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Molecular docking of 11β-HSD1 with (1,2,4-triazole derivatives) inhibitors in a solvated medium

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Research

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CONFLICTS OF INTEREST

There are no conflicts of interest for any of the authors.

ABSTRACT

Background: The scope of molecular modeling techniques is enormous, reflecting the spectrum of knowledge and scientific domains that may be involved. It can be valuable in the identification of therapeutic targets, typically protein receptors whose specific role in a pathology is characterized. It may then prove indispensable in the development of chemical inhibitors for this target.1, 2, 4 triazol derivatives are recommended in treatment of hypertension.
Methods: The study of the interaction of the enzyme 11β-HSD1 - derived from 1, 2, 4-triazol by molecular modeling and precisely the molecular docking in solvated and unsolvated medium leads to the most stable complex. This study is based on the comparison of the theoretical and experimental results of the literature.
Results: Molecules 1,2,4 triazol derivatives interact differently with blood pressure enzyme (11β-HSD1) and confirm primary studies concerning1,2,4-triazol derivativesare good inhibitors for high blood pressure.
Conclusion: 11β-HSD1) enzyme with by molecular modeling by using molecular docking to confirm the experimental studies of 11β-HSD1 inhibitors reduce Medium.

Keywords: Enzyme 11β-HSD1, molecular docking, solvation

Introduction

Hypertension is the most important risk factor associated with stroke and heart disease. We talk about high blood pressure when blood pressure is high in the arteries, so the heart makes more effort to pump blood into the blood vessels [1].

Theoretical methods, such as molecular modeling [2], now make it possible to study the interaction between enzymatic and biologically active molecules. Water plays a very important role in the biomolecular structure, so it is essential to represent the solvent around the solutes in the molecular modeling studies.

The explicit solvation method represents the solvent in a microscopic manner. In this case, a solvation cage is generated around the molecule. Quite simply, a number of solvent molecules (water) corresponding to its density are added randomly. A box or sphere of a defined size is created around the molecule that is filled with water molecules [3]. Many molecular docking software has been used in solvated media [4] such as Chemira, Hex, MolegroVertualDocker, and MOE (Molecular Operating Environment) soft-

ware [4]. For our work we use the software MOE

Preparation of protein and ligands
1-Preparation of protein

We downloaded our hypertension protein from the database "protein data bank (www.rcsb.org/pdb)" 11β-HSD1 (code: 4yyz) [5].
The enzyme was prepared for molecular docking by adding all the hydrogen atoms using standard procedures. The heteroatoms of co-crystallization were suppressed.

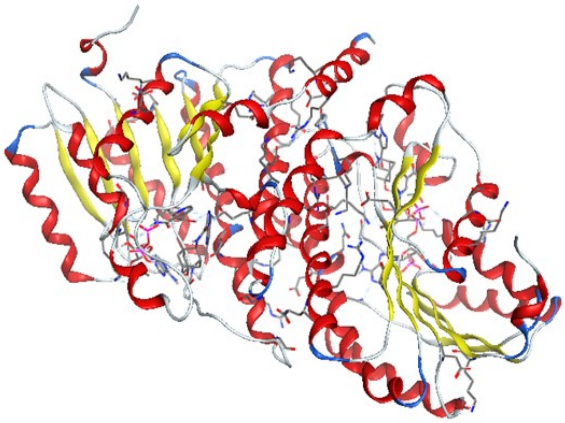


Fig1: 11β-HSD1 enzyme:atom number equal 3960 atoms

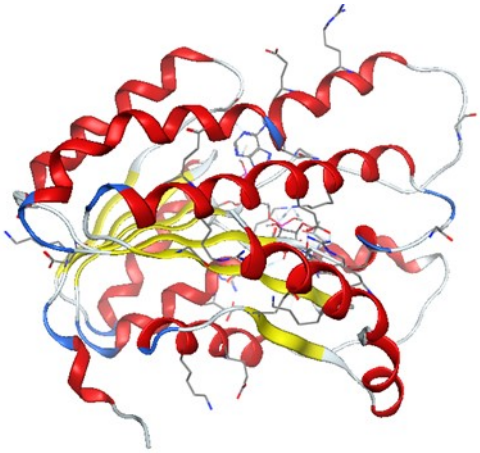


Fig 2:11β-HSD1 Enzyme simplified: atom number equal to188 atoms

Minimization of the energy of the enzyme simplify equal to 3.928kcal / mol.
The preparation of the enzyme is done by creating the active site and isolating it to do the molecular docking in a well-designated active site.

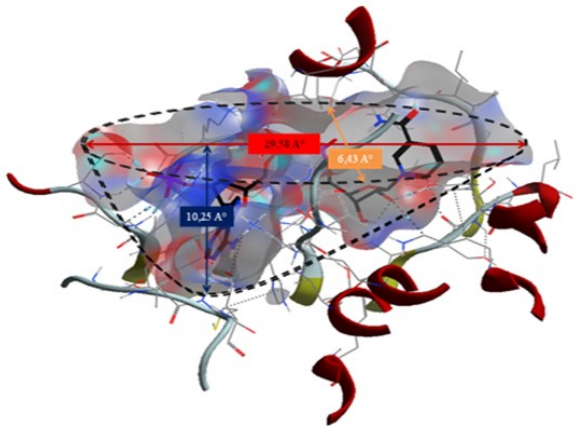


Fig3: active site size

2-Prepartion of ligands

The 1, 2, 4-triazole molecule have been downloaded from the PubChemdatabase (www.pubchem.com). For the 1,2,4-triazole derivatives, the 1,2,4-triazole skeleton was retained and the side chain was modified

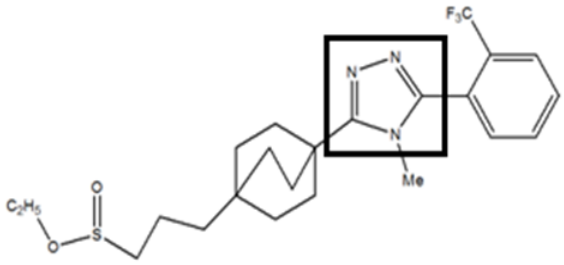


Fig4: 1, 2, 4-triazole

Lipinski Rule

Before calculating the interactions between the enzyme and the four compounds, it is necessary to evaluate the parameters allowing their validation as a drug.

The Lipinski rule also known as the five rule (RO5) is a basic rule for evaluating or determining whether a chemical compound possesses pharmacological or biological activity. 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 [6,7].

Table1:Lipinski rule of inhibitors of 11b-HSD1

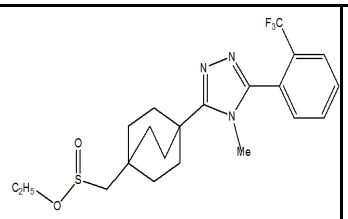
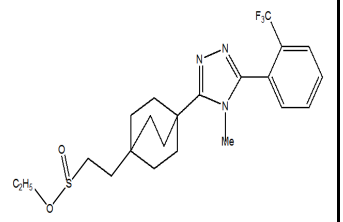
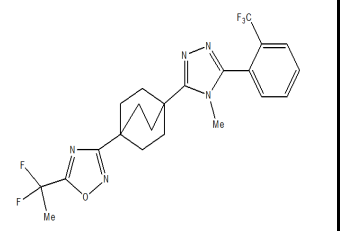
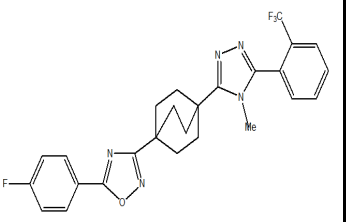
	Toxic: no Weight:441.52g/mol Logp:5.46 Logs:-5.54 Groupe d'hydrogene : Donneur :0 ; Accepteur :4
	Toxic: no Weight:455.54g/mol Logp:5.85 Logs:-6.68 Groupe d'hydrogene : Donneur : 0 ; Accepteur :4
	Toxic: no Weight:467.44g/mol Logp:6.52 Logs:-6.27 Groupe d'hydrogene : Donneur : 0 ; Accepteur : 4
	Toxic: no Weight:497.50g/mol Logp:6.90 Logs:-8.42 Groupe d'hydrogene : Donneur : 0 ; Accepteur : 4

Table2: Energy optimization of molecules

molécules	Energies (kcal/mol)
Molécule01	-1851.97
Molécule02	-2133.77
Molécule03	-1933.89
Molécule04	-2560.45

After the preparation of our enzyme and the four inhibitors, the examination of the enzymatic cavity and the calculation of the distances between the inhibitors and the side chains of the amino acids constituting the active site and the calculated energies is done using Of MOE molecular docking program.

The set of simulations that will be presented in this work was done using a solvent model explicitly represented. To study an explicit solvent molecule, it is necessary to solvate it, that is to say to immerse it entirely in a "solvent box". This method represents each molecule of water around solute as a given triatomic molecule, as shown schematically in Fig5.

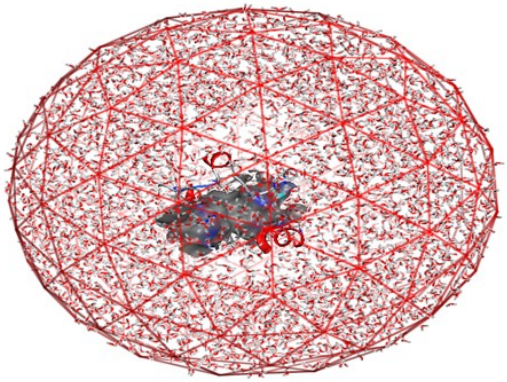


Fig 5: formation of a solvent sphere

A sphere (shape) of a defined dimension is created around the complex that is filled with water molecules (solvent).

Table 3: Solventparameter

Mode	Droplet
shape	Sphere
margin	2.00
solvent	Water
delete	far
salt	"
center	0
align	0
UpdatePotential	1
ClashCutoff	10.00
wallForce	100.00
add_H	1
verbose	1

The best placement of the ligand in the active site of the enzyme was chosen according to the best score.

The results of the interaction energies obtained by the MOE software are in the form ΔG (free energy), the latter being correlated with inhibitor constant Ki of the same complex according to the following formula [9-10]:

Constant of inhibition Ki is given in the following relation:

$\Delta G = -RT \ln Ki$
With R: constant gas (1.937cal .mol^{-1}k^{-1}),

Ic50 values are determined experimentally in the literature [11].

Table 4: Positions of L4 Ligand

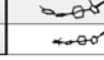
	mol	rseq	mseq	S	rmsd_refine	E_conf	E_place	E_score1	E_refine	E_score2
1		1	1	-11.7119	0.8803	110.3024	-115.4555	-14.0198	-15.4875	-11.7119
2		1	1	-11.5698	2.5317	106.5940	-45.4826	-12.9866	-20.8902	-11.5698
3		1	1	-11.0829	1.1248	99.6140	-88.2702	-13.9216	-12.1789	-11.0829
4		1	1	-10.8060	1.3991	110.3295	-121.5264	-13.1389	-11.8219	-10.8060
5		1	1	-10.5635	1.2256	113.1086	-73.1899	-13.3215	-6.0819	-10.5635
6		1	1	-8.2359	1.3727	114.1966	-78.0917	-14.2648	14.6465	-8.2359
7		1	1	-8.2023	1.3777	120.0791	-40.1224	-13.8718	19.1371	-8.2023
8		1	1	-5.2369	1.3517	115.8709	-70.4597	-13.0380	43.4727	-5.2369
9		1	1	-4.8620	1.1156	120.8904	-1.9548	-13.5825	59.2194	-4.8620

Table 5: The energy of complexes and Biochemical properties of the 11b-HSD1 inhibitors

complexe	Rmsd-refine(A°)	Ic50(nM)	ln Ic50	ki	ΔG(kcal/mol)
11β-HSD1_MOL1	1.43	31.2	1.49	$101.62.10^{-2}$	-9.31
11β-HSD1_MOL2	1.76	7.5	0.87	$101.81.10^{-2}$	-10.46
11β-HSD1_MOL3	0.73	30.4	1.48	$101.72.10^{-2}$	-9.90
11β-HSD1_MOL4	0.88	3.0	0.47	$102.72.10^{-2}$	-11.71

From the results obtained, it can be seen that for the 11β-HSD1_MOL4 complex at energy equal to -11.71 Kcal / Mol with a weak RMSD it is the most stable complex. It is concluded that MOL4 is probably the best inhibitor for the enzyme.

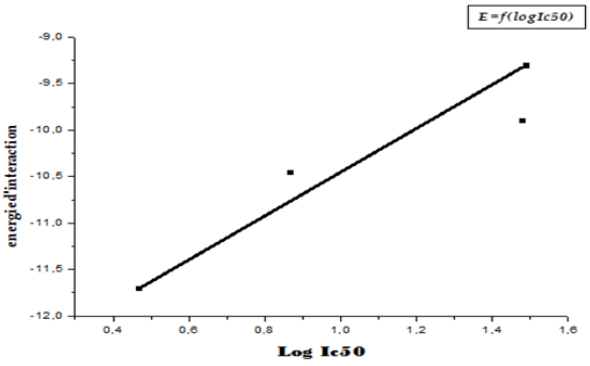


FIG34: correction between the biological activity log IC50 of the ligands, and theire energies of interactions with the enzyme11β-HSD1.

The linear regression analysis performed between the interaction energies and IC50 (log IC50) provides a scatter diagram with a correlation coefficient equal to 0.693. This value indicates that the two variables are highly correlated and thus demonstrate the high performance of the MOE program.

From the results obtained, it can be seen that the 11β-HSD1_MOL4 complex with an energy equal to -11.71 Kcal / Mol with an RMSD equal to 0.88 (Å) is the most stable complex. It is concluded that L4 is probably the best inhibitor for the enzyme

The results of the molecular docking of the four complexes have an RMSD value of less than 2Å. The RMSD between 0Å and 2Åshe is considered low and between 2Å and 4Å is assumed to be average. RMSD greater than 4 Å is strong. The prediction of the ligand is acceptable if the value does not exceed 2 Å [12].

From the results obtained, the interactions formed between our ligands and the residues of the active site of the enzyme 11β-HSD1 are between 2.65 Å, and 4.31 Å.

Interactions between 2.5 Å and 3.1 Å are considered strong and those between 3.1 Å and 3.55 Å are assumed to be average. Interactions greater than 3.55 Å are weak or absent [13].

Following the results obtained, the ligand MOL4 forms strong interactions with the active site of the enzyme (11β-HSD1) and thus a better complementarity, it is concluded that the ligand MOL4 is probably the best inhibitor for enzyme (11β-HSD1)

Table 6: Table of interactions distances enzymes_ligand

molecule	Ligand	Receptor	Interaction	Distance (Å)	E (kcal/mol)
Mol1	O 45	NH2 ARG 66	(A) H-acceptor	2.95	-7.8
Mol2	O 43	N ARG 66	(A) H-acceptor	2.95	-7.8
	O 43	NE ARG 66	(A) H-acceptor	3.36	-1.2
	O 43	NH2 ARG 66	(A) H-acceptor	3.34	-1.2
	5-ring	N ILE 46	(A) pi-H	4.31	-0.6
Mol3	F 28	NH2 ARG 66	(A) H-acceptor	2.65	-1.0
Mol4	N 9	CA GLY 45	(A) H-acceptor	3.30	-1.0
	N 22	N ILE 121	(A) H-acceptor	3.61	-0.6
	F 32	N MET 93	(A) H-acceptor	2.82	-1.0

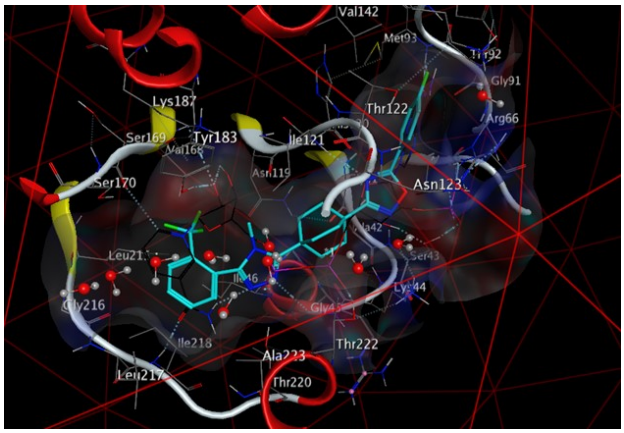


Fig 6: the interactions 11β-HSD1-ligand 4 in the cavity (3D)

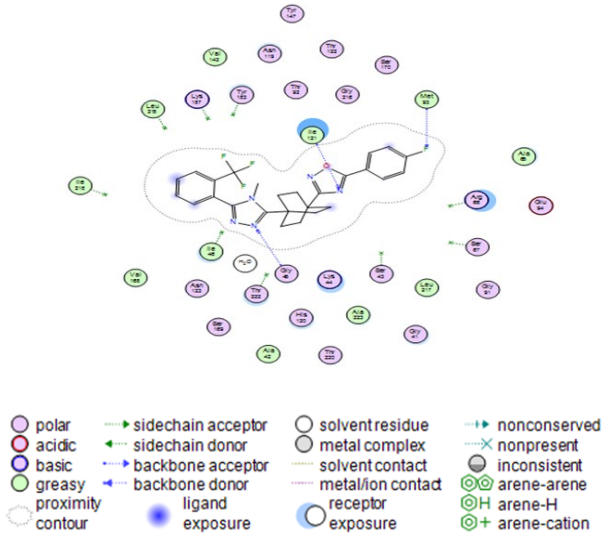
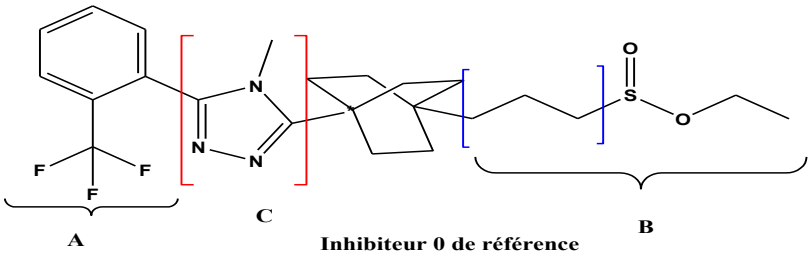
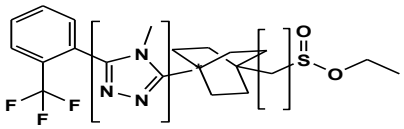


Fig 7: H_bond interactions of E-L4 complex (2D)

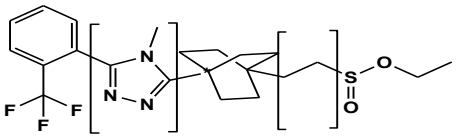
The formation of a stable complex depends on the binding of the inhibitor to the active site. Fig 6 presented above shows that the ligand MOL4 forms in the enzymatic cavity formed by the residues of the active site, which means that there are interactions which stabilize the complex and then a better fixation of this inhibitor at the level of the cavity of the enzyme.



Inhibiteur 0 de référence

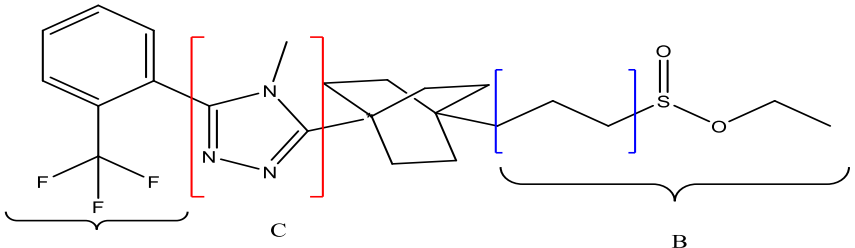


inhibiteur 1



Inhibiteur 3

The results of molecular docking reveal that the energy of the complex formed by the inhibitor 2 is less than that of the complex formed by the inhibitor1; the complex inhibitor 2 is the most stable. It is concluded that the length of the chain (number of -CH2) increases the stability of the complex.



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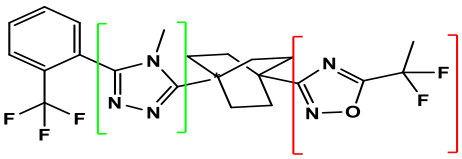

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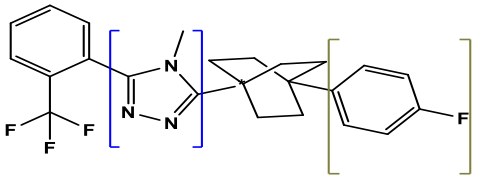
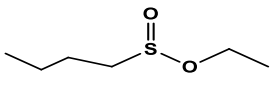


Inhibiteur 4 B



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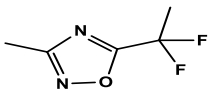

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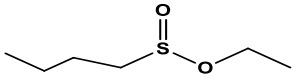

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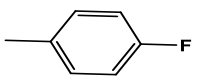

III

In the second step, the side chain B has been replaced by other groups:

⇒ The substituent I by the substituent II,
⇒ The substituent I by the substituent III

According to molecular docking calculations, the complex formed with inhibitor 4 is more stable than the complex formed with inhibitor 2.

CONCLUSION:

In order to determine 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.

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.

The results of molecular docking show that the four compounds exhibit inhibitory activity, but the MO L4 inhibitor is the most stable because it has the lowest energy and the lowest IC50 inhibitory concentration according to the literature [11]. Therefore, theoretical calculations by molecular docking have confirmed the experimental results [11]. In conclusion the MOL4 inhibitor is probably the best inhibitor of our enzyme.

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