Synthesis , Spectroscopic and Antibacterial Studies of Zinc(II) Complexes Derived from Salicylaldehyde, Leucylalanine and Glycylglycine

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Abstract:

Two Schiff base ligands L_1 and L_2 have been obtained by condensation of salicylaldehyde respectively with leucylalanine and glycylglycine then their complexes with Zn(II)were prepared and characterized by elemental analyses , conductivity measurement , IR and UV-Vis .The molar conductance measurement indicated that the Zn(II) complexes are 1:1 non-electrolytes. The IR data demonstrated that the tetradentate binding of the ligands L_1 and L_2 . The in vitro biological screening effect of the investigated compounds have been tested against the bacterial species *Staphlococcus aureus, Escherichia coil , Klebsiella pneumaniae, Proteus vulgaris and Pseudomonas aeruginosa* by the disc diffusion method . A comparative study of inhibition values of the Schiff base ligands and their complexes indicated that the complexes exhibit higher antimicrobial activity than the free ligands . Zinc ions are proven to be essential for the growth-inhibitor effect. The extent of inhibition appeared to be strongly dependent on the initial cell density and on the growth medium .

Key words: Dipeptide , Schiff base, Antibacterial, Zn(II)complexes

Introduction:

The coordination chemistry of amino acid Schiff base is of considerable interest due to their biological importance[1,2]. However, little attention has been paid to systems in which the Schiff bases derived from simple peptides. A vanadium complex VO(sal–glygly)$(H_2O)_n$(sal–glygly= N-salicylideneglycylglycine); n=1.5–3.0 has been isolated from relatively concentrated solutions containing oxovandium (IV) , glycylglycine and salicylaldehyde [3].Synthesis ,crystal structure and magnetic studies of cis–configuration copper (II) – M(II) (M= Ba , Ca) complexes of the sal – glygly Schiff base have been determined [4] . Sallam and coworkers have been prepared and characterized the uranyl complexes of Schiff base obtained by condensing glygly with hydroxybenzaldehyde [5]. Recently , tow copper (II) tripeptide Schiff base complexes: [$Mg(H_2O]$ $[CuL]2.3.5H_2O$ and $[Cd(H_2O)_4(CuL)_2].3.5H_2O$ (H_3L = N-sal–glygly) have been synthesized and structurally characterized [6]. Also, Binuclear copper, nickel and cobalt of the Schiff bases have been prepared by condensation of glycylglycine with acetylacetone, benzoylacetone, dibenzoylmethane and thenoyltrifluoroacetone[7]. Many metals complexes have powerful antimicrobial activities and are already common day-to-day use in medicinal field such as silver bandages for treatment of burns ,zinc antiseptic creams , bismuth drugs for the treatment of ulcers and metal clusters

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as anti-HIV drugs . The potential for further development of metal-based drugs and treatment as an antimicrobial agent[8,9]is enormous and also of great importance with the evolution of drug-resistant bacteria and threats from a range of viral diseases . The discovery and development of antibiotics are among the most powerful and successful achievements of modern science and technology for the control of infectious diseases. Metal-based drugs represent a novel group of anti fungal agents with potential applications for the control of fungal infection . This inspires synthetic chemists to search for new metal complexes for bioactive compounds and zinc in particular has attracted the researchers . The field of macrocyclic chemistry of metals is developing very rapidly because of its application and importance in the area of coordination chemistry [10] .The finding that the tetrahedral zinc complexes in its cavities generally represent the optimal , least strained structures among various zinc polyhedra may explain why four-coordinate zinc is chosen to play a structural role in zinc fingers and enzymes. Recently, Nair and coworkers have been synthesized and characterized some Schiff base metal complexes and their in *vitro* antimicrobial activities have been investigated [11,12]. In the present paper , I report the result on the synthesis, characterization and antimicrobial activities of Zn(II) complexes of Schiff base ligands L1 and L2 derived from silicylaldehyde and leucylalanine and glycylglycine respectively.

Materials and Methods :

Reagents and apparatus.

The dipeptide, leucylalanine and glycylglycine has been purchased from Fluka (LTD) and used without further purification .Salicylaldehyde have been obtained from Fluka and Zn(II) acetate was obtained from Merck (LTD) .All other reagent and solvent have been purchased from commercial sources and were of analytical grade. Solvent have been purified and dried by standard methods. Elemental analysis was done using a Perkin-Elmer elemental analyzer .IR spectra have been recorded in KBr disc on a (8300) (FT-IR) Shimadzu spectrophotometer in the range 4000-400 cm^{-1} region. The electronic spectra have been recorded on a Shimadzu,160,using a quartz cell of (1.0) cm length spectrophotometer .Molar conductance of the complexes has been measured in DMSO (10^{-3}M) solution using a coronation digital conductivity meter.

***In vitro* antimicrobial activity.** Antibacterial activity of the ligands and their complexes have been tested against the bacterial species *Staphlococcus aureus, Escherichia coil, Klebsiella pneumaniae, Proteus vulgaris and Pseudomonas aeruginosa* by Kirby bauer Disc diffusion method [13]. *Amikacin, Ofloxacine* and *Ciprofloxacine* have been used as the standard antibacterial agent .The test organisms were grown on nutrient agar medium in petri plates. The compounds have been prepared in DMSO and soaked in filter paper disc of 5mm diameter and 1mm thickness .The disc were placed on the previously seeded plates and incubated at 37 C° and the diameter inhibition zone [14] around each disc has been measured after 24 h for bacteria .

Synthesis of the Dipeptide Schiff base Potassium Salt. A solution containing (1.01 gm, 5mmol) of leucylalanine and (0.66gm,5 mmol) of glycylglycine in 20 ml of water was added to 15 mL of an ethanol solution containing (0.36 gm ,5 mmol) of KOH. The resulting solution was

stirred on a water bath at 25 C˚ for half an hour and then filtered . The filtrate was added dropwise to 20 mL of an ethanol solution of Salicylaldehyde (0.61 gm , 5 mmol) with stirring on a water bath at 25 C˚ for one hour . The volume of the solution was reduced by distillation to 5 mL and then ethanol (10 mL) was added . The yellowish precipitate formed was separated by filtration . The precipitate was recrystalled from methanol . [15]

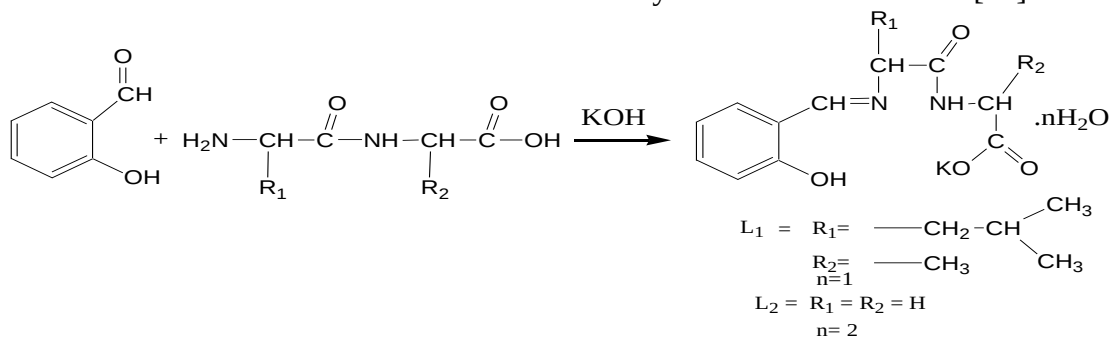


Fig.1 Synthesies and structures of ligands

Synthesis of Zn(II **) Schiff base complexes.** The Zinc acetate (1.09 gm , 5mmol) was dissolved in 20 mL of water . The solution was filtered and added dropwise into 25 mL of an ethanol solution of the Schiff base ligands (1.81 and 1.55 gm .respectively ,5mmol). The reaction mixture was stirred at 25 C˚ on water bath for 3 h. The resulting precipitate has been filtered , washed with ethanol and diethyl ether ,then recrystallized from methanol , and dried in vacuum desiccator .[15] The analytical data are summarized in Table 1.

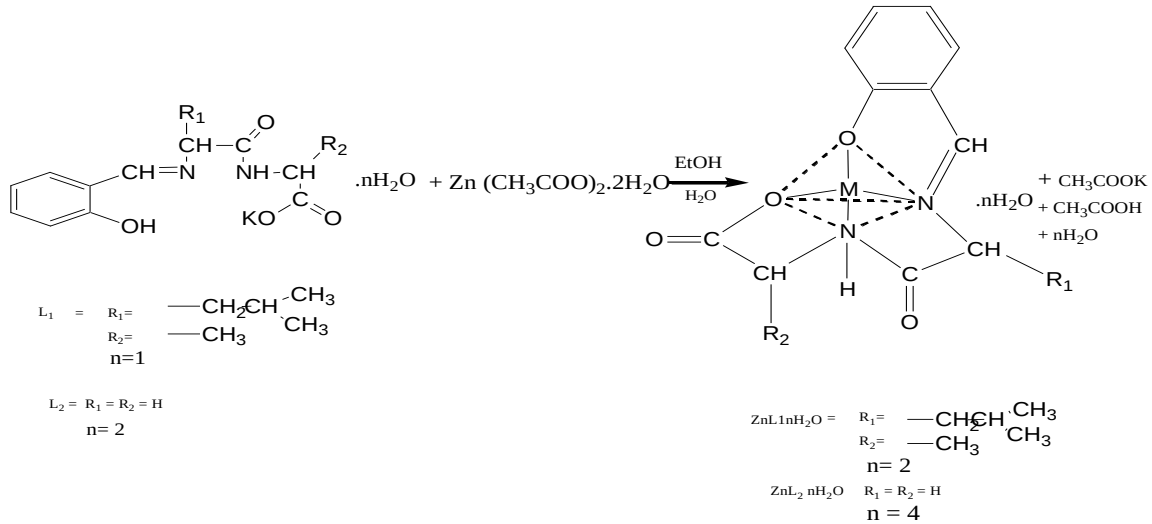


Fig.2 Synthesies and proposed structure for ZnL_1 and ZnL_2 Schiffbase complexes

Results and Discussion:

Zn(II) complexes are stable at room temperature, insoluble in water but soluble in DMF and DMSO. The physical properties and analytical data of the ligands and their complexes are given in Table 1. Elemental analysis data of the complexes are in good agreement with theoretical values. The analytical data (Table 1) indicate that the metal to ligand ratio is 1:1 in all the complexes systems and it can be represented as $[ZnL_1]. nH_2O$ and $[ZnL_2]. nH_2O$, where L_1 and L_2 are

Schiff base ligands obtained by the condensation of salicylaldehyde respectively with leucylalanine and glycylglycine. The values of the conductivities of the Zn(II) complexes are in the (7.2 – 12.5) Ω^{-1} mol^{-1} cm^2 range, indicating that the proposed complexes are 1:1 non-electrolytes [16].

Table 1. Physical and analytical data of the Schiff base ligands and their complexes

Compound	Formula	Mol. Wt. gm/mol	M.p (C°)	Yield (%)	Conductivity Ohm^{-1} cm^2mol^{-1}	Found (calc.) (%)			
						C	H	N	M
$KHL_1.H_2O$	$C_{16}H_{23}KN_2O_5$	362.46	134	35	–	53.09 (53.02)	6.31 (6.40)	8.01 (7.73)	–
$KHL_2.2H_2O$	$C_{11}H_{15}KN_2O_6$	310.06	120	38	–	42.79 (42.57)	4.97 (4.87)	9.43 (9.03)	–
$ZnL_1.2H_2O$	$C_{16}H_{24}N_2O_6Zn$	405.78	> 265	68	7.2	47.44 (47.36)	5.88 (5.96)	7.29 (6.90)	16.24 (16.12)
$ZnL_2.4H_2O$	$C_{11}H_{18}N_2O_8Zn$	371.68	> 250	65	12.5	35.40 (35.55)	4.53 (4.88)	7.66 (7.54)	17.44 (17.60)

IR spectra. The Schiff base ligands L_1 and L_2 show (C=N) azomethine bands observed at 1618 cm^{-1} and 1615 cm^{-1} respectively . On complexation , this band was shifted to 1610 cm^{-1} and 1600 cm^{-1} regions [17] due to the coordination of azomethine nitrogen to the Zn (II) ion . In the spectra of Schiff base ligands , the peptide bands were observed at 1521 $cm^{-1}$and 1518 cm^{-1} . On complexation , this band was shifted to 1525 cm^{-1} and 1525 cm^{-1} region , indicating the linkage between metal ion and the peptide nitrogen atoms. The asymmetric carboxyl stretching $\upsilon_{asy}(COO^-)$ was shifted to higher and lower frequency in the 1600 cm^{-1} and 1560 cm^{-1} range and the symmetric carboxyl stretching $\upsilon_{sym}(COO^-)$ was shifted to higher and lower frequency in the 1520 cm^{-1} and 1440 range , indicating the linkage between the metal ion and carboxylato oxygen atom.The asymmetric and symmetric stretching vibration of the carboxylato group in the complexes shows the separation value ($\Delta\upsilon$) greater than 150 cm^{-1} .This indicates monodentate binding of carboxylato group in Zinc (II) complexes. Furthermore, the presence of coordinated and lattice water molecules appeared respectively at 3375 and 3380 cm^{-1} in ZnL_1 and ZnL_2 complexes may be attributed to O-H stretching vibration . The appearance of two bands at 510 and 520 cm^{-1} corresponds to υ (M-O) and the bands at 430 and 425 cm^{-1} corresponds to υ (M-N) stretching vibrations respectively (see Fig 3) . Thus, the IR spectral data indicate that ZnL_1 and ZnL_2 complexes tetradentate binding through azomethine nitrogen , amide nitrogen, phenolic oxygen and carboxylato oxygen atoms. The IR data are summarized in Table 2

Table.2. Important IR Absorption Bands (cm^{-1}) of the Schiff base ligands and their complexes

Compound	υOH	υC=N	$\upsilon_{as}COO^-$	υ(CONH)	$\upsilon_{sym}COO^-$	υC-N	υC-O	δcoo^-	υM-O	υM-N
$KHL_1.H_2O$	3380 s,br	1618 s	1598 s	1521 s	1460 m	1398 s	1240 w	765 s	-	-
$KHL_2.2H_2O$	3385 s,br	1615 s	1600 m	1518 s	1450 m	1395 s	1245 w	765 s	-	-
$ZnL_1.2H_2O$	3375 s,br	1610 s	1600 s	1525 m	1520 m	1390 m	1160 s	755 s	430 w	510 w
$ZnL_2.4H_2O$	3380 s,br	1600 s	1560 s	1523 m	1442 s	1380 s	1242 m	768 m	425 w	520 w

s= strong , br= broad , m= medium , w= weak

UV/Vis. Spectra. The Schiff base ligands L1 and L2 show the absorption bands at 291 nm and 280 nm, which is assigned to π-π* transition of the C=N chromophore. On complexation , this band was shifted to lower wavelength region 285 nm and 275nm, suggesting the coordination of azomethine nitrogen with Zn(II) ion [18](see Fig 4) . Zn(II) complex does not exhibit d-d electronic transition due to the completely filled (d) orbital. Four coordinate Zn(II)complexes would have tetrahedral geometry (Fig.2) .

Antimicrobial activity. The *in vitro* biological screening effect of the investigated compounds were tested against some bacterial species(isolated from patients) by the disc diffusion method . The results of the antibacterial activities were given in Table 2. The results show that both the Schiff base ligands have moderate activity in the antibacterial species. Against all organisms , ZnL_1 and ZnL_2 complexes were found to be highly active in the bacterial species of *S. aureus* , *E. coil* and *P. aeruginosa* . However, ZnL_1 has moderate activity in the species of *K. penunaniae*. Moreover, the results point out that in *P.vulgaris*, ZnL_1 complex is less active and ZnL_2 is moderately active . Again, the comparison of the above results with *Amikacin, Ofloxacine* and *Ciprofloxacine* antibacterial standards demonstrates that *S. aureus, K. penunaniae*, *P.vulgaris* and *P. aeruginosa* are moderately active . However, the standards *Amikacin* and *Ciprofloxacine* show higher activity in the *E. coil* species , while *Ofloxacine* is less active in the *P. aeruginosa* species . Table 3.

Table 3. Antibacterial activity of Schiff base ligands and their complexes

Compound	Gram positive bacteria	Gram negative bacteria			
	S. aureus	*K. penunaniae*	*P.vulgaris*	*E. coil*	*P. aeruginosa*
$KHL_1.H_2O$	++	++	++	++	++
$KHL_2.2H_2O$	++	++	++	++	++
$ZnL_1.2H_2O$	+++	++	+	+++	+++
$ZnL_2.4H_2O$	+++	+++	++	+++	+++
Amikacin[a]	++	++	++	+++	++
Ofloxacin[a]	++	++	++	++	+
Ciprofloxacin[a]	++	++	++	+++	++

Inhibition values = 0.1-0.5 cm beyond control = + (less active); inhibition values = 0.6-1.0 cm beyond control = ++ (moderate active) ; inhibition values = 1.1-1.5 cm beyond control = +++ (highly active) . [a]Standards.

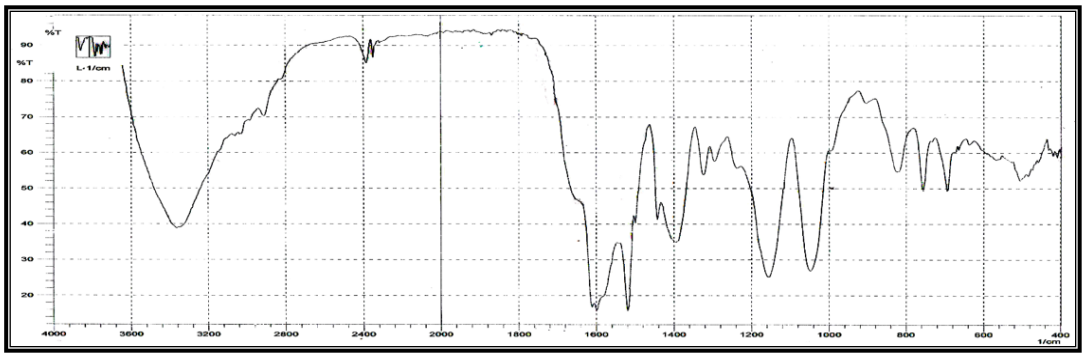
Mode of action. Although the exact mechanism hasn't been understood biochemically , mode of action of antimicrobils may involve various target in microorganisms.

(i) Interference with the cell wall synthesis, damage as a result of which cell permeability may be altered (or) they may disorganize the lipoprotein leading to the cell death.

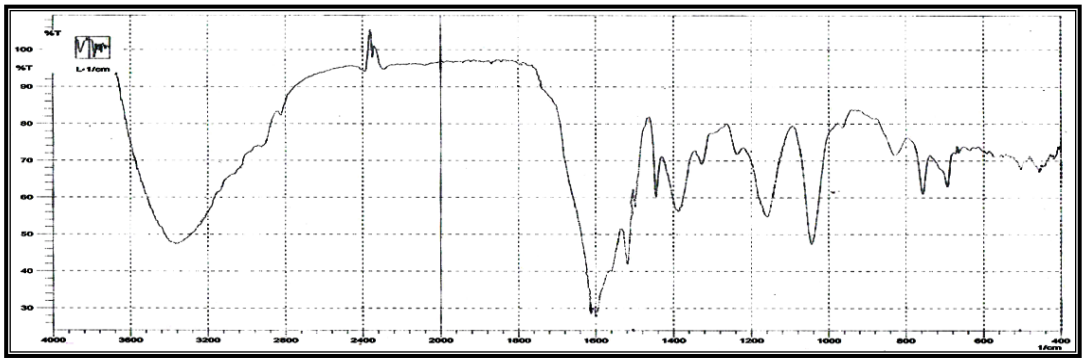
(ii) Deactivate various cellular enzymes, which play a vital role in different metabolic pathways of these microorganisms .

(iii) Formation of a hydrogen bond through the azomethine group with the active center of cell constituents, resulting in interference with the normal process.

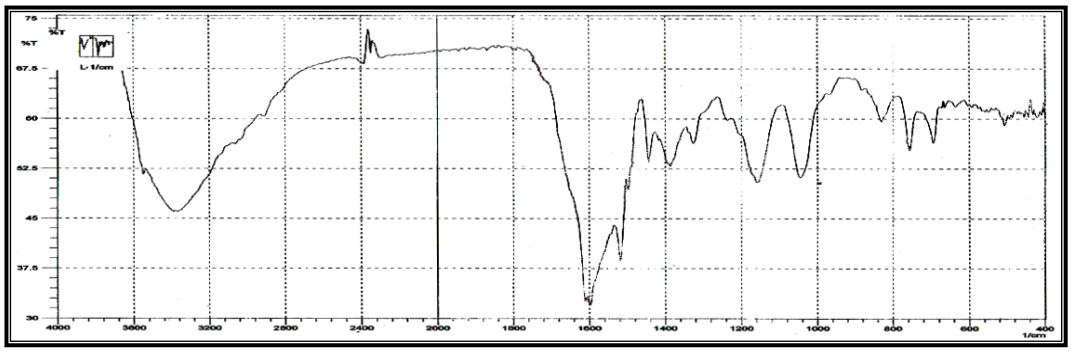
Effect of azomethine (C=N) group. The mode of action of the compounds may involve formation of a hydrogen bond through azomethine group (C=N) with the active centers of cell constituents[19] resulting in interferences with the normal process.



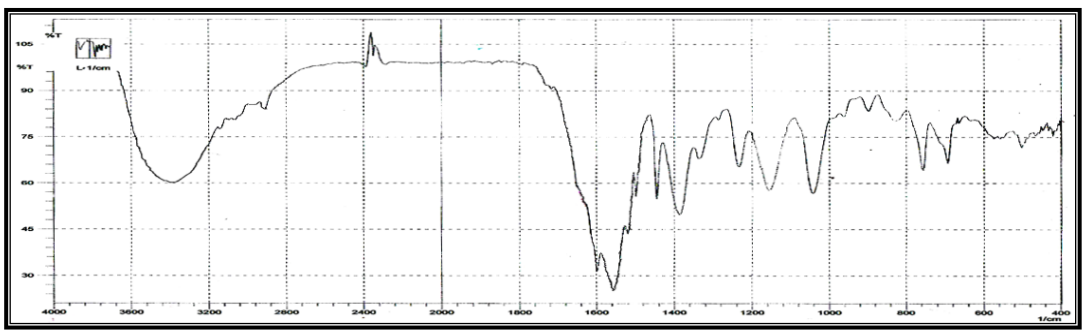
IR spectra of ligand L_1



IR spectra of ligand L_2

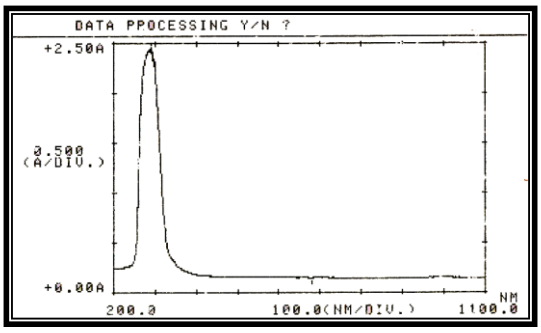


IR spectra of $ZnL_1.2H_2O$

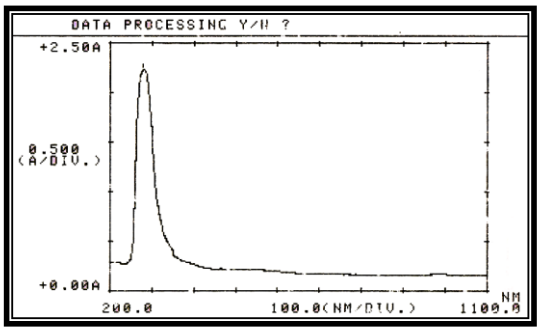


IR spectra of $ZnL_2.4H_2O$

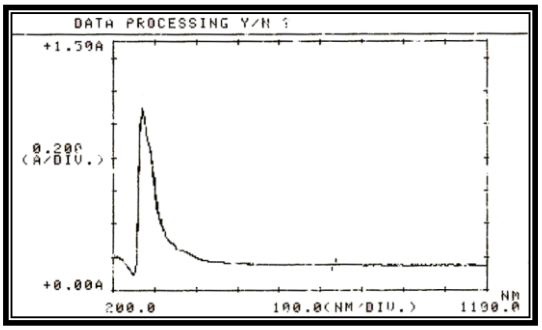
Fig. 3 IR spectra for the prepared compounds



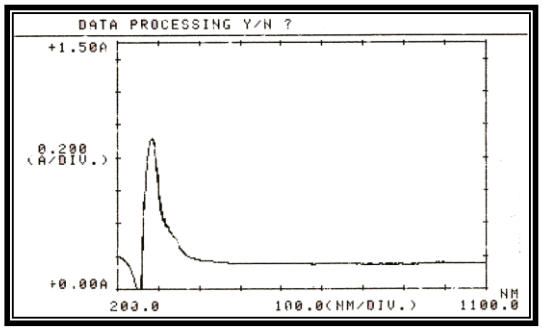
UV-Vis of Ligand L_1



UV-Vis of Ligand L_2



UV-Vis of $ZnL_1.2H_2O$



UV-Vis of $ZnL_2.4H_2O$

Fig. 4 UV-Vis spectra for the prepared compounds

References:

1. Mathews, I.I. , Joy, P.A. and Vasudevan , S. 1991.Synthetic, spectroscopic, magnetic, and x-ray structural studies on a vitamin B_6 – amino acid Schiff base complex, aqua(5-phosphopyridoxylidenetyrosinato) copper(II) tetrahydrate, Inorg. Chem., 30(9):2181-2185 .
2. Angoso, A., Marin-Lorento, J.M. , Manzano, J.L., Martin, M. , Martin, R. and Rodriguez, E. 1992.Preparation and study of amino acid (DL- leucine, L-isoleucine, L-histidine) Schiff bases with ethyl-α-ketocyclopentylcarboxylate and the corresponding copper(II) complexes, Inorg. Chim . Acta, 195(1):45-49 .
3. Costa Pessoa , J., Cavaco , I.; Correia , I., Costa, D., Henriques, R. T. and Gillard , R. D. 2000. Preparation and characterization of new oxovanadium (IV) Schiff base complexes derived from salicylaldehyde and simple dipeptides , Inorg. Chim . Acta, 305(1): 7-13 .
4. Hu, C. J., Ren ,X. M., Lu, C. S., Zou, Y., Zhang , W.W.,Duan C.Y. and Meng, Q.J. 2003.Synthesis ,crystal structure and magnetic studies of *cis*-configuration copper(II)-M(II) (M= Ba ,Ca) complexes of novel Schiff bases derived from salicylaldehyde and dipeptides ,Transition Met. Chem. , 28(3):350-355.
5. Sallam ,Sh.A. and Ayad, M.I. 2003. Spectral and thermal properties of some uranyl complexes of some Schiff bases derived from glycylglycine , J. Kor. Chem. Soc., 47(3):199- 205 .
6. Liu , W.L., Zou, Y. , Ni, C.L.,Ni, Z.P., Li, Y.Z., Yao, Y.G. and Meng, Q.J. 2004. Synthesis and characterization of copper (II)

Schiff base complexes derived from salicylaldehyde and glycylglycylglycine , Polyhedron, 23(5): 849-855.

7. Sallam, Sh.A. 2006. Binuclear copper (II) , nickel (II) and cobalt (II) complexes with N_2O_2 chromophores of glycylglycine Schiff bases of acetylacetone, benzoylacetone and thionyltrifluoroacetone , Transition Met. Chem. ,31(1):46-55.
8. Scozzafava, A., Menabuoni, L. , and Mincione, F. 2001. Carbonic anhydrase inhibitors:Synthesis of sulfonamides incorporating dtpa tails and of their zinc complexes with powerful topical antiglaucoma properties , Bioorg. Med. Chem. Lett., 11(4):575-582.
9. Scozzafava, A. and Supuran , C. 2000.Carbonic anhydrase and matrixmetalloproteinase inhibitors: Sulfonylated amino acid hydroxamates with MMP inhibitory properties act as efficient inhibitors of CA isozymes I,II, and IV, and N-hydroysulfonamides inhibit both these zinc enzymes , J. Med. Chem., 43(20):3677-3687.
10. Ashu , C., Nidhi , B., Gajraj , A. and Singh , R. 2003. Antifertility , antibacterial ,antifungal and perecent disease incidence aspects of macrocyclic complexes of Mn(II), J. Inorg. Bio-chem., 96(2-3) :393-400 .
11. Nair , M. S. and Raj , C. R. S. 2007. Furfuraldenevalinate system: Solution chemistry of denticity reduction , gas and solid phase complexing behavior , J. Mol. Liquids , 131-133:196-199
12. Nair , M. S. , Sudhakumari , S. and Neelakantan, M. A, 2007. Studies on some novel Schiff base complexes in solution and solid phase, J. Coord. Chem. 60(12):1291-1303.
13. Bauer, A. W., Kirby, W. M. M. , Sherries , J. C. and Truck, M. 1996. Antibiotic susceptibility testing by a standardized single disk method , Am. J. Clin. Pathol. 45(3):493-496.
14. Ferrari , M. B., Capacchi, S., Reffo, G , Tarasconi , P., Albertini, R., Pinelli, S. and Lunghi, P. 1999. Synthesis structural characterization and biological activity of helicin thiosemicarbazone momnohydrate and a Cu(II) complex of salicylaldehyde thiosemicarbazone, Inorg. Chim. Acta,286(2):134-141.
15. Wang , G. 2000. Synthesis and characterization of novel complexes of a dipeptide Schiff base ligand containing DL- alanyl-DL- alane, Synth. React. Inorg. Met-Org. Chem., 30(4):601-608.
16. Geary ,W. J. 1971. The use of conductivity measurements in organic solvents for the characterization of coordination compounds , Coord. Chem. Rev. ,7(1):81-122.
17. Nakamoto, K. 1992. Infra-red and Raman Spectra of Inorganic and Coordination Compounds, John Wiley and Sons, New York , 3rd Ed, pp. 91-112 .
18. Lever , A. B. P. 1984. Inorganic Electronic Spectroscopy, Elsevier , 2nd Ed , Amsterdam, pp.77-85.
19. Mishra, L. and Sing ,V. K. 1993. Synthesis , structural and antifungal studies of Co(II) ,Ni (II) ,Cu(II) and Zn(II) complexes with Schiff bases bearing benzimidazoles, Indian J. Chem. ,32A:440- 449 .

تحضير ودراسة طيفية وبكتيرية لمعقدات الزنك الثنائية والمشتقة من السالسلديهايد و ليوسيل-الانين و كلايسيل- كلايسين

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الخلاصة:

تم الحصول على ليكاندين لقواعد شف (L_1,L_2) بواسطة تكثيف السالسلديهايد على التوالي مع ليوسيل-الانين وكلايسيل- كلايسين ومن ثم تحضير معقداتهما مع ايون الزنك الثنائي وقد تم تشخيص هذه المركبات باستخدام التحليل الدقيق للعناصر والتوصيلية المولارية. كذلك تم استخدام التقنيات الطيفية مثل الأشعة ما تحت الحمراء والأشعة فوق البنفسجية – المرئية . بينت قياسات التوصيلية المولارية ان معقدات الزنك الثنائية هي بنسبة 1:1 وغير الكتروليتية . كذلك بينت الأشعة ما تحت الحمراء الارتباط الرباعي لليكاندين (L_1,L_2) .وقد درست الفعالية الحياتية المضادة للبكتريا للمركبات المحضرة على مجموعة من البكتريا وباستخدام طريقة (Disc diffusion). وقد تم أجراء دراسة مقارنة لقيم التثبيط لليكاندت قواعد شف ومعقداتها وبينت الدراسة أن معقدات قواعد شف أظهرت فعالية حياتية عالية ضد البكتريا على عكس ليكاندات قواعد شف الحرة . ايون الزنك الثنائي ضروري للتأثير على عملية نمو التثبيط . وان التوسع في عملية التثبيط تظهر بقوة اعتمادا على كثافة الخلية الأولية وعلى نمو الوسط.