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ORIGINAL PAPER

Green chemical multicomponent approach for the synthesis of C3-pyranopyrazole-substituted coumarins

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Abstract
An efficient and rapid method was developed for the synthesis of C3-pyranopyrazole-substituted coumarins from one-pot five-component reaction of *β*-keto ester, hydrazine, *O*-hydroxy aromatic aldehydes, 6-methyl, 4-hydroxy pyranone and aromatic aldehyde in the presence of tri-ethylamine in solvent-free conditions. The microwave-assisted method reported herein offers advantageous shorter reaction times, higher yields and cleaner reaction compared with conventional heating methods.

Keywords Multicomponent · C3-pyranopyrazole-substituted coumarin · Solvent free · Microwave synthesis

Introduction

Coumarins are one of the important structural units with assorted biological [1–4] and pharmacological activities ranging from antimicrobial, anti-arrhythmic, antitumour, antifungal, anti-HIV and anti-osteoporosis to inflammatory [5–11]. Apart from this, coumarins have been used as additives in foods, perfumes and cosmetics and also in the preparation of optical brighteners, laser dyes, fluorescent labels and in nonlinear optics [12–18].

Microwave-assisted organic synthesis (MAOS) has emerged as a new "lead" in organic synthesis. The technique offers simple, clean, fast, efficient and economic for the synthesis of a large number of organic molecules [19–22]. In the recent years, microwave-assisted organic reaction has emerged as new tool in organic synthesis. Important advantage of this technology includes highly accelerated rate of the reaction, reduction in reaction time with an improvement in the yield and quality of product [23, 24]. Nowadays, this technique is considered as an important approach towards green chemistry, because this technique is more environmental friendly and in addition, due to assimilation of green chemistry principles, solvent-free multicomponent reactions have been enticed.

Recently we have developed a methodology for the synthesis of C3-dihydrofuran-substituted coumarins from one-pot four-component reaction of *O*-hydroxy aromatic aldehydes, 6-methyl, 4-hydroxy pyran, aromatic aldehyde and pyridinium ylides in the presence of tri-ethylamine under microwave irradiation in solvent-free conditions [25, 26]. As a part of our continuous efforts towards the development of new green chemistry synthetic approaches for important heterocyclic compounds [27–31], in the present work we reported an efficient and ecofriendly five-component reaction protocol in microwave-mediated regioselective synthesis of C3-pyranopyrazole-substituted coumarins from one-pot reaction of *β*-keto ester, hydrazine, *O*-hydroxy aromatic aldehydes, 6-methyl, 4-hydroxy pyranone, aromatic aldehyde and in the presence of tri-ethylamine in solvent-free conditions.

Results and discussion

We contemplated to synthesize novel dihydropyrano[2,3-*c*] pyrazol-6-yl)-2*H*-chromen-2-one derivatives **6** by the one-pot four-component reaction of *O*-hydroxy aromatic aldehydes **1**, 6-methyl, 4-hydroxy pyranone **2**, *β*-keto ester **3**,

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aromatic aldehyde **4** and hydrazine **5** utilizing microwave irradiation under solvent-free conditions (Scheme 1). We decided to perform the preparation of these compounds under microwave irradiation from green chemistry point of view, when associated with neat conditions it represents an environmentally benign alternative in organic synthesis. In the reaction protocol, when equimolar amounts of *O*-hydroxy aromatic aldehydes **1**, 6-methyl, 4-hydroxy pyranone **2**, *β*-keto ester **3**, aromatic aldehyde **4** and hydrazine **5** were reacted in the presence of 0.1 equivalents of Et_3N in a sealed vial under microwave irradiation at 90 °C for 5 min afforded after work-up, dihydropyrano[2,3-*c*]pyrazol-6-yl)-2*H*-chromen-2-one derivatives **6a** were obtained in very good yield.

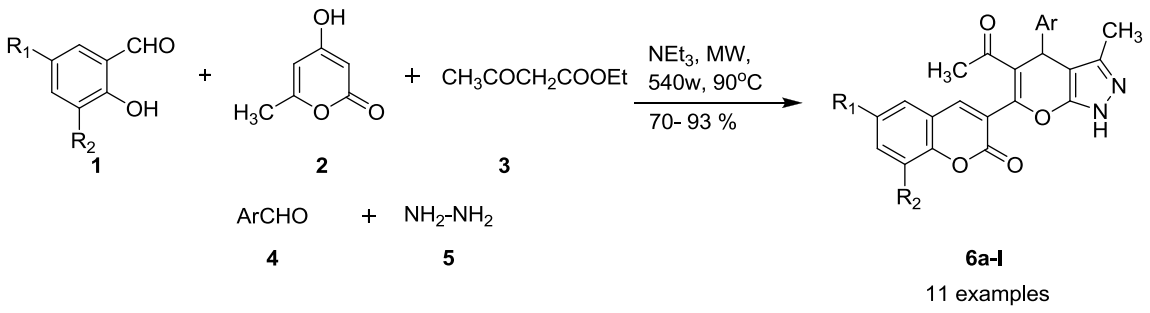
The structure of the compound was fully characterized by ^1H and ^{13}C NMR, MS and IR spectra and elemental analysis. The mass spectrum shows a sharp distinguishable peak of compound **6a** at 485.1315 $[M + Na]^+$. Initially, the reaction was investigated in the absence of catalyst (Table 1, entry 1) under microwave, but no product was formed. Then, we studied the reaction by using different catalysts (Table 2, entries 2–7) but no such satisfactory results were obtained. When the reaction was carried out in the presence of catalytic amount of NEt_3, the reaction was occurred within 5 min. Use of 0.1 eq of Et_3N (Table 1, entry 8) at 540 W for 5 min in microwave irradiation at 90 °C was found to be sufficient for obtaining optimum yield of the desired product, and an increase in the amount of catalyst (Table 2, entry 8) did not improve the yield of the product. The reaction was also carried out in the presence of different solvents under microwave irradiation, but no optimum increase in the yield of desired product was observed (Table 2, entries 10–18).

Compound **6a** was obtained with 27% of yield by conventional method (Entry 13) and 89% by microwave-assisted synthesis (Entry 17). Table 1 shows the comparison between percentage yields and total reaction times for synthesized compound **6a** in both conventional and microwave-mediated conditions. Conventional synthesis was completed within 5–8 h and microwave-assisted synthesis was completed within 3–15 min. In all the cases, microwave-assisted synthesis gave better yield and was completed in much shorter period of time.

Similarly, compounds **6b–q** were synthesized and characterized. Then, the substrate scope of the reaction was explored by using various aromatic aldehydes in the model reaction. All the reactions proceed smoothly giving C3-pyranopyrazole-substituted coumarins in moderate to high yields. Electronic effects were also observed in the reaction process.

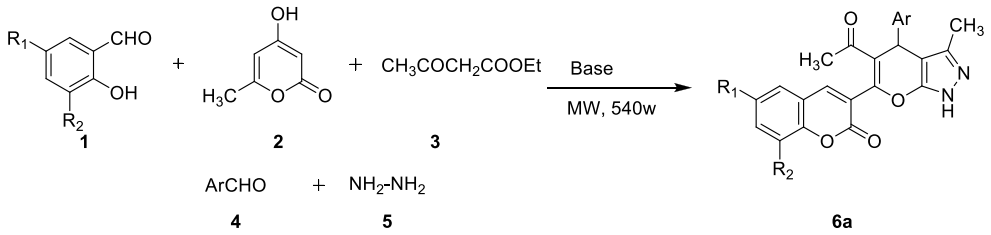
The electron-donating group (EDG) at the para position of the aldehyde required less reaction time to give comparatively high yields of the product (Table 2, entries 9 and 11) while stronger EWG-substituted ones gave evidently poor yields (Table 2, entry 10). The aliphatic aldehyde did not show any effect in the above said reaction. The synthetic route is facile, convergent and allows easy placement of a variety of substituents around the periphery of the heterocyclic ring system (Scheme 1).

A probable mechanism for the formation of product is depicted in Scheme 2. The mechanism most likely involves the initial nucleophilic attack of hydrazine on the *β*-ketoester and subsequent cyclization to form the pyrazolone **A**. Further the reaction occurs via an initial Knoevenagel condensation between 1,3-pyrazolone **A** and aromatic aldehyde **5** to give the intermediate **D**. In the next step, the reaction can be continued via a Knoevenagel condensation followed by attack of the acetoacetonyl coumarin **F** on intermediate **D** that leads to the formation of **G**. Finally, nucleophilic attack of hydroxyl group in intermediate **G** followed by intramolecular cyclization leads to form the final product **6**. The eliminated pyridine releases tri-ethylamine from the Et_3N/HBr salt which further catalyses the reaction. Isolation of intermediates **D** and **F** from the reaction mixture supporting the proposed reaction mechanism.



Scheme 1 Multicomponent synthesis of dihydropyrano [2,3-*c*]pyrazol chromenone derivatives

Table 1 Optimization of reaction conditions[a] under microwave irradiation and conventional heating methods



Entry	Base	Solvent	Time		Yield[c]	
			MW (min)	CH[b] (h)	MW	CH
1	No	No	5	–	0	–
2	Piperidine	No	5	–	57	–
3	Piperidine	EtOH	3	6	63	24
4	Piperidine	Water	3	6.5	60	18
5	Marpholine	No	3	–	55	–
6	Piperizine	No	3	–	58	–
7	K_2CO_3	No	3	–	50	–
8.	NEt_3 (1 eq)	No	3	–	89	–
9.	NEt_3 (0.8 eq)	No	3	–	89	–
10.	NEt_3 (0.5 eq)	No	3	–	89	–
11.	NEt_3 (0.3 eq)	No	3	–	89	–
12.	NEt_3 (0.2 eq)	No	3	–	89	–
13.	NEt_3 (0.1 eq)	No	3	–	89	–
14.	NEt_3 (0.07 eq)	No	3	–	69	–
15.	NEt_3 (0.1 eq)[e]	No	15	–	Trace	–
16	$NHEt_2$	No	3	–	65	–
17	NEt_3	EtOH	5	5	61	27
18	NEt_3	Water	5	5	40	24
19	NEt_3	DD Water[d]	10	6	43	18
20	NEt_3	DMF	15	6.5	51	16
21	NEt_3	MeCN	15	6	45	16
22	NEt_3	THF	15	8	55	18
23	NEt_3	CH_2Cl_2	15	7	58	20
24	NEt_3	Toluene	15	9	32	12
25	NEt_3	$CHCl_3$	15	8	54	17

[a]The reaction of 2-hydroxybenzaldehyde (1.0 mmol) **1a**, 6-methyl 4-hyroxy pyranone (1.0 mmol) **2**, benzaldehyde **3a** (1.0 mmol), ethylaceto acetate **4** (1.0 mmol), hydrazine **5** (1.0 mol)

[b]Conventional heating

[c]Yields for isolated pure products

[d] Deuterium-depleted water

[e]Reaction in the absence of microwave irradiation (by simple heating in the absence of solvent)

Overall, this microwave-promoted five-component domino reaction leads to the generation of one C–O and three C–C bonds. This methodology can be further explored towards the synthesis of diverse C3-pyranopyrazole-substituted coumarins derivatives by using different β-ketoesters with active methylene compounds and study of their biological evolution.

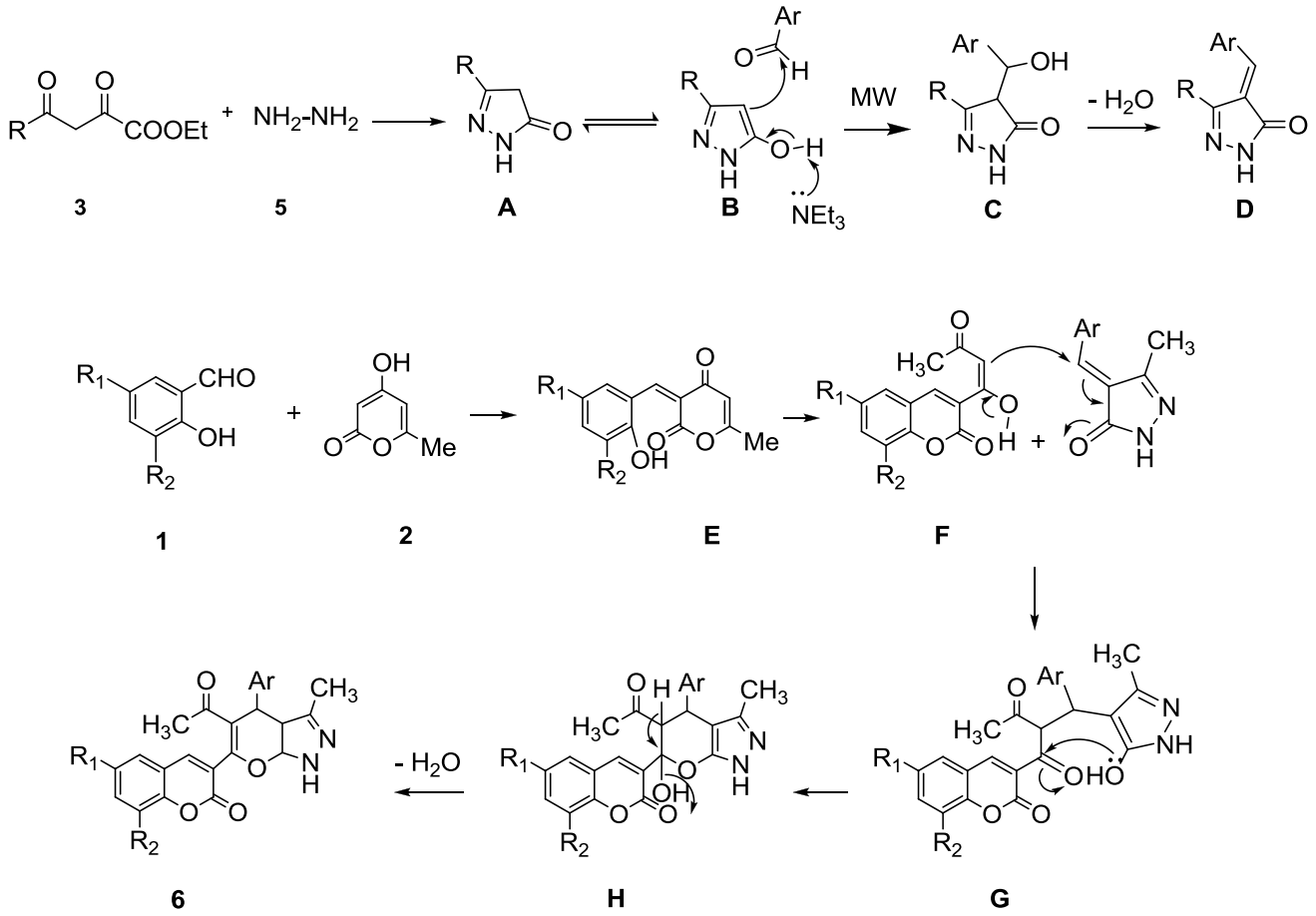
Conclusion

In conclusion, we have developed an efficient microwave-promoted reaction protocol for the synthesis of C3-pyranopyrazole-substituted coumarins via one-pot five-component reaction of *O*-hydroxy aromatic aldehydes, 6-methyl, 4-hydroxy pyranone, β-keto ester, hydrazine and aromatic

Table 2 Multicomponent synthesis of C3-dihydropyranopyrazole-substituted coumarins (**6a–l**)

Entry	Compound	R_1	R_2	Ar	Yield (%)[c]
1.	6a	H	H	C_6H_5	85
2.	6b	Cl	H	C_6H_5	87
3.	6c	Br	H	C_6H_5	89
4.	6d	H	OCH_3	C_6H_5	91
5.	6e	H	OC_2H_5	C_6H_5	89
6.	6f	Cl	Cl	C_6H_5	75
7.	6g	Cl	Br	C_6H_5	79
8.	6h	Br	Br	C_6H_5	77
9.	6i	H	H	*p*-ClC_6H_4	81
10.	6j	H	H	*P*-$(NO_2)C_6H_4$	70
11.	6k	H	H	*p*-*N*$(CH_3)_2$ C_6H_4	93

aldehyde in the presence of tri-ethylamine under microwave-mediated solvent-free conditions. Short reaction times in microwave-assisted conditions along very simple work-up, better yields as well as the absence of the solvent make the protocol more environmentally benign for the synthesis of pyranopyrazole chromenones. The versatility of the reaction to allow the formation of a variety of functionalities such as amido, hydroxyl and amino groups makes these compounds attractive candidates as precursors for drug discovery, combinatorial chemistry and chemical biology. The simple performance, green and mild conditions, good yields and easy purification of the products are among the advantages of this protocol.



Scheme 2 Plausible mechanism for the formation of C3-pyranopyrazole-substituted coumarin

Experimental section

General Methods

Melting points were recorded using open-ended capillary tubes on VEEGO VMP-DS instrument. The progression of all the reactions was monitored by TLC using a mixture of hexanes (60–80 °C boiling mixture) and ethyl acetate. Column chromatography was performed on silica gel (100–200 mesh, SRL Chemicals) using increasing percentage of ethyl acetate in hexanes. All microwave reactions were performed in a monomode Biotage Emery's Creator 540 W system with sample absorption set to "normal". ^{1}H NMR spectra (400 MHz) and ^{13}C NMR (100 MHz) and DEPT -135 spectra were recorded for $CDCl_3$ + CCl_4 (2:1) solutions on a Bruker—400 spectrometer with tetramethylsilane (TMS) as internal standard; *J* values are given in Hz. IR spectra were recorded as KBr solid solution on a Nicolet-6700 spectrometer. High-resolution mass spectra were recorded on a waters micromass Q-TOF micromass spectrometer using electron spray ionization mode. Organic solvents were distilled and dried before use. Melting points were measured in open capillary tubes and are uncorrected. Elemental analyses were performed on a Perkin Elmer 2400 Series II Elemental CHNS analyser.

General synthetic procedure (conventional heating), exemplified by 3-(5-acetyl-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazol-6-yl)-2*H*-chromen-2-one **6a**

Mixture of 2-hydroxybenzaldehyde (198 mg, 0.163 mmol) **1a**, 6-methyl 4-hyroxy pyranone (205 mg, 0.163 mmol) **2**, benzaldehyde **3a** (172 mg, 0.153 mmol), ethylaceto acetate **4** (211 mg, 0.153 mmol), hydrazine **5** (81 mg, 0.153) and 0.1 equivalents of trimethylamine (16 mg, 0.015 mmol) as a catalyst was added in 25 mL of three-neck flask. Then, ethyl alcohol (5 mL) was added as the solvent. The resulting mixture was refluxed at 80 °C for 5 h. During this time, precipitate was formed. Completion of reaction was ensured by TLC, and the reaction mixture was cooled to room temperature. Then, the precipitate was removed by filtration and washed with a little cold ethanol to give the pure product (Yield 27%).

General synthetic procedure (microwave heating), exemplified by 3-(5-acetyl-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazol-6-yl)-2*H*-chromen-2-one **6a**

Mixture of 2-hydroxybenzaldehyde (198 mg, 0.163 mmol) **1a**, 6-methyl 4-hyroxy pyranone (205 mg, 0.163 mmol) **2**, benzaldehyde **3a** (172 mg, 0.153 mmol), ethylaceto acetate **4** (211 mg, 0.153 mmol), hydrazine **5** (81 mg, 0.153) and 0.1 equivalents of trimethylamine (16 mg, 0.015 mmol) was mixed in process glass vial. The vial was capped properly, and thereafter, the mixture was heated under microwave irradiating conditions at power level 540 W at 90 °C for 3 min without solvent. Yield 85% (551 mg), Mp 138.4 °C, R_f 0.24 (1:1 hexane–EtOAc), IR (KBr) υ_{max} 3204, 3011, 1756, 1688, 1613, 1450, 1318, 1013, 981, 704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 12.26 (s, 1H), 8.5 (s, 1H),7.83 (d, *J* = , 1H), 7.41 (t, *J* = , 1H), 7.35 – 7.38 (m, 2H), 7.34 (t, *J* = , 1H), 7.13 -7.08 (m, 2H), 6.89 (t, *J* = , 1H), 5.35 (s, 1H), 2.51 (s, 3H), 1.89 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 163.4, 162.0, 157.7, 152.1, 144.3, 141.7, 136.8, 133.1, 152.1, 144.3, 141.7, 136.8, 133.1, 129.0, 126.7, 126.1, 123.9, 123.3, 121.0, 118.8, 117.1, 112.2, 106.2, 34.2, 26.8, 10.3 ppm; HRMS (ESI, m/z): 421.1159 calcd for $C_{24}H_{18}N_2O_4$ (M + Na) found: 421.1156. Analysis calcd for $C_{24}H_{18}N_2O_4$: C, 72.35; H, 4.55; N, 7.03; Found C, 72.33; H, 4.54; N, 7.01.

3-(5-Acetyl-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazol-6-yl)-6-chloro-2*H*-chromen-2-one **6b**

Yield 87% (612 mg), Mp 140.6 °C, R_f 0.24 (1:1 hexane–EtOAc), IR (KBr) υ_{max} 3217, 3034, 1754, 1692, 1621, 1454, 1321, 1025, 982, 724 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 12.26 (s, 1H), 8.54 (s, 1H), 7.83 (d, *J* = 7.2 Hz, 1H), 7.62 (d, *J* = 7.4 Hz, 1H), 7.42–7.34 (m, 2H), 7.13–7.08 (m, 2H), 6.90 (d, *J* = 6.8 Hz, 1H), 5.35 (s, 1H), 2.51 (s, 3H), 1.89 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 164.4, 163.0, 157.0, 152.3, 149.3, 146.7, 137.0, 133.2, 129.3, 126.7, 124.6, 123.5, 121.5, 118.4, 117.2, 112.3, 106.0, 34.2 ppm; HRMS (ESI, m/z) 455.0769 calcd for $C_{24}H_{17}ClN_2O_4$ (M + Na) found 455.0767. Analysis calcd for $C_{24}H_{17}ClN_2O_4$: C, 66.59; H, 3.96; N, 6.47; Found C, 66.57; H, 3.94; N, 6.46.

3-(5-Acetyl-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazol-6-yl)-6-bromo-2*H*-chromen-2-one **6c**

Yield 89% (690 mg), Mp 140.8.4 °C, R_f 0.23 (1:1 hexane–EtOAc), IR (KBr) υ_{max} 3214, 3016, 1753, 1692, 1618, 1448, 1320, 1021, 985, 728 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 12.25 (s, 1H), 8.52 (s, 1H), 7.85 (t, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 6.95 (s, 1H), 6.69 (d, *J* = 8.6 Hz, 1H), 5.37 (s, 1H, 2.45 (s, 3H), 1.85 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1, 167.0, 166.1, 156.2, 150.1, 148.6, 146.3, 145.6, 133.6, 129.0, 127.6, 126.3, 125.6, 124.9, 123.4, 118.8, 117.3, 112.1, 104.1, 35.6, 26.1, 10.3 ppm; HRMS (ESI, m/z) 499.0264 calcd for $C_{24}H_{17}BrN_2O_4$ (M + Na)

found 499.0261. Analysis calcd for $C_{24}H_{17}BrN_2O_4$: C, 60.39; H, 3.59; N, 5.87; Found C, 60.37; H, 3.58; N, 5.84.

3-(5-Acetyl-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazol-6-yl)-8-methoxy-2*H*-chromen-2-one **6d**

Yield 91% (634 mg), Mp 139.9 °C, R_f 0.23 (1:1 hexane–EtOAc), IR (KBr) υ_{max} 3212, 3010, 1750, 1690, 1611, 1448, 1306, 1010, 980, 783 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.24 (s, 1H), 8.57 (s, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.61 (t, J = 5.2 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.34 (t, J = 7.6 Hz, 2H), 6.82 (dd, J = 6.2 Hz, 1.4 Hz, 2H), 6.73 (s, 1H), 5.34 (s, 1H), 3.81 (s, 3H), 2.57 (s, 3H), 1.82 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.4, 166.2, 164.8, 156.6, 155.4, 155.3, 140.9, 139.2, 137.6, 132.8, 124.1, 123.0, 120.6, 120.1, 117.0, 112.4, 110.4, 104.1, 56.2, 35.4, 27.7, 10.3 ppm; HRMS (ESI, m/z) 451.1264 calcd for $C_{25}H_{20}N_2O_5$ (M + Na) found 451.1261. Analysis calcd for $C_{25}H_{20}N_2O_5$: C, 70.08; H, 4.71; N, 6.54; Found C, 70.07; H, 4.69; N, 6.51.

3-(5-Acetyl-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazol-6-yl)-8-ethoxy-2*H*-chromen-2-one **6e**

Yield 89% (641 mg), Mp 142.7 °C, R_f 0.22 (1:1 hexane–EtOAc), IR (KBr) υ_{max} 3211, 3031, 2998, 1749, 1697, 1618, 1450, 1319, 1021, 991, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.23 (s, 1H), 8.56 (s, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7.60 (t, J = 7.2 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.34 (t, J = 7.6 Hz, 1H), 6.80 (dd, J = 4.2 Hz, 1.2 Hz, 1H), 6.73 (m, 3H), 5.38 (s, 1H), 4.24 (q, J = 6.8 Hz, 2H), 2.56 (s, 3H), 1.95 (s, 3H), 1.43 (t, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.4, 163.7, 159.5, 156.1, 148.7, 142.2, 140.1, 138.3, 126.7, 126.2, 124.5, 123.7, 121.5, 118.3, 117.5, 112.3, 109.4, 107.8, 102.1, 58.1, 37.2, 26.3, 14.9, 13.3 ppm; HRMS (ESI, m/z) 465.1421 calcd for $C_{26}H_{22}N_2O_5$ (M + Na) found 465.1419. Analysis calcd for $C_{26}H_{22}N_2O_5$: C, 70.58; H, 5.01; N, 6.33; Found C, 70.56; H, 4.98; N, 6.31.

3-(5-Acetyl-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazol-6-yl)-6,8-dichloro-2*H*-chromen-2-one **6f**

Yield 75% (570 mg), Mp 148.5 °C, R_f 0.32 (4:6 hexane–EtOAc), IR (KBr) υ_{max} 3213, 3029, 1751, 1691, 1619, 1450, 1319, 1022, 979, 716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.26 (s, 1H), 8.29 (s, 1H), 7.96 (d, J = 8.4 Hz, 1H), 7.53 (t, J = 8.4 Hz, 1H), 7.30–7.28 (m, 3H), 7.00 (s, 1H), 6.84 (s, 1H), 5.38 (s, 1H), 2.46 (s, 3H), 1.88 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.4, 163.7, 159.8, 154.0, 144.0, 142.2, 139.5, 132.6, 131.1, 128.3, 126.4, 124.3, 123.8, 122.2, 116.8, 116.7, 115.5, 109.8, 107.3, 35.5, 27.8, 13.1 ppm; HRMS (ESI, m/z) 489.0379 calcd for $C_{24}H_{16}Cl_2N_2O_4$ (M + Na) found 489.0377. Analysis calcd for $C_{24}H_{16}Cl_2N_2O_4$: C, 61.69; H, 3.45; N, 5.99; Found C, 61.67; H, 3.43; N, 5.97.

3-(5-Acetyl-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazol-6-yl)-8-bromo-6-chloro-2*H*-chromen-2-one **6 g**

Yield 79% (658 mg), Mp 147.9 °C, R_f 0.31 (4:6 hexane–EtOAc), IR (KBr) υ_{max} 3217, 3034, 1754, 1692, 1621, 1451, 1322, 1025, 982, 724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.27 (s, 1H), 8.28 (s, 1H), 7.96 (d, J = 8.2 Hz, 1H), 7.53 (t, J = 8.4 Hz, 1H), 7.29–7.27 (m, 3H), 7.00 (s, 1H), 6.83 (s, 1H), 5.37 (s, 1H), 2.46 (s, 3H), 1.88 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.2, 163.4, 159.7, 154.0, 144.6, 142.2, 138.4, 132.6, 131.1, 128.3, 125.8, 124.3, 124.2, 122.2, 116.8, 116.7, 115.5, 109.8, 107.2, 35.7, 27.5, 13.1 ppm; HRMS (ESI, m/z) 532.9874 calcd for $C_{24}H_{16}BrClN_2O_4$ (M + Na) found 532.9872. Analysis calcd for $C_{24}H_{16}BrClN_2O_4$: C, 56.33; H, 3.15; N, 5.47; Found C, 56.30; H, 3.14; N, 5.45.

3-(5-Acetyl-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazol-6-yl)-6,8-dibromo-2*H*-chromen-2-one **6h**

Yield 77% (698 mg), Mp 151.3 °C, R_f 0.30 (1:1 hexane–EtOAc), IR (KBr) υ_{max} 3214, 3003, 1747, 1689, 1619, 1454, 1321, 1023, 977, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.29 (s, 1H), 8.36 (s, 1H), 7.98 (d, J = 8.2 Hz, 1H), 7.54 (t, J = 8.4 Hz, 1H), 7.30–7.28 (m, 3H), 7.00 (s, 1H), 6.85 (s, 1H), 5.38 (s, 1H), 2.46 (s, 3H), 1.88 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.2, 163.6, 159.7, 154.0, 145.4, 142.2, 138.4, 132.6, 130.9, 128.7, 125.8, 124.3, 124.2, 122.4, 120.8, 119.7, 115.7, 109.2, 107.3, 35.7, 25.7, 13.1 ppm; HRMS (ESI, m/z) 576.9369 calcd for $C_{24}H_{16}Br_2N_2O_4$ (M + Na) found 576.9367. Analysis calcd for $C_{24}H_{16}Br_2N_2O_4$: C, 51.83; H, 2.90; N, 5.04; Found C, 51.80; H, 2.87; N, 5.01.

3-(5-Acetyl-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazol-6-yl)-2*H*-chromen-2-one **6i**

Yield 81% (570 mg), Mp 141.3 °C, R_f 0.25 (1:1 hexane–EtOAc), IR (KBr) υ_{max} 3201, 3012, 1758, 1687, 1620, 1449, 1317, 1018, 978, 716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.20 (s, 1H), 8.48 (s, 1H), 8.10 (d, J = 7.4 Hz, 2H), 7.96 (d, J = 8.2 Hz, 1H), 7.78 (t, J = 7.4 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.08 (d, J = 7.8 Hz, 1H), 5.39 (s, 1H), 2.46 (s, 3H), 1.82 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.4, 163.7, 159.3, 154.5, 151.3, 142.9, 139.2, 129.9, 126.7, 126.5, 124.2, 122.3, 121.4, 118.2, 117.9, 112.5,

109.6, 107.4, 102.4, 37.2, 25.2, 13.3 ppm; HRMS (ESI, m/z) 455.0769 calcd for $C_{24}H_{17}ClN_2O_4$ (M + Na) found 455.0768. Analysis calcd for $C_{24}H_{17}ClN_2O_4$: C, 66.59; H, 3.96; Cl, 8.19; N, 6.47; Found C, 66.57; H, 3.95; N, 6.45.

3-(5-Acetyl-3-methyl-4-(4-nitrophenyl)-1,4-dihydropyrano-[2,3-*c*]pyrazol-6-yl)-2*H*-chromen-2-one **6j**

Yield 70% (505 mg), Mp 142.1 °C, R_f 0.23 (1:1 hexane–EtOAc), IR (KBr) υ_{max} 3212, 3005, 1758, 1695, 1613, 1573, 1454, 1384, 1321, 1025, 982, 724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 12.2 (s, 1H), 8.47 (s, 1H), 8.10 (d, $J = 7.2$ Hz, H), 7.96 (d, $J = 7.8$ Hz, 1H), 7.80 (t, $J = 7.3$ Hz, 1H), 7.48 (d, $J = 8.3$ Hz, 2H), 7.40 (t, $J = 7.52$ Hz, 1H), 7.10 (t, $J = 7.5$ Hz, 1H), 5.39 (s, 1H), 2.42 (s, 3H), 1.88 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.2, 164.1, 160.7, 159.4, 158.3, 156.2, 142.9, 139.4, 129.5, 126.7, 124.0, 123.9, 121.5, 118.1, 116.9, 112.4, 109.1, 108.1, 37.3, 26.4, 13.2 ppm; HRMS (ESI, m/z) 466.1010 calcd for $C_{24}H_{17}N_3O_6$ (M + Na) found 466.1008. Analysis calcd for $C_{24}H_{17}N_3O_6$: C, 65.01; H, 3.86; N, 9.48; Found C, 65.00; H, 3.84; N, 9.46.

3-(5-Acetyl-4-(4-(dimethylamino)phenyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazol-6-yl)-2*H*-chromen-2-one **6k**

Yield 93% (666 mg), Mp 149.5 °C, R_f 0.26 (1:1 hexane–EtOAc), IR (KBr) υ_{max} 3211, 3001, 2861, 1761, 1690, 1620, 1451, 1314, 1025, 976, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.24 (s, 1H), 8.59(s, 1H), 7.82 (d, $J = 7.4$ Hz, 1H), 7.61(t, $J = 6.8$ Hz, 1H), 7.41(d, $J = .4$ Hz, 2H), 7.39(t, $J = 7.2$ Hz, 1H), 6.82(d, $J = 6.8$ Hz, 2H), 6.75(t, $J = 7.2$ Hz, 1H), 5.38 (s, 1H), 3.33(s, 6H), 2.33(s, 3H), 1.89 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 164.1, 159.6, 154.4, 151.0, 143.4, 139.2, 129.3, 126.8, 126.1, 124.6, 123.5, 122.6, 119.0, 116.1, 111.7, 108.4, 108.1, 101.0, 43.9, 36.5, 26.7, 13.10 ppm; HRMS (ESI, m/z) 464.1581 calcd for $C_{26}H_{23}N_3O_4$ (M + Na) found 464.1579. Analysis calcd for $C_{26}H_{23}N_3O_4$: C, 70.73; H, 5.25; N, 9.52; Found C, 70.71; H, 5.22; N, 9.53.

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