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SYNTHESIS AND BIOLOGICAL EVALUATION OF PYRAZOLE BASED CURCUMIN ANALOGUES AS PROMISING ANTIMICROBIAL AND ANTICANCER AGENTS

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ABSTRACT: In present work, we reported the synthesis of series of some new pyrazole based curcumin analogues (5a-l). The chemical structures of synthesized derivatives were confirmed from their physical and ^{1}H-NMR, ^{13}C-NMR, IR and Mass spectral data. The confirmed compounds were screened for their antimicrobial and anticancer activity. Investigation of antimicrobial activity of synthesized compounds demonstrated the ability to inhibit microorganisms with MIC ranging between 0.4 to 25 µg/mL. Among the tested derivatives, 5d and 5l showed highest potency against both *S. aureus* and *E. coli*. Investigation of anticancer activity of synthesized compounds demonstrated the ability to inhibit the growth of cancer cell with IC_{50} values in moderate range. Among tested derivatives, compound 5i showed moderate anticancer activity for MCF-7, Breast cancer cell line.

KEYWORDS: Pyrazole based curcumin, pyrazole carbaldehyde, anticancer, MCF-7 etc.

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1.INTRODUCTION

Extensive research related with antimicrobial activity leads to the synthesis of several heterocycles with antimicrobial activity. But many of such therapeutic agents suffer from bacterial resistance problem; hence there is need to development of new antibacterial drugs that could overcome the resistance problem. On the hand cancer is still major health problem worldwise as it causes about 13% of all the death. Accordingly development of new anticancer therapeutic agents is one of the fundamental goals for researchers in medicinal chemistry. For such purpose there is need to keep the window of research always open and try to development new methodologies, novel structural modifications in order to enhance the biological activity of synthesized compounds with trace side effects as well as target selected activity. In last decade, several pyrazole derivatives have been synthesized and proved to be having antimicrobial and anticancer activity. In the Present work, we synthesized pyrazole based curcumin derivativesas promising antimicrobial and anticancer activity. Literature survey revealed that lot of research groups spent their efforts for inventing the modification in the structure of pyrazole derivatives so as to enhance the biological activity. pyrazole derivatives showed large spectrum of biological activities like anticancer [1-3], antimicrobial [4-5], antifungal [6], anti-depressant [7], anti-inflammatory [8], anti-convulsant [9], anti-diabetic [10], α-amylase inhibitor [11] etc. Curcumin derivatives from literature also showed broad range of activities like anticancer [12, 13], anti-inflammatory [14, 15], antioxidant [16], antibacterial [17, 18], antifungal [19], analgesic [20], antidepressant [21], antidiabetic [22], COX1 inhibitor [23], anti-alzheimer [24] etc. Because of such beneficial activities related with pyrazole and curcumin derivatives we decided to synthesize some new modified pyrazole derivatives consisting of both pyrazole and curcumin moiety and in continuation we synthesized pyrazole based curcumin analogues.

2. MATERIALS AND METHODS

All the chemicals used were of research grade from Acros Organics and were directly used without further purification. Purity of the synthesized compounds was checked by TLC on silica G plates. Melting points were determined in open capillary tubes and were uncorrected. The IR spectra were recorded on FT-IR- 4600 type A spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ with TMS as internal standard on Brucker spectrometer at 400 MHz and chemical shift values expressed in ppm. LC-MS was recorded on LC-MSD-Trap-SL_ 01046.

Experimental Procedure:

General Procedure for the synthesis of 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (2):

A mixture of ethyl acetoacetate (5.2g, 5.2 mL, 0.04 mol) and phenyl hydrazine (4.3g, 3.94 mL, 0.04 mol) was taken in a 100 mL round bottomed flask and heated at 120ºC with constant stirring under solvent-free condition for 4h on oil bath to get the compound (2) in excellent yield. Yield: 6.68 g (96%), MF/FWt: $C_{10}H_{10}N_2O$/174, MP: 126-127ºC.

General procedure for the synthesis of 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carboxaldehyde (3): A mixture of 3-methyl-1-phenyl-2-pyrazolin-5-one (2) (2.205g, 0.018 mol) and dimethyl formamide (DMF) (10 mL, 0.13 mol) was taken in a three neck round bottomed flask equipped with reflux condenser under inert atmosphere. The reaction mixture was cooled at 0ºC and treated with $POCl_3$ (4.6g, 2.8mL, 0.03 mol), maintaining the temperature between 10-15ºC. 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 yellow coloured compound (3) in good yield. Yield: 0.340g, (77%), MF/FWt: $C_{11}H_9ClN_2O$/ 220.5, MP: 144-145ºC.

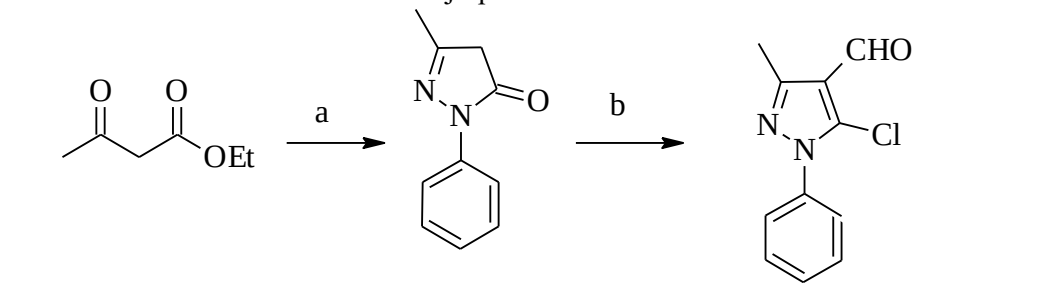
General procedure for the synthesis of (3*E*)-4-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)but-3-en-2-one (4): A mixture of 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carboxaldehyde (3) (0.44g, 2mmol) and acetone (0.116g, 0.14 mL, 2mmol) was taken in a three neck round bottomed flask equipped with air condenser and magnetic stirrer. The reaction mixture was cooled to 0^0C using 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 at 0^0C to get off-white solid compound (4). The solid obtained was recrystallized from ethanol to obtain pure compound (4). Yield: 0.426 gm, (82%), MF/FWt: $C_{14}H_{13}ClN_2O$/260.5, MP: 144-145 ºC.

General procedure for the synthesis of aryl pyrazole based chalcones (5a-l):

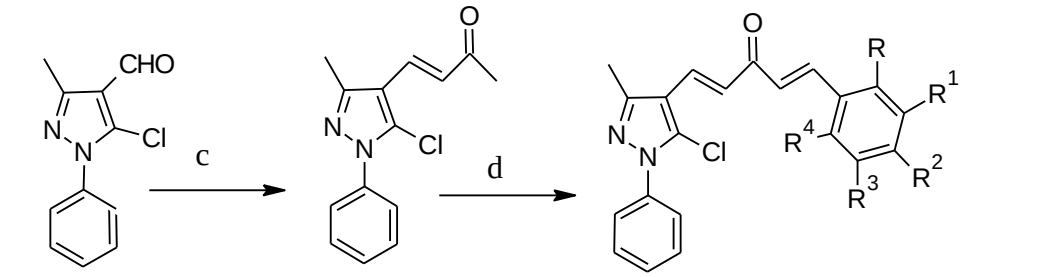
In round bottomed flask, a mixture of compound (4) (3*E*)-4-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl) but-3-en-2-one (0.260g, 1mmol) and aromatic aldehydes (1mmol) was dissolved in ethanol (15ml) under stirring. To this solution was added sodium hydroxide (0.04g, 1mmol) dissolved in minimum quantity of water and stirring continued further to obtain the faint yellow solid products.

3. RESULTS AND DISCUSSION

Herein, we have reported the synthesis of various pyrazole based curcumins (5a-l) from pyrazolyl butenone (4) and different aromatic or hetroaromatic aldehydes by using the method which easily afforded the desired products with higher yields in pure form. The formations of curcumins are supported by the spectral and physical data. The four signals in pmr near about (6.82-6.97, d, J = 16 Hz, 1H ***=CH-***) clearly indicate the trans coupled protons and supports the successful condensation between intermediate compound (4) and substituted aromatic aldehyde molecules. Also the IR bands in the range of 1650-1700 cm^{-1} indicates (***-C=O***) stretching of α-β unsaturated carbonyl structure in pyrazole based curcumin analogues. The Mass and ^{13}C values are in good agreement with proposed structures.



EAA (1) Pyrazolone (2) Carbaldehyde (3)



Carbaldehyde (3) Compound (4) Pyrazole based curcumin analogues (5a-l)

Scheme 1: Reagents and conditions

(a) $PhNHNH_2$, Solvent free, reflux 3h (b) DMF/ $POCl_3$ 2h reflux at 10-15^{0}C

(c) Acetone, NaOH, EtOH. 1:1 Selective and slow stirring at 0^{o}C

(d) Substituted aromatic aldehydes, NaOH, EtOH, Reflux (Claisen-Schmidt Reaction)

Table 1: Physical data of aryl pyrazole based chalcone analogues (5a-l)

Comp. Code	Nature of R group					Yield %	M.P. ^{0}C	Molecular Formula
	R	R^1	R^2	R^3	R^4			
5a	H	H	H	H	H	78	191-193	$C_{21}H_{17}ClN_2O$
5b	H	H	$-CH_3$	H	H	82	177-180	$C_{22}H_{19}ClN_2O$
5c	H	H	$-NO_2$	H	H	75	209-210	$C_{21}H_{16}ClN_3O_3$
5d	H	H	-OH	H	H	75	171-172	$C_{21}H_{17}ClN_2O_2$
5e	H	H	-Cl	H	H	92	185-186	$C_{21}H_{16}Cl_2N_2O$
5f	H	H	$-OCH_3$	H	H	77	180-182	$C_{22}H_{19}ClN_2O_2$
5g	H	$-OCH_3$	-OH	H	H	73	204-206	$C_{22}H_{19}ClN_2O_3$
5h	$-OCH_3$	H	H	$-OCH_3$	H	71	216-218	$C_{23}H_{21}ClN_2O_3$
5i	$-OCH_3$	H	$-OCH_3$	H	$-OCH_3$	77	221-223	$C_{24}H_{23}ClN_2O_4$
5j	H	$-OCH_3$	$-OCH_3$	$-OCH_3$	H	79	206-207	$C_{24}H_{23}ClN_2O_4$
5k	H	-Br	-OH	$-OCH_3$	H	78	218-220	$C_{22}H_{18}BrClN_2O_3$
5l	2-Napthaldehyde					77	195-197	$C_{25}H_{19}ClN_2O$

Analytical and spectral data of compounds:

Synthesis of (1*E*,4*E*)-1-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-5-phenylpenta-1,4-dien-3-one (5a) Yield: 0.272 g, 78% MF/FWt: $C_{21}H_{17}ClN_2O$/348.8 MP: 191-193ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.40 (s, 3H, ***-CH₃ Pyr***), δ 6.95 (d, 1H, J= 16 Hz, ***=CH-CO***), δ 7.03 (d, J= 16 Hz, 1H, ***=CH-CO***), δ 7.39 (dd, J = 1.6 Hz, 7.4 Hz, 2H, ***–ArH***), δ 7.42 – 7.56 (m, 8H, ***–ArH*),** δ 7.58 (d, J= 14.2 Hz, 1H, ***-CH***=CH-CO-), δ 7.69 (d, J= 13.2 Hz, 1H, -***CH***=CH-CO-). ^{13}C NMR: 13.19, 117.83, 121.83 x 2, 124.5, 124.72, 127.33 x 2, 128.74 x 2, 128.92, 129.15 x 2, 129.23, 132.17, 132.60, 134.71, 139.36, 143.55, 145.22, 188.82.

Synthesis of (1E,4E)-1-(5-Chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-5-p-tolyl-penta-1,4-dien-3-one (5b) Yield: 0.298 g, 82%, MF FWt: $C_{22}H_{19}ClN_2O$/362.5, MP: 177-180 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.11 (s, 3H, ***Ar-CH₃***), δ 2.49 (s, 3H, ***-CH₃* Pyr**, δ 6.98 (d, J = 16 Hz, 2H, ***2 x*** =***CH***-CO), δ 7.21 (d, J= 7.0 Hz, 2H, **-ArH**), δ 7.45 (d, J= 7.2 Hz, 1H, ***-ArH***), δ 7.49-7.57 (m, 6H, ***2 x-ArH, 4 x –ArH***), δ 7.66 (d, J= 16 Hz, 2H, 2 x ***-CH*** =CH-CO), ^{13}C NMR: 13.19, 21.26, 117.83, 121.83 x 2, 124.5, 124.72, 127.47 x 2, 129.15 x 2, 129.23, 129.56 x 2, 131.02, 132.17, 132.60, 139.36, 139.75, 143.55, 145.22 188.82.

Synthesis of (1*E*,4*E*)-1-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-5-(4-nitrophenyl)-penta-1,4-dien-3-one (5c) Yield: 0.296 g, 75% , MF/FWt: $C_{21}H_{16}ClN_3O_3$/393.8, MP: 209-210 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.49 (s, 3H, ***-CH₃ Pyr***), δ 7.15 (d, J= 16 Hz, 2H, ***2 x =CH-CO-*),** δ 7.41 (d, 2H, J= 6.8 Hz, ***-ArH***), δ 7.45 (d, J= 7.2, 1H, ***-ArH***), δ 7.51- 7.58 (m, 6H, ***2 x –ArH , 4 x –ArH***), δ 7.69 (d, J= 16 Hz, 2H, ***2 x CH***=CH-CO-), ^{13}C NMR: 13.19, 117.83, 121.83 x 2, 123.94 x 2, 124.50, 124.72, 127.50 x 2, 129.15 x 2, 129.23, 132.17, 132.60, 139.36, 140.88, 143.55, 145.22, 147.98, 188.82.

Synthesis of (1*E*,4*E*)-1-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-5-(4-hydroxyphenyl)-penta-1,4-dien-3-one (5d) Yield: 0.272 g, 75%, MF/FWt: $C_{21}H_{17}ClN_2O_2$/ 364.8**,** MP: 171-172 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.53 (s, 3H, ***-CH₃ Pyr***), δ 4.12 (bs, 1H, -OH), δ 6.91 – 6.96 (m, 3H, ***2 x –ArH 1 =CH-CO-*),** δ 7.03 (d, 1H, J= 16 Hz, ***=CH-CO***), δ 7.41 (dd, J= 7.2 Hz, 1.6 Hz, 1H, ***-ArH***), δ 7.47- 7.59 (m, 6H, ***2 x –ArH , 4 x –ArH***), δ 7.64 (d, J= 14.2 Hz, 1H, ***-CH***=CH-CO-), δ 7.69 (d, J= 13.8 Hz, 1H, ***CH***=CH-CO-), ^{13}C NMR: 13.19, 116.50 x 2, 117.83, 121.83 x 2, 124.5, 124.72, 127.39, 129.15 x 2, 129.23, 130.09 x 2, 132.17, 132.60, 139.36, 143.55, 145.22, 157.82, 188.82.

Synthesis of (1*E*,4*E*)-1-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-5-(4-chlorophenyl)-penta-1,4-dien-3-one (5e) Yield: 0.352 g, 92%, MF / FWt: $C_{21}H_{16}Cl_2N_2O$/ 383**,** MP: 185-186 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.52 (s, 3H, ***-CH₃ Pyr***), δ 7.04 (d, J= 16 Hz, 2H, ***2 x =CH-CO-*),** δ 7.40 (d, 2H, J= 6.8 Hz, ***-ArH***), δ 7.46 (d, J= 7.2, 1H, ***-ArH***), δ 7.50- 7.58 (m, 6H, ***2 x –ArH , 4 x –ArH***), δ 7.70 (d, J= 16 Hz, 2H, ***2 x CH***=CH-CO-), ^{13}C NMR: 13.19, 117.83, 121.83 x 2, 124.5, 124.72, 129.15 x 2, 129.23, 129.29 x 2, 129.54 x 2, 132.17, 132.60, 133.75, 135.68, 139.36, 143.55,

145.22, 188.85.

Synthesis of (1*E*,4*E*)-1-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)5-(4-methoxyphenyl)-penta-1,4-dien-3-one (5f) Yield: 0.292 g, 77%, MF/FWt: $C_{22}H_{19}ClN_2O_2$ / 378.8, MP: 180-182 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.52 (s, 3H, ***-CH₃* Pyr**, δ 3.86 (s, 3H, ***-OCH₃***), δ 6.93- 6.97 (m, 3H, ***2 x –ArH, 1* =*CH*-CO**), δ 7.05 (d, J= 16 Hz, 1H, =***CH***-CO), δ 7.45 (dd, J= 1.6 Hz, 7.2 Hz, 1H, ***-ArH***), δ 7.49-7.60 (m, 6H, ***2 x-ArH, 4 x –ArH***), δ 7.68 (d, J= 13.2 Hz, 1H, ***-CH*** =CH-CO), δ 7.72 (d, J= 12.8 Hz, 1H, ***-CH*** =CH-CO), ^{13}C NMR: 13.19, 55.46, 114.33 x 2, 117.83, 121.82 x 2, 124.50, 124.72, 127.39, 128.92 x 2, 129.15 x 2, 129.23, 132.17, 132.60, 139.36, 143.55, 145.22, 160.41, 188.90.

Synthesis of (1*E*,4*E*)-1-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-5-(4-hydroxy-3-methoxy-phenyl)-penta-1,4-dien-3-one (5g) Yield: 0.284 g, 73%, MF/FWt: $C_{22}H_{19}ClN_2O_3$ /394.8**,** MP: 204-206 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.44 (s, 3H, **Pyr-*CH₃***), δ 3.78 (s, 3H, **-O*CH₃***), δ 4.18 (bs, 1H, **-O*H***), δ 5.92 – 5.99 (m, 3H, **–ArH**), δ 6.86 (d, J= 15.8 Hz, 1H, =***CH***-CO), δ 6.95 (d, J= 15.8 Hz, 1H, **=*CH***-CO), δ 7.41 (dd, J= 1.6 Hz, 7.2 Hz, 1H, ***–ArH***), δ 7.49 - 7.55 (m, 4H, ***-ArH***), δ 7.62 (d, J= 14.6 Hz, 1H, ***-CH*** =CH-CO-), δ 7.67 (d, J= 13.8 Hz, 1H, ***-CH*** =CH-CO-), ^{13}C NMR: 13.19, 56.15, 111.69, 115.67, 117.83, 121.83 x 2, 123.13, 124.50, 124.72, 127.82, 129.15 x 2, 129.23, 132.17, 132.60, 139.36, 141.39, 145.22, 147.83, 148.81, 188.78.

Synthesis of (1*E*,4*E*)-1-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-5-(2,5-dimethoxy-phenyl)-penta-1,4-dien-3-one (5h) Yield: 0.292 g, 71%, MF/FWt: $C_{23}H_{21}ClN_2O_3$/408**,** MP: 216-218 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.48 (s, 3H, **Pyr-*CH₃***), δ 3.84 (s, 3H, **-O*CH₃***), δ 3.90 (s, 3H, **-O*CH₃***), δ 5.97 – 6.08 (m, 3H, ***–ArH***), δ 6.88 (d, J= 16 Hz, 1H, =***CH***-CO), δ 6.98 (d, J= 16 Hz, 1H, **=*CH***-CO), δ 7.42 (dd, J= 1.6 Hz, 7.4 Hz, 1H, ***–ArH***), δ 7.48 - 7.56 (m, 4H, ***-ArH***), δ 7.63 (d, J = 14.4 Hz, 1H, ***-CH*** =CH-CO-), δ 7.70 (d, J= 13.6 Hz, 1H, ***-CH*** =CH-CO-), ^{13}C NMR: 13.19, 55.46, 55.87, 112.40, 112.46, 115.26, 120.39, 121.83 x 2, 124.50, 124.72, 129.15 x 2, 129.23, 129.99, 132.17, 132.62, 139.36, 140.34, 145.22, 151.80, 152.56, 189.

Synthesis of (1*E*,4*E*)-1-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-5-(2,4,6-trimethoxy-phenyl)-penta-1,4-dien-3-one (5i) Yield: 0.338 g, 77%, MF/FWt: $C_{24}H_{23}ClN_2O_4$/438.9**,** MP: 221-223 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.47 (s, 3H, ***-CH₃* Pyr**), δ 3.88 (s, 3H, **-O*CH₃***), δ 3.89 (s, 6H, ***2 x -OCH₃***), δ 6.08 (s, 2H, ***–ArH***), δ 6.90 (d, J= 16 Hz, 1H, =***CH***-CO), δ 7.02 (d, J= 1.6 Hz, 1H, **=*CH***-CO), δ 7.44 (dd, J= 1.6 Hz, 7.4 Hz, 1H, ***–ArH***), δ 7.50-7.58 (m, 4H, ***-ArH***), δ 7.65 (d, J= 13.2 Hz, 1H, ***-CH*** =CH-CO-), δ 7.71 (d, J= 12.8 Hz, 1H, ***-CH*** =CH-CO-), ^{13}C NMR: 13.19, 55.46, 55.87 x 2, 91.97 x 2, 110.25, 120.49, 121.83 x 2, 124.50, 124.72, 129.15 x 2, 129.23, 132.17, 132.60, 139.36, 141.10, 145.22, 157.91 x 2, 162.77, 188.85.

Synthesis of (1*E*,4*E*)-1-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-5-(3,4,5-trimethoxy-phenyl)-penta-1,4-dien-3-one (5j) Yield: 0.346 g, 79%, MF/FWt: $C_{24}H_{23}ClN_2O_4$/438.9**,** MP: 206-207 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.47 (s, 3H, ***-CH₃* Pyr**), δ 3.94 (s, 6H, **2 x -O*CH₃***), δ 3.95

(s, 3H, **-O*CH₃***), δ 6.93 (s, 2H, **–ArH**), δ 6.95 (d, J= 16 Hz, 1H, =***CH***-CO), δ 7.05 (d, J= 16 Hz, 1H, **=*CH***-CO), δ 7.49 (dd, J= 1.6 Hz, 7.4 Hz, 1H, ***–ArH***), δ 7.52-7.59 (m, 4H, ***-ArH***), δ 7.69 (d, J= 13.2 Hz, 1H, -***CH*** =CH-CO-), δ 7.76 (d, J= 12.8 Hz, 1H, -***CH*** =CH-CO-), ^{13}C NMR: 13.19, 56.15 x 2, 60.90, 105.31 x 2, 117.83, 121.83 x 2, 124.50, 124.72, 129.15 x 2, 129.23, 130.25, 132.17, 132.60, 139.36, 13975, 144.45, 145.22, 153.44 x 2, 188.92.

Synthesis of (1*E*,4*E*)-1-(3-bromo-4-hydroxy-5-methoxy-phenyl)-5-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-penta-1,4-dien-3-one (5k) Yield: 0.372 g, 78%, MF/FWt: $C_{22}H_{18}ClN_2O_3Br$/474.5**,** MP: 218-220 ^{o}C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.48 (s, 3H, **Pyr-*CH₃***), δ 3.82 (s, 3H, **-O*CH₃***), δ 4.22 (bs, 1H, **-O*H***), δ 5.88 – 5.94 (m, 2H, **–ArH**), δ 6.72 (d, J= 16 Hz, 1H, =***CH***-CO), δ 6.92 (d, J= 16 Hz, 1H, **=*CH***-CO), δ 7.41 (dd, J= 1.5 Hz, 7.4 Hz, 1H, ***–ArH***), δ 7.46 - 7.53 (m, 4H, ***-ArH***), δ 7.61 (d, J= 13.8 Hz, 1H, -***CH*** =CH-CO-), δ 7.65 (d, J= 12.8 Hz, 1H, -***CH*** =CH-CO-), ^{13}C NMR: 13.19, 56.15, 108.69, 110.70, 117.83, 121.83 x 2, 124.50, 124.72, 129.15 x 2, 129.23, 132.17, 132.50, 133.06, 134.32, 139.36, 144.45, 145.22, 148.50, 149.80, 189.

Synthesis of (1*E*,4*E*)-1-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-5-naphthalen-1-yl-penta-1,4-dien-3-one (5l) Yield: 0.308 g, 77%, MF/FWt: $C_{25}H_{19}ClN_2O$/398.9, MP: 195-197 ^{o}C.^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.39 (s, 3H, ***-CH₃ Pyr***), δ 6.93 (d, 1H, J= 16 Hz, ***=CH-CO***), δ 6.97 (d, J= 16 Hz, 1H, ***=CH-CO***), δ 6.99 – 7.22 (m, 4H, ***–ArH*),** δ 7.36 (dd, J = 1.6 Hz, 7.4 Hz, 1H, ***–ArH***), δ 7.54 (d, J= 13.8 Hz, 1H, ***-CH***=CH-CO-), δ 7.66 (d, J= 13.6 Hz, 1H, -***CH***=CH-CO-), ^{13}C NMR: 13.19, 117.83, 121.83 x 2, 123.62, 124.5, 124.72, 126.19, 126.56 x 2, 127.72, 127.74, 128.5, 129.15 x 2, 129.23, 131.84, 132.17, 132.60, 132.66 137.10, 139.36, 144.45, 145.22, 188.75.

Biological Activity:

Antimicrobial activity was determined by using *S. aureus* (Gram positive) and *E. coli* (Gram negative) organism and find out the MIC values of tested compounds. Anticancer activity was determined by MTT method using MCF-7 Breast cancer cell line.

Antibacterial activities of pyrazole based curcumin analogues.

The in-vitro antibacterial activitity [25, 26] of some selected pyrazole based curcumin analogues **(Scheme-1)** was performed on two types of bacteria strains: *S. aureus* (Gram positive) and *E. coli* (Gram negative) organism. MIC values were found out by aerobic MIC test using the material HIMEDIA M210-500G and BRAIN HEART INFUSION BROTH 500g. The results was compared with **Ciprofloxacin** as a reference compound and are shown in **Table 2.**

Table 2 MIC values of pyrazole based curcumin derivatives.

Sr. No.	Sample Code	MIC Values in µg/mL	
		S. aureus	*E. coli*
1	5a	0.8	0.8
2	5b	1.6	**0.4**
3	5d	**0.4**	0.8
4	5f	0.8	25.0
5	5i	0.8	25.0
6	5k	3.12	25.0
7	5l	**0.4**	0.8
8	Ciprofloxacin	2.0	2.0

From the **Table 2** it is clear that majority of tested compounds showed good antibacterial activity. Table clearly indicates the potency against Gram positive organism is greater than Gram negative organism. Out of the tested compounds, compounds **5d** and **5l** showed highest activity against *S. aureus* while compounds **5a, 5b, 5f** and **5i** are next to them. Compound **5k** showed moderate activity against *S. aureus*. On the other hand compound **5b** showed highest activity against *E. coli*, while compounds **5a**, **5d**, and **5l** are next to him. Remaining compounds **5f, 5i** and **5k** showed moderate antibacterial activity against *E. coli*. Among the series compounds **5d** and **5l** are more potent antibacterial compounds against both Gram positive and Gram negative organisms.

Anticancer activities of pyrazole based curcumin analogues:

Anticancer activity of some selected pyrazole based curcumin analogues **(Scheme-1)** were determined by MTT assay method [27, 28] and IC_{50} values were found out by using MCF-7 Breast cancer cell line and the results are compared with **Paclitaxel** as reference compound for anticancer activity and shown in **Table 3**.

Table 3 IC 50 values of pyrazole based curcumin derivatives in µM

Sr. No.	Comp. Code	IC 50 Values in µM
1	5a	188.8
2	5b	330.2
3	5d	71.03
4	5f	152.8
5	**5i**	**28.75**
6	5k	209.6
7	5l	121.0
8	**Paclitaxel**	**0.35**

Table 4 Cell Viability (MCF-7)							
Conc. µg/mL	5a	5b	5d	5f	5i	5k	5l
500	21.00	22.29	22.29	21.86	25.71	19.29	23.14
400	23.14	28.29	28.29	24.86	30.36	31.79	25.71
300	32.86	31.29	31.29	30.43	31.79	40.00	26.64
200	43.71	41.14	41.14	39.86	40.29	52.14	28.29
100	75.00	49.71	49.71	68.57	42.00	71.79	36.86
50	90.43	50.14	50.14	73.29	42.86	87.14	94.45
NC	100						

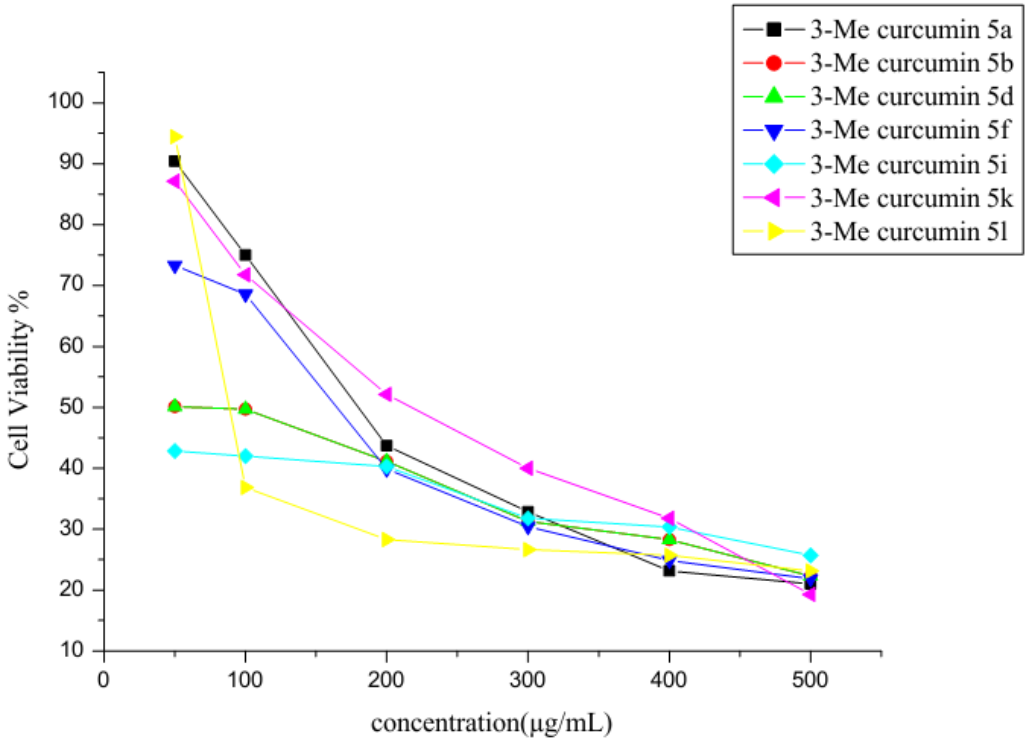


Fig. Cell viability of tested compounds

From the **Table 3** it is clear that tested compounds are moderate to weak in their anticancer activity. The compound **5i** shows moderate anticancer activity while compounds **5a, 5b, 5d, 5f, 5k** and **5l** are weak towards anticancer activity. Among tested compounds, compound **5i** is more potent anticancer compound.

4. CONCLUSION

We have synthesized series of pyrazole based curcumins and evaluated their antibacterial activities against Gram-positive and Gram-negative bacteria as well as anticancer activity against MCF-7, Breast cancer cell line. For antibacterial activity the molecules 5d and 5l most effectively inhibit *S. aureus* and *E. coli* with MIC ranging between 0.4 and 0.8 µg/mL and are the most potent molecules

among the tested compounds. For anticancer activity only the compound 5i showed moderate anticancer activity while other tested compounds are weak in their activity. In conclusion, more extensive study is needed to optimize the effectiveness of pyrazole based curcumin type compounds and to determine their mode of action. This could be accomplished by preparing a variety of such derivatives and screen their antibacterial and anticancer activities.

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CONFLICT OF INTEREST

Authors have no conflict of interest.

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