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Research Article

Designing Novel Angiotensin Receptor Blockers and their Antihypertensive Potentials

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ABSTRACT

Background: Hypertension is a pervasive and incurable disease that requires an effective management throughout life. Sartans are the most commonly used prescription drugs. These drugs are specific angiotensin II receptor type 1 (AT_1R) antagonists and are commonly called Angiotensin Receptor Blockers (ARBs). However, further development of the drugs is necessary since none of the sartans that are clinically available possess all the desired pharmacological properties such as bioavailability, high efficacy and safety. **Materials and Methods:** Five novel AT_1R antagonists were computationally designed using the molecular configuration of olmesartan as a base molecule. The compounds were analyzed *in silico* for their pharmacodynamics, pharmacokinetics, toxicity, druglikeness, binding affinity to AT_1R and molecular dynamics. **Results:** Among the novel compounds, compound 1, 2 and 3 showed promising properties as effective and safe ARBs. Compound 4 is unsuitable for further development due to its high molecular weight, high toxicity and low pharmacological activities. Compound 5 also lacked many of the desired drug properties and showed high toxicity and mutagenicity. **Conclusion:** Compound 1, 2 and 3 appeared to have AT_1R antagonistic activity and pharmacological properties to be developed as antihypertensive compounds. The findings encourage further investigations into the precise mode of action and experimental tests for the novel compounds.

Keywords: Angiotensin II receptor type 1 blockers, Hypertension, Molecular docking, Molecular dynamic simulation, Toxicity.

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INTRODUCTION

Hypertension is often called the "silent killer" due to its menacing physiological effects. When the force of blood against the arterial walls increases to the pressure 140/90 mmHg and above, the symptoms of hypertension appear. The condition poses major risks for life-threatening renal, cardiovascular and cerebrovascular diseases.[1,2] According to the "Global Report on Hypertension" of the World Health Organization, there has been a sharp increase in the global incidence of hypertension among adults during 1991–2019. There was 41% increase in the European and American regions, and 144% increase in the South-East Asia and Western Pacific regions.[3] The Global Burden of Disease Study 2021 estimates 85.62% average increase of the incidence and 81.46% average increase of the prevalence.[4] There has been an annual global increase of 7.20% clinical cases of hypertension among young people, specifically below 19 years of age, between 2006 and 2021, which indicates that the disease prevalence is unlikely to improve in the near future.[5]

The pathogenesis of hypertension is not yet fully understood since it involves a complex interplay of different but functionally interrelated signalling pathways. The fundamental molecular mechanisms involve disruption of the Renin-Angiotensin-Aldosterone System (RAAS), an endocrine system that regulates blood volume, plasma pressure and electrolyte balance. Within RAAS, the hormone angiotensin II seems to play the most pivotal roles in the regulation of blood pressure. Angiotensin II elicits its effect through a group of receptors, called the angiotensin II receptors, among which AT_1R and AT_2R are implicated with the development of hypertension.[6] Angiotensin II receptors belong to a family of G-protein-coupled receptors and are most critical in hypertension as they exert a range of cellular functions including vasoconstriction, production of aldosterone and release of vasopressin. These physiological processes intricately form a network of regulatory systems for blood pressure.[7] AT_1R specifically modulates signalling molecules of the most critical pathways such as AT_1R/JAK/STAT, Ras/Raf/MAPK, NF-κB and Cyclic AMP Response Element-Binding (CREB) pathways. Consequently, it is involved

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in all major types of hypertensions including aldosterone-induced hypertension, angiotensin II-induced hypertension, arginine-induced hypertension, diabetic hypertension, obesity-induced hypertension, salt-sensitive hypertension, renovascular hypertension, spontaneous hypertension, and stress-induced hypertension.[8]

Several prescription drugs have been developed for the clinical management of hypertension. β-adrenergic blockers, angiotensin-converting-enzyme inhibitors, calcium channel blockers, diuretics, and vasodilators are conventionally used. However, none of them are fully effective or free from adverse effects.[9,10] Drugs targeting AT_2R are also being developed, but none are approved for usage.[11] The development of losartan in the early 1990s as the first AT_1R antagonist marked the arrival of sartans. The analogues of losartan such as azilsartan, candesartan, eprosartan, irbesartan, olmesartan, telmisartan and valsartan were eventually developed (Figure 1). These AT_1R antagonists are well tolerated and effective thus creating a new milestone in hypertension management.[12] The sartans are now the most commonly used antihypertensive drugs. However, they are not fully satisfactory in terms of specific pharmacological properties. For instance, losartan has low solubility and bioavailability, azilsartan and omelsartan are practically insoluble, azilsartan has low bioavailability, olmesartan has weak receptor affinity, eprosartan, valsartan and temisartan have low bioavailability.[13] In addition, they are not totally safe as clinical trials and meta-analyses show that they cause more cardiovascular mortality and myocardial infarctions than the conventional drugs.[14] Olmesartan is known for its severe side effects characterized by a medical condition called sprue-like enteropathy that is indicated by severe diarrhoea, weight loss and gastrointestinal pain.[15]

Development of ideal drugs are labour intensive, arduous, risky and expensive, and also hugely wasteful since most synthesised molecules are ultimately discarded. To overcome the problem, Computer-Aided Drug Design (CADD) has become a major procedure in drug design as it simplifies selection of compounds from a myriad of possible sources. CADD had been successfully used to correctly simulate more than 70 pharmaceutical drugs that are now available in clinical applications.[16] It has not only eased the experimental procedures but also widened the application and scopes of drug development for different medical conditions.[17] With the recent development of AT_1R antagonists and understanding of their limitations, the importance of CADD became pronounced as several potential antihypertensive molecules had been reported.[18,19] We therefore attempt to provide insights into the modified compounds of sartans as AT_1R blockers using olmesartan as the base compound, since the drug is established to be one of the most effective and safest sartans.[20,21]

MATERIALS AND METHODS

Preparation of sartan derivatives

Five compounds were computationally designed with ChemBioDraw Ultra 12.0 using the chemical configuration of olmesartan (CID: 158781). Alterations were made by addition or removal of different presumptive chemical groups to olmesartan that could improve the pharmacological properties. These compounds were labelled as compound 1 (C-1), compound 2 (C-2), compound 3 (C-3), compound 4 (C-4) and compound 5 (C-5). The IUPAC names, isomeric SMILES and InChI were obtained. Molecular docking and dynamic simulations were performed using Maestro 2024-2 of Schrodinger Suite.

Retrieval of receptor and ligands

Human angiotensin II receptor type 1 (AT_1R) (PDB code: 4ZUD) in complex with olmesartan was retrieved from RCSB Protein Data Bank (https://www.rcsb.org/). The receptor was further processed using protein preparation module where unwanted molecules were removed. The structures of AT_1R such as azilsartan (CID: 135415867), candesartan (CID: 2541), eprosartan (CID: 5281037), irbesartan (CID: 3749), losartan (CID: 3961), olmesartan (CID: 158781), telmisartan (CID: 65999) and valsartan (CID: 60846) were retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov/) and were processed in LigPrep module for minimization of energy.

Molecular descriptor, ADMET analyses and druglikeness

The molecular descriptor of the compounds, pharmacokinetic parameters such as absorption, distribution, metabolism, excretion and toxicity were analyzed with pkCSM online database (https://biosig.lab.uq.edu.au/pkcsm/) following a standard protocol.[22] To determine the druglike nature of the novel compounds, druglikeness analyses were performed with SWISSADME online tool (http://www.swissadme.ch/).

Molecular docking

Glide module was used to analyze the binding affinity of different compounds to AT_1R. The receptor was defined by allowing the grid box to cover all the surface of the protein. Molecular dockings were separately performed on the receptor for all the ligands. The docking score expressed in kilocalorie/mole (kcal/mol) and Root Mean Square Deviation (RMSD) values were obtained. Novel compounds with low binding energy were selected for molecular dynamic simulation. For ARBs, the drug with the lowest binding energy was selected for molecular dynamic simulation.

Molecular dynamic simulation

After analyses of the molecular docking results, five compound including C-1, C-2, C-3, C-4 and eprosartan were selected for molecular dynamic simulations using Desmond simulation

package of Schrodinger suite. Orthorhombic cubic box was generated and filled with water molecules using SPC water model. The simulated system was neutralized with Na^+ and Cl^- ions and OPLS force field was applied. The simulation was performed for 100 ns with fs steps.

RESULTS

Five novel compounds were generated from olmesartan, designated C-1, C-2, C-3, C-4 and C-5. The IUPAC names, SMILES, InChI and structures of the novel compounds are given in Table 1 and Figure 2. The molecular properties of the compounds and ARBs including chemical formulae, molecular weights, number of rotatable bonds, number of electron acceptors and donors, surface area and partition coefficient (LogP) values are given in Table 2. All the compounds were found to be hydrophobic in nature. However, the partition coefficient values of C-1, C-4 and C-5 were found to be moderate while C-2 and C-3 exhibited low LogP values.

Water solubility prediction showed that all the compounds have relatively low solubility in water at 25°C. C-1 and C-2 are predicted to be highly absorbed orally while C-3, C-4 and C-5 showed no oral absorption. All the compounds were predicted to be readily absorbed in the intestine with absorption percentage of 84.19, 49.72, 68.01, 49.55 and 68.99 for C-1, C-2, C-3, C-4 and C-5 respectively. All the compounds were found to have relatively low skin permeability and were also substrates of P-glycoprotein. Only C-1 was predicted to act as inhibitor of P-glycoprotein I. C-1, C-3 and C-5 were also predicted to inhibit P-glycoprotein II while the analyses showed no inhibitory properties for C-2 and C-4 (Table 3).

C-3 was found to have intermediate steady state Volume of Distribution (VDss), while C-1, C-2, C-4 and C-5 showed relatively low VDss. C-1 and C-4 were predicted to have low fraction unbound, C-3 has intermediate fraction unbound while C-2 and C-5 were predicted to have high fraction unbound. All the compounds showed no permeability to the blood-brain barrier and central nervous system. Our prediction showed

Table 1: IUPAC nomenclature, SMILES and InChI of five novel compounds.

C-1	IUPAC name	:	(2'-(2,3-dihydro-1,2,3,5-oxatriazol-4-yl)-[1,1'-biphenyl]-4-yl)(6-hydroxy-4-methyl-3a,7a-dihydro-1H-benzo[d]imidazol-1-yl)methanone
	SMILES	:	CC1=CC(O)=CC2C1N=CN2C(C3=CC=C(C=C3)C4=CC=CC=C4C5=NONN5)=O
	InChI	:	InChI=1S/C22H19N5O3/c1-13-10-16(28)11-19-20(13)23-12-27(19)22(29)15-8-6-14(7-9-15)17-4-2-3-5-18(17)21-24-26-30-25-21/h2-12,19-20,26,28H,1H3,(H,24,25)
C-2	IUPAC name	:	6-(2-(1H-tetrazol-5-yl)phenyl)-1,4-dimethyl-2,4-dihydro-1H-benzo[d]imidazole-2-carboxylic acid
	SMILES	:	CC(C1=NC(C(O)=O)N(C)C1=C2)C=C2C3=CC=CC=C3C4=NN=NN4
	InChI	:	InChI=1S/C17H16N6O2/c1-9-7-10(8-13-14(9)18-16(17(24)25)23(13)2)11-5-3-4-6-12(11)15-19-21-22-20-15/h3-9,16H,1-2H3,(H,24,25)(H,19,20,21,22)
C-3	IUPAC name	:	7-hydroxy-1-((3-methoxy-2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-1,4-diazaspiro[4.4]nonan-2-one
	SMILES	:	OC(C1)CCC1(NCC2=O)N2CC3=CC=C(C=C3OC)C4=CC=CC=C4C5=NNN=N5
	InChI	:	InChI=1S/C22H24N6O3/c1-31-19-10-14(17-4-2-3-5-18(17)21-24-26-27-25-21)6-7-15(19)13-28-20(30)12-23-22(28)9-8-16(29)11-22/h2-7,10,16,23,29H,8-9,11-13H2,1H3,(H,24,25,26,27)
C-4	IUPAC name	:	(1-((1-((2'-(2,3-dihydro-1,2,3,5-oxatriazol-4-yl)-[1,1'-biphenyl]-4-yl)(hydroxy)methyl)-2-methoxy-2,3-dihydro-1H-benzo[d]imidazol-5-yl)methyl)-4,5-dihydro-1H-imidazol-5-yl)methyl hydrogen carbonate
	SMILES	:	OC(N1C(OC)NC2=CC(CN3C=NCC3COC(O)=O)=CC=C21)C4=CC=C(C=C4)C5=CC=CC=C5C6=NONN6
	InChI	:	InChI=1S/C28H29N7O6/c1-39-27-30-23-12-17(14-34-16-29-13-20(34)15-40-28(37)38)6-11-24(23)35(27)26(36)19-9-7-18(8-10-19)21-4-2-3-5-22(21)25-31-33-41-32-25/h2-12,16,20,26-27,30,33,36H,13-15H2,1H3,(H,31,32)(H,37,38)
C-5	IUPAC name	:	6-(2'-(2H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)-7-acetyl-1-amino-4-hydroxy-1,3-dihydro-2H-benzo[d]imidazol-2-one
	SMILES	:	O=C(N1N)NC2=C1C(C(C)=O)=C(C=C2O)C3=CC=C(C=C3)C4=CC=CC=C4C5=NNN=N5
	InChI	:	InChI=1S/C22H17N7O3/c1-11(30)18-16(10-17(31)19-20(18)29(23)32)24-19)13-8-6-12(7-9-13)14-4-2-3-5-15(14)21-25-27-28-26-21/h2-10,31H,23H2,1H3,(H,24,32)(H,25,26,27,28)

that all the compounds were neither substrate nor inhibitor of Cytochrome 2D6 (CYP2D6). C-2 was not a substrate of Cytochrome 3A4 (CYP3A4) while the other four compounds were found to be substrates of CYP3A4. C-1 and C-3 were found to inhibit CYP3A4 while C-2, C-4 and C-5 showed no inhibition. None of the compounds showed inhibition against Cytochrome 1A2 (CYP1A2) and Cytochrome 2C19 (CYP2C19), except C-1 which showed inhibitory property for CYP2C19. C-1 and C-4 were also found to have inhibitory property for Cytochrome 2C9 (CYP2C9). C-2 and C-3 showed higher total clearance values expressed as log(ml/min/kg) compared to C-1, C-4 and C-5. It was also found that all the compounds were not substrate of renal organic cation transporter (Table 3).

C-5 was predicted to be mutagenic while the other compounds showed no mutagenicity according to Ames test. The maximum recommended tolerated dose for C-3 was high while the other compounds were found to exhibit low maximum recommended tolerated dose. Prediction of the inhibiting properties of the compounds for human ether a-go-go genes (hERG I and II) showed that none of the investigated compounds inhibited hERG I while C-1, C-3 and C-5 were found to inhibit hERG II. The oral rat acute toxicity (LD_{50}) was found to be 2.397, 2.532, 3.002, 2.453 and 2.482 mol/kg for C-1, C-2, C-3, C-4 and C-5 respectively. The oral rat chronic toxicity (LOAEL) was found to be 1.544, 0.686, 2.369, 2.428 and 2.693 expressed in log (mg/kg bw/day) for C-1, C-2, C-3, C-4 and C-5 respectively. All the compounds were predicted to be hepatotoxic, however, with no skin sensitization. Tests for *Tetrahymena pyriformis* toxicity and Minnow toxicity showed that all the compounds were toxic (Table 3).

All the ARBs exhibited relatively low water solubility. Eprosartan, irbesartan and telmisartan were found to be orally absorbed. Irbesartan had the highest rate of intestinal absorption while valsartan had the lowest rate. All the ARBs had relatively low skin permeability and were all substrates of P-glycoprotein. Only irbesartan was predicted to inhibit P-glycoprotein I while only valsartan was predicted to act as P-glycoprotein II inhibitor. Telmisartan was found to have comparatively high intermediate steady state volume of distribution. Irbesartan, losartan and valsartan were predicted to have low fraction unbound and all the ARBs showed no blood brain barrier and central nervous system permeability. Losartan had the highest total clearance value while olmesartan had the lowest value. Only telmisartan was predicted to be substrate of renal organic cation transporter. Ames toxicity test predicted irbesartan and telmisartan to be toxic. Valsartan exhibited the highest tolerated dose while telmisartan showed the lowest tolerated dose. Eprosartan and telmisartan were predicted to be hERG I inhibitor while only losartan was predicted to be hERG II inhibitor. The oral rat acute toxicities were comparable to one another; however, oral rat chronic toxicity was highest for candesartan and lowest for telmisartan. Only telmisartan was predicted to be hepatotoxic. No ARBs were predicted to be positive for skin sensitization. Tests for *T. pyriformis* toxicity showed that all the ARBs were cytotoxic while Minnow toxicity predicted that only irbesartan, losartan and olmesartan were cytotoxic (Table 4).

Druglikeness analyses predicted C-1 to follow Lipinski, Veber, Egan and Muegge except Ghose and has a bioavailability score of 0.55. C-2 and C-3 do not violate any of the laws under consideration and have bioavailability score of 0.56 and 0.55 respectively. C-4 violates all the laws and has a bioavailability of 0.17. C-5 follows Lipinski and Ghose but violates Veber, Egab and Muegge and has bioavailability of 0.11 (Table 5).

Table 2: Molecular properties of the novel compounds and angiotensin II type 1 receptor blockers.

Compound	Chemical formula	Molecular weight	LogP	#Rotatable bonds	#Acceptors	#Donors	Surface area
C-1	$C_{22}H_{19}N_5O_3$	401.426	2.678	3	7	3	172.339
C-2	$C_{17}H_{16}N_6O_2$	336.355	1.581	3	6	2	143.131
C-3	$C_{22}H_{24}N_6O_3$	420.473	1.715	5	7	3	178.971
C-4	$C_{28}H_{29}N_7O_6$	559.583	2.815	9	12	5	235.106
C-5	$C_{22}H_{17}N_7O_3$	427.424	2.466	4	8	4	179.854
Azilsartan	$C_{25}H_{20}N_4O_5$	456.458	4.192	7	7	5	192.799
Candesartan	$C_{24}H_{20}N_6O_3$	440.463	4.029	7	7	2	188.226
Eprosartan	$C_{23}H_{24}N_2O_4S$	424.522	7.744	10	5	2	178.696
Irbesartan	$C_{25}H_{28}N_6O$	428.540	4.777	7	5	1	187.503
Losartan	$C_{22}H_{23}ClN_6O$	422.920	4.267	8	6	2	179.302
Olmesartan	$C_{24}H_{26}N_6O_3$	446.511	3.657	8	7	3	190.684
Telmisartan	$C_{33}H_{30}N_4O_2$	514.629	7.264	7	5	1	226.754
Valsartan	$C_{24}H_{29}N_5O_3$	435.528	4.162	10	5	2	187.211

LogP: Partition coefficient#Rotatable bonds: Number of bonds that can rotate#Acceptor: Number of electron acceptor#Donor: Number of electron donor

Table 3: Absorption, distribution, metabolism, excretion (ADME) and toxicity properties of the novel compounds.

Property	Model Name	C-1	C-2	C-3	C-4	C-5
Absorption	Water solubility	-3.887	-2.656	-3.182	-3.665	-2.892
	Caco-2 permeability	0.998	0.436	-0.267	-0.701	-0.842
	Intestinal absorption (human)	84.191	49.718	68.013	49.547	68.987
	Skin Permeability	-2.825	-2.735	-2.735	-2.735	-2.735
	P-glycoprotein substrate	Yes	Yes	Yes	Yes	Yes
	P-glycoprotein I inhibitor	Yes	No	No	No	No
	P-glycoprotein II inhibitor	Yes	No	Yes	No	Yes
Distribution	VDss (human)	0.007	-0.044	0.493	-1.104	-0.048
	Fraction unbound (human)	0.083	0.395	0.134	0.034	0.303
	BBB permeability	-0.76	-1.274	-1.645	-1.345	-2.698
	CNS permeability	-2.458	-3.124	-3.853	-3.676	-3.729
Metabolism	CYP2D6 substrate	No	No	No	No	No
	CYP3A4 substrate	Yes	No	Yes	Yes	Yes
	CYP1A2 inhibitor	No	No	No	No	No
	CYP2C19 inhibitor	Yes	No	No	No	No
	CYP2C9 inhibitor	Yes	No	No	Yes	No
	CYP2D6 inhibitor	No	No	No	No	No
	CYP3A4 inhibitor	Yes	No	Yes	No	No
Excretion	Total Clearance	0.03	0.619	0.651	0.028	0.223
	Renal OCT2 substrate	No	No	No	No	No
Toxicity	AMES toxicity	No	No	No	No	Yes
	Max. tolerated dose (human)	-0.156	0.311	0.501	0.286	0.438
	hERG I inhibitor	No	No	No	No	No
	hERG II inhibitor	Yes	No	Yes	No	Yes
	Oral Rat Acute Toxicity (LD50)	2.397	2.532	3.002	2.453	2.482
	Oral Rat Chronic Toxicity (LOAEL)	1.544	0.686	2.369	2.428	2.693
	Hepatotoxicity	Yes	Yes	Yes	Yes	Yes
	Skin Sensitisation	No	No	No	No	No
	T. pyriformis toxicity	0.369	0.285	0.291	0.285	0.285
	Minnow toxicity	2.858	2.41	3.997	3.399	5.39

VDss: Steady state volume of distributionBBB: Blood-brain barrierCNS: Central nervous system

The molecular docking affinities and site of docking of the novel compounds and ARBs were given in Table 6 and Figures 3-7. All the analyzed compounds shared similar binding site on AT_1R. However, the amino acid residues with which they interacted were not similar. All the compounds except olmesartan interacted with valine located in the position 108. In a similar fashion only C-1 does not interact with tryptophan in the position 84. Other common interacting amino acids include arginine (position 167) and isoleucine (position 288). Among the standard ARBs, eprosartan exhibited lowest binding energy (-11.421 kcal/mol) while losartan interacted with the highest binding energy (-7.960 kcal/mol). Among the novel compounds, C-4 has the lowest binding energy (-13.236 kcal/mol) while C-5 has the highest binding energy (-3.920 kcal/mol).

Molecular dynamic simulation demonstrated that the interaction between eprosartan and AT_1R showed fluctuations with similar trend between the ligand and the receptor (Figure 8). Fluctuations were observed in both the protein and ligand root mean square fluctuation (RMSF). Ligand RMSF value exceeded 3.5 at ligand atom index 25. The incorporation of C-1 in the binding pocket of AT_1R did not cause extensive conformational change (Figure 9). Protein RMSF showed fluctuation between 300-350 residue index. Ligand RMSF showed that the ligand is stable during the interaction. As high interactions were observed with alpha helices, the interaction between the C-1 and AT_1R is found to be

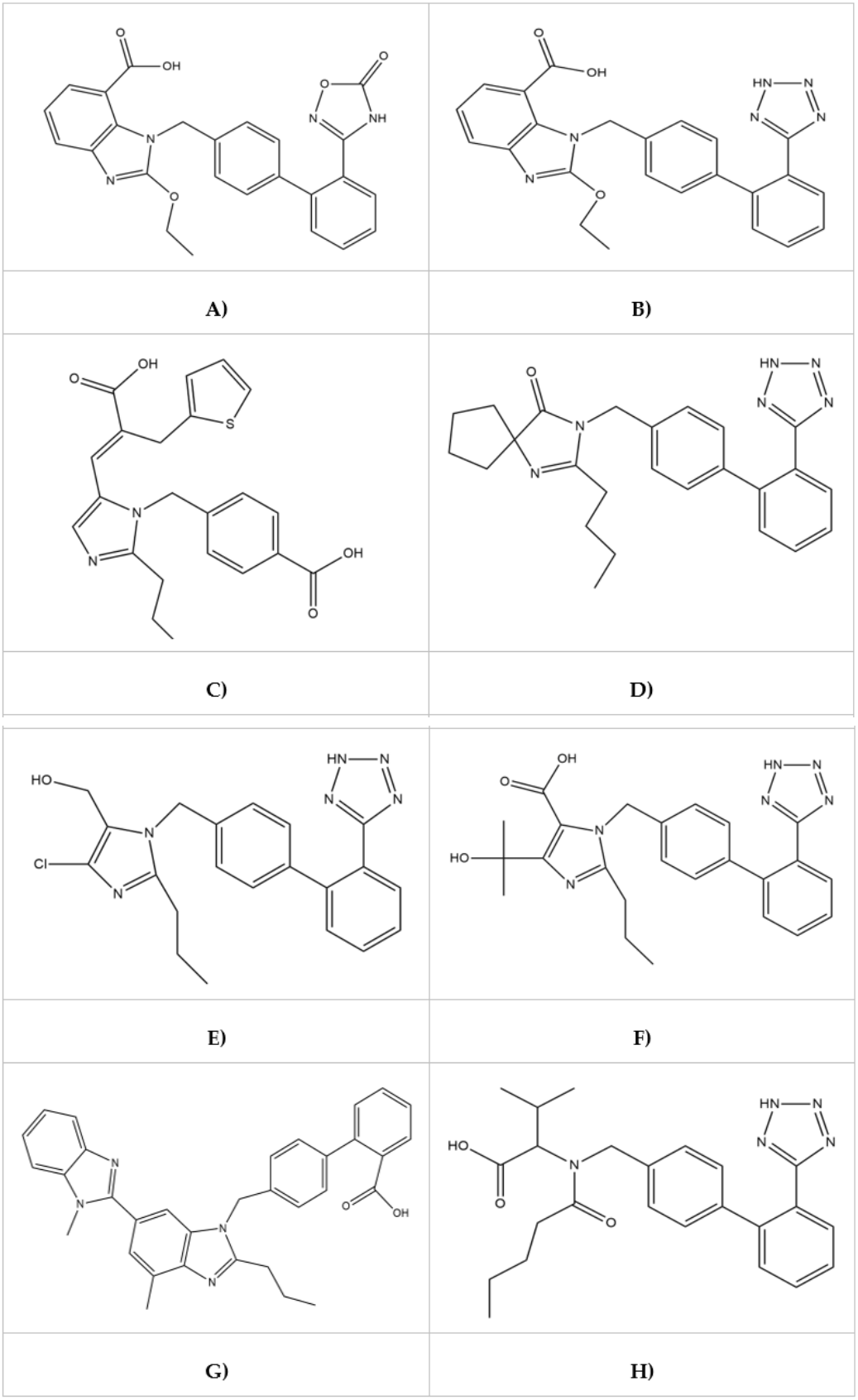

Figure 1: Molecular structure of angiotensin II receptor blockers A) Azilsartan B) Candesartan C) Eprosartan D) Irbesartan E) Losartan F) Olmesartan G) Telmisartan H) Valsartan.

stable. The interaction of C-2 with the receptor showed an initial conformational change in the protein before 20 ns of simulation. However, the receptor stabilized its conformation later on (Figure 10). Protein and ligand RMSF showed no extensive fluctuations. Interaction between C-3 and AT_1R showed moderate stable interaction. Protein and ligand RMSF indicated no extensive fluctuations. The protein-ligand RMSD of interaction between C-4 and AT_1R showed that the interaction is unfavorable. Extensive fluctuations were observed in both protein and ligand RMSF.

Table 4: Absorption, distribution, metabolism, excretion (ADME) and toxicity properties of angiotensin II type 1 receptor blockers.

Property	Model Name	Azilsartan	Candesartan	Eprosartan	Irbesartan	Losartan	Olmesartan	Telmisartan	Valsartan
Absorption	Water solubility	-2.892	-2.892	-2.890	-3.545	-2.915	-2.891	-2.892	-3.059
	Caco-2 permeability	-0.358	-0.674	0.675	1.024	-0.195	-0.386	1.107	-0.382
	Intestinal absorption (human)	73.199	64.975	57.173	91.296	79.338	45.989	89.941	45.046
	Skin permeability	-2.735	-2.735	-2.735	-2.735	-2.735	-2.735	-2.735	-2.735
	P-glycoprotein substrate	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	P-glycoprotein I inhibitor	No	No	No	Yes	No	No	No	No
	P-glycoprotein II inhibitor	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Distribution	VDss (human)	-0.59	-0.597	-0.725	0.127	0.082	-0.251	0.874	-1.517
	Fraction unbound (human)	0.24	0.251	0.139	0.026	0.056	0.142	0.194	0.022
	BBB permeability	-1.426	-1.861	-0.870	-1.434	-1.737	-1.956	-0.082	-1.710
	CNS permeability	-3.334	-3.650	-2.477	-2.537	-2.792	-3.581	-1.583	-3.421
Metabolism	CYP2D6 substrate	No	No	No	No	Yes	No	No	No
	CYP3A4 substrate	No	No	No	Yes	Yes	No	No	Yes
	CYP1A2 inhibitor	No	No	No	No	Yes	No	No	No
	CYP2C19 inhibitor	No	No	No	Yes	Yes	No	No	No
	CYP2C9 inhibitor	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
	CYP2D6 inhibitor	No	No	No	No	No	No	No	No
	CYP3A4 inhibitor	No	No	No	Yes	Yes	No	No	No
Excretion	Total clearance	0.249	0.328	0.670	0.440	0.674	0.244	0.365	0.577
	Renal OCT2 substrate	No	No	No	No	No	No	Yes	No

Property	Model Name	Azilsartan	Candesartan	Eprosartan	Irbesartan	Losartan	Olmesartan	Telmisartan	Valsartan
Toxicity	Ames toxicity	No	No	No	Yes	No	No	Yes	No
	Max. tolerated dose (human)	0.437	0.438	0.443	0.471	0.454	0.454	0.407	0.537
	hERG I inhibitor	No	No	Yes	No	No	No	Yes	No
	hERG II inhibitor	No	No	No	No	Yes	No	No	No
	Oral rat acute toxicity (LD_{50})	2.496	2.486	2.409	2.673	2.538	2.500	2.482	2.683
	Oral Rat Chronic Toxicity (LOAEL)	2.359	3.114	1.474	0.734	2.359	2.984	-0.387	3.144
	Hepatotoxicity	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
	Skin sensitisation	No	No	No	No	No	No	No	No
	T. pyriformis toxicity	0.285	0.285	0.285	0.292	0.285	0.285	0.285	0.285
	Minnow toxicity	-0.720	-0.775	-0.738	1.469	0.532	1.562	-3.717	1.950

VDss: Steady state volume of distributionBBB: Blood-brain barrierCNS: Central nervous system

DISCUSSION

The homeostasis of blood pressure is largely regulated by the renin-angiotensin-aldosterone system that involves several hormones.[23] The RAAS hormonal cascade begins when the juxtaglomerular cells of the kidney produce renin in response to lowering of arterial blood pressure.[24] Renin is the rate-limiting enzyme of the RAAS cascade that convert angiotensinogen to angiotensin I. Angiotensin I is further cleaved into a biologically active angiotensin II by a group of enzymes called angiotensin converting enzymes. Angiotensin II elicits its physiological effects through its high affinity-binding receptors, AT_1R and AT_2R.[25] Activation of the AT_1R by angiotensin II causes tyrosine phosphorylation of several downstream proteins and activation of MAPK/ERK in various cell types including the vascular smooth muscle.[8] This activation in turn causes vasoconstriction and increases renal reabsorption via aldosterone, a terminal hormone of RAAS, thereby causing hypertension. In contrast, activation of AT_2R is associated with vasodilation response by stimulating the release of nitric oxide and bradykinins.[26] Malfunction of RAAS causes systemic hypertension with associated conditions like renal dysfunction and cardiac arrest.

Drugs that diminish or inhibit overactivation of RAAS pathway by acting as AT_1R blockers or Angiotensin-Converting Enzyme (ACE) inhibitors are commonly used in the treatment of hypertension.[27] ARBs inhibit the binding of angiotensin II to AT_1R thereby acting as antagonists or inverse agonists. The advantage of using ARBs over ACE inhibitors is the reduced adverse effects.[10] ARBs selectively bind to the AT_1R and prevent the binding of angiotensin II. In this way, the hypertensive effects such as vasoconstriction, stimulation for the synthesis of aldosterone and renal sodium reabsorption are stopped. The effects maintain low blood pressure and aldosterone level to a physiologically safe range.[6] As shown in our result, all the standard ARBs bind to a similar domain and exhibited binding affinity to AT_1R as expected.[28] The novel compounds generated in our study also interacted with the similar domain on AT_1R and at the same time exhibited higher binding affinity. This may suggest that the new compounds likely exert similar inhibiting, but better activity to AT_1R compared to standard ARBs.

Analyses of the pharmacokinetic and pharmacodynamic parameters of drug candidates are essential to establish their suitability.[29] One of the major factors is the size of a compound. Majority of pharmaceutical drugs have molecular weights less than 500, with few drugs within the range of 500-600. Thus, smaller molecular weight is considered more suitable for drug molecules.[30] Among the novel compounds, C-4 violated all the druglikeness parameters because of its high molecular weight. Telmisartan with a molecular weight higher than 500 also violated Lipinski, Ghose, Egan and Muegge except Veber. Larger molecular weight generally contributes to increase number of rotatable bonds, poorer modified LogP and higher topological polar surface area. It has been indicated that ideal drugs will have LogP value ranging between 0.4-5.6.[31] Our analyses showed that all the novel compounds fall within this range, except eprosartan and telmisartan that showed higher values than the ideal range.

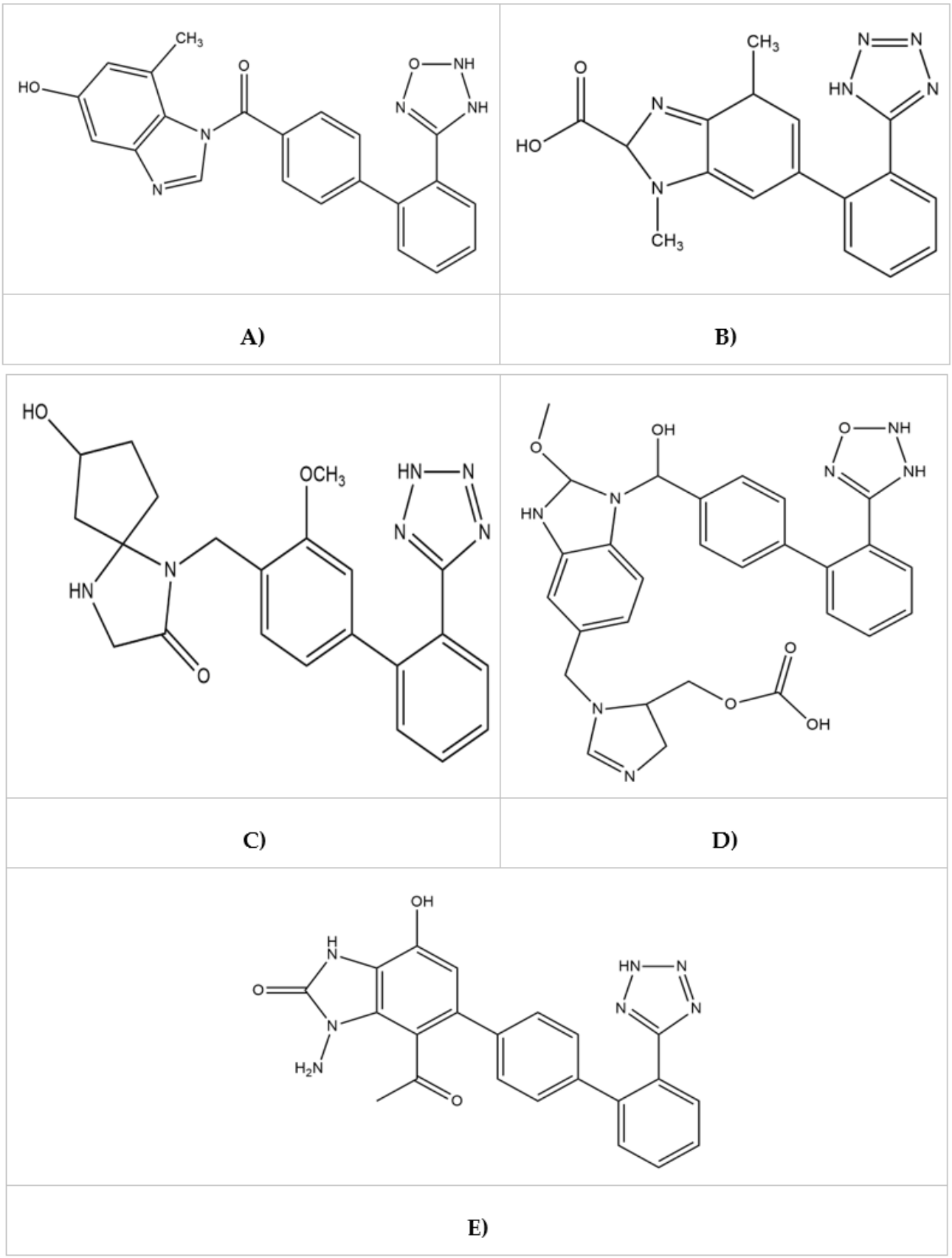

Figure 2: Molecular structures of the novel compounds C-1 (A), C-2 (B), C-3 (C) ,C-4 (D) and C-5 (E).

Table 5: Druglikeness of the novel compounds and angiotensin II type 1 receptor blockers.

Compound	Parameters					
	Lipinski	Ghose	Veber	Egan	Muegge	Bioavailability score
C-1	Yes	No; 1 violation; MR>130	Yes	Yes	Yes	0.55
C-2	Yes	Yes	Yes	Yes	Yes	0.56
C-3	Yes	Yes	Yes	Yes	Yes	0.55
C-4	No; 2 violations: MW>500. NorO>10	No; 3 violations: MW>480, MLOGP<-0.4, MR>130	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	No; 1 violation: TPSA>150	0.17
C-5	Yes	Yes	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	No; 1 violation: TPSA>150	0.11
Azilsartan	Yes	Yes	Yes	Yes	Yes	0.56
Candesartan	Yes	Yes	Yes	Yes	Yes	0.56
Eprosartan	Yes	Yes	Yes	Yes	Yes	0.56
Irbesartan	Yes; 1 violation: MLOGP>4.15	No; 1 violation: MR>130	Yes	Yes	Yes	0.55
Losartan	Yes	Yes	Yes	Yes	Yes	0.56
Olmesartan	Yes	Yes	Yes	Yes	Yes	0.56
Telmisartan	No; 2 violations: MW>500, MLOGP>4.15	No; 3 violations: MW>480, WLOGP>5.6, MR>130	Yes	No; 1 violation: WLOGP>5.88	No; 1 violation: XLOGP3>5	0.85
Valsartan	Yes	Yes	No; 1 violation: Rotor>10	Yes	Yes	0.56

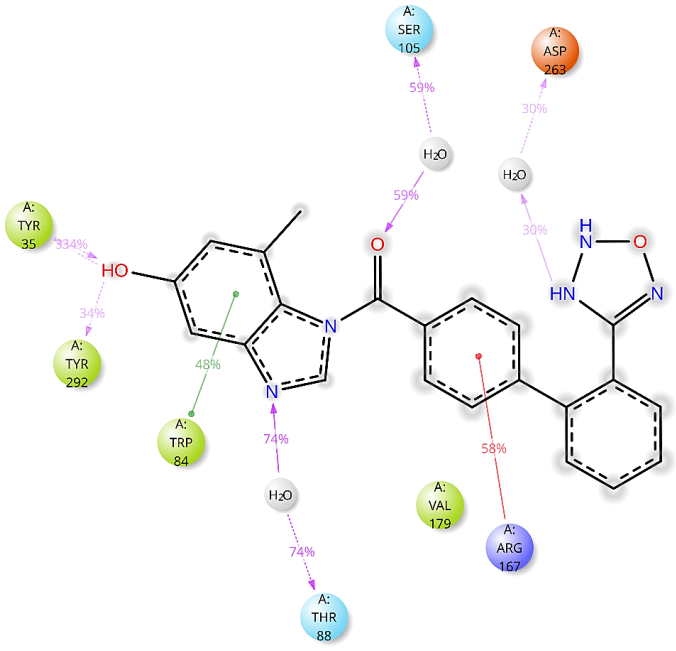

Figure 3: Interaction of the novel compound, C-1 with different amino acid residues on AT1R.

Table 6: Molecular docking score of the novel compounds and angiotensin II type 1 receptor blockers.

Ligand	Molecular Docking Score (kcal/mol)	Amino acid			
		Residue	Position	Residue	Position
C-1	-7.619	Tryptophan	19	Valine	108
		Arginine	167	Lysine	199
		Tryptophan	253	Histidine	256
		Isoleucine	288		
C-2	-8.808	Tyrosine	35	Tryptophan	84
		Valine	108	Proline	285
		Isoleucine	288		
C-3	-8.210	Tryptophan	84	Threonine	88
		Valine	108	Arginine	167
		Alanine	181	Isoleucine	288
C-4	-13.236	Tryptophan	84	Tyrosine	92
		Valine	108	Arginine	167
		Histidine	256	Isoleucine	288
C-5	-3.920	Tryptophan	84	Valine	108
		Tyrosine	113	Arginine	167
		Isoleucine	288		
Azilsartan	-8.720	Tyrosine	35	Tryptophan	84
		Tyrosine	87	Tyrosine	92
		Valine	108	Arginine	167
		Alanine	181	Tyrosine	184
Candesartan	-8.496	Tyrosine	35	Tryptophan	84
		Tyrosine	87	Tyrosine	92
		Valine	108	Arginine	167
		Alanine	181	Tyrosine	184
		Proline	285	Isoleucine	288
Eprosartan	-11.421	Tryptophan	84	Tyrosine	92
		Valine	108	Arginine	167
		Proline	285	Isoleucine	288
Irbesartan	-10.215	Tyrosine	35	Tryptophan	84
		Valine	108	Arginine	167
		Methionine	284	Isoleucine	288
Losartan	-7.960	Isoleucine	31	Tryptophan	84
		Tyrosine	92	Serine	105
		Valine	108	Serine	109
		Alanine	163	Arginine	167
		Proline	285		
Olmesartan	-8.048	Proline	19	Arginine	23
		Tryptophan	84	Tyrosine	87
		Tyrosine	92	Arginine	167

Ligand	Molecular Docking Score (kcal/mol)	Amino acid			
		Residue	Position	Residue	Position
Telmisartan	-10.638	Tyrosine	35	Tryptophan	84
		Tyrosine	87	Valine	108
		Serine	109	Alanine	181
		Tryptophan	253	Isoleucine	288
Valsartan	-9.032	Tryptophan	84	Tyrosine	87
		Tyrosine	92	Valine	108
		Arginine	167	Cysteine	180

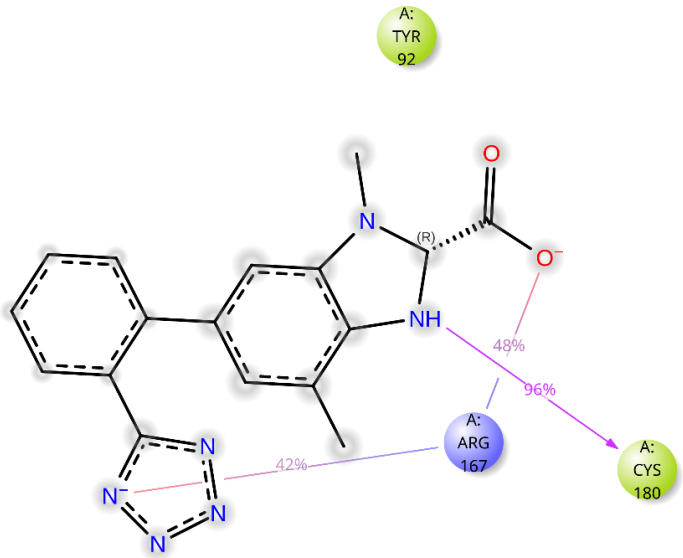

Figure 4: Interaction of the novel compound, C-2 with different amino acid residues on AT1R.

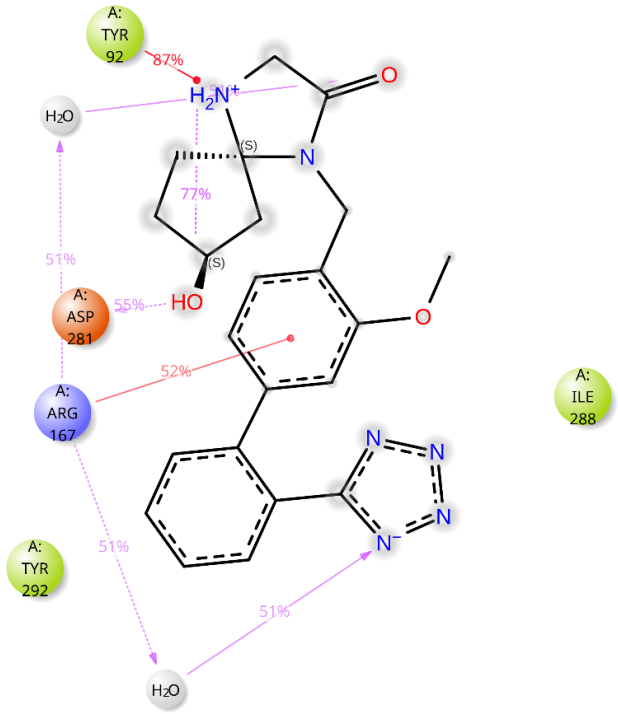

Figure 5: Interaction of the novel compound, C-3 with different amino acid residues on AT1R.

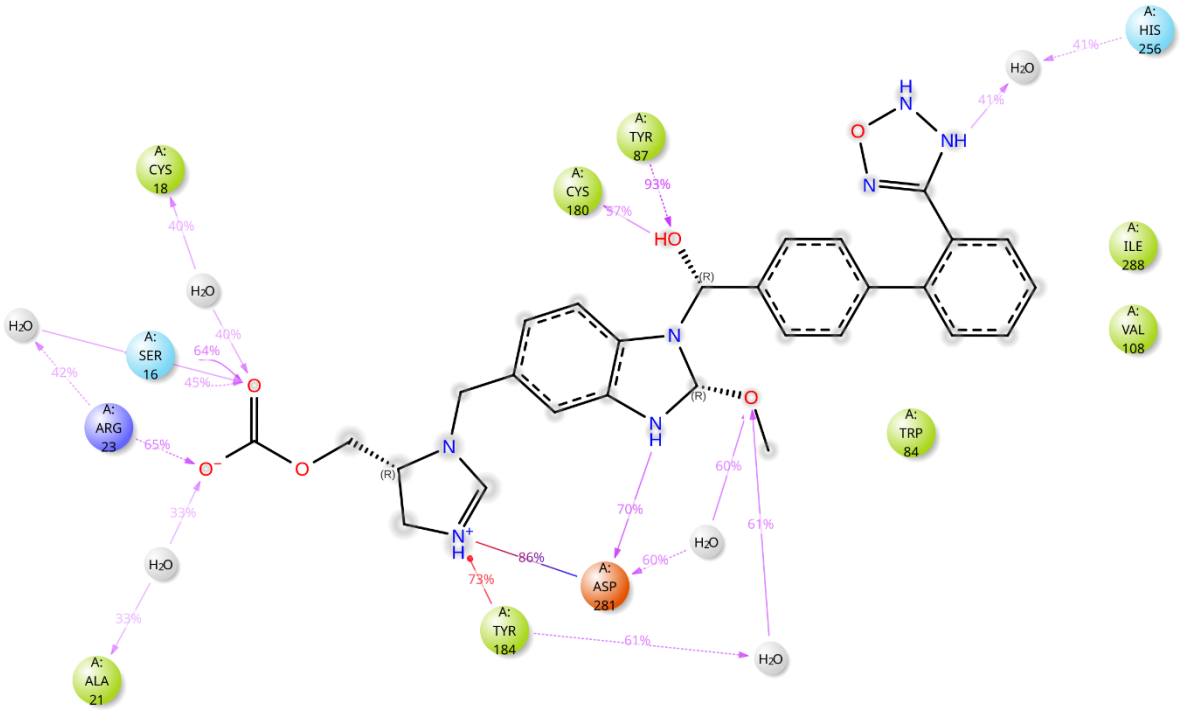

Figure 6: Interaction of the novel compound, C-4 with different amino acid residues on AT1R.

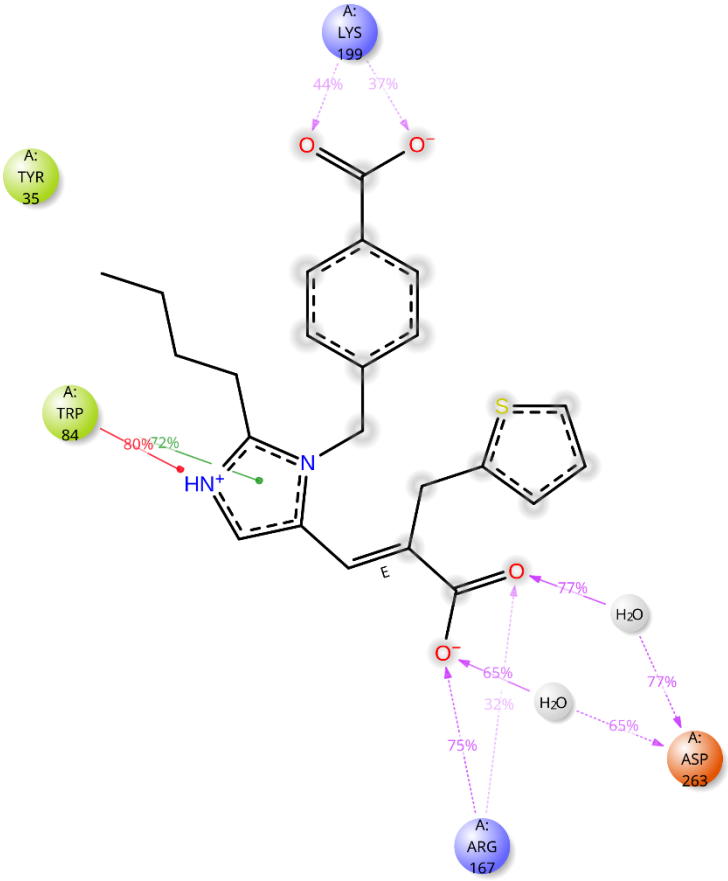

Figure 7: Interaction of eprosartan with different amino acid residues on AT1R.

Specifically, C-1, C-2 and C-3 showed comparable bioavailability to standard ARBs.

AT_1R proteins, like other G-protein coupled receptors, are present on the cell membranes. Comparison of the novel compounds with standard ARBs showed that ARBs are more hydrophobic in nature which may contribute to their binding on AT_1R. However, even though the novel compounds are less likely to be hydrophobic, their predicted values indicated that they may not cross the plasma membrane. Most ARBs are generally administered orally as they can be absorbed in the intestine.[28] Our result also demonstrated that all the ARBs are intestinally absorbed. The novel compounds also exhibited similar route of absorption. Depending on the nature of the drugs and the location of their target receptors, their distribution inside the body is an important parameter.[32] C-3 and telmisartan have intermediate to high steady state volume of distribution indicating that they may migrate to various body parts other than the blood vessel. All the other compounds may be confined to the blood vessel which is an ideal condition. Additionally, C-1, C-4, irbesartan, losartan and valsartan are predicted to be highly available pharmacologically while C-3, eprosartan, olmesartan and telmisartan are present in free form in a lower state. Analyzing the toxicity of compounds is crucial in the development of novel drugs.[33] The inhibition of Human Ether a-go-go Genes (hERG I and II) is considered pharmaceutically unsuitable. Eprosartan and telmisartan inhibit hERG I while losartan may inhibit hERG II. On the other hand, none of the novel compounds inhibited hERG I. However, C-1, C-3 and C-5 inhibited hERG II. All the compounds except telmisartan were predicted to be hepatotoxic, but with no skin sensitization. *T. pyriformis* toxicity test showed that all the

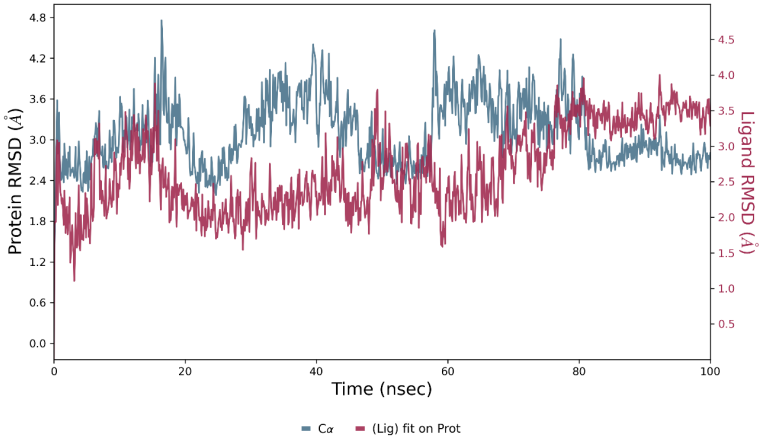

Figure 8: Molecular dynamic simulation of AT_1R and eprosartan showing RMSD trajectory (blue = protein; red = eprosartan).

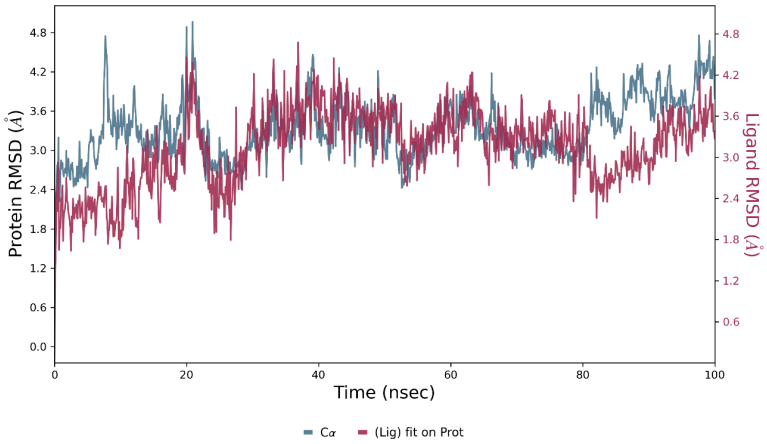

Figure 9: Molecular dynamic simulation of AT_1R and compound 1showing RMSD trajectory (blue = protein; red = C-1).

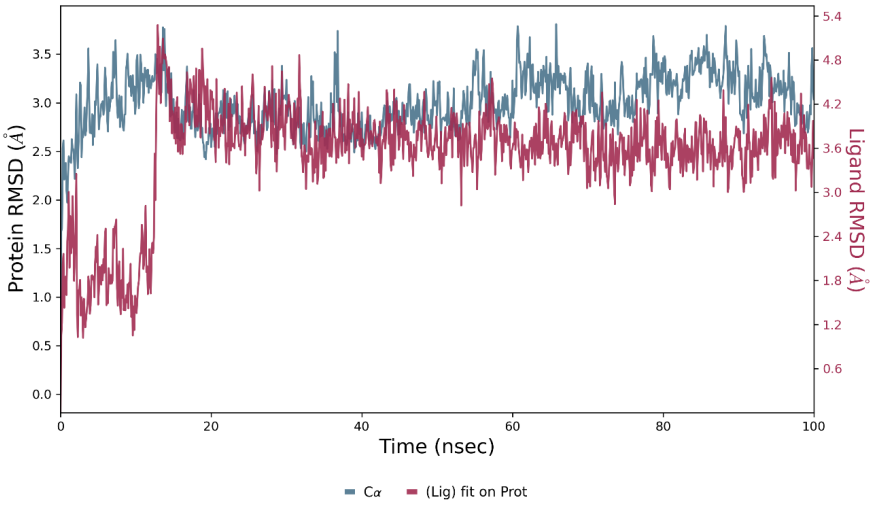

Figure 10: Molecular dynamic simulation of AT_1R and compound 2 showing RMSD trajectory (blue = protein; red = C-2).

compounds are toxic while tests for Minnow toxicity showed that irbesartan, losartan, olmesartan and valsartan are non-toxic.

Extensive alterations in the structure of either the ligand or receptor are considered unsuitable for use as medication.[34] Our molecular dynamic simulation demonstrated that the interaction of eprosartan with AT_1R showed fluctuations in both the ligand and receptor, but with comparable pattern. Interaction of C-1 and AT_1R showed stable interaction. The binding of C-2 to the receptor caused an initial conformational change in the receptor which later stabilized. Interaction of C-3 and the receptor was stable. The interaction between C-4 and AT_1R was unfavorable as extensive fluctuations were observed in both the ligand and receptor. It is therefore plausible that the novel compounds, especially C-1, C-3 and C-5 may be suitable candidates that may act as antagonists or inverse agonists of AT_1R in the treatment of hypertension. Further screening and synthesis will be essential for the development of these compounds.

CONCLUSION

Angiotensin Receptor Blockers (ARBs) were designed by computational method by modifying olmesartan, one of the most well-known Angiotensin II Receptor Type 1 (AT_1R) blockers that is used in the clinical management of hypertension. Five novel hydrophobic compounds (C-1 to C-5) were generated and identified. C-1 and C-2 were most suitable for oral administration based on their water solubility. All the compounds showed high values for absorption in the intestine, with the highest value for C-1. C-1 was further predicted to have inhibitory effect against P-glycoprotein I and P-glycoprotein II, membrane transporters that efflux drugs. C-1 and C-3 inhibit Cytochrome 3A4 (CYP3A4). Only C-1 showed inhibitory potential against Cytochrome 2C19 (CYP2C19) and Cytochrome 2C9 (CYP2C9). Ames test showed mutagenicity only for C-5. Except for C-3, the compounds indicated low maximum recommended tolerated dose. C-1, C-3 and C-5 were capable of inhibiting human ether a-go-go genes (hERG II) but not hERG I. The oral rat acute toxicity (LD_{50}) was on the low range of 2.4 to 3 mol/kg, while the oral rat chronic toxicity (LOAEL) was found to be between 0.68 and 2.69 mg/kg bw/day. C-1 and C-5 showed higher binding affinity to AT_1R compared standard ARBs. These findings suggest that some of these compounds could be further analysed and may be suitable for pharmaceutical development.

FUNDING

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY

All data are provided within the manuscript.

ABBREVIATIONS

ACE: Angiotensin-converting enzyme; **ADMET:** Absorption, distribution, metabolism, excretion and toxicity; ARB: Angiotensin receptor blockers; AT_1R: Angiotensin II receptor type 1; **CADD:** Computer-aided drug design; **CID:** PubChem compound

identity; **CREB:** cyclic AMP response element-binding protein; **CYP:** Cytochrome P450; hERG: Human ether a-go-go genes; **InChI:** International chemical identifier; **IUPAC:** International Union of Pure and Applied Chemistry; **LD_{50}:** Median lethal dose; **LOAEL:** Lowest-observed-adverse-effect level; **RAAS:** Renin-angiotensin-aldosterone system; **RMSD:** Root mean square deviation; **RMSF:** Root mean square deviation; **SMILES:** Simplified molecular input line entry system; **VDss:** Steady state volume of distribution.

AUTHORS CONTRIBUTIONS

Conceptualization: BLR; Data generation: DMS and LNH; Data analysis: LNH, PBL and BLR; supervision: LZS and KLC; Facilities: LZS; Funding: KLC; Writing manuscript: DMS, PBL and BLR. Compilation and finalization: KLC.

SUMMARY

The study involved computer-aided drug design of antihypertensive compounds from olmesartan. Olmesartan and other sartans are the best and most commonly used medications in the management of hypertension but are associated with several undesirable pharmacological properties. To search for sartans that are highly effective, safe and with high bioavailability, five novel compounds were generated as analogues of olmesartan. Compounds 4 and 5 did not exhibit the complete desired properties as they were large in size and highly toxic to normal cells. Compounds 1, 2 and 3 showed the ideal drug properties including high efficacy, low toxicity and efficient interaction with angiotensin II receptor type 1 (AT1R), the key receptor in the physiological homoeostatis of blood pressure. Thus, our findings advocate further studies into the chemical nature and biological effects of these novel compounds.

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