Synthesis and Biological Evaluation of Ligand (E)-1,1-dimethyl-2-(7-methyl-3H-benzo[b][1,4] diazepin-3-ylidene)-2,3-dihydro-1H-benzo[e]indole and its complexes with some metal(II) ions

Adel Salim Khayoon
Department of Chemistry, College of Science, University of Diyala, Iraq.

Jinan Mohammed Mahmood Al-Zinkee
Department of Chemistry, College of Science, University of Diyala, Iraq.

Areej Ali Jarullah
Department of Chemistry, College of Science, University of Diyala, Iraq.

Abstract

A new compound 1,1-dimethyl-2-(7-methyl-3H-1,5-benzodiazepin-3-ylidene)-2,3-dihydro-1H-benzo[e]indole have synthesized from the reaction of 2-(1,1-Dimethyl1,3-dihydro-benzo[e] indol-2-ylidene)-malonaldehyde with 4-methyl-O-phenylene diamine. This compound was used as a ligand for the synthesis of novel complexes [M(C24H20N3)2] from its reaction with some salts of transition elements (CdCl2, CoCl2.6H2O, NiCl2.6H2O, CuCl2.2H2O, and ZnCl2). The newly prepared complexes [M(C24H20N3)2] had been characterized by (FTIR, UV-Vis, atomic absorption spectroscopy(A. A.), elemental analysis(CHN), magnetic susceptibility μeff, and conductivity measurements. On the other hand, (E.Coli) and (S. Aureus) bacteria were used to estimate the biological activities of the complexes.

Keywords: *Heterocyclic compounds, E.Coli, S. Aureus, ligand, complexes, indole.*

INTRODUCTION

Heterocyclic compounds are a special type of organic compound that contains a ring structure that contains atoms such as nitrogen, oxygen, and sulfur as well as carbon atoms as part of the ring, most of the medicines currently being marketed contain heterocyclic compounds in their structure, new medicines contain more than 90% of these compounds in their structure [1]. The presence of heterogeneous atoms gives heterocyclic compounds physical and chemical properties that differ from their counterparts with a homogenous carbon ring, most heterocyclic compounds are those that contain five or six members and a heterogeneous atom of nitrogen or oxygen or sulfur, the most famous of these compounds is pyridine, pyrrole, furan, thiophene, heterocyclic compounds have wide uses in the fields of medicine, agriculture, veterinary medicine, antioxidants, corrosion inhibitors, dyestuffs, and in the preparation of other organic compounds [2-5]. Indole is a heterocyclic compound formed by the fusion of the pyroyl ring with a benzene ring [6]. Indole is a major component of natural plant hormones such as tryptophan, melatonin and serotonin, which play an important role in the biochemistry of animals [7]. Indoles and their derivatives have a wide range of pharmacological and biological activities such as anticonvulsants, anti-inflammatory, antiviral, antimicrobial, and anticancer analgesics [8]. Complexes of transition elements with Schiff bases used as ligands have wide applications such as

medicinal and industrial chemistry, biological and pharmaceutical studies, catalysis properties, bioinorganic modeling studies, polymer chemistry, and material science [9]. For these purposes, we objective to synthesize (E)-1,1-dimethyl-2-(7-methyl-3H-benzo[b] [1,4]diazepin-3-ylidene)-2,3-dihydro-1H-benzo[e]indole and its complexes. We believe that our compounds will exhibit good antibacterial efficiency.

Materials

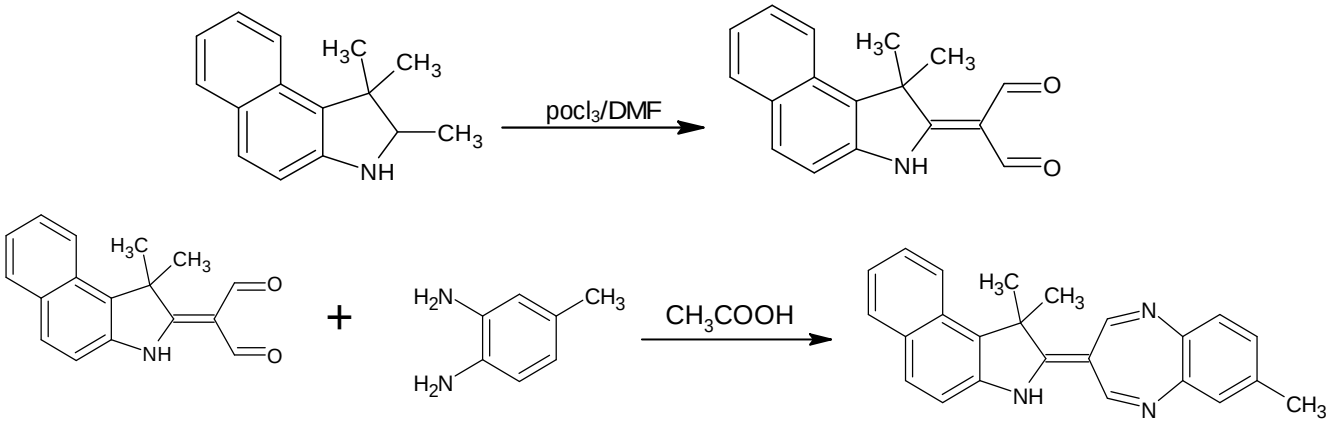
The chemicals utilized in this paper were equipped from a number of companies like (Aldrich, ACS, Macklin, BDH, Scharlu, Fluka, CDH, and SCRC).

Synthesis methods

Synthesis of C24H21N3

(2.5g, 9.42 mmol) of starting material C17H15O2N prepared by Ali, W. B. [10] was dissolved in 50 ml ethanol and added to a solution of (1.15 g, 9.42 mmol of 4-methyl-O-phenylenediamine with 50 ml of ethanol) then, added 1ml of glacial acetic acid into the reaction mixture. The mixture of reaction was refluxed for 5 hours at 80°C in a water bath; the reaction left with stirring at room temperature overnight; the next day filters a yellow precipitate and washed with C2H5OH. Scheme 1 shows the working method.

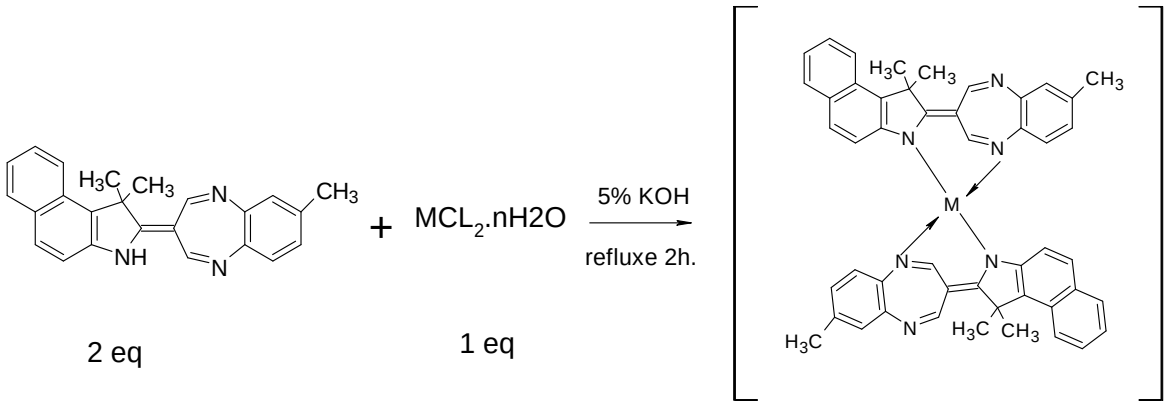
SCHEME 1. The synthetic pathway of C24H21N3



Synthesis of [M(C24H20N3)2]

The transition element complexes [M(C24H20N3)2] were synthesized from the reaction of one equivalent of transition element ions dissolved in 20 ml of hot ethanol, which was gradually added into two equivalents of the ligand dissolved in 30 ml of hot ethanol, then added 5% of KOH (a few drops) to a mixture and leave to refluxed in a water bath with a degree of at a temperature of 78 ° C for two hours, then leave for 4 hours, filter and wash in sufficient quantity in ethanol. (Scheme 2)

SCHEME 2. Synthesis of [M(C24H20N3)2]



M = Cd (ll) andZn(ll) ,n=0
M = Cu(ll) n=2
M = Co (ll) and Ni (ll) ,n=6

Biological activity of [M(C24H20N3)2]

Staphylococcus aureus was cultivated on blood agar, mannitol salt agar, eosin, methylene blue, and E. coli isolates on macCkonky agar. The preparation solution provided by the business (biomerix) was used to calibrate the number of bacterial cells since it provides an approximation of 1.5 x 108 cells/ml. You may make Muller Hinton Agar by dissolving 38 grams of agar in 1L of distillated water, sterilizing it in an autoclave for 15 minutes at 121 oC and 15 pounds of pressure, and then cooling it down. To prepare the suspended bacteria and place them in tubes containing brain heart infusion broth, bacteria colonies were conveyed via a loop. The tubes were incubated at 37 oC for (18–24) hours. after which the muller hinton agar-coated plates were covered with the bacteria suspension, and the plates were permitted to dry for a time. A cork borer that had been sanitized was used to drill holes in the culture material. Using a micropipette, 100ml of the substance (concentration 100/150/200) was administered to each hole separately. After that, incubate the plate for 24 hours at 37 oC. The use of sterilized DMSO serves as a positive control. The diameter of the inhibition zone surrounding each hole was used to gauge the potency of each concentration.

Results and Discussion

Characterization of ligand C24H21N3

1H-NMR, (DMSO-d6, 400 MHz,) δ (ppm) Fig.1: 14.67(s, 1H, NH inole ring), 8.11 and 8.09 (s, 2H, 2HC=N) , 7.86- 7.35 (m , 9H, Ar-H), 2.17 (s, 3H, CH3-Ar), 1.85 and 1.87 (s,6H, 2CH3-indol ring) [11,12]. The characteristic FT-IR bands in (cm-1) Fig.2 and Table (1): 3123 (υ NH inole ring), 3063 (υ C-H aromatic) and 1637 (υ HC=N)[13]. UV-Vis (DMSO), λmax/nm (cm-1) Fig. 3 and Table (2): 410.2 (24378) ILCT, 395.6 (25278) n→ π*, 299.6 (33377) and 262.6(38080) π→ π* [14]. Anal calc. for C24H21N3 (MW= 351.44) Table (3): C, 82.02; H, 6.02; N, 11.96. Found:82.30; H, 6.42; N, 12.14. Total yield: 88 %.

Fig. 1:- ^{1}H-NMR of $C_{24}H_{21}N_3$

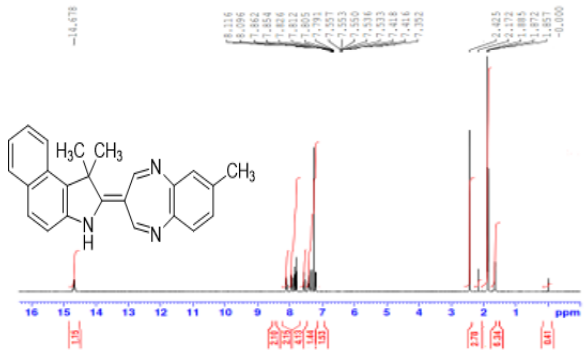


Fig. 2:- FT-IR of $C_{24}H_{21}N_3$

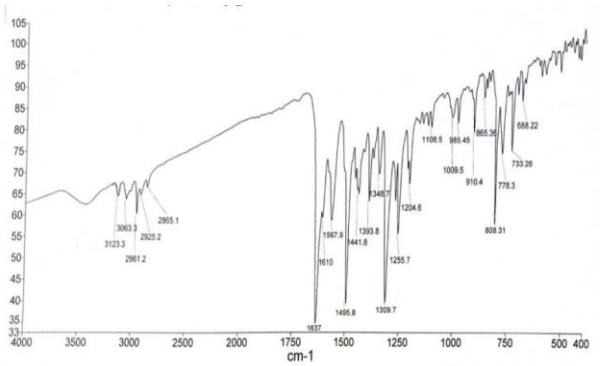
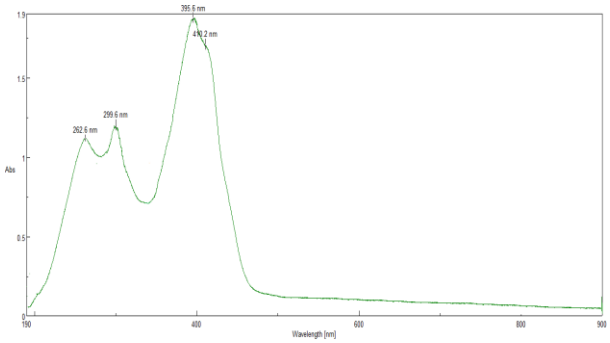


Fig. 3:- UV. Vis. of $C_{24}H_{21}N_3$



FT-IR Spectra of complexes

The FT-IR spectra of all synthesized complexes Table (1) exhibited changes in the shape and location of stretching vibration for the C=N group value and the disappearance of stretching vibration for the NH indole group compared to the spectrum of the free ligand, this means the ligand coordinates with the metal ion from the nitrogen atoms of an azomethine group, nitrogen atoms of indole group. in addition, appeared new bands in the spectra at (514, 520, 525, 529, and 544) cm-1 which indicates M-N stretching vibration [15,16].

TABLE 1. bands spectra of FT-IR (cm^{-1})

Compound	C-H alph	C-H ar.	N-H indole	C=N	M-N
$C_{24}H_{21}N_3$	2961 2925 2865	3063	3123	1637	------
$[Cd(C_{24}H_{20}N_3)_2]$	296 2919 2865	3068	-------	1630	541
$[Co(C_{24}H_{20}N_3)_2]$	2958 2930 2865	3053	-------	1628	514
$[Cu(C_{24}H_{20}N_3)_2]$	2973 2919 2865	3051	-------	1604	544
$[Ni(C_{24}H_{20}N_3)_2]$	2961 2919 2865	3060	-------	1628	520
$[Zn(C_{24}H_{20}N_3)_2]$	2964 2868	3060	-------	1624	529

The magnetic properties, electronic spectra and molar conductance for [M(C24H20N3)2]

The electronic spectra of complexes Fig. (4-8) are summarized in Table (2) [17,18] . In nature, the magnetic susceptibility of the square planar Ni (II) complex is probable to be small paramagnetic or diamagnetic. The observed magnetic moment value for Ni (II) complex exhibit (0BM). The measured magnetic moment value exhibit (2.61 BM). Co (II) square planar complexes have low spin magnetic values (2.2-2.9). The complex's magnetic moment (1.68BM) corresponds to the anticipated magnetic moment for square planar Cu (II) complexes (1.7 B.M.) [19]. However, the produced Zn (II) and Cd (II) complex were diamagnetic, as predicted for d10 ion. Table (2) explains the magnetic susceptibility of the complexes. Conductivity values of the complexes in DMSO ranged from (7-17 S.cm2.mole-1) Table (2), indicating that these complexes are non-electrolytes (non-conductive).

TABLE 2. Electronic spectrum, molar conductivity and magnetic properties

Comp.	λ nm ($\bar{\upsilon}$ cm^{-1})	Transition	μ_{eff} BM	Conductivity in DMSO $S.cm^2.mol^{-1}$	Suggested Geometry
$C_{24}H_{21}N_3$	410.2(24378) 395.6(25278) 299.6(33377) 262.6(38080)	ILCT n→ π* π→ π* π→ π*	-----	-----	-----
$[Co(C_{24}H_{20}N_3)_2]$	734.8(13609) 415.6(24061) 340.6(29359) 292.6(34176) 260(38461)	$^2A_1g \rightarrow {}^2A_2g$ ILCT n→ π* π→ π* π→ π*	2.61	7.69	Square planner
$[Ni(C_{24}H_{20}N_3)_2]$	686.8(14560) 495.4(20185) 398(25125) 342(29239) 298(33557) 258(38759)	$^1A_1g \rightarrow {}^1A_2g$ $^1A_1g \rightarrow {}^1B_1g$ C.T. n→ π* π→ π* π→ π*	0	15.33	Square planner
$[Cu(C_{24}H_{20}N_3)_2]$	734.2(13620) 498.4(20064)	$^2B_1g \rightarrow {}^2B_2g$ $^2B_1g \rightarrow {}^2Eg$	1.68	8.34	Square planner

	413(24213) 391.4(25549) 300.4(33288) 261.2(38284)	C.T. n→ π* π→ π* π→ π*			
$[Zn(C_{24}H_{20}N_3)_2]$	385(25974) 319(31347) 248(40322)	n→ π* π→ π* π→ π*	0	17.08	Tetrahedral
$[Cd(C_{24}H_{20}N_3)_2]$	388(25773) 306(32679) 256.8(38940)	n→ π* π→ π* π→ π*	0	8.34	Tetrahedral

Fig. 4:- UV. Vis. of $[Co(C_{24}H_{20}N_3)_2]$

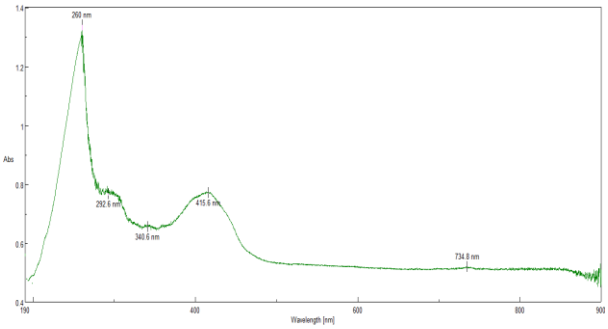


Fig. 5:- UV. Vis. of $[Ni(C_{24}H_{20}N_3)_2]$

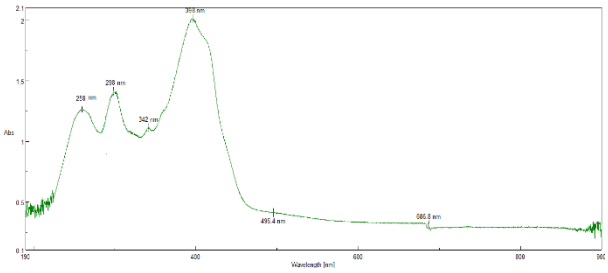


Fig. 6:- UV. Vis. of $[Cu(C_{24}H_{20}N_3)_2]$

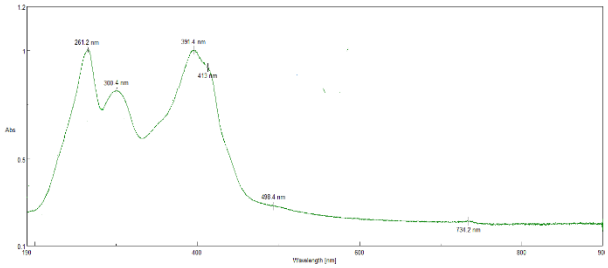


Fig. 7:- UV. Vis. of $[Zn(C_{24}H_{20}N_3)_2]$

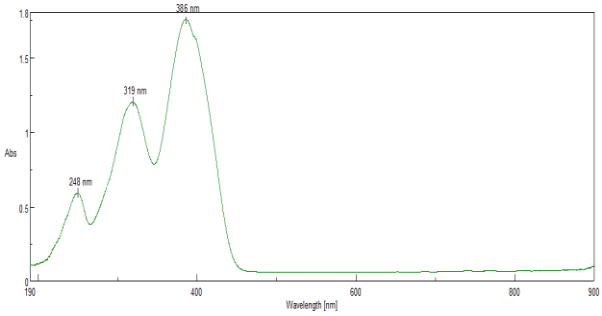
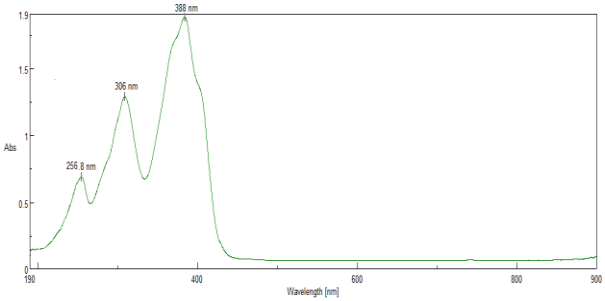


Fig. 8:- UV. Vis. of $[Cd(C_{24}H_{20}N_3)_2]$



Physical characteristics, elemental analysis, and atomic absorption of [M(C24H20N3)2]

The values of the percentage for carbon, hydrogen, nitrogen, and metal in all prepared complexes (calculated and discovered) were compatible with each other and were in agreement with the structure of the synthesized

compounds. Analytical data and physical characteristics for all complexes were provided in Table (3)

TABLE 3. Physical characteristics, elemental analysis (C.H.N.) and atomic absorption (A.A.) data for C24H21N3 and [M($C_{24}H_{20}N_3$)$_2$]

Compounds	Color	m.p. °C	Yield %	M.Wt g.mol^{-1}	C % Found (Calc.)	H % Found (Calc.)	N % Found (Calc.)	M % Found (Calc.)
$C_{24}H_{21}N_3$	Drak yellow	>300	88	351.44	82.30 (82.02)	6.42 (6.02)	12.14 11.96	-------
[Cd($C_{24}H_{20}N_3$)$_2$]	Orange	>300	83	813.28	70.01 (70.89)	5.23 (4.96)	10.66 (10.33)	14.00 (13.82)
[Co($C_{24}H_{20}N_3$)$_2$]	Charcoal	290	90	759.80	76. 02 (75.88)	5.43 (5.31)	11.56 (11.06)	7.95 (7.76)
[Cu($C_{24}H_{20}N_3$)$_2$]	Brown	295	78	764.27	75.65 (75.42)	5.44 (5.27)	11.27 (10.99)	8.66 (8.31)
[Ni($C_{24}H_{20}N_3$)$_2$]	Light orange	>300	82	759.56	76. 02 (75.90)	5.57 (5.31)	11.38 (11.06)	8.00 (7.73)
[Zn($C_{24}H_{20}N_3$)$_2$]	Burnt Orange	>300	86	766.25	75.53 (75.24)	5.47 (5.26)	11.17 (10.97)	9.00 (8.53)

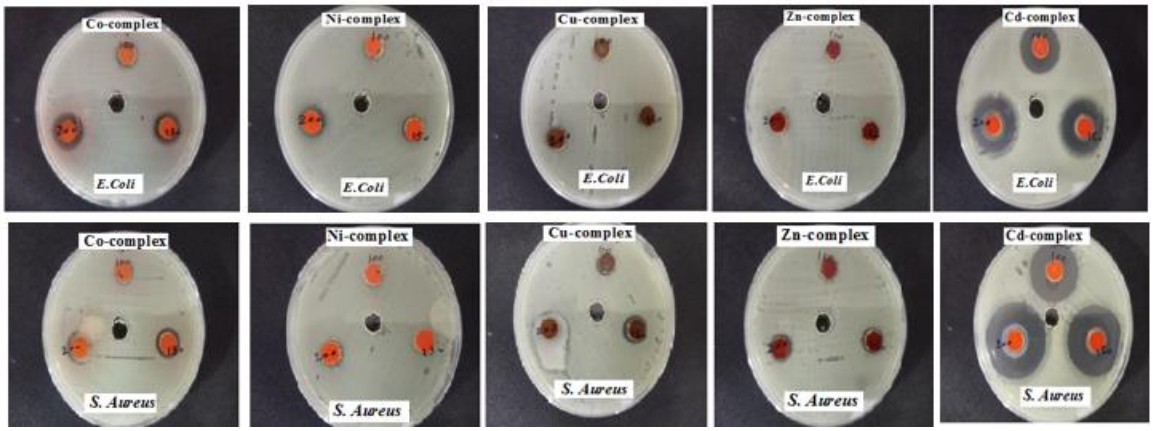
Biological activity of the complexes

The findings of biological activity of metal complexes in concentration (200mg/ml) against (S. aureus) bacteria after 24 hours of exposure showed a rise in inhibitory zones according to [Cd(C24H20N3)2]< [Cu(C24H20N3)2]< [Co(C24H20N3)2]< [Zn(C24H20N3)2] whereas increased inhibitory zones in biological activity against (E.colias) bacteria according to [Cd(C24H20N3)2]< [Co(C24H20N3)2]< [Ni(C24H20N3)2]. The Cd(II) combination displays antibacterial action against Gram-positive and Gram-negative bacterial species [20]. Table (4) and Fig. 9. shown briefly antibacterial activities of the experience complexes

TABLE 4. antibacterial activities of the experience complexes (inhibition zones in mm)

Microorganism / Tested materials	E. Coli			S. aureus		
	100	150	200	100	150	200
[Co($C_{24}H_{20}N_3$)$_2$]	---	13	16	---	13	15
[Ni($C_{24}H_{20}N_3$)$_2$]	---	11	13	---	---	---
[Cu($C_{24}H_{20}N_3$)$_2$]	---	---	---	---	13	17
[Zn($C_{24}H_{20}N_3$)$_2$]	---	---	---	---	11	12
[Cd($C_{24}H_{20}N_3$)$_2$]	21	24	27	26	31	34

Fig. 9:- Biological activity of [M($C_{24}H_{20}N_3$)$_2$]



Conclusions

A new synthesized complexes were synthesized from the ligand (E)-1,1-dimethyl-2-(7-methyl-3H-benzo[b][1,4]diazepin-3-ylidene)-2,3-dihydro-1H-benzo[e] indole. The structure of the synthesized ligand was investigated by using (FTIR, 1H-NMR, and UV.–Vis.). The FTIR data showed that the ligand bonds to the metal ions via nitrogen atoms of isometane and nitrogen of the indole ring. The measured molar conductivity of the metal complexes indicated these complexes were non-electrolytes. All data obtained from the measurements proved the geometrical structure of Ni(II), Co(II), and Cu(II) complexes were square planer but Zn(II) and Cd(II) tetrahedral. Among the prepared metal complexes, compounds with Cd (II) showed higher antibacterial activities against both bacteria strains tested in this study. This suggested that Cd complex would be a better therapeutic drug for bacteria therapy.

Acknowledgment

The researchers thank the Chemistry Department in the Science College, Diyala University to help us with this work.

Reference

Farshbaf, S., Sreerama, L., Khodayari, T., and Vessally, E. (2018). Propargylic ureas as powerful and versatile building blocks in the synthesis of various key medicinal heterocyclic compounds. Chemical Review and Letters, 1(2):56-67.

Arora, P., Arora, V., Lamba, H. S., and Wadhwa, D. (2012). Importance of heterocyclic chemistry: a review. International Journal of Pharmaceutical Sciences and Research, 3(9), 2947.

Gupta, R. R., Kumar, M., & Gupta, V. (2013). Heterocyclic Chemistry: Volume II: Five-Membered Heterocycles. Springer Science & Business Media.

Katritzky, A. R., & Lagowski, J. M. (2013). The principles of heterocyclic chemistry. Elsevier.

Jacobi, P. A. (2018). Introduction to Heterocyclic Chemistry. John Wiley & Sons.

Karaaslan, C., and Suzen, S. (2011). Electrochemical behavior of biologically important indole derivatives. International Journal of Electrochemistry, 2011.

Han, Y., Dong, W., Guo, Q., Li, X., & Huang, L. (2020). The importance of indole and

azaindole scaffold in the development of antitumor agents. European Journal of Medicinal Chemistry, 203, 112506.

Sulthana, S., and Pandian, P. (2019). A review on Indole and Benzothiazole derivatives its importance. Journal of Drug Delivery and Therapeutics, 9(1-s), 505-509.

Gaspar, A., Matos, M. J., Garrido, J., Uriarte, E., and Borges, F. (2014). Chromone: a valid scaffold in medicinal chemistry. Chemical reviews, 114(9), 4960-4992.

Ali, W. B. (2018). Synthesis, Characterization and Theoretical Study of Some Pyrazole Compounds Derived From 1, 1, 2-Trimethylbenz [e] Indole. Diyala Journal For Pure Science, 14(03), 206-219.

Ghaidan, A. F., Faraj, F. L., and Abdulghany, Z. S. (2018). Synthesis, characterization and cytotoxic activity of new indole schiff bases derived from 2-(5-chloro-3, 3-dimethyl-1, 3-dihydro-indol-2-ylidene)-malonaldehyde with aniline substituted. Oriental Journal of Chemistry, 34(1), 169-181.

Lateef, H. S., Jarullah, A. A. and Faraj, F. L. (2019). Cytotoxicity effecting of new Ligand (LCl) and it's complexes on a breast cancer. International Journal of Pharmaceutical Research, 11(4): 1-10.

Paula, S. S. P., Yardilyb, A., and Rejia, T. A. F. (2014). Synthesis, characterization and DFT studies of 4-amino-5-(indol-3-oyl)-2-phenylaminothiazole. Synthesis, 2: 89-95.

Al-Shaalan, N. H.(2011). Synthesis, characterization and biological activities of Cu(II), Co(II), Mn(II), Fe(II), and UO2(VI) complexes with a new Schiff base hydrazone: O-hydroxyacetophenone-7-chloro-4-quinoline hydrazone, Molecules, 16(10): 8629-8645.

Numan, A. T., Sanak, K. A., Atiyah, E. M., & Sadiq, S. A. (2015). Synthesis and characterization of new bidentate chalcone ligand type (NO) and its Mn II, Co II, Ni II and Cu II complexes with study of their antibacterial activity. Diyala Journal For Pure Sciences, 11(3), 19-30.

Al-Shemary, R. K. R. (2017). Microwave Preparation, Spectral Studies and Antimicrobial Activities Evaluation of Mn (II), Ni (II), Hg (II), Co (II) and Cu (II) Complexes with Schiff Base Ligand. Ibn AL-Haitham Journal For Pure and Applied Sciences, 30(3): 58-67.

Lever, A.B.P., Inorganic Electronic Spectroscopy, Elsevier, 1968, p. 320, 318.

Hameed, R. F., Jarullah, A. A. and Faraj, F. L.(2019). Synthesis and evaluation of cytotoxicity effect of new ligand (LBe) and it's complexes on a cervical cancer. Oriental Journal Of Chemistry, 35(3): 1208-1214.

Yallur B. C., Krishna P. M., and Challa M.(2021). Bivalent Ni(II), Co(II) and Cu(II) complexes of [(E)-[(2-methyl-1,3-thiazol-5-yl)methylidene]amino]thiourea: synthesis, spectral characterization, DNA and in-vitro anti-bacterial studies. Heliyon, 7:1-12.

Dahlous, K. A., Alotaibi, A. A., Dege, N., El-Faham, A., Soliman, S. M., & Refaat, H. M. (2022). X-ray structure analyses and biological evaluations of a new Cd (II) complex with S-Triazine based ligand. Crystals, 12(6), 861.