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α-Functionalization of the Carbonyl Group for the Construction of Pyrazoline Rings Derived from 1,3-Indandione

Raniah T. Ali , Rafid S. Dawood*

Department of Chemistry, College of Science, University of Baghdad, Baghdad, Iraq Al-Jadriya Campus, Baghdad 10071, Iraq

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Abstract

This work includes the synthesis of new pyrazoline derivatives **5-13** over three steps starting from 1,3-indandione. The first step included the acylation of 1,3-indandione with acetyl chloride to produce compound **1** with excellent yield (90%). In the second step, the enolate form of **1** was condensed with various aromatic aldehydes (benzaldehyde, *p*-nitrobenzaldehyde, and *p*-chlorobenzaldehyde) to afford the corresponding α,β-unsaturated carbonyl derivatives **2-4** in high yields (93-95%). The third step involved a reaction of **2-4** with hydrazine hydrate, phenyl hydrazine, and *p*-nitrophenyl hydrazine to give the desired pyrazoline derivatives **5-13** in yields ranging from 70 to 83%. The structure of the synthesized compounds was verified through FT-IR and ^{1}H NMR spectroscopy. Additionally, a subset of the synthesized compounds underwent testing to evaluate their antibacterial and antioxidant properties.

Keywords: Antibacterial, Antioxidant, 1,3-Indandione, Pyrazoline.

توظيف الفا–مجموعة كاربونيل لبناء حلقات البايرازولين المشتقة من 1،3–انداندیون

رانيه تحسين علي ، رافد سعد داود*

جامعة بغداد ، كلية العلوم ، قسم الكيمياء ، مجمع الجادرية ، بغداد 10071 ، العراق.

الخلاصة

يتضمن هذا العمل تخليق مشتقات جديدة للبايرازولين **5–13** على ثلاث خطوات بداية من 1،3–انداندیون. تضمنت الخطوة الاولى اسيلة 1،3–انداندیون مع كلوريد الاسيتيل لانتاج مركب **1** بنسبة منتوج ممتازة (90%). في الخطوة الثانية، تم تكثيف شكل الاينوليت لمركب **1** مع الديهايدات اروماتية مختلفة (بنزلديهايد، بارا–نايترو بنزلديهايد و بارا–كلورو بنزلديهايد) لتوفير مشتقات الكاربونيل α,β–غير المشبعة المقابلة **2–4** بمنتوج عالي (93–95%). تضمنت الخطوة الثالثة تفاعل **2–4** مع هيدرات الهيدرازين، فينيل هيدرازين و بارا–نايترو فينيل هيدرازين لأعطاء مشتقات البايرازولين المرغوبة **5–13** في نسب منتوج تتراوح من 70 الى 83%. تم تاكيد تراكيب المركبات من خلال القياس الطيفي للاشعة تحت الحمراء و الرنين النووي المغناطيسي. بالإضافة إلى ذلك، خضعت مجموعة من المركبات المحضرة للاختبار لتقييم خصائصها المضادة للبكتيريا و مضادات الأكسدة.

*Email: rafid.s@sc.uobaghdad.edu.iq

1. Introduction

α,β-Unsaturated carbonyl compounds play a vital role as intermediates in the synthesis of numerous organic compounds, including heterocyclic compounds and natural products. These compounds serve as valuable building blocks for the creation of bioactive compounds such as medicines [1], precursors for materials [2], tastes [3], perfumes [4], and physiologically [5] or optically significant molecules [6]. Therefore, the synthesis of α,β-unsaturated carbonyl compounds continues to be a fascinating task in the context of developing better synthetic methodologies. Traditionally, these compounds have been prepared through various methods such as the Horner-Wadsworth-Emmons reactions [7], aldol reactions [8], Knoevenagel condensations [9], or particular oxidations like the Saegusa oxidation [10]. More subsequently, new pathways based on dehydrogenations [11], coupling reactions [12], or other techniques [13] were also discovered to yield structurally varied compounds. The majority of the synthesis techniques mentioned above use an existing carbonyl group to create the desired products. Among these, pyrazoline emerges as a vital precursor for the synthesis of novel chemical compounds possessing therapeutic properties [14]. Due to their significance in heterocyclic synthesis and medical applications, pyrazolines hold a prominent position as essential compounds within the field of organic chemistry [15]. Moreover, pyrazolines possess a wide range of biological activities, for instance, anti-inflammatory [16,17], anti-depressant [18], antimicrobial [17,19], calcium channel blockers [20], antihypertensive [21], antitumor [22], antiviral [23], antibacterial [24], monoamine oxidase inhibitor [25], anti-HIV [26], anticancer [27], antimalarial [28]. Our research aims to synthesize new pyrazolines derived from 1,3-indandione through a three-step process. Firstly, acylation of 1,3-indandione will be carried out to obtain 2-acetyl-1,3-indandione. Subsequently, this compound will be utilized to synthesize α,β-unsaturated carbonyl compounds containing 1,3-indandione. Finally, a cyclocondensation reaction will be performed between the synthesized products and hydrazine or its derivatives to yield the desired pyrazoline derivatives.

2. Experimental part

2.1. Materials and instruments

Unless stated otherwise, all chemicals were acquired from commercial sources (such as Merck, BDH, Sigma Aldrich, and Fluka companies) and utilized without additional purification. Merck silica gel 60 F_{254} plates were employed for thin-layer chromatography (TLC), which was visualized using a UV lamp and aqueous alkaline potassium permanganate. Melting points were determined using Stuart Scientific SMP3 apparatus with open capillary tubes, and the reported values are uncorrected. A Shimadzu 8400 FT-IR spectrometer was used to record infrared spectral data in 500-4000 cm^{-1} region. Spectral data for ^1H NMR were captured using a Bruker AV400 spectrometer. Chemical shifts are expressed in ppm downfield from tetramethylsilane (TMS) as an internal standard or deuterated DMSO in ^1H NMR as a reference (δ_H 2.50 ppm). The antioxidant activity data were recorded using a spectrophotometer (Shimadzu UV-1800 Spectrophotometer).

2.2. Chemistry

*2.2.1. Synthesis of 2-acetyl-1,3-indandione (**1**)*

This compound was prepared according to modification of a literature procedure [29]. In a 100-mL round-bottom flask, a solution of 1,3-indandione (2 g, 10 mmol, 1.0 eq.) in THF (20 mL) was stirred for a few minutes in an ice bath before adding a solution of sodium hydride (50% dispersion in mineral oil, 230 mg, 10 mmol, 1.0 eq.) in THF (5 mL) and stirring for 15 minutes. Acetyl chloride (700 μΛ, 780 mg, 10 mmol, 1.0 eq.) was then slowly added to the reaction mixture. After completion of the addition, the ice bath was removed, and the reaction mixture was stirred for 30 hours at room temperature. The reaction was monitored by TLC (eluent with petroleum ether/ethyl acetate, 3:1) until no 1,3-indandione remained. A solution

of HCl (10 mL, 4%) was then added to the reaction mixture, and the organic phase was extracted with ethyl acetate (10 mL), washed with brine (10 mL), dried over anhydrous sodium sulfate, and concentrated to give the title product **1**. The physical properties and FT-IR spectral data of product **1** are shown in Tables 1 and 2, respectively.

*2.2.2. General procedure A for the synthesis of α,β-unsaturated carbonyl compounds derived from 1,3-indandione **2-4** [30]*

In a 100-mL round-bottom flask, a solution of sodium hydroxide (3 drops, 5%) and absolute EtOH (10 mL) was stirred for 5 minutes at 0 °C. Compound **1** (0.5-1 g, 2-5 mmol, 1.0 eq.) was then added to the reaction mixture and stirred for 10 minutes at 0 °C before adding benzaldehyde, *p*-nitrobenzaldehyde, or *p*-chlorobenzaldehyde (200-500 mg, 2-5 mmol, 1.0 eq.). The reaction mixture was then stirred at room temperature for 22-30 hours, after which TLC (eluent with petroleum ether/ethyl acetate, 3:1) indicated the consumption of the starting materials. The solid crude material was filtered and recrystallized using a suitable solvent to give the desired products **2-4**. The physical properties and FT-IR spectral data of these products (**2-4**) are shown in Tables 1 and 2, respectively.

*2.2.3. General procedure B for the synthesis of pyrazoline derivatives **5-13** [31]*

To a solution of compounds **2-4** (83-96 mg, 300 μμολ, 1.0 eq.) in absolute EtOH (20 mL), hydrazine hydrate, phenyl hydrazine, or *p*-nitrophenyl hydrazine (10–40 μγ, 300 μμολ, 1.0 eq.) were slowly added. The reaction mixture was heated to reflux for 28-38 hours, as determined by TLC (eluent with petroleum ether/ethyl acetate). The mixture was then allowed to cool to room temperature before adding ice-water. The solid crude material was then filtrated, washed with water, and recrystallized from ethanol to provide the desired products **5-13**. The physical properties and FT-IR spectral data of these products (**5-13**) are listed in Tables 1 and 2, respectively.

2.3. Antibacterial activity test

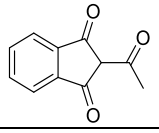
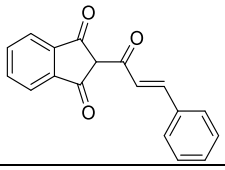
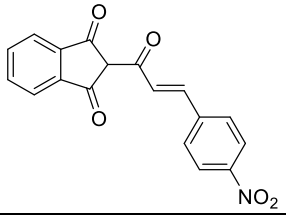
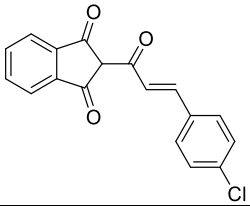
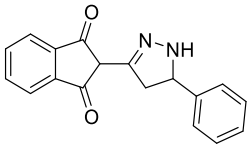
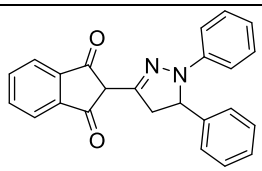
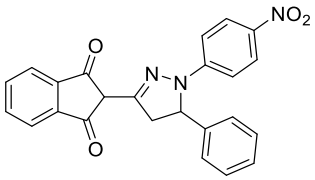
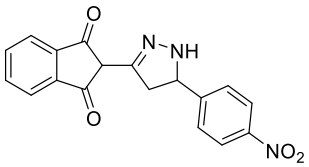
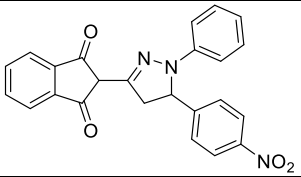
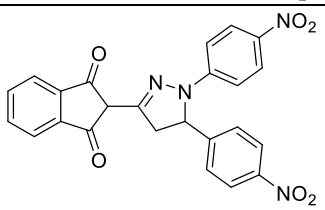
For the *in vitro* antibacterial activity assay, various samples [32], were tested against *Escherichia coli* and *Staphylococcus aureus* - two bacterial strains used in the study. The antibiotic Amikacin served as the standard reference. Test samples and standard references were prepared in a DMSO solution at a concentration of 1 mg/mL. Sterilized, liquefied agar was poured into Petri plates to a depth of approximately 3 mm, along with a suspension of the microbes (1 mL/100 mL of medium). The prepared test samples and references were added to wells created in the solidified medium. Subsequently, the plates were chilled at 5 °C for one hour and then incubated at 37 °C for 18 hours.

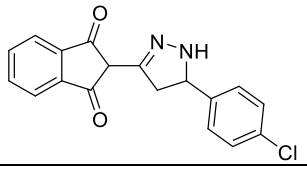
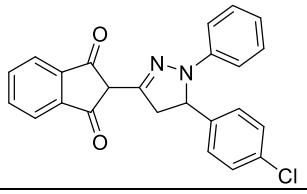
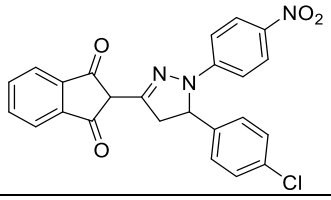
2.4. Antioxidant activity test

The scavenging ability of the generated compounds against free radicals was assessed using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay [33]. In a nutshell, the chemical was synthesized in three concentrations of 25, 50, and 100 ppm, and one milliliter of each concentration was coupled with one milliliter of DPPH solution (400 mg in 100 mL). After that, the mixture was allowed to stand at room temperature in the dark for 30 minutes. Finally, the absorbance at 517 nm of each sample was measured using a spectrophotometer. The ability to scavenge DPPH was calculated using the following equation, with ascorbic acid acting as a reference.

I% = (Abs blank - Abs sample) / Abs blank × 100 [34]

Table 1: Some physical properties of the prepared compounds **1-13**

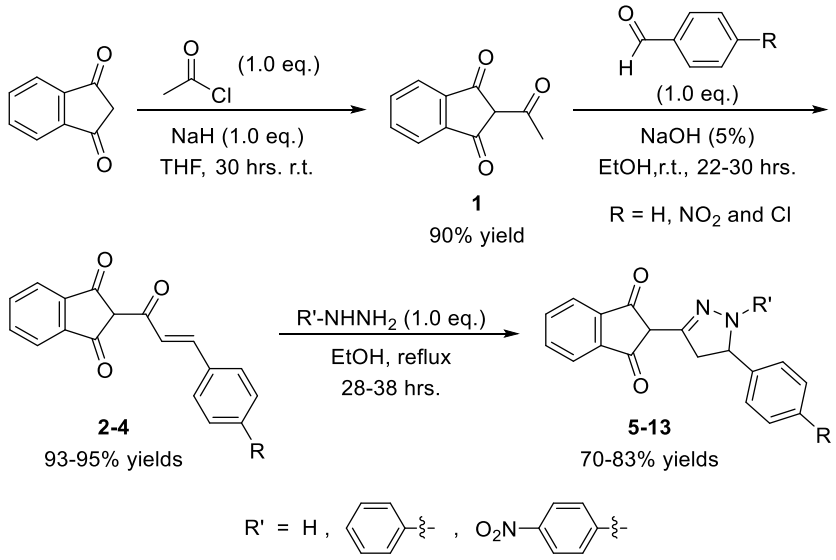
No.	Structure	m.p. (°C)	M.wt (g/mol)	Chemical formula	Color	Time (hour)	Yield (%)
1		118-121	188.18	$C_{11}H_8O_3$	Deep brown	30	90
2		Dec. 142	276.29	$C_{18}H_{12}O_3$	Brown	30	95
3		>360	321.29	$C_{18}H_{11}NO_5$	Green	22	93
4		>360	310.04	$C_{18}H_{11}ClO_3$	Red	22	95
5		136-140	290.32	$C_{18}H_{14}N_2O_2$	Red-brown	28	73
6		114-118	366.14	$C_{24}H_{18}N_2O_2$	Black	28	70
7		152-156	411.42	$C_{24}H_{17}N_3O_4$	Deep brown	28	77
8		164-170	335.32	$C_{18}H_{13}N_3O_4$	Orange	35	72
9		78-81	411.42	$C_{24}H_{17}N_3O_4$	Deep red	38	80
10		334-338	456.41	$C_{24}H_{16}N_4O_6$	Brown	35	70

11		Dec. 210	324.76	$C_{18}H_{13}ClN_2O_2$	Yellow	35	72
12		Up to 360	400.86	$C_{24}H_{17}ClN_2O_2$	Orange	35	76
13		230-234	445.86	$C_{24}H_{16}ClN_3O_4$	Brown	35	83

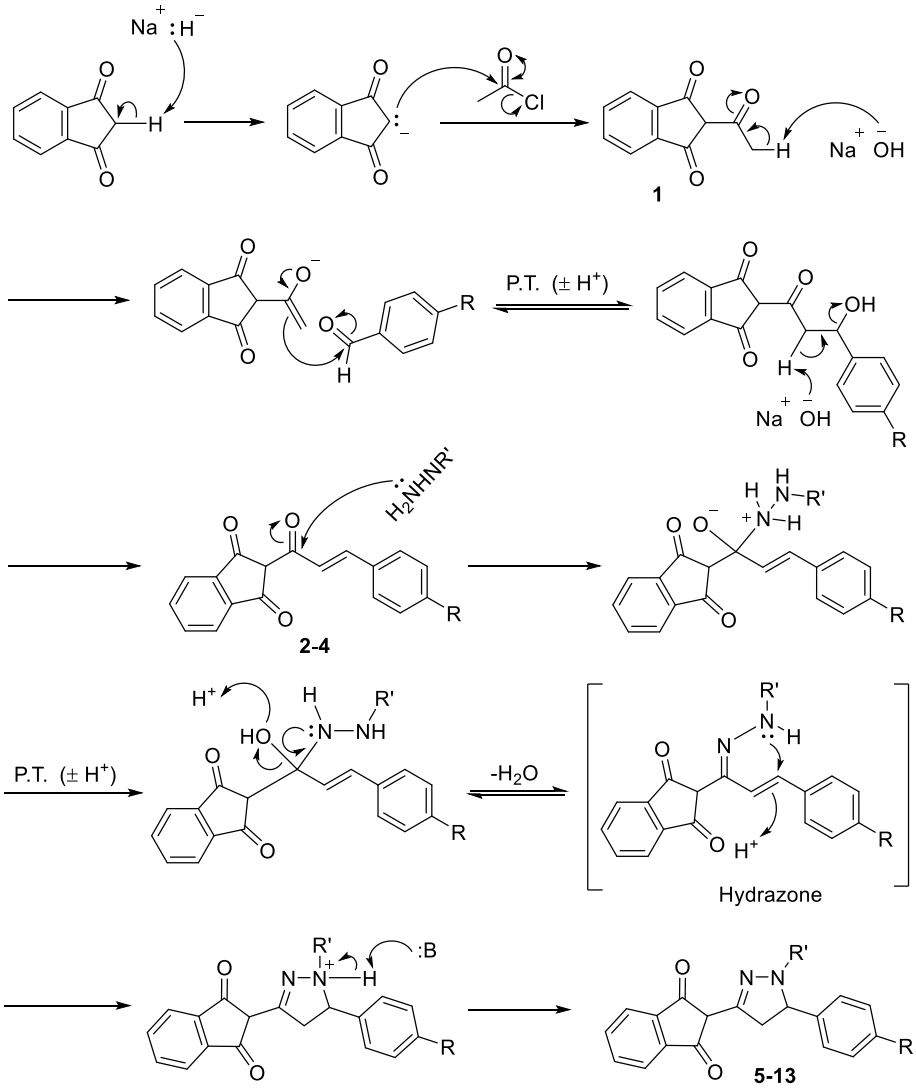
3. Results and discussion

3.1. Chemistry

Scheme 1 illustrates the reaction sequence employed for the synthesis of compounds **1-13**. Scheme 2 proposes the mechanism for the formation of pyrazoline derivatives **5-13** starting from 1,3-indandione. Compound **1** was obtained with a yield of 90% through the reaction between 1,3-indandione and acetyl chloride. The FT-IR spectrum of compound **1** exhibited a new absorption peak at 1743 cm^{-1}, which was attributed to the carbonyl group of the newly formed ketone. Successful synthesis of α,β-unsaturated carbonyl compounds **2-4** was achieved using Claisen-Schmidt condensation. This reaction involved the treatment of compound **1** with three different types of aromatic aldehydes in an ethanoic sodium hydroxide solution, serving as a basic medium to form the enolate of compound **1**, which is more reactive towards aldehyde reactions. The FT-IR spectra of compounds **2-4** showed new absorption peaks in the range of 1610-1688 cm^{-1}, corresponding to the olefinic bond of the α,β-unsaturated carbonyl compounds [35]. In addition, the absorptions of the enone carbonyl groups of compounds **2-4** were lower than the carbonyl group in compound **1**. This is due to the conjugation of the double bond with the carbonyl group. Two absorption bands at 1418 and 1350 cm^{-1} appeared in compound **3** due to the asymmetric and symmetric stretching absorptions of the NO_2 group, respectively [36]. The products **2-4** were then employed in the next step to synthesize the pyrazoline derivatives **5-13** through reactions with hydrazine hydrate, phenyl hydrazine, and *p*-nitrophenyl hydrazine. The desired products **5-13** were obtained in good yields (70-83%). Each product of **5-13** is likely to be a mixture of two enantiomers. The FT-IR spectral data of compounds **5-13** showed the absence of an olefinic bond and the appearance of new absorptions at 1591-1680 cm^{-1} attributed to the C=N absorption bands [37]. Table 2 displays all FT-IR spectral data for compounds **1-13**. The ^1H NMR spectral data of compound **4** showed multiple signals between 7.80 and 4.89 ppm due to the aromatic and alkene protons [35,38]. A singlet signal appeared at 4.34 ppm, attributed to the aliphatic proton of the indandione ring. In the ^1H NMR spectral data of compound **5**, the chemical shifts of the fourteen aromatic protons appeared at 7.99-6.80 ppm. The C-H aliphatic proton of the indandione ring appeared at 4.30 ppm. The signals at 3.80-3.45 ppm and 2.70-2.55 ppm belong to the C-H and CH_2 protons of the pyrazoline ring, respectively. The ^1H NMR spectral data of compound **9** showed a singlet signal at 8.75 ppm attributed to the N-H proton. Eight protons of the aromatic rings appeared at 8.20-6.55 ppm, and the aliphatic proton of the indandione ring appeared at 4.30 ppm. Finally, the chemical shifts of the C-H and CH_2 protons of the pyrazoline ring appeared at 3.75-3.38 ppm and 2.69-2.53 ppm, respectively. All the details of the ^1H NMR data are shown in Table 3.



Scheme 1; Synthesis of pyrazoline compounds **5-13** derived from 1,3-indandione

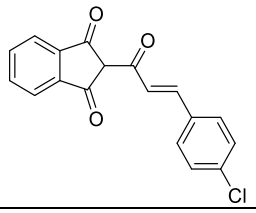
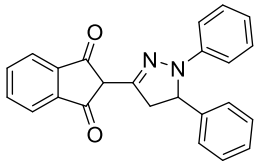
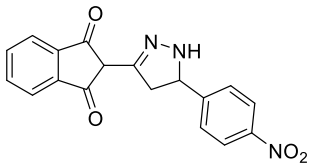


Scheme 2: The full mechanism for the transformation of the 1,3-indandione to the pyrazolines **5-13**

Table 2: Characteristic FT-IR spectral data (υ, cm^{-1}) of compounds **1-13**

Compound number	C=O Carbonyl	C=C Aliphatic	C=C Aromatic	C=N Imine	C-H Aromatic	C-H Aliphatic	Other bands
1	1743 1705	-	1578	-	3084 3011	2959 2922	-
2	1730 1695	1636	1574	-	3059	2934	-
3	1730 1711	1688	1572	-	3099	2984	1418 (NO_2 asym.) 1350 (NO_2 sym.)
4	1745 1707	1610	1591	-	3072	2962	1092 (C-Cl)
5	1713	-	1578	1664	3059	2926	-
6	1705	-	1572	1628	3061	2924	3354 (N-H)
7	1709	-	1580	1680	3063	2922	1499 (NO_2 asym.) 1302 (NO_2 sym.)
8	1715	-	1560	1601	3086	2924	1528 (NO_2 asym.) 1348 (NO_2 sym.)
9	1730	-	1572	1649	3007	2924	1528 (NO_2 asym.) 1337 (NO_2 sym.) 3371 (N-H)
10	1717	-	1562	1591	3075 3096	2926	1529 (NO_2 asym.) 1321 (NO_2 sym.)
11	1711	-	1555	1649	3059	2928	1094 (C-Cl)
12	1717	-	1568	1591	3080	2926	3414 (N-H) 1092 (C-Cl)
13	1715	-	1553	1593	3067	2924	1094 (C-Cl)

Table 3: ^{1}H NMR spectral data (δ, ppm) of compounds **4**, **5**, and **9**

No.	Compound structure	^{1}H NMR spectral data (δ, ppm)
4		7.80-4.89 (m, 10H, Ar-H + CH=CH), 4.34 (s, 1H, C-H)
5		7.99-6.80 (m, 14H, Ar-H), 4.30 (s, 1H, C-H), 3.80-3.45 (m, 1H, C-H), 2.70-2.55 (m, 1H, CH_2)
9		8.75 (s, 1H, N-H), 8.20-6.55 (m, 8H, Ar-H), 4.30 (s, 1H, C-H), 3.75-3.38 (m, 1H, C-H), 2.69-2.53 (m, 1H, CH_2)

3.2. Antibacterial activity

In this experiment, the antibiotic Amikacin was used as a control, and DMSO was employed as a solvent (Table 4). Some of the prepared products (**5**, **7**, **10**, and **13**) were tested to evaluate their antibacterial activity against two types of bacteria (*Staphylococcus aureus* as a gram-positive bacteria and *Escherichia coli* as gram-negative bacteria). The results revealed varying activities among the tested compounds. For instance, compound **13** exhibited the highest effectiveness in inhibiting the growth of gram-positive bacteria, while its efficacy

against gram-negative bacteria was comparatively lower. Compound **7** demonstrated almost equal effectiveness against both types of bacteria. Compound **5** showed higher activity against gram-negative bacteria than gram-positive bacteria. In contrast, compound **10** showed higher activity against gram-negative bacteria than gram-positive bacteria.

Table 4: Antibacterial activity of the tested prepared compounds (**5**, **7**, **10**, and **13**) based on mm of the inhibition zone

Compound number	Gram-negative bacteria (*Escherichia coli*)	Gram-positive bacteria (*Staphylococcus aureus*)
5	18	10
7	8	10
10	8	16
13	8	22
DMSO	8	8
Amikacin	34	40

3.3. Antioxidant activity

The DPPH radical test was used to spectrophotometrically evaluate the *in vitro* antioxidant activity of compounds at three distinct dosages (25, 50, and 100 ppm) (**5**, **7**, **10**, and **13**). At a 25% concentration, compound **5** outperformed ascorbic acid, whereas the other compounds had a lower impact than ascorbic acid at all concentrations. Table 5 displays all the information about the antioxidant activity.

Table 5: Free radical-scavenging activity (%) for some of the prepared compounds (**5**, **7**, **10**, and **13**)

Compound number	Inhibition (%) for the concentrations (ppm)		
	100	50	25
5	81.83	78.07	94.89
7	66.36	64.71	59.15
10	75.67	73.87	72.97
13	70.57	83.93	75.37
Ascorbic acid	93.54	89.25	80.95

4. Conclusion

Three novel α,β-unsaturated carbonyl compounds incorporating the 1,3-indandione moiety were synthesized in a three-step process, providing excellent yields. The compounds were thoroughly characterized using various spectroscopic techniques. Through a cyclocondensation reaction with hydrazine or its derivatives, the desired pyrazoline derivatives were obtained with yields ranging from 70% to 83%. Some of the synthesized compounds were subjected to testing for their antibacterial and antioxidant activities. Compounds **10** and **13** exhibited significant inhibitory effects against gram-positive bacteria, effectively impeding their growth. Compound **5** demonstrated successful suppression of

gram-negative bacteria. In terms of antioxidant activity, compound **5** displayed noteworthy results at a concentration of 25%, surpassing the scavenging capacity of ascorbic acid against detected free radicals. However, no significant effects were observed at concentrations of 50% or 100% for the tested compounds.

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