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Microwave assisted template synthesis of metal based EGFR, TRK inhibitors, molecular docking and *in vitro* biological studies

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Metal based biologically active compounds have been synthesized by microwave assisted template condensation method and characterized by spectro-analytical techniques like molar conductance, UV-visible, infrared and mass spectroscopy and thermogravimetric analysis. The metal is arranged in octahedral geometry surrounded by tetradentate ligand framework. The binding affinity of all the metal complexes has been evaluated theoretically by molecular docking studies against epidermal growth factor receptor (EGFR) and tyrosine kinase (TRK) receptor molecules which are further verified by in vitro anticancer activity. Complex $[Cr(C_{16}H_{11}N_4O_2)(NO_3)_2]NO_3$ have showed potent *in vitro* cytotoxicity (IC_{50} value 39.5µM) against SCC4 cancer cell line. Antioxidant study has also performed by DPPH assay and significant results are found. $[Fe(C_{16}H_{11}N_4O_2)(OAc)_2]OAc$ and $[Cr(C_{16}H_{11}N_4O_2)\ (OAc)_2]OAc$ are most effective antioxidants with 78.7% and 76.8% free radical scavenging activity, respectively.

Keywords: Antioxidant, EGFR, microwave method, Molecular docking, Template synthesis

Nitrogen and oxygen containing ligand moiety has a strong affinity to form stable transition metals complexes and received a huge attention because of their considerable biological activities[1-4]. This kind of molecules has shown diverse applications such as catalysis, enzyme mimetic activity, chemical sensors, selective metal ion recovery, and pharmacology[5]. Isatin is one of such kind of ligand systems which has a wide variety of pharmacological applications including anticancer activity[6-7]. Isatin is a versatile ligand with one nitrogen and two oxygen donor atoms and it is a core constituent of many alkaloids, drugs, dyes, pesticides and analytical reagents. A large number of structurally diverse derivatives of isatin have been developed due to its synthetic versatility which includes, analogues derived from aryl ring modification or by substituting/modifying the nitrogen/carbonyl groups of indole ring[8]. It has been proven by research that biological activity of such type of molecules generally increases on their complexation with transition metal ions[9]. These compounds generally inhibit the cancerous tumor growth by interacting with a number of intracellular targets like Protein kinases, DNA, telomerase, P-glycoprotein etc.[10].

The coordination potential of these ligand frameworks and their diverse applications motivated us to explore new coordination compounds derived from isatin, evaluating their antioxidant potential and anticancer activity against human cancer cell line. This article deals with microwave assisted template synthesis of macrocyclic metal complexes derived from benzene-1,4-dicarbohydrazide and 1H-indole-2, 3-dione (isatin) with trivalent transition metal Cr(III) and Fe(III) salts. The metal complexes were assessed for their antioxidant activity and cytotoxicity against head and neck cancer cell line Squamous cell carcinoma (SCC4). Moreover, molecular docking studies were performed to predict the binding energy of synthesized compounds to the molecular target Epidermal Growth Factor Receptor (EGFR) Kinase and tyrosine kinase (TRK). EGFR and TRK are important molecular targets for the development of novel anticancer drugs. In many solid tumors like head and neck, ovarian and colon tumors cell lines an over expression of EGFR has been detected[11] which signals through tyrosine kinase. Both of these have been proven as attractive oncology targets for therapeutic intrusions due to their significant roles of abnormal signaling in cancer cells.

Materials and Methods

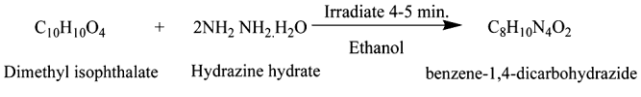
The chemicals used in study including isatin, dimethyl-phenyl-isophthalate, hydrazine hydrate, metal salts were purchased from Sigma Aldrich. Solvents used in the study were purchased from Merck India. The CHN analysis was recorded using a Perkin Elmer 2400 elemental analyzer. The FTIR spectra were recorded in the range 4000–400 cm^{-1} on Thermo Scientific Nicolet S 50 FTIR spectrophotometer using KBr pallets. Ultraviolet–visible spectra were recorded in DMSO on Perkin Elmer Lambda 25 spectrophotometer at room temperature. The thermogravimetric analysis (TGA) was performed on Perkin Elmer thermoanalyzer between temperatures 0-1000 ºC at a heating rate of 10 ºC/min.

Synthesis of benzene-1,4-dicarbohydrazide

A mixture of dimethyl-phenyl-isophthalate (10 mmol) and 2 mL hydrazine hydrate (98%) in 4-5mL ethanol was irradiated at 300 W for 4-5 min. The resulting mixture was kept to get the room temperature and then the reaction mixture was poured onto ice cold water. The precipitate thus obtained was filtered and recrystallized by using ethanol. Yield ~85% (Scheme 1).

Template synthesis of Cr(III) and Fe(III) complexes of benzene-1, 4-dicarbohydrazide and 1H-indole-2, 3-dione

Benzene-1, 4-dicarbohydrazide and respective metal salt were mixed in 1:1 molar ratio in a grinder. After that the mixture was irradiated at 300 W. in UWave-1000, microwave synthesizer by taking 8-10 ml of methanol and 4-5 drops of dil. HCl. After 3-4 min, an equimolar amount of 1*H*-indole-2, 3-dione (isatin) was added to the reaction mixture and it was further irradiated for 8-10 min. Colored precipitates were produced (~75-82%) which were washed with methanol, diethyl ether and dried in vacuum desiccator over anhydrous $CaCl_2$ (Scheme 2). The purity of synthesized metal complexes has been checked by TLC run in 80:20 ratio of dimethylsulfoxide (DMSO) and acetonitrile[12].



Scheme 1 — Microwave synthesis of benzene-1, 4-dicarbohydrazide

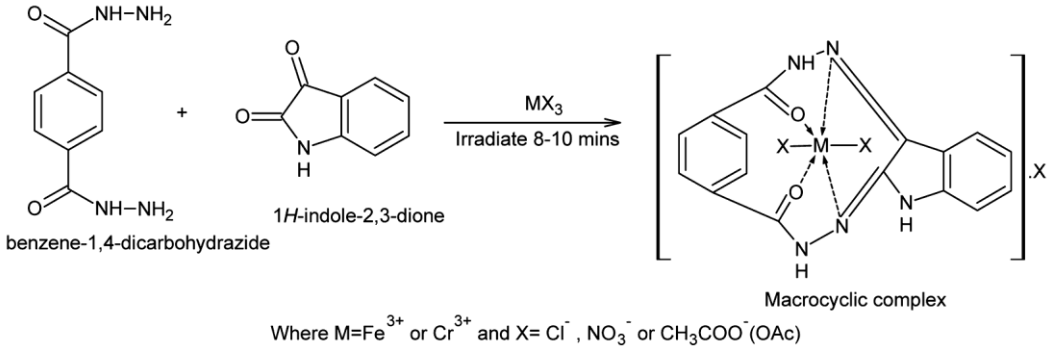
Physicochemical characterization

Metal complexes containing desired ligand framework were synthesized by template method in good yield in 1:1:1 molar ratio of isatin, metal salt and benzene-1, 4-dicarbohydrazide. The formation of ligand framework in macrocyclic complexes has been inferred on the basis of results obtained from elemental analyses, molar conductance, mass spectra (Table 1) and FTIR analysis. The molar conductance values in dimethylformamide (DMF) have indicated them to be 1:1 electrolyte (60-80 $ohm^{-1}cm^2mol^{-1}$) in nature[13]. The position of the absorption bands in electronic spectra and observed values of magnetic moment have revealed the overall geometry of molecules. Evidence of the absence of water molecules and thermal stability of the complexes was studied by their TG analysis.

Biological activity

Molecular Docking study

AutoDock 4.2 program was used for the prediction of binding energy and searching for the best possible binding site together using the Lamarckian genetic algorithm. AutoDock Tools were used to carry out molecular docking calculations of the synthesized metal complexes with protein receptors EGFR kinase and tyrosine kinase (TRK)[14-16]. The co-crystal structure of EGFR-erlotinib complex (PDB ID: 1M17, resolution of 2.6 Å) was downloaded from Protein Data Bank and the co-crystal structure of tyrosine complex (1t46) obtained with a resolution of 1.60 Å. The downloaded protein structures were undergone



Scheme 2 — Microwave template synthesis of trivalent metal complexes

Table 1 — Molecular formula, Elemental analysis, M.P., Color, Molar mass of the metal complexes

S. N.	Mol. Formula	Melting point (^oC)	Color	Molar mass gm/mol Calculated	Elemental analysis calculated(found)% C	H	N	M
I	[$Cr(C_{16}H_{11}N_4O_2)Cl_2]Cl$	278	Greenish orange	448.2	42.8 (41.9)	2.2 (2.2)	23.7 (23.5)	11.5 (11.4)
II	$[Cr(C_{16}H_{11}N_4O_2)(NO_3)_2]NO_3$	275	Greenish brown	528.0	36.3 (36.1)	1.9 (1.8)	33.3 (33.1)	9.8 (9.7)
III	$[Cr(C_{16}H_{11}N_4O_2)(OAc)_2]OAc$	280	Green	519.1	50.8 (50.2)	3.6 (3.6)	24.6 (24.2)	9.9 (9.7)
IV	$[Fe(C_{16}H_{11}N_4O_2)(NO_3)_2]NO_3$	280	Brown	532.3	36.0 (36.1)	1.8 (1.8)	33.0 (33.7)	10.4 (10.5)
V	$[Fe(C_{16}H_{11}N_4O_2)(OAc)_2]OAc$	276	Light brown	523.7	50.5 (50.2)	3.6 (3.5)	24.4 (24.3)	10.6 (10.4)

"Energy Minimization" by using SPDBV 4.10-version. All water molecules and ligands were removed from the protein complex while hydrogen atoms and Kollman charges were added. Active site with a radius of 10.5 Å was defined in the receptor protein molecule. The three dimensional structure of synthesized ligand was drawn by Chem Sketch software and the structure was cleaned by using Chem Sketch tools and a mol file was generated which was converted into PDB format using "Open Babel Gui 2.3.2". The minimized ligand and metal complexes were docked into the active site of EGFR kinase and tyrosine kinase receptor molecules. The binding free energy of the compounds inside the target receptors was calculated for best docked poses[16].

In vitro antioxidant activity

The free radical scavenging activity of complexes was evaluated by using DPPH (2, 2-diphenyl-1-picrylhydrazyl 1, 1-diphenyl-2-picrylhydrazyl) method as reported in literature. 10^{-3} M of stock solution of DPPH in methanol and solutions of all test compounds prepared in the concentration range of 25-500 µg/ml in DMF were prepared and by measuring their absorbance at characteristic wavelength of DPPH i.e. 517 nm[17-18]. DMF and DPPH were used as negative and positive control, respectively. The results were compared with the standard antioxidant butylated hydroxyanisole (BHA) in the same concentration range.

In vitro cytotoxicity

SCC4 (Squamous Cell Carcinoma) cell line was taken for investigating the cytotoxicity of synthesized metal complexes. The growth inhibitory effect of the synthesized complexes on human SCC4 cancer cell line was evaluated by applying MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium-bromide) assay, in which MTT can be easily transformed by living cells to produce a DMSO soluble product formazan that can be simply detected using colorimetric analysis[19-20]. 200 µL ml of medium containing the complex at five variable concentrations (ranging from 10 µM to 100 µM) and 20 µL of MTT solution (5 mg/ml) were used for the assay. Three different test timescales (24 h, 48 h, and 72 h) were established for each treatment. After discarding the medium with MTT, 150 µL of DMSO was added to each well to dissolve the formazan crystals. The untreated cells containing DMSO and media were used as control. BIOTEK ELISA PLATE READER was used to check the absorbance at 570 nm wavelength. The % cell inhibition was determined by reported method [21].

Results and Discussion

FTIR analysis

A pair of bands at 3300 cm^{-1} and 3350 cm^{-1} corresponding to $\nu(NH_2)$ were present in the IR spectrum of benzene-1,4-dicarbohydrazide, but absent in the spectrum of complexes (Fig. 1). However a single medium intensity broad band at 3250–3270cm^{-1} was observed in the spectrum of complexes, which may be assigned to N-H stretching vibrations[14]. Furthermore no absorption band was observed at ~1715 cm^{-1} in the spectrum of complexes which indicates the absence of C=O group of 1H-indole-2,3-dione. It reveals the condensation reaction of C=O group of 1H-indole-2, 3-dione and NH_2 group of benzene-1,4-dicarbohydrazide in all metal complexes[22, 23]. This fact is further supported by the appearance of a new strong absorption band at 1605 cm^{-1} and 1615 cm^{-1} in the spectrum of complexes, respectively which may be assigned to $\nu(C{=}N)$ stretching vibrations[23-25]. A medium intensity

band at 1650–1657 cm^{-1} in the spectra of metal complexes supports the involvement of C=O group in coordination with central metal atom. All these results strongly give evidence of the formation of N_2O_2 donor macrocyclic frame in the complexes. The peak corresponding to N-H stretching has appeared at expected position which infers that NH group is not contributing in coordination. The bands observed at 3057–3092 cm^{-1} and 1455–1565 cm^{-1} are assigned to C–H and C=C stretching vibrations of aromatic rings respectively[26-29]. In the acetate complexes a strong band at 1620–1632cm^{-1} and 1320–1375 cm^{-1} was also obtained. The difference in frequencies of these two bands in IR spectrum suggests that these acetate groups are bonded to metal ion in monodentate fashion. Moreover the appearance of medium intensity band at 530–524 cm^{-1} and 425–436 cm^{-1} evident the presence of M-O and M-N bonds and further supports the coordination through oxygen and nitrogen atom of the ligand framework with metal ion[29]. All the significant peaks required for characterization of metal complexes are summarized in Table 2.

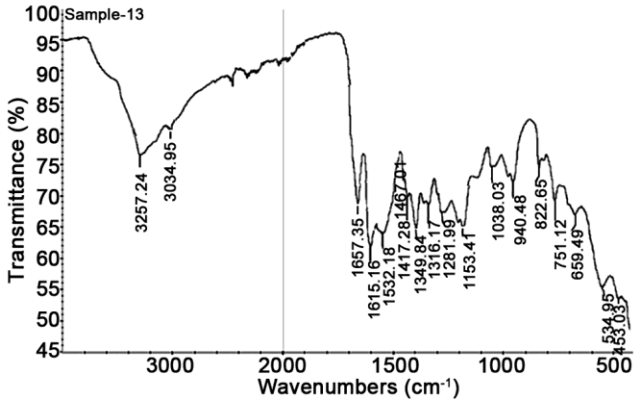


Fig. 1 — FTIR spectrum of $[Cr(C_{16}H_{11}N_4O_2)(NO_3)_2]NO_3$ in the range of 4000-400 cm^{-1}.

Electronic spectra and magnetic moment analysis

UV-visible spectra of metal complexes were recorded in DMSO at room temperature (Table 3).

Chromium complexes

Chromium (III) complexes showed magnetic moments in the range of 3.72–3.85 B.M which indicates the presence of three unpaired electrons[30]. The electronic spectrum of the chromium complexes recorded in DMSO displays three bands at 14,860–15,000 cm^{-1} (ν_1), 22,196–22,355 cm^{-1} (ν_2) and 30,111–30,469 cm^{-1}(ν_3) corresponding to $^4A_2g(F)\rightarrow{}^4T_2g(F)$, $^4A_2g(F)\rightarrow{}^4T_1g(F)$ and $^4A_2g(F)\rightarrow{}^4T_1g(P)$ transitions, respectively. The peak appeared at 14860–15,000 cm^{-1} corresponds to the d-d transition while the other two peaks raised due to n–π* and π–π* transitions of ligand framework around the metal. The position of peaks is in good agreement with the earlier reported results for the octahedral geometry around the Cr(III) ion reported by S. Chandra *et al.* [31]. The ligand field parameters like ligand field splitting energy (10 Dq), Racah inter-electronic repulsion parameter (B′), covalency factor (β) and ν_2/ν_1 were calculated for the complexes and are listed in Table 4. The Cr(III) complexes having a low value of B′ i.e. 812-817, in comparison to that of free ion (918 cm^{-1}) suggests a significant degree of covalence. The values of ν_2/ν_1 are lying between 1.47–1.48 which suggests the octahedral geometry of the complexes[32].

Table 2 — IR spectral data for synthesized metal complexes

S.N.	Compound	Significant IR peaks (cm^{-1})				
		(ν_{-NH})	($\nu_{-C=O}$)	($\nu_{-C=N}$)	(ν_{-M-O})	(ν_{-M-N})
I	$[Cr(C_{16}H_{11}N_4O_2)Cl_2]Cl$	3260	1632	1610	530	425
II	$[Cr(C_{16}H_{11}N_4O_2)(NO_3)_2]NO_3$	3257	1657	1615	534	453
III	$[Cr(C_{16}H_{11}N_4O_2)(OAc)_2]OAc$	3253	1646	1607	521	432
IV	$[Fe(C_{16}H_{11}N_4O_2)(NO_3)_2]\ NO_3$	3250	1639	1595	521	450
V	$[Fe(C_{16}H_{11}N_4O_2)(OAc)_2]OAc$	3257	1657	1615	524	436

Table 3 — Electronic spectra, Magnetic moment and Molar conductance data of synthesized metal complexes

Compound	Bands in UV-visible (cm^{-1})	Assignment	Magnetic moment (B.M.)	Molar conductance ($ohm^{-1}\ cm^2\ mole^{-1}$)	Geometry
Cr(III) complexes	14,860-15,000 22,196-22,355 30,111-30,469	$^4A_2g(F)\rightarrow{}^4T_2g(F)$; $^4A_2g(F)\rightarrow{}^4T_1g(F)$; $^4A_2g(F)\rightarrow{}^4T_1g(P)$	3.72-3.85	64.0-75.0	Octahedral
Fe(III) complexes	17,145-17,280 25,518-25,585	$^6A_{1g}\rightarrow{}^4T_{1g}$ (E) $^6A_{1g}\rightarrow{}^4T_{2g}$	5.91–5.98	69.0-76.0	Octahedral

Table 4 — Calculated ligand field parameters of metal complexes

S.N.	Complex	LFSE10Dq (cm^{-1})	B′ (cm^{-1})	β	ν_2/ν_1
1.	$[Cr(C_{16}H_{11}N_4O_2)(OAc)_2]$ (OAc)	14860	812	0.88	1.48
2.	$[Cr(C_{16}H_{11}N_4O_2)$ $(NO_3)_2]$ (NO_3)	14950	817	0.89	1.47
3.	$[Cr(C_{16}H_{11}N_4O_2)Cl_2]Cl$	15000	815	0.88	1.47

Iron complexes

Fe(III) complexes showed magnetic moments in the range 5.91–5.98 BM which is close to the predicted value corresponding to five unpaired electrons. For iron complexes, Rana *et al.* have reported absorption peak at 17500cm^{-1} and at 25000 cm^{-1} due to $^6A_{1g}\rightarrow{}^4T_{1g}$ (E) and $^6A_{1g}\rightarrow{}^4T_{2g}$ transitions, respectively[32-33]. Our Fe(III) complexes have shown absorption peaks at 17,145–17,280 cm^{-1} and 25,518–25,585 cm^{-1}, corresponding to above said transitions, respectively and were consistent with the octahedral geometry around Iron (III) ion [21]. These peaks correspond to d-d transition and ligand based transition, respectively.

Mass spectral analysis

The ESI mass spectra of metal complexes were recorded and analyzed. The molecular ion (Mþ) peaks obtained for metal complexes are as following: $[Cr\ (C_{16}H_{11}N_4O_2)\ (Cl)_2]$ Cl m/z (447.67), $[Cr\ (C_{16}H_{11}N_4O_2)\ (NO_3)_2]$ NO_3 m/z (527.00), $[Cr(C_{16}H_{11}N_4O_2)(OAc)_2]$ OAc, m/z (518.10), $[Fe(C_{16}H_{11}N_4O_2)(NO_3)_2]$ NO_3 m/z (531.37) (Fig. 2), $[Fe(C_{16}H_{11}N_4O_2)(OAc)_2]$ m/z (522.10). This data is in full agreement with the calculated molecular weight for these complexes.

Thermal studies

Evidence of the absence of water molecules and thermal stability of the complexes was studied by analyzing their TGA data. The thermal degradation of metal complexes started at ~240 ºC which confirms the absence of coordinated or lattice water in the complexes (Fig. 3). All TG curves are showing stepwise degradation of molecules in the temperature range 520–710 ºC which may be attributed to the removal of anions and organic moiety from the complexes. The weight% of the left over matches with the weight% of the corresponding air stable metal oxides which further supports the composition of the complexes[34].The results related to TGA analysis of all complexes are summarized in Table 5.

Biological study

Molecular Docking

The best binding mode of docked compounds with

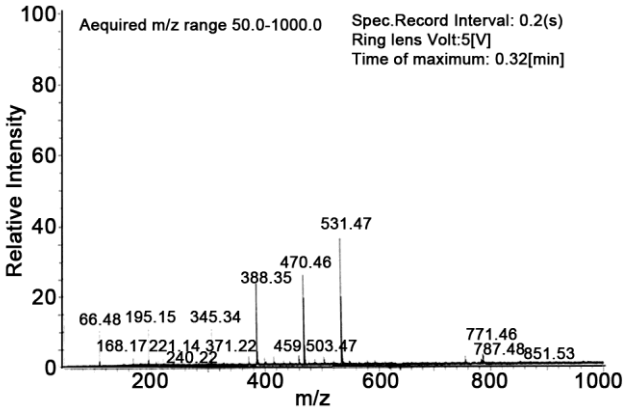


Fig. 2 — Mass spectrum of $[Fe(C_{16}H_{11}N_4O_2)(NO_3)_2]NO_3$.

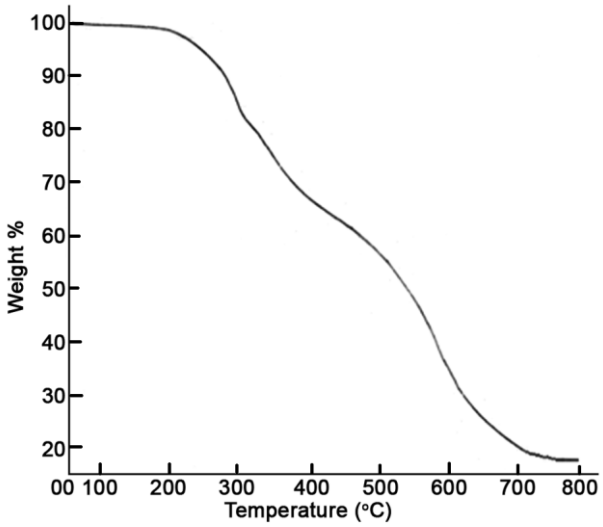


Fig. 3 — Thermogravimetric (TG) curve of $[Cr(C_{16}H_{11}N_4O_2)$-$(NO_3)_2]NO_3$.

ATP binding site of EGFR kinase (1M17) (Fig. 4) and TRK (1T46) was analyzed to find out different types of molecular interactions like H-bonding, electrostatic and hydrophobic. The complex was extended into the active site of EGFR kinase created by amino acid residues LEU764, LEU694, GLN767, LEU768, ALA719, THR766, PRO770, MET769, GLY772, PHE771, THR830, ASP831 and LEU820[30]. The metal complexes have shown affinity to the amino acid residues of EGFR through H-bonding. These interactions reveal significant binding of the synthesized Fe(II) complex with the protein receptor

Table 5 — Thermo gravimetric analysis (TGA) of metal complexes

Complex	Temp (°C)	Weight loss % calc. (found)
$[Cr(C_{16}H_{11}N_4O_2)Cl_2]Cl$	271–352	20.28(20.96)
	519–689	68.58(67.89)
	At 689	Remaining mass 11.14(11.20)
$[Cr(C_{16}H_{11}N_4O_2)(NO_3)_2]NO_3$	284–367	13.29 (13.57)
	503–710	76.22(75.87)
	At 710	Remaining mass 9.89(9.96)
$[Cr(C_{16}H_{11}N_4O_2)(OAc)_2]OAc$	277–349	21.12 (20.79)
	523–668	68.87(69.15)
	At 668	Remaining mass 10.01(10.11)
$[Fe(C_{16}H_{11}N_4O_2)(NO_3)_2]\ NO_3$	242–375	20.30 (20.07)
	536–706	69.59(69.24)
	At 706	Remaining mass 10.11(10.21)
$[Fe(C_{16}H_{11}N_4O_2)(OAc)_2]OAc$	267–342	20.42 (20.79)
	513–692	**68.77(69.1)**
	At 692	Remaining mass 10.81(10.86)

Table 6 — Summarized, Molecular docking results of complexes against the receptor molecules

Compound	Receptor protein	Amino acid residue	Type of interaction	Bond length	Binding affinity ΔG (Kcal/mol)
Complex II	EGFR Kinase (1M17)	THR830	H-bond	2.911	-8.82
		THR830		3.027	
		ASP831		2.933	
		GLU738		3.155	
Complex II	Tyrosine kinase (1t46)	LYS 642	H-bond	2.982	-6.44

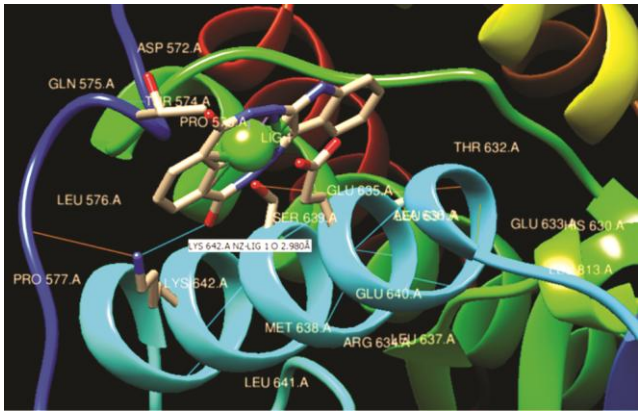


Fig. 4 — Molecular docking of complex II with molecular target 1M17.

molecule contributing to a favourable free binding energy The active site of TRK (1T46) is formed by TYR846, VAL845, CYS844, THR847, ARG791, PHE848, TYR570, ASN566, CYS788, ASN787, ILE571 amino acid residues Best binding affinity (ΔG) was shown by complex II with these receptor molecules with a binding energy of -8.82 and -6.64 kcal/mol, respectively. The results obtainedby molecular docking of synthesized compounds with both the receptor molecules are summarized in Table 6

Antioxidant activity

It was observed that antioxidant potential of synthesized complexes increased with increasing concentration of the metal complexes and standard**.** Complex (III) and (V) have shown significant radical scavenging activity with a maximum value 76.8% and 78.7%, respectively at 500 µg/ml concentration. Complex (I) was found least effective antioxidant than other complexes. Other complexes have shown average antioxidant potential**.** The results of DPPH assay in the form of percentage DPPH scavenging activity are summarized in the Table 7.

In vitro anticancer activity

Results of cytotoxicity of complexes were expressed in terms of IC_{50} values and compared with that of standard drug Cisplatin. All the complexes have shown significant IC_{50} value (Table 8, Fig. 5) at 72 h. It was found that the average cell viability ratio decreased with increasing concentration of the tested compounds. Complexes exhibited clearly reduced cell viability in a dose-dependent manner showing cytotoxicity IC_{50} values against SCC4 cancer cell line. Cr(III) complexes were exhibiting better cytotoxicity than the Fe(III) complexes. Among all the tested compounds complex (II) was found most effective inhibitor for SCC4 cancer

Table 7 — DPPH scavenging activity of metal complexes at different concentrations

S. N.	Compounds	% antioxidant activity at different concentration (μg/ml)				
		25	50	100	250	500
Standard	BHA	26.7	32.3	47.2	74.6	88.3
I	$[Cr(C_{16}H_{11}N_4O_2)Cl_2]Cl$	23.5	30.6	37.8	42.5	48.6
II	$[Cr(C_{16}H_{11}N_4O_2)(NO_3)_2]NO_3$	32.5	39.8	45.7	53.4	64.3
III	$[Cr(C_{16}H_{11}N_4O_2)(OAc)_2]OAc$	34.6	51.7	67.9	72.5	76.8
IV	$[Fe(C_{16}H_{11}N_4O_2)(NO_3)_2]NO_3$	24.6	32.4	39.8	44.6	51.7
V	$[Fe(C_{16}H_{11}N_4O_2)(OAc)_2]OAc$	39.3	46.8	54.6	62.5	78.7

Table 8 — Cytotoxicity of test compounds against SCC4 cell line at different time scale

Sl. no.	Compounds	IC_{50} (μM)		
		24hrs	48hrs	72hrs
I	$[Cr(C_{16}H_{11}N_4O_2)Cl_2]Cl$	62.1	55.7	42.3
II	$[Cr(C_{16}H_{11}N_4O_2)(NO_3)_2]NO_3$	54.1	47.0	39.5
III	$[Cr(C_{16}H_{11}N_4O_2)(OAc)_2]OAc$	68.9	57.1	44.5
IV	$[Fe(C_{16}H_{11}N_4O_2)(NO_3)_2]NO_3$	86.7	80.4	77.4
V	$[Fe(C_{16}H_{11}N_4O_2)(OAc)_2]OAc$	>100	>100	90.7
Standard	Cisplatin	10.1	7.9	5.2

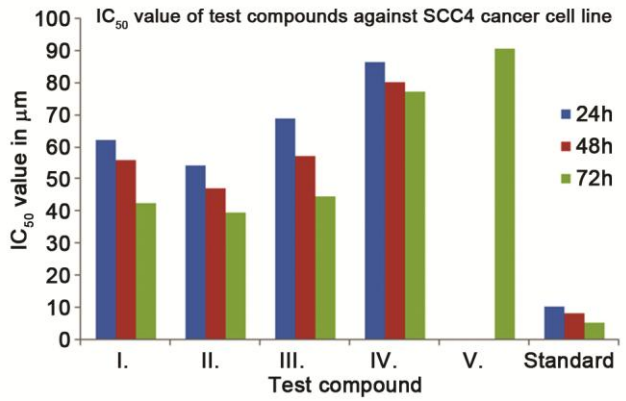


Fig. 5 — Cytotoxicity of synthesized compounds/standard at different time scale.

cell line with IC_{50} value being 39.5 μM at 72 h time scale. These results are in full agreement with the results of molecular docking study against EGFR and TRK biomolecules. The IC_{50} value shown by this complex was found to be better than the earlier reported isatin based macrocyclic complexes[16] against SCC4 cancer cell line.

Conclusions

The metal complexes were synthesized using ecofriendly microwave assisted method successfully. The metal complexes of tetradentate ligand framework are stable in air, colored and biologically active. The structure of the ligand and the complexes was established by using UV-visible, IR, Mass and TGA techniques. The ligand acted as N_2O_2 donor system to form mono-nuclear complexes having octahedral geometry. Molecular docking analysis revealed that complex II has best binding affinity with EGFR and TRK receptor molecules. In vitro antioxidant activity of complex V was the best among all. Complex II showed potent *in vitro* cytotoxicity (IC_{50} value 39.5 μM) against SCC4 cancer cell line indicating that these complexes may be very promising candidates as antitumor agents.

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