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Metal Based α-glucosidase Inhibitors: Synthesis, Characterization and α-glucosidase Inhibition Activity of Transition Metal Complexes

I. P. Tripathi[1*], Aparna Dwivedi[1] and Mahendra Mishra[1]

[1]Department of Physical Sciences, Faculty of Science and Environment, Mahatma Gandhi Chitrakoot Gramodaya Vishwavidyalaya, Chitrakoot, Satna (M.P.), India.

Authors' contributions

This work was carried out in collaboration between all authors. Author MM designed the study, performed the statistical analysis and wrote the protocol. Author AD wrote the first draft of the manuscript. Author IPT managed the analyses of the study. All authors managed the literature searches, read and approved the final manuscript.

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ABSTRACT

Aims: The aim of current study to examine percentage inhibition of α-glucosidase by synthesized transition metal complexes of 1,6-diaminohexane.
Study Design: Current study is based on given experimental methodology.
Place and Duration of Study: Faculty of Science and Environment and Department of Physical Sciences, between June 2009 and July 2010.
Methodology: In current work we have synthesized metal complexes by various salts of Co(II), Cu(II), Ni(II) and Zn(II) with 1,6-diaminohexane and characterized by means of infrared and ultraviolet spectroscopy. α-glucosidase inhibition activity has performed by standardize method of Tripathi et al. and calculated their IC_{50} value.
Results: All synthesized metal complexes of 1,6-diaminohexane are showing α-glucosidase inhibition activity among them $[Zn(dahe)_3]2Cl$ having highest α-glucosidase inhibition activity with

**Corresponding author: E-mail: tripathi.ip@gmail.com;*

lowest IC_{50} value 1.196 mg/ml while $[Ni(dahe)_3]2Cl$ having lowest α-glucosidase inhibition activity with highest IC_{50} value 3.633 mg/ml.

Conclusion: α-glucosidase inhibitors are oral antidiabetic drugs, which are widely used as chemotherapeutic agents in the clinical treatment of diabetes and obesity. Synthetic α-glucosidase inhibitor may be effective for antidiabetic treatment and other disorders because it is easy to synthesize and also having a great possibility to inhibit α-glucosidase. We have performed *in-vitro* α-glucosidase inhibition activity of transition metal complexes of 1,6-diaminohexane; however, need further work to validate reliability.

Keywords: α-glucosidase; diabetes; chemotherapy; IC_{50} value.

1. INTRODUCTION

The syndrome diabetes mellitus is best discussed in the light of the knowledge of the functions of insulin. Changes in fat and protein metabolism are involved in diabetes mellitus, these changes were thought to be consequent on abnormal glucose metabolism. It is now appreciated that insulin is directly involved not only in the synthesis of carbohydrate from glucose but also in the formation of fatty acids, neutral fat, amino acids and protein [1].

To treat diabetes therapeutic process includes inhibiting the absorption of glucose by retarding the action of gastro-intestinal enzymes such as *α*-glucosidase and *α*-amylase. Complication of diabetes is mainly due to the higher glucose level in blood which dysfunction the other organs of body [2]. *α*-glucosidase is an enzyme which converts polyasaccharides into monosaccharides and increase the glucose level in blood, thus we can say that the effective *α*-glucosidase inhibitors may serves as chemotherapeutic agents for clinical use in the treatment of diabetes.

The idea of using metal ions for the treatment of diabetes reported in 1899. Metal ions play an important role in biological activities. The research on the role of metal ions may contribute to the improvements of diabetes began. The orally active metal complex containing vanadyl [oxovanadium(iv)] ion and cysteine or other ligands were first proposed in 1990 and a wide class of vanadium, copper and zinc complexes was found to be effective for treating diabetes in experimental animals [3].

In current research article we have synthesized complexes of Co(II), Ni(II), Cu(II) and Zn(II) salts with 1,6-diaminohexane and characterized by IR and UV spectroscopy. Transition metal complexes are interesting due to their capability to cure several metabolic disorders. Synthesized complexes have used for evaluating the *α*-glucosidase inhibitory effect.

2. EXPERIMENTAL

2.1 Synthesis of Complexes

Complexes were prepared by stirring method suggested by Cheng et al. [4] with slight modification. Metal complexes synthesized from different salts (chloride, sulphate and nitrate) of metals [Co(II), Ni(II), Cu(II) and Zn(II)] and 1,6-diaminohexane as ligand. 2 mM of aqueous solution of metal salt was taken in a beaker and 6 mM solution of ligand was added drop wise with continuous stirring and stirred or three hours. 2-3 ml of ethyl alcohol was added for precipitation. Colored solution was obtained, which was transferred in a petri dish and to remove solvent put in incubator at 45℃. After 4-5 days colored complex obtained in the form of crystalline solid which was collected in vials and stored in dessicator.

2.2 Physical Measurement of Metal Complexes

Infrared (IR) spectra were obtained by the KBr method using a Bruker Alfa-T model Fourier transform (FTIR) spectrometer (Bruker Instrument, Germany). The spectrometer was equipped with a Globar IR source, KBr beam splitter, and detector. For each spectrum, 16 scans were obtained with the resolution of 4 cm^{-1}. The obtained IR spectra were processed by means of the program OPUS 7.0 at Faculty of Science and Environment, MGCGV Chitrakoot, Satna [MP] [5].

The UV-visible transmittance spectra of the complexes were recorded at 25℃ on a shimadzu UV-VIS 160 spectrophotometer, in quartz cells at the desired wave length region. 3 mM solution of complexes in DMSO was used in

all UV–visible measurements at Faculty of Science and Environment, MGCGV Chitrakoot, Satna [MP] [6].

2.3 α-glucosidase Inhibition

α-glucosidase inhibitory activity was performed by following method of Tripathi et al. [7]. In brief, Rat-intestinal acetone powder was dissolved in 100 ml of saline water and sonicated properly at 4℃. After sonication, the suspension was centrifuged (3,000 rpm, 4℃, 30 minutes) and the resulting supernatant was used for the assay. A reaction mixture containing 50 µl of phosphate buffer (50 mM; pH 6.8), 20 µl of rat α-glucosidase and 25 µl of sample of varying concentrations was pre-incubated for 5 min at 37℃, and then 25 µl of 3 mM PNPG was added to the mixture as a substrate. After incubation at 37℃ for 30 min, enzymatic activity was quantified by measuring the absorbance at 405 nm in a micro titer plate reader (Bio-TEK, USA). Acarbose was used as a positive control and water as negative control. Experiments were done in triplicates.

IC_{50} value was quantified using formula, $Y = 0.026(x) - 46.26$, $R^2 = 0.958$. The percentage of enzyme inhibition by the sample was calculated by the following formula:

Percentage of Inhibition = {[(AC - AS)/AC] ×100}

Where, AC is the absorbance of the control and AS is the absorbance of the tested sample. The concentration of an inhibitor required to inhibit 50% of enzyme activity under the mentioned assay conditions is defined as the IC_{50} value.

3. RESULTS AND DISCUSSION

3.1 Infra Red Spectroscopy of Metal Complexes

In order to study the bonding mode of 1,6-diaminohexane to the metal complexes infrared spectroscopy is a useful technique. Band shifting from higher to lower frequencies tells about the co-ordination of ligand with metal through the nitrogen atom at the amine group [8]. IR spectrum bonded hydroxyl group. Absence of this band in the metal complexes indicates the breaking of the hydrogen bond and co-ordination of oxygen atom to the metal after deprotonation [9]. A high intensity band around 1284 cm^{-1} in the Schiff base due to the phenolic C-O stretching frequency. C=N azomethine band occurs at 1638 cm^{-1} in the Schiff base ligand, shifting in bands from higher to lower frequency indicating the co-ordinating of the azomethine nitrogen to the metal ion and co-ordination of the water molecule is indicated by the appearance of a broad band in the 3550-3400 cm^{-1} [10].

We have taken infrared spectrum of all given complexes under the range 600-4000 cm^{-1}. In the IR spectrum of complex 1 N-H bending vibration observed as strong band at 1582 cm^{-1}, which is observed for chelated 1,6-diaminohexane complex. The N-H stretching vibration is found at the 3216 cm^{-1} which is showing presence of primary amines. C-H stretching vibration observed at 3134 cm^{-1} and band for O-H is observed at 3291 cm^{-1}. C-N stretching vibrations are observed between 1043-1125 cm^{-1} where 1043 cm^{-1} and 1125 cm^{-1} are showing primary and secondary amines group.

IR assignments of the complex 1 to 12 are given in Table 1 and IR spectrum of the complex 3, 6, 8 and 11 are shown in Figs. 1, 2, 3 and 4 respectively.

3.2 Ultraviolet Spectroscopy of Metal Complexes

The electronic spectra of metal complexes were recorded in 100% DMSO at room temperature. The UV spectra of synthesized transition metal complexes with the ligand show absorption bands around 198–355 nm. The spectra of the free Schiff base exhibit two absorption bands in the regions 252–275 and 305–324 nm. These bands are attributed to π→π* transitions the first band is due to transitions of the benzene ring and second to the imines group. The bands in the region 464–337 nm may be assigned to the n→π* transitions of the azomethine group. In the spectra of this type of complexes, the bands due to the azomethine chromophore are shifted to lower frequencies indicating that the imines nitrogen atom is involved in co-ordination to the metal ion [11].

In the electronic spectrum of Co(II) complexes with 1,6-diaminohexane λ_{max} shown at 221–235 nm, Cu(II) complexes with 1,6-diaminohexane λ_{max} shown at 252–279 nm, Zn(II) complexes with 1,6-diaminohexane λ_{max} shown at 335 nm and Ni(II) complexes with 1,6-diaminohexane λ_{max} shown at 198–207 nm. Representative graphs of four metal complexes among all twelve complexes are given in Figs. 5, 6, 7 and 8.

Table 1. Representing the band assignment for complexes

S. no.	Complex	Group	Band (cm^{-1})
1.	[Cu $(dahe)_3$]2Cl	-NH (bending) bounded with metal	1582
		-NH (stretching)	3216
		-CH (stretching)	3134
		-OH	3306
		-CN (stretching)	1043-1323
2.	[Cu $(dahe)_3$]SO_4	-NH (bending) bounded with metal	1582
		-NH (stretching)	3216
		-CH (stretching)	3136
		-OH	3303
		-CN(stretching)	1043-1338
3.	[Cu $(dahe)_3$]$2NO_3$	-NH (bending) bounded with metal	1587
		-NH (stretching)	3222
		-CH (stretching)	3119
		-OH	3401
		-CN(stretching)	1048-1167
4.	[Co $(dahe)_3$]2Cl	-NH (bending) bounded with metal	1588
		-NH (stretching)	2972
		-CH (stretching)	3202
		-OH	3682
		-CN(stretching)	1138-1385
5.	[Co $(dahe)_3$]SO_4	-NH (bending) bounded with metal	1587
		-NH (stretching)	-
		-CH (stretching)	-
		-OH	-
		-CN(stretching)	1032-1140
6.	[Co $(dahe)_3$]$2NO_3$	-NH (bending) bounded with metal	1590
		-NH (stretching)	3216
		-CH (stretching)	3124
		-OH	3392
		-CN(stretching)	1036-1283
7.	[Ni $(dahe)_3$]2Cl	-NH (bending) bounded with metal	1616
		-NH (stretching)	3210
		-CH (stretching)	3099
		-OH	3441
		-CN(stretching)	1086-1292
8.	[Ni $(dahe)_3$]SO_4	-NH (bending) bounded with metal	1585
		-NH (stretching)	3286
		-CH (stretching)	-
		-OH	3338
		-CN(stretching)	1053-1284
9.	[Ni $(dahe)_3$]$2NO_3$	-NH (bending) bounded with metal	1622
		-NH (stretching)	-
		-CH (stretching)	-
		-OH	3386
		-CN(stretching)	1120

S. no.	Complex	Group	Band (cm^{-1})
10.	$[Zn(dahe)_3]2Cl$	-NH (bending) bounded with metal	1587
		-NH (stretching)	3222
		-CH (stretching)	3119
		-OH	3401
		-CN(stretching)	1048-1167
11.	$[Zn(dahe)_3]SO_4$	-NH (bending) bounded with metal	1593
		-NH (stretching)	3245-3288
		-CH (stretching)	3164
		-OH	3334-3482
		-CN(stretching)	1102-1331
12.	$[Zn(dahe)_3]2NO_3$	-NH (bending) bounded with metal	1588
		-NH (stretching)	3245-3288
		-CH (stretching)	3163
		-OH	3332-3483
		-CN(stretching)	1146-1331

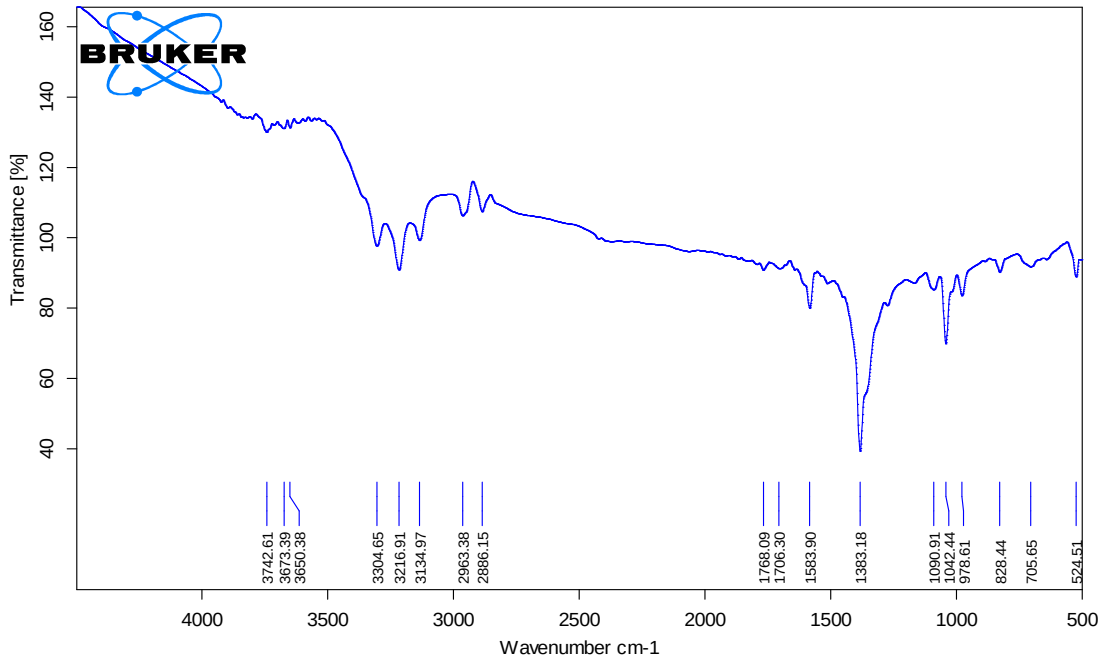

Fig. 1. Infrared spectrum of $[Cu(dahe)_3]2NO_3$

3.3 α–glucosidase Inhibition

In current study metal complexes of different salts (chloride, nitrate and sulphate) of each metal (copper, cobalt, nickel and zinc) with 1,6-diaminohexane have been synthesized to evaluate their anti diabetic activity by α-glucosidase inhibition. After searching and reviewing number of literature, found that lots of metal complexes have been synthesized and their α-glucosidase inhibition activity evaluated. α-glucosidase inhibition is an activity by which α-glucosidase enzyme is inhibited. α-glucosidase is a digestive enzyme which converts glycogen into glucose. Glucose can be easily dissolved in blood, thus glucose level increases in blood and causes hyperglycemia. α-glucosidase inhibitors play an important role to maintain the level of glucose in a diabetic patient.

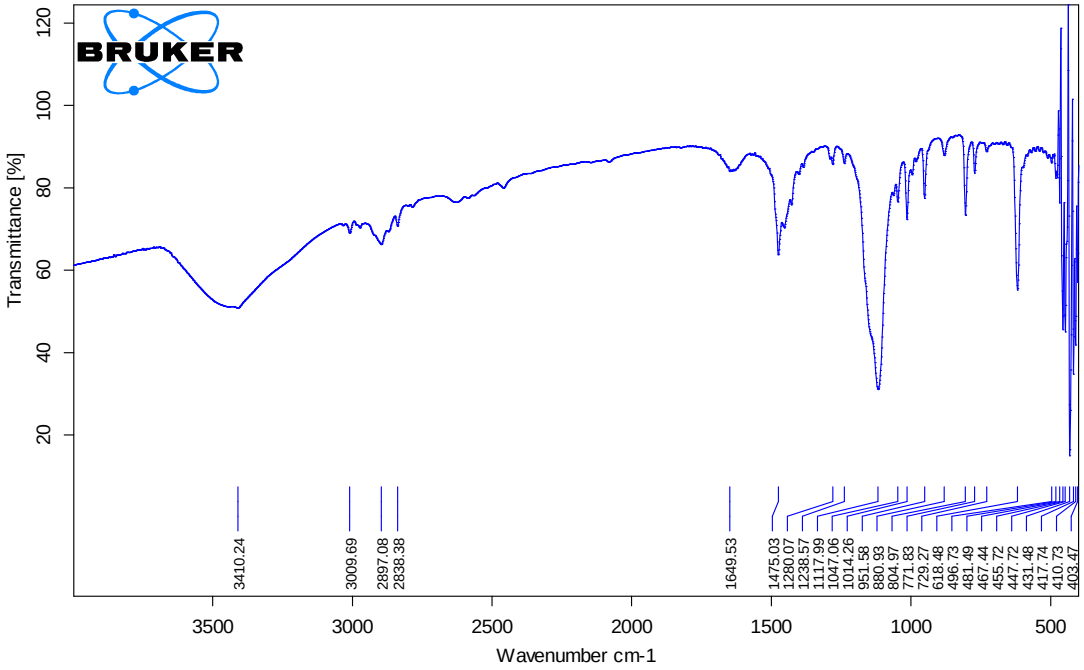

Fig. 2. Infrared spectrum of $[Co(dahe)_3]\ 2NO_3$

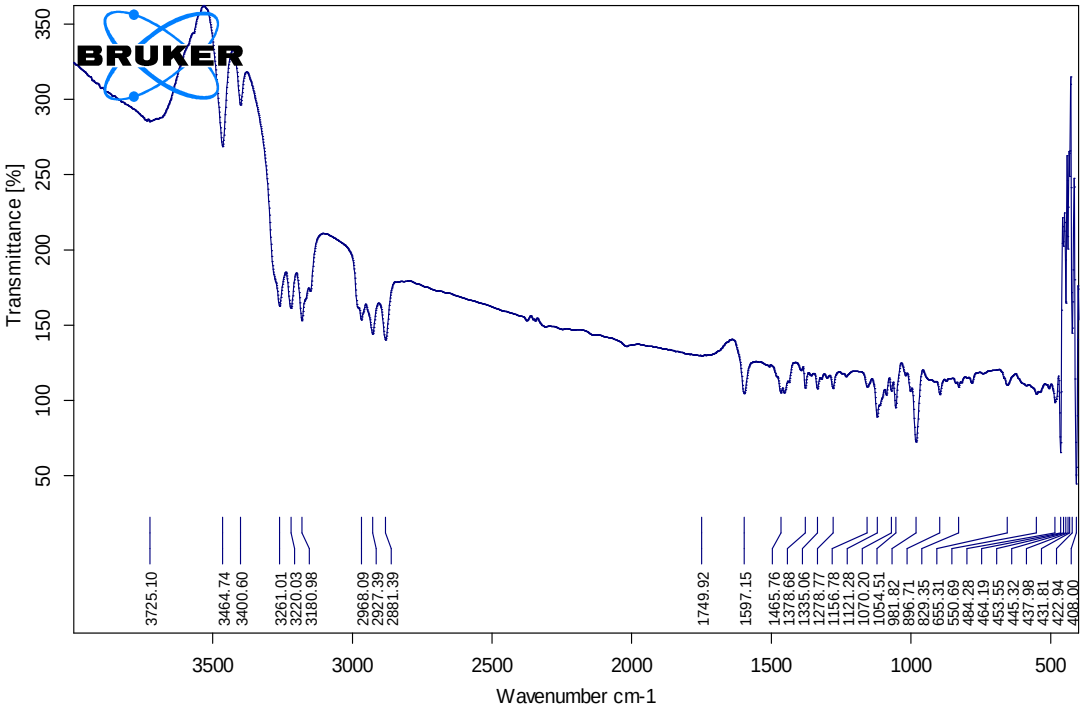

Fig. 3. Infrared spectrum of $[Ni(dahe)_3]\ SO_4$

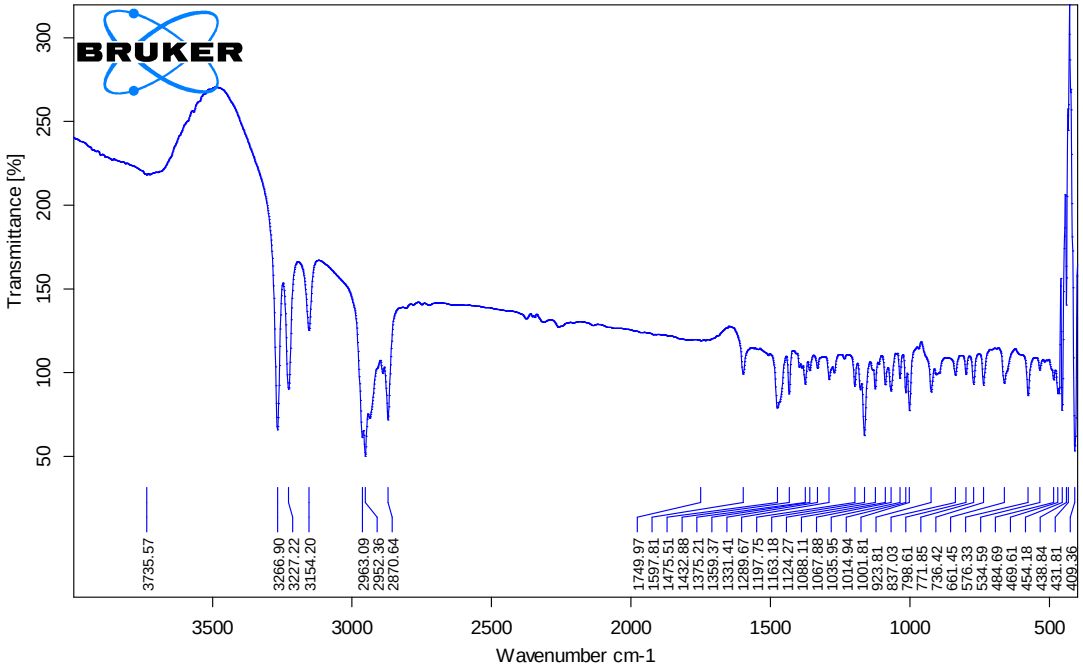

Fig. 4. Infrared spectrum of $[Zn(dahe)_3]SO_4$

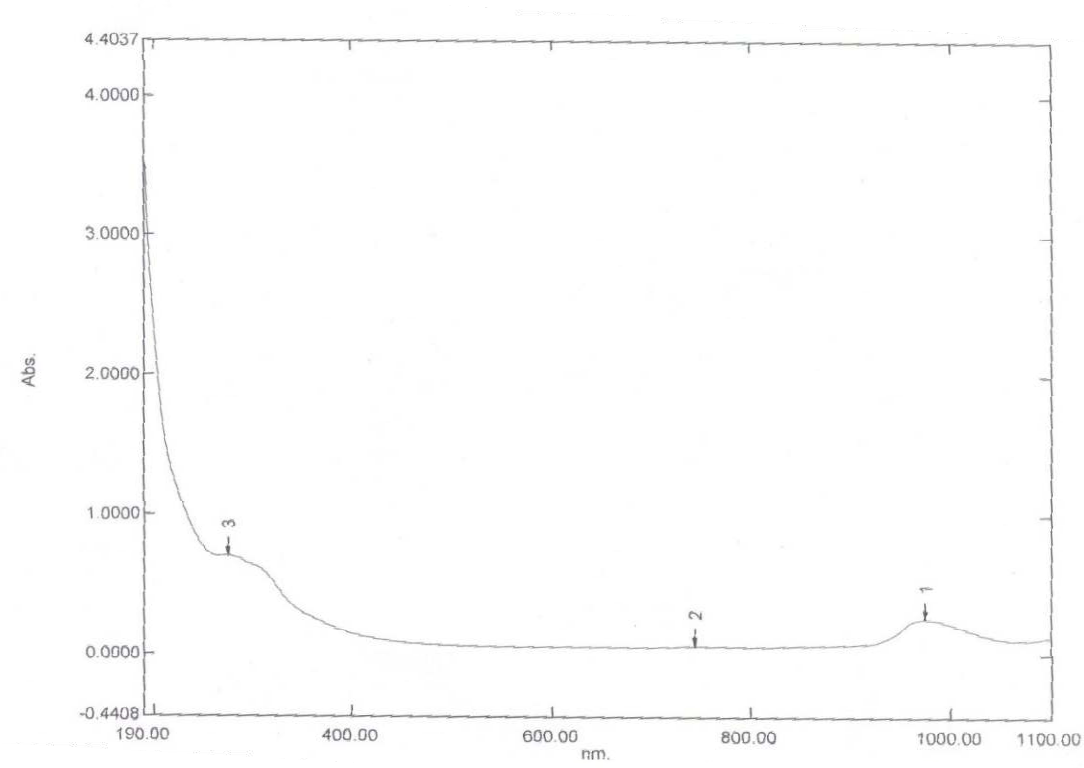

Fig. 5. Ultraviolet spectrum of $[Cu(dahe)_3]2Cl$

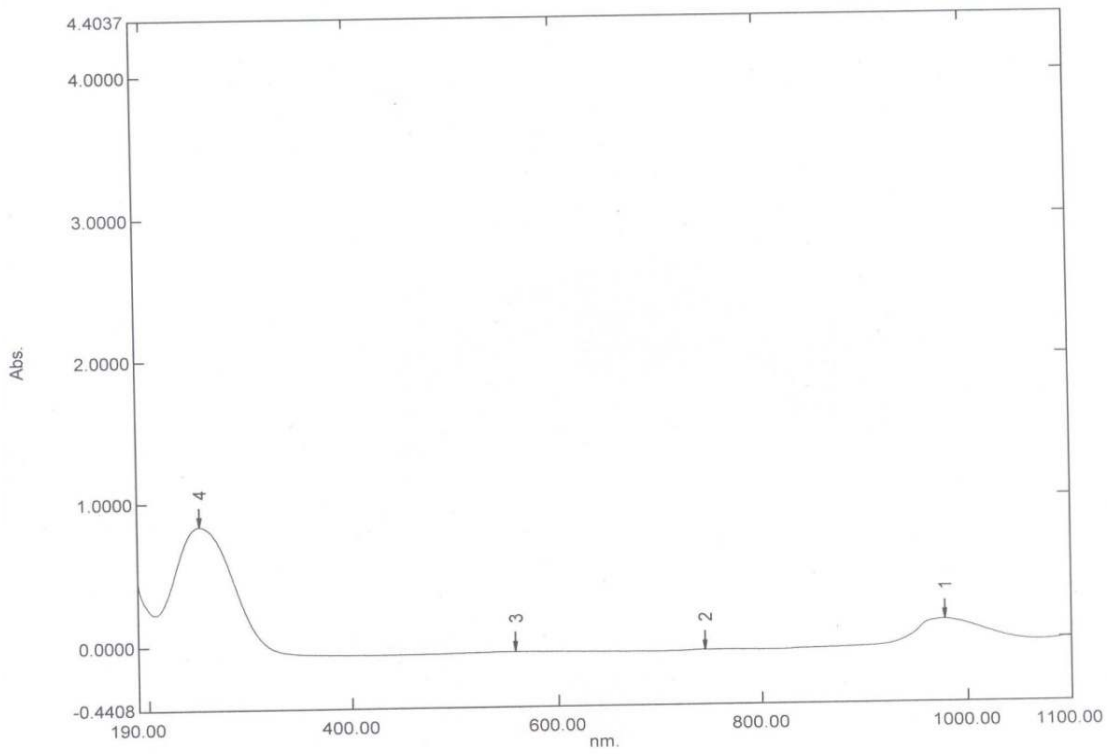

Fig. 6. Ultraviolet spectrum of $[Co(dahe)_3]SO_4$

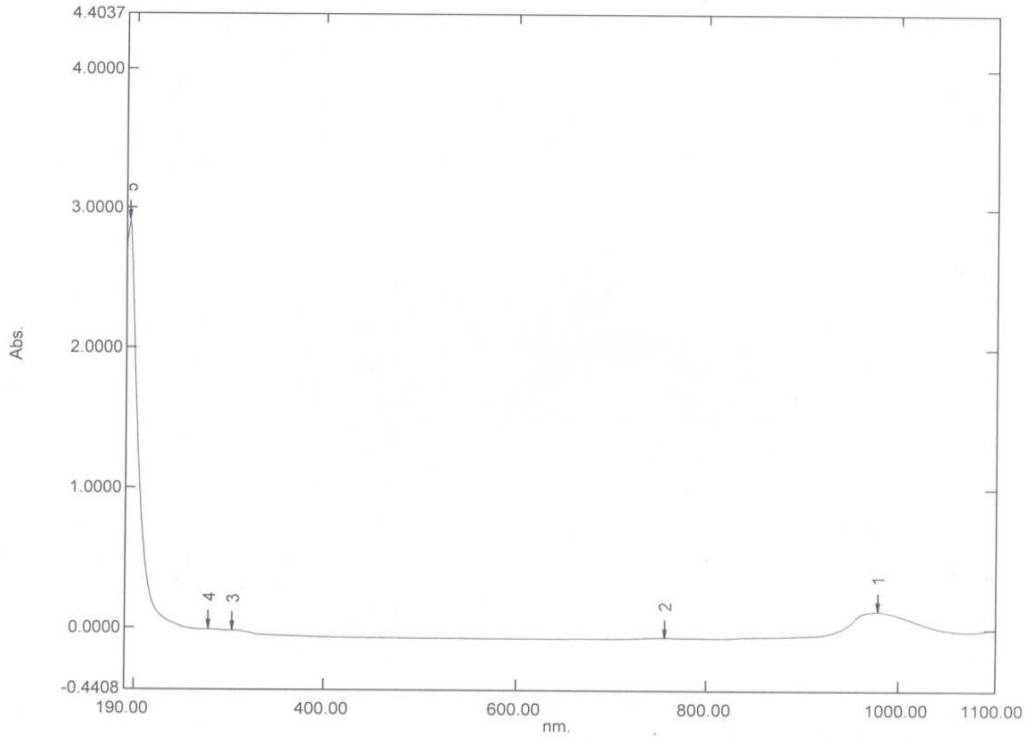

Fig. 7. Ultraviolet spectrum of $[Ni(dahe)_3]SO_4$

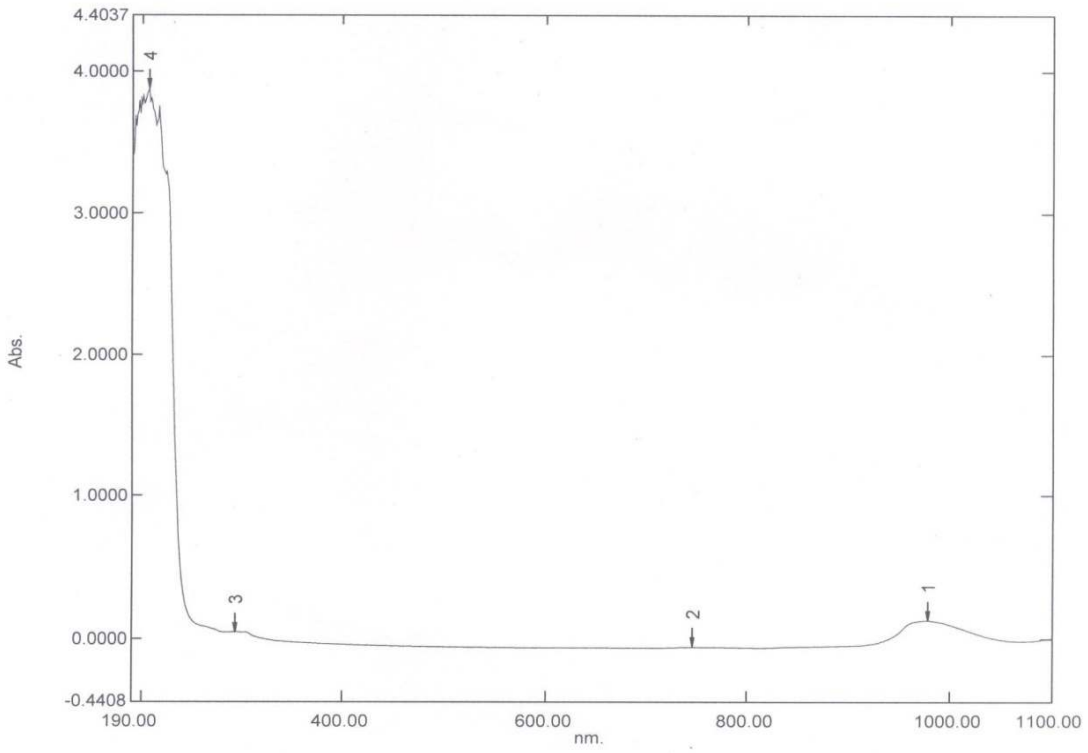

Fig. 8. Ultraviolet spectrum of $[Zn(dahe)_3]2Cl$

Ligands containing phenyl hydroxyl group show inhibitory potential because phenyl hydroxyl group is fundamental for their inhibition activities. Substituent groups present on ligand may influence the hydrogen bond donor capability of the phenyl hydroxyl group. It may also act as hydrogen bond acceptors to appropriate hydrogen bonds donors of protein side chains and causes variations in the inhibitory potential [12]. In α-glucosidase, side chain of Threonine 215 acts as the hydrogen bond acceptor and the side chain hydroxyl group of Serine 244 serves as a hydrogen bond donor [13]. Bond formation between the metal ion and protein side chain is important for inhibition or activation of the enzyme. Metal complexes as α-glucosidase inhibitor can be further stabilized in the active site through hydrogen bonds with catalytic residues and the establishment of hydrophobic contacts in a cooperative fashion [14].

The percentage inhibition activity data of α-glucosidase are given in Table 2. Table 3 is describing the IC_{50} value of acarbose and all 12 metal complexes. All complexes are showing α-glucosidase inhibition activity where complex 1, complex 5 and complex 10 are showing most potent inhibition activity. Complex 10 having lower IC_{50} value 1.196 mg/ml with higher percentage inhibition activity while complex 7 having higher IC_{50} value 3.633 mg/ml with lower percentage inhibition activity. Fig. 9 is representing Percentage inhibition activity of acarbose and Figs. 10, 11, 12 and 13 are representing percentage inhibition activity of metal complexes.

Table 2. Representing the λ_{MAX} for metal complexes

SN	Name of metal complexes	λ_{max} (nm)
1.	$[Cu\ (Ben)_3]2Cl$	276
2.	$[Cu\ (Ben)_3]SO_4$	266
3.	$[Cu\ (Ben)_3]2NO_3$	279
4.	$[Co\ (Ben)_3]2Cl$	221
5.	$[Co\ (Ben)_3]SO_4$	252
6.	$[Co\ (Ben)_3]2NO_3$	279
7.	$[Ni\ (Ben)_3]2Cl$	276
8.	$[Ni\ (Ben)_3]SO_4$	194
9.	$[Ni\ (Ben)_3]2NO_3$	198
10.	$[Zn\ (Ben)_3]2Cl$	207
11.	$[Zn\ (Ben)_3]SO_4$	215
12.	$[Zn\ (Ben)_3]2NO_3$	223

Table 3. Percent inhibition of α-glucosidase

SN	Conc. (mg/ml)	Acarbose	Complexes											
			1	2	3	4	5	6	7	8	9	10	11	12
1	0.1	45.8	4.011	3.438	1.719	8.505	5.412	3.865	5.867	2.933	3.178	6.515	5.382	6.232
2	0.2	53.85	11.17	12.60	6.876	14.69	11.08	9.536	9.290	5.378	6.601	15.01	11.89	11.04
3	0.4	58.74	19.19	16.61	9.455	21.13	22.42	15.97	10.02	11.73	11.00	22.66	18.41	16.14
4	0.6	62.24	22.63	18.05	18.05	26.28	26.28	24.22	12.71	17.60	12.95	28.61	25.77	23.22
5	0.8	67.13	29.22	20.63	32.95	33.76	36.34	33.76	14.66	20.29	15.89	37.39	28.32	27.47
6	1.0	72.38	39.25	32.95	39.82	37.62	40.20	37.62	18.22	24.69	20.29	40.22	35.69	34.84

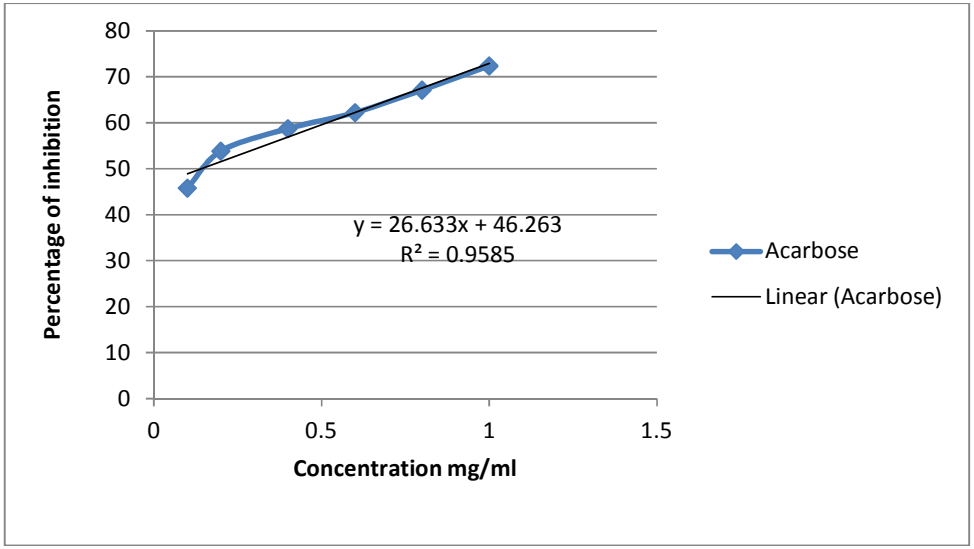

Fig. 9. Percent inhibition of α-glucosidase by acarbose

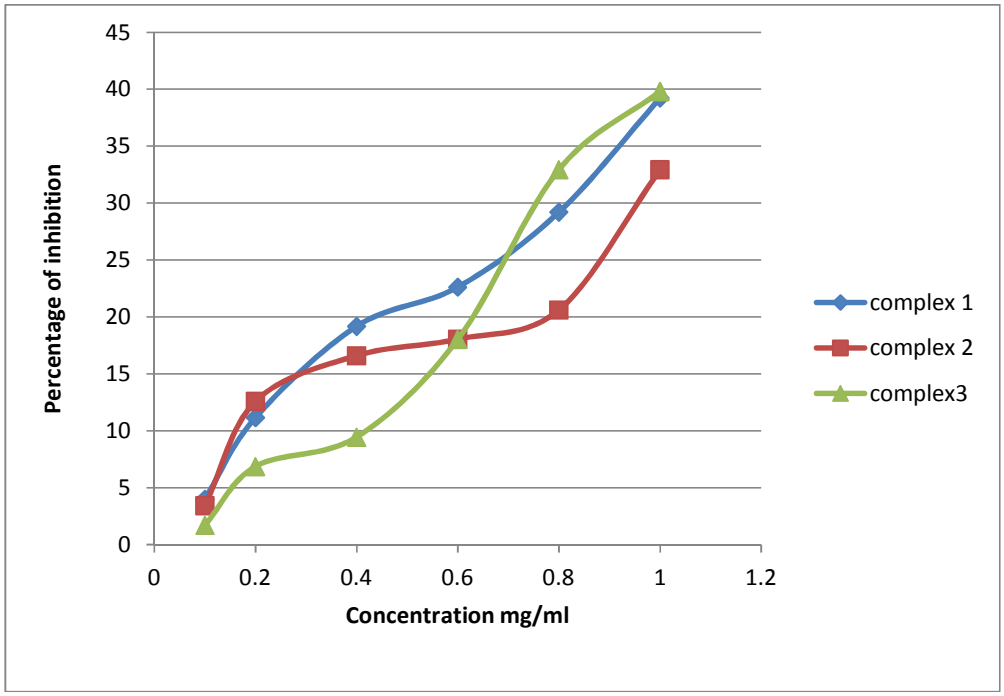

Fig. 10. Percent inhibition of α-glucosidase by Cu(II) metal complexes

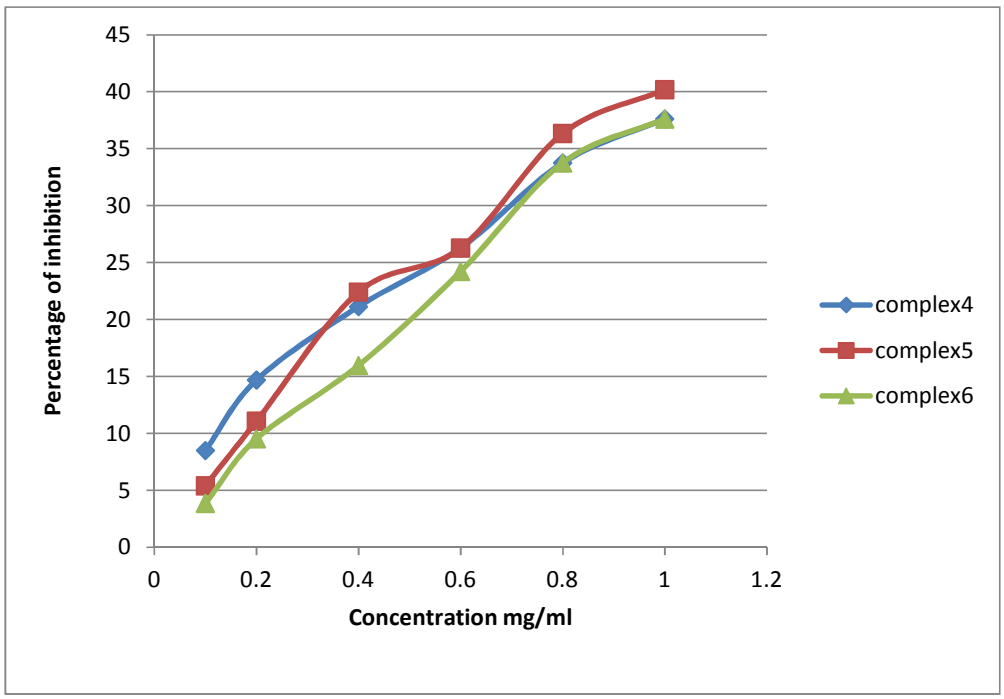

Fig. 11. Percent inhibition of α-glucosidase by Co(II) metal complexes

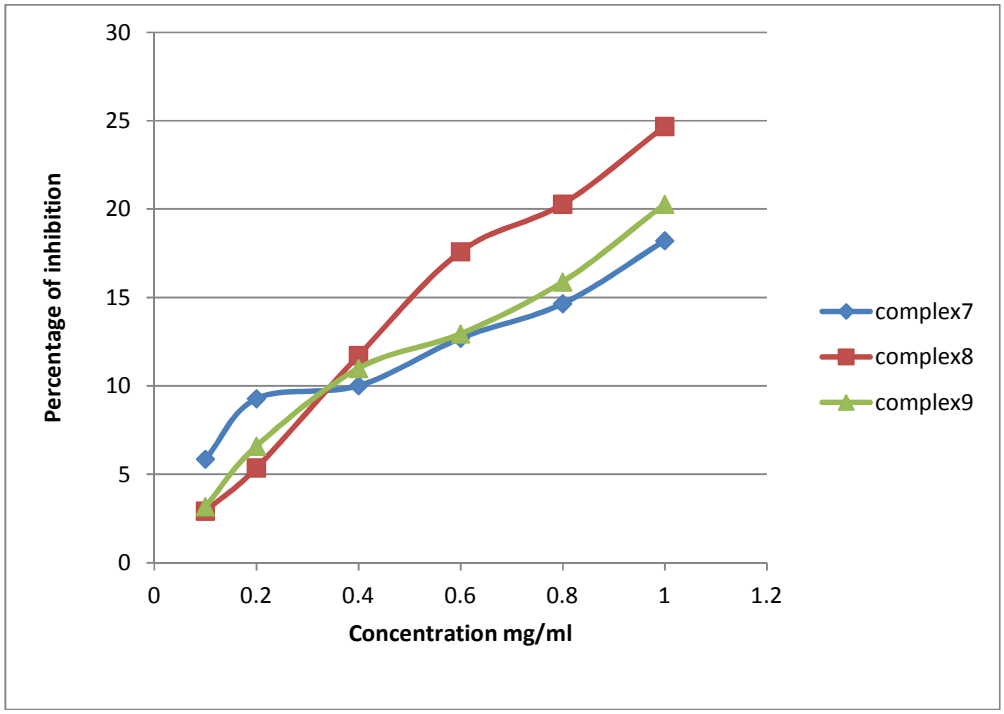

Fig. 12. Percent inhibition of α-glucosidase by Ni(II) metal complexes

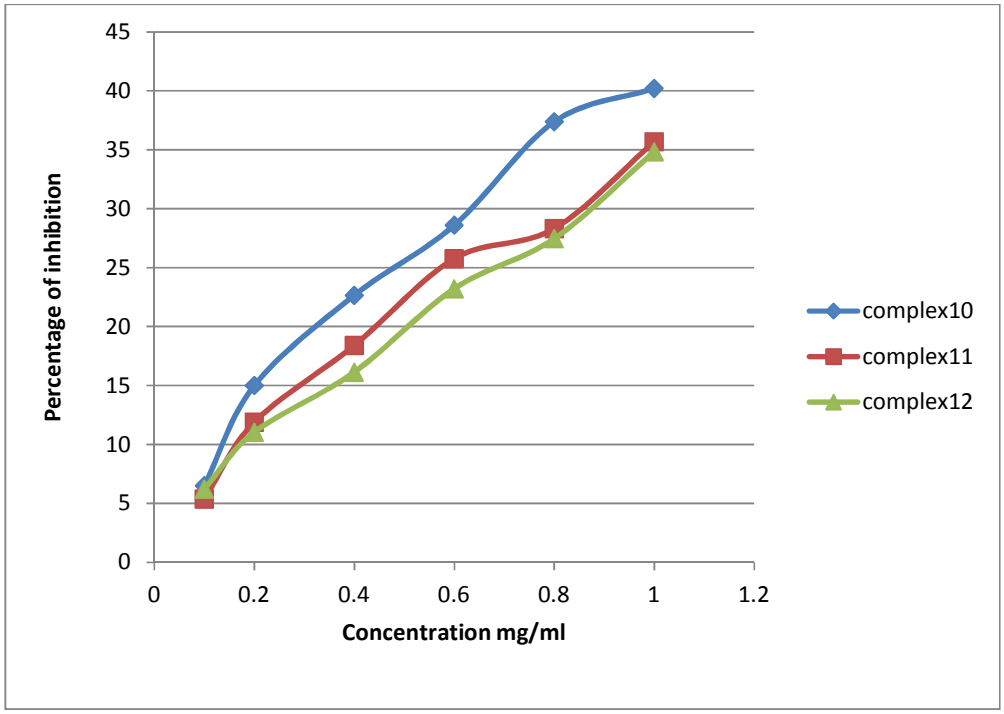

Fig. 13. Percent inhibition of α-glucosidase by Zn(II) metal complexes

Table 4. IC_{50} value of complexes

SN	Name of Complex	IC_{50} (mg/ml)
1.	[Cu $(dahe)_3$]2Cl	1.332
2.	[Cu $(dahe)_3$]SO_4	1.763
3.	[Cu $(dahe)_3$]2NO_3	1.259
4.	[Co $(dahe)_3$]2Cl	1.348
5.	[Co $(dahe)_3$]SO_4	1.198
6.	[Co $(dahe)_3$]2NO_3	1.279
7.	[Ni $(dahe)_3$]2Cl	3.633
8.	[Ni $(dahe)_3$]SO_4	2.000
9.	[Ni $(dahe)_3$]2NO_3	2.699
10.	[Zn $(dahe)_3$]2Cl	1.196
11.	[Zn $(dahe)_3$]SO_4	1.435
12.	[Zn $(dahe)_3$]2NO_3	1.504
	Acarbose	0.140

4. CONCLUSION

Transition metals have an essential role in biological system. In current work we have synthesized and characterized metal complexes via infrared and ultraviolet spectral properties. Sharp and intense peak between 1582-1616 cm^{-1} in IR spectrum represents metal-ligand bonding which represents that [$M(dahe)_3$] complexes have synthesized. UV spectral bands in region of 194 – 279 nm are showing $\pi \rightarrow \pi^*$ transition which is indicating involvement of imines nitrogen atom in synthesized metal complexes and assuring metal ligand coordination. All twelve complexes possess α-glucosidase inhibition activity, among them [Zn $(dahe)_3$]2Cl have the highest α-glucosidase inhibition, having lowest IC_{50} value 1.196 mg/ml and [$Ni(dahe)_3$]2Cl have the lowest α-glucosidase inhibition, having highest IC_{50} value 3.633 mg/ml. synthetic α-glucosidase inhibitor may be effective for antidiabetic treatment and other disorders because it is easy to synthesize and also having a great possibility to inhibit α-glucosidase.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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