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RESEARCH ARTICLE

Synthesis, Characterization, Antibacterial and Antifungal Activity of Some Bis (1, 3, 4-oxadiazole) Polymer

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Abstract

Pyridine-2, 6-dicarbohydrazide comp (2) was synthesized from ethanolic solution of diethyl pyridine-2, 6-dicarboxylate comp (1) with excess of hydrazine hydrate. Newly five polymers ($\mathbf{P}_1$-$\mathbf{P}_5$) were synthesized from reaction of pyridine-2, 6-dicarbohydrazide comp (2) with five different di carboxylic acid in the presence of poly phosphoric acid (PPA). The antibacterial activity of the synthesized polymers was screened against some gram positive and gram negative bacteria. Antifungal activity of these polymers was evaluated in vitro against some yeast like fungi such as albicans (*candida albicans*). Polymers P_3, P_4 and P_5 exhibited highest antibacterial and antifungal against all microorganisms under test.

Keywords: *Bis 1, 3, 4-oxadiazole, Polymer, Antibacterial, Antifungal.*

Introduction

Oxadiazole, a hetero cyclic nucleus has attracted wide attention of the chemists in search of new therapeutic molecules. 1, 3, 4-oxadiazole is widely exploited for various applications. 1,3,4-oxadiazole have a wide range of biological activities ranging from antibacterial [1, 2], anti convulsant [3], antifungal [4], used in treatment of rheumatoid, osteo and jaundice arthritis [5], anti-flammatory [6], anti-cancer [7], anti-malarial [8], anti HIV [9], insecticidal activities [10], anti-protozoal [11], anti-diabetic [12], anti-allergic [13], anti-oxidant [14], anti-tumor [15], anti-viral [16], anti-tubercular [17] and activity of some transfer enzymes [18].

Some material applications of 1,3,4-oxadiazole derivatives lie in the fields of electro chemical properties[19], in the field of liquid crystal [20], photo luminescent properties [20], act as corrosion inhibitors [21], high thermal stability [22],optical properties [23], photo sensitizer [24] and light emitting diodes [25].

Methodology

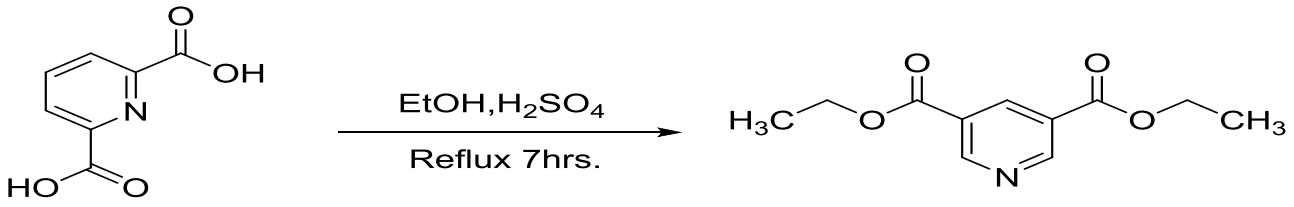
Materials

All substances (Chemicals and solvents) which utilized for synthesis the monomer and their corresponding polymers were taken up from Sigma-Aldrich, Romil, and Merck. The Melting point of synthesized compounds was finding out by open capillary tube method utilizing OMEGA MPS10 apparatus and it is uncorrected. The IR spectra were located at Shimadzu 8300 Fourier Transform Infrared spectrophotometer (FTIR), The NMR spectra were recorded on NMReady 60 pro 60 MHz using DMSO-d_6 as a solvent and TMS as internal standard and the element analysis (CHN) was recognized by EURO EA 3000 at Central Service Laboratory/ College of Education For Pure Science (Ibn Al-Haitham), University of Baghdad.

The biological activities of these compounds were tested using agar disc diffusion method, in Central Service Laboratory/ College of Education For Pure Science (Ibn Al-Haitham), University of Baghdad.

Methods

Synthesis of diethyl pyridine-2, 6-dicarboxylate Comp.1



Comp 1

A solution of 2, 6- pyridinedicarboxylic acid (15g, 89.8 mmol) in absolute ethanol (25 mL) and three drops of concentrated sulfuric acid was heated under reflux for 7 hrs. The reaction was monitored by TLC utilizing hexane: ethyl acetate (3:1) as eluent. The excess of solvent was evaporated under reduced pressure and then extracted three times with25 mL ethyl acetate. The organic layer washed with saturated solution of sodium hydrogen carbonate (5%) several times then washed with distilled water. The combined organic layer was dried under anhydrous sodium sulfate, filtered and evaporated under reduced pressure to afford pale yellow oil, Yeild80% BP 43-45˚C. (lit44-46˚C) [26].The ranger of differences between the melting point of compound (**1)** and the literature was about 2-3˚C that could be attributed to the differences in percentage of purity. IR (KBr, υ max\ cm^{-1}); 3062 (CH_{Ar}), 2985-2871 (CH_{aliph}), 1745 (C=O), 1576 -1446 (C=C), ^{1}H NMR (60 MHz, DMSO-d_6) δ, ppm; 1.47 (t, 6H, *J* 7.2Hz, $2CH_3$), 3.29 (q, 4H, *J* 7.2Hz, $2CH_2$), 7.82-8.14 (m, 3H, $H_{pyridine}$). The CHN element analysis of compound (**1**) was in a good agreement with the proposed structure as tabulated in Table (1).

Table1: C.H.N. analysis of Comp1

Compound	Theoretical Value	Practical Value
1	**C**:59.19 **H**:5.87 **N**:6.27	**C**:59.21 **H**:5.90 **N**:6.29

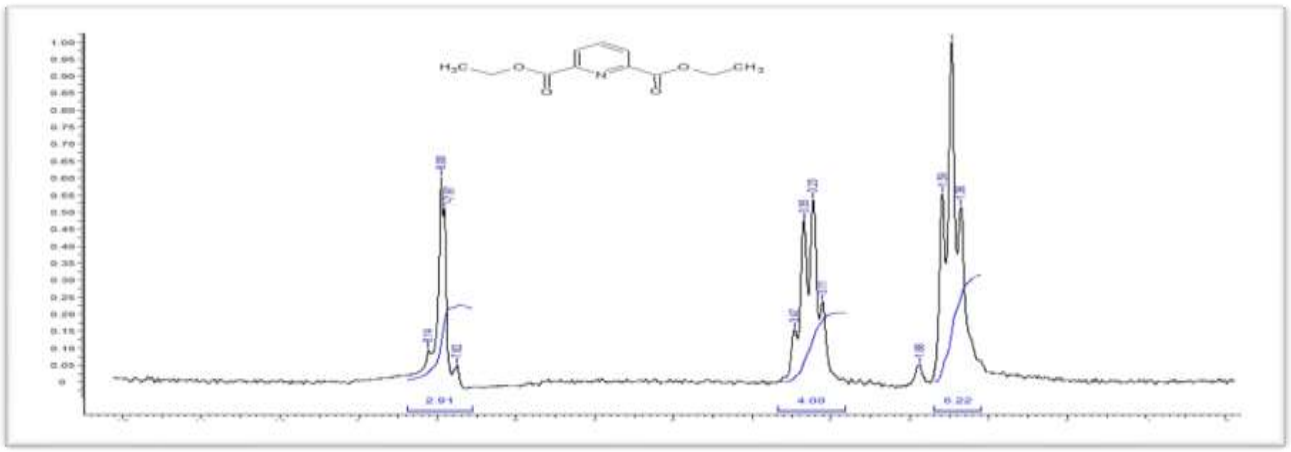
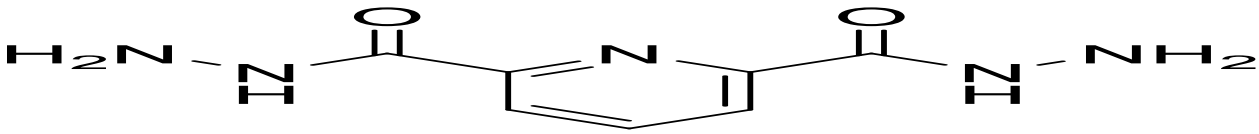


Figure 1: ^{1}H NMR Spectrum of (compound 1)

Synthesis of Pyridine-2, 6-dicarbohydrazide Comp. (2)



Dimethyl pyridine-2,6-dicarboxylate (8g, 36mmol) was dissolved in (65mL) of ethanol and stirred with heating for 60°C at 15 min. Excess of hydrazine hydrate 80% (10mL) was added drop wise. The mixture was refluxed for 1hr. Upon cooling , the product was filtered and dried , recrystallized from ethanol to give white prouder (6.2g), Yield 89%, MP 278-282 ˚C, (lit 280-284˚C) [27].

IR (KBr, υ max\ cm^{-1}); 3276-3186 (NH_2 & NH), 3016 (CH_{Ar}), 1689 (C=O), 1639 (C=N), 1518-1441 (C=C); ^{1}H NMR (60 MHz, DMSO-d_6) δ, ppm; 4.58 (bs, 4H, $2NH_2$), 8.11-8.43 (m, 3H, $H_{pyridine}$) 10.58 (bs, 2H, 2NH). The experimental percentage of CHN analysis was too matched to the theoretical results as illustrated in Table (2).

Table2: C.H.N. analysis of Comp2

Compound	Theoretical Value	Practical Value
2	**C**:43.08 **H**:4.56 **N**:35.88	**C**:43.06 **H**:4.61 **N**:35.85

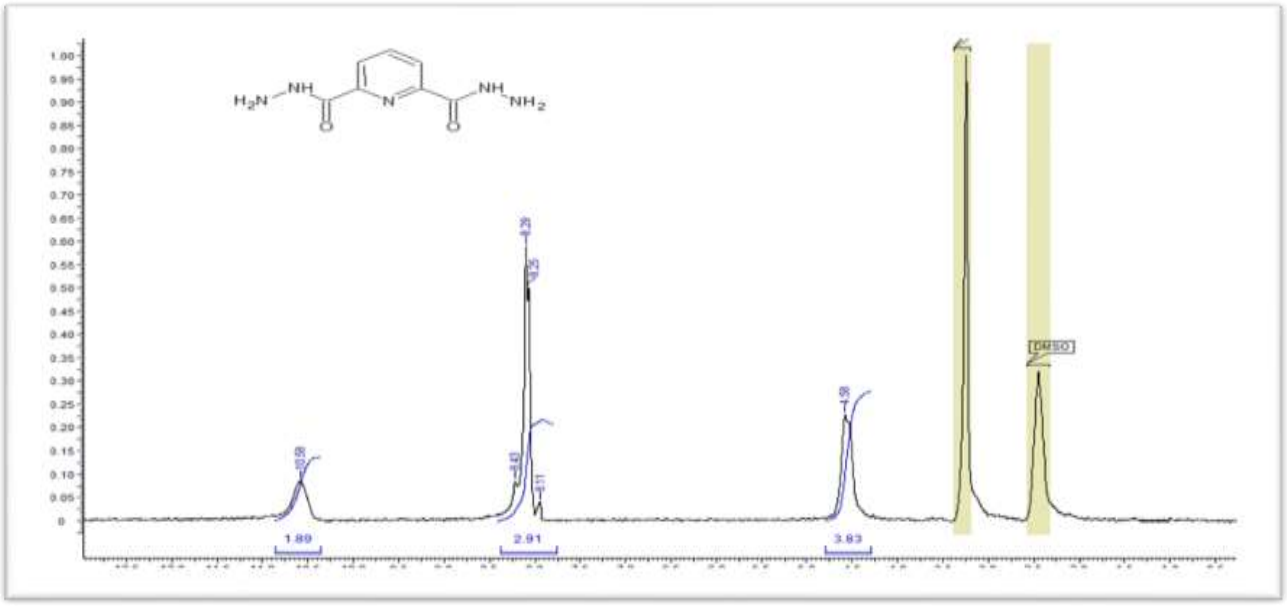
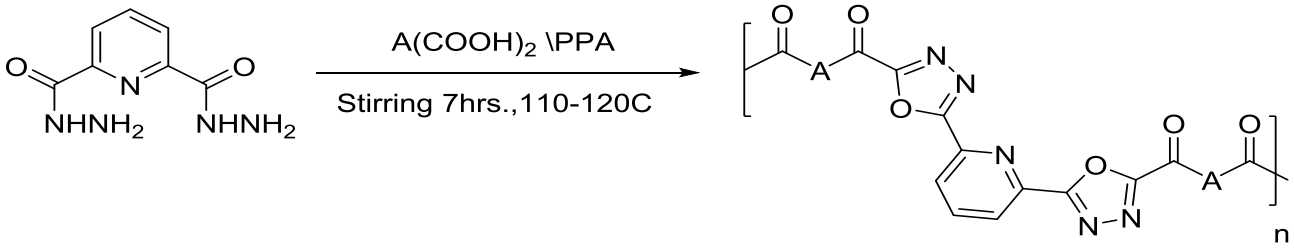
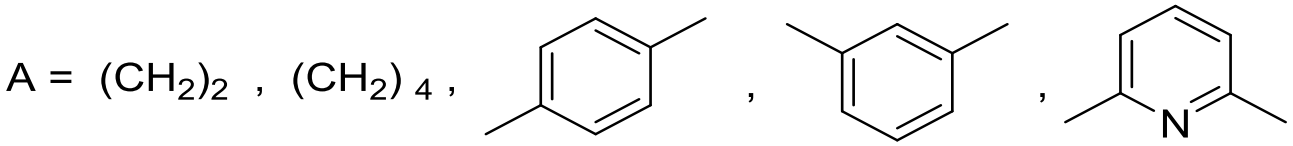


Figure 2: ^{1}H NMR Spectrum of (compound 2)

General Synthesis of Bis 1, 3, 4-oxadiazole Polymerization (P_1-P_5)



P(1,2,3,4,5)



Pyridine -2, 6-dicarbohydrazide (0.5g, 2.56mmol) and dicarboxylic acid (1gm) was mixed and grinding to finny powder then poured into hot stirring liquid of poly phosphoric acid at 110-120˚C. The mixture left under heating and stirring for7 hrs. After cooling the mixture poured into (50mL) crashed ice. PH of the solution was adjusted to (7-8) by adding a solution of sodium hydroxide 10%.

The mixture was evaporated under reduced pressure to obtain the target polymer. The synthesized polymers were characterized by FTIR but cannot characterize by ^{1}H-NMR spectrum because they were insoluble in most of known deuterated solvents. The resulting polymers were tabulated in Table (3).

Synthesis of P1:

IR (KBr, υ max\ cm^{-1}); 1668 (C=O), 1651 (C=N).

Synthesis of P2:

IR (KBr, υ max\ cm^{-1}); 1631(C=N), 1579 (C=C).

Synthesis of P3:

IR (KBr, υ max\ cm^{-1}); 1670(C=N), 1572-1485 (C=C).

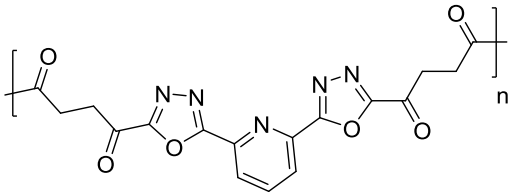
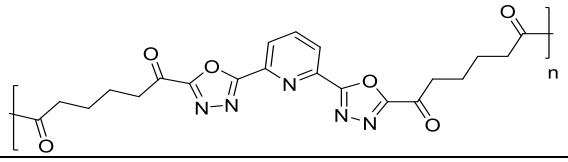
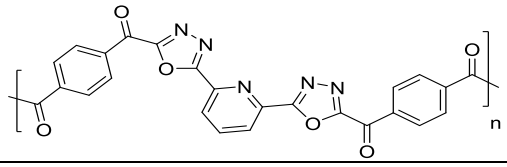
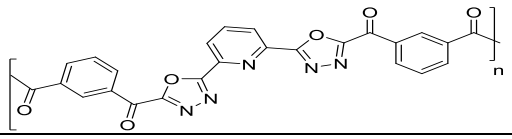
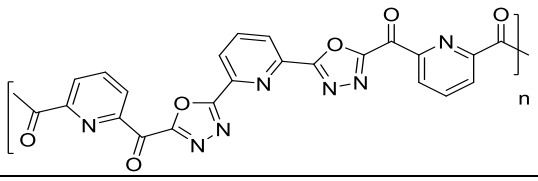
Synthesis of P4:

IR (KBr, υ max\ cm^{-1}); 3072(CH_{AR}), 1658(C=O), 1616 (C=N), 1541-1450(C=C).

Synthesis of P5:

IR (KBr, υ max\ cm^{-1}); 3381(CH_{AR}), 1691 (C=O), 1643(C=N), 1583-1520 (C=C).

Table3: The synthesized polymers and their physical properties

NO.	Structure	M.P.	Color
P_1		133.3	Pale pink
P_2		183.5	white
P_3		184.9	Greenish Yellow
P_4		354.4	Blue
P_5		205.2	white

Results and Discussions

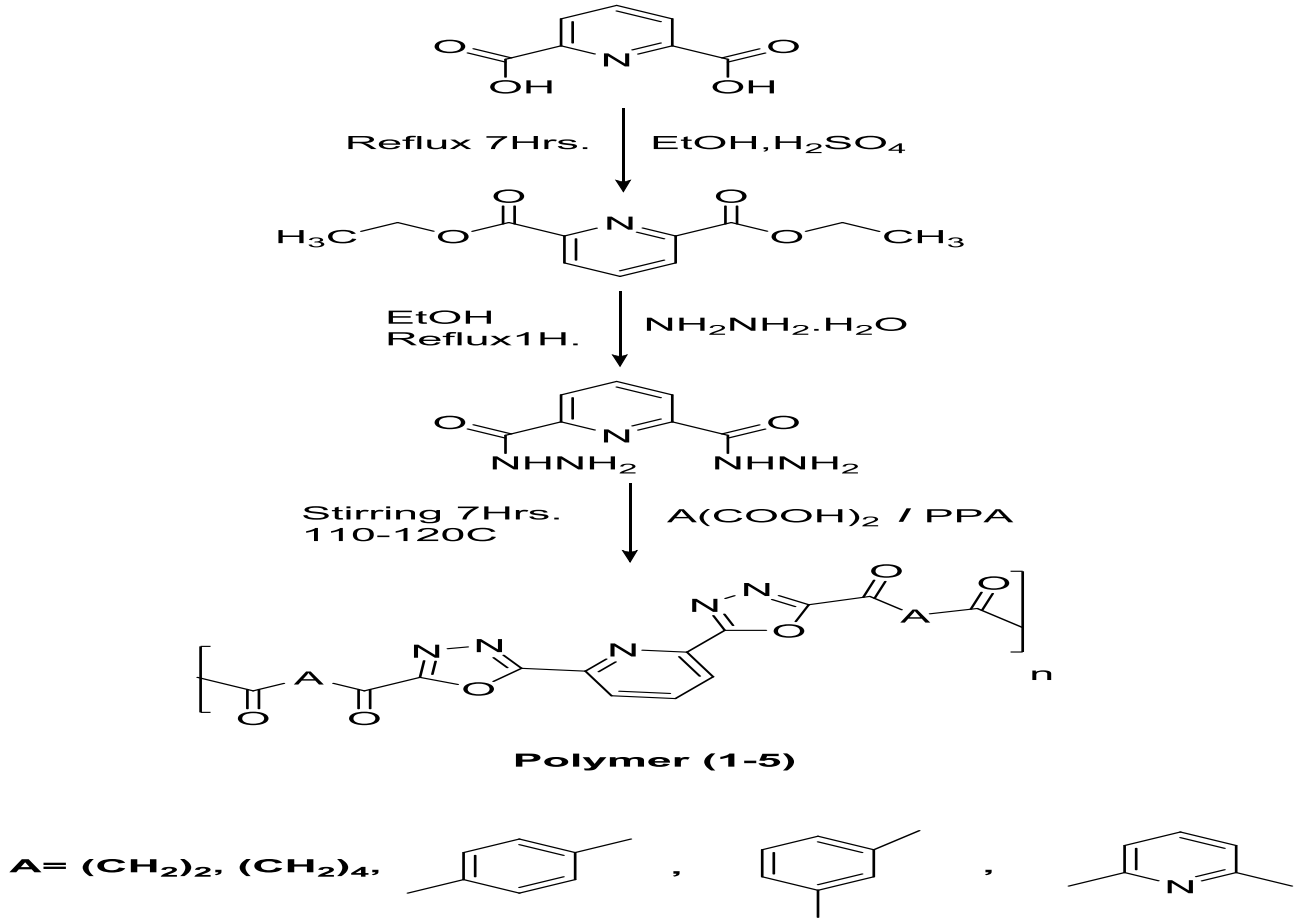
Chemistry

Diethyl pyridine-2, 6-dicarboxylate comp.(1) was synthesized from a solution of 2,6-pyridine di carboxylic acid in absolute ethanol in the presence of concentrated sulfuric acid. The target compound was characterized by FTIR and ^{1}H NMR spectra besides to CHN analysis. The FTIR of this compound reveled disappeared the OH peak of pyridine 2,6-di carboxylic acid which is consist good evidence for success the reaction. Furthermore the spectrum showed new band at 2985 and 2871 cm^{-1} attributed to(CH_{aliph}).The band of carbonyl ester (C=O) was located at 1745 cm^{-1} ,the (CH_{Ar}) at 3060 cm^{-1} and two peaks of (C=C) at 1576 and 1466 cm^{-1}. The ^{1}H NMR spectrum of this compound confirmed the suggested structure.

The spectrum showed triplet peak for six protons of two CH_3 groups assigned at 1.47ppm with coupling constant equal 7.2 Hz, four protons of two CH_2 group located at 3.29 ppm as quartet peaks with coupling constant equal 7.2 Hz and the protons of pyridine groups were located at 7.82-8.14 ppm as multiplet peaks. The CHN elements analysis was constantly harmonically with the calculated percentage. The pyridine-2, 6-dicarbohydrazide comp. (2) was synthesized from reacted ethanolic solution of diethyl pyridine-2, 6-dicarboxylate comp.(1) with excess of hydrazine hydrate.

The FTIR spectrum exhibited appearing of new peaks at 3276-3186 cm^{-1} attributed to (NH_2 and NH) and new band at 1639 for (C=N) cm^{-1}. Furthermore (C=O) showed shifting in peak of amide group at 1689 cm^{-1} besides to (C=C) which was located at 1518-1441cm^{-1}. The ^{1}H NMR spectrum agreed with FTIR results and showed broad singlet peak at 4.58 ppm attributed to four protons of two NH_2 groups, multiplet peak for pyridine protons at 8.11-8.43ppm and broad singlet peak for two protons of two NH group at 10.58ppm.

The experimental percentage of CHN was too matched to the theoretical results. Five newly polymers were synthesized from reaction of pyridine-2,6-dicarbohydrazide comp.(2) With five di carboxylic acid in presence of PPA as illustrated in Scheme 1.



Scheme 1: synthetic route for synthesis polymers (P_1-P_5)

The structures of newly synthesized polymers were confirmed by FTIR but cannot characterize by ^{1}H NMR because all synthesized polymers were insoluble in most of known deutrated solvents.

All FTIR spectra of the polymers showed new peak corresponding to the carbonyl of ester at range (1658-1691) cm^{-1} besides to the OH which could be attributed to the end of polymer as either phenolic or carbocyclic acid hydroxyl. The $\mathbf{P}_4$ and $\mathbf{P}_5$ showed CH aromatic at range (3072-3381) cm^{-1} and C=C at (1450-1583) cm^{-1}. All spectrum showed the C=N of the oxadiazole at range (1616 -1651) cm^{-1}.

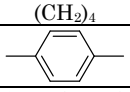
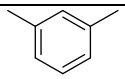
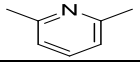
Biological Activity of the Synthesized Polymers

There has been considerable interest in the development of novel compounds as antibacterial, antifungal, antimalarial, antimicrobial and analgesic Multiple antibacterial resistances of the bacterial pathogens have a great attention in production of drugs and preservatives in food industry. Antibacterial and antifungal are important problems in the treatment of human patients with infectious disease and food contaminated with some bacterial pathogens. The newly synthesized polymers were tested for their inhibitory activity in vitro growth against *Escherichia coli* (gram-negative bacteria), *Bacillus subtilis* and *Staphylococcus aureus* (gram-positive bacteria), and the yeast- like pathogenic fungus *candida albicans*.

The bioactivities were carried out using the agar disc diffusion method using Müller-Hintor agar medium. The agar plate surface is inoculated by spreading of the microbial inoculum over the entire agar surface. Then, a hole with a diameter of 8mm is punched aseptically with a sterile tip. Then it was moistened with the polymer solution in dimethylsulfoxide (DMSO) of specific concentration (50µg\mL) and carefully placed on the agar culture plates, the solution diffuse in the agar medium to inhibit the growth of microbial strain. The plates were incubated at 37°C, and the diameters of the growth inhibition zone around the hole were

measured after 24 hrs, in case of bacteria while were calculated after 48 hrs. in case of *candida albicans*. The results point that the presence of phenyl group is an important factor for increase the biological activity both in antibacterial and antifungal [28, 29] so that polymers **P**3, **P**4 and **P**5 exhibited more significant results than polymer **P**1and **P**2. The results were tabulated in Table 4.

Table4: Antibacterial and antifungal zone of inhibition (mm) of synthesized polymers

Polymer	A	*Escherchia coli*	*Staphylococcus aureus*	*Bacillus subtilis*	*Candida albicans*
P_1	$(CH_2)_2$	11	___	___	___
P_2	$(CH_2)_4$	16	___	___	13
P_3		13	14	12	21
P_4		22	15	15	22
P_5		20	16	20	22

(--): inactive polymer against the specified microorganisms

As well, the Figures (3, 4, 5, 6) exhibited the inhibitions zones for the synthesized polymers against the microorganisms and fungal.

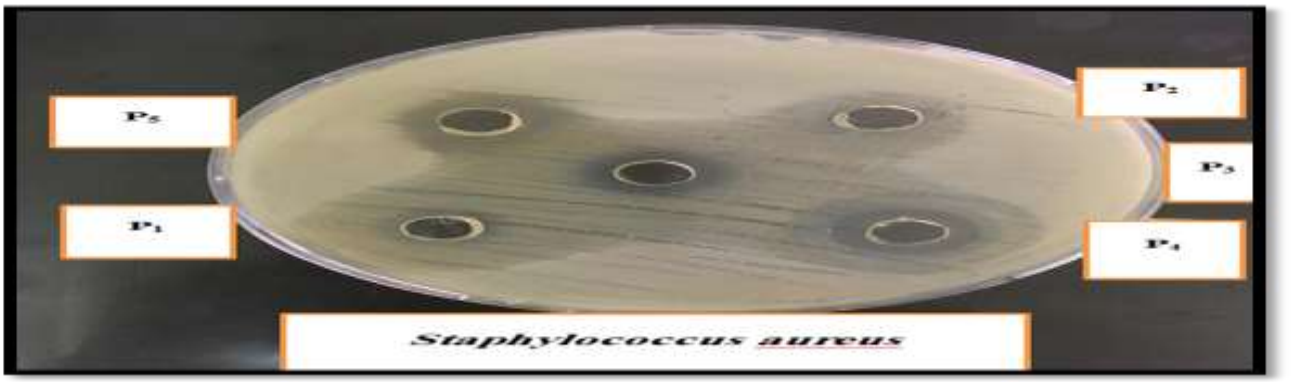


Figure 3: Inhibition zone of (P_1-P_5) against *Staphylococcus aureus*

Figure4: Inhibition zone of (P_1-P_5) against *Bacillus subtilius*

Figure5: Inhibition zone of (P_1-P_5) against *Escherichia coli*

Figure6: Inhibition zone of (P_1-P_5) against *candida albicans*

Conclusion

Successfully five newly synthesized polymers were obtained from reaction of pyridine-2, 6-dicarbohydrazide comp (2) with five different di carboxylic acid in the presence of PPA. The synthesized polymers characterized from their FTIR spectra. The antibacterial activities were screened against gram positive and gram negative bacteria as well antifungal activity was screened against *candida albicans* fungal. Meanwhile, the polymers gained from aromatic di carboxylic acid showed highest antibacterial and antifungal activity than those gained from aliphatic di carboxylic acid.

Acknowledgments

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Investigation of potential anti-malarial lead candidate 2-(4-fluorobenzylthio)-5-(5-bromothiophen-2-yl)-1,3,4-oxadiazole: Insights from crystal structure, DFT, QTAIM and hybrid QM/MM binding energy analysis. Journal of Molecular Structure, 1175: 230-240.

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