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Synthesis and Characterization of Novel Mono Carbonyl Curcumin Analogues of Pyrazole Derivatives

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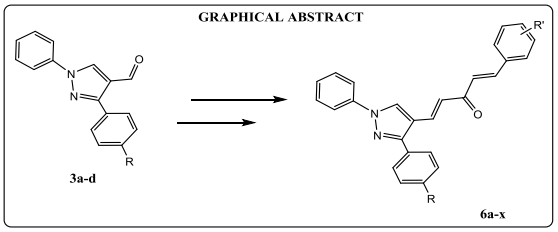
ABSTRACT

(E)-4-aryl-1-phenyl-1H-pyrazol-4-yl)but-3-en-2-one derivatives were (4a-d) synthesized by the condensation of 3-aryl-1-phenyl-1H-pyrazole-4-carbaldehyde derivatives (3a-d) with acetone in the presence of sodium hydroxide. Compounds (4a-d) on condensation with different aldehydes give mono carbonyl curcumin analogues (MACs) of pyrazole derivatives (6a-x) in good yield.

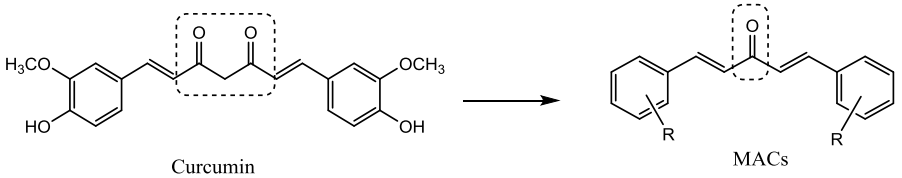


Keywords: Mono-carbonyl analogs of curcumin, Synthesis, Pyrazoles, Chalcone, Acetone

INTRODUCTION

Curcumin, 5-hydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,4,6-trien-3-one (diferuloylmethane), is a secondary metabolite of the well-known Indian spice turmeric, derived from the rhizomes of Curcuma longa, of the Zingiberaceae family. Curcumin is a polyphenol, and it is the main component of the yellow-pigmented fraction of turmeric [1]. To date, no studies in either animals or humans have discovered toxicity associated with the use of curcumin, even when tested at high doses [2].

Curcumin and its derivatives owns a broad spectrum of therapeutic activities viz., antibacterial [3], antifungal [4], antiviral [5], anti-HIV [6], anti-inflammatory [7], anti-Parkinson's [8], anti-Alzheimer's [9], anti-angiogenesis [10], free radical scavenging activity [11], antirheumatic [12], antimalarial [13], anticancer [14], antiprotozoan [15], antimutagenic [16], wound treatment [17], hepatoprotective activity [18], anti-leishmanial activity [19] and amyloid heart disease [20]. Among the active curcumin analogs, mono-carbonyl analogs of curcumin (MACs) are important which were designed by deleting the reactive β-diketone moiety. This class of analogs has received much attention due to their improved chemical stability and pharmacokinetic profiles.



MATERIALS AND METHODS

All the reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F254 (mesh); spots were visualized with UV light. Merck silica gel (60–120 mesh) was used for column chromatography. ^{1}H NMR (400 MHz), and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker AMX 400 MHz NMR spectrometer in $CDCl_3$/DMSO solution using TMS as an internal standard. All chemical shifts are reported in δ (ppm) using TMS as an internal standard. Elemental analysis was determined using a Vario Microcube Elemental Analyzer. Melting points were determined in open capillaries on a Mel Temp apparatus and are uncorrected.

General procedure for the synthesis of acetophenone phenyl hydrazones (2a-d)

A mixture of appropriate ketone (1a-e) (1 mmol) and phenyl hydrazine (1 mmol) in ethanol was refluxed in the presence of few drops of glacial acetic acid for 2 h. The progress of reaction was monitored by TLC using n-hexane: ethyl acetate (7:3) as a mobile phase. The mixture was cooled and the solid product obtained was filtered, washed with water and recrystallized from ethanol.

Z)-1-(1-(4-methoxyphenyl)ethylidene)-2-phenylhydrazine (2a): White solid; Yield: 89%; mp: 125-127 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.23 (s, 3H), 4.12 (s, 3H), 7.25-7.34 (m, 5H), 7.54 (s, 1H), 7.68 (d, *J* = 8.72 Hz, 2H), 7.75 (d, *J* = 8.75 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 26.9, 114.8, 122.5, 123.7, 125.8, 129.4, 137.5, 145.3, 147.8, 160.2; LCMS (positive ion mode) (*m/z*): 241.4 $[M+H]^+$ for $C_{15}H_{16}N_2O$.

(Z)-1-(1-(4-chlorophenyl)ethylidene)-2-phenylhydrazine (2b): White solid; Yield: 92%; mp: 120-122 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.25 (s, 3H), 7.14-7.26 (m, 5H), 7.65 (s, 1H), 7.69 (d, *J* = 8.56 Hz, 2H), 7.84 (d, *J* = 8.57 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 26.3, 113.2, 120.6, 123.5, 124.2, 129.5, 136.5, 144.6, 145.7, 160.1; LCMS (positive ion mode) (*m/z*): 245.2 $[M+H]^+$ for $C_{14}H_{13}ClN_2$.

(Z)-1-phenyl-2-(1-phenylethylidene)hydrazine (2c): White solid; Yield: 88%; mp: 117-119 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 2.25 (s, 3H), 7.02 (t, *J* = 7.50 Hz, 1H), 7.32-7.35 (m, 4H), 7.42-7.45 (m, 1H), 7.45 (s, 1H), 7.56 (d, *J* = 8.76 Hz, 2H), 7.73 (d, *J* = 8.74 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 25.4, 112.6, 120.5, 122.9, 124.5, 129.8, 136.7, 145.3, 146.4, 160.2; LCMS (positive ion mode) (*m/z*): 211.3 $[M+H]^+$ for $C_{14}H_{14}N_2$.

(Z)-1-(1-(4-fluorophenyl)ethylidene)-2-phenylhydrazine (2d): White solid; Yield: 91%; mp: 118-120 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 2.27 (s, 3H), 7.15 (d, *J* = 7.56 Hz, 2H), 7.25-7.32 (m, 3H), 7.67 (s, 1H), 7.75 (d, *J* = 8.46 Hz, 2H), 7.83 (d, *J* = 8.47 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.3, 115.7, 121.4, 123.9, 125.3, 129.7, 137.2, 145.2, 146.5, 160.5; LCMS (positive ion mode) (*m/z*): 229.3 $[M+H]^+$ for $C_{14}H_{13}FN_2$.

General procedure for the synthesis of 3-aryl-1-phenyl-1*H*-pyrazole-4-carbaldehyde (3a-d)

To an ice cold dimethyl formamide (10 ml), $POCl_3$ (3 mmol) was added drop wise with continuous stirring over a period of 30 min. Stirring was continued for further 60 min, keeping the reaction temperature at 0^{o}C. Acetophenone phenyl hydrazone derivative (2a-d) (1 mmol) was then added and the reaction mixture was allowed to attain room temperature. The mixture was then refluxed for 5 h, allowed to cool and poured onto ice. The mixture was neutralized with saturated sodium bicarbonate solution. The solid product obtained was filtered, washed with water and recrystallized from methanol. The completion of reaction was monitored by TLC using n-hexane: ethyl acetate (7:3) as a mobile phase.

3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (3a): Off-white solid; Yield: 74%; mp: 136-138^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.87 (s, 3H), 7.03 (d, *J* = 8.69 Hz, 2H), 7.38 (d, *J* = 7.39 Hz, 1H), 7.51 (t, *J* = 7.85 Hz, 2H), 7.78-7.80 (m, 4H), 8.52 (s, 1H), 10.04 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 55.9, 114.8, 120.3, 122.9, 124.4, 128.4, 130.2, 130.8, 131.8, 139.6, 155.1, 161.1, 185.7; LCMS (positive ion mode) (*m/z*): 279.15 $[M+H]^+$, 301.10 $[M+Na]^+$ for $C_{31}H_{23}ClN_6O$.

3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (3b): Off-white solid; Yield: 75%; mp: 128-130^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 7.13 (d, *J* = 8.69 Hz, 2H), 7.57 (d, *J* = 7.85 Hz, 2H), 7.91-7.94 (m, 5H), 8.45 (s, 1H), 10.07 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 116.8, 121.5, 123.2, 124.8, 127.4, 129.5, 130.8, 131.7, 138.6, 156.7, 160.6, 185.2; LCMS (positive ion mode) (*m/z*): 283.10 $[M+H]^+$ for $C_{16}H_{11}ClN_2O$.

1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde (3c): Off-white solid; Yield: 82%; mp: 129-131^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.14-7.19 (m, 3H), 7.36 (d, *J* = 7.92 Hz, 2H), 7.53-7.58 (m, 5H), 8.63 (s, 1H), 10.19 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 114.8, 121.5, 122.5, 123.5, 129.8, 130.1, 130.3, 131.9, 136.6, 158.7, 161.1, 185.1; LCMS (positive ion mode) (*m/z*): 249.05 $[M+H]^+$ for $C_{16}H_{12}N_2O$.

3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (3d): Off-white solid; Yield: 79%; mp: 134-136^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 7.15 (d, *J* = 8.69 Hz, 2H), 7.63 (d, *J* = 7.85 Hz, 2H), 7.81-7.85 (m, 5H), 8.57 (s, 1H), 10.12 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 115.9, 120.5, 123.9, 124.4, 127.4, 129.5, 130.8, 131.7, 138.6, 156.7, 160.6, 185.2; LCMS (positive ion mode) (*m/z*): 267.10 $[M+H]^+$ for $C_{16}H_{11}FN_2O$.

General procedure for the synthesis of (E)-4-aryl-1-phenyl-1*H*-pyrazol-4-yl)but-3-en-2-one (4a-d):

To a stirred solution of pyrazole derivatives (3a-d) (1 mmol) in ethanol (3 mL) was added 0.5 mL of acetone and 15% aqueous NaOH (1 mL) solution at 0^{o}C. The reaction was allowed to stir at room temperature till it was completed. The reaction was quenched by the addition of water and the formed precipitate was filtered and dried. Further, it was purified by column chromatography (Silica gel, 60-120 mesh, 9:1 hexane/ethyl acetate) to obtain pure chalcone(4a-d).

(E)-4-(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)but-3-en-2-one (4a): Yellow solid; Yield: 75%; mp: 143-145 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 2.31 (s, 3H), 3.87 (s, 3H), 6.56 (d, *J* = 16.4 Hz, 1H), 7.03 (d, *J* = 8.8 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.53 (s, 1H), 7.57-7.61 (m, 2H), 7.76 (d, J = 8.4 Hz, 2H), 8.24 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 27.2, 55.4, 114.3, 117.4, 119.3, 124.6, 126.3,

126.6, 127.2, 129.4, 129.9, 134.3, 139.4, 153.5, 160.1, 198.2. Anal.calcd for $C_{20}H_{18}N_2O_2$: C, 75.45%; H, 5.70%; N, 8.80%. Found: C, 75.63%; H, 5.41%; N, 8.59%.

(E)-4-(1,3-diphenyl-1*H*-pyrazol-4-yl)but-3-en-2-one (4b):Yellow solid; Yield: 78%; mp: 142-144 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ= 2.27 (s, 3H), 6.58 (d, *J* = 16.4 Hz, 1H), 7.05 (d, *J* = 8.8 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.54 (s, 1H), 7.58-7.63 (m, 3H), 7.78 (d, *J* = 8.4 Hz, 2H), 8.23 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.5, 114.9, 117.5, 119.6, 125.2, 126.3, 126.8, 128.3, 129.6, 131.2, 133.4, 138.4, 153.2, 159.2, 198.0. Anal.calcd for $C_{19}H_{16}N_2O$: C, 79.14%; H, 5.59%; N, 9.72%. Found: C, 79.43%; H, 5.41%; N, 9.89%.

(E)-4-(3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)but-3-en-2-one (4c): Off-white solid; Yield: 77%; mp: 146-148 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ= 2.25 (s, 3H), 6.50 (d, J = 16 Hz, 1H), 7.29 (t, *J* = 7.2 Hz, 1H), 7.39-7.46 (m, 5H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 2H), 8.18 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 27.4, 117.6, 118.9, 119.4, 126.5, 127.0, 127.5, 129.0, 129.6, 130.7, 133.5, 134.8, 139.2, 152.4, 198.0. Anal.calcd for $C_{19}H_{15}ClN_2O$: C, 70.70%; H, 4.68%; N, 8.68%. Found: C, 70.50%; H, 4.92%; N, 8.34%.

(E)-4-(3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)but-3-en-2-one (4d): Off-white solid; Yield: 75%; mp: 145-147 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ = 2.27 (s, 3H), 6.56 (d, J = 16 Hz, 1H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.42-7.47 (m, 5H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 2H), 8.20 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 27.6, 118.2, 118.9, 120.5, 125.6, 127.2, 127.9, 129.2, 129.6, 131.2, 133.8, 135.4, 141.2, 152.6, 198.5. Anal.calcd for $C_{19}H_{15}FN_2O$: C, 74.50%; H, 4.94%; N, 9.14%. Found: C, 74.63%; H, 4.61%; N, 9.09%.

General procedure for the synthesis of compounds (6a-x)

To a stirred solution of chalcone (4a-d) (0.5 mmol) in ethanol (5 mL) was added 15% aqueous NaOH (2 mL) solution and appropriate aldehyde (5a-f) (0.5 mmol) at 0 ^oC. The resulting solution was stirred at room temperature till the completion of the reaction. The reaction mixture was quenched by the addition of water and the formed precipitate was filtered and dried. Further, it was purified by column chromatography (Silica gel, 60-120 mesh, 9:1 hexane/ethyl acetate) to obtain pure compounds (6a-x).

(1E,4E)-1-(3,4-dimethoxyphenyl)-5-(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)penta-1,4-dien-3-one (6a): Off-white solid; Yield: 72%; mp: 176-178 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ = 3.98-4.00 (m, 9H), 6.96 (d, *J* = 15.89 Hz, 1H), 7.03 (d, *J* = 15.77 Hz, 1H), 7.34 (s, 1H), 7.45 (t, *J* = 7.34 Hz, 1H), 7.56-7.61 (m, 5H), 7.67 (d, *J* = 15.89 Hz, 1H), 7.74 (d, *J* = 8.19 Hz, 2H), 7.82-7.87 (m, 4H), 8.40 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 57.0, 61.8, 106.3, 118.9, 120.2, 125.7, 125.9, 127.6, 128.2, 129.8, 130.4, 130.8, 131.0, 131.6, 134.1, 135.6, 137.8, 139.6, 140.1, 141.2, 144.0, 153.3, 154.3, 189.0. Anal.calcd for $C_{29}H_{26}N_2O_4$: C, 74.66%; H, 5.62%; N, 6.00%. Found: C,74.74%; H, 5.82%; N, 6.12%.

(1E,4E)-1-(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-5-(3,4,5-trimethoxyphenyl)penta-1,4-dien-3-one (6b): Light yellow solid; Yield: 74%; mp: 175-177 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ= 3.87 (s, 3H), 3.90-3.91 (m, 9H), 6.81 (s, 2H), 6.89 (d, *J* = 15.89 Hz, 1H), 6.94 (d, *J* = 15.89 Hz, 1H), 7.03 (d, *J* = 8.56 Hz, 2H), 7.35 (t, *J* = 7.34 Hz, 1H), 7.59 (d, *J* = 15.77 Hz, 2H), 7.64 (d, *J* = 8.56 Hz, 2H), 7.76-7.82 (m, 4H), 8.31 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 55.3, 56.1, 61.0, 105.4, 114.2, 118.0, 119.3, 124.5, 124.8, 125.1, 126.5, 127.2, 129.5, 130.0, 130.3, 134.0, 139.4, 140.2, 142.9, 153.4, 153.6, 160.1, 188.4. Anal.calcd for $C_{30}H_{28}N_2O_5$: C, 72.56; H, 5.68%; N, 5.64%. Found: C, 72.64%; H, 5.72%; N, 5.81%.

(1E,4E)-1-(4-(dimethylamino)phenyl)-5-(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)penta-1,4-dien-3-one (6c):Pale yellow solid; Yield: 74%; mp: 175-176 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ= 3.03 (s, 6H), 3.88 (s, 3H), 6.68 (d, *J* = 8.31 Hz, 2H), 6.80 (d, *J* = 15.53 Hz, 1H), 6.92 (d, *J* = 15.65 Hz, 1H), 7.03 (d, *J* = 7.95 Hz, 2H), 7.33 (t, *J* = 7.17 Hz, 1H), 7.47-7.49 (m, 4H), 7.64-7.68 (m, 3H), 7.73-7.79 (m, 3H), 8.28 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 40.1, 55.3, 111.8, 114.2, 118.3, 119.2, 120.9, 122.6, 125.0, 125.4, 126.3, 127.0, 129.5, 130.0, 130.2, 132.6, 139.5, 143.9, 151.9, 153.4, 160.0, 188.5. Anal.calcd for $C_{29}H_{27}N_3O_2$: C, 77.48%; H, 6.05%; N, 9.35%. Found: C, 77.21%; H, 6.32%; N, 9.47%.

(1E,4E)-1-(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-5-(4-nitrophenyl)penta-1,4-dien-3-one (6d):Yellow solid; Yield: 75%; mp: 179-180 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ= 3.92 (s, 3H), 6.92 (d, *J* = 15.89 Hz, 1H), 6.99 (d, *J* = 15.89 Hz, 1H), 7.12 (d, *J* = 8.34 Hz, 2H), 7.35-7.39 (m, 3H), 7.49-7.53 (m, 4H), 7.61-7.67 (m, 4H), 7.77-7.82 (m, 2H), 8.32 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 55.3, 114.3, 117.4, 119.3, 124.2, 124.6, 126.3, 126.6, 127.2, 128.8, 128.9, 129.5, 129.6, 129.9, 130.1, 134.3, 139.4, 139.6, 153.5, 160.1, 187.8. Anal.calcd for $C_{27}H_{21}N_3O_4$: C, 71.83%; H, 4.69%; N, 9.31%. Found: C, 71.95%; H, 4.79%; N, 9.13%.

(1E,4E)-1-(4-chlorophenyl)-5-(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)penta-1,4-dien-3-one (6e): Light yellow solid; Yield: 72%; mp: 175-177 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ= 3.88 (s, 3H), 6.89 (d, *J* = 15.89 Hz, 1H), 6.95 (d, *J* = 15.89 Hz, 1H), 7.04 (d, *J* = 8.07 Hz, 2H), 7.33-7.38 (m, 3H), 7.47-7.52 (m, 4H), 7.60-7.65 (m, 3H), 7.77-7.81 (m, 3H), 8.29 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 55.4, 114.3, 117.9, 119.3, 124.7, 125.9, 126.6, 127.2, 129.2, 129.4, 129.5, 129.9, 130.0, 133.4, 134.4, 136.2, 139.4, 141.4, 153.6, 160.1, 188.3. Anal.calcd for $C_{27}H_{21}ClN_2O_2$: C, 73.55%; H, 4.80%; N, 6.35%. Found: C, 73.62%; H, 5.01%; N, 6.49%.

(1E,4E)-1-(4-fluorophenyl)-5-(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)penta-1,4-dien-3-one (6f): Light yellow solid; Yield: 74%; mp: 177-179 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ = 3.97 (s, 3H), 6.98 (d, *J* = 15.89 Hz, 1H), 7.04 (d, *J* = 15.89 Hz, 1H), 7.13 (d, *J* = 8.07 Hz, 2H), 7.42-7.47 (m, 3H), 7.56-7.60 (m, 4H), 7.69-7.74 (m, 3H), 7.86-7.90 (m, 3H), 8.38 (s, 1H);^{13}C NMR (100 MHz, DMSO-d_6): δ= 55.4, 114.4, 118.0, 119.4, 124.8, 125.9, 126.7, 127.3, 129.3, 129.5, 129.6, 130.0, 130.1, 133.4, 134.4, 136.3, 139.5, 141.4, 153.7, 160.2, 188.4. Anal.calcd for $C_{27}H_{21}FN_2O_2$: C, 76.40%; H, 4.99%; N, 6.60%. Found: C, 76.23%; H, 5.14%; N, 6.52%.

(1E,4E)-1-(3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-5-(3,4-dimethoxyphenyl)penta-1,4-dien-3-one (6g):Yellow solid; Yield: 72%; mp: 177-179 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ= 3.93 (s, 6H), 6.85 (d, *J* = 15.77 Hz, 1H), 6.93 (d, *J* = 16.13 Hz, 1H), 7.11-7.26 (m, 3H), 7.37 (t, *J* = 7.45 Hz, 1H), 7.47-7.53 (m, 4H), 7.61-7.67 (m, 3H), 7.72-7.79 (m, 3H), 8.31 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 55.9, 109.9, 111.2, 118.2, 119.4, 123.0, 123.8, 125.2, 126.7, 127.4, 127.7, 129.0, 129.6, 130.0, 130.9, 132.9, 134.8, 139.3, 143.2, 149.3, 151.4, 152.4, 188.3. Anal.calcd for $C_{28}H_{23}ClN_2O_3$: C, 71.41%; H, 4.92%; N, 5.95%. Found: C, 71.63%; H, 4.71%; N, 6.09%.

(1E,4E)-1-(3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-5-(3,4,5-trimethoxyphenyl)penta-1,4-dien-3-one (6h): Yellow solid; Yield: 76%; mp: 179-180 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ = 3.90-3.92 (m, 9H), 6.82 (s, 2H), 6.88 (d, *J* = 15.77 Hz, 1H), 6.95 (d, *J* = 15.77 Hz, 1H), 7.37 (t, *J* = 7.34 Hz, 1H), 7.48-7.53 (m, 5H), 7.59 (d, *J* = 15.89 Hz, 1H), 7.66 (d, *J* = 8.19 Hz, 2H), 7.77-7.79 (m, 2H), 8.32 (s, 1H); ^{13}C NMR (100 MHz,

DMSO-d_6): δ= 56.2, 61.0, 105.5, 118.1, 119.4, 124.9, 125.1, 126.8, 127.4, 129.0, 129.6, 130.0, 130.2, 130.8, 133.3, 134.8, 139.3, 140.4, 143.2, 152.5, 153.4, 188.2. Anal.calcd for $C_{29}H_{25}ClN_2O_4$: C, 69.53%; H, 5.03%; N, 5.59%. Found: C, 69.73%; H, 5.19%; N, 6.05%.

(1E,4E)-1-(3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-5-(4-(dimethylamino)phenyl)penta-1,4-dien-3-one (6i):Orange solid; Yield: 69%; mp: 179-181 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ= 3.03 (s, 6H), 6.69 (d, *J* = 8.68 Hz, 2H), 6.79 (d, *J* = 15.77 Hz, 1H), 6.93 (d, *J* = 15.77 Hz, 1H), 7.47-7.52 (m, 7H), 7.67 (d, *J* = 8.44 Hz, 2H), 7.71 (d, *J* = 15.89 Hz, 2H), 7.78 (d, *J* = 8.19 Hz, 2H), 8.30 (s,1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 40.1, 111.8, 118.4, 119.3, 120.7, 122.4, 125.9, 126.6, 127.3, 129.0, 129.6, 130.0, 130.1, 130.3, 130.9, 131.9, 144.2, 152.0, 152.3, 157.7, 188.4. Anal.calcd for $C_{28}H_{24}ClN_3O$: C, 74.08%; H, 5.33%; N, 9.26%. Found: C, 74.21%; H, 5.52%; N, 9.35%.

(1E,4E)-1-(3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-5-(4-nitrophenyl)penta-1,4-dien-3-one (6j):Yellow solid; Yield: 71%; mp: 175-177 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ= 6.77 (d, *J* = 8.68 Hz, 2H), 6.88 (d, *J* = 15.89 Hz, 1H), 7.01 (d, *J* = 15.87 Hz, 1H), 7.44 (t, *J* = 7.45 Hz, 2H), 7.55-7.58 (m, 5H), 7.72-7.76 (m, 3H), 7.81-7.87 (m, 3H), 8.38 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 114.3, 117.4, 119.4, 124.2, 124.7, 126.4, 126.7, 127.2, 127.4, 128.8, 129.5, 129.6, 130.0, 130.1, 134.4, 139.4, 139.7, 153.5, 160.1, 187.8. Anal.calcd for $C_{26}H_{18}ClN_3O_3$: C, 68.50%; H, 3.98%; N, 9.22%. Found: C, 68.62%; H, 4.03%; N, 9.42%.

(1E,4E)-1-(4-chlorophenyl)-5-(3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)penta-1,4-dien-3-one (6k): Off-white solid; Yield: 73%; mp: 176-178 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ= 6.98 (d, *J* = 15.89 Hz, 2H), 7.18 (t, *J* = 8.31 Hz, 2H), 7.45 (t, *J* = 7.33 Hz, 1H), 7.56-7.60 (m, 4H), 7.64-7.67 (m, 2H), 7.70-7.74 (m, 3H), 7.81-7.87 (m, 3H), 8.39 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 116.1, 116.3, 118.2, 119.5, 125.3, 126.9, 127.5, 129.1, 129.7, 130.0, 130.1, 130.3, 130.4, 130.9, 131.1, 133.5, 134.9, 139.4, 141.9, 188.3. Anal.calcd for $C_{26}H_{18}Cl_2N_2O$: C, 70.12%; H, 4.07%; N, 6.29%. Found: C, 70.35%; H, 4.21%; N, 6.35%.

(1E,4E)-1-(3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-5-(4-fluorophenyl)penta-1,4-dien-3-one (6l):Off-white solid; Yield: 71%; mp: 178-180 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ= 6.90 (d, *J* = 15.89 Hz, 2H), 7.10 (t, *J* = 8.31 Hz, 2H), 7.37 (t, *J* = 7.33 Hz, 1H), 7.47-7.51 (m, 4H), 7.56-7.59 (m, 2H), 7.63-7.67 (m, 3H), 7.73-7.79 (m, 3H), 8.31 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 116.0, 116.2, 118.1, 119.4, 125.2, 126.8, 127.4, 129.0, 129.6, 129.9, 130.0, 130.2, 130.3, 130.8, 131.0, 133.4, 134.8, 139.3, 141.8, 188.2. Anal.calcd for $C_{26}H_{18}ClFN_2O$: C, 72.81%; H, 4.23%; N, 6.53%. Found: C, 72.99%; H, 4.35%; N, 6.67%.

(1E,4E)-1-(3,4-dimethoxyphenyl)-5-(1,3-diphenyl-1*H*-pyrazol-4-yl)penta-1,4-dien-3-one (6m):Off-white solid; Yield: 71%; mp: 177-179 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ= 3.93 (s, 6H), 6.86 (d, *J* = 14.91 Hz, 1H), 6.94 (d, *J* = 15.89 Hz, 1H), 7.11-7.26 (m, 3H), 7.35 (t, *J* = 7.33 Hz, 1H), 7.43-7.52 (m, 6H), 7.62 (d, *J* = 15.89 Hz, 1H), 7.72 (d, *J* = 7.70 Hz, 2H), 7.78-7.81 (m, 3H), 8.32 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 55.9, 109.9, 111.1, 118.2, 119.3, 123.0, 123.7, 125.0, 126.5, 127.2, 127.8, 128.6, 128.7, 128.8, 129.5, 132.4, 133.4, 139.4, 143.0, 149.3, 151.4, 153.7, 188.5. Anal.calcd for $C_{28}H_{24}N_2O_3$: C, 77.04%; H, 5.54%; N, 6.42%. Found: C, 77.25%; H, 5.31%; N, 6.62%.

(1E,4E)-1-(1,3-diphenyl-1*H*-pyrazol-4-yl)-5-(3,4,5-trimethoxyphenyl)penta-1,4-dien-3-one (6n): Off-white solid; Yield: 74%; mp: 178-180 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ= 3.99-4.01 (m, 9H), 6.91 (s, 2H), 6.97 (d, *J* = 15.89 Hz, 1H), 7.04 (d, *J* = 15.89 Hz, 1H), 7.46 (t, *J* = 7.34Hz, 1H), 7.57-7.62 (m, 5H), 7.68 (d, *J* = 15.89 Hz, 1H), 7.75 (d, *J* = 8.19 Hz, 2H), 7.83-7.88 (m, 3H), 8.41 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 56.0, 60.9, 105.3, 118.0, 119.2, 124.7, 125.0, 126.6, 127.3, 128.8, 129.5, 129.9, 130.1, 130.7, 133.2, 134.6, 139.1, 140.2, 143.0, 152.4, 153.3, 188.1. Anal.calcd for $C_{29}H_{26}N_2O_4$: C, 74.66%; H, 5.62%; N, 6.00%. Found: C, 74.52%; H, 5.75%; N, 6.13%.

(1E,4E)-1-(4-(dimethylamino)phenyl)-5-(1,3-diphenyl-1*H*-pyrazol-4-yl)penta-1,4-dien-3-one (6o):
Orange solid; Yield: 68%; mp: 175-176 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ= 3.03 (s, 6H), 6.67 (d, *J* = 8.80 Hz, 2H), 6.79 (d, *J* = 15.77 Hz, 1H), 6.93 (d, *J* = 15.77 Hz, 1H), 7.34 (t, *J* = 7.45 Hz, 1H), 7.47-7.51 (m, 6H), 7.65 (d, *J* = 15.77 Hz, 1H), 7.71-7.74 (m, 3H), 7.76-7.80 (m, 3H), 8.31 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 40.1, 111.8, 118.4, 119.3, 119.4, 120.8, 122.5, 125.6, 126.5, 127.1, 128.6, 128.7, 128.8, 129.5, 130.2, 132.4, 139.5, 144.0, 151.9, 153.6, 188.6.Anal.calcd for $C_{28}H_{25}N_3O$: C, 80.16%; H, 6.01%; N, 10.02%. Found: C, 80.37%; H, 6.19%; N, 10.20%.

(1E,4E)-1-(1,3-diphenyl-1*H*-pyrazol-4-yl)-5-(4-nitrophenyl)penta-1,4-dien-3-one (6p):Yellow solid; Yield: 73%; mp: 179-180 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ= 6.72 (d, *J* = 8.76 Hz, 2H), 6.72 (d, *J* = 15.77 Hz, 1H), 6.98 (d, *J* = 15.77 Hz, 1H), 7.28 (t, *J* = 7.42 Hz, 1H), 7.45-7.49 (m, 6H), 7.62 (d, *J* = 15.77 Hz, 1H), 7.75-7.78 (m, 3H), 7.81-7.85 (m, 3H), 8.34 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 110.9, 118.7, 119.6, 119.9, 120.4, 121.7, 124.7, 126.8, 127.7, 128.2, 128.4, 129.1, 129.5, 130.0, 132.8, 139.3, 144.9, 151.5, 154.7, 188.3. Anal.calcd for $C_{26}H_{19}N_3O_3$: C, 74.10%; H, 4.54%; N, 9.97%. Found: C, 74.27%; H, 4.62%; N, 10.01%.

(1E,4E)-1-(4-chlorophenyl)-5-(1,3-diphenyl-1*H*-pyrazol-4-yl)penta-1,4-dien-3-one (6q): Off-white solid; Yield: 70%; mp: 177-178 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ= 6.69 (d, *J* = 8.76 Hz, 2H), 6.71 (d, *J* = 15.77 Hz, 1H), 6.95 (d, *J* = 15.77 Hz, 1H), 7.24 (t, *J* = 7.42 Hz, 2H), 7.42-7.47 (m, 5H), 7.60 (d, *J* = 15.77 Hz, 1H), 7.73-7.76 (m, 2H), 7.81-7.85 (m, 4H), 8.36 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 110.5, 117.9, 119.2, 119.7, 120.2, 121.6, 123.5, 125.8, 127.3, 127.8, 128.8, 129.3, 129.8, 131.3, 132.5, 138.1, 143.6, 149.5, 153.4, 188.7. Anal.calcd for $C_{26}H_{19}ClN_2O$: C, 76.00%; H, 4.66%; N, 6.82%. Found: C, 76.20%; H, 4.80%; N, 6.95%.

(1E,4E)-1-(1,3-diphenyl-1*H*-pyrazol-4-yl)-5-(4-fluorophenyl)penta-1,4-dien-3-one (6r):Off-white solid; Yield: 70%; mp: 172-174 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ= 6.72 (d, *J* = 8.76 Hz, 2H), 6.77 (d, *J* = 15.77 Hz, 1H), 6.98 (d, *J* = 15.77 Hz, 1H), 7.29 (t, *J* = 7.42 Hz, 1H), 7.48-7.53 (m, 6H), 7.63 (d, *J* = 15.77 Hz, 1H), 7.75-7.78 (m, 2H), 7.91-7.95 (m, 4H), 8.38 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 111.5, 118.5, 118.9, 119.4, 120.1, 122.4, 123.2, 124.9, 126.9, 128.1, 128.9, 129.6, 129.9, 130.7, 133.5, 138.6, 145.8, 148.5, 152.7, 188.5. Anal.calcd for $C_{26}H_{19}FN_2O$: C, 79.17%; H, 4.86%; N, 7.10%. Found: C, 79.35%; H, 4.97%; N, 7.35%.

(1E,4E)-1-(3,4-dimethoxyphenyl)-5-(3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)penta-1,4-dien-3-one (6s):Off-white solid; Yield: 73%; mp: 177-178 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ = 3.95 (s, 6H), 6.87 (d, *J* = 15.77 Hz, 1H), 7.03 (d, *J* = 15.77 Hz, 1H), 7.15-7.21 (m, 4H), 7.39 (t, *J* = 7.47 Hz, 1H), 7.52-7.56 (m, 3H), 7.63-7.66 (m, 3H), 7.72-7.76 (m, 3H), 8.32 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 56.2, 110.9, 111.8, 117.1, 120.4, 123.3, 123.8, 124.9, 126.5, 127.4, 128.3, 129.3, 129.7, 130.2, 131.3, 132.7, 135.4, 139.8, 144.2, 149.6, 151.3, 152.9, 188.7. Anal.calcd for $C_{28}H_{23}FN_2O_3$: C, 73.99%; H, 5.10%; N, 6.16%. Found: C, 74.02%; H, 5.15%; N, 6.28%.

(1E,4E)-1-(3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-5-(3,4,5-trimethoxyphenyl)penta-1,4-dien-3-one (6t): Off-white solid; Yield: 75%;

mp: 178-179 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.98-4.03 (m, 9H), 6.82 (s, 2H), 6.91 (d, *J* = 15.77 Hz, 1H), 6.97 (d, *J* = 15.77 Hz, 1H), 7.25 (t, *J* = 7.84 Hz, 1H), 7.51-7.55 (m, 5H), 7.61 (d, *J* = 15.89 Hz, 1H), 7.69 (d, *J* = 8.19 Hz, 2H), 7.79-7.83 (m, 2H), 8.37 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 56.4, 61.5, 106.7, 117.6, 120.4, 124.4, 125.3, 126.4, 128.4, 129.2, 129.6, 130.2, 130.8, 131.8, 133.3, 135.7, 138.9, 141.4, 144.7, 151.5, 154.5, 188.8. Anal.calcd for $C_{29}H_{25}FN_2O_4$: C, 71.89%; H, 5.20%; N, 5.78%. Found: C, 72.01%; H, 5.41%; N, 5.96%.

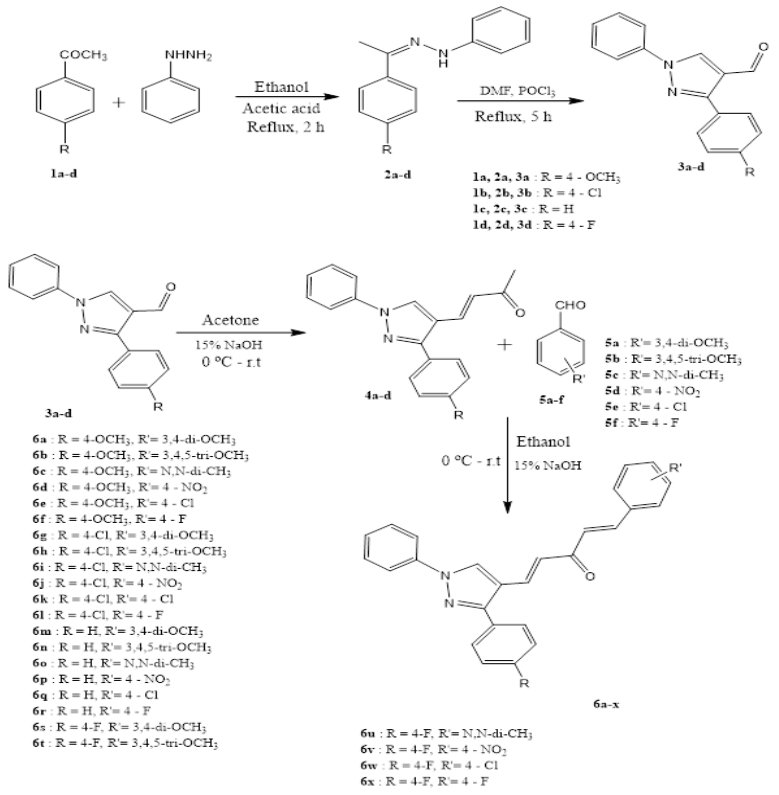
(1E,4E)-1-(4-(dimethylamino)phenyl)-5-(3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)penta-1,4-dien-3-one (6u): Orange solid; Yield: 68%; mp: 179-180 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 3.08 (s, 6H), 6.65 (d, *J* = 8.74 Hz, 2H), 6.81 (d, *J* = 15.77 Hz, 1H), 6.95 (d, *J* = 15.77 Hz, 1H), 7.51-7.54 (m, 7H), 7.68 (d, *J* = 8.43 Hz, 2H), 7.75 (d, *J* = 15.89 Hz, 2H), 7.82 (d, *J* = 8.19 Hz, 2H), 8.35 (s,1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 40.4, 112.5, 117.6, 119.8, 120.9, 122.6, 126.1, 126.8, 127.6, 129.2, 129.7, 130.2, 130.5, 130.8, 131.3, 132.5, 144.6, 152.1, 153.5, 157.9, 188.7. Anal.calcd for $C_{28}H_{24}FN_3O$: C, 76.87%; H, 5.53%; N, 9.60%. Found: C, 76.52%; H, 5.65%; N, 9.76%.

(1E,4E)-1-(3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-5-(4-nitrophenyl)penta-1,4-dien-3-one (6v):Yellow solid; Yield: 70%; mp: 177-179 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 6.81 (d, *J* = 8.65 Hz, 2H), 6.92 (d, *J* = 15.89 Hz, 1H), 7.12 (d, *J* = 15.87 Hz, 1H), 7.46 (t, *J* = 7.37 Hz, 2H), 7.63-7.65 (m, 5H), 7.75-7.78 (m, 3H), 7.84-7.87 (m, 3H), 8.34 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 114.6, 118.3, 120.1, 123.5, 124.9, 126.4, 126.9, 127.4, 127.8, 129.1, 129.4, 129.8, 130.3, 131.7, 135.8, 139.5, 139.7, 154.6, 159.8, 188.2. Anal.calcd for $C_{26}H_{18}FN_3O_3$: C, 71.06%; H, 4.13%; N, 9.56%. Found: C, 71.21%; H, 4.27%; N, 9.31%.

(1E,4E)-1-(4-chlorophenyl)-5-(3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)penta-1,4-dien-3-one (6w): Off-white solid; Yield: 70%; mp: 175-176 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ= 6.94 (d, *J* = 15.89 Hz, 2H), 7.23 (t, *J* = 8.45 Hz, 2H), 7.47 (t, *J* = 7.35 Hz, 1H), 7.54-7.57 (m, 3H), 7.65-7.69 (m, 3H), 7.70-7.74 (m, 4H), 7.81-7.87 (m, 2H), 8.41 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ= 116.5, 117.2, 118.5, 120.7, 125.8, 126.5, 127.8, 128.9, 129.6, 129.8, 130.2, 130.3, 130.6, 130.9, 132.0, 133.6, 135.4, 139.8, 142.6, 188.7. Anal.calcd for $C_{26}H_{18}ClFN_2O$: C, 72.81%; H, 4.23%; N, 6.53%. Found: C, 72.96%; H, 4.45%; N, 6.72%.

(1E,4E)-1-(4-fluorophenyl)-5-(3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)penta-1,4-dien-3-one (6x):Off-white solid; Yield: 71%; mp: 174-176 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.92 (d, *J* = 15.89 Hz, 2H), 7.10 (t, *J* = 8.34 Hz, 2H), 7.39 (t, *J* = 7.33 Hz, 1H), 7.47-7.51 (m, 3H), 7.58-7.61 (m, 3H), 7.65-7.69 (m, 3H), 7.82-7.87 (m, 3H), 8.38 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 116.7, 117.1, 118.5, 119.9, 124.8, 125.8, 127.7, 129.2, 129.5, 129.9, 130.1, 130.2, 130.6, 130.9, 132.5, 133.8, 134.6, 140.1, 142.8, 188.5. Anal.calcd for $C_{26}H_{18}F_2N_2O$: C, 75.72%; H, 4.40%; N, 6.79%. Found: C, 75.91%; H, 4.72%; N, 6.86%.

Scheme-1: Synthesized of a series of asymmetric curcuminoid analogs



RESULTS AND DISCUSSIONS

In the present study, we have synthesized a series of asymmetric curcuminoid analogs (6a-x) by taking two core structural elements aldehydes (3a-d) and chalcones (4a-d). Initially, for the preparation of aldehyde derivatives (3a-d), the appropriate phenyl hydrazones were prepared by treating different aldehydes with phenyl hydrazine in the presence of acetic acid. Then they were refluxed with VilsmeierHaack reagent (DMF+$POCl_3$) at 80 ^{o}C to yield 3-(substituted phenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (3a-d). Chalcones (4a-d) were prepared by NaOH-madiatedClaisen-Schmidt condensation of aldehydes (3a-d) with acetone[21]. Finally, NaOH-madiatedClaisen-Schmidt condensation of chalcones (4a-d) and substituted benzaldehydes (5a-f) furnished the target compounds 6a-x in good yields (Scheme 1).

All the synthesized compounds were purified by column chromatography and well characterized by spectroscopic techniques such as ^{1}H NMR, ^{13}C NMR spectra and elemental analysis. The formation of compounds 3a-d was confirmed by the appearance of aldehyde proton in the range of δ 10.04-10.19 ppm. The ^{1}H NMR spectrum of compound 6c showed a singlet of two methyl groups on nitrogen at δ 3.03 ppm, a singlet of methoxy protons at δ 3.88 ppm and pyrazole –CH proton was assigned at δ 8.28 ppm. All the aromatic protons and four olefinic protons appeared in the region of δ 6.68-8.28 ppm. In the ^{13}C NMR spectrum, the aliphatic carbons appeared in the region between δ 40.1-55.3 ppm while the aromatic carbons and four olefinic carbons were assigned in the region of δ 119.8-160.0 ppm. The most deshielded carbon at δ 188.5 ppm was assigned to carbonyl carbon. Almost similar patterns were observed in ^{1}H and ^{13}C NMR spectra of rest of the compounds (6a-x).

CONCLUSION

In summary, we have synthesized a series of curcumin inspired pyrazole derivatives (6a-x) by using Claisen Schmidt reaction. Intiallychalcones (4a-d) were prepared from pyrazolecarbaldehyde derivatives (3a-d) by treating with acetone in the presence of potassium carbonate. Finally monocarbonyl analogs of curcumins were synthesized by Claisen Schmidt condensation of chalcones with benzaldehyde derivatives (5a-f). All the MCAs were characterized by 1H NMR, 13C NMR spectra and elemental analysis.

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