RESEARCH ARTICLE Am. J. PharmTech Res. 2015; 5(1) ISSN: 2249-3387

AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

A Novel Bioinformatics Approach: to Design Novel 1, 4-Benzothiazine Derivatives for the Treatment of Hypertension

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ABSTRACT

Angiotensin I-converting enzyme (ACE) is a key therapeutic target for combating hypertension and related cardiovascular diseases. ACE inhibitory novel designed substituted 1, 4-benzothiazine derivatives offer the prospect of enhanced potency, high specificity, and no or low side effect. Novel 1,4-benzothiazine derivatives were designed keeping in view the structural requirement of pharmacophore and Quantitatively structure Activity Relationship (QSAR).In the docking study, the most active compounds of the series were, AR 1, AR 2 and AR 3 exhibited good binding properties. Result reveals that the protein-ligand interaction energy of derivatives AR 1, AR 2 and AR 3 were -7.51 kcal/mol, -8.80 kcal/mol and -7.63 kcal/mol, which is slightly greater than the marketed antihypertensive Losartan drug as -5.51 kcal/mol, so that the derivatives have satisfactory affinity with established hypertensive receptor namely Angiotensin converted enzyme II. A computational study was also carried out including prediction of pharmacokinetic properties, toxicity and bioactivity studies. The percentage of absorption (%ABS) was calculated and observed that all titled compounds exhibited a better %ABS %ABS ranging 90.54, 91.42 and 90.55 respectively and compared than standard Losartan drug as %ABS 77.06.Although other pharmacological parameters were better than the standard drug. The above observation suggested that these compounds would serve as better lead compound for antihypertensive screening for future drug design perspective.

Keywords: 1, 4-benzothiazine derivatives, Anti hypertension activity, Computational study and ACE-II.

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Received 29 December 2014, Accepted 1 February 2015

Please cite this article as: Rai A *et al.*, A Novel Bioinformatics Approach: to Design Novel 1, 4-Benzothiazine Derivatives for the Treatment of Hypertension. American Journal of PharmTech Research 2015.

INTRODUCTION

Hypertension or high blood pressure is a major risk factor for cardiovascular disorder; therefore, blood pressure should be controlled and properly regulated in hypertensive patients[1].Drugs available for the treatment of hypertension include diuretics, β-Blockers, aldosterone receptor antagonist, angiotensin converting enzyme (ACE) inhibitors and angiotensin-II receptor blockers (ARBs). Nonetheless, hypertension is poorly controlled in many patients and the drugs prescribed may produce significant side effects[2].Angiotensin I-converting enzyme (ACE) is a key therapeutic target for combating hypertension and related cardiovascular diseases because angiotensin-I-converting enzyme (ACE) is a zinc metallopeptidase that can catalyze the proteolysis angiotensin-I to the vasopressor angiotensin-II, which is a potent vasoconstrictor, and inactivate bradykinin, which is a peptide that causes blood vessels to enlarge[3]. Toward this end, much of the efforts have been focused on library search for and structure-based rational design of inhibitors that target ACE[4&5].Synthetic ACE inhibitors, such as captopril, lisinopril, enalapril and fosinopril, are used as pharmaceuticals to treat hypertension, congestive heart failure, and myocardial infarction[6]. However, these synthetic ACE inhibitors are known to have strong side effects, such as cough, skin rashes, and angioedema [7, 8]. A part of search[6,6] fused ring system such as 1,4-benzothiazine derivatives show the antihypertensive activity.1,4-benzothiazine derivatives are important molecules, which are common heterocyclic scaffold in biological activities like central nervous system depressant[9], calcium antagonist[10], antibacterial activity[11], and anti-tubercular activity[12]. Docking techniques have been used in modern drug designing to understand drug-receptor interaction. It has been shown in the literature that computational procedures may strongly support and help the design of new, more potent drugs by revealing the mechanism of drug-receptor interaction[13].

MATERIALS AND METHOD

For carrying out this, National center for Biotechnology Information (NCBI) website and Protein Data Bank (PDB) website were used as chemical sources.

For designing the derivatives: Chemdraw Ultra 10.0

For optimizing the geometry of derivatives: ArgusLab software

For docking studies: Molegro Virtual docker and autodocking software

For characterization of the derivatives: Molinspiron software toolkit, MedChem Designer and EPA DSSTox Structure Browser v2.0 service.

Losartan structure data file was draw by Chemdraw Ultra 10.0 and protein target was downloaded from Protein Data Bank with PDB id 1R4L.

Protocol

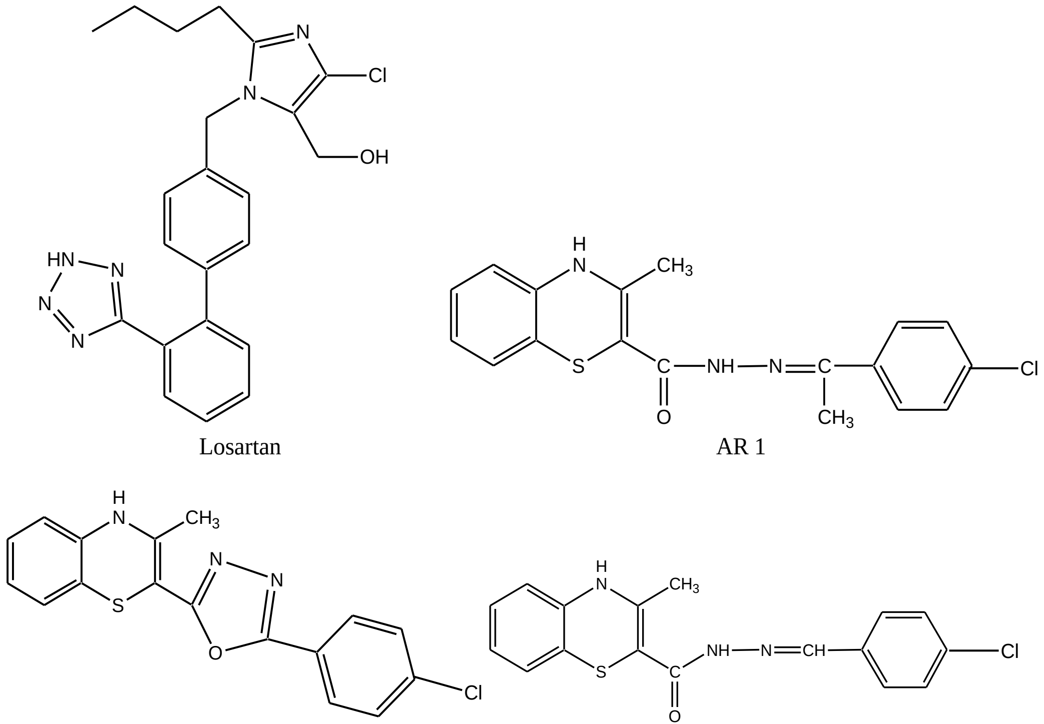
Drawing of Losartan and AR1, AR 2, AR 3 and AR 4 (Figure.1)

↓

Generation and geometry optimization of 3D structure

↓

Docking analysis of Losartan and 1, 4-benzothiazine derivatives with Inhibitor bound human Angiotensin converting enzyme-Related carboxypeptidase (ACE2)



Losartan

AR 1

AR 2

AR 3

Figure:1 Show the chemical structure of standard Losartan drug and 1, 4-benzothiazine derivatives (AR 1, AR 2 & AR 3).

Computational Study

A computational study of all compounds was performed for prediction of ADME properties such as absorption (%ABS), polar surface area (TPSA), miLog P etc by using Molinspiration property calculation toolkit. Docking study of titled compounds was performed with established hypertension molecular targets namely Angiotensin converting enzyme (ACE2), by using Autodock 4.0 and Argus lab software along with its LGA algorithm for automated flexible ligand docking and affinity (Kcal/mol).

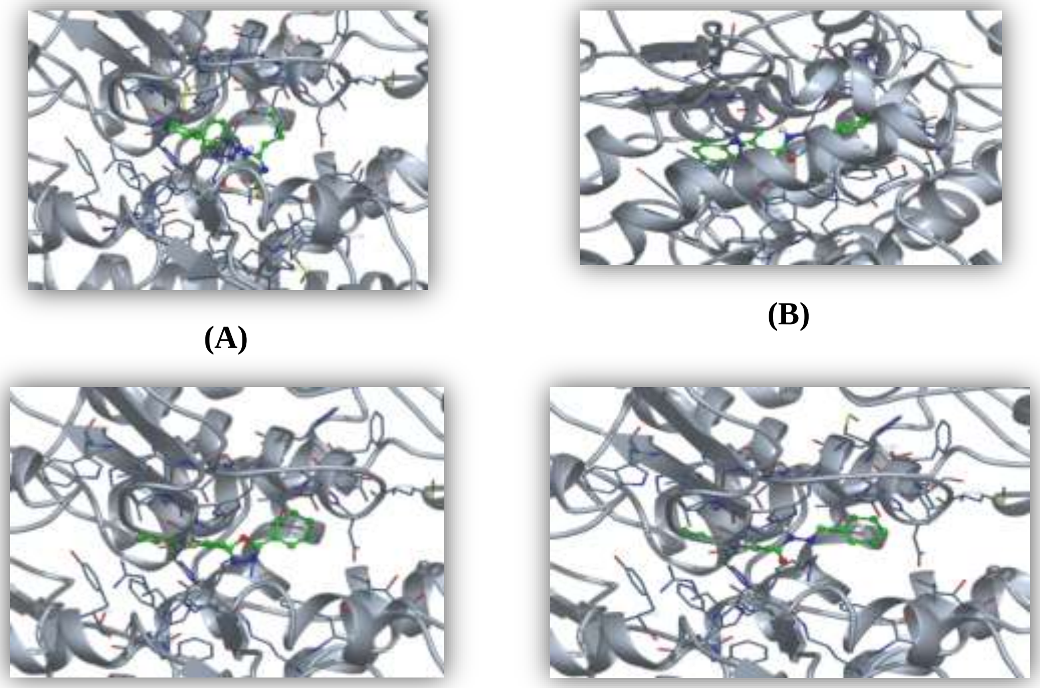
Prediction of ADME properties

A computational study for prediction of ADME properties of titled compounds was performed. Topological polar surface area (TPSA), i.e., surface belonging to polar atoms, is a descriptor that was shown to correlate well with passive molecular transport through membranes. The percentage of absorption was calculated using TPSA. From all these parameters, it can be observed that all titled compounds exhibited a great %ABS ranging. These all parameters were calculated using Molinspiration online property calculation toolkit[14]. The results are shown in Table 2. Absorption (%ABS) was calculated by:

% ABS = 109-(0.345×TPSA) [15].

Docking study

In this study, we have used Auto Dock 4.0 along with its LGA algorithm for automated flexible ligand docking of compounds AR 1, AR 2, AR 3 and Standard Losartan drug with one established hypertension molecular targets namely Angiotensin converted enzyme-II and evaluated docking affinity (Kcal/mol) and count of probable hydrogen bonds. All compounds have exhibited good binding properties (the comparison of protein-ligand interaction energy, much lower interaction energy is being associated with higher stability) compared than Losartan with receptor. The docking images are given in Figure:2. the results are shown in Table: 1.



(A) (B)

(C) (D)

Figure:2 It shows docking images (a) Losartan with ACE 2 (1R4L), (b) AR 1 with ACE 2, (c) AR 2 with ACE 2 and (d) AR 3 with ACE 2.

Bioactivity prediction and Toxological comparative studies

The designed derivatives and original drugs, bioactivity predictions have been compared along with some selected activity GPCR (G-Protein coupled receptor) etc. The score of bioactivity prediction of Losartan and 1, 4-benzothiazine derivatives (AR 1, AR 2& AR 3) are show in Table 3. The score of Toxological comparative studies of Losartan and 1, 4-benzothiazine derivatives (AR 1, AR 2& AR 3) are show in Table: 4.these all parameters were calculated using Molinspiration property calculation toolkit and EPA DSSTox.in-silico toxicity prediction.

RESULTS AND DISCUSSION

Docking study

In this study, we have used Autodock 4.0 along with its LGA algorithm for automated flexible ligand docking of compounds **AR 1, AR 2** and **AR 3** with one established antihypertensive molecular target namely ACE-2 and evaluated docking affinity (Kcal/mol). Compounds **AR 1, AR 2** and **AR 3** have exhibited good binding properties with Inhibitor bound human Angiotensin converting enzyme-Related carboxypeptidase (ACE2) (affinity value were -7.51 kcal/mol, -8.80 kcal/mol and -7.63 kcal/mol, respectively) which is better than the standard antihypertensive Losartan drug (affinity value -5.51 kcal/mol). The docking images are given in Figure: 2 and the docking results are shown in Table: 1.

Table:1 Table shows Protein-Ligand interaction Energy of Std. Losartan drug and 1, 4-Benzothiazine derivatives, AR1, AR2, & AR3 with ACE2 (1R4L)

S. No.	Compound	Est. Free Energy of Binding	Est. Inhibition Constant, Ki	vdW+Hbond+desolv Energy	Electrostatic Energy	Total Intermolec. Energy	Frequency	Interact Surface
1	Losartan	-5.51 kcal/mol	91.30 uM	-7.88 kcal/mol	-0.19 kcal/mol	-8.07 kcal/mol	20%	959.134
2	AR1	-7.51 kcal/mol	3.11 uM	-8.25 kcal/mol	-0.03 kcal/mol	-8.27 kcal/mol	10%	816.51
3	AR2	-8.80 kcal/mol	355.03 nM	-9.34 kcal/mol	+0.11 kcal/mol	-9.23 kcal/mol	50%	808.519
4	AR3	-7.63 kcal/mol	2.57 uM	-8.46 kcal/mol	+0.05 kcal/mol	-8.42 kcal/mol	10%	799.506

Predication of ADME properties

A computational study for prediction of ADME properties of titled compounds was performed. The percentage of absorption (%ABS) was calculated using TPSA. From all these parameters, it can be observed that all titled compounds exhibited a great %ABS ranging 90.54, 91.42 and 90.55, respectively and compared than standard Losartan drug as %ABS 77.06 (Table: 2). None of the compounds violated Lipinski's parameters, making them potentially promising agents for hypertension therapy.

Table: 2 Table shows ADME Properties Prediction of standard Losartan drug and 1, 4 benzothiazine derivatives, AR 1, AR 2 & AR 3

S.No.		Rule	Losartan	AR 1	AR 2	AR 3
1	S+ log P	–	3.421	4.669	4.346	4.440
2	S +log D	–	1.269	4.517	4.346	4.322
3	M logP	–	3.667	3.486	3.659	3.253
4	M.Wt	< 500	422.920	357.869	341.821	343.837
5	n-OHNH donor	<5	2.000	2.000	1.000	2.000
6	M_NO.	–	7.000	4.000	4.000	4.000
7	T_PSA(Topological polar surface area)	_	92.570	53.490	50.950	53.490
8	Rule of 5	≤ 1	0.000	0.000	0.000	0.000
9	%ABS(% of absorption)	–	77.06	90.54	91.42	90.55
10	MV	–	465.001	407.583	349.459	351.475
11	n-ON acceptor	<10	7	4	4	4
12	Volume	–	423.74	403.113	326.944	353.48
13	n-ROTB	–	9	5	3	4

[a]**MlogP**, Moriguchi estimation of logP. S+ log P logP calculated using Simulations Plus' highly accurate internal model; **S+logD**, logD at user-specified pH (default 7.4), based on S+logP;**n-OHNH donor**, Number of Hydrogen bond donor protons; **M_NO**, Total number of Nitrogen and Oxygen atoms; **T_PSA**, Topological polar surface area in square angstroms; **Rule Of Five**, Lipinski's Rule of Five: a score indicating the number of potential problems a structure might have with passive oral absorption;miLog P, logarithm of compound partition coefficient between n-octanol and water; log D, logarithm of compound distribution coefficient; n-ROTB, number of rotatable bonds; MV, molecular volume; n-ON acceptor, number of Hydrogen bond acceptor protons.

Bioactivity prediction and Toxological comparative studies

In this study, for prediction of Bioactivity and Toxological properties of titled compounds were carried out. From all calculated parameters, it can be observed that all titled compounds compared than standard Losartan drug shown less affinity with GPCR(G-Protein coupled receptor) ligand, Ion channel Modulator, Kinase inhibitor, Kinase inhibitor, Nuclear receptor ligand, Protease inhibitor and Enzyme inhibitor and the toxological comparative studies of all titled compounds compared than standard Losartan drug having very less toxicity effect such as acute toxicity to fish (lethality), carcinogenicity, mutagenicity and repeated dose toxicity that mean these compounds can be make good bioactivity and minor toxicity drug compared than standard Losartan drug for hypertension. The Bioactivity and Toxological data are given in Table 3-4.

Table: 3 Table shows score of bioactivity prediction of Losartan and 1, 4-benzothiazine derivatives, AR 1, AR 2 & AR 3.

S.No.		Losartan	AR 1	AR 2	AR 3
1	GPCR(G-Protein coupled receptor) ligand	0.98	-0.13	-0.05	-0.28
2	Ion channel Modulator	0.19	-0.47	-0.25	-0.72
3	Kinase inhibitor	0.02	-0.47	-0.14	-0.46
4	Nuclear receptor ligand	0.01	-0.17	-0.13	-0.43
5	Protease inhibitor	0.33	-0.29	-0.16	-0.52
6	Enzyme inhibitor	0.43	-0.30	-0.09	-0.46

Table: 4Table shows score of Toxological comparative studies of Losartan and 1, 4-benzothiazine derivatives, AR 1, AR 2 & AR 3.

S.No.	DSSTox toxicity origin	Losartan	AR 1	AR 2	AR 3
1.	DSSTox Carcinogenic Potency DBS MultiCell Call: non-carcinogen	0.0117	0.0143	0.0641	0.0143
2.	DSSTox Carcinogenic Potency DBS Mutagenicity: non-mutagenic	0.00859	0.0357	0.0221	0.0357
3.	DSSTox Carcinogenic Potency DBS Rat: non-carcinogen	0.0695	0.0488	0.0515	0.0446
4.	Kazius-Bursi Salmonella mutagenicity: non-mutagenic	0.0416	0.0303	0.0371	0.0303
5.	FDA v3b Maximum Recommended Daily Dose mmol:0.0152722115276765	0.0422	0.0878	0.106	0.0926
6.	DSSTox Carcinogenic Potency DBS SingleCellCall: non-carcinogen	0.219	0.042	0.0222	0.0278
7.	EPA v4b Fathead Minnow Acute Toxicity LC50_mmol: 0.00359162218026281	0.164	0.168	0.195	0.195
8.	DSSTox ISSCAN v3a Canc: carcinogen	0.0394	0.0533	0.0621	0.0533
9.	DSSTox Carcinogenic Potency DBS Hamster: non-carcinogen	0.108	0.165	0.19	0.165
10.	DSSTox Carcinogenic Potency DBS Mouse: non-carcinogen	0.153	0.0696	0.067	0.0696

CONCLUSION

A series of novel1,4-benzothiazine derivatives were designed and a computational study was also carried out including docking studies, ADME, bioactivity and toxicity prediction of titled compounds. All compounds displayed significant binding affinity compared than the standard antihypertensive drug and very less toxicity found. The docking study data strongly support the assumption that this receptor may be involved in observed antihypertensive activity of 1, 4-benzothiazine derivatives. However further studies need to be carried out to synthesis, *in-vivo* evaluation of pharmacological activity and ascertain the precise mechanism of action of antihypertensive activity of these compounds. These titled compounds emerged as a lead in this series and making them potentially promising agents for hypertension therapy.

ACKNOWLEDGEMENTS

The authors would like to express their gratitude to Babasaheb Bhimrao Ambedkar Cental Government University Lucknow for providing the software and research data.

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