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Synthesis and Characterization of New Substituted Coumarin Derivatives and Study Their Biological Activity

Ali Y. Mohammed, Luma S. Ahamed*

Department of Chemistry, College of Science, University of Baghdad, Baghdad, Iraq

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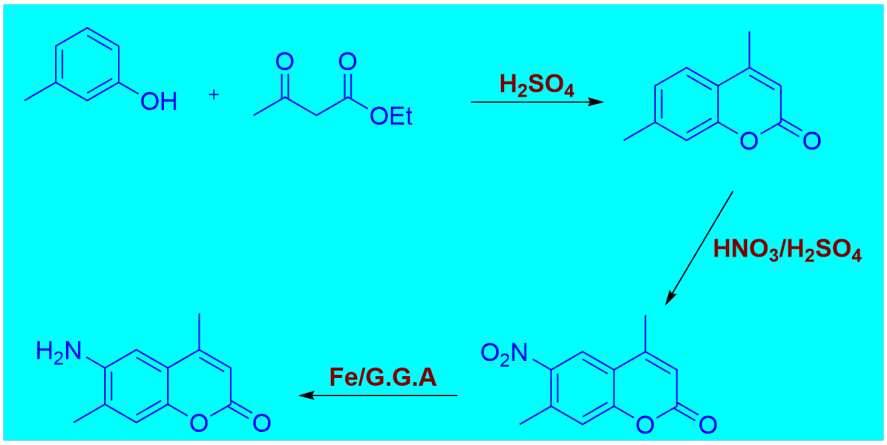
ABSTRACT

New substituted coumarins derivatives were synthesized by using nitration reaction to produce different nitro coumarin isomers which were separated from these isomers by using different solvent, and the reduction of nitro compounds was done to give corresponding amino coumarins. Temperature and reaction time of reaction were very important factors in determining the most productive nitro isotopes. A low temperature for three hours was sufficient to give a high product of a compound 6- nitro coumarin while increasing the temperature for a period of twenty-four hours that gave a high product of 8-nitro-coumarin. The synthesized compounds were confirmed by FT-IR, ^{1}H-NMR, and ^{13}C-NMR spectroscopy and all final compounds were tested for their antifungal and antibacterial activity. Some of them showed more biological activity than the standard drugs. Some synthesized compounds showed a variation in their anti-oxidant activities according to IC50 values. Some of these compounds had a very good antioxidant compared with ascorbic acid as a standard.

GRAPHICAL ABSTRACT



* Corresponding author: Luma S. Ahamed
✉ E-mail: Forat. lama.s@sc.uobaghdad.edu.iq

Introduction

Heterocyclic compounds synthesis and their biological activities: Pharmacologically relevant heterocyclic compounds play a key role in the fight against diseases affecting both human and animal living organisms, as well as plants and they lead to new results about new molecules with a potential biological effect [1]. The shortage of novel antifungal drugs, the emergence of new infectious diseases, the resurgence of several infections, and the increased resistance of fungi to available chemotherapeutic agents are the essential issues in drug design and development, which prompted researchers to look for novel compounds that can combat with multidrug-resistant organisms [2]. Field of chemistry is forging ahead progressively, and hence newer molecules are synthesized in the laboratory to identify leads with target specific activity [3]. All synthesized compounds were tested for their biological activity as anti-fungal and antibacterial and also, they were tested for antioxidant. Bacterial and fungal diseases significantly influence on public health, and their resistance to antibiotics has prompted increased medical concerns, human contract bacterial infections from the air, food, water, or living vectors. Despite this, many bacterial organisms in human bodies do not cause disease [4]. Coumarins are classify under the benzopyrone family of heterocyclic compounds in which 6-membered α-pyrone ring fused with benzene ring and generally occurs in various natural products as a benzo derivative. Another efficient method for coumarin synthesis includes the interaction of resorcinol and ethyl acetoacetate by Pechmann condensation to provide pyrano coumarin derivatives with a good yield and atom-economy [5]. Several methods can be used to synthesize coumarins such as Pechmann condensation [6], Knoevenagel reaction [7], Claisen rearrangement [8], Baylis-Hill man reaction [9], and Wittig reaction [10].

Coumarins are heterocyclic compounds and have many medical properties [11] such as antifungal [12], antibacterial [13], antioxidants activity [14], and anti-inflammatory [15]. Coumarin and its derivatives possess anticancer activity against different types of cancers such as prostate, renal, breast, laryngeal, lung, colon, CNS, leukemia, and malignant melanoma [16]. Anti-HIV antiviral coumarin-based derivatives have the potential to inhibit different stages in the HIV replication cycle, inclusive of virus-host cell attachment, and cell membrane fusion [17]. Also, coumarins have been proven efficient pharmacophores in rest of coumarins studies as important biological activities, as depicted in Figure 1.

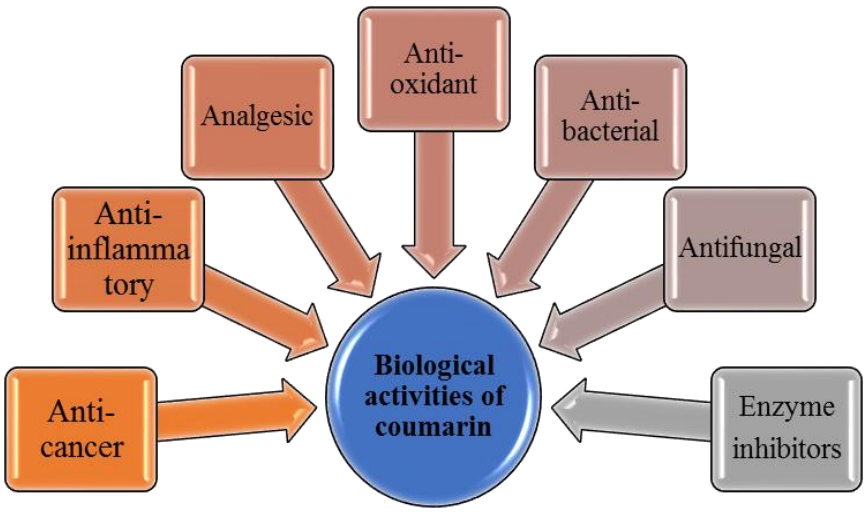


Figure 1: Biological activity of coumarin

We tried to synthesize new substituted coumarins as heterocyclic compounds having oxygen as a hetero atom, which has been reported as a common denominator of pharmacological and biochemical activities [18] so that we tested them as antibacterial, antifungal, and antioxidants.

Materials and methods

^{1}H-NMR spectra solvent DMSO-d_6 was recorded on a 500 MHz spectrometer with TMS as an internal standard in Isfahan university, Iran and some in Jourdan. Melting points were determined on a Gallen-Kamp MFB-600 melting point apparatus and are uncorrected. Analytical thin layer chromatography (TLC) was performed on plates coated with silica gel (Merck 60 F254, 0.25 mm) and was visualized with ultraviolet light [19]. This process was conducted by using the preparative TLC method with preparative TLC plates and a solvent containing hexane: ethyl acetate (6:4). This experiment relied on visual observation with long-wave UV-light (365 nm) [19]. The biological activity test was performed at the University of Baghdad, College of Science.

*Preparation of 6-nitro-4,7-dimethyl-chromen-2-one **2***

Preparation of compound **2** was carried out according to the same method in literature [20] by using 4,7-dimethyl coumarin, nitric acid, and sulfuric acid at 0-5 °C [21].

*Synthesis of 8-nitro-4,7-dimethyl-chromen-2-one **3***

1 g from 4,7-dimethyl-chromen-2-on was dissolved in 15 mL of H_2SO_4 by stirring in an ice bath. The solution was added to a mixture of (0.4 ml) of HNO_3 and (1.2 mL) of H_2SO_4 dropwise at 0–5 °C. The resulting solution was stirred for overnight at 0–5 °C. After the reaction was completed, the solution was added to the ice to produce the desired product. Then, the formed solid precipitate was filtered and washed from ethanol.

Synthesis of dinitro-4,7-dimethylcoumarin

It was prepared with some modifications by using double amounts of nitrate mixture (nitric acid and sulfuric acid) at 0-5 °C. In initial (3 h), the reaction which was kept overnight, and then the temperature increased gradually to 15 °C. Two isomers, 3,6-dinitro-4,7-dimethylcoumarin **4**, which were insoluble in dioxane, and 6,8-dinitro-4,7-dimethylcoumarin **5**, which was soluble in dioxane, were produced.

*Synthesis of 3,6,8 -tri nitro-4,7-dimethylcoumarin **6***

It was conducted by using thrice amount of nitrate mixture comprised of nitric acid and sulfuric acid under a gradual increase in temperature to 28 °C in which the reaction was kept overnight. Then, the solid product was poured in ice and after that, the precipitate was separated by filtration, washed with water, and dried.

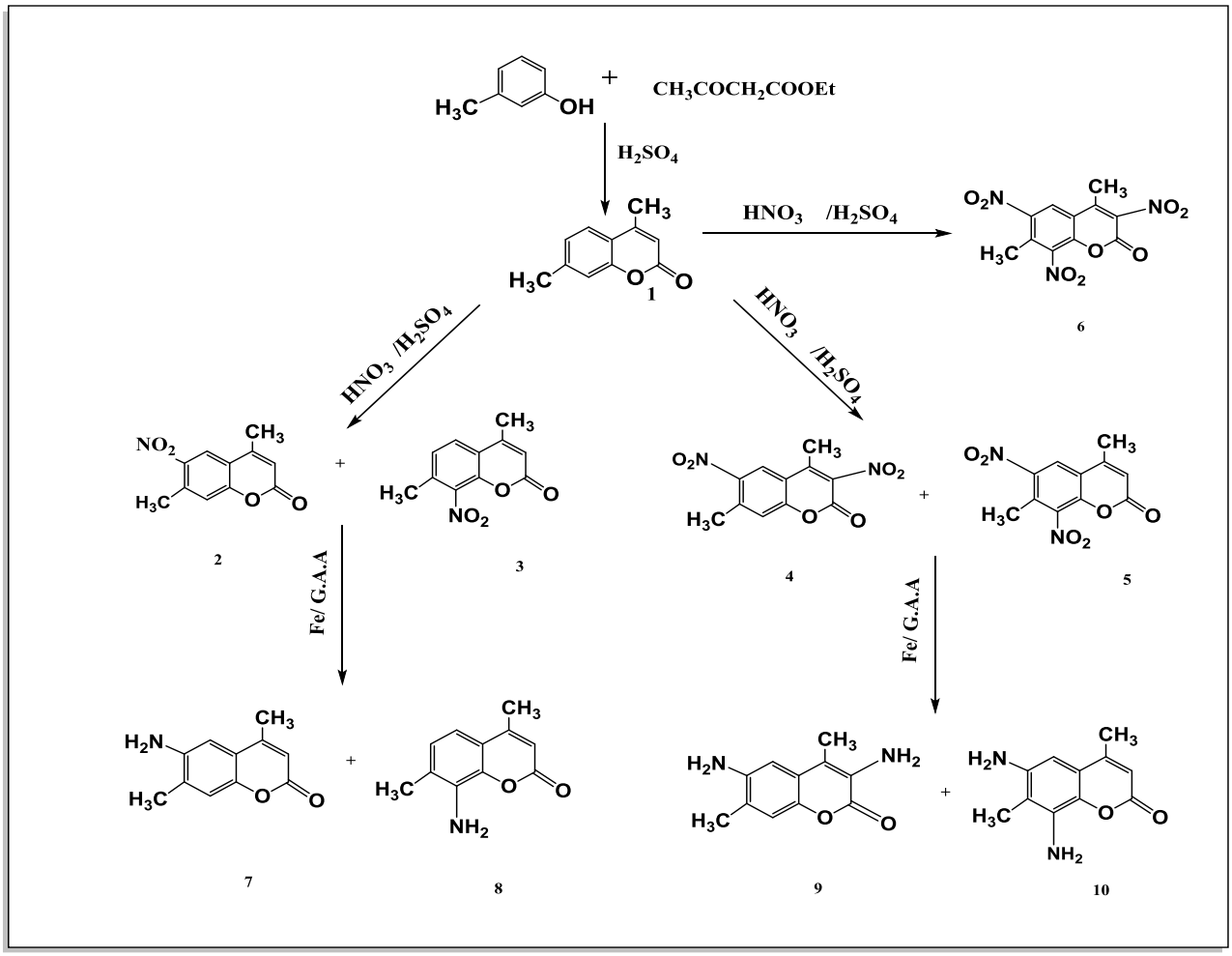
*Synthesis of amino-4,7-dimethyl-chromen-2-one **7-10***

1 g of nitro-4,7-dimethyl-chromen-2-on was dissolved in 15 mL of dioxane by heating, and then the solution was added to a mixture of 0.83 g of iron, 2.3 mL of H_2O, and 1.2 mL of G.A.A. The resulting solution was refluxed for 10 hours. The hot mixture was filtered to get rid of unreacted iron, and then the filtrate was neutralized with sodium bicarbonate. After that, the solution was added to the ice to produce the desired product. Then, the formed solid precipitate was filtered and recrystallized from benzene.

Results and Discussion

In the present work, nitro cumarins were synthesized by nitration of cumarin by using nitric acid in the presence of sulfuric acid. The temperature of this reaction is very important to direct the nitro group in the molecule, which gives two isomers: 6-nitro-4,7-dimethyl-chromen-2-one **2** and 8-nitro-4,7-dimethyl-chromen-2-one **3**. The isomer **2** would be high in percentage yield if the mixture reaction stirring at room temperature for three hours after stirring at ice bath for one hour. However, the

isomer **3** would be more in percentage yield if the temperature is kept under 5 °C at overnight, as displayed in Scheme 1.



Scheme 1: Synthesis of new amino coumarin from nitro coumarin

New nitro coumarin compounds were created by varying the concentration of nitric mixture and temperature of the reaction. Two nitro isomers of dinitro-4,7-dimethyl coumarin are 4,7-dimethyl-3,6-dinitro-2*H*-chromen-2-one **4** and 4,7-dimethyl-6,8-dinitro-2*H*-chromen-2-one **5** with trinitro-4,7-dimethyl coumarin that was 4,7-dimethyl-3,6,8-trinitro-2*H*-chromen-2-one **6** were confirmed by T.L.C, ^{1}H-NMR, and ^{13}C-NMR, as demonstrated in Table 1 and 2.

FT-IR spectrum of compound 7 showed a decrease in absorption band at 1691 cm^{-1} due to carbonyl group for lactone ring that was due to the electrons releasing of the amino group instead of withdrawing nitro group which was disappereance of two absorption bands of the V NO_2 and the appearance of absorption band at 3435 and 3360 cm^{-1} due to NH_2 group.

8-amino-4,7-dimethyl-2*H*-chromen-2-one **8**, 3,6-diamino-4,7-dimethyl-2*H*-chromen-2-one **9**, and 6,8-diamino-4,7-dimethyl-2*H*-chromen-2-one **10** compounds: It was obtained by reducing compounds **3**, **4**, and **5**, respectively. Likewise, compound **7** with double concentration of the reduction mixture was compared with the preparation of compounds **4** and **5**. See Scheme 1.

Biological activity

In in vitro antifungal studies

The synthesized compounds were tested for antifungal activity against *candida albicans* by using DMSO as a solvent by the agar well diffusion method (well diameter was 6 mm). Fluconazole was used as a standard drug for three days. Compounds **4** and **5** revealed a good

antifungal activity and were better than the standard drug, as indicated in Table 3.

Table 1: The physical properties and FT-IR spectral data cm^{-1} of synthesized compounds **2-10**

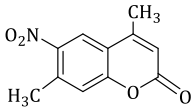
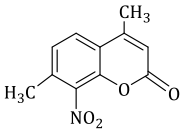
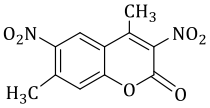
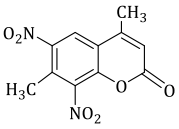
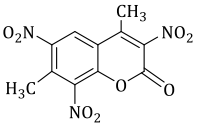
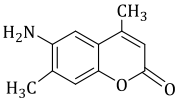
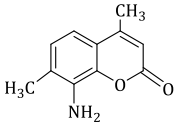
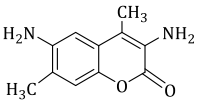
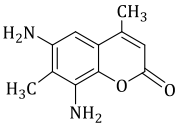
Physical properties					Major FT-IR absorption cm^{-1}					
No. of compound	Structure of compounds	m.p. (°C)	RF	Yield%	υ (C-H) Aromatic	υ (C-H) Aliphatic as sy	Υ (C=O) lacton	υ C=C aromatic	υ (C-OC)	Other band as sy
2		256-258	0.88	60	3095	2960	1734	1622	1251	1354 1527 υNO2
3		189-190	0.73	40	3060	2945 as 2885sy	1737	1625 1525	1255	1352 1525 υNO2
4		156-158	0.74	35	3080	2993	1766 1739	1623	1253	1537 1350 υNO2
5		164-166	0.76	65	3085	2360	1737	1623	1253	1527 1352 υNO2
6		235	0.8	90	3001	2935	1764	1627	1226	1556 1342 υNO2
7		210	0.14	70	3060 3035	2918 2948	1691	1556 1616	1220 1172	3434 3361 υ (NH2)
8		155-156	0.32	65	3056	2974 2918	1693	1558 1620	1176	3433 3359 υ (NH2)
9		188-189	0.23	55	3053	2974	1693	1556	1249 1222	3425 3361 υ (NH2)
10		204 dec	0.21	65	3072	2968 2918	1681	1564 1620	1255 1234	3444 3425 υ (NH2)

Table 2: ^{1}H-NMR and ^{13}C-NMR spectral of some synthesized compounds

No. of compund	^{1}H-NMR & ^{13}C-NMR
2	^{1}H-NMR (500 MHz, DMSO): δ 2.4 (s, 3H, CH_3), 2.6 (s, 3H, CH_3), 6.5 (s, 1H, H-lactam ring), 7.5 (s, 1H, Ar-H), 8.3 (s, 1H, Ar-H).
3	^{1}H-NMR (500 MHz, DMSO): δ 2.49 (d, 3H, CH_3), 2.54 (d, 3H, CH_3), 6.53 (s, H, H-lactone ring), 7.73 (d, Ar-H5), 8.38 (d, Ar-H6).
6	^{1}H-NMR (500 MHz, DMSO): δ 8.8 (s, 1H, Ar-H). ^{13}C-NMR (125 MHz, DMSO): δ 14.4, 14.7, 118, 126, 134, 138, 139, 145, 151.
7	^{1}H-NMR (500 MHz, DMSO): δ 2.34 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 6.23 (s, 1H, H-lactam ring), 8.19 (s, 2H, Ar-H), and 8.12 (s, 2H, Ar-H), 5.02 (s, 2H, NH_2).
8	^{1}H-NMR (500 MHz, DMSO): δ 2.12 (3, 3H, CH_3), 2.72 (s, 3H, CH_3), 5.1 (d, 2H, NH_2), 6.2 (s, 1H, H-lactam ring), 6.7 (d, *J*=8.4Hz, 1H, Ar-H), 6.9 (d, *J*=8.4Hz, 1H, Ar-H). ^{13}C-NMR (125 MHz, DMSO): δ 17.7, 18.5, 106, 107, 140, 144, 145, 151, 153, 159, 160.
9	^{1}H-NMR (500 MHz, DMSO): δ 1.9 (s, 3H, CH_3), 2 (s, 3H, CH_3), 3.39 (d, 2H, NH_2), 5.0 (d, 2H, NH_2), 6.1 and 6.7 for (2 H, Ar-H). ^{13}C-NMR (125 MHz, DMSO): δ 12.2, 17.3, 95, 129, 133, 143, 144, 155, 159.

Table 3: Antifungal and antibacterial activities for synthesized compounds **1-10** by using agar well diffusion method. The concentration of compounds is 10 mg/mL

No.of sample	Escherichia coli	Staphylococcus aureus	Candida albicans
1	16	17	16
2	17	19	16
3	18	19	16
4	17	22	16
5	16	20	18
6	30	23	25
7	16	21	17
8	16	21	15
9	20	20	14
10	22	20	19
Amoxillin	21 mm	25	-
Cephalexin	21 mm	20	-
Fluconazole	-	-	16

In vitro antibacterial studies

The synthesized compounds **2-10** were tested for antibacterial activity against *Escherichia coli* and *staphylococcus aureus* by using cephalexin and amoxicillin as standard drugs by the agar well disc diffusion method, and the study showed that compound **6** was found to be more effective against *E.coli* than the standard drug.

Antioxidant activity

DPPH radical scavenging activity [22]

DPPH (2,2-diphenyl-1-picryl-hydrazyl-hydrate) [23]

DPPH (1.434 mg) was dissolved in 100 mL of methanol, and by shielding the aluminum foil test tubes, various concentrations (100, 50, 25, 12.5, and 6.25 ppm) were prepared for seven compounds (**3**, **4**, **5**, **6**, **7**, **8**, and **10**) by using methanol to prepare the mentioned concentration above, ascorbic acid (vitamin C) was used as the reference compound. The absorbance of each solvent was measured with a spectrophotometer at 517 nm, after which incubation was done at 37 °C for 1 hour. Triple measurements were made by the following equation, which was able to determine the potential to scavenge DPPH (2, 2- diphenyl-1-picryl-hydrazyl-hydrate):

$$\% \text{ inhibition} = \frac{(A_0 - A_t)}{A_t} \times 100$$

DPPH: Radical scavenging activity

Some newly synthesized compounds showed antioxidant activity against DPPH (2, 2- diphenyl-1-picryl-hydrazyl-hydrate) free radical and gave good scavenging percentage [24]. Hence, the compounds that were tested that showed antioxidant properties were selected for further testing (Figure 2). Accordingly, inhibitory concentrations (IC50) values were recorded and listed in Table 4. In this project, we applied the anti-oxidant activity classification, which was depended on IC50 range values published by Phongpaichit. For more details about these ranges, see Table 5.

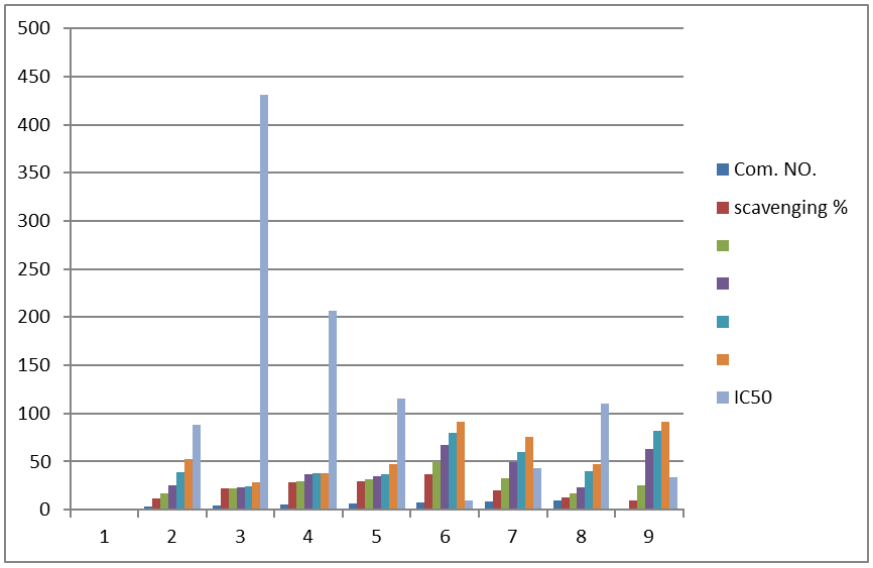


Figure 2: DPPH scavenging activity of all compounds

Table 4: Anti-oxidant activities for synthesized compounds (**3**, **4**, **5**, **6**, **7**, **8**, and **10**)

No of compound	Scavenging %					IC50
	6.25 µg\mL	12.5 µg\mL	25 µg\mL	50 µg\mL	100 µg\mL	
3	12.1	16.9	24.8	39.1	52.1	88.5
4	21.76	22.45	23.29	24.2	28.24	431
5	28.66	29.29	37.03	37.38	38.21	206.1
6	28.94	31.1	35.08	37.03	47.28	115.2
7	36.8	50.3	67	80.1	91.2	10
8	20.1	33.1	49.3	60.3	75.9	42.9
10	12.2	16.9	22.9	39.9	46.9	110.2
Ascorbic acid	9.48	25.52	63.18	81.94	90.86	33.48

Table 5: Antioxidant activity according to Phongpaichit, 2017

IC50 (µg/mL)	Mark
10-50	Strong Antioxidant Activity
50-100	Intermediate Antioxidant Activity
>100	Weak Antioxidant Activity

The compounds showed a variation in their anti-oxidant activities according to IC50 values, which revealed a range of high, intermediate, and low activities, as can be seen in Table 2. The compound **7** has a very good antioxidant compared with ascorbic acid as a standard, as represented in Table 2 and Table 3 (Activity according to Phongpaichit) [24].

Conclusion

In this work, different conditions were used to synthesize different nitro coumarin isomers. These compounds were reduced to corresponding amino coumarins by using Fe in dioxane in the presence of glacial acetic acid. All synthesized compounds were tested against different antibacterial, *Escherichia coli*, *Staphylococcus aureus* and tested against Candida albicans as anti-fungal. Compound 6 was found to be more effective against *E. coli* than the standard drug, Amoxicillin, which may be due to the presence of three nitro groups. The synthesized compounds were also tested for antioxidants by IC50 measurement by using (DPPH) and the result showed that compound 7 has a very good antioxidant compared with ascorbic acid as a standard.

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Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

There are no conflicts of interest in this study.

ORCID:

Ali Y. Mohammed
https://www.orcid.org/0000-0002-1077-7556
Luma S. Ahamed
https://www.orcid.org/0000-0002-6482-6747

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