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Microwave-assisted one-pot synthesis of pyrazolyl-substituted benzochroman-4-one derivatives and evaluation of their anticancer activity

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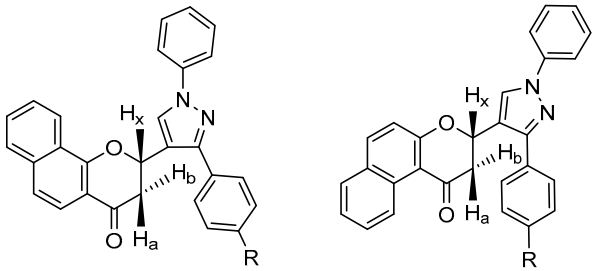


Hybrid compounds containing both flavanone and pyrazole moieties have been synthesized from acetylnaphthols and pyrazole-4-carbaldehydes in good yields using microwave irradiation in a one-step procedure. The synthesized compounds were evaluated for their anticancer activity against four human cancer cell lines.

Keywords: 1-(1-hydroxynaphthalen-2-yl)ethanone, 1-(2-hydroxynaphthalen-2-yl)ethanone, anticancer activity, microwave irradiation.

Pyrazole, a five-membered aromatic nitrogen heterocycle forms a part of the structure of several natural products and drugs.[1–3] Pyrazole derivatives are known to possess antimicrobial,[4] antiviral,[3] antitumor,[5,6] antihypertensive,[7] antidepressant,[8] insecticidal,[9] antifungal,[10] 5α-reductase inhibitory,[11] antiproliferative,[12] antiparasitic,[13] herbicidal,[14] anti-inflammatory,[15,16] antiprotozoal,[17] analgesic,[16] and androgen receptor modulatory[18] activities. The pyrazole ring is present as the core in a variety of leading drugs such as lonazolac,[19] rimonabant (Fig. 1).[20]

Flavanoids are a group of common and naturally occurring compounds that are widely found in the plant kingdom.[21] They occur naturally as plant pigments in many fruits and vegetables, as well as beverages, such as tea, red wine, coffee, and beer.[22] Natural and synthetic flavanones have attracted considerable attention because of their broad spectrum of biological activities[23] including antimycobacterial, antimicrobial, antilung cancer, antibacterial, antiproliferative, antituberculosis, antifungal, antiarrhythmic, antiviral, antihypertensive, antioxidant, anti-inflammatory. Flavanoids, such as eriodictyol and pinocembrin are associated with reduced risk of certain chronic diseases.[24] Natural flavanones (chromen-4-ones) isolated from flowers of *Chromolaena odorata*, such as 4'-hydroxy-5,6,7-trimethoxyflavanone are reported to have antimycobacterial activity (Fig. 1).[25] Flavanones are generally synthesized by cyclization of 2'-hydroxychalcones in acetic acid, ethanol, or other suitable solvent in the presence of an acid catalyst such as sulfuric acid,[26] polyphosphoric acid,[27] or basic reagents, such as pyridine,[28] DBU,[29] and TEA,[30] or a neutral reagent such as DMFDMA,[31] under conventional heating or microwave irradiation.

Microwave (MW) irradiation is known to provide enhanced reaction rate and improved product yield in organic synthesis, and its application has been quite successful in the formation of a variety of carbon–heteroatom bonds. In recent years, microwaves have been extensively applied to different chemical reactions as a useful non-conventional energy source.[32, 33]

In present work, we have synthesized some new 2-(pyrazol-4-yl)flavanones in one step from acetyl-(hydroxy)naphthalenes and pyrazole aldehydes using microwave irradiation. All synthesized compounds have been tested for their *in vitro* anticancer activity as a part of the search for new anticancer drugs.

When 1-(1-hydroxynaphthalen-2-yl)ethanone (**1**) was reacted with 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde (**2a**) in ethanol in the presence of pyrrolidine as base the expected

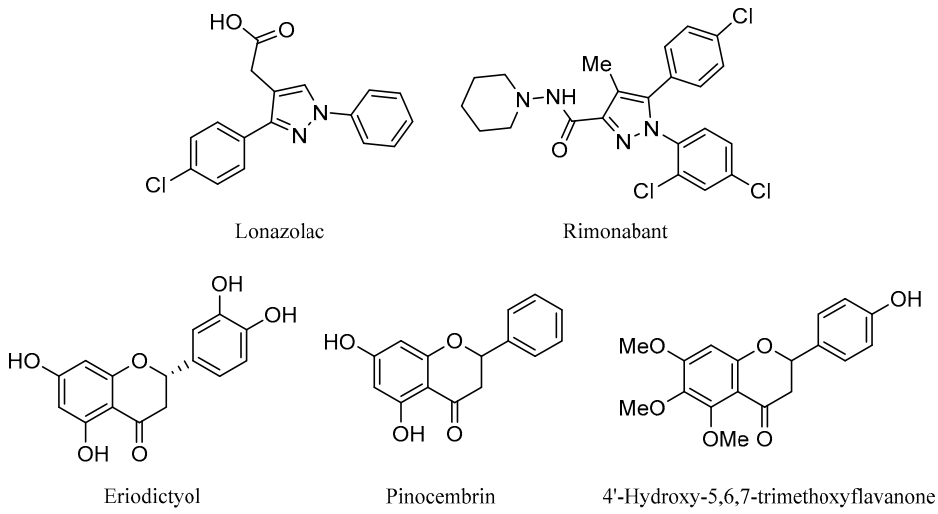


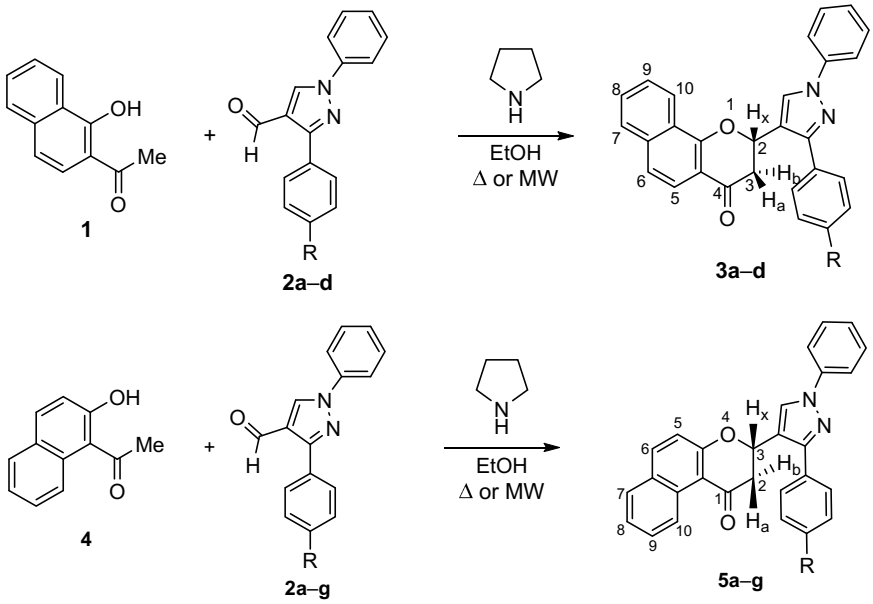
Figure 1. Structures of some biologically active pyrazoles and flavanoids.

corresponding 2'-hydroxychalcone could not be isolated. Instead, the isomeric cyclic product 2-(1,3-diphenyl-1*H*-pyrazol-4-yl)-2,3-dihydro-4*H*-benzo[*h*]chromen-4-one (**3a**), i.e., the corresponding flavanone, was obtained (Scheme 1).

In the IR spectrum of compound **3a**, the characteristic peak was at 1671 cm^{-1} corresponding to a carbonyl group. The ^1H NMR spectrum of flavanone **3a** featured three characteristic signals due to aliphatic protons forming an ABX system (H_a, H_b, and H_x). The H_a proton which is in the *cis* position relative to the H_x proton resonated at 3.08 ppm as a doublet of doublets (J = 3.2 and 16.8 Hz), while the H_b proton which is in the *trans* position relative to the H_x proton was shifted downfield to 3.34 ppm (J = 12.4 and 16.8 Hz). The signal of the H_x proton had the corresponding vicinal constants 3.2 and 12.4 Hz. The formation of a flavanone ring system was further supported by the ^{13}C NMR spectrum of compound **3a**, in which the CH_aH_b and CH_x carbons of the pyrane ring resonated at 55.4 and 66.1 ppm, respectively. These values are in close agreement with the previously reported values for the respective flavanone carbons.[34] The mass spectrum of compound **3a** showed the protonated molecular ion peak at *m*/*z* 417.

Analogously, the reaction of compound **1** with pyrazole aldehydes **2a**–**d** gave flavanones **3a**–**d**. If instead of compound **1** its isomer 1-(2-hydroxynaphthalen-1-yl)-ethanone (**4**) was used flavanones **5a**–**g** with a different ring fusion pattern were produced (Scheme 1). All the synthesized compounds were characterized by elemental and spectral

Scheme 1



2, **3**, **5 a** R = H, **b** R = Me, **c** R = OMe, **d** R = F;
2, **5 e** R = Cl, **f** R = Br, **g** R = NO_2

Table 1. Reaction time and yields for the synthesis of compounds **3a**–**d**, **5a**–**g**

Compound	Conventional heating		MW heating	
	Time, h	Yield, %	Time, min	Yield, %
3a	10	63	6	75
3b	10	69	5	79
3c	11	66	5	86
3d	11	71	5	84
5a	10	62	6	78
5b	10	66	5	82
5c	12	61	6	76
5d	11	69	5	88
5e	11	71	5	86
5f	12	61	7	79
5g	12	59	6	71

Table 2. Anticancer activity of compounds **3a**–**d**, **5a**–**g** (GI_{50}, μM)

Compound	Cell line			
	MCF-7	KB	Colo-205	A-549
3a	<0.1	–*	–	<0.1
3b	1.1	–	1.8	<0.1
3c	4.3	5.9	2.5	–
3d	<0.1	–	<0.1	–
5a	<0.1	–	<0.1	<0.1
5b	<0.1	2.3	2.7	2.9
5c	3.2	4.9	–	13.6
5d	<0.1	–	–	<0.1
5e	–	2.2	–	–
5f	1.6	–	–	2.4
5g	–	16.2	–	16.3
Adriamycin	0.13	0.13	<0.1	<0.1

* En dash represents no activity.

data. The combination of IR, ^{1}H and ^{13}C NMR spectral data provides a strong evidence in support of structures assigned to pyrazole flavanones **3a**–**d** and **5a**–**g**. The synthesis was carried out both under conventional heating and with MW irradiation. The use of MW irradiation produced a much higher reaction yield along with a significant decrease of the reaction time in comparison with conventional heating (Table 1).

The synthesized compounds **3a**–**d**, **5a**–**g** were evaluated for their anticancer activity in selected human breast (MCF-7), oral (KB), colon (Colo-205), and lung (A-549) cancer cell lines by using sulforhodamine B method.[35] The growth inhibition of cancer cell lines was expressed as GI_{50}, which is defined as the concentration for 50% of maximal inhibition of cell proliferation. The compounds that exhibited $GI_{50} \leq 10$ μM were considered to be active against the respective cell lines. All the compounds **3a**–**d**, **5a**–**g** exhibited significant anticancer activity with GI_{50} values ranging from ≤ 0.1 to 16.3 μM, while the positive control, adriamycin demonstrated the GI_{50} in the range of <0.1 to 0.13 μM against the cell lines employed (Table 2). Compound **5b** showed promising anticancer activity against all cell lines, while all the compounds except **5e** and **5g**, showed potent anticancer activity on MCF-7 cell lines. Compounds **5b**,**e** showed a good anticancer activity on KB cell lines, but not as good as that of adriamycin. Compounds **3d** and **5a** have shown potent anticancer activity on Colo-205 cell lines while compounds **3a**, **3b**, **5a** and **5d** showed promising activity against A-549 cell lines. However, in the present case, the activity did not significantly depend on the electronic nature of the compounds. This is evident from the GI_{50} values of compounds **3d** (R = 4-F), **3e** (R = 4-Cl) and **5d** (R = 4-F), **5e** (R = 4-Cl), and **5f** (R = 4-Br), which showed no significant difference in the levels of activity.

A series of some new 2-(pyrazol-4-yl)flavanones have been synthesized by conventional and microwave irradiation methods. These compounds were evaluated for their anticancer activity against four human cancer cell lines (breast, oral, colon, and lung). Majority of compounds showed potent activity, which is comparable with reference drug adriamycin. Thus, the they can be considered as lead compounds for further development of more potent anticancer agents.

Experimental

IR spectra were recorded in KBr on a Shimadzu FTIR 8400S spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance II 400 spectrometer (400 and 100 MHz, respectively) in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Shimadzu LCMS-2020 mass spectrometer. The elemental analysis was carried out on a Vario-11 CHN analyzer. Melting points were determined in open glass capillaries on a Stuart SMP30 apparatus and are uncorrected. Purity of the compounds was checked by TLC on silica gel 60 F254 plates (Merck). All the microwave irradiation experiments were performed in a multiSYNTH series microwave system (Milestone). The cell cultures were supplied by the National Center for Cell Science, Pune, and other apparatus used for carrying out anticancer activity were supplied by Sri Venkateswara Enterprizes. Pyrazole aldehydes **2a**–**g**[36–38] were prepared according to a literature procedure.[36] All solvents and chemicals were obtained commercially, mostly from Sigma-Aldrich, and were used without further purification.

Synthesis of 2-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)-2,3-dihydro-4*H*-benzo[*h*]chromen-4-ones 3a–d and 3-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)-2,3-dihydro-1*H*-benzo[*f*]chromen-1-ones 5a–g (General method). I (Conventional heating). A mixture of 1-(1-hydroxynaphthalen-2-yl)ethanone (**1**) or 1-(2-hydroxynaphthalen-1-yl)ethanone (**4**) (1.86 g, 0.01 mol) and pyrazole aldehyde **2a**–**g** (0.01 mol) in the presence of pyrrolidine (0.7 g, 0.01 mol) in ethanol (20 ml) was refluxed for 10–12 h (Table 1). The progress of the reaction was monitored by TLC (hexane–EtOAc, 7:3). After completion of the reaction, the reation mixture was poured onto crushed ice, and the separated solid was filtered off, washed with water, and recrystallized from methanol to afford a pale-yellow crystalline product.

II (Microwave irradiation). A mixture of 1-(1-hydroxynaphthalen-2-yl)ethanone (**1**) or 1-(2-hydroxynaphthalen-1-yl)ethanone (**4**) (218 mg, 0.01 mol) and pyrazole aldehyde **2a**–**g** (0.01 mol) in the presence of pyrrolidine (0.7 g, 0.01 mol) in ethanol (5 ml) was taken in a quartz tube, inserted into a screw-capped teflon vial, and subjected to microwave irradiation at 180 W for 5–7 min (Table 1). After completion of the reaction (as indicated by TLC, hexane–EtOAc, 7:3), the reaction mixture was worked up as above.

2-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-2,3-dihydro-4*H*-benzo-[*h*]chromen-4-one (3a). Mp 246–248°C. IR spectrum, ν, cm^{-1}: 3058 (C–H Ar), 1671 (C=O), 1626 (C=C), 1573 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.08 (1H, dd, *J* = 3.2, *J* = 16.8, 3-CH_a); 3.34 (1H, dd, *J* = 12.4, *J* = 16.8, 3-CH_b); 5.88 (1H, dd, *J* = 3.2, *J* = 12.4, 2-CH_x); 7.30–7.52 (7H, m, H Ar); 7.58–7.64 (1H, m, H Ar); 7.75–7.86 (5H, m, H Ar); 7.91 (1H, d, *J* = 8.8, H Ar); 8.16 (1H, s, H pyrazole); 8.20 (2H, d, *J* = 8.4, H Ar). ^{13}C NMR spectrum, δ, ppm: 55.4 (C-3); 66.1 (C-2); 110.3; 113.7; 114.1; 114.4; 114.5; 115.1; 117.5; 121.4; 123.8; 125.9; 129.2 (2C); 130.0; 132.3; 137.2; 144.7; 151.2; 158.3; 160.9; 163.9; 172.7; 186.1 (C-4). Mass spectrum, *m*/*z* (I_{rel}, %): 417 $[M+H]^+$ (100). Found, %: C 80.72; H 4.89; N 6.70. $C_{28}H_{20}N_2O_2$. Calculated, %: C 80.75; H 4.84; N 6.73.

2-[3-(4-Methylphenyl)-1-phenyl-1*H*-pyrazol-4-yl]-2,3-dihydro-4*H*-benzo[*h*]chromen-4-one (3b). Mp 264–266°C. IR spectrum, ν, cm^{-1}: 3063 (C–H Ar), 1663 (C=O), 1622 (C=C), 1570 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.39 (3H, s, CH_3); 3.12 (1H, dd, *J* = 3.2, *J* = 16.8, 3-CH_a); 3.37 (1H, dd, *J* = 12.2, *J* = 16.8, 3-CH_b); 5.89 (1H, dd, *J* = 3.2, *J* = 12.2, 2-CH_x); 7.24 (2H, d, *J* = 8.0, H Ar); 7.33–7.37 (1H, m, H Ar); 7.47–7.54 (4H, m, H Ar); 7.63–7.67 (1H, m, H Ar); 7.74–7.85 (5H, m, H Ar); 7.93–7.95 (1H, d, *J* = 8.0, H Ar); 8.19 (1H, s, H pyrazole); 8.25 (1H, d, *J* = 7.6, H Ar). ^{13}C NMR spectrum, δ, ppm: 21.4 (CH_3); 44.6 (C-3); 72.5 (C-2); 114.1; 118.2, 119.1; 119.2; 121.5, 122.3, 123.2, 124.5, 125.3; 126.1; 127.3; 128.0; 128.2; 129.4; 131.3; 132.5; 133.4; 137.3; 140.1; 152.1; 163.4; 184.5 (C-4). Mass spectrum, *m*/*z* (I_{rel}, %): 431 $[M+H]^+$(100). Found, %: C 80.95; H 5.19; N 6.56. $C_{29}H_{22}N_2O_2$. Calculated, %: C 80.91; H 5.15; N 6.51.

2-[3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl]-2,3-dihydro-4*H*-benzo[*h*]chromen-4-one (3c). Mp 256–258°C. IR spectrum, ν, cm^{-1}: 3060 (C–H Ar), 1658 (C=O), 1625 (C=C), 1574 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.09 (1H, dd, *J* = 3.6, *J* = 17.2, 3-CH_a); 3.34 (1H, dd, *J* = 12.8, *J* = 17.2, 3-CH_b); 3.81 (3H, s, OCH_3); 5.86 (1H, dd, *J* = 3.6, *J* = 12.8, 2-CH_x); 6.94 (2H, d, *J* = 8.6, H Ar); 7.30–7.34 (1H, m, H Ar); 7.45–7.50 (4H, m, H Ar); 7.62 (1H, d, *J* = 8.4, H Ar); 7.77–7.83 (5H, m, H Ar); 7.92 (1H, d, *J* = 8.8, H Ar); 8.16 (1H, s, H pyrazole); 8.24 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 42.5 (C-3); 55.3 (OCH_3); 72.8 (C-2); 114.2; 115.6; 118.8; 119.3; 121.4; 121.7; 123.5; 124.9; 125.1; 126.4; 126.8; 127.0 (2C); 127.9; 129.5; 129.7; 137.6; 139.7; 152.0; 159.5; 159.9; 191.5 (C-4). Mass spectrum, *m*/*z* (I_{rel}, %): 447 $[M+H]^+$ (100). Found, %: C 78.03; H 4.94; N 6.24. $C_{29}H_{22}N_2O_3$. Calculated, %: C 78.01; H 4.97; N 6.27.

2-[3-(4-Fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-2,3-dihydro-4*H*-benzo[*h*]chromen-4-one (3d). Mp 260–262°C. IR spectrum, ν, cm^{-1}: 3048 (C–H Ar), 1658 (C=O), 1622 (C=C), 1568 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.08 (1H, dd, *J* = 3.0, *J* = 16.8, 3-CH_a); 3.22 (1H, dd, *J* = 11.5, *J* = 16.4, 3-CH_b); 5.72 (1H, dd, *J* = 3.0, *J* = 11.5, 2-CH_x); 7.02–7.12 (2H, m, H Ar); 7.31–7.49 (7H, m, H Ar); 7.59–7.62 (2H, m, H Ar); 7.73 (2H, d, *J* = 7.7, H Ar); 8.04 (1H, s, H pyrazole); 8.28 (2H, d, *J* = 8.8, H Ar). ^{13}C NMR spectrum, δ, ppm: 42.5 (C-3); 71.9 (C-2); 112.0; 112.2; 118.4; 119.3; 119.9; 121.5; 122.5; 122.8; 123.8; 124.0; 126.2; 126.9; 127.1; 127.6; 129.5; 131.2; 133.2; 134.3; 139.4; 146.3; 156.3; 157.2; 158.7; 191.0 (C-4). Mass spectrum, *m*/*z* (I_{rel}, %): 435 $[M+H]^+$ (100). Found, %: C 77.38; H 4.43; N 6.41. $C_{28}H_{19}FN_2O_2$. Calculated, %: C 77.41; H 4.41; N 6.45.

3-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-2,3-dihydro-1*H*-benzo-[*f*]chromen-1-one (5a). Mp 244–246°C. IR spectrum, ν, cm^{-1}: 3053 (C–H Ar), 1658 (C=O), 1624 (C=C), 1570 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.11 (1H, dd, *J* = 3.2, *J* = 16.8, 2-CH_a); 3.42 (1H, dd, *J* = 12.4, *J* = 16.8, 2-CH_b); 5.81 (1H, dd, *J* = 3.2, *J* = 12.4, 3-CH_x); 7.21 (1H, d, *J* = 9.2, H Ar); 7.38–7.84 (13H, m, H Ar); 7.99 (1H, d, *J* = 8.8, H Ar); 8.19 (1H, s, H pyrazole); 9.50 (1H, d, *J* = 8.8, H Ar). ^{13}C NMR spectrum, δ, ppm: 44.5 (C-3); 72.0 (C-2); 112.8; 118.7; 119.1; 119.3 (2C); 122.8, 124.9; 125.3; 126.8 (2C); 126.9; 128.3; 128.6; 129.4; 129.6; 131.6; 132.7; 132.8; 137.6; 139.9 (2C); 152.3; 163.2; 192.6 (C-4). Mass spectrum, *m*/*z* (I_{rel}, %): 417 $[M+H]^+$ (100). Found, %: C 80.70; H 4.88; N 6.71. $C_{28}H_{20}N_2O_2$. Calculated, %: C 80.75; H 4.84; N 6.73.

3-[3-(4-Methylphenyl)-1-phenyl-1*H*-pyrazol-4-yl]-2,3-dihydro-1*H*-benzo[*f*]chromen-1-one (5b). Mp 247–249°C. IR spectrum, ν, cm^{-1}: 3050 (C–H Ar), 1657 (C=O), 1620 (C=C), 1568 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.40 (3H, s, CH_3); 3.13 (1H, dd, *J* = 3.6, *J* = 16.4, 2-CH_a); 3.36 (1H, dd, *J* = 12.8, *J* = 16.4, 2-CH_b); 5.79 (1H, dd, *J* = 3.6, *J* = 12.8, 3-CH_x); 7.23 (1H, d, *J* = 9.2, H Ar); 7.25–7.30 (2H, m, H Ar); 7.31–7.38 (1H, m, H Ar); 7.51–7.81 (9H, m, H Ar); 7.99 (1H, d, *J* = 8.8, H Ar); 8.18 (1H, s, H pyrazole); 9.52 (1H, d, *J* = 8.4, H Ar). ^{13}C NMR spectrum, δ, ppm: 21.2 (CH_3); 44.5 (C-3); 72.1 (C-2); 112.7; 118.7; 119.0; 119.2; 124.9; 125.9; 126.7; 126.8; 128.2; 128.3; 129.3; 129.4; 129.7; 129.8; 131.5; 137.5 (2C); 138.2; 139.9; 152.1; 163.3; 192.7 (C-4). Mass spectrum, *m*/*z* (I_{rel}, %): 431 $[M+H]^+$ (100). Found, %: C 80.88; H 5.18; N 6.48. $C_{29}H_{22}N_2O_2$. Calculated, %: C 80.91; H 5.15; N 6.51.

3-[3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl]-2,3-dihydro-1*H*-benzo[*f*]chromen-1-one (5c). Mp 260–262°C. IR spectrum, ν, cm^{-1}: 3045 (C–H Ar), 1661 (C=O), 1623 (C=C), 1568 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.14 (1H, dd, *J* = 3.6, *J* = 16.4, 2-CH_a); 3.39 (1H, dd, *J* = 12.4, *J* = 16.4, 2-CH_b); 3.85 (3H, s, OCH_3); 5.79 (1H, dd, *J* = 3.6, *J* = 12.4, 3-CH_x); 6.98–6.99 (2H, m, H Ar); 7.21 (1H, d, *J* = 9.2, H Ar); 7.35 (1H, t, *J* = 7.4, H Ar); 7.52–7.82 (9H, m, H Ar); 7.99 (1H, d, *J* = 8.8, H Ar); 8.17 (1H, s, H pyrazole); 9.51 (1H, d, *J* = 8.4, H Ar). ^{13}C NMR spectrum, δ, ppm: 44.7 (C-3); 55.4

(OCH_3); 72.5 (C-2); 113.1; 114.2; 114.5; 118.8; 119.1; 119.2; 119.4; 125.1; 125.6; 126.1; 126.8; 126.9; 128.4; 129.4; 129.8; 131.8; 137.5; 140.2; 151.1; 160.3; 163.4; 192.6 (C-4). Mass spectrum, *m*/*z* (I_{rel}, %): 447 $[M+H]^+$ (100). Found, %: C 77.71; H 4.93; N 6.23. $C_{29}H_{22}N_2O_3$. Calculated, %: C 78.01; H 4.97; N 6.27.

3-[3-(4-Fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-2,3-dihydro-1*H*-benzo[*f*]chromen-1-one (5d). Mp 264–266°C. IR spectrum, ν, cm^{-1}: 3054 (C–H Ar), 1658 (C=O), 1621 (C=C), 1576 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.10 (1H, dd, *J* = 3.2, *J* = 16.8, 2-CH_a); 3.38 (1H, dd, *J* = 12.8, *J* = 16.8, 2-CH_b); 5.78 (1H, dd, *J* = 3.2, *J* = 12.8, 3-CH_x); 7.19 (1H, d, *J* = 8.8, H Ar); 7.35–7.37 (1H, m, H Ar); 7.68–7.88 (11H, m, H Ar); 7.98 (1H, d, *J* = 8.6, H Ar); 8.17 (1H, s, H pyrazole); 9.53 (1H, d, *J* = 8.4, H Ar). ^{13}C NMR spectrum, δ, ppm: 44.4 (C-3); 71.8 (C-2); 118.6; 119.0; 119.4; 121.5; 124.3; 125.9; 126.0; 127.2; 127.3; 128.4; 128.9; 129.5; 129.6; 130.8; 131.2; 131.7; 134.6; 137.7; 139.6; 140.2, 150.1; 163.1; 192.5 (C-4). Mass spectrum, *m*/*z* (I_{rel}, %): 435 $[M+H]^+$ (100). Found, %: C 77.43; H 4.44; N 6.42. $C_{28}H_{19}FN_2O_2$. Calculated, %: C 77.41; H 4.41; N 6.45.

3-[3-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-2,3-dihydro-1*H*-benzo[*f*]chromen-1-one (5e). Mp 250–252°C. IR spectrum, ν, cm^{-1}: 3065 (C–H Ar), 1664 (C=O), 1624 (C=C), 1573 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.07 (1H, dd, *J* = 3.6, *J* = 16.8, 2-CH_a); 3.35 (1H, dd, *J* = 12.8, *J* = 16.8, 2-CH_b); 5.74 (1H, dd, *J* = 3.6, *J* = 12.8, 3-H_x); 7.17 (1H, d, *J* = 9.6, H Ar); 7.32-7.34 (1H, m, H Ar); 7.54–7.80 (11H, m, H Ar); 7.97 (1H, d, *J* = 9.2, H Ar); 8.16 (1H, s, H pyrazole); 9.48 (1H, d, *J* = 8.4, H Ar). ^{13}C NMR spectrum, δ, ppm: 44.3 (C-3); 71.8 (C-2); 118.7; 119.1; 119.3; 122.4; 123.8; 125.0; 125.9; 127.0; 127.1; 128.3; 128.8; 129.4; 129.5; 129.7; 131.2; 131.5; 134.5; 137.6; 139.7; 150.9; 163.0; 192.4 (C-4). Mass spectrum, *m*/*z* (I_{rel}, %): 451 $[M+H]^+$ (100). Found, %: C 74.54; H 4.21; N 6.19. $C_{28}H_{19}ClN_2O_2$. Calculated, %: C 74.58; H 4.25; N 6.21.

3-[3-(4-Bromophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-2,3-dihydro-1*H*-benzo[*f*]chromen-1-one (5f). Mp 273–275°C. IR spectrum, ν, cm^{-1}: 3055 (C–H Ar), 1664 (C=O), 1625 (C=C), 1575 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.09 (1H, dd, *J* = 3.6, *J* = 16.4, 2-CH_a); 3.35 (1H, dd, *J* = 12.4, *J* = 16.4, 2-CH_b); 5.74 (1H, dd, *J* = 3.6, *J* = 12.4, 3-CH_x); 7.16 (1H, d, *J* = 9.2, H Ar); 7.35 (1H, t, *J* = 7.4, H Ar); 7.52–7.96 (11H, m, H Ar); 7.99 (1H, d, *J* = 8.8, H Ar); 8.14 (1H, s, H pyrazole); 9.47 (1H, d, *J* = 8.4, H Ar). ^{13}C NMR spectrum, δ, ppm: 44.3 (C-3); 71.8 (C-2); 112.8; 118.5; 119.0; 119.3; 122.8; 122.3, 124.6, 125.0; 125.9; 127.0; 127.1; 128.3; 129.4; 129.7; 129.8; 131.8; 137.6; 139.7 (2C); 150.9; 163.0; 192.3 (C-4). Mass spectrum, *m*/*z* (I_{rel}, %): 497 $[M+H]^+$ (100). Found, %: C 67.86; H 3.90; N 5.63. $C_{28}H_{19}BrN_2O_2$. Calculated, %: C 67.89; H 3.87; N 5.66.

3-[3-(4-Nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-2,3-dihydro-1*H*-benzo[*f*]chromen-1-one (5g). Mp 245–247°C. IR spectrum, ν, cm^{-1}: 3054 (C–H Ar), 1656 (C=O), 1628 (C=C), 1578 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.10 (1H, dd, *J* = 2.8, *J* = 16.8, 2-CH_a); 3.65 (1H, dd, *J* = 13.6, *J* = 16.8, 2-CH_b); 6.01 (1H, dd, *J* = 2.8, *J* = 13.6, 3-CH_x); 7.24 (1H, d, *J* = 8.8, H Ar); 7.42–7.68 (5H, m, H Ar); 7.96–8.15 (6H, m, H Ar); 8.32 (2H, d, *J* = 8.8, H Ar); 9.0 (1H, s, H pyrazole); 9.38 (1H, d, *J* = 8.4, H Ar). ^{13}C NMR spectrum, δ, ppm: 44.8 (C-3); 72.6 (C-2); 112.6; 118.8; 119.5; 120.6, 121.8; 122.9; 125.2; 125.7;126.3; 127.1; 127.2; 128.4; 129.4; 129.5; 129.7; 132.1; 133.2; 137.9; 139.9; 159.9; 163.2; 192.6 (C-4). Mass spectrum, *m*/*z* (I_{rel}, %): 462 $[M+H]^+$ (100). Found, %: C 72.85; H 4.18; N 8.81. $C_{28}H_{19}N_3O_4$. Calculated, %: C 72.88; H 4.15; N 9.11.

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