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Research Article

SYNTHESIS, CHARACTERIZATION, AND BIOLOGICAL ACTIVITIES OF SOME NEW FIVE AND SIX MEMBERED HETEROCYCLIC RINGS DERIVED FROM CHALCONES BY FUSION METHOD

Muath Jabbar Tarfa Al-Abbasee[1]., Baraa Mohammed Ibrahim Al-Hilali[2] and Ahmed Khaled Hussein[1]

[1]Dept. of Chemistry, College of Education, University of Samarra, Samarra, Iraq
[2]Dept. of Biology, College of Education, University of Samarra, Samarra, Iraq

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ABSTRACT

Some novel heterocyclic derivatives such as dihydropyrimidine, dihydropyrimidine –thione, Isoxazoline, Pyrazoline, (II,III,IV,V) were synthesized from chalcone. Chalcone (I) were prepared by direct fusion method Claisen-schmidt condensation of suitable brominated acetophenones with suitable brominated benzaldehyde in the presence of sodium hydroxide up to fusion point. The newly synthesized compounds were characterized viaTLC, melting points, FT-IR, H^1-NMR, C^{13}-NMR spectral data. All the compounds were tested for their antibacterial and antifungal activities by the cylinder-plate method.

INTRODUCTION

Heterocyclic synthesis has been emerging as effective technique for discovering scaffold to design and build for useful versatilemoieties. Heterocyclic systems supply moieties can arrange pharmacophoreon which to yield powerful and selected drugs [1].The essential structure of chalcones consist of two aromatic rings joined by an α,β-unsaturated group of carbonyl [**2,3**].

The reactive group of α, β-unsaturated keto functional in chaconne was accountable for their wide spectrum activity, which may altered depending on position and type of substituent on aromatic rings [4].

Chalcones represent an essential moiety of natural as well as synthetic products and some of them have wide ranges of pharmacological activity such as anti-inflammatory, anti-fungal, antibacterial and anti-oxidant agents [5]. anticonvulsant[6], antibacterial[7] hypoglycemic[8], anti-inflammatory [9] antimalarial activity [10].

The Chalcone derivatives are important intermediate and also act as precursor for the synthesis of novel cyanopyridines[11], pyrazolines[12], isoxazolines[13], pyrimidines[14], Pyrazole[15], and sulfur containing heterocycles, thiazolidines and thiazine [16] that have been reported to possess different pharmacological activities[17-20]. In the view of the varied biological, pharmacological, we have planned to synthesis some isoxazoline derivatives containing, pyrazoline unit.

METHODOLOGY

The used of chemicals were synthesis of analytical reagents grade. Melting points was uncorrected and were taken throughout open capillaries. TLC used to check purity of compounds.(Shimadzu Infrared Spectrophotometer Fourier Transform FTIR-8400S) using KBr pallets were used to record IR Spectra . The recorded NMR peaks were on NMR bruker 500 MHz; which recorded on δ scale (ppm) against TMS. The utilized solvent was DMSO (3.33-3.35).

Corresponding author:* **Muath Jabbar Tarfa Al-Abbasee
Dept. of Chemistry, College of Education, University of Samarra, Samarra, Iraq

Synthesis of 1,3-bis(4-bromophenyl)propenal (I)

4-Bromobenzaldehyde(0.02 mole,3.7 gm) and 4-bromoacetophenone(0.02 mole,3.98 gm) in the presence of (0.02 mole,0.8 gm)sodium hydroxide were ground together and heated gently up to fusion into oil bath for 1 hrs. The resulting mixture was acidified by 5% hydrochloric acid and small amount of ice was added. The obtained solid product was filtered off, dried and recrystallized from ethanol to get yellow precipitate. The physical properties and yield are listed in Table 1. The TLC was used for monitoring reaction progress (ethyl acetate 3: 1 n-hexane).

Synthesis of4,6-bis(4-bromophenyl)-5,6-dihydropyrimidin-2(1H)-one and 4,6-bis(4-bromophenyl)-5,6-dihydropyrimidine-2(1H)-thione (II,III)

An equimolar of (0.002 mole,0.732 gm) of chalcone (I) with urea (0.002 mole,0.12 gm) and thiourea (0.002 mole,0.152 gm) respectively in the presence of (0.002 mole,0.08 gm) sodium hydroxide were ground together and heated gently up to fusion in an oil bath for 2hr. The resulting mixture was acidified by 5% hydrochloric acid. The solid product was filtered off, dried and then recrystallized from ethanol to get the products. The physical properties and yield are listed in Table 1. The TLC was used for monitoring reaction progress (ethyl acetate 3: 1 n-hexane).

Synthesis of 3,5-bis(4-bromophenyl)-4,5-dihydroisoxazole (IV)

An equimolar of (0.002 mole,0.732 gm)of chalcone (I) with of hydroxylamine hydrochloride(0.002 mole,0.139 gm) in the presence of (0.002 mole,0.08 gm)sodium hydroxide were ground together and heated gently up to fusion in an oil bath for 2hr . The gained solid product was filtered off, washed, dried and recrystallized from ethanol to get yellow-orange crystals. The physical properties and yield are listed in Table 1. The TLC was used for monitoring reaction progress (ethyl acetate 3: 1 n-hexane).

Synthesis of 3,5-bis(4-bromophenyl)-4,5-dihydro-1H-pyrazole (V)

An equimolar of (0.002 mole,0.732 gm) of chalcone (I) and hydrazine hydrate (0.002 mole ,0.5mL) in absolute ethanol(10 mL) the reaction mixture was stirred for 30 minute and then refluxed for 1hr at room temperature. The obtained solid product was filtered off, washed, dried and recrystallized from ethanol to get orange-brown crystals. The physical properties and yield are listed in Table 1. The TLC was used for monitoring reaction progress (ethyl acetate 3: 1 n-hexane)[21].

Table No. 1 Physical properties of synthesized compounds I-V

Compound No.	Molecular formula	Molecular weight	Yield	Melting points	Color
I	$C_{15}H_{10}Br_2O$	366	85	182-184	Yellow
II	$C_{16}H_{12}Br_2N_2O$	408	68	203-205	Bright yellow
III	$C_{16}H_{12}Br_2N_2S$	424	77	171-173	Orange-red
IV	$C_{15}H_{11}Br_2NO$	381	65	165-167	Yellow-orange
V	$C_{15}H_{12}Br_2N_2$	380	74	109-111	Orange-brown

Biological activity

Examination the antibacterial and antifungal activity of synthesized compounds were conducted in plates method.

Standard solutions*:* Preparing a stock solution by dissolve a suitable quantity of the USP Standard Reference of a given antibiotic, where appropriate in the specified solvent as in Table 2; and diluted to the required concentrations. Stored at 2^o-8^o, and use within the period indicated. Stock solution increase stepwise in concentrations, usually in the ratio of 1:1.25.

Table No. 2

Antibiotic	Stock Solutions				
	Initial solvent	Initial concentration	Further Diluent	Final concentration	Use Within
Neomycin	B.3	–	–	1 mg/mL	14 days

Media and solutions

The media were prepared depending on the listed tables below

Media1

Peptone	6.0 g
Pancreatic digest of casein	4.0 g
Yeast extract	3.0 g
Beef extract	1.5 g
Dextrose	1.0 g
Ager	15.0 g
Water	1000 mL
PH after sterilization	6.6 ± 0.1

Media19

Peptone	9.4 g
Yeast extract	4.7 g
Beef extract	2.4 g
sodium hydroxide	10.0 g
Dextrose	10.0 g
Ager	23.5 g
Water	1000 mL
PH after sterilization	6.1 ± 0.1

Solutions

Buffers were prepared as directed in Table **(**12**)**

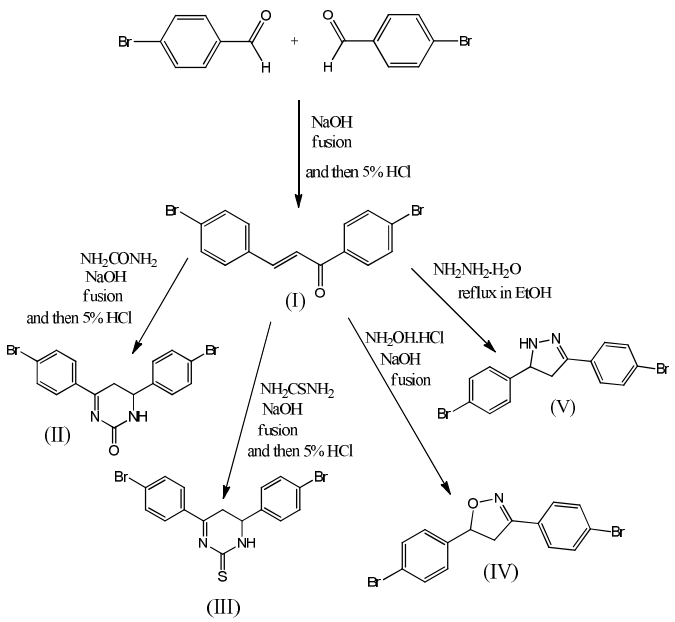
Table No 2 Buffers

Buffer	Concentration of Dibasic potassium phosphate (g/L)	Concentration of Monobasic potassium phosphate (g/L)	Volume of 10 N potassium hydroxide (mL)	PH after sterilization
Buffer B.3(0.1 M , pH 8.0)	16.73	0.523	–	8.0 ± 0.1
Buffer B.6(10% , pH 6.0)	20	80	–	6.0 ± 0.05

[a] Adjust the pH with 18 N phosphoric acid or 10 N potassium hydroxide

RESULTS AND DISCUSSION

The synthesis of chalcones (I), dihydropyrimidine(II), dihydropyrimidine –thione(III), dihydroisoxazole(IV), dihydropyrazole(V),derivatives were performed as shown in scheme (1). The starting chalcones, namely1,3-bis(4-bromophenyl) propenal were synthesized by direct fusion technique via the Claisen- Schmidt reaction of 4-bromoacetophenone and 4-bromobenzaldehyde with soudium hydroxide. The structural assignments of all above mentioning derivatives based on TLC, melting points, FTIR,^{1}H-NMR,^{13}C-NMR spectroscopy.



Scheme 1 state synthesized compounds

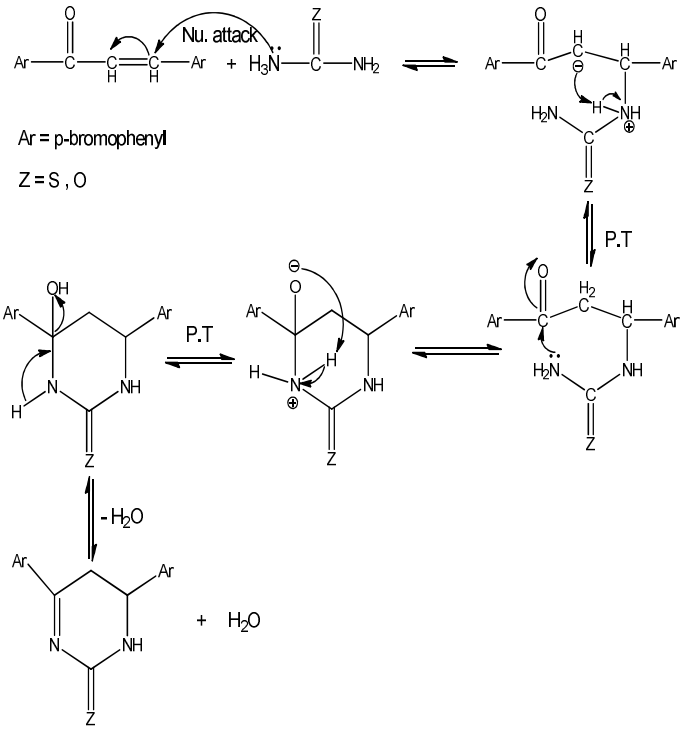
FT-IR Spectra

Chalcone (I) is the starting material of this research were synthesized by Claisen –Schemidt condensation which are characterized by TLC, melting points, FT-IR stretching bands indicated the appearance of the olefinic (-C-H) at 3053cm^{-1} and also aromatic (-C-H) at 3168 cm^{-1} and conjugation (-C=O) at 1652 cm^{-1} and olefinic (-C=C) at 1600 cm^{-1} and the aromatic (-C=C) at 1573-1558 cm^{-1}fig. (1). The FT-IR spectra of compounds six-membered heterocycles (II and III) respectively shown appear of (NH) stretching absorption band at 3380cm^{-1} and 3340 cm^{-1} and absorption band for aromatic (-C-H) near 3030 cm^{-1} for both two compounds and absorption band for (-C=O) at 1650 cm^{-1} and for (-C=S) at 1270 cm^{-1} and stretching bands of aromatic (-C=C) at 1520-1460 cm^{-1} and 1580-1480 cm^{-1} and for (-C=N) at 1590 cm^{-1} and 1600 cm^{-1} and finally bands of (-C-Br) at 520 cm^{-1} and 550 cm^{-1} fig(4,6)**.** The FT-IR spectra of compound five-membered heterocyclic (V) shown stretching bands indicated the appearance of (NH) absorption band at 3340cm^{-1} and for aromatic (-C-H) near 3030 cm^{-1} and for (-C=N) at 1589 cm^{-1} and the aromatic (-C=C) at 1487-1450 cm^{-1} and finally bands of (-C-Br) at 590 cm^{-1}(fig.9) [22].

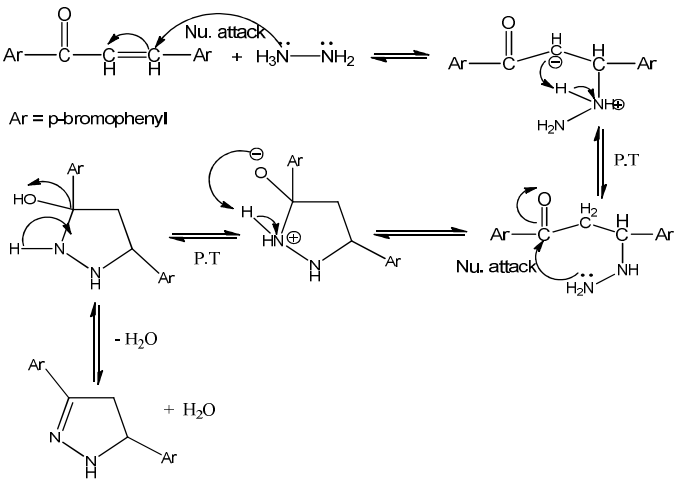
^{1}HNMR and ^{13}C-NMR spectra

The ^{1}HNMR spectrum of compound (I), (in DMSO as a solvent) showed the following characteristic chemical shifts: a sharp singletsignal at δ (7.56-7.87) ppm refers to two olefinic protons, the other multi signals between δ (7.00-8.01) ppm refers to aromatic protons (fig.2). The ^{13}C-NMR spectrum of compound (I) showed the most important signal of conjugated C=O (1) group at~ δ189.06 ppm, C (2)at δ142.55 ppm,C (3)at δ122.84 ppm, aromatic C-Br (4) at δ 128.5 ppm, aromatic C-Br (5) at δ 123.92 ppm, the remaining signals attributed to other aromatic carbons (fig.3). The ^{1}HNMR spectrum of compound (II), showed the following Signal: a sharp singlet signal at δ 9.12 ppm refers to NH proton (1), and signal triplet at δ 5.13ppmrefers to CH proton (2), Signal at δ 3.3 ppm refers to CH_2protons (3), the signals near δ 7.5 ppm refers to other aromatic protons (fig.5). The ^{13}C-NMR spectrum of compound (III) showed the most important signal of thiocarbonyl group C=S (1) at δ175.72 ppm, azomethine group C=N (4) at δ143.66 ppm, C (5) and C (6) respectively at δ134.21 ppm and δ 132.89 ppm, C (7) and C (8) respectively at δ132.05 ppm and δ 131.71 ppm, C (9) and C (10) respectively at δ129.06 ppm and δ 128.60 ppm, C (11) and C (12) respectively at δ122.54 ppm and δ 121.81 ppm, C (2) near δ 68 ppm, C (3) near δ 55 ppm fig (7). The ^{13}C-NMR spectrum of compound (IV) showed the following signals : C (1) at δ161.36 ppm, C (2)at δ150.28 ppm, C (3) at δ149.62 ppm, C (4) at δ 149.33 ppm, C (5) at δ125.41 ppm, C (6)at δ123.30 ppm, C (7)at δ122.48 ppm, C (8)at δ121.50 ppm, C (9)at δ115.50 ppm, C (10) near δ 89 ppm, , C (11) near δ 65 ppm (fig 8).The ^{1}HNMR spectrum of compound (V), showed a sharp singletsignal at δ 7.72 ppm refers to NH proton (1), multisignals between δ 7.5-8.13 ppm refers to aromatic protons, triplet signal at δ 4 ppm refers to CH proton (2), a doublet signalatδ3.7 ppm refers toCH_2 (3) fig(10) [22].

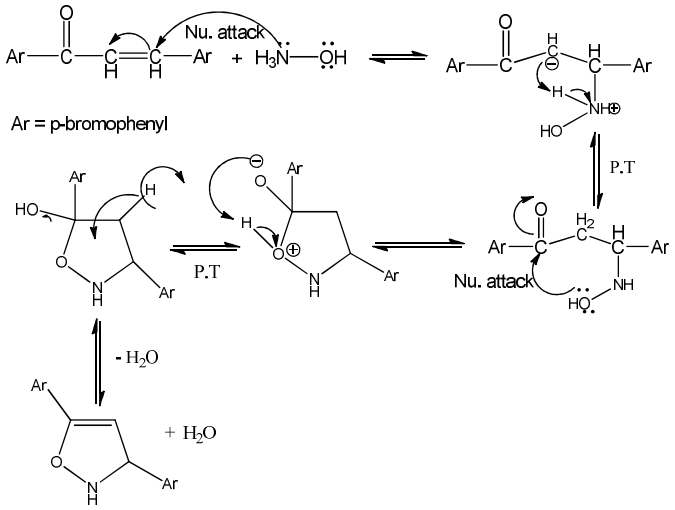
The suggested mechanism:- six-membered heterocyclic rings



Mechanism of five-membered rings synthesis (Michael route):



Mechanism of five-membered isoxazole ring synthesis (Michael route):



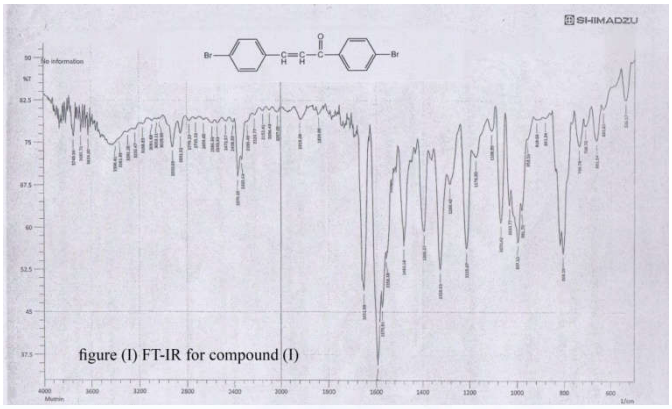


figure (I) FT-IR for compound (I)

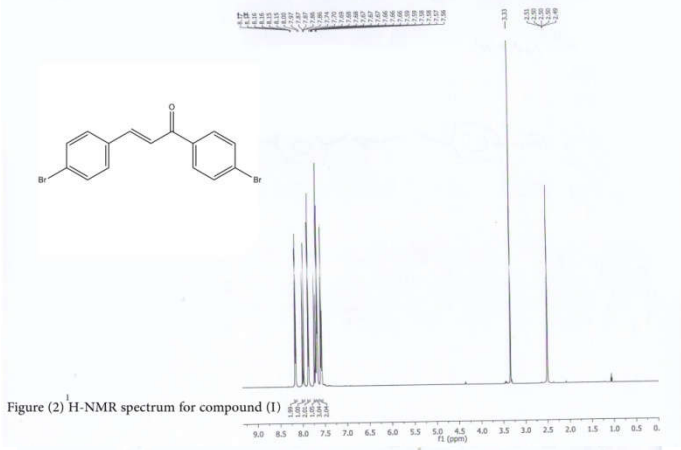


Figure (2) ^{1}H-NMR spectrum for compound (I)

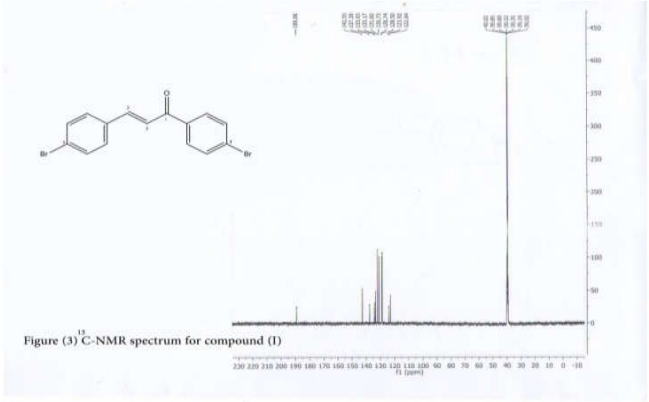


Figure (3) ^{13}C-NMR spectrum for compound (I)

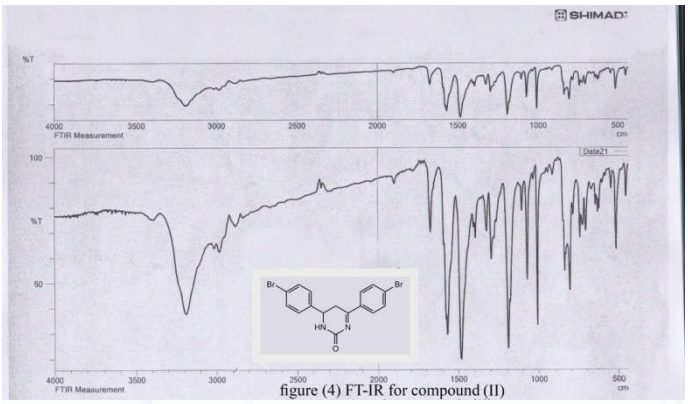


figure (4) FT-IR for compound (II)

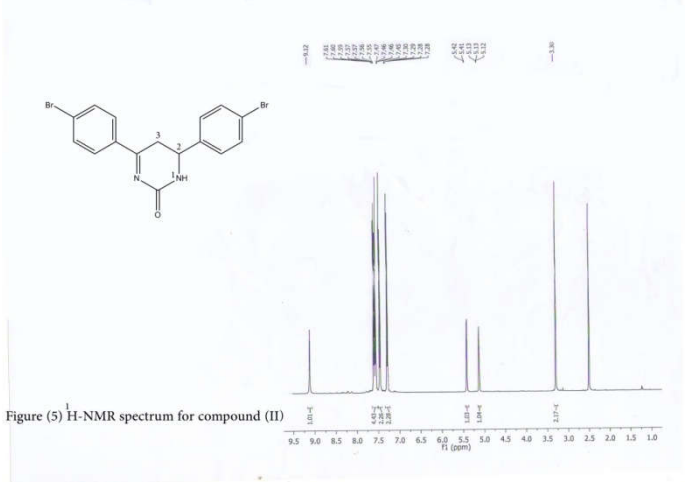


Figure (5) ^{1}H-NMR spectrum for compound (II)

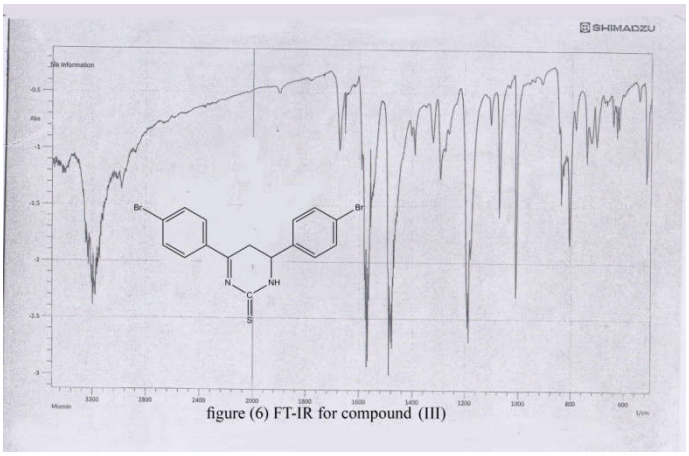


figure (6) FT-IR for compound (III)

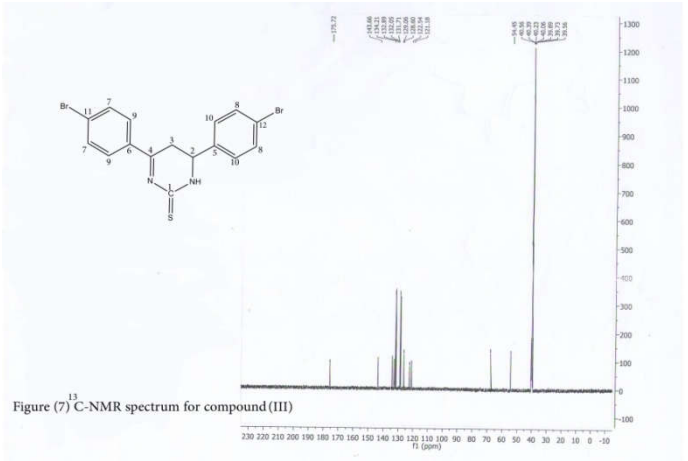


Figure (7) ^{13}C-NMR spectrum for compound (III)

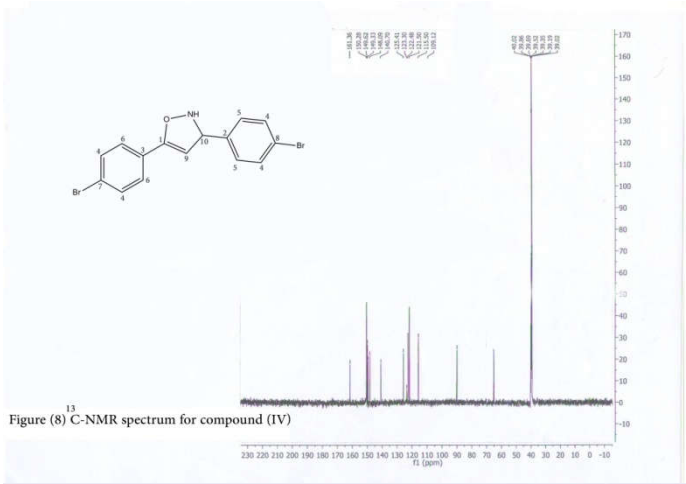
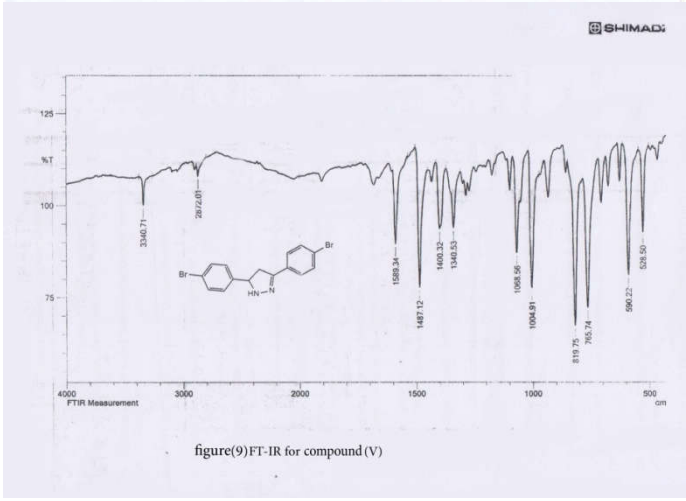


Figure (8) ^{13}C-NMR spectrum for compound (IV)



figure(9)FT-IR for compound (V)

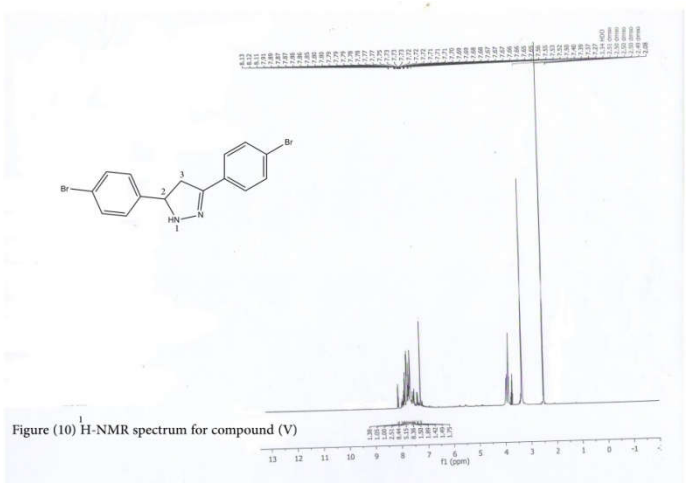


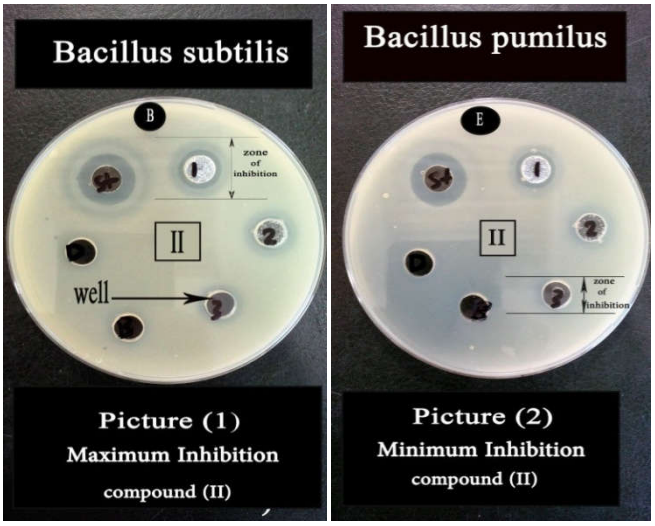
Figure (10) ^{1}H-NMR spectrum for compound (V)

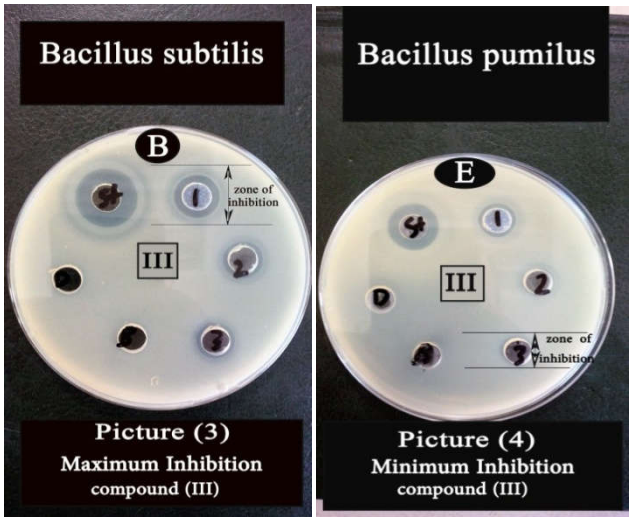
Biological activity

In our study, new series of heterocyclic derivatives showed moderate to significant antibacterial activity when compared with standard drug Neomycin and powerful antifungal activity.

The maximum inhibition for synthesized compound (II) was (18 mg/mL) against Bacillus subtilis (picture 1) while the minimum inhibition for synthesized compound (II) was (6 mg/mL) against Bacillus pumilus (picture 2). The maximum inhibition for synthesized compound (III) was (14 mg/mL) against Bacillus subtilis (picture 3) while the minimum inhibition for synthesized compound (III) was (8 mg/mL) against Bacillus pumilus (picture 4) .The maximum inhibition for synthesized compound (IV) was (13 mg/mL) against Bacillus subtilis (picture 5) while the minimum inhibition for synthesized compound (IV) was (7 mg/mL) against Bacillus pumilus (picture 6) table (3).

Concerning with fungi, all the synthesized compound revealed good activity against candida albicans in all testified concentrations.





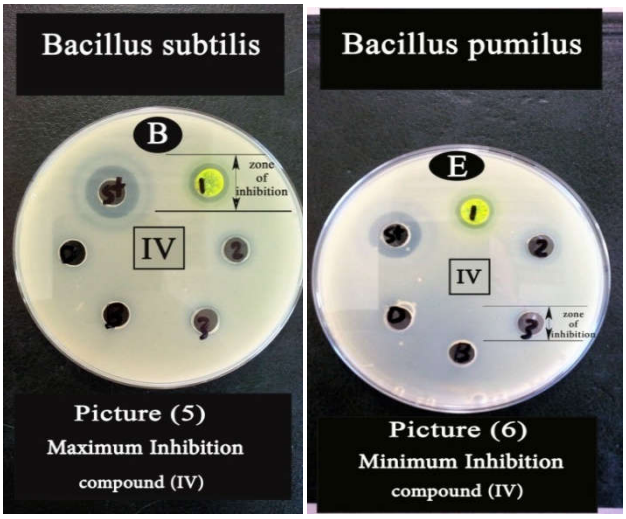


Table No 3

Materials	Bacillus subtilis (B)				Bacillus pumilus (E)				Staphylococcus aureus (S)				Candida albicans (C)			
	st. 0.1 mg/mL	25 mg/mL	15 mg/mL	5 mg/mL	st. 0.1 mg/mL	25 mg/mL	15 mg/mL	5 mg/mL	st. 0.1 mg/mL	25 mg/mL	15 mg/mL	5 mg/mL	st.	25 mg/mL	15 mg/mL	5 mg/mL
II	15	18	13	11	16	17	12	6	14	11	–	–	/	17	17	12
III	15	14	11	10	16	11	8	–	14	11	–	–	/	12	11	10
IV	15	13	11	8	16	11	10	7	14	12	–	–	/	18	8	6
V	15	17.5	12	10	16	12	10	8	14	–	–	–	/	13	12	10

-Inhibition zone in (mm).
- St. "References Standard USP" = Neomycin (as Sulfate).

CONCLUSION

Newly synthesized compounds (I,II,III,IV) were gained by direct fusion method, short reaction time, ease of workup and good yield. All the gained derivatives were detected by TLC, melting points, IR, ^{1}H-NMR, ^{13}C-NMR. The compounds (II-V) were evaluated for their antibacterial and antifungl activity by cylinder-plate method against various Gram positive bacteria and fungi (Candida albicans). All synthesized compounds show significant activity against Bacillus subtilis and Bacillus pumilus and against Candida albicans too while toward Staphylococcus aureus showed comparable activity compared with standard drug (Neomycin) at the concentrations used.

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