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Study of the interaction of the enzyme "mineralocorticoid receptor (MR)" and derivatives spironolactone by molecular docking in solvated medium

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ABSTRACT

Hypertension is a serious complication that can cause infarctions, stroke [ACV] ... our work is based on the study of spironolactone and its derivatives interaction with the enzyme minéralocorticoïde (MR) by molecular modeling precisely docking using two different software. Our various calculations are performed in medium solvated and non solvated.

Keywords: molecular docking; hypertension; spironolactone; solvent (H_2O)

INTRODUCTION

Spironolactone belongs to the class of medicines called diuretics (water pills increase the excretion of urine). It is used to treat edema (water retention in the body tissues) which can be caused by congestive heart failure, livercirrhosis, and nephrotic syndrome. It is also used in the treatment of high blood pressure and a primary hyper-aldosteronism (the condition resulting from an over production of aldosterone from the adrenal glands) which it serves also to the diagnosis [1].

Our work is to study the activity of some molecules of the family of spironolactone by a theoretical method such as molecular modeling, which provides for example the structure of the given transition state of a chemical reaction, which is difficult, impossible, for experimental chemistry [2].

Water plays a very important role in the structure of biomolecular structures and therefore it appears essential to represent the solvent around the solutes in molecular modeling studies [3], specifically the molecular docking, which is a method that gives direction preferably of a molecule to a second when they are linked to from a stable complex [4].

We took as enzyme miniracorticoid receptor (MR) (code: 3VHU).

The mineralocorticoid receptor (MR) is a protein of the superfamily of nuclear receptors, steroid receptor family, binder aldosterone, whichis the main mineralocorticoid hormone regulating inter alia hydro-sodio balance of organisms through the expression of specific genes [5].

The MR also has a role in the central nervous system that is poorly understood. It is expressed in the hippocampus

and involved in the regulation of different cellular mechanisms (apoptosis, etc.), and physiological (regulation of blood pressure and appetite for salt, etc.) [6].

MATERIALS AND METHODS

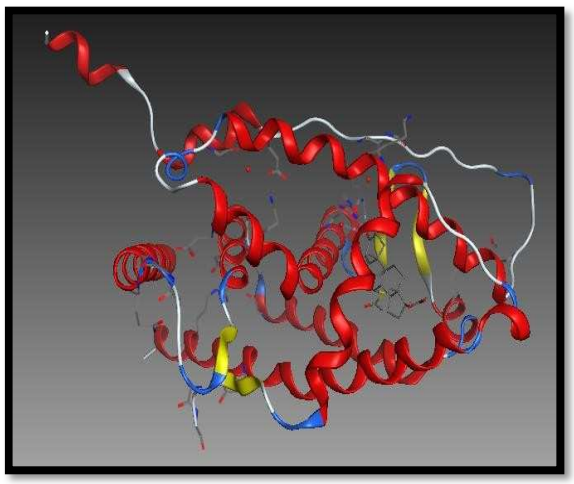

Figure 1: Enzyme "3VHU"

We downloaded our protein of hypertension from the Data Bank "protein data bank (www.rcsb.org/pdb)" miniracorticoid receptor (code: 3VHU).

The protein was prepared for molecular docking by adding all the hydrogen atoms using standard procedures. The molecules of water and other co-crystallization hetero atoms have been removed; the binding energy was observed for each ligand-protein, using the MOE software (Modeling Operating environment) [7], and UCSF Chimera1.8.1software [8].

The PubChem data base (www.pubchem.com) allows the download of structures from a variety of vendors as SDF files. We downloaded the Spironolocatone structure (CID: 5833), groups or the substituent were changed by keeping the skeleton of the main structure.

Table 1: Properties Spironolocatone

Toxic	No
Weight	416.58 g/mol
Log p	4.85
Hydrogen donor group	0
Hydrogen acceptor moiety	3

The Lipinski's rule also known as the rule of five (RO5) is a basic rule for estimating or determining whether a chemical compound has a certain pharmacological or biological activity. The rule was formulated by Christopher A. Lipinski in 1997, based on the observation that medicines administered orally are relatively small and moderately lipophilic [9.10].

This additional information about other molecular properties confirms that these biologically active molecules whose inhibitory effect is to be verified experimentally.

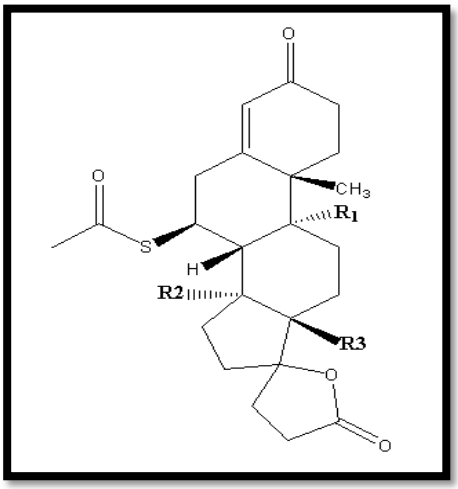

Figure 2: spironolactone structure

Table 2: Prepared ligands

R / molecules	R1	R2	R3
L1	─OH	─H	─CH3
L2	─H	─OH	─CH3
L3	─OH	─OH	─CH3
L4	─OH	─OH	─OH
L5	─OH	─OH	─Cl

The energy optimization of ligands has been achieved with the Hyperchem software [11]

Molecular docking using the Software MOE:

1- Medium unsolvated

Table 3: The score of the energy complex

Complexes	E (kcal/mol)	RMSD (Å)
E-L1	-11.37	0.93
E-L2	-10.83	1.04
E-L3	-11.29	1.39
E-L4	-11.71	1.67
E-L5	-11.18	1.32

Note that for E-L4 complex has energy equal to -11.71 kcal / mol, this is the most stable complex. It concluded that L4 is probably the best inhibitor for the enzyme. More RMSD is low so our complex was more stable.

The RMSD between 0 Å and 2 Å is considered low, and between 2 Å and 4 Å is supposed to mean. The above 4 Å RMSD is strong. The RMSD of our ligands is between 0 and 2, predicting the ligand is acceptable if the value does not exceed 2 Å [12].

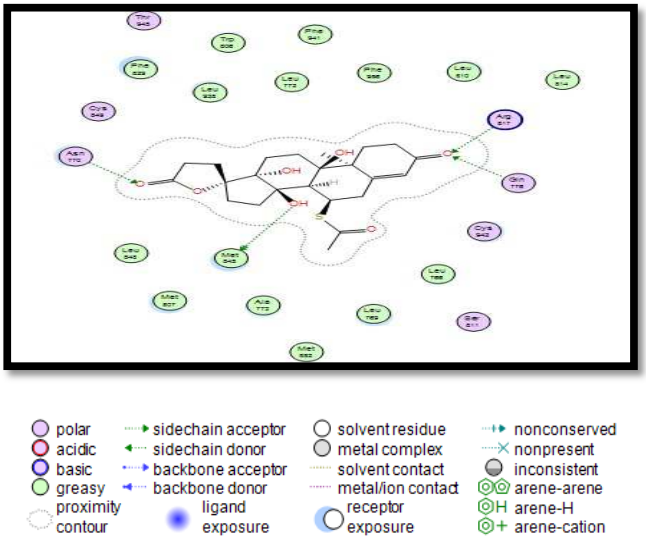

Figure 3: H-bond interactions of the E-L4 complex Table 4: H-bond interactions of the E-L4 complex

Ligand		Receptor			Interaction		Distance(Å)	E (kcal/mol)
O	29	SD	MET	845	(A)	H-donor	3.27	-1.7
O	3	ND2	ASN	770	(A)	H-acceptor	3.27	-1.2
O	4	NE2	GLN	776	(A)	H-acceptor	3.33	-1.0
O	4	NH2	ARG	817	(A)	H-acceptor	2.80	-3.7

The formation of stable complex depends on the binding of the inhibitor in the active site.

Figure 3 presented above show that ligand L4 take a form in the enzymatic cavity formed by the active site residues, which means that there are interactions that stabilize the complex and subsequently, better fixation of this inhibitor at active site.

Interactions between 2.5 Å and 3.1 Å are considered strong and those between 3.1 Å and 3.55 Å are assumed averages. Greater interactions to 3.55 Å are weak or absent [13].

2- Medium solvated:

Creating a box of a size defined around the complex which is filled with water molecules. We launch a calculating molecular docking, and finally made a comparative study of the results obtained in solvated and unsolvated medium.

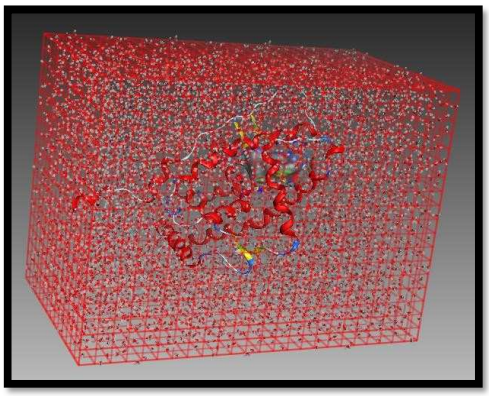

Figure 4: The box of solvent

Table5: The score of the energy complex

complexes	E (kcal/mol)	RMSD(Å)
E-L1	-13.31	1.40
E-L2	-13.57	1.11
E-L3	-13.37	1.02
E-L4	-13.69	1.04
E-L5	-13.28	1.68

From the table we notice that the energy of complexation is lower than in unsolvated environment. The solvent effect increases the complexes stability.

Table 6: H-bond interactions of the E-L4 complex

Ligand		Receptor			Interaction		Distance(A°)	E (kcal/mol)
O	29	SD	MET	845	(A)	H-donor	3.27	-1.7
O	3	ND2	ASN	770	(A)	H-acceptor	3.27	-1.2
O	4	NE2	GLN	776	(A)	H-acceptor	3.37	-0.8
O	4	NH2	ARG	817	(A)	H-acceptor	2.81	-2.9

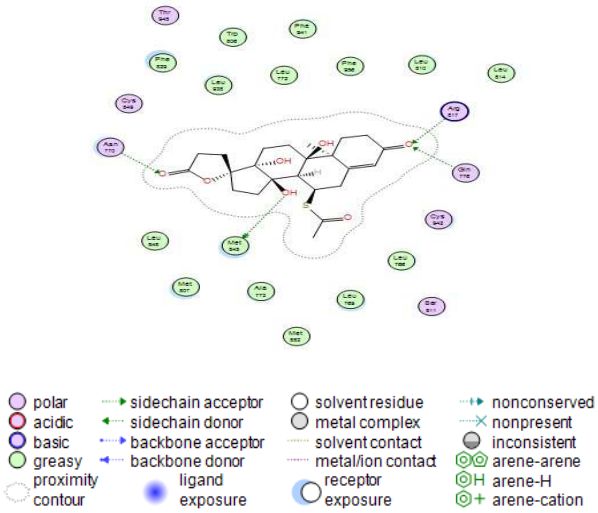

Figure 5: H-bond interactions of complex E-L4

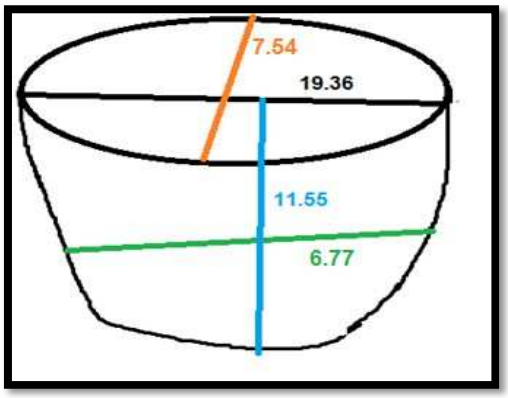

Figure 6: The size of active site of the enzyme

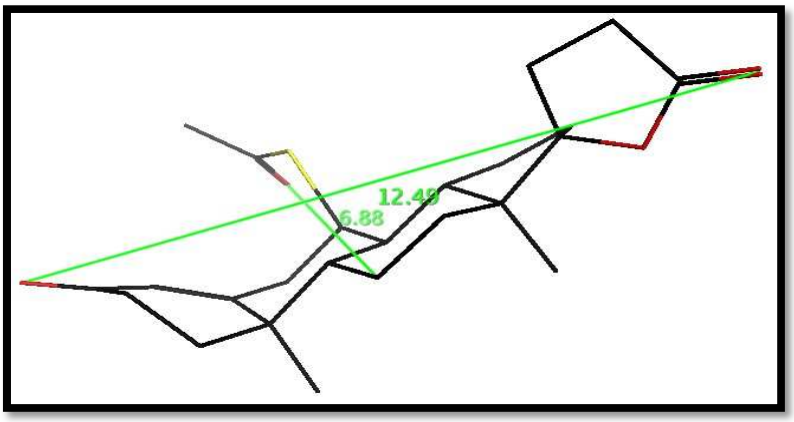

Figure 7: The size of spironolactone ligand

With solvent or without solvent the ligand L4 has the smallest energy. We concluded that this is probably the best inhibitor.

L4 Energy with solvent < energy L4 the solvent. It is concluded that the solvent stabilizing ligand L4, Note that we can discuss complementarity by increasing or decreasing the size of interval of active site pocket [14, 15], in our case, width of 19.36 Å and 11.56 Å for depth.

The molecular docking using Chimera software.

1- Medium solvated

After preparation of the enzyme, was placed the enzyme and the ligand in a box of known parameters and starts the molecular docking.

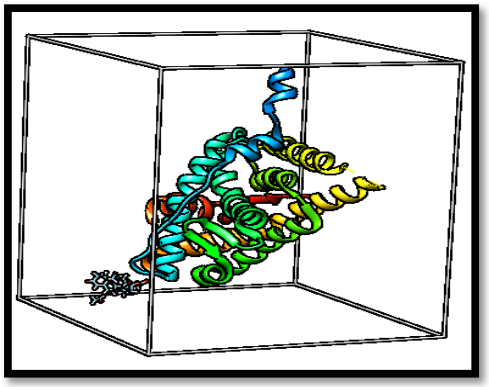

Figure 8: Box of complex

Table 7: The score of the energy complex

complexes	**E (kcal/mol)**
E-L1	-6.6
E-L2	-7.9
E-L3	-7.4
E-L4	-8.0
E-L5	-7.0

In light of the results obtained (Table 7), the scores are energies of interaction between bound and unbound atoms and the energy of interaction between receptor and ligand. In view of these results, we notice that E- L4 complex has energy equal to -8.0 kcal / mol is the best for inhibition.

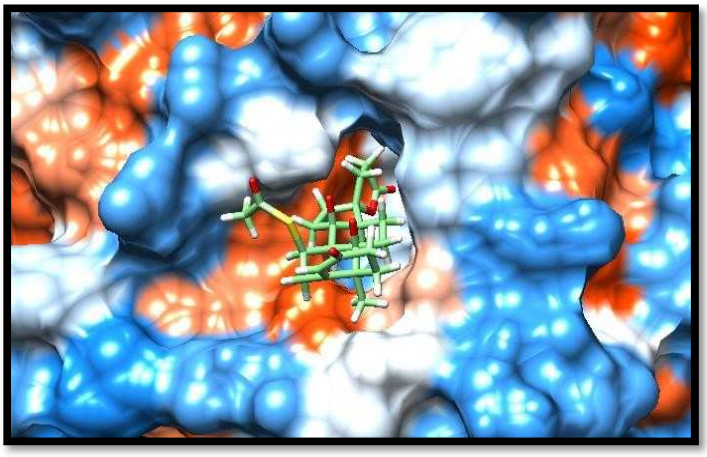

Figure 9: L4 ligand in the active site

2- Medium solvate:

To study an explicit solvent molecule, it is necessary to solvate that is to say to plunge fully into a "solvent box". This solvent box, each water molecule is shown around a given solute in the form of triatomic molecule, such as schematically shown in Figure 10.

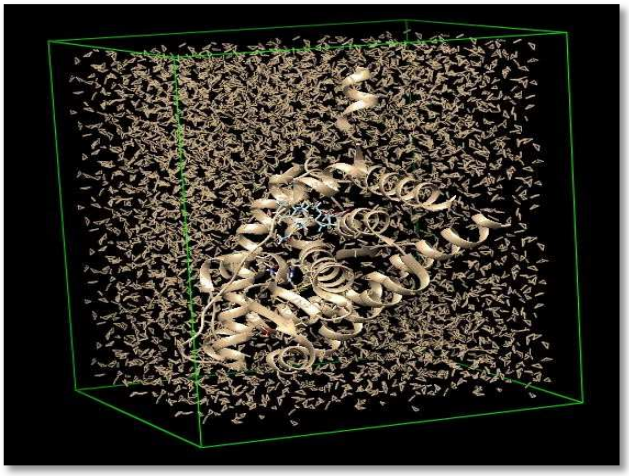

Figure 10: Complex in a solvent box (water)

Table 8: The score of the energy complex

complexes	E (kcal/mol)
E-L1	-11.0
E-L2	-8.0
E-L3	-8.0
E-L4	-12.3
E-L5	-12.1

According to the result, we notice that the energy of the complexes of complexations decreases when water is added, so it is more stable. E-L4 has the lowest energy therefore the most stable complex. The ligand L4 is the most effective inhibitor for this enzyme.

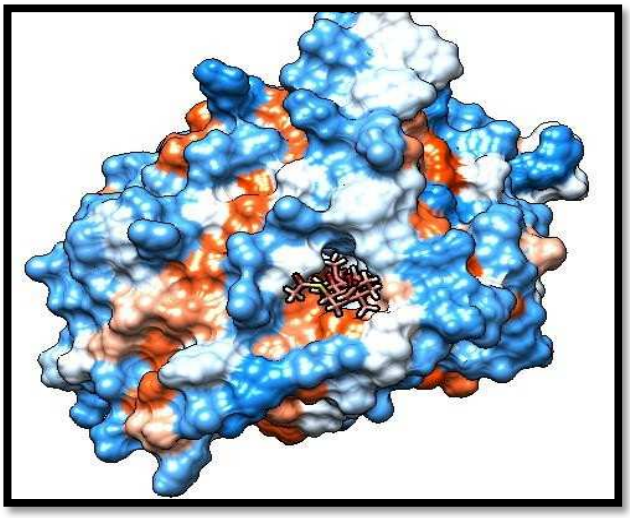

Figure 11: Ligand in the active site in solvated medium

CONCLUSION

In order to determine the enzyme-substrate interactions we performed molecular docking calculations to find the most stable conformation which corresponds to the lowest energy adopted by the complex formed.

The results obtained using two molecular docking programs confirm that the molecule L4 is probably the best of our enzyme inhibitor.

Both programs have generally comparable results. Indeed, in the study of the inhibition of 3HVU by the five known ligands, both programs highlight the same compound L4 as the better inhibitor of the enzyme.

In the explicit solvation or the presence of water, energies obtained are lower than in non solvated medium, so the addition of water increases the interactions between ligand and amino acids of the active site, the effect of solvent (water) is to stabilize the complexes, and to help inhibitors for decreases biological activity of the hypertension enzyme.

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