Synthesis of 1,3-Diaryl Substituted Pyrazole Based Curcuminoids as Potent Antibacterial Agents

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Abstract-

*Some new 5-substituted (1E,4E)-1-[3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl]-1,4-dien-3-one derivatives has been synthesized and confirmed on the basis of IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectroscopic techniques. The synthesized derivatives then screened for their antimicrobial activity against S. aureus and E. coli bacteria. Among the tested compounds, derivative **5g, 5h** and **5k** are most active against S. aureus while derivative **5h** is most active against E. coli. Out of these tested derivatives, compound **5h** with electron donating **2,5-dimethoxy** substitution on aromatic aldehyde ring of curcumin structure is more potent in their anti-microbial activity.*

Keywords- *Hydrazone, Pyrazole-4-carboxaldehyde, Vilsmeier-Haack Reaction, antimicrobial activity, MIC.*

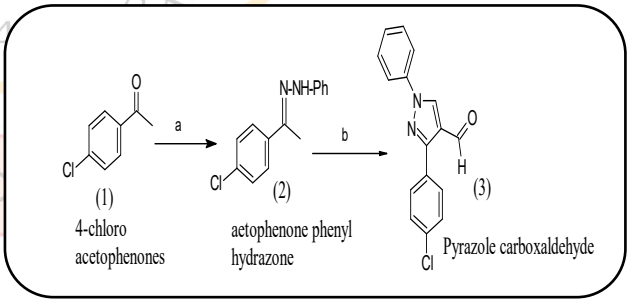
Introduction-

1,3-diaryl pyrazole based dienones are the mimics of curcumin analogues. Presence of α-β unsaturation on both side of carbonyl group makes it more important precursor in the field of pharmacology [1,2] as well as in organic transformations [3]. Modification to the central β-diketone structure of natural curcumin analogues enhances its biological properties [4,5].These derivatives are used to cure Parkinson's disease [6]. Extensive literature survey shown that 1,3 diaryl pyrazole based curcumins exhibit diverse variety of bio-activities like anticancer [7,8], antibacterial [9], antioxidant and antihypoglycemic[10], antimalarial [11], anti-tuberculosis [12], antimicrobial [13], antioxidant [14] and antiviral[15] which revealed that 1,3-diaryl pyrazole based curcumins are potent bioactive molecules.

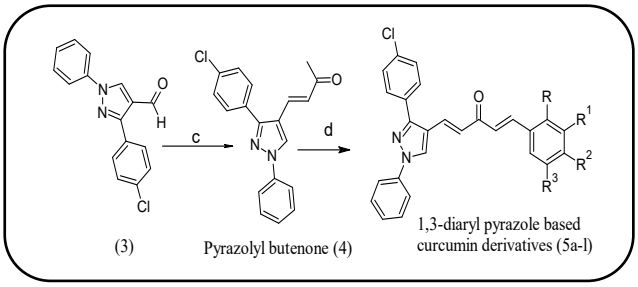
Result And Discussion-

Chemistry-

The required intermediate pyrazole-4-carboxaldehyde (3) was generated by Vilsmeier-Haack reaction on acetophenone hydrazone (2) which in turn obtained by the reaction of 4-chloro acetophenone (1) with phenyl hydrazine. [Scheme 1]. The pyrazole-4-carboxaldehyde (3) on further reaction with acetone gave another one precursor compound pyrazolyl butenone (4), which on subsequently condensation with differently substituted aromatic as well as hetero aromatic aldehydes gave 1,3-diaryl substituted pyrazole based curcumin derivatives in good yield. [Scheme 2].



Scheme 1: Reagents and conditions



Scheme 2: Reagents and conditions

(a) $PhNHNH_2$, Glacial AcOH, EtOH, reflux;
(b) DMF / $POCl_3$, 0-100°C (Vilsmeier-Haack Reaction)
(c) Acetone, NaOH, EtOH, 1:1 Selective and slow stirring under cold reaction condition;
(d) Different substituted aromatic or heteroaromatic aldehydes, NaOH, EtOH, Reflux.

Antimicrobial activity-:

All the synthesized 1,3-diaryl substituted pyrazole based curcumin derivatives (5a-l) were screened for their in vitro antimicrobial potential against Gram positive (*S. aureus*) and Gram negative (*E. coli*) bacteria. Among the tested compounds, curcumin derivatives 5c, 5h, 5k exhibited MIC 0.4 µg/mL against *S. aureus* while curcumin derivative 5h exhibited MIC 6.25 µg/mL against *E. coli*. The standard drug Ciprofloxacin showed MIC 2.0 µg/mL against both *S. aureus* and *E. coli*.

Experimental-:

The melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded in KBr on FT/IR-4600 type A spectrophotometer and frequencies are presented as cm^{-1}. ^1H NMR and ^{13}C spectra were taken in $CDCl_3$ on Bruker 400MHz spectrometer using TMS as an internal standard in $CDCl_3$ as solvent. Chemical shift values are expressed in δ (ppm). Mass spectra were recorded with a Shimadzu LCMS-2010EV. Homogeneity of the compounds was checked on TLC silica gel G plates and spots were located by exposure to iodine vapors.

Synthesis of acetophenone hydrazone derivatives N-[1-(4-chloro-phenyl)-eth-(*E*)-ylidene]-N'-phenyl-hydrazine (2)

A mixture of 4-chloro acetophenone (**1**) (0.309 g, 0.23 mL, 2 mmol) and solution of phenyl hydrazine (0.216 g, 0.2 mL, 2 mmol) in ethanol (15 mL) is taken in a 100 mL round bottomed flask equipped with reflux condenser and magnetic stirrer. To this reaction mixture, catalytic amount of glacial acetic acid (2-3 drops) was added and heated at reflux with constant stirring for 2h on oil bath. After completion of reaction observed on TLC, the reaction mixture was cooled to separate out colorless solid of N-[1-(4-chloro-phenyl)-eth-(*E*)-ylidene]-N'-phenyl-hydrazine (**2**). The obtained solid was filtered, washed with water and recrystallized from ethanol to obtain the pure product.

Synthesis of 3-(4-chloro-phenyl)-1-phenyl-1*H*-pyrazole-4-carboxaldehyde (3)

A mixture of acetophenone hydrazone (**2**) N-[1-(4-chloro-phenyl)-eth-(*E*)-ylidene]-N'-phenyl-hydrazine (0.489 g, 2 mmol) and dimethyl formamide (DMF) (0.146 g 0.15 mL, 2 mmol) was taken in a three neck round bottomed flask equipped with reflux condenser under inert atmosphere. The reaction mixture was cooled at 0°C and treated with $POCl_3$ (0.306 g, 0.19 mL, 2 mmol) maintaining the temperature between 10-15°C. After complete addition, the reaction mixture was heated on water bath for about 3h, cooled, and poured into ice water with vigorous stirring to obtain the desired compound **(3)** in good yield. The product obtained was recrystallized from ethanol as yellow needles.

Synthesis of (3*E*)-4-[3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-but-3-en-2-one (4)

A mixture of 3-(4-chloro-phenyl)-1-phenyl-1*H*-pyrazole-4-carboxaldehyde **(3)** (0.564 g, 2 mmol) and acetone (0.116 g, 0.14 mL, 2 mmol) was taken in a three neck round bottomed flask equipped with air condenser and magnetic stirrer. The resulting mixture was cooled in ice-bath and cooled solution of 10% NaOH was added very slowly drop wise with slow stirring. After complete addition, the stirring continued for 2 hours using ice bath. After completion of reaction monitored with TLC, the resulting mixture was poured on crushed ice to get white coloured solid compound **(4)** (3*E*)-4-[3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-but-3-en-2-one. The solid obtained was filtered, washed with water, dried and recrystallized from ethanol to obtain pure 1,3-diaryl pyrazol-4-yl-but-3-en-2-one (**4**) which was used for further synthesis of target compounds.

Yield: 0.504 g, 78.00%, m.p. 164-166 °C, M.F. $C_{19}H_{15}ClN_2O$, F.Wt. 322.

Synthesis of 1,3-diaryl pyrazole based curcumin derivatives. (5 a-l)

In round bottomed flask, a mixture of (3*E*)-4-[3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-but-3-en-2-one (**4**) (0.322 g, 1 mmol) and substituted aromatic / hetero-aromatic aldehyde (1 mmol) was dissolved in ethanol (15 mL) under stirring. To this

solution was added sodium hydroxide (0.12 g, 3 mmol) dissolved in minimum quantity of water and stirring continued further for 2-3h. After completion of reaction observed with TLC, the yellow solid product obtained was filtered off and washed with little cold ethanol. The crude product was dried and recrystallized from ethanol to get desired product in pure form.

(1*E*,4*E*)-1-[3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-5-phenylpenta-1,4-dien-3-one (5a)
Yield 85%, m.p. 195-197 °C, **M.F.** $C_{26}H_{19}ClN_2O$, F. Wt. 410.91; **FT-IR υ_{max} cm^{-1}:** 671, 690, 756, 956, 1078, 1197, 1325, 1456, 1618, 1686, 2987, 3022. **^{1}H NMR ($CDCl_3$ 400 MHz):** δ 6.88 (d, J = 15.4 Hz, 2H, 2 x ***=CH-CO***), 7.23 (d, J = 7.4 Hz, 4H, 4 x ***–ArH***), 7.35-7.39 (m, 6H, 6 x ***–ArH***), 7.41- 7.47 (m, 3H, 3 x ***–ArH***), 7.53-7.58 (m, 3H, 2 x ***–CH***=*CH-CO* & 1 x ***–ArH***), 8.38 (s, 1H, ***Pyr-H***). **^{13}C NMR ($CDCl_3$ 100 MHz):** 119.71, 125.81, 127.75, 128.68, 129.30, 129.36, 129.95, 130.33, 130.83, 133.70, 135.07, 143.51, 146.85 210.85. **MS (EI) *m/z:*** 410.90 $(M)^+$. **Molecular Composition:** calculated (Found) C 76.00% (76.03%), H 4.66% (4.68%), N 6.82% (6.80%), O 3.89% (3.90%), Cl 8.63% (8.66%).

(1*E*,4*E*)-1-[3-(4-Chloro-phenyl)-1-phenyl-1*H*-pyrazol-4-yl]-5-p-tolyl-penta-1,4-dien-3-one (5b).
Yield 76%, m.p. 183-185 °C, M.F. $C_{27}H_{21}ClN_2O$, F.Wt. 424.93; **FT-IR υ_{max} cm^{-1}:** 496, 543, 685, 754, 841, 981, 1091, 1184, 1242, 1305, 1441, 1536, 1577, 1618, 1651, 2920, 3122. **^{1}H NMR ($CDCl_3$ 400 MHz):** δ 2.99 (s, 3H, ***-Ar-CH$_3$***), 6.93 (dd, J = 8Hz, 16 Hz, 2H, 2 x ***=CH-CO***), 7.21 (d, J = 8Hz, 2H, ***-ArH***), 7.37 (m, 1H, ***-ArH***), 7.47-7.52 (m, 6H, ***-ArH***), 7.64-7.78 (m, 6H, ***2 x –CH***=*CH-CO* ***& 4 x -ArH***), 8.31 (s, 1H, ***Pyr-H***). **^{13}C NMR ($CDCl_3$ 100 MHz):** 21.54, 118.18, 119.38, 125.29, 129.03, 129.61, 129.73, 130.00, 131.90, 139.32, 141.08, 143.28, 152.49, 188.53. **MS (EI) *m/z:*** 424.88 $(M)^+$ **Molecular Composition:** calculated (Found) C 76.32% (76.33%), H 4.98% (4.99%), N 6.59% (6.60%), O 3.77% (3.79%), Cl 8.34% (8.36%).

(1*E*,4*E*)-1-[3-(4-Chloro-phenyl)-1-phenyl-1*H*-pyrazol-4-yl]-5-(4-nitro-phenyl)-penta-1,4-dien-3-one (5c).
Yield 82%, m.p. 213-214 °C, M. F. 213-214 °C, F.Wt. 455.90; **FT-IR υ_{max} cm^{-1}:** 685, 778, 923, 1078, 1219, 1460, 1525, 1656, 1675, 2978, 3012. **^{1}H NMR ($CDCl_3$ 400 MHz):** δ 6.97 (d, J = 16.2 Hz, 2H, 2 x ***=CH-CO***), 7.42 (d, J = 7.8 Hz, 3H, 3 x ***–ArH***), 7.45--7.49 (m, 6H, 6 x ***–ArH***), 7.53- 7.58 (m, 3H, 3 x ***–ArH***), 7.69-7.74 (m, 3H, 2 x ***–CH***=*CH-CO* & 1 x ***–ArH***), 8.43 (s, 1H, ***Pyr-H***). **^{13}C NMR ($CDCl_3$ 100 MHz):** 119.71, 1256.71, 127.95, 128.98, 129.33, 129.46, 129.95, 130.63, 130.93, 134.60, 135.27, 144.74, 146.95 198.845. **MS (EI) *m/z:*** 455.96 $(M)^+$ **Molecular Composition:** calculated (Found) C 68.50% (68.52%), H 3.98% (4.01%), N 9.22% (9.23%), O 10.53% (10.55%), Cl 7.78% (7.80%).

(1*E*,4*E*)-1-[3-(4-Chloro-phenyl)-1-phenyl-1*H*-pyrazol-4-yl]-5-(4-hydroxy-phenyl)-penta-1,4-dien-3-one (5d)
Yield 81.00%, m.p. 179-180 °C, M. F. $C_{26}H_{19}ClN_2O_2$, F.Wt. 426.91; **FT-IR υ_{max} cm^{-1}:** 685, 965, 1069, 1198, 1323, 1435, 1616, 1694, 2994, 3034, 3488. **^{1}H NMR ($CDCl_3$ 400 MHz):** δ 6.90 (d, J = 16.4 Hz, 2H, 2 x ***=CH-CO***), 7.28 (d, J = 6.4 Hz, 3H, 3 x ***–ArH***), 7.33-7.37 (m, 6H, 6 x ***–ArH***), 7.40-7.46 (m, 3H, 3 x ***–ArH***), 7.53-7.59 (m, 3H, 2 x ***–CH***=*CH-CO* & 1 x ***–ArH***), 8.13 (bs, 1H, ***-Ar-OH***), 8.38 (s, 1H, ***Pyr-H***). **^{13}C NMR ($CDCl_3$ 100 MHz):** 116.11, 116.61, 117.85, 119.63, 119.98, 120.76, 122.68, 124.55, 124.76, 127.49, 128.62, 128.77, 128.89, 129.22, 129.98, 130.19, 131.98, 133.27, 134.69, 135.79, 138.88, 143.63, 152.94, 157.89, 179.85. **MS (EI) *m/z:*** 426.86 $(M)^+$ **Molecular Composition:** calculated (Found) C 73.15% (7.18%), H 4.49% (4.51%), N 6.56% (6.57%), O 7.50% (7.51%), Cl 8.30% (8.33%).

(1*E*,4*E*)-1-[3-(4-Chloro-phenyl)-1-phenyl-1*H*-pyrazol-4-yl]-5-(4-methoxy-phenyl)-penta-1,4-dien-3-one (5e).
Yield 82.00%, m. p. 167-168 °C, M. F. $C_{27}H_{21}ClN_2O_2$, F. Wt. 440.93; **FT-IR υ_{max} cm^{-1}:** 613, 838, 980, 1027, 1108, 1230, 1372, 1407, 1598, 1644, 1687, 2969. **^{1}H NMR ($CDCl_3$ 400 MHz):** δ 3.80 (s, 3H, ***-OCH$_3$***), 6.57 (dd, J = 7.6Hz, 16 Hz, 2H, 2 x ***=CH-CO***), 6.61 (d, J = 7.4 Hz, 2H, ***-ArH***), 7.38 (m, 1H, ***-ArH***), 7.49-7.54 (m, 6H, ***-ArH***), 7.62-7.79 (m, 6H, 2 x ***–CH***=*CH-CO* & 4 x ***–ArH***), 8.27 (s, 1H, ***Pyr-H***). **^{13}C NMR ($CDCl_3$ 100 MHz):** 55.52, 117.25, 119.05, 126.21, 126.73, 127.12, 128.72, 129.28, 130.36, 133.16, 134.51, 138.94, 152.06,

197.63. **MS (EI)** ***m/z:*** 440.90 $(M)^+$ **Molecular Composition:** calculated (Found) C 73.55% (73.56%), H 4.80% (4.82%), N 6.35% (6.37%), O 7.26% (7.27%), Cl 8.04% (8.06%).

(1*E*,4*E*)-1-(2-chlorophenyl)-5-[3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]penta-1,4-dien-3-one (5f).

Yield 84.00%, m.p. 156-158 ºC, M.F. $C_{26}H_{18}Cl_2N_2O$, F. Wt. 445.33; **FT-IR υ_{max} cm^{-1}:** 671, 689, 758, 998, 1086, 1216, 1366, 1418, 1499, 1623, 1689, 2969, 3016. **^{1}H NMR ($CDCl_3$ 400 MHz):** δ 6.90 (d, J = 16.2 Hz, 2H, 2 x ***=CH-CO***), 7.33 (d, J = 6.8 Hz, 4H, 4 x ***–ArH***), 7.37-7.42 (m, 3H, 3 x ***–ArH***), 7.47 (d, 6.8 Hz, 2H, 2 x ***–ArH***), 7.55-7.59 (m, 4H, 2 x ***–CH***=*CH-CO* & 2 x ***–ArH***), 7.63 (d, J = 6.6 Hz, 2H, ***-ArH***), 8.41 (s, 1H, ***Pyr-H***). **^{13}C NMR ($CDCl_3$ 100 MHz):** 119.72, 124.63, 127.46, 127.77, 127.97, 128.64, 129.94, 130.33, 130.57, 134.17, 139.05, 139.59, 152.89, 188.77. **MS (EI)** ***m/z:*** 445.45 $(M)^+$ **Molecular Composition:** calculated (Found) C 70.12% (70.13%), H 4.07% (4.09%), N 6.29% (6.31%), O 3.59% (3.61%), Cl 15.92% (15.95%).

(1*E*,4*E*)-1-(4-chlorophenyl)-5-[3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]penta-1,4-dien-3-one (5g).

Yield 79.00%, m.p. 146-148 ºC, M.F. $C_{26}H_{18}Cl_2N_2O$, F.Wt. 445.33; **FT-IR υ_{max} cm^{-1}:** 452, 541, 755, 842, 1012, 1093, 1185, 1241, 1292, 1505, 1536, 1598, 1617, 1653, 2923, 3050, 3124. **^{1}H NMR ($CDCl_3$ 400 MHz):** δ 6.92 (dd, J = 8Hz, 16 Hz, 2H, 2 x ***=CH-CO***), 7.38 (d, J = 8Hz, 3H, 3 x ***–ArH***), 7.40-7.50 (m, 6H, 6 x ***–ArH***), 7.51-7.64 (m, 3H, 3 x ***–ArH***), 7.66-7.77 (m, 3H, 2 x ***–CH***=CH-CO & 1 x ***–ArH***), 8.31 (s, 1H, ***Pyr-H***). **^{13}C NMR ($CDCl_3$ 100 MHz):** 118.09, 119.43, 125.17, 125.88, 127.48, 129.07, 129.28, 129.50, 129.65, 130.03, 133.65, 134.89, 141.67, 152.59, 188.15.**MS (EI)** ***m/z:*** 445.38 $(M)^+$ **Molecular Composition:** calculated (Found) C 70.12% (70.13%), H 4.07% (4.09%), N 6.29% (6.31%), O 3.59% (3.60%), Cl 15.92% (15.94%).

(1*E*,4*E*)-1-[3-(4-Chloro-phenyl)- 1-phenyl-1*H*-pyrazol-4-yl] -5-(2,5-dimethoxy-phenyl)-penta-1,4-dien-3-one (5h).

Yield 88.00%, m.p. 213-215 ºC, M.F. $C_{28}H_{23}ClN_2O_3$, F.Wt. 470.96; **FT-IR υ_{max} cm^{-1}:** 508, 607, 682, 754, 840, 997, 1093, 1131, 1182, 1240, 1274, 1333, 1416, 1504, 1536, 1597, 1620, 1652, 2833 2931, 3124. **^{1}H NMR ($CDCl_3$ 400 MHz):** δ 3.82 (s, 3H, ***-OCH$_3$***), 3.88 (s, 3H, ***-OCH$_3$),*** 6.88 (d, J = 8Hz, 1H, ***-ArH***), 6.95 (d, J = 8Hz, 1H, ***-ArH***), 7.03 (d, J = 6 Hz, 1H, ***-ArH***), 7.13 (d, J = 6 Hz, 1H, ***-ArH***), 7.36-7.42 (m, 1H, ***-ArH***), 7.48-7.52 (m, 4H, ***2 x =CH-CO & 2 x -ArH***), 7.67-7.80 (m, 6H, ***2 x -CH***=*CH-CO* ***& 4 x -ArH***), 7.83 (s, 1H, ***Ar-H***), 8.33 (s, 1H, ***Pyr-H***). **^{13}C NMR ($CDCl_3$ 100 MHz):** 55.80, 56.10, 112.45, 113.22, 117.43, 119.39, 126.65, 127.37, 128.99, 129.61, 130.01, 133.07, 138.24, 152.49, 153.10, 153.55, 189.08. **MS (EI)** ***m/z:*** 470.90 $(M)^+$ **Molecular Composition:** calculated (Found) C 71.41% (71.42%), H 4.92% (4.95%), N 5.95% (5.97%), O 10.19% (10.20%), Cl 7.53% (7.56%).

(1*E*,4*E*)-1-[3-(4-Chloro-phenyl)- 1-phenyl-1*H*-pyrazol-4-yl] -5-(2,4-dichloro-phenyl)-penta-1,4-dien-3-one (5i).

Yield 89.00%, m.p. 172-174 ºC, M.F. $C_{26}H_{17}Cl_3N_2O$, F.Wt. 479.78; **FT-IR υ_{max} cm^{-1}:** 561, 765, 862, 1027, 1088, 1169, 1261, 1296, 1526, 1567, 1587, 1630, 1653, 2983, 3008, 3024. **^{1}H NMR ($CDCl_3$ 400 MHz):** δ 6.86 (d, J = 16 Hz, 2H, 2 x ***=CH-CO***), 7.18 (d, J = 7.6 Hz, 2H, 2 x ***–ArH***), 7.23 (d, J = 7.6 Hz, 2H, 2 x ***–ArH***), 7.28 (dd, J = 2.4 Hz, 7.4 Hz, 1H, ***–ArH***), 7.33 (d, J = 7.4 Hz, 4H, 4 x ***–ArH***), 7.41-7.47 (m, 3H, 3 x ***–ArH***), 7.58 (d, J = 16 Hz, 2H, 2 x ***–CH***=*CH-CO*), 8.35 (s, 1H, ***Pyr-H***). **^{13}C NMR ($CDCl_3$ 100 MHz):** 119.72, 124.61, 127.36, 127.81, 127.93, 12.68, 129.38, 129.95, 130.33, 130.40, 134.44, 137.80, 139.56, 152.91, 188.47. **MS (EI)** ***m/z:*** 479.80 $(M)^+$ **Molecular Composition:** calculated (Found) C 65.09% (65.10%), H 3.57% (3.60%), N 5.84% (5.86%), O 3.33% (3.35%), Cl 22.17% (22.19%).

(1*E*,4*E*)-1-[3-(4-Chloro-phenyl)- 1-phenyl-1*H*-pyrazol-4-yl] -5-(3,4,5-trimethoxy-phenyl)-penta-1,4-dien-3-one (5j).

Yield 82.00%, m.p. 221-223 ºC, M.F. $C_{29}H_{25}ClN_2O_4$, F.Wt. 500.99; **FT-IR υ_{max} cm^{-1}:** 547, 686, 754, 845, 1042, 1092, 1178, 1218, 1348, 1418, 1494, 1536, 1589, 1620, 1650, 2837, 2926, 3007, 3067, 3119. **^{1}H NMR ($CDCl_3$ 400 MHz):** δ 3.93 (s, 3H, ***-OCH$_3$***), 3.96 (s, 6H, 2 x ***–OCH$_3$***), 6.92 (d, J = 16 Hz, 2H, 2 x ***=CH-CO***), 7.02 (d, J = 7.4 Hz, 2H, 2 x ***–ArH***), 7.21 (d, J = 7.6 Hz, 2H, ***-ArH***), 7.28-7.34 (m, 3H, 3 x ***–ArH***), 7.37 (d, J = 7.6 Hz, 4H, 4 x ***–ArH***), 7.45 (d, J = 16 Hz, 2H, 2 x ***–CH***=*CH-CO*), 8.38 (s, 1H, ***Pyr-H***). **^{13}C NMR ($CDCl_3$ 100 MHz):** 56.41, 61.26, 105.71, 119.52, 125.12, 125.41, 127.70, 129.23,

129.88, 130.30, 130.46, 143.42, 153.71, 188.49. **MS (EI) *m/z:*** 501.12 $(M)^+$ **Molecular Composition:** calculated (Found) C 69.53% (69.56%), H 5.03% (5.05%), N 5.59% (5.61%), O 12.77% (12.80%), Cl 7.08% (7.10%).

(1*E*,4*E*)-1-[3-(4-Chloro-phenyl)- 1-phenyl-1*H*-pyrazol-4-yl] -5-naphthalen-1-yl-penta-1,4-dien-3-one (5k).

Yield 85.00%, m.p. 188-189 ºC, M.F. $C_{30}H_{21}ClN_2O$, F.Wt. 460.97; **FT-IR υ_{max} cm^{-1}:** 637, 767, 993, 1068, 1113, 1219, 1398, 1479, 1619, 1634, 2918, 2989. **^{1}H NMR ($CDCl_3$ 400 MHz):** δ 6.92 (d, J = 16 Hz, 2H, =***CH-CO***), 7.24 (d, J = 7.6 Hz, 2H, ***-ArH***), 7.28-7.33 (m, 3H, ***-ArH***), 7.34 (d, J = 7.6 Hz, 7H, 7 x ***–ArH***), 7.45 (d, J = 16 Hz, 2H, 2 x ***–CH***=*CH-CO*), 7.62 (d, J = 7.4 Hz, 4H, 4 x ***–ArH***), 8.28 (s, 1H, ***Pyr-H***). **^{13}C NMR ($CDCl_3$ 100 MHz):** 119.38, 125.07, 125.45, 126.28, 126.96, 128.78 129.04, 129.61, 130.00, 130.76, 133.71, 140.02, 152.52, 188.31. **MS (EI) *m/z:*** 460.92 $(M)^+$ **Molecular Composition:** calculated (Found) C 78.17% (78.19%), H 4.59% (4.60%), N 6.08% (6.11%), O 3.47% (3.50%), Cl 7.69% (7.70%).

(1*E*,4*E*)-1-[3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-5-(thiophen-2-yl)penta-1,4-dien-3-one (5l).

Yield 86.00%, m.p. 169-171 ºC , M.F. $C_{24}H_{17}ClN_2OS$, F.Wt. 416.93; **FT-IR υ_{max} cm^{-1}:** 556, 657, 775, 983, 1098, 1143, 1229, 1376, 1488, 1636, 1656, 2998, 3033. **^{1}H NMR ($CDCl_3$ 400 MHz):** δ 6.90 (d, J = 16 Hz, 2H, =***CH-CO***), 7.21 (d, J = 7.4 Hz, 3H, ***-ArH***), 7.30-7.34 (m, 5H, ***-ArH***), 7.47 (d, J = 16 Hz, 2H, 2 x ***–CH***=*CH-CO*),7.68 (d, J = 7.4 Hz, 4H, 4 x ***–ArH***), 8.33 (s, 1H, ***Pyr-H***). **^{13}C NMR ($CDCl_3$ 100 MHz):** 119.63, 119.89, 120.71, 122.68, 124.56, 124.78, 128.33, 128.62, 1128.69, 128.77, 128.93, 129.11, 129.19, 129.24, 129.27, 130.36, 132.26, 132.38, 133.22, 135.70, 138.88, 139.17, 139.73, 152.96, 188.89. **MS (EI) *m/z:*** 416.86 $(M)^+$ **Molecular Composition:** calculated (Found) C 69.14% (69.16%), H 4.11% (4.13%), N 6.72% (6.70%), O 3.84% (3.86%), Cl 8.50% (8.52%), S 7.69% (7.71%).

Antimicrobial Activity-:

All the synthesized 1,3-diaryl substituted pyrazole based curcumin derivatives (5a-l) were screened for their in vitro antimicrobial potential against Gram positive (*S. aureus*) and Gram negative (*E. coli*) bacteria using BHI broth dilution method at maximum concentration of 50 µg/mL in DMSO [16-19]. The drug dilutions were made serially. The test was performed at 25°C with pH 7.4+/-0.2 and minimum inhibitory concentration (MIC) in µg/mL was recorded by visual observation after 24 h incubation and compared with Ciprofloxacin as standard drug.

Table 1. Antibacterial activities of 1,3-diaryl pyrazole based curcumin derivatives **(MIC Values in µg/mL)**

Sr. No.	Compound Code	MIC Values in µg/mL	
		S. aureus	*E. coli*
1	3-Ph curcumin 5a	50.0	50.0
2	3-Ph curcumin 5b	0.8	100.0
3	3-Ph curcumin 5c	**0.4**	12.5
4	3-Ph curcumin 5d	0.8	50.0
5	3-Ph curcumin 5e	0.8	12.5
6	3-Ph curcumin 5f	3.12	50.0
7	3-Ph curcumin 5g	25.0	25.0
8	3-Ph curcumin 5h	**0.4**	**6.25**
9	3-Ph curcumin 5i	0.8	50.0
10	3-Ph curcumin 5j	0.8	100.0
11	3-Ph curcumin 5k	**0.4**	12.5
12	3-Ph curcumin 5l	0.8	25.0
13	Ciprofloxacin	2.0	2.0

From the **Table 1** it is clear that majority of tested compounds shows good antibacterial activity. Table clearly indicates the potency against Gram positive organism is greater than Gram negative organism. Out of the tested compounds, compounds **5c, 5h** and **5k** shows highest activity against *S. aureus* while compounds **5b, 5d, 5e, 5f, 5i, 5j** and **5l** are next to them. Compound **5a** and **5g** shows moderate activity against *S. aureus*. On the other hand compound **5h** shows highest activity against *E. coli*. While remaining compounds shows moderate antibacterial activity against *E. coli*. Among the series compound **5h** with electron donating 2,5-dimethoxy substitution is more potent antibacterial compound against both Gram positive and Gram negative organisms. Similar to **5h**, compounds **5c** and **5k** with electron with drawing 4-nitro ($-NO_2$) substitution and 1-napthyl substitution showed highest activity but showed less activity against *E. coli.* as compared to **5h**. Except **5a** and **5g** other

compounds showed better to good antimicrobial activity.

Conclusion-

New derivatives of 5-substituted (1*E*,4*E*)-1-[3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-1,4-dien-3-one have been synthesized easily by employing environmentally benign reaction conditions. The present method have some advantages viz. high yield, low reaction time, less side products, easy workup procedure. Some of the synthesized derivatives found to possess potent anti-microbial activity against *S. aureus* and *E. coli.* The substitution on benzene ring found to affect the activity.

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