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The Effect of Ligand Exchange and Group Substituent on Biological Activity of Anticancer Ruthenium (III) Complexes (NAMI-A)

Ahmed Abdul Sattar Ali

Assistant Lecturer, Al-Rasheed University College / Medical Laboratory Technology Department

Abstract: ***The most spread illnesses nowadays and be afraid so far largely in the world are "Cancer Diseases" because these illnesses represent complicated and tricky to cure. The main methods of new cancer curing is "drug therapy". "cell killing (cytotoxic)" and "cell stabilizing (cytostatic)" are two wide categories medications used to fight cancer. Many ruthenium based metallodrugs for anticancer diseases has produced as alternates to platinum compounds, the first ruthenium metallodrug enter clinical trials was NAMI-A "trans-[tetrachloro (DMSO) (imidazole) ruthenate(III)]", this compound explain to have low toxicity and high selectivity against solid tumor metastases when pharmacologically effectiveness doses. In this paper, we describe the building, characterization and designing crystal structure of a novel ruthenium complex, NAMI-A "trans-[tetrachloro (DMSO) (imidazole) ruthenate(III)]" and it's derivative based on density functional theory (DFT) method using Gaussian 03 program"Gaussian 2003". Thefrontier molecular orbital energies "HOMO, LUMO", "Mulliken charges distribution", "complex activity", and "stability" of the complexes werediscussed.The obtained results of building complexes in addition to standard complex are explained that both (C_2, C_3, C_6, C_7) are more suitable as anticancer activity compared toward standard complex (C_1), while (C_4, C_5) is lower activity than (C_1)***

Keywords: Cancer Diseases; NAMI-A;ruthenium (III) metallodrug; density functional theory (DFT);dimethyl sulfoxide (DMSO); (HOMO, LUMO) energies.

1. Introduction

Coordination field of transition metal compound are anionic, cationic, or neutral species during which a coordinated transition metal by ligands[1]. Research has shown important progress in utilization of transition metal ions and their compounds as medication to many human illnessestreatment. Transition metals exhibit totally different oxidation states and might move with negatively charged of variety molecules. This transition metals activity has started the event of metal based medication with promising medicine application and should supply distinctive therapeutic chances[2].

The inorganic chemistry advances included provide the best chances appropriateness to use metal complexes as chemotherapeutic agents. The activity of compounds containing metal ion on living organism is differing from non metals. These complexes appear a great variety in action[3].Because the unparalleled properties of metal ions, the medicinal inorganic chemistry can take advantage of these metals to design of new drugs. This has; for instance, lead to the clinical application of metal compounds as chemotherapeutic agents for tumor therapy, such as "cis-platin"[4]. These compound show a large variety in their effectiveness; not only have anti-tumor properties but have also been used as "anti-diabetic","anti-infective" and "anti-inflammatory" compounds[5].

The most spread illnesses nowadays and be afraid so far largely in the world are "Cancer Diseases" because these illnesses represent complicated and tricky to remediation. The major cause ofcancer difficulty is that disease occur consequence the not disciplined reduplication of "normal human cells". Drug therapy is one of the main methods of new cancer remediation."Cell Killing (cytotoxic)" and "Cell Stabilizing (cytostatic)" are two wide categories medications used to fight cancer. Both of these categories lead to reduction in the cancermagnitude[6].In this area, the universal research efforts included (i) evolution of new powerful "antineoplastic" factor and (ii) invention of new biological objectives; for example, cytotoxic drug "cisplatin" is today one of the most widely used in medical applicationsfor cancer curing [7].

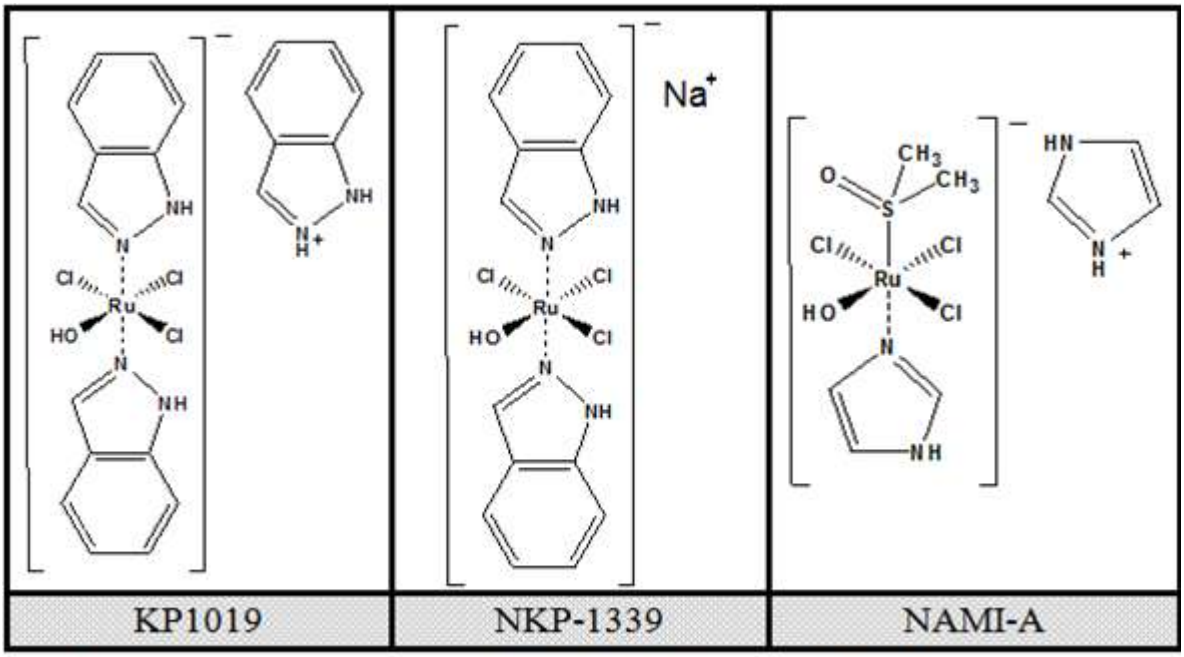

Fig (1-1): Structural formula of (KP1019, NKP1339, and NAMI-A) complexes.

Many ruthenium based metallodrugs for anticancer diseases has produced as alternates to platinum compounds, the first ruthenium metallodrug enter clinical trials was NAMI-A "trans-[tetrachloro (DMSO) (imidazole) ruthenate(III)]"; Figure (1-1), this compound explain to have low toxicity and high selectivity against solid tumor metastases when pharmacologically effectiveness doses[8].The second ruthenium based metallodrug which also entered clinical trials after proof its effectiveness against diverse tumor types and exhibit cytotoxic activity of cisplatin-resistant human colon carcinoma was KP1019 "indazolium trans-[tetrachlorobis (1H-indazole) ruthenate (III)]" and its sodium salt analogue NKP-1339[9], figure (1-1).

Research studies and comparisons between ruthenium compounds and platinum compounds showed that ruthenium complexes cause fewer (and less severe) side effects. the small difference in the energy barriers to inter transformation between ruthenium oxidation states (+2) and (+3) lead to become suitable compounds for pharmacological applications as antitumor agents and letting for preparednesschanges the oxidation state when inside the cell.

On the other hand, ruthenium tends in its compounds to form octahedral forms, allowing two additional ligands atoms to be exploited compared to platinum (II) compounds which have a square planar geometry as well as the ruthenium nature can be forming strong chemical bonds with a number of molecules that have different "hardness and electronegativities". Thus, Ru metal ion can bind to (not just a DNA) a number of bio-molecules.

One of the postulation theorythat explain why Ru complexes are less poisonous than Pt compounds is "Activation by Reduction" which is depend on (i) the observation that Ru (+3) compounds are inert and more than Ru (+2) compounds and (ii) behave cancer cells to more chemically reducing environment than healthy cells. These two factors explain the behavior of the ruthenium complexes. The ruthenium oxidation state (+3) causes minimal damage to the healthy cells (relatively inert), while the ruthenium are reduced in the cancer cells to oxidation state (+2) and its compounds become more effective[11,12].

In recent years, there have been many studies conducted on various compounds of the ruthenium metal, where some have proved effective in inhibiting the activities of cancer cells[13,14].In this paper, we describe the building, characterization and designing crystal structure of a novel ruthenium complex, NAMI-A "trans-[tetrachloro (DMSO) (imidazole) ruthenate(III)]" and it's derivative. Additionally, based on crystal data, density functional theory (DFT) studies of the complexes were performed and completedusing the Gaussian 03 program suite. Thefrontier molecular orbital energies "HOMO, LUMO", "Mulliken charges distribution","complex activity",and"stability" of the complexes werediscussed.

Aim of this work

In the present work we are studying the effectiveness of chemical groups substitution or ligand exchange on the central atom [ruthenium (III)] of known anticancer drugs NAMI-A "trans-[tetrachloro (DMSO) (imidazole) ruthenate(III)]".

2. Calculation Method

The molecular designing was performed and accomplished using computations of Gaussian 03 (2003) program package. In the presentwork, the computations have been accomplished at "DFT/B3LYP" method with "6-31G(d,p)" basis set. Electron interconnection were included using "Becke3-Lee-Yang-Parr (B3LYP)"procedure[15].

These study and investigation included calculated numerous physical and chemical properties of building complexes which represent an anti-diabetic drug. The Calculating of balance geometrical shape (Optimization) of molecules and the Electronic Density of the atoms in molecules (ligands

and complexes), especially of metal ion and coordinated atoms of ligands, in addition HOMO"Highest occupiedmolecular orbital" andLUMO "lowest unoccupied molecular orbital"are the most critical to describe the biological activity of complexes, optical properties, andchemical reactivity.

3. Result and Discussion

Ruthenium compounds with oxidation number (II) and (III), have been evaluated for therapeutic applications and especially for cancer treatments because they have characteristics similar to platinum compounds (II) in terms of ligands exchange as well as their ability to interact with large molecules such as "protein", "DNA",or small "P-, S-"donor compounds and/or water. These reactions are necessary in measuring the effectiveness of the metallodrugs compounds.

There are three essential characteristics that must be availability in the compound to be suitable for medical applications (i) ability to be ligand exchange (ii) the oxidation states range which can be accessible and (iii) the ability of metal in the compound to mimic iron mechanism in binding to particular biological molecules[16].

In the present work,sixruthenium (III) derivative complexes modeling were performed using Gaussian 03 program package for calculations. the calculations have been carried out at (DFT/B3LYP) method with 6-31Gbasis set. These complexes deferent about known drugs (C_1: NAMI-A) by ligand exchange (OH^- ion, or NH_2^- ion instead of Cl^- ion) or group substituent instead of hydrogen atom on the (DMSO) ligand.

The complex C_2 is similar to C_1 except one amino group substitutioninstead of the chloride ligand, the complex C_3 is similar to C_1 except two amino group substitution is found instead of chlorideligand, the complex C_4 is similar to C_1 except two ethyl group substitution is found instead of methyl group of DMSO ligand, C_5 complex is similar to C_1 except one ethyl group substitution is found instead of methyl group of DMSO ligand, C_6 complex is similar to C_5 except one hydroxyl group substitution is found instead of chlorideligand,C_7 complex is similar to C_5 except two hydroxyl group substitution is found instead of chlorideligand,table (3-1) figure (3-1).

Table (3-1): Symbol, chemical formula, and names of the calculated complexes (C_1-C_7).

Symbols	*Chemical formula*	*Name*
C_1	$C_5H_{10}Cl_4N_2SORu$	trans-[tetrachloro (dimethyl sulfoxide) (imidazole) ruthenate (III)]
C_2	$C_5H_{12}Cl_3N_3SORu$	trans-[amino trichloro (dimethyl sulfoxide) (imidazole) ruthenate (III)]
C_3	$C_5H_{14}Cl_2N_4SORu$	trans-[diamino dichloro (dimethyl sulfoxide) (imidazole) ruthenate (III)]
C_4	$C_7H_{14}Cl_4N2SORu$	trans-[tetrachloro (diethyl sulfoxide) (imidazole) ruthenate (III)]
C_5	$C_6H_{12}Cl_4N_2SORu$	trans-[tetrachloro (ethyl methyl sulfoxide) (imidazole) ruthenate (III)]
C_6	$C_6H_{13}Cl_3N_2SO_2Ru$	trans-[trichloro hydroxy (ethyl methyl sulfoxide) (imidazole) ruthenate (III)]
C_7	$C_6H_{14}Cl_2N_2SO_3Ru$	trans-[dichloro dihydroxy (ethyl methyl sulfoxide) (imidazole) ruthenate (III)]

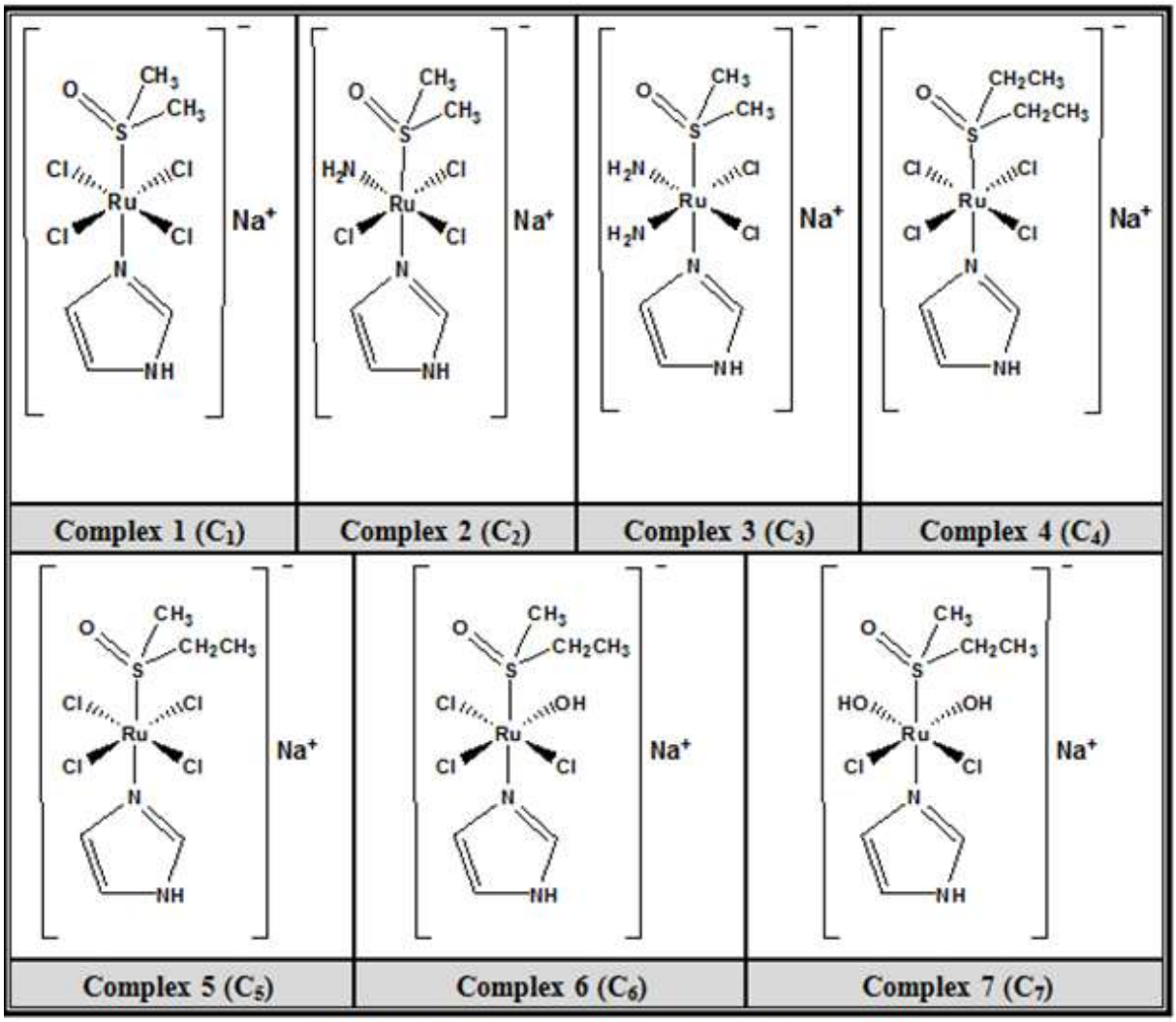

Fig (3-1): derivative complexes of Ruthenium (III).

The conformations of the Ruthenium (III) derivative complexes in addition to known drug obtained from "DFT" method for calculation. The optimization process "the global minimum energy information of the compounds is achieved" was fully done to assessment the electronic density of atoms in all compounds. in these oxidation states, the ruthenium centre is predominantly hexacoordinate with essentially octahedral geometry, by coordinate the central ruthenium ion (III) to two chloride ion and (Cl-, NH_2-, or OH-) group in the third and forth attack, while the hetrocyclic ligand (imidazole) occupied the five coordinate attack, on the other hand, the six coordinate attack is occupied with R2-sulfoxide (R: methyl, ethyl) table (3-2) figure [(3-2) to (3-8)].

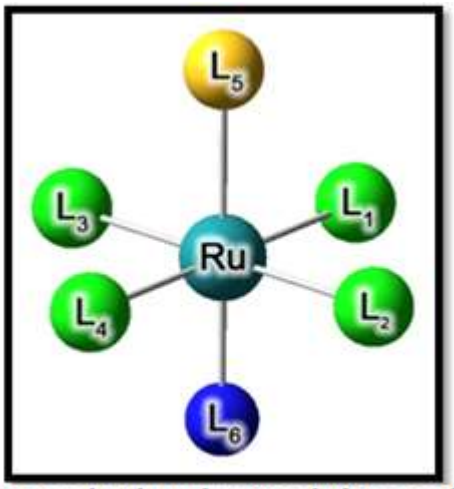

Figure (3-2): ruthenium (III) ion and coordinated atom of the ligands.

Table (3-2): Electronic density of ruthenium (III) ion and coordinated atom of the ligands.

Complex	Ru	L_1	L_2	L_3	L_4	L_5	L_6
C_1	42.930201	17.323464	17.350692	17.331174	17.228623	15.131017	6.935803
* C_2	42.869949	17.455094	17.407880	6.881290	17.365311	15.173406	6.944031
* C_3	42.980478	17.464824	17.496460	6.863920	6.891188	15.175322	6.926681
C_4	42.856317	17.322324	17.344323	17.324157	17.230802	15.177931	6.934948
C_5	42.892389	17.322078	17.345917	17.329711	17.229994	15.151208	6.935831
* C_6	42.932109	8.049411	17.408690	17.398964	17.297604	15.171644	6.944306
* C_7	42.968806	8.092037	17.449980	8.032019	17.334513	15.192222	6.962890

* Ligand exchange

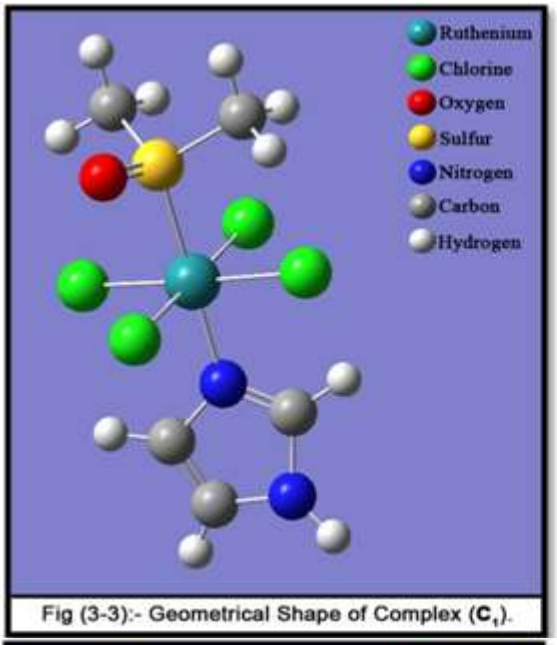

Fig (3-3):- Geometrical Shape of Complex (C_1).

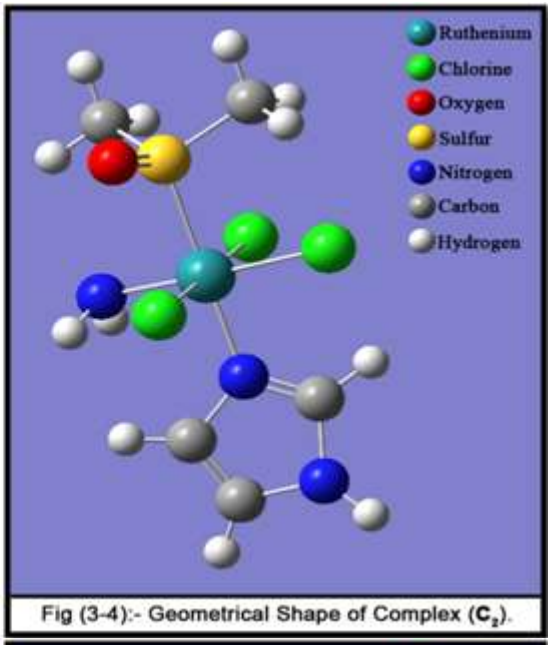

Fig (3-4):- Geometrical Shape of Complex (C_2).

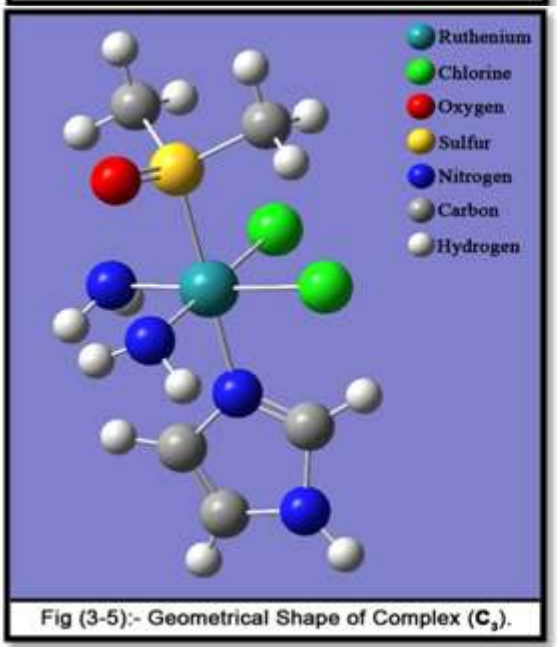

Fig (3-5):- Geometrical Shape of Complex (C_3).

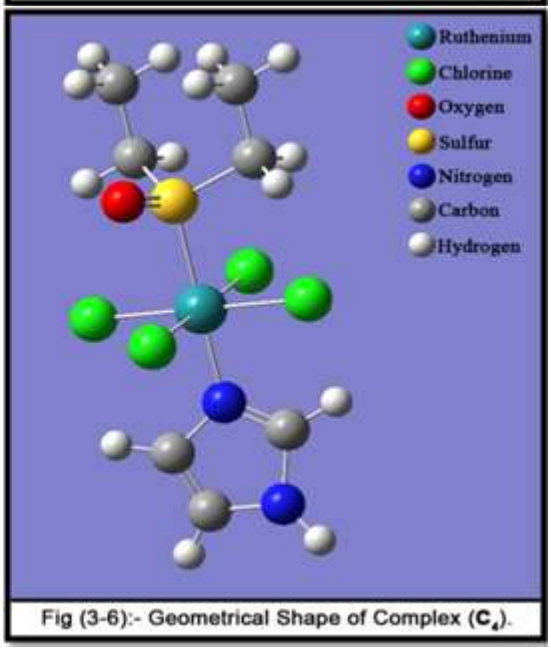

Fig (3-6):- Geometrical Shape of Complex (C_4).

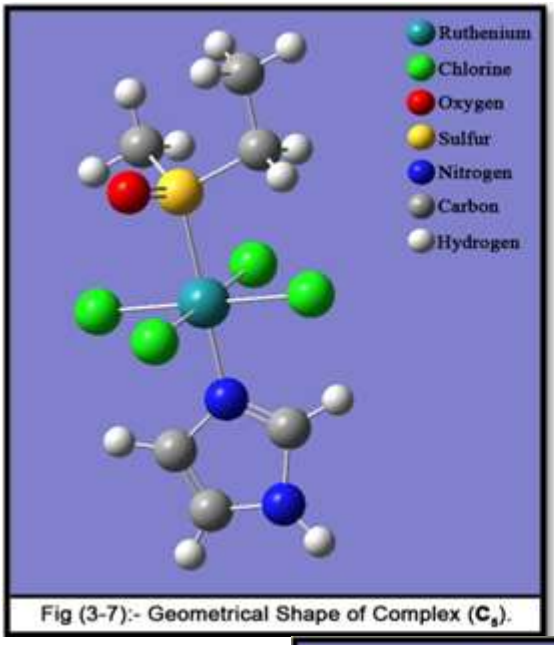

Fig (3-7):- Geometrical Shape of Complex (C_6).

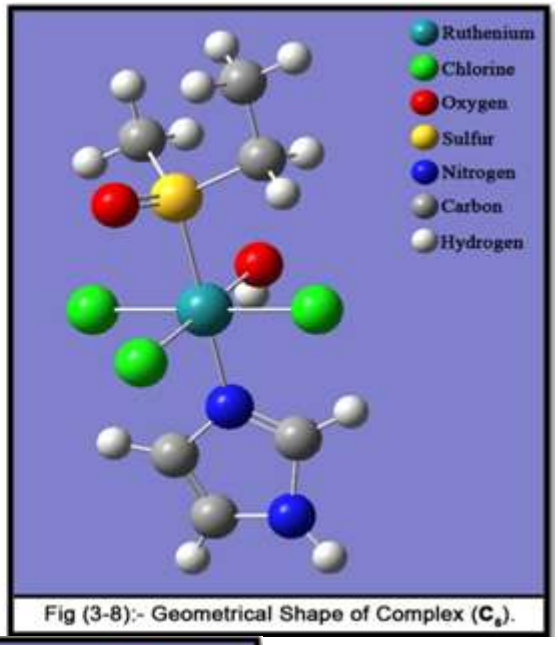

Fig (3-8):- Geometrical Shape of Complex (C_8).

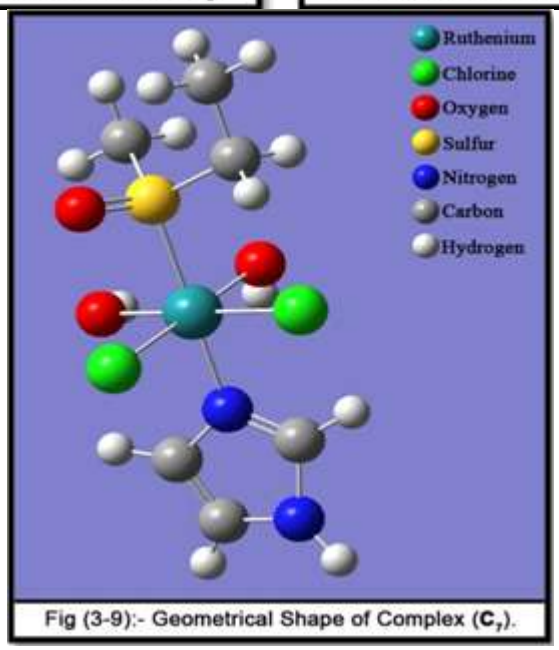

Fig (3-9):- Geometrical Shape of Complex (C_7).

The building ruthenium (III) complexes are represent stable according to mulliken charge data.These data explain that all (Cl) and(N-) ligands carry negative charges and(S-) ligand carry positive chargewhich coordinate with the positive charge of metal ion (ruthenium).on the other hand, the ruthenium (III) charge value is decreased from (+3) to [(0.35<Ru<0.48)] which explain that portion of the electrons have transferred from the ligands to (Ru) ion, table (3-3).

Table (3-3): Mulliken atomic charges of ruthenium (III) ion and coordinated atoms of the ligand

	Ru	L_1	L_2	L_3	L_4	L_5	L_6
C_1	0.412989	-0.465308	-0.478560	-0.462296	-0.386797	0.865449	-0.586136
C_2	0.474752	-0.589633	-0.564808	-0.691076	-0.522988	0.861098	-0.595649
C_3	0.368353	-0.609700	-0.628049	-0.690837	-0.703210	0.850257	-0.577940
C_4	0.431201	-0.463185	-0.477003	-0.460214	-0.389546	0.835727	-0.587630
C_5	0.421127	-0.463694	-0.477643	-0.461462	-0.388517	0.857768	-0.586933
C_6	0.404731	-0.536050	-0.516798	-0.520923	-0.466188	0.863816	-0.593377
C_7	0.359535	-0.577241	-0.588608	-0.538776	-0.493353	0.876200	-0.590904

The most essential orbitals to describe the optical properties of the compound, and chemical and biological activityof the chemical speciesarethe frontier highest occupied MO'sand lowest unoccupied MO's(HOMO, LUMO). Higher value of HOMO of a moleculemean its act as a "Lewis Base" or itcould be oxidationand has ability to donate electrons to convenient acceptor molecule with low energy(or empty molecular orbitals),while higher valueof lowest unoccupied molecular orbital LUMOof a moleculemeanits act as a "Lewis Acid"or itcould bereductionand has a ability to accept electrons fromconvenientdonor molecule.

On the other hand, numerous theoretical studies[17] shown that the mechanism between DNA and ruthinium complexes is depending on the binding and an intercalation (or part intercalation) through the following ideas:

- The base pairs of DNA helix represent an "electron donor", while the drug complexes represent an "electron acceptor".
- The higher values of E_{HOMO}"highest occupiedmolecular orbital" of DNA base-pairs and low values (all values are negative) of E_{LUMO}"lowest unoccupiedmolecular orbital" of the intercalated complex.
- The aqueous environment allow to ligand changes and intercalation occurs.

The obtained results of building complexes in addition to standard complex are explained that both (C_2, C_3, C_6, C_7) are more suitable as anticancer activity compared toward standard complex (C_1), while (C_4, C_5) is lower activity than (C_1),table (3-4) figure [(3-10) to (3-23)].

Additionally and according to ΔE_{gap}, the (C_2, C_3, C_6, C_7) represented more stable complexes than C_1 (standard complex), while the (C_4, C_5) to be more reactive complexes (less stable), table(3-4).

Table (3-4): The energy of Highest Occupied Molecular Orbitals, Lowest Unoccupied Molecular Orbitals, ΔE.

Compound	E_{HOMO} (e.v.)	E_{LUMO} (e.v.)	ΔE (e.v.)
C_1	-0.09388	0.04546	0.13934
C_2	-0.05765	0.08560	0.14325
C_3	-0.03597	0.11591	0.15188
C_4	-0.09458	0.04355	0.13813
C_5	-0.09438	0.04458	0.13896
C_6	-0.07448	0.06526	0.13974
C_7	-0.06334	0.09838	0.16172

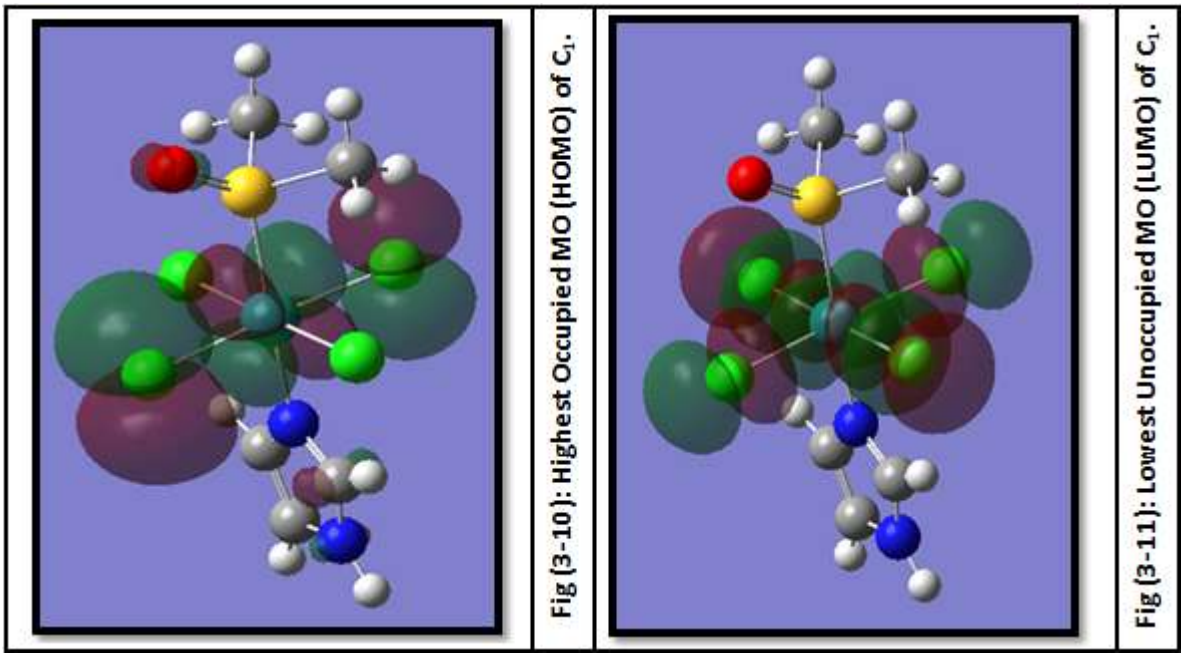

Fig (3-10): Highest Occupied MO (HOMO) of C_1.

Fig (3-11): Lowest Unoccupied MO (LUMO) of C_1.

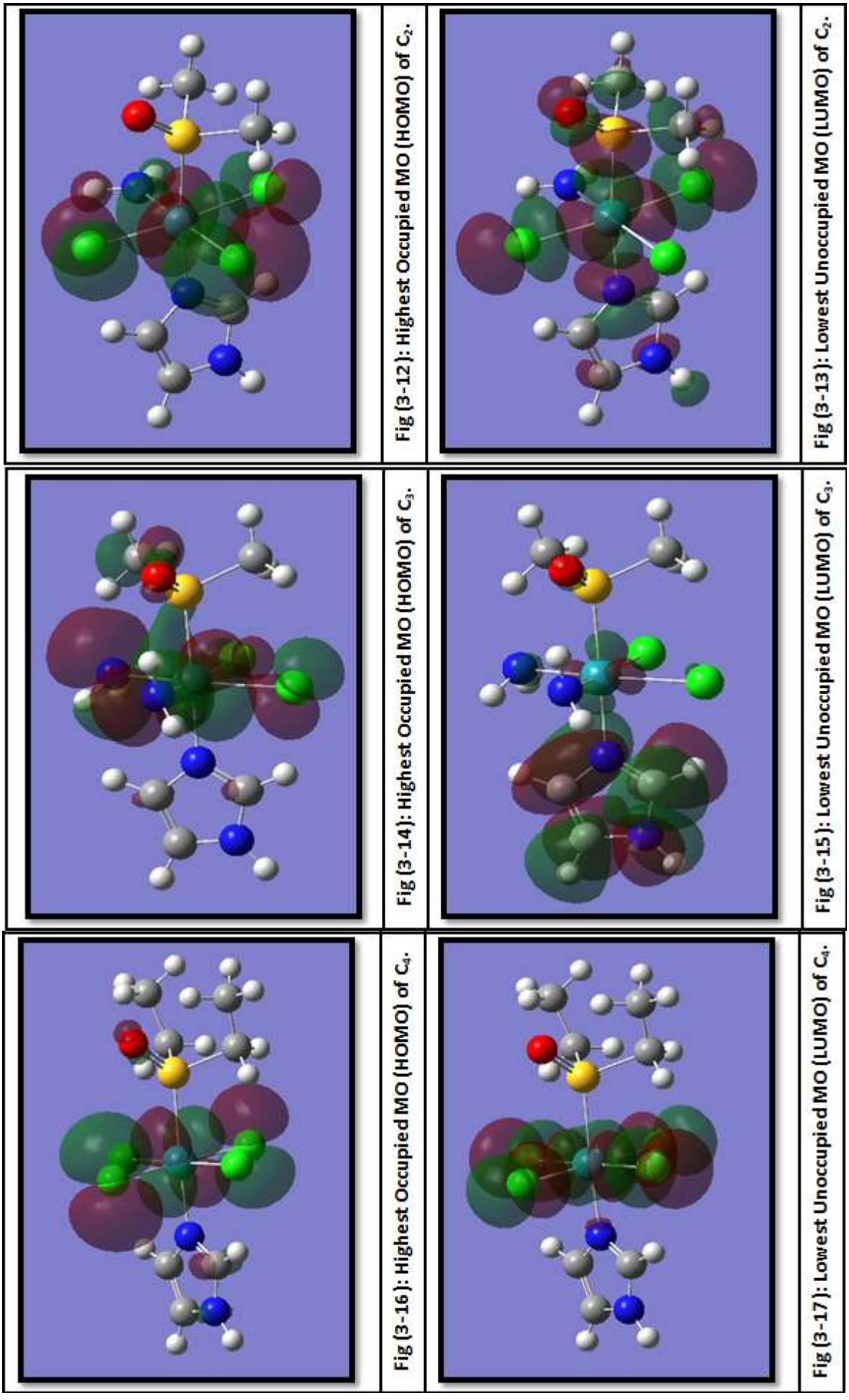

Fig (3-12): Highest Occupied MO (HOMO) of C_2.

Fig (3-13): Lowest Unoccupied MO (LUMO) of C_2.

Fig (3-14): Highest Occupied MO (HOMO) of C_3.

Fig (3-15): Lowest Unoccupied MO (LUMO) of C_3.

Fig (3-16): Highest Occupied MO (HOMO) of C_4.

Fig (3-17): Lowest Unoccupied MO (LUMO) of C_4.

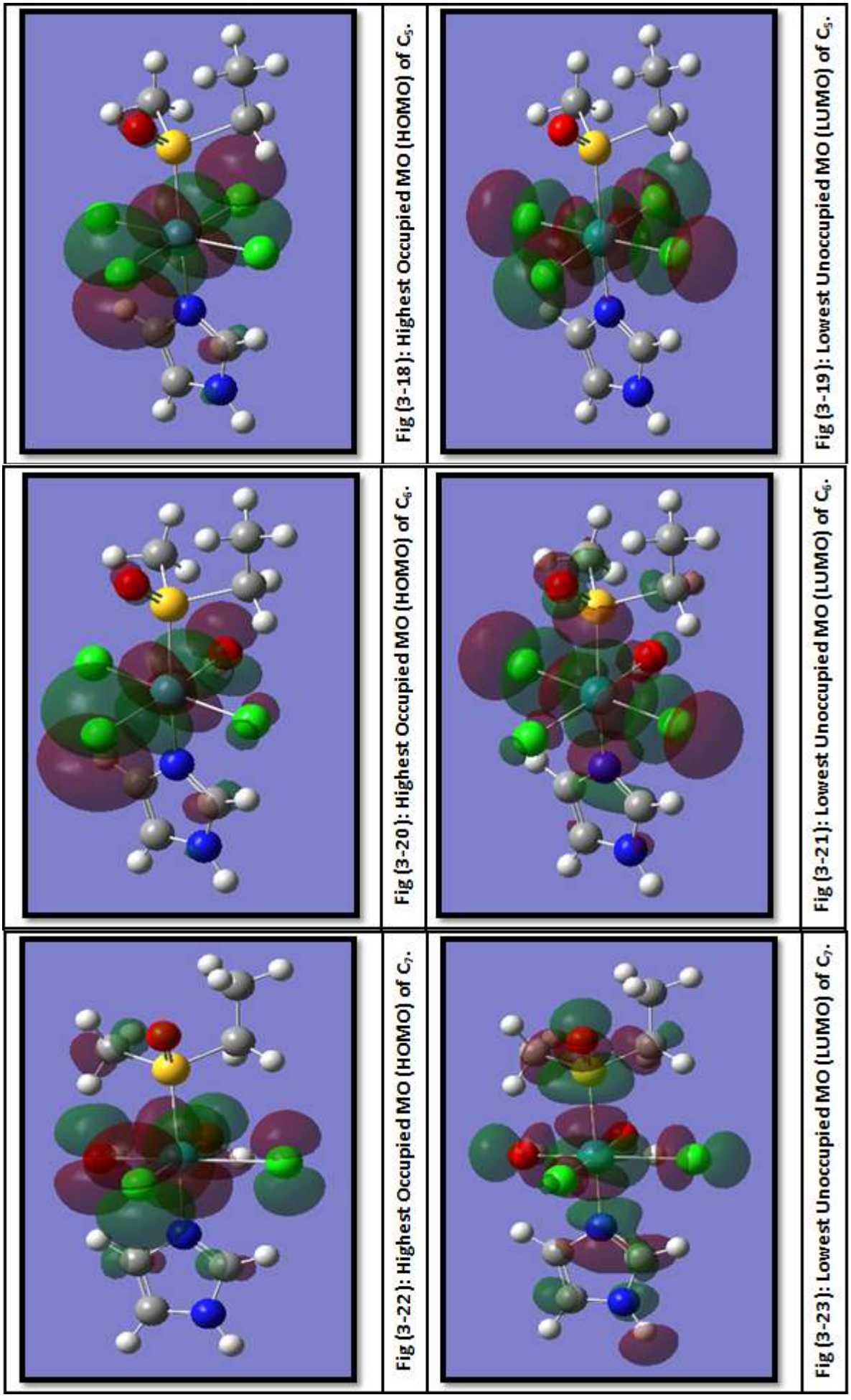

Fig (3-18): Highest Occupied MO (HOMO) of C_5.

Fig (3-19): Lowest Unoccupied MO (LUMO) of C_5.

Fig (3-20): Highest Occupied MO (HOMO) of C_6.

Fig (3-21): Lowest Unoccupied MO (LUMO) of C_6.

Fig (3-22): Highest Occupied MO (HOMO) of C_7.

Fig (3-23): Lowest Unoccupied MO (LUMO) of C_7.

One of the important physical propertyfor the moleculesdescribed are infrared spectrum technique. In that capacity, the (IR) spectrum can be utilized as a unique fingerprint for distinguishing and comparison between the derivative complexes and reference complex (NAMI-A) (standard complex).This first rules approach depends on the fact that structural properties of the complex, regardless of whether they are the spine of the complex or the functional groups attached to the complex ligands.The following figures [(3-24) to (3-30)] show infrared vibration spectra of all building complexes.

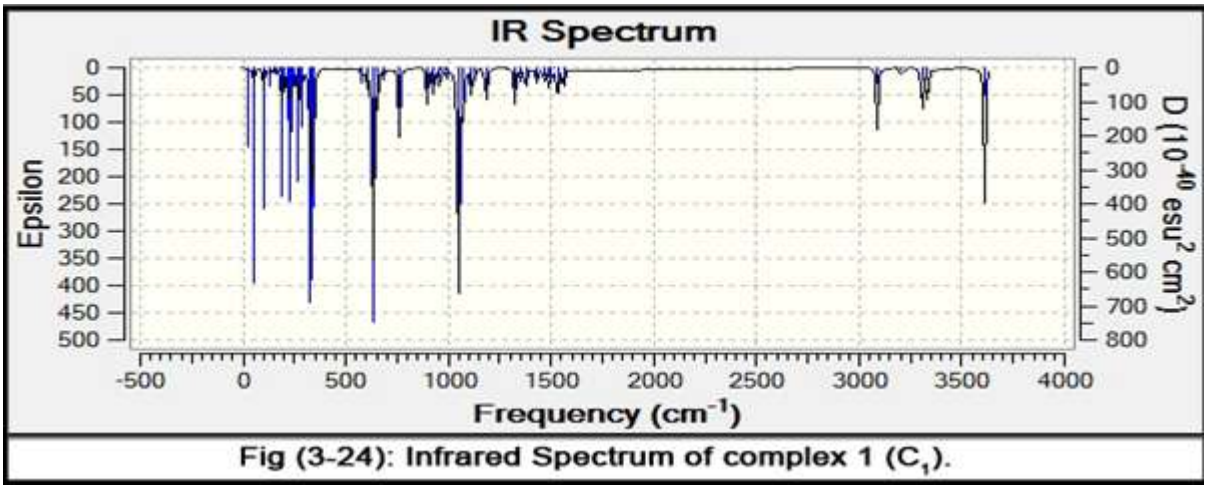

Fig (3-24): Infrared Spectrum of complex 1 (C_1).

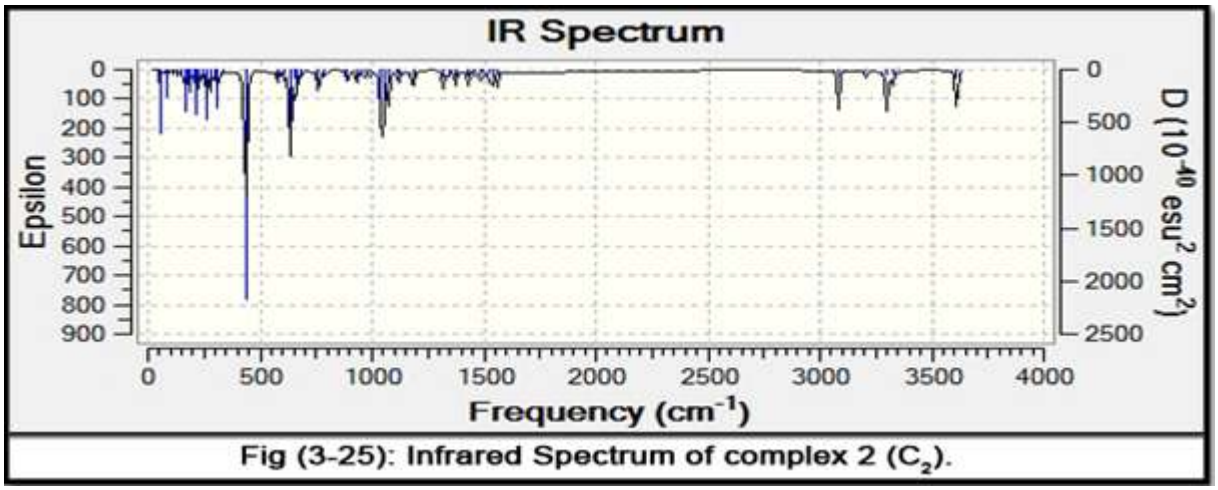

Fig (3-25): Infrared Spectrum of complex 2 (C_2).

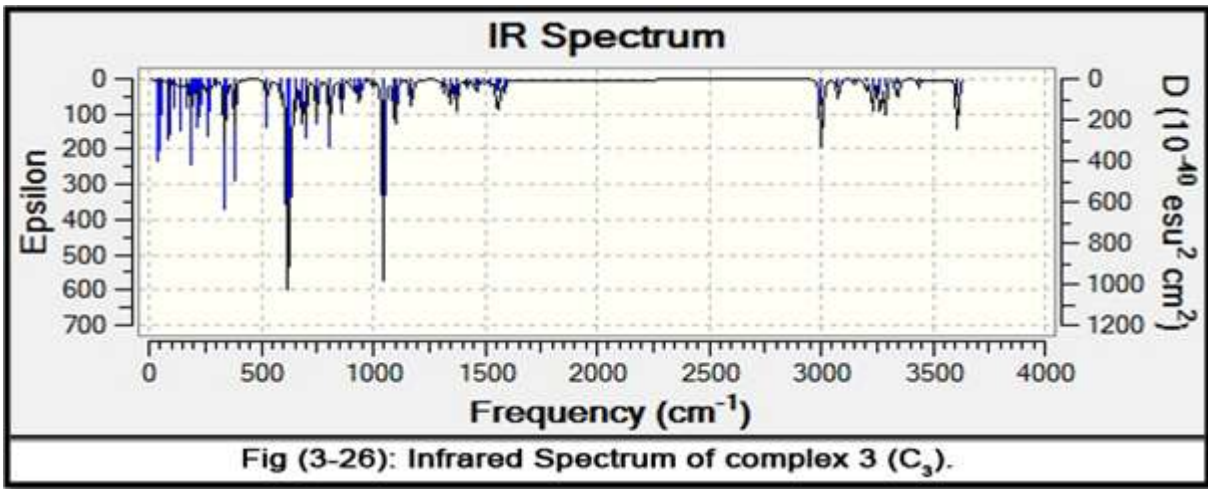

Fig (3-26): Infrared Spectrum of complex 3 (C_3).

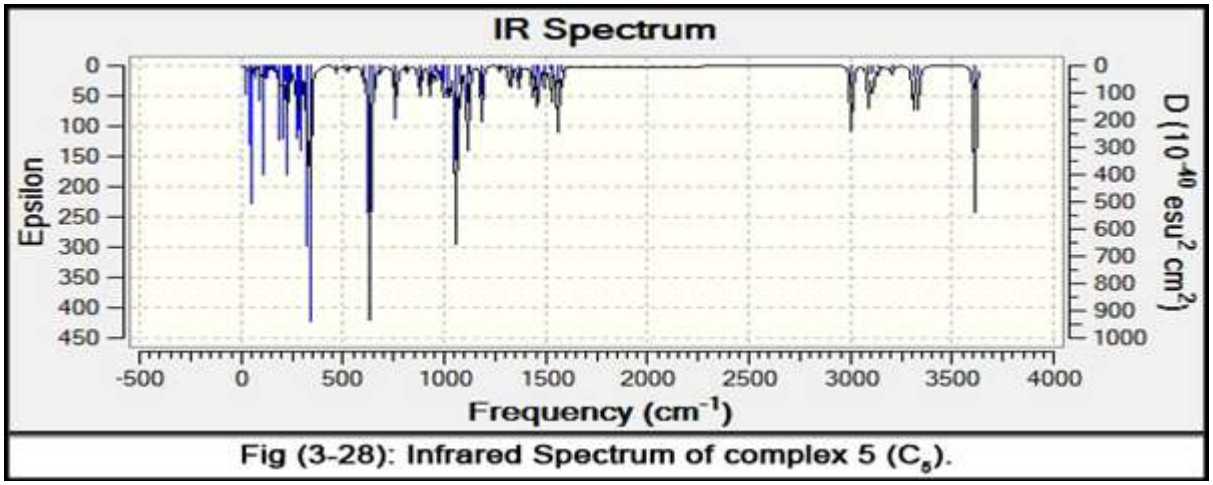

Fig (3-28): Infrared Spectrum of complex 5 (C_5).

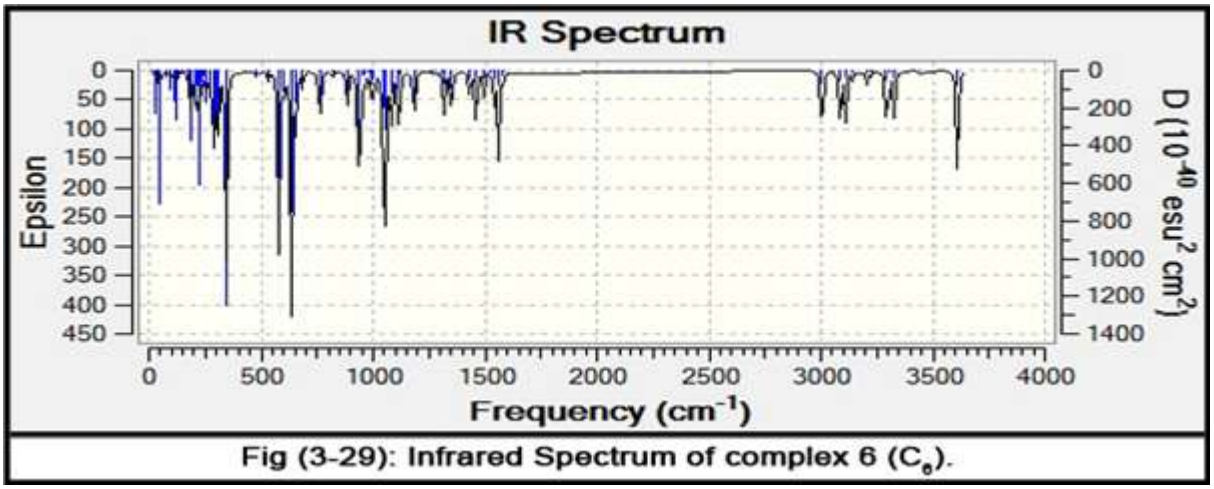

Fig (3-29): Infrared Spectrum of complex 6 (C_6).

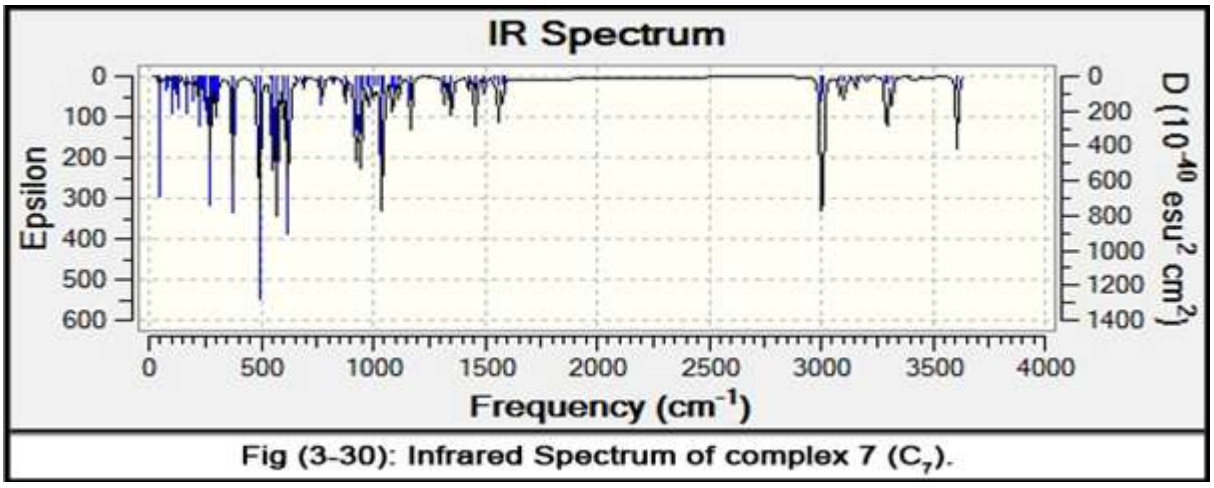

Fig (3-30): Infrared Spectrum of complex 7 (C_7).

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