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Synthesis of some novel coumarin-pyrazoline hybrid compounds from 6- and 8-acetyl-7-hydroxy-4-methylcoumarin

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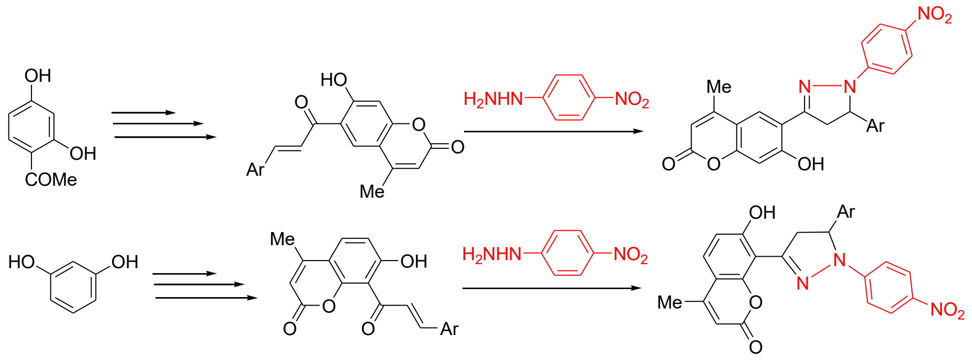
Abstract

Coumarin–pyrazoline hybrids are of considerable interest due to their broad spectrum of biological activities, including antimicrobial, anticancer, and antioxidant properties. In this study, twenty-one novel derivatives of 6- and 8-(5-aryl-1-(4-nitrophenyl)pyrazoline-3-yl)-7-hydroxy-4-methylcoumarin were synthesized starting from 6- and 8-acetyl-7-hydroxy-4-methylcoumarin. The structures of the compounds were confirmed using spectral and elemental analysis. The antimicrobial activity of all synthesized compounds was evaluated against *Klebsiella pneumoniae*, *Staphylococcus epidermidis* and *Candida albicans*. The results indicated notable inhibitory effects, particularly against *C. albicans*, with zones of inhibition reaching up to 31 mm at concentrations of 150 µg/µL



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Introduction

Coumarins represent a versatile class of heterocyclic compounds found widely in nature as phytochemicals and are also readily synthesized in the laboratory. These molecules are recognized for their broad spectrum of pharmacological and biological activities, including antidiabetic,[1] anticancer,[2,3] antifungal,[4] anti-HIV, and antibacterial properties.[5] In recent decades, an increasing number of naturally occurring and synthetically derived coumarins have been identified and studied for their diverse bioactivities.[6]

The coumarin scaffold is present in several clinically approved drugs. For example, Warfarin, Acenocoumarol, and Phenprocoumon act as anticoagulants by inhibiting vitamin K-dependent clotting factors.[7] Novobiocin, a coumarin-based antibiotic, exerts its antibacterial effect by targeting bacterial DNA gyrase.[8] Additionally, compounds such as 4-hydroxycoumarin have shown promising anticancer potential against various cancer cell lines.[9]

Beyond their medicinal applications, coumarin derivatives have demonstrated the ability to inhibit platelet aggregation[10] and steroid 5α-reductase,[11] highlighting their therapeutic potential in cardiovascular and hormonal disorders. Coumarins are also valued for several non-therapeutic applications, including their use as optical brighteners,[12] photosensitizers,[13] fluorescent and laser dyes,[13,14] and aromatic additives in perfumes and cosmetic formulations.[15]

Due to this wide range of applications, the design and synthesis of novel coumarin-based molecules continue to be a focus of interest in drug discovery and material sciences.

Pyrazoline, a five-membered nitrogen-containing heterocycle featuring two adjacent nitrogen atoms, has emerged as a key structural motif in medicinal chemistry. Due to its electron-rich nature and structural versatility, the pyrazoline nucleus has been extensively explored for a broad spectrum of biological activities, including antimicrobial,[16,17] anticancer,[18-22] anti-inflammatory,[22,23] antioxidant,[19,24] antidepressant and anticonvulsant properties.[25,26] Among these, 2-pyrazoline derivatives have attracted particular interest owing to their multifaceted therapeutic potential. These compounds continue to serve as promising scaffolds for the design of novel agents targeting infectious diseases, chronic inflammatory disorders, neurological conditions, and cancer. Accordingly, the exploration of pyrazoline-based pharmacophores remains an important focus in drug discovery and development.

Recent advances have highlighted the therapeutic promise of pyrazoline-based scaffolds across multiple pharmacological domains. A number of newly synthesized thiazolyl–pyrazoline hybrids have demonstrated potent antiproliferative activity against MCF-7 cells, acting as dual EGFR/HER2 inhibitors with IC_{50} values in the nanomolar range.[27] Diphenylpyrazole carbothioamides have shown notable inhibition of angiogenesis-related targets such as APN, VEGFR2, and MMP9, inducing apoptosis in breast cancer models.[28] Furthermore, pyrazoline–thiazole conjugates and pyrazoline–chalcone–benzothiazole hybrids exhibited significant anti-diabetic and anti-Helicobacter pylori activities, respectively.[29,30] Other recent studies have reported pyrazoline–isoniazid derivatives with strong acetylcholinesterase inhibition for potential Alzheimer's therapy.[31] These findings reaffirm the versatility of the pyrazoline core as a privileged structure in drug design, particularly in the development of multi-target therapeutic agents.

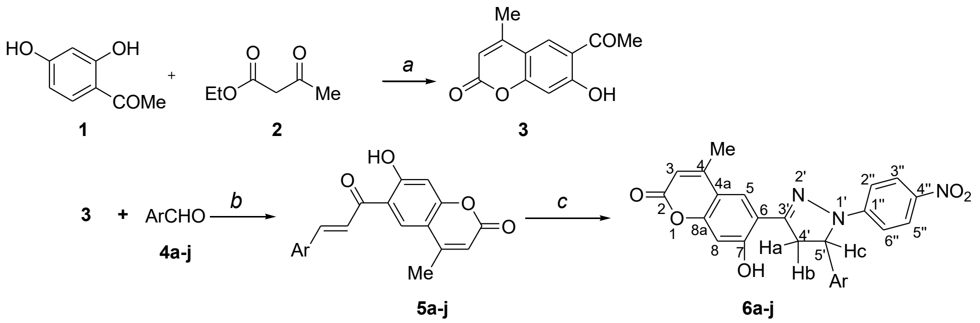
The coumarin scaffold was combined with nitrogen-containing heteroatom molecules, such as pyrazoline, to enhance its biological activity. This combination showed a wide range of activities.[32] In addition, researchers found that coumarin and pyrazoline were tested for their ability to inhibit telomerase. The results indicated that the compound was effective against various types of breast cancer[33] and MCF-7 breast cancer cell lines.[34]

Therefore, the molecular hybridization technique is essential in developing new drugs to treat various complex disorders.[35]

Results and Discussion

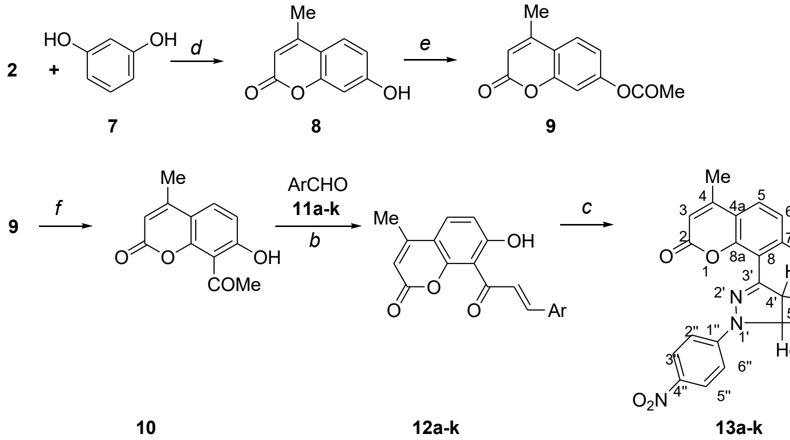
We have applied Pechmann's condensation reaction for the synthesis of required 6-acetyl-7-hydroxy-4-methylcoumarin (**3**) from 2,4-dihydroxyacetophenone and ethyl acetoacetate according to the literature procedure.[36] This process was carried out in the presence of $POCl_3$ as a catalyst in nitrobenzene.

8-Acetyl-7-hydroxy-4-methylcoumarin (**10**) has been synthesized from resorcinol (Scheme 2). The synthesis of the 7-hydroxy-4-methylcoumarin (**8**) was achieved via the Pechmann reaction, catalyzed by H_2SO_4, from resorcinol and ethyl acetoacetate. Compound (**8**) was subsequently acetylated to yield 7-acetoxy-4-methylcoumarin (**9**). The Fries rearrangement reaction of (**9**) at 160°C, in which dry $AlCl_3$ was used as a catalyst, gave 8-acetyl-7-hydroxy-4-methylcoumarin (**10**).[37,38]



Ar=C_6H_5 (**a**); 4-$CH_3C_6H_4$ (**b**); 4-$CH_3OC_6H_4$ (**c**); 4-HOC_6H_4 (**d**); 2-HOC_6H_4 (**e**); 4-ClC_6H_4 (**f**); 3-ClC_6H_4 (**g**); 3-$O_2NC_6H_4$ (**h**); 4-BrC_6H_4 (**i**); 3-C_5H_4N (**j**)

Scheme 1. Synthetic path to coumarin-pyrazoline hybrids **6a–j** from 2,4-dihydroxyacetophenone. Reaction conditions: (a) $POCl_3$, nitrobenzene, room temperature for seven days; (b) Piperidine (catalyst), abs. EtOH, 20–40 h, under reflux; (c) CH_3COOH, under reflux, 30–40 h.



Ar=C_6H_5 (**a**); 4-$CH_3C_6H_4$ (**b**); 4-$CH_3OC_6H_4$ (**c**); 4-$(CH_3)_2NC_6H_4$ (**d**); 4-ClC_6H_4 (**e**); 3-ClC_6H_4 (**f**); 4-$O_2NC_6H_4$ (**g**); 3-$O_2NC_6H_4$ (**h**); 4-BrC_6H_4 (**i**); 4-HO-3-$CH_3OC_6H_3$ (**j**); 3,4-$O_2CH_2C_6H_3$ (**k**)

Scheme 2. Synthetic path to coumarin-pyrazoline hybrid compounds **13a–k** from resorcinol. Reaction conditions: (d) H_2SO_4, room temperature for 24 h; (e) $(CH_3CO)_2O$, under reflux, 1.5 h; (f) $AlCl_3$ (catalyst), 2 h, 160°C; (b) Piperidine (catalyst), abs. EtOH, 20–40 h, under reflux conditions; (c) CH_3COOH, under reflux, 30–40 h.

Required *α,β*-unsaturated ketones 6- and 8-[(2*E*)-3-(aryl)-prop-2-enoyl]-7-hydroxy-4-methylcoumarin (**5a-j** and **12a-k**) were prepared by Claisen-Schmidt reaction of 6- and 8-acetyl-7-hydroxy-4-methylcoumarin (**3** and **10**) with the corresponding aromatic and heteroaromatic aldehydes **4a-j** and **11a-k,** according to our previous procedure (Scheme 1, Scheme 2).[39,40] Weak bases such as piperidine, trimethyl amine, and pyridine were used as catalysts in chloroform or ethanol, for this reaction. Inorganic catalysts such as KOH and NaOH are strong and produce smaller yields because we observed a coumarin ring opened product under these conditions.

Pyrazolines **6a-j** and **13a-k** were synthesized by the reaction of the corresponding *α,β*-unsaturated ketones **5a-j** and **12a-k** with *p*-nitrophenyl hydrazine in the presence of glacial acetic acid as a catalyst (**Scheme 1**). The pyrazoline ring was formed through the aldol addition of the first amino group of *p*-nitrophenyl hydrazine with the carbonyl group, followed by dehydration. This process continued with the second amino group that attacked the vinyl group to produce 2-pyrazoline.[41]

The synthesis of 2-pyrazolines was relatively slow, reaction time was 20-40 h, while the reaction was monitored by TLC. The molar ratio of **5a-j** and **12a-k** and *p*-nitrophenyl hydrazine was 1:1, in ethanol and glacial acetic acid as a solvent and catalyst, respectively. The reaction mixture was heated under reflux. 2-Pyrazoline derivatives containing coumarin are solids, have high melting points (258-313^{o}C), and are difficult to dissolve in organic solvents such as ethanol, acetone, and chloroform. The successful synthesis of 2-pyrazoline derivatives was confirmed through spectral analysis, including IR, NMR and MS.

The infrared spectra of 2-pyrazoline derivatives showed the absorption peaks characterized by the C=C str. and C=N str. groups appearing in the region of 1633-1587 cm^{-1} in ring pyrazoline. The IR spectra of 2-pyrazolines revealed that the characteristic absorption bands for out-of-plane bending vibration of C−H in the *trans*-alkene group (in the 960-990 cm^{-1} region) had disappeared. Instead, two strong absorption bands appeared at 1304-1333 cm^{-1} and 1505-1558 cm^{-1}, representing symmetric and asymmetric stretching vibrations of the NO_2 group in the 4-nitrophenyl hydrazine component.

In the ^{1}H-NMR of all 2-pyrazoline derivatives, the appearance of the new resonance signals in the regions at 2.84-4.21 ppm, 3.38-3.56 ppm, and 5.26-5.60 ppm, which were assigned to the proton Hb, Ha and Hc, respectively, is also proof for the ring-closure of enones **5a-j** and **12a-k** with *p*-nitrophenyl hydrazine.

The ^{13}C NMR spectra showed distinguished signals at 132.0-139.4 ppm and 159.0-161.9 ppm corresponding to C=N and C=O, respectively. Additionally, the appearance of chemical shifts at 31.1-46.8 ppm and 61.0–76.7 ppm for alkane carbon atoms at CH_2-4'and CH-5', respectively, gave further evidence of the structure of 1,3,5-substituted-2-pyrazolines.

Low-resolution mass spectrometry analysis by ESI, in the positive or negative mode, confirmed the expected molecular ions and formulas of new compounds. Furthermore, It was easy to detect the presence of chlorine or bromine in a molecule or ion by observing the intensity ratios of ions that differ by 2 amu.

All synthesized compounds **6a-j and 13a-k** were screened for their antimicrobial activity against the Gram-negative bacteria *Klebsiella pneumonia* (K.p), Gram-positive bacteria *Staphylococcus epidermidis* (S.e), and *Candida albicans* fungi (C.a) in the 19-8 hospital (Vietnam) using disc diffusion method.[42] All the compounds **6a-j and 13a-k** showed activity against *K. pneumoniae*, *S. epidermidis*, and especially *C. albicans* at 50, 100, and 150 µg/µl with aseptically circle diameters up to 31 mm (compounds **6b** and **13h**). The details of the results are given in Table 1.

Table 1. Antibacterial and antifungal activity of **6a-j and 13a-l**

Compd	*K.pneumonia*			*S.epidamisdis*			*C.albicans*		
	50μg/μl	100μg/μl	150μg/μl	50μg/μl	100μg/μl	150μg/μl	50μg/μl	100μg/μl	150μg/μl
6a	0	16	18	0	17	22	14	26	28
6b	**0**	**14**	**17**	**0**	**16**	**21**	**13**	**27**	**31**
6c	0	15	18	0	19	24	14	26	29
6d	0	11	17	9	20	26	18	24	29
6e	0	14	18	10	21	27	9	22	27
6f	0	16	20	11	21	27	12	25	29
6g	0	15	21	10	22	27	14	24	28
6h	0	13	19	12	21	25	12	28	30
6i	0	16	21	15	23	26	15	26	30
6j	0	15	22	14	22	24	17	24	29
13a	0	11	16	0	14	18	11	25	29
13b	0	10	15	9	15	18	11	24	29
13c	0	10	14	0	0	14	11	22	26
13d	0	12	16	14	19	25	16	24	28
13e	0	9	15	11	18	22	10	24	27
13f	0	8	14	9	17	21	9	23	28
13g	0	9	15	0	12	19	10	24	27
13h	**0**	**9**	**16**	**10**	**18**	**22**	**9**	**25**	**31**
13i	0	10	14	0	0	14	8	20	26
13j	0	13	16	0	0	16	9	21	27
13k	0	12	16	0	9	17	12	24	29

Conclusions

In the present study, a series of novel coumarin–pyrazoline hybrid compounds were synthesized from 6- and 8-acetyl-7-hydroxy-4-methylcoumarin precursors. The structures of the obtained compounds were confirmed by IR, NMR, and LRMS spectral analysis.

Biological evaluation revealed that several of the synthesized hybrids exhibited notable antimicrobial activity against Klebsiella pneumoniae, Staphylococcus epidermidis, and Candida albicans. Particularly, strong inhibitory effects were observed against C. albicans, with inhibition zones reaching up to 31 mm at a concentration of 150 μg/μL. These findings highlight the potential of coumarin–pyrazoline hybrids as promising antimicrobial agents and underscore the beneficial effect of pharmacophore hybridization in enhancing biological activity.

Overall, this study provides meaningful insights into the synthetic development and biological potential of coumarin–pyrazoline hybrid molecules. The promising antimicrobial activities observed underscore the significance of molecular hybridization as a strategy to enhance bioactivity. Future work will focus on mechanistic investigations, molecular docking studies, and in vivo evaluations to further elucidate the mode of action and improve the drug-like properties of these compounds.

Experimental Section

General. Stuart SMP3 was used to confirm the melting point of the synthetic compounds. IR spectrum was analyzed by an Impact 410-Nicolet Spectrometer using KBr pellets. NMR spectra were obtained at 500 MHz for ^{1}H and 125 MHz for ^{13}C by an Avance AV500 Spectrometer made by Bruker, a company based in Germany, using DMSO-d_6 as the solvent and TMS as the internal standard. ESI-MS data was recorded by LC-MS-ORBITRAP-XL. We use Merck Kieselgel 60F254 pre-coated plates for conducting thin-layer chromatography (TLC). The R_f value of the compounds was determined by using a mixture of *n*-hexane/ethyl acetate 1:1.2 (for **6a-j**) and chloroform/ethyl acetate 1:4 (for **13a-k**). Chemical reagents with high purity were bought from Merck Chemical Company. All reagents were of a grade for organic synthesis.

General procedure for synthesis of 6- and 8-(5-aryl-1-(4-nitrophenyl)pyrazoline-3-yl)-7-hydroxy-4-methylcoumarin (6a-j and 13a-k): A mixture of the appropriate intermediate (**5a–j** or **12a–k**, 1 mmol), *p*-nitrophenylhydrazine (1 mmol), and glacial acetic acid (0.25 mL) was dissolved in 30 mL of ethanol and heated under reflux for 20–40 hours. The reaction progress was monitored by thin-layer chromatography (TLC). Upon completion, the reaction mixture was cooled to room temperature, resulting in the precipitation of the crude product. The solid was collected by filtration, washed thoroughly with cold water to remove residual impurities, and dried under vacuum.

The crude product was purified by recrystallization using a mixture of dimethylformamide (DMF) and 96% ethanol. Specifically, the solid was dissolved in a minimal amount of hot DMF, followed by the slow addition of 96% ethanol under stirring until the solution reached saturation. The mixture was then allowed to cool gradually to room temperature, and crystallization was induced by slow evaporation. The resulting crystals were collected by filtration, washed with cold ethanol, and dried under vacuum to afford the pure compounds **6a–j** and **13a–k** in high purity.

6-(5-Phenyl-1-(4-nitrophenyl) pyrazoline-3-yl)-7-hydroxy-4-methylcoumarin (6a). From **5a** (Ar=C_6H_5, 1mmol, 306 mg): Reaction time: 30 h, yield 198.5 mg (45%) of **6a**, crystallized from a mixture of DMF and 96% ethanol (1:2) as bright yellow crystals. Mp: 288-290 °C; R_f: 0.75. IR (KBr): 3279 (OH); 1687 (C=O), 1624 (C=C), 1587 (C=N); 1531 (NO_2, asym.), 1323 (NO_2 sym.). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.19 (1H, s, HO-7), 8.32 (1H, s, H-5), 8.12 (2H, d, J = 9.0 Hz, 3′′,5′′, Ar), 7.57 (2H, d, J = 7.5 Hz, Ar), 7.44-7.47 (2H, m, Ar), 7.39-7.42 (1H, m, Ar-H), 7.36 (2H, d, J = 9.0 Hz, 2′′, 6′′, Ar), 6.94 (1H, s, H-8), 6.23 (1H, d, J = 1.0 Hz, H-3), 5.38 (1H, dd, J = 11.5, 3.5 Hz, H-c), 3.48 (1H, dd, J = 17.0, 3.5 Hz, H-a), 2.90 (1H, dd, J = 17.0, 11.5 Hz, H-b), 2.49 (3H, d, J 1.5 Hz, CH_3-4). ^{13}C NMR (125 MHz, DMSO-d_6): δ 159.1 (C-2), 158.3 (C-8a), 154.1 (C-7), 152.4 (C-4), 150.6 (C-1′′), 138.9 (C-3′), 138.8 (C-4″), 136.1 (Ar-C), 128.1 (2C, Ar), 128.0 (Ar-C), 126.0 (2C, Ar), 125.7 (2C, C-3″, 5″), 120.2 (C-5), 117.6 (C-6), 114.3 (C-4a), 112.1 (C-3), 111.7 (2C, C-2″, 6″), 76.73 (C-5′), 31.31 (C-4′), 17.59 (CH_3-4). LRMS (ESI-) *m/z* calcd. for $C_{25}H_{18}N_3O_5$ [M-H]$^-$ 440.13, found 440.08.

6-(5-*p*-Tolyl-1-(4-nitrophenyl)pyrazoline-3-yl)-7-hydroxy-4-methylcoumarin (6b). From **5b** (Ar=*p*-$CH_3C_6H_4$, 1mmol, 320 mg): Reaction time: 25 h, yield 211.7 mg (48%) of **6b**, crystallized from a mixture of DMF and 96% ethanol (1:2) as bright yellow crystals. Mp: 301–303 °C; R_f: 0.82. IR (KBr, cm^{-1}): 3283 (OH), 1692 (C=O), 1626 (C=C), 1598 (C=N), 1521 (NO_2 asym.), 1325 (NO_2 sym.). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.21 (1H, s, HO-7), 8.35 (1H, s, H-5), 8.14 (2H, d, J = 9.0 Hz, H-3″,5″), 7.45 (2H, d, J = 8.0 Hz, Ar-H), 7.38 (2H, d, J = 9.0 Hz, H-2″,6″), 7.26 (2H, d, J = 8.0 Hz, Ar-H), 6.95 (1H, s, H-8), 6.26 (1H, s, H-3), 5.37 (1H, dd, J = 11.0, 3.0 Hz, H-c), 3.45 (1H, dd, J = 17.0, 3.0 Hz, H-a), 2.95 (1H, dd, J = 17.0, 11.0 Hz, H-b), 2.49 (3H, s, CH_3-4), 2.34 (3H, s, Ar-CH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ 159.2 (C-2), 158.4 (C-8a), 154.2 (C-7), 152.6 (C-4), 150.6 (C-1″), 139.3 (C-3′), 138.8 (C-4″), 137.5, 136.1 (Ar-C), 128.6 (2C, Ar-C), 126.1 (2C, Ar-C), 125.3 (C-3″,5″), 120.3 (C-5), 117.7 (C-6), 114.3 (C-4a), 112.0 (C-3), 111.8 (C-2″,6″), 104.1 (C-8), 76.63 (C-5′), 31.16 (C-4′), 20.27 (Ar-CH_3), 17.64 (CH_3-4).

6-(5-(4-Methoxyphenyl)-1-(4-nitrophenyl)pyrazoline-3-yl)-7-hydroxy-4-methylcoumarin (**6c**). From **5c** (Ar=*p*-$CH_3OC_6H_4$, 1mmol, 336 mg): Reaction time: 25 h, yield 240.2 mg (51%) of **6c**, crystallized from a mixture of DMF and 96% ethanol (1:2) as yellow crystals. Mp**:** 288–289 °C; R_f: 0.80. IR (KBr, cm^{-1}): 3293 (OH), 1698 (C=O), 1624 (C=C), 1594 (C=N), 1515 (NO_2 asym.), 1323 (NO_2 sym.). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.40 (1H, s, HO-7), 8.34 (1H, s, H-5), 8.15 (2H, d, J = 8.5 Hz, H-3″,5″), 7.51 (2H, d, J = 8.5 Hz, Ar-H), 7.39 (2H, d, J = 8.5 Hz, H-2″,6″), 7.02 (2H, d, J = 8.5 Hz, Ar-H), 7.01 (1H, s, H-8), 6.31 (1H, d, J = 1.0 Hz, H-3), 5.34 (1H, dd, J = 12.0, 3.0 Hz, H-c), 3.78 (3H, s, Ar-OCH_3), 3.42 (1H, dd, J = 17.0, 3.0 Hz, H-a), 2.96 (1H, dd, J = 17.0, 12.0 Hz, H-b), 2.53 (3H, s, CH_3-4). ^{13}C NMR (125 MHz, DMSO-d_6): δ 159.2 (C-2), 159.0 (Ar-C), 158.4 (C-8a), 154.1 (C-7), 152.4 (C-4), 150.6 (C-1″), 139.3 (C-3′), 138.8 (C-4″), 130.9 (2C, Ar-C), 127.5 (Ar-C), 125.3 (C-3″,5″), 120.2 (C-5), 117.6 (C-6), 114.3 (C-4a), 113.7 (2C, Ar-C), 111.9 (C-3), 111.7 (C-2″,6″), 104.0 (C-8), 76.45 (C-5′), 54.93 (Ar-OCH_3), 31.12 (C-4′), 17.56 (CH_3-4).

6-(5-(4-Hydroxyphenyl)-1-(4-nitrophenyl)pyrazoline-3-yl)-7-hydroxy-4-methylcoumarin (**6d**). From **5d** (Ar=*p*-HOC_6H_4, 1mmol, 322 mg): Reaction time: 32 h, yield 246.7 mg (54%) of **6d**, crystallized from a mixture of DMF and 96% ethanol (1:2) as yellow crystals. Mp: 284–286 °C; R_f: 0.71. IR (KBr, cm^{-1}): 3536, 3280 (OH), 1684 (C=O), 1624 (C=C), 1595 (C=N), 1534 (NO_2 asym.), 1320 (NO_2 sym.). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.20 (1H, s, HO-7), 9.32 (1H, s, Ar-OH), 8.34 (1H, s, H-5), 8.14 (2H, d, J = 8.0 Hz, H-3″,5″), 7.38 (2H, d, J = 8.0 Hz, H-2″,6″), 7.38 (2H, d, J = 8.0 Hz, Ar-H), 6.91 (1H, s, H-8), 6.85 (2H, d, J = 8.0 Hz, Ar-H), 6.25 (1H, s, H-3), 5.27 (1H, dd, J = 11.5, 3.0 Hz, H-c), 3.42 (1H, dd, J = 17.0, 3.0 Hz, H-a), 2.91 (1H, dd, J = 17.0, 11.5 Hz, H-b), 2.49 (3H, s, CH_3-4). ^{13}C NMR (125 MHz, DMSO-d_6): δ 159.1 (C-2), 158.6 (C-8a), 157.3 (Ar-C), 154.1 (C-7), 152.5 (C-4), 150.6 (C-1″), 139.4 (C-3′), 138.8 (C-4″), 129.2 (2C, Ar-C), 127.6 (Ar-C), 125.3 (C-3″,5″), 120.2 (C-5), 117.6 (C-6), 114.9 (2C, Ar-C), 114.2 (C-4a), 111.9 (C-3), 111.8 (C-2″,6″), 104.1 (C-8), 76.74 (C-5′), 31.17 (C-4′), 17.61 (CH_3-4).

6-(5-(2-Hydroxyphenyl)-1-(4-nitrophenyl)pyrazoline-3-yl)-7-hydroxy-4-methylcoumarin (**6e**). From **5e** (Ar=*o*-HOC_6H_4, 1mmol, 322 mg): Reaction time: 40 h, yield 274.2 mg (54%) of **6e**, crystallized from a mixture of DMF and 96% ethanol (1:2) as bright yellow crystals. Mp: 278–280 °C; R_f: 0.83. IR (KBr, cm^{-1}): 3243 (OH), 1725 (C=O), 1623 (C=C), 1591 (C=N), 1531 (NO_2 asym.), 1321 (NO_2 sym.). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.28 (1H, s, HO-7), 9.88 (1H, s, Ar-OH), 8.25 (1H, s, H-5), 8.09 (2H, d, J = 8.5 Hz, H-3″,5″), 7.45 (1H, d, J = 7.0 Hz, Ar-H), 7.38 (2H, d, J = 8.5 Hz, H-2″,6″), 7.22 (1H, t, J = 7.5, 7.0 Hz, Ar-H), 6.87–6.93 (2H, m, Ar-H), 6.91 (1H, s, H-8), 6.23 (1H, s, H-3), 5.49 (1H, dd, J = 12.5, 2.5 Hz, H-c), 3.39 (1H, dd, J = 17.5, 3.0 Hz, H-a), 2.77 (1H, dd, J = 17.5, 12.0 Hz, H-b), 2.49 (3H, s, CH_3-4). LRMS (ESI-) m/z 455.99 $[M – H]^-$ (100%).

6-(5-(4-Chlorophenyl)-1-(4-nitrophenyl)pyrazoline-3-yl)-7-hydroxy-4-methylcoumarin (**6f**). From **5f** (Ar=*p*-ClC_6H_4, 1mmol, 340.5 mg): Reaction time: 40 h, yield 233.5 mg (43%) of **6f**, crystallized from a mixture of DMF and 96% ethanol (1:2) as yellow crystals. Mp: 311–313 °C; R_f: 0.78. IR (KBr, cm^{-1}): 3339, 3283 (OH), 1707 (C=O), 1624 (C=C), 1595 (C=N), 1523 (NO_2 asym.), 1326 (NO_2 sym.). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.20 (1H, s, HO-7), 8.34 (1H, s, H-5), 8.14 (2H, d, J = 9.0 Hz, H-3″,5″), 7.60 (2H, d, J = 8.5 Hz, Ar-H), 7.51 (2H, d, J = 8.5 Hz, Ar-H), 7.38 (2H, d, J = 9.0 Hz, H-2″,6″), 6.97 (1H, s, H-8), 6.26 (1H, s, H-3), 5.43 (1H, dd, J = 11.5, 3.0 Hz, H-c), 3.49 (1H, dd, J = 17.0, 3.0 Hz, H-a), 2.92 (1H, dd, J = 17.0, 11.5 Hz, H-b), 2.51 (3H, s, CH_3-4). ^{13}C NMR (125 MHz, DMSO-d_6): δ 159.1 (C-2), 158.1 (C-8a), 154.1 (C-7), 152.4 (C-4), 150.5 (C-1″), 138.9 (C-3′), 138.8 (C-4″), 137.9, 132.8, 128.1, 128.1, 127.9, 127.9 (Ar-C), 125.3 (C-3″,5″), 120.2 (C-5), 117.6 (C-6), 114.4 (C-4a), 112.1 (C-3), 111.8 (C-2″,6″), 104.1 (C-8), 75.96 (C-5′), 31.10 (C-4′), 17.60 (CH_3-4).

6-(5-(3-Chlorophenyl)-1-(4-nitrophenyl)pyrazoline-3-yl)-7-hydroxy-4-methylcoumarin (**6g**). From **5g** (Ar=*m*-ClC_6H_4, 1mmol, 340.5 mg): Reaction time: 38 h, Yield 233.0 mg (49%) of **6g**, crystallized from a mixture of DMF and 96% ethanol (1:2) as bright yellow crystals. Mp: 288-290 °C, R_f: 0.73. IR (KBr, cm^{-1}): 3304 (OH), 1697 (C=O), 1626 (C=C), 1594 (C=N), 1558 (NO_2, asym.), 1322 (NO_2 sym.). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.21 (1H, s, HO-7), 8.34 (1H, s, H-5), 8.14 (2H, d, J = 9.0 Hz, H-3″,5″), 7.65 (1H, s, Ar-H), 7.55 (1H, d, J = 7.5 Hz, Ar-H), 7.51 (1H, d, *J* = 7.5 Hz, Ar-H), 7.47 (1H, t, *J* = 7.5 Hz, Ar-H), 7.38 (2H, d, *J* = 9.0 Hz, H-2″,6″), 6.99 (1H, s, H-8), 6.26 (1H, s, H-3), 5.43 (1H, d, *J* = 9.5 Hz, H-c), 3.52 (1H, dd, *J* = 16.5, 3.0 Hz, H-a), 2.91 (1H, dd, *J* = 16.5, 11.5 Hz, H-b), 2.51 (3H, s, CH$_3$-4). ^{13}C NMR (125 MHz, DMSO-d_6): δ 159.0 (C-2), 158.0 (C-8a), 154.1 (C-7), 152.4 (C-4), 150.5 (C-1″), 141.4 (Ar-C), 138.8 (C-3′), 138.7 (C-4″), 133.0 (Ar-C), 130.1 (Ar-C), 128.0 (Ar-C), 125.9 (Ar-C), 125.3 (C-3″,5″), 124.6 (Ar-C), 120.3 (C-5), 117.6 (C-6), 114.5 (C-4a), 112.2 (C-3), 111.8 (C-2″,6″), 104.1 (C-8), 75.88 (C-5′), 31.14 (C-4′), 17.60 (CH$_3$-4).

6-(5-(3-Nitrophenyl)-1-(4-nitrophenyl)pyrazoline-3-yl)-7-hydroxy-4-methylcoumarin (**6h**). From **5h** (Ar=*m*-O$_2$NC$_6$H$_4$, 1mmol, 351 mg): Reaction time: 38 h, yield 209 mg (43%) of **6h**, crystallized from a mixture of DMF and 96% ethanol (1:2) as bright yellow crystals. Mp 258-260 °C, R_f: 0.74. IR (KBr, cm^{-1}): 3270 (OH), 1732 (C=O), 1623 (C=C), 1600 (C=N), 1531 (NO$_2$ asym.), 1324 (NO$_2$ sym.). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.41 (1H, s, HO-7), 8.47 (1H, s, Ar-H), 8.44 (1H, s, H-5), 8.28 (1H, dd, *J* = 7.5, 1.0 Hz, Ar-H), 8.15 (2H, d, *J* = 9.0 Hz, H-3″,5″), 8.08 (1H, t, *J* = 7.0, 1.0 Hz, Ar-H), 7.94 (1H, t, *J* = 7.0, 1.0 Hz, Ar-H), 7.39 (2H, d, *J* = 9.0 Hz, H-2″,6″), 7.18 (1H, s, H-8), 6.32 (1H, s, H-3), 5.59 (1H, d, *J* = 11.0 Hz, H-c), 3.56 (1H, dd, *J* = 16.5, 3.0 Hz, H-a), 2.94 (1H, dd, *J* = 16.5, 11.0 Hz, H-b), 2.51 (3H, s, CH$_3$-4).

6-(5-(4-Bromophenyl)-1-(4-nitrophenyl)pyrazoline-3-yl)-7-hydroxy-4-methylcoumarin (**6i**). From **5i** (Ar=*p*-BrC$_6$H$_4$, 1mmol, 384 mg): Reaction time: 35 h, yield 270.4 mg (52%) of **6i**, crystallized from a mixture of DMF and 96% ethanol (1:2) as yellow crystals. Mp 301-303 °C, R_f: 0.69. IR (KBr, cm^{-1}): 3283 (OH), 1686 (C=O), 1626 (C=C), 1595 (C=N), 1548 (NO$_2$ asym.), 1326 (NO$_2$ sym.). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.21 (1H, s, HO-7), 8.34 (1H, s, H-5), 8.13 (2H, d, *J* = 7.5 Hz, H-3″,5″), 7.65 (2H, d, *J* = 6.5 Hz, Ar-H), 7.54 (2H, s, Ar-H), 7.37 (2H, s, H-2″,6″), 6.96 (1H, s, H-8), 6.25 (1H, s, H-3), 5.41 (1H, d, *J* = 7.0 Hz, H-c), 3.48 (1H, d, *J* = 14.0 Hz, H-a), 2.92 (1H, dd, *J* = 17.5 Hz, H-b), 2.49 (3H, s, CH$_3$-4). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 159.1 (C-2), 158.2 (C-8a), 154.1 (C-7), 152.5 (C-4), 150.5 (C-1″), 138.9 (C-3′), 138.8 (C-4″), 138.3, 131.2, 131.1 (Ar-C), 131.1, 128.2 (Ar-C), 128.2, 125.3 (C-3″,5″), 120.2 (C-5), 117.6 (C-6), 114.3 (C-4a), 112.1 (C-3), 111.8 (C-2″,6″), 104.2 (C-8), 76.00 (C-5′), 31.06 (C-4′), 17.61 (4-CH$_3$). LRMS (ESI-) *m/z* calcd. for $C_{25}H_{18}BrN_3O_5$ [M-H]$^-$ 518.04, 519.04, [M–H+2]$^-$ 520.04, found 518.93 (29.6%), 519.90 (100%), 520.97 (28.1%).

6-(5-(Pyridin-3-yl)-1-(4-nitrophenyl)pyrazoline-3-yl)-7-hydroxy-4-methylcoumarin (**6j**). From **5j** (Ar=C$_5$H$_4$N, 1mmol, 307 mg): Reaction time: 28 h, Yield 252 mg (57%) of **6j**, crystallized from a mixture of DMF and 96% ethanol (1:2) as pale yellow crystals. Mp 296-297 °C, R_f: 0.86. IR (KBr, cm^{-1}): 3341, 3399 (OH), 1707 (C=O), 1626 (C=C), 1594 (C=N), 1505 (NO$_2$ asym.), 1333 (NO$_2$ sym.). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.36 (1H, s, HO-7), 8.79 (1H, s, Ar-H), 8.32 (1H, d, *J* = 3.5 Hz, Ar-H), 8.30 (1H, s, H-5), 8.13 (2H, d, *J* = 8.5 Hz, H-3″,5″), 8.01 (1H, d, *J* = 8.0 Hz, Ar-H), 7.50 (1H, dd, *J* = 7.0, 2.5 Hz, Ar-H), 7.37 (2H, d, *J* = 8.5 Hz, H-2″,6″), 7.01 (1H, s, H-8), 6.28 (1H, s, H-3), 5.47 (1H, dd, *J* = 12.0, 2.5 Hz, H-c), 3.49 (1H, dd, *J* = 16.5, 2.5 Hz, H-a), 2.94 (1H, dd, *J* = 16.5, 12.0 Hz, H-b), 2.50 (3H, s, CH$_3$-4). ^{13}C NMR (125 MHz, DMSO-d$_6$) δ: 159.5 (C-2), 158.3 (C-8a), 154.2 (C-7), 153.0 (C-4), 150.7 (C-1″), 149.8 (Ar-C), 148.0 (Ar-C), 138.8 (C-3′), 138.7 (C-4″), 134.8, 134.3 (Ar-C), 125.8 (C-3″,5″), 123.7 (Ar-C), 120.5 (C-5), 117.8 (C-6), 114.8 (C-4a), 112.5 (C-3), 112.0 (C-2″,6″), 104.6 (C-8), 75.0 (C-5′), 31.3 (C-4′), 18.1 (CH$_3$-4).

8-(5-Phenyl-1-(4-nitrophenyl)pyrazoline-3-yl)-7-hydroxy-4-methylcoumarin (**13a**). From **12a** (Ar=C$_6$H$_5$, 1mmol, 306 mg): Reaction time: 36 h, yield 150 mg (34%) of **13a**, crystallized from a mixture of DMF and 96% ethanol (1:2) as pale yellow crystals. Mp 262-264 °C, R_f: 0.50. IR (KBr, cm^{-1}): 3315 (OH), 1711 (C=O), 1587 (C=N, C=C), 1535 (NO$_2$ asym.), 1320 (NO$_2$ sym.). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.43 (1H, s, HO-7), 8.08 (2H, d, *J* = 8.5 Hz, H-3″,5″), 7.68 (1H, d, *J* = 9.0 Hz, H-5), 7.59–7.40 (5H, m, Ar-H), 7.58 (2H, d, *J* = 8.5 Hz, H-2″,6″), 7.02 (1H, d, *J* = 9.0 Hz, H-6), 6.33 (1H, s, H-3), 5.36 (1H, t, *J* = 12.5, 2.5 Hz, H-c), 3.45 (1H, t, *J* = 16.5, 2.5 Hz, H-a), 2.90 (1H, dd, *J* = 16.5, 12.5 Hz, H-b), 2.44 (3H, s, CH$_3$-4). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 160.1 (C-2), 159.5 (C-7), 153.5 (C-8a), 151.3 (C-1″), 151.2 (C-4), 138.8 (Ar-C), 139.3 (C-4″), 137.7 (C-3′), 135.3 (Ar-C), 128.5 (Ar-C), 128.5 (Ar-C), 126.4 (C-5), 126.0 (C-3″,5″), 125.5 (Ar-C), 125.5 (Ar-C), 114.4 (C-4a), 114.0 (C-6), 112.6 (C-2″,6″), 111.5 (C-3), 109.3 (C-8), 76.66 (C-5′), 32.29 (C-4′), 18.58 (CH$_3$-4).

8-(5-*p*-Tolyl-1-(4-nitrophenyl)pyrazoline-3-yl)-7-hydroxy-4-methylcoumarin (**13b**). From **12b** (Ar=CH$_3$C$_6$H$_4$, 1mmol, 320 mg): Reaction time: 30 h yield 209.3 mg (46%) of **13b**, crystallized from a mixture of DMF and 96% ethanol (1:2) as bright yellow crystals. Mp 248-250 °C, *R$_f$*: 0.75. IR (KBr, cm^{-1}): 3238 (OH), 1713 (C=O), 1598 (C=C, C=N), 1502 (NO$_2$ asym.), 1313 (NO$_2$ sym.). ^{1}H NMR (500 MHz, DMSO-*d$_6$*) δ: 10.45 (1H, s, HO-7), 8.10 (2H, d, *J* = 9.5 Hz, H-3″,5″), 7.69 (1H, d, *J* = 9.0 Hz, H-5), 7.57 (2H, d, *J* = 9.5 Hz, H-2″,6″), 7.47 (2H, d, *J* = 8.0 Hz, Ar-H), 7.28 (2H, d, *J* = 8.0 Hz, Ar-H), 7.03 (1H, d, *J* = 9.0 Hz, H-6), 6.35 (1H, s, H-3), 5.35 (1H, dd, *J* = 12.0, 3.0 Hz, H-c), 3.45 (1H, dd, *J* = 16.5, 3.0 Hz, H-a), 2.93 (1H, dd, *J* = 16.5, 12.0 Hz, H-b), 2.45 (3H, s, CH$_3$-4), 2.35 (3H, s, Ar-CH$_3$). ^{13}C NMR (125 MHz, DMSO-*d$_6$*) δ: 160.6 (C-2), 160.1 (C-7), 154.1 (C-8a), 151.9 (C-4), 151.8 (C-1″), 139.3 (C-4″), 138.4 (C-3′), 138.1, 136.8, 129.5, 129.5, 127.0, 127.0 (Ar-C), 126.5 (C-5), 126.1 (C-3″,5″), 114.9 (C-4a), 114.6 (C-6), 113.1 (C-2″,6″), 111.9 (C-3), 109.8 (C-8), 77.05 (C-5′), 32.65 (C-4′), 19.12 (CH$_3$-4). LRMS (ESI+) *m/z* calcd. for C$_{26}$H$_{21}$N$_3$O$_5$ [M+H]$^+$ 456.14, found 456.29 (100%).

8-(5-(*p*-Methoxyphenyl)-1-(4-nitrophenyl)pyrazoline-3-yl)-7-hydroxy-4-methylcoumarin (**13c**). From **12c** (Ar=*p*-CH$_3$OC$_6$H$_4$, 1mmol, 336 mg): Reaction time: 24 h, yield 226 mg (48%) of **13c**, crystallized from a mixture of DMF and 96% ethanol (1:2) as yellow crystals. Mp 276-278 °C, *R$_f$*: 0.49. IR (KBr, cm^{-1}): 3290 (OH), 1707 (C=O), 1596 (C=N, C=C), 1508 (NO$_2$ asym.), 1313 (NO$_2$ sym.). ^{1}H NMR (500 MHz, DMSO-*d$_6$*) δ: 10.40 (1H, s, HO-7), 8.13 (2H, d, *J* = 8.0 Hz, H-3″,5″), 8.07 (2H, d, *J* = 8.5 Hz, Ar-H), 7.65 (1H, d, *J* = 8.0 Hz, H-5), 7.50 (2H, d, *J* = 8.0 Hz, H-2″,6″), 7.35 (2H, d, *J* = 8.5 Hz, Ar-H), 7.01 (1H, d, *J* = 8.0 Hz, H-6), 6.32 (1H, s, H-3), 5.30 (1H, dd, *J* = 12.0, 3.0 Hz, H-c), 3.78 (3H, s, Ar-OCH$_3$), 3.41 (1H, dd, *J* = 16.5, 3.0 Hz, H-a), 2.92 (1H, dd, *J* = 16.5, 12.0 Hz, H-b), 2.41 (3H, s, CH$_3$-4). LRMS (ESI+): *m/z* 472.39 [M+H]$^+$ (8.05%), 494.16 [M+Na]$^+$ (56%).

8-(5-(*p*-Dimethylaminophenyl)-1-(4-nitrophenyl)pyrazoline-3-yl)-7-hydroxy-4-methylcoumarin (**13d**). From **12d** (Ar=*p*-(CH$_3$)$_2$NC$_6$H$_4$, 1mmol, 349 mg): Reaction time: 30 h, yield 251.7 mg (52%) of **13d**, crystallized from a mixture of DMF and 96% ethanol (1:2) as yellow crystals. Mp 299-301 °C, *R$_f$*: 0.52. IR (KBr, cm^{-1}): 3141 (OH), 1737 (C=O), 1588 (C=N, C=C), 1506 (NO$_2$ asym.), 1304 (NO$_2$ sym.). ^{1}H NMR (500 MHz, DMSO-*d$_6$*) δ: 11.36 (1H, s, HO-7), 8.06 (2H, d, *J* = 8.5 Hz, H-3″,5″), 7.72 (1H, d, *J* = 9.0 Hz, H-5), 7.19 (2H, d, *J* = 8.5 Hz, Ar-H), 7.02 (2H, d, *J* = 8.5 Hz, H-2″,6″), 7.01 (1H, d, *J* = 9.0 Hz, H-6), 6.68 (2H, d, *J* = 8.5 Hz, Ar-H), 6.21 (1H, s, H-3), 5.60 (1H, dd, *J* = 12.0, 5.0 Hz, H-c), 4.17 (1H, dd, *J* = 18.5, 5.0 Hz, H-a), 3.40 (1H, dd, *J* = 18.5, 12.0 Hz, H-b), 2.85 (6H, s, Ar-N(CH$_3$)$_2$), 2.40 (3H, s, CH$_3$-4). ^{13}C NMR (125 MHz, DMSO-*d$_6$*) δ: 160.8 (C-2), 159.5 (C-7), 153.0 (C-8a), 152.4 (C-1″), 149.7 (C-4), 147.6 (Ar-C), 138.3 (C-4″), 138.2 (C-3′), 126.9 (C-5), 126.3 (Ar-C), 126.3 (Ar-C), 125.1 (C-3″,5″), 114.3 (C-4a), 112.7 (C-6), 112.4 (Ar-C), 112.4 (Ar-C), 112.0 (C-3), 111.7 (C-2″,6″), 110.4 (C-8), 61.0 (C-5′), 46.8 (C-4′), 40.08 (Ar-N(CH$_3$)$_2$), 17.78 (CH$_3$-4).

8-(5-(*p*-Chlorophenyl)-1-(4-nitrophenyl)pyrazoline-3-yl)-7-hydroxy-4-methylcoumarin (**13e**). From **12e** (Ar=*p*-ClC$_6$H$_4$, 1mmol, 340.5 mg): Reaction time: 36 h, yield 204.5 mg (43%) of **13e**, crystallized from a mixture of DMF and 96% ethanol (1:2) as bright yellow crystals. Mp 243-245 °C, *R$_f$*: 0.68. IR (KBr, cm^{-1}): 3304 (OH), 1714 (C=O), 1591 (C=C, C=N), 1527 (NO2 asym.), 1314 (NO$_2$ sym.). ^{1}H NMR (500 MHz, DMSO-*d$_6$*) δ: 10.44 (1H, s, HO-7), 8.08 (2H, d, *J* = 8.5 Hz, H-3″,5″), 7.66 (1H, d, *J* = 9.0 Hz, H-5), 7.62–7.53 (4H, m, Ar-H), 7.54 (2H, d, *J* = 8.5 Hz, H-2″,6″), 7.02 (1H, d, *J* = 9.0 Hz, H-6), 6.33 (1H, s, H-3), 5.30 (1H, d, *J* = 11.0 Hz, H-c), 3.45 (1H, d, *J* = 16.5 Hz, H-a), 2.86 (1H, t, *J* = 16.5, 11.5 Hz, H-b), 2.43 (3H, s, CH$_3$-4).

8-(5-(*m*-Chlorophenyl)-1-(4-nitrophenyl)pyrazoline-3-yl)-7-hydroxy-4-methylcoumarin (**13f**). From **12f** (Ar=*m*-ClC$_6$H$_4$, 1mmol, 340.5 mg): Reaction time: 40 h, yield 185.5 mg (39%) of **13f**, crystallized from a mixture of DMF and 96% ethanol (1:3) as brown crystals. Mp 248-250 °C, R_f: 0.73. IR (KBr, cm^{-1}): 3299 (OH), 1712 (C=O), 1585 (C=C, C=N), 1520 (NO$_2$ asym.), 1315 (NO$_2$ sym.). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.39 (1H, s, HO-7), 8.07 (2H, d, *J* = 8.0 Hz, H-3″,5″), 7.66 (1H, s, Ar-H), 7.64 (1H, d, *J* = 8.0 Hz, H-5), 7.56–7.47 (3H, m, Ar-H), 7.51 (2H, d, *J* = 8.0 Hz, H-2″,6″), 7.01 (1H, d, *J* = 8.0 Hz, H-6), 6.33 (1H, s, H-3), 5.37 (1H, dd, *J* = 12.0, 3.0 Hz, H-c), 3.46 (1H, dd, *J* = 16.5, 2.5 Hz, H-a), 2.84 (1H, dd, *J* = 16.5, 12.0 Hz, H-b), 2.42 (3H, s, CH$_3$-4). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 160.0 (C-2), 159.1 (C-7), 153.4 (C-8a), 151.4 (C-1″), 151.2 (C-4), 141.7 (Ar-C), 138.9 (C-4″), 137.2 (C-3′), 133.3 (Ar-C), 130.5 (Ar-C), 128.3 (Ar-C), 126.3 (C-5), 125.9 (C-3″,5″), 125.5 (Ar-C), 125.1 (Ar-C), 114.5 (C-4a), 113.9 (C-6), 112.6 (C-2″,6″), 111.6 (C-3), 109.3 (C-8), 75.74 (C-5′), 32.02 (C-4′), 18.57 (CH$_3$-4). LRMS (ESI+) *m/z* calcd. for $C_{25}H_{18}ClN_3O_5$ [M+Na]$^-$ 498.09, [M+Na+2]$^-$ 500.09, found 498.55 (100%), 500.46 (30.1%).

8-(5-(*p*-Nitrophenyl)-1-(4-nitrophenyl)pyrazoline-3-yl)-7-hydroxy-4-methylcoumarin (**13g**). From **12g** (Ar=*p*-$O_2NC_6H_4$, 1mmol, 351 mg): Reaction time: 40 h, yield 155.5 mg (32%) of **13g**, crystallized from a mixture of DMF and 96% ethanol (1:3) as blight brown crystals. Mp 245-247 °C, R_f: 0.37. IR (KBr, cm^{-1}): 3307 (OH), 1710 (C=O), 1587 (C=C, C=N), 1522 (NO$_2$, asym.), 1317 (NO$_2$ sym.). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.51 (1H, s, HO-7), 8.35 (2H, d, *J* = 8.5 Hz, Ar-H), 8.10 (2H, d, *J* = 8.0 Hz, H-3″,5″), 7.88 (2H, d, *J* = 8.5 Hz, Ar-H), 7.73 (1H, d, *J* = 8.0 Hz, H-5), 7.56 (2H, d, *J* = 8.0 Hz, H-2″,6″), 7.10 (1H, d, *J* = 8.0 Hz, H-6), 6.38 (1H, s, H-3), 5.59 (1H, dd, *J* = 12.0, 3.5 Hz, H-c), 3.56 (1H, dd, *J* = 16.5, 3.5 Hz, H-a), 2.91 (1H, dd, *J* = 16.5, 12.0 Hz, H-b), 2.46 (3H, s, 4-CH$_3$). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 161.8 (C-2), 159.4 (C-7), 158.4 (C-8a), 152.7 (C-4), 150.9 (C-1″), 147.2 (Ar-C), 146.1 (Ar-C), 138.9 (C-4″), 136.3 (C-3′), 127.1 (Ar-C), 125.5 (C-5), 124.9 (C-3″,5″), 123.2 (Ar-C), 114.4 (C-4a), 113.5 (C-6), 112.4 (C-2″,6″), 111.3 (C-3), 109.2 (C-8), 75.25 (C-5′), 31.40 (C-4′), 17.98 (CH$_3$-4). LRMS (ESI-) *m/z* calcd. for $C_{25}H_{18}N_4O_7$ [M-H]$^-$ 485.11, found 485.01.

8-(5-(*m*-Nitrophenyl)-1-(4-nitrophenyl)pyrazoline-3-yl)-7-hydroxy-4-methylcoumarin (**13h**). From **12h** (Ar=*m*-$O_2NC_6H_4$, 1mmol, 351 mg): Reaction time: 40 h, yield 179.8 mg (37%) of **13h**, crystallized from a mixture of DMF and 96% ethanol (1:3) as blight yellow crystals. Mp 281-283 °C, R_f: 0.62. IR (KBr, cm^{-1}): 3297 (OH), 1718 (C=O), 1587 (C=C, C=N), 1531 (NO$_2$ asym.), 1314 (NO$_2$ sym.) ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.46 (1H, s, HO-7), 8.46 (1H, s, Ar-H), 8.29 (1H, dd, *J* = 8.5, 1.0 Hz, Ar-H), 8.08 (2H, d, *J* = 8.0 Hz, H-3″,5″), 8.07 (1H, dd, *J* = 8.5, 1.0 Hz, Ar-H), 7.79 (1H, t, *J* = 7.5, 7.0 Hz, Ar-H), 7.68 (1H, d, *J* = 8.0 Hz, H-5), 7.54 (2H, d, *J* = 8.0 Hz, H-2″,6″), 7.06 (1H, d, *J* = 8.0 Hz, H-6), 6.34 (1H, s, H-3), 5.56 (1H, dd, *J* = 12.0, 3.5 Hz, H-c), 3.55 (1H, dd, *J* = 16.5, 3.5 Hz, H-a), 2.90 (1H, dd, *J* = 16.5, 12.0 Hz, H-b), 2.43 (3H, s, CH$_3$-4). ^{13}C NMR (125 MHz, DMSO-d$_6$) δ: 161.8 (C-2), 159.5 (C-7), 158.4 (C-8a), 153.4 (C-8a), 152.7 (C-4), 150.9 (C-1″), 147.8 (Ar-C), 141.1 (Ar-C), 138.9 (C-4″), 136.4 (C-3′), 132.3 (Ar-C), 129.7 (Ar-C), 125.5 (C-5), 124.9 (C-3″,5″), 122.7 (Ar-C), 120.5 (Ar-C), 114.3 (C-4a), 113.5 (C-6), 111.3 (C-3), 109.1 (C-8), 75.09 (C-5′), 31.36 (C-4′), 17.98 (CH$_3$-4).

8-(5-(*p*-Bromophenyl)-1-(4-nitrophenyl)pyrazoline-3-yl)-7-hydroxy-4-methylcoumarin (**13i**). From **12i** (Ar=*p*-BrC_6H_4, 1mmol, 384 mg): Reaction time: 36 h, yield 208 mg (40%) of **13i**, crystallized from a mixture of DMF and 96% ethanol (1:2) as blight yellow crystals. Mp 245-247 °C, R_f: 0.68. IR (KBr, cm^{-1}): 3306 (OH), 1713 (C=O), 1586 (C=C, C=N), 1509 (NO$_2$ asym.), 1315 (NO$_2$ sym.). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.31 (1H, s, HO-7), 8.08 (2H, d, *J* = 9.0 Hz, H-3″,5″), 7.68 (2H, d, *J* = 8.5 Hz, Ar-H), 7.66 (1H, d, *J* = 9.0 Hz, H-5), 7.57 (2H, d, *J* = 8.5 Hz, Ar-H), 7.56 (2H, d, *J* = 9.0 Hz, H-2″,6″), 7.02 (1H, d, *J* = 9.0 Hz, H-6), 6.31 (1H, s, H-3), 5.39 (1H, dd, *J* = 12.0, 3.0 Hz, Hc), 3.50 (1H, dd, *J* = 16.5, 3.0 Hz, Ha), 2.90 (1H, dd, *J* = 16.5, 12.0 Hz, Hb), 2.44 (3H, s, CH$_3$-4). ^{13}C NMR (125 MHz, DMSO-d$_6$) δ: 161.7 (C-2), 159.6 (C-7), 158.9 (C-8a), 153.0 (C-4), 151.0 (C-1″), 138.9 (C-4″), 138.4 (Ar-C), 137.1 (C-3′), 136.9 (Ar-C), 131.2 (2C-Ar), 128.2 (2C-Ar), 125.7 (C-5), 125.1 (C-3″,5″), 114.3 (C-4a), 113.6 (C-6), 112.4 (C-2″,6″), 111.3 (C-3), 109.2 (C-8), 75.66 (C-5′), 31.57 (C-4′), 18.12 (CH$_3$-4).

8-(5-(*4*-Hydroxy-3-methoxyphenyl)-1-(4-nitrophenyl)pyrazoline-3-yl)-7-hydroxy-4-methylcoumarin (13j). From **12j** (Ar=4-HO-3-OMeC_6H_3, 1mmol, 352 mg): Reaction time: 24 h, yield 229 mg (47%) of **13j**, crystallized from a mixture of DMF and 96% ethanol (1:3) as yellow crystals. Mp 284-286 °C, R_f: 0.81. IR (KBr, cm^{-1}): 3407 (OH), 1729 (C=O), 1585 (C=C, C=N), 1509 (NO_2 asym.), 1304 (NO_2 sym.). ^{1}H-NMR (500 MHz, DMSO-*d$_6$*), δ 8.86 (1H, s, Ar–OH), 8.05 (2H, d, *J* = 9.0 Hz, H-3″,5″), 7.70 (1H, d, *J* = 8.0 Hz, H-5), 7.06 (2H, d, *J* = 9.0 Hz, H-2″,6″), 7.01 (1H, d, *J* = 8.0 Hz, H-6), 6.95 (1H, d, *J* = 1.5 Hz, Ar–H), 6.79 (1H, dd, *J* = 8.5, 1.5 Hz, Ar–H), 6.75 (1H, d, *J* = 8.5 Hz, Ar–H), 6.17 (1H, s, H-3), 5.56 (1H, dd, *J* = 12.0, 5.0 Hz, H-c), 4.21 (1H, dd, *J* = 18.5, 5.0 Hz, H-a), 3.75 (3H, s, Ar–OCH_3), 3.45 (1H, dd, *J* = 18.5, 12.0 Hz, H-b), 2.40 (3H, s, CH_3-4). ^{13}C-NMR (125 MHz, DMSO-*d$_6$*), δ: 159.6 (C-2), 158.9 (C-7), 153.2 (C-8a), 152.4 (C-1″), 149.6 (C-4), 147.9 (Ar-C), 147.8 (Ar-C), 146.1 (Ar-C), 138.3 (C-4″), 132.0 (C-3′), 126.9 (C-5), 125.2 (C-3″,5″), 118.2 (Ar-C), 115.7 (C-4a), 112.8 (C-6), 112.0 (C-3), 111.8 (C-2″,6″), 110.3 (Ar-C), 110.2 (C-8), 105.8 (Ar-C), 61.31 (C-5′), 55.61 (Ar-OCH_3), 46.87 (C-4′), 17.88 (CH_3-4).

8-(5-(3,4-Methylenedioxyphenyl)-1-(4-nitrophenyl)pyrazoline-3-yl)-7-hydroxy-4-methylcoumarin (13k). From **12k** (Ar=3,4-$O_2CH_2MeC_6H_3$, 1mmol, 350 mg): Reaction time: 20 h, yield 223 mg (46%) of **13k**, crystallized from a mixture of DMF and 96% ethanol (1:2) as yellow crystals. Mp 243-245 °C, R_f: 0.82. IR (KBr, cm^{-1}): 3238 (OH), 1711 (C=O), 1599 (C=C, C=N), 1508 (NO_2 asym.), 1311 (NO_2 sym.). ^{1}H-NMR (500 MHz, DMSO-*d$_6$*), δ 10.28 (1H, s, HO-7); 8.08 (2H, d, *J* = 9.0 Hz, H-3″,5″); 7.96 (1H, d, *J* = 8.0 Hz, Ar-H); 7.65 (1H, d, *J* = 8.0 Hz, H-5); 7.56 (2H, d, *J* 9.0 Hz, H-2″,6″); 7.14 (1H, d, *J* = 1.0 Hz, Ar-H); 7.06 (1H, dd, *J* = 8.0, 1.0 Hz, Ar-H); 6.98 (1H, d, *J* = 8.0 Hz, H-6); 6.29 (1H, d, *J* = 1.0 Hz, H-3); 6.04 (2H, s, Ar-3,4-O_2CH_2); 5.28 (1H, dd, *J* = 12.0, 3.0 Hz, H-c); 3.45 (1H, dd, *J* = 16.5, 3.0 Hz, H-a); 2.91 (1H, dd, *J* = 16.5, 12.0 Hz, H-b); 2.43 (3H, s, CH_3-4). ^{13}C-NMR (125 MHz, DMSO-d_6): δ 161.9 (C-2); 159.6 (C-7); 159.2 (C-8a); 152.9 (C-1″); 151.1 (C-4); 147.2, 147.1 (Ar-C); 138.9 (C-4″); 137.5 (C-3′); 132.8 (Ar-C); 125.6 (C-5); 125.1 (C-3″,5″); 119.9 (Ar-C); 114.1 (C-4a); 113.6 (C-6); 112.4 (C-2″,6″); 111.1 (C-3); 109.1 (C-8); 107.7 (Ar-C); 106.7 (Ar-C); 100.8 (Ar-3,4-O_2CH_2); 76.24 (C-5′); 31.70 (C-4′); 18.11 (CH_3-4).

Biological activity. Each disc contained 50-150 µg/ml of the tested compounds. The agar was allowed to solidify and then three wells/cups were made using a sterile cork borer for each organism. This was done to ensure the proper distribution of the wells, with three in the periphery and one in the center. Agar plugs were removed, and the test samples (each compound at three concentrations) were poured into the corresponding marked wells using micropipettes. Antibacterial and antifungal activity was assessed by the aseptically circle diameter (mm).

Supplementary Material

Copies of NMR and IR spectra associated with this paper are provided in the accompanying Supplementary Material.

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