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A Novel Oxopyrimidine and Pyrazole Derivatives: Synthesis, Characterization and Biological Activity Study

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Abstract:
Novel oxopyrimidine (3,7) and pyrazole (4,8) compounds bearing an azo group were successfully synthesized and characterized using FTIR, ^{1}HNMR, and ^{13}CNMR spectroscopy. The diazonium salt was first synthesized by reacting p-amino acetophenone with nitrous acid. This salt was added to activated aromatic rings (o-nitro phenol, β-naphthol) to produce azo compounds (**1**,**5**). Following the reaction of these azo compounds with salicylaldehyde, chalcone derivatives (**2**,**6**) were produced. Subsequently, these synthetic compounds were cyclized to create pyrazole derivatives (**4**,**8**) and oxopyrimidine (**3**,**7**) using urea and 2,4-dinitrophenyl hydrazine. Furthermore, the antibacterial activity of synthesized compounds was elevated against two types of bacteria (*Pseudomonas* and *Staphylococcus aureus*. According to the results, compounds 1-[4-(4-Hydroxy-3-nitro-phenylazo)-phenyl]-ethanone (**1**) and 1-[4-(2-Hydroxy-naphthalen-1-ylazo)-phenyl]-ethanone (**5**) were effective in treating the selected bacterium, while the other compounds are inactive

Keywords: Synthesis, Azo compounds, Antimicrobial activity, Chalcone, Oxopyrimidine, Pyrazole

مشتقات الأوكسو بيريميدين والبيرازول الجديدة: تحضير،تشخيص و دراسةالفعالية البيولوجية لها

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الخلاصة

تم تحضير مشتقات الأوكسوبيريميدين **(3،7)** والبيرازول **(4،8)** الجديدة التي تحمل مجموعة الآزو بنجاح و تشخيصها بواسطة التحليل الطيفي FTIR – ^{1}HNMR و^{13}C–NMR. تم تحضير ملح الدايازونيوم بداية من تفاعل بارامينواسيتوفينون مع حامض النتروز . تم اضافة الملح المحضر الى حلقات الاروماتية المنشطة (β–naphthol، o–nitro phenol) لتحضير مركبات الآزو **(1،5)**. وبعد التفاعل بين مركبات الآزو هذه والساليسيلالدهيد، تم انتاج مشتقات الجالكون **(2،6)**. بعد ذلك، تم الغلق الحلقي للمركبات المحضرة للحصول على مشتقات أوكسوبيريميدين **(3،7)** والبيرازول **(4،8)** باستخدام اليوريا و2،4–داي نيتروفينيل هيدرازين على التوالي. علاوة على ذلك، تم اختبار فعالية المركبات المحضرة ضد نوعين من

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البكتيريا (*Pseudomonas* و *Staphylococcus aureus*) .طبقا للنتائج التي تم الحصول عليها، وجد ان مركبات 1-[4-(4-هيدروكسي-3-نيترو-فينيلازو)-فينيل]-إيثانون (**1**) و1-[4-(2-هيدروكسي-نفثالين-1-يلازو)-فينيل] -كان الإيثانون (**5**) نشطة وفعالة في معالجة البكتيريا المختارة، بينما كانت المركبات الأخرى غيرنشطة وغير فعالة.

1.Introduction:

Dyes and their derivatives play a crucial role in various fields, including medicine, industry, and chemistry, due to their diverse applications. Over the years, scientists and researchers have explored numerous direct methods to synthesize these compounds [1-7]. Azo dyes are commonly used to color leather items, clothes, and foods [8-12]. A significant class of naturally occurring flavonoids with a broad range of biological activity is the group of molecules known as chalcones, which contain two aromatic rings joined by a Keto vinyl chai [13-17]. The synthesis of chalcones has been described using various methods and ideas. Aldol condensation and Claisen-Schmidt condensation remain two of the most widely used techniques. The Wittig reaction, Fridel-Crafts acylation of cinnamoyl chlorides, and Suzuki coupling reaction are other well-known methods [18-22]. Chalcones serve as important synthetic intermediates in the production of various five-, six-, and seven-membered heterocyclics, such as isoxazoles, pyrazoles, and other heterocyclic systems, chalcones play a crucial role as intermediates [23, 24]. In numerous chemical and biological research, oxo pyrimidines and their nucleoside derivatives have been investigated due to their interesting pharmacological characteristics, consequently as a part of the ongoing program for synthesizing fused heterocyclic systems with anticipated biological characteristics [25-28]. A heterocyclic five-membered ring molecule called pyrazole has nitrogen atoms in the 1st and 2nd places. Pyrazole has intriguing pharmacological properties, including activating tumor cell growth, analgesic, anti-leishmanial, anti-inflammatory, enzyme inhibitory, anticancer effects, and antioxidant [29-34]. The objective of this study is to design and synthesize new oxopyrimidine and pyrazole derivatives and assess their potential as antibacterial agents.

2.Experimental part

2.1. Materials and Instruments:

All solid and liquid chemicals used in this study were obtained from the Fluka and BDH chemical suppliers. The FTIR spectra were recorded using a Japanese Shimadzu Spectrophotometer model 8300 FT-IR device with a potassium bromide disc. 1HNMR and 13CNMR spectra were recorded at 300 MHz using a Brüker ACF 300 spectrometer with DMSO-d6 as a solvent and TMS as the internal standard. Also, a Gallen Kamp capillary melting point instrument was utilized to record melting points.

2.2. Methods for the synthesized compounds

*Synthesis of Azo compounds (**1**,**5**) [35]*

A sodium nitrite (cold solution) (2 g, 2 mmol) in 3.5 ml of water was used to diazotize a well-stirred solution of p-(amino acetophenone) (1.3 g, 1 mmol) in 5 mL of concentrated HCl. The reaction mixture was stirred at the same temperature for 2 hrs. Prior to the addition of the cold diazonium salt solution, the coupling chemical solution was thoroughly mixed with the dampened KOH solution under vigorous stirring. The resultant mixture was stirred. The resultant product underwent filtering, drying, and recrystallization using ethanol.

*Synthesis of Chalcone derivatives (**2**,**6**) [36]*

Salicylaldehyde (1.3 ml, 1 mmol) was added to the ethanol absolute (5 ml) containing a ketone derivative (1,5) (1 mmol). Sodium hydroxide (30%) was then added at a volume of 2

ml. Using a magnetic stirrer, the liquid was swirled in the cold bath for 30 minutes at room temperature. The reaction mixture was then stirred all night. The precipitation was re-crystallized from absolute ethanol after the solvent was evaporated.

*Synthesis of oxopyrimidine derivatives (**3**,**7**) [37]*

The reaction mixture containing sodium carbonate (1.05 g, 1 mmol) and urea (0.6 g, 1 mmol), which were gradually added to the mixture of chalcone derivatives (**2**,**6**) (0.01 mmol). After that, the mixture was refluxed for six hours. After evaporating the solvent, the resulting solid product was recrystallized from ethanol.

*Synthesis of pyrazole derivatives (**4**,**8**) [38]*

A mixture of chalcones derivatives (**2**,**6**) (2 mmol) and 2,4-dinitrophenyl hydrazine (0.39 g, 2 mmol) was refluxed for about 10 to 11 hrs. Then, the formed solution was poured into a petri dish, the solvent was evaporated, and the resulting product was recrystallized using ethanol.

Table 1: Physical characteristics of the synthetic compounds

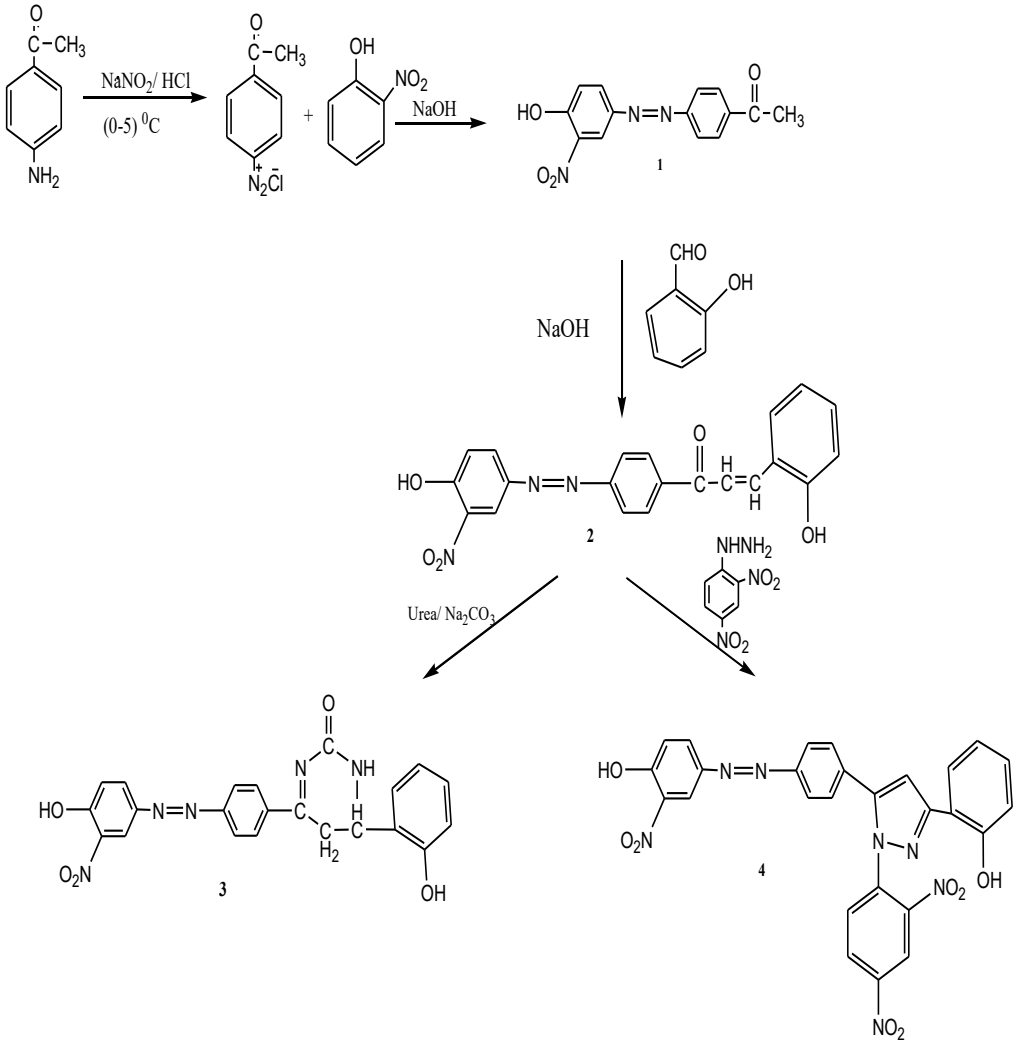
Compound number	Color	m.p. °C	Yield %
1	Yellow	Gum	88
2	Orange	188 - 190	92
3	Pale Orange	223 - 225	91
4	Black	298 - 300	94
5	Pale Yellow	210 - 212	65
6	Pale Orange	238 - 240	60
7	Yellowish- orange	278 - 280	63
8	Brown	198 - 200	73

Antibacterial activity [39-41]

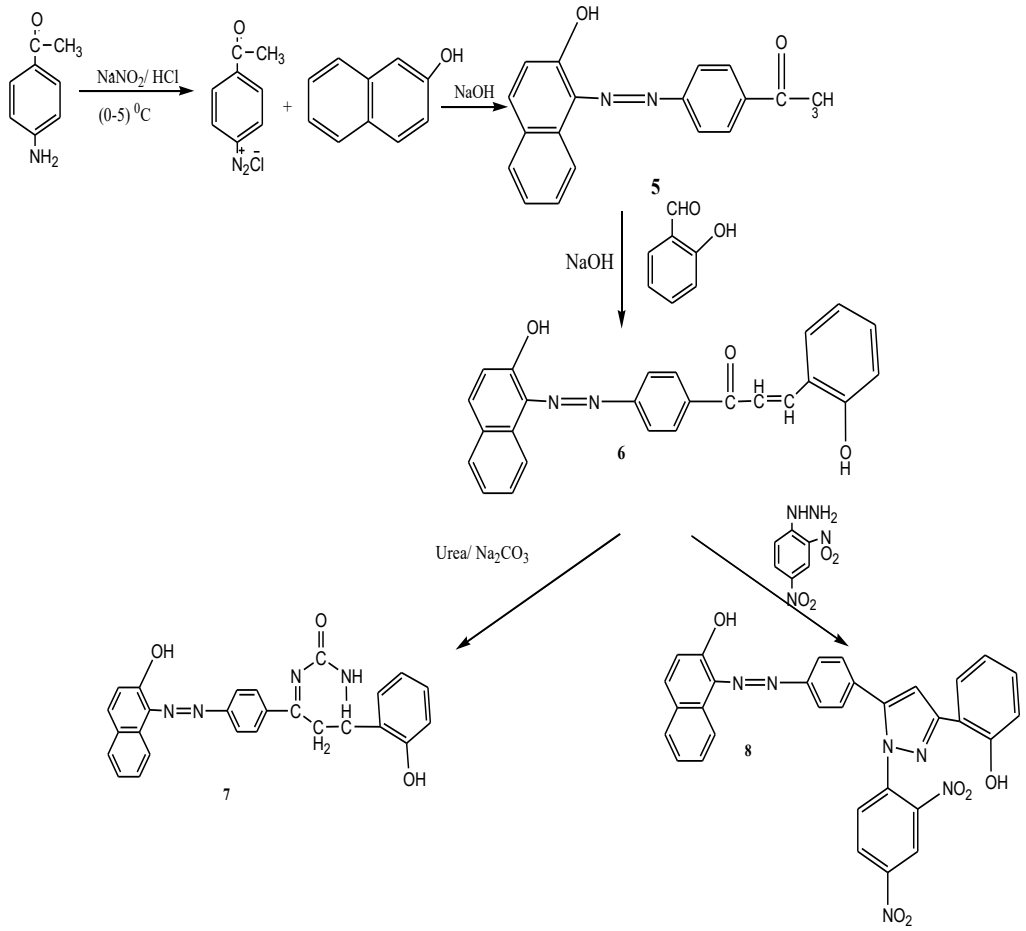
Using the agar diffusion method, the antibacterial activity of each produced molecule was evaluated using *Pseudomonas* (gram-negative bacteria) and *Staphylococcus aureus* (gram-positive bacteria). The nutrient agar plates were inoculated with 0.1 ml of each isolate, and then a cork-borer was utilized to create 8 mm wells in the agar. These wells were subsequently filled with 0.1 ml of the synthesized compounds. Following a 24-hour incubation period at 37°C, the diameter of the inhibition zones on the inoculation plates with various isolates was measured.

3. Results and discussion

In the first step of this research, azo compounds were synthesized by reacting of diazonium salt of amine derivative (*p*-amino acetophenone) with phenolic derivatives, and a distinctive band of the azo group appeared in the spectrum of FTIR. The next step included synthesizing chalcone derivatives from the reaction of ketones containing azo dyes, which were synthesized in the previous step, with salicylaldehyde. In this stage, the spectrum exhibits characteristic bands attributable to the CH=CH and C=O functional groups present in the chalcone structure. The synthesis of oxopyrimidine was then achieved by facilitating a reaction between these chalcones and urea. The disappearance of the double bond and C=O of chalcones and the appearance of the C=O amide and NH bond were observed in FTIR spectra [42,43]. Finally, pyrazole derivatives were synthesized from reacting chalcones with 2,4-dinitrophenyl hydrazine. These bands and others are listed in Table 2.



Scheme 1. The synthetic route of compounds **1-4.**



Scheme 2: The synthetic route of compounds **5-8**.

Table 2: Infrared absorption (cm^{-1}) for compounds 1-8

Compound number	υC-H Aliphatic	υC-H Aromatic	υC=C Aromatic	υN=N	υNO_2	υO-H	υC=C chalcone	Others
1	2873 2931	3014	1585 1600	1535	1359 1514	3359	-----	C=O, 1720
2	2871 2937	3062	1580 1600	1546	1361 1506	3427	1654	C=O 1679
3	2815 2933	3050	1590 1604	1481	1355 1546	3438	-----	C=N, 1618, C=O, 1670
4	2833 2931	3035	1593 1616	1454	1338 1512	3392	-----	C=N, 1630
5	2858 2927	3056	1556 1600	1512	-----	3433	----	C=O ketone, 1720
6	1869 2945	3051	1580 1600	1488	-----	2433	1620	C=O, 1662
7	2813 2975	3030	1600 1620	1490	-----	3438	----	C=N, 1635, C=O, 1672, N-H, 3210
8	2871 2929	3045	1590 1600	1537	1350 1517	3421	----	C=N, 1610

The ^{1}H-NMR and ^{13}C-MNR spectra were done for all the synthesized compounds, as shown in Tables 3 and 4.

Table 3: ^{1}H-NMR of the synthesized compounds.

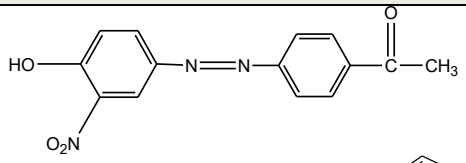
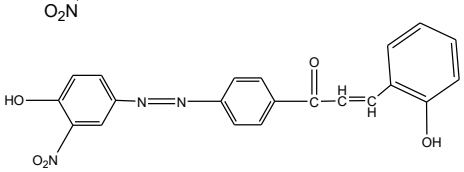
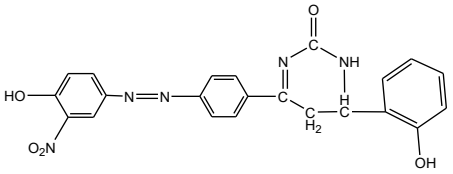
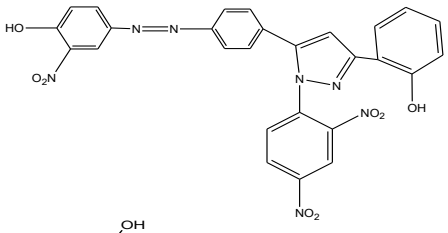
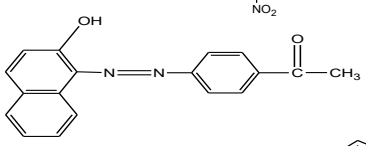
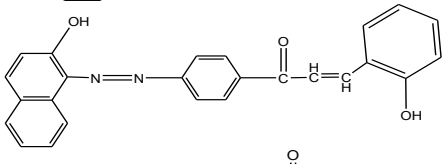
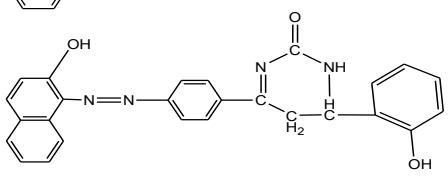
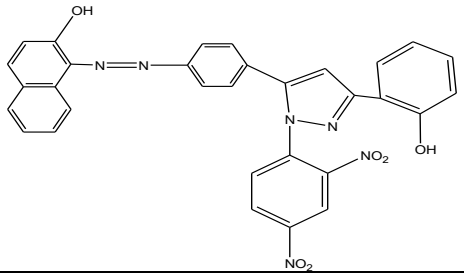
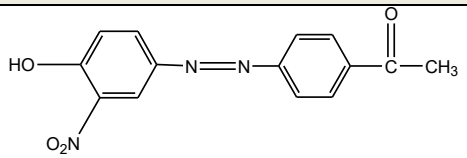
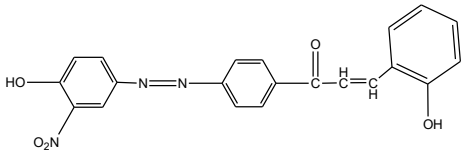
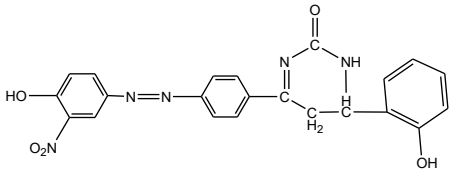
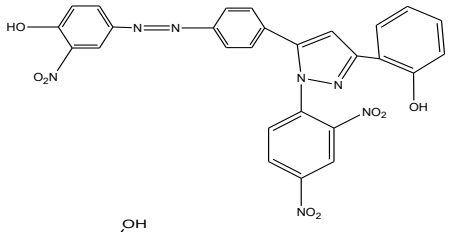
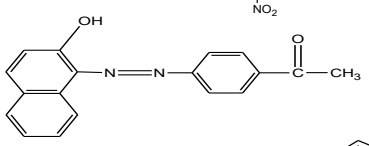
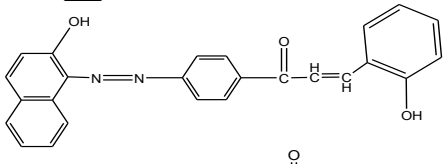
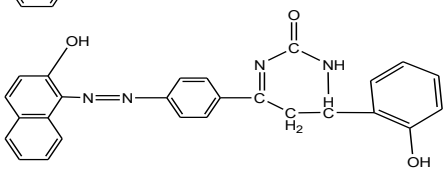
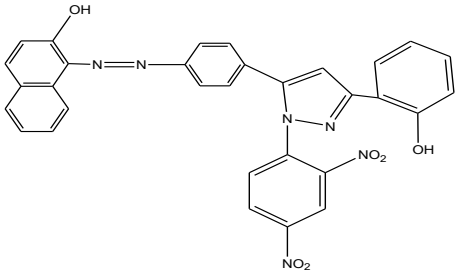
Compound number	Compound structure	HNMR spectral data (δ ppm)
1		2.4 (s, 3H, CH_3), 6.8-8 (m, 7H, Ar), 10.53 (s, 1H, OH)
2		6.1 (d, 2H, CH=CH), 6.5-8 (m, 11H, Ar), 9.7 (s, 1H, OH)
3		2.6 (d, 2H, CH_2), 3.7 (t, 1H, CH), 6.5-7.7 (m, 11H, Ar), 8.4 (s, 1H, NH), 9.5 (s,1H, OH)
4		5 (s, 1H, CH), 6.8-8.8 (m,14H, Ar), 10 (s, 1H, OH)
5		2.4 (s, 3H, CH3), 7.1-8 (m, 10H, Ar), 9.9 (s, 1H, OH)
6		6.5 (d, 2H, CH=CH), 6.5-8 (m, 14H, Ar), 10.2 (s, 2H, OH)
7		2.5 (d, 2H, CH_2), 3.6 (t, 1H, CH), 6.7-8 (m, 14H, Ar), 8.4 (s, 1H, NH), 9.5 (s,2H, OH)
8		5.5 (s, 1H, CH), 6.7-8.6 (m, 17H, Ar), 9.7 (s, 2H, OH)

Table 4: ^{13}C-NMR of the synthesized compounds.

Compound number	Compound structure	^{13}CNMR spectral data (δ ppm)
1		26 (CH_3), 40 (C-N), 115 (C-NO_2), 120 (C-OH), 123-154 (C-C, Ar), 167(C=O)
2		40 (C-N), 110 (C-NO_2), 114 (C-OH), 122-159 (C-C, Ar), 197(C=O)
3		26 (C-CH), 40 (C-CH_2), 40 (C-NH), 109 (C-NO_2), 116 (C-OH), 116-136 (C-C, Ar), 167(C=O)
4		38, 40 (C-CH) pyrazole ring, 40 (C-N), 111 (C-NO_2), 116 (C-OH), 116-149 (C-C, Ar), 157(C=O)
5		27 (CH_3), 40 (C-N), 109 (C-OH), 115-155 (C-C, Ar), 157(C=O)
6		40 (C-N), 115 (C-OH), 118-145(C-C, Ar), 197(C=O)
7		29 (C-CH), 40 (C-CH_2), 40 (C-NH), 109 (C-OH), 116-136 (C-C, Ar), 167(C=O)
8		39, 40 (C-CH) pyrazole ring, 40 (C-N), 116 (C-NO_2), 117 (C-OH), 118-148 (C-C, Ar), 158(C=O)

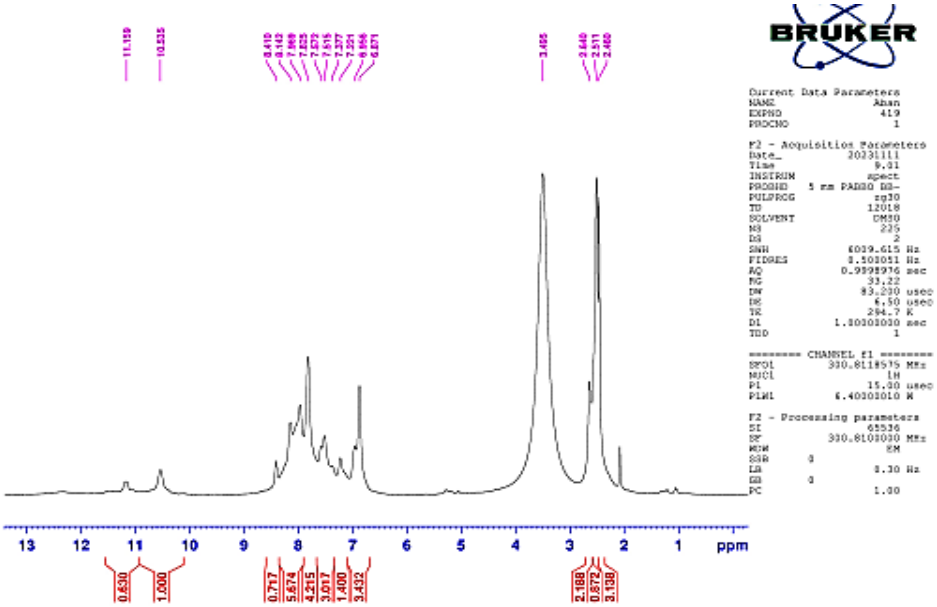


Figure 1: [1]HNMR spectrum of the compound **1**

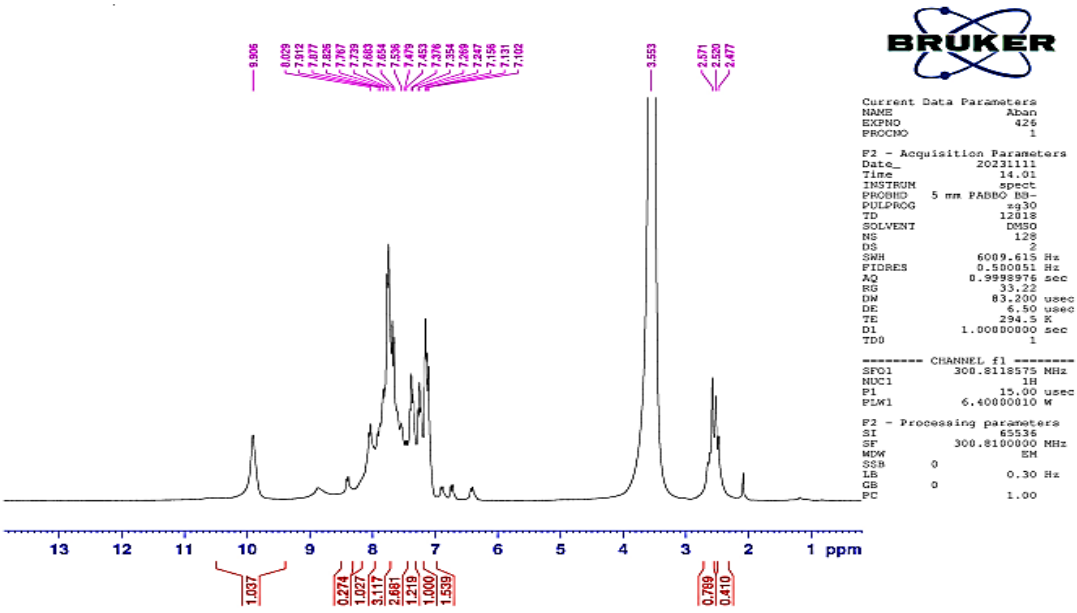


Figure 2: [1]HNMR spectrum of the compound **5**

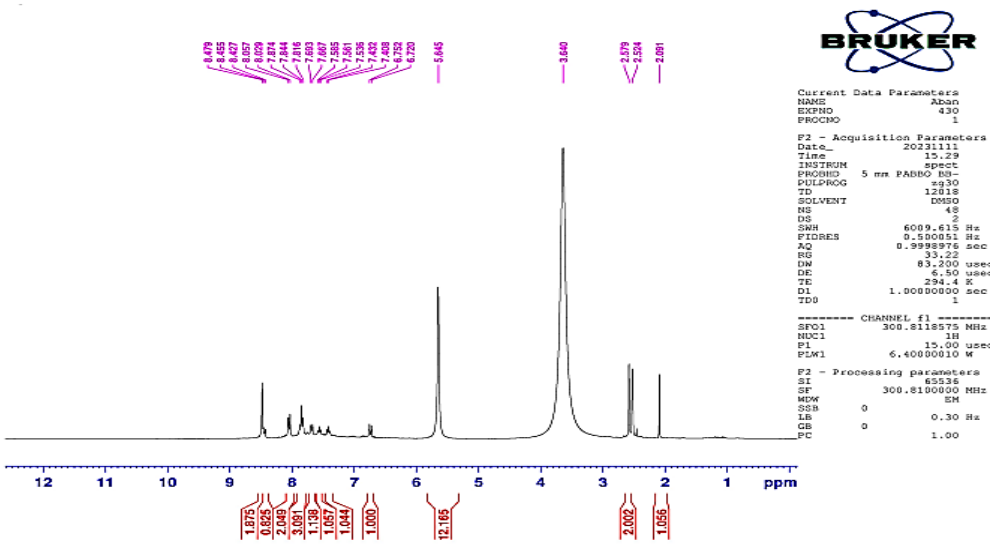


Figure 3: [1]HNMR spectrum of the compound **7**

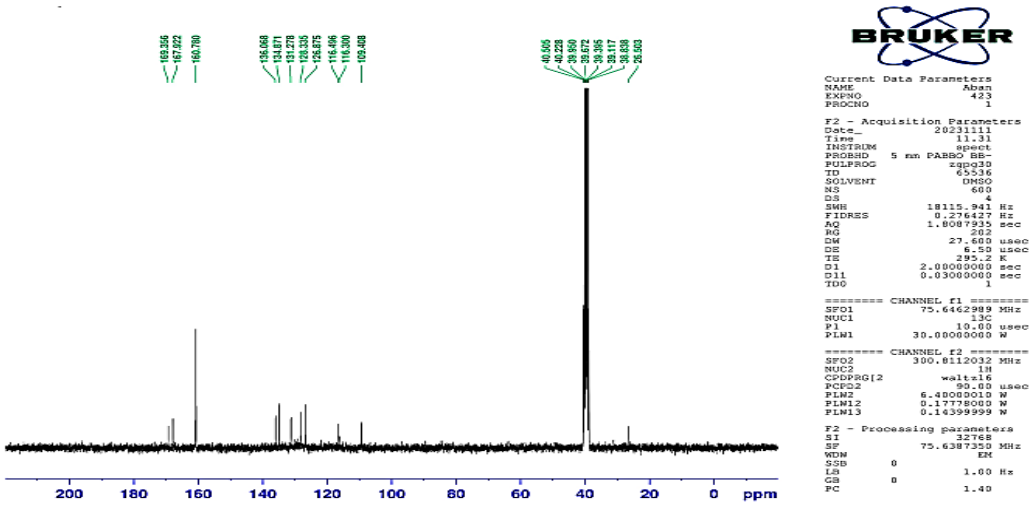


Figure 4: [13]CNMR spectrum of the compound **3**

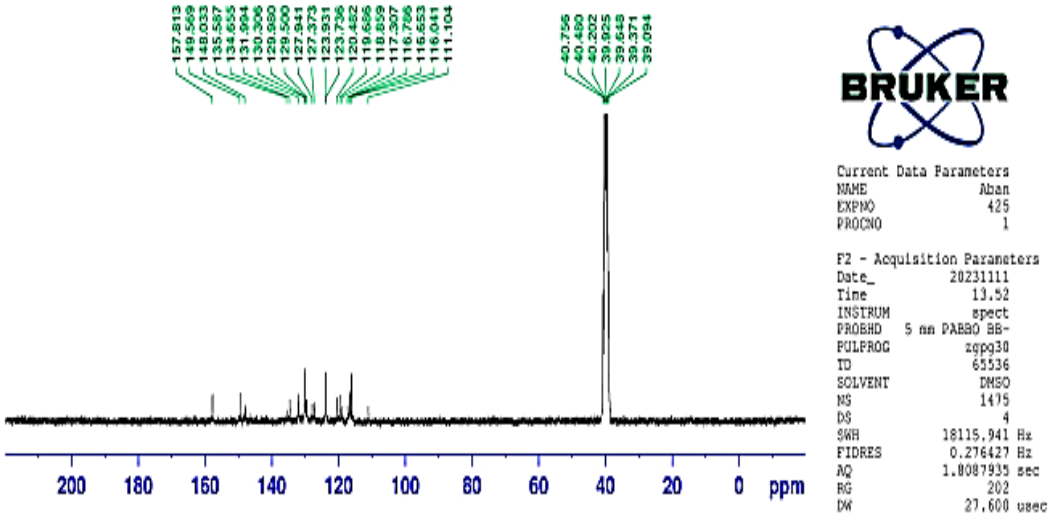


Figure 5: [13]CNMR spectrum of the compound **4**

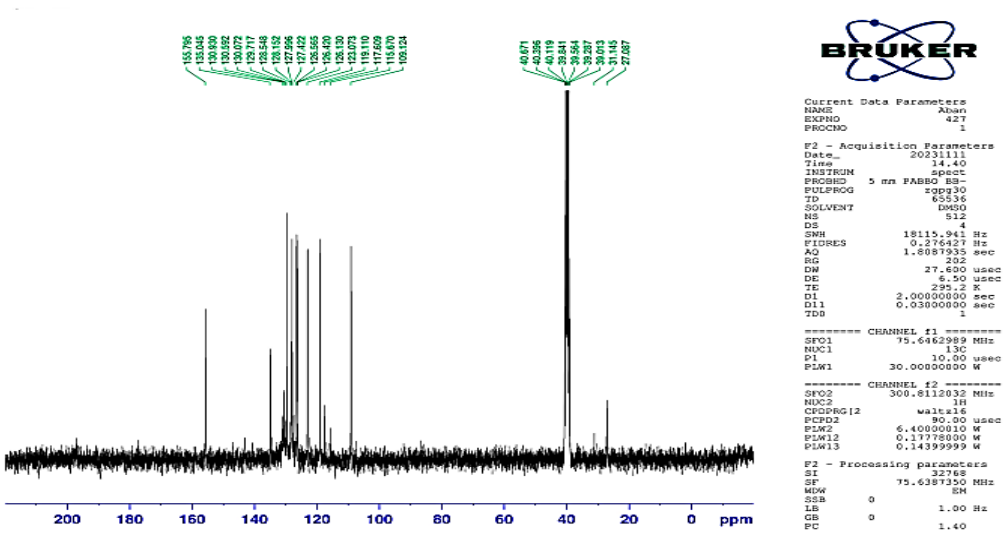


Figure 6: ^{13}CNMR spectrum of the compound **5**

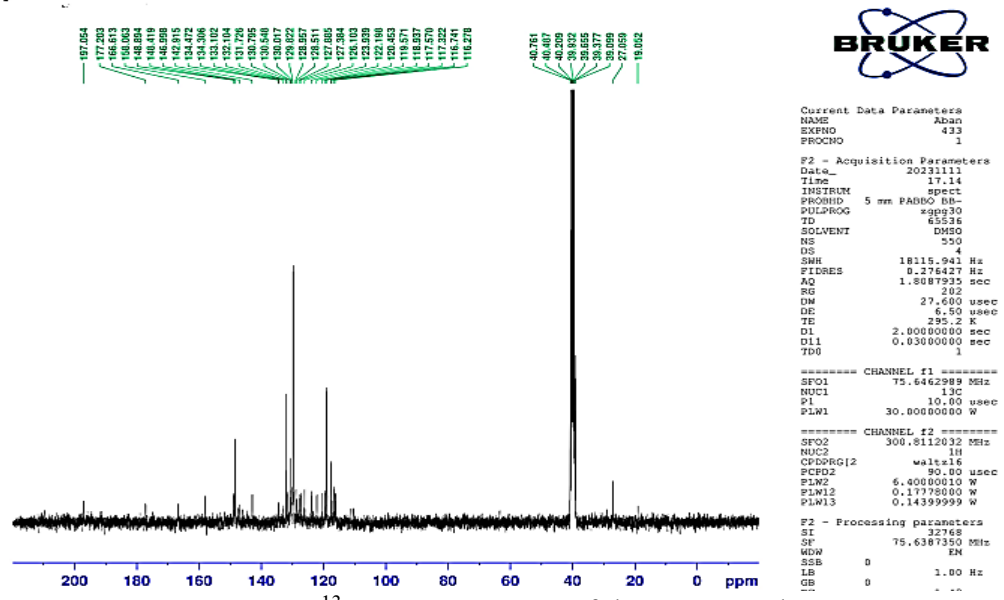


Figure 7: ^{13}CNMR spectrum of the compound **8**

3.2. Antibacterial activity[44-49]

To evaluate antibacterial properties, all the synthesized compounds were evaluated against *Pseudomonas* (gram-negative bacteria) and *Staphylococcus aureus* (gram-positive bacteria) compared to amoxicillin as a standard. The results obtained indicate that out of the compounds under examination, only two compounds (**1** and **5**) have effects on the microorganisms under study as shown in Table 5, Figs. 8 and 9. This can be attributed to the presence of the carbonyl group of ketones.

Table 5: Antibacterial activity of the synthesized compounds

Compound number	Compound-number in Petri-dish	Inhibition zone (mm) Conc. 0.02 (g/mL)	
		Pseudomonas	*Staphylococcus aureus*
1	8	18	23
2	4	---	---
3	5	---	---
4	1	---	---
5	3	17	22
6	7	---	---
7	6	---	---
8	2	---	---
Amoxicillin		---	33

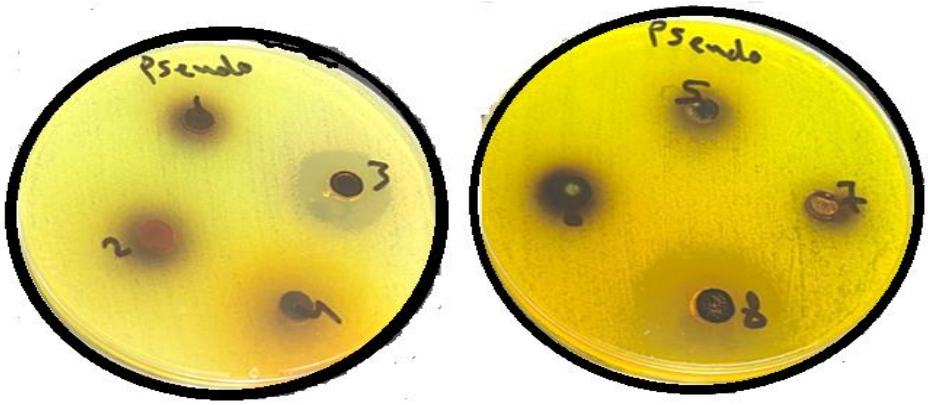


Figure 8: Effects of the synthesized compounds against *Pseudomonas*

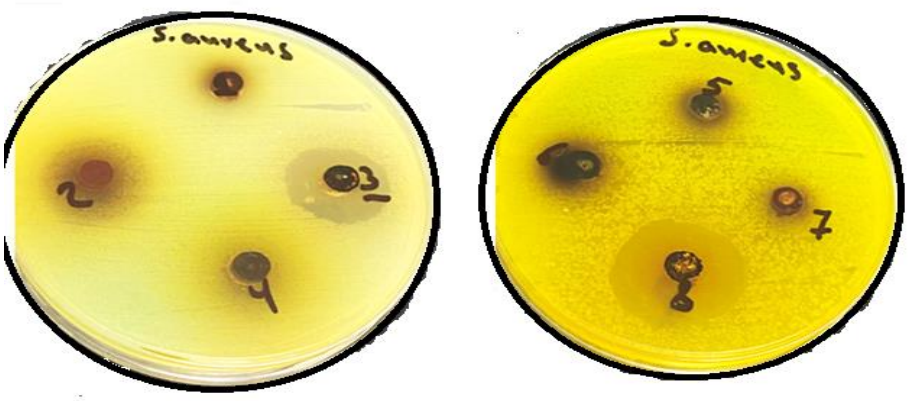


Figure 9: Effects of the synthesized compounds against *Staphylococcus aureus*

Conclusion

A range of oxopyrimidine and pyrazole derivatives, featuring the azo group, were successfully synthesized and characterized. The structures of these compounds were confirmed through spectroscopic analysis, including FTIR, 1HNMR, and 13CNMR, which were found to be consistent with the predicted molecular architecture. Additionally, two synthesized compounds (**1** and **5**) exhibited antibacterial activity against the selected Gram-positive and Gram-negative bacterial strains, while the other synthesized compounds were inactive.

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