Synthesis, Characterization, Biological Activities and Antioxidant Study of Gabapentin Derivatives and Their Complexes with [Cu(II), Zn(II]

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Abstract

Synthesis of some gabapentin derivatives derived from condensation of one mole of selected acid chlorides with one mole of Gabapentin in basic medium have been carried out. These derivatives which act as ligands, were characterized by FT-IR, CHN, ^{1}HNMR,^{13}CNMR and mass spectra measurements. Complexes of gabapentin derivatives were prepared by adding MCl2, where M = Cu(II) and Zn(II), to gabapentin derivatives (L1, L2, L3, L4 and L5), in 1:2 molal ratio. The complexes (L6 – L13) have been characterized by FT-IR, ^{1}HNMR, ,^{13}CNMR and CHN elemental analysis. The biological activities of the ligands and their complexes showed appreciable antibacterial activities against two types of bacteria, E.coli and staphylococcus aureus. Antioxidant properties of some derivatives and complexes showed excellent properties and others gave lower antioxidant properties.

Keywords: Gabapentin derivatives, biological activity, antioxidant, metal complexes, metal chlorides, acid chlorides.

1. Introduction

Gabapentin, 1-(aminomethyl) cyclohexaneacetic acid which is called Neurontin (Gpn)structurally belongs to the neurotransmitter gammaaminobutyric acid (GABA). It is studied to a large degree for its significant inhibitory action in the central nervous system (Loscher, W. C. 2002). Gabapentin is an artificial amino acid due to the presence of acidic groups (COOH) and the basic group (NH2) (Satzinger, G. 1994, Schwarz, J. B., et.al. 2005). Gabapentin has been applied in the treatment of neuropathic pain. It is a new generation antiepileptic used as add on therapy and mono therapy in patients with partial seizures (Ananda, K., Aravinda, S. et.al. 2003,Ameringen MV, Rynn MA, Murphy TK, Mandel F. 2008, Ameringen MV, Rynn MA, Murphy TK, Mandel F. 1993,Attal N, Cruccu G, Baron R, Haanpää M, Hansson P, Jensen TS, et al, 2006, Vedula SS, Bero L, Scherer RW, Dickersin K, 2009). Many gabapentin derivatives have been synthesized as schiff bases which were derived from Gabapentin condensation with 2-hydroxy 1-napthaldehyde in equal molar ratios in absolute ethanol and at room temperature (Shokohi-pour Z, 2016). Another gabapentin derivatives were synthesized and studied such as salicylaldhyde derivative which were evaluated to explore any potential benefit in comparison with GBP in rat model of CIPN, and administration of cisplatin (3.0mg/Kg/week) for five connect five weeks generated reproducible paw withdrawal this hold comfrey filament application (Ahmad N. and Sewwell D. E. 2017). Various amide gabapentin derivatives have been synthesized (Hussain E.A., Kanwal N., Khan I. U., Mutahir S. and Yar M., 2018). Green one pot synthesis of new gabapentin- lactamase (G2-G8) has been achieved by reacting gabapentin with a variety of substituted sulfonyl chlorides (Hekmat S., Balalaie S., Ramezanpour S., Rominger F., Vavsari V. and Kabiri-Fard H. 2017). Nitroalkanes. synthesis from gabapentin by reduction, cyclization, hydrolysis cascade reaction from highly enantioselective β-aryl-γ-nitroalkanes Michael adducts were predicted(Amirani M. & Mohammadi M. 2018). Considering their great flexibility and various structural aspects, a wide range of transition metal complexes of amide ligands have been synthesized and the structure function relationships of the resulting complexes have been extensively studied in recent years (Singh R.K., Duvedi R. 2014, Radwan M. O., M, Ismail A.H., Mekkawy El-, Ismail N.S.M., Hanna A.G. 2016).

A wide range of coordination network of gabapentin with La3+, Ce3+, Nd3+Er3+, Y3+ and Mn2+ were obtained by mechanosynthesis and characterized by physical methods (Nadgi A., Mhlong N. and Esoliman M. 2017, Quaresma, S., Andre, V., Alxandra, L., Cunha Silva and M. Teresa. 2017).In the current article we have tried to synthesize some new derivatives of gabapentin by condensing some acid chlorides with basic solution of gabapentin in 1:1 molal ratioin dichloromethane. And preparing some metal complexes for them, then studying some of their biological activities and antioxidant properties.

2. Experimental

2.1 Materials

All solvents which were used for synthesis were commercially available, reagent grade and were used without further purification. 4-Nitrobenzoul chloride, 3-Nitobenzoyl chloride, 4-Chlorobenzoyl chloride and Isobutaryl chloride were from Merck. Transition metal chlorides were from B.D.H. Sodium hydroxide and dichloromethane were from Sigma Aldrich. Chloroform, absolute ethanol, dimethyl sulfoxide and absolute methanol were from Alpha Aldrich. The bilogical activities tests of the gabapentin derivatives and their complexes were carried out using two types of bacteria, Staphylococcus aureus (NCTC6571) and Escherichia coli (NCTC 5933). The diffusion technique was used across the nutrient medium, where DMSO was used as a solvent and as a feed medium. .

2.2 Physical Measurements

Silica gel60F254 aluminum TLC sheets were supplied by Merck, The melting points weredetermined by using a VeeGO Digital model VMP-D (Jenway) apparatus. Fourier transforminfrared (FT-IR) spectra were recorded on FT-IR JASCO-4200 spectrophotometer within 4000–400 cm^{-1} range, by using KBr pellets technique. The elemental analysis were performed on a Vario EL cube apparatus. NMR spectra were measured on a Bruker spectrometer at 300 MHz by using TMS as reference and in DMSO as a solvent. Mass spectra measurements were recorded on Agilent device with electronic energy estimated at 70ev.

2.3 General procedure for synthesis of the gabapentin derivatives:

2.3.1 Synthesis of Gabapentin derivatives (Ligands: L1-L5)

10 mmole of gabapentin was mixed with 10 mmole of acid chloride and made basic with20 mmole of NaOH, and were dissolved in 10 ml of dichloromethane. The acid chloride wasadded gradually to the mixture in an ice bath and then ice bath removed to reach room temperature and kept stirring for about 90-120 min. The reactions were controlled by TLC and using (MeOH :Chloroform) mixture in (4: 6) eluent ratio. Then a white to a warm white precipitates were formed. Then each derivative was recrystallized in absolute ethanol, and dried in desiccator, giving yield around 80% -90% with different melting points.

2.3.2 Synthesis of metal complexes of the ligands (L1-L5):

2.3.2.1 Synthesis of Cu(II)-complex : (L6)

The synthesis of copper(II)-complex was done by adding copper(II) chloride (0.852 g, 5.0 mmol) to the basic solution of ligand (L1) (3.2 g, 10.0 mmol) by dissolving in 20 mmole NaOH solution. The mixture was stirred for 90 min at r.t.. The formed precipitate of Cu(II) complex was filtered and washed with distilled water many times and followed by TLC for purity, then kept in desiccator.

2.3.2.2 Synthesis ofZn(II)-complex : (L7)

The synthesis of Zinc complex was done by adding Zinc Chloride (0.677 g, 5.0 mmol) to thebasic solution of ligand L1 (3.2 g, 10.0 mmol) by dissolving in 20 mmole NaOH solution.Themixture was stirred for 90 min. at r.t . The formed precipitate of Zn (II) complex was worked up as above (item 2.3.2.1), then kept in desiccator.

2.3.2.3 Synthesis of Cu(II)-complex : (L8)

The synthesis of copper complex was done by adding copper chloride (0.852 g, 5.0 mmol) to the basic solution of ligand L2 (3.2 g, 10.0 mmol) by dissolving in 20 mmole NaOH solution. The mixture was stirred for 90 min at r.t . The formed solid of Cu (II) complex was worked up as above,then was kept in desiccator,

2.3.2.4 Synthesis of Zn(II)-complex : (L9)

The synthesis of Zinc complex was done by adding Zinc Chloride (0.677 g, 5.0 mmol) to thebasic solution of ligand L2 (3.2 g, 10.0 mmol) by dissolving in 20 mmole NaOH solution. Themixture was stirred for 90 min in rt. The formed solid of Zn (II) complex was worked up as above, then was kept in desiccator.

2.3.2.5 Synthesis of Cu(II)-complex : (L10)

The synthesis of copper(II)-complex was done by addingcopper(II) Chloride (0.852 g, 5.0 mmol) to the basic solution of ligand L3 (3.09 g, 10.0 mmol) by dissolving in 20 mmole NaOH solution. The mixture was stirred for 90 min. at r.t . The formed Cu (II) complex was worked up as above,then it was kept in desiccator.

2.3.2.6 Synthesis of Cu(II)-complex : (L11)

The synthesis of copper(II)- complex was done by adding copper (II) chloride (0.852 g, 5.0 mmol) to the basic solution of ligand L4 (2.14 g, 10.0 mmol) by dissolving in 20 mmole NaOH solution. The mixture was stirred for 90 min. at r.t. The formed Cu (II) complex was worked up as above, then it was kept in desiccator.

2.3.2.7 Synthesis of Cu(II)-complex : (L12)

The synthesis of copper complex was done by adding copper (II) Chloride (0.852 g, 5.0 mmol) to the basic solution of ligand L5 (2.42 g, 10.0 mmol) by dissolving in 20 mmole NaOH solution. The mixture was stirred for 90 min at r.t. The formed Cu (II) complex was worked up as above,then it was kept in desiccator.

2.3.2.8 Synthesis of Zn(II)-complex : (L13)

The synthesis of Zinc(II)- complex was done by adding Zinc(II) Chloride (0.677 g, 5.0 mmol) to thebasic solution of ligand L5 (2.42 g, 10.0 mmol) by dissolving in 20 mmole NaOH solution. The mixture was stirred for 90 min. at r.t .The formed Zn (II) complex was worked as above, then it was kept in desiccator.

2.4 Biological Activity

The biological activities study of the (10-3) M concentration compounds was carried out by using two types of bacteria, gram positive Staphylococcus aureus (NCTC6571) and another bacteria was gram negatives E. coli (NCTC 5933). The diffusion technique was used for the feeder medium and DMSO was used as a solvent.The inhibition diameters of the compounds synthesized, in millimeters (mm), were measured, as shown in (Table 1).

Table(1) Growth Inhibition by compounds prepared (L1- L13) against bacteria

Symbol	Staphylococcus aureus (mm)	Escherichia coil (mm)
L1	0	14
L2	0	16
L3	0	15
L4	0	18
L5	0	19
L6	21	15
L7	16	18
L8	15	17
L9	18	14
L10	14	16
L11	11	13
L12	14	19
L13	11	20

2.5 Antioxidant properties

The antioxidant activities of gabapentin derivatives and their complexes compounds (L1-L13) were evaluated against 2,2-diphenyl-1-picrylhydrazyl (DPPH) as hydrogen acceptor. DPPH absorbs visible light at 517 nm and therefore to test the antioxidant properties. Each prepared compound (L1-L13) was mixed thoroughly with DPPH and then incubated the in the dark for one hour. The DPPH radical scavenging activity with ascorbic acid was also assayed for comparison. The percentage of antioxidant activities was calculated using the following equation (Venkatesan K., Satyanarayana V.S. and Sivakumar, 2011) :

Antioxidant activity (%) = A0-A1/ A0 x100%

Where A0 is the absorbance of the control reaction and A1 is the absorbance of the sample orstandard ascorbic acid (ASC). Figure (1&2) shows the antioxidant activities of preparedcompounds (L1-L13) together with ASC as standard reference.

The synthesized compounds (L1- L13) showed a pronounced antioxidant activities compared to that of (ASC). And the higher gabapentin derivative is L1 and then L2 and L3, but the less one are the complex compounds L11

and L13.From these evidences confirmed about the biological activities of the gabapentin derivatives (L1-L5),and their complexes (L6-L7),we changed gabapentin as anti-seizer into these new biological properties confirmed as antibacterial and antioxidants compounds.

3. Results and Discussion

3.1 Elemental analysis

Elemental analyses (CHN data)of the prepared compounds indicate the formation of sixcoordination complexes containing two ligands of gabapentin derivatives as bidentate ligand and two water molecules, in addition to the formation of the ligands (L1- L13), as shown in Table(3).

Symbol	Molecular Formula	m.p. ^{o}C	Color	Founded %N (Theoretical)	Founded %H (Theoretical)	Founded %C (Theoretical)
L1	$C_{16}H_{19}N_2O_5$	128	Off white	8.62 (8.74)	6.91 (6.29)	60.11 (59.99)
L2	$C_{16}H_{19}N_2O_5$	130	white	8.34 (8.74)	6.33 (6.29)	60.82 (59.99)
L3	$C_{16}H_{19}NO_3Cl$	129	white	3.92 (4.52)	6.81 (6.51)	61.11 (62.03)
L4	$C_{11}H_{19}NO_3$	124	white	6.41 (6.6)	9.17 (8.55)	61.43 (62.24)
L5	$C_{13}H_{23}NO_2$	95	Off white	5.94 (5.83)	9.41 (9.23)	63.48 (64.98)
L6	$[Cu(C_{16}H_{19}N_2O_5)_2].2H_2O$	282	Light green	7.64 (7.84)	6.07 (5.90)	54.20 (53.77)
L7	$[Zn(C_{16}H_{19}N_2O_5)_2].2H_2O$	178	white	7.99 (7.82)	6.00 (5.88)	53.82 (53.64)
L8	$[Cu(C_{16}H_{19}N_2O_5)_2].2H_2O$	285	Light blue	7.47 (7.84)	6.12 (5.90)	53.55 (53.77)
L9	$[Zn(C_{16}H_{19}N_2O_5)_2].2H_2O$	190	white	7.71 (7.82)	5.97 (5.88)	53.24 (53.64)
L10	$[Cu(C_{16}H_{19}NO_3Cl)_2].2H_2O$	264	Light green	3.92 (4.04)	6.42 (6.08)	55.31 (55.40)
L11	$[Cu(C_{11}H_{19}NO_3)_2].2H_2O$	240	Light blue	5.72 (5.57)	8.11 (8.38)	52.90 (52.56)
L12	$[Cu(C_{13}H_{23}NO_3)_2].2H_2O$	263	Deep green	4.81 (5.01)	9.22 (8.99)	55.64 (55.88)
L13	$[Zn(C_{13}H_{23}NO_3)_2].2H_2O$	144	white	5.17 (5.00)	8.74 (8.96)	55.92 (55.72)

Tablet (3) Some physical properties and CHN of compounds (L1-L13)

3.2 Infra-red spectra

The gabapentin derivatives (L1-L5) show an intense band at 3258 cm-1 and 3394 cm-1 for amide groups and show an intense bands at 1581cm-1 and 1619cm-1 for carbonyl of carboxylic acid and bands at 1683cm-1 and 1713cm-1 for carbonyl of amide group , indicate that the reaction of gabapentin and carboxylic chloride is successful . The Gabapentin derivatives may coordinate in complexes (L6-L13) with metal ions through the nitrogen of the amide and the appearance of N-H intense band at lower wavenumber because the bonding acts on the restriction of the signal and reduces the oscillatory motion. The disappearance of the Carboxylic O-H band from the spectra of the complexes may be due to bonding with metal.

The coordination of metal ion may be through one oxygen of carboxylic group and through nitrogen of amide group of each gabapentin derivative. Table(4) shows the important IR frequencies of ligands (L1- L5) and their metal complexes (L6-L13).

Compund	υ_{CH} bending Arom.	υ_{CH} bending Aliph.	υ_{COO-sy}	$\upsilon_{COO-asy,}$	$\upsilon_{C=O}$ Amide	$\upsilon_{C=OCarboxylic}$	υOH_{COO}	Aliph υCH_{asy} υCH_{sy}	υCH_{Arom}	$_{NH}\upsilon$	υOH_{H2O}
L1	717	1207	1351	1526	1615	1734	2630	2929 2864	3084	3394	-
L2	717	1207	1348	1526	1591	1711	2619	2931 2855	3106	3385	
L3	760	1175	1321	1424	1590	1683	2670	2933 2851	3052	3386	-
L4	-	1201	1391	1526	1581	1713	2583	2933 2855	-	3385	-
L5	-	1200	1391	1526	1619	1713	2650	2934 2856	-	3385	-
L6	720	1204	1348	1530	1568	1623	-	2925 2856	3080	3387	3410
L7	724	1197	1374	1451	1576	1619	-	2925 2853	3084	3258	3431
L8	721	1200	1348	1408	1528	1653	-	2928 2858	3080	-	3402
L9	720	1200	1348	1425	1528	1651	-	2929 2857	3080	-	3403
L10	775	1095	1403	1430	1550	1594	-	2927 2857	3052	3347	3402
L11	-	1112	1407	1444	1564	1671	-	2854 2927	-	3244	3342
L12	-	1112	1409	1457	1552	1680	-	2931 2855	-	3325	3574
L13	-	1047	1389	1512	1556	1682	-	2886	-	-	3407

Table (4) the most importation vibrational IR frequencies of functional groups in compounds (L1-L13)

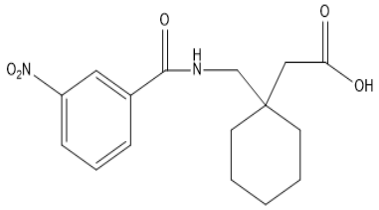
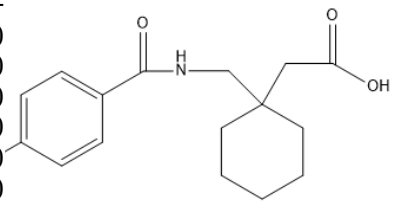
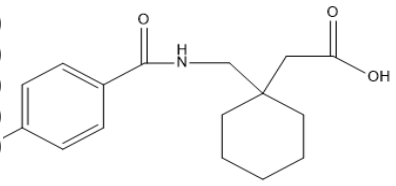
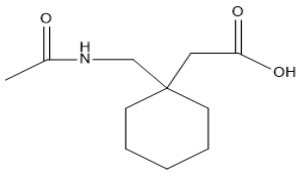
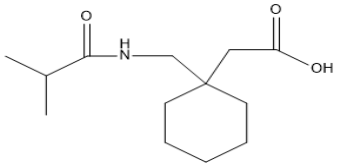
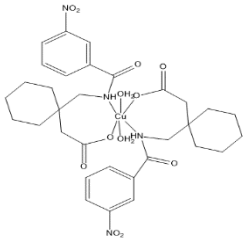
3.3 ^{1}H NMR spectra

All gabapentin derivative compounds (L1-L5) exhibited bands with chemical shift at the range (12.22-12.6) ppm related to proton of OH carboxylic acid group in addition to single bands at (7.6-7.8) ppm related to NH of amide group. And for (L1-L3) ligands multi bands at (6.5-7.7) ppm for aromatic Protons. Also, the compounds give multi signal at (1.3-2.6) ppm to cyclohexane protons of gabapentin. The gabapentin complexes showed groups of signals were almost identical in their chemical shifts with the spectra of the gabapentin derivatives, i.e. the ligands (L1-L5), except some displacements toward a weak magnetic field (higher chemical shift) for amide group, and the absence of the OH proton bands of carboxylic group between (12.22-12.62) ppm. This confirms formation of complexing of metal ions through carboxylic oxygen group. The amide proton in complexes showed a higher chemical shift compared with amide protons in ligand due to coordination of the metal ions through nitrogen atom of the amide group too, in complexes (L6- L13). Therefore we suggest the coordination of each metal ion(Cu(II),or Zn(II) for complexes will be through oxygen atom of carboxylic group and nitrogen atom of amide in each derivative.as shown in Table (2) and in Figs.(from 9 to 21).

3.4 ^{13}C NMR spectra

All ^{13}C NMR spectra of the prepared compounds showed all signals and the predicted relativeintensity of each carbon The ^{13}C NMR spectra of gabapentin derivatives (L1, L2, L3, L4, L5) showed various signals at 39-21ppm due to cyclohexane carbon atoms, L1, L2, L3 gave multiple signals between 154-123 ppm were attributed to carbon atoms of the aromatic ring. All ligands prepared shown a signal at the range 165-173 ppm were attributed to the carbon atom of the carbonyl amide group, and signal in the range 172-177 ppm are attributed to carbon of carboxyl carbonyl group.

The ^{13}C NMR spectra of the complexes (L6-L13) shows sets of signals that are almost identical in their chemical shifts with the spectra of the prepared ligands, but some signals appeared at lower magnetic field (larger chemical shift) for carbon atom of carboxylic group and carbon atom attached to amide group of derivatives, which confirm the formation of complexes through coordination of metal ion Zn(II) or Cu(II) through one oxygen atom of carboxylic group and nitrogen atom of amide group in the ligands(L1-L5).as shown in Figs. (22 to 34) and in Table (2)

Symbol	Chemical Shift (PPM) ^{13}C-NMR	Compound structure	Chemical Shift(PPM) H^1-NMR
L1	22.34-39.21(m-6C-Cyclohexan) 40.53(S-C-NH) 41.70(S-C-COOH) 133.30-148.44(m-6C-Ar) 167.45(S-CO-NH) 174.30(S-CO-OH)		1.3-2.5(m-10H-Cyclohexan-H) 3.425(s-2H-CH_2-NH) 3.444(s-2H-CH_2-COOH) 7.76-8.15 (m-5H-(4H-Ar)+ 1H-NH) 12.49(s-OH)
L2	21.58-39.91(m-6C-Cyclohexan) 40.19(S-C-NH) 46.26(S-C-COOH) 123.84-154.70(m-6C-Ar) 165.91(S-CO-NH) 173.67(S-CO-OH)		1.15-2.8(m-10H-Cyclohexan-H) 3.55(s-2H-CH_2-NH) 3.97(s-2H-CH_2-COOH) 7.95-8.74 (m-5H-(4H-Ar)+ 1H-NH) 12.222(s-OH)
L3	21.89-38.11(m-6C-Cyclohexan) 40.32(S-C-NH) 41.88(S-C-COOH) 127.92-138.44(m-6C-Ar) 168.48(S-CO-NH) 172.93(S-CO-OH)		1.25-2.7(m-10H-Cyclohexan-H) 2.94(s-2H-CH_2-NH) 3.74(s-2H-CH_2-COOH) 6.52-7.83 (m-5H-(4H-Ar)+ 1H-NH) 12.62 (s-OH)
L4	21.16-38.29(m-7C-Cyclohexan + CH_3CO) 41.77(S-C-NH) 45.98(S-C-COOH) 173.78(S-CO-NH) 176.11(S-CO-OH)		0.95-1. 54(m-10H-Cyclohexan-H) 1.96 (s-3H-CH_3-CO) 2.46(s-2H-CH_2-NH) 3.42(s-2H-CH_2-COOH) 7.68(s- 1H-NH) 12.42(s-OH)
L5	20.02(S-2CH_3-CH) 21.23-39.89(m-7C-Cyclohexan + CHCO) 40.80(S-C-NH) 45.52(S-C-COOH) 173.33(S-CO-NH) 177.20(S-CO-OH)		1.03(s-6H-2CH_3-CH) 1.32-2.50(m-10H-Cyclohexan-H) 2.89 (m-1H-CH-CO) 2.97(s-2H-CH_2-NH) 3.44(s-2H-CH_2-COOH) 7.66(s- 1H-NH)- 12.22(S-OH)
L6	22.44-38.54(m-6C-Cyclohexan) 41.55(S-C-NH) 45.80(S-C-COOH) 128.51-151.60(m-6C-Ar) 170.68(S-CO-NH) 178.25(S-CO-OH)		1.33-2.9(m-10H-Cyclohexan-H) 3.36(s-2H-CH_2-NH) 3.46(s-2H-CH_2-COOH) 7.68-8.39 (m-5H-(4H-Ar)+ 1H-NH)

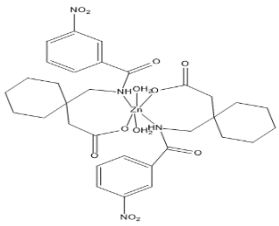
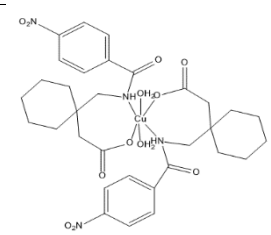
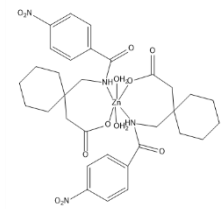
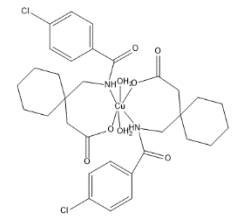
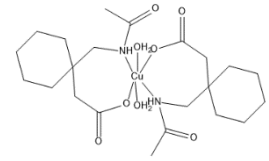
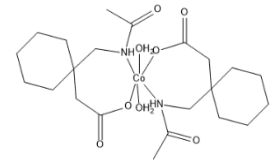
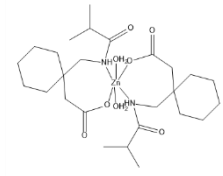
L7	22.57-38.87(m-6C-Cyclohexan) 39.80(S-C-NH) 44.63(S-C-COOH) 127.70-151.31(m-6C-Ar) 171.42(S-CO-NH) 175.72(S-CO-OH)		1.33-2.64(m-10H-Cyclohexan-H) 3.426(s-2H-CH_2-NH) 3.45(s-2H-CH_2-COOH) 7.79-8.45 (m-5H-(4H-Ar)+ 1H-NH)
L8	24.15-41.34(m-6C-Cyclohexan) 43.57(S-C-NH) 48.18(S-C-COOH) 126.96-152.87(m-6C-Ar) 178.11(S-CO-NH) 182.42(S-CO-OH)		1.39-2.92(m-10H-Cyclohexan-H) 3.71(s-2H-CH_2-NH) 4.10(s-2H-CH_2-COOH) 7.47-8.95 (m-5H-(4H-Ar)+ 1H-NH)
L9	21.83-39.31(m-6C-Cyclohexan) 40.96(S-C-NH) 44.56(S-C-COOH) 124.37-148.19(m-6C-Ar) 179.44(S-CO-NH) 182.86(S-CO-OH)		1.30-2.59(m-10H-Cyclohexan-H) 3.27 (s-2H-CH_2-NH) 3.34(s-2H-CH_2-COOH) 7.95-8.30 (m-5H-(4H-Ar)+ 1H-NH)
L10	22.93-39.27(m-6C-Cyclohexan) 41.15(S-C-NH) 45.26(S-C-COOH) 134.76-142.19(m-6C-Ar) 177.61(S-CO-NH) 181.77(S-CO-OH)		1.30-2.94(m-10H-Cyclohexan-H) 3.15(s-2H-CH_2-NH) 3.90(s-2H-CH_2-COOH) 6.63-8.10 (m-5H-(4H-Ar)+ 1H-NH)
L11	21.16-38.29(m-7C-Cyclohexan + CH_3CO) 41.97(S-C-NH) 46.32(S-C-COOH) 181.58(S-CO-NH) 187.02(S-CO-OH)		0.95-1.86(m-10H-Cyclohexan-H) 2.42 (s-3H-CH_3-CO) 2.89(s-2H-CH_2-NH) 3.54(s-2H-CH_2-COOH) 8.42(s- 1H-NH)
L12	21.82-39.14(m-7C-Cyclohexan + CH_3CO) 40.90(S-C-NH) 47.11(S-C-COOH) 178.28(S-CO-NH) 182.69(S-CO-OH)		0.95-1. 78(m-10H-Cyclohexan-H) 2.34 (s-3H-CH_3-CO) 2.76(s-2H-CH_2-NH) 3.48(s-2H-CH_2-COOH) 7.90(s- 1H-NH)
L13	21.88(S-2CH_3-CH) 22.19-39.89(m-7C-Cyclohexan + CHCO) 41.24(S-C-NH) 43.61(S-C-COOH) 179.11(S-CO-NH) 183.61(S-CO-OH)		1.10(S-6H-2CH_3-CH) 1.42-2.67 (m-10H-Cyclohexan-H) 3.11 (m-1H-CH-CO) 3.30(s-2H-CH_2-NH) 3.63(s-2H-CH_2-COOH) 8.14(s- 1H-NH)

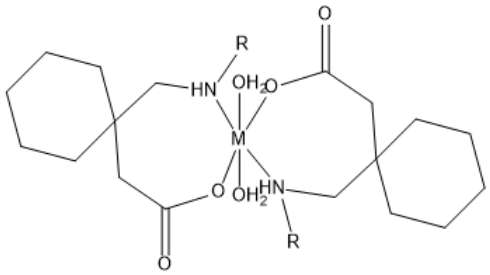
Table (2) shows the results of H^1-NMR &^{13}C-NMR of the ligand and their complexities

3.5 Mass spectra

The mass spectrometry used to record [M+] ions at the proposed [M.Wt] confirming the expected molecular weights of the ligands. The ligand L1 was characterized by a peak of the partial ion atom at m / z = 321 with relative abundance (14%). Ligand L2 showed a peak of the partial ion atom at m / z = 321 with relative abundance (10%). Ligand L3 showed a peak of the partial ion atom at m / z = 310 with relative abundance (21%). Ligand L4 is characterized by a peak of the partial ions (m / z = 214) with relative abundance (16%). The mass

spectrometry of the ligandsL5 was characterized by the base peak of the partial ion atom at m / z = 242, and as shown in spectra Figs.(from 35 to 39).

From the above physical measurements; FTIR,CHN,^{1}HNMR,^{13}CNMR, and Mass spectra, we confirm the formation of gabapentin derivatives (L1-L5) and their Cu(II)- & Zn(II)- complexes (L6-L13).And we suggest the formation of octahedral complexes as the followingstructure:



Where M = Cu (II) or Zn (II)

4. Conclusion

The present measurments by IR, CHN, ^{1}HNMR, ^{13}C NMR, and Mass spectra confirmed the formation of the new ligands of gabapentin derivatives (L1-L5) and their complexes(L6-L13), which exhibited appreciable antibacterial and antioxidant activities. And the antioxidant activities of all compounds which were synthesized in this research urge us to do anticancer activities in future work.

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References

Loscher, W.C. (2002),Current status and future in the pharmacology of epilepsy, Trends Pharmacol .Sci.23, 113–118.

Satzinger, G., (1994),Antiepileptics from gamma-aminobutyric acid, Forsch. 44, 261–266

Schwarz, J. B, Gibbons S. E., Graham S. R., Colbry, N. L., Guzzo P. R., Van-Duc Le,;

Vartanian, M. G., Kinsora J. J., Lotarski, S. M.. et al.(2005), Ca2+ Channel α2-δ Ligands for the Treatment of Neuropathic Pain,J. Med. Chem., 48, 3026–3035.

Ananda, K., Aravinda S., Vasudev P.G., Raja K.M.P., Sivaramakrishnan H., Nagarajan K., Shamala N., Balaram P.(2003), Stereochemistry of gabapentin and several derivatives: Solid state conformations and solution equilibria, Curr. Sci.,85 (7) 1002–1011. .

Ameringen MV, Rynn MA, Murphy TK, Mandel F. (2008), Influence of gender on the clinical presentation of generalized anxiety disorder, and response to treatment with Pregabalin, Eur Psych., 23, S221-S222.

Ameringen MV, Rynn MA, Murphy TK, Mandel F. (1993), Gabapentin, A review of its pharmacological properties and clinicalpotential in epilepsy. Drugs, 46,409-427.

Attal N, Cruccu G, Baron R, Haanpää M, Hansson P, Jensen TS, et al. (2006) EFNS guidelineson the pharmacological treatment of neuropathic pain. Eur J Neurol.,13, 1153-1169.

Vedula SS, Bero L, Scherer RW, Dickersin K,(2009).Outcome reporting in industry, sponsoredtrials of gabapentin for off-label use.

Shokohi-pour Z, (2016), A novel Schiff base derived from the gabapentin drug and copper (II) complex: Synthesis, characterization, interaction with DNA protein and Cytotoxicactivity, Journal of Photochemistry & Photobiology, B:Biology,162, 34–44.

Ahmad N. and Sewwell D. E.(2017), Gabapentin and its salicylaldehyde derivative alleviate allodynia and hypoalgesia in a cisplatin-induced neuropathic pain model,European Journal of Pharmacology,814, 302-312.

Hussain E.A., Kanwal N., Khan I. U. (2017) Mutahir S. and Yar M.,Green and Facile Reaction of Gabapentin with Sulfonyl Chlorides to Synthesize Lactams and Sulfonamides Derivatives in Aqueous Medium,Letters in organic Chemistry., 15,163-170.

Hekmat S., Balalaie S., Ramezanpour S., Rominger F., Vavsari V. and Kabiri-Fard H. (2017), SBA-Pr-SO3H: an efficient catalyst for the combinatorial synthesis of functional 2-aryl-4-quinazolinones using unusual γ-amino acids, Journal Of Chemical Society , 14, 833-841.

Amirani M. & Mohammadi M. (2018), Gabapentin-base synthesis and theoretical studies of biologically active compounds: N-cyclohexyl-3-oxo-2-(3-oxo-2-azaspiro[4.5] decan-2-yl)-3-arylpropanamides and N-(tert-butyl)-2-(3-oxo-2-azaspiro[4.5]deca2-yl)-2-arylacetamide derivatives, Journal of Molecular Structure, 1152, 44-52.

Singh R.K., Duvedi R. (2014),Synthesis, antimicrobial and of amido sulfonamido methane linked bis heterocycles, Arabian Journal of Chemistry, 7, 385–395.

Radwan M. O., M, Ismail A.H., Mekkawy El-, Ismail N.S.M., Hanna A.G. (2016,) Synthesis and biological activity of new 18β-glycyrrhetinicacid derivatives, Arabian Journal of Chemistry, 9, 390–399.

Nadgi A., Mhlong N. and Esoliman M.,(2017), Metal complexes in cancer therapy update from drug design perspective, Drug Design Development and therapy,11, 599-618.

Quaresma S., Andre V., Alxandra L. Cunha Silva and M. Teresa,(2017)American ChemicalSociety, 13, 5007-5017.

Furniss B.S., Hannaford A.J., Smith P.W.G. and Tatchell A.R.(1989). , Vogels, Text book of practical organic chemistry, Longman Scientific and Technical, 5th edition, New York,680

Pang X. and song M;(2012). Anti-synchronization of Duffing Double-Well Chaotic Oscillators via Integral Sliding Mode Control; International Journal of ChemTech Research,4, 346.

Venkatesan K., Satyanarayana V.S. and Sivakumar, 2011,Ultrasonic Assisted Synthesis of Naphthalene Substituted Schiff BaseDerivatives and Their Antioxidant ActiveStudies, Journal of the Chinese Chemical Society, 58, 583-589.