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Microwave Synthesis and Biological Evaluation of Coumarins Substituted Furylpyrazolylpyrazoline

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Some new furaylpyrazolylpyrazoline substituted coumarins were synthesized under microwave irradiation. Target compounds were obtained by cyclization of coumarin chalcones with various substituted hydrazine hydrate and arylhydrazines to give the corresponding pyrazoline by Michael addition reaction (1,4-addition on α,β-unsaturated carbonyl group). Establishment of the structure of the synthesized compounds were based on ^{1}H NMR, ^{13}C NMR, IR, mass spectrometry and elemental analysis data. The synthesized compounds were screened for antibacterial *in vitro* against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Salmonella typhi* (bacteria) and *Aspergillus niger*, *Candida albicans* (fungi) and some of the compounds are acted as potential antimicrobials.

Keywords: Pyrazoline substituted coumarins, Furaylpyrazolyl aldehyde, Antimicrobial activity.

INTRODUCTION

During the last decade, the microwave assisted organic synthesis has revolutionized organic syntheses. Microwave reaction significantly accelerated the organic reactions and shortened the reaction time from days or hours to minutes as well as improved yield and selectivity [1-3]. Synthesis of heterocycles is one of the most broadly used areas in the microwave chemistry. The coumarins are heterocyclic compounds belonging to the class of benzopyrone possesses antitumour [4], anti-HIV and anti-platelet aggregation [5]. In addition, pyrazoline is also reported to have considerable biological activities *e.g.* antimicrobial [6] and pyrazoline derivatives are potent anti-inflammatory [7,8], anticancer [8] and antidepressant [9]. On the other hand, furan derivatives are very important heterocycles that exhibit remarkable biological activities such as antibacterial analgesic, anti-inflammatory, antifungal, antitumor avtivities, *etc*. [10].

Considering the significance of pyrazolyl-pyrazoline-substituted coumarins [11], incorporation of furan moiety further in the above said substituted coumarins are expected to show remarkable cytotoxic activities in the form of multiple heterocyclic based hybrids and thus various furanylpyrazolyl-pyrazoline substituted coumarins were synthesized in this work using microwave reaction.

EXPERIMENTAL

The microwave reactions were performed on a Raga electromagnetic system. 3-Acetylcoumarin and 8-methoxy-3-acetylcoumarin [12-14] and 3-(furan-2-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde [15] were synthesized according to the procedures as described in the literature.

Synthesis of 3-[3-(1-phenyl-3-furan-1*H*-pyrazol-4-yl)-acryloyl]coumarin (1a-b): In a 100 mL round bottom flask, a mixture of 3-acetylcoumarin (0.01 mol), 3-(furan-2-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (0.015 mol) in 50 mL ethyl alcohol (solvent) was taken. A catalytic amount of piperidine (1.0 mL) was added to the reaction mixture, stirred at room temperature for 10 min, refluxed in a water bath for 4 h and then cooled at room temperature. The separated solid was filtered, washed with ethanol, dried and recrystallized from absolute ethanol.

Compound 1a (R = H): Yield 78%; m.p.: 222-223 ºC; IR (KBr, ν_{max}, cm^{-1}): 3045, 1722, 1665, 1605, 1535, 685; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.31-8.45 (15H, m, 13 aromatic protons

+ 2 olefinic protons), 8.59 (1H, s, pyrazole ring protons); Anal. calcd. (found) % for $C_{25}H_{16}N_2O_4$: C, 73.52 (73.48); H, 3.95 (3.91); N, 6.86 (6.81).

Compound 1b (R=OCH$_3$): Yield 75%; m.p.: 160 ºC; IR (KBr, ν_{max}, cm^{-1}): 3047, 1725, 1651, 1601, 1540, 755, 685; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 4.1 (3H, singlet, OCH_3), 7.22-8.58 (14H, multiplet, twelve aromatic protons + two olefinic protons), 8.65 (1H, singlet, proton of pyrazole ring); Anal. calcd. (found) % for $C_{25}H_{16}N_2O_4$: C, 73.80 (73.88); H, 4.14 (4.19); N, 6.39 (6.31).

Synthesis of 3-[1-acetyl/propionyl-5-(1-phenyl-3-furan-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-pyrazol-3-yl]coumarins (2a-d): A mixture of 3-[3-(1-phenyl-3-furan-1*H*-pyrazol-4-yl)acryloyl]coumarins (**1a-b**) (0.003 mol), NH_2NH_2 (0.009 mol) in AcOH/CH_3CH_2COOH (8 mL) was stirred at room temperature for 15 min and irradiated in a 240 W microwave oven for 4 min. Then a reaction mixture was poured into water (50 mL) and the solid product was isolated which was filtered, washed with distilled water, dried and then recrystallized from methanol to obtain 3-[1-acetyl/propionyl-5-(1-phenyl-3furan-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-pyrazol-3-yl]coumarins (**2a-d**) (**Scheme-I**).

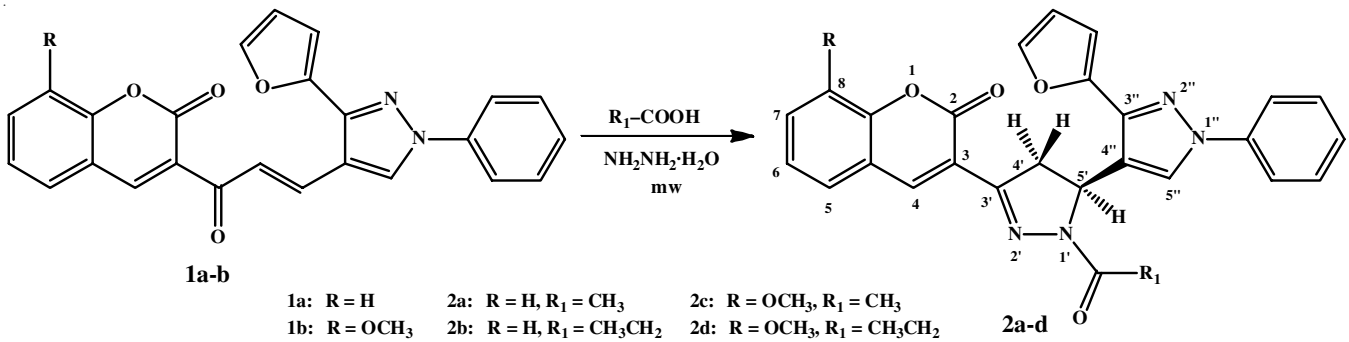
Compound 2a: Yield 82%; m.p.: 241 ºC; IR (KBr, ν_{max}, cm^{-1}): 3022, 2926, 1739, 1654, 1593, 1498; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.28 (3H, >N-CO-C$\underline{H}_3$), 3.28 (1H, dd, *J* = 18.8 & 5.2 Hz, C_4'-H-$_{trans}$), 3.90 (1H, dd, *J* = 18.8 & 12.8 Hz, C_4'-H-$_{cis}$), 5.51 (1H, m, C_5'-H), 7.36-7.90 (12H, m, aromatic protons + C_4-H coumarin proton), 8.60 (1H, s, C_5''-H pyrazole ring proton); ^{13}C NMR (400 MHz, $CHCl_3$) δ ppm: 8.97 (CH_3), 27.74 (CH_2), 44.31 (CH_2), 56.97 (CH), 113.85 (CH), 116.49 (C),118.97 (CH), 119.43 (C), 120.23 (C), 121.89 (C), 124.75 (CH), 125.42 (CH), 125.77 (CH), 126.33 (CH), 126.59 (CH), 127.74 (CH), 128.21 (CH), 129.15 (CH), 129.32 (C), 129.55 (CH), 131.67 (CH), 137.96 (C), 143.57 (C), 143.77 (C), 159.32 (coumarin CO), 169.21 (>N-$\underline{CO}$-CH_2-CH_3); Anal. calcd. (found) % $C_{27}H_{20}N_4O_4$: C, 69.82 (69.78); H, 4.34 (4.38); N, 12.06 (12.09).

Compound 2b: Yield 85%; m.p.: 221-223 ºC; IR (KBr, ν_{max}, cm^{-1}): 3048, 2935, 1735, 1666, 1600, 1501; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.06 (3H, t, *J* = 7.2 Hz, -$CH_2C\underline{H}_3$), 2.70 (2H, m, -$C\underline{H}_2CH_3$), 3.27 (1H, dd, *J* = 18.8 & 5.6 Hz, C_4'-H-$_{trans}$), 3.88 (1H, dd, *J* = 18.8 & 12.4 Hz, C_4'-H-$_{cis}$), 5.50 (1H, m, C_5'-H), 7.36-7.89 (13H, m, aromatic protons + C_4-H coumarin proton), 8.59 (1H, singlet, C_5''-H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 8.97 (CH_3), 27.74 (CH_2), 44.31 (CH_2), 56.97 (CH), 113.85 (CH), 116.49 (C), 118.97 (CH), 119.43 (C), 120.23 (C), 121.89 (C), 124.75 (CH), 125.42 (CH), 125.77 (CH), 126.33 (CH), 126.59 (CH), 127.74 (CH), 128.21 (CH), 129.15 (CH), 129.32 (C), 129.55 (CH), 131.67 (CH), 137.96 (C), 143.57 (C), 143.77 (C), 159.32 (coumarin CO), 169.21 (>N-$\underline{CO}$-CH_2-CH_3). Anal. calcd. (found) % for $C_{28}H_{22}N_4O_4$: C, 70.28 (70.35); H, 4.63 (5.22); N, 11.71 (12.19).

Compound 2c: Yield 88%; m.p.: 220-222 ºC; IR (KBr, ν_{max}, cm^{-1}): 3030, 2935, 1701, 1650, 1605, 1504; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.27 (3H, s, >N-CO-C$\underline{H}_3$), 3.28 (1H, dd, *J* = 19.4 & 5.2 Hz, C_4'-H-$_{trans}$), 3.87 (1H, dd, *J* = 19.4 & 12.0 Hz, C_4'-H-$_{cis}$), 3.94 (3H, s, OCH_3), 5.51 (1H, m, C_5'-H), 7.32-7.51 (12H, m, aromatic protons + C_4-H coumarin proton), 8.56 (1H, s, C_5''-H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm:17.56 (>N-CO-C$\underline{H}_3$), 44.08 (CH_2), 55.56 (CH), 56.08 (OCH_3), 117.88 (C), 119.24 (CH), 120.15 (C), 123.69 (CH), 124.41 (C), 124.89 (CH), 126.16 (CH), 126.46 (CH), 126.65 (CH), 126.75 (CH), 127.10 (CH), 127.51 (CH), 127.59 (CH), 127.98 (C), 128.86 (CH), 129.60 (CH), 130.54 (C), 142.29 (C), 149.79 (C), 153.17 (C), 159.50 (coumarin CO), 169.86 (>N-$\underline{CO}$-CH_3), 169.39 (>N-$\underline{CO}$-CH_3); Anal. calcd. (found) % for $C_{28}H_{22}N_4O_5$: C, 68.01 (68.08); H, 4.48 (4.58); N, 11.33 (11.22).

Compound 2d: Yield 86%; m.p.: 259 ºC; IR (KBr, ν_{max}, cm^{-1}): 3050, 2920, 1735, 1665; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.05 (3H, t, -$CH_2C\underline{H}_3$, *J* = 7.2 Hz), 2.69 (2H, m, -$C\underline{H}_2CH_3$), 3.24 (1H, dd, *J* = 18.8 &5.6 Hz, C_4'-H-$_{trans}$), 3.85 (1H, dd, *J* = 18.8 & 12.8 Hz, C_4'-H-$_{cis}$), 3.89 (3H, s, OCH_3), 5.46 (1H, m, C_5'-H), 7.01-7.81 (12H, m, aromatic protons + C_4-H coumarin proton), 8.53 (1H, s, C_5''-H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 8.82 (CH_3), 28.82 (CH_2), 43.82 (CH_2), 53.99 (CH), 56.28 (OCH_3), 113.72 (C), 114.65 (C), 116.06 (CH), 117.91 (CH), 119.76 (C), 120.74 (CH), 123.32 (CH), 123.88 (CH), 125.36 (CH), 126.65 (CH), 128.56 (CH), 130.09 (CH), 130.89 (CH), 131.69 (CH), 133.72 (CH), 136.49 (C), 137.29 (C), 138.96 (C), 139.45 (C), 154.59 (C), 159.45 (coumarin CO), 168.59 (>N-$\underline{CO}$-CH_2-CH_3); Anal. calcd. (found) % for $C_{29}H_{24}N_4O_5$; : C, 68.49; H, 4.76; N, 11.02%; found: C, 68.36; H,4.09; N, 11.05%.

Synthesis of 3-[5-(1-phenyl-3-furan-1*H*-pyrazol-4-yl)-1-aryl-4,5-dihydro-1*H*-pyrazol-3-yl]coumarins (4a-f): A mixture of 3-[3-(1-phenyl-3-furan-1*H*-pyrazol-4-yl)acryloyl]-coumarins (**1a-b**) (0.003 mol), $PhNHNH_2$ (0.009 mol) in acetic acid (8 mL) was stirred for 15 min at room temperature and then irradiated in a 240 W microwave oven for 6 min. The reaction mixture was poured onto the crushed ice and filtered the the solid product, washed with water and dried. It is



1a: R = H 2a: R = H, R_1 = CH_3 2c: R = OCH_3, R_1 = CH_3

1b: R = OCH_3 2b: R = H, R_1 = CH_3CH_2 2d: R = OCH_3, R_1 = CH_3CH_2

Scheme-I

recrystallized from methanol to obtain 3-[5-(1-phenyl-3-furan-1*H*-pyrazol-4-yl)-1-aryl-4,5-dihydro-1*H*-pyrazol-3-yl]coumarins **(4a-f)** (**Scheme-II**).

Compound 4a: Yield 81%; m.p.: 230-232 ºC; IR (KBr, ν_{max}, cm^{-1}): 3040, 2924, 1730, 1595, 1497, 750, 690; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.27 (1H, dd, *J* = 18.0 & 7.2 Hz, C_4'-H-*trans*), 3.97 (1H, dd, *J* = 18.0 & 14.4 Hz, C_4'-H-*cis*), 5.53 (1H, m, C_5'-H), 6.79-7.86 (18H, m, Ar-H), 8.50 (1H, s, C_5''-H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 44.80 (CH_2), 55.42 (CH), 115.16 (CH), 115.86 (CH), 116.47 (CH), 117.86 (CH), 118.77 (CH), 119.93 (C), 121.59 (CH), 121.90 (CH), 122.87 (CH), 123.56 (CH), 123.97 (CH), 124.97 (C), 125.47 (CH), 126.27 (CH), 127.02 (C), 127.40 (C), 128.71 (CH), 129.48 (CH), 129.80 (CH), 130.84 (C), 132.10 (C), 137.55 (C), 142.15 (C), 143.58 (C) & 159.95 (coumarin CO); Anal. calcd. (found) % for $C_{31}H_{22}N_4O_3$: C, 74.69 (74.72); H, 4.45 (4.48); N, 11.24 (11.20).

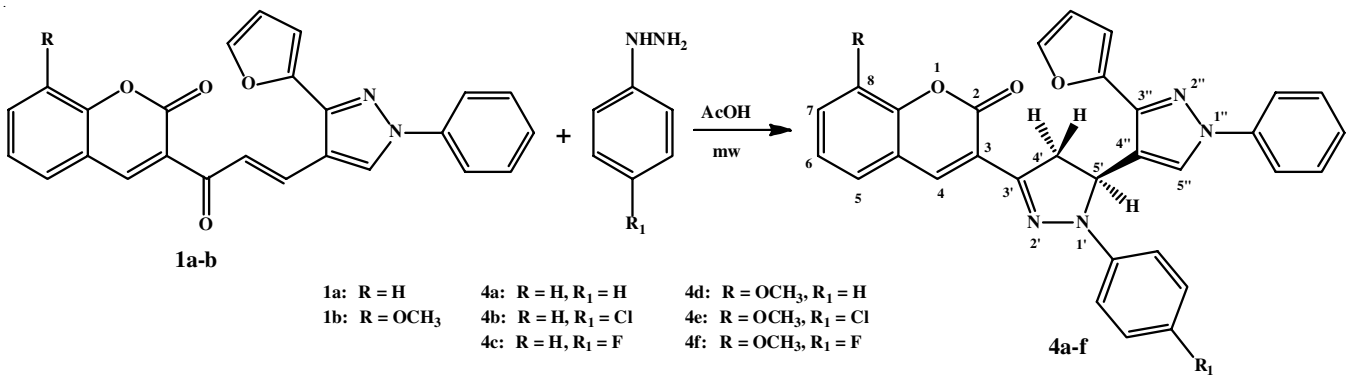
Compound 4b: Yield 85%; m.p.: 160-162 ºC; IR (KBr, ν_{max}, cm^{-1}): 3060, 2928, 1730, 1595, 1498, 825; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.29 (1H, dd, *J* = 18.4 and 6.8 Hz, C_4'-H-*trans*), 3.99 (1H, dd, *J* = 18.4 & 12.4 Hz, C_4'-H-*cis*), 5.53 (1H, m, C_5'-H), 7.05-7.86 (17H, m, aromatic protons + C_4-H coumarin proton), 8.51 (1H, s, C_5''-H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 44.50 (CH_2), 55.45 (CH), 106.92 (CH), 109.03 (C), 110.89 (CH), 112.57 (CH), 114.05 (CH), 114.30 (CH), 115.74 (CH), 119.62 (CH), 120.68 (CH), 121.31 (CH), 123.68 (CH), 125.24 (CH), 126.77 (C), 126.88 (CH), 128.17 (C), 128.53 (C), 128.76 (CH), 128.82 (CH), 130.40 (C), 130.47 (C), 132.64 (C), 134.62 (C), 137.23 (C), 139.04 (C), 161.39 (coumarin CO); Anal. calcd. (found) % for $C_{31}H_{21}N_4O_3Cl$: C, 69.86 (69.81); H, 3.97 (3.99); N, 10.51 (10.59).

Compound 4c: Yield 82%; m.p.: 288-289 ºC; IR (KBr, ν_{max}, cm^{-1}): 3059, 2925, 1725, 1590, 1490, 828; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.27 (1H, dd, *J* = 18.4 & 7.6 Hz, C_4'-H-*trans*), 3.96 (1H, dd, *J* = 18.4 &13.6 Hz, C_4'-H-*cis*), 5.49 (1H, m, C_5'-H), 7.05-7.85 (17H, m, aromatic protons + C_4-H coumarin proton), 8.65 (1H, s, C_5''-H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 44.32 (CH_2), 55.68 (CH), 106.12 (CH), 111.86 (CH), 116.44 (CH), 119.39 (C), 119.61 (CH), 121.12 (C), 121.83 (CH), 123.04 (CH), 123.68 (CH), 124.85 (C), 125.27 (CH), 125.32 (CH), 127.70 (CH), 128.58 (C), 130.01 (CH), 130.18 (CH), 133.23 (CH), 139.34 (C), 141.13 (C), 143.48 (CH), 149.19 (C), 151.65 (C), 153.95 (C), 154.70 (C), 159.83 (coumarin CO); Anal. calcd. (found) % for $C_{31}H_{21}N_4O_3F$: C, 72.08 (72.01); H, 4.10 (4.15); N, 10.85 (10.82).

Compound 4d: Yield 84%; m.p.: 189-190 ºC; IR (KBr, ν_{max}, cm^{-1}): 3045, 2930, 1730, 1595, 1495, 742, 684; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.24 (1H, dd, *J* = 18.0 & 7.2 Hz, C_4'-H-*trans*), 3.91 (3H, s, OCH_3), 3.94 (1H, dd, *J* = 18.0 & 12.4 Hz, C_4'-H-*cis*), 5.46 (1H, m C_5'-H), 6.77-7.77 (17H, m, aromatic protons + C_4-H coumarin proton), 8.49 (1H, s, C_5''-H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 43.62 (CH_2), 54.43 (CH), 56.26 (OCH_3), 109.58 (C), 110.08 (CH), 112.90 (CH), 113.10 (CH), 114.26 (CH), 114.80 (C), 115.77 (CH), 117.64 (CH), 118.56 (C), 119.48 (CH), 121.15 (CH), 124.60 (CH), 124.91 (CH), 127.19 (C), 127.98 (C), 128.84 (C), 129.56 (CH), 129.72 (CH), 131.39 (CH), 140.80 (C), 144.47 (C), 149.23 (C), 155.54 (C), 160.56 (coumarin CO); Anal. calcd. (found) % for $C_{32}H_{24}N_4O_4$: C, 72.72 (72.78); H, 4.58 (4.52); N, 10.60 (10.69).

Compound 4e: Yield 85%; m.p.: 240-241 ºC; IR (KBr, ν_{max}, cm^{-1}): 3068, 2919, 1732, 1601, 1504, 823; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.45 (1H, dd, *J* = 18.4 &7.2 Hz, C_4'-H-*trans*), 4.03 (3H, s, OCH_3), 4.09 (1H, dd, *J* = 18.4 &12.8 Hz, C_4'-H-*cis*), 5.31 (1H, m, C_5'-H), 7.06-7.48 (16H, m, aromatic protons + C_4-H coumarin proton), 8.46 (1H, s, C_5''-H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 43.23 (CH_2), 53.23 (CH), 55.29 (OCH_3), 108.02 (C), 108.58 (CH), 109.67 (C), 110.41 (C), 113.72 (CH), 117.34 (C), 118.59 (C), 120.21 (CH), 123.56 (CH), 125.20 (CH), 126.01 (CH), 126.11 (CH), 127.11 (CH), 127.75 (CH), 128.21 (CH), 128.71 (CH), 134.72 (CH), 136.41 (C), 140.30 (CH), 143.39 (C), 151.36 (C), 153.39 (C), 157.93 (C), 160.61 (coumarin CO); Anal. calcd. (found) % for $C_{32}H_{23}N_4O_4Cl$: C, 68.27 (68.21); H, 4.12 (4.15); N, 9.95 (9.98).

Compound 4f: Yield 84%; m.p.: 238-239 ºC; IR (KBr, ν_{max}, cm^{-1}): 3060, 2918, 1730, 1605, 1506, 825;^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.43 (1H, dd, *J* = 18.0 &7.2 Hz, C_4'-H-*trans*), 3.90 (3H, s, OCH_3), 4.04 (1H, dd, *J* = 18.0 & 12.8 Hz, C_4'-H-*cis*), 5.28 (1H, m, C_5'-H), 6.85-7.52 (16H, m, aromatic protons + C_4-H coumarin proton), 8.35 (1H, s, C_5''-H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 44.83 (CH_2), 53.42 (CH), 56.62 (OCH_3), 115.15 (CH), 115.97 (CH), 116.87 (C), 117.15 (C), 118.27 (CH), 119.18 (CH), 121.5 (CH), 121.99 (CH), 122.97 (CH), 123.22 (CH), 123.87 (CH), 124.18 (C), 125.57 (CH), 126.19 (C), 127.12 (C), 127.56 (C), 128.87 (CH), 129.18 (CH), 129.8 (CH), 130.71 (C), 132.29 (C), 137.30 (C), 142.13 (C), 143.37 (C), 159.43 (CO of coumarin); Anal. calcd. (found) % for



Scheme-II

$C_{32}H_{23}N_4O_4F$: C, 70.32 (70.28); H, 4.24 (4.21); N, 10.25 (10.32).

RESULTS AND DISCUSSION

Various 3-[1-acetyl/propionyl-5-(1-phenyl-3-furan-1*H*-pyrazol-4-yl)-4,5-dihydro-1*H*-pyrazol-3-yl]coumarins (**2a-d**) and 3-[5-(1-phenyl-3-furan-1*H*-pyrazol-4-yl)-1-aryl-4,5-dihydro-1*H*-pyrazol-3-yl]coumarins (**4a-f**) were synthesized using microwave reaction. The structures of all the synthesized compounds were evaluated using IR, ^{1}H NMR, ^{13}C NMR and mass data.

In the IR spectra of compounds **2a-d**, strong bands about 1739 cm^{-1}and 1654 cm^{-1} were found due to elongation of δ-lactone of coumarin ring and elongation of carbonyl of >N-CO-CH_3 group, respectively. The bands observed about 1593 cm^{-1} and 1498 cm^{-1} represent C=C (aromatic) and C=N stretching vibrations, respectively. The compound also exhibited bands around 2926 cm^{-1} and 3022 cm^{-1} due to aliphatic C-H stretching and aromatic C-H stretching, respectively.

^{1}H NMR spectra of compounds **2a-d** in $CDCl_3$ solvent appeared a signal of about at 2.23 δ with integrating over three protons due to the methyl group (> N-CO-C<u>H</u>$_3$). About at 3.28 δ (*J* = 18.8 and 5.2 Hz), doublet of doublet observed for one proton, is due to C_4'-H-$_{trans}$. About 3.90 δ (*J* = 18.8 and 12.8 Hz), doublet of doublet observed for one proton, is due to C_4'-H-$_{cis}$. Around at 5.51 δ, multiplet observed for one proton, is due to C_5'-H. Around at 8.60 δ, the C_5''-H of ring pyrazole observed as a singlet. About at 7.36-7.90 δ, twelve aromatic protons and C_4-H proton of coumarin were merged as a multiplet.

^{13}C APT spectra of compounds **2a-d** in $CDCl_3$ solvent appeared signals about at 17.12-169.12 δ for 25 different types of carbon atoms present in the compound. About at 17.12 δ, signal observed is due to methyl group carbon (>N-CO-C<u>H</u>$_3$). About at 44.48 and 56.93 δ, signals observed are due to C_4' and C_5', respectively. About at 159.83 δ, the signal observed that can be attributed to the carbon of carbonyl of the coumarin ring δ-lactone. About at 169.12 δ, most downfield signal observed that can be attributed to the carbon of carbonyl of > N-CO-CH_3 group of pyrazoline ring nucleus. About at 56.93-133.21 δ, the inverted signals related to thirteen non-equivalent tertiary carbon atoms of the compound.

In mass spectrum of compound **2a**, the M$^+$ peak was detected at 464 (100%), *m/z* (%) and the peaks of some other fragments were detected at 368 (11%), 289 (20%), 91 (55%), 77 (80%), *etc*. A molecular ion peak observed at 464 units confirms the structure of compound **2a.**

In the IR spectra of compounds **4a-f**, strong band at 1730 cm^{-1} were found due to elongation of carbonyl carbon of δ-lactone of coumarin ring. The bands appeared about 1595 cm^{-1} and 1497 cm^{-1} represent C=C and C=N aromatic stretching vibrations, respectively. The strong bands appeared about 690 cm^{-1} and 750 cm^{-1} represent the monosubstituted phenyl ring C-H out of plane bending vibrations. The bands observed about 2924 cm^{-1} and 3040 cm^{-1} due to the aliphatic C-H stretching and aromatic C-H stretching vibrations, respectively.

^{1}H NMR spectra of compounds **4a-f** in $CDCl_3$ solvent observed 3.27 δ (*J* = 18.0 and 7.2 Hz), doublet of doublet centered for one proton due to C_4'-H-$_{trans}$. About at 3.97 δ (*J* = 18.0 and 14.4 Hz, doublet of doublet centered for one proton, is due to C_4'-H-$_{cis}$. About at 5.53 δ, multiplet centered for one proton due to C_5'-H. About at 8.50 δ, C_5''-H of ring pyrazole observed as a singlet. About at 6.79-7.86 δ, seventeen aromatic and C_4-H of coumarin protons merged between as a multiplet.

^{13}C APT spectra of compounds **4a-f** in $CDCl_3$ solvent observed signals at about 44.80 and 55.42 δ are due to C_4' and C_4', respectively. Around at 159.95 δ, the signal observed that can be attributed to the carbon of carbonyl of the δ-lactone of coumarin nucleus.

In the mass spectrum of compound **4a**, M$^+$ peak was detected at 498 (10%) (*m/z*%), 498 units including 471 (15%), 260 (14%), 77 (12%) and 44 (100%). The appearance of molecular ion peaks at 498 mass unit confirms the structure of compound **4a**.

Antimicrobial activity: Compounds **2a-d** and **4a-f** were tested for *in vitro* antibacterial activity against Gram-positive bacteria (*Bacillus subtilis*, MTCC 441), *Staphylococcus aureus*, MTCC 96)) and Gram-negative bacteria (*Escherichia coli*, MTCC 443). Antifungal activity against *Aspergillus niger* (MTCC 282) and *Candida albicans* (MTCC 227) by Broth dilution method [16]. The antimicrobial activity data of the synthesized compounds are shown in Table-1.

Compound **2c** (MIC = 100 μg/mL) was found to be more effective than ampicillin (MIC = 250 μg/mL) and equivalent to norfloxacin (MIC = 100 μg/mL) against Gram-positive bacteria *B. subtilis* when evaluating the antimicrobial activity data. Compounds **2b** and **4f** (MIC = 125 μg/mL) exhibited good activity against Gram-positive bacteria *B. subtilis* compared to ampicillin (MIC = 250 μg/mL). Compounds **2a** and **4d** (MIC = 200 μg/mL) showed moderate activity against ampicillin (MIC = 250 μg/mL) against Gram-positive bacteria *B. subtilis.*

Compounds **2b** (MIC = 100 μg/mL) and **2c** (MIC = 125 μg/mL) excerted the better activity than ampicillin (MIC = 250 μg/mL) against Gram-positive bacteria *S. aureus.* Compounds **2a** and **4d** (MIC = 200 μg/mL) observed moderate activity than ampicillin (MIC = 250 μg/mL) against Gram-positive bacteria *S. aureus*

Compound **4a** (MIC = 50 μg/mL) exhibit good activity against Gram-negative bacteria *E. coli* than ampicillin (MIC = 100 μg/mL) and similar activity to chloramphenicol (MIC = 50 μg/mL). Compounds **4b and 4c** (MIC = 100 μg/mL) and compounds **2a** and **4f** (MIC = 100 μg/mL) observed equivalent activity as ampicillin (MIC = 100 μg/mL) against *E. coli* and *S. typhi,* respectively.

Upon evaluating the antifungal activity data of the target compounds showed that compound **2a** (MIC = 250 μg/mL) was more active against *C. albicans* than griseofulvin (MIC = 500 μg/mL). Compounds **2c** and **4f** (MIC = 500 μg/mL) were equivalent to griseofulvin (MIC = 500 μg/mL) against *C. albicans.* None of the compounds found better activity against *A. niger* than the standard drugs.

Thus, compounds **2c** and **4a** have the maximum antimicrobial effectiveness amongst all the tested compounds.

TABLE-1
ANTIMICROBIAL ACTIVITY OF **2a-d** AND **4a-f** COMPOUNDS

Compound	Minimum inhibitory concentration (MIC, μg mL^{-1})					
	Gram-positive bacteria		Gram-negative bacteria		Fungi	
	Bacillus subtilis	*Staphylococcus aureus*	*Escherichia coli*	*Salmonella typhi*	*Aspergillus niger*	*Candida albicans*
2a	200	200	250	100	>1000	250
2b	125	100	250	250	500	>1000
2c	100	125	250	500	>1000	500
2d	500	500	500	500	>1000	>1000
4a	500	500	50	200	500	1000
4b	500	250	100	200	500	>1000
4c	500	250	100	500	>1000	1000
4d	200	200	200	250	500	1000
4e	500	500	250	500	1000	1000
4f	125	500	200	100	>1000	500
Ampicillin	250	250	100	100	–	–
Chloramphenicol	50	50	50	50	–	–
Ciprofloxacin	50	50	25	25	–	–
Norfloxacin	100	10	10	10	–	–
Gentamycin	1	0.25	0.05	5	–	–
Griseofulvin	–	–	–	–	100	500
Nystatin	–	–	–	–	100	100

Conclusion

The coumarin pyrazoline derivatives clubbed with furan pyrazole moiety were successfully synthesized, characterized and the antimicrobial studies. Screening results showed that all the synthesized compounds possessed moderate to good activities against the pathogenic strains. Compounds **2c** and **4a** have the highest antimicrobial efficacy among all the compounds tested.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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