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Synthesis and biological activity of 2-(4,5-dihydro-1*H*-pyrazol-1-yl)-1,3-benzothiazole derivatives

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Abstract

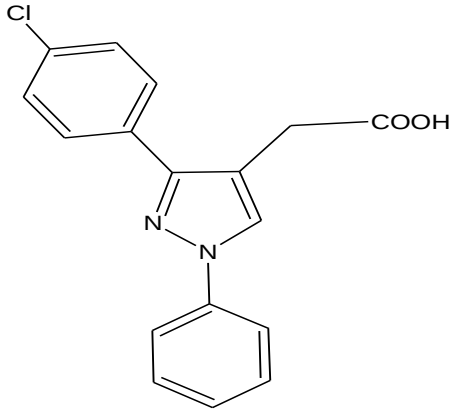
In this work include synthesis some of 2-(4,5-dihydro-1*H*-pyrazol-1-yl)-1,3-benzothiazole derivatives were synthesized from 2-hydrazino-1,3-benzothiazole with dicarbonyl compounds, compounds (**8** and **9**) synthesis with microwave assistance. The biological activity for some compounds (**2-5**) were studied against (gram +ve) bacteria, (gram –ve) bacteria; and antifungal activity against and the data obtained show that all compounds show activity against all bacteria and candida. The prepared compounds were characterized by FT-IR, ^{1}HNMR and also studied the physical properties.

Key words: Benzothiazole, Antibacterial activity, Antifungal activity, Pyrazole.

Introduction

Pyrazoles are five-membered heterocycles that constitute a class of compounds particularly useful in organic synthesis. They are one of the most studied groups of compounds among the azole family. Indeed, a huge variety of synthesis methods and synthetic analogues have been reported over the years. The presence of the pyrazole nucleus in different structures leads to diversified applications in different areas such as technology, medicine and agriculture[1]. Pyrazole has interesting biological activities such as tumour cell growth activation[2]. Anti leishmanial[3,4], anti-inflammatory agents analgesic activity, antimicrobial activity[5-7], anti-inflammatory activity[8,9], α glycosidase inhibitory[10],

anti bacterial activity[11,12], This heterocycle can be traced in a number of well-established drugs belonging to different categories with diverse therapeutic activities (I) [13].



anti inflammatory

(I)

Benzothiazole is a heterocyclic aromatic compound. The compound is bicyclic which consists of a fusion of benzene with thiazole ring. It is an important pharmacophore as benzothiazole and its novel analogs have been found to have a wide variety of therapeutic activities in medicinal chemistry such as in anticancer(14-17), anti-HIV(18), antioxidant(19), anticonvulsant(20), trypanocidal agent(21), antitumor(22- 24), antimicrobial (25) , COX inhibitor (26) , hypoglycemic(27), antidiabetic(28), antituberculosis (29) , anti-urease(30) and inhibitor of α-glucosidase(31). Various benzothiazole derivative such as 2-arylbenzothiazole is in the eyes of most scientists due to its diverse structure and its uses as radioactive amyloid imaging agents. It is reported that the isosters and derivatives of benzothiazole have antimicrobial activity against various types of gram positive and gram negative bacterias (e.g., *E. coli*، *Pseudomonas aeruginosa*, *Enterobacter Staphylococcus epidermis*, etc.). (32)

2. Experimental

2.1. Chemical materials

All reactants and solvents used in this study were reagents grade and they are available from Sigma- Aldrich and Fluka companies Melting points are determined in open capillary tubes in a Germany, Stuarts, SMP30 Melting points apparatus and are un corrected. Infrared spectra (FT-IR) were recorded using a SHIMADZU FT-IR8400S spectrophotometer at the Department of Chemistry/Collage of Science/ University of Mustansiriyah.

^{1}HNMR spectra were recorded on a Bruker, in Iran, Ultra Shield 400Mhz, spectrometer (Switzerland) using DMSO-d6 as a solvent with a tetramethylsilane (TMS) as an internal standard, all progress of the reactions and checking the purity were performed with thin layer chromatography (TLC) technique and revealed by mixture of n-hexane and ethyl acetate (3 : 2) as eluent in the staining jar and irradiation with UV. light chromatograms.

2.1.1. Synthesis of 2-hydrazino-1,3-benzothiazole (1)[33]

A mixture of 2-Mercaptobenzothiazole (0.01 mole, 1.67g) with (0.01mole, 0.5g) from hydrazine in 15 mL ethanol refluxed for 3 hrs . the mixture cooled to precipitate product and then filtered of and washed with cold water to remove hydrazine excess and give compound (1). The physical properties of compound [1] are listed in table (1).

2.1.2. Synthesis of 1-(1,3-benzothiazol-2-yl)pyrazolidine-3,5-dione (2)[34]

A Mixture of compound (1) (0.006mole, 1g) with diethyl malonate (0.006 mole, 0.76g), 2drops from acetic acid (0.015 mole) and absolute ethanol (30mL) were taken in a round bottom flask. The mixture.

refluxed for about 11-12 hr. The solvent was evaporated to precipitate product and then filtered and recrystallized from ethanol to give compound (2) The physical properties of compound [2] are listed in table (1).

2.1.3. Synthesis of 5-amino-2-(1,3-benzothiazol-2-yl)-2,4-dihydro-3*H*-pyrazol-3-one (3)[34]

Mixture from compound (1), (0.003mole, 0.5g) and ethyl 2-cyanoacetate (0.003mole, 0.4g) was taken 20.0 mL of ethanol and the mixture was refluxed for 10-11 hours. The reaction mixture was allowed to attain the room temperature. The mixture was then poured into the ice-cold water. The resulting solid product was filtered, dried, and recrystallized from methanol to give compound [3]. The physical properties of compound [3] are listed in table (1).

2.1.4. Synthesis of 1-acetyl-2-(1,3-benzothiazol-2-yl)pyrazolidine-3,5-dione (4)[34]

A mixture of compound (1) (0.01 moles) and diethyl malonate (0.01mole) were taken in a round bottom flask and dissolved in (30.00 mL) glacial acetic acid. Then the well-stirred mixture was refluxed for 24 hr. The solvent was evaporated to precipitate product and then filtered and recrystallized from Ethanol to give compound [4]. The physical properties of compound [4] are listed in table (1).

2.1.5. Synthesis of (4*Z*)-1-(1,3-benzothiazol-2-yl)-4-(4-hydroxy or nitro or chlorobenzylidene) pyrazolidine-3,5-dione (5, 6, 7)[35]

A mixture of compound (2) (0.001mol, 0.30g) , p-hydroxy benzaldehyde or p-nitrobenzaldehyde or p-chlorobenzaldehyde (0.001mol) , 3 drops of piperidine, and ethanol (20 mL). The reaction mixture was heated under reflux and continuously stirred for a period of

24h. The course of the reaction was monitored by TLC. The reaction mixture was poured into water and acidified with acetic acid. The resulting precipitate was filtered off and recrystallized from acetic acid to give compound [5-7]. The physical properties of compound [5-7] are listed in table (1).

2.1.6. Synthesis of 2-(1,3-benzothiazol-2-yl)-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one (8)[34]

A mixture of compound (2) (0.006mol, 1g) and ethyl acetoacetate (0.006mol, 0.78g) were mixed in a closed microwave tube and subjected to microwave irradiation on a CEM Discover™ SP microwave system in standard mode at(120°C for 30 min,600 watt). Upon completion of the reaction, the crude product may be purified by recrystallized from ethanol afford the pure product [8]. The physical properties of compound [8] are listed in table (1).

2.1.7. Synthesis of 2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-1,3-benzothiazole (9)[34]

A mixture from compound (2) (0.006mol, 1g) and Acetylacetone (0.006mol, 0.60g) were mixed in a closed microwave tube and subjected to microwave irradiation on a CEM Discover™ SP microwave system in standard mode at(120°C for 20 min,600 watt). Upon completion of the reaction, the crude product may be purified by recrystallized from Ethanol afford the pure product [9]. The physical properties of compound [9] are listed in table (1).

2.1.8. Synthesis of (4*Z*)-2-(1,3-benzothiazol-2-yl)-4-(4-chloro or nitrobenzylidene)-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one (10, 11)[35]

A mixture of compound (8) (0.004mol, 1g) , p-nitrobenzaldehyde or p-chlorobenzaldehyde (0.004mol) , 3drops of piperidine, and ethanol (25

mL). The reaction mixture was heated under reflux and continuously stirred for a period of 24h. The course of the reaction was monitored by TLC. The reaction mixture was poured into water and acidified with acetic acid. The resulting precipitate was filtered off and recrystallized from acetic acid to give compound [10 or 11]. The physical properties of compound [10 and 11] are listed in table (1).

2.2 . Biological activity

Applying the agar plate diffusion technique[36], some of the synthesized compounds were screened in vitro for antibacterial activity against (gram +ve) bacteria (*Staphylococcus aureus and Staphylococcus epidermidis*), and (gram –ve) bacteria (*Escherichia coli* and *Klebsiella pneumniae*); and antifungal activity against (*Candida albicans*). Prepared agar and petri-dishes were sterilized by autoclaving for (15 min) at 121°C. The ager plates were surface inoculated uniformly from the broth culture of the tested microorganisms. In the solidified medium suitably spaced apart holes were made all (6 mm) in diameter, were filled with (100 µl) of the prepared compounds. The synthesized compounds [2-5were dissolved in DMSO in concentration (10^{-3} mol.L^{-1}). These plates were incubated at (37°C) for (24hrs.). The inhibition zones caused by the various compounds on the bacteria were examined as in the table (2).

Table (1) : The physical properties of compounds (1-11)

Comp. symbol	M.F	M.W *gm/mole*	Rec. solvent	R_f	Yield (%*t*)	Color	m.p/°C
1	$C_7H_7N_3S$	165	ethanol	0.30	92	pale yellow	199-201

2	$C_{10}H_7N_3O_2S$	233	ethanol	0.34	85	yellow	168-170
3	$C_{10}H_8ON_4S$	232	ethanol	0.41	80	light yellow	187-189
4	$C_{12}H_9O_3N_3S$	275	glacial acetic acid	0.89	57	dark brown	232-234
5	$C_{17}H_{11}O_3N_3S$	337	ethanol	0.42	70	light brown	207-209
6	$C_{17}H_{10}O_4N_4S$	366	ethanol	0.53	84	Light brown	226-228
7	$C_{17}H_{10}O_2ClN_3S$	355	ethanol	0.40	87	Light orange	192-194
8	$C_{11}H_9ON_3S$	231	Diethyl-malonate	0.36	88	orange	159-161
9	$C_{12}H_{11}N_3S$	299	Acetyl acetone	0.23	97	golden yellow	144-146
10	$C_{18}H_{12}OClN_3S$	353	ethanol	0.31	83	reddish brown	179-181
11	$C_{18}H_{12}O_3N_4S$	364	ethanol	0.38	78	brown	209-211

3. Results and Discussion

The compound 2-hydrazino-1,3-benzothiazole (1) was selected as key to prepare all derivatives in this work. The compounds (2,4,8,9) include synthesis pyrazole ring from cyclization of hydrazine compound (1) with diketone, while compound (3) from compound (1) and ethylcyano acetate. The compounds (8 and 9) were synthesis by microwave assistance. The FT-IR of compound (3) shows stretching bands symmetrical and asymmetrical at 3319, 3200 cm^{-1} for (NH_2) group, 3126 cm^{-1} for (CH arom.), 2983-2868 cm^{-1} for (CH aliph.), 1743 cm^{-1} for (C=O), 1651 cm^{-1} for (C=N) and 1597 cm^{-1} for (C=C). The ^{1}HNMR of

compound (3), figure (3) show signals at δ=3.30 ppm (s, 2H, CH_2 overlapping with protons of DMSO-d_6 solvent), δ=5.01 ppm (s, 2H, NH_2), and δ=6.88-9.00 ppm (m, 4H, Ar-H). The FT-IR of compound (4) shows stretching bands at 3109 cm^{-1} for (CH arom.), 2983-2897 cm^{-1} for (CH aliph.), 1747 cm^{-1} for (C=O outer), 1734 cm^{-1} for (C=O inner), 1641 cm^{-1} for (C=N) and 1593 cm^{-1} for (C=C). The ^{1}HNMR of compound (4) show signals at δ=1.98 ppm (s, 3H, CH_3), δ=2.80 ppm (s, 2H, CH_2), δ=7.02-7.91 ppm (m, 4H, Ar-H) and other signals are impurities. The FT-IR of compound (2), figure (1), shows stretching bands at 3188 cm^{-1} for (NH endo cyclic.) 3036 cm^{-1} for (CH arom.), 2935-2978 cm^{-1} for (CH aliph.), 1737 and 1732 cm^{-1} for (two C=O), , 1614 cm^{-1} for (C=N) and 1583 cm^{-1} for (C=C). The ^{1}HNMR of compound (2) show signals at δ=4.14 ppm (s, 2H, CH_2), δ=6.93-8.08 ppm (m, 4H, Ar-H), and δ=10.52 ppm (s, 1H, NH). The compounds (5-7) was synthesized by reaction compound (2) with aldehyde substituted (p-hydroxy , p-nitro and p-chloro benzaldehyde) respectively in presence of pipredine as base. The FT-IR of compounds (5-7) shows disappearance of (CH aliph.), and other bands shows in table (2).

Table (2) : The Stretching bands (cm^{-1}) of compounds (5-7)

Comp.	Stretching bands (cm^{-1})							
	OH	NH	C-H arom.	C=O	C=N	C=C	NO_2	Cl
5	3353	3180	3056	1735,1730	1614	1600	-	-
6	-	3120	3061	1658,1653	weak	1597	Sym. 1340, asym. 1505	-
7	-	3200	3066	1743,1701	1627	1599	-	1091

The ^{1}HNMR of compound (5) show signals at δ=7.14-7.89 ppm (m, 9H, Ar-H and C=CH) and δ=9.68 ppm (s, 2H, NH overlapping with OH).

The FT-IR of compound (8), figure (2), shows stretching bands at 3072 cm^{-1} for (CH arom.), 2949-2854 cm^{-1} for (CH aliph.), 1735 cm^{-1} for (C=O), 1662 cm^{-1} for (C=N) and 1612 cm^{-1} for (C=C).

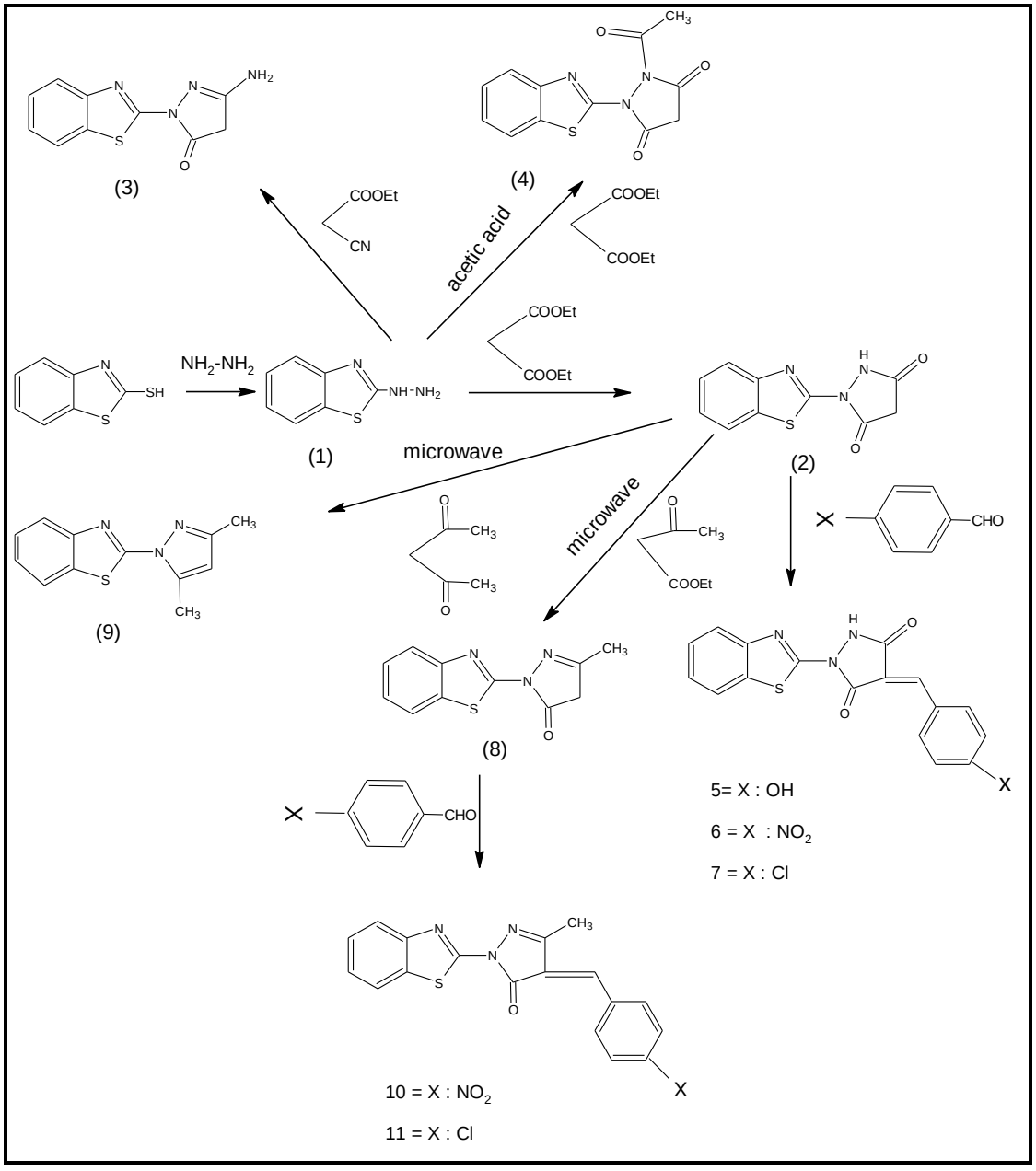
The compounds (10,11) was synthesized by reaction compound (8) with aldehyde substituted (p-nitro and p-chloro benzaldehyde) respectively in presence of pipredine as base. The FT-IR of compounds (10 and 11) shows stretching bands as in table (3).

Table (3) : The Stretching bands (cm^{-1}) of compounds (10 and 11)

Comp.	Stretching bands (cm^{-1})						
	C-H arom.	C-H aliph.	C=O	C=N	C=C	NO_2	Cl
10	3107	2850	1703	1633	1604	Sym. 1344, asym. 1535	-
11	3061	2825-2929	1699	1649	1612	-	1091

The FT-IR of compound (9) shows stretching bands at 3147 cm^{-1} for (CH arom.), 2974-2856 cm^{-1} for (CH aliph.), and 1599 cm^{-1} for (C=C).

The ^{1}HNMR of compound (9), figure (4), show signals at δ=2.22 ppm (s, 3H, CH_3) δ=2.71 ppm (s, 3H, CH_3 - b), δ=6.25 ppm (s, 1H, CH of pyrazole ring) and δ=7.36-8.03 ppm (m, 4H, Ar-H).



Scheme (1): Synthesis of compounds (1-11)

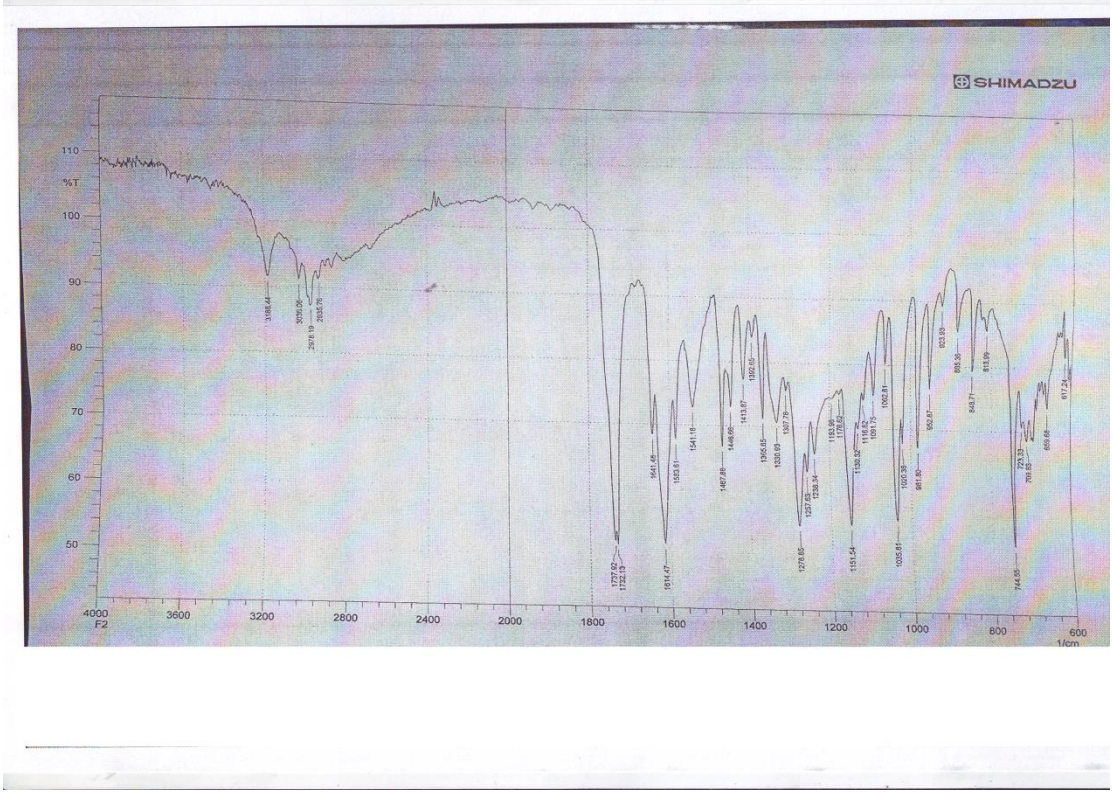


Figure (1): FT-IR spectrum of compound (2)

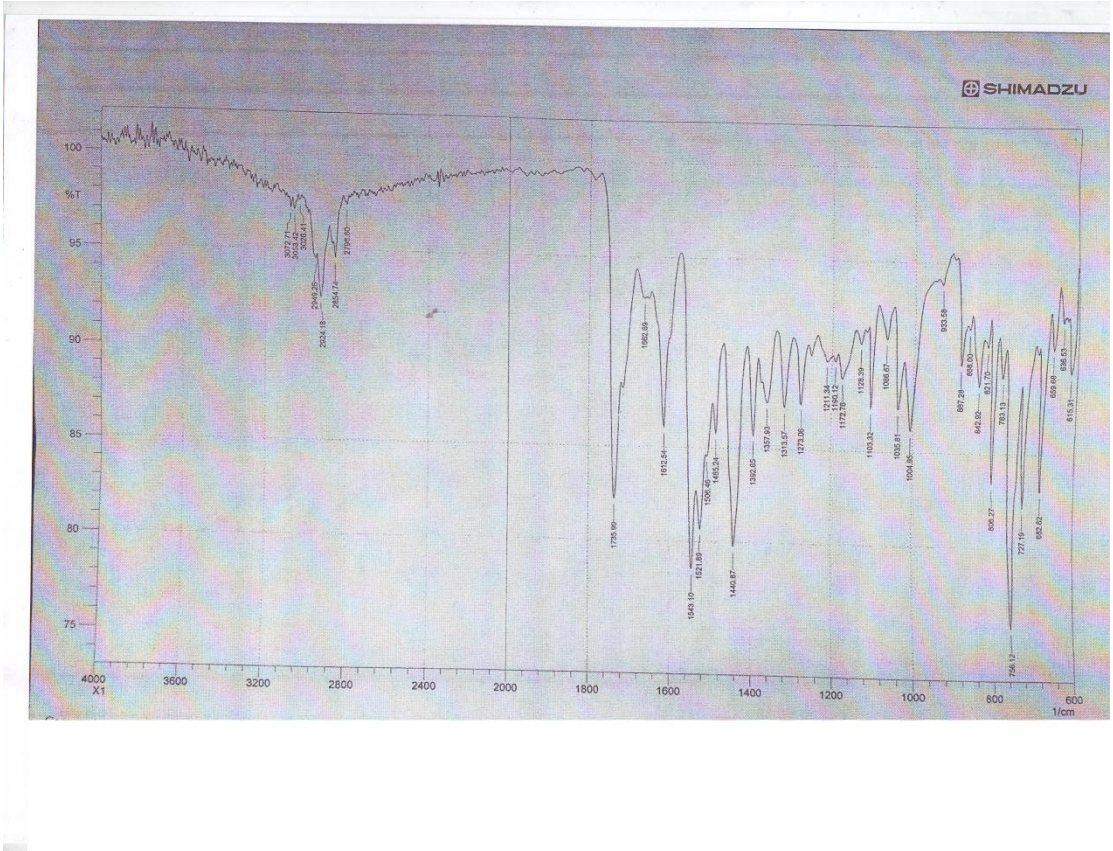


Figure (2): FT-IR spectrum of compound (8)

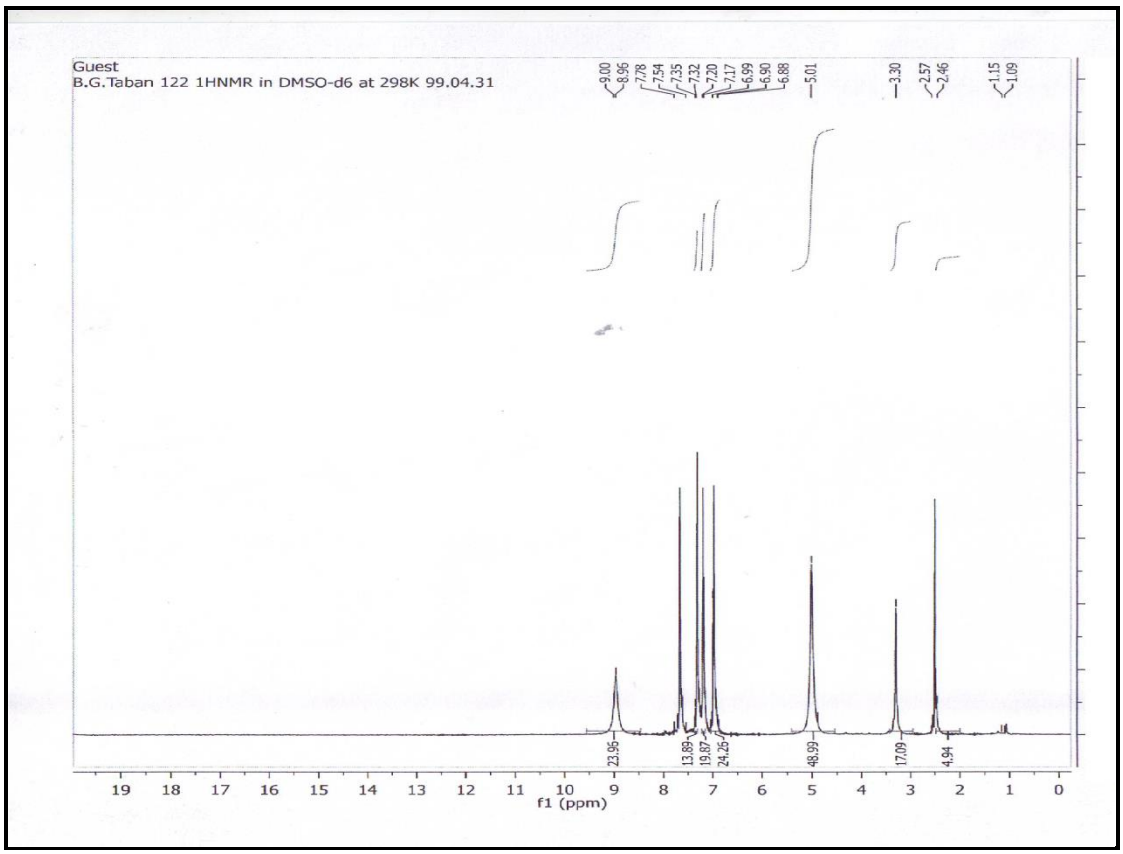


Figure (3): ^{1}HNMR spectrum of compound (3)

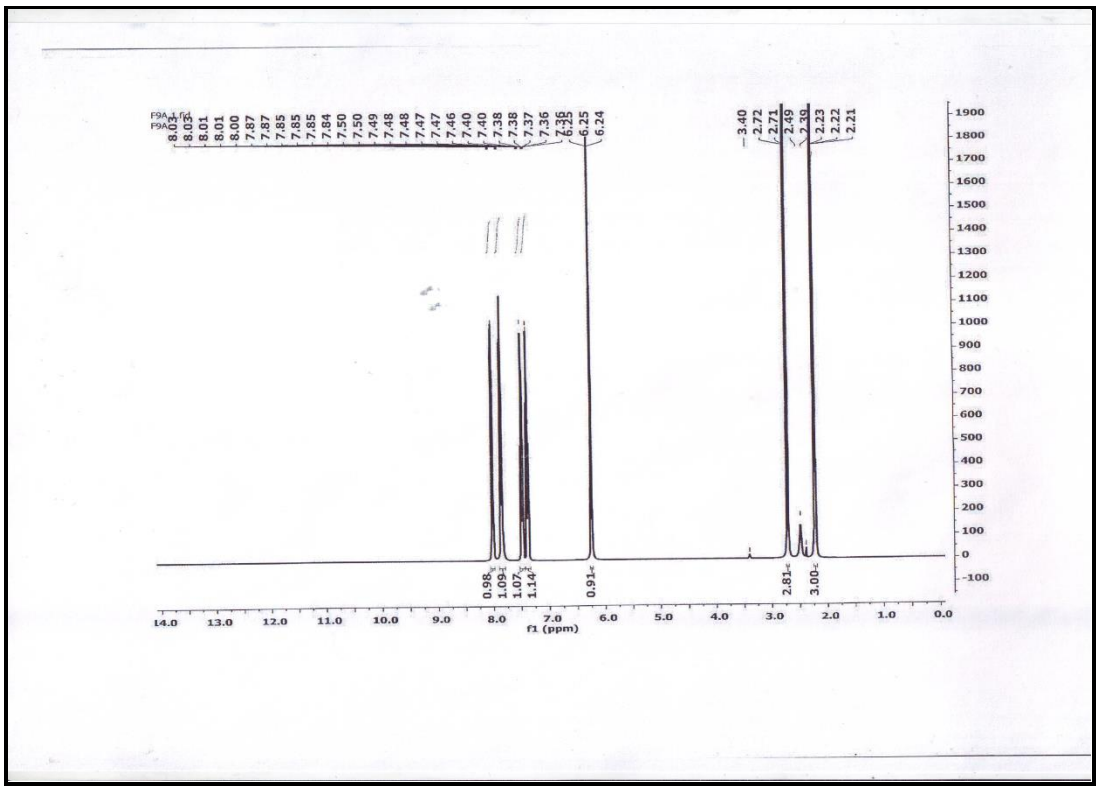


Figure (4): ^{1}HNMR spectrum of compound (9)

3.1. Biological activity

With the development of new strains of bacteria resistant to many currently available antibiotic treatments, there is increasing interest in the discovery of new antibacterial agents. Antimicrobial resistance refers to microorganism that develop the ability to inactivate, exclude or block the inhibition or lethal mechanism of the antimicrobial agents .

The results of the preliminary screening test are listed in table (4), from the data obtained in table (4) and it's found that compound [**8**] have highest activity against *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli*, and *Candida albicans*, while the other compounds show activity for some bacteria and candida. These activity due to heterocyclic and hetero atoms.

Table (4) : Antibacterial activities of some of synthesized compounds

Comp. symbol	Grame positive		Grame negative		Fungi
	S. aureus	***S. epidermidis***	***E. coli***	***Klebsiella pneumniae***	***Candida albicans***
2	-	17	-	11	20
3	-	16	11	11	16
4	-	19	-	10	20
5	-	16	16	12	23
6	19	15	10	10	-
7	17	14	12	16	18
8	19	19	13	7	20
9	20	-	-	14	12
10	12	10	16	6	7
11	14	17	12	11	6

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