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Synthesis and characterization of novel 2-(1-benzyl-3-[4-fluorophenyl]-1*H*-pyrazol-4-yl)-7-fluoro-4*H*-chromen-4-one derivatives

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Abstract

Novel 1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazole-4-carbaldehydes **3a** to **3e** were synthesized via Vilsmeier-Haack reaction of the appropriate 1-benzyl-2-(1-(4-fluorophenyl)ethylidene)hydrazines, derived from 4-fluoroacetophenone **1** with substituted 2-benzylhydrazines **2a** to **2e**. The base catalyzed condensation of 1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazole-4-carbaldehydes **3a** to **3e** with 1-(4-fluoro-2-hydroxyphenyl)ethanone **4** gave (*E*)-3-(1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-1-(4-fluoro-2-hydroxyphenyl)prop-2-en-1-ones **5a** to **5e**. On cyclization with dimethyl sulfoxide (DMSO)/I_2, compounds **5a** to **5e** gave 2-(1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-7-fluoro-4*H*-chromen-4-ones **6a** to **6e**. Structures of all novel compounds were confirmed by infrared (IR), proton nuclear magnetic resonance (^{1}H NMR), carbon nuclear magnetic resonance (^{13}C NMR), and mass spectral data. All the synthesized compounds were screened for their antibacterial activities.

1 | INTRODUCTION

Chromones (4*H*-1-benzopyran-4-one, 4*H*-chromen-4-one) are the heterocyclic compound widely distributed in nature.[1] Chromone-containing compounds display various pharmacological properties such as antifungal,[2] antimalarial,[3] anticancer,[4] antibacterial,[5] and are also well known as an antidiabetic and cardiovascular agents.[6,7] Pyrazole-containing compounds show antiangiogenic,[8] antimalarial,[9] antifungal,[10] antitubercular,[11] antimicrobial,[11] and anticancer[12] activities.

Currently, there are more than 200 pharmaceutical drugs available in market containing fluorine atom. Fluorine and fluorine-containing substituent can impart many effects on properties of organic compounds.[13,14] Fluorine-containing compounds exhibit fungicidal,[15] herbicidal,[16] antiviral,[17] antipyretic,[18] and analgesic[19] activities.

Considering the biological importance of chromone, pyrazole, and fluorine nucleus, we have reported the synthesis, characterization, and antibacterial screening of novel 1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazole-4-carbaldehydes **3a** to **3e**, (*E*)-3-(1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-1-(4-fluoro-2-hydroxyphenyl)prop-2-en-1-ones **5a** to **5e** and 2-(1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-7-fluoro-4*H*-chromen-4-one derivatives **6a** to **6e**.

2 | RESULT AND DISCUSSION

1-Benzyl-3-(4-fluorophenyl)-1*H*-pyrazole-4-carbaldehydes **3a** to **3e** were synthesized via the Vilsmeier-Haack reaction of the appropriate 1-benzyl-2-(1-(4-fluorophenyl)ethylidene)hydrazines, derived from 4-fluoroacetophenone **1** with substituted 2-benzylhydrazines **2a** to **2e**.[20] (*E*)-3-(1-Benzyl-3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-1-(4-fluoro-2-hydroxyphenyl)prop-2-en-1-ones **5a** to **5e** were synthesized from the reaction of 1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazole-4-carbaldehydes **3a** to **3e** with 1-(4-fluoro-2-hydroxyphenyl)ethanone **4** in 10% aq. KOH. The synthesis of 2-(1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-

7-fluoro-4*H*-chromen-4-ones **6a** to **6e** was achieved by reaction of (*E*)-3-(1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-1-(4-fluoro-2-hydroxyphenyl)prop-2-en-1-ones **5a** to **5e** with dimethyl sulfoxide (DMSO)/I_2 (Scheme 1 and Section 3).

Structures of all the synthesized compounds were confirmed by using infrared (IR), proton nuclear magnetic resonance (^{1}H NMR), carbon nuclear magnetic resonance (^{13}C NMR), and liquid chromatography-mass spectrometry (LC-MS) spectroscopic techniques.

2.1 | Antibacterial activities

All the synthesized compounds were screened for their antibacterial activities. The bacterial strains *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, and *Pseudomonas aeruginosa* were used. The zone of inhibition in millimeter was determined by the well diffusion method at 1 mg/mL of concentration, and Ampicillin was used as reference drugs. The results of antibacterial activity are shown in Table 1.

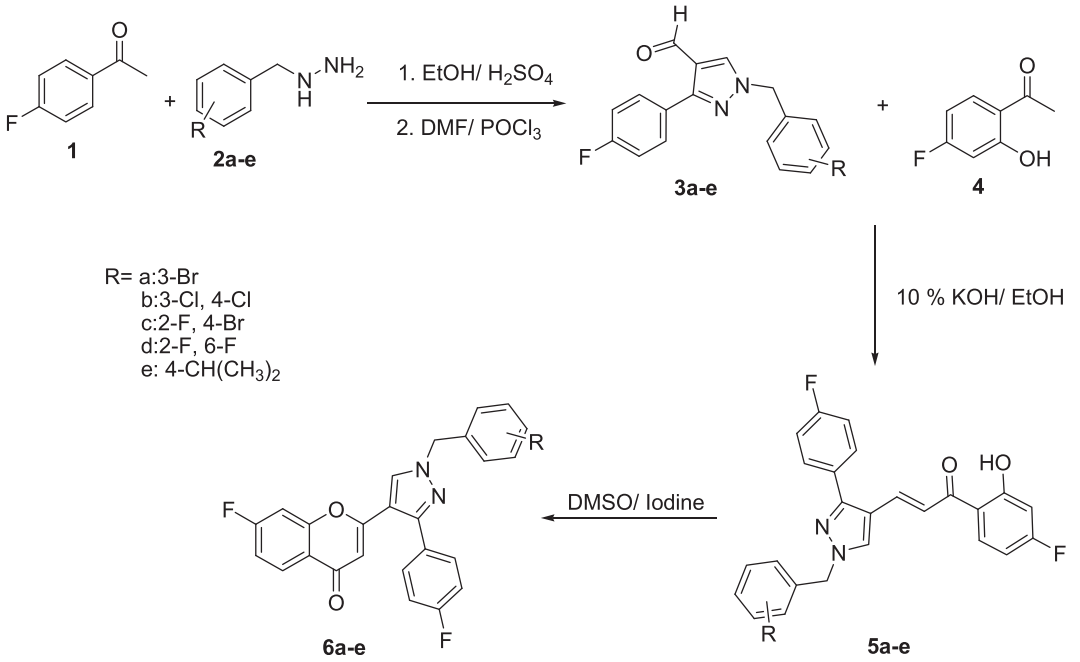
The results given in Table 1 indicated that compounds **3c**, **3d**, **3d**, **6a**, **6b**, **6c**, and **6d** exhibited good antibacterial activity against *E. coli* bacterial strain. Compounds **3c** to **3e**, **5e**, and **6a** to **6e** exhibited good antibacterial activity against *P. aeroginosa*. While compounds **3e** and **6a** to **6d** exhibited good antibacterial activity against *B. subtilis* and *S. aureus* compared with the standard Ampicillin. While other compounds were found to be less to moderately active against all bacterial strains.

3 | EXPERIMENTAL

The melting points were measured on a DBK melting point apparatus and are uncorrected. IR spectra were recorded on Shimadzu IR Affinity 1S (attenuated total reflection [ATR]) Fourier transform infrared (FTIR) spectrophotometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on Varian 400 spectrophotometer using tetramethylsilane (TMS) as an internal standard and DMSO-d_6 as solvent, and chemical shifts were expressed as δ parts per million units. Mass spectra were obtained on Shimadzu (LC-MS) mass spectrometer.

3.1 | General procedure for synthesis of 1-benzyl-3-(4-fluorophenyl)-1H-pyrazole-4-carbaldehydes (3a-e)

A mixture of substituted 1-benzylhydrazine (0.01 mol) and catalytic amount of concencentated H_2SO_4 was added to a solution of 1-(4-fluorophenyl)ethanone (0.01 mol) in 20 mL of ethanol. The mixture was refluxed for 1 hour, and the 1-benzyl-2-(1-(4-fluorophenyl)ethylidene)hydrazine formed was filtered and dried. A mixture of dimethylformamide (DMF) and phosphoryl chloride ($POCl_3$) was cooled with constant stirring at 0°C. A solution of 1-benzyl-2-(1-(4-fluorophenyl)ethylidene)hydrazine in DMF was added dropwise to the reaction mixture and then heated at 70 to 80°C for 5 hours. After completion of reaction, contents were cooled to room temperature and poured onto ice-cold water, and then it was made alkaline with saturated K_2CO_3 solution. The



SCHEME 1 Synthetic approach to the title compounds

TABLE 1 Antibacterial activities of the synthesized compounds (zone of inhibition in millimeter)

Compound	*Escherichia coli*	*Pseudomonas aeroginosa*	*Bacillus subtilis*	*Staphylococcus aureus*
3a	8	10	10	12
3b	9	10	10	11
3c	14	13	12	12
3d	15	14	12	13
3e	16	15	14	17
5a	9	11	12	11
5b	9	10	10	12
5c	8	10	10	9
5d	10	11	10	9
5e	12	14	13	12
6a	16	15	14	16
6b	14	15	14	16
6c	16	14	16	17
6d	14	15	15	16
6e	12	14	9	10
Ampicillin	16	15	17	18

precipitate formed was crystallized from ethanol to get pure 1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazole-4-carbaldehydes **3a-e**.

3.2 | 1-(3-Bromobenzyl)-3-(4-fluorophenyl)-1H-pyrazole-4-carbaldehyde (3a)

Yield: 71%, White solid, mp 58-60°C. IR (ν_{max}/cm^{-1}): 3112 (═C—H), 2820 (aldehyde C—H), 1674 (C═O), 1655 (C═N); ^{1}H NMR spectrum (400 MHz, DMSO-d_6): δ = 5.45 (s, 2H, —CH_2), 7.25-7.35 (m, 4H, Ar—H), 7.52-7.60 (m, 2H, Ar—H), 7.86-7.90 (m, 2H, Ar—H), 8.72 (s, 1H, pyrazolyl-H), 9.86 (s, 1H, —CHO); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 53.92, 115.17, 115.38, 120.48, 127.96, 128.36, 130.10, 130.52, 130.61, 130.85, 131.24, 137.09, 138.35, 150.91, 161.21, 163.66, 184.33; MS (LC-MS): *m/z* 358.95 $(M + H)^+$.

3.3 | 1-(3,4-Dichlorobenzyl)-3-(4-fluorophenyl)-1H-pyrazole-4-carbaldehyde (3b)

Yield: 65%, White solid. mp 190-192°C; IR (ν_{max}/cm^{-1}): 3112 (═C—H), 2820 (aldehyde C—H), 1674 (C═O), 1655 (C═N); ^{1}H NMR spectrum (400 MHz, DMSO-d_6): δ = 5.46 (s, 2H, —CH_2), 7.26-7.36 (m, 3H, Ar—H), 7.64-7.68 (m, 2H, Ar—H), 7.86-7.89 (m, 2H, Ar—H), 8.72 (s, 1H, pyrazolyl-H), 9.86 (s, 1H, —CHO); MS (LC-MS): *m/z* 349 $(M + H)^+$.

3.4 | 1-(4-Bromo-2-fluorobenzyl)-3-(4-fluorophenyl)-1H-pyrazole-4-carbaldehyde (3c)

Yield: 69%; White solid; mp 64-66°C; IR (ν_{max}/cm^{-1}): 3113 (═C—H), 2822 (aldehyde C—H), 1673 (C═O), 1656 (C═N); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.49 (s, 2H, —CH_2), 7.29 (t, 2H, *J* = 8.8 Hz, Ar—H), 7.35 (t, 1H, *J* = 8 Hz, Ar—H), 7.45 (d, 1H, *J* = 8.4 Hz, Ar—H), 7.61 (d, 1H, *J* = 8.4 Hz, Ar—H), 7.86 (dd, 2H, *J* = 8 and 6 Hz, Ar—H), 8.67 (s, 1H, pyrazolyl-H), 9.86 (s, 1H, —CHO); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 49.66, 115.40, 115.62, 116.20, 116.42, 119.34, 119.58, 121.08, 121.23, 123.26, 123.35, 127.44, 127.85, 128.02, 128.05, 130.53, 130.61, 131.57, 131.60, 131.77, 131.86, 134.57, 152.82, 159.01, 161.53, 161.97, 164.45, 184.20; MS (LC-MS): *m/z* 376.95 $(M + H)^+$.

3.5 | 1-(2,6-Difluorobenzyl)-3-(4-fluorophenyl)-1H-pyrazole-4-carbaldehyde (3d)

Yield: 61%; White solid; mp 68-70°C; IR (ν_{max}/cm^{-1}): 3112 (═C—H), 2824 (aldehyde C—H), 1677 (C═O), 1654 (C═N); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.52 (s, 2H, —CH_2), 7.18 (t, 2H, *J* = 8 Hz, Ar—H), 7.26 (t, 2H, *J* = 8.8 Hz, Ar—H), 7.50 (t, 1H, *J* = 8 Hz, Ar—H), 7.83 (m, 2H, Ar—H), 8.66 (s, 1H, pyrazolyl-H), 9.85 (s, 1H, —CHO); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 43.32, 111.38, 111.57, 111.75, 112.00, 115.17, 115.38, 120.24,

127.96, 130.49, 130.57, 131.43, 131.53, 131.64, 138.50, 150.59, 159.75, 161.20, 162.15, 163.64, 184.38; MS (LC-MS): *m/z* 317.05 $(M + H)^+$.

3.6 | 1-(4-Isopropylbenzyl)-3-(4-fluorophenyl)-1H-pyrazole-4-carbaldehyde (3e)

Yield: 64%; White solid; mp 52-54°C; IR (ν_{max}/cm^{-1}): 3111 (=C—H), 2821 (aldehyde C—H), 1672 (C=O), 1656 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.1 (d, 6H, —CH_3), 2.8 (m, 1H, —CH), 5.4 (s, 2H, —CH_2), 7.23-7.30 (m, 6H, Ar—H), 7.86-7.90 (m, 2H, Ar—H), 7.45 (d, 1H, *J* = 8.4 Hz, Ar—H), 7.61 (d, 1H, *J* = 8.4 Hz, Ar—H), 7.86 (dd, 2H, *J* = 8 and 6 Hz, Ar—H), 8.67 (s, 1H, pyrazolyl-H), 9.85 (s, 1H, —CHO); MS (LC-MS): *m/z* 323.05 $(M + H)^+$.

3.7 | General procedure for synthesis of (E)-3-(1-Benzyl-3-(4-fluorophenyl)-1H-pyrazol-4-yl)-1-(4-fluoro-2-hydroxyphenyl) prop-2-en-1-ones (5a-e)

A mixture of 1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazole-4-carbaldehydes **3a** to **3e** (0.005 mol) with 1-(4-fluoro-2-hydroxyphenyl)ethanone **4** (0.005 mol) was stirred in ethanolic KOH (10%) for 16 hours at room temperature. After completion of reaction, contents were poured onto ice-cold water and then acidified with concentrated hydrochloric acid (HCl). The precipitate formed was filtered off, washed with water, and crystallized from ethanol to get the pure product **5a-e**.

3.8 | (E)-3-(1-(3-Bromobenzyl)-3-(4-fluorophenyl)-1H-pyrazol-4-yl)-1-(4-fluoro-2-hydroxyphenyl)prop-2-en-1-one (5a)

Yield: 74%; Yellow solid; mp 80-82°C; IR (ν_{max}/cm^{-1}): 1637 (C=O), 1590 (C=N), 1569 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.46 (s, 2H, —CH_2), 6.82-6.89 (m, 2H, Ar—H), 7.33-7.39 (m, 4H, Ar—H), 7.53-7.61 (m, 4H, Ar—H), 7.70-7.81 (AB quartet, 2H, *J* = 15.6 Hz, =C—H), 8.21 (dd, 1H, *J* = 8 and 6.8 Hz, Ar—H), 8.75 (s, 1H, pyrazolyl-H), 13.09 (s, 1H, —OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 54.73, 104.12, 104.36, 106.79, 107.02, 115.65, 115.86, 117.58, 119.62, 121.84, 126.97, 128.52, 130.36, 130.44, 130.63, 130.90, 132.31, 133.04, 133.16, 135.87, 139.10, 151.29, 161.01, 163.46, 164.46, 164.60, 165.14, 167.67, 192.09; MS (LC-MS): *m/z* 495.10 $(M + H)^+$.

3.9 | (E)-3-(1-(3,4-Dichlorobenzyl)-3-(4-fluorophenyl)-1H-pyrazol-4-yl)-1-(4-fluoro-2-hydroxyphenyl)prop-2-en-1-one (5b)

Yield: 72%; Yellow solid; mp 158-160°C; IR (ν_{max}/cm^{-1}): 1641 (C=O), 1594 (C=N), 1524 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.47 (s, 2H, —CH_2), 6.81-6.87 (m, 2H, Ar—H), 7.33-7.44 (m, 3H, Ar—H), 7.59 (dd, 2H, *J* = 8 and 6 Hz, Ar—H), 7.66-7.68 (m, 2H, Ar—H), 7.69-7.81 (AB quartet, 2H, *J* = 15.6 Hz, =CH), 8.19 (t, 1H, *J* = 8 Hz, Ar—H), 8.73 (s, 1H, pyrazolyl-H), 13.07 (s, 1H, —OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 55.34, 104.98, 105.22, 106.86, 107.08, 115.76, 115.97, 116.83, 118.83, 127.23, 128.22, 129.90, 129.97, 130.48, 130.56, 131.06, 131.49, 131.60, 132.92, 133.22, 135.43, 136.10, 152.44, 166.03, 166.18, 192.06; MS (LC-MS): *m/z* 485.05 $(M + H)^+$.

3.10 | (E)-3-(1-(4-Bromo-2-fluorobenzyl)-3-(4-fluorophenyl)-1H-pyrazol-4-yl)-1-(4-fluoro-2-hydroxyphenyl)prop-2-en-1-one (5c)

Yield: 71%; Yellow solid; mp 118-120°C; IR (ν_{max}/cm^{-1}): 1638 (C=O), 1587 (C=N), 1574 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.48 (s, 2H, —CH_2), 6.81-6.89 (m, 2H, Ar—H), 7.32-7.40 (m, 3H, Ar—H), 7.48 (dd, 1H, *J* = 8 and 2 Hz, Ar—H), 7.57 (dd, 2H, *J* = 8 and 6 Hz, Ar—H), 7.63 (dd, 1H, *J* = 8 and 2 Hz, Ar—H), 7.69-7.82 (AB quartet, 2H, *J* = 15.6 Hz, =CH), 8.23 (dd, 1H, *J* = 8 and 6.8 Hz, Ar—H), 8.72 (s, 1H, pyrazolyl-H), 13.10 (s, 1H, —OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 49.07, 104.13, 104.37, 106.82, 107.03, 115.66, 115.74, 115.87, 117.60, 118.92, 119.16, 119.67, 121.97, 122.07, 122.64, 122.79, 128.00, 128.46, 130.39, 130.47, 132.29, 132.38, 132.43, 133.12, 133.23, 135.80, 151.35, 158.82, 161.02, 161.32, 163.47, 164.47, 164.60, 165.16, 167.68, 192.13; MS (LC-MS): *m/z* 515 $(M + H)^+$.

3.11 | (E)-3-(1-(2,6-Difluorobenzyl)-3-(4-fluorophenyl)-1H-pyrazol-4-yl)-1-(4-fluoro-2-hydroxyphenyl)prop-2-en-1-one (5d)

Yield: 74%; Yellow solid; mp 184-186°C; IR (ν_{max}/cm^{-1}): 1640 (C=O), 1596 (C=N), 1568 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.49 (s, 2H, —CH_2), 6.81-6.89 (m, 2H, Ar—H), 7.17 (t, 2H, *J* = 8 Hz, Ar—H), 7.33 (t, 2H, *J* = 8 Hz, Ar—H), 7.48-7.56 (m, 3H, Ar—H), 7.7 (d, 1H, *J* = 15.8 Hz, =C—H), 7.83 (d, 1H, *J* = 15.6 Hz, =C—H), 8.26 (dd, 1H, *J* = 8 and 6.8 Hz, Ar—H), 8.74 (s, 1H, pyrazolyl-H), 13.14 (s, 1H, —OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 43.47, 104.09, 104.32, 106.73, 106.95, 111.37, 111.56,

111.75, 111.93, 111.99, 115.59, 115.65, 115.81, 117.45, 119.49, 128.45, 128.48, 130.37, 130.45, 131.37, 131.47, 131.57, 132.10, 133.17, 133.28, 135.82, 151.32, 159.71, 159.79, 161.02, 162.20, 162.27, 163.47, 164.63, 164.77, 165.19, 167.71, 193.20; MS (LC-MS): m/z 453.15 $(M + H)^+$.

3.12 | (E)-3-(1-(4-Isopropylbenzyl)-3-(4-fluorophenyl)-1H-pyrazol-4-yl)-1-(4-fluoro-2-hydroxyphenyl)prop-2-en-1-one (5e)

Yield: 77%; Yellow solid; mp 130-132°C; IR (ν_{max}/cm^{-1}): 1635 (C═O), 1595 (C═N), 1567 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.17 (d, 6H, CH_3), 2.87 (m, 1H, —C—H), 5.39 (s, 2H, —CH_2), 6.82-6.89 (m, 2H, Ar—H), 7.25-7.37 (m, 6H, Ar—H), 7.57-7.61 (m, 2H, Ar—H), 7.70-7.81 (AB quartet, 2H, J = 15.8 Hz, ═C—H), 8.23 (dd, 1H, J = 8 and 6.8 Hz, Ar—H), 8.74 (s, 1H, pyrazolyl-H), 13.13 (s, 1H, —OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.75, 33.12, 55.41, 104.13, 104.36, 106.79, 107.01, 115.63, 115.75, 115.84, 117.56, 119.36, 126.06, 127.92, 128.63, 130.35, 130.43, 132.01, 133.06, 133.17, 133.90, 136.05, 148.22, 151.04, 160.98, 163.42, 164.49, 164.63, 165.14, 167.67, 192.13; MS (LC-MS): m/z 459.15 $(M + H)^+$.

3.13 | General procedure for synthesis of 2-(1-benzyl-3-(4-fluorophenyl)-1H-pyrazol-4-yl)-7-fluoro-4H-chromen-4-ones (6a-e)

Compound **5a** to **5e** (0.002 mol) was dissolved in 15-mL DMSO. To this solution, catalytic amount of iodine was added. The reaction mixture was heated to 140°C for 2 hours. After completion of reaction (checked by thin-layer chromatography [TLC]), content were cooled and poured over crushed ice. The product obtained was filtered, washed with cold water and 10% sodium thiosulphate solution followed by cold water, and crystallized from ethanol to get the pure product **6a** to **6e**.

3.14 | 2-(1-(3-Bromobenzyl)-3-(4-fluorophenyl)-1H-pyrazol-4-yl)-7-fluoro-4H-chromen-4-one (6a)

Yield: 77%; White solid; mp 200-202°C; IR (ν_{max}/cm^{-1}): 3112 (═C—H), 1641 (C═O), 1622 (C═N), 1597 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.46 (s, 2H, —CH_2), 6.32 (s, 1H), 7.19 (dd, 1H, J = 8 and 2 Hz, Ar—H), 7.30-7.62 (m, 9H, Ar—H), 8.19 (dd, 1H, J = 8 and 6.8 Hz, Ar—H), 8.71 (s, 1H, pyrazolyl-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 54.87, 104.56, 104.82, 107.24, 110.95, 112.30, 113.82, 115.32, 115.54, 116.69, 119.55, 120.72, 122.07, 127.24, 127.74, 127.84, 129.20, 130.97, 131.12, 133.66, 139.25, 149.39, 158.12, 158.50, 158.89, 159.28, 159.63, 163.82, 175.80; MS (LC-MS): m/z 495.10 $(M + H)^+$.

3.15 | 2-(1-(3,4-Dichlorobenzyl)-3-(4-fluorophenyl)-1H-pyrazol-4-yl)-7-fluoro-4H-chromen-4-one (6b)

Yield: 65%; White solid; mp 148-150°C; IR (ν_{max}/cm^{-1}): 3059 (═C—H), 1645 (C═O), 1620 (C═N), 1598 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.47 (s, 2H, —CH_2), 6.32 (s, 1H), 7.19 (d, 1H, J = 8 Hz, Ar—H), 7.27-7.70 (m, 8H, Ar—H), 8.19 (t, 1H, J = 8 Hz, Ar—H), 8.70 (s, 1H, pyrazolyl-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 54.13, 104.83, 107.23, 110.87, 113.74, 115.32, 115.54, 116.61, 120.59, 127.80, 128.53, 129.00, 130.25, 131.06, 131.39, 133.71, 137.48, 157.96, 158.34, 158.73, 159.10, 175.70; MS (LC-MS): m/z 483.10 $(M + H)^+$.

3.16 | 2-(1-(4-Bromo-2-fluorobenzyl)-3-(4-fluorophenyl)-1H-pyrazol-4-yl)-7-fluoro-4H-chromen-4-one (6c)

Yield: 69%; White solid; mp 220-222°C; IR (ν_{max}/cm^{-1}): 3065 (═C—H), 1643 (C═O), 1620 (C═N), 1594 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.49 (s, 2H, —CH_2), 6.31 (s, 1H), 7.19 (dd, 1H, J = 8 and 6.8 Hz, Ar—H), 7.25-7.78 (m, 8H, Ar—H), 8.05 (dd, 1H, J = 8 and 6.8 Hz, Ar—H), 8.67 (s, 1H, pyrazolyl-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 48.46, 104.43, 104.69, 107.01, 111.87, 113.66, 113.89, 115.14, 115.35, 118.85, 119.09, 120.41, 121.87, 121.96, 122.62, 122.77, 127.48, 127.59, 127.96, 128.77, 130.43, 130.83, 130.91, 132.24, 133.50, 149.04, 156.26, 156.40, 158.73, 159.23, 161.01, 161.24, 163.46, 165.97, 175.44; MS (LC-MS): m/z 513.10 $(M + H)^+$.

3.17 | 2-(1-(2,6-Difluorobenzyl)-3-(4-fluorophenyl)-1H-pyrazol-4-yl)-7-fluoro-4H-chromen-4-one (6d)

Yield: 72%; White solid; mp 140-142°C; IR (ν_{max}/cm^{-1}): 3110 (═C—H), 1648 (C═O), 1622 (C═N), 1594 (C═C); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.51 s (2H, —CH_2), 6.31 (s, 1H), 7.16-7.57 (m, 9H, Ar—H), 8.04 (dd, 1H, J = 8 and 6.8 Hz, Ar—H), 8.66 (s, 1H, pyrazolyl-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 43.31, 104.41, 104.66, 106.95, 111.43, 111.70, 111.75, 111.93, 113.58, 113.80, 115.09, 115.30, 120.38, 127.43, 127.54, 128.80, 130.81, 130.89, 131.44, 131.54, 133.25, 148.96, 156.23, 156.37, 159.17, 159.74, 161.00, 162.16, 163.44, 165.94, 175.41; MS (LC-MS): m/z 451.05 $(M + H)^+$.

3.18 | 2-(1-(4-Isopropylbenzyl)-3-(4-fluorophenyl)-1H-pyrazol-4-yl)-7-fluoro-4H-chromen-4-one (6e)

Yield: 67%; White solid; mp 280-282°C; IR (ν_{max}/cm^{-1}): 3066 (=C—H), 1644 (C=O), 1620 (C=N), 1592(C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.18 (d, 6H, —CH_3), 2.87 (m, 1H, —C—H), 5.39 (s, 2H, —CH_2), 6.30 (s, 1H), 7.18-7.36 (m, 8H, Ar—H), 7.58-7.62 (m, 2H, Ar—H), 8.05 (dd, 1H, J = 8 and 6.8 Hz, Ar—H), 8.68 (s, 1H, pyrazolyl-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.76, 33.12, 55.20, 104.44, 104.70, 106.90, 111.81, 113.67, 113.90, 115.16, 115.37, 120.44, 126.57, 127.52, 127.98, 128.98, 130.85, 130.93, 133.17, 133.83, 148.22, 148.76, 156.30, 156.43, 159.46, 161.00, 163.44, 165.99, 175.46; MS (LC-MS): m/z 457.15 $(M + H)^+$.

4 | CONCLUSION

In conclusion, we have synthesized a series of novel 2-(1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-7-fluoro-4*H*-chromen-4-ones **6a** to **6e** from 1-benzyl-3-(4-fluorophenyl)-1*H*-pyrazole-4-carbaldehydes **3a** to **3e**. All synthesized compounds are characterized by using spectral methods and screened for their antibacterial activities.

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REFERENCES

[1] J. Reis, A. Gaspar, N. Milhazes, F. M. Borges, *J. Med. Chem.* **2017**, *60*(19), 7941.

[2] O. Prakash, R. Kumar, V. Parkash, *Eur. J. Med. Chem.* **2008**, *43*, 435.

[3] P. Lerdsirisuk, C. Maicheen, J. Ungwitayatorn, *Bioorg. Chem.* **2014**, *57*, 142.

[4] K. N. Gopalan, A. Joseph, S. Moorkoth, *Int. J. Pharm. Biosci. Technol.* **2013**, *1*, 130.

[5] M. Momin, D. Ramjugernath, H. Chenia, N. A. Koorbanally, *J. Chem.* **2013**, *13*, 50.

[6] O. Bozdag-Dundar, M. Ceylan-Unlusoy, E. J. Verspohl, R. Ertan, *Arzneim. Forsch.* **2007**, *57*, 532.

[7] M. Ceylan-ÜnlÜsoy, E. J. Verspohl, R. Ertan, *J. Enzyme. Inhib. Med. Chem.* **2010**, *25*, 784.

[8] M. S. Christodoulou, S. Liekens, K. M. Kasiotis, S. A. Haroutounian, *Bioorg. Med. Chem.* **2010**, *18*, 4338.

[9] A. A. Bekhit, A. Hymete, H. Asfaw, A. A. Bekhit, *Arch. Pharm. Chem. Life Sci.* **2012**, *345*, 147.

[10] C. B. Vicentini, C. Romagnoli, E. Andreotti, D. Mares, *J. Agric. Food Chem.* **2007**, *55*, 10331.

[11] R. B. Pathak, P. T. Chovatia, H. H. Parekh, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5129.

[12] I. Bouabdallah, L. A. M'Barek, A. Zyad, A. Ramdani, I. Zidane, A. Melhaoui, *Nat. Pro. Res.* **2006**, *20*(11), 1024.

[13] Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Acen, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.* **2016**, *116*(2), 422.

[14] J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*(4), 2432.

[15] A. Guan, C. Liu, G. Huang, H. Li, S. Hao, Y. Xu, Y. Xie, Z. Li, *J. Fluorine Chem.* **2014**, *160*, 82.

[16] G. Li, X. Qian, J. Cui, Q. Huang, D. Cui, R. Zhang, F. Liu, *J. Fluorine Chem.* **2006**, *127*, 182.

[17] H. Chen, S. Q. Huang, J. Y. Xie, *J. Fluorine Chem.* **2006**, *127*, 1130.

[18] S. G. Kucukguzel, S. Rollas, H. Erdeniz, A. C. Kiraz, M. Ekinci, A. Vidin, *Eur. J. Med. Chem.* **2000**, *35*, 761.

[19] T. P. Gregory, C. D. Darlene, M. S. David, *Pestic. Biochem. Phys.* **1998**, *60*, 177.

[20] M. A. Kira, M. O. Abdel-Rahman, K. Z. Gadalla, *Tetrahedron Lett.* **1969**, *10*, 109.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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