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MOLECULAR DOCKING FOR ANTICOAGULANT ACTIVITY EVALUATION OF BIS-PHENOLIC LIGAND

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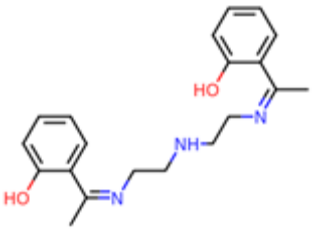
Abstract

The aim of this study was performed to assess *in silico* inhibition effect of the ligand 2-[(1*E*)-*N*-{2-[(2-{(*Z*)-[1-(2-hydroxyphenyl) ethylidene] amino}ethyl) amino]ethyl}ethanimidoyl] phenol on coagulation factor VIIa and IXa. Results indicate the moderate effect of this ligand.

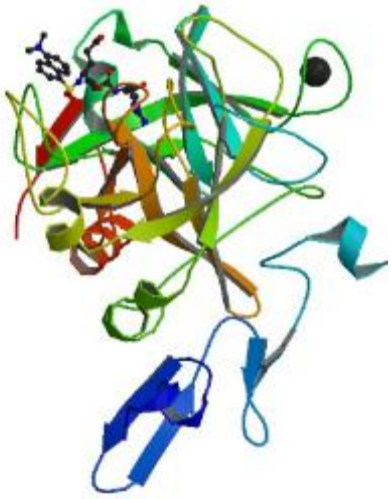
Keyword: coagulation, docking, anticoagulant

Introduction

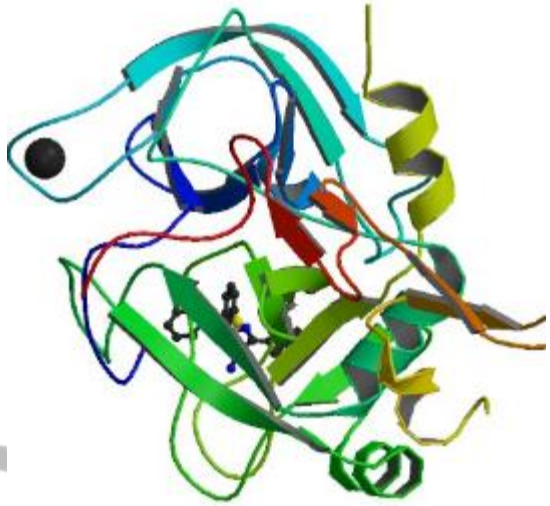
Cardiovascular disease is an important cause of death in the world (1). Blood clotting in the arteries is the principle origin of this disease, causing strokes and heart attacks (2). Clotting factors are mainly formed by the liver, secreted in inactive forms (3). The coagulation cascade composed of two pathways; extrinsic and intrinsic (4) and it is a finely tuned system that, along with cellular elements promotes hemostasis. In this study, the ligand 2-[(1*E*)-*N*-{2-[(2-{(*Z*)-[1-(2-hydroxyphenyl) ethylidene] amino}ethyl) amino]ethyl}ethanimidoyl] phenol was selected for to evaluate inhibition effect of coagulation factor VIIa and IXa by molecular docking.



Scheme.1. Schiff base ligand structure



Crystal structure of active site-inhibited human coagulation factor VIIA



Selective Benzothiophine Inhibitors of Factor IXa

Scheme.2. Enzymes structures

Methods

Molecular docking was carried out using the software package MOE (Molecular Operating Environment). **MOE (The Molecular Operating Environment) Version 2005.06, Chemical Computing Group Inc. Available from: http://www.chemcomp.com.** Energy minimization algorithm of MOE tool was employed for protein minimizing energy with Force Field: Amber 99.

Results and Discussion

Complexes energy minimization

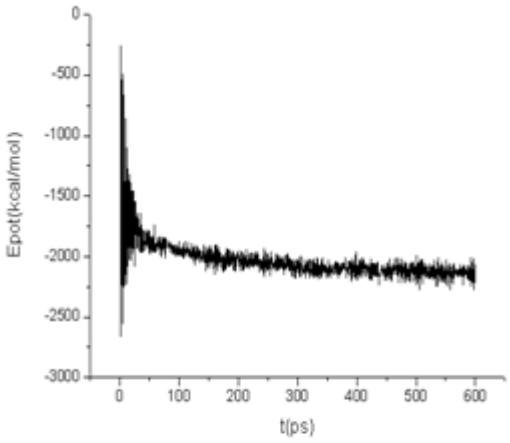
Minimization is necessary to bring the energy state of the molecule as low as possible. In our study, we used force field Amber 99.

Tableau 1 : *The steric energy of complexes*

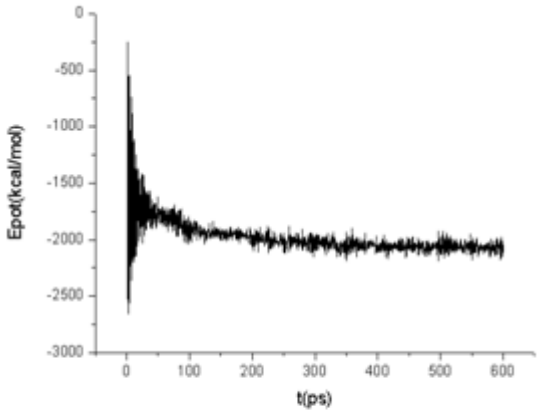
E.Stéric (KJ/mole)	**E.** éle.	**E.** Tor	**E.**VDW.	**E**. Str.	**E**. Ang.	**E.** Oop.	**Energy TOTAL**
Complex_1	-10550.4	2686.813	-381.227	398.179	846.439	47.398	-6952.81
Complex_2	-5813.19	2499.111	-1043.56	181.586	649.089	42.784	-3484.19

Molecular dynamics of complexes

When the complexes are formed, we performed the geometry optimization and a molecular dynamics calculation to look for the most stable conformation.



Complexe_ (1cvw)



Complex_2 (3lc5)

Molecular Docking

Once the complex (enzyme-inhibitor) is formed, it will adopt the most stable conformation corresponding to the lowest energy level and take RSMD as a value less than 2 Å, and this conformation sought during simulations.

Enzyme (1cvw) –Inhibition

Conformation values

Compounds	***S(SCORD)***	***RMSD***
Ligand reference	-7.90831995	9.34143162
Test 1	-6.74243069	2.74233985

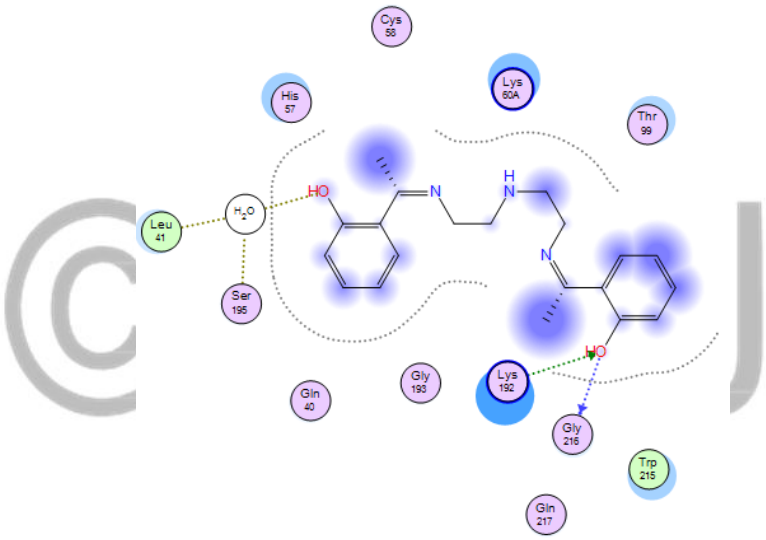
Enzyme (3lc5) -Inhibition

Les valeurs de conformation.

Compounds	***S(SCORD)***	***RMSD***
LIGAND REFERENCE	-8.88067436	0.473244101
Test 2	-6.79163313	3.00148058

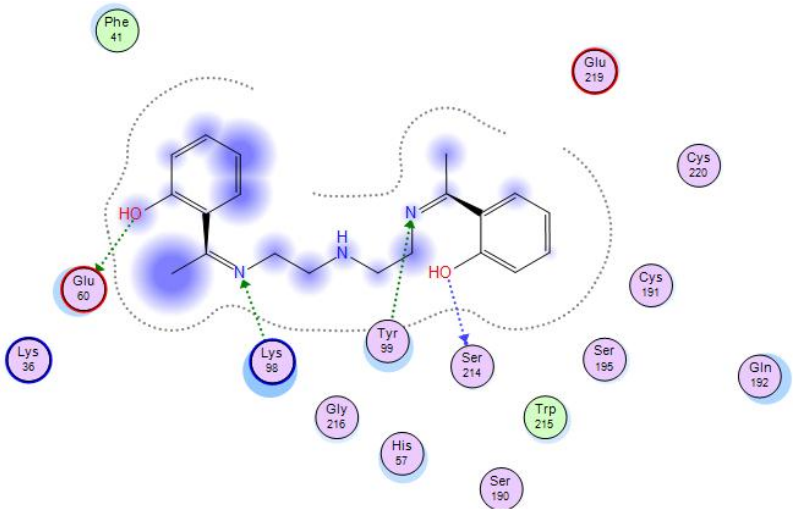
Interactions (Enzyme-ligand référence 1)

- **Test 1**



Ligand	Réceptor	interaction	distance	E (kcal/mol)
O 47	O GLY 216 (H)	H-donneur	2.68	-4.5
O 49	O HOH 506 (H)	H-donneur	2.39	6.7
O 47	NZ LYS 192 (H)	H-accepteur	2.60	-2.9

- **Test 2**



Ligand	Récepteur	interaction	distance	E (kcal/mol)
O 47	O GLY 214 (A)	H-donor	2.57	-2.5
O 49	OE1 GLU 60 (A)	H-donor	2.37	5.7
N 15	NZ LYS 98 (A)	H-acceptor	2.86	-10.1
N 16	OH TUR 99 (A)	H-acceptor	2.68	-2.1

We measured the distances between two enzymes (1cvw, 3lc5) and ligand which constitute the active site. The distances measured vary between 3.25 Å and 3.83 Å for all the studied complexes. According to **Anne Imbertet**, interactions with distances between 2.5 Å and 3.1Å are considered strong and those between 3.1Å and 3.55Å are assumed medium and when their distances are greater than 3.55Å, they are considered weak [5].

In the previous table we can easily find that the distances between the amino acids of the active site between 2.39 and 2.86 and the test 1 three interaction forest bonds and test 2 four strong interaction bonds.

Interaction energy

The interaction energies between the different substrates studied and the 1XKK are obtained using the following relation:

E interactions = (total potential E complex - substrate) - (E potential total enzyme alone +E potential total Substrate).

Van der Waals interactions must also be taken into account since it is the interactions between unbound atoms that stabilize the Enzyme-Inhibitor complexes.

Enzymes	VDW Energy	Electrostatic Energy	stéric Energy
Enzyme **(1cvw)**	4190,837	-6090,48	1936,006
Enzyme **(3lc5)**	3055,762	-3267,08	3172,814

Energies

	***E**-Total Du **(E-S)**.*	***E**-Total Du **(s)**.*	***E- VdwDu (E-S).***	***E**- Vdw Du **(s)**.*	***E**-Intera. De **vdw**.*	***E**-intera. De **Total**.*
Test 1	3655,174	149,227	3680,552	47,253	-1,4	1569,941
Test 2	3366,225	149,227	3040,502	47,253	-1	44,184

- Based on the total interaction energy, we note that the inhibitory activity is more active (Test 2 most active Test1).
- For the interaction energy of Van Der Waals (generally used to explain the interactions between unbound atoms that stabilize the Enzyme-Substrate complex). It is noticeable that the inhibitors are more stable (Test 2 the most stable Test 1).

ACKNOWLEDGMENTS

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