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Research Article

Study of Interaction between Angiotensin-Converting Enzyme (ACE) and Beta Blocker Inhibitors Including Solvatation Parameter with Molecular Modeling

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Abstract

Background: Nowadays molecular docking is widely practiced in different areas of scientific research. Mainly in medical and pharmaceutical research molecular modeling allows miserly time and money in conception of new drugs by comprehension of interaction between disease's enzymes and inhibitors for probable formation of stable complex. The inhibition of Angiotensin-converting enzyme (ACE) is an governing approach in the treatment of Heart failure (HF). The Beta blocker cardio selective, not – cardio selective are expended for inhibiting ACE. Our work is the attempt of molecular interaction between the enzyme (Angiotensin Converting) and the substrates (inihibitor for ACE). Various tools of molecular modeling are applied to carry out this work (molecular mechanics, molecular dynamics and molecular docking) (MOE). The introduction of bulky groups causes adjustment rearrangement in the active site pocket, which will presumably be reinforced and thus complement its activity. The results performed from this work, in which the inhibitions of Angiotensin Converting by molecular modeling process have been demonstrated. In conclusion, taking into account the results obtained in this study, inhibition of Angiotensin Converting by molecular modeling methods has been elucidated, which allow us to conclude that Carvedilol (β-blocker non-cardioselective) when water is included in the docking simulation has a better inhibition 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: Molecular Modelling; Angiotensin - Converting Enzyme (ACE); Inhibitors of ACE; MOE (Molecular Operating Environment)

Introduction

Heart failure (HF), often referred to as congestive heart failure (CHF), occurs when the heart is unable to pump sufficiently to maintain blood flow to meet the body's needs [1]. Signs and symptoms commonly include shortness of breath, excessive tiredness, and leg swelling. The shortness of breath is usually worse with exercise, while lying down, and may wake the person at night. A limited ability to exercise is also a common feature. Chest pain, including angina, does not typically occur due to Heart Failure [1].

In best of our knowledge no studies interaction by docking between these inhibitor Beta blocker cardioselectifs, not – cardioselectifs and ECA enzyme has been done. The purpose of this study is to minimize the formation of the complex and consequently to delay its progression [2]. In order to rationalize the properties of the inhibitors and to determine the reaction processes involving these compound [2]. Our objective main thing in this research and to determine the mode of interaction of the complex for the binding of the inhibitor to the enzyme, with a better complementarity (better activity). These results will probably help with the development of an effective therapeutic tool to fight against the development of the disease cardiac Failure.

Materials and Methods

Angiotensin-converting enzyme (ACE)

Angiotensin-converting enzyme, or ACE, is a central component of the renin-angiotensin system (RAS), which controls blood pressure by regulating the volume of fluids in the body [3,4]. It converts the hormone angiotensin I to the active vasoconstrictor angiotensin II [5]. Therefore, ACE indirectly increases blood pressure by causing blood vessels to constrict [5]. Other less known functions of ACE are degradation of bradykinin [6] and amyloid beta-protein [5]. ACE is a zinc metalloenzyme [5]. The zinc ion is essential to its activity, since it directly participates in the catalysis of the peptide hydrolysis [3].

Angiotensin-converting ACE inihibitors

Angiotensin-converting enzyme (ACE) inhibitors help relax blood vessels [7]. Angiotensin converting enzyme inhibitors (ACE inhibitors) are medications that slow (inhibit) the activity of the enzyme ACE, which decreases the production of angiotensin II [8]. 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 [9].

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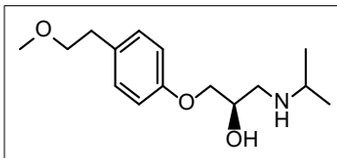
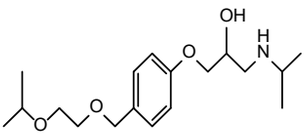
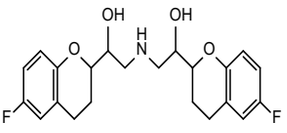
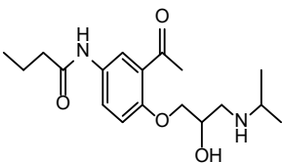
ACE inhibitors also have beneficial effects on left ventricular hypertrophy, another clinical marker of therapy in the hypertensive patient. ACE inhibitors also avoid some of the detrimental metabolic effects of other antihypertensive medications, such as dyslipidemia, glucose intolerance, and hyperinsulinemia. The inhibitors for ACE chosen are given in table 1.

Molecule	Name	IUPAC name	Pub Chem CID	Molar mass g/mol	Formula
1	Metoprolol	(2R)-1-[4-(2-methoxyethyl) phenoxy]-3-(propan-2-ylamino) propan-2-ol	157717	267,3639	$C_{15}H_{25}NO_3$
2	Bisoprolol	1-(4-((2-isopropoxyethoxy)methyl)phenoxy)-3-(isopropylamino)propan-2-ol	2405	325,443	$C_{18}H_{31}NO_4$
3	Nebivolol	2,2'-azanediylbis(1-(6-fluorochroman-2-yl) ethan-1-ol)	71301	405,435	$C_{22}H_{25}F_2NO_4$
4	Acebutolol	N-(3-acetyl-4-(2-hydroxy-3-(isopropylamino) propoxy) phenyl) butyramide	1978	336,4259	$C_{18}H_{28}N_2O_4$
5	Atenolol	2-(4-(2-hydroxy-3-(isopropylamino)propoxy) phenyl) acetamide	2249	266,3361	$C_{14}H_{22}N_2O_3$
6	Betaxolol	1-(4-(2-(cyclopropylmethoxy)ethyl)phenoxy)-3-(isopropylamino)propan-2-ol	2369	307.428	$C_{18}H_{29}NO_3$
7	Celiprolol	3-(3-acetyl-4-(3-(tert-butylamino)-2-hydroxypropoxy)phenyl)-1,1-diethylurea	2663	379.50	$C_{20}H_{33}N_3O_4$
8	Esmolol	methyl3-[4-[2-hydroxy-3-(propan-2-ylamino)propoxy]phenyl]propanoate	59768	295.374	$C_{16}H_{25}NO_4$
9	Carvedilol	1-((9H-carbazol-4-yl)oxy)-3-((2-(2-methoxyphenoxy)ethyl)amino)propan-2-ol	2585	406,4742	$C_{24}H_{26}N_2O_4$
10	Labetalol	2-hydroxy-5-[1-hydroxy-2-(4-phénylbutan-2-ylamino)éthyl]benzamide	3869	328,4055	$C_{19}H_{24}N_2O_3$
11	Levobunolol	5-[(2S)-3-(tert-butylamino)-2-hydroxypropoxy]-3,4-dihydro-2H-naphthalen-1-one	39468	291.385	$C_{17}H_{25}NO_3$
12	Nadolol	(2R,3S)-5-[3-(tert-butylamino)-2-hydroxypropoxy]-1,2,3,4-tetrahydronaphthalene-2,3-diol	39147	309.401	$C_{17}H_{27}NO_4$
13	Oxprenolol	1-(propan-2-ylamino)-3-(2-prop-2-enoxyphenoxy) propan-2-ol	4631	265.348	$C_{15}H_{23}NO_3$
14	Propranolol	1-naphthalen-1-yloxy-3-(propan-2-ylamino) propan-2-ol	4946	259,3434	$C_{16}H_{21}NO_2$
15	Pindolol	1-(1H-indol-4-yloxy)-3-(propan-2-ylamino)propan-2-ol	4828	248.321	$C_{14}H_{20}N_2O_2$
16	Sotalol	(N-[4-[1-hydroxy-2-(propan-2-ylamino)ethyl]phenyl]methanesulfonamide	5253	272.3624	$C_{12}H_{20}N_2O_3S$
17	Timolol	(2S)-1-(tert-butylamino)-3-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxy]propan-2-ol	33624	316.421	$C_{13}H_{24}N_4O_3S$
18	Carteolol	5-[3-(tert-butylamino)-2-hydroxypropoxy]-3,4-dihydro-1H-quinolin-2-one	2583	292.373	$C_{16}H_{24}N_2O_3$

Table 1: Physico- Chemical properties of inihibitors Synthetic for Cyclooxygenase COX_2.

Preparation and optimization of both enzyme and inhibitors

Download of ACE was done from database Bookhaven Protein (www.rcsb.org/pdb) (code 4BZR).With three-dimensional structure obtained by X-ray diffraction (resolution 1.84 Å). Note that the Angiotensin-converting enzyme (ACE) crystallizes as a monomer (Figure 1) with 589 residues and 4726 atoms [2]. Compounds of inhibitors for ACE were downloading from Pub Chem data base. (www.pubchem.com) see table 2 Using MOE software (Molecular operating environment) [10]. We select the active site in the enzyme and we minimize the energy of both enzyme and molecules. Energy minimizing was done under following conditions: Temperature = 300 °K, pH = 7, the geometry was performed using the field strengths in the MMFF94x implanted in MOE [10] and Hamiltonian AM1 [2]. Figure 2 shows the active site of the enzyme with molecule of co-crystallization Minimized energy of ligands and their toxicity are obtained by MOE software [2].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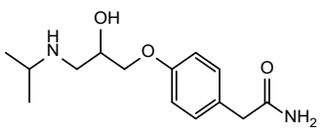	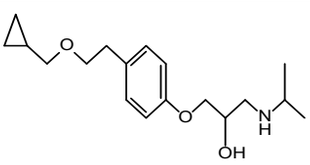	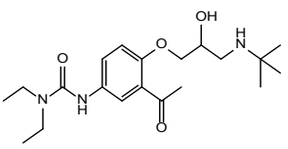	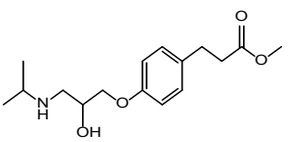
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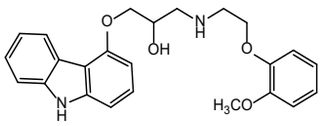
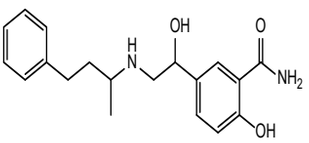
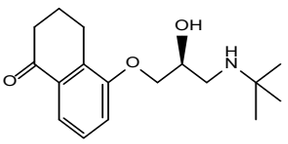
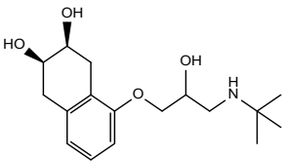
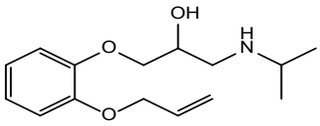
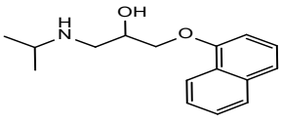
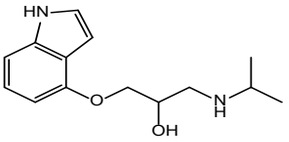
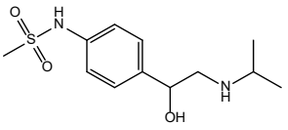
			
B-blocker 9 (CID2585)	B-blocker 10(CID 3869)	B-blocker 11(CID 39468)	B-blocker12(CID 39147)
			
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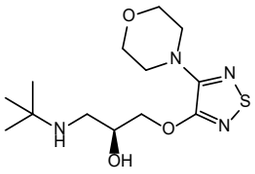
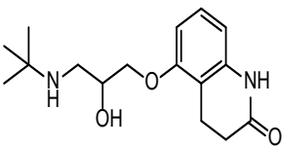
			
	B-blocker 17(CID33624)	B-blocker 18(CID 2583)	

Table 2: Beta-blocker inhibitors used for ACE.

A/ Ligand	Molecules	Energies (Kcal/mol)	LogP	LogS	Toxicity
1	Metoprolol	5.86602 e+001	0.59	-1.81	No
2	Bisoprolol	7.11106e+001	1.61	-2.54	No
3	Nebivolol	9.36839e+001	1.34	-3.98	No
4	Acebutolol	4.12731e+001	1.34	-2.87	No
5	Atenolol	5.09331e+001	-0.57	-1.94	No
6	Betaxolol	6.88535e+001	1.37	-2.44	No
7	Celiprolol	4.16625e+001	1.86	-2.86	No
8	Esmolol	5.07490e+001	0.50	-1.95	No
9	Carvedilol	1.02452e+002	2.71	-5.01	No
10	Labetalol	6.71388e+001	1.20	-3.15	No
11	Levobunolol	6.80706e+001	1.31	-2.53	No
12	Nadolol	7.98990e+001	-0.39	-1.77	No
13	Oxprenolol	6.27391e+001	0.96	-2.18	No
14	Propranolol	6.77687e+001	1.55	-3.51	No
15	Pindolol	5.10022e+001	0.88	-1.92	No
16	Sotalol	2.51585e+001	0.16	-1.39	No
17	Timolol	7.76451e+001	-0.52	-1.49	No
18	Carteolol	5.52941e+001	0.67	-2.22	No

Table 3: Minimization energy of molecules (Kcal/mol)A Beta blocker.

These ligands is able to present a very important biological activity in accordance with the rule of Lipinski., *et al.* (1997) [11].

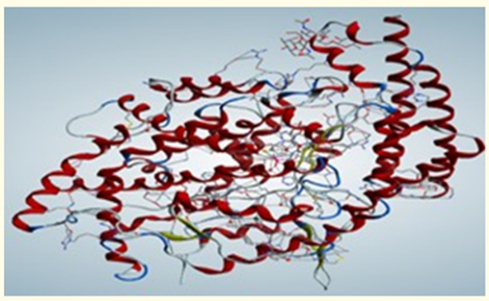


Figure 1: ACE simplified 3D structure.

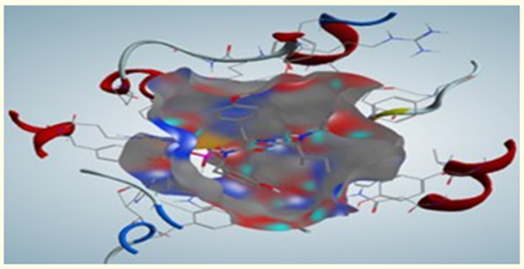


Figure 2: ACE active site isolated.

Docking and building complexes

The next step, after the construction of the ligand, is the positioning of this molecule in the active site of Angiotensin Converting (ACE) [2]. For this, we used the Molecular Docking Module using MOE software [2-10]. Once the ligand -receptor complex is formed, it will adapt the most stable conformation, i.e. the lowest energy level [2]. 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 [2-12]. For each ligand, a number of conformations called poses were generated to identify favorable binding modes [2]. The search for binding modes is generally constrained to a small specific region of the receptor called the active site [2].

Results and Discussion

The results given in tables 4,5 show that the orientation of the ligands plays a significant role for the positioning of the ligands in the active site of the enzyme, one 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 consequently the activity [2-14]. 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 [2-15]. Residues are marked with their amino acid code of 3 letters, and job classification [2-16,17]. If there are multiple channels in the system, the positions are prefixed by the letters of the alphabet [2]. 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 [2-18].

To get more valid results we do our calculation with and without water and we studied the water effect in the interaction. So our results are given with and without water.

Synthetic inhibitors approach without water

These results show that the complex- 10 has the lowest energy (-7.2475 Kcal/mol) and is more active than complex -9 (-7.0196 Kcal/mol) which is more active than complex -2 (-6.8338 kcal/mole) [2].

For complex 10: Labetalol interacts with the amino acids [GLU 411 (A) H-donor, (A) ionic] at a distance of 3.47, 3.47 Å respectively (for the 1st, 2nd average interaction; and interaction with HIS 387 [(A) ionic(ND1, NE2), (A) cation-pi;]. at a distance of (3.82,3.85,3.89) Å for (for 1st; 2nd; 3th weak interaction and interaction with HIS 410 ((A) H-pi) at a distance of 3.72 Å (weak interaction) and interaction with Zink ((A) metal) Zn at a distance of 2.75 Å (strong interaction)

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	-6.1019	1.6614	14.2425	-77.9882	-12.6985	-23.9830	-6.1019
Complexe-2	-6.8338	2.1718	31.5191	-58.9168	-12.9865	-24.1349	-6.8338
Complexe-3	-6.1579	4.4428	41.8055	-75.2202	-13.6334	-21.3060	-6.1579
Complexe-4	-6.1176	2.9156	-13.4259	-56.7821	-15.4462	-14.5139	-6.1176
Complexe-5	-5.7681	1.9745	-16.2213	-61.2165	-11.7814	-15.8087	-5.7681
Complexe-6	-6.8002	1.8909	29.7989	-53.6413	-12.0233	-13.8208	-6.8002
Complexe-7	-6.2981	2.2629	-38.8001	-64.3493	-11.7346	-13.9010	-6.2981
Complexe-8	-5.8666	3.7208	-10.1412	-82.9636	-12.5764	-17.1322	-5.8666
Complexe-9	-7.0196	2.6543	53.0200	-61.4781	-13.9041	-23.1147	-7.0196
Complexe-10	-7.2475	1.8552	-12.9471	-82.3414	-11.7073	-35.7651	-7.2475
Complexe-11	-5.7195	1.3207	23.8135	-76.4104	-11.3651	-9.2848	-5.7195
Complexe-12	-6.2993	2.6536	36.7381	-57.7777	-12.1091	-21.4960	-6.2993
Complexe-13	-5.7138	1.4578	39.3543	-55.2332	-11.0545	-12.6817	-5.7138
Complexe-14	-6.0584	2.1735	17.6185	-73.4523	-11.7239	-17.5620	-6.0584
Complexe-15	-5.5215	2.8106	-161.1925	-67.5111	-14.7628	-15.3991	-5.5215
Complexe-16	-5.6279	1.4549	-71.2300	-92.2873	-12.1789	-15.8673	-5.6279
Complexe-17	-5.3919	2.4570	41.9921	-102.7313	-10.9497	-24.6594	-5.3919
Complexe-18	-6.6201	1.8269	-27.5773	-96.4527	-11.2149	-20.9932	-6.6201

Table 4: Energy Balance of 18 complexes Beta blocker -ACE Without Water (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 [13].

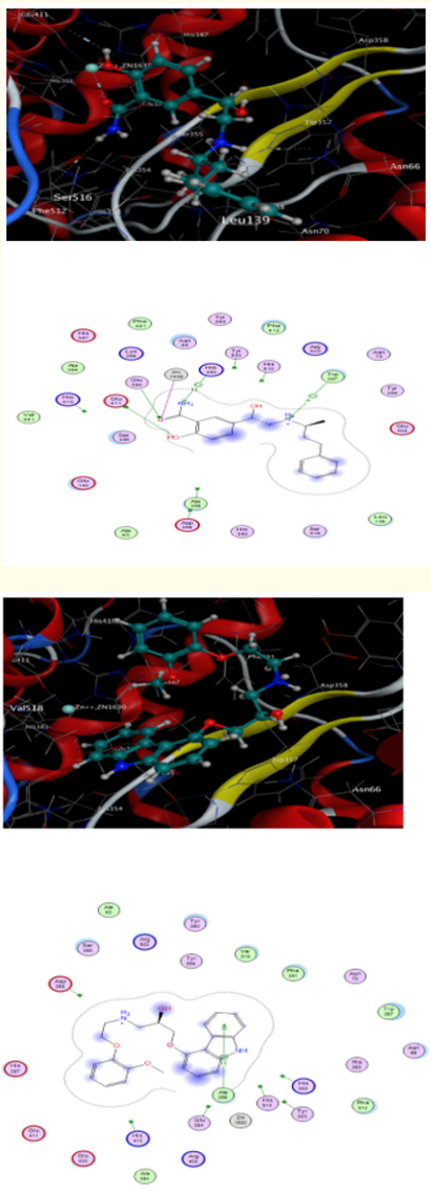
Mol	score	Rmsd-refine	E-Conf	E-PLACE	E-SCORE1	E-REFINE	E-SCORE2
Ligref	-13.6675	2.7837	-222.2882	-107.0895	-18.8538	-76.8066	-13.6675
Complexe-1	-8.02151299	1.78913164	14.5016499	-65.651962	-15.765262	-14.712783	-8.02151299
Complexe-2	-9.10876751	2.60233521	36.1677933	-47.044918	-16.352117	-12.203584	-9.10876751
Complexe-3	-9.787076	2.39357805	39.8967094	-67.660148	-19.203273	-19.243463	-9.787076
Complexe-4	-9.13803196	3.98257351	-2.04681087	-44.990409	-15.450089	-14.169252	-9.13803196
Complexe-5	-7.6812005	1.22421634	-24.2205734	-67.133361	-17.498580	-7.9016475	-7.6812005
Complexe-6	-9.06015873	2.60167432	29.2688255	-62.225696	-17.526674	-7.862563	-9.06015873
Complexe-7	-9.17838383	3.07364035	-41.54562	-48.737407	-16.150613	-11.618090	-9.17838383
Complexe-8	-8.39698315	1.2392801	-0.135879129	-46.850513	-14.800361	-9.2966222	-8.39698315
Complexe-9	-10.581053	3.34600234	57.1051636	-37.53375	-16.71735	-18.84925	-10.581053
Complexe-10	--9.24532223	1.39020622	-4.73803949	-64.90832	-19.93404	-22.53537	-9.24532223
Complexe-11	-8.9317998	2.32224369	20.3306217	-50.48353	-14.37519	-17.36423	-8.9317998
Complexe-12	-8.4824304	0.84692639	45.5280457	-86.35620	-16.65194	-10.34206	-8.4824304
Complexe-13	-7.7656774	2.44758749	41.1435738	-54.65490	-15.84378	-19.18963	-7.7656774
Complexe-14	-8.0904417	3.50845027	16.4806328	-63.12503	-12.75469	-19.40169	-8.0904417
	-6.5019054	2.05447626	-154.191574	-77.33808	-14.22684	-12.28352	-6.5019054
Complexe-16	-7.2906031	3.7798903	-71.0258942	-60.00892	-14.60831	-10.71572	-7.2906031
Complexe-17	-8.3725681	1.65543127	52.8794785	-55.09284	-14.01877	-23.62775	-8.3725681
Complexe-18	-8.4415369	1.61853886	-32.200943	-79.06652	-14.56211	-14.56681	-8.4415369

Table 5

wich suggesting that Labetalol can inhibit Angiotensin - Converting (ACE) and interfere with GLU 411 (A) H-donor, (A) ionic [19].

For complex 9: Carvedilol has an interaction with the amino acid ALA 356 ((A) pi-H) at a distance of 4.71 Å (weak interaction) which suggests that Carvedilol can inhibit Angiotensin - Converting (ACE) and interfere with ALA 356 (A) pi-H [19].

For complex 2: Bisoprolol interacts with amino acids GLU 123[(A) H-donor, (A) ionic)]. at a distance of 2.93, 2.93 Å respectively (for the 1st, 2nd strong interaction, and interaction with MET 223 (A) H-donor at a distance of 3.71 Å (weak interaction) which suggesting that Bisoprolol can inhibit Angiotensin - Converting (ACE) and interfere with GLU 123[(A) H-donor, (A) ionic)], MET 223 (A) H-donor [19].



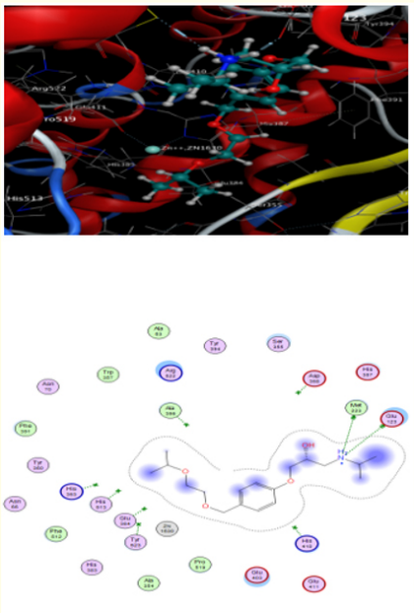


Figure 3: Diagrams of interactions (enzyme-ligands) 3 complex (a, b, c).

Figure (a): Diagram interaction of complex-10 (ACE + Labetalol)

Figure (b): Diagram interaction of complex-9 (ACE + Carvedilol)

Figure (c): Diagram interaction of complex-2 (ACE + Bisoprolol)

Synthetic inhibitors approach in water

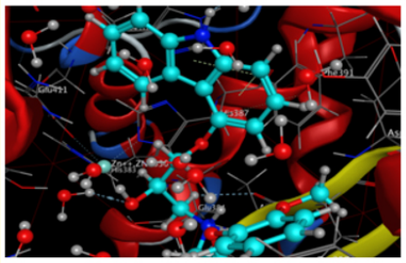
These results show that the complex- 9 has the lowest energy (-10.581053 Kcal/mol) and is more active than complex -3 (- 9.787076 Kcal/mol) which is more active than complex - 10 (-9.2441692 Kcal/mole).

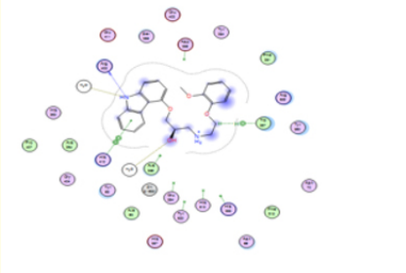
For complex 9: Carvedilol interacts with the amino acids [ARG 402 (A) H-donor; 6-ring TRP 357 (A) H-pi; 5-ring HIS 410 (A) pi-pi] at a distance of 3.09, 3.62, 3.72 Å respectively (for the 1st strong interaction, 2nd and 3rd weak interaction and interaction with water (H-donor N5, H-acceptor O2) at a distance of 3.27; 2.96 Å for (for 1st average interaction and for 2nd strong interaction, which suggesting that Carvedilol can inhibit Angiotensin - Converting (ACE) and interfer with [ARG 402 (A) H-donor; 6-ring TRP 357 (A) H-pi; 5-ring HIS 410 (A) pi-pi] [19].

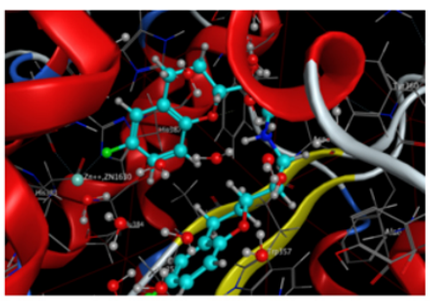
For complex 3: Nebivolol interacts with the amino acid [ARG 402 (A) H-donor] at a distance of 3.10 Å for the 1st strong interaction; wich suggesting that Nebivolol can inhibit Angiotensin - Converting (ACE) and interfer with [ARG 402 (A) H-donor] [19].

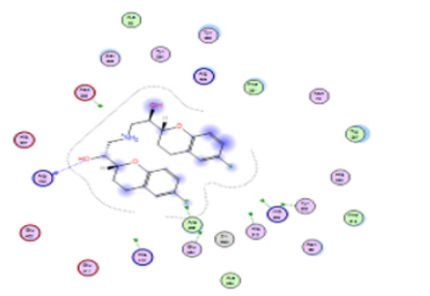
For complex 10: Labetalol interacts with the amino acids [ASP 358 (A) H-donor; 5-ring HIS 410 (A) pi-pi] at a distance of 3.16, 3.84 Å respectively (for the 1st strong interaction, 2nd weak interaction); and interaction with HOH (H-donor (O2, N4)) at a distance

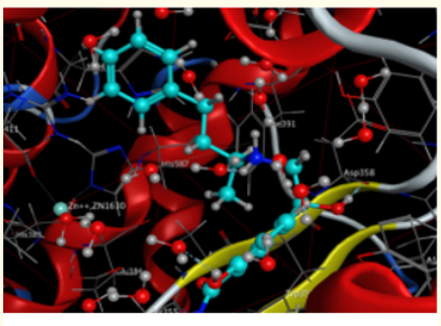
of 2.93, 2.95 Å (strong interaction) wich suggesting that Labetalol can inhibit Angiotensin - Converting (ACE) and interfer with [ASP 358 (A) H-donor; 5-ring HIS 410 (A) pi-pi] [19].











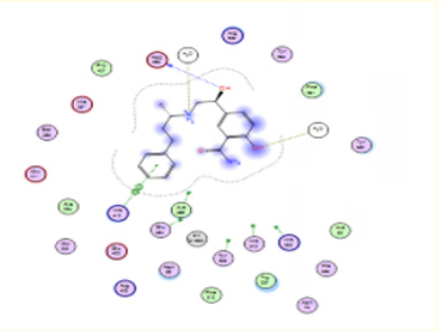


Figure 4: Diagrams of interactions (enzyme-ligands) 3 complex (a, b, c).

Figure (a): Diagram interaction of complex-9 (ACE + Carvedilol

Figure (b): Diagram interaction of complex-3 (ACE + Nebivolol)

Figure (c): Diagram interaction of complex-10 (ACE + Labetalol)

The value of IC50 with the inhibitor of the K27 co-crystallization is 14.4 nM [2-20].

Energy (Labetalol -7.2475 Kcal/mol < Carvedilol -7.0196 Kcal/mol < Bisoprolol -6.8338 Kcal/mole).

Energy (Carvedilol -10.581053 Kcal/mol < Nebivolol - 9.787076 Kcal/mol < Labetalol - 9.2441692 Kcal/mole).

Carvedilol (Beta blocker) when water is included in the docking simulation will be the best inhibitors to slow the evolution of the pathology studied (Heart Failure HF).

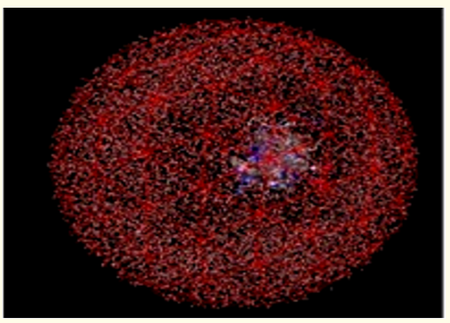


Figure 5: Solvation Ligand –Substrat in Spherical box.

Inhibition of enzymes plays an important role in the control of biological mechanisms, and in particular in the regulation of metabolic pathways.

The majority of enzymes need to be in an aqueous medium to function. The presence of the first adjacent layer allows better inhibition and good stability of the complex by providing the outer layer.

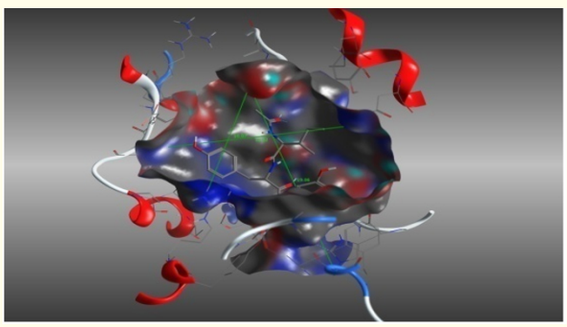


Figure 6: Size of the enzyme cavity.

The cavity enzymatic confirms that the structure of Labetalol with the groupings of the atoms (N4, N4 and C15) presents a strong interaction hydrogen bond with GLU 411, HIS 387, HIS 410 and Carvedilol with the groupings of the atom (N5) presents a strong interaction hydrogen bond with [ARG 402 (A) H-donor] and one better complementarity with Angiotensin Converting enzyme (ACE).

Conclusions

The results obtained from this work, into which the inhibition of Angiotensin Converting (ACE) by molecular modeling methods was elucidated, allow us to conclude that inhibitor-9 Carvedilol (β-blocker non-cardioselective) when water is included in the docking simulation presents a more optimised inhibition of Angiotensin Converting (ACE) for the treatment of Heart Failure (HF). We can speculate that solvatation is important parameter to ensure a relay between the ligand and the active site.

Acknowledgements

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Conflict of Interest

The authors declare no conflict interest.

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