Prediction of Binding Sites of Zinc Complex Using Experimental and Computational ModelingApproach

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ABSTRACT

The binding modes of a new zinc complex derived from 3-(5-bromo-2-hydroxybenzylideneamino)-2-(5-bromo-2-hydroxyphenyl)-2,3-dihydroquinazoline-4(1H)-one withdivalent zinc was studied using both experimental and computational chemistry. ^{1}H NMR, IR, molar ratio and atomic absorption were used to predict the characterization of zinc complex. Hartree–Fock (HF) method was selected to determine the HOMO-LUMO gap of several possibilities of binding sites to describe the more stable structure which reflects the more possible coordination sites of ligand to Zn^{+2} ion. Good matching between theoretical and experimental results was found which concluded the tetra dentate behavior of the ligand.

الخلاصة

تم في هذا البحث دراسة طريقة ارتباط معقد الخارصين الثنائي مع الليكاند
3-(5-bromo-2-hydroxybenzylideneamino)-2-(5-bromo-2-hydroxyphenyl)-2,3-
dihydroquinazoline-4(1H)-one
باستخدام الطرق العملية والحاسوبية. تم استخدام تقنيات مختلفة مثل مطيافية الامتصاص الذري وتحت الحمراء
والرنين المغناطيسي بالاضافة الى النسبة المولية باستخدام Uv visible لتشخيص معقد الخارصين. حاسوبيا، تم
اختيار طريقة هاتري فوك لحساب الفرق بين هومو لومو لمجموعة من احتمالات الربط لهذا المعقد لتحديد المعقد
الاكثر استقرارا والذي يستدل من خلاله على الشكل الاكثر احتمالا في طبيعة التناسق. تم الحصول على تطابق جيد بين
الطرق الحاسوبية والنتائج العملية في تحديد طبيعة الشكل النهائي لعملية التناسق بين الفلز والليكاند

INTRODUCTION

An understanding and predicting of metal-binding sites through complexation is so important in the biological systems especially in proteins to assist in rational design of suitable chemical drugs [1]. Binding sites can be determinates theoretically by several methods using computational modeling which can be considered as useful way to calculate some of important parameters falls under this topic, such as MEP (molecular electrostatic potential) and electronic energy. MEP can be considered as very useful for predicting the possible coordination sites. Its values represent the electron density which reflects the electrophilic attack power. Most favorable sites are those have minima MEP [2,3]

Stability of species evaluated by interaction energy using DFT modeling, can also be used in predicting the real binding mode. The more the negative energy, the more probable stable species.[4] .

Ring size and the number of chelating rings play an important role in predicting the most probable structure of the studied possibilities. Complexes contain 5 membered chelate ring without pi-bond been the most stable while 6 membered chelate ring with double bond be the favorite[5,6]. Due to the metal ligand complexation, increasing the number of chelate rings result in more stable of the complex formed [7,8,9].

In this study and on the continuation of our previous work which involved the preparation of new quinazoline compounds which have potent biological activities, especially against cancer, we aim to synthesize new zinc complex. Attempts were curried out to find the relation between HOMO-LUMO energy gap (highest occupied molecular orbital and lowest unoccupied molecular orbital) and binding modes of the ligand using several possibilities of chelation from different donor atoms. The larger the gap, the more stable species due to the higher energy needed for transition state to convert [1, 2].

MATERIALS AND METHODS

All chemicals and solvents (2-Aminobenzhydrazide, 2-Hydroxy-5-bromo benzaldehyde, Glacial acetic acid ,Deuterated dimethyl sulfuoxide, Ethanol, Zinc(II) acetate dihydrate, Triethylamine, Hexane and Ethyl acetate) used for the synthesis of zinc complex were obtained from Merck and Sigma-Aldrich. Melting point of the synthesized complex was determined by the open capillary melting point apparatus without further corrections. The purity of the complex was checked using pre-coated thin layer chromatography TLC plates by MERCK (60F254) with a mixture of hexane : ethyl

acetate 4:1 as an eluent. The developed chromatography plates were visualized under UV-Vis light at 254nm.

Infrared spectra was performed by a Perkin Elmer Spectrum 4000-400 FT.IR Spectrophotometer, ^{1}H NMR spectra were recorded on an AVN Bruker 400 MHz system. Tetramethylsilane TMS was used as an internal standard; deuterated DMSO-d_6 was used as a solvent for NMR spectrophotometer. The electronic spectra of the compound was obtained using Uv-visible spectrophotometer type shimadzu 160 in the range (1000-200 nm) using quartz cell of 1.0 cm length. Metal analysis were measured with atomic absorption spectrophotometer [phoenix 986]. Both ^{1}H NMR and FTIR analysis were recorded in the department of chemistry, Faculty of science, University of Malaya, Kuala lumpur, Malaysia, while other analysis were done in the ministry of science and technology, Materials Research Directorate, Baghdad, Iraq.

Synthesis of the ligand
The ligand was synthesized according to literature using the synthetic pathway as shown in scheme 1 .
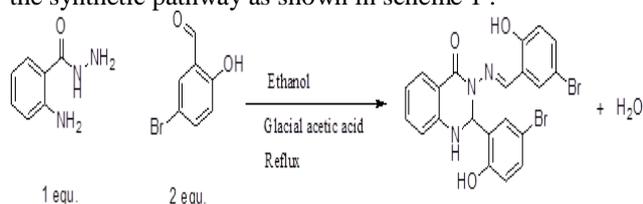


Scheme 1: Synthetic pathway of ligand

Solution of 2-Aminobenzyhydrazide (0.755 g, 5mmol) in ethanol reacted with solution of 2-hydroxy-5-bromo benzaldehyde (2.01 g,10mmol) in ethanol in the presence of 1 ml glacial acetic acid. Reflux at 75°C for 3h, yellow precipitate was formed and then collected by filtration. Yield :(2.55 g, 98%);mp 236–238°C;

Procedure for Synthesis of zinc complex
Zinc complex was synthesized according to the below synthetic pathway using one equivalent of 3-(5-bromo-2-hydroxybenzylideneamino)-2-(5-bromo-2-hydroxyphenyl)-2,3-dihydroquinazoline-4 (1H)-one (0.1 g, 2.0 mmol) dissolved in 50 mL of ethanol with one equivalent of zinc acetate (0.044g, 2.0 mmol) dissolved in 20 mL of ethanol. To this solution a few drops of trimethylamine was added as a catalyst. The reaction mixture was refluxed for 18 h at 80℃. Yellow precipitate of zinc complex was formed during the reaction. Three quarters of the solvent was evaporated. The precipitate was removed by filtration, washed with a cold ethanol and then dried in an oven. Yield: (0.085g, 76%), m.p. 350 °C.
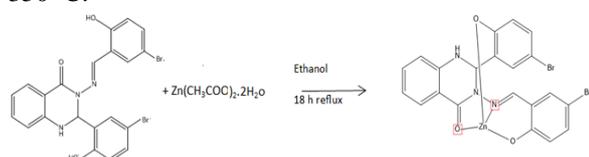
The synthetic pathway for zinc complex

Computational method
AbinitioHartree–Fock (HF) method at 6-31G level calculations were performed on the 3-(5-bromo- 2 - hydroxybenzylideneamino) - 2- (5 - bromo -2-hydroxyphenyl) -2,3- dihydroquinazoline-4(1H)-one with divalent zinc using ChemBio3D ultra supported with Gaussian program. The calculations carried out by PC.computer, type Lenovo icore-7

RESULTS AND DISCUSSION
Geometry optimizationZinc (II) complex was optimized at HF/6-31G levels. A series of divalent zinc chelating possibilities was studied to identify the more possible binding mode. Figure1 shows the optimized molecular structures of all chelating options studied. HOMO-LUMO energy gap values are listed in table 1.
Comparison of all possibilities were done depend on the energy gap values. As can be observed from table-1, which arranged into three subclasse of bidentate, tridentate then tetradentate chelating modes. It is clearly observed that the most probable chelating sites of the ligand has been started with the two deprotonated oxygen (O19 and O30) with divalent Zinc due its high stability according to the larger HOMO-LUMO energy gap compared to the others [1,2], and from this point, the next possibilities was done to determine which is be the most probable tridentate choice. Nitrogen imine (N11) in addition to both O19,O30 being the best probability chelation sites. Finally, the forth probable donor atom introduce in the donation system of this complex is the carbonyl oxygen (O28). All the three selected possibilities being the most stable due the larger value of E-gap in each subclass. Figure 1 shows the optimized geometry of the three most probale complexes yield from the mentioned donation modes.

Table-1: HOMO-LUMO gap for several chelating possibilities calculated by HF /6-31G

Bidentate chelating mode		
Complex No.	Chelation sites	HOMO-LUMO gap eV

| 1	Zn + O19+ N10	0.799
2	Zn + O30+ N11	0.975
3	Zn + O30+N10	1.124
4	Zn + O19+ N11	1.322
5	Zn + O30+ N8	1.72
6	Zn + O28+ N11	2.9
7	Zn + O28+ N8	3.517
8	Zn + O30+O19	5
Tridentate chelating mode		
1	Zn+O30+O19+N8	*
2	Zn+O28+O30+N11	1.692
3	Zn+O28+O19+N11	2.59
4	Zn+O30+O19+O28	4.988
5	Zn+O30+O19+N10	5.137
6	Zn+O30+O19+N11	5.4
Tetradentate chelating mode		
1	Zn + O30 +O19+N11+N8	**
2	Zn + O30 +O19+N11+N10	5.016
3	Zn + O30 +O19+N11+O28	5.388

*distorted geometry in which abnormal N8-Zn bond length that equal 2.963 A° .

** distorted geometry: abnormal N11-Zn bond length that equal 2.98 A° due to three membered ring strains.

IR study

Characteristic IR of ligand shows the following data by cm−1 unit: 3223 υ(NH), 3012 υ(CH aromatic), *1643* υ(C=O), *1608* υ(C=N), *1206* υ(N-N), *1148* υ(C-N), *1044* υ (C-O).

Fig. 2 shows a comparison in IR spectra between the ligand and zinc complex spectrums. Appearance absorption band of hydroxyl groups in ligand spectrum and disappear these bands from zinc complex spectrum by deprotonation is an evidence on coordination between hydroxyl groups and zinc ion. As well as occurring shiftingof amidic carbonyl absorption band from 1643 cm-1 to 1615 cm-1 and azomethine group from 1608 cm-1 to 1589 cm-1. In addition, also appearance a new absorption bands at 538cm-1 and 488 cm-1 were assigned to and υ(M-N), υ(M–O) bonds, respectively. All these main absorption bands confirmed the formation of zinc complex [11].
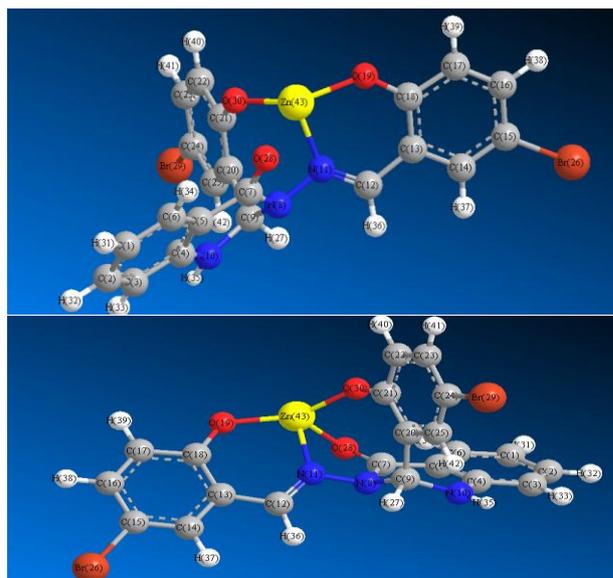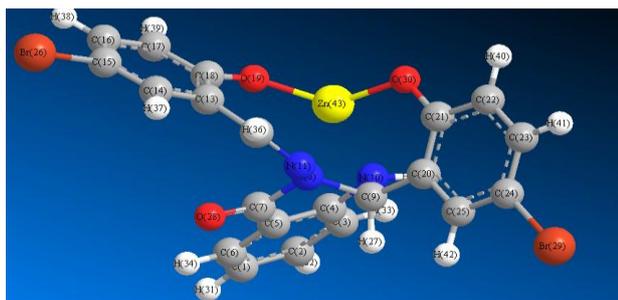
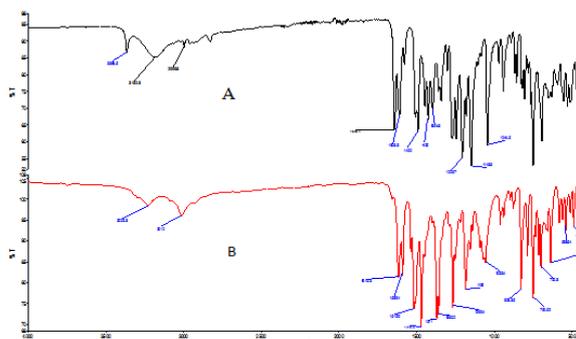(Fig-1) Optimized structure of the most stable complex calculated by HF/ 6-31G

Figure 2: IR spectra comparison between the ligand (A) and zinc complex (B)

NMR study:

1H NMR of zinc complex Fig. 3 showed disappeared two singlet signals from zinc complex spectrum compared to 1H NMR spectrum of ligand (Fig. 4) [10] at 11.27 ppm and 10.57 ppm belonged to two hydroxyl groups this is evidence the coordination between the zinc ion and two oxygen atoms of hydroxyl groups by deprotonation. As well as occurrence shifting of azomethine group (-N=CH-) from 8.56ppm in ligand spectrum to 8.49ppm in zinc complex spectrum, this a good evidence to form the complex [12].Also ten signals appeared in region between 7.91 -6.48 ppm were assigned to proton atoms of aromatic rings [13]. In addition, two signals, one signal belonged to proton of NH and another signal attributed to proton of CH of quinazoline ring [14]. The signal at 3.3 ppm is attributed to the usual existence of low percentage of moisture contamination in DMSO solvent, while the signal at 2.5 ppm is attributed to residual DMSO-d5[15,16] . All these signals confirm the formation of the zinc complex.
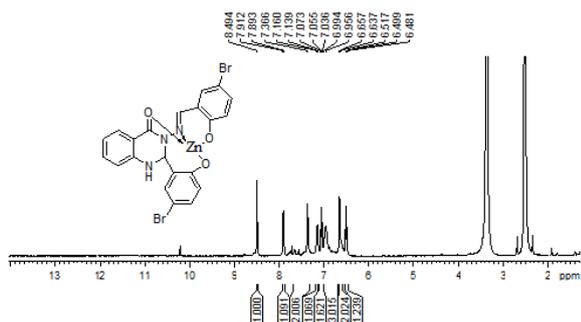
Figure 3: ^{1}H NMR spectrum of zinc complex in DMSO-d_6 solvent using TMS as reference
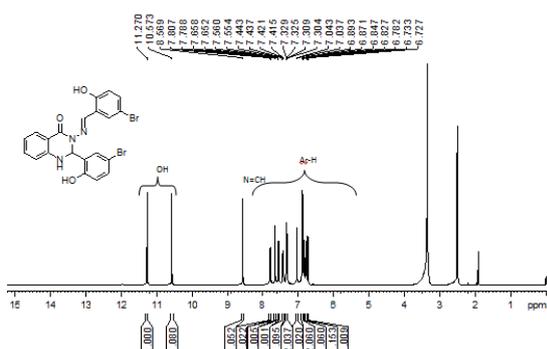

Figure 4: ^{1}H NMR spectrum of ligand in DMSO-d_6 solvent using TMS as reference

Uv-Visible

As shown in table-2, the electronic spectrum of ligand showed three absorption bands 272, 324 and 402 nm attributed to π-π* and n-π* respectively, these bands shifted to lower energy 308, 389 and 413 nm due to the complex formation which confirmed by the appearance of new band in the visible region 440 nm that assigned mainly to charge transfer, no d-d transitions were observed for d^{10} configuration of zinc ion.

Table-2: electronic transitions of both the ligand and complex

	π-π* nm		n-π* nm	charge transfer nm
Ligand	272	324	402	
complex	308	389	413	440

Geometry of complex

Suggested tetrahedral geometry of complex has been confirmed by three factors. Theoretical calculations obtained reflect the high stability of tetrahedral geometry compared to octahedral geometry. 0.089 eV , 5.502 eVHOMO-LUMO gap for both octahedral and tetrahedral complex respectively was observed .

Theoretical concentration of metal ion in complex have similar values with those of the synthesized complex which demonstrates the complete reaction took place.

The proposal geometry (1:1) metal:ligand of zinc complex was confirmed by metal analysis AAs (11.29% calculated and 10.5% found) as well as molar ratio method [17,18] as shown in figure (fig-5) using two

wave length that could not appear in the Uv- Visible spectrum of both starting materials metal salt and the ligand.
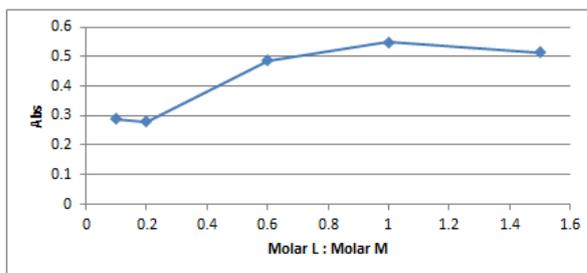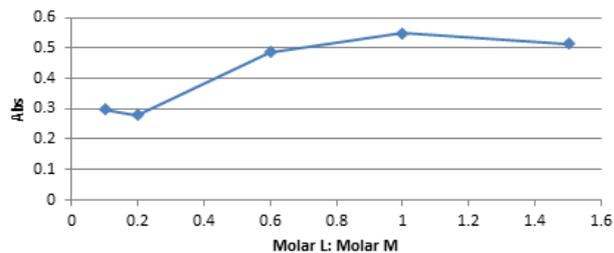

Fig- 5 : molar ratio of ligand:metal , (A): at wave length 302 nm , (B): at 297 nm

CONCLUSIONS

In this study, zinc complex has been synthesized *via* reaction of 3-(5-bromo- 2 - hydroxybenzylideneamino)-2-(5–bromo–2–hydroxyphenyl)-2,3-dihydroquinazoline-4(1H)-one with zinc acetate dihydrate. Theoretical calculations were performed to predict the binding modes of the synthesized zinc complex between zinc ion and the ligand. This investigation study has been supported by NMR and FTIR which confirmed the ligand acts as a tetradentate chelating agent, bonded to the metal ion via the one nitrogen atom of Schiff base (-C=N), two oxygen atoms by deprotonation of hydroxyl groups and oxygen atom of carbonyl group of quinazoline ring

Based on the data obtained, tetrahedral geometry of complex has been determined due to the computational calculations supported by both UV-Visible and atomic absorption.

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