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Research Article

Investigating Heart Failure Disease by Studying Interaction between Angiotensin -Converting Enzyme (ACE) and Different Inhibitors including Solvatation Parameter with Molecular Docking

Mesli Fouzia[1,5], Bouchentouf Salim[2,5]*, Ghomri Amina[3,5], Missoum Noureddine[4,5] and Ghalem Saïd[1,5]

[1]*Department of Chemistry, Aboubekr Belkaid University of Tlemcen, Algeria*

[2]*Faculty of Technology, Doctor Tahar Moulay University of Saïda, Algeria*

[3]*High school of Applied sciences ESSA, Tlemcen, Algeria*

[4]*Hassiba Benbouali University of Chlef, Algeria*

[5]*Laboratory of Natural and Bioactive Substances (LASNABIO), Algeria*

***Corresponding Author:** Bouchentouf Salim, Faculty of Technology, Doctor Tahar Moulay University, Saïda, Algeria.

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Abstract

Study interaction of Angiotensin-converting enzyme (ACE) for probable inhibition presents an efficient way to contribute to elucidation of drugs used in treatment of Heart failure (HF). Captopril analogous present one of the most used ACE inhibitors. In this work we study the molecular interaction between Angiotensin Converting enzyme (ACE) and different substrates (bioactive molecules) including solvatation parameter. To carry out this work, we used different molecular modeling approaches as molecular mechanics, molecular dynamics and molecular docking. The introduction of bulky groups causes a conformational rearrangement in the active pocket site, which will probably reinforce and thus complements its activity. Theoretical studies were done using molecular operating environment software (MOE). Obtained results show considerable improvement. Successful docking simulations were found when including flexible water molecules solvating hydrogen bonding groups of the ligand. Taking into account obtained results from study of Angiotensin enzyme interaction with molecules, we can conclude that Moexcipril (Similar of Captopril) present better interaction of Angiotensin Converting Enzyme in presence of water molecules while docking and consequently can be the best inhibitor candidate to be *in vitro* and *in vivo* investigated.

Keywords: Heart Failure; Angiotensin Converting Enzyme (ACE); Molecular Docking; Solvatation; Molecular Operating Environment (MOE)

Introduction

Heart failure (HF) frequently referred as congestive heart failure (CHF), occurs when the heart is unable to pump sufficiently to maintain blood flow to meet the bodies needs [1]. Signs and symptoms generally consist to breathe shortness with a long tiredness period, and leg swelling. The shortness of breath is usually worse with exercise, while lying down, and may wake the person at night. In addition a limited ability to exercise is an ordinary aspect. Heart failure don't cause typically chest pain and angina [2]. On the other hand, heart failure can be caused by myocardial failure but may also happen in the existence of near-normal cardiac function under situation of high require. We note that, heart failure always causes circulatory failure, but the converse is not necessarily the case, because various noncardiac conditions (e.g. hypovolemic shock, septic shock) can produce circulatory failure in the presence of normal, modestly impaired, or even supranormal cardiac function [3]. To maintain the pumping function of the heart, compensatory mechanisms augment blood volume, cardiac filling pressure, heart rate, and cardiac muscle mass. However, despite these mechanisms, there is progressive decline in the ability of the heart to contract and relax, resulting in worsening heart failure [3]. Additionally, there are many methods for evaluating the ACE inhibitory activity in vitro, such as spectrophotometric, fluorometric, radiochemical, high-performance liquid chromatography (HPLC) and capillary electrophoresis (CE) methods [4,5]. Identification basée sur ionisation-tandem de la spectrométrie de masse de chromatographie-electrospray liquide (LC-ESI-MS/MS) [6]. Kinetics assays of ACE inhibition by PAs purified extracts from skin and grape seed. The analysis was performed using a previously described HPLC method [7].

Actually molecular modeling methods present powerful tools in the development and the study of the drug design, and it is largely used as a predictive step, before using products and synthesizes new molecules. Our aim in this work is to study interactions between Angiotensin Converting Enzyme (ACE) and its famous inhibitors to get clear idea about factors encouraging interactions to lead and help for development of new drugs against the cardiac failure disease. In order to reach our objective, we used molecular modeling methods to rationalize the properties of inhibitors and determine interaction modes of complex formed between inhibitor and the enzyme looking for the better complementarily (better activity).

Materials and Methods

Angiotensin-converting enzyme (ACE)

One of the important components of the rennin-angiotensin system (RAS) is the Angiotensin-converting enzyme (ACE), which controls blood pressure by regulating the volume of fluids in the body [8,9]. The role of the ACE is the conversion of the angiotensin I to the angiotensin II (the active vasoconstrictor). But can increases indirectly the blood pressure by causing blood vessels to constrict. For this reason the ACE inhibitors are considered as a pharmeceutical drugs in the treatment of cardiovascular deseases. The degradation of bradykinin and amyloid beta –protein present other functions of ACE which are less known [10].

ACE is a zinc metalloenzyme. Indeed the zinc ion is essential to its activity, since it directly participates in the catalysis of the peptide hydrolysis. Therefore, ACE can be inhibited by metal-chelating agents. The importance of ACE in circulatory homeostasis is well documented. Besides being present as a membrane-bound enzyme on the surface of vascular endothelial cells, ACE also circulates in plasma. The plasma enzyme may be synthesized in vascular endothelium. In normal individuals, plasma ACE levels can show as much as a 5-fold inter-individual variation; on the other hand, intra-individual variation is small [11].

ACE inhibitors

An Angiotensin Converting Enzyme inhibitor (ACE inhibitor) is a pharmaceutical drug used primarily for the treatment of hypertension (elevated blood pressure) and congestive heart failure. This group of drugs causes relaxation of blood vessels as well as a decrease in blood volume, which leads to lower blood pressure and component of the renin–angiotensin system. Frequently prescribed ACE inhibitors include zofenopril, perindopril, trandolapril, captopril, enalapril, lisinopril, and ramipril. ACE inhibitors have also been used in chronic kidney failure and kidney involvement in systemic sclerosis (hardening of tissues, as scleroderma renal crisis) [12]. ACE inhibitors also have beneficial effects on left ventricular hypertrophy, another clinical marker of therapy in the hypertensive patient. ACE inhibitors also avoid some of the detrimental metabolic effects of other antihypertensive medications, such as dyslipidemia, glucose intolerance, and hyperinsulinemia. Finally, ACE inhibitors may be used in African Americans successfully, although higher doses or combination with a diuretic may be necessary for optimal effect [13]. The inhibitors for ACE chosen are given in table 1.

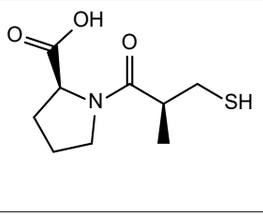
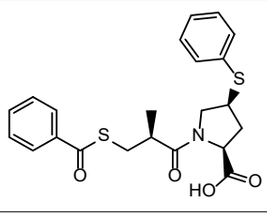
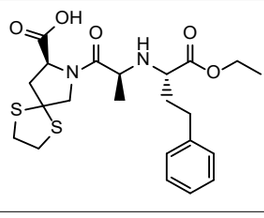
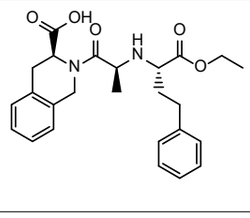
Preparation and optimization of both enzyme and inhibitors

Structure of ACE was downloaded from Bookhaven Protein database under code 4BZR, with three-dimensional structure obtained by X-ray diffraction (resolution 1.84 Å). We note that the Angiotensin-converting enzyme (ACE) crystallizes as a monomer (Figure 1) with 589 residues and 4726 atoms. ACE Inhibitors (Table 2) were downloaded from Pub Chem data base. We select the active site in the enzyme and we minimize the energy of both enzyme and molecules by means of MOE software (Molecular operating environment) [14].

Molecule	Name	IUPAC name	Pub Chem CID	Molar mass g/mol	Formula
1	Captopril	(2S)-1-[(2S)-2-methyl-3-sulfanylpropanoyl]pyrrolidine-2-carboxylic acid	44093	217,285	$C_9H_{15}NO_3S$
2	Zofenopril	(2S,4S)-1-[(2S)-3-benzoylsulfanyl-2-methylpropanoyl]-4-phenylsulfanylpyrrolidine-2-carboxylic acid	92400	429.552	$C_{22}H_{23}NO_4S_2$
3	Spirapril	(8S)-7-[(2S)-2-[[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]-1,4-dithia-7-azaspiro[4.4]nonane-8-carboxylic acid	5311447	466.616	$C_{22}H_{30}N_2O_5S_2$
4	Quinapril	(3*S*)-2-[(2*S*)-2-[[(2*S*)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]-3,4-dihydro-1*H*-isoquinoline-3-carboxylic acid	54892	438.516	$C_{25}H_{30}N_2O_5$
5	Lisinopril	(2*S*)-1-[(2*S*)-6-amino-2-[[(1*S*)-1-carboxy-3-phenylpropyl]amino]hexanoyl]pyrrolidine-2-carboxylic acid	5362119	405.488	$C_{21}H_{31}N_3O_5$
6	Perindopril	(2*S*,3*aS*,7*aS*)-1-[(2*S*)-2-{[(2*S*)-1-ethoxy-1-oxopentan-2-yl]amino}propanoyl]-octahydro-1*H*-indole-2-carboxylic acid	107807	368.468	$C_{19}H_{32}N_2O_5$
7	Trandolapril	(2*S*,3*aR*,7*aS*)-1-[(2*S*)-2-{[(2*S*)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino}propanoyl]-octahydro-1*H*-indole-2-carboxylic acid	5484727	430.537	$C_{24}H_{34}N_2O_5$
8	Benazepril	2-[(3*S*)-3-[[(2*S*)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino]-2-oxo-4,5-dihydro-3*H*-1-benzazepin-1-yl]acetic acid	5362124	424.49	$C_{24}H_{28}N_2O_5$
9	Imidapril	(4*S*)-3-[(2*S*)-2-[[(2*S*)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]-1-methyl-2-oxoimidazolidine-4-carboxylic acid	5464343	405.444	$C_{20}H_{27}N_3O_6$
10	Cilazapril	(4*S*,7*S*)-7-[[(2*S*)-1-Ethoxy-1-oxo-4-phenylbutan-2-yl]amino]-6-oxo-1,2,3,4,7,8,9,10-octahydropyridazino[1,2-a]diazepine-4-carboxylic acid	56330	417.51	$C_{22}H_{31}N_3O_5$

11	Moexipril	(3*S*)-2-[(2*S*)-2-[[(2*S*)-1-ethoxy-1-oxo-4-phenylbutan-2-yl] amino]propanoyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinoline-3-carboxylic acid	91270	498.568	$C_{27}H_{34}N_2O_7$
12	Enalapril	(2*S*)-1-[(2*S*)-2-{[(2*S*)-1-ethoxy-1-oxo-4-phenylbutan-2-yl] amino}propanoyl]pyrrolidine-2-carboxylic acid	5388962	376.447	$C_{20}H_{28}N_2O_5$
13	Ramipril	(2*S*,3a*S*,6a*S*)-1-[(2*S*)-2-[[(2*S*)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]-3,3a,4,5,6,6a-hexahydro-2*H*-cyclopenta[b]pyrrole-2-carboxylic acid	5362129	416.511	$C_{23}H_{32}N_2O_5$
14	Fosinopril	(2*S*,4*S*)-4-cyclohexyl-1-[2-[hydroxy(4-phenylbutyl)phosphoryl]acetyl]pyrrolidine-2-carboxylic acid	55891	563.663	$C_{30}H_{46}NO_7P$

Table 1: Physico- Chemical properties of ACE inhibitors similar to Capopril.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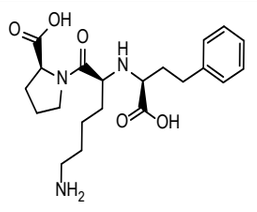	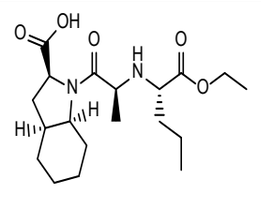	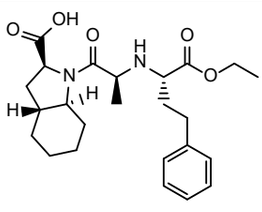	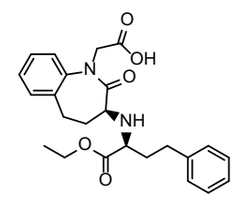
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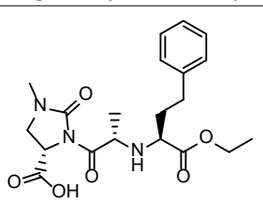	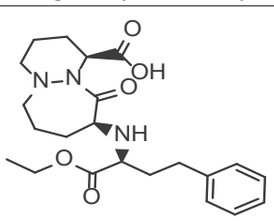	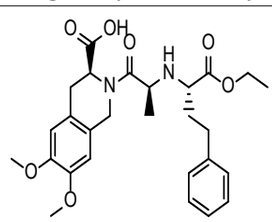	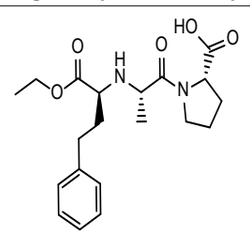
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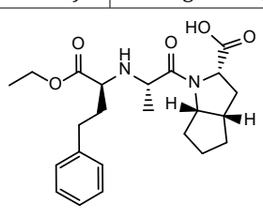
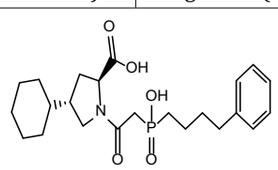
			
Ligand 13(CID5362129)		Ligand 14(CID 55891)	

Table 2: Ligands Similar to Capopril used for ACE inhibition.

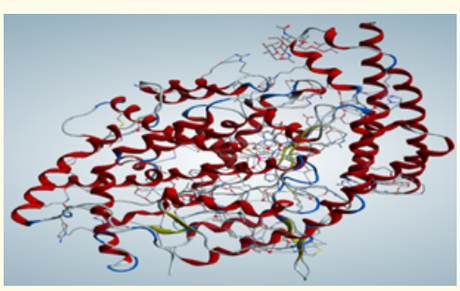


Figure 1: ACE simplified 3D structure.

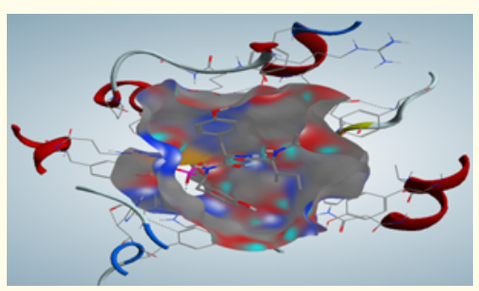


Figure 2: ACE active site isolated.

Ligand	Molecules	Energies (Kcal/mol)	LogP	LogS	Toxcicity
1	Captopril	3.71043e+001	0.63	-1.28	No
2	Zofenopril	8.82248e+001	2.71	-6.31	No
3	Spirapril	1.09391e+002	2.39	-5.05	No
4	Quinapril	1.08650e+002	2.83	-4.47	No
5	Lisinopril	1.08624e+002	2.83	-4.47	No
6	Perindopril	7.33520e+001	1.94	-3.22	No
7	Trandolapril	9.91545e+001	2.77	-4.21	No
8	Benazepril	1.10233e+002	2.57	-4.40	No
9	Imidapril	5.64409e+001	0.88	-2.79	No
10	Cilazapril	6.64713e+001	1.60	-3.06	No
11	Moexipril	1.29945e+002	2.85	-4.57	No
12	Enalapril	8.73084e+001	0.27	-3.33	No
13	Ramipril	9.70705e+001	2.38	-3.69	No
14	Fosinopril	5.02531e+001	5.05	-6.42	No

Table 3: Energy molecules minimizing (Kcal/mol).

Log S: aqueous solubility and intestinal permeability

Log P: distribution coefficient

These ligands are able to present a very important biological activity in accordance with the rule of Lipinski [16].

Docking and building complexes

In this step and after construction of the ligand, we proceed to positioning of molecule in the active site of Angiotensin Converting (ACE). For this, we used the Molecular Docking Module using MOE software [15]. Once the ligand -receptor complex is formed, it will adapt the most stable conformation, i.e. the lowest energy level. The purpose of the Dock application is looking at favorable conformational binding between medium size ligands and a not so soft macromolecular target, which is usually a protein [16]. For each ligand, a number of conformations called poses were generated to identify favorable binding modes. The search for binding modes is generally constrained to a small specific region of the receptor called the active site. Solvatation parameter has been taken in account. Obtained results are given in table 4 and 5.

Results and Discussion

Obtained results show that the orientation of ligands plays a significant role in positioning of the in this latter into enzyme active site, we can conclude that the introduction of bulky groups causes a rearrangement of conformation inside the cavity of the active site, which will be probably the complementarity and

Mol	Score	Rmsd-refine	E-Conf	E-PLACE	E-SCORE1	E-REFINE	E-SCORE2
Ligref	-13.6675	2.7837	-222.2882	-107.0895	-18.8538	-76.8066	-13.6675
Complexe-1	-7.4305	1.3150	-39.2358	-107.7534	-15.3519	-37.5473	-7.4305
Complexe-2	-9.0546	1.9345	15.8962	-87.9883	-16.6709	-42.6432	-9.0546
Complexe-3	-9.5882	2.9950	81.9127	-83.2609	-16.1842	-48.5037	-9.5882
Complexe-4	-8.7041	2.7971	82.1892	-76.6736	-14.6588	-35.9554	-8.7041
Complexe-5	-9.7351	2.3431	73.2402	-85.2919	-13.7907	-48.0109	-9.7351
Complexe-6	-7.8733	3.6298	48.1347	-60.4407	-15.6235	-35.6675	-7.8733
Complexe-7	-9.3291	2.6212	103.7711	-65.5980	-15.6460	-34.7081	-9.3291
Complexe-8	-8.1315	2.6223	75.1878	-88.0575	-23.1205	-38.4729	-8.1315
Complexe-9	-8.0730	1.7627	-18.0368	-112.7908	-16.7113	-29.0007	-8.0730
Complexe-10	-7.9074	2.9713	31.0412	-90.6845	-13.6002	-37.0146	-7.9074
Complexe-11	-9.8324	2.9390	101.3867	-76.0799	-14.9193	-41.7895	-9.8324
Complexe-12	-8.9613	1.9133	54.9907	-102.9565	-16.2971	-39.9821	-8.9613
Complexe-13	-8.6982	1.9664	70.8351	-84.4398	-15.6932	-43.2500	-8.6982
Complexe-14	-10.3304	2.3093	-54.7690	-60.8599	-15.6751	-41.4670	-10.3304

Table 4: Energy balance of complexes formed with -ACE Without Water molecules (Kcal/mol).

S: The Final Score; is the score of the last step; rmsd_refine: The mean square deviation between the laying before refinement and after refinement pose; E_conf: Energy Conformer; E_place: Score of the placement phase; E_scor1: Score the first step of notation; E_refine: Score refinement step and number of conformations generated by ligand; E_scor2: Score the first step notation; number of poses: Number of conformations [18].

Mol	Score	Rmsd-refine	E-Conf	E-PLACE	E-SCORE1	E-REFINE	E-SCORE2
Ligref	-13.6675	2.7837	-222.2882	-107.0895	-18.8538	-76.8066	-13.6675
Complexe-1	-7.90205097	0.865433633	-39.61753	-83.62424	-13.11081	-30.67458	-7.9020509
Complexe-2	-10.7658653	2.17372656	23.350462	-81.8878	-15.76332	-39.55902	-10.765865
Complexe-3	-9.92536068	2.46874738	123.9994	-87.10417	-17.30550	-9.135173	-9.9253606
Complexe-4	-9.59552574	2.70885062	120.54825	-39.59576	-17.87198	-2.897480	-9.5955257
Complexe-5	-10.291316	1.41206253	89.415939	-89.70933	-19.50791	-1.801922	-10.291316
Complexe-6	-9.5085907	2.20588112	66.944358	-56.96804	-15.53754	-22.72537	-9.508590
Complexe-7	-10.4118309	1.97213018	82.714698	-32.45192	-15.99796	-25.28024	-10.411
Complexe-8	-9.64621353	2.92878866	91.486648	-81.18762	-19.41166	-21.27453	-9.6462135
Complexe-9	-11.0151653	1.4450103	-24.68374	-79.86515	-16.13713	-26.39874	-11.015165
Complexe-10	-11.7562275	3.51483274	34.381721	-34.50009	-18.35927	-36.31149	-11.756227
Complexe-11	-12.5532837	1.58603287	108.91011	-106.6410	-19.73938	-31.38470	-12.553283
Complexe-12	-11.4617662	1.59836376	54.242935	-81.41729	-18.23189	-37.75716	-11.461766
Complexe-13	-9.78623962	1.89591479	109.97189	-80.83955	-16.87877	-20.99597	-9.7862396
Complexe-14	-10.9001017	1.70253134	-20.31206	-25.91220	-15.77829	2.032264	-10.900101

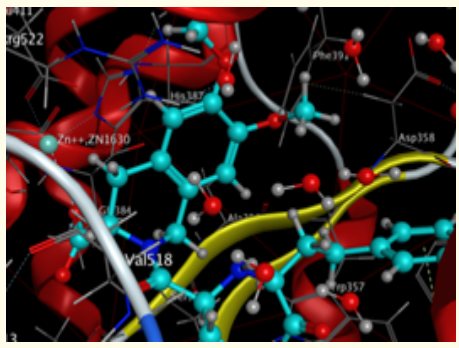
Table 5: Energy balance of complexes formed with -ACE With Water molecules (Kcal/mol).

consequently the activity. 2D molecular method of the screen has been attributed to the MOE (Molecular Operating Environment) software, which is designed to visualize the active sites of the complex (protein-ligand). The ligand is prepared and made with an improved 2D depiction layout algorithm, and protein residues version are arranged around it to indicate links spatial proximity [17,18]. Residues are marked with their amino acid code of 3 letters, and job classification [19,20]. If there are multiple channels in the system, the positions are prefixed by the letters of the alphabet. Interactions between 2.5 Å and 3.1 Å are considered high and those between 3.1Å and 3.55Å are average. Greater than 3.55Å interactions are weak [21].

Docking without water molecules

Table 4 shows that the complex- 14 (Figure 3) has the lowest energy (-10.3304 Kcal/mol) and is more stable than complex – 11 (Figure 4) (-9.8324 Kcal/mol). The third important low energy is obtained for the complex – 5 (Figure 4) (-9.7351 Kcal/mole). For complex 14: Fosinopril interacts with the amino acids [SER 355 (A) H-acceptor, GLU 384 (A) H-acceptor, TYR 523 (A) H-acceptor] at a distance of 3.54 Å, 3.18 Å, 2.74 Å respectively (for the 2nd and 3rd strong interaction, 1st weak interaction), with the existence of six electric forces HIS 410, HIS387, HIS 513; HIS 353; ALA356, ASP 358 and interaction with Zink Zn 1630 (metal, ionic) at a distance of 2.70 Å and 2.50 Å for metal and ionic strong interaction witch suggesting that Fosinopril can be candidate for inhibiting of Angiotensin - Converting (ACE) and interfere with [SER 355 (A) H-acceptor, GLU 384 (A) H-acceptor, TYR 523 (A) H-acceptor] [22].

For complex 11 (Figure 4), Moexcipril has an interaction with the amino acids [ALA356 (A) H-acceptor, HIS 387 (A) H-pi, ASN 66 (A) pi-H] at a distance of 3.25 Å, 3.95 Å, 3.75 Å respectively (for the 1st average interaction, 2nd and 3rd weak interaction) with the existence of six electric forces HIS 513; HIS 353; TYR523; GLU 384, HIS 410, ASP 358 and interaction with Zink Zn1630 (metal, ionic) at a distance of 2.52 Å for metal and ionic strong interaction which suggests that Moexcipril can also be good candidate for inhibiting of Angiotensin - Converting (ACE) and interfere with acid [ALA356 (A) H-acceptor, HIS 387 (A) H-pi, ASN 66 (A) pi-H] [22].



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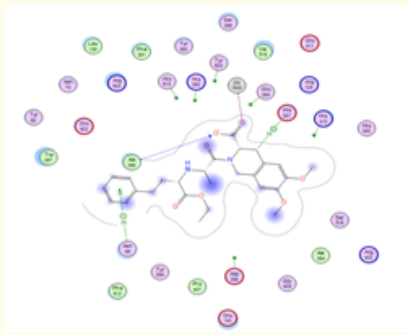

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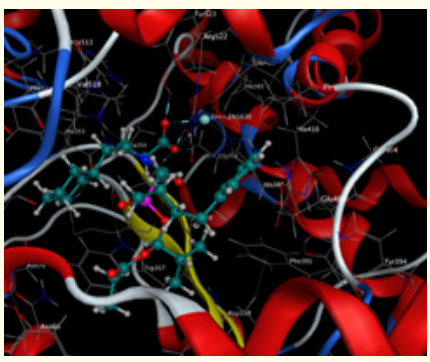
Figure 4: Diagram interaction of complex-11 (ACE + Moexcipril).

For complex 5 (Figure 5) Lisinopril interacts with amino acids [HIS 513 (A) H-acceptor, TYR 523 (A) H-acceptor, TYR 360 (A) pi-H] at a distance of 3.06 Å, 3.01 Å, 3.94 Å respectively (for the 1st, 2nd strong interaction, and 3rd weak interaction), with the existence of five electric forces HIS 410; HIS 353, ALA 356, HIS 513, HIS 353; ASP 358 and interaction with Zink Zn 1630 (metal, ionic) at a distance of 2.38 Å for metal and ionic strong interaction which suggesting that Lisinopril can also be good candidate for inhibition of Angiotensin - Converting (ACE) and interfere with [HIS 513 (A) H-acceptor, TYR 523 (A) H-acceptor, TYR 360 (A) pi-H] [22].



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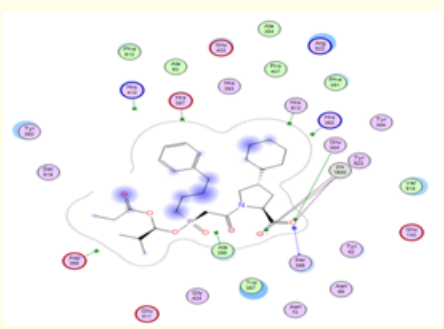

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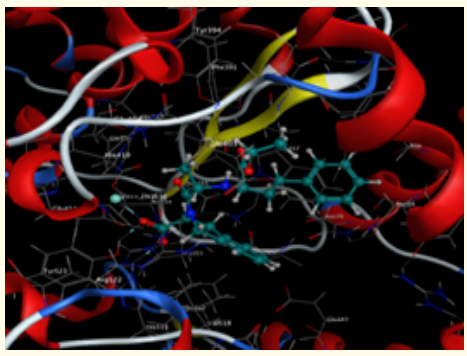
Figure 3: Diagram interaction of complex-14 (ACE + Fosinopril).



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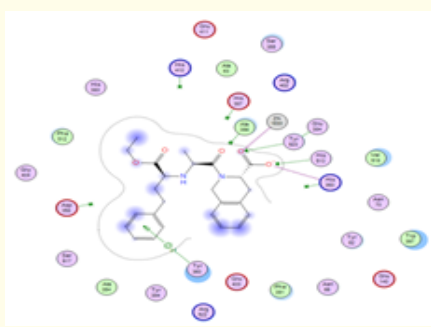

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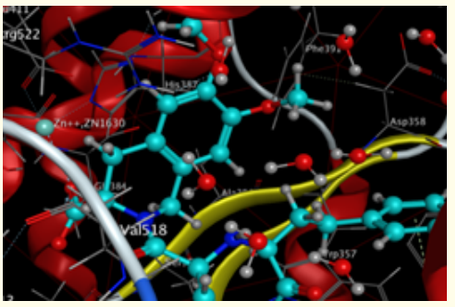
Figure 5: Diagram interaction of complex-5 (ACE + Lisinopril).

Docking with water molecules

Obtained results form table 5 show that complex- 11 has the lowest energy (-12.5532837 Kcal/mol) and is more active than complex - 10 (-11.7562275 Kcal/mol). The third important low energy is from complex -12 (-11.4617662 Kcal/mole).

For complex 11 (Figure 6), Moexipril interacts with the amino acids [GLU 384 (A) H-acceptor; GLU 411 (A) ionic HIS 353 (A) ionic; ASN 66 (A) pi-H] at a distance of 2.77 Å, 3.24 Å; 3.42 Å, 4.48 Å respectively (for the 1st strong interaction, 2nd, 3rd average interaction and 4th weak interaction), with the existence of three electric forces HIS 410, TYR 523, ASP 358 and interaction with Zink Zn 1630 ionic at a distance of 3.16 Å strong interaction witch suggest that Moexipril is good inhibitor candidate of Angiotensin - Converting (ACE) and interfere with [GLU 384 (A) H-acceptor; GLU 411 (A) ionic] [22].



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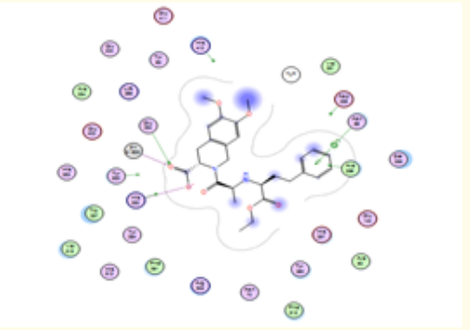

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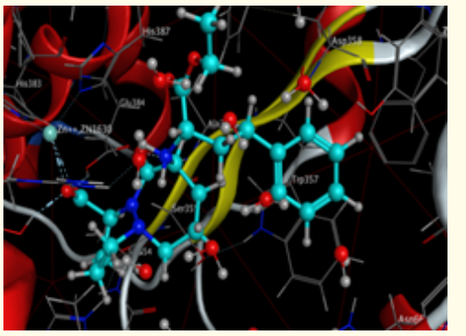
Figure 6: Diagram interaction of complex-11 (ACE + Moexipril).

For complex 10 (Figure 7), Cilazapril interacts with the amino acids [ALA 356 (A) H-acceptor 3.13; TYR 523 (A) H-acceptor; GLU 384 (A) H-acceptor, GLU 411 (A) ionic] at a distance of 3.13 Å, 2.79 Å and 3.24 Å. Å respectively (for the 1st and 2nd and strong interaction, 3rd average interaction), with the existence of two electric forces HIS 353, ASP 358 and interaction with Zink Zn 1630 (metal, ionic) at a distance of 2.50 Å and 2.63 Å for metal and ionic strong interaction witch suggest that Cilazapril is good inhibitor candidate of Angiotensin - Converting (ACE) and interfere with [ALA 356 (A) H-acceptor 3.13; TYR 523 (A) H-acceptor; GLU 384 (A) H-acceptor, GLU 411 (A) ionic] [22].



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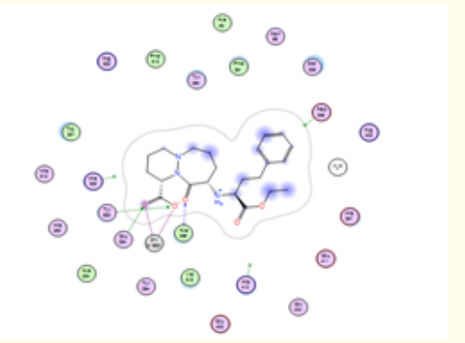

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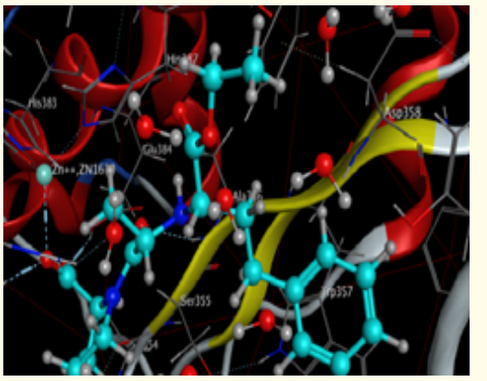
Figure 7: Diagram interaction of complex-10 (ACE + Cilazapril).

For complex 12 (Figure 8) Enalapril interacts with the amino acids [TYR 523 (A) H-acceptor; GLU 384 (A) H-acceptor; GLU 411 (A) ionic] at a distance of 2.77 Å, 2.77 Å and 3.24 Å respectively (for the 1st and 2nd strong interaction, 3rd average interaction), with the existence of four electric forces HIS 410, ASP 358, HIS 353; and ALA 356 interaction with Zink Zn 1630 ionic at a distance of 3.16 Å strong interaction witch suggest that Enalapril is candidate to inhibit Angiotensin - Converting (ACE) and interfere with [TYR 523 (A) H-acceptor; GLU 384 (A) H-acceptor; GLU 411 (A) ionic] [22].



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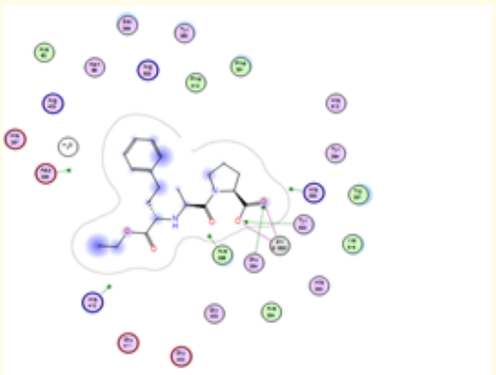

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Figure 8: Diagram interaction of complex-12 (ACE + Enalapril).

The value of IC_{50} with the inhibitor of the K27 co-crystallization is 14.4 nM [23]. Energy (Fosinopril - 10.3304 Kcal/mol < Moexcipril - 9.8324 Kcal/mol < Lisinopril -9.7351 Kcal/mol). Energy (Moexcipril -12.5532837 Kcal/mol < Cilazapril -11.7562275 Kcal/mol < Enalapril -11.4617662 Kcal/mol). Moexcipril (Similar of Capopril) when water is included present best inhibition to the evolution of the pathology studied (heart failure HF). The behavior of water molecules in direct contact with the solute is very important and it is therefore crucial to ensure that not only the solute but also the first solvation layers are surrounded by a sufficient number of water molecules for ensure a realistic behavior of all the molecules of solvent (Figure 9). Refinements of certain terms of the force field describing the water molecule are imperative to ensure good results. For example, the explicit treatment of the electronic polarizability of water molecules can be included as an additional term in an empirical force field. The presence of water is sometimes paramount to ensure a relay between the ligand and the active site [24].

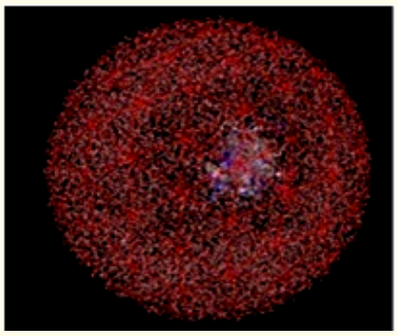

Figure 9: Solvation Ligand –Substrate in Spherical box.

We note that we can discuss complementarity increasing or decreasing in the range of dimensions of the active site pocket, in our case with a deep geometry of 19.06 Å an opening and 15.92 Å, this pocket shrunk up a width of 10.07 Å (Figure 10). Taking into account different geometrical constraints, the approach considered inhibitors may influence the complementarity and later activity. The examination of the enzymatic cavity confirms that the structure of Fosinopril with the groupings of the atoms (O_{22}, O_{23}) presents a strong interaction hydrogen bond with [GLU 384 (A) H-acceptor, TYR 523 (A) H-acceptor] and Moexcipril with the atom (O_5) present a strong interaction hydrogen bond with [GLU 384 (A) H-acceptor] and one better complementarity with Angiotensin Converting enzyme (ACE).

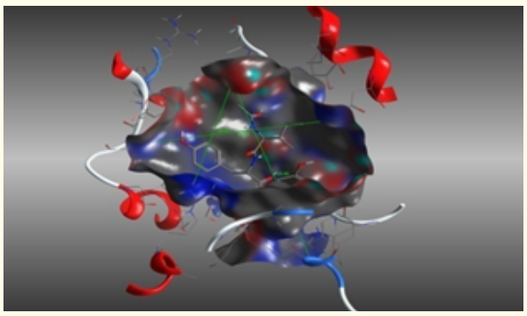

Figure 10: ACE active site size (target size).

Conclusion

In this work, we studied the Angiotensin Converting (ACE) interactions with known inhibitors using molecular modeling (molecular docking) and solvatation parameter. Interaction energy (scores) with water molecules and without water molecules has been calculated. In presence of water molecules interaction of ACE with Moexcipril (Similar of Capopril), is better compared to other molecules and also because of flexibility of the active site. We can conclude that solvatation is important parameter permitting better selection of potential inhibitors candidate of ACE.

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Conflict of Interest

The authors declare no conflict of interest.

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