New Oxidovanadium(IV) Mixed Ligand Complexes: Antidibetic, Anticancer activities and Cytotoxicity Study Using MTT Assay

Sonaji Gayakwad
Swami Ramanand Teerth Marathwada University
Dnyaneshwar Wankhede (dswchem@yahoo.co.in)
Swami Ramanand Teerth Marathwada University https://orcid.org/0000-0002-5787-1013
Vikas Ragole
Swami Ramanand Teerth Marathwada University
Satish Maulage
Mrs. K. S. K. College

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New Oxidovanadium(IV) Mixed Ligand Complexes: Antidibetic, Anticancer activities and Cytotoxicity Study using MTT Assay

Sonaji Gayakwad[1]. Dnyaneshwar Wankhede[1,*]. Vikas Ragole[1] . Satish Maulage[2]

[1]School of Chemical Sciences, Swami Ramanand Teerth Marathwada University, Nanded-431606, Maharashtra State, India

[2]Department of Chemistry, Mrs. K. S. K. College, Beed-431122, Maharashtra State, India

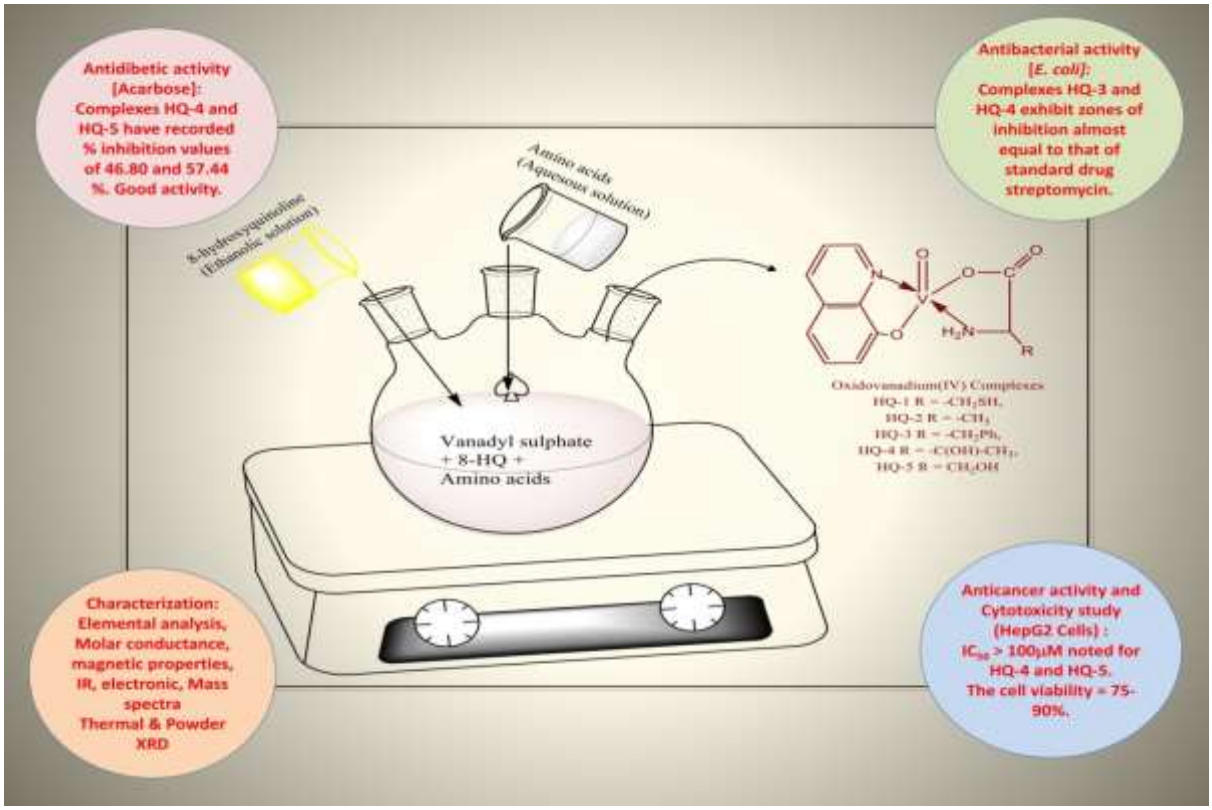
Corresponding author e-mail: dswchem@yahoo.co.in

ORCID id of Dnyaneshwar Wankhede: 0000-0002-5787-1013

Abstract

Five new (**HQ-1 to HQ-5**) oxidovanadium(IV) mixed ligand complexes using 8-hydroxyquinoline as primary ligand and amino acids like L-cystein, L-alanine, L-phenylalanine, L-threonine and L-serine as secondary ligands in 1:1:1 ratio were synthesized. All the complexes were characterized using various characterization techniques such as elemental analysis, IR, electronic, mass spectra, thermal (TGA/DTA) and powder XRD analysis, molar conductance and magnetic susceptibility measurements. Based on the results obtained all the complexes were proposed to have square pyramidal geometry. All the complexes were screened for their antibacterial activities against *E. coli* and antifungal activities against *C. albicans*. *In vitro* antidibetic activities of all the complexes were studied by screening them for α-amylase inhibition activities. The complexes **HQ-4** and **HQ-5** were also screened for their anticancer activities against human cancer cells HepG2 using MTT assay.

Graphical Abstract



Keywords Molar conductance . magnetic susceptibilities . α-amylase . antimicrobial . Powder XRD

1 Introduction

Diabetes mellitus (DM) resulting from insulin deficiency or insulin resistance is a serious chronic disorder around the world [1-3]. The increasing population failing to this disease around the world has become a serious issue today. Two types of situations are identified regarding this disease viz. type 1 DM called as insulin dependent DM and type 2 called as non-insulin dependent DM. Although various drugs are used to treat type 2 disease, the complications involved with this disease such as kidney failure, micro-and macrovascular disease, retinopathy, neuropathy and atherosclerosis has created an urgent need for the search of orally active drugs [1-3].

Vanadium is an important trace element and essential for human body [1, 4]. Vanadium compounds are known to possess insulin mimetic activity, inhibit lipolysis, decrease blood glucose levels (BGL) in animals and in clinical trials, and stimulate insulin secretion in experimental models of Diabetes Mellitus (DM) [5-10]. 8-hydroxyquinoline is monoprotic bidentate ligand and is widely used in complex formation [11]. 8-hydoxyquinoline and its metal complexes exhibit antiseptic, disinfectant and pesticide properties [12]. Mixed ligand complexes involving amino acids as secondary ligands are significant owing to their potential to act as models for enzyme metal ion substrate complexes [13].

We report synthesis of new oxidovanadium(IV) mixed ligand complexes using 8-hydroxyquinoline and amino acids like L-cystein, L-alanine, L-phenylalanine, L-threonine and L-serine as ligands, their characterization using various characterization methods and their screening for antimicrobial, antidibetic, anticancer activities and cytotoxicity study using MTT assay.

2 Materials and Methods

2.1 Materials

Chemicals used in the present investigation were purchased from S. D. Fine Chemicals, Spectrochem Private Limited, Qualigens Fine Chemicals and Merck Chemicals. All the chemicals used were of AR grade. Solvents were double distilled and dried using molecular sieves before use [14].

2.2 Methods

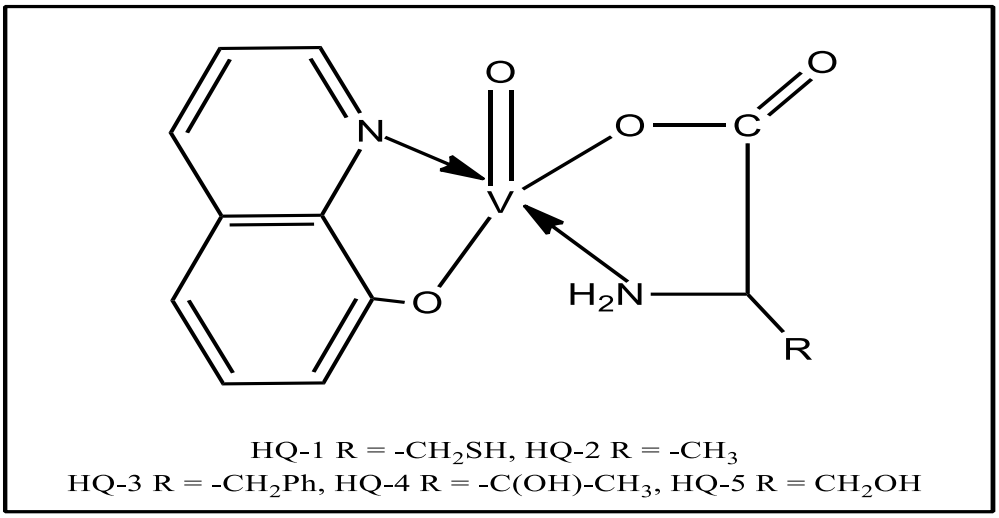
Melting point or decomposition temperature for all the synthesized compounds was measured using a simple capillary tube method. Elemental analyses of complexes were done using Thermo finnigan (Model: Flash EA 1112 series) analyzer. Molar conductance values of all the synthesized complexes were measured by preparing 10^{-3} M solutions in DMSO solvent using Equiptronics conductivity meter with an inbuilt magnetic stirrer (Model:Eq-664) at room temperature. Magnetic susceptibilities were determined on the SES Instrument's magnetic susceptibility Gouy's balance (Model:EMU-50) at room temperature using copper(II) sulphate as a standard.

IR spectra were recorded as KBr pellets in the region of 4000-400 cm^{-1} on a Perkin Elmer Spectrophotometer. Electronic spectra were recorded by preparing 10^{-3} M solutions of complexes in DMSO using Shimadzu UV-1800 UV/Visible Scanning spectrophotometer (double beam). Mass spectra were recorded using Alliance 2795 Q-TOF Micromass mass spectrometer. The TGA/DTA curves were recorded using DTG 60H module with heating rate 10.00 k/min. The experiments were carried out in a nitrogen atmosphere with heating rate of 10.00 K/Min and in temperature range 30 to 1000^{o}C using alumina crucible. The amount of samples taken was 9 mg. The Powder XRD was recorded on an Ultima IV instrument with X-Ray 40kV/20mA.

2.3 Synthesis of mixed ligand Complexes

General procedure used for synthesis of mixed ligand complexes is given below:

To an aqueous solution (20 mL) of vanadyl sulphate (1.63 g, 0.01 mol) an ethanolic solution (20 mL) of 8-hydroxyquinoline (1.45 g, 0.01 mole) was added. The mixture was stirred for 30 min at room temperature. To this reaction mixture an aqueous solution (20 mL) of respective amino acid (0.01 mol) was added drop wise with constant stirring. The resulting reaction mixture was then allowed to stir at room temperature. After 5h black coloured complexes were precipitated, which were filtered, washed with cold distilled water followed by ethanol. The complexes were dried at room temperature and used for further study. **Fig. 1** represents the generalized proposed structure of all the synthesized mixed ligand complexes.



HQ-1 R = $-CH_2SH$, HQ-2 R = $-CH_3$
HQ-3 R = $-CH_2Ph$, HQ-4 R = $-C(OH)-CH_3$, HQ-5 R = CH_2OH

Fig. 1 Generalized proposed structure of all the synthesized mixed ligand complexes

2.4 Antimicrobial activity

The complexes were screened for their antibacterial activity against bacterial pathogen *E. coli* using well plate method. The complexes (10 mg) were dissolved in DMSO, so as to prepare solution of concentration 1000 μg/mL. The test solution was spread uniformly on the surface of agar medium in a Petri plate by using spreader. In each plate up to four discs were used. Similarly all the complexes were screened for their antifungal activity using well diffusion method. In this method the agar plate surface is inoculated by spreading a volume of the microbial inoculums over the entire agar surface. Then, a hole with a diameter of 6 to 8 mm is punched aseptically with a sterile cork borer or a tip and a volume (20-100 mL) of the antimicrobial agent or extract solution at desired concentration is introduced into the well. Then, Agar plates are incubated under suitable conditions depending upon the test microorganism. The antimicrobial agent diffuses in the agar medium and inhibits the growth of the microbial strain tested [15] against *C. albicans* fungi and is compared with standard drug used. The inhibitory concentration used for testing was 1000 μg/mL.

2.5 Anti-diabetic activity using α-amylase inhibition

2.5.1 Importance α-amylase enzyme in the body

In humans, the digestion of starch involves several stages. Initially, partial digestion by the salivary amylase results in the degradation of polymeric substrates into shorter oligomers. Later on in the gut these are further hydrolyzed by pancreatic α-amylases into maltose,

maltotriose and small malto-oligosaccharides. The digestive enzyme (α-amylase) is responsible for hydrolyzing dietary starch (maltose), which breaks down into glucose prior to absorption. Inhibition of α-amylase can lead to reduction in post prandial hyperglycemia in diabetic condition [16-17]. Treatment of diabetes include improvement of the activity of insulin at the objective tissues, with the utilization of sensitizers (biguanides, thiozolidinediones); incitement of endogenous insulin discharge with the utilization of sulfonylureas (glibenclamide, glimepiride) and decrease of the interest for insulin utilizing particular enzyme inhibitors (**Acarbose**, miglitol)

2.5.2 Assay of Amylase Inhibition

In vitro amylase inhibition was studied using method of Bernfeld [18]. A 100 µL (100 µg/) of the test extract was allowed to react with 200 µL of α-amylase enzyme (Hi media 638) and 100 µL of 2 mM of phosphate buffer (pH-6.9). After 20 min incubation, 100 µL of 1% starch solution was added. The same procedure was performed for the controls where 200 µL of the enzyme was replaced by buffer. After incubation for 5 min, 500 µL of dinitrosalicylic acid reagent was added to both control and test samples. They were kept in boiling water bath for 5 min. The absorbance was recorded at 540 nm using spectrophotometer and the percentage inhibition of α-amylase enzyme was calculated using the formula (1) given below:

$$Percent\ Inhibition\ (\%) = \frac{[(Abs\ 540\ (control) - Abs\ 540\ (extract)]}{Abs\ 540\ (control)}\ X\ 100 \quad (1)$$

Suitable reagent blank and inhibitor controls were simultaneously carried out.

2.6 Anticancer activity and cytotoxicity study using MTT assay

The anticancer activity of complexes **HQ-4** and **HQ-5** were determined using MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide] assay against human liver cancer cell lines HepG2 to assess the cytotoxicity [19-20]. The cancer cell line used in this work was selected due to easy availability and wide use found in literature survey with cisplatin.

Cells were incubated at a concentration of $1x10^4$ cells/ in culture medium for 24h at 37°C and 5% CO_2. Cells were seeded at a concentration (70 µL) 10^4 cells/well in 100 µL culture medium and 100 µL herbal extracts into micro plates respectively (tissue culture grade, and 96 wells). Control wells were incubated with DMSO (0.2% in PBS) and cell line. All

Samples were incubated in triplicate. Controls were maintained to determine the control cell survival and the percentage of live cells after culture. Cell cultures were incubated for 24h at 37°C and 5% CO_2 in CO_2 incubator. After incubation the medium was completely removed and added 20 μL of MTT reagent (5mg/min PBS). After addition of MTT, cells incubated for 4h at 37°C in CO_2 incubator. The wells were observed for formazan crystal formation under microscope. The yellowish MTT was reduced to dark coloured formazan by viable cells only. After removing the medium completely added 200 μL of DMSO (kept for 10 min) and incubated at 37°C (wrapped with aluminium foil). Triplicate samples were analyzed by measuring the absorbance of each sample by microplate reader at a wavelength of 550 nm. Measurements were performed and the concentration required for a 50% inhibition of viability (IC_{50}) was determined graphically.

3 Result and Discussion

3.1 Physicochemical data

The synthesis of mixed ligand complexes of vanadium using 8-hydroxyquinoline and amino acids in 1:1:1 proportion can be represented as follows:

$$VOSO_4 + HQ + HL \longrightarrow [VO(Q)(L)]$$

Where, HQ = 8-hydroxyquinoline and HL= L-Amino Acids. All the synthesized complexes are obtained in 70-78% yield, black coloured, non-hygroscopic and thermally stable indicating presence strong metal-ligand bonding. The complexes are insoluble in common organic solvents, but are found to be soluble in DMSO and DMF.

3.2 Molar conductance

The molar conductance values recorded for all the synthesized complexes (0.12 – 0.29 Mhos mol^{-1} cm^{-2}) are very low which indicates non-electrolytic nature of complexes [21].

3.3 Magnetic measurements

The observed values of magnetic moments (1.72 to 1.87 B.M.) indicate presence of one unpaired electron in these complexes [21]. The results obtained from molar conductance and

magnetic susceptibility measurements along with elemental analysis data recorded for all the synthesized mixed ligand complexes are represented in **Table 1**.

Table 1 Elemental analysis, molar conductance and magnetic susceptibility values

Complexes	Elemental Analysis Calculated/Found (%)						Molar Conductance (Mhos mol^{-1} cm^{-2})	μ_{eff} (B.M.)
	C	H	N	O	S	M(V)		
HQ-1 $C_{12}H_{12}N_2O_4SV$	43.51 (43.47)	3.65 (3.62)	8.46 (8.45)	19.32 (19.34)	9.68 (9.66)	15.38 (15.39)	0.12	1.75
HQ-2 $C_{12}H_{12}N_2O_4V$	48.18 (48.13)	4.04 (4.01)	9.36 (9.35)	21.39 (21.39)	---	17.03 (17.04)	0.21	1.84
HQ-3 $C_{18}H_{16}N_2O_4V$	57.61 (57.56)	4.30 (4.26)	7.46 (7.45)	17.05 (17.05)	---	13.57 (13.59)	0.18	1.87
HQ-4 $C_{13}H_{14}N_2O_5V$	47.43 (47.38)	4.29 (4.25)	8.51 (8.50)	24.30 (24.30)	---	15.47 (15.49)	0.26	1.72
HQ-5 $C_{12}H_{12}N_2O_5V$	45.73 (45.68)	3.84 (3.80)	8.89 (8.88)	25.38 (25.38)	---	16.16 (16.18)	0.29	1.73

3.4 IR spectra

The broad peak observed in the range of 3410 to 3442 cm^{-1} due to symmetric stretching of O-H bond in free 8-hydroxyquinoline molecule was found to be absent in case of complexes which indicates complex formation between vanadium and 8-hydroxyquinoline through oxygen atom of –OH group.

The broad peak at 2920-2972 cm^{-1} due to –NH vibrations of free amino acids are shifted to higher wave number in the range of 2981-3057 cm^{-1} in the spectra of metal complexes which indicates amino group bonded through nitrogen atom with metal [13]. The C=N stretching vibration observed at 1580 cm^{-1} in free 8-hydroxyquinoline ligand is shifted to lower wave number up to 1460-1465 cm^{-1} in the spectra of complexes. This indicates coordination of 8-hydroxyquinoline molecule with vanadium through ternary nitrogen.

The asymmetric and symmetric (COO^-) bands observed in the region 1580-1597 and 1402-1408 cm^{-1} in free amino acids were observed to be shifted to lower wave numbers region of 1571-1575 and 1373-1377 cm^{-1} respectively in the spectra of complexes. This indicates bonding of COO^- group with metal with oxygen atom of carboxylic group of amino acids. The band observed between 945-950 cm^{-1} in the spectra of complexes indicates ν(V=O) stretching vibrations. Finally the bands observed in the range of 445-447 cm^{-1} and 621-632 cm^{-1} indicates ν(M-N) and ν(M-O) bonding in complexes respectively.

3.5 Electronic spectra

The electronic absorption spectra of synthesized mixed ligand complexes were recorded using freshly prepared solution in DMSO at room temperature. The electronic spectra of all the five complexes show three absorption bands.

The first band at 203-264 nm indicates $\pi \rightarrow \pi^*$ transition due to aromatic rings of ligand. The second peak observed in the range 364-501 nm in electronic spectra of complexes indicate charge transfer transition from ligand to metal atom (LMCT) [21].

Third absorption band observed in the region 479-791 nm in electronic spectra of complexes can be caused by $d \rightarrow d^*$ transition of the central metal vanadium [22]. The results obtained from electronic spectra of all the synthesised complexes indicated presence of square pyramidal geometry in all these complexes [23].

3.6 Mass spectra

The ESI-MS spectra of complexes **HQ-4** and **HQ-5** were recorded as a representative case. The peaks of appreciable intensity have been observed in both these complexes viz. peaks at m/z 146, 252, 301, 338, 355, 437, 453, 582, 727 and 749 for **HQ-4** complex and 146, 252, 355, 301, 413, 582, 727 and 749 for **HQ-5** complex.

Although molecular ion peaks are not observed in both these spectra, the peak at m/z 338 in mass spectrum of **HQ-4** and at m/z 301 in mass spectrum of **HQ-5** complexes is nearest to the composition of **HQ-4 [$C_{13}H_{14}N_2O_5V$]** and **HQ-5 [$C_{12}H_{12}N_2O_5V$]** respectively [24].

3.7 Thermal analysis (TGA/DTA)

The TGA and DTA curves were recorded for mixed ligand complexes **HQ-1** and **HQ-2** as a representative case. Two major weight loss steps are observed in both these complexes. For complex **HQ-1** the weight loss of -37.36% observed in first step in the temperature range 220-300^oC is attributed to loss of coordinated 8-hydroxyquinoline molecule. While the second major weight loss of -47.13% in the temperature range 300-600^oC is attributed to loss of another coordinated ligand molecule.

For complex **HQ-2** the first weight loss is observed in the temperature range 250-400^oC which is attributed to loss of coordinated 8-hydroxyquinoline ligand molecule. While the second weight loss in the temperature range 400-650^oC indicates loss of second ligand molecule.

The DTA curve of both these complexes exhibit two broad peaks in the range of 300-650ºC. It was observed that decomposition of complex is started at 300ºC and completed at 600-650ºC. After complete decomposition, formation of fine powder of metal atom with reducing gaseous products like CO, NH_3 etc. was observed which confirms the loss of both coordinated ligands from metal during decomposition of complexes [25].

3.8 Powder XRD analysis

The nature of synthesized mixed ligand complexes were studied by powder X-ray method. The XRD pattern indicates microcrystalline nature of complexes. The particle sizes of complexes were calculated using Scherer's formula [26] given as in equation (2).

$$Particle\ size\ (D) = \frac{0.9\,\lambda}{\beta\, Cos\theta} \quad (2)$$

Where λ = wavelength of x-ray radiation, β = FWHM and θ = diffraction angle.

The mean particle size of complexes HQ-1, HQ-2, HQ-3, HQ-4 and HQ-5 is found to be 15.75, 24.98, 10.60, 37.26 and 25.86 nm respectively. The inter planner spacing (d) of complexes were calculated by using Bragg's equation (3).

$$n\lambda = 2d\ Sin\theta \quad (3)$$

Where, λ= Wavelength of x-ray, and θ = is the angle of diffraction. The results obtained from powder XRD analysis of all the complexes are represented in **Table 2**.

Table 2 Powder XRD analysis

Complex	Reflexes	2θ	Miller Indices	Inter Planner Spacing d (Aº)	Crystal Size D (nm)	FWHM
$C_{12}H_{12}N_2O_4SV$ (HQ-1)	Peak1	9.94	111	8.89	08.92	1.5587
	Peak2	12.81	210	6.90	31.18	0.4474
	Peak3	18.85	311	4.70	26.62	0.5278
	Peak4	22.79	400	3.95	03.18	4.9398
	Peak5	28.50	422	3.12	08.85	1.6146
			Average crystal size		15.75 nm	
$C_{12}H_{12}N_2O_4V$ (HQ-2)	Peak1	7.41	111	11.9	24.50	0.5669
	Peak2	11.90	220	7.42	28.51	0.4888
	Peak3	22.65	511	3.92	22.52	0.6275
	Peak4	24.15	521	3.68	24.38	0.5813
			Average crystal size		24.98 nm	
$C_{18}H_{16}N_2O_4V$ (HQ-3)	Peak1	11.96	111	7.39	07.60	1.8320
	Peak2	19.90	220	4.45	12.97	1.0847
	Peak3	22.97	311	3.86	07.42	1.9058
	Peak4	30.80	420	2.89	14.68	0.9789
			Average crystal size		10.60 nm	
	Peak1	11.89	111	7.44	32.68	0.4265
	Peak2	13.13	200	6.74	47.59	0.2932
	Peak3	19.18	220	4.62	55.17	0.2548

$C_{13}H_{14}N_2O_5V$	Peak4	22.73	311	3.90	15.84	0.8920
(HQ-4)	Peak5	24.20	222	3.67	24.19	0.5859
	Peak6	27.75	400	3.21	48.09	0.2969
			Average crystal size		37.26 nm	
	Peak1	11.96	111	7.39	33.08	0.4213
	Peak2	13.21	200	6.70	49.11	0.2842
	Peak3	20.24	221	4.38	17.44	0.873
$C_{12}H_{12}N_2O_5V$	Peak4	22.64	311	3.92	22.14	0.6385
(HQ-5)	Peak5	24.43	222	3.63	07.54	1.8807
			Average crystal size		25.86 nm	

3.9 Antimicrobial activity

The complexes **HQ-3** and **HQ-4** exhibited zones of inhibition 20 and 19 mm respectively which is almost equal to that of standard drug streptomycin (20 mm). Hence these two complexes exhibit excellent antimicrobial activity against *E. Coli.* Out of the remaining complexes, **HQ-1** and **HQ-5** exhibited moderate to good activity with the zone of inhibition values of 17 mm and 12 mm respectively, whereas the complex **HQ-2** exhibited moderate activity with the zone of inhibition 9 mm.

Fig. 2 represents results obtained from antibacterial screening of all the complexes.

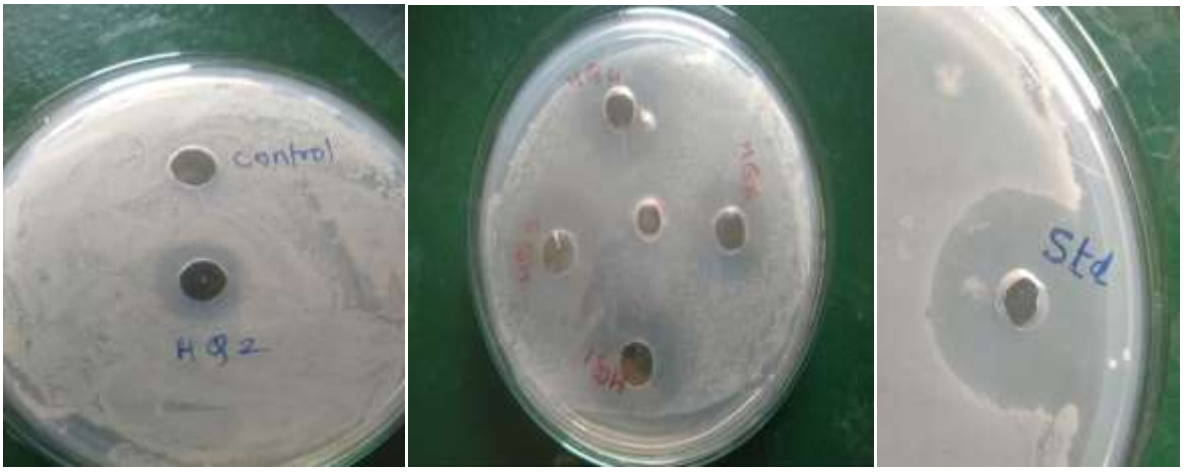


Fig. 2 **A**ntibacterial activity against *E. coli*

All the complexes exhibited very poor antifungal activity with zone of inhibition values ranging from 0 to 7 mm as compared to standard drug with zone of Inhibition value of 16 mm [13, 27-28].

Fig. 3 represents results obtained for antifungal screening of all the mixed ligand complexes.

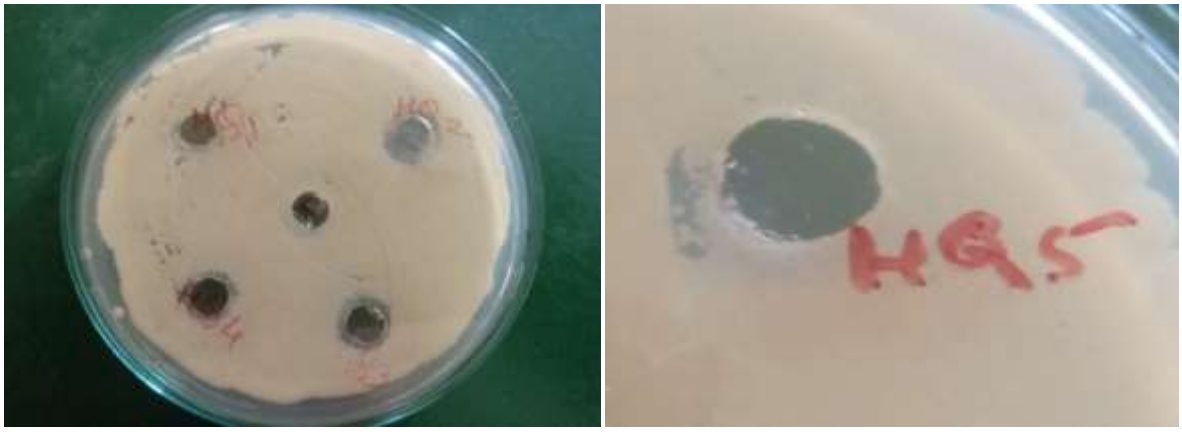


Fig. 3 Antifungal activity against *C. albicans*

3.10 Anti-diabetic activity using α-amylase inhibition

Table 3 given below represents the results obtained from antidibetic activity i.e. percent inhibition of α-amylase inhibitory assay for all the synthesized mixed ligand complexes.

Table 3 Antidibetic activity using α-amylase inhibition

Sample Code	Concentration (µg/mL)	ABS at 540 nm	% inhibition
Blank	---	0.47	---
HQ-1 $C_{12}H_{12}N_2O_4SV$	1000	0.38	19.14
HQ-2 $C_{12}H_{12}N_2O_4V$	1000	0.37	21.27
HQ-3 $C_{18}H_{16}N_2O_4V$	1000	0.46	02.12
HQ-4 $C_{13}H_{14}N_2O_5V$	1000	0.25	46.80
HQ-5 $C_{12}H_{12}N_2O_5V$	1000	0.20	57.44
Standard – Acarbose	1000	0.13	72.34

The complexes **HQ-4** and **HQ-5** have recorded % inhibition values of 46.80 and 57.44 % which means these complexes show good activity as compared to standard acarbose (72.34%). The remaining three complexes **HQ-1**, **HQ-2** and **HQ-3** exhibited poor activities (i.e. 19.14, 21.27 and 02.21 % inhibition) respectively.

3.11 Anticancer activities and cytotoxicity study using MTT assay

To evaluate cytotoxicity two of the synthesized complexes **HQ-4** and **HQ-5**, against human hepatocarcinoma (HepG2) cells, were incubated with different doses (10, 30 and 100 µg/mL)

for 24h and cell viability was determined by the MTT assay. **Table 4** represents results obtained from anticancer activity and cytotoxicity study using MTT assay.

Table 4 Anticancer activity and cytotoxicity study using MTT Assay

Complex	Concentration (µg/mL)	Cell Viability (%)	Cell inhibition (%)	IC50 (µM)
HQ-4 $C_{13}H_{14}N_2O_5V$	10	87.45	12.55	>100
	30	82.75	17.25	
	100	77.32	22.68	
HQ-5 $C_{12}H_{12}N_2O_5V$	10	88.48	11.52	>100
	30	85.69	14.31	
	100	75.92	24.08	
Standard 5-FU (Fluorouracil)	10	62.05	37.95	42.80
	30	53.68	46.32	
	100	30.18	69.82	

The IC_{50} values above 100µM are noted for both these complexes which indicate both these complexes were able to inhibit proliferation of the cancer cells HepG2 [19]. The cell viability values are within expected range i.e. 75-90% which indicates these complexes are more toxic to cancer cells than normal cells. Considering all these observed results both these complexes could be considered as potential anticancer agents.

4 Conclusions

All the complexes (**HQ-1 to HQ-5**) are proposed to have square pyramidal geometry. The complexes **HQ-3** and **HQ-4** exhibited excellent antibacterial activities against *E. Coli* i.e. close to that of standard streptomycin which seems to be inspiring and indicating towards potential of these compounds to act as antibacterial agents.

The complexes **HQ-4** and **HQ-5** show good percent inhibition of α-amylase activities as compared to standard acarbose and thus good antidibetic activities. The complexes **HQ-4** and **HQ-5** were screened for their anticancer activities and cytotoxicity studies using MTT assay as a representative case. The IC_{50} values (below 50 µM) recorded indicated towards the potential of these complexes to act as anticancer agents.

Compliance with Ethical Standards

Conflicts of interest There is no conflicts of interests.

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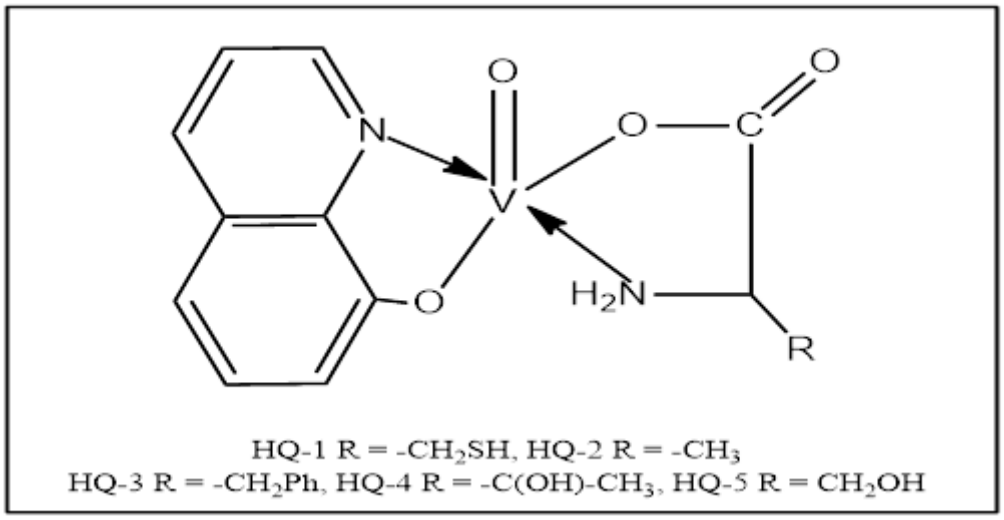
Figures



HQ-1 R = -CH_2SH, HQ-2 R = -CH_3
HQ-3 R = -CH_2Ph, HQ-4 R = -C(OH)-CH_3, HQ-5 R = CH_2OH

Figure 1

Generalized proposed structure of all the synthesized mixed ligand complexes

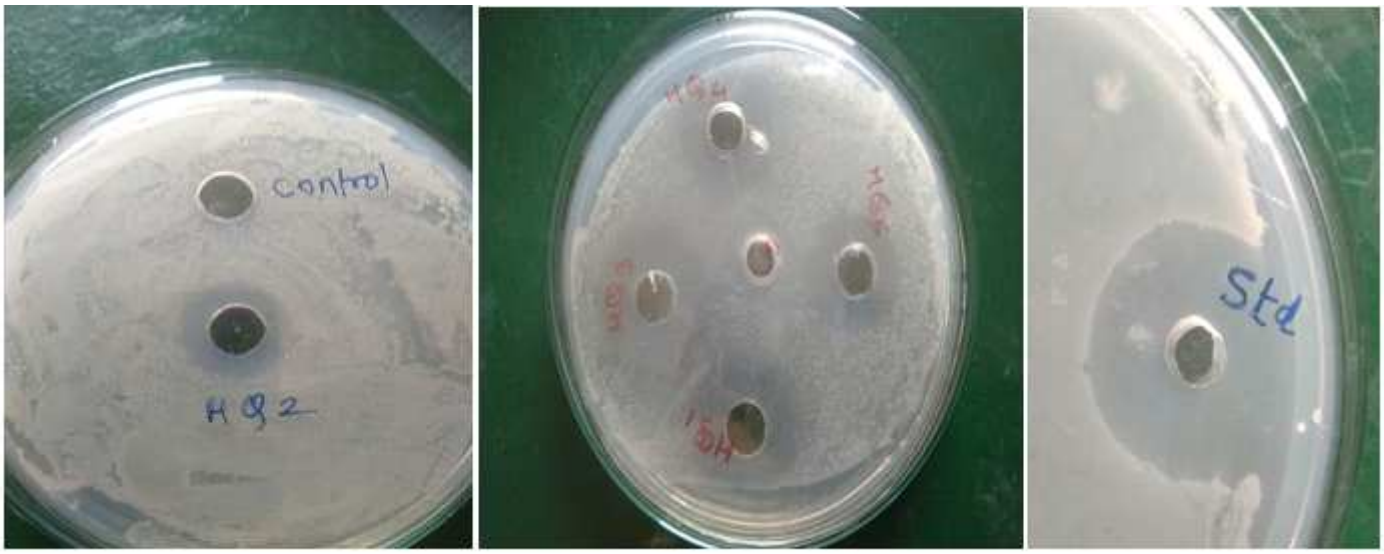


Figure 2

Antibacterial activity against E. coli

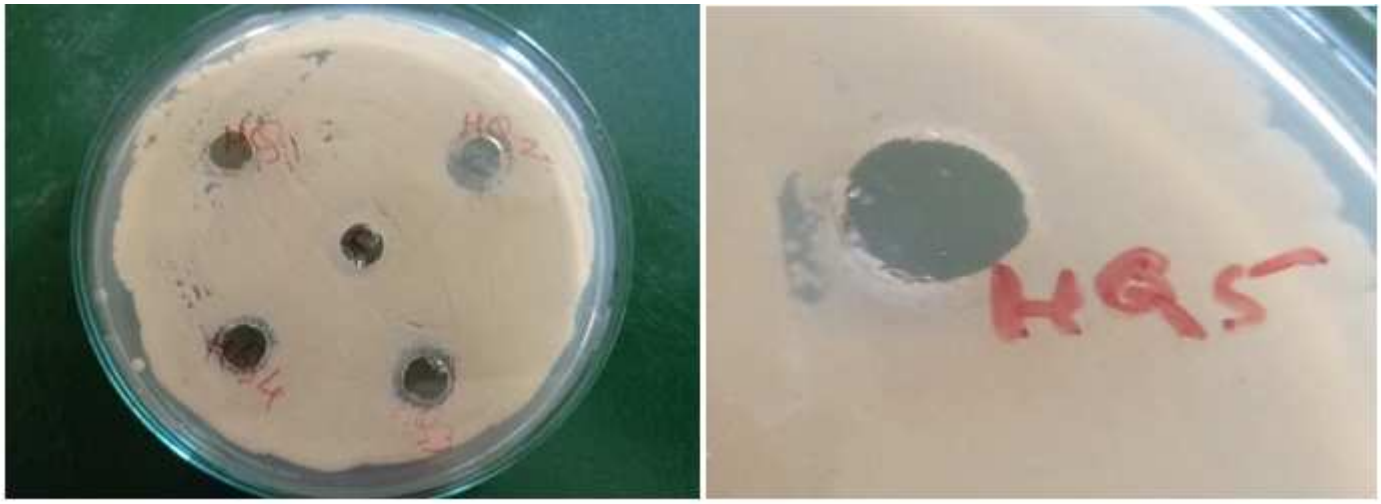


Figure 3

Antifungal activity against C. albicans

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