*Full Length Research Paper*

# Isolation, synthesis and pharmacological evaluation of some novel curcumin derivatives as anticancer agents

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Microwave assisted a series of novel curcumin analogues that were synthesized by altering β-diketone system with olifinic bond (4 to 12) and evaluated their anticancer activity against KB-oral and mouth, CaCo2-colon, MCF-7-breast, WRL-68 liver, HepG-2-liver human cancer cell lines. The naturally occurring curcuminods (A, B and C) showed excellent $IC_{50}$ ranging from 0.0006 to 6.0 μg/ml. Analogues 5, 7, 10 and 12 showed very good anticancer activity with $IC_{50}$ value 0.003, 0.0012, 0.33 and 0.067 μg/ml, respectively as compare to curcumin and taxol with $IC_{50}$ 0.044 and 0.001 μg/ml, respectively.

**Key words:** Curcumin, anticancer, curcuminoids, turmeric, natural product and microwave.

## INTRODUCTION

Curcumin (diferuloylmethane), a polyphenol, is an active principle of the perennial herb *Curcuma longa* commonly known as turmeric. Turmeric contains curcumin (Compound 1) (77%) demethoxycurcumin (Compound 2) (17%), bisdemethoxycurcumin (Compound 3) (3%) and cyclocurcumin. Curcuminoids are present in 3 to 5% of turmeric. (Gautam et al., 2007; Goel et al., 2008). Curcuminoids are recognized for their broad spectrum of biological activities. The potential use of curcumin in the prevention of cancer and in the treatment of infection with human immunodeficiency virus (HIV) is the subject of intensive laboratory and clinical research (Jayaprakash et al, 2005). Anticancer potential of curcumin has reported and reviewed by many groups (Agarwal et al, 2003); Shishodia, 2005; Mehta et al, 1997). Recently we have reported few analogues of compounds 1 and 2, with significantly good antitubercular activity (Agrawal et al., 2008, Agrawal and Mishra et al., 2010).

Structurally, curcumin has two pharmacophores: First is the two substituted aromatic rings and the second part is the linking chain of the two substituted aromatic ring systems which is a β–diketone with two symmetrical olefinic bonds. Several studies indicated that changing the substituents of the aromatic ring system is significantly altering the activity of the analogues and is explored well. Whereas alterations in the second pharmacophore are not explored well, therefore we decided to prepare analogues by altering the β–diketone system with olefinic bonds. Introduction of a substituted phenyl ring attached to heterocyclic aromatic system at the point of β–diketone system was our target for the preparation of various analogues. This hypothesis is derived from the fact that free hydroxyl group must be there and further addition of hetero atom containing moiety will improve activity.

In continuation of our work on Curcumin, we have isolated all three curcuminoids from root and rhizome of *C. longa*, confirmed their structure with the help of modern nuclear magnetic resonance (NMR) experimentation and went ahead for microwave assisted synthesis of few more promising semisynthetic analogues with effectively reduced reaction time up to 30 s. Three naturally occurring curcuminoids (Compounds 1 to 3) and semisynthetic analogues (Compounds 4 to 12) were screened for their anticancer potential in different cell lines (Figure 1).

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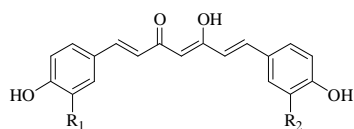
**1**.Curcumin (A): $R_1=R_2=OCH_3$
**2**.Demethoxycumin (B) : $R_1=H$ ,$R_2=OCH_3$
**3**.Bisdemethoxycurcumin (C): $R_1=R_2=H$

**Figure 1.** Chemical structures of curcuminoids.

## MATERIALS AND METHODS

All the reagents were purchased from Sigma Aldrich and were used as received. Reaction progress was monitored by TLC using Merck silica gel 60 F254 with detection by UV. Column chromatography was performed using Merck silica gel 60 to 120 mesh. 1 H NMR spectra was recorded on 300 MHz Bruker NMR spectrometers using tetramethylsilane as internal standard and the chemical shifts are reported in (δ) units. Multiplicities are reported as follows: s singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broadened). Human KB-oral cancer cells, CaCo2-colon cancer cell, MCF-7-breast cancer cell, WRL-68 liver cancer cell, and HepG-2-liver cancer cells were procured from the cell repository of the National Center for Cell Lines, Pune.

### Isolation and characterization of Curcuminoids (1 to 3)

The curcuminoids rich crude was charged on silica gel (60 to 120 meshes) column and eluted successively with hexane, chloroform: hexane (20 to 80% v/v), chloroform and acetone-chloroform (1 to 8% v/v). Similar fractions were pooled on the basis of TLC profile.

### General procedure for the synthesis of N-(substituted) phenylcurcumin pyrazole compounds (4 to 12)

Curcumin (1.2 mmol) was dissolved in glacial acetic acid (5 mL), and different hydrazine derivatives (1.5 mmol) (4-methylphenylhydrazine hydrochloride, 4-chlorophenylphenylhydrazine hydrochloride, 4-sulphonamidophenylhydrazine hydrochloride, 4-bromophenylphenylhydrazine hydrochloride, 2,4dimethylphenylphenylhydrazine hydrochloride, 3-methylphenylpyrazolephenylhydrazine hydrochloride, 3-chlorophenylpyrazolephenylhydrazine hydrochloride, 3, 4 dimethylphenyl phenylhydrazine hydrochloride, 2-chlorophenyl phenylhydrazine hydrochloride) were added to the solution. The solution was heated in microwave oven for 35 s, and then the solvent was removed in vacuo. Residue was dissolved in ethyl acetate and washed with water. Organic portion was collected, dried over sodium sulfate, and concentrated in vacuum. Crude extract was further purified by column chromatography. All the products (4 to 12) were prepared by using the same procedure[6.] All the synthesized derivatives were characterized by using modern spectroscopic techniques such as NMR and Mass spectroscopy

### Spectral analysis of compounds

#### Curcumin (A)

m.p. = 182 [183℃];  ^{1}H NMR (300MHz, DMSOd6): δ 3.82 (s, 6H, 2

× OC$H_3$), 6.05 (s, 1H, CO - C$H$ = C - OH), 6.71-6.76 (d, 2H, = C$H$-CO, J = 15.84 Hz), 6.79 - 6.82 (d, 2H, *aromatic protons*, J = 8.14 Hz), 7.12 - 7.15 (dd, 2H, *aromatic protons*, J = 8.18 and 1.14 Hz), 7.30 (bs, 2H, *aromatic protons*), 7.50 - 7.55 (d, 2H, C$H$ = C-CO-, J = 15.81 Hz), 9.72 (s, 2H, exchangeable, 2 × phenolic O$H$); ^{13}C NMR (75 MHz, DMSOd6): δ 56.74, 101.51, 112.62, 116.74, 122.12, 123.82, 127.37, 141.46, 148.97, 150.27, 184.03; IR (KBr): 3426, 1628, 1598, 1511, 1280, 1157, 963.
Electrospray mass (MeOH): 391 [M+Na]⁺, 406.9 [M+K]⁺, 759 [2M+Na]⁺; Negative ESI mass: 367 [M-1]⁻

#### Demethoxycurcumin (B)

m.p. = 165℃ [170℃]; ^{1}H NMR (300MHz, DMSOd6): δ 3.76 (s, 3H, OC$H_3$), 5.98 (s, 1H, CO - C$H$ = C - OH), 6.59-6.64 (d, 2H, = C$H$ - CO, J = 15.89 Hz), 6.73 - 6.76 (d, 4H, *aromatic protons*, J = 8.2 Hz), 7.05 - 7.08 (d, 1H, *aromatic proton*, J = 8.13 Hz), 7.45 - 7.51 (m, 2H, *aromatic protons*), 7.44 -7.49 (d, 2H, C$H$ = C - CO -, J = 15.62 Hz), 9.53 (s, 1H, exchangeable, phenolic O$H$); ^{13}C NMR (75 MHz, DMSOd6): δ 56.76, 101.50, 112.64, 116.76, 116.86, 121.86, 122.12, 123.84, 126.84, 127.41, 131.02, 141.18, 141.45, 148.99, 150.24, 160.58, 183.95, 184.11.
Electrospray mass (MeOH): 360.9 [M+Na] ⁺, 376.9 [M+K]⁺, 699.0 [2M+Na]⁺; Negative ESI: 336.9 [M-1]⁻

#### Bisdemethoxycurcumin (C)

m.p. = 215°C [222°C]; ^{1}H NMR (300MHz, DMSOd6): δ 5.81 (s, 1H, CO – C$H$ = C - OH), 6.45 - 6.50 (d, 2H, = C$H$ - CO, J = 15.77 Hz), 6.85 - 6.88 (d, 4H, *aromatic protons*, J = 8.51 Hz), 7.42 - 7.44 (d, 4H, *aromatic protons*, J = 8.53 Hz), 7.53 - 7.59 (d, 2H, C$H$ = C – CO -, J = 15.72 Hz), 9.62 (s, 2H, exchangeable, phenolic O$H$s); ^{13}C NMR (75 MHz, DMSOd6): δ 101.59, 116.83, 121.78, 126.79, 131.06, 141.18, 160.57, 184.04;
Electrospray mass (MeOH): 330.9 [M+Na] ⁺, 639.0 [2M+Na] ⁺; Negative ESI: 306.9 [M-1]⁻.

#### N-(4-Methylphenylpyrazole) Curcumin (4)

The silica gel eluent was hexane/ethyl acetate, 70:30. Rf = 0.60 (MeOH/CHCl₃ 6:100), yield: 81%, mp 205, Elemental Analysis- C (74.0 %), H (5.74 %), N (6.16 %).
^{1}H NMR (300 MHz, CDCl₃):  δ 2.3(s, 3H, CH₃)  3.82 (s, 6H, 2 · OCH₃), 6.63 (s, 1H, C4-H), 6.76 (d, 2H, J = 15.8 Hz, C2 - H and, C6 - H), 7.04 (d, 2H, J = 15.8 Hz, C1 - H and C7-H), 7.16 – 7.21 (m, 4H, Ar-H). ESI – MS m/z [M+H]⁺ 454.60

#### N-(4-Chlorophenylpyrazole) Curcumin (5)

The silica gel eluent was hexane/ethyl acetate, 70:30. Rf = 0.60 (MeOH/CHCl₃ 6:100), yield: 74%, mp 209, Elemental analysis- C (68.25 %), H (4.90 %), N (5.90 %).
^{1}H NMR (300 MHz, CDCl₃): δ 3.82 (s, 6H, 2 · OCH₃), 6.63 (s, 1H, C4-H), 6.76 (d, 2H, J = 15.8 Hz, C2-H and, C6-H), 7.04 (d, 2H, J = 15.8 Hz, C1-H & C7-H), 7.21 (d, 2H, Ar-H), 7.23 (d, 2H, Ar-H). ESI– MS m/z [M+H]⁺ 474.80

#### N-(4-Sulphonamidophenylpyrazole) Curcumin (6)

The silica gel eluent was hexane/ethyl acetate, 60:40. Rf = 0.60 (MeOH/CHCl₃ 6:100), yield: 68%, mp 212, Elemental anaysis- C (62.45 %), H (4.87 %), N (8.11 %).

^{1}H NMR (300 MHz, CDCl3): δ 2.1 (s, 2H, 2. NH2) 3.82 (s, 6H, 2 · OCH3), 6.63 (s, 1H, C4 - H), 6.76 (d, 2H, J = 15.8 Hz, C2 - H and, C6 - H), 7.04 (d, 2H, J = 15.8 Hz, C1-H and C7-H), 7.51 (d, 2H, Ar-H), 7.91 (d, 2H, Ar-H). ESI – MS m/z [M+H]$^+$ 519.89

## N-(4-Bromophenylpyrazole) Curcumin (7)

The silica gel eluent was hexane/ethyl acetate, 60:40. Rf = 0.60 (MeOH/CHCl3 6:100), yield: 56%, mp 202, Elemental analysis- C (62.45 %), H (4.46 %), N (5.41 %).
^{1}H NMR (300 MHz, CDCl3): δ 3.82 (s, 6H, 2 · OCH3), 6.63 (s, 1H, C4-H), 6.76 (d, 2H, J = 15.8 Hz, C2-H and, C6-H), 7.04 (d, 2H, J = 15.8 Hz, C1-H and C7-H), 7.2 (d, 2H, Ar-H), 7.4 (d, 2H, Ar-H). ESI– MS m/z [M+H]$^+$ 519.14.

## N-(2, 4 dimethylphenylpyrazole) Curcumin (8)

The silica gel eluent was hexane/ethyl acetate, 60:40. Rf = 0.60 (MeOH/CHCl3 6:100), yield: 74%, mp 211, Elemental analysis- C (74.37 %), H (6.05 %), N (6.00 %).
^{1}H NMR (300 MHz, CDCl3): δ 2.35 (d, 3H, CH3 ), 2.31 (d, 3H, CH3), 3.82 (s, 6H, 2 · OCH3), 6.63 (s, 1H, C4-H), 6.76 (d, 2H, J = 15.8 Hz, C2-H and, C6-H), 7.04 (d, 2H, J = 15.8 Hz, C1-H & C7-H), 7.2 (d, 2H, Ar-H), 7.4 (d, 2H, Ar-H). ESI–MS m/z [M+H]$^+$ 468.89.

## N-(3-Methylphenylpyrazole) Curcumin (9)

The silica gel eluent was hexane/ethyl acetate, 60:40. Rf = 0.60 (MeOH/CHCl3 6:100), yield: 69%, mp 204, Elemental analysis- C (74.10 %), H (6.01 %), N (6.16 %).
^{1}H NMR (300 MHz, CDCl3): δ 2.35 (d, 3H, CH3) 3.82 (s, 6H, 2 · OCH3), 6.63 (s, 1H, C4 - H), 6.76 (d, 2H, J = 15.8 Hz, C2-H and, C6-H), 7.04 (d, 2H, J = 15.8 Hz, C1-H and C7-H), 7.2 (d, 2H, Ar - H), 7.1 (d, 2H, Ar-H). ESI–MS m/z [M+H]$^+$ 454.14.

## N-(3-Chlorophenylpyrazole) Curcumin (10)

The silica gel eluent was hexane/ethyl acetate, 60:40. Rf = 0.60 (MeOH/CHCl3 6:100), yield: 79%, mp 202, Elemental analysis- C (68.30 %), H (4.89 %), N (5.90 %).
^{1}H NMR (300 MHz, CDCl3): δ 2.35 (s, 3H, CH3) 3.82 (s, 6H, 2 · OCH3), 6.63 (s, 1H, C4 - H), 6.76 (d, 2H, J = 15.8 Hz, C2 - H and, C6-H), 7.04 (d, 2H, J = 15.8 Hz, C1-H and C7 - H), 7.2 (d, 2H, Ar - H), 7.3 (s, 4H, Ar - H). ESI–MS m/z [M+H]$^+$ 474.84.

## N-(3,4 Dimethylphenylpyrazole) Curcumin (11)

The silica gel eluent was hexane/ethyl acetate, 60:40. Rf = 0.60 (MeOH/CHCl3 6:100), yield: 66%, mp 205, Elemental analysis- C (74.35 %), H (6.05 %), N (6.00 %).
^{1}H NMR (300 MHz, CDCl3): δ 2.35 (s, 6H, CH3) 3.82 (s, 6H, 2 · OCH3), 6.63 (s, 1H, C4-H), 6.76 (d, 2H, J = 15.8 Hz, C2-H and, C6-H), 7.04 (d, 2H, J = 15.8 Hz, C1-H & C7-H), 7.2 (d, 2H, Ar-H), 6.9 (s, 3H, Ar-H). ESI–MS m/z [M+H]$^+$ 468.24.

## N-(2-Chlorophenylpyrazole) Curcumin (12)

The silica gel eluent was hexane/ethyl acetate, 60:40. Rf = 0.60 (MeOH/CHCl3 6:100), yield: 66%, mp 205, Elemental analysis- C

(68.30 %), H (4.90 %), N (6.00 %). ^{1}H NMR (300 MHz, CDCl3): δ 3.82 (s, 6H, 2 · OCH3), 6.63 (s, 1H, C4-H), 6.76 (d, 2H, J = 15.8 Hz, C2-H and, C6-H), 7.04 (d, 2H, J = 15.8 Hz, C1-H and C7-H), 7.2 (d, 2H, Ar-H), 7.3 (s, 2H, Ar-H). ESI–MS m/z [M+H]$^+$ 474.18.

## *In vitro* anticancer activity using MTT assay

Cytotoxicity testing in *in-vitro* mode was done by Woerdenbag et al. (1993) method. [7]2 × 10$^3$ cells/well were incubated in the 5% $CO_2$ incubator for 24 h to enable them to adhere properly to the 96 well polystyrene microplates (Grenier, Germany).

All the test compounds were completely soluble in Dimethyl sulfoxide (DMSO) and dissolved in 100% DMSO (Merck, Germany), in at least five doses (100 to 0.0001 µg/ml), were added and left for 6 h. The compound plus media was replaced with fresh media and the cells were incubated for another 48 h in the $CO_2$ incubator at 37°C.

The concentration of DMSO used in our experiments never exceeded 1.25%, which was found to be non-toxic to cells. Then, 10 µl of a 5 mg/ml stock solution of MTT [3-(4,5-dimethylthiazol-2-yl)-2,5- diphenyltetrazolium bromide; Sigma M 2128] in phosphate-buffered saline (PBS: 1.6 mM $KH_2PO_4$, 6.5 mM $Na_2HPO_4$.12 $H_2O$, 0.137 mM NaCl, 2.7 mM KCl, pH 7.4) was added, and plates were incubated at 37°C for 4 h. 100 µl dimethyl sulphoxide (DMSO, Merck, Germany) was added to all wells and mixed thoroughly to dissolve the dark blue crystals. After a few minutes at room temperature to ensure that all crystals were dissolved, the plates were read on a SpectraMax 190 Microplate Elisa reader (Molecular Devices Inc. USA), at 570 nm. Plates were normally read within 1 h of adding the DMSO. The experiment was done in triplicate and the inhibitory concentration (IC) values were calculated as follows:

% inhibition = [1 - OD (570 nm) of sample well / OD (570 nm) of control well] × 100.

$IC_{50}$ is the concentration µg/mL required for 50% inhibition of cell growth as compared to that of untreated control (Woerdenbag et al, 1993). Curcumin, demethoxycurcumin, bisdemethoxycurcumin and all semi synthetic derivatives of curcumin were evaluated for *in vitro* anticancer activity against human KB-oral cancer cells, CaCo2-colon cancer cell, MCF-7-breast cancer cell, WRL-68 liver cancer cell, and HepG-2-liver cancer cells. Taxol (Paclitaxel) was used as a standard compound.
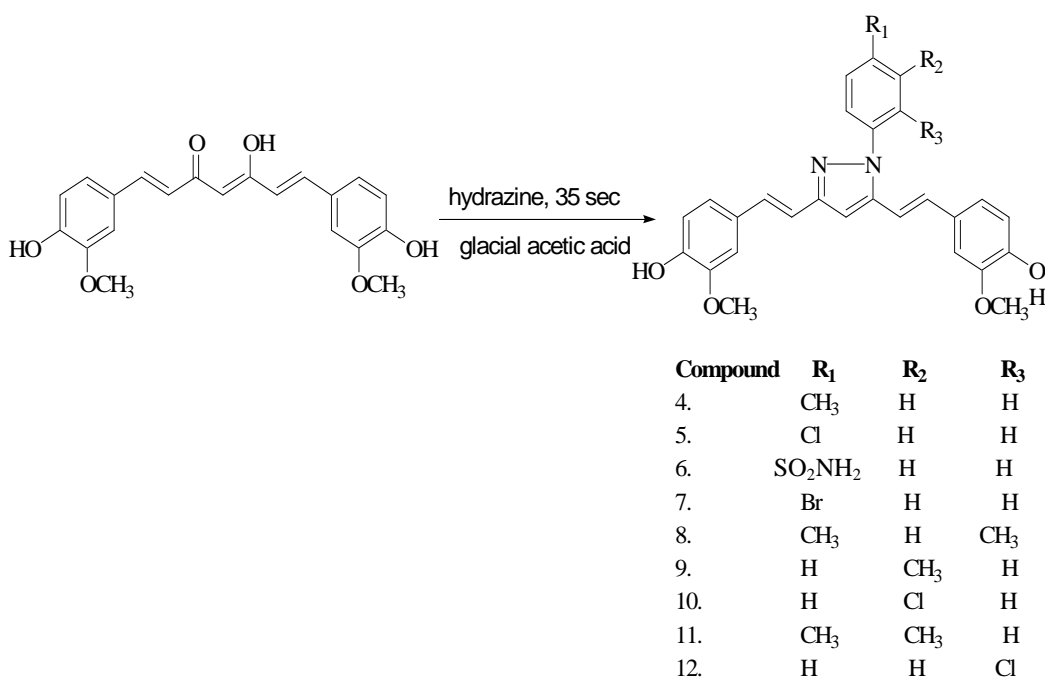
## RESULTS AND DISCUSSION

All the synthesized curcumin analogues along with isolated compounds were screened for anticancer activity in various cell lines that is on KB, MCF-7, CaCo2, WRL-68, HepG-2 (Table 1) to determine $IC_{50}$ and $IC_{90.}$ Among the three naturally occurring curcuminoids bisdemethoxy curcumin (Curcumin-C,**3**) was found most active with $IC_{50}$ of 0.0006 and $IC_{90}$ of 0.043 µg/ml against KB-oral cancer cell line followed by demethoxycurcumin and curcumin with $IC_{50}$ of 0.0011 and 0.044 µg/ml, respectively (Figure 2). Since our aim was to sysnthesize economically viable semisynthetic analogues, therefore we tried microwave assisted synthesis to obtain active compounds by modifying the linker chain of the curcumin-A (1), which can be isolated very easily in good amount from the turmeric.

Curcumin analogues with N-Phenyl Pyrazoles

**Table 1.** Anticancer activity of curcuminoids and semisynthetic analogs against various cancer cell lines using MTT assay. (Concentrations in µg/ml).

| Compound No. | Test samples | KB | | MCF-7 | | CaCo2 | | WRL-68 | | HepG-2 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | $IC_{50}$ | $IC_{90}$ | $IC_{50}$ | $IC_{90}$ | $IC_{50}$ | $IC_{90}$ | $IC_{50}$ | $IC_{90}$ | $IC_{50}$ | $IC_{90}$ |
| 1. | A | 0.044 | 0.84 | 0.073 | 7.3 | 2.0 | 8.0 | 1.0 | 30 | 0.5 | 7.0 |
| 2. | B | 0.0011 | 0.075 | 6.0 | 15 | 0.84 | 5.0 | 0.08 | 7.0 | 1.0 | 9.0 |
| 3. | C | 0.0006 | 0.043 | 0.071 | 7.3 | 0.93 | 6.5 | 0.0073 | 1.0 | 3.8 | 15 |
| 4. | 4 | 0.47 | 7.5 | 0.56 | 2.7 | 3.0 | 6.89 | 2.56 | 13.0 | 2.7 | 8.7 |
| 5. | 5 | 0.003 | 0.065 | 0.086 | 6.8 | 1.9 | 8.76 | 2.3 | 9.96 | 0.7 | 7.9 |
| 6. | 6 | 0.16 | 5.6 | 0.34 | 9.45 | 3.1 | 9.0 | 1.2 | 12.4 | 3.4 | 45 |
| 7. | 7 | 0.0012 | 0.023 | 0.76 | 4.3 | 3.4 | 8.9 | 2.93 | 33.4 | 2.97 | 18.9 |
| 8. | 8 | 0.74 | 12.34 | 0.76 | 5.4 | 4.23 | 8.79 | 3.26 | 15.6 | 3.2 | 15.6 |
| 9. | 9 | 0.35 | 5.6 | 0.46 | 1.98 | 2.99 | 8.91 | 2.55 | 11.9 | 2.56 | 7.0 |
| 10. | 10 | 0.033 | 0.73 | 0.23 | 7.8 | 4.9 | 7.3 | 1.1 | 8.85 | 0.76 | 7.8 |
| 11. | 11 | 0.71 | 11.23 | 0.87 | 6.87 | 2.34 | 8.68 | 3.21 | 18.9 | 0.24 | 17.6 |
| 12. | 12 | 0.067 | 1.78 | 1.34 | 8.45 | 4.15 | 9.87 | 3.2 | 11.2 | 0.54 | 9.8 |
| 13. | Taxol | 0.001 | 0.0470 | 0.005 | 0.85 | 0.007 | 0.065 | 0.0035 | 2.5 | 0008 | 1.0 |



| Compound | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|
| 4. | $CH_3$ | H | H |
| 5. | Cl | H | H |
| 6. | $SO_2NH_2$ | H | H |
| 7. | Br | H | H |
| 8. | $CH_3$ | H | $CH_3$ |
| 9. | H | $CH_3$ | H |
| 10. | H | Cl | H |
| 11. | $CH_3$ | $CH_3$ | H |
| 12. | H | H | Cl |

**Figure 2**. Scheme of synthesis of derivatives.

are already reported as potent antimalarials (Mishra et al, 2008) but their antiproliferative activity is not explored so far, therefore we decided to test these novel compounds for their antiproliferative activity on different cancer cell lines using MTT assay. Starting from curcumin, we have investigated the effect of different substituents on N-phenylpyrazole system introduced on the linker chain of curcumin. A series of nine analogues (4 to 12) were synthesized in which most of the substituents were either

electron withdrawing or electron releasing groups. Among all semisynthetic compounds, compounds 7 was found to be most active with $IC_{50}$ 0f   0.0012 µg/ml followed by compounds 5, 10, and 12 with $IC_{50}$ of 0.003, 0.033 and 0.067 µg/ml, respectively against KB- oral and mouth cancer cell line. Anticancer activity data of all compounds shows that the introduction of a electronegative elements like Bromine (7) and Chlorine (5) at Para position of the phenyl group of the N-Phenyl Pyrazole system increases

activity whereas substitution of the electronegative element at ortho (12) and meta (10) positions decreases the activity subsequently. Introduction of methyl group at any position (4, 8, 9, and 11) or introduction of Sulphonamide group (6) at para position decreases activity.

Compound **7** with bromo substitution at para position of N-Phenyl Pyrazole exhibited better activity then its parent compound curcumin which is comparable to existing drug taxol and can be studied further for lead optimization. Demethoxycurcumin **2** and bisdemethoxycurcumin **3** with excellent anticancer activity also showed a light of hope to become a good lead in future if explored well.

## ACKNOWLEDGEMENT

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