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Research Article

Development of New Multicomponent Reactions in Eco-Friendly Media-Greener Reaction and Expeditious Synthesis of Novel Bioactive Benzylpyranocoumarins

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Multicomponent cyclocondensation of hydrazine derivatives, ethyl acetoacetate, aromatic aldehydes, and 4-hydroxycoumarin has been reported. The optimization details of the developed novel protocol are recorded. The novel procedure features short reaction time, moderate yields, and simple workup. In addition, BMIM[triflate] was chosen as a green solvent. The structures of the obtained benzylpyrazolyl coumarins were determined and confirmed by ^{1}H NMR, ^{13}C NMR, IR, and elemental analysis. The MIC values of benzylpyrazolyl coumarin derivatives were determined by the microbroth dilution method using 96-well plates. However, the derivatives **5a**, **5b**, **5d**, and **5g** possess the strongest activities. Compound **5b** was the most active derivative against *Candida albicans*. Moreover, the antioxidant activity determination of these coumarins derivatives **5**(**a**–**g**)–**6**(**a**–**g**) were studied with the DPPH and compared with gallic acid (GA)and butylated hydroxytoluene (BHT). Molecular modelling studies using DFT (density functional theory) calculations showed that there two tautomers **A** and **B** in which **A** is more stable than **B**. The benzylpyrazolyl coumarin derivatives 5e and 6f exhibited the most cytotoxic effect on the promising cytotoxic activity with IC50 values 4.45 μg/mL against MDA-MB-231 and 4.85 μg/mL against MCF7, respectively.

1. Introduction

Coumarin scaffolds are commonly bioactive compounds [1–23]. Pyrazolone derivatives also exhibit a broad spectrum of biological activities [24–26] and are also important structural moieties in many drug substances of medicinal applications [22, 27, 28], such as phenazone, propyphenazone, ampyrone, and metamizole sodium (Figure 1).

Multicomponent reactions convert three or more starting materials in one pot to a highly functionalized product displaying maximum molecular diversity [29–35].

At present, ionic liquids (ILs) are playing a more and more important role in organic synthesis as green catalysts and solvents. Compared with traditional catalysts, these ionic liquids have shown special advantages and potential due to their ideal catalytic performance and the unusual characteristics.

Here, we report the synthesis of pyrazolone-linked coumarin derivatives which were obtained via the four-component domino reaction of 4-hydroxycoumarin, hydrazine derivatives, ethyl acetoacetate, and arylaldehydes; then, the structures of these new coumarin derivatives were characterized by spectroscopic methods (^{1}H and ^{13}C NMR, FT-IR, and elemental analysis). In addition, the benzylpyrazolyl coumarin derivatives were tested for their antimicrobial and antioxidant activities, which have not been studied in the past.

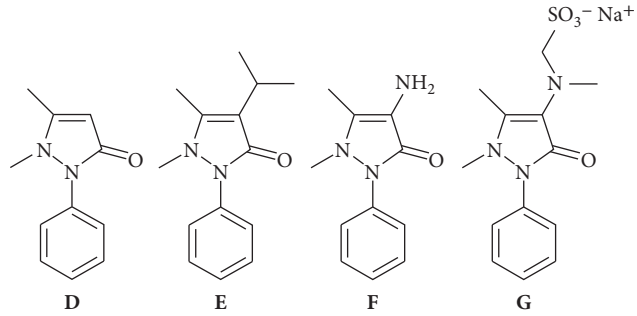


Figure 1: Structures of (**D**) phenazone, (**E**) propyphenazone, (**F**) ampyrone, and (**G**) metamizole.

2. Results and Discussion

The cyclocondensation of hydrazine derivatives, ethyl acetoacetate, and arylaldehydes with 4-hydroxycoumarins to generate benzylpyrazolyl coumarin derivatives was investigated under a variety of conditions (solvents, reaction time, temperature, and catalysts) (Scheme 1).

Initially, for examination of the catalytic activity, different catalysts such as TFA, HCOOH, $Cu(OAc)_2$, ZnO, and glacial acetic acid were selected. Then, a model study was carried out by the condensation reaction of hydrazine derivatives, ethyl acetoacetate, aromatic aldehydes, and 4-hydroxycoumarin under conventional conditions at different temperatures in the presence of each catalyst, separately. The corresponding results are summarized in Table 1.

Several catalysts were tested to check their effects such as TFA, HCOOH, $Cu(OAc)_2$, ZnO, and glacial acetic acid (Table 1, entries **10**–**15**). The obtained results indicated that glacial AcOH is the best catalyst for this reaction. Then, several amounts of this catalyst were evaluated: It was found that 5 mol% of the catalyst gave 65% of yield. When we increased the amounts of the catalyst to 10 mol%, 15 mol%, and 20 mol%, the yields were also found to be increased up to 95%, 94%, and 85%, respectively. After 20 mol%, there is no significant improvement of the yield of the reaction; consequently, 10 mol% of the catalyst was chosen as the maximum quantity of the catalyst for the reaction. The reaction was also performed at different reaction times, and the obtained results showed that the best reaction time was 30 min (Table 1, entries **1** and **15**–**17**). Based on all of these experiments, the optimum reaction conditions were identified as $[BMIM][CF_3SO_3]$ for 30 min using 10 mmol% of glacial acetic acid. The reaction was then carried out with different series of substituted aromatic aldehydes in order to check the limitations of this methodology. The results are summarized in Table 2.

The aromatic aldehydes carrying both electron-withdrawing and electron-donating functional groups (Table 2, entries **2**–**7**) underwent successful condensation with ethyl acetoacetate and hydrazines derivatives. The structures of compound **5** were confirmed from their spectroscopic data including ^{1}H NMR, ^{13}C NMR spectra, and elemental analysis.

In the ^{1}H NMR of compound **5c**, two characteristic singlets at 3.34 and 3.55 ppm were assigned to the methyl protons (a) and (b, d), whereas the proton H_c appears as a singlet at about 4.17 ppm in accordance with the literature data for other 4-hydroxycoumarin derivatives [36, 37]. ^{13}C NMR showed the $C_{2'}$ signal at $\delta = 168.06$ ppm, the C_4 signal had a chemical shift of $\delta = 164.90$ ppm, while the C_2, C_3, Ca, Cc, $C_{b,d}$, C_1, and C_5 signals were assigned at $\delta = 162.87$, 103.59, 13.66, 36.34, 40.01, 128.53, and 152.9 ppm, respectively.

The compound **5** thus obtained can exist in the form of two tautomers **A** and **B**. Theoretical calculations with the Gaussian program 09 carried out with the DFT (density functional theory) level with the base 6-31G + (d) and the functional B_3LYP confirm the stability of the structure **A** with respect to that of **B** ($\Delta E = 2$ kcal). Optimized geometries for compounds **A** and **B** are shown in Figure 2.

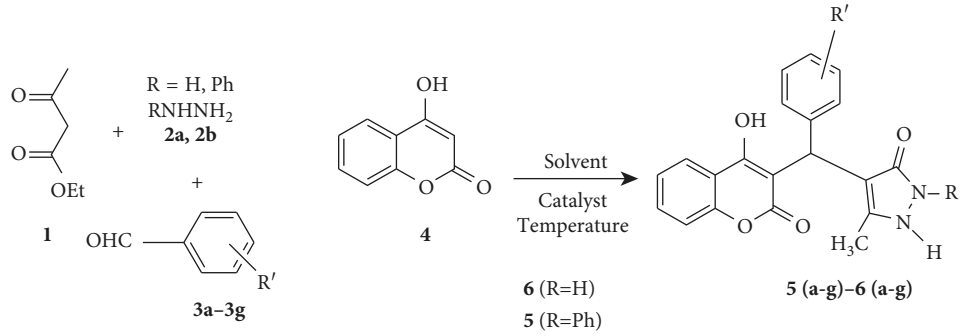
Encouraged by the obtained results, we tried to extrapolate our method to the condensation with hydrazine. The reaction seemed to be tolerant with different aromatic aldehydes. Overall, yields in the range of 75%–95% were obtained (Table 3).

The structure of the benzylpyrazolyl coumarin **6** derivatives has been confirmed by their spectroscopic data, and their melting points are compared with literature reports. The presence of signal at 3425 cm^{-1} in IR spectra was assigned to NH.

3. Antimicrobial Activity

The in vitro antimicrobial activity of the novel benzylpyrazolyl coumarin derivatives **5**(**a**–**g**)–**6**(**a**–**g**) were evaluated for in vitro antimicrobial activity by the well diffusion method. All products were screened for activity against Gram-positive bacteria (*Micrococcus luteus*, *Listeria monocytogenes*, and *Staphylococcus aureus*), Gram-negative bacteria (*Pseudomonas aeruginosa* and *Escherichia coli*), and fungi (*Candida albicans*). The minimum inhibitory concentrations (MICs) were determined and are given in Table 4.

As can be seen, most of the benzylpyrazolyl coumarin derivatives exhibit considerable activity against the tested microorganisms. The results obtained by these tests showed that our different molecules have antimicrobial activity. In fact, regarding the activity against Gram-negative bacteria (*Pseudomonas aeruginosa*), **5a** showed excellent activity and compounds **5b**–**5g** showed good activity. On the contrary, compound **5b** was the most active against *Candida albicans*.

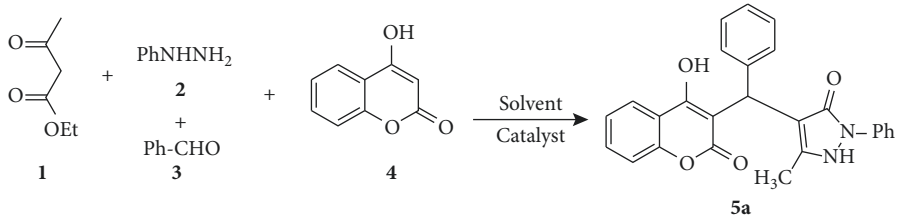


2a, R/= H, and **2b**, R/= Ph

3a–3g where a = H, b = p-CH_3, c = p-$N(CH_3)_2$, d = p-NO_2, e = m-Br, f = m-OCH_3, g = m-OH

Scheme 1: Synthesis of benzylpyrazolyl coumarin derivatives **5**(**a**–**g**)–**6**(**a**–**g**).

Table 1: Optimization of the conditions' reaction using different solvents.



Entry	Catalysts (mmol%)	Solvent	Time (h)	Temperature (°C)	Yield[a,b,c] (%)
1	No	([BMIM][CF_3SO_3])	24	210	—
2	No	DMC	24	90	—
3	No	H_2O	24	100	—
4	No	EtOH	24	78	—
5	No	CH_3CN	24	82	—
6	No	THF	24	66	—
7	No	CH_2Cl_2	24	40	—
8	No	Toluene	24	110	—
9	No	Glacial AcOH	24	119	—
10	TFA (10)	([BMIM][CF_3SO_3])	24	210	40
11	HCOOH (10)	([BMIM][CF_3SO_3])	24	210	45
12	$Cu(OAc)_2$ (10)	([BMIM][CF_3SO_3])	24	210	—
13	ZnO (10)	([BMIM][CF_3SO_3])	24	210	Trace
14	Gl. AcOH (5)	([BMIM][CF_3SO_3])	24	210	65
15	Gl. AcOH (10)	([BMIM][CF_3SO_3])	24	210	95
16	Gl. AcOH (15)	([BMIM][CF_3SO_3])	24	210	94
17	Gl. AcOH (20)	([BMIM][CF_3SO_3])	24	210	85
18	Gl. AcOH (10)	([BMIM][CF_3SO_3])	30 min	210	95
19	Gl. AcOH (10)	([BMIM][CF_3SO_3])	40 min	210	85
20	Gl. AcOH (10)	([BMIM][CF_3SO_3])	1	210	76
21	Gl. AcOH (10)	([BMIM][CF_3SO_3])	1 : 5 h	210	72
22	Gl. AcOH (10)	([BMIM][CF_3SO_3])	2	210	75

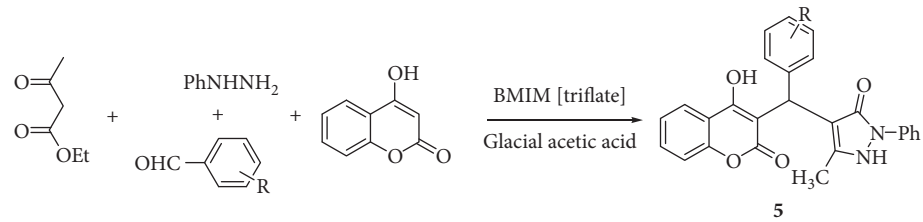
[a]All reactions were carried with hydrazine (0.005 mol), ethyl acetoacetate (0.005 mol), benzaldehyde (0.005 mol), and 4-hydroxycoumarin (0.005 mol). [b]Yield of the isolated product. [c]The reaction failed to provide a product. [BMIM][CF_3SO_3], 1-butyl-3-methylimidazolium trifluoromethanesulfonate.

In addition, we evaluated the antimicrobial activity of four synthetic products (**5a**, **5b**, **5d,** and **5g**) possessing the strongest activities against two Gram-positive bacteria (*S. aureus*) and Gram-negative bacteria (*P. aeruginosa*) against a fungus (*Candida albicans*) by the determination of the MIC in a liquid medium.

We determined the MIC values of the products tested against two bacteria and a fungus. Then, the minimal inhibitory concentration (MIC) values of benzylpyrazolyl coumarin derivatives were determined against *Staphylococcus aureus* ATCC 6538, *Pseudomonas aeruginosa* ATCC 49189, and *Candida albicans*. The obtained results are given in Table 5.

We have noticed that the compounds **6a**, **6b**, and **6g** are very active by comparing with ampicillin used as a control antibiotic against the strain *Staphylococcus aureus*. These

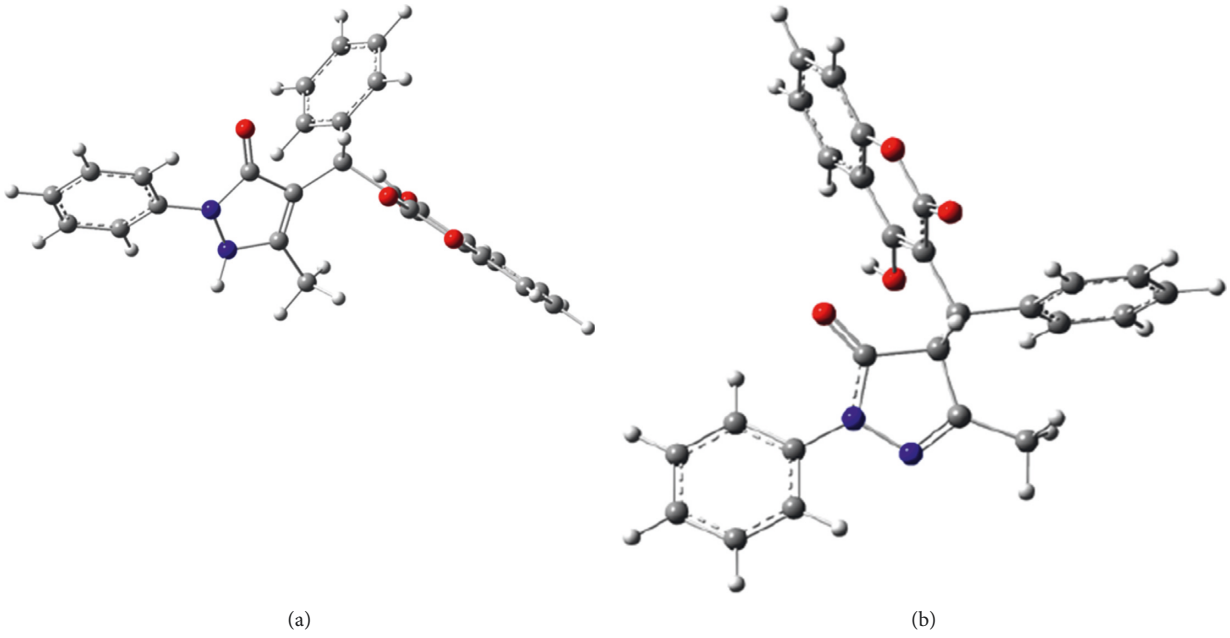
Table 2: Chemical yields and physical properties of coumarins derivatives **5a**–**5g**.



5

Entry	R	Compound[b]	Yield[a] (%)	Melting point (°C)
1	H	**5a**	60	204
2	*p*-CH_3	**5b**	70	221
3	*p*-$N(CH_3)_2$	**5c**	75	176
4	*p*-NO_2	**5d**	80	138
5	m-Br	**5e**	75	242
6	m-OCH_3	**5f**	85	138
7	m-OH	**5g**	90	174

[a]All reactions were carried with hydrazine (0.005 mol), ethyl acetoacetate (0.005 mol), benzaldehyde (0.005 mol), and 4-hydroxycoumarin (0.005 mol). [b]Yield of the isolated product. [BMIM][CF_3SO_3], 1-butyl-3-methylimidazolium trifluoromethanesulfonate.



(a) (b)

Figure 2: Optimized 3D geometrical structures for compounds (a) **A** and (b) **B**.

same results showed that the compounds **6a** and **5a** are very active against the fungus *Candida albicans* by comparing with a standard antifungal "fluconazole."

4. Antioxidant Activities

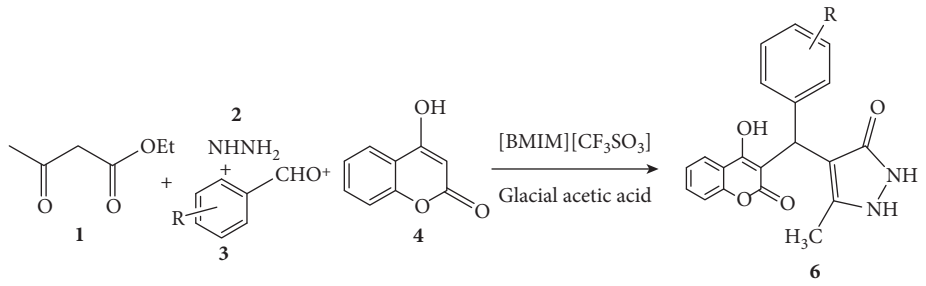
The scavenging activity of the synthesized benzylpyrazolyl coumarin derivatives **5** with DPPH (1,1-diphenyl-2-picrylhydrazyl) was investigated (Figure 3).

The analysis of the results showed that the profiles of the antiradical activity obtained reveal that the synthetic products tested compound **5** have a very important antiradical activity. For a used concentration (0.0625 mg/ml), the product **5e** has a radical activity lower than gallic acid and BHT (butylated hydroxytoluene). Of the same way, the compound **5b** for a concentration equal to 0.01575 mg/ml has a lower radical activity than gallic acid and BHT (butylated hydroxytoluene). At a concentration of 1 mg/ml, these products revealed a very interesting activity of DPPH in comparison with the activity of the synthetic antioxidants used.

5. Conclusion

In this study, the synthesis of pyrazolone-linked coumarin derivatives through a four-component, one-pot

Table 3: Chemical yields and physical properties of coumarins derivatives **6a**–**6g**.



Entry	R	Compound	Yield (%)	Melting point (°C)
1	H	**6a**	95	120
2	*p*-CH_3	**6b**	75	142
3	*p*-$N(CH_3)_2$	**6c**	80	160
4	*p*-NO_2	**6d**	85	210
5	m-Br	**6e**	87	160
6	m-OCH_3	**6f**	90	236
7	m-OH	**6g**	95	240

Table 4: Antibacterial activity of the prepared compounds **5(a–g)**–**6(a–g)**.

Compounds	Microorganisms					
	Micrococcus luteus LB 14110	*Listeria monocytogenes* ATCC 19117	*Staphylococcus aureus* ATCC 6538	*Pseudomonas aeruginosa* ATCC 49189	*E. coli*	*Candida albicans*
5a	—	—	—	24 ± 0.1	—	25 ± 0.1
5b	—	12 ± 0.2	16 ± 0.5	18 ± 0.4	—	26 ± 0.5
5c	—	—	20 ± 0.1	16 ± 0.1	—	20 ± 0.2
5d	—	—	12 ± 0.5	15 ± 0.1	—	18 ± 0.3
5e	—	10 ± 0.2	12 ± 0.5	20 ± 0.6	—	20 ± 0.6
5f	—	10 ± 0.2	14 ± 0.2	20 ± 0.3	—	22 ± 0.2
5g	—	—	14 ± 0.5	16 ± 0.4	—	18 ± 0.2
6a	—	—	15 ± 0.4	30 ± 0.1	—	28 ± 0.4
6b	—	—	15 ± 0.2	28 ± 0.2	—	28 ± 0.5
6c	—	10 ± 0.2	14 ± 0.2	24 ± 0.12	—	20 ± 0.6
6d	—	—	15 ± 0.2	24 ± 0.3	—	26 ± 0.3
6e	—	—	—	22 ± 0.5	—	12 ± 0.3
6f	—	—	14 ± 0.3	24 ± 0.4	15 ± 0.2	28 ± 0.1
6g	18 ± 0.3	16 ± 0.5	20 ± 0.2	22 ± 0.3	24 ± 0.3	28 ± 0.2

Table 5: Determination of the minimum inhibitory concentrations (MICs) expressed in mg/ml.

Microorganisms	Compounds					
	6a	**6b**	**6g**	**5a**	Ampicillin	Fluconazole
Staphylococcus aureus ATCC 6538	0.3125	0.3125	0.1562	0.625	0.04	—
Pseudomonas aeruginosa ATCC 49189	0.1562	0.3125	0.625	0.625	0.04	—
Candida albicans	0.00975	0.039	0.0781	0.00975	—	0.00125

condensation of ethyl acetoacetate, aromatic aldehydes, hydrazines, and 4-hydroxycoumarin using ([BMIM][CF_3SO_3]) as a green solvent was described. In addition, their structures were confirmed by elemental and spectral analyses. The antibacterial and antioxidant property of the synthesized compounds were assessed against Gram-positive and Gram-negative bacteria. Some of the compounds were very effective as antimicrobial agents. The results of the research were promising, and some of the synthesized derivatives represent good candidates for MIC determination during future studies. This study further presents benzylpyrazolyl coumarin derivatives as a new class of antioxidant agents, and it may serve as a model compound for design and development of therapeutic-based anticancer inhibitors.

6. Experimental

6.1. General Information. All manipulations were performed using Standard Schlenk techniques under the Argon

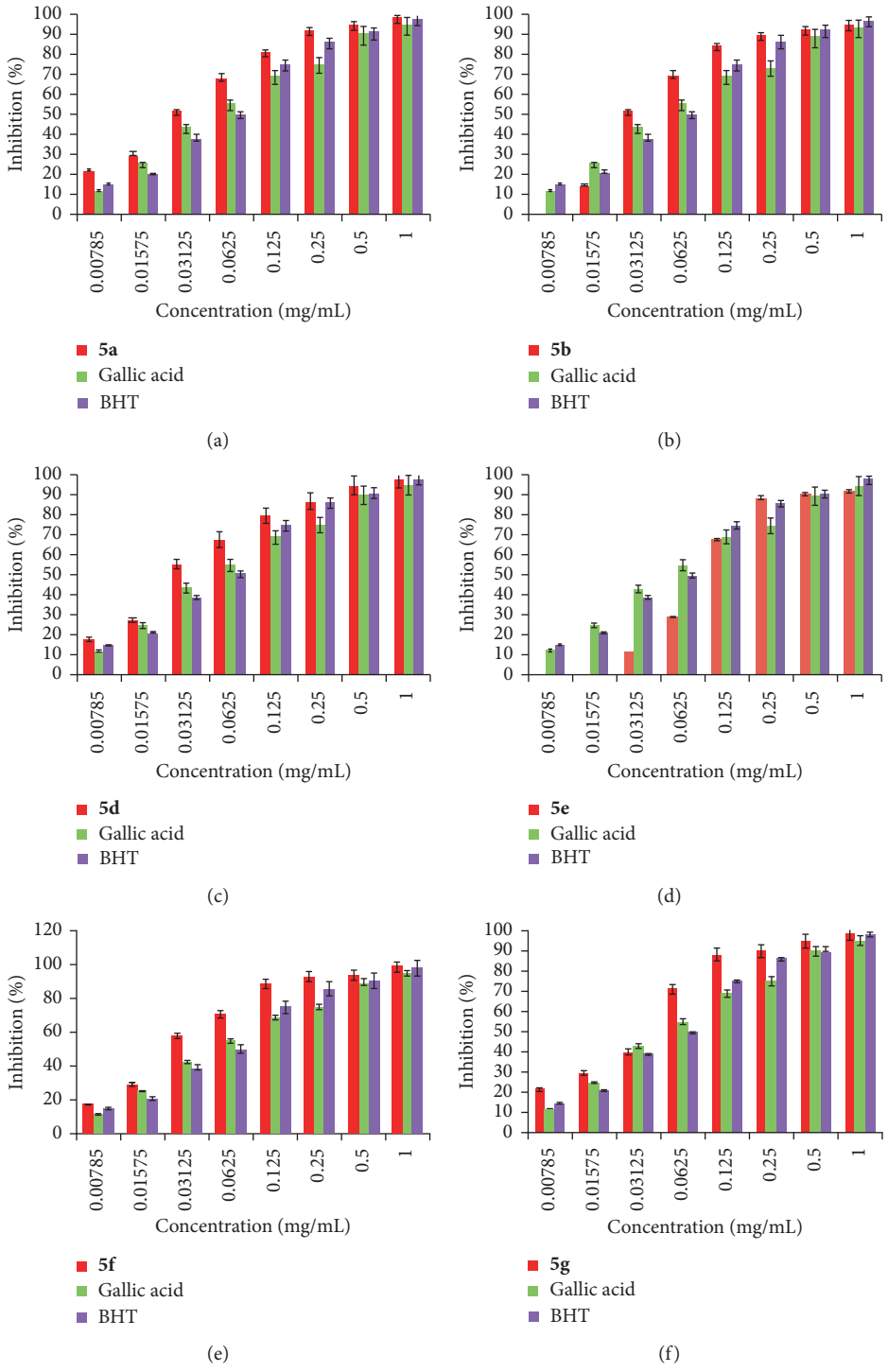


Figure 3: Scavenging activity of benzylpyrazolyl coumarin derivatives **5** on DPPH radicals.

atmosphere. Chemicals were purchased from Sigma-Aldrich and were used without further purification. All solvents were purified and dried by the MBRAUN SPS 800 solvent purification system. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. Chemical shifts, δ, are reported in ppm relative to the internal standard TMS for both ^{1}H and ^{13}C NMR. The products were characterized by GC (gas chromatography). Quantitative GC analyses were performed with the GC-2010 Plus gas chromatography (SHIMADZU). The NMR studies were carried out in high-quality 5 mm NMR tubes. Signals are quoted in parts per million as δ downfield from tetramethylsilane ($\delta = 0.00$) as an internal standard. NMR multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, and m = multiplet signals. IR spectra were recorded on a 398 spectrophotometer.

Elemental microanalysis was performed on an Elementar Vario El III Carlo Erba 1108 elemental analyzer, and the values found were within ±0.4% of the theoretical values. Melting points were determined with the Kofler bench. The biological analysis was done regarding our previous work [36, 37].

6.2. General Procedure for the Synthesis of Coumarin Derivatives **5**(**a**–**g**)–**6**(**a**–**g**). A mixture of hydrazine (5 mmol, 0.157 mL) or phenylhydrazine 1 (5 mmol, 0.491 mL), ethyl acetoacetate **2** (5 mmol, 0.6 mL), aromatic aldehyde **3** (benzaldehyde (5 mmol, 0.510 mL), para tolyl benzaldehyde (5 mmol, 0.589 mL), 4-(dimethylamino)benzaldehyde (5 mmol, 0.745 g), 4-nitrobenzaldehyde (5 mmol, 0.755 g), 3-bromobenzaldehyde (5 mmol, 0.582 mL), m-anisaldehyde (5 mmol, 0.609 mL), 3-hydroxybenzaldehyde (5 mmol, 0.610 g)), 4-hydroxycoumarin 4 (5 mmol, 0.810 g), and glacial acetic acid (10 mmol%, 0.02 mL) in 5 ml of ionic liquid [BMIM][CF_3SO_3] was stirred at 210°C. After completion of the reaction (indicated by TLC), the reaction mixture was then cooled to the room temperature to give a precipitate, and the free-flowing solid was filtered and washed with water. The precipitated crude product was purified by recrystallization from hot ethanol. The isolated compounds were well characterized by IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis.

6.2.1. 1,2-Dihydro-4-((4-hydroxy-2-oxo-2H-chromen-3-yl)(phenyl)methyl)-5-methyl-l-2-phenylpyrazol-3-one (**5a**). Yield: 1.72 g (60%); m.p. 204°C–206°C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.42 (s, 3H, H_a), 5.74 (s, 1H, $H_{4'}$), 6.38 (s, 1H, H_c), 7.21 (s, 1H, $H_{9'}$), 7.31 (m, 2H, $H_{2'',6''}$), 7.35 (m, 3H, $H_{3'',4'',5''}$), 7.43 (d, 2H, $H_{6,8}$), 7.51 (m, 2H, $H_{8',10'}$), 7.62 (m, 2H, $H_{7',11'}$), 7.87 (d, 1H, H_7), 7.89 (d, 1H, H_5); ^{13}C NMR (DMSO-d_6, 100 MHz,): δ 34.14 (C_a), 39.60 (C_c), 104.46 (C_3), 105.95 ($C_{1'}$), 107.18 (C_8), 116.36 ($C_{7'}$), 118.50 ($C_{11'}$), 121.29 ($C_{9'}$), 124.31 (C_5), 126.48 (C_6), 127.26 ($C_{4''}$), 128.68 ($C_{2''}$), 129.73 ($C_{3''}$), 132.42 (C_7), 135.59 ($C_{8'}$), 139.93 ($C_{10'}$), 147.44 ($C_{6'}$), 152.45 ($C_{1''}$), 162.69 (C_{10}), 163.98 (C_2), 164.74 (C_4), 165.31 ($C_{2'}$); Anal. Calc. $C_{26}H_{20}N_2O_4$: C, 73.573%; H, 4.749%; N, 6.600%; Found: C, 73.9; H, 4.5; N, 6.8%.

6.2.2. 1,2-Dihydro-4-((4-hydroxy-2-oxo-2H-chromen-3-yl)-(p-tolyl)methyl)-5-methyl-2-phenylpyrazol-3-one (**5b**). Yield: 1.53 g (70%); m.p. 221°C–223°C; IR (cm^{-1}) 3585 (O-H), 3425 (NH), 1542 (C=C), 1715 (CO lactone), 1742 (CO ketone); δ 2.24 (s, 3H, H_a), 2.40 (s, 3H, H_b), 3.17 (s, 1H, $H_{4'}$), 5.67 (s, 1H, H_c), 7.01 (s, 2H, $H_{3'',5''}$), 7.06 (s, 2H, $H_{2'',6''}$), 7.30 (m, 3H, $H_{6,8',10'}$), 7.52 (t, 1H, H_8), 7.58 (m, 2H, $H_{7',9'}$), 7.68 (d, 1H, $H_{11'}$), 7.79 (dd, 1H, H_7), 7.86 (dd, 1H, H_5); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 20.91 (C_b), 33.81 (C_a), 39.72 (C_c), 104.73 (C_3), 106.16 ($C_{1'}$), 107.3 (C_8), 116.3 ($C_{11'}$), 121.19 ($C_{9'}$), 124.25 (C_5), 127.16 (C_6), 129.24 (C_7), 129.70 ($C_{3''}$), 132.29 ($C_{2''}$), 135.39 ($C_{8'}$), 136.80 ($C_{4''}$), 147.39 ($C_{1''}$), 152.42 ($C_{6'}$), 162.74 ($C_{5'}$), 163.84 (C_{10}), 164.70 (C_2), 165.33 (C_4), 165.72 ($C_{2'}$); Anal. Calc. for $C_{27}H_{22}N_2O_4$: C, 73.9%; H, 5.0%; N, 6.3%; Found: C, 73.5; H, 6.1; N, 6.2%.

6.2.3. 1,2-Dihydro-4-((4-hydroxy-2-oxo-2H-chromen-3-yl)-(p-N,N-dimethyl phenyl)methyl)-5-methyl-2-phenylpyrazol-3-one (**5c**). Yield: 75 g (75%); m.p. 176°C–178°C; IR (cm^{-1}) 3585 (O-H), 3425 (NH), 1542 (C=C), 1715 (CO lactone), 1745 (CO amide); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.34 (s, 3H, H_a), 3.55 (s, 6H, $H_{b,d}$), 4.17 (s, 1H, H_c), 7.32 (s, 1H, $H_{3''}$), 7.88 (d, 1H, $H_{5''}$), 8.20 (t, 2H, $H_{2'',6''}$), 8.33 (m, 2H, $H_{6,8}$), 8.46 (t, 1H, $H_{9'}$), 8.56 (t, 2H, $H_{8',10'}$), 8.62 (s, 2H, $H_{7',11'}$), 8.86 (dd, 1H, H_7), 9.00 (dd, 1H, H_5), 9.68 (s, 1H, H_4); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 36.34 (C_a), 39.59 ($C_{b,}$), 103.59 (C_3), 111.80 ($C_{1'}$), 116.0 ($C_{2''}$), 118.58 (C_8), 120.2 ($C_{7'}$), 121.68 ($C_{9'}$), 123.42 (C_5), 124.56 (C_6), 128.53 ($C_{3''}$), 129.15 ($C_{5''}$), 131.53 (C_7), 137.89 ($C_{8'}$), 139.36 ($C_{1''}$), 148.61 ($C_{6'}$), 152.0 ($C_{4''}$), 152.99 ($C_{5'}$), 154.28 (C_{10}), 162.87 (C_2), 164.90 (C_4), 168.06 ($C_{2'}$); Anal. Calc. for $C_{28}H_{25}N_3O_4$: C, 71.93%; H, 5.39%; N, 8.9%; Found: C, 71.7%; H, 5.4%; N, 8.7%.

6.2.4. 1,2-Dihydro-4-((4-hydroxy-2-oxo-2H-chromen-3-yl)-(4-nitrophenyl)methyl)-5-methyl-2-phenylpyrazol-3-one (**5d**). Yield: 1.87 g (80%); m.p. 138°C–140°C. IR (cm^{-1}) 3585 (O-H), 3425 (NH), 1540 (C=C), 1715 (CO lactone), 1742 (CO amide); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.06 (s, 3H, H_a), 3.44 (s, 1H, $H_{4'}$), 6.35 (s, 1H, H_c), 6.84 (s, 1H, $H_{9'}$), 7.16 (d, 2H, $H_{6,8}$), 7.27 (m, 1H, $H_{8'}$), 7.37 (m, 1H, $H_{10'}$), 7.53 (m, 1H, $H_{2''}$), 7.69 (d, 1H, $H_{6''}$), 7.82 (d, 1H, $H_{7'}$), 7.89 (d, 1H, $H_{11'}$), 7.94 (s, 1H, H_7), 8.05 (d, 1H, H_5), 8.13 (d, 1H, $H_{3''}$), 8.22 (m, 1H, $H_{5''}$), 10.89 (s, 1H, H_4); ^{13}C NMR δ (DMSO-d_6, 100 MHz): δ 34.87 (C_a), 39.82 (C_c), 103.60 (C_3), 105.00 ($C_{1'}$), 106.78 (C_8), 113.03 ($C_{7'}$), 116.22 ($C_{11'}$), 120.37 ($C_{9'}$), 121.46 (C_5), 124.48 (C_7), 126.43 ($C_{3''}$), 129.67 (C_6), 134.05 ($C_{2''}$), 143.07 ($C_{6''}$), 144.90 (C_7), 146.44 ($C_{8'}$), 147.30 ($C_{10'}$), 148.46 ($C_{6'}$), 151.05 ($C_{4''}$), 152.55 ($C_{5'}$), 152.95 (C_{10}), 162.24 (C_2), 164.89 (C_4), 167.42 ($C_{2'}$); Anal. Calc. for $C_{26}H_{19}N_3O_6$: C, 66.5%; H, 4.0%, N, 8.9%; Found C, 66.4%; H, 4.2%; N, 8.8%.

6.2.5. 4-((3-Bromo-phenyl)-(4-hydroxy-2-oxo-2H-chromen-3-yl)methyl)-5-methyl-1,2-dihydro-5-methyl-2-phenylpyrazol-3-one (**5e**). Yield: 88 g (75%); m.p. 242°C–244°C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 240 (s, 3H, H_a), 3.43 (s, 1H, $H_{4'}$), 5.71 (s, 1H, H_c), 7.22–7.80 (m, 13H, H_{arom}); ^{13}C NMR δ (DMSO-d_6, 100 MHz): δ 34.03 (C_a), 39.72 (C_c), 105.10 (C_3), 106.75 ($C_{1'}$), 116.41 (C_8), 121.38 ($C_{7'}$), 122.14 ($C_{9'}$), 124.35 (C_6), 126.62 ($C_{6''}$), 127.24 (C_7), 129.75 ($C_{8'}$), 130.86 ($C_{5''}$), 132.52 ($C_{2''}$), 135.59 ($C_{6'}$), 143.16 ($C_{1''}$), 147.38 ($C_{5'}$), 152.50 (C_{10}), 162.12 (C_2), 164.61 (C_4), 166.12 ($C_{2'}$); Anal. Calc. for $C_{26}H_{19}BrN_2O_4$: C, 62.04%; H, 3.805%; N, 5.565%; Found: C, 62.1; H, 3.9; N, 5.6%.

6.2.6. 1,2-Dihydro-4-((4-hydroxy-2-oxo-2H-chromen-3-yl)(3-methoxyphenyl)methyl)-5-methyl-2-phenylpyrazol-3-one (**5f**). Yield: 1.92 g (85%); m.p. 138°C–140°C: ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.39 (s, 3H, H_a), 3.66 (s, 3H, H_b), 5.68 (s, 1H, H_c), 6.71 (s, 1H, $H_{4'}$), 6.78 (d, 2H, $H_{2'',6''}$), 7.26 (m, 5H, $H_{6,8,9',5'',4''}$), 7.51 (m, 2H, $H_{8',10'}$), 7.59 (t, 1H, H_7), 7.71 (d, 2H, $H_{7',11'}$), 7.83 (t, 1H, H_5); ^{13}C NMR δ (DMSO-d_6, 100 MHz): δ 33.66 (C_a), 39.86 (C_c), 54.83 (C_b), 105.21 (C_3), 106.43 ($C_{1'}$), 110.42 ($C_{4''}$), 113.48 ($C_{2''}$), 115.85 (C_8), 118.19

($C_{6''}$), 119.23 ($C_{7'}$), 120.75 ($C_{9'}$), 123.76 (C_5), 126.55 (C_6), 129.71 (C_7), 131.86 ($C_{8'}$), 135.35 ($C_{5''}$), 141.42 ($C_{6'}$), 146.94 ($C_{1''}$), 151.98 ($C_{10,}$), 159.20 ($C_{3''}$), 161.76 (C_2), 163.83 (C_4), 164.25 ($C_{2'}$); IR (cm^{-1}) 3588 (O-H), 3425 (NH), 1542 (C=C), 1715 (CO lactone), 1742 (CO amide); Anal. Calc. for $C_{27}H_{22}N_2O_5$: C, 71.3%; H, 4.8%; N, 6.1%; Found: C, 71.5; H, 5.1; N, 5.8%.

6.2.7. 1,2-Dihydro-4-((4-hydroxy-2-oxo-2H-chromen-3-yl)-(3-hydroxyphenyl)methyl)-5-methyl-2-phenylpyrazol-3-one (**5g**). Yield: 1.98 g (90%); m.p. 174°C–176°C; IR (cm^{-1}) 3585 (O-H), 3425 (NH), 1535 (C=C), 1710 (CO lactone), 1745 (CO amide); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 22.41 (s, 3H, H_a), 3.44 (s, 1H, $H_{4'}$), 5.66 (s, 1H, H_c); 6.57 (s, 1H, $H_{9'}$), 6.76 (m, 2H, $H_{4'',5''}$), 6.97 (d, 2H, $H_{2'',6''}$), 7.30 (m, 2H, $H_{6,8}$), 7.37 (m, 2H, $H_{8',10'}$), 7.68 (d, 2H, $H_{7',11'}$), 7.79 (d, 1H, H_7), 7.84 (t, 1H, H_5);^{13}C NMR (DMSO-$d_{6,}$ 100 MHz): δ 33.61 (C_a), 39.56 (C_c), 33.61 (C_3), 105.65 ($C_{1'}$), 112.9 ($C_{4''}$), 114.7 ($C_{2''}$), 116.4 (C_8), 120.3 ($C_{6''}$), 121.1 ($C_{7'}$), 122.8 ($C_{9'}$), 123.3 (C_5), 125.4 (C_6), 130.1 ($C_{5''}$), 137.3 ($C_{6'}$), 143.7 ($C_{1''}$), 152.3 ($C_{5'}$), 157.35 ($C_{3''}$), 162.7 (C_2), 163.57 (C_4), 164.34 ($C_{2'}$); Anal. Calc. for $C_{26}H_{20}N_2O_5$: C, 70.9%; H, 4.5%; N, 6.3%; Found: C, 71.8%, H, 4.6%; N, 6.4%.

6.2.8. 1,2-Dihydro-4-((4-hydroxy-2-oxo-2H-chromen-3-yl)phenyl)methyl)-5-methyl-pyrazol-3-one (**6a**). Yield: 95%; m.p. 120°C–122°C; IR (cm^{-1}) 3589 (O-H), 3423 (NH), 1539 (C=C), 1705 (CO lactone), 1741 (CO amide); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.50 (s, 3H, H_a), 6.32 (s, 1H, H_c), 7.14 (d, 3H, $H_{3'',4'',5''}$), 7.18 (d, 2H, $H_{2'',6''}$), 7.31 (m, 2H, $H_{6,8}$), 7.56 (t, 2H, $H_{5,7}$), 7.85 (d, 2H, $H_{3',4'}$); ^{13}C NMR (DMSO-$d_{6,}$ 100 MHz): δ 36.42 (C_a); 39.96 (C_c), 104.74 (C_3), 116.51 ($C_{1'}$), 117.99 (C_8), 124.34 (C_5), 126.19 (C_6), 127.18 ($C_{2''}$), 128.61 ($C_{3''}$), 132.55 ($C_{1''}$), 139.86 (C_{10}), 152.62 ($C_{2'}$), 165.31 (C_2), 165.39 (C_4); Anal. Calc. for $C_{20}H_{16}N_2O_4$: C, 68.9%; H, 4.6%; N, 8.0%; Found: C, 68.9%, H, 4.6%; N, 8.0%.

6.2.9. 1,2-Dihydro-4-((4-hydroxy-2-oxo-2H-chromen-3-yl)(p-tolyl)methyl)-5-methyl-pyrazol-3-one (**6b**). Yield: 75%; m.p. 142°C–144°C; IR (cm^{-1}) 3440 (O-H), 3423 (NH), 1539 (C=C), 1741 (CO lactone), 1797 (CO amide); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.76 (s, 6H, $H_{a,b}$), 6.55 (s, 1H, H_c), 7.27 (s, 4H, $H_{2',3',5',6'}$), 7.59 (m, 4H, $H_{5,6,7,8}$), 7.84 (t, 1H, $H_{4'}$), 8.13 (d, 1H, $H_{3'}$); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 20.53 (C_a); 35.61 (C_b); 39.52 (C_c); 104.44 (C_3), 116.07 ($C_{1'}$), 117.46 (C_8), 123.85 (C_5), 126.64 (C_6), 128.78 ($C_{2''}$), 132.11 ($C_{1''}$), 134.69 ($C_{4''}$), 136.10 (C_{10}), 152.13 ($C_{2'}$), 164.66 (C_2), 164.94 (C_4); Anal. Calc. for $C_{21}H_{18}N_2O_4$: C, 69.6%; H, 5.0%; N, 7.7%; Found: C, 69.9%, H, 5.0%; N, 7.7%.

6.2.10. 1,2-Dihydro-4-((4-hydroxy-2-oxo-2H-chromen-3-yl)-(4-N,N-dimethylphenyl)methyl)-5-methyl-pyrazol-3-one (**6c**). Yield: 80%; m.p. 160°C–162°C; IR (cm^{-1}) 3584 (O-H), 3420 (NH), 1545 (C=C), 1715 (CO lactone), 1735 (CO amide), ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.03 (s, 3H, H_a), 3.11 (s, 6H, $H_{b,d}$), 6.28 (s, 1H, H_c), 6.82 (s, 1H, $H_{4'}$), 6.82 (s, 1H, $H_{4'}$), 7.29(m, 4H, $H_{2'',3'',5'',6''}$), 7.52 (t, 2H, $H_{6,8}$), 7.71 (d, 1H, H_7), 7.80 (d, 1H, H_5), 8.56 (s, 1H, $H_{3'}$); ^{13}C NMR (DMSO-$d_{6,}$ 100 MHz): δ 26.91 (C_a), 36.38 (C_b), 45.69 (C_c), 103.56 (C_3), 112.37 ($C_{1''}$), 116.02 ($C_{2''}$), 120.17 (C_8), 123.45 (C_5), 124.57 (C_7), 128.59 ($C_{1''}$), 131.57 ($C_{4''}$), 152.99 (C_{10}), 159.56 ($C_{4'}$), 164.91 (C_2), 168.07 (C_4); Anal. Calc. for $C_{22}H_{21}N_3O_4$: C, 67.5%; H, 5.4%; N, 10.7%; Found: C, 67.5%, H, 5.4%; N, 10.7%.

6.2.11. 1,2-Dihydro-4-((4-hydroxy-2-oxo-2H-chromen-3-yl)(4-nitrophenyl)methyl)-5-methyl-pyrazol-3-one (**6d**). Yield: 85%; m.p. 210°C–212°C; IR (cm^{-1}) 3585 (O-H), 3425 (NH), 1545 (C=C), 1712 (CO lactone), 1745 (CO amide); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.50 (s, 3H, H_a), 3.43 (s, 1H, $H_{4'}$), 6.36 (s, 1H, H_c), 7.29 (m, 4H, $H_{6,8,2'',6''}$), 7.39 (d, 1H, H_7), 7.54 (t, 1H, H_5), 7.82 (d, 2H, $H_{3'',5''}$), 8.06 (d, 1H, $HH_{3'}$); ^{13}C NMR (DMSO-$d_{6,}$ 100 MHz): δ 37.20 (C_a), 40.00 (C_c), 103.46 (C_3), 116.17 ($C_{1'}$), 119.64 (C_8), 123.70 (C_5), 124.58 ($C_{2''}$), 128.41 (C_6), 131.91 ($C_{4''}$), 145.86 ($C_{1''}$), 151.35 (C_{10}), 152.96 ($C_{2'}$), 164.49 ($C_{1'}$), 167.68 (C_4); Anal. Calc. for $C_{20}H_{15}N_3O_6$: C, 61.0%; H, 3.8%; N, 10.6%; Found: C, 61.0%, H, 3.8%; N, 10.6%.

6.2.12. 4-((3-Bromo-phenyl)-(4-hydroxy-2-oxo-2H-chromen-3-yl)methyl)-5-methyl-1,2-dihydro-5-methyl-pyrazol-3-one (**6e**). Yield: 87%; m.p. 160°C–162°C; IR (cm^{-1}) 3592 (O-H), 3425 (NH), 1543 (C=C), 1715 (CO lactone), 1745 (CO amide); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.53 (s, 3H, H_a), 5.52 (s, 1H, $H_{3'}$), 6.42 (s, 1H, H_c), 7.50(m, 4H, $H_{6,8,5'',6''}$), 7.79(m, 3H, $H_{7,2'',4''}$), 7.92(d, 1H, H_5), 8.00 (d, 1H, $H_{3'}$); ^{13}C NMR (DMSO-$d_{6,}$ 100 MHz): δ 22.30 (C_a), 40.01 (C_c), 91.46 (C_3), 114.28 ($C_{1'}$), 116.84 (C_9), 117.1 (C_8), 123.65 ($C_{3''}$), 125.63 (C_5), 128.73 (C_6), 131.37 ($C_{6''}$), 132.19 (C_7), 153.07 ($C_{2''}$), 153.98 ($C_{1''}$), 156.13 (C_{10}), 158.05 ($C_{2'}$), 162.31 (C_2), 166.0824 (C_4); Anal. Calc. for $C_{20}H_{15}N_2O_4Br$: C, 56.2%; H, 3.5%; N, 6.5%; Found: C, 56.2%, H, 3.5%; N, 6.5%.

6.2.13. 1,2-Dihydro-4-((4-hydroxy-2-oxo-2H-chromen-3-yl)(3-methoxyphenyl)methyl)-5-methyl-pyrazol-3-one (**6f**). Yield: 90%; m.p. 236°C–238°C; IR (cm^{-1}) 3585 (O-H), 3425 (NH), 1535 (C=C), 1710 (CO lactone), 1735 (CO amide); δ 2.51 (s, 3H, H_a), 3.64 (s, 3H, H_b), 6.31 (s, 1H, H_c), 6.66 (d, 2H, $H_{4'',6''}$), 7.14 (t, 1H, $H_{2''}$), 7.35 (m, 3H, $H_{6,8,5''}$), 7.58 (t, 2H, $H_{5,7}$), 7.88 (d, 2H, $H_{3',4'}$); ^{13}C NMR (DMSO-$d_{6,}$ 100 MHz): δ 36.42 (C_a), 39.97 (C_c), 55.33 (C_b), 104.62 (C_3), 110.74 ($C_{1'}$), 113.73 ($C_{2''}$), 116.46 (C_8), 118.2 ($C_{6''}$), 119.63 (C_5), 124.27 (C_6), 124.35 (C_7), 129.57 ($C_{5''}$), 132.43 ($C_{1''}$), 141.96 (C_{10}), 152.65 ($C_{2'}$), 159.73 ($C_{3'}$), 165.29 (C_2), 165.60 (C_4); Anal. Calc. for $C_{21}H_{18}N_2O_5$: C, 66.6%; H, 4.7%; N, 7.4%; Found: C, 66.5%, H, 4.8%; N, 7.5%.

6.2.14. 1,2-Dihydro-4-((4-hydroxy-2-oxo-2H-chromen-3-yl)(3-hydroxyphenyl)methyl)-5-methyl-pyrazol-3-one (**6g**). Yield: 95%; m.p. 204°C–206°C; IR (cm^{-1}) 3588 (O-H), 3425 (NH), 1545 (C=C), 1715 (CO lactone), 1742 (CO amide); δ 2.51 (s, 3H, H_a), 6.31 (s, 1H, H_c), 6.66 (d, 2H, $H_{4'',6''}$), 7.14 (t, 1H, $H_{2''}$), 7.35 (m, 3H, $H_{6,8,5''}$), 7.58 (t, 2H, $H_{5,7}$),7.88 (d, 2H, $H_{3',4'}$); ^{13}C NMR (DMSO-$d_{6,}$ 100 MHz): δ 36.4 (C_a), 39.9

(C_c), 104.6 (C_3), 110.7 ($C_{1'}$), 113.7 ($C_{4''}$), 114.3 ($C_{2''}$), 116.4 (C_8), 120.3 ($C_{6''}$), 123.7 (C_5), 128.3 (C_7), 152.1 ($C_{5'}$), 156.9 ($C_{3''}$), 157.3 ($C_{2'}$), 165,2 (C_2), 165,4 (C_4); Anal. Calc. for $C_{20}H_{16}N_2O_5$: C, 65.9%; H, 4.4%; N, 7.6%; Found: C, 65.9%, H, 4.4%; N, 7.6%.

Data Availability

Data are available on request to the corresponding author.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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