A(25,26,55)	111,4338
A(12,11,32)	110,3041	A(22,18,23)	109,4199	A(53,26,54)	108,7161
A(31,11,32)	108,2129	A(2,19,6)	123,2313	A(53,26,55)	108,4597
A(8,12,11)	103,9	A(2,19,17)	114,0812	A(54,26,55)	106,5436
A(8,12,33)	111,52	A(6,19,17)	122,6872	A(25,27,28)	131,8754
A(8,12,34)	111,3774	A(5,20,17)	108,5073	A(25,27,56)	114,6884
A(11,12,33)	112,1565	A(5,20,24)	110,2124	A(28,27,56)	113,4323
A(11,12,34)	110,3313	A(5,20,40)	104,4908	A(27,28,57)	113,5444
A(33,12,34)	107,5975	A(17,20,24)	119,3883	A(27,28,58)	109,7989
A(9,13,15)	110,0286	A(17,20,40)	103,8546	A(27,28,59)	109,4414
A(9,13,16)	124,7614	A(24,20,40)	109,2385	A(57,28,58)	108,0134
A(15,13,16)	125,2042	A(1,21,7)	122,917	A(57,28,59)	109,4586
A(8,14,15)	104,0933	A(1,21,25)	115,3681	A(58,28,59)	106,325
A(2,16,39)	107,2087	A(7,21,25)	121,6946		

Table 3. The dihedral values of optimized echimidine molecule.

Dihedral	Degree(°)	Dihedral	Degree(°)	Dihedral	Degree(°)
D(21,1,10,9)	106,6397	D(1,10,11,31)	42,7373	D(18,17,20,40)	75,141
D(21,1,10,11)	-142,1149	D(1,10,11,32)	162,3243	D(19,17,20,5)	-47,0553
D(21,1,10,30)	-18,285	D(9,10,11,12)	37,5617	D(19,17,20,24)	80,2945
D(10,1,21,7)	-4,0904	D(9,10,11,31)	160,7876	D(19,17,20,40)	-157,808
D(10,1,21,25)	177,5263	D(9,10,11,32)	-79,6253	D(4,18,22,41)	64,4626
D(19,2,16,13)	-175,9019	D(30,10,11,12)	159,0629	D(4,18,22,42)	-175,6821
D(19,2,16,38)	-53,8575	D(30,10,11,31)	-77,7113	D(4,18,22,43)	-54,202
D(19,2,16,39)	62,7482	D(30,10,11,32)	41,8758	D(17,18,22,41)	-175,0097
D(16,2,19,6)	5,978	D(10,11,12,8)	-36,3639	D(17,18,22,42)	-55,1544
D(16,2,19,17)	-173,8507	D(10,11,12,33)	-156,9475	D(17,18,22,43)	66,3257

D(50,3,17,18)	116,1846	D(10,11,12,34)	83,1183	D(23,18,22,41)	-54,1343
D(50,3,17,19)	-2,1398	D(31,11,12,8)	-158,7044	D(23,18,22,42)	65,721
D(50,3,17,20)	-120,3387	D(31,11,12,33)	80,712	D(23,18,22,43)	-172,7989
D(51,4,18,17)	87,5893	D(31,11,12,34)	-39,2223	D(4,18,23,44)	60,4099
D(51,4,18,22)	-153,1311	D(32,11,12,8)	79,5011	D(4,18,23,45)	-58,455
D(51,4,18,23)	-34,7139	D(32,11,12,33)	-41,0825	D(4,18,23,46)	-178,1839
D(52,5,20,17)	95,3723	D(32,11,12,34)	-161,0168	D(17,18,23,44)	-62,5319
D(52,5,20,24)	-37,0578	D(9,13,15,14)	-2,4788	D(17,18,23,45)	178,6031
D(52,5,20,40)	-154,3039	D(9,13,15,37)	176,9338	D(17,18,23,46)	58,8742
D(12,8,9,10)	3,1538	D(16,13,15,14)	178,3584	D(22,18,23,44)	177,1148
D(12,8,9,13)	131,7405	D(16,13,15,37)	-2,229	D(22,18,23,45)	58,2499
D(12,8,9,29)	-110,8922	D(9,13,16,2)	-34,3118	D(22,18,23,46)	-61,479
D(14,8,9,10)	-127,0152	D(9,13,16,38)	-155,1561	D(5,20,24,47)	-57,559
D(14,8,9,13)	1,5716	D(9,13,16,39)	84,0255	D(5,20,24,48)	-178,1757
D(14,8,9,29)	118,9389	D(15,13,16,2)	144,7308	D(5,20,24,49)	61,7288
D(9,8,12,11)	20,4841	D(15,13,16,38)	23,8864	D(17,20,24,47)	175,8877
D(9,8,12,33)	141,4956	D(15,13,16,39)	-96,932	D(17,20,24,48)	55,2711
D(9,8,12,34)	-98,2828	D(8,14,15,13)	3,3593	D(17,20,24,49)	-64,8245
D(14,8,12,11)	146,3056	D(8,14,15,37)	-176,0708	D(40,20,24,47)	56,7027
D(14,8,12,33)	-92,6829	D(35,14,15,13)	-116,9549	D(40,20,24,48)	-63,914
D(14,8,12,34)	27,5387	D(35,14,15,37)	63,615	D(40,20,24,49)	175,9905
D(9,8,14,15)	-2,8785	D(36,14,15,13)	124,0176	D(1,21,25,26)	166,4001
D(9,8,14,35)	117,5299	D(36,14,15,37)	-55,4126	D(1,21,25,27)	-15,391
D(9,8,14,36)	-123,3767	D(3,17,18,4)	-178,7229	D(7,21,25,26)	-12,0049
D(12,8,14,15)	-128,6647	D(3,17,18,22)	63,6284	D(7,21,25,27)	166,204
D(12,8,14,35)	-8,2563	D(3,17,18,23)	-56,7411	D(21,25,26,53)	-179,287
D(12,8,14,36)	110,8371	D(19,17,18,4)	-62,911	D(21,25,26,54)	59,9852
D(8,9,10,1)	89,2652	D(19,17,18,22)	179,4403	D(21,25,26,55)	-58,567
D(8,9,10,11)	-25,3709	D(19,17,18,23)	59,0708	D(27,25,26,53)	2,4009
D(8,9,10,30)	-147,9615	D(20,17,18,4)	64,3549	D(27,25,26,54)	-118,3269
D(13,9,10,1)	-28,6614	D(20,17,18,22)	-53,2938	D(27,25,26,55)	123,1209
D(13,9,10,11)	-143,2975	D(20,17,18,23)	-173,6633	D(21,25,27,28)	-0,4908
D(13,9,10,30)	94,1119	D(3,17,19,2)	-167,1485	D(21,25,27,56)	-179,7178
D(29,9,10,1)	-153,5459	D(3,17,19,6)	13,0218	D(26,25,27,28)	177,5918
D(29,9,10,11)	91,818	D(18,17,19,2)	77,1024	D(26,25,27,56)	-1,6353
D(29,9,10,30)	-30,7726	D(18,17,19,6)	-102,7273	D(25,27,28,57)	-13,4654
D(8,9,13,15)	0,567	D(20,17,19,2)	-52,6561	D(25,27,28,58)	107,5574
D(8,9,13,16)	179,7343	D(20,17,19,6)	127,5142	D(25,27,28,59)	-136,0911
D(10,9,13,15)	119,3895	D(3,17,20,5)	68,2752	D(56,27,28,57)	165,7692
D(10,9,13,16)	-61,4432	D(3,17,20,24)	-164,3751	D(56,27,28,58)	-73,208
D(29,9,13,15)	-117,4522	D(3,17,20,40)	-42,4775	D(56,27,28,59)	43,1435
D(29,9,13,16)	61,7151	D(18,17,20,5)	-174,1063		
D(1,10,11,12)	-80,4886	D(18,17,20,24)	-46,7566		

Molecular Docking

Molecular docking study of echimidine molecule was realized with AChE using Autodock Vina program. The binding profile and binding affinities of echimidine were determined. The best binding affinity was calculated as -8.5 kcal/mol and the binding interactions was provided by hydrogen bond, pi interactions, and van der Waals interactions (see Figure 2). Echimidine made weak hydrogen bonds (3.05 Å and 3.14 Å) and pi-alkyl interactions with Tyr-121 residue in the PAS region of AChE. Echimidine made a pi-sigma interaction with Tyr-279, another important residue in the PAS region. Trp-84, Phe-330 and Phe-331 residues on the anionic site are other residues that make pi-alkyl interactions with echimidine. Echimidine had a van der Waals interaction with the His-440 residue from the CAS region. As a result of molecular docking, van der Waals interactions were observed with Gly-118 and Gly-119, which are important

residues in the oxyanion hole. In the binding profile where van der Waals interactions were dominant, other residues participating in the van der Waals interaction was Gly-335, Ile-287, Arg-289, Ser-122, Asn-85, Ser-81, Asp-72, Tyr-70, Phe-290 and Tyr-334. Additionally, echimidine made unfavorable donor-donor interaction with Phe-288 residue of AChE. The echimidine molecule interacted with most of the residues that Galantamine, used in Alzheimer's disease, interacts with in the active site of AChE [17]. Considering that the binding affinity value of Rivastigmine, a cholinesterase inhibitor, in the molecular docking study performed with AChE using Autodock Vina was -7.7 kcal/mol [18], the binding affinity obtained as a result of the molecular docking study of the Echimidine molecule with AChE had a lower value, and it was predicted that it could provide a strong binding profile. Additionally, considering that the AChE structure used is important for the docking result, a docking study was performed again for Rivastigmine with the prepared protein structure in this study. As a result of the study, it was determined that the binding affinity was again lower than echimidine.

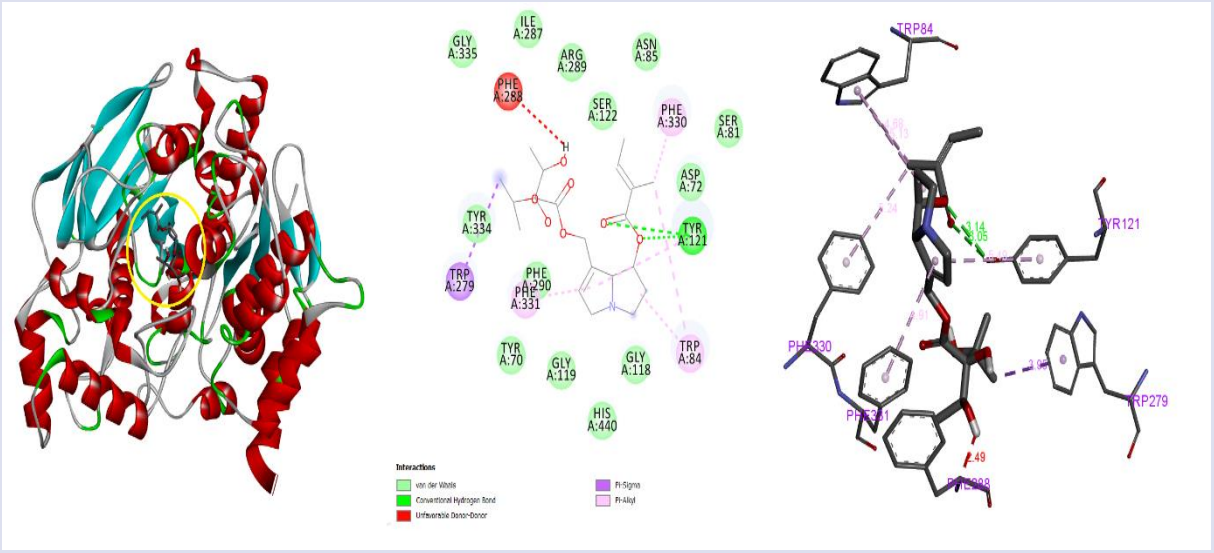

Figure 2. The molecular docking profile of echimidine at AChE active site

ADMET Analysis

Pharmacokinetic properties of echimidine were obtained by ADMET (absorption, distribution, metabolism, excretion, toxicity) analysis by using SwissADME and pkCSM servers, and tabulated in Table 4. It is stated that drug candidates that can be taken orally may violate at most 1 of the 4 criteria specified according to Lipinski's rules [19]. These 4 criteria are called the Lipinski's rule of five and consist of the principles that the molecular weight (MW) should not exceed 500 Daltons, the hydrogen bond donors (HBD) should not be greater than 5, the hydrogen bond acceptors (HBA) should not be greater than 10, and the octanol-water partition coefficient (logP) should not exceed 5. Apart from the Lipinski rule, other rules such as Ghose and Veber, which contain different rules, can also be evaluated for drug candidates. The Ghose filter indicates that the absorption rate will be high if the molecular weight, logP, molar refractivity and total number of atoms are within certain ranges [20, 21]. Veber's rule for oral bioavailability states that a drug should have fewer than 10 rotatable bonds and its polar surface area should not exceed 140 Å2 [22, 23]. Egan's rule states that polar surface area (PSA) and logP values must be within a certain range [24, 25]. The Muegge's rule selects even more specific ranges. The ranges of MW, LogP, PSA, number of rings, number of carbons, number of heteroatoms, rotatable bonds, HBD and HBA was stated by this rule [26]. According to SwissADME server results, it was determined that echimidine complies with all the rules. The results of echimidine showed poor BBB penetration and did not inhibit CYP450 enzymes according to the SwissADME server results. On the other hand, the molecule displayed optimum bioavailability scores and showed high GI absorption. P-glycoprotein, another prominent parameter in ADME estimation, is an important protein in the elimination of toxins and the absorption and disposition of the drug [27]. These substances that use the P-glycoprotein transporter for such activities are called p-glycoprotein substrates. In the prediction made according to the SwissADME server, echmidine was evaluated to be a P-gp substrate. When the skin permeability parameter was evaluated, it was predicted that echimidine had low skin permeability. When the echimidine molecule was evaluated using pkCSM server, it was determined that it was not mutagenic according to the AMES toxicity estimate, had no skin sensitization, and had no potential as a hERG I-II inhibitor in this study. However, it was evaluated in the toxicity prediction study that it should not be ignored that the molecule may have a hepatotoxic effect. It was observed that the prediction that echimidine, a pyrrolizidine alkaloid, may have a hepatotoxic effect is supported by literature studies [6, 28].

Table 4. Predicted ADMET properties of Echimidine.

Physicochemical Properties		**Lipophilicity**	
MW	397.46 g/mol	$LogP_{O/W}$(iLOGP)	3.43
No. of heavy atoms	28	$LogP_{O/W}$(XLOGP3)	0.74
No. rotatable bonds	9	$LogP_{O/W}$(WLOGP)	-0.08
No. of HBA	8	$LogP_{O/W}$(MLOGP)	0.30
No. of HBD	3	$LogP_{O/W}$(SILICOS-IT)	1.00
Polar surface area	116.53 Å²	Consensus LogPO/W	1.08
Water Solubility		**Pharmacokinetics**	
Log S (ESOL)	-2.18	GI absorption	High
Solubility	2.65e+00 mg/ml; 6.66e-03 mol/l	BBB permeant	No
Class	Soluble	P-gp substrate	Yes
Log S (Ali)	-2.77	CYP1A2 inhibitor	No
Solubility	6.81e-01 mg/ml; 1.71e-03 mol/l	CYP2C19 inhibitor	No
Class	Soluble	CYP2C9 inhibitor	No
Log S (SILICOS-IT)	-0.60	CYP2D6 inhibitor	No
Solubility	9.98e+01 mg/ml; 2.51e-01 mol/l	CYP3A4 inhibitor	No
Class	Soluble	Log K_P (skin permeation)	-8.20 cm/s
Druglikeness		**Toxicity**	
Lipinski	Yes, 0 violation	AMES toxicity	No
Ghose	Yes	Max. tolerated dose (human)	0.37 (log mg/kg/day)
Veber	Yes	hERG I inhibitor	No
Egan	Yes	hERG II inhibitor	No
Muegge	Yes	Hepatotoxicity	Yes
Bioavailability Score	0.55	Skin Sensitisation	No

Conclusion

In this study, the structure of the echimidine molecule was elucidated for the first time, its interactions with AChE were examined in detail, and predictions regarding its pharmacokinetic properties and toxicity were provided. The three-dimensional structure of the echimidine molecule, which plays a role in AChE inhibition, was optimized, and the interaction profile of the optimized structure with AChE was elucidated by molecular docking study. The binding profile and binding affinity of echimidine with molecules with proven interactions with AChE, such as galantamine and rivastigmine, were compared. As a result of the studies, it was evaluated that Echimidine has similar binding points to Galantamine used in Alzheimer's disease and can provide a stronger binding than the binding affinity of rivastigmine, a cholinesterase inhibitor. Additionally, the ADMET profile of echimidine was examined and it was determined that it complied with Lipinski's rules and other druglikeness rules, but its hepatotoxicity should not be ignored. This study is a molecular modeling study on echimidine, and it is anticipated that the different properties of this molecule can be further elucidated through experimental studies.

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Conflict of interest

There are no conflicts of interest in this work.

Acknowledgement

I would like to thank the editor and referees for their contributions to the review and evaluation of the manuscript.

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