IN-SILICO MOLECULAR DOCKING AND CHEMO-INFORMATIC PROPERTIES EVALUATION OF SOME IMIDAZOLE CANDIDATE AS POTENT AND SPECIFIC ANGIOTENSIN II RECEPTOR ANTAGONISTS

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Abstract

Imidazole has a unique place in heterocyclic chemistry, and its derivatives have piqued interest in recent years due to their diverse chemistry and pharmacology features. Hence, we designed a series of tetracyclic imidazole derivatives and perform molecular docking against Angiotensin II receptor protein (PDB ID:1O8A). The docking result showed binding energy ranging from – 5.42 to -9.56 kcal/mol. The top binding ligands 2,15, 16, 19, and 20were compared with the Azilsartan drug. Among 25 imidazole derivatives, 1-(2-(4,5-diphenyl-2-(p-tolyl)-1H-imidazol-1-yl)ethyl)piperazine (19) showed good interaction with standard drug Azilsartan. Further, the Lipinski rule of five was evaluated with help of the SWISS-ADME server. The pharmacokinetic properties of the selected substances were assessed using pkCSM. Overall, the in-silico results confirmed that the compound 1-(2-(4,5-diphenyl-2-(p-tolyl)-1H-imidazol-1-yl)ethyl)piperazine (19) could be used as s promising angiotensin II receptor inhibitor. We believe that the insights gained from the in-silico study may be of great value for the discovery and development of the novel angiotensin II receptor inhibitor drug.

Keywords: Imidazole; Angiotensin II; Azilsartan; molecular docking, SWISS-ADME

1. Introduction

Hypertensive heart disease is regularly referred to as hypertension and is quite possibly the most well-known human diseases in developed countries [1]. Angiotensin converting enzyme (ACE) assumes a significant part in hypertension, failure of which is the most widely recognized reason for hypertension [2]. The most well-known biological reason behind hypertension is the production of the enzyme angiotensin II, which is created by changing angiotensin I over to angiotensin II [3]. Thusly, managing the change of angiotensin I to angiotensin II might be a compelling methodology to control hypertension. ACE is viewed as significant in this pathway and has gotten impressive

consideration as a therapeutic target for the control of hypertension. Repressing of ACE expression has been demonstrated to be a successful system for controlling hypertension in light of the fact that its decrease prevents the conversion of angiotensin I to angiotensin II [4]. In this review, the binding affinities of different natural, synthetic, and herbal inhibitors to ACE active sites were predicted was anticipated utilizing the molecular docking approach, which is turning into the main tool in drug plan. Ang II receptor inhibitors (ARBs) viably lower pulse and have less incidental effects than different sorts of antihypertensive medications [5,6]. Nowadays, ARBs are generally utilized in the treatment of hypertension and show another pharmacological impacts in the treatment of diabetes [7-9] and heart illness [10, 11].As a general rule, imidazole has been viewed as a essential medication for bioactivity of AT1 receptor antagonists. The incredible accomplishment of ACE inhibitors includes [12,13] Losartan, Eprosartan, Olmesartan medoxomil , Candesartan cilexetil , Telmisartan and others, which inhibit the formation of angiotensin II (AII) [14-17] from angiotensin I (AI) . The ACE inhibitors have been stuided throughout the previous few decades. The utilization of ACE inhibitors, like as dry cough and angioedema [18]

2. Materials and methods

2.1. Preparation of ligand and protein

The 25 imidazole derivatives (Fig.1) were designed based on the literature [19]. The selected structures were drawn using chem draw software. Then its mol. file and smiles were extracted. The imidazole derivatives (1-25) in SDF format were entered into the database after protonation and energy minimization with Amber12: EHT Force field. The crystal structure of the angiotensin II receptor (PDB ID:108A)was retrieved from the Protein Data Bank (http://www.rcsb.org/pdb/). The crystal structure of the ERα is displayed in Fig. 2. The protein structure was prepared using MOE 09 docking tools [20]. The removal of water molecules, structure correction, and 3D protonation was done. The energy minimization was performed using Amber12:EHT Forcefield.

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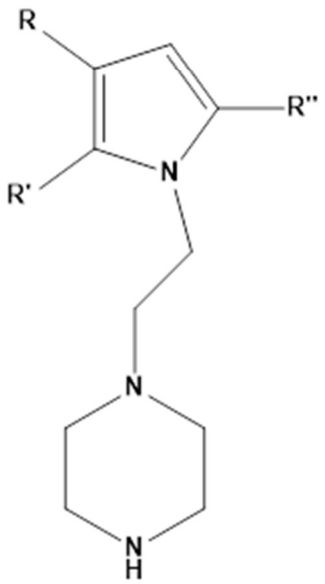

1-25

Ligand No	R	R'	R''
1	CH_3	CH_3	C_6H_5
2	CH_3	CH_3	*p*-F C_6H_4
3	CH_3	CH_3	*p*-Br C_6H_4
4	CH_3	CH_3	*p*-NO_2 C_6H_4
5	CH_3	CH_3	*p*-OH C_6H_4
6	CH_3	CH_3	*p*-CH_3 C_6H_4
7	CH_3	CH_3	*p*-OCH_3 C_6H_4
8	CH_3	CH_3	*p*-$N(CH_3)_2$ C_6H_4
9	CH_3	CH_3	C_5H_4N
10	CH_3	CH_3	C_4H_3S
11	CH_3	CH_3	C_4H_3O
12	CH_3	CH_3	C_4H_4N
13	C_6H_5	C_6H_5	C_6H_5
14	C_6H_5	C_6H_5	*p*-F C_6H_4
15	C_6H_5	C_6H_5	*p*-Cl C_6H_4
16	C_6H_5	C_6H_5	*p*-Br C_6H_4
17	C_6H_5	C_6H_5	*p*-NO_2 C_6H_4
18	C_6H_5	C_6H_5	*p*-OH C_6H_4
19	C_6H_5	C_6H_5	*p*-CH_3 C_6H_4
20	C_6H_5	C_6H_5	*p*-OCH_3 C_6H_4
21	C_6H_5	C_6H_5	*p*-$N(CH_3)_2$ C_6H_4
22	C_6H_5	C_6H_5	C_5H_4N
23	C_6H_5	C_6H_5	C_4H_3S
24	C_6H_5	C_6H_5	C_4H_3O
25	C_6H_5	C_6H_5	C_4H_4N

Fig.1 Scheme of Imidazole derivatives 1-25

2.2. Molecular docking analysis

The docking analysis of Angiotensin II receptor with imidazole derivatives (1-25) was carried out by MOE 09 docking tool. Azilsartan was used as a standard drug. The 5 finest docked positions were created by applying a scoring job London dG and using induce-fit model. The probable binding conformations of ligands were extracted by using Discovery studio visualizer.

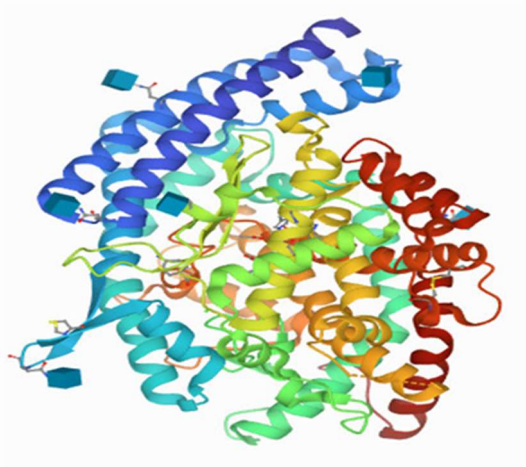

Fig. 2 Crystal structure of Angiotensin II receptor (PDB ID:108A)

2.3. Drug-likeness and ADMET properties analysis

Drug-likeness properties of selected ligands such 2,15, 16, 19, and 20 were analyzed using SwissADME online server [21]. Lipinski's rule was used to fitter the bioactive compounds based on their physicochemical properties [22]. The condition for the rule molecular mass less than 500 Da, hydrogen bond donors no more than 5, hydrogen bond acceptors no more than 10, total polar surface area not more than 140 and partition coefficient (log P) not greater than 5. The Absorption, Distribution, Metabolism, Excretion, And Toxicity (ADMET) properties analysis of the ligand 1-25 was performed by pkCSM server [23]. The ligand SMILES was retrieved from NCBI PubChem database and was used as the input fie for the SwissADME and pkCSM online servers.

3. Results and discussion

3.1 Molecular docking analysis

The Angiotension II receptor crystal structure was docked with the designed imidazole ligands 1-25. The outcome of the docking results is summarized in Table 1.

Table 1 Docking scores of deigned imidazole derivatives

Ligand No	Binding energy kcal/mol	Ligand No	Binding energy kcal/mol
1	-7.32	14	-6.59
2	-8.03	15	-9.02
3	-5.62	16	-9.04
4	-6.36	17	-7.49
5	-6.2	18	-7.02

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6	-5.48	19	-9.56
7	-6.19	20	-8.65
8	-7.98	21	-7.13
9	-7.17	22	-5.99
10	-7.12	22	-5.92
11	-6.92	24	-6.32
12	-5.46	25	-7.27
13	-5.35		

The ligands 1-25 have higher binding affinities which range from -5.42 to -9.56 kcal/mol. We have chosen the top five scoring namely ligands 2,15, 16, 19, and 20 were compared with the Azilsartan drug. Their interactions and results have been displayed in Table 2. From Table 2, molecule 19 was identified to have the highest binding energy (-9.56 kcal/mol) among the other selected ligands which are probably a result of pi-alkyl interactions formed with HIS 387, PHE 391, and VAL 518 amino acid residues in the active site of Angiotension II receptor. Besides pi-alkyl interactions, it also formed a carbon-hydrogen bond with HIS 410 amino acid in the protein, whereas the standard drug showed binding energy -6.26 kcal/mol and forms a hydrogen bond with ARG 522 amino acid residue in the protein pocket. Looking at ligand 16 which is second in the ranking in terms of binding energy (-9.04kcal/mol). It formed a hydrogen bond with LYS 117 amino acid residue in the active site. Not only has hydrogen bond has it interacted with, but also interacted with LYS 118, SER 219, PHE 570, GLU 403, MET 223, GLU 123, LYS 1170 in the active site of the Angiotension II receptor. The ligand 15 also interacts very well in the active site of the protein pocket with a binding energy of -9.02 kcal/mol. The amino acids such as HIS 387, VAL 518, and PHE 391 interact with ligands through pi-alkyl interactions. The methoxy substituted ligand 20 has -8.65 kcal/mol binding energy and it forms pi-alkyl interaction with VAL 518 amino acids. Further, it showed a carbon-hydrogen bond with HIS 410, GLU 411, ALA 354, and ASN 66 amino acids in the active pocket. As seen in Table 2, compound 2 has the least binding energy (-8.03 kcal/mol). It also interacts with ASN 70 in the active site of the Angiotension II receptor via hydrogen bond. Apart from the hydrogen bond, it interacts with PHE 391 amino acid through pi-alkyl interaction.

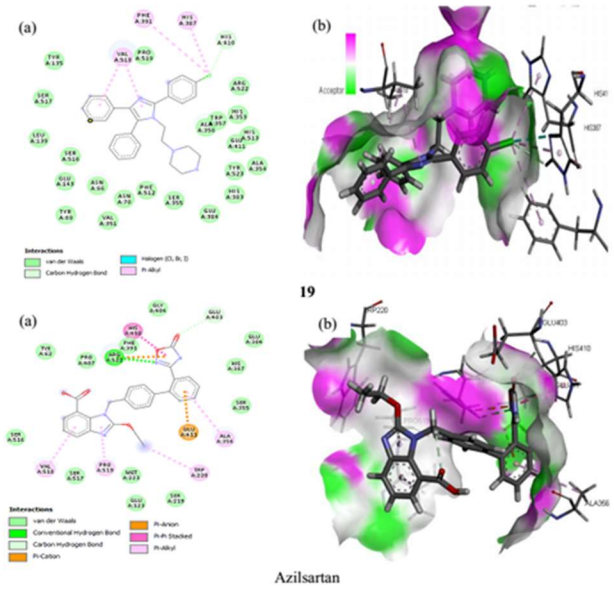

Fig. 3 (a) 2D and (b) 3D images of ligand 19 and Azilsartan drug

Table 2 Docking result of Imidazole derivatives and standard drug

Ligand No	Binding energy kcal/mol	Interactions	H-bond
2	-8.03	GLU 143, PHE 391, SER 355, ALA 356	ASN 70
15	-9.02	HIS 387, VAL 518, PHE 391, HIS 410	
16	-9.04	LYS 118, SER 219, PHE 570, GLU 403, MET 223, GLU 123, LYS 117	LYS 117
19	-9.56	HIS 410, HIS 387, PHE 391, VAL 518	
20	-8.65	HIS 410, GLU 411, ALA 354, ASN 66, VAL 518	
Azilsartan	-6.26	GLU 403, ALA 356, GLU 411, TRP 220, PRO 519, VAL 518, ARG 522, HIS 410	ARG A:522

3.2. Drug-likeness properties analysis

Lipinski's rule of five was used to evaluate the drug-like qualities of compounds 2,15, 16, 19, and 20. This study is based on the structure of the drug material and serves as a starting point for determining its structural similarity to a perfect drug. Compound 2 violates Lipinski's rule of five, as seen in Table 3, while the rest of the compounds do not. To be a potential drug application, however, a drug does not have to follow all of the rules. Bickerton et al. proposed in 2012 that the

oral bioavailability of ligands has no effect on a drug candidate's bioactivity or pharmacological potencies [24]. This research found that all of the candidates had excellent structural characteristics.

Table 3 Drug-likeness properties of compounds 2,15, 16, 19, and 20

Ligand	MM	Log p	HBA	HBD	TPSA	Molar refractivity
2	302.39	2.45	1	4	33.09	94.26
15	442.98	4.65	3	1	33.09	140.26
16	487.43	4.73	3	1	33.09	142.95
19	422.56	4.45	3	1	33.09	140.21
20	438.56	4.12	4	1	42.32	141.74

3.3. ADMET profile analysis

The ADMET study is remarkably beneficial in the initial phase of drug discovery to enable significant reduction of clinical trial disappointments [23]. The designed compounds 2,15, 16, 19, and 20 were subjected to ADMET analysis. The absorption parameter such as water solubility, GI absorption, skin and Caco2 permeability are in the drug development process. It is implied that an intestinal absorption value more than 30% implies good absorbance. The subjected compounds showed good GI absorption character and the values are ranges from 81.98 to 90.84 %. A skin permeability value greater than -2.5 cm/h is deemed as low skin permeability and all drug compounds exhibited acceptable skin permeability. All the drug candidates had low Caco2 permeability (<0.9 cm/s) except compound 2. Another important factor during ADMET analysis was to predict the P-glycoprotein non-substrate candidature. All compounds were observed to be a substrate for P-glycoprotein. The VDss, CNS and BBB membrane permeability was used to study the drug distribution [25]. The log VDss greater-than 0.45 were considered to be relatively high. The compound 2 showed greater distribution volumes than other ligands. (Table 4). For BBB membrane permeability, log BB values > 0.3 but < −1 indicated that the drug molecules crossed the BBB membrane. Expect compound 16, others have not crossed the BBB membrane. For CNS permeability, range of log PS values > −2 to < −3 specified impenetrability. It is evidenced from Table 4, that compounds 15 and 20 do not penetrate CNS, others such as 2, 16, and 19 are capable of penetrating the CNS. The CYP450 plays an important role in drug metabolism in the liver system [26].

Table 4 ADMET properties of compounds 2,15, 16, 19, and 20 using pkCSM server

	Model Name	2	15	16	19	20	Unit

	Water solubility	-2.56	-2.89	-2.89	-2.89	-2.89	Numeric (log mol/L)
	Caco2 permeability	-1.35	-0.85	0.65	-0.82	-0.94	Numeric (log Papp in 10 cm/s)
	Intestinal absorption (human)	90.84	81.98	83.12	85.38	87.69	Numeric (% Absorbed)
	Skin Permeability	-2.74	-2.74	-2.74	-2.74	-2.74	Numeric (log Kp)
	P-glycoprotein substrate	Yes	Yes	Yes	Yes	Yes	Categorical (Yes/No)
	P-glycoprotein I inhibitor	No	Yes	Yes	Yes	Yes	Categorical (Yes/No)
Absorption	P-glycoprotein II inhibitor	No	Yes	Yes	Yes	Yes	Categorical (Yes/No)
	VDss (human)	1.06	0.133	0.15	0.13	0.04	Numeric (log L/kg)
	Fraction unbound (human)	0.28	0.305	0.31	0.3	0.31	Numeric (Fu)
Distribution	BBB permeability	0.45	0.671	-0.07	0.58	0.46	Numeric (log BB)

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	CNS permeability	-2.23	-1.56	-2.02	-2.61	-1.99	Numeric (log PS)
Metabolism	CYP2D6 substrate	No	Yes	No	Yes	Yes	Categorical (Yes/No)
	CYP3A4 substrate	Yes	Yes	Yes	Yes	Yes	Categorical (Yes/No)
	CYP1A2 inhibitior	Yes	Yes	Yes	Yes	Yes	Categorical (Yes/No)
	CYP2C19 inhibitior	Yes	Yes	Yes	Yes	Yes	Categorical (Yes/No)
	CYP2C9 inhibitior	No	Yes	Yes	Yes	Yes	Categorical (Yes/No)
	CYP2D6 inhibitior	Yes	Yes	No	Yes	Yes	Categorical (Yes/No)
	CYP3A4 inhibitior	No	Yes	Yes	Yes	Yes	Categorical (Yes/No)
Excretion	Total Clearance	0.79	0.50	0.33	0.56	0.57	Numeric (log ml/min/kg)
	Renal OCT2 substrate	Yes	Yes	Yes	Yes	Yes	Categorical (Yes/No)
Toxicity	AMES toxicity	Yes	Yes	Yes	Yes	Yes	Categorical (Yes/No)
	Max. tolerated dose (human)	0.16	0.25	0.27	0.23	0.07	Numeric (log mg/kg/day)

	hERG I inhibitor	No	Yes	Yes	Yes	No	Categorical (Yes/No)
	hERG II inhibitor	Yes	Yes	Yes	Yes	Yes	Categorical (Yes/No)
	Oral Rat Acute Toxicity (LD50)	2.83	2.48	2.48	2.47	2.48	Numeric (mol/kg)
	Oral Rat Chronic Toxicity (LOAEL)	1.43	2.74	3.36	2.71	2.05	Numeric (log mg/kg_bw/day)
	Hepatotoxicity	No	No	No	No	No	Categorical (Yes/No)
	Skin Sensitisation	No	No	No	No	No	Categorical (Yes/No)
	*T.Pyriformis*toxicity	0.29	0.29	0.29	0.29	0.29	Numeric (log ug/L)
	Minnow toxicity	0.99	-0.187	-0.001	0.01	2.18	Numeric (log mM)

The metabolism scores showed that the drug compound 2 and 16 did not affect/inhibit CYP2D6 enzymes. The metabolism scores showed that all the drug compounds inhibit CYP3A4 enzymes. The total drug clearance is measured by a combination of hepatic and renal clearance. Total clearance defies the concentration of drug in the body using its elimination rate [27]. The predicted results showed that the drug candidates' excretion ranges from 0.33 to 0.79 mL/min/kg. Toxicity is an important benchmark in drug development, and it influences the selection of the best drug candidates [25]. All of the medication compounds studied in this study had no skin allergy or hepatotoxic effects. hERG inhibition (I and II) is an important factor for toxicity analysis and it also involves cardiotoxicity. The compounds 2 and 20 exhibited inhibitory actions for hERG-I. None of the compounds exhibited inhibitory actions for hERG-II. All the drug candidates have not expressed any AMES toxicity and T. Pyriformis toxicity. The LD50, LOAEL and maximum tolerated dosage range of drug candidates were predicted by the toxicity analysis server and the predicted scores are shown in Table 4.

Conclusion

The goal of this study is to develop a reliable method for predicting the Angiotensin II receptor inhibitor using imidazole (1-25) derivatives. Molecular docking research was used to investigate the important interactions of imidazole derivatives with the Angiotensin II receptor inhibitor. The binding energies of the proposed medicines ranged from -5.42 to -9.56 kcal/mol. In comparison to the regular Azilsartan drug, ligand 19 had a high binding energy in the proposed candidates. The binding mode analysis of ligand 19 revealed that HIS 387, PHE 391, and VAL 518 amino residues play important roles in stabilizing the Angiotension II receptor-imidazole interaction. The imidazole candidates had excellent structural characteristics, according to Lipinski's rule of five. The current study concluded that these imidazole compounds could be exploited as possible protease inhibitor medicines based on the ADMET results.

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