RESEARCH ARTICLE

Synthesis, Characterization and Studying Biological Activity of Heterocyclic Compounds

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ABSTRACT

Heterocyclic moiety was mentioned to present diverse biological activities such as inhibitors of protein glycation, antibacterial, antifungal, anticancer, antidepressant, anti-inflammatory, antituberculosis, antioxidant, and as antiviral agents, in addition to other biological activities; therefore, many medicines containing heterocyclic moiety have been observed. Due to the pharmacological importance of heterocyclic derivatives, the present work comes as attempt to synthesis of heterocyclic compound involved (tetrazole and pyrazole rings) by series of steps starting from pyrimidin-2-amine, which reacted with 2-chloroacetyl chloride gave compound (1) [2-chloro-N-(pyrimidin-2-yl) acetamide], then the reflex reaction of the compound (1) with the hydrazine hydrate in ethanol led to compound (2) [2-hydrazinyl-N-(pyrimidin-2-yl)acetamide], the last one reacted with acetyl acetone to form pyrazole ring compound (3) [2-(3,5-dimethyl-1H-pyrazol-1-yl)-N-(pyrimidin-2-yl)acetamide]. In other line another pyrazole derivative was prepared by diazotization of pyrimidin-2-amine with $NaNO_2$/HCl to azo derivative compound (4), which is reacted with acetyl acetone gave compound (5) [3-(2-(pyrimidin-2-yl)hydrazono)pentane-2,4-dione] to react with hydrazine gave pyrazole moiety compound (6) [(2-((1H-pyrazol-4-yl)diazenyl)pyrimidine]. Pyrimidin-2-amine was reacted with 4-hydroxybenzaldehyde in ethanol and glacial acetic acid gave Schiff base compound (7) , which reacted with sodium azide in dioxane to form tetrazole ring compound (8) [4-(1-(pyrimidin-2-yl)-4,5-dihydro-1H-tetrazol-5-yl)phenol]. The spectroscopic techniques were used to confirmed the chemical structures are FTIR, ^{1}H-NMR. The biological study of pyrazole and tetrazole derivative was evaluated as anti-bacterial against gram-negative *(Klebsiella pneumoniae*), gram-positive (*Enterococcus faecalis*) and as anti-fungal against the *Candida trichomonas* and *Candida dubliniensis* in concentration 25, 75, 50, and 100 mg/mL. It was found that pyrazole and tetrazole derivative have biological activity against the bacteria and fungi where the tetrazole ring has biological effect more than pyrazole ring.

Keywords: Biological activity, Heterocyclic compounds, Pyrazole, Tetrazole.

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INTRODUCTION

The pyrazole ring is one of the most important chemical skeletons in medicinal chemistry and advanced organic materials.[1] In reality, pyrazole compounds have a variety of pharmacological activities, including anticancer, analgesic, anti-inflammatory, antidepressant, and cardiovascular benefits.[2] It is widely accepted that pyrazole's pharmacological activity is attributable to its chemical features, notably the presence of two nitrogen atoms with highly distinct chemical capabilities and the aromatic heterocycle's planar structure.[3-5] The pyrazole nucleus, which is also seen in natural substances, has three carbon atoms and two nitrogen atoms next to it.[6] The nitrogen atom N1 "pyrrole-like," owns unshared electrons which conjugate with the aromatic system. Nitrogen atom N2 "pyridine-like" is characterized *via* the unshared electrons not affected by resonance, similar of pyridine systems. pyrazole can react with acids and bases due to chemical differences between N1 and N2.[7] The pyrazole rings are currently found in a variety of commercialized drugs, including potent anti-inflammatory compounds that inhibit COX-2 (celecoxib), nonsteroidal anti-inflammatory drugs (NSAIDs) (tepoxalin), anticancer agents (crizotimib), anti-obesity agents (surinabant, difenamizole), tranquilizers (mepiprazole), insecticides (finopril), thus demonstrating the pyrazole nucleus' pharmacological potential.[4] The most interesting molecule will be interested in pyrazole-containing molecules with antimicrobial effects

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to meet the" World Health Organization's (WHO)" and Drugs for Neglected Diseases Initiative's (DNDI) joint initiative, which encourages research and development of new antibiotic drugs throughpublic–private partnerships.[8] Tetrazole are five heterogeneous ring having four nitrogen, one carbon and hydrogen atoms, the most basic of which is the compound (Tetrazole) with molecular formula CH_2N_4.[9] Due to the nitrogen-rich conjugated system, tetrazoles are characterized by acceptor and electronic donor properties.[10] The planar form works on stabilizing negative charge via delocalization, which is thought to be optimal for receptor-ligand interactions. Tetrazolate anions, compared with carboxylates, are higher lipophilicity allowing medication molecules to pass through cell membranes more easily. On the other hand, Tetrazoles are resistant to metabolic breakdown pathways and hence have a longer duration of action.[11] Because of their unusual structure and excellent pharmacokinetic characteristics, tetrazoles and their heterocyclic analogs are essential pharmacophores in medicinal chemistry. Antihypertensive, antianalgesic, antiallergic, and antiulcer actions are all part of their pharmacological profile.[12-18] Tetrazole-based heterocycles are widely used in synthetic applications and serve as a precursor for the production of powerful heterocycles in industries such as explosives, medicines, and propellants.[9] Tetrazole heterocyclic analogs are the first validated therapy for dopamine D2 receptors.[19] Heterocycles based on tetrazoles are effective antibacterial and anticancer drugs.[20,21]

Experimental

Without additional purification, commercially available reagents were used. The melting points were calculated using the Stuart SMP 30 equipment and were not adjusted. At the Faculty of Pharmacy, University of Kufa, FTIR spectra were recorded on an IR Prestige-21 SHIMADZE as KBr disc (Iraq). Chemical shifts in ^{1}H-NMR spectra were measured in ppm using a BRUKER spectrometer at 400 MHz with d6-DMSO as the solvent and TMS as the internal standard at Basra University (Iraq). Chemical reactions were monitored using thin layer chromatography (TLC) on 0.2 mm percolated plates of silica gel G60 F254 (Merck) with Benzene/ethanol (4:1) as mobile phase, and spots were examined with iodine vapor.

Synthesis of compound (1) 2-Chloro-N-(pyrimidin-2-yl) acetamide][22]

After stirring the mixture of pyrimidin-2-amine (0.0033 mole, 0.313 gm), absolute alcohol 10 mL, and anhydrous K_2CO_3 (0.1 gm), 2-chloroacetyl chloride (0.0033 mole, 0.26 mL) was added dropwise under chilled at 0–5°C. At 60–70°C, the mixture was refluxed for 7–8 hours. The solution was filtered, and the residue was washed with ethanol before the solvent was evaporated at reduced pressure, resulting in a solid product that was recrystallized with ethanol. Table 1 shows the physicochemical parameters of the compound (1)

The FTIR spectrum of compound (1) Figure 1, signifies the following characteristic absorption bands: ν 3 415 cm^{-1} (s) of NH (single band for secondary amine group); ν 3064 cm^{-1} (s) of (C-H Ar.); ν 2922 cm^{-1} (s) of (C-H alph.); ν 1647 cm^{-1} (s) of (C=O , amide group) ν 1627 cm^{-1} (s) of C=N band; ν 1544, 1400 cm^{-1} (s) of (C=C Ar.); ν 702 cm^{-1} (s) of C-Cl. ^{1}H-NMR (DMSO-d_6,δ) ppm (Figure 2): 3.3 (S, 2*H*, CH_2) 6.6-7.7 (m, 3*H*, aromatic protons), 9.6 (S, 1*H*, NH) .

Synthesis of compound (2) 2-hydrazinyl-N-(pyrimidin-2-yl) acetamide[23]

In 25 mL of ethanol, a combination of compound (1) (0.002 mole, 0.342 gm) and hydrazine hydrate (0.01 mole, 0.5 mL) was refluxed for 3 hours. The solid product was filtered and washed in ethanol before being recrystallized from ethanol. Table 1 shows the physicochemical parameters of the compound (2).

The FTIR spectrum of compound (2) (Figure 3), signifies the following characteristic absorption bands : ν 3444-3321 cm^{-1} (s) of NH (amine group) ; ν 2966,2929 cm^{-1} (s) of (C-H); ν 1649 cm^{-1} (s) of (C=O , amide group) ν 1604 cm^{-1} (s) of C=N band; ν 1539, 1454 cm^{-1} (s) of (C=C Ar.) ; 1317 bend of amine group, with the disappearance of band at 702 cm^{-1} of C-Cl.

Synthesis of compound (3) 2-(3,5-dimethyl-1H-pyrazol-1-yl)-N-(pyrimidin-2-yl) acetamide[23]

In abs. ethanol (15 mL), a mixture of compound (2) (0.0024 mole, 0.409 gm) and acetylacetone (0.0024 mole, 0.24 mL) was refluxed for 6 hours. Solid product was recovered, dried, and recrystallized from ethanol. Table 1 shows the physicochemical parameters of the compound (3)

The FTIR spectrum of compound (3) (Figure 4), signifies the following characteristic absorption bands: ν 3325 cm^{-1} (s) of NH (amine group); ν 2947,2723 cm^{-1} (s) of (C-H); ν 1647 cm^{-1} (s) of (C=O, amide group) ν 1627 cm^{-1} (s) of C=N band; 1402cm^{-1} (s) of (C=C Ar.) ; 1317 bend of amine group.

Synthesis of compound (5) 3-(2-(pyrimidin-2-yl)hydrazono) pentane-2,4-dione[23]

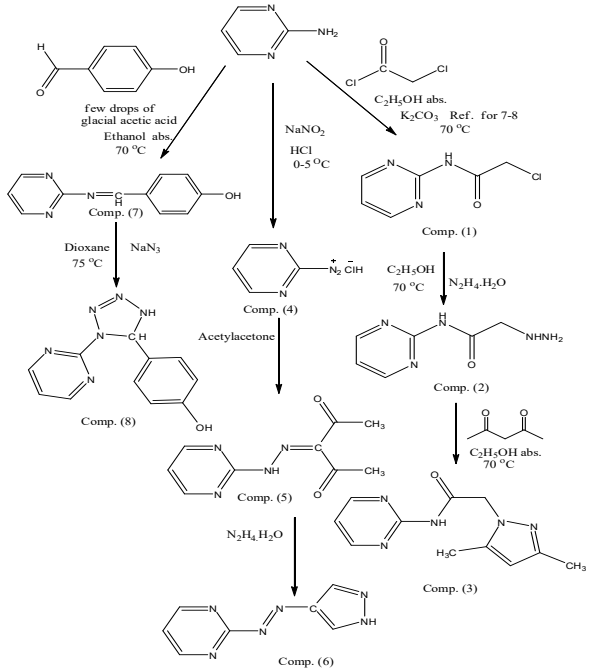
In abs, a cold combination of acetyl acetone (0.005 mole, 0.5 gm) and sodium acetate (0.005 mole, 0.42 gm). ethanol (12 mL) was added dropwise to the diazonium salt (4) solution over 10 minutes, stirring for 30 minutes, and the reaction mixture was allowed for roughly 2 hours at room temperature. The orange solid was filtered, dried, and recrystallized from ethanol. Table 1 shows the physicochemical parameters of the compound (5).

The FTIR spectrum of compound (5) Figure 5, signifies the following characteristic absorption bands: ν 3435 cm^{-1} (s) of NH (amine group); ν 3066 cm^{-1} (s) of (C-H Ar.); ν 3933 cm^{-1} (s) of (C-H alph.); ν 1685 cm^{-1} (s) of (C=O, ketone) ν 1666 cm^{-1}; 1639(s) of C=N band; 1556; 1544 cm^{-1} (s) of (C=C Ar.).

Synthesis of compound (6) 2-((1H-pyrazol-4-yl)diazenyl) pyrimidine[23]

Compound (5) (0.005 mole, 1 gm) and hydrazine hydrate (0.01 mole, 0.5 gm) were heated in ethanol (25 mL) under reflux for 10–12 hours. Chilled and a yellow solid was produced. The solid was filtered, dried and recrystallized from ethanol. Table 1 shows the physicochemical parameters of the compound (6).

The FTIR spectrum of compound (6) (Figure 6), signifies the following characteristic absorption bands: ν 3398 cm^{-1} (s)



Scheme 1: Synthesis of target compounds.

Table(1) The physiochemical properties of the synthesized compounds

No. comp.	Molecular formula	Molecular weight	Melting point (°C)	Description	Yield %	Rf
1	$C_6H_6ClN_3O$	171	277-276	Dark purple precipitate	62	08
2	$C_6H_9N_5O$	167	216	Yellow precipitate	83	0.8
3	$C_{11}H_{13}N_5O$	231	>300 decomposition	Yellow precipitate	87	0.8
5	$C_9H_{10}N_4O_2$	206	viscous compound	Orange	79	0.8
6	$C_7H_6N_6$	174	viscous compound	yellow	79	0.9
7	$C_{11}H_9N_3O$	199	110	Pale yellow precipitate	64	0.8
8	$C_{11}H_{10}N_6O$	242	83	Yellow precipitate	82	0.7

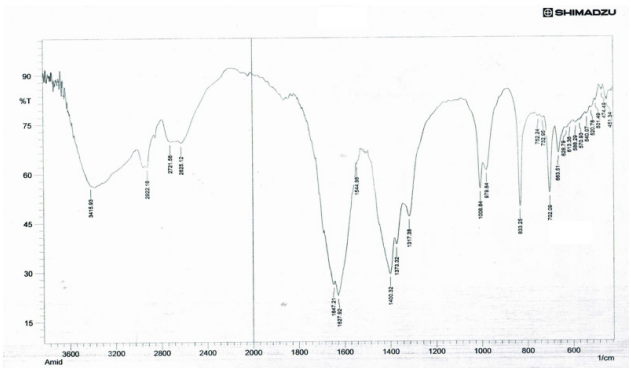


Figure 1: FTIR spectrum of compound (1).

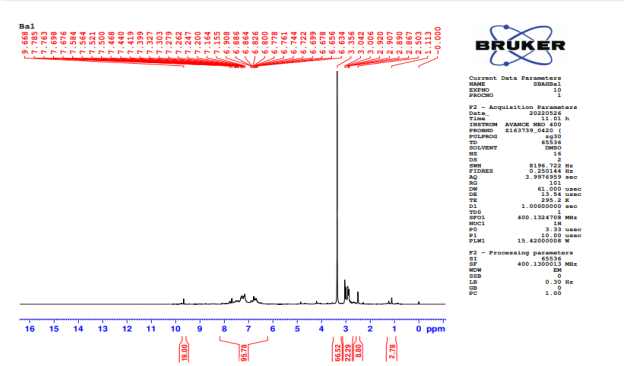


Figure 2: ^{1}H-NMR spectrum of compound (1).

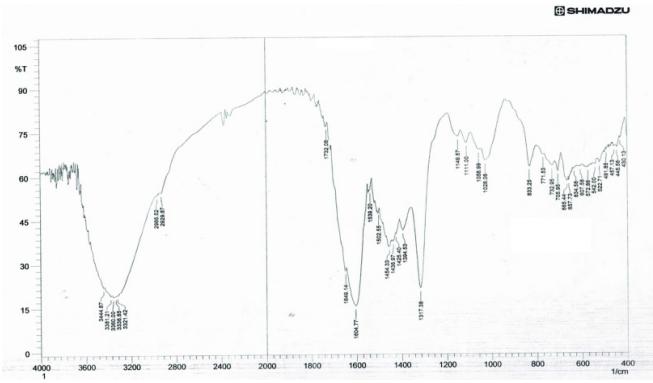


Figure 5: FTIR spectrum of compound (2).

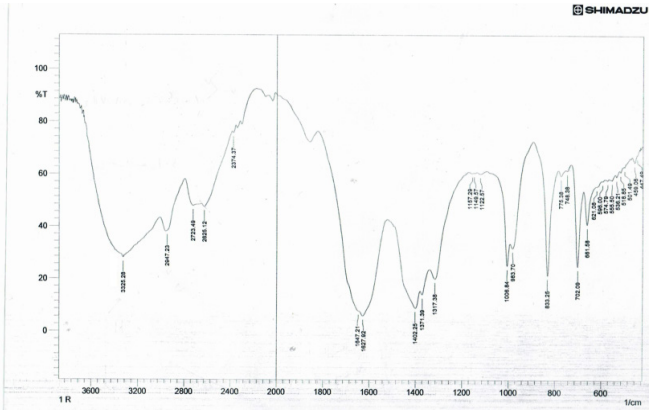


Figure 5: FTIR spectrum of compound (3).

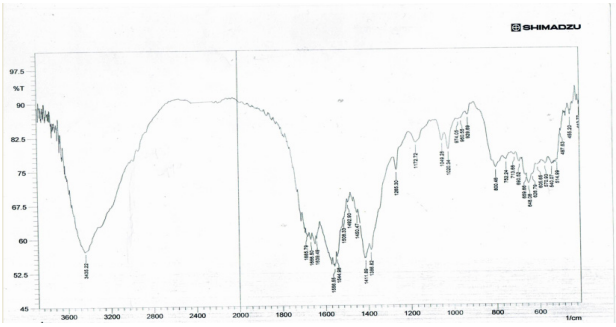


Figure 5: FTIR spectrum of compound (5).

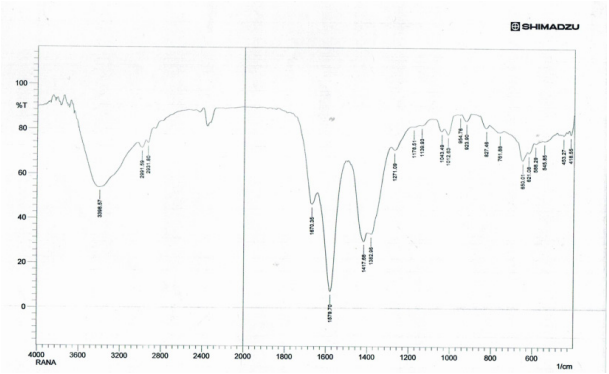


Figure 6: FTIR spectrum of compound (6).

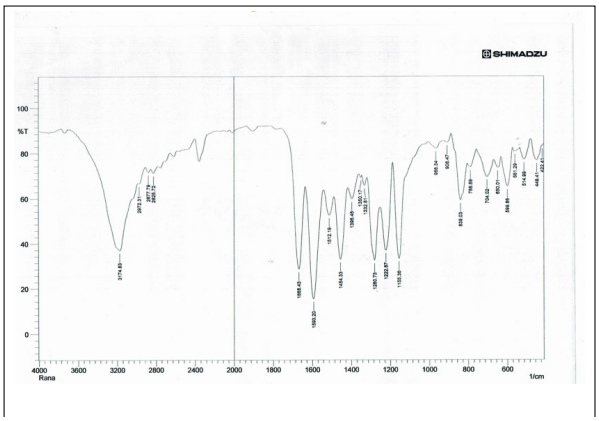


Figure 7: FTIR spectrum of compound (7).

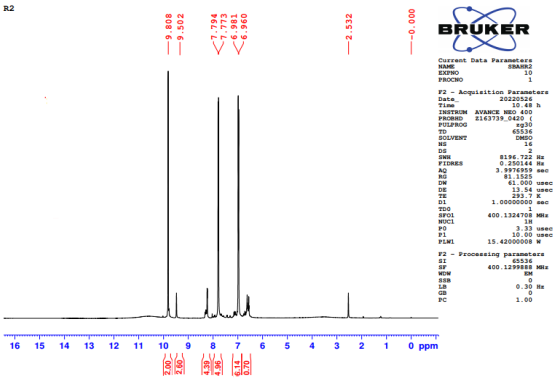


Figure 8: ^{1}H-NMR spectrum of compound (7).

of NH (amine group); ν 2991 cm^{-1} (s) of (C-H Ar.); ν 281 cm^{-1} (s) of (C-H alph.); ν 1670 cm^{-1} (s), (C=N) ν, 1579cm^{-1} (s) of C=C cyclic; 1417 N=N .

Synthesis of compound (7) 4-((pyrimidin-2-ylimino)methyl) phenol[24]

In ethanol (15 mL) with one drop of glacial acetic acid, pyrimidin-2-amine (0.002 mole, 0.19 gm) and 4-hydroxybenzaldehyde (0.002 mole, 0.24 gm) were refluxed for 5 hours and held overnight until the precipitate was formed. From ethanol, the solid was filtered, dried, and recrystallized. Table 1 shows the physicochemical parameters of the compound (1).The FTIR

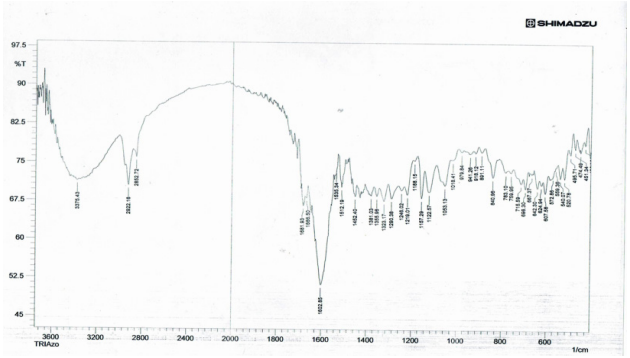


Figure 9: FTIR spectrum of compound (8).

spectrum of compound (7)

The FTIR spectrum of compound (7) Figure 7, signifies the following characteristic absorption bands: ν 3174 cm^{-1} (s) of OH (phenol group); ν 2972 cm^{-1} (s) of (C-H Ar.); ν 2877 cm^{-1} (s) of (C-H alph.); ν 1668 cm^{-1} (s) of (C=N schiff base) ν 1593 cm^{-1} (s) of C=N cyclic; 1512,1454 C=C Ar.

^{1}H-NMR (DMSO-d$_6$,δ) ppm Figure 8: 6.9 (2*H*,2CH-C-OH) 7.7 (3*H*,CHAr.), 7.79 (2*H*,CH-C=N) 9.5 (S, 1*H*, OH phenol),9.8 (S,1H,C=NH)

Synthesis of compound (8) 4-(1-(pyrimidin-2-yl)-4,5-dihydro-1H-tetrazol-5- yl)phenol[25]

Compound (7) (0.002 mol, 0.42 gm) was dissolved in dioxane (5 mL) and mixed with sodium azide (0.002 mol, 0.13 gm). The mixture was warmed in a water bath for 7 hours at 75°C. From ethanol, the precipitate was filtered and recrystallized. Table 1 shows the physicochemical parameters of the compound (8)

The FTIR spectrum of compound (8) Figure 9, signifies the following characteristic absorption bands: ν 3375 cm^{1} (s) of OH (phenol group) overlap with NH group; ν 3066, 2922 cm^{-1} (s) of (C-H); 1681cm^{-1} due to the υ(C=N) inside pyrimidine ring; ν 1602 cm^{-1} (s) of N=N inside pyrimidine ring. The weak and medium absorption bands at 1512 and 1452 cm^{-1} are attributed to the υ (C= C) aromatic ring.

RESULTS AND DISCUSSION

Following the chemical sequences illustrated in Scheme 1, novel pyrazole and tetrazole derivatives containing diverse moieties such as pyrimidine ring, azo, and amid group were produced. The starting material for synthesizing the labeled compounds (1-8) is 2-amino pyrimidine, which reacted with chloroacetyl chloride in boiling ethanol with K_2CO_3 as a base serving as a catalyst in the generation of the amide group in compound (1). The NH stretching absorption band near 3488cm-1 appeared as a single band in the FTIR spectrum, along with new stretching absorption bands at 1647 cm^{-1} for C=O, amide, and appearance absorption bands at 702 cm^{-1} for C-Cl. Nucleophilic substitution reaction of compound (1) with hydrazine in ethanol generated product (2). The synthesis of the target compound was confirmed by the emergence of a stretched absorption band of the amine group at frequency 3444-3321 cm^{-1} and the elimination of the C-Cl band at 702 cm^{-1} in the FTIR spectrum (Figure 3). In boiling ethanol,

Table 2: Study the biological activity

Comp. No.	*Concentration mg/mL*	*Bacteria*		*Fungi*	
		Gram-negative K. pneumoniae	*Gram-positive E. faecalis*	*C. dubliniensis*	*C. trichomonas*
		Zone inhibition in mm			
8	25	16	17	19	18
	50	17	19	20	19
	75	18	21	21	21
	100	19	24	23	23
6	25	16	17	Zero	17
	50	16	18	12	18
	75	17	19	14	19
	100	18	20	15	20

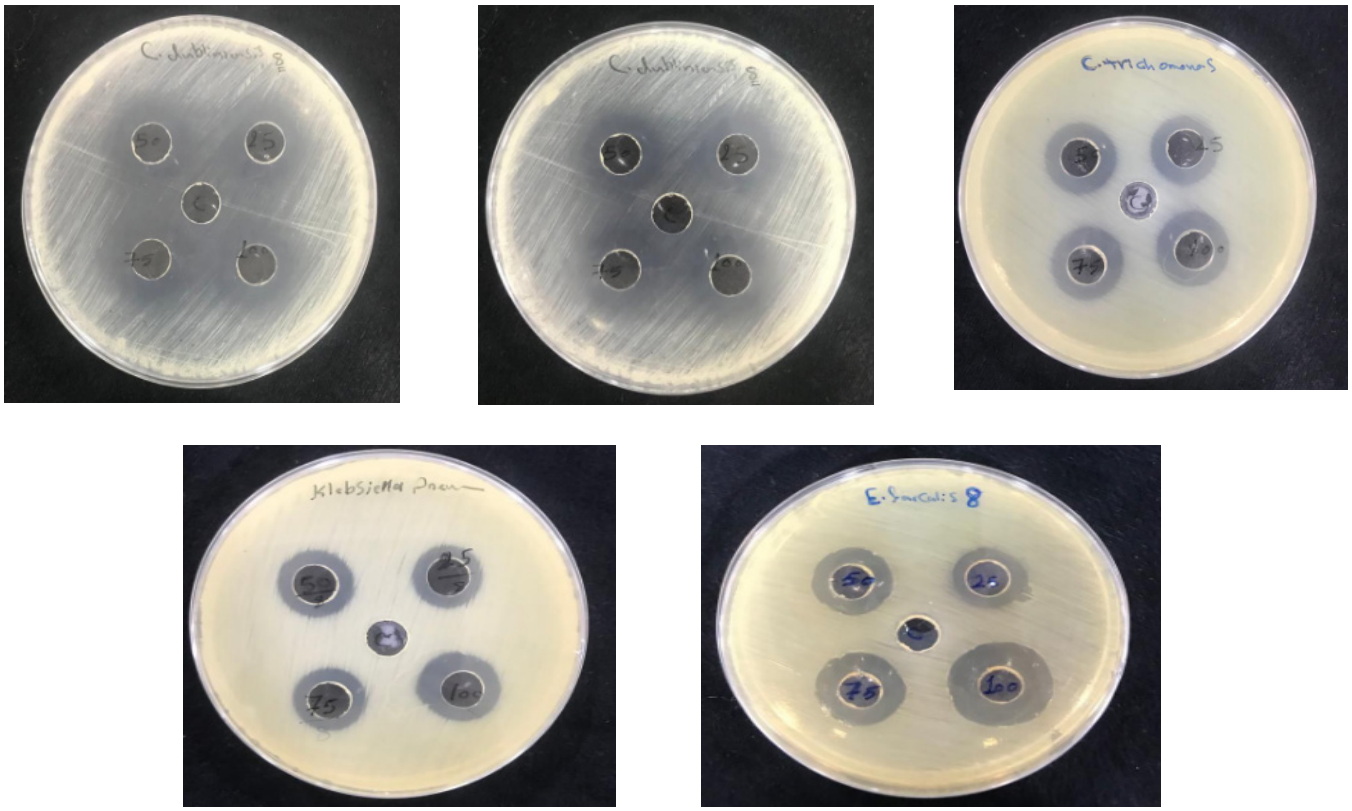


Figure 10: The biological effect of compound (8).

chemical (2) reacts with acetylacetone lead to ring closure in compound (3). FTIR shows an NH stretching band at 3325 cm^{-1} and a C=N cyclic band at 1627 cm^{-1}. The diazotation of 2-aminopyrimidine afforded the diazonium salt (4), which was then coupled with an active methylene molecule such as acetyl acetone to generate the azo derivative (5). The existence of absorption bands at 3205, 3234 cm^{-1} (NH), 1683 cm^{-1} (C=O), and 1624 cm^{-1} (C=N) confirmed its structure. The Schiff base (7) was created via condensation of 2-aminopyrimidine with 4-hydroxybenzealdehyde in abs. ethanol with glacial acetic acid. The existence of the azomethine (CH=N) stretching band at 1668 cm^{-1} in its FTIR spectra and the absence of the NH2 stretching band suggested the production of schiff base. Finally, following reacting chemical (7) with sodium azide in dioxane for 7-8 hours, the tetrazole ring (8) was formed. The mechanism of this reaction has been studied thoroughly as [2+3] cycloaddition, also known as 1,3-dipolar cycloaddition. The addition of unsaturated systems, dipolarphiles, to 1,3-dipoles, a molecule with resonance contributors in which the positive and negative charges are in 1,3-positions relative to each other, is involved. The outcome is a ring with five members.[26,27] The elimination of the strong absorption band at 1637 cm^{-1} due to the (C=N) exocyclic and the emergence of an absorption band at 1602 cm^{-1} due to the (N=N) inside tetrazole ring were observed in the FTIR spectrum, indicating the formation of the tetrazole ring; ν1681 cm^{-1} (s) of C=N inside

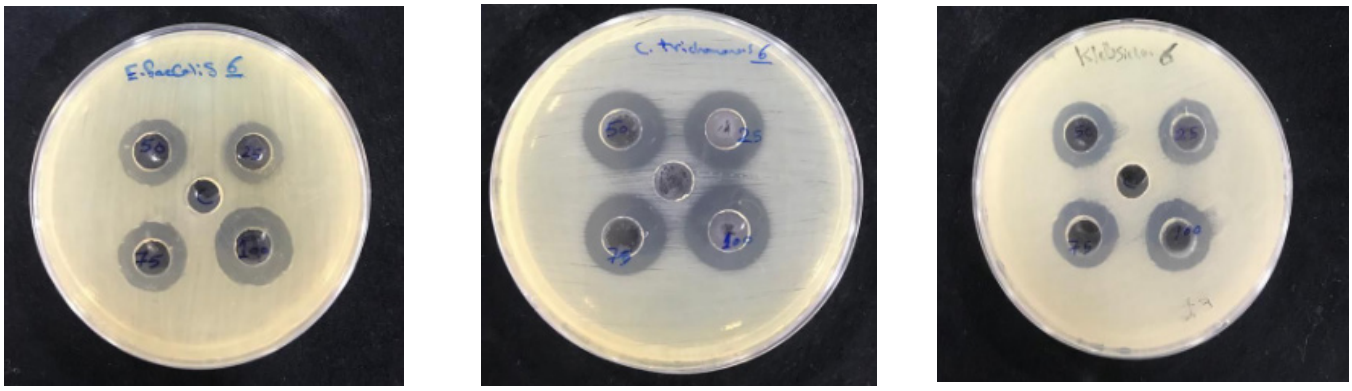


Figure 11: The biological effect of compound (6).

pyrimidine ring . The (C=C) aromatic ring is responsible for the weak and medium absorption bands at 1512 cm^{-1} and 1452 cm^{-1}, respectively.

The biological effect of pyrazole derivative compound (7) and tetrazole derivative compound (8) as antibacterial against Gram-positive (*E. faecalis*) and Gram-negative (*K. pneumoniae*) also was studied their biological activity as antifungals against *C. dubliniensis* and *C. trichomonas* in concentration (25, 75, 50 and 100) mg/mL. Pyrazole and tetrazole derivative showed biological activity against bacteria and fungi, but the biological effect of tetrazole derivative is higher than that of the pyrazole ring on the microbial growth (Table 2).

CONCLUSION

In conclusion, Schiff base, azo compounds and amide derivatives were synthesized in this study in good yield as good intermediate for synthesis of pyrazole and tetrazole derivatives (Scheme 1) These derivatives also were synthesized in good yield. Pyrazole and tetrazole derivatives have high melting point, that refer to their stability. These derivative , compounds (6,8) were evaluated their biological activity as antibacterial by using two types from bacterial (*E. faecalis* as positive bacterial) and (*K. pneumoniae* as negative bacterial) and as anti-fungal against *C. dubliniensis* and *C. trichomonas* in concentration 25, 75, 50 and 100 mg/mL. These tested compound show biological activity against the chosen microbial especially tetrazole ring which appeared zone of inhibition higher than pyrazole ring.

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