Synthesis, Characterization of some gabapentin derivatives by Green Chemistry

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Abstract

*Two new gabapentin derivatives were synthesized without solvent as green chemistry, by mixing gabapentin with sebacoylchioride in (2:1) molal ratio to give derivative **(1).** The second derivative**(2)**was synthesized by mixing one mole of benzoyl chloride with one mole of gabapentin without solvent. These derivatives**(1)** and **(2)**which act as ligands, were characterized by FT-IR, CHN, ^{1}HNMR, ^{13}CNMR measurements and thermal analysis. Complexes of gabapentin derivatives were prepared by adding MNO^{3}. $3H_2O$, where M = Cu(II) , to gabapentin derivatives **(1)** in 2:1molal ratio and to derivative **(2)** in 1: 2 molal ratio of Cu(II) to the derivative **(2)**. The complexes**(3)**and**(4)**have been characterized by FT-IR, CHN and thermal analysis.*

Keywords: Gabapentin, benzoyl chloride, sebacoyl chloride, copper(II) nitrate, green chemistry.

1. Introduction

Gabapentin is a medication which is used to treat partial seizers, neuropathic pain, hot flashing and restlesslegs syndrome (Goa KL et al,1993),(Goa KL, *et al* 2015), (Wijemanna S.*et al*, 2015). Many gabapentin derivatives have been synthesized and studied (Shokohi-pour Z,2016),(Ahmad N.,Senwell D. 2017), (Husain E.A., Kanwal, N. *et al*, 2017),(Hekmat S.et al, 2017). Unprecedented example of metal complexes with 1-aminomethyl-1-cyclohexane acetic acid were synthesized and giving $Co(Gbn.)_4$ and Ni(Gbn.) complexes, and the study revealed that cobalt complex has better activity than gabapentin(11a)(Amshumali MK *et al* Jan 2018). Recently another gabapentin derivatives were synthesized by condensation of gabapentin with some acid chlorides, and showed some antibacterial activities and antioxidant properties (Al-Mudhaffar Dh. et al, 2018).

Nitroalkane- gabapentin derivatives have been predicted (Amirani M. & Mahamnade M., 2018). A new gabapentin-base synthesis and theoretical studies of active compound ; N-cyclohexyl-3- oxo-2-(3-oxo-2-azospiro[4,5] decan-2-yl)-3-aryipropanamids and N-(tert-butyl)-2-(3-oxo-2-azospiro[4,5]decan-2-yl)-2-arylacetamide derivatives have been reported(MahboobAmericaniPoor *et al*2018).Unpresented example of metal complexes with 1-aminomethyl cyclohexane acetic acid was reported(Amshumali MK, *et al*, Jan 2018).

Another example of gabapentin derivatives which have been synthesized by green chemistry and facile reaction with sulfonide chlorides to produce lactams and sulfonamides derivatives (11) had been achieved (Hussain Erum A. et al March 2018).

In the current article, we have synthesized, by a greenchemistry, two new gabapentin derivatives by condensation of gabapentin directly, without solvent, with two acid chlorides and preparing their Cu(II)- complexes.

2. Experimental

2.1. Materials:

Gabapentin was from (Actavis). $CuCl_2$. $2H_2O$ was from (BDH). CCl_4 was from (BDH) and used without further purification.Sebacoyl Chloride was from Alpha Aldrich. BenzoylChloridewas from (Merck).Silica gel60F254 aluminum TLC sheets were supplied by Merck.

2.2. Physical measurements:

Melting points were done by using Gallenkamp apparatus .Infra-red spectra were reported on shimadzu spectrophotometer in the range 4000-400 cm^{-1} with KBr disc. Thermal analysis, (TGA and DTG) were done by using TGA 4000, PerkinElmer by heating from 30 $^{\circ}$C to 900 $^{\circ}$Cat 40.0 $^{\circ}$C\min. heating rate with alumina crucible.

Elemental analysis were performed on a Vario EL cube apparatus.NMR spectra were reportedon a Bruker spectrometer at 300 MHz by using TMS as reference and in DMSO as a solvent.

2.3. Synthesis of gabapentin derivatives:

2.3.1. (Sebacoyl – gabapentin) derivative (1):

(0.242 gm; 2mmol) of gabapentin (gabn.) was mixed with (0.239 gm; 1 mmol) of sebacoyl chloride and mixed by stirringwithout solvent at 50˚C for 1hr. Then the white resultant mixture Solid was washed with CCl_4 many times and followed by TLC in (2:1) ratio for (Ethanol: CCl_4), giving white solid (76% yield), m.p.:(96-98)˚C, then was kept in a desiccator.

2.3.2. (Benzoyl- gabapentin) derivative (2):

Similar procedure was done as in **(2.3.1)** by mixing(0.1710 gm.; 1 mmol) gabapentin (gabn.) with (0.1350 gm ; 1 mmol) benzoyl chloride without solvent and stirred for 1hr. Then was worked up as in **(2.3.1**) giving white solid(m.p.: 98-100)℃, (76 % yield),then was kept in desiccator.

2.3.3. Preparation of Cu (II)-(Sebacoyl- gabapentin) derivative)complex (3):

(0.100 gm:0.50 mmol) of the derivative **(1)**was added to basic solution of Cu(NO3)2.3H2O (0.240 gm,1mmol) which dissolved in minimum volume of distilled water, and the mixture was stirred at room temperature till completion by following with TLC giving a green precipitate.The resultant precipitate was filtered and washed many times with water,and the resultant green solid was dried and kept in desiccator,(72% yield).

2.3.4. Cu (II)-(Benzoyl- gabapentin) derivative complex (4):

Similar procedure was done as in **(2.3.3)** above to prepare this complex by mixing (0.0550 gm: 0.2 mmol) of benzoyl-gabapentin derivative **(1)**with hydrated Cupric nitrate (0.0241 gm: 1 mmol) dissolved in minimum volume of distilled water and giving green solution and worked up as above item**(2.3.3)** to give a green solid and was kept in a desiccator. (67 % yield)

3. ***Results and discussions:***

3.1.Infra- red spectra:

In case of sebacoyl-gabapentin derivative (**1**)gives band at 1697.41cm^{-1} which is attributed to carbonyl group due to the formation of amide group beside the disappearance of (NH2) bands of gabapentin that appear at 2857 cm^{-1} and 2931 cm^{-1} and appearance NH of amide group at 3398.69 cm^{-1} . On complexation of this derivative (**1**) with Cu(II) ion the resultant infrared spectrum is similar to that of gabapentin derivative (**1**) except the disappearance of OH band of gabapentinand shift of amide carbonyl stretching frequency to 1697.4cm^{-1}, indicating the coordination of Cu(II) ion with oxygen atom of carboxylic group of gabapentin.

Infra-red spectrum of the synthesized benzoyl-gabapentin derivative **(2)**shows theidentical spectral bands as that of gabapentin and benzoyl chloride alone, but with additional bands at about 1678 cm^{-1} attributed to $\upsilon_{c=o}$ of amide group which is formed due to condensation of benzoyl chloride with gabapentin (Al- Mudhaffar Dh. 2018), and disappearance of (NH_2) band of gabapentin. This givesan indication of the formation of the amide derivative compound (**1**)**.**And on complexation of this derivative (**1**) with Cu^{2+} ion,the OH band disappeared as a result of coordination of the metal ion with oxygen atom of carboxylic group in basic medium in formation of complex compound (**3**).

3.2. Elemental analysis:

Elemental analyses (CHN data)of the prepared compounds indicated the formation of bidentate ligands (**1 & 2**), in addition to formation four coordination complexes containing one ligand of gabapentin derivative **(3)** and two ligands of the second gabapentin derivative**(4),** as as shown in Table (1). Table 1: CHN and some physical properties of compounds (1, 2, 3 & 4)

Symbol	Molecular formula	m.p. ˚C	Color	Founded (Theoretical) % C	Founded (Theoretical) % H	Founded (Theoretical) % N
1	$C_{28}H_{48}N_2O_6$	-96 98	White	66.0615 (66.1085)	9.3572 (9.5112)	5.3281 (5.5068)
2	$C_{16}H_{21}NO_3$	-98 100	White	69.5682 (69.7931)	7.4297 (7.6878)	4.8299 (5.0870)
3	Cu ($C_{28}H_{46}N_2O_6$)	>300	Green	66.0004 (66.3002)	8.9061 (9.1413)	5.4608 (5.5223)
4	Cu ($C_{16}H_{20}NO_3)_2$	>300	Green	62.8047 (62.9860)	6.4168 (6.6076)	4.3822 (4.5908)

3.3. Thermal analysis:

Thermal analysis hadbeen done for the two derivatives **(1)** and **(2)** and their Cu(II) complexes **(3& 4),** as shown in the Figs. **(1,2,3& 4):**

3.3.1. Sebacoyl- gabapentin derivative (1):

This derivative shows one step weight loss (wt. loss) at 314.55 °C of 91.717 % as practical wtloss, with complete breakdown of the compound **(1),** but leaving radical as C_2O_2 (ethene-1,2-dione)corresponding to 56 g \mol and the theoretical wt. loss value is 88.99 % which is nearly equal the practical one, leaving char residue with 8.02 % wt. of the derivative (**1),**at 361.36 ° C . The TGA gives one step with one DTG band as in Fig.**(1),** and according to the following equation:

314.55°C361.36 °C

($C_{28}H_{48}O_6N_2$)(1) ----------→Complete breakdown--------→C_2O_2 ↓+ Char

3.3.1.1.Cu (II) complex of Sebacoyl –gabapentin derivative (3):

While for this derivative- Cu(II)-complex **(3)** shows two wt. loss steps, and the first one occurs at 314.01 ° C with 80.009 % wt. loss which indicates the breakdown of all the complex **(3)** but leaving the coordinated part of the derivative (1) with Cu(II) ion as Cu(C_2O_2), indicating the coordination of one molecule of Sebacoyl-gabn. derivative**(1)** with Cu^{2+} through carboxylic acid oxygen atoms of two gabapentin molecules, and the wt. loss 80.009 % corresponding to one molecule of gab-sebacoyl derivative **(1),** but without two molecules of (CO).and that the coordination reaction is 1:1 between Cu(II) ion and the derivative **(1).**The left char is 20.54 % decomposed further giving two molecules of CO with 8.305 % practical wt. loss which is near to theoretical value 9.821 %,.and Cu atom as residue.The TGAthermogramis shown in Fig**.(3).** The breakdown of the complex is according to thefollowing equations:

314.01 ° C
1. [($C_{28}H_{46}N_2O_6$) Cu (II)] ----------→ (Breakdown part) + Cu (C_2O_2) ↓
> 450 °C
2. Cu (C_2O_2) ----------→ Cu ↓+ 2 CO ↑

3.3.2. Benzoyl-gabn.-derivative(2):

This derivative shows three wt. loss steps The first one is at 170.85 ° C with 9.294 % wt. loss and we suggest loss of one CO molecule (M.wt = 28.01 g/ mol) with theoretical wt. loss = 10.173%. The second step occurs at 234.80°C with 30.105 % wt. lossand it may be (C_6H_{11}) as cyclohexene(M.wt.= 83.105 g/ mole), and its B.P = 82.9 °C, thus at 234.8° Cit should be evaporated, with theoretical wt. loss = 30.152 %. The second formed compound is suggested to be**(B)** which is called N-(2-Hydroxyethyl) benzamide,(MitsuoSekine, Masaki Satoh, Hikaru Yamagata, and Tsujiaki Hata,1980). And the third wt. loss is at 234.80 ° C with wt. loss = 54.047 % which may correspond to complete breakdown of compound (2b),$C_9H_{11}NO_2$, (M.wt.= 151.16256), and the theoretical wt. loss=54.849 %.

The remaining is char from 281 ° C up to 900 ° C (2). The details is shown in Fig.**(3).** And we suggest the following equations for the three steps:

170.85 ° C

1. **$C_{16}H_{21}NO_3$ ----------→ $C_{15}H_{21}NO_2$ + CO ↑**
(2)A
197.31 °C
2. **A----------→ $C_9H_{11}NO_2$+C6H9**(30.105 %)
B (Cyclohexene)
234.80 °C
3. **B ----------→$C_9H_{11}NO_2$(Complete breakdown) -------→ Char↓**

3.3.3. Cu (II)-complex of Benz. - gabn.- derivative (4):

It shows first step at 195.15 °C with 14.292 % wt. loss and we suggest loss of two moles (CONH) radicals**(B)** (Theoretical. Wt. loss 13.6174 %) This step indicates that the coordination of Cu(II) ion is through carboxylate- two oxygen atoms but not with nitrogen atom and oxygen atom of amide group giving probability of tetrahedral or square planar complex.

In the second step of wt. loss = 54.330 % we suggest loss of two moles of (C_6H_{11}) radical**(D)**and two moles of benzyl radical (C_7H_7)**(E),**with theoretical wt. loss = 55.103 %,leaving $Cu(CH_2\text{-}CO_2)_2$as a char,and the thermogram ,Fig. **(4)** shows these wt. losses, according to the following equations:

195.15 °C

1.[Cu (II) ($C_{32}H_{40}N_2O_6$)] ----------→2 (CONH) ↑ + [Cu(II) (C30H38)]
A B C
M.wt. = (631.546)
272.28 °C
2.(C) ----------→ 2 $\dot{C}_6H_{11}$↑+ 2 $\dot{C}H_2$- C6H5↑+ $Cu(CH_2\text{-}CO2)_2$↓
D E F
And the third step at about 370 °C gives wt. loss of 21.102 % which correspond to the char containing Cu residue, and evolution of one mole of ethylene and two moles of CO_2 which means that the theoretical wt. loss will be 23.946 % :
370 °C
3.(F) ----------→ Cu ↓ + C_2H_4↑ +2CO_2↑

4. NMR spectra:

4.1. Sebacoyl- gabapentin derivative (1):

^{1}HNMR spectrum of sebacoyl- gabapentin derivative **(1)** shows cyclohexylprotons bands of gabapentin at range (1.8 - 2.2) ppm, and at 2.8 ppm for CH_2 – protons attached to carboxylic group of gabapentin that compared to the free gabapentin which occurs at (1.33- 1.479) ppm and at 2.415 ppm for CH_2 group attached to carboxylic group (Hussain E.A. et al 2017, Al-Mudhaffar D.M. et al 2018), this shift is due to coordination with sebacoylchroride. Single sharp band occurs at about 8 ppm due to (-NH) amide proton due to condensation of gabapentin with sebacoyl chloride. Hydroxyl proton gives broad band at about 12.9 ppm. Another methyl group protons ($CH_2 – NH_2$) occurs at 2.503 ppm that correspond to gabapentin molecule. Another bands occur in the range (1.4 -2.9) ppm due to sebacoyl group but are little shifted as result of condensation with gabapentin (www.hanhonggroup.com/en/) The spectrum is shown in Fig**(5)**, and detailed data in Table **(2).**

Table (2) NMR chemical shifts of Gabapentin derivatives (1) & (2)

Compound no.	**Structure**	**^{1}H NMR (ppm)**	**^{13}C NMR (ppm)**
(1)		H (Cycl.-Gabn.): (1.8-2.8), H (HN-amide):8.393, H(CH_2 – NH): 2.4, H(Sebacoyl): (1.4-2.9), H(CH2-carboxylic): 2.5	(Sebl.): C1: 173.28, C3:25, C4 : 24.8, C2: 39.694, C5: 23, C-O-OH: 175, C-NH: 40.25.
(2)		H(cycl-gabn.): (1.4-2.9), CH2-CO2H): 2.502,, -NH: 7.6, Ar.(H): (7.5-8.3), OH: 12.669, CH2-NH: 2.409	(m-6C-Cyclohexan) : (25.821-39.695), (S-C-NH) :40.244, (S-C-COOH) :40.521, (m-6C-Ar) : (127.76-135.183),

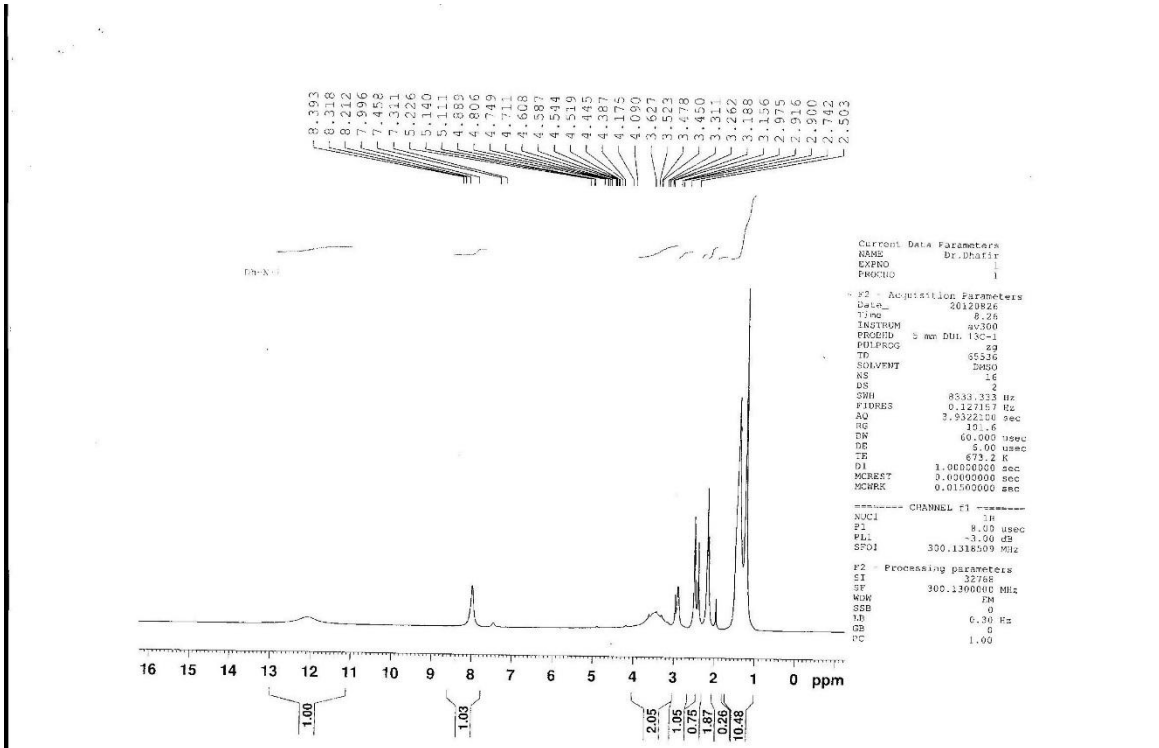
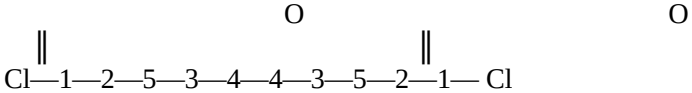


Fig.(5):[1]HNMR spectrum of Sebacoyl-gabn.-derivative (1)

[13]C NMR spectrum for this derivative **(1)**shows the band of gabapentin-carbon amide atoms at 173.28 ppm but with little shift due to the condensation withsebacoylchloride ,and for free sebacoyl chloride occurs at 173.60 ppm.Single band appears at 174.92 ppm may beattributed to carbon of carboxyl carbonyl group. (Al-Mudhaffar Dh. M. et al 2018). Carbon-amide signal occurs at 173.28 ppm.Another two bands occur at 25 ppm and 24.8 ppm due to $\mathbf{C_3}$and $\mathbf{C_4}$ respectively of sebacoyl group with little shift than that of free sebacoyl chloride which occur at 28.78 ppm and 28.32 ppm respectively, due to coordination in forming the derivative **(1)**(www.hanhonggroup.com/en/)**.**This spectrum is shown in Fig.**(5),**and the detailed data is given in Table **(3)**:



Sebacoyl Chloride

4.2. Benzoyl- gabapentin derivative (2):

[1]H NMR spectrum of this derivative **(2)**shows cyclohexane protons of gabapentin bands at (1.2-2.9) ppm , and at 3.5 ppm for methyl (CH_2 -) which attached to cyclohexylic group of gabapentin compared to free gabapentin molecule occurs at 2.629 -1.33) ppm and at2.415 ppm respectively.Hydroxyl group of gabapentin occurs at 7.6 ppm embedded with the aromatic protons bands of benzoyl group which gives the aromatic protons bands in the range (7.5-8.3) ppm (Al-Mudhaffar Dh. M. et al 2018). Hydroxyl group occurs at 12.7 ppm, and for the free gabapentin molecule gives bands in the range (12.22-12.62)ppm and this shift occurs due to coordination. The [1]HNMR spectra is shown in Fig**.(6),** and the detailed data in Table **(2).**

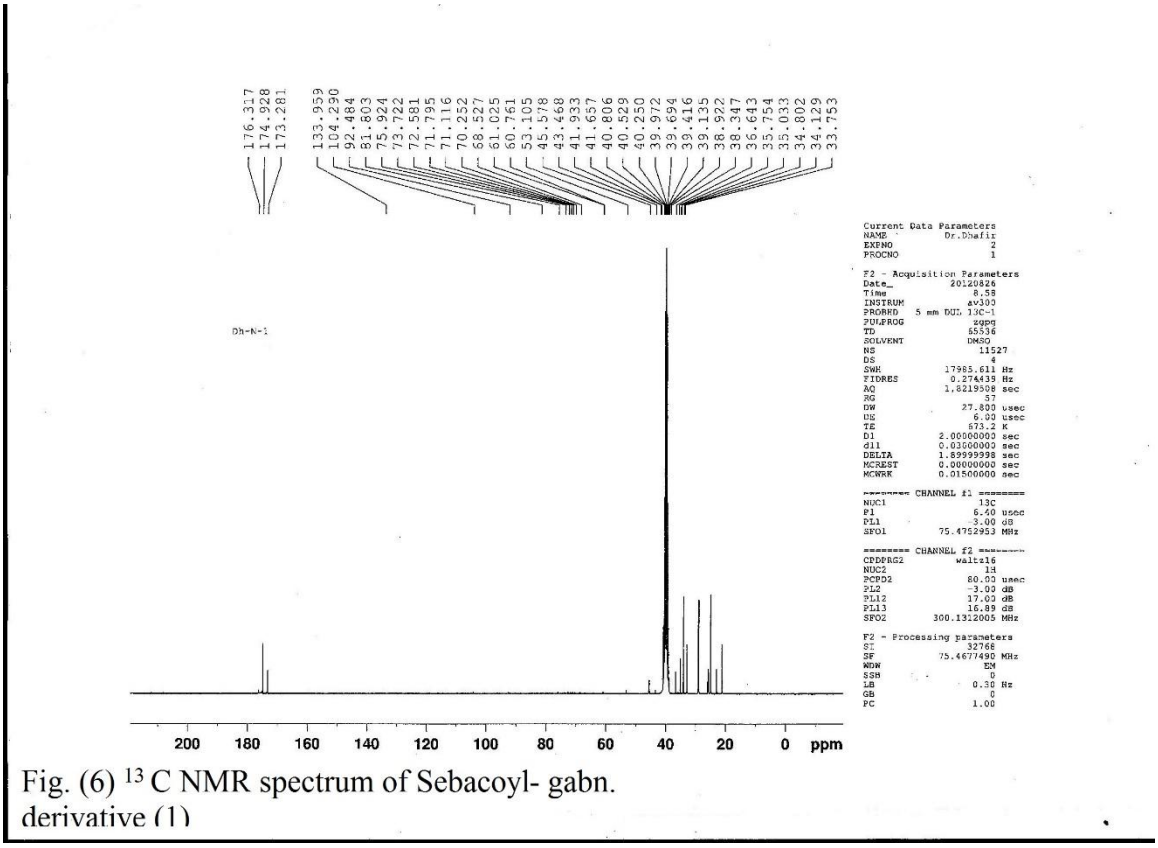


Fig. (6) [13] C NMR spectrum of Sebacoyl- gabn. derivative (1)

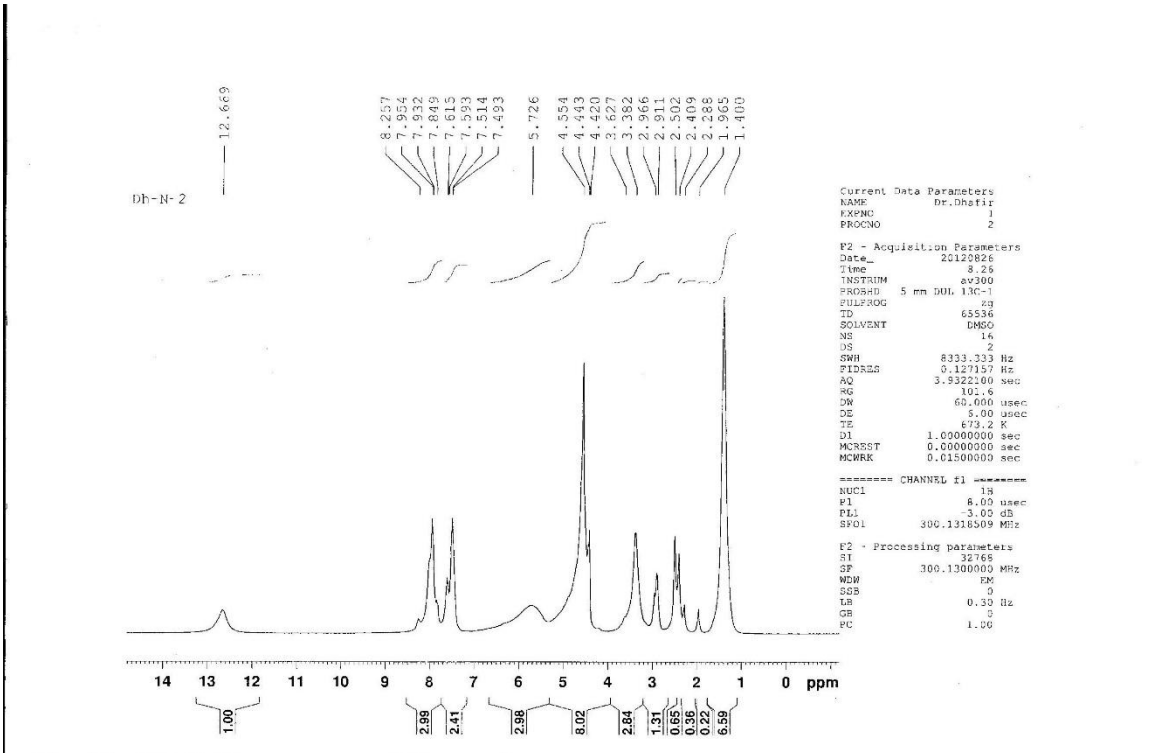


Fig.(7): [1]HNMR spectrum of Benzoyl-gabn.derivative (2)

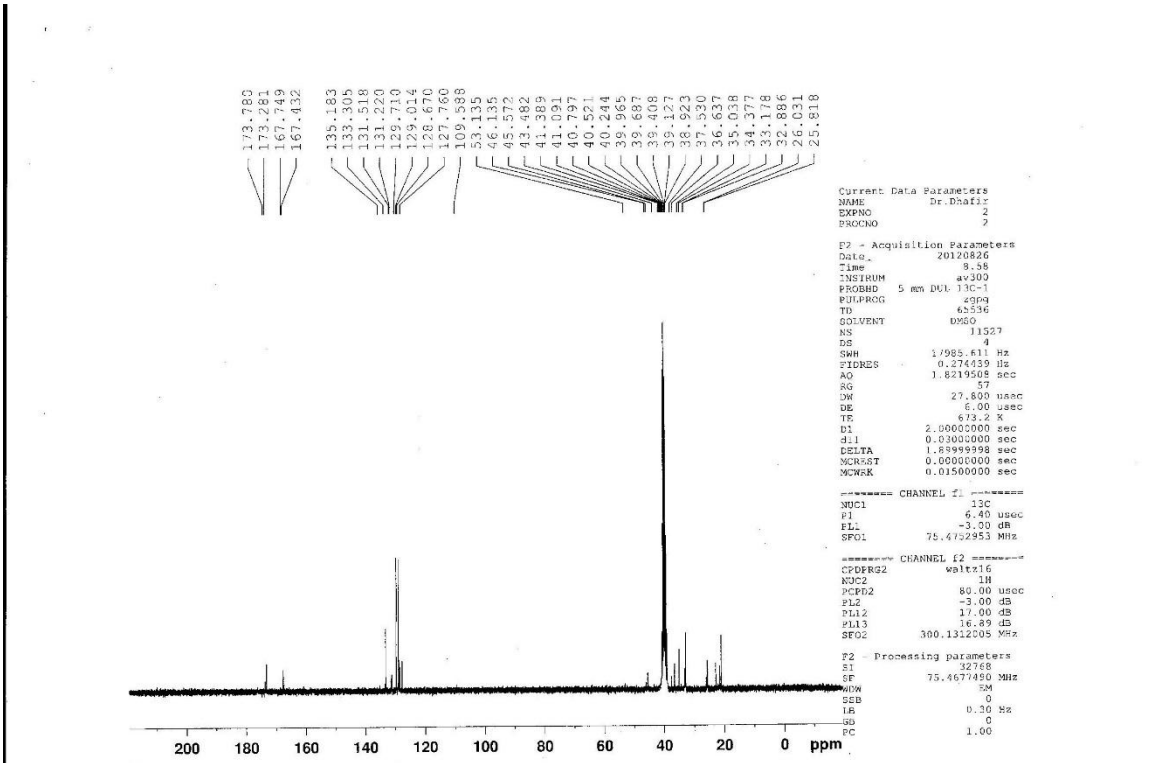


Fig.(8): ^{13}C NMR spectrum of Benzoyl-gabn.derivative (2)

[13]C NMR of this derivative **(2)**shows the characteristic bands for cyclohexyl carbon atoms at (21-39) ppm with little shift due to condensation with benzoyl chloride. Aromatic carbon atoms of benzoyl group occur in the range (127.76-135.183) ppm whereas for the free benzoyl chloride occur at (129-135.3) pm. Carbonyl carbon atom of benzoyl group shows band at about 168 ppm and for that of the free benzoyl chloride occurs at 167.9 ppm. The spectrum shows carbon atoms bands of cyclohexylic gabapentin group in the range(21.08- 37.53) ppm nearly similar to that of free gabapentin- cyclohexyl carbon atoms which occur in the range (21.1-32.2) ppm with little shift due to the condensation with benzoyl chloride (Wishart DS, et al.: HDMB. Epub 2008 Oct).

From IR spectra, CHN, thermal analysis, and NMR spectra we confirm the formation of gabapentin derivatives, i.e. derivative **(1)** as**(sebacoyl- gabapentin)derivative** with the following formula:

(1)

And**(benzoyl-gabapentin)** derivative **(2)**with the following formula:

(2)

In addition, for Cu (II) complexes **(3)**and **(4),** copper ion forms two coordinated complexes, either tetrahedral or square planar through carboxylic oxygen atoms, according to soft and hard (acid-base)criteria, as in the followings:

[(Sebacoyl- gabapentin) Cu(II)]-Complex:(3)

[Benzoyl-gabapentin) $_2$Cu(II)]- Complex(4)

5. ***Conclusion*****:**

The present measurements by IR, CHN, ^{1}HNMR, ^{13}C NMR, and TGA confirm the formation of the two gabapentin derivatives by green chemistry and their copper(II) complexes. These compounds may exhibit antioxidant and/ or anticancer activities, which need further study..

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