



SYNTHESIS, CHARACTERISATION, ANTIBACTERIAL AND DOCKING STUDIES OF COPPER AND IRON TYRAMINE DITHIOCARBAMATE METAL COMPLEXES

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Abstract: Tyramine dithiocarbamate Metal complexes of Copper and Iron were synthesized. Initially, the Tyramine dithiocarbamate ligand was synthesized by condensation of Tyramine with carbon disulfide and characterized. This dithiocarbonate was used to prepare the copper and iron metal complexes. These metal complexes were confirmed by ¹H-NMR, ESR, powder XRD, Electronic spectra, Infrared, Conductivity, and Magnetic Susceptibility Studies. All the data confirms that these metals forms complexes with octahedral geometry. Antibacterial activity of ligand and metal complexes was tested against Escherichia coli, Bacillus subtilis, and Klebsiella. Ligand and metal complexes were exhibited moderate antibacterial activity. Tyramine dithiocarbamate ligand and their metal complexes are used for docking studies with Dopamine D₁ receptor for interactive studies by Auto Dock 4.0. All the interactions were reported.

Keywords: Tyramine dithiocarbamate; metal complexes; antibacterial activity and docking studies.

Introduction: There has been intense interest in the coordination compounds of unsaturated sulfur donor chelating ligands, Dithiocarbamate, and their related molecules for chemists, physicists, biologists, and theoreticians alike owing to their interesting chemical properties and possible wide applications^{I-IV}. Interest in molecular structural investigations and chemical studies of these metal chelates covers a whole gamut of areas ranging from general considerations of metal-sulfur bonding, and the formation of four-membered chelate rings to the employment of these ligands in inorganic qualitative analysis^V, their practical application in organic synthesis^{VI}, medicine^{VII}, and biology^{VIII} and their uses as vulcanization accelerators^{IX}, floatation agents, fungicides^X, pesticides^{XI}, radiation protectors^{XII}, antioxidants^{XIII} and photo stabilizers of polymers^{XIV}. Their role in material science has also been quite significant. Guschinet al.,^{XV} has synthesized the diethyl carbamodithiolates, which are potential antiallergic drugs and inhibit the activation of Mast cells. Wong et al.,^{XVI} prepared Dinuclear

Zn (II) carbamodithiolate macrocycles, which show inhibition activity on tumor growth and potentiate other anticancer agents' effect. Mann et al.,^{XVII} has synthesized the carbamodithiolate complexes of copper which shows inhibition on prostate cancer cellular proteasome activity associated with suppression of proliferation and induction of apoptosis. Luca Ranconiet al.,^{XVIII} synthesized Gold (I), Gold (III) carbamodithiolate derivatives with increased bioavailability, higher cytotoxicity, and lower side effects than cisplatin. Diethyl carbamodithiolate^{XIX} has extensive clinical use in the treatment of Wilson's disease, i.e. copper poisoning and a variety of other heavy-metal poisoning, and inhibits the progression of HIV implicated in AIDS. Diethyl carbamodithiolates are also hampering the activity of Cu/Zn-superoxide dismutase (SOD) through the withdrawal of copper from the protein both in-vitro and invitro^{XX}. Carbamodithiolate is effective in the reduction of several secondary effects associated with chemotherapeutic agents such as cisplatin^{XXI}.

Materials and Methods

All the chemicals used were analytical grade, used without purification.

Synthesis of Tyramine Dithiocarbamateligand

0.1 mol of Tyramine (bought from merk chemicals) was dissolved in 50 ml of absolute ethyl alcohol in a clean beaker placed in ice. To this cold solution, add 10 ml of Sodium hydroxide (10N) solution, and then add Carbon disulfide(Fisher scientific chemicals) (0.1 mol) in dropwise through separating funnel in about 30 min with constant stirring. The contents were stirred mechanically for about 30 min, sodium salt of Dithiocarbamate precipitated out. It was dried and recrystallised from methanol and dried in vacuum over calcium chloride. Synthetic procedures yield and melting points were mentioned below.

Synthesis of copper and iron metal complexes of Tyramine Dithiocarbamate

The aqueous solution of 0.1 Mol of metal salts ferric chloride(Aldrich Chemicals) copper chloride(Aldrich chemicals)was added with constant stirring to an aqueous solution of 0.1mol of Sodium Dithiocarbamateligand. The reaction mixture was stirred at room temperature for 2 hours. The coloured precipitates were obtained. The precipitates were filtered and washed with water and then with Methanol and dried over calcium chloride in a desiccator. All the complexes were prepared in 1:2 ratios of Metal to Ligand. The newly synthesized ligands and their metal complexes with their elemental analysis data Magnetic, conductivity, I.R, NMR, ESR.UV and XRD

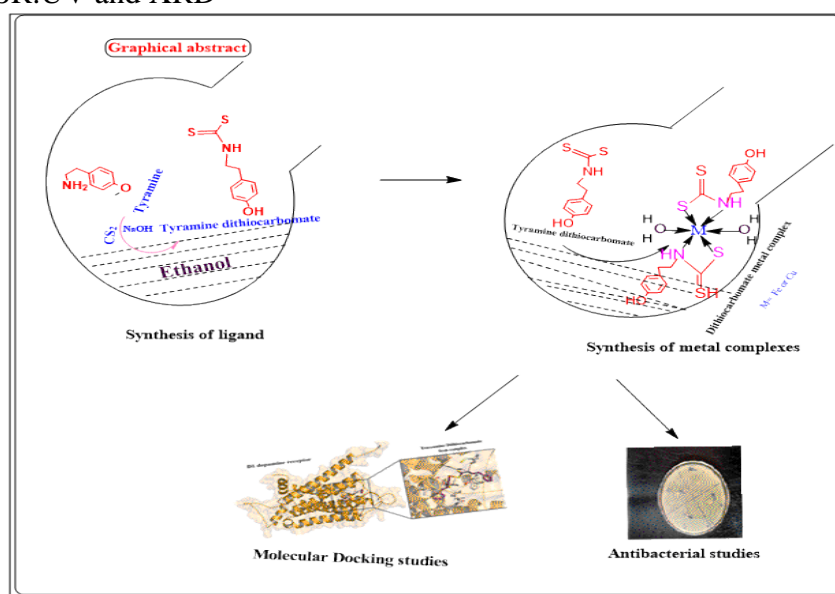


Fig:1.Graphical abstract showing of synthesis and their applications of newly synthesised metal complexes

Results and Discussion

Infrared spectral analysis

The analysis of IR spectra of Dithiocarbamate complexes of transition metals had arisen and considerable interest both diagnostically to determine the mode of coordination and as a means of assessing the nature of bonding in these complexes. The Infrared spectrum of Cu (II) complex was compared the ligand. The typical IR Spectrum of [Cu(TRACT)₂] complex is presented in Fig-3 A strong band exhibited at 1498.82cm⁻¹ in the I.R spectrum of the ligand, which was assigned to the thioureide bond, was shifted to 1498.82-1540.68cm⁻¹ region. On Passage from the free Dithiocarbamate ligand to their complex, the ν(N-CSS) mode is shifted to higher energies, showing a increase of Carbon-Nitrogen double-bond character and hence a greater contribution of the structure. The appearance of broadband at 3411.4 cm⁻¹ can be assigned to the stretching vibrations of ν- NH and coordinated water molecules present in their complexes. In the spectra of both ligand and complex, significant change was observed for molecular vibrational stretching mode. The one weaker band at 1027.7-672.52 cm⁻¹ were assigned respectively to -OH rocking and wagging vibrations of co-ordinated water in the complex. The band in the region 878.18 cm⁻¹ was assigned to the ν (M-S) metal-ligand bond of the complex. The typical IR Spectrum of [Fe(TRACT)₂] was shown in fig-4. The appearance of broadband at 3390.05cm⁻¹ can be assigned to the stretching vibrations of ν- NH and coordinated water molecules present in their complexes. In the spectra of both ligand and complex, significant changes were observed for molecular vibrational stretching mode. The two weaker bands at 878.18 cm⁻¹ were assigned respectively to -OH rocking and wagging vibrations of co-ordinated water in the complex.

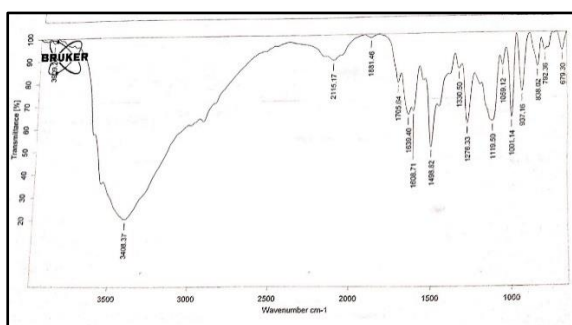


Fig: 2, IR Spectrum of the TRACT Ligand

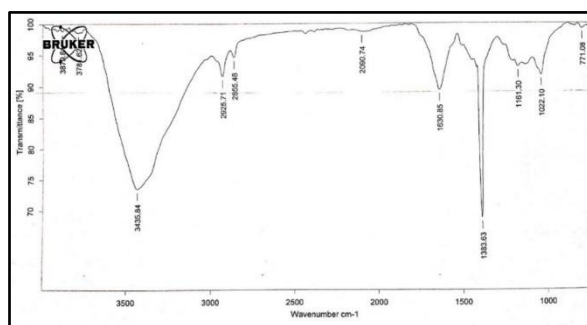


Fig:3. IR Spectrum of the [Cu(TRACT)₂] Metal Complex

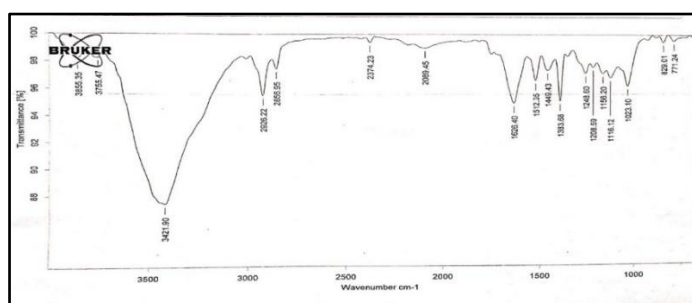


Fig: 4, IR Spectrum of the [Fe(TRACT)₂] Metal Complex.

Table :1. I.R spectral data of Tyramine Dithiocarbamate and its metal complexes

Compound name	Thioureied bond	-NH-	-C=C-	C-S	M-S
TRADE	1498.82	3408.37	1608.71	1001.71	-----
[Cu(TRADTC) ₂]	1540.68	3411.4	1620.0	1027.7	772.62
[Fe(TRADTC) ₂]	1528.0	3390.05	1628.0	1020.6	878.18

¹HNMR Spectral analysis

¹HNMR spectrum of Tyramine Dithiocarbamate (TRADTC)(Fig:5). Phenyl ring of Dithiocarbamate ligand forms a signal at 7.25 ppm and one more singlet appeared in the region 5.5 ppm due to OH proton and 3.25ppm was due to NH₂proton. The main characteristic peak appears in the region of 7.25 ppm indicate NH proton of in thioureide region of Dithiocarbamate ligand. ¹HNMR spectrum of Cu and Fe metal complex shown in Fig:6&7. In the complexes signal due to proton bonded to Nitrogen in the thioureide bond was observed in the 7.25 to 7.27 ppm. The down field shift of the complex may be attributed to an increase of the - bond character and the delocalization of electrons along the C-N bond contributed by the substituents and also by the bidentate nature of the dithiocarbamate ligand.

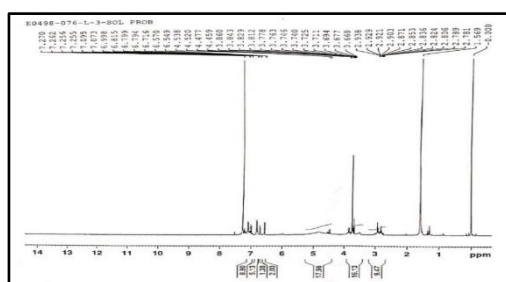


Fig.:5, ¹HNMR Spectrum of the TRADTC ligand

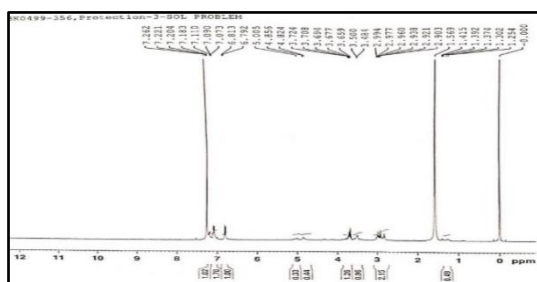


Fig.6, ¹HNMR Spectrum of the [Cu(TRAADTC)₂] Metal Complex

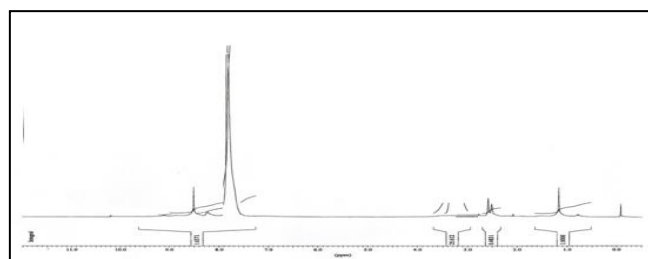


Fig:7. ¹HNMR Spectrum of the [Fe(TRAADTC)₂] Metal Complex

Table:2. ¹H-NMRSpectral Analysis data of Tyramine Dithiocarbamate Metal Complexes

Compound	H-N-C (thioureide bond)	(H ₂ O) Coordinated water
TRACT	7.25	-----
[Cu(TRACT) ₂]	7.27	10.8
[Fe(TRACT) ₂]	7.97	9.9

Ultraviolet –Visible spectral analysis

The solution electronic spectra of the ligand and the complexes were recorded in DMF as solvent in the UV-Visible region. The electronic spectra of the Sodium salt of Tyramine

Dithiocarbamate (TRADTC)ligand shown in **Fig-8**, it shows alone intense absorption bands at 274.00 nm These band may be due to $\pi-\pi^*$ and $n-\pi^*$ transitions of N- C-S group and S-C-S. On complexation these bands were shifted. In all the complexes, bands below 300 nm were attributed to the intra ligand transitions. The Electronic spectrum of the [Cu(TRACT)₂]and [Fe(TRACT)₂] complexes were shown in the **Fig-9 and Fig-10**. The Copper complex shows one intense band observed at 276.00 nm were assigned to the intra molecular charge transfer of ligand $\pi-\pi^*$ and $n-\pi^*$ in the N-C = S group).The complex shows two less intense broad bands in the high wavelength region corresponding to intra ligand d – d metal orbital's transitions. In particular this broadband can be assigned to the $d_{xy} d_x^2 - y^2$ and $d_{xz, yz} d_x^2 - y^2$ transitions. The Electronic spectrum of the [Fe (TRACT)₂] complex was shown in the **Fig-10**. The Ruthenium complex shows two intense bands observed at 278.00 was assigned to the intra molecular charge transfer of ligand $\pi-\pi^*$ and $n-\pi^*$ in the N-C = S group).The complex shows two less intense broad bands in the high wavelength region corresponding to intra ligand d – d metal orbital's transitions. In particular this broadband can be assigned to the $d_{xy}d_x^2 - y^2$ and $d_{xz, yz} d_x^2 - y^2$ transitions.

Table:3. UV-Vis spectral data of the ligand TRADCT and its metal complexes

Compound	max/nm	Possible assignment
L = VCCDT	274.00	$\pi-\pi^*$, $n-\pi^*$
[Cu(L) ₂ (H ₂ O) ₂]	276.00	$n-\pi^*$
[Fe(L) ₂ (H ₂ O) ₂]	278.00	$\pi-\pi^*$ $n-\pi^*$

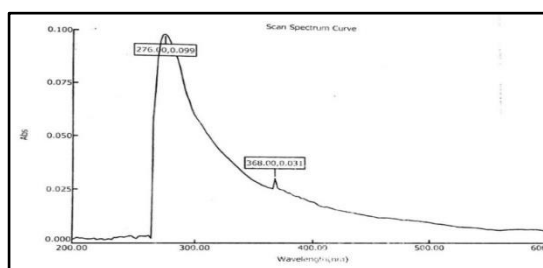


Fig:8. UV-Visible Spectrum of the TRACT ligand Complex

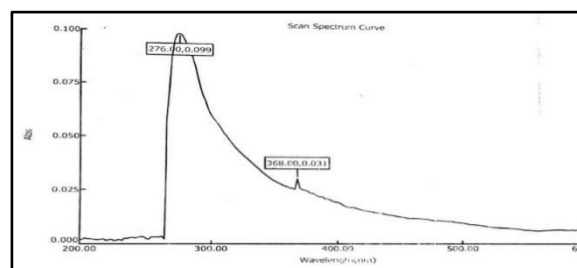


Fig:9. UV-Visible Spectrum of the [Cu(TRACT)₂] Metal Complex

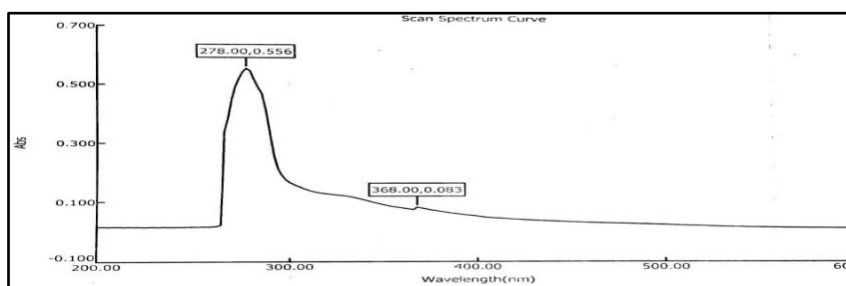


Fig:10. UV-Visible Spectrum of the [Fe(TRACT)₂] Metal Complex

ESR Spectral Analysis of Tyramine Dithiocarbamate (TRADTC) Metal Complexes

ESR spectra obtained for copper complex in DMF at liquid nitrogen temperature and representative ESR spectrum was presented in Fig.11. In this low temperature spectrum, the three peaks of small intensity have been identified, which are considered to originate from $g\parallel$ component. The spin Hamiltonian, orbital reduction and bonding parameters of the complex

were given in Table.4. $g_{||}$ value is less than 2.3 the covalent bond character can be predicted to exist between the metal and the ligand for complex. The trend $g_{||} > g_{ave} > g_{\perp} > 2.0023$ observed of the complex suggests that the unpaired electron was localized in $d_{x^2-y^2}$ orbital [16] of the copper (II) complex. The lowest g value (>2.0027) is also consistent with $d_{x^2-y^2}$ ground state. The $g_{||}/A_{||}$ quotient value was 112.86 cm^{-1} , evidence in support of the octahedral geometry with no appreciable distortion. According to Heathway^{XXII}, for the present complex the $G=4.464$, indicates the formation of monomeric complexes^{XXIII}.

The reduction of P-value of the free ion value (0.036 cm^{-1}) might be attributed to the strong covalent bonding. The shape of ESR lines, ESR data together with the electronic spectral data suggest octahedral geometry for copper complex^{XXIV}.

Table:4. Spin Hamiltonian and orbital reduction parameters of copper complex in DMF solution

Parameters	[Cu(TRACT) ₂]
$g_{ }$	2.4041
g_{\perp}	2.0923
g_{ave}	2.2321
G	4.4644
$A_{ }^*$	0.0103
A_{\perp}^*	0.0102
A_{ave}^*	0.0287
$K_{ }$	0.0276
K_{\perp}	0.0288
P^*	0.0063
α^2	0.9234

* Values are given as cm^{-1} units.

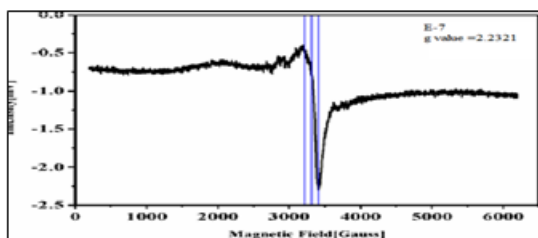


Fig:11. ESR Spectrum of the [Cu(TRACT)₂] Metal Complex

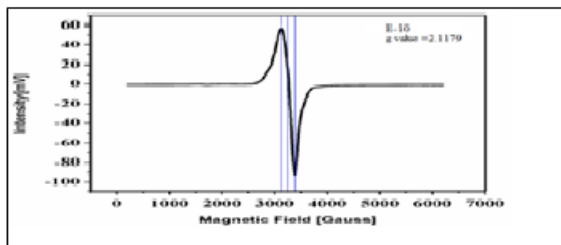


Fig:12. ESR Spectrum of the [Fe(TRACT)₂] Metal Complex

Powdered X-ray diffraction analysis

The X-Ray diffractogram of [M(TRACT)₂] Complexes were shown in the Fig.13&14 which were ranging between $5-50\theta$, Where θ is the Bragg's angle. All the main peaks were indicated and calculated values of Miller indices (h k l) along with observed d-specified. All the peaks have been indexed and 2θ values compared in the graph. The patterns were qualitative and dispersive in intensity for Cu and Ru metal complexes. The XRD patterns were used to explain qualitatively the degree of crystallinity. The diffraction patterns of the complex had been indexed by standard methods, and the (h k l) values were calculated from the indexed data by trial-and-error method. Cu 651,742,531,442, 753,543, 442, 321, 211, 432,.....Fe(TRACT)₂ complexes 120,311,322,330,430,410,421,422,400,510,.....

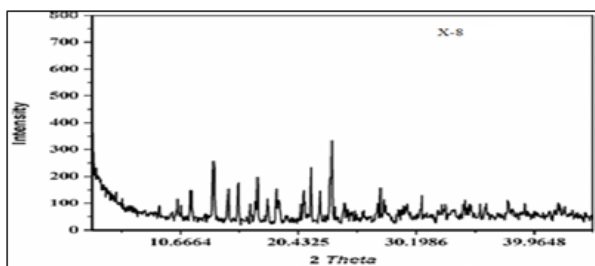


Fig.13 : X-Ray diffractogram of the [Fe(TRADTC)₂] Metal Complex

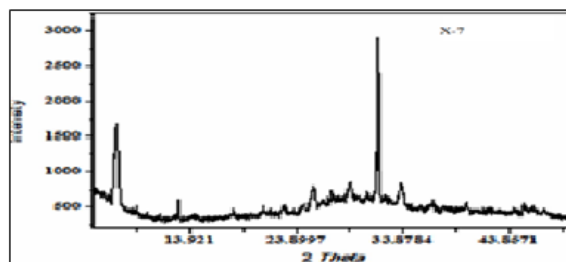


Fig.14 : X-Ray diffractogram of the [Cu(TRADTC)₂] Metal Complex

Conductivity Measurements

The molar conductance of the complex in DMF (1×10^{-3} M) was determined at $27 \pm 2^\circ\text{C}$ using systronic 303 direct reading conductivity of the bridge. The specific and molar conductance value was calculated. If molar conductance value is more than $20 \text{ Ohm}^{-1}\text{cm}^{-1}$ the metal complex is said to be electrolytic in nature if the k value is less than $20 \text{ Ohm}^{-1}\text{cm}^{-1}$, the metal complex are said to be non-electrolytic in nature^{XXV}. The conductance values of all metal complexes were given in the table; molar conductance value for all the newly synthesized complexes were in the range $730\text{-}750 \text{ Ohm}^{-1} \text{ cm}^2, \text{ mol}^{-1}$ the molar conductance of all metal complexes shows them to be electrolytic in nature.^{XXVI-XXVIII}

Table:5. Conductance data for [M(TRADTC)₂] complexes (with cell constant 1.01)

Metal Complex	Conductance (Ohm ⁻¹)	Specific conductance (Ohm ⁻¹ . Cm ⁻¹)	Molar conductance (Ohm ⁻¹ . Cm ² . Mol ⁻¹)
[Cu(TRADTC) ₂ (H ₂ O) ₂]	0.75	0.75	750
[Ru(TRADTC) ₂ (H ₂ O) ₂]	0.73	0.73	730

Magnetic susceptibility measurement

The effective magnetic moment values of synthesized Cu and Ru complexes show magnetic moment 1.83, and 4.78 B.M.

Table:6. Antibacterial activities of ligands and their transition metal complexes (Zone formation in mm)

Compound	Escherichia coli	Klebsiella	Bacillus subtilis
TACT	20	30	21
[Cu(TADCT) ₂]	22	32	25
[Fe(TADCT) ₂]	25	35	22

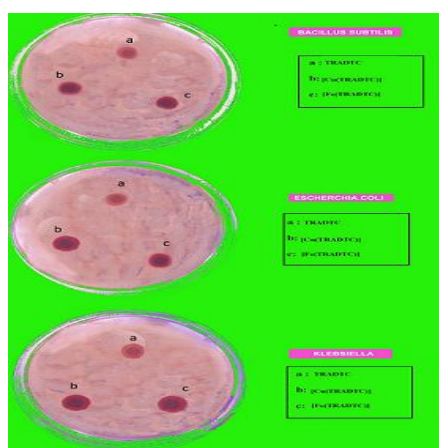


Fig:15. Antibacterial activities of ligands and their transition metal complexes (Zone formation in mm)

Docking Studies of Ligands and Metal Complexes

In the present all the calculations were performed on a workplace by AMD 64 bits dual processing hi-end server machines. Molecular docking calculations^{XXIX-XXXII} were performed with AutoDock 4.0. If not otherwise stated, default settings were used during all calculations., Tyramine ligand and its metal complexes are docking with Dopamine D1receptor the interactions studied shown in table-7.

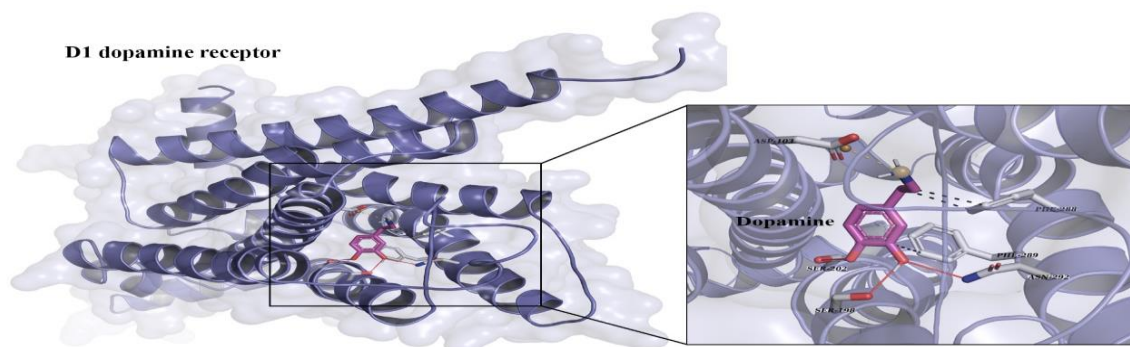


Fig.16. Dopamine receptor with tyramine dithiocarbamate ligand

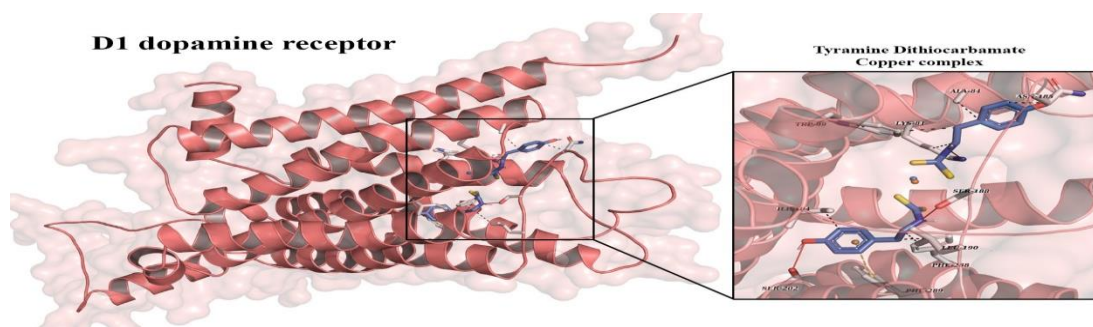


Fig.18. Tyramine dithiocarbamate Copper Complex docking with D1 dopamine receptor

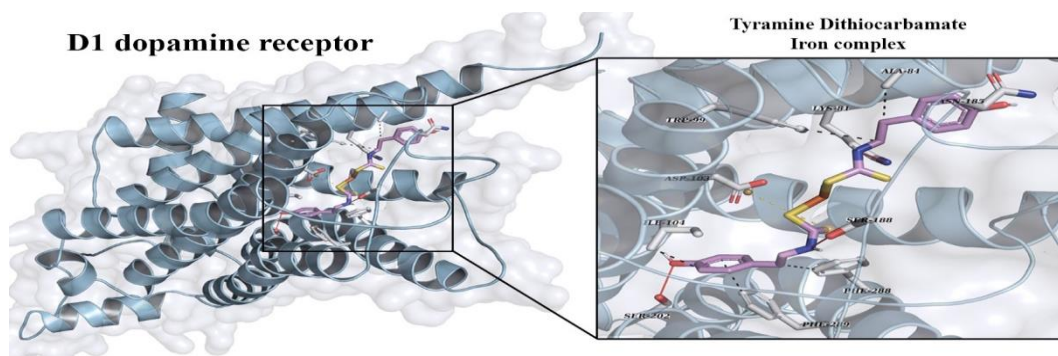


Fig.19. Tyramine dithiocarbamate Iron dithiocarbamate complex docking with D1 dopamine receptor.

Conflict of interest: Author has no conflict of interest.

Conclusion: Tyramine dithiocarbamate Metal complexes of Copper and Iron were synthesized. All the data confirms that these metals forms complexes with octahedral geometry. Antibacterial activity of ligand and metal complexes was tested against *Escherichia coli*, *Bacillus subtilis*, and *Klebsiella*. Ligand and metal complexes were exhibited moderate antibacterial activity. Tyramine dithiocarbamate ligand and their metal complexes are used for docking studies with Dopamine D₁ receptor for interactive studies. All the interactions were reported. We wish this study may help in development of organometallic chemistry

Table: 7. Results of the docking interactions of Tyramine ligand and its metal complexes with Dopamine D₁receptor.

S.N O.	Ligands	Binding Energy (Kcal/Mol)	Hydrogen Bonds			Hydrophobic Interactions		Salt Bridges			π-Stacking					Metal Complexes		
			Residues	Bond Distance (Å)	Donor Angle (°)	Residues	Bond Distance (Å)	Residues	Distance (Å)	Ligand Group	Residues	Bond Distance (Å)	Angle (°)	Offset	Type	Residues	Bond Distance (Å)	Location
1	Tyramine dithiocarbamate Iron Complex	-7.7	Lys81	3.28	122.04	Ala84	3.58	Asp103	5	Sulfonium	Phe289	5.25	75.1	1.84	T-shaped	-	-	-
			Ser188	2.22	169.44	Trp99	3.93	-	-	-	-	-	-	-	-	-	-	-
			Ser202	2.14	128.37	Ile104	3.36	-	-	-	-	-	-	-	-	-	-	-
			-	-	-	Asn185	3.8	-	-	-	-	-	-	-	-	-	-	-
			-	-	-	Phe288	3.82	-	-	-	-	-	-	-	-	-	-	-
			-	-	-	Phe289	3.75	-	-	-	-	-	-	-	-	-	-	-
2	Tyramine dithiocarbamate Copper Complex	-7.7	Lys81	3.16	126.38	Lys81	3.89	-	-	-	-	-	-	-	-	-	-	
			Ser188	2.1	167.23	Ala84	3.7	-	-	-	-	-	-	-	-	-	-	
			Ser202	2.29	137.19	Trp99	3.61	-	-	-	-	-	-	-	-	-	-	
			-	-	-	Ile104	3.7	-	-	-	-	-	-	-	-	-	-	
			-	-	-	Asn185	3.68	-	-	-	-	-	-	-	-	-	-	
			-	-	-	Leu190	3.75	-	-	-	-	-	-	-	-	-	-	
*	681_Dopamine	-5.7	Ser198	2.1	142.65	Phe288	3.75	Asp103	2.95	Tertamine	-	-	-	-	-	-	-	
			Ser202	1.98	135.93	Phe288	3.8	-	-	-	-	-	-	-	-	-		
			Asn292	2.61	110.75	Phe289	3.67	-	-	-	-	-	-	-	-	-		

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