Received: 6 November 2019 | Revised: 8 December 2019 | Accepted: 10 December 2019

DOI: 10.1002/jhet.3873

ARTICLE

WILEY

Synthesis and antimicrobial activity of some new coumarin and dicoumarol derivatives

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Abstract

PTC reaction of coumarin derivative **1** with alkyl halides afforded C_4 oxygen alkylation products **2a-d** in appreciative yield, whereas with phenyl isothiocyanate gives the C_3 addition product **4**; also, one-pot three-component PTC reaction was investigated. Treatment of coumarin **1** with aromatic aldehydes in different molar ratios gives 3-arylidene derivatives **7a,b** and the dicoumarol derivatives **8a,b**. Pyrano chromene **9** and pyrano pyridine **10** were obtained by reaction of arylidene **7a** with ethyl acetoacetate through Michael cycloaddition reaction. The stability of pyrone ring in 3-arylidene **7** and dicoumarol **8** towards different nucleophilic reagents under reflux and/or fusion conditions has been studied by the action of hydrazine hydrate, ammonium acetate, methyl amine, and *p*-toluidine afforded compounds **11** and **13a-c**. The antimicrobial activity of some synthesized compounds has been investigated.

1 | INTRODUCTION

Coumarins (1,2-benzopyrones) are worthy scaffold among heterocyclic compounds; many coumarins have been synthesized and also are present in nature (exist in therapeutic plants, flavors, and vegetables). Over the past decades, coumarin-linked and fused heterocyclic derivatives have attracted strong scientific interest arising from their broad spectrum of pharmacological and biochemical activities, acting as antidepressants,[1] antimicrobials,[2] anti-oxidants,[3] anti-inflammatories,[4] antinociceptives,[5] anti-tumor agents,[6] antiasthmatics,[7] antiviral (including anti-HIV),[8] and anti-coagulants.[9] 4-Hydroxycoumarins (Figure 1) have gained a lot of attention due to their important pharmacological features, including analgesic,[10] anti-arthritis,[11] anti-inflammatory,[12] anti-pyretic,[13] anti-bacterial,[14] anti-viral,[15] and anticancer.[16] 4-Hydroxycoumarin and its derivatives have been effectively and efficiently utilized as anticoagulants for the treatment of thrombophlebitis[17] and pulmonary embolism[18] and treatment of limited and specific cardiac cases[19] and have shown good anticoagulant activity combined with low side effects and little toxicity.[20] Dicoumarol was brought to light as a naturally occurring anticoagulant.[21] Different dicoumarol derivatives also show antimicrobial and antioxidant activity.[22]

2 | RESULTS AND DISCUSSION

In continuation to our previous studies on the synthesis and reactivity of coumarin and their derivatives,[23–26] the present work is aimed to synthesize new coumarins and dicoumarol derivatives and to study their antimicrobial activity. Reaction of coumarin **1** with primary alkyl halides such as allyl chloride, benzyl chloride, *p*-nitro benzyl chloride, and/or ethyl chloro acetate under phase transfer catalysis conditions, using potassium carbonate as base and tetra butyl ammonium chloride as catalyst, results in oxygen alkylation through nucleophilic displacement to give **2a-d** in appreciative yield and smaller amount of C_3 alkylation product **3** in case of benzyl chloride (Scheme 1). The success of *O*-alkylation over C_3 alkylation may be explained by using primary alkyl halides (sp^3 C-X) through nucleophilic displacement

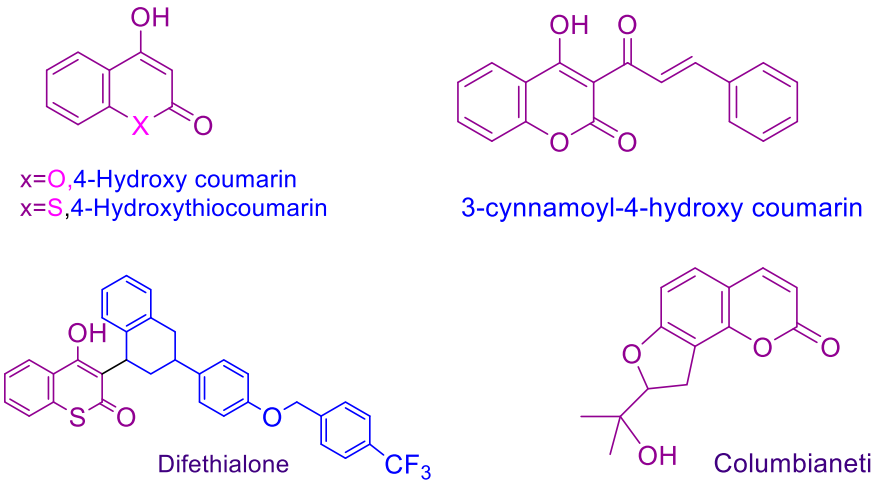
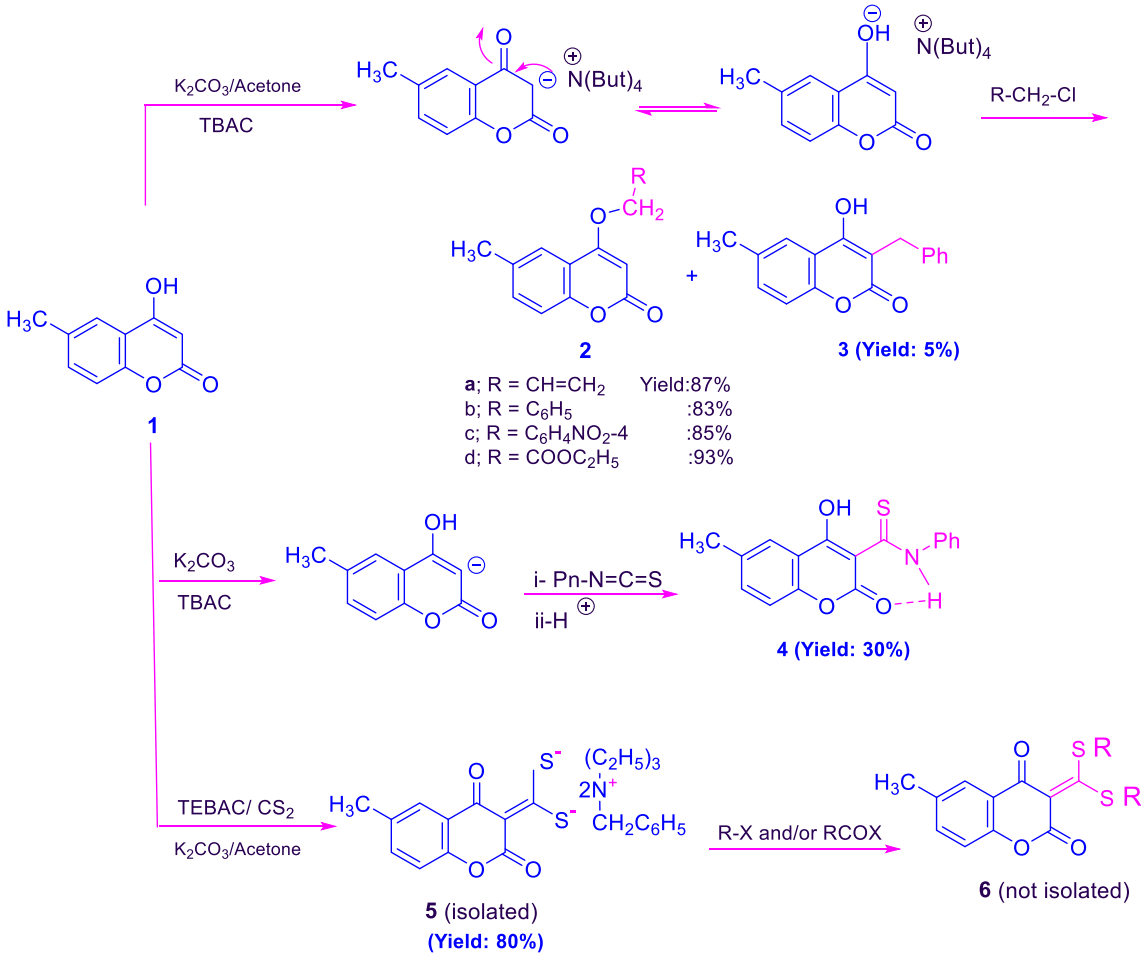


FIGURE 1 Structure of 4-hydroxycoumarin and coumarin derivatives have antimicrobial activity



SCHEME 1 PTC reaction of coumarin derivative **1** with alkyl halides, phenyl isothiocyanate, and CS_2

reactions, whereas C_3-alkylation reaction of coumarin **1** with compounds containing multiple bonds (sp^2 and/or sp) through addition reactions. The structure of compounds **2a-d** was evidenced by studying their spectral data. Their IR spectra showed absorption bands for C=O lactone as well as C=O for ester in case of compound **2d** and devoid of any absorption for OH and/or ketonic carbonyl groups. The appearance of a singlet signal for the olefinic protons at C_3– as well as signals of O-CH_2 and absence of any exchangeable singlet signal in the down field region corresponding to OH proton in their ^{1}HNMR spectra is a good evidence for O-alkylation rather than

C-alkylation. The structure of compound **3** was proved by IR spectrum that established a band for OH group as well as ^{1}HNMR that revealed an exchangeable singlet signal for OH proton at δ 13.8 ppm and lack of signal for the olefinic proton at C_3–.

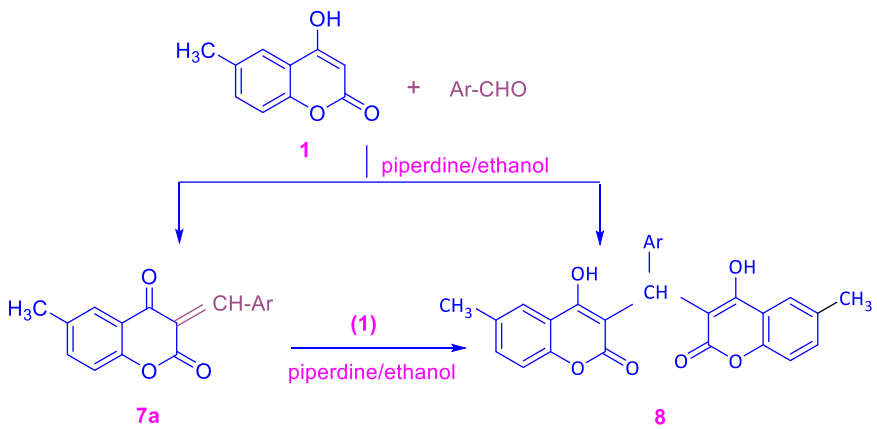
PTC reaction of the coumarin derivative **1** with phenylisothiocyanate in equimolar amount at room temperature proceed via carbanion C_3– addition on the carbon nitrogen double bond of the isothiocyanate to give 3-(*N*-phenyl) thiocarbamido coumarin **4**. One-pot three-component phase transfer catalysis reaction of the coumarin derivative **1** with carbon disulfide and different alkyl halides and/or aroyl halides, to form the dithioalkylation and/or dithioacylation at C_3 of the coumarin **1** through ambident anion intermediate **5**, using K_2CO_3 as base and triethylbenzyl ammonium chloride (TEBAC) as catalyst failed, this may be attributed to the high stability of the dithiolate anion **5** and more crowding around the nucleophilic center (Scheme 1). The IR and ^{1}HNMR spectral data were in accordance with the proposed structure of the dithiolate derivative **5**

Reaction of coumarin **1** with aromatic aldehydes, namely, 3,4-methylene dioxybenzaldehyde and/or 4-methoxy benzaldehyde in equal molar ratio in the presence of piperidine as a base catalyst, afforded the condensation product 3-arylidene-6-methyl-4-oxocomarin (**7a,b**),[27–30] but when the reaction is repeated in excess of 4-hydroxy coumarin **1**, the dicoumarol derivatives **8a,b** were obtained in high yield. Also, the dicoumarol **8a**[31] was prepared authentically by the addition of coumarin **1** to 3-arylidine of **7a** in the presence of base as piperidine. (Scheme 2).

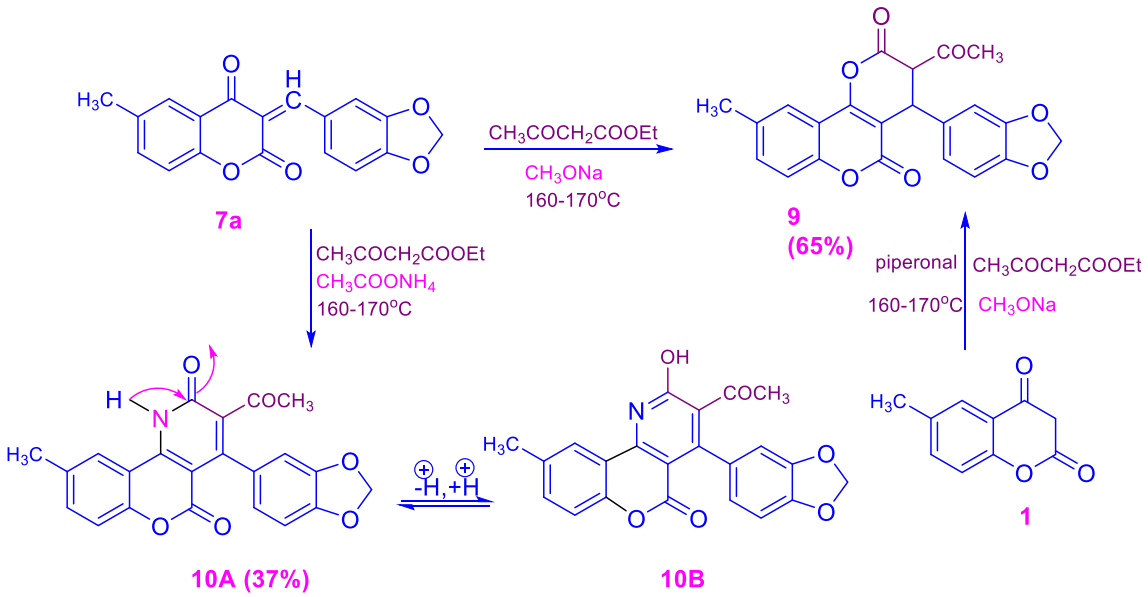
The structure of the 3-arylidene **7a,b** was proved from its IR spectrum by the appearance of an absorption bands at 1685 and 1660 cm^{-1} for **7a** and 1690 and 1650 cm^{-1} for **7b** due to the conjugated carbonyl group of lactone and ketone, respectively; also, the ^{1}HNMR spectrum for **7a,b** showed two singlet peak at 6.2 ppm due to two proton of CH=, in addition to signals at 5.94 ppm for CH_2O_2 and 3.69 for OCH_3 in case of **7a** and **7b**, respectively. Its mass spectrum also showed a parent peak at *m/z* 308 (85%) of $[M]^+$ and 307 (100%) for $[M\text{-}1]^+$. The structure of both **8a** and **8b** was confirmed by the presence of a band at 3400 cm^{-1} corresponding to enolic –OH and carbonyl absorption bands at 1670 and 1680 cm^{-1}, respectively. The ^{1}HNMR spectra of both two compounds showed signals corresponding to double number of protons for CH_3 at 2.44 ppm relative to CH_2O_2 at 5.96 ppm corresponding to **8a** while in **8b** showed singlet signal for CH_3 and OCH_3 protons at δ 2.45 3.79 ppm. Further evidence was gained from their mass spectra that revealed molecular ion peaks as well as some of important peaks.

The arylidene derivative of **7a** can be considered as α,β-unsaturated ketone, which undergoes Michael type of cycloaddition reactions, when react with ethyl acetoacetate in the presence of sodium methoxide and/or ammonium acetate as base catalyst under fusion conditions, to give the cyclo addition products of pyranochromene **9** and pyrano pyridone **10**, respectively. The pyranochromene **9** was also obtained by one-pot three-component reaction of coumarin **1** with piperonal and ethyl acetoacetate in the presence of sodium methoxide as a base catalyst under fusion condition (Scheme 3).

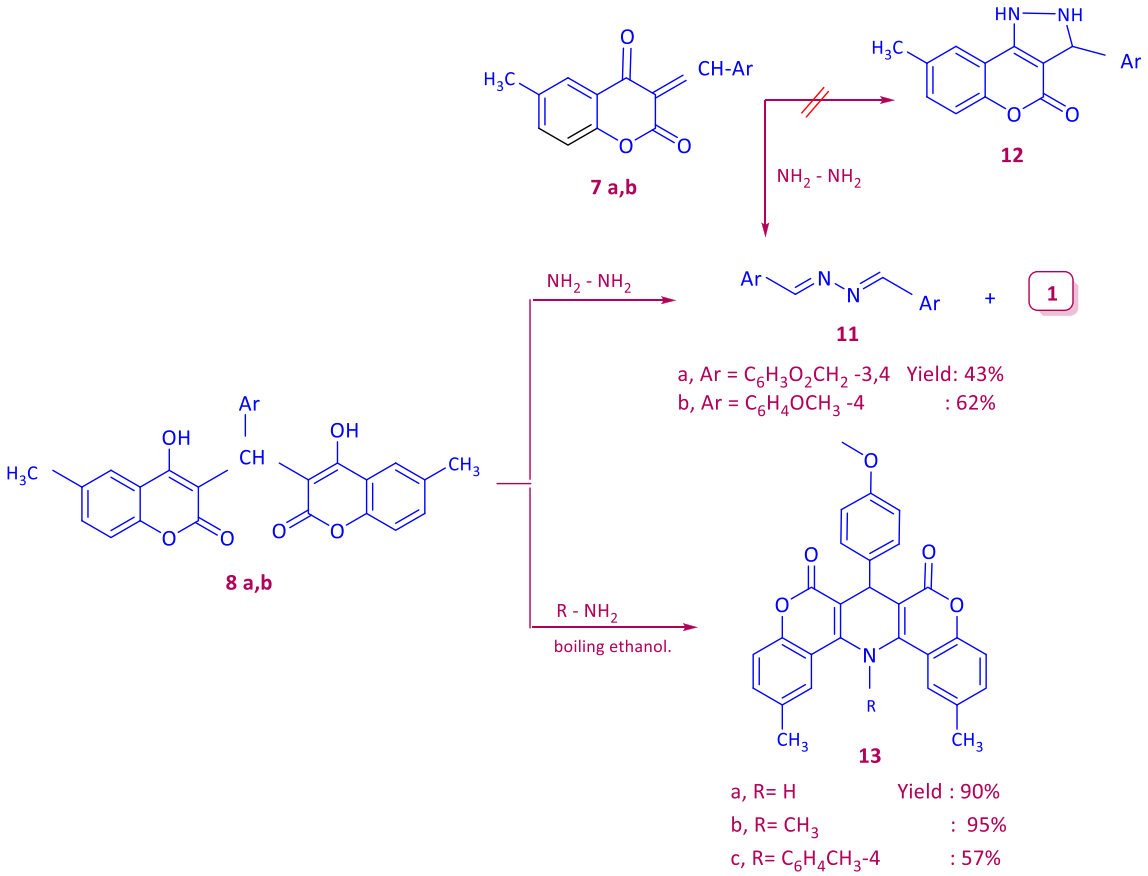
The structures of compounds **9** and **10** were substantiated from their spectral data. Their IR spectra exhibited absorption bands for C=O lactone and ketone as well as C=O amide in case of compound **10**. Further evidence was gained from their ^{1}HNMR spectra that revealed signals for existence of two methine protons. The appearance of two exchangeable broad singlet signals in the down field region at δ 8.4 ppm (N–H) and 12.42 ppm (O–H) with an equimolar ratio in case of compound **10** is a good evidence for its existence as a mixture of lactam **10A** and lactim **10B** tautomers (Scheme 3).



SCHEME 2 Reaction of coumarin derivative **1** with aromatic aldehydes

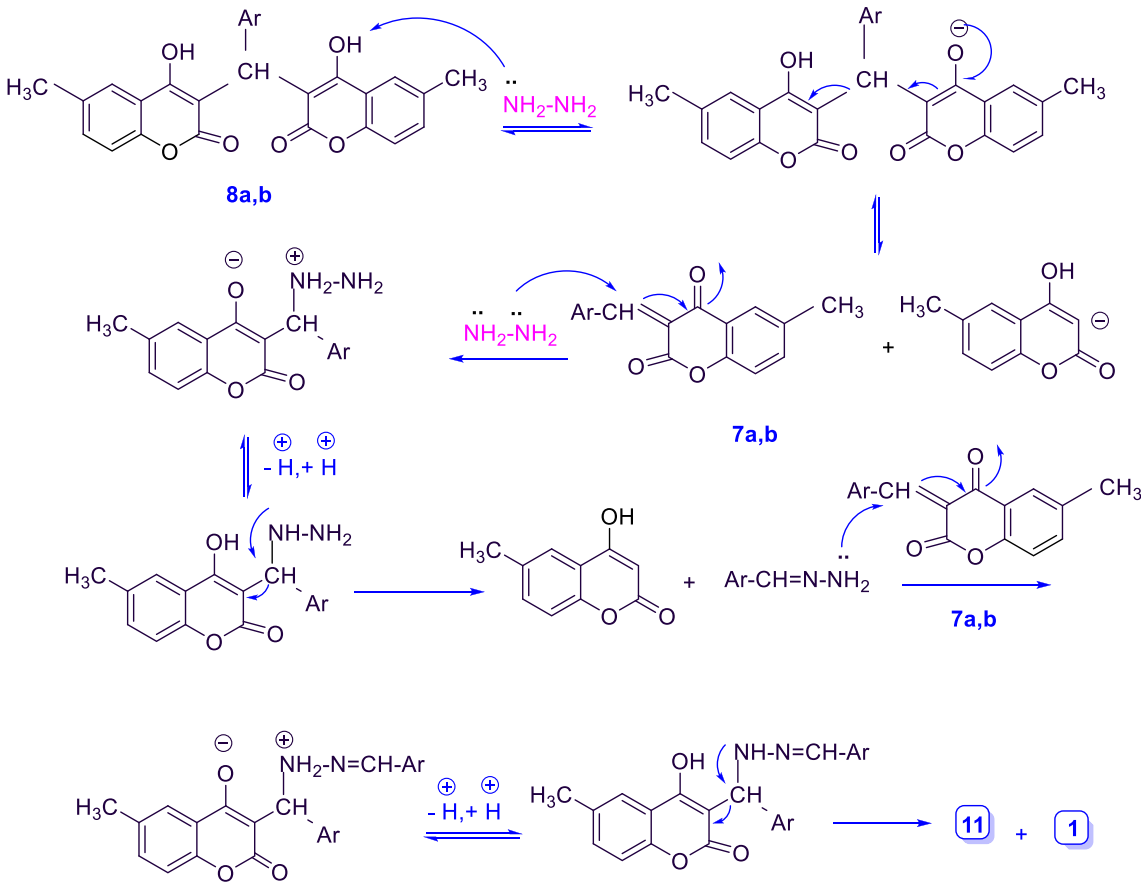


SCHEME 3 Michael cycloaddition reactions of coumarin derivative **1** with ethyl acetoacetate



SCHEME 4 Reaction of 3-arylidenes **7a**,**b** and/or dicoumarols **8a**,**b** with nitrogen nucleophiles

The reaction of hydrazine hydrate with 3-arylidenes **7a,b** and/or dicoumarols **8a,b** in boiling ethanol afforded the corresponding 1,2-dibenzyldene hydrazine derivatives **11a,b** beside the starting coumarin **1** instead of the expected product of pyrazolocoumarin **12** (Scheme 4). A chemical proof for the suggested structure is gained by



SCHEME 5 The suggested mechanism for the formation of compound **11**

preparing an authentic sample through reacting of piperonal and/or *p*-anisaldehyde with hydrazine hydrate. It was identical in all respects mp, mmp, and TLC with compounds **11a,b**.[32] The mechanistic pathway for the formation of compound **11** is depicted in Scheme 5. Whereas treatment of dicoumarol **8b** with ammonium acetate, methyl amine, and/or *p*-toluidine in boiling ethanol under reflux condition, it gives the corresponding pyridine derivatives **13a-c**, respectively, through cyclocondensation reaction of two carbonyl groups with nitrogen nucleophiles.

2.1 | Antimicrobial activity

Antimicrobial activity of newly synthesized products has been evaluated.[33] The results are listed in Table 1.

The selected compounds were tested in vitro for antibacterial activity against Gram-positive bacteria (*Staphylococcus aureus*) and Gram-negative bacteria (*Escherichia coli*). The antifungal activity of the compounds was tested against *Candida albicans*, using disc diffusion method[34] at 1 mg/mL disc concentration. The antibacterial activity of a common standard antibiotic ampicillin and antifungal colitrimazole was also recorded using the same procedure as above at the same concentration and solvents. DMSO was used as solvent. The zone of inhibition of bacterial and fungal growth was observed. The % activity index was calculated using the following formula:

$$\%\text{Activity Index} = \frac{\text{Zone of inhibition by test compound (diameter)}}{\text{Zone of inhibition by standard (diametre)}} \times 100.$$

The results showed that most of the compounds (81%) were active against the most of the screened microorganisms. Only two compounds (**7a** and **7b**) had no activity. Minimum antimicrobial activities were exhibited by compounds **2c-d** whose activity index value did not exceed 40%. Compounds **2a**, **2b**, **4**, **8a**, **8b**, **9**, and **10** showed promising antibacterial and antifungal activity. The activity index value ranged between 50% and 87%.

3 | EXPERIMENTAL

All melting points were recorded on a Gallen Kamp electric melting point apparatus (Shimadzu, Japan) and

TABLE 1 : Response of diverse microorganisms toward some selected products in in vitro culture

No.	Compound	*Escherichia coli*, mg/mL		*Staphylococcus aureus*, mg/mL		*Candida albicans*, mg/mL	
		Diameter of Inhibition Zone, mm	% Activity Index	Diameter of Inhibition Zone, mm	% Activity Index	Diameter of Inhibition Zone, mm	% Activity Index
1	**2a**	14	56	12	50	14	54
2	**2b**	14	56	12	50	15	58
3	**2c**	9	36	10	42	9	35
4	**2d**	8	32	ND	—	ND	—
5	**4**	21	84	20	83	22	85
6	**7a**	ND	—-	ND	—	ND	—
7	**7b**	ND	—-	ND	—	ND	—
8	**8a**	18	72	19	79	14	54
9	**8b**	19	76	20	83	16	62
10	**9**	22	88	20	83	22	85
11	**10**	22	88	19	79	21	81
12	**13a**	18	72	18	75	16	62
Ampicillin		25	100	24	100	ND	——
Colitrimazole		ND	——	ND	——	26	100

Abbreviation: ND, not detected.

uncorrected. All the infrared spectra were recorded on a PyeUnicamSP-3-300 infrared spectrophotometer (Thermo Scientific, Nitolet is in waltham,MA02451, USA) using potassium bromide disks. ^{1}H NMR spectra were run at 200 MHz, on a Varian Mercury VX-200 NMR spectrophotometer (Billerica, Massachusetts) using TMS as an internal standard in deuterated dimethyl sulfoxide and deuterated chloroform. Chemical shifts are quoted in ppm. The mass spectra were recorded on Shimadzu GCMS-QP-1000EX mass spectrophotometer at 70eV All the spectral measurements were carried out at the NMR laboratory of Faculty of Science, Cairo University, Egypt, at the NMR laboratory of Faculty of Pharmacy, Ain Shams University, and Mass laboratory, Al-Azhar University, Egypt. The micro analytical data were measured in Central Lab of Faculty of Science, Cairo University, Egypt, and the Ministry of Defense Chemical Laboratories, Egypt. All the chemical reactions were monitored by TLC on silica gel coated aluminum sheets (Silica Gel 60 F254, Merck).

3.1 | General procedure for the formation of 4-alkoxy and 3-alkyl-6-methyl coumarin derivatives 2a-d and 3

A mixture of coumarin **1** (1.76 g; 0.01 mol), anhydrous potassium carbonate (5 g; 0.16 mol), tetra butyl ammonium chloride (0.5 g; 0.01 mol), and alkyl halides, namely, allyl chloride, benzyl chloride, *p*-nitrobenzyl chloride, and/or ethyl chloro acetate (0.01 mol) in acetone (30 mL), was stirred at room temperature for 3 hours. When the reaction was completed, the organic layer was separated, the solvent was evaporated, and the solid products crystallized from the appropriate solvent.

3.1.1 | 6-Methyl-4(2-propenyloxy)-2*H*-chromen-2-one (2a)

Crystallized from benzene as white crystals, Yield: 1.87 g (87%); m.p.: 106°C. IR (KBr) no absorption bands for (OH) and (C=O) of ketone, but showed band at 1720 cm^{-1} for (C=O lactone); ^{1}HNMR ($CDCl_3$) δ (ppm): 2.35 (s, 3H, CH_3), 4.02 (d, J = 6 Hz, 2H, CH_2–O), 5.19 (d, J = 6.2 Hz, 1H, =CH), 5.31 (d, J = 13.3 Hz, 1H, =CH), 5.6 (s, 1H, C_3–H), 5.88-5.9 (m, 1H, =CH), 7.05 (d, J = 8.1 Hz, 1H, aromatic CH), 7.42 (d, J = 8.2 Hz, 1H, aromatic CH), 7.71 (s, 1H, aromatic CH). Anal for $C_{13}H_{12}O_3$ (216.24). Calcd: C, 72.21; H, 5.59; Found: C, 71.98; H, 5.56.

3.1.2 | 4-(Benzyloxy)-6-methyl-2*H*-chromen-2-one (2b)

Crystallized from petroleum ether (60-80) as white crystals, Yield: 2.2 g (83%), m.p.: 150°C. IR (KBr) no absorption bands for (OH) and (C=O) of ketone, but showed band at 1750 cm^{-1} for (C=O lactone); ^{1}HNMR ($CDCl_3$) δ

(ppm): 2.39 (s, 3H, CH_3) 5.19 (s, 2H, CH_2O), 5.76 (s, 1H, C_3–H), 7.08-7.56 (m, 7H, aromatic CH), 7.70 (s, 1H, aromatic CH). Anal for $C_{17}H_{14}O_3$ (266.30). Calcd: C, 76.68; H, 5.30; Found: C, 76.53; H, 5.15.

3.1.3 | 6-Methyl-4-(4-nitrobenzyloxy)-2*H*-chromen-2-one (2c)

Crystallized from benzene/methanol with ratio (1:1) as yellow crystals, Yield: 2.64 g (85%), m.p.: 252°C. IR (KBr) no absorption bands for (OH) and (C=O) of ketone, but showed band at 1700 cm^{-1} (C=O lactone); ^{1}HNMR ($CDCl_3$) δ (ppm): 2.42 (s, 3H, CH_3), 5.30 (s, 2H, CH_2O), 5.70 (s, 1H, C_3–H), 7.16 (d, J = 8 Hz, 1H, aromatic CH), 7.38 (d, J = 8.1 Hz, 1H, aromatic CH), 7.64 (d, J = 8.6 Hz, 2H, aromatic CH), 7.72 (s, 1H, aromatic CH), 8.31 (d, J = 8.5 Hz, 2H, aromatic CH). Anal for $C_{17}H_{13}NO_5$ (311.26). Calcd: C, 65.59; H, 4.21; N, 4.50; Found: C, 65.51; H, 4.12; N4.45.

3.1.4 | Ethyl 2-((6-methyl-2-oxo-2*H*-chromen-4-yl) oxy) acetate (2d)

Crystallized from diethyl ether as white crystals, Yield: 2.1 g (93%), m.p.: 120°C. IR (KBr) no absorption bands for (OH) and (C=O) of ketone, but showed bands at 1760, 1720 cm^{-1} (C=O) lactone and ester, respectively. ^{1}HNMR ($CDCl_3$) δ (ppm): 1.35 (t, J = 6.9 Hz, 3H, CH_2–$\underline{CH_3}$), 2.35 (s,3H, CH_3), 4.30 (q, J = 6.9 Hz, 2H, $\underline{CH_2}$-CH_3), 4.70 (s, 2H, CH_2), 5.56 (s, 1H, C_3-H), 7.20 (d, J = 8.1 Hz, 1H, aromatic CH), 7.67(d, J = 8 Hz, 1H, aromatic CH), 7.80 (s, 1H, aromatic CH). Anal for $C_{14}H_{14}O_5$ (262.08). Calcd: C, 64.12; H, 5.38; Found: C, 63.98; H, 5.28.

3.1.5 | 3-Benzyl-4-hydroxy-6-methyl-2*H*-chromen-2-one (3)

Crystallized from ethanol as white crystals, Yield: 0.13 g (5%), m.p.: 180°C. IR (KBr) showed absorption bands at 3300 cm^{-1} (OH) and 1715 cm^{-1} (C=O lactone); ^{1}HNMR ($CDCl_3$) δ (ppm): 2.42 (s, 3H, CH_3), 2.90 (s, 2H, CH_2), 7.20-7.56 (m, 8H, aromatic CH), 13.8 (br.s, 1H, –OH). Anal for $C_{17}H_{14}O_3$ (266.30). Calcd: C, 76.68; H, 5.30; Found: C, 76.64; H, 5.26.

3.1.6 | Synthesis of 4-hydroxy-6-methyl-2-oxo-*N*-phenyl-2*H*-chromene-3-carboxamide (4)

A mixture of the coumarin derivative **1** (1.76 g; 0.01 mol), anhydrous potassium carbonate (5 g; 0.16 mol), tetra butyl ammonium chloride (0.5 g; 0.01 mol), and phenyl isothiocyanate (1.3 g; 0.01 mol) in acetone (30 mL) was stirred for 24 hours at room temperature. When the reaction being completed, the organic layer was separated, the solvent was evaporated, and the solid product was obtained crystallized from petroleum ether (40-60), to give **4** as yellow crystals, Yield: 0.93 g (30%), m.p.: 174-176°C. IR (KBr) cm^{-1} showed absorption bands at 3450 cm^{-1} (OH), 3300 cm^{-1} (NH), 1640 cm^{-1} (chelated C=O). ^{1}HNMR ($CDCl_3$) δ (ppm): 2.42 (s, 3H, CH_3), 6.87-7.42 (m, 8H, aromatic CH), 12.40 (br.s, 1H, NH); 14.45 (br.s, 1H, OH); MS showed the parent peak at *m/z*: (% abundance) 311(8) [M^+]. Anal for $C_{17}H_{13}NO_3S$ (311.36). Calcd: C, 65.58; H, 4.21; N, 4.50; Found: 65.49; H, 4.16; N, 4.43.

3.1.7 | Synthesis of diammonium salt of dithiolate anion 5

A mixture of coumarin derivative **1** (1.76 g; 0.01 mol), anhydrous potassium carbonate (5 g; 0.16 mol), benzyl triethyl ammonium chloride (0.5 g; 0.01 mol), carbon disulfide (20 mL) in acetone (30 mL), and added different aryl halides, namely, benzyl chloride and/or *p*-nitro benzyl chloride (0.01 mol), was stirred at room temperature for 3 hours. The solid layer was separated and washed by dil. HCl (100 mL, 10%) and then filtered off, dried, and crystallized from ethanol afforded compound **5** as yellow crystals, Yield: 5.1 g (80%); m.p.: above 350°C. IR (KBr) showed absorption bands at 1690 and 1680 cm^{-1} (C=O) of lactone and ketone; ^{1}HNMR ($CDCl_3$) δ (ppm): 0.94-0.96 (m, 6H, $2CH_3$), 1.21-1.23 (m, 12H, $4CH_3$), 2.34 (s, 3H, CH_3), 2.72 (q,4H, $2CH_2$-N), 3.42 (q, 8H, $4CH_2$-N), 4.62 (S, 4H, $2CH_2$-ph), 7.15-8.4 (m, 13H, aromatic CH). Anal for $C_{37}H_{50}N_2O_3S_2$ (634.56). Calcd: C, 69.98; H, 7.93; N, 4.41; Found: C, 70.14; H, 7.81; N, 4.59.

3.2 | General procedure for the reaction of 4-hydroxy-6-methylcoumarin 1 with aromatic aldehydes

A mixture of 4-hydroxy coumarin derivative **1** (1.76 g; 0.01 mol) and aromatic aldehydes such as piperonal and/or *p*-anisaldehyde (0.01 mol) and piperidine (0.5 mL) as a base catalyst in ethanol (20 mL) was refluxed for 1 hour. After completion, the reaction was left to cool and poured onto crushed ice and then acidified with dilute HCl solution (10 mL, 10%); the separated solid was filtered off, washed with water, dried, and crystallized from the appropriate solvent.

3.2.1 | 3-(Benzo[*d*][1,3]dioxol-5-ylmethylene)-6-methylchroman-2,4-dione 7a

Crystallized from methanol as yellow crystals, Yield: 2.93 g (95%); m.p.: 213-215°C. IR (KBr) showed absorption bands at 1685 and 1660 cm^{-1} of conjugated (C=O) lactone and ester, respectively. ^{1}HNMR (DMSO-d_6) δ (ppm): 2.38 (s, 3H, CH_3), 5.94 (s, 2H, CH_2O_2), 6.2 (s, 1H, =CH), 6.68 (d, J = 8.1 Hz, 1H, aromatic CH), 6.89 (s, 1H, aromatic CH), 6.79 (d, J = 8.2 Hz, 1H, aromatic CH), 7.27 (d, J = 8.1 Hz, 1H, aromatic CH), 7.42 (d, J = 8.1 Hz, 1H, aromatic CH), 7.71 (s, 1H, aromatic CH). MS showed the parent peak at *m/z*: (% abundance) 308 (85%) [M^+], and the following fragments 307 (100) [M^+-1], 279 (14), 176 (29), 134 (66). Anal for $C_{18}H_{12}O_5$ (308.29). Calcd: C, 70.13; H, 3.92; Found: C, 69.95; H, 4.07.

3.2.2 | 3-(4-Methoxybenzylidine)-6-methyl-2*H*-chromen-2,4-dione 7b

Crystallized from methanol as white crystals, Yield: 1 g (34%); m.p.: 203°C-206°C. IR (KBr) cm^{-1} showed absorption bands at 1690 and 1650 cm^{-1} (C=O) of conjugated lactone and ketone, respectively. ^{1}HNMR (DMSO-d_6) δ (ppm): 2.36 (s, 3H, CH_3), 3.69 (s, 3H, OCH_3), 6.2 (s, 1H, =CH), 6.71 (d, J = 8.1 Hz, 2H, aromatic CH), 7.10 (d, J = 8 Hz, 2H, aromatic CH), 7.18 (d, J = 7.9 Hz, 1H, aromatic CH), 7.51 (d, J = 8 Hz, 1H, aromatic CH), 7.62 (s, 1H, aromatic CH). MS showed the parent peak at *m/z*: (% abundance) 294 (56) [M^+] and 293 (75) [M^+-1]. Anal for $C_{18}H_{14}O_4$ (294.31). Calcd: C, 73.46; H, 4.79; Found: C, 73.45; H, 4. 68.

3.3 | General procedure for the formation of aryl-bis(4-hydroxy-6-methyl coumarin-3-yl) methane 8a,b

The mixture of 4-hydroxy coumarin derivative **1** (1.76 g; 0.01 mol) and aromatic aldehydes such as piperonal and/or *p*-anisaldehyde (0.005 mol) and piperidine (0.5 mL) as a base catalyst in ethanol (20 mL) was refluxed for 3 hours. After completion, the reaction was left to cool and poured onto crushed ice and then acidified with a solution of dilute HCl (10 mL, 10%); the solid product obtained was washed with water and filtered off, dried and crystallized from the appropriate solvent.

3.3.1 | 3,4-Methylenedioxy phenyl bis (4-hydroxy-6-methyl coumarin-3-yl) methane 8a

Crystallized from diethyl ether as pale yellow crystals, Yield: 2.76 g (57%); m.p.: 268°C-270°C. IR (KBr) showed absorption bands at 3400 cm^{-1} of enolic (OH) and 1670 cm^{-1} (C=O) of lactone. ^{1}HNMR ($CDCl_3$) δ (ppm): 2.38 (s, 6H, $2CH_3$), 5.96 (s, 2H, CH_2O_2), 6.00 (s, 1H, CH), 6.70 (d, J = 8 Hz, 1H, aromatic CH), 6.76 (s, 1H, aromatic CH), 6.97 (d, J = 8.2 Hz, 1H, aromatic CH); 7.30 (d, J = 7.8 Hz, 2H, aromatic CH), 7.46 (d, J = 7.9 Hz, 2H, aromatic CH), 7.8 (s, 2H, aromatic CH), 11.31 (br.s, 2H, 2OH). MS showed the parent peak at *m/z*: (% abundance) 484 (12) [M^+]. Anal for $C_{28}H_{20}O_8$ (484.21). Calcd: C, 69.40; H, 4.16; Found: C, 69.63; H, 4.34.

3.3.2 | 4-Methoxyphenyl bis(4-hydroxy-6-methyl coumarin-3-yl) methane 8b

Crystallized from ethanol as white crystals, Yield: 2.96 g (63%); m.p.: 256°C-258°C. IR (KBr) cm^{-1} showed absorption bands at 3400 cm^{-1} (OH) enolic and 1680 cm^{-1} (C=O) of lactone. ^{1}HNMR ($CDCl_3$) δ (ppm): 2.45 (s, 6H, $2CH_3$), 3.79 (s, 3H, OCH_3), 6.03 (s, 1H, CH), 6.83 (d, J = 8.4 Hz, 2H, aromatic CH), 7.09 (d, J = 8.3 Hz, 2H, aromatic CH), 7.29 (d, J = 7.8 Hz, 2H, aromatic CH), 7.43 (d, J = 7.8 Hz, 2H, aromatic CH), 7.83 (s, 2H, aromatic CH), 11.62 (br.s, 2H, 2 OH enol). MS showed the parent peak at *m/z*: (% abundance): 470(3) [M^+], and the following fragments 293 (100), 263 (74), 176 (22), 134 (56). Anal for $C_{28}H_{22}O_7$ (470.21). Calcd: C, 71.47; H, 4.72; Found: C, 71.61; H, 4.85.

3.3.3 | Reaction of 3-arylidine derivatives 7a,b with coumarin 1: formation of dicoumarol 8a,b

Heating a mixture of 3-arylidene **7a** and/or **7b** (0.01 mol) with coumarin **1** (1.76 g; 0.01 mol) and piperidine (0.5 mL) in ethanol 50 mL under reflux condition for 2 hours. The reaction mixture was allowed to cool and poured onto crushed ice and then acidified with dilute HCl solution (10 mL, 10%); the separated solid was filtered off, washed with water, dried, and crystallized from the appropriate solvent to give the dicoumarol **8a** and/or **8b** that are identical of m.p., TLC and IR as well as the products produced in last experiment.

3.3.4 | Synthesis of 3-acetyl-4-(benzo[*d*][1,3]dioxol-5-yl)-9-methyl-3,4-dihydro-2*H*,5*H*-pyrano[3,2-*c*]chromene-2,5-dione 9

Method A

A mixture of arylidene derivative **7a** (1.55 g; 0.005 mol), ethyl acetoacetate (0.005 mol), and sodium methoxide (0.53 g; 0.01 mol) was heated under fusion condition at temperature between 160°C and 170°C for 3 hours, cooling the reaction mixture, triturated with dil. HCl solution (100 mL; 10%), and then filtered off, washing with water (150 mL). The solid obtained was crystallized from benzene-diethyl ether (2:1) to give the pyranochromene derivative **9** as yellow crystals; m.p. 196°C-198°C; Yield 0.92 g (47%); IR (KBr) showed absorption bands at 1740, 1720, and 1690 cm^{-1} corresponding to (C=O) of two lactones and ketone, respectively. ^{1}HNMR (DMSO-d_6) δ (ppm): 2.38 (s, 3H, CH_3-CO), 2.42 (s, 3H, CH_3), 3.56 (d, J = 6.2 Hz, 1H, CH), 4.42 (d, J = 6.1 Hz, 1H, CH), 5.97 (s, 2H, CH_2O_2), 6.72-7.66 (m, 5H, aromatic CH), 7.72 (s, 1H, aromatic CH). Anal for $C_{22}H_{16}O_7$ (392.36). Calcd: C, 67.35; H, 4.11; Found: C, 67.27; H, 4.0.

Method B

A mixture of 4-hydroxy coumarin derivative **1** (1.76 g; 0.01 mol), piperonal (1.5 g; o.o1mol), ethyl acetoacetate (1.3 g; 0.01 mol), and sodium methoxide (0.53 g; 0.01 mol) was heated under fusion condition at temperature between 160°C and 170°C for 3 hours, cooling the reaction mixture, triturated with dil. HCl solution (100 mL; 10%) and then filtered off, washing with water (150 mL). The solid product was crystallized from benzene-diethyl ether (2:1) to give the pyranochromene derivative **9** as yellow crystals; Yield 2.14 g (65%).

3.3.5 | Synthesis of 3-acetyl-4-(benzo[*d*][1,3]dioxol-5-yl)-9-methyl-2*H*-chromeno[4,3-*b*] pyridine-2,5(1*H*)-dione 10

A mixture of the arylidene derivative **7a** (1.55 g; 0.005 mol), ethyl acetoacetate (0.005 mol), and ammonium acetate (5.0 g; 0.065 mol) is heated at temperature between 160°C and 170°C for 3 hours under fusion condition. The reaction mixture was cooled, triturated with HCl solution (10%, 100 mL) and then filtered off, washed with water (150 mL); the solid product obtained was dried and crystallized from methanol to give pyridine derivative **10** as yellow crystals. Yield: 0.72 g (37%), m. p. 308°C. IR (KBr) showed absorption bands at 3100 cm^{-1} (NH), 1760 cm^{-1} (C=O lactone), and 1650 cm^{-1} (C=O amide). ^{1}HNMR (DMSO-d_6) δ (ppm): 2.40 (s, 3H, CH_3-CO), 2.46 (s, 3H, CH_3), 6.44 (s, 2H, CH_2O_2), 7.29-7.49 (m, 5H, aromatic CH), 7.78 (s, 1H, aromatic CH), 8.40 (br.s, 1H, NH), 12.42 (s, 1H, OH enolic). Anal for $C_{22}H_{15}NO_6$ (389.36). Calcd: C, 67.87; H, 3.88; N, 3.60; Found: C, 67.68; H, 3.76; N, 3.55.

3.4 | General procedure for the formation of 1,2-diarylidine hydrazine 11a,b

A mixture of the arylidene derivatives **7a,b** and/or dicoumarol derivatives **8a,b** (0.01 mol) and hydrazine hydrate (0.5 mL; 0.01 mol) in ethanol (50 mL) was refluxed for 2 hours, the reaction mixture was allowed to cool, and the solid product was separated dissolve in $NaCO_3$ solution (50 mL, 20%); the residue separated, dried, and crystallized from ethanol to give **11a,b**, and the filtrate contains coumarin **1** that acidified with dilute HCl (10 mL, 10%) was filtered off then crystallized from ethanol.

3.4.1 | 1,2-Bis(benzo[*d*][1,3]dioxol-5-ylmethylene) hydrazine 11a

Crystallized from ethanol as creamy crystals, Yield: 1.27 g (43%); m.p.: 208°C-210°C. IR (KBr) showed absorption band at 1620 cm^{-1} (C=N). ^{1}HNMR (DMSO-d_6) δ (ppm): 6.20 (s, 4H, $2CH_2O_2$), 7.25 (d, J = 9.1 Hz, 2H, aromatic CH), 7.59 (s, 2H, aromatic CH), 7.54 (d, J = 9.2 Hz, 2H, aromatic CH), 8.69 (s, 2H, 2CH=N). Anal for $C_{16}H_{12}N_2O_4$ (296.08). Calcd: C, 64.86; H, 4.08; N, 9.46; Found: C, 64.82; H, 4.04; N, 9.44.

3.4.2 | 1, 2-Bis(4-methoxybenzylidene) hydrazine 11b

Crystallized from ethanol as yellow crystals, Yield: 1.66 g (62%); m.p.: 167°C-168°C. IR (KBr) cm^{-1} showed absorption band at 1620 cm^{-1} (C=N). ^{1}HNMR (DMSO-d_6) δ (ppm): 3.75 (s, 6H, $2OCH_3$), 7.06 (d, J = 8.9 Hz, 4H, aromatic CH), 7.83 (d, J = 9 Hz, 4H, aromatic CH), 8.65 (s, 2H, 2CH=N). Anal for $C_{16}H_{16}N_2O_2$ (268.15). Calcd: C, 71.61; H, 6.01; N, 10.45; Found: C, 71.60; H, 5.97; N, 10.41.

3.5 | General procedure for the formation of pyridine derivatives 13a-c

A mixture of dicoumarol **8b** (1.39 g; 0.003 mol) and ammonium acetate, methyl amine, and/or *p*-toluidine

(0.01 mol) in ethanol (50 mL) was refluxed for 3 hours. After the reaction being completed, it was left to cool and poured onto crushed ice and then acidified with dilute HCl solution (10 mL, 10%); the solid product obtained was filtered off, washed with water, dried, and crystallized from the appropriate solvent to give pyridine derivatives **13a-c**.

3.5.1 | 7-(4-Methoxyphenyl)-2,12-dimethyl-7,14-dihydro-6*H*,8*H*-dichromeno[4,3-*b*:3′,4′-e]pyridine-6,8-dione 13a

Crystallized from ethanol as white crystals, Yield: 1.22 g (90%); m.p.: 288°C-289°C. IR (KBr) cm^{-1} showed absorption bands at 3280 cm^{-1} (NH) and 1685 cm^{-1} (C=O) of lactone. ^{1}HNMR (DMSO-d_6) δ (ppm): 2.34 (s, 6H, 2 CH_3), 3.69 (s, 3H, OCH_3), 6.17 (s, 1H, CH), 6.84 (d, J = 8.1 Hz, 2H, aromatic CH), 7.02 (d, J = 8.1 Hz, 2H, aromatic CH), 7.21-7.43 (m, 4H, aromatic CH), 7.81 (s, 2H, aromatic CH), 17.83 (s, 1H, NH). Anal for $C_{28}H_{21}NO_5$ (451.48). Calcd: C, 74.49; H, 4.69; N, 3.10. Found: C, 74.57; H, 4.61; N, 3.18.

3.5.2 | 7-(4-Methoxyphenyl)-2,12,14-trimethyl-7,14-dihydro-6*H*,8*H*-dichromeno[4,3-*b*:3′,4′-*e*]pyridine-6,8-dione 13b

Crystallized from ethanol as white crystals, Yield: 1.32 g (95%); m.p.: 228°C-230°C. IR (KBr) showed absorption band 1690 cm^{-1} (C=O) of lactone and absent of bands for (OH) and (NH). ^{1}HNMR (DMSO-d_6) δ (ppm): 2.31 (s, 6H, 2CH_3), 3.38 (s, 3H, N–CH_3), 3.69 (s, 3H, OCH_3), 6.21 (s, 1H, CH), 6.83 (d, J = 7.9 Hz, 2H, aromatic CH), 7.04 (d, J = 7.9 Hz, 2H, aromatic CH), 7.17 (d, J = 8 Hz, 2H, aromatic CH), 7.36 (d, J = 8 Hz, 2H, aromatic CH); 7.83 (s, 2H, aromatic CH). Anal for $C_{29}H_{23}NO_5$ (465.51). Calcd: C, 74.83; H, 4.98; N, 3.01. Found: C, 75.04; H, 4.87; N, 3.00.

3.5.3 | 7-(4-Methoxyphenyl)-2,12-dimethyl-14-(*p*-tolyl)-7,14-dihydro-6*H*,8*H*-dichromeno[4,3-*b*:3′,4′-*e*]pyridine-6,8-dione 13c

Crystallized from benzene-methanol (1:1) as white crystals, Yield: 0.93 g (57%), m.p.: 221°C-222°C. IR (KBr) showed absorption band at 1695 cm^{-1} (C=O) of lactone and absent of bands for (OH) and (NH). ^{1}HNMR ($CDCl_3$) δ (ppm): 2.32 (s, 6H, 2CH_3), 2.41 (s, 3H, CH_3), 3.69 (s, 3H, OCH_3), 6.21 (s, 1H, CH), 6.72 (d, J = 8.1 Hz, 2H, aromatic CH), 6.97 (d, J = 8.1 Hz, 2H, aromatic CH), 7.14-7.38 (m, 8H, aromatic CH), 7.62 (s, 2H, aromatic CH). Anal for $C_{35}H_{27}NO_5$ (541.60). Calcd: C, 77.62; H, 5.03; N, 2.59. Found: C, 77.58; H, 5.00; N, 2.66.

4 | CONCLUSION

6-Methyl-4-hydroxy coumarin undergoes O-alkylation easily at room temperature under PTC conditions; also, it can form the 3-arylidene derivatives by treatment with aromatic aldehydes in similar molar ratios, whereas in excess of coumarin, the dicoumarol is well formed. Pyrano coumarin can be obtained either by Michael cycloaddition and/or one-pot reaction of coumarin with aldehyde and ethyl acetoacetate. The arylidine group is easily decomposed by reaction of 3-arylidine and/or dicoumarol with hydrazine hydrate to give the corresponding diarylidene hydrazine. Also, treatment of dicoumarol with different amines gives pyridine derivatives. Most of the synthesized compounds (81%) showed promising antibacterial and antifungal activity.

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How to cite this article: Regal MKA, Shaban SS, El-Metwally SA. Synthesis and antimicrobial activity of some new coumarin and dicoumarol derivatives. *J Heterocycl Chem*. 2020;1–11. https://doi.org/10.1002/jhet.3873