ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

The Role of Platinum (II) β -Carboline Complexes in Autophagy and Cancer Developement by Molecular Modeling.

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ABSTRACT

The autophagy, or type II: cellular death programme dis proposed like third cellular mode of death and the apoptose in addition to necrosis [1.2] the role of the autophagy in the development of cancer and the response of the therapy of cancer to summer a subject of debate [3]. This study was carried out with goal to predict the inhibition of AuroraB Kinase by a series of Ruthenium complexes (II) β-carboline by molecular modeling. During last years Kinases Aurora were emerged like one of the important targets of drug in several pharmaceutical companies and industries of research and it plays a main function in the regulation of the mitosis and the cytocinèse [4] Aurora Kinases has close links with cancer and guides the current growth of new classes of anti-cancer drugs wich precisely to target the field binding the ATP of Kinases Aurora[5] and for this reason one inhibited these Kinases Aurora with a series of Rethenium (II) containing an alkaloid β-carboline as legand can simultaneously induce the autophagy and apoptose in the tumoral cells[3].

Keywords: Ruthenium (II) β-carboline complex Aurora Kinases, Molecular (EMO,MM,DM,Docking Molecular)

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ISSN: 0975-8585

INTRODUCTION

The development of the metal complexes with bioactive molecule like legends offer of the possibilities for the discoveries of new against-cancer drugs [3]. A series of Ruthenium (II) containing alkaloid β-carboline as legend which was synthesized and characterized [3]. These complexes [Ru (NN) 2 (1 – Py-βC)]2 are nuclear permeable and very active against a panel of cancerous cellular lines human [3]:

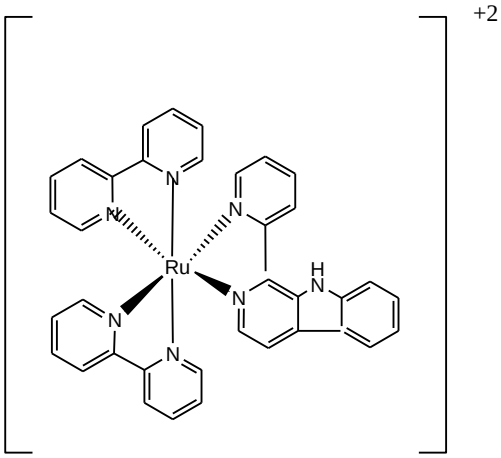

Figure1: Complex1 of Ruthenium

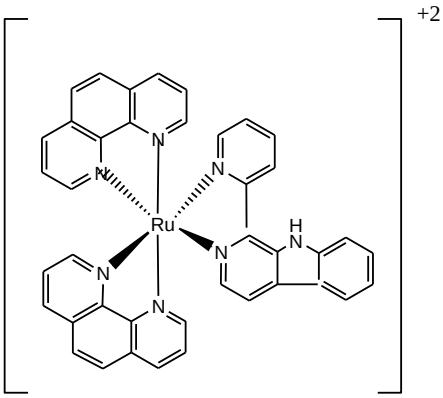

Figure2: Complex2 of Ruthenium

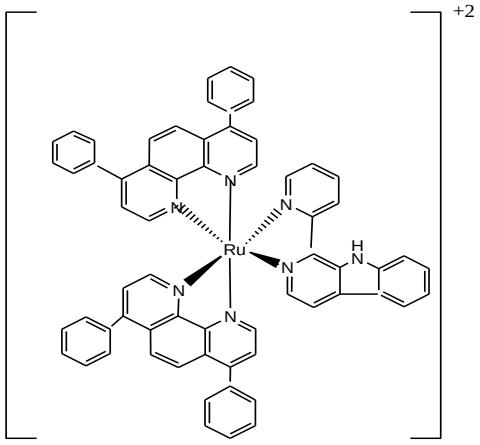

Figure3: Complex 3 of Ruthenium

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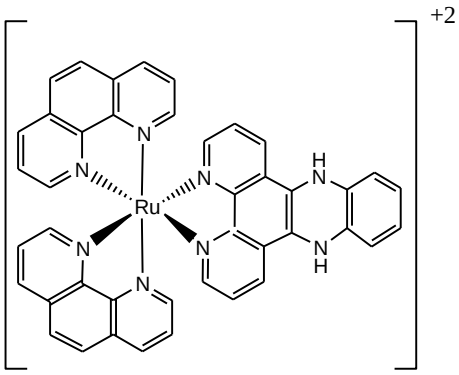

Figure 4: Complex4 of Ruthenium

The Ru combination (II) complex arena with the staurosporine, a powerful inhibitor for various Kinases, leads to the inhibiting discovery of nanomolaire and even protein picomolaires Kinases [6].

In our work we used these complexes to inhibit Kinase Aurora B/A maped to the region of 20q13.2-13.3 and human chromosome 17p13, respectively, amplified in cancer cell lines and primary tumors. The expression levels of Aurora B/A Kinases were elevated in several Aurora Kinases could be a novel chemotherapeutic strategy against the fight cancer [3]. Inhibition of Kinase Aurora yield distinct phenotype, were he may have tow void for the anti-cancer drugs [7].

Kinase Aurora(PDB: 2VRX) was chosen as the best model for human Kinase Aurora B showed the best sequence identity with 77 percent ASP 157,Glu 155 and Lys 106.

RESULTS AND DISCUSSION

Optimisation of Aurora Kinases

The geometry optimization of the Aurora Kinase B was performed using the force field Amber99 [9] plemented in the software version. The main chain was kept rigid, Hyperchem7.5 professional chains are flexible. This approximation allows where as the side chains of proteins more easily find the position in which side interactions are most favorable. The value of the energy optimization is:

Eopt= 6340, 57 Kcal/mol

Optimization of the Inhibitors

The construction and the optimization of legend were made by program EMO (Energy of Molecule) [10]. The results obtained are show in the following **Table1**:

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Table 1: Results obtained using program EMO

Energy steric (KJ/mol)(	EStretching	EBending	ETorsion	EVdw	Eelectrostatique	Esteric
Complex1	10.16	151.60	-150.80	169.30	.00	180.253
Complex2	20.36	792.23	-32.29	206.99	.00	987.278
Complex3	25.44	798.90	-170.43	346.00	.00	999.914
Complex4	9.74	696.49	-265.11	195.55	.00	635.672

Molecular dynamique of the Ruthenum Complexes

We began dynamics with an initialization of the system: with t=0 we R(T)=0 have, i.e. the initial structure previously minimized. Then we heated the system up to 300k during 1000 steps with an integration step of 1Ps. In 300 k , there is a balance: the speeds are adjusted to keep the temperature constant(there is exchange between the kinetic energy). Then, there is production of conformation. The time of simulation ofthe molecular dynamics is 100 picoseconds.

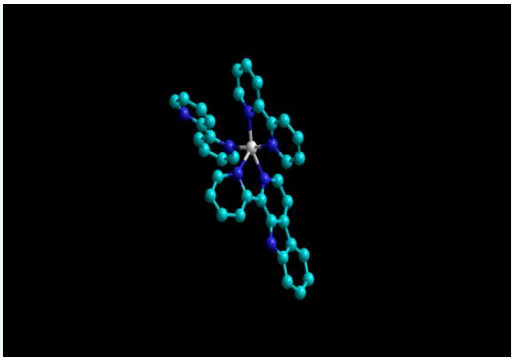

Figure 5 : Complex 1 optimized by EMO

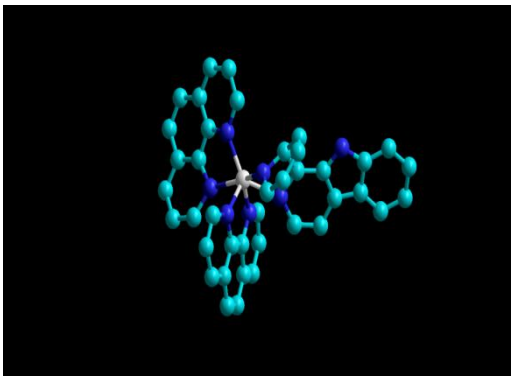

Figure 6: Complex 2 optimized by EM

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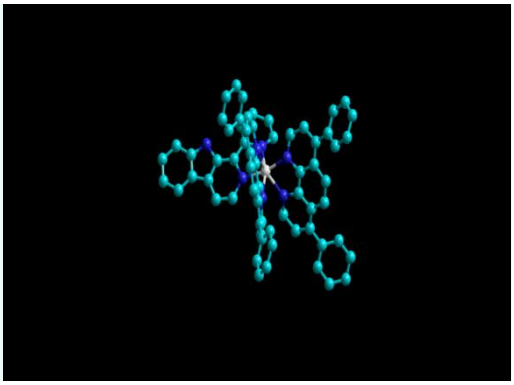

Figure7: Complex 3 optimized by EMO

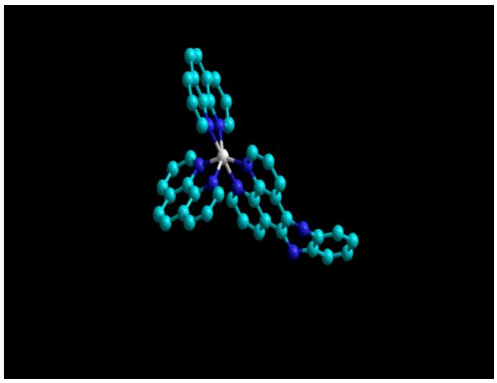

Figure8: Complex 4 optimized by EMO

Molecular Dynamics of Kinases Aurora

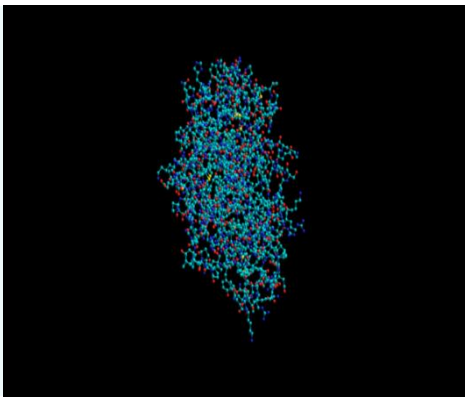

Figure9: Kinases Aurora Obtained by Molecular Dynamics

Docking of Substrates and the Construction of the Complex (Ruthenum complexes+Aurora Kinases)

The next stage, after the construction of the legends, is the positioning of these molecules in the active site of Aurora Kinase to do this, we used molecular docking module of the software planed molecular dynamics calculations to find the most stable conformation module of the software Hex4. Once all the complexes formed, we will perform a geometry optimization planed molecular dynamics calculations to find the most stable conformation.

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Complexe1 formed by Ruthenum complex1 and Aurora Kinase

Figure10: Complex 1 Obtained by molecular docking

Complex 2 formed by the complex 2 of Ruthenum and Aurora Kinase

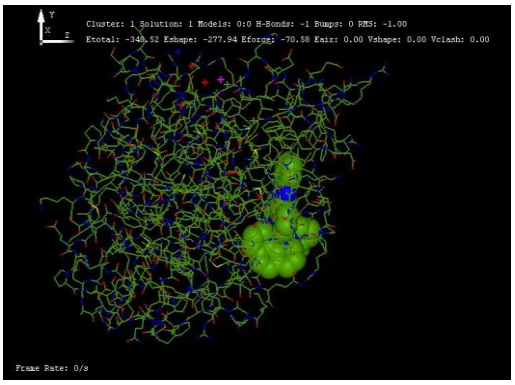

Figure11: Complex 2 Obtained by molecular docking

Complex 3 formed by the complexe3 of Ruthenum and Aurora Kinases

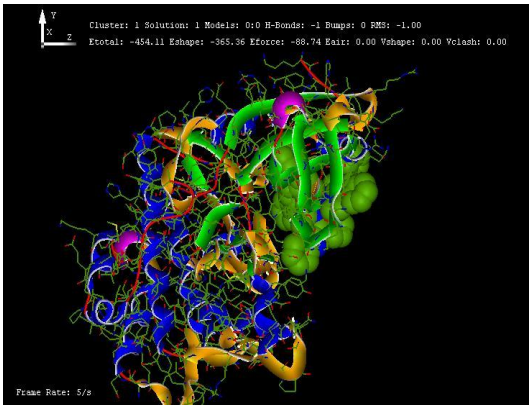

Figure12: Complex 3 obtained by the molecular docking

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Complex 4 formed by the complex 3 of Ruthenium and Aurora Kinases

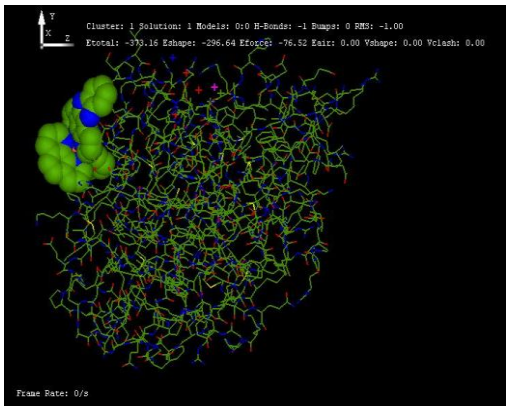

Figure13: Complex 4 obtained by the molecular docking

Table 2: the energies of the complexes formed by the ruthenium complexes with Aurora Kinases

Complexes	Complex1 of Ru(II)	Complex2 of Ru(II)	Complex3 of Ru(II)	Complex4 of Ru(II)
Energies (Kcal/mol)	-339.72	-348.52	-454.11	-373.16

Based on the obtained in table 2 we see that the complex 3 is the most stable i.e. the complex 3 Ruthenium is the best inhibitor after complex 4 then complex2.

Table3: IC_{50} experimental values obtained in vitro (cell lines cancer Ruthenium complexes with anti-tumor). [3]

	HepG2	Hela	MCF-7	MCF-10
Complex1 of Ru(II)	86.2±12.3	61.2±3.9	102.5±14.5	2052±12.3
Complex2 of Ru(II)	50.3±2.2	20.2±1.6	56.7±2.8	133.6±7.2
Complex3 of Ru(II)	3.5±0.3	1.9±0.2	5.9±0.4	40.6±3.1
Complex4 of Ru(II)	170.2±12.0	152.1±13.1	260.3±26.3	286.4±9.7

HepG2 (human hepatocellular liver carcinoma), Hela and MCF-7 (human breast adenocarcinoma) and Mcf-10 (immortalized breast epithelial cells) [3].

The IC_{50} resulting values for the compounds tested indicating that, in general based on the values of IC_{50} calculated after the end of anti proliferative activity in vitro of compounds can be envisaged: 3> 2> 1> 4 [3].

Distances between the Amino Acids of the Active site and Groups of Inhibitors

In general **[12]**

2.5 A°< R <3.1A° ⟶ Interction strong
3.1 A°< R < 3.55A° ⟶ average interaction
R > 3.55A° ⟶ weak interaction

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Complex 1

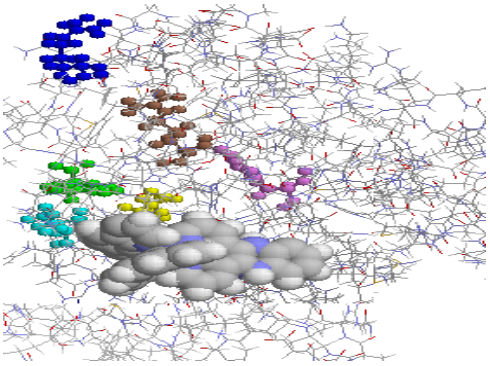

Table 4: Measuring distances between the complexe-1 and groups of side chains of amino acids responsible for interaction.

Residues	Pro151	Tyr206	Arg149	Tyr355	Leu351	Tyr157
Distances (A°)	7.49	9.47	7.55	4.910	9.17	11.30

Complex 2

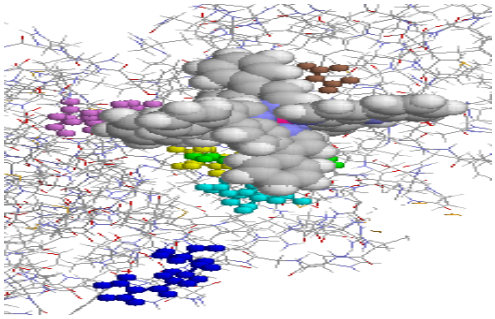

Table5: Measuring distances between the complexe-2 and groups of side chains of amino acids responsible for interaction.

Residues	Pro151	Tyr206	Arg149	Tyr355	Leu351	Tyr157
Distances (A°)	4.01	4.47	4.45	4.91	3.50	5.23

Complex 3

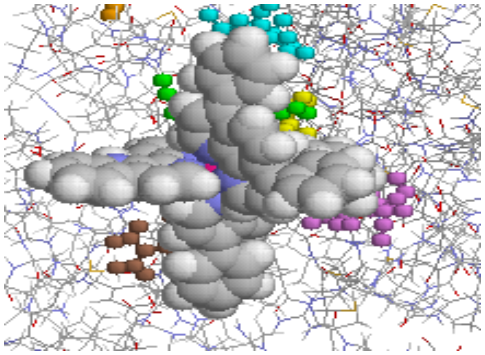

Table 3: Measuring distances between the complexe-3 and groups of side chains of amino acids responsible for interaction.

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Residues	Pro151	Tyr206	Arg149	Tyr355	Leu351	Tyr157
Distances (A°)	2.85	4.47	3.45	2.61	3.03	5.23

Complex4

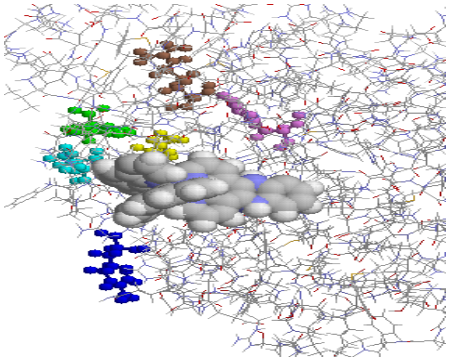
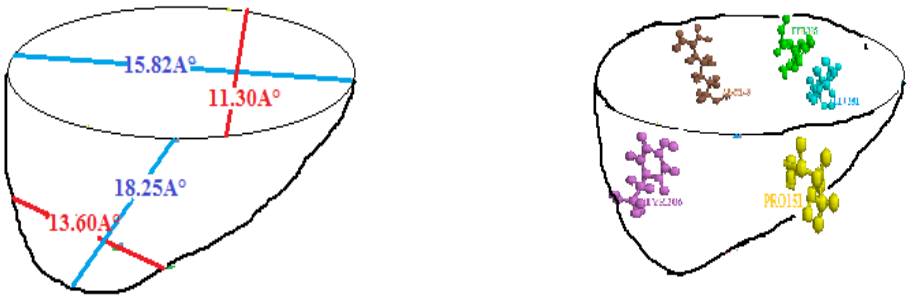


Table 4: Measuring distances between the complexe-4 and groups of side chains of amino acids responsible for interaction.

residues	Pro151	Tyr206	Arg149	Tyr355	Leu351	Arg348
Distances (A°)	20.41	13.63	10.20	16.39	9.58	7.23

We note that we can discuss complementarities in increasing or decreasing the interval size of the active site pock-et [13], in our case with a geometry of 18.25 Å depths, opening 15.82 Å 11.30 Å, this pocket is narrowed up to a width of 13.60 Å.



Dimensions of active site of the enzyme

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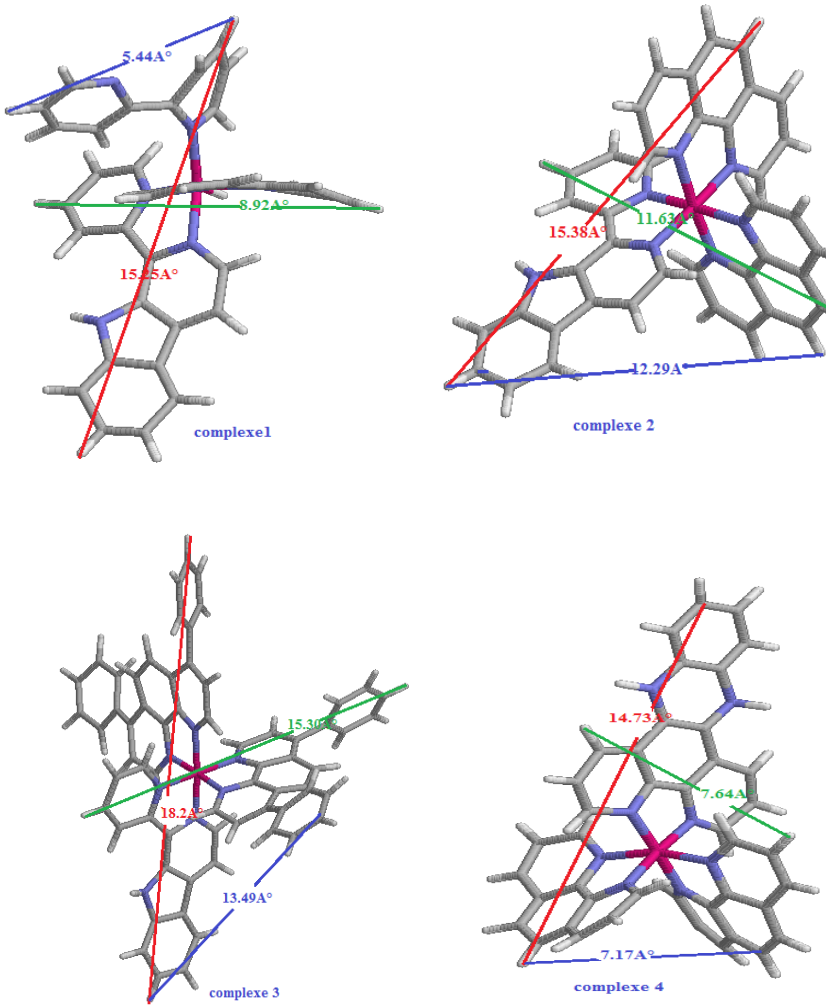

CONCLUSIONS

According to our results the theoretical calculations of the energies of complication of ruthenium complexes and enzyme Aurora Kinases and distance cavity, we concluded that the ruthenium complex 3 has strong interactions with the active site and results molecular docking, the complex 3 is more stable than other complexes then the enzyme Aurora Kinases this complex is the best inhibitor against a cancer cell Lines.

Ruthenium complexes of β-carboline alkaloids are anti-cancer agents, the most active drug is complex 3 exhibits cytotoxic activity than the chemotherapeutic agent cisplatin clinical widely used [3].This Ru (II) complexes β-carboline are double acting and inducing autophagy appoptose agent.

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