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VIRTUAL SCREENING OF TRIAZOLES INHIBITORS OF 11B-HYDROXYSTEROID DEHYDROGENASE ENZYMES USING -ADME - MOLECULAR DOCKING, AND MOLECULAR DYNAMICS SIMULATION STUDIES

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ABSTRACT

Hypertension, or elevated arterial blood pressure, is a substantial public health problem. The two 11β-hydroxysteroid dehydrogenase (11β-HSD) isozymes catalyze the interconversion of cortisol and cortisone. Our research consists in studying the inhibition of the enzymes with some derivatives of 1,2,4-triazoles by means of molecular docking and dynamics approaches.The interactions between the studied inhibitors and our target were further explored through molecular docking and molecular dynamics simulations, in the presence of water molecules. The molecular dynamics study was done for the best derivatives of 1,2,4-triazoles inhibitors (deducted from the docking best scores for L2 and L1, and lowest score for Lref). A few key residues (N-14 with oxygen receptor interaction H- donor) at the binding site of of (11β-HSD1) and (11β-HSD2) were identified. Obtained Docking and molecular dynamics result, both leads to the same conclusion and predict that L2 subsisted derivatives of 1, 2, 4-triazoles is the best inhibitor candidate.

Keywords: 11β-HSD1; 11β–HSD2; Hypertension ; 1,2,4-Triazoles ; Bioactivity Properties ; (Molecular Operating Environment)

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1. INTRODUCTION

11-Beta-Hydroxysteroid dehydrogenase 11β-HSD are enzymes that exert a regulating action on the metabolism of cortisol before access to the receptors. The isoform 11-beta-hydroxysteroid dehydrogenase type 1 (11-β-HSD-1) is widely expressed in liver, adipose tissue, brain, lung and other glucocorticoid tissuerere1, while the isoform expression 2 (11-β- HSD-2) is limited to tissues that express the mineralo corticoid receptor, such as kidney, gut and placenta. The disease is due to a mutation of the CYP11B1 gene located on chromosome 8q21. Steroid 11-beta-hydroxylase deficiency causes decreased cortisol secretion and hypertension due to accumulation of glucocorticoid precursors and mineralocorticoids. The enzyme 11-β hydroxysteroid dehydrogenase 11-beta-hydroxysteroid dehydrogenase type 1 (11-β-HSD-1) plays a major role in blood pressure regulation. 11β-OHSD 2 assures the conversion of cortisol to cortisone. Excess cortisol is associated with numerous disorders, including diabetes, obesity, dyslipidemia, insulin resistance and hypertension.The administration of 11.beta.-HSD1 inhibitors decreases the level of cortisol and other 11.beta hydroxysteroids in target tissues, thereby reducing the effects of excessive amounts of cortisol and other 11-β-hydroxyesteroides. Thus 11-beta-HSD-1 is a potential target for therapy associated with numerous disorders that my be ameliorated by reduction of glucocorticoid action. Therefore, inhibition of 11-β-HSD-1 may be used to prevent, treat or control diseases mediated by abnormally high levels of cortisol and other 11-β-hydroxyesteroides as diabetes, obesity, hypertension or dyslipidemia. Inhibition activity of 11-β- HSD-1 in the brain [1] such as to lower cortisol levels may also be useful to treat or reduce anxiety, depression, cognitive impairment or age –related cognitive dysfunction [2].

The understanding of the mechanisms of action of these two enzymes led us to try to find the best inhibitors thus opening up new therapeutic perspectives. After optimization of both ligands and enzyme, we proceed to positioning of ligands into active site of the enzymes (4YYZ) and (3HFG) using (Molecular Docking) with MOE software (Molecular operating environment). The search for binding modes is generally constrained to a small specific region of the receptor called the active site [3]. We then recorded the best score, i.e. the one with the lowest energy corresponds to the best interactions between the ligand and the active site of the enzyme. Water molecules in enzyme cavities can sometimes be a fundamental element. They are able to ensure the relay between the receptor and the ligand and thus create networks of hydrogen bonds. So, we set ourselves the goal of studying our complexes by

solvation.

This study aimed at theoretically elucidating the inhibition activity of two enzymes 11-Beta-Hydroxysteroid dehydrogenase 11β-HSD (11β-HSD1 and 11β-HSD2 by a some derivatives of 1,2,4-triazoles using the two simulation methods, molecular dynamics and molecular docking.

The synthetics inhibitors chosen for (11β-HSD1 and 11β-HSD2 are given in (Fig 1). These results can help in the development of an effective therapeutic tool to prevent arterial hypertension 1 (PAH) treatment.

2. MATERIALS AND METHODS

2.1 Ligand structure retrieval

For our study we chose the ligands of the literature [4]. The structures L1 CID: 59255569 and L5 CID: 5231054 were retrieved in SDF format and were changed to PDB format using PyMol. (www.pubchem.com), but L2, L3 and L4 have been schematized with Chemdraw in order to resemble those of the reference [4]. (www.chemdraw.Com). In our previous work we have already studied the enzyme 11-Beta-Hydroxysteroid dehydrogenase (11β-HSD1 by other inhibitors taken in the same reference [5].

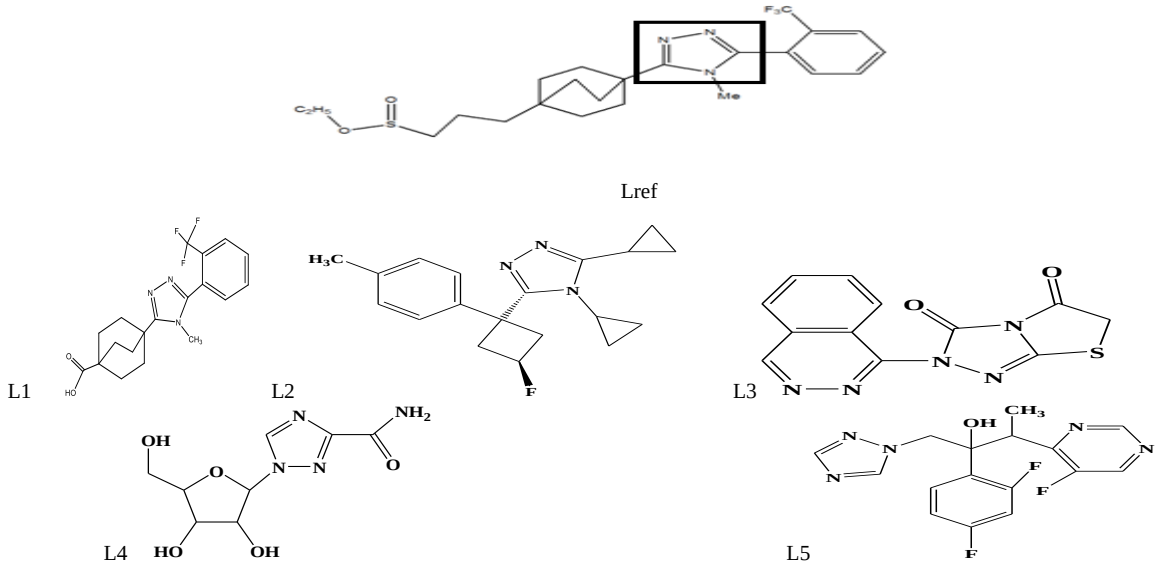

Fig.1. Substited derivatives of 1,2,4-triazoles [3]

2.2 Macromolecules structure retrieval

Download of 11-beta-hydroxysteroid dehydrogenase of type 1 (11β-HSD1) was done from PROTEIN DATA BANK (http://www.rcsb.org/pdb) (ID: 4YYZ) With three dimensional

structure obtained by X-ray diffraction (resolution 3.2 Å (Fig 2 and 3) and type 2 (11β-HSD2) was done from (NCBI reference sequence: NM_000196.3). Details related to the 11β-HSD1 is given in (Table 1). First, we tried to align the 11β-HSD1 enzyme from the code (4YYZ) and the 11β-HSD2 enzyme (NCBI reference sequence: NM_000196.3) [6] in order to generate a model for 11bHSD2 but it was difficult to achieve, so we based ourselves on ref [7] and we chose another '11β-HSD1 enzyme from the code: (3HFG) and it was doable.

11bHSD2 (NCBI reference sequence: NM_000196.3) [6] and the coordinates of the crystal structure of 11bHSD1 (PDB code: 3HFG) [7] were loaded into the MOE. The primary structures of 11β-HSD1 and 11β-HSD2 were aligned, carefully checked to avoid deletions or insertions in the preserved and corrected regions wherever necessary. A series of the 11bHSD2 model was constructed using a randomized procedure weighted by Boltzmann [8] combined with specialized logic for the treatment of sequence insertions and deletions [9]. Among the 6 models generated for 11bHSD2, the best was selected in our study for a complete energy minimization and a more thorough inspection. The energy of the enzyme was minimized and geometry was conducted using Hamiltonian AM1 implanted in MOE software and then isolation of the active site of the enzyme (target). The most stable geometry of each molecule structure (ligand) was minimized by the same method (AM1). Other chains and water molecules were removed using PyMol (Fig. 1). PyMol is a useful open source software tools to perform molecular graphics [10]. The MOE (Molecular operating environment), software allowed us to identify and present the residues that form the active site using the "Site Finder" module which includes a tool for the detection of the enzymatic cavity, as well as the most favorable site [11, 12].

Table 1. Details related to the 11β-HSD1

Proteins	**Methods**	**Resolution (Å)**	**R-Value Free**	**Residue Count**	**Co-crystallized ligands**
11β-HS1 **(4YYZ)**	X-ray diffraction	3.2	0.267	518	Query on 4JX

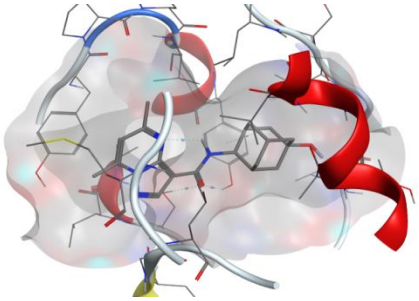

Fig.2. Simplified model of 11β-HSD1

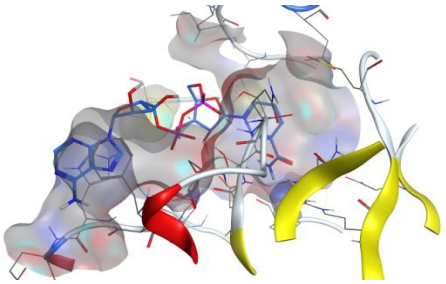

Fig.3. Simplified model of 11β-HSD2

2.3 Drug scan

Before calculating the interactions between the enzyme and the five compounds, it is necessary to evaluate the parameters allowing their validation as a drug [5]. The Lipinski rule also known as the five rules (RO5) gives us an information if this drug would be an orally active compounds in human.Molinspiration (http://www.molinspiration.com/cgi-bin/properties) was used for calculating Lipinski's properties. The rule was formulated by Christopher A. Lipinski in 1997; it is based on observation and informs us that the drugs administered orally are relatively smaller and moderatelylipophilic [13, 14]. According to (Table 2), the ligands satisfy the Lipinski rule. This additional information on other molecular properties confirms that these molecules are biologically active [5].

Table 2. Minimization energy of derivatives compounds of triazole (Kcal/mol) and solvent parameter.

Ligand	**Toxicity**	**Rsynth 100%**	**Weight g/mol**	**TPSA (Å²)**	**logp**	**logs**
Ligref	No	62.50%	469.57g/mol	76.22A(donor :0 ;acceptor : 4)	6.24	-7.19
Mol1	No	100%	379.38g/mol	68.01(donor :1 ;acceptor : 4)	4.85	-4.37
Mol2	No	73.91%	311.40g/mol	30.71(donor :0 ;acceptor : 5)	4.31	-3.46
Mol3	No	100%	285.29g/mol	78.76(donor :0 ;acceptor : 5)	1.42	-4.47
Mol4	No	100%	244.21g/mol	143.72(donor :4 ;acceptor : 7)	-2.92	0.47
Mol5	No	100%	349.32g/mol	76.72(donor :1 ;acceptor : 5)	2.75	-3.41
Mode	**Shape**	**Margin**	**Update Potentiel**	**Clash Cutoff**	**Wall Force**	**Verbose**
Droplet	Sphere	2.00	01.0	10.00	100.00	01.00

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

2.4 Molecular Dynamics (MD) Simulation

The best conformer of two 11β-hydroxysteroid dehydrogenase isozymes proteins with ligands was subjected to Molecular Dynamics Simulations MD was performed for both the complex using the MOE software [15]. MOE dynamics simulation uses the Nosé-Poincaré Andersen (NPA) equations of motion [16,17]. The coordinates were stored every 0.5ps to get an accurate view of molecular movement. In all simulations the van der Waals cut-out distance was set to 8Å. The interactions of the system's amino acids were defined using the NPA algorithm and MMFF94x force field. The default protocols and steps of the MD were used to optimize the system's equilibrium for 50 ps and the production run in 800 ps. We used MD simulation for each ligand-protein complex to evaluate the interactions' stability for each docking pose. Here, we have shown the detailed analysis of MD simulation results of only two compounds (L1, L2) with target 11β-HSD1 and 11β-HSD2 (Fig 4 and 5) because these compounds show better binding affinity for both receptors. In the end and according to the molecular dynamics simulation analysis among these 2 compounds the most active compounds were L1 and L2 in 11β-HSD1 proteins.

2.5 ADME Properties

ADME/T prediction Absorption, distribution, metabolism, excretion, and toxicity (ADMET) of the molecules are their pharmacokinetic properties and are needed to be evaluated to resolve their activity inside the body. The ADMET properties of the molecules were analyzed using admetSAR, an online ADMET prediction tool (http://lmmd.ecust.edu.cn:8000/) [18].

3 RESULTS AND DISCUSSION

3.1 Molecular Docking

As a means to resolve the enzyme-substrate interactions we have carried out molecular docking calculations in order to find the most stable conformation which corresponds to the lowest energy adopted by the complex formed. We have done the calculations by employing water as a solvent. (Table 3- 4) show that L2 and L1 both interact with the different amino acid presenting an H-acceptor strong kind of interaction with comparable distances of (2.99Å - 3.85Å) and 2.82Å consecutively. However, results show also that complex2 has the lowest energy (-8.34 Kcal/mol) and is more active than complex -1 (-7.86 Kcal/mol) contrarily with (11β-HSD2) the complexe-1- (-7.48 Kcal/mol) has the lowest energy and is more active than complexe-2 (-6.18 Kcal/mol)even at that time also L2 and L1 both interact with the different amino acid presenting an H-acceptor strong kind of interaction 2.82 Å and (2.99 Å

-3.85 Å) (Fig 4 and 5). One important point is also obtained from Table 1 that, The energy of (complexe-ref -5.67 Kcal/mol) for (11β-HSD1 is important in comparison with that obtained by the 5 ligands. contrarily with (11β-HSD2) The energy of (complexe- ref -9.98 Kcal/mol) is weak compared to those of the5 ligands. therefore, these ligands better inhibit the enzyme 11β-HSD1. Therefore, we can validate L2 subsisted derivatives of 1,2,4-triazole as a best inhibitor.

Table 3. Energy Balance of complexes formed by 5 derivatives of triazoles compounds (Kcal/mol)

Complexes	E(kcal/mol)	Rmsd-refine(Å)	E_conf	E_place	E_refine
11β-HSD1_LIG Ref	**-5.67**	**2.19**	**-14.70**	**-14.70**	**47.54**
11β-HSD1_LIG01	-7.86	-65.82	-48.32	-48.32	-4.81
11β-HSD1_LIG 02	-8.34	-32.79	-41.84	-41.84	-10.25
11β-HSD1_LIG 03	-6.84	-94.00	-105.53	-105.53	-15.16
11β-HSD1_LIG 04	-6.12	-107.19	-72.64	-72.64	-10.83
11β-HSD1_LIG 05	-6.67	-48.82	-61.79	-61.79	2.49
11β-HSD2_LIG Ref	**-9.98**	**2.11**	**68.43**	**-33.73**	**-7.94**
11β-HSD2_LIG01	-7.48	1.70	-70.82	-60.47	-8.50
11β-HSD2_LIG 02	-6.18	1.776	-23.10	7.14	14.10
11β-HSD2_LIG 03	-6.81	3.66	-89.34	-111.11	-4.39
11β-HSD2_LIG 04	-6.22	2.97	-104.77	-102.77	-4.13
11β-HSD2_LIG 05	-6.80	2.68	52.25	-32.88	-6.98

S: The final score; is the last step's score. rmsd_refine: The mean square deviation between the laying before refinement and after refinement poses. E_conf: Energy conformer. E_place: Score of the placement phase. E_scor1: Score of the first step of notation. E_refine: Score of the refinement step and the number of conformations generated by ligand. E_scor2: Score of the first step notation, number of poses: Number of conformations.

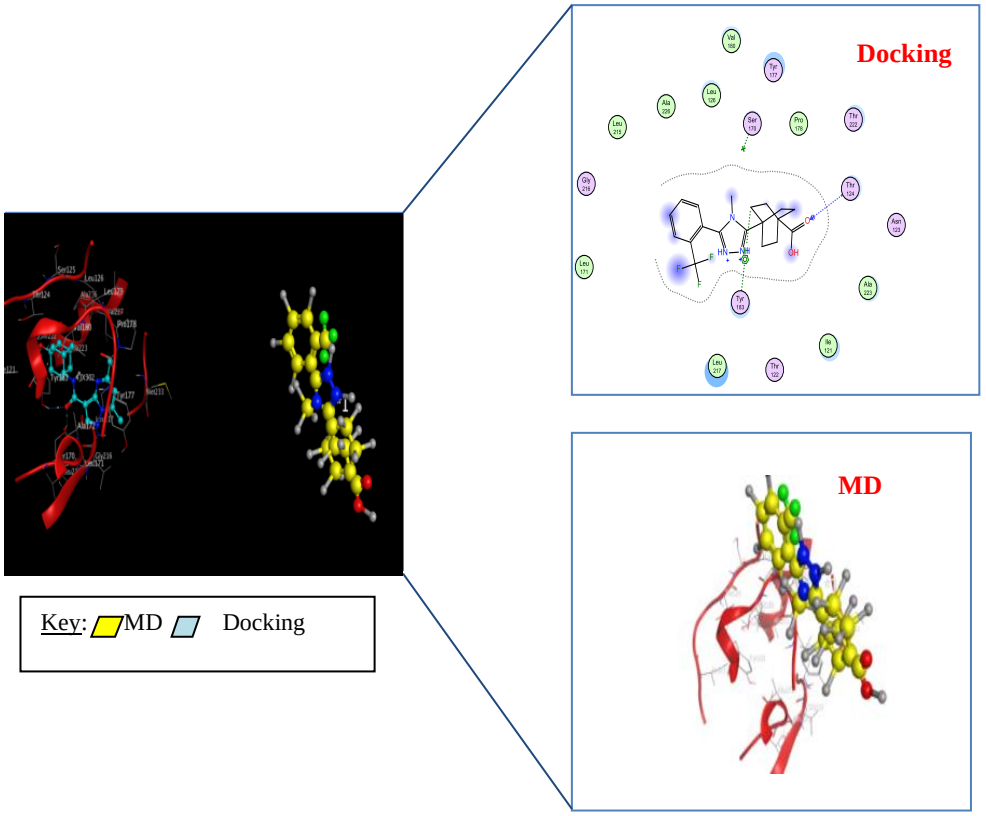

Fig.4. The compound -1, is docked well into the binding site of protein 1-beta-hydroxysteroid dehydrogenase of type 1, and has the highest dock score. There is also a clear difference between the docking pose and the final ligand pose after a molecular dynamics (MD) simulation of 800 ps.

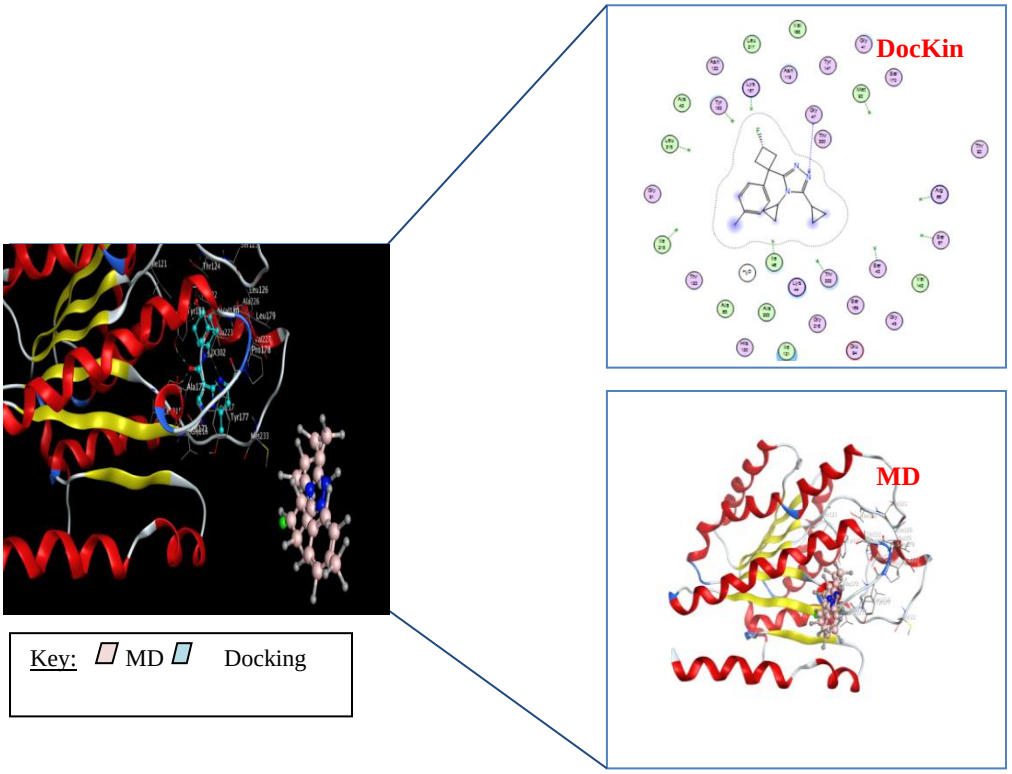

Fig.5. The compound -2, is docked well into the binding site of protein 1-beta-hydroxysteroid dehydrogenase of type 1, and has the highest dock score. There is also a clear difference between the docking pose and the final ligand pose after a molecular dynamics (MD) simulation of 800 ps

Table 4. Results Bonds between atoms of compounds and residues of active site into 11β-HSD1 and 11β-HSD2

Compounds	Atom of compound	Involved receptor atoms	Involved receptor residues	Type of interaction bond	Distance (Å)	Eenrgies (kcal/mol)
11β-HSD2_LIGRef	**N 14** **6-ring**	**O** **6-ring**	**HOH(0)** **PHE (282)**	**H-acceptor** **Pi-pi**	**3.42** **3.76**	**-0.7** **0.0**
11β-HSD2_LIG01	N3 13 5-ring	O O	HOH(0) HOH(0)	H-donor Pi-H	3.25 4.22	-3.7 -1.1
11β-HSD2_LIG 02	N14 14 N15 15 N14 14 N15 15	O OD2 OD2 OD2	ASP(274) ASP(274) ASP(274) ASP(274)	H-donor H-donor Ionic ionic	2.86 3.21 3.45 3.21	-9.7 -7.4 -2.1 -3.2
11β-HSD2_LIG 03	N12 12 N12 12 S16 16 N12 12 N12 12 5-ring	OD1 OD2 OD1 OD1 OD2 O	ASP(274) ASP(274) ASP(274) ASP(274) ASP(274) HOH(0)	H-donor H-donor H-donor Ionic Ionic Pi-H	3.25 3.68 3.35 3.25 3.68 4.73	-0.8 -12.5 -2.2 -3.0 -7.0 -0.8
11β-HSD2_LIG 04	N13 15 O9 11 O9 11 C3 3	O O O 5-ring	HOH(0) HOH(0) HOH(0)	H-donor H-acceptor H-acceptor H-Pi	2.65 3.10 2.87 4.00	-4.8 -3.2 -1.0 -1.4
11β-HSD2_LIG 05	N 30 5-ring	OG1 NE2	THR(252) HIS(253)	H-acceptor Pi-cation	2.78 3.76	-1.6 -1.7
11β-HSD1_LIGRef	**O** **48** **C** **60** **6-ring** **5ring**	**O** **6-ring** **CB** **6-ring**	**HOH (0)** **TYR(177)** **TYR(177)** **TYR(183)**	**H-acceptor** **H-Pi** **Pi-H** **PI-Pi**	**2.87** **3.87** **4.05** **3.33**	**-1.8** **-0.6** **-0.7** **-0.0**
11β-HSD1_LIG01	O25 25 C17 17	N 6-ring	THR(124) THR(183)	H-acceptor H-Pi	2.99 3.85	-3.6 -1.0
11β-HSD1_LIG 02	N14 14	O	HOH(0)	H-donor	2.82	-7.6
11β-HSD1_LIG 03	6-ring	OG	SER(170)	Pi-H	3.87	-0.8
11β-HSD1_LIG 04	O7 7	OG	SER(170)	H-acceptor	2.82	-0.6
11β-HSD1_LIG 05	N20 20	O	GLY(216)	H-donor	2.72	-4.2

In vitro, many studies were focused on the inhibitory effect of triazoles on key enzymes linked to arterial hypertension 1 (PAH), 11-beta-hydroxysteroid dehydrogenase of type 1 (11β-HSD1) and type 2 (11β-HSD2. Beck et al have identified that itraconazole is a stronger inhibitor of 11β-HSD2 (IC_{50} 139 ± 14 nM), its active metabolite hydroxyitraconazole (IC_{50} 223 ± 31 nM) and posaconazole (IC_{50} 460 ± 98 nM) [19]. Also Chapman *et al* had showed that 11β-HSD2 inhibition causes apparent mineralocorticoid excess and hypertension due to inappropriate glucocorticoid activation of renal MR [20]. Roberto *et al* have identified that diethylcarbamate is the most potent inhibitor of 11β-HSD2 (IC_{50} 6.3 microM), and suggest that Abietic acid inhibited both 11beta-HSD1 (IC_{50} 27 μM for reduction and 2.8 microM for oxidation) and 11beta-HSD2 (IC_{50} 12 microM) [21]. By that means the software

adapted MOE (Molecular operating environment), does not scout up any trace of the hydrophobic interactions between L2 (best inhibitor) subsisted derivatives of 1, 2, 4-triazoles and both the enzymes; what may be connected to the large size of this ligand and the high number of torsion angles.

3.2 Molecular Dynamics

Thermodynamic properties

Using the MD simulation approach, we have studied the evolution thermodynamic properties of the two complexes in NVT ensemble (Table 5).

Table 5. Thermodynamic properties calculated in reels units. Pressure Wp = Wp* ε/ σ^{-3} , Energy of configuration EC = EC* Nε, Translation Energy ET = ET* Nε and Enthalpy EH=EH* Nε

Stage	Method	EH	EC	ET	Wp	V
SP_1	NVT11β-HSD2_LIG01 NVT11β-HSD2_LIG02	0.02455±0.00550 0.52140±0.01524	32356.36±0.2451 42536.23±0.4152	2523.00±0.0214 5425.00±0.0142	110.2356±0.2251 54.230±0.4451	35423.00±0.5541 3423.00±0.6523
	NVT11β-HSD2_LIG01 NVT11β-HSD2_LIG02	-0.12450±0.0245 1.21450±0.24510	3025.326±0.0215 3203.236±0.1425	2543.00±0.0012 4523.00±0.0012	105.550±0.5542 85.365±0.5623	2054.23±0.0025 3425.30±0.2415
	NVT11β-HSD2_LIG01 NVT11β-HSD2_LIG02	2.23562±0.0256 2.1252±1.2560	2153.00±125420 52142.00±1.0250	5421.00±0.0145 2745.00±0.2451	55.236±0.4525 -155.236±0.4414	3243.00±0.555 2542.00±0.5562
SP_2	NVT11β-HSD2_LIG01 NVT11β-HSD2_LIG02	3.12540±1.5425 -2.2356±0.5485	41253.00±0.5122 2232.00±0.54215	15412.00±0.1458 3523.00±0.4152	104.552±0.4174 144.55 ± 0.542	3856.22±0.0125 3482.33±0.0215
	NVT11β-HSD2_LIG01 NVT11β-HSD2_LIG02	3.2542±0.5623 2.3256±0.4585	2523.00±1.4521 4526.00±0.5255	1423.00±0.0215 2426.00±0.0022	145.236±0.5662 -25.369±0.5425	6458.22±0.00236 4533.00±0.2351
	NVT11β-HSD2_LIG01 NVT11β-HSD2_LIG02	5.2563±0.24510 -4.2536±0.5632	2421.00±0.0015 3423.00±0.0256	1586.00±0.1444 14523.00±0.5424	-1045.66±0.5552 -55.2365±0.6532	3805.33±0.0245 3859.33±0.025

The results presented in table 5 revealed that compound L1 and compound L2 have high energy. The complex formed by L2 has a very important energy. In contrast to the complex formed by L2 their energies obtained are low. By against on pressure fluctuations are significant for the complex formed by L2 is of order 0.2251-0.6532 which explains the instability of the system by its strong therefore the movement rotational and vibration energy is important oscillation. In regard to variation in the average temperature of translation is fixed as at the outset in considering isochors-isotherms ensemble. Therefore, L2 is predicted to be the most interactive system. These results are in total agreement with the Docking prediction results (Table 1). A computational study of two top scoring lead compounds was performed for assessment of ADME properties and the obtained value is depicted in (Table 6).

3.3 In silico assessment of the ADME properties and drug likeness

A computational study of two top-scoring lead compounds was performed for the assessment

of ADME properties and the obtained value is depicted in (Table 6).

Table 6. ADME bioactivity properties for two top scoring lead compounds

Entry	ABS	TPSA (Å²)	n-ROTB	MW	MLog P	n-ON acceptors	n-OHNH donors	n violations	n rotb	Volume
Rule	-	-	-	<500	≤5	<10	<5	≤1	-	-
L2	High	30.72	4	311.40	3.15	3	0	0	4	289.27
L1	High	68.02	4	379.38	3.23	5	1	0	4	319.50

Ligands	GPCR Ligand	Ion Channel modulator	Kinase inihibitor	Nuclear receptor ligand	Protease inihibitor	Enzyme inhibitor
L2	**0.09**	-0.11	-0.15	0.10	-0.10	0.46
L1	**0.24**	-0.09	-0.27	0.41	-0.09	0.44

ABS: absorption, **TPSA**: topological polar surface area, **n-ROTB:** number of rotatable bonds**, MW**: molecular weight, **MLog*P*:** logarithm of partition coefficient of the compound between water and n-octanol: **n-OHNH donors:** number of hydrogen bonds donors, **n-ON acceptors:** number of hydrogen bond acceptors.

Many potential therapeutic agents fail to reach the clinic trials because of their unfavorable absorption, distribution, metabolism, and elimination (ADME) parameters; also it is not checking the drug-likeness. miLogP represents the octanol/water partition coefficient, TPSA is the molecular polar surface area, natoms is the number of atom of the molecule, nON and nOHNH are the number of hydrogen bond acceptors and hydrogen bond donors respectively, nviol is the number of violations of the Lipinsky Rule of Five [12], nrotb is the number of rotatable bonds, volume is the molecular volume, and MW is the molecular weight of the studied system. were calculated using Calculation of molecular properties and bioactivity score (https://www.molinspiration.com/cgi-bin/properties#) online property calculation. From all these parameters for the top scoring lead compounds. The results presented in table 5 revealed that compound L2 and compound L1 have high absorption. Also, the two compounds L2 and L1 comply with Lipinski's rule of 5, Veber's rule and Egan's rule. where log*P* values ranged between 3.15-3.23), MW range 311.40– 379.38 (<500), HBA range 3-5 (≤10) and HBD range 0-1 (<5) (Table 6), suggesting that these compounds would not be expected to cause problems with oral bioavailability and thus showing possible utility of both compounds for developing the compound with good drug like properties.

To study an explicit solvent molecule, it is necessary to solvate it, that is to say to immerse it entirely in a "solvent box"(Table.3).This method represents each molecule of water around solute as a given triatomic molecule, as shown schematically in (Fig 6). For that, we used molecular simulation to predict solvation (see table 2).

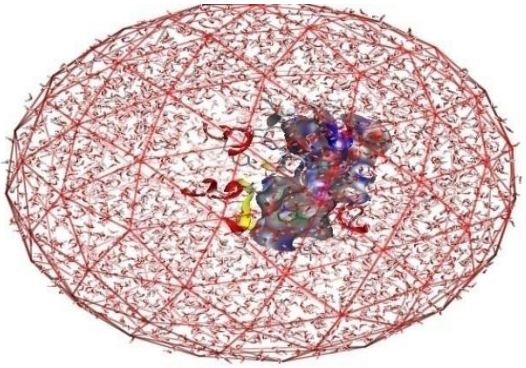

Fig.6. Solvation Ligand–Substrate in cube

When water is included, the best inhibition to the evolution of the pathology studied (Hypertension 1 (PAH) is provided. The use of solvation is premendial allows a relative stability of the different protein conformations, (Figures 4-5). In addition, the latter allows to estimate the free energy of binding of ligands to proteins. Precisely, atomic level descriptions of hydrophobicity and amphiphilicity.The presence of water is sometimes paramount to ensure a relay between the ligand and the active site [23].

4 CONCLUSION

In this investigation, the inhibitions of two 11β-hydroxysteroid dehydrogenase (11β-HSD) isozymes were theoretically examined by molecular docking analyses taking into account solvatation parameter MD simulations. Our calculations showed that the synthetic inhibitor- 2 of subsisted derivatives of 1,2,4-triazoles provides more optimized inhibition of 11-beta-hydroxysteroid dehydrogenase type 1 (11-β-HSD-1) for hypertension 1 (PAH) treatment. These interactions between 11-beta-hydroxysteroid dehydrogenase type 1 (11-β-HSD-1) and those inhibitors are undergoing different interactions between N-14 with oxygen receptor interaction H- donor of synthetic ones. However, the docking simulation results are optimized under dynamic conditions by MD simulations to prove the stability of the interaction between both proteins and each ligand. Although compounds L1 and L2 have binding affinity with 11-β-HSD-1 protein in the docking simulation, the ligand-protein interactions mentioned in docking simulation are almost stable in dynamic conditions. The solvation model involving the coordination of the solvent molecules with the interacting complex for 11-beta-hydroxysteroid dehydrogenase type 1 (11-β-HSD-1) shows a considerable decrease of the complex energy of these ligands compared with the energies for 11-beta-hydroxysteroid dehydrogenase type 2 (11-β-HSD-2) and there by an increase of the inhibition activity. We also propose further studies to develop L2 subsisted

derivatives of 1,2,4-triazole into a new drug.

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