RESEARCH ARTICLE

Synthesis, Characterization and Evaluation of the Antibacterial Activity of Some Heterocyclic Compounds

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ABSTRACT

This work includes preparing various heterocyclic compound types, which include the phthalazin**,** pyridazin**,** pyrazol**,** phthalazin-3,8-dione [5] and pyridazin-3,6-dione [6] derivatives which derived from hydrazide compound [3]. The structures of those compounds have been identified by the fourier-transform infrared spectroscopy (FTIR), proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy and checked with the use of the TLC technique, and evaluated the antibacterial activities for some of the synthesized compounds. Those activities have been characterized in *v*itro using the well diffusion approach against three types of the pathogenic strains of the bacteria *Escherichia coli* and *Pseudomonas* (G-) and *S. aureus* (G+). Results have shown that some of those compounds have shown good activity.

Keywords: Hydrazide, Phthalazin, Pyrazole, Pyridazin.

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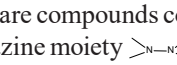
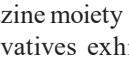
INTRODUCTION

The heterocyclic compounds represent the core of a wide range of pharmaceutical agents and are natural, bio-active products that are beneficial as well for herbicides and corrosion inhibitors. For example, nitrogen-containing heterocyclic compounds have been considered as highly important concepts in pure as well as the applied chemistry.[1-3]

Ibuprofen, a non-steroidal anti-inflammatory drug (NSAID), is the gold standard in pain relievers. It is included in the "Essential Medicines List" issue-1d by the World Health Organization (WHO).[4,5] The mechanism of action involves inhibition of Cyclooxygenase-II (COX-II), inhibiting the synthesis of prostaglandins from arachidonic acid.[6]

Hydrazides are compounds containing the group  where the hydrazine moiety  is attached to an acyl group.[7] Hydrazide derivatives exhibit different biological activities such as antiviral, anti-cancer, anti-depressant, and anti-inflammatory.[8,9] Pyrazoles in heterocyclic rings are classified as diazol. A family of five contains two nitrogen and three carbon. Class As alkaloids despite their scarcity in nature.[10] Pyridazine can be defined as one of the heterocyclic organic compounds with a molecular formula of $(CH)_4N_2$. It includes a 6-membered ring that has two adjacent atoms of nitrogen, and it is aromatic. It's a colorless liquid with a 208°C boiling point. It's isomeric with two other rings of $(CH)_4N_2$, pyrazine and pyrimidine.[11] The pyridazine ring belongs to the structures of several medications that can be found in markets,[12] such as the minaprine, hydralazine, pipofezine, cefozopran, and so on. The derivatives of the Pyridazine were found to be having a variety of pharmacological activities, which include the antibacterial[13-16] anti-fungal, anti-tubercular[17-19] anticonvulsant,[20,21] antihypertensive,[22] anti-inflammatory, and analgesic.[23,24]

MATERIAL AND METHODS

Acetic acid, absolute ethanol, sulfuric acid, hydrazine hydrate, succinic anhydride, 3-nitro-phthalic anhydride, maleic anhydride. All chemicals and solvents used were of the highest purity from BDH, Fluka, Aldrich, GCC, and Merck.

Instrumentation

FTIR has been recorded in Central Service Lab, College of Sciences, Al-Mustansiriyah University. The melting points have been recorded by the use of the apparatus of (Gallen Kamp) melting point. Thin TLC (i.e., layer chromatography) has been performed using the Alumina plates that have been pre-coated by silica-gel, and the vapor of the Iodine has detected the compound. ^{1}H-NMR spectrum have been registered on BRUKER-400MHz that operates at 400MHZ with tetramethyl silane as an internal standard in the dimethyl-d6 sulfoxide (DMSO-d6) as a solvent; the measurements have been taken at Kashan University, Iran. The biological activity has been conducted at Univ. of Baghdad College of Sciences, Biology Department, Advisory Office, and Central Lab.

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Method of Preparation

Preparation of ethyl 2-(4-isobutylphenyl) propanoate [2][10]

2-(4-isobutylphenyl) propanoic acid [1] (0.048 mol, 10 g) dissolved in (20.0ml) of the absolute ethanol, (4 mL) concentrated sulfuric acid was added, then this mix has been refluxed for a 4 hours. period, then cooled, filtered the reaction mixture and the residue formed to give the compound [2].

Preparation of 2-(4-isobutylphenyl) propanehydrazide [3][11]

Compound [3] was prepared by adding hydrazine hydrate (10 ml) to (0.008 mol, 2 g) of compound [2] and dissolving it in (20 mL) of the absolute ethanol, and after that, the mix was refluxed for 5 hours. Following the cooling, the precipitate was filtered and then re-crystallized by the ethanol.

Synthesis of 1-[2-(4-(4-isobutylphenyl] propane]2,4,5-trihydropyridazine-3,6-dione [4][12]

Compound [3] (0.001mol, 0.4g) was mixed with succinic anhydride (0.001 mol, 0.1g) in the presence of acetic acid (20mL) and heated by reflux for 8 hours. The reaction mix has been cooled, and the precipitate has been filtered to produce the compound [4].

Synthesis of 2-(2-(4-isobutylphenyl) propanoyl)-5-nitro-2,3-di-hydrophthalazine-1,4-dione [5][13]

Compound [3] (0.002 mol, 0.5 g) was mixed with 3nitro-phthalic anhydride (0.002 mol, 0.43 g) in (15 mL) acetic acid then the mixture was refluxed for 6 h. and cooled after that, then added to crushed ice. Then this precipitate has been filtered and washed with the water to produce the compound [5].

Synthesis of 1-(2-(4-isobutylphenyl)propanoyl)-1-2-dihydropyridazine-3,6-dione [6][13]

This compound was prepared by reacting compound [3] (0.001mol, 0.3g) with maleic anhydride (0.001mol, 0.1g) in the presence of acetic acid (20 mL), this mix has been refluxed for 8 hours. and cooled afterwards and added to the crushed ice. The precipitate that has been obtained was filtered and washed by the water in order to produce the final products.

RESULTS AND DISCUSSION

Characterization of Compound 2

The FT-IR spectrum showed the disappearance of the υ (O-H) hydroxyl group band, of 2-[4-isobutyl phenyl] propanoic acid at 3,000 cm^{-1} and the appearance of the band at 1,732 cm^{-1} as a result of the carbonyl ester group. Also, the (C-H) aliphatic group appeared at (2848,2926)cm^{-1}, besides the (C-H)aromatic at 3026 cm^{-1}.

The spectrum of the ^{1}H-NMR of the compound (2), Figure 2 illustrates the following characteristic chemical shifting (DMSO – d 6, ppm): aromatic ring protons appears as several signals at (δ7.12ppm- δ7.79ppm), signal at (δ4.04ppm) as a result of

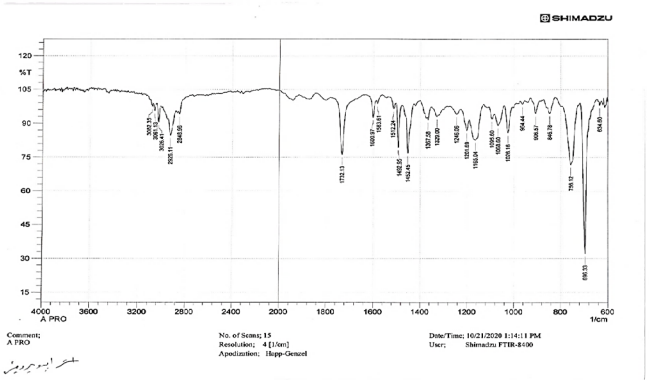

Figure 1: FTIR spectrum of compound 2.

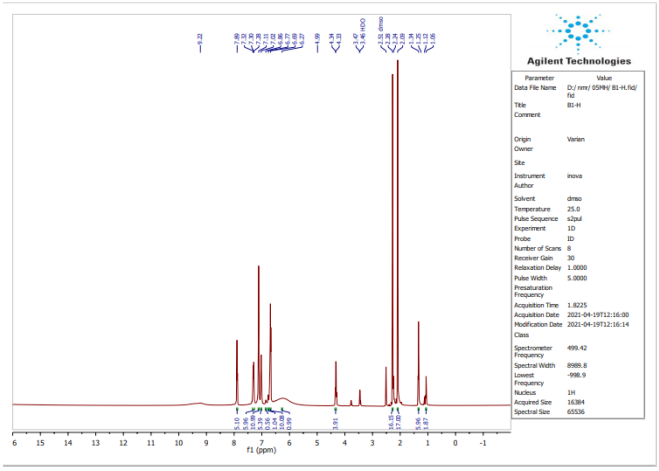

Figure 2: ^{1}H-NMR spectrum of compound 2.

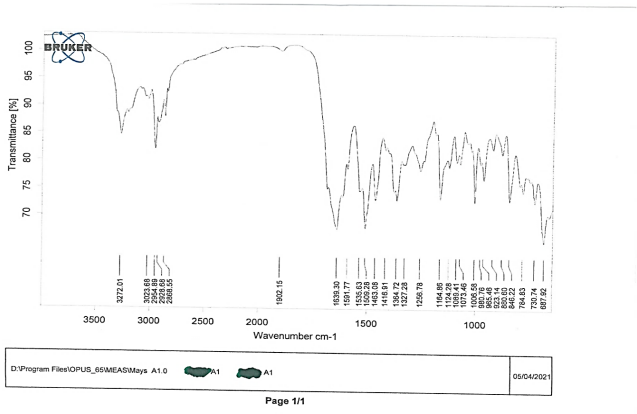

Figure 3: FTIR spectrum of compound 3.

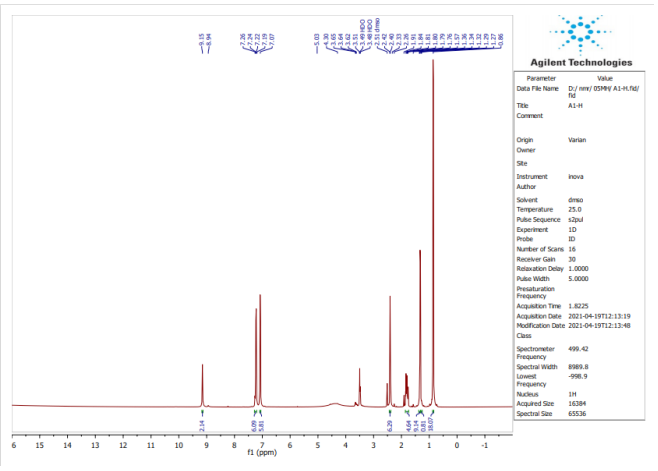

Figure 4: ^{1}H-NMR spectrum of compound 3.

(-CH_2-) group, Single signal at (3.88ppm) a result of (OCH_3) group, signals at δ 1.08ppm and δ 1.45ppm (6 H), which might be assigned to (CH_3) protons and δ2.48ppm for the DMSO.

Characterization of Compound 3

The FTIR spectrum for the compound of hydrazide [3], had shown the appearance of characteristic absorption bands in the (3,272cm^{-1} and 3,297cm^{-1}) regions as a result of the symmetric and asymmetric stretching vibration of the (NH_2) group, the appearance of υ(N-H) group band in 3,120 cm^{-1} region. The FTIR spectrum had shown as well the absorption band appearance in 1,639 cm^{-1} region as a result of the amide carbonyl group's stretching vibration.[14]

The spectrum of the ^{1}H-NMR (as solvent in the DMSO) of the acid hydrazide [3], Figure 4, shows a signal at δ9.22ppm (1 H) as a result of the proton of NH, signal at δ1.42ppm (3 H), which might be assigned to (CH_3) protons, a singlet at δ3.63 ppm (1 H), which might be a result of 1 (C-H) group proton and several signals at δ7.10ppm - δ7.76 ppm), which might be a result of the 6 aromatic protons, which have shown a sharp singlet at δ3.83 ppm for 3 OCH_3 group protons.

Characterization of Compound [4]

FTIR spectrum which showed bands at 3334, 3020, (2955, 2868) and 1651 cm^{-1} that may be a result of the NH, CH (arom.), CH (aliph.) and C=O respectively.[15]

Characterization of compound 5,6

The FTIR spectrum of compounds.5,6 Were an indication of the disappearance of the NH_2 band (3304 and 3279 cm^{-1}) of the starting material [1], and the appearance of N-H band at (3330 cm^{-1}) in compound [5], shows the appearance of the band of υ (N-H) group in the region (3400 cm^{-1}) in compound [6] and carbonyl group band at (1728 cm^{-1}) in compounds [5]and [6], and carbonyl group at (1614cm^{-1}) compound.[5].[15]

The ^{1}H-NMR spectrum of the compounds [5], numerous signals at (δ7.78- δ7.84) belong to aromatic protons. A sharp singlet at δ3.84ppm as a result of three protons of the (CH2) group, signal at δ1.45ppm (3H), which might be assigned to the (CH3) protons, a singlet at δ3.35ppm (1 H) which might be a result of one (C-H) group proton and signal at δ4.04ppm as a result of (N-H) group, the pyridazine (N-H) peak at δ(9.71-9.98).

Biological Activities

This part is concerned with studying the antibacterial activities of some synthesized compounds. Those activities have been characterized in vitro using the well diffusion approach against the bacteria *S. aureus (G+), E.coli.* The results that have been obtained, showed that some at those compounds had shown measurable activities.

CONCLUSION

- Throughout the present study, the heterocyclic compounds have been prepared. Analytical as well as spectral data (1 H – NMR, FTIR) of the synthesized

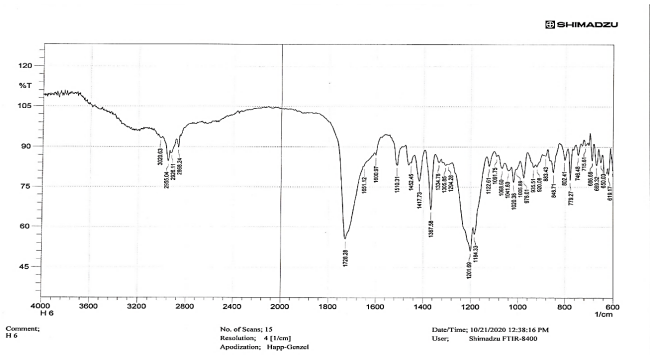

Figure 5: FT-IR spectrum of compound 4.

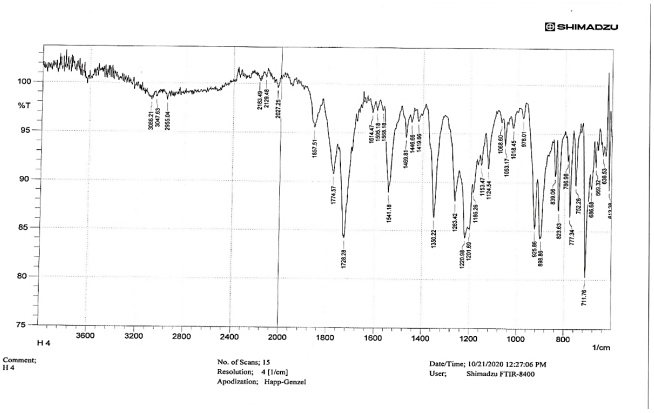

Figure 6: FTIR spectrum of compound 5

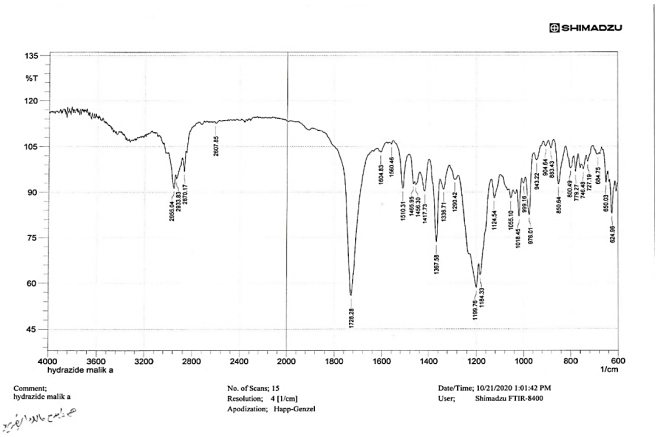

Figure 7: FTIR spectrum of compound 6.

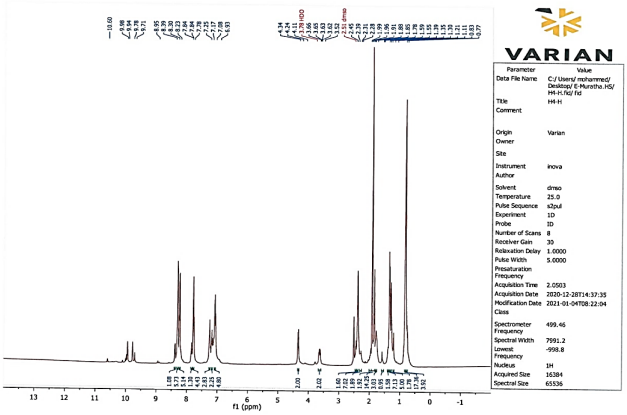

Figure 8: ^{1}H-NMR spectrum of compound.

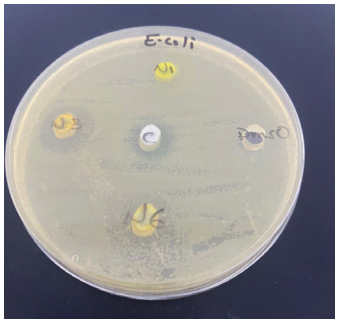

Figure 9: Effect of compounds D1, N3, N6 and S1against E.coli (G-).

Figure 10: Effect of compounds D1, N3, N6 and S1 against E.coli (G-).

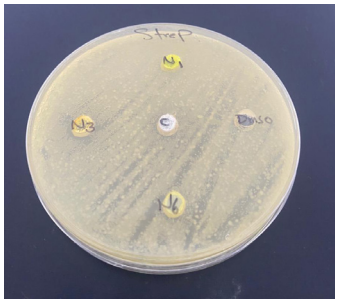

Figure 11: Effect of compounds D1, N3, N6, and S1 against Staphylococcus(G+).

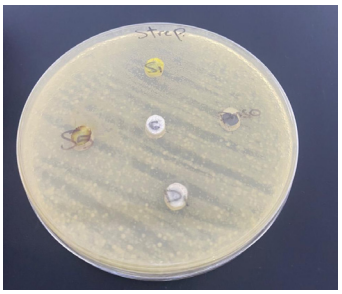

Figure 12: Effect of compounds D1, N3, N6, and S1 against Staphylococcus(G+).

compounds some of them have been in agreement with the suggested structure; in addition to that, biological activities of some of the prepared compounds have been researched, and shown inhibition impacts, as explained below:

Compounds [3 and 5] are moderately active against *E.coli a*; Compound [5] are moderately active against Pseudomonas; Compound [5] are active against Pseudomonas, and Compounds [3 and 5] are moderately active.

- The new heterocyclic compounds with aromatic units are high melting points than the others.
- The six rings heterocyclic compound are more stable than that for the five and four rings heterocyclic compounds against Staphylococcus .

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