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Synthesis, Design, Biological and Anti-oxidant Assessment of Some New 9H-Carbazole Derivatives

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Abstract

This research includes the synthesis of 9H-carbazole compounds (1-7) through the prepared compound (2) by condensation 9H-Carbazole with chloroacetic acid in the presence of triethylamine and benzene as a solvent. The compound (3) was prepared from compound (2) and ethanol in the presence of H_2SO_4 as catalyst by using MWI. The synthesis of amide carbazole derivatives (3,4,5) was accomplished by using microwave irradiation with aromatic amine (p-, o-bromoaniline and m-chloroaniline). The synthesis of derivatives (6,7) was performed by Suzuki coupling reaction during which derivative (5) was treated with aryl boronic acid using $pd(pph_3)_4$ "palladium-tetrakis(triphenyl phosphine)" as a catalyst via oxidation, transformation and reduction steps (Scheme 1). The synthesized compounds were evaluated by FT-IR, 1H-NMR, 13C-NMR spectra. The assay of biological activity of synthesized compounds against two types of bacteria i.e. gram-positive (Staphy. Aureus) and gram-negative (E. coli) were performed. The results exhibited excellent activity of all synthesized compounds as compared with ciprofloxacin drug. The antioxidant activity of the synthesized compounds using DPPH test showed good findings.

Keywords: Carbazole, Aryl Boronic Acid, Oramtic Amine, Ethanol, Antioxdanit Activity.

1. Introduction:

Carbazole (Cz) is a heterocyclic compound. It contains two benzene rings and a pentagonal ring containing nitrogen or having a benzene ring with an indole [1]. The pharmacological properties of Cz derivatives are well recognized, and many are looking for novel physiologically active substanceshaving antibacterial and antifungal properties [2][3], cytotoxic against cancer cell lines [4-6], antinociceptive action [7][8], antiobesitic [8], antidiabetic [9], antipsychotic activity [10], and antiemetic medicine [11] . "Suzuki coupling reaction" is one of the useful reactions for preparing carbon-carbon compounds as polymers, pharmaceutical from aryl halides and borones in the presence of palladium catalysts [12-14]. In this study, microwave technology was combined to employ the Suzuki reaction under straightforward conditions for a brief period. In comparison to other organometallic reagents, boric acids are less hazardous and safer. [15-17].

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2. Materials and Method:

2.1. General:

New compounds (1-7) were prepared via "Suzuki reaction" from Carbazole derivatives with aryl boronic used MWI (Scheme 1). Carbazole and other chemicals were obtained from Fluka, CDH Company and BDH Company. The compounds were recognized by FT-IR; "Testseon Shimadzu (FT-IR 8400Series, Japan)", 1H-NMR and 13C-NMR" (Bruker, UltraShield 500 MHZ and 100 MHz)".

2.2. Synthesis of Compound (1):

9H-carbazole (2g; 0.01mol) , chloroacetic acid (1 mL; 0.01 mol) in benzene (15 mL), and then added triethylamine (TEM) (1 mL) while stirring. Then, refluxed for 9 h on a water bath and washed with 5% $NaHCO_3$ [18]. The physical data is given in Table 1.

FT-IR spectrum (cm^{-1}, vmax): Compound (1) Fig (1): (3447-2431) OH acid, (3024, 3049) $CH_{ar.}$, (2839) $CH_{al.}$, (1342) C-N, (1722) C=O, (1521) C=C ar. and (1217-1273) C-O.

1HNMR (500MHz, DMSO-d6, ppm) :12.06 (s,1H, OH acid), (4.9) (s, 2H, N-CH_2) and (7.24-8.37) (m,8H, Ar-H).

2.3 Synthesis of Ester (2):

Compound (1) (0.5 g, 0.001 mol) was added in ethanol (30 ml) and H_2SO_4 (1 mL) and refluxed for 20 min in the microwave oven. The yield then filtrated, washed with ethanol to give ester [19] (Table 1).

FTIR: 3083 (CH ar.), 2945 (CH al.), 1718 (C=O), (1165-1274) C-O, 1342 (C-N).

^{1}HNMR: 4.3 (t, 2H, CH_2), 4.7 (s, 2H, CH_2), 2.3 (d, 3H, CH_3), 7.3-7.9 (m, 8H, Ar.).

2.4. Synthesis of Compounds (3, 4 and 5):

Ester (2) (0.5 g, 0.001 mol) was added in ethanol (10 mL) and 2-bromoaniline (0.17 g, 0.001 mol.), 3-chloroaniline (0.13 g, 0.001 mol), *p*-bromoaniline (0.17 g, 0.001 mol), respectively were added. Then refluxed for 20 min in microwave oven, filtered, washed, and recrystallized in ethanol [20] (Table1).

FTIR Compound (3): 3437 (NH), 1722 ($C=O_{amide}$), 3081, 3049 ($CH_{ar.}$), 2857, 2972 ($CH_{al.}$), 1527 ($CH_{ar.}$), 1228-1259 (C-O), 1362 (C-N) and 578 (C-Br).

1HNMR: 7.3 (s, 1H, NH), 4.9 (s, 2H, CH_2), 6.7-8.3 (m,12H, Ar-H.).

FTIR Compound (4): 3022 ($C\text{-}H_{ar.}$), 2845, 2994 ($C\text{-}H_{al.}$), 1672 (C=O), 3415 (NH), 1575 (C=C), 1182-1294 (C-O), 1331 (C-N) and 748 (C-Cl).

^{1}HNMR: 4.9 (d, 2H, CH_2), 7.5 (s, 1H-NH), 6.7-8.5 (m, 12H, Ar-H.).

^{13}C-NMR: 165 (1C, C=O), 103-136 (12C, $C_{aromatic}$), 45 (2C, CH_2).

FTIR compound (5): 3041 ($C\text{-}H_{ar.}$), 2826, 2972 (C-H al.), 1724 (C=O), 3414 (NH), 1575 (C=C), 1182-1284 (C-O), 1331 (C-N), 691 (C-Br).

1HNMR: 4.7 (d, 2H, CH2), 9.1 (s, 1H-NH), 7.06-7.9 (m, 12H, Ar-H.).

^{13}C-NMR: 169 (1C, C=O), 105-134 (12C, $C_{aromatic}$), 42 (2C, CH_2).

Table1: Physical properties of compounds (1-7).

Com. NO.	Molecular Formula	M.Wt	Colour	m.p. °C	Yield %	Rf	(TLC)
1	$C_{14}H_{11}NO_2$	225	Deep violet	150-151	80	0.79	ethanol: n-hexane 1:3
2	$C_{16}H_{15}NO_2$	253	White	240-242	73	0.82	ethylacetate: n-hexane 1:1
3	$C_{20}H_{15}BrN_2O$	378	Brown	277-279	62	0.77	Acetone : n-hexane 1:2
4	$C_{20}H_{15}ClN_2O$	334	yellow	281-282	67	0.85	Acetone: n-hexane 1:1
5	$C_{20}H_{15}BrN_2O$	378	White	285-288	61	0.71	Acetone: n-hexane 1:2
6	$C_{26}H_{19}N_3O_3$	421	Orange	176-178	80	0.98	ethylacetate: n-hexane 3:2
7	$C_{26}H_{20}N_2O_2$	392	Brown	270-272	82	0.87	ethylacetate: n-hexane 3:2

2.5. Synthesis of Compounds (6 and 7):

Compound (5) (0.2 g, 0.0004 mol) with 4-nitrophenyl boronic acid (0.0668 g), 5-formyl-2-thienyl boronic acid (0062 g) were added, respectively, to 0.05 g of $Pd(pph_3)_4$ with 20 mL ethanol (EtOH) under N_2 gas. Then, 5 mL of 5% Na_2CO_3 was added, stirred for 5-6 h and heated at 75 °C. Finally, filtrated, washed by ethanol, and dried [21][22] (Table 1).

FTIR Compound (6): 3495 (NH), 3099 ($CH_{ar.}$), 2941 ($CH_{al.}$), 1725 (C=O), 1172-1196-1272 (C-O), 1525 (C=C) and 1334 (C-N).

1HNMR: δ 7.24 (NH), 7.5-8.3 (m,12H, Ar) ,4.9 (s, 2H, CH_2).

^{13}CNMR: 165 (1C, C=O), 109- 139 (12C, $C_{ar.}$), 44 (2C, CH_2), 148 (C-N).

FTIR Compound (7): 3412 (NH), 3047-3063 ($CH_{ar.}$), 2954, 2931 ($CH_{al.}$), 1718 (C=O), 1649 (C=O), 1136-1247 (C-O-C), 1525 (C=C) and 1375 (C-N).

1HNMR: δ 8.2 (NH), 9.1 (s, 1H, COH), 6.5-7.9 (m, 12H, Ar-H) and 4.6, 4.7, 4.98, 4.99 (8H, CH_2).

^{13}CNMR: 160 (1C, C=O), 185 (1C, COH), 103- 134 (12C, $C_{ar.}$), 46 (2C, CH_2) and 148 (COH).

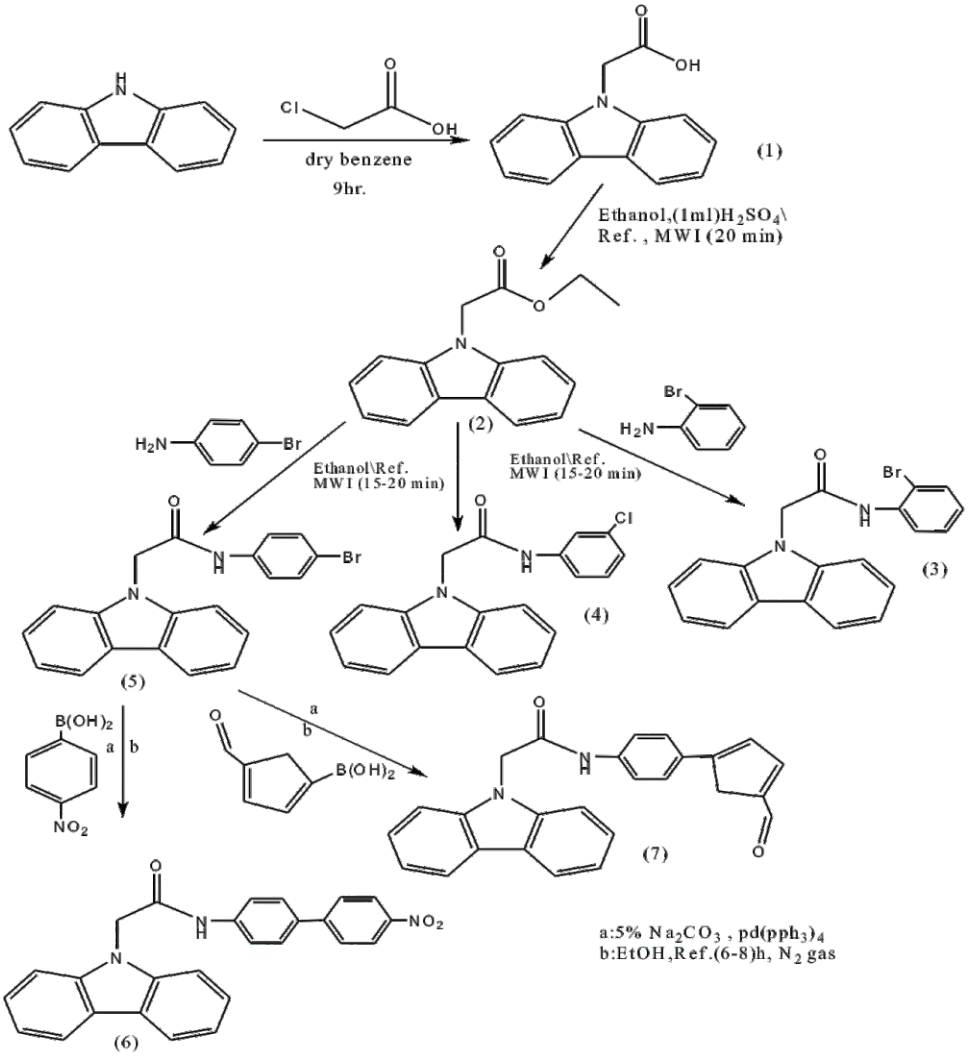

Figure1: Scheme for synthesis of compounds (1-7).

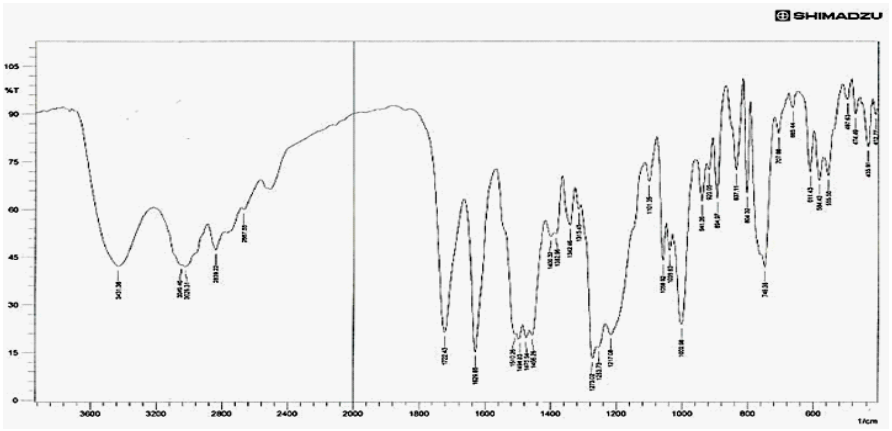

Figure 2: FT-IR of prepared compound (1).

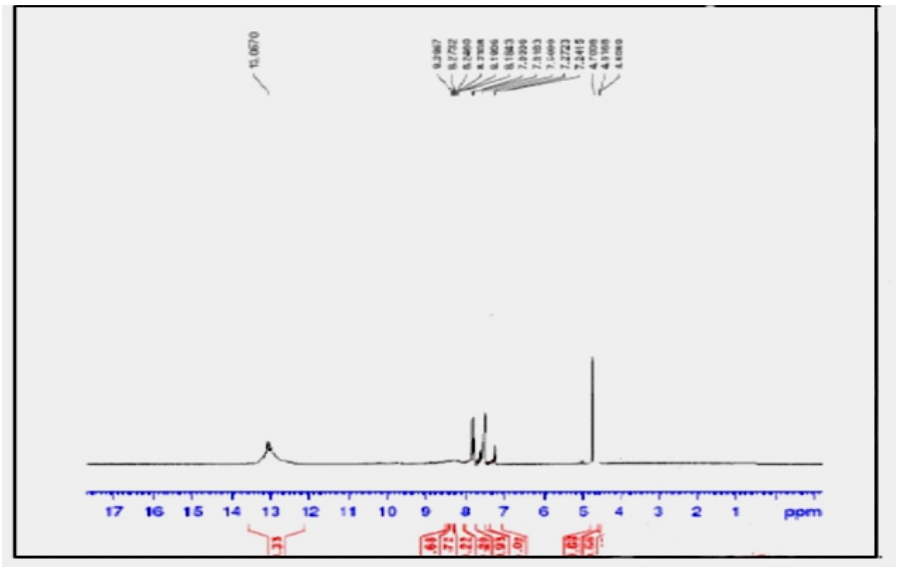

Figure 3: ^{1}HNMR of compound (1).

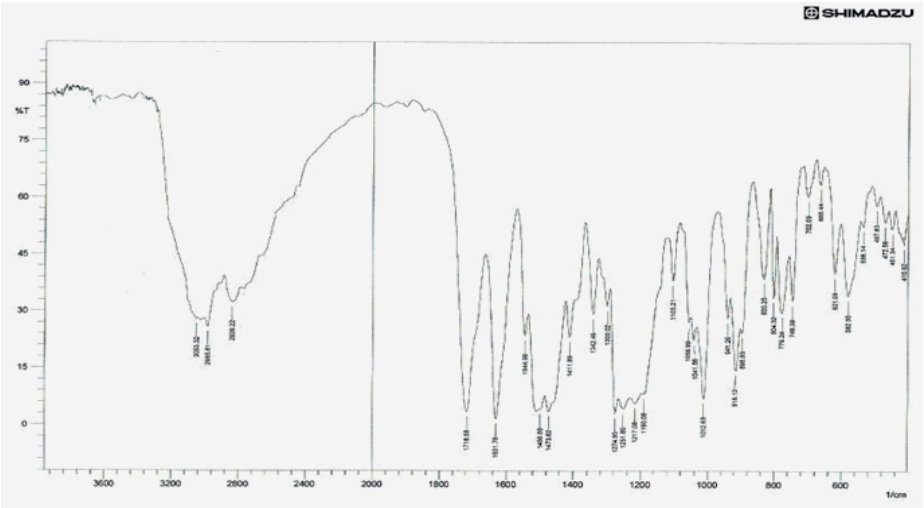

Figure 4: FTIR of compound (2).

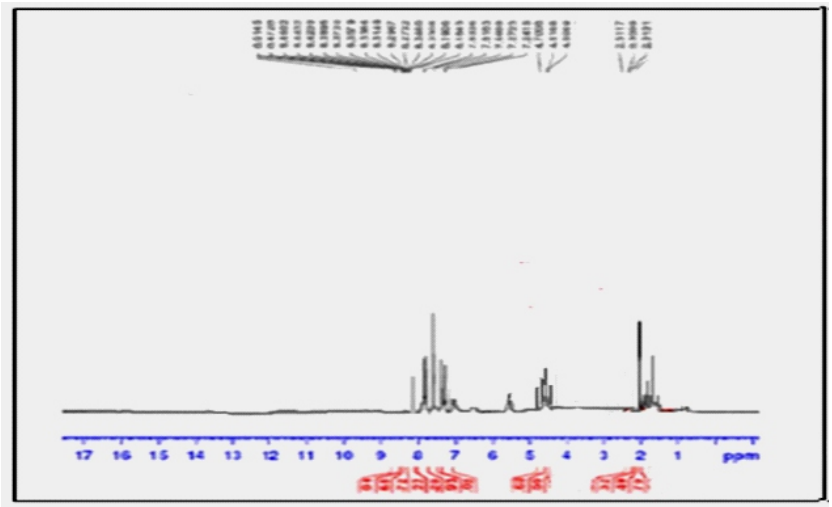

Figure 5: [1]HNMR of compound (2).

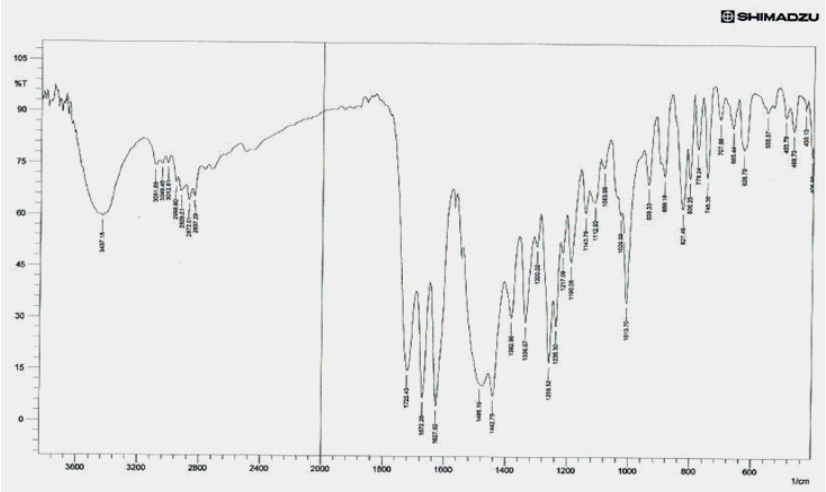

Figure 6: FTIR of compound (3).

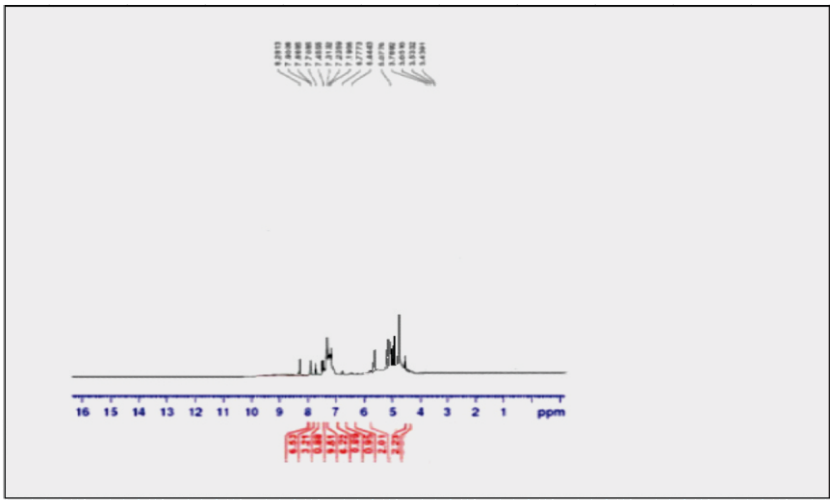

Figure 7: [1]HNMR of compound (3).

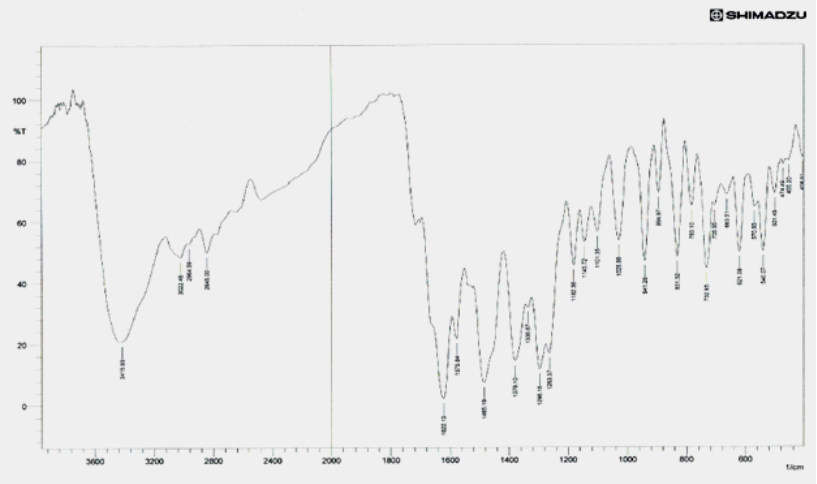

Figure 8: FTIR of compound (4).

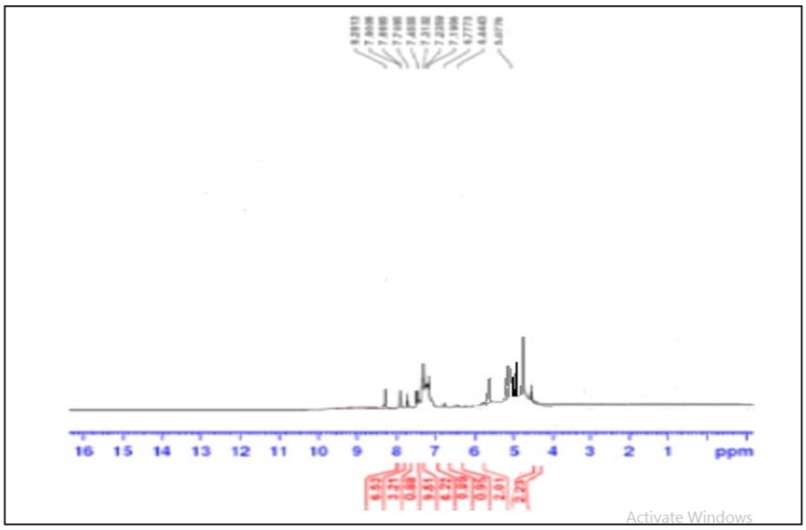

Figure 9: [1]HNMR of compound (4).

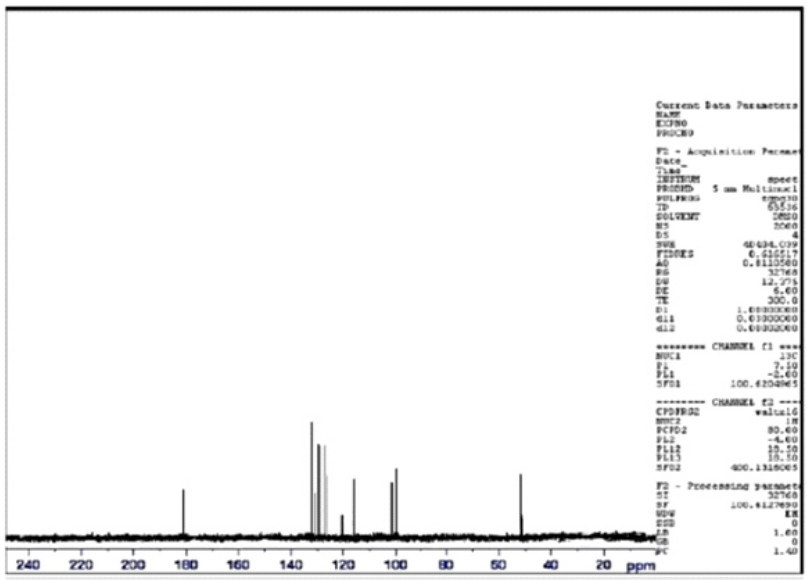

Figure 10: [13]CNMR of compound (4).

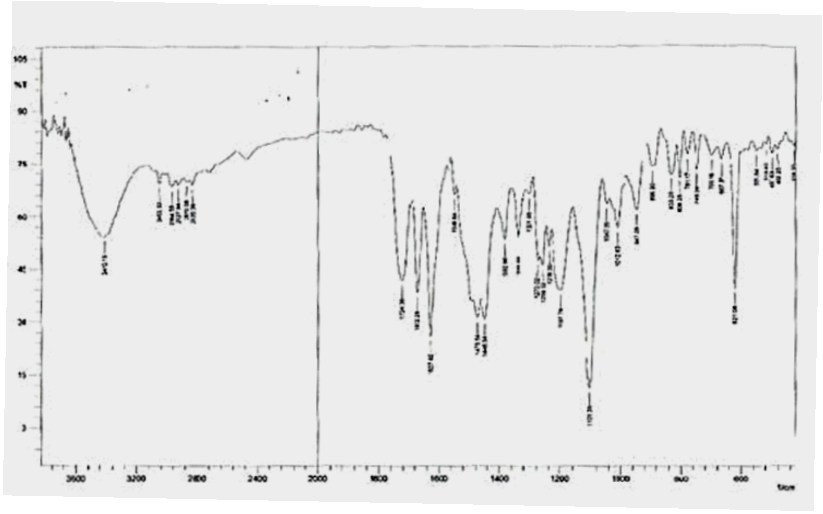

Figure 11: FT-IR of compound (5).

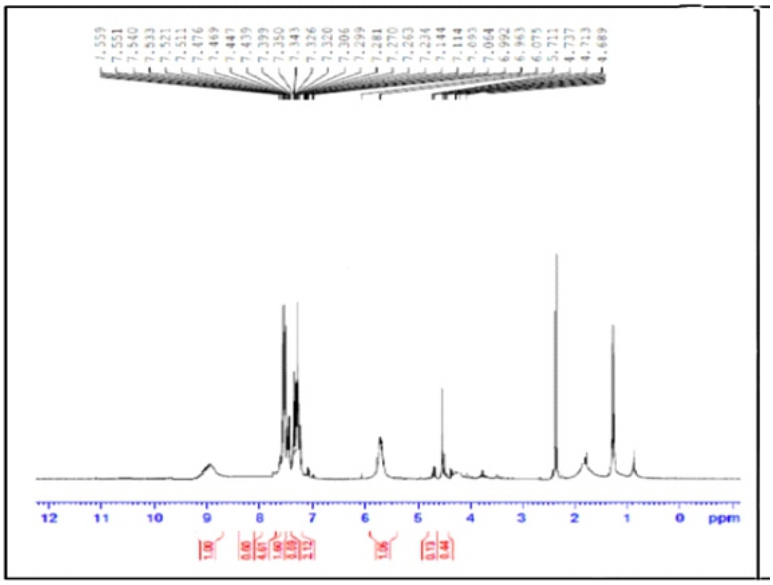

Figure 12: [1]HNMR of compound (5).

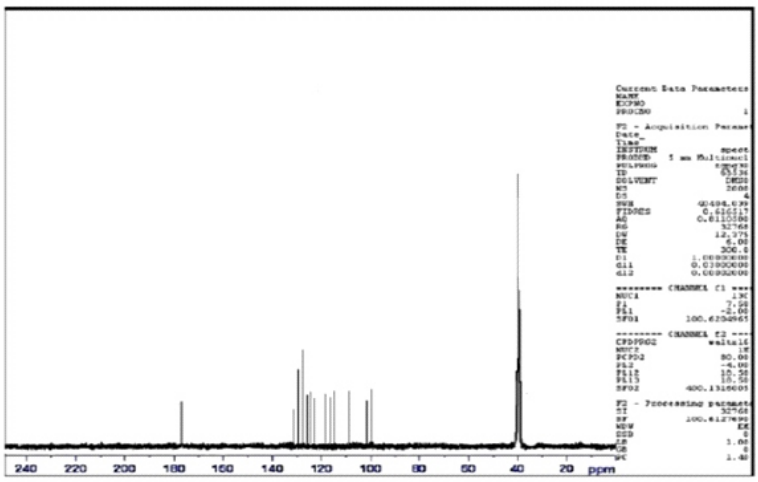

Figure 13: [13]CNMR of compound (5).

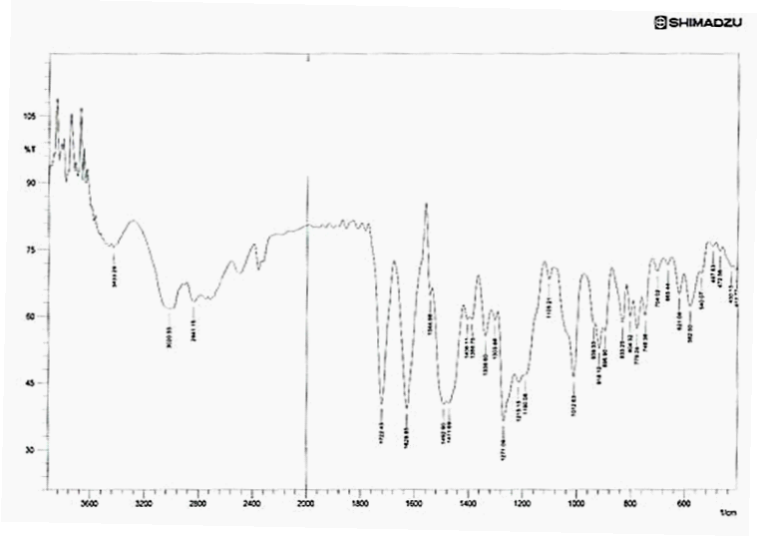

Figure 14: FTIR compound of (6).

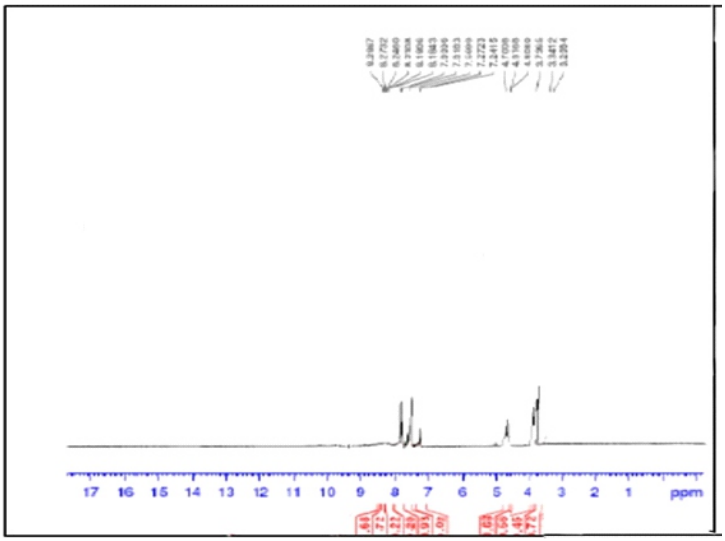

Figure 15: [1]HNMR of compound (6).

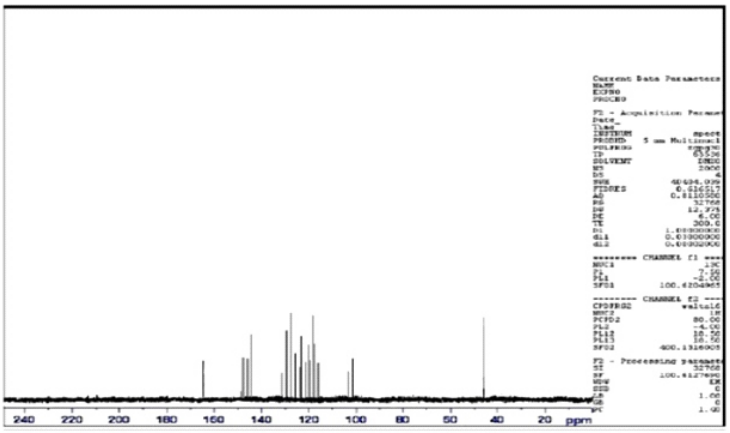

Figure 16: [13]CNMR of compound (6).

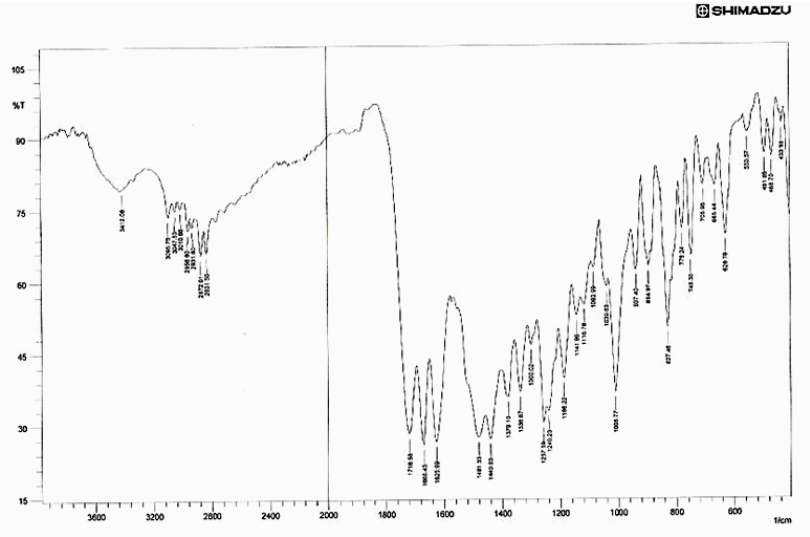

Figure 17: FT-IR of compound (7).

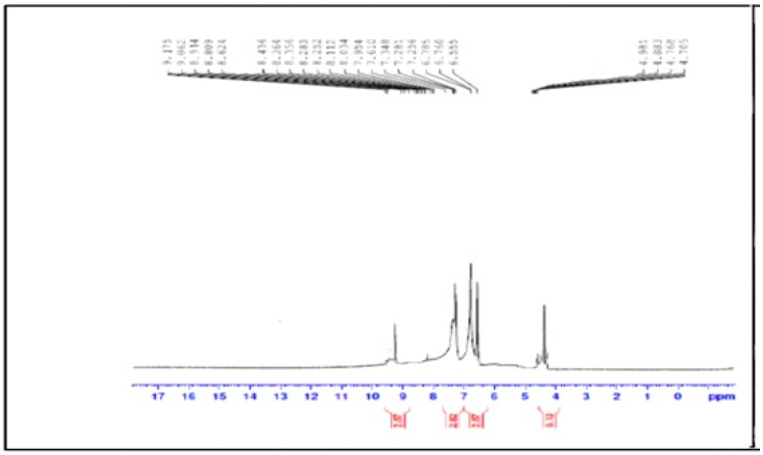

Figure 18: ^{1}HNMR of compound (7).

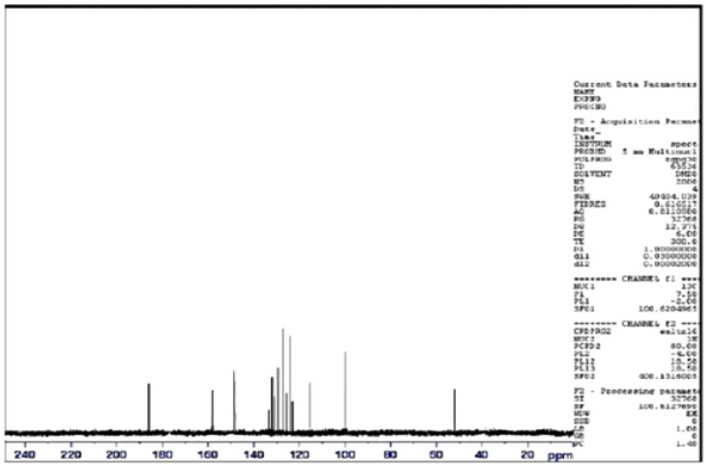

Figure 19: ^{13}CNMR of compound (7).

3. Biological Activity:

The findings demonstrated that the compounds activity against S. aureus bacteria was strong for prepared compounds 2, 3, 4, 5 and 7 but it was low for 1 and 6. The compounds 4, 5 and 7 exhibited strong anti-*E. Coli* activity, while compounds (1, 2, 3 and 6) showed poor activity.

Table 2: Biological action of derivatives (1-7).

Comp. No.	E-coli (G-)	Staph. Aureus (G+)
Ciprofloxacin Standard	16	13
1	9	11
2	12	13
3	14	16
4	18	13
5	16	15
6	14	12
7	17	14

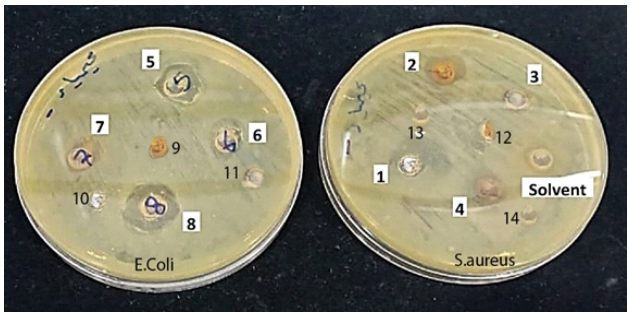

Figure 19: Biological effect of compounds (1-7).

4. Antioxidant Action:

The antioxidant effects of the prepared compounds (1-7) were assessed using an DPPH test . The best outcomes were determined to be the following compounds: 2 and 3 comparing with ascorbic acid control (IC50 µg\ml=31.95).Figure(20).

Table 3: Antioxidant action of derivatives (1-7).

conc. µg\ml	% Inhibition (DPPH-Scavenging)							
	1	2	3	4	5	6	7	STD (Ascorbic acid)
25	36.56	56.13	51.05	38.04	18.06	39.46	34.22	46.12
50	40.73	59.11	55.12	51.05	28.56	53.02	41.44	60.14
75	50.67	60.02	58.6	59.12	30.91	55.16	51.03	65.01
100	60.24	65.13	69.08	65.05	52.75	66.21	61.21	78.3
IC50 µg\ml	71.81	27.95	25.74	53.19	103.44	51.98	70.72	31.95

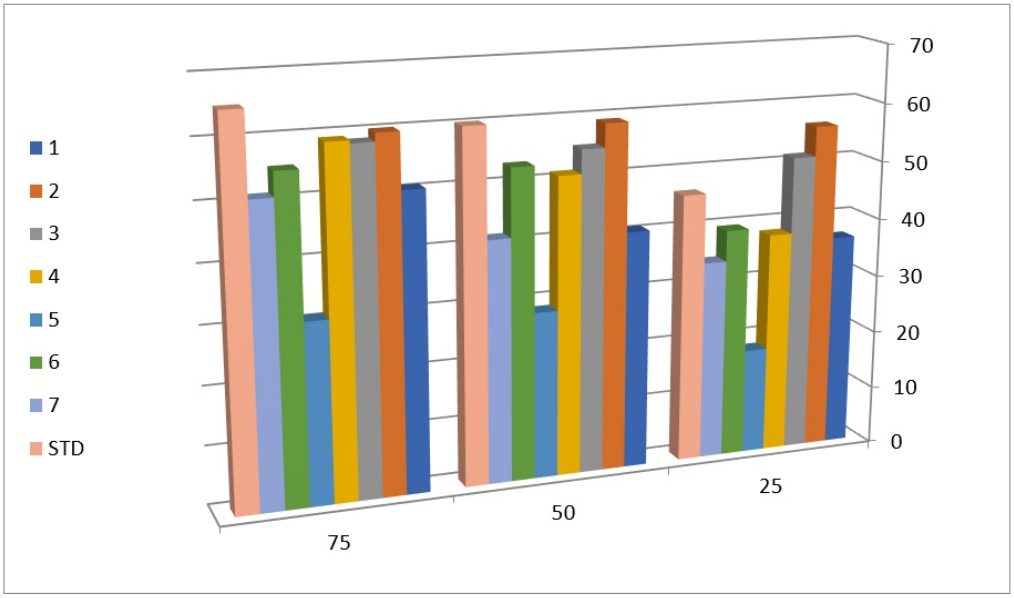

Figure 20: DPPH test of compounds (1-7).

5. Conclusions:

New derivatives were synthesized using the MWI approach with a high yield and reaction times shortened from hours to minutes and confirmed by FTIR and NMR. The study of biological and antioxidant activity of all compounds against two types of bacteria (gram-positive) and (*E. coli*) gram-negative showed good biological activity much higher than the of drug [23].

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