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Pryparation, Characterization And Biological Activity of New Derivatives of 2-Biphenyl-3-Aminomethylimidazo(1,2-a)Pyrimidine

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Abstract

New Fourteen compounds were synthesized in four steps. The first step included synthesis of 2-biphenyl fused ring of imidazo(1,2-a)pyrimidine from the reaction of 2-aminopyrimidine and biphenyl phenacyl bromide . The second step was introduced aldehyde group from the reaction of 2-biphenyl fused rings of imidazo(1,2-a)pyrimidine with $POCl_3$ in presence of DMF and $CHCl_3$. 3-Carbaladehyde derivatives of fused imidazo/pyrimidine was reacted with different aromatic amines to afford new Schiff bases. These new 3- imines derivatives was reduced by using sodiumborohydride to yield another new 3-aminomethyl-2-biphenyl imidazo (1,2-a)pyrimidine derivatives in moderate yield .Some new prepared compounds were identified by melting point, FT- IR , ^{13}C-NMR and ^{1}H-NMR spectra. Most of the new products compounds were tested against different bacteria to evaluate them as antimicrobial agents.

Keywords: Imidazo/pyrimidine, Schiff bases, Reduction, microbial, Biological activity

INTRODUCTION

Fused rings of imidazo/pyrimidine were attracted a numerous attention due to of their massive advantage in both pharmaceutical and medical chemistry. [(1)]. Pyrimidine compounds were well known in most of publications where the pyrimidine ring is linked to various heterocyclic such as imidazo pyrimidine , purine ,triazolo pyrimidines , pyrazolopyrimidine and pyridopyrimidine[(2-4)]. Pyrimidine's compound showed activities, antiviral, antibacterial, anti-HIV, antitumor as well as in the cure of neurodegenerative disorders such as, anti-depression cases, anti-anxiety disorders and Parkinson's disease [(5-10)]. The chemistry of fused rings of imidazo/pyrimidine played important rule in pharmacological science. They are really well known for their analgesic, neurolepic , cardiovascular and anxiolytic properties[(11-13)]. A. Vidal et al. examined the effects of a series of six imidazo[1,2-a] pyrimidines derivatives on cell functions regarding to the inflammatory response by using mouse peritoneal macrophages and human neutrophils . Moreover, they have studies their anti-inflammatory activity in the mouse air pouch injected with zymosan to determine their effects on leukocyte infiltration into the inflammatory site and the production of arachidonate metabolites[(14)]. Schiff bases are imine compounds produced from condensation of aromatic aldehydes with aromatic amines, and they have also a wide biological applications[(15)]such as antioxidant, analgesic, antimicrobial, anti-tubercular, anti-inflammatory , anticancer and antifungal activities[(16-19)] . Borohydride reduction of azomethine bond in Schiff bases has been studied [(20)]. In this contribution [(21)], various procedures of enhancement of selectivity and reactivity of NaBH4 as reducing agent and other applications in organic synthesis are described.

MATERIAL AND METHOD

Chemicals and reagents

All chemicals used in this article were purchased from Sigma-aldrich unless otherwise stated.

Instrumentation

Melting points were assessed in Gallen Kamp melting point apparatus and were uncorrected. FTIR spectra were measured on SHIMADZU FTIR - 8400 Fourier Transform Infrared spectrophotometer as KBr disc. ^{1}HNMR and C^{13}NMR spectra were measured on Bruker spectrospin ultra shield magnets 400 MHz instrument using tetramethyl silane (TMS) as an internal standard and DMSO-d_6 as a solvent in Ahl-Albate University in Jordan.

1. Preparation of 2-biphenyl imidazo(1,2-a)pyrimidine (1) [(22)]

A mixture of (0.01 mole) (0.95 g) of 2-amino pyrimidine , (0.01 mole) (2.77g) of biphenyl phenacylbromide and (0.01 mole) (1.68 g) of sodium bicarbonate were clear up in ethanol 20 Ml. Tese mixture was refluxed for 6 hrs. After that, 5% of sodium hydroxide was added to a mixture to make the PH =10. The solid compound was filtered and recrystallized from ethanol.

2. Preparation of 2-biphenyl imidazo [1,2-a]pyrimidine -3-carbaldehyde(2) [(23)]

Freshly distilled phosphourous oxychloride (0.0091 mole) was added dropwise with stirring to dry N,N-dimethyl formamide (0.7 mole) in the flask protected from moisture in presence of chloroform (20 ml). The temperature being kept at 0-5 ^{0}C. 2-biphenyl imidazo(1,2-a)pyrimidine **1** was then slowly added with stirring . The reaction mixture was heated under reflux for 2 hours. The residue was poured into ice and water , the obtained solid compound was filtered and purified from ethanol. All physical properties and FTIR data of compound (1) and (2) are listed in Table (1).

3. Preparation of Schiffs bases (3-8) [(24)]

A series of Schiff bases were prepared from the reaction of compound **(2)** (0.01 mole), with different aromatic amine (0.01 mole), in 20ml ethanol absolute and 2 ml of glacial acetic acid. This mixture was heated under reflux for 6hrs and then cooled; The obtained solid was recrystallized from ethanol . All physical properties and FTIR data of compound **(3-8)** are listed in Table (2).

4. Preparation of compounds [9-14] [(25)]

Sodium borohydride (0.03 mole) was added to a methanolic solution of Schiff bases (0.0002 mole) over a period of 30 min. at temperature 5-10 ^{0}c with stirring. The reaction mixture was kept overnight at room temperature. The mixture was filtered and recrystallized from methanol. All physical properties and FTIR data of compound (**9-14**) are listed in Table (3).

Biological activity [(26)]

Some of new prepared compounds were examined *in vitro* for potential antibacterial activity against gram negative *Escherichia coli* and Gram positive *staphylococcus aureus* by agar diffusion method. Chlorophenicol and flucanazol were used as control drugs. The final resulted data on the antimicrobial activity of some new compounds and control drugs are given in Table 6. Microdilution broth susceptibility method was choiced for the antibacterial evaluation of the compounds and chloramphenicol was candiduted as standard antibacterial agent. Agar plates were surface vaccinated uniformly with 100 µl from both cultures of tasted microorganism. The impregnated disks were placed in the middle, and the plates kept warm to promot growth at 278 K for 1 h to allow good dispersion and relocated to another an incubator at 310 K for 24 h. The inhibition zones caused by various

compounds on the microorganisms were determined biological activity for prepared compounds is listed in Table 6.

RESULT AND DISCUSSION

New six imine compounds were synthesized from the reaction of compound (**2**) with different aromatic amine, after that, these new six Schiffs bases were reduced by using sodiumborohydride as shown in scheme (2). These compounds (**3-14**) were showed a moderate biological activities. The first step was synthesis of 2-biphenyl imidazo(1,2-a)pyrimidine from the reaction between 2-aminopyrimidine and biphenyl phenacylbromide. FT-IR spectrum of compound (**1**) showed characteristic absorption bands at (1610) cm $^{-1}$, (1559) cm $^{-1}$ and (1230) cm $^{-1}$ due to stretching of the (C=N) pyrimidine, (C=C) aromatic and (C-N) respectively as shown in table (1) . The second step was introduced carbaldehyde group to give 2-biphenyl imidazo[1,2-a]-pyrimidine-3-carbaldehyde from the reaction between 2-biphenyl imidazo(1,2-a)pyrimidine with $POCl_3$ in presence of DMF and $CHCl_3$(Scheme 1). FT-IR spectrum of compound [**2**] displayed characterized absorption bands at (1558) cm $^{-1}$, (1537) cm $^{-1}$, (1647) cm $^{-1}$, (1602) cm $^{-1}$, (1234) cm $^{-1}$ and (2831) cm $^{-1}$ due to (C=N) pyrimidin, (C=C) aromatic, (C=O) aldehyde , (C=N) , (C-N) and (CH) aliphatic respectively as shown in table (1).

Then, the prepared compound (**2**) was condensed with different aromatic amines to form a new Schiffs bases. Finally, Schiff bases underwent reduction reaction with sodium borohydride as reducing agent to give new derivatives of 3-aminomethyl .

^{1}-H-NMR spectrum of compounds (**4**and 5) (Figure 2 and 3)displayed a multiple signals at (7.1-8.8) ppm due to the aromatic ring protons and aromatic amine protons, another singlet signal appeared at 7.6-8.5 ppm due to proton of Shiff bases. While compound (**5**) exhibited singlet signal at 2.2 ppm due to CH_3 group as shown in table (4).13C-NMR spectra of products (**4** and 5) (Figure 4 and 5) showed signals at 119-158 ppm due to aromatic carbon and aromatic carbone of amine and signal at 160-168 ppm due to carbone of Shiff bases. While compound (**6**) exhibited signal at 5.5-14.5 ppm due to carbon of methyl group, compound [**4**] also showed a signal at 126 ppm due to resonance of (C-Cl) as shown in table (5) .

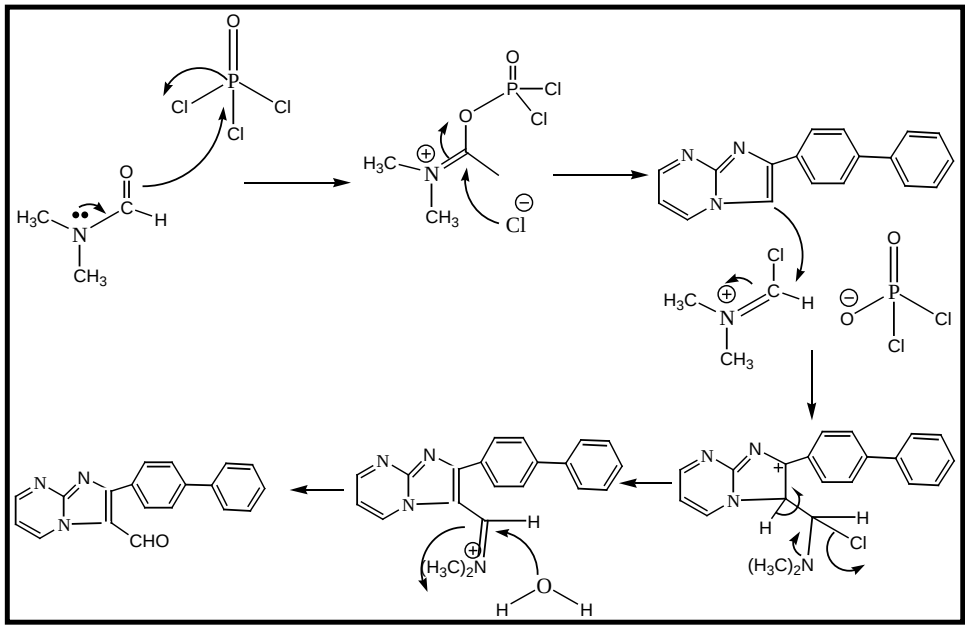
Moreover, FT-IR spectra of reduced Schiffs bases(**9-14**) displayed characterized stretching bands at (1674-1679 cm $^{-1}$, (1550-1580) cm $^{-1}$, (2920-3485) cm $^{-1}$ and (2810-2951) cm $^{-1}$ due to stretching of (C=N) imidazo, (C=C) aromatic , (N-H) and (C-H) aliphatic. As well as, FT-IR spectrum of product (**10**) displayed absorption band at (1004)cm $^{-1}$ due to vibration of (C-Cl).

Furthermore, 1-H-NMR spectrum of compound (**9**)(Figure 6) appeared a multiple signals at 7.4-8.8 ppm due to the aromatic ring protons and aromatic amine protons, another triplet signal appeared at (7.7) ppm owing to N-H , doublet signals at (4.8) ppm owing to CH_2-N. and singlet signal at 2.5 ppm belong to CH_3 group as shown in table (4). 13C-NMR spectra of compound (**9**) (Figure 7) showed signals at (109-158) ppm due to resonance of aromatic carbon and aromatic carbons of amine, another signal appeared at (138.7) ppm belong to C-N . also signals at (52.3) ppm due to CH_2-N and signal at 19.4 ppm due to carbon of methyl group as shown in table (5).

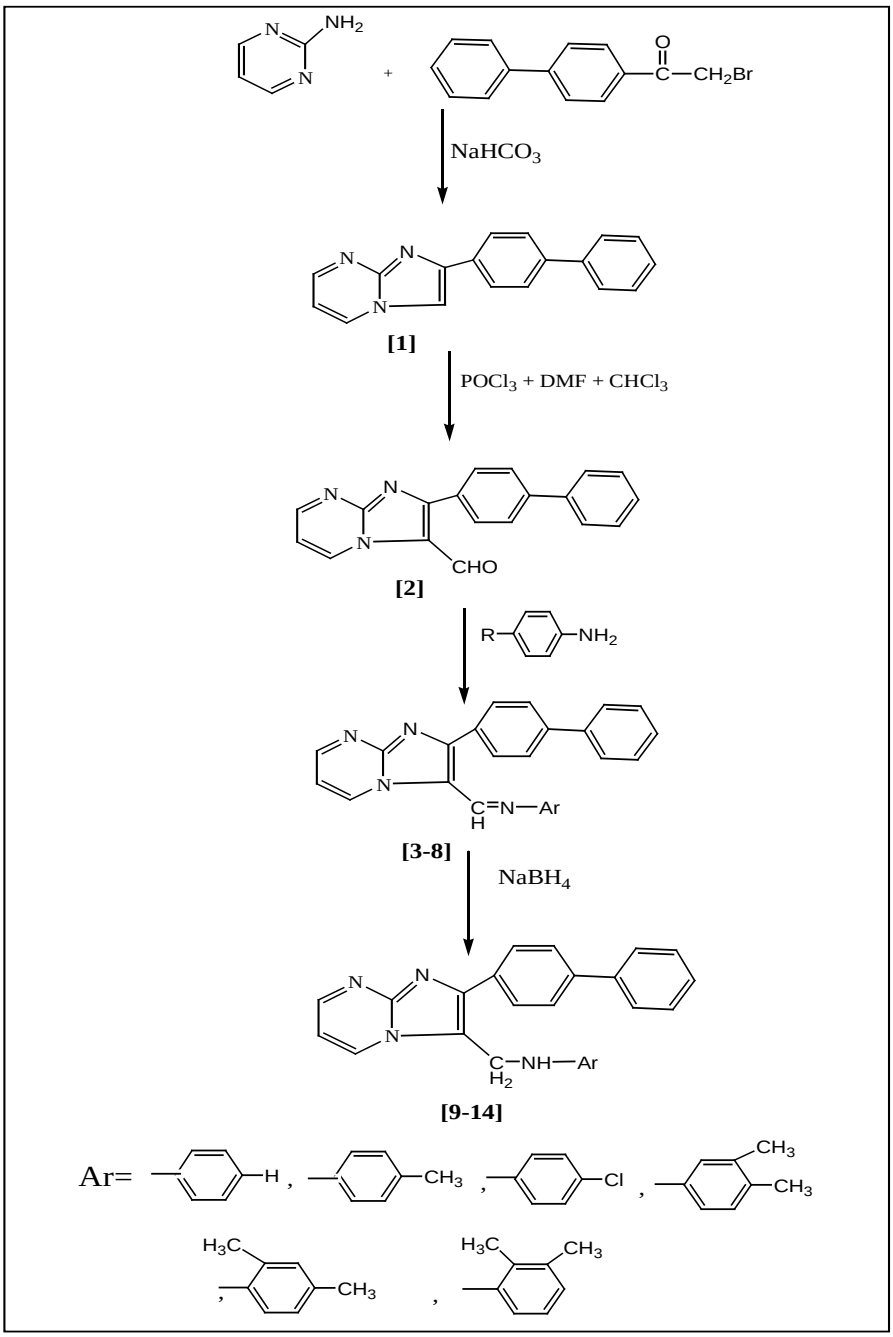
Biological activity

Since heterocyclic compounds like fused imodazo/pyrimidine rings showed different biological activities as mansion above, the new prepared derivatives of imidazo/ pyrimidine's were evaluated against different bacteria. These compound exhibited a good biological activity. The results of antibacterial activity of compounds (**1**,**2**,**3**, **4**,**5**,**9**,**10** and **13**) showed inhibition activities against two types of bacteria gram positive and gram negative bacteria including ***staphylococcus aureus*** *and* ***E.coli*** These inhibition studies exhibited that the compounds (**1** ,**9** and **10**) were inactive against *staphylococcus aureus*, while compounds (**2**,**3** and **4**) showed moderately activity against this bacteria. While product (**5** and **13**) were very highly activity against this bacteria.

Moreover, compounds [**1** and **2**] showed a highly activity against ***E.coli*** while compounds [**3-10**] exhibited moderately activity against same bacteria. These results interpreted the diversity of substituent's at position -3 of these interested bridgehead nitrogen compounds could be contributed to variety of biological activities. All these result were shown in Table (6).



Scheme (1): Synthesis mechanism of compound (**2**)



Scheme (2): Formation of compounds [1-14]

Table 1: Physical properties and FT-IR spectra data of compounds (1) and (2)

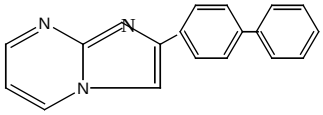
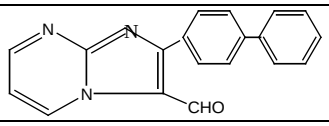
					υ C=N pyrimidino	υ C=C aromatic	υ C=O	υ C-N	**others**
1		200-201 dec.	93	Off White	1610	1559	---	1230	--
2		**175-178**	**40**	**Pale Yellow**	**1585**	**1537**	**1647**	**1234**	**C-H aliphatic 2831**

Table (2): Physical properties and FT-IR spectral data of compounds (3-8)

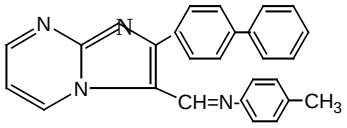
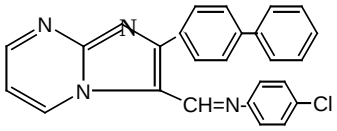
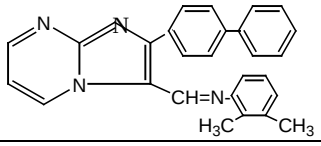
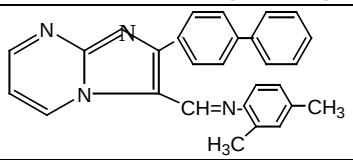
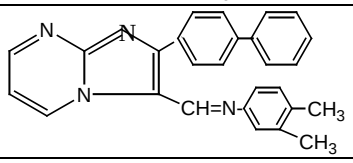
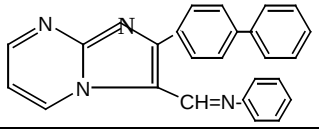
					υC=N Imidazo	υ C=N schiffs	υ C-H aromatic	υC=C aromatic	**Other**
3		201-205	40	Brown	1679	1600	3064	1560	**CH aliphatic 2922**
4		240-241 Dec.	30	Brown	1679	1616	3058	1560	**C-Cl 1078**
5		205-210 Dec.	30	Brown	1677	1604	3083	1570	**CH aliphatic 2921**
6		185-187	48	Brown	1676	1600	3120	1558	**CH aliphatic 2925**
7		210-212 Dec.	25	Orange	1677	1620	3110	1560	**CH aliphatic 2925**
8		**190-194**	**52**	**Orange**	**1610**	**1667**	**3037**	**1565**	---

Table (3): Physical properties and FT-IR spectral data of compounds (9-14)

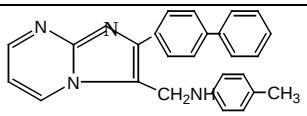
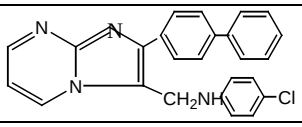
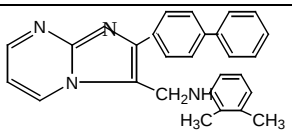
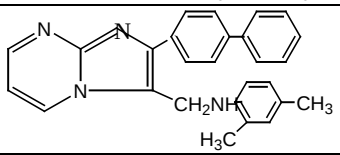
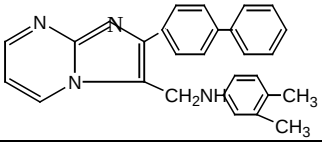
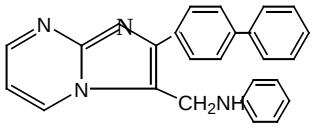
					υC=N Imidazo	υ C=C aromatic	υ N-H	υC-H aliphatic	**Other**
9		210-212	57	Off White	1679	1560	3249 Sym. 3101 Asym.	2925	---
10		198-202	50	Off White	1674	1579	2921 Sym. 2850 Asym.	2830	**C-Cl 1004**
11		216-218 Dec.	50	Off White	1679	1580	2920 Sym. 2850 Asym.	2810	---
12		194-196 Dec.	25	Off White	1676	1550	3168 Sym. 3078 Asym.	2951	---
13		180-182	62	Off White	1674	1562	3485 Sym. 3436 Asym.	2920	---
14		**170-172 Dec.**	**64**	**Off White**	**1674**	**1550**	**3438 Sym. 3406 Asym.**	**2852**	---

Table (4): 1H-NMR-spectrum data of compounds (4,5and 9)

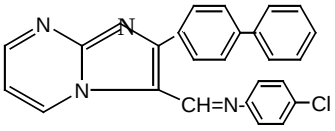
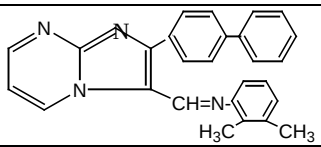
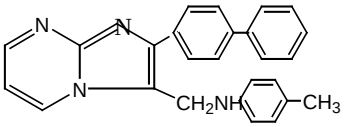
4		**7.1-8.6 (m,12H, aromatic), 7(m,4H, aromatic amine), 8.5 (s,H, shiff bases)**
5		**7.4-8.8 (m, 12H, aromatic and m,3H, aromatic amine), 7.6 (s,H, shiff bases), 2.2(H of methyl group)**
9		**7.4-8.8 (m,12H, aromatic and m,4H, aromatic amine), 2.5 (s,3H,CH_3), 7.7(t,H,N-H), 4.8(d,2H, CH_2-N)**

Table (5): ^{13}C-NMR-spectrum data of compounds (4,5and 9)

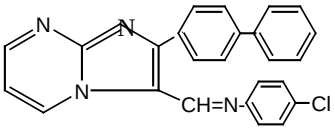
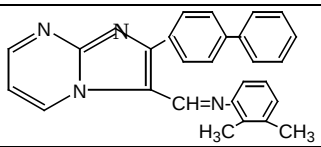
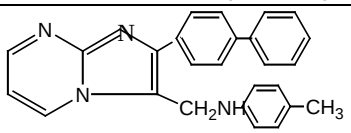
4		**119-140 (aromatic carbon and aromatic amine), 168(carbon of shiff bases), 126(C-Cl)**
5		**120-158(aromatic carbon and aromatic amine), 160(carbon of shiff bases), 5.5-14.5(carbon of methyl group)**
9		**109-158(aromatic carbon and aromatic amine), 19.4(carbon of methyl), 138.7 (C-N), 52.3 (CH_2-N)**

Table (6): Biological activities of some of the prepared compounds

	Staph.areus	***E.coli***
1	---	**17**
2	14	**13**
3	14	**6**
4	7	**---**
5	20	**10**
9	4	**4**
10	**----**	**---**
13	**19**	**4**

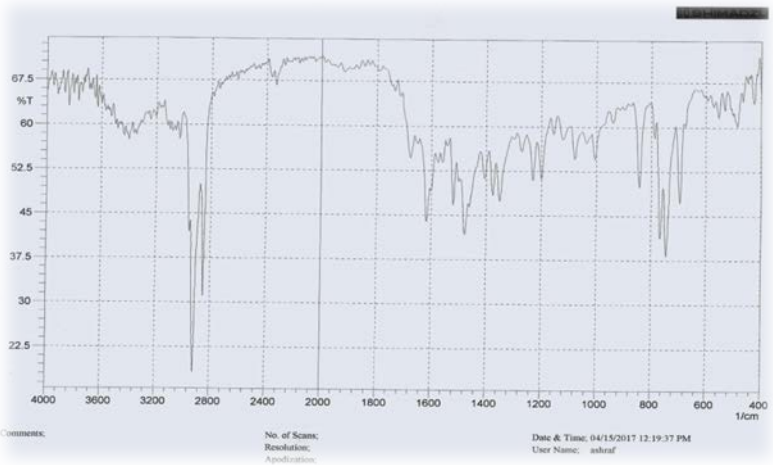


Figure (1): FTIR data of compound

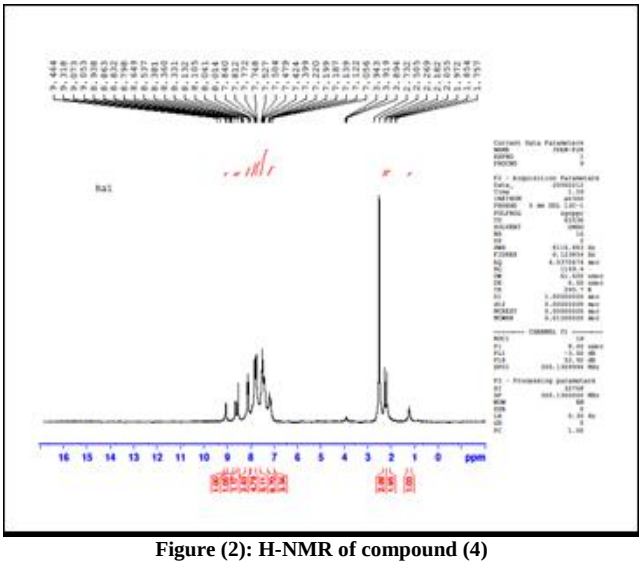


Figure (2): H-NMR of compound (4)

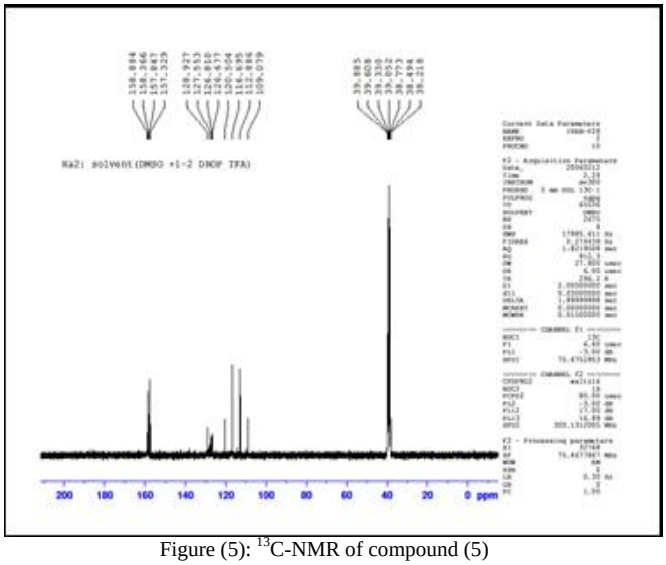


Figure (5): ^{13}C-NMR of compound (5)

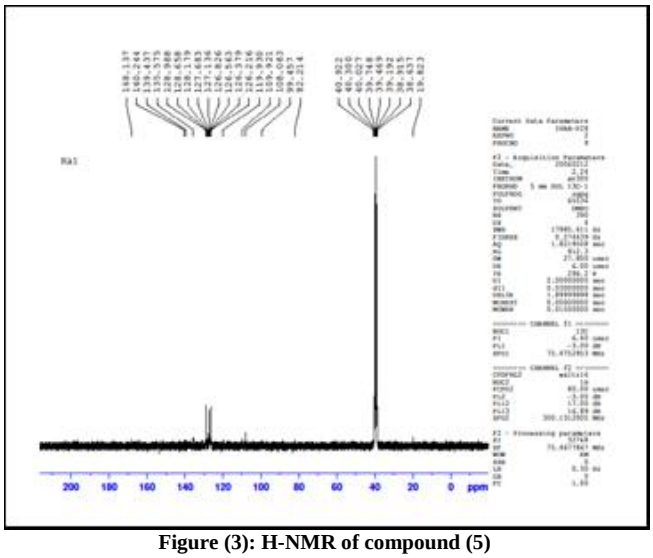


Figure (3): H-NMR of compound (5)

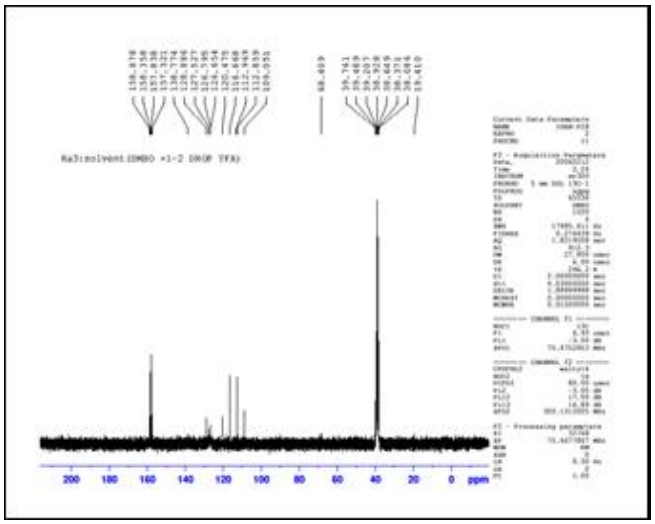


Figure (6): H-NMR of compound (9)

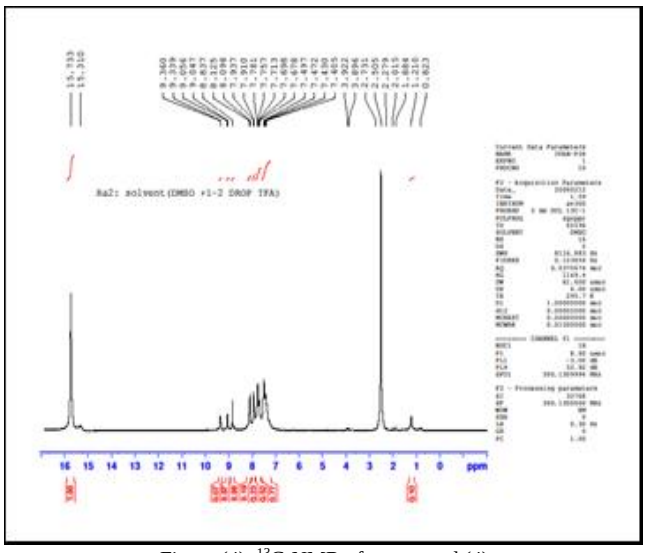


Figure (4): ^{13}C-NMR of compound (4)

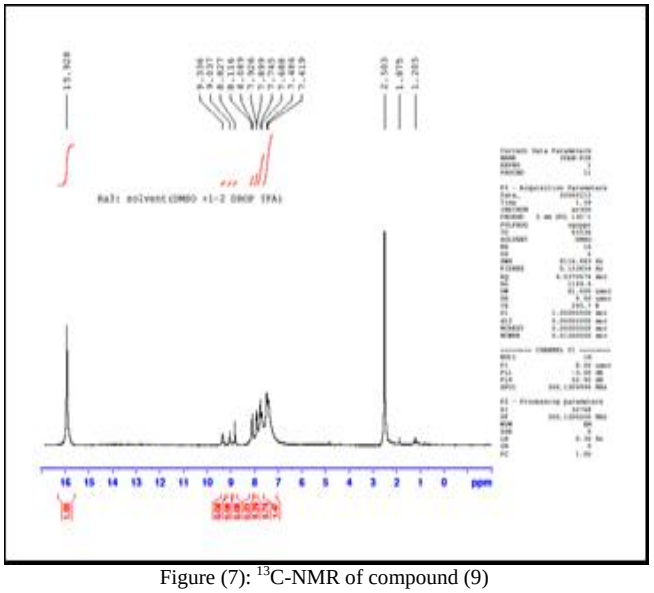


Figure (7): ^{13}C-NMR of compound (9)

ACKNOWLEDGEMENT:

We would like to thank Dr.Mohanad Masad in Ahl-Albate University in Jordan for conducting H-NMR and ^{13}C-NMR measurements

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