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Pramod K. Sahu

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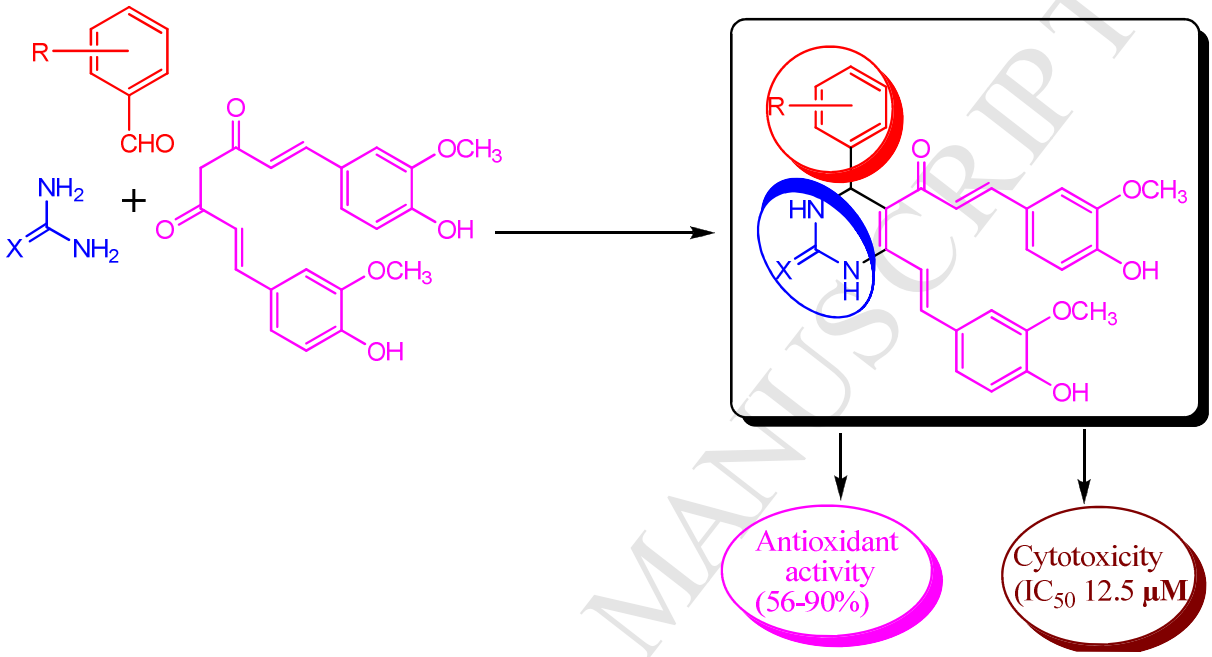
Graphical abstract



Design, structure activity relationship, cytotoxicity and evaluation of antioxidant activity of curcumin derivatives/analogues

Pramod K. Sahu*[a,b]

[a]*School of Studies in Chemistry, Jiwaji University, Gwalior-474011, Madhya Pradesh, India*

[b]*Department of Industrial Chemistry, Jiwaji University, Gwalior-474011, Madhya Pradesh, India .*

*To whom correspondence should be addressed; Email: sahu.chemistry@gmail.com, researchdata6@gmail.com (Pramod K. Sahu)

Abstract

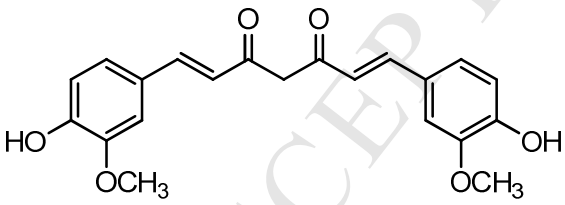
New fourteen 3,4-dihydropyrimidine derivatives/analogues of curcumin (**2a**-**2n**) were designed, synthesized and biologically evaluated for their cytotoxicity and antioxidant activity. Cytotoxicity effect has been evaluated against three cell lines HeLa, HCT-116 and QG-56 by MTT assay method. From SAR study, it has been revealed that particularly, compound **2e** and **2j** (IC_{50} value 12.5 µM) have shown better cytotoxicity effect against three cell lines. According to results of SAR study, it was found that 3,4-dihydropyrimidines of curcumin, **2c**, **2d**, **2j** and **2n** exhibited better antioxidant activity than curcumin. A correlation of structure and activities relationship of these compounds with respect to drug score profiles and other physico-chemical properties of drugs are described and verified experimentally. Therefore, we conclude that physico-chemical analyses may prove structural features of curcumin analogues with their promising combined cytotoxicity/antioxidant activity and it is also concluded from virtual and practical screening that the compounds were varied to possess a broad range of lipophilic character, revealed by Log *P* values.

Keywords: Structure-activity Relationship, Drug Design, Curcumin Derivatives/Analogues, Antioxidant Activity, Physico-Chemical Analyses.

1. Introduction

Curcumin is well-known chemical constituents abundantly found in turmeric (*Curcuma longa L.*), is an herbaceous plant of Zingiberaceae family, originated from India and Southeast Asia. The curcuminoids complex is also referred to as Indian saffron, ukon, yellow root, yellow ginger, kacha haldi or natural yellow, curcuminoids are present in 3-5% of turmeric. The powdered rhizome of turmeric is widely used as spice and coloring agent in food by virtue of its yellowish-orange color and pleasant aroma [1]. Yellowish orange color present in turmeric is chemically 1,6-heptadiene-3,5-dione-1,7-bis(4-hydroxy-3-methoxy phenyl)-(1E,6E) or curcumin (Figure 1). Curcumin is a naturally occurring phytochemical which is used for centuries in a variety of pharmaceutical applications [2,3]. Literature survey reveals that curcumin, and its derivatives have various pharmacological activities such as antiviral [4], anti-inflammatory [5], antimicrobial [6,7], antioxidant [8-10], anti-HIV [11], cancer preventive properties [12.13], anti-parkinson [14], anti-Alzheimer's [15], anti-angiogenesis [16], free radical scavenging activity [17], and anticancer [18].

Figure 1. Structure of curcumin



Number of curcumin analogs/derivatives have been designed and synthesized in order to enhance metabolic stability and antiproliferative activity against human cancer cells [19,20]. By looking at variation on carbonyl moiety and active methylene group, recently many structural modification efforts were carried out and it was found that some of the active methylene and carbonyl substituted curcumin derivatives/analogues showed better antioxidant activity than

curcumin [21-29]. One of the most important aspects of curcumin is its effectiveness against various types of cancer with both chemopreventive and chemotherapeutic properties [30,31]. Unfortunately, due to poor bioavailability [32], and stability in physicological media [33], the potential utility of curcumin is somewhat limited. It is believed that the presence of the active methylene group and β-diketone moiety contributes to the instability of curcumin under physiological conditions, poor absorption, and fast metabolism [34].

In order to develop the molecules with enhances properties and stability, recently synthetic modifications on carbonyl and active methylene moiety of curcumin has been studied intensively [35,36]. It seems from these studies that compounds synthesized using carbonyl and active methylene moiety of curcumin have enhanced activity and stability in biological medium compared to curcumin [34-36]. However, 3,4-dihydropyrimidine derivatives of curcumin have not been reported so far for their antioxidant activity, cytotoxicity, drug scores and physico-chemical analyses. In an attempt to better understand the curcumin pharmacophore and to improve its pharmacodynamic profile, we designed molecules retaining the E,E-1,7-diarylhepta-1,6-diene-3,5-dione backbone and synthesized curcumin analogues/derivatives on carbonyl and active methylene moiety of curcumin. Further, synthesized compounds have been evaluated for their cytotoxicity against human cancer lines using standard MTT assay method and antioxidant activity by adopting DPPH [37], and nitric oxide radical [38] scavenging activity evaluation.

2. Results and discussion

2.1 Chemistry

3,4-Dihydropyrimidine derivatives/analogues of curcumin (**2a-2n**) were synthesized with good yield as outlined in Scheme 1 by condensation of curcumin (5 mmol), aldehydes (5 mmol) and urea/thiourea (5 mmol) in the presence of piperidine using conventional heating (Table 1).

The structures of 3,4-dihydropyrimidines of curcumin were confirmed by IR, NMR, Mass spectra and elemental analysis. Various aromatic aldehydes containing electron-withdrawing and electron-donating substituents at ortho, meta or para positions show equal ease towards the product formation (Table 1). There was no significant effect of electron donating and electron withdrawing substituents on yield and reaction time.

Scheme 1. Synthesis of 3,4-dihydropyrimidine derivatives of curcumin (**2a-2n**).

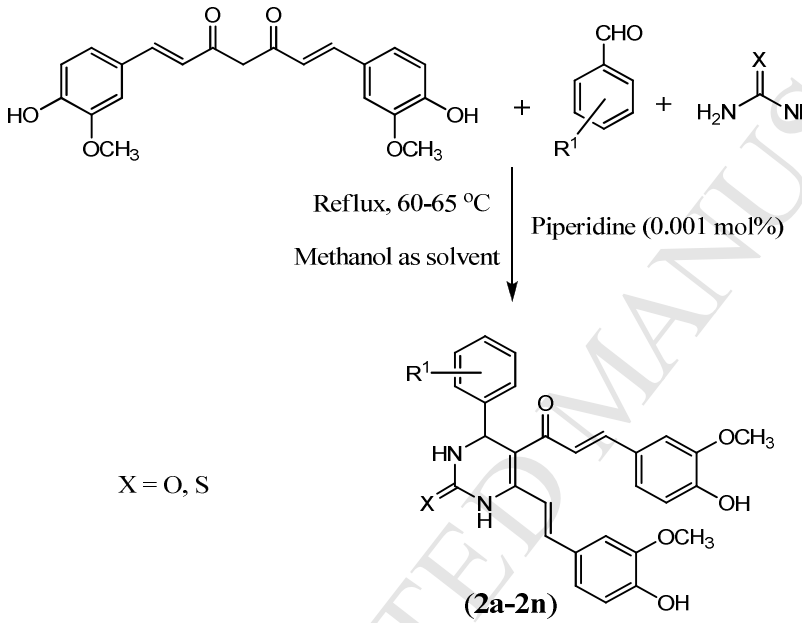


Table 1. Synthesis of dihydropyrimidine derivatives/analogues of curcumin

Entry	R	X	Product	Time (hrs)/ Yield (%)[a]
1	H	O	**2a**	16/76
2	4-CH_3	O	**2b**	16/81
3	2-OH	O	**2c**	18/75
4	4-OH	O	**2d**	18/62
5	4-$N(CH_3)_2$	O	**2e**	18/55
6	2,6-Cl_2	O	**2f**	20/78
7	3-NO_2	O	**2g**	20/72
8	2-Cl	O	**2h**	20/80
9	H	S	**2i**	16/76
10	4-CH_3	S	**2j**	18/78
11	2-OH	S	**2k**	16/86
12	4-$N(CH_3)_2$	S	**2l**	16/80

13	2,6-Cl_2	S	**2m**	18/86
14	2-Cl	S	**2n**	16/87

[a]Isolated yield

2.2 Antioxidant activity

It is believed that curcumin moiety is responsible for antioxidant effect as biological activity. To facilitate the explore whether target compounds maintain the antioxidant activity, synthesized curcumin derivatives were evaluated for their antioxidant activity by $DPPH^{\cdot}$ and nitric oxide radical scavenging activity evaluation methods. Preliminary evaluation for DPPH inhibitory activity was conducted at 50 µM test concentration. Four bioactive compounds (**2c**, **2d**, **2l** and **2k**) were found to exhibit strong DPPH inhibitory activity giving 88.9%, 90.9%, 89.5% and 86.3% respectively. Meanwhile, nitro derived derivative (**2g**) displayed moderate inhibitory activity. Rest of compounds showed lower activity. From structure activity relationship, it can be seen in Table 2 that antioxidant activity of derivatives **2c**, **2d** and **2k** showed the higher free radical scavenging activity due to attachment of hydroxyl moiety in the benzene ring which may be involved in free radical mechanism. Literature survey also shows that phenolic hydroxyl group is responsible for antioxidant activity [39].

Table 2. Antioxidant activity by $DPPH^{\cdot}$ method

Compound	X	$DPPH^{\cdot}$ FRSA%			
		50 µM	20 µM	10 µM	2 µM
2a	O	40.2	38.2	26.4	15.2
2b	O	46.0	38.2	29.9	17.2
2c	O	88.9	81.0	73.6	33.6
2d	O	90.3	84.6	75.0	25.0
2e	O	56.0	48.0	37.6	17.9
2f	O	43.2	31.9	19.2	11.2
2g	O	71.0	66.3	51.2	17.0
2h	O	55.5	46.0	40.0	20.2
2i	S	48.0	38.0	26.5	15.5
2j	S	62.0	51.0	43.2	15.5
2k	S	86.3	72.3	60.2	25.0
2l	S	89.5	83.0	72.0	30.2

2m	S	50.2	43.2	29.0	17.7
2n	S	60.0	56.6	43.2	16.2
Curcumin		50.2	42.2	33.2	6.0

From structure activity relationship, it is clear that phenolic group is essential for antioxidant activity. Besides, it has also been found that the substitution at para position as dimethylammino group (**2l**) does effect the DPPH activity due to strong effect of electron donating moiety. However, **2c**, **2d** and **2k** are hydroxyl derived dihydropyrimidone derivatives of curcumin but **2k** showed slightly lower DPPH activity as compared to **2c** and **2d** derivatives, it may be due to atomic size of oxygen and sulphur which may be also involved in the activity because oxygen atom is smaller than sulphur. Along with all derivatives, four 3,4-dihydropyrimidines of curcumin showed promising effect in DPPH scavenging property which follow the order; **2d**>**2c**>**2l**>**2k**>**2g**>**2j**>**2n**>**2e**>**2h**>**2m**>**2i**>**2b**>**2f**>**2a**.

Synthesized curcumin dihydropyrimidines have been evaluated for their nitric oxide (NO) inhibitory activity radical scavenging assay. Nitric oxide is an important mediator involved in the inflammatory process. It is biosynthesized endogenously from L-arginine, oxygen and NADPH, and catalyzed by various nitric oxide synthase (NOS) enzymes. Appropriate level of NO produced is responsible for body's defense mechanism against abnormalities [40]. Therefore, pharmacological intervention of NO production is a rapid and promising strategy in the search for new potent drugs against inflammatory related degenerative diseases.

In term of NO inhibitory activity, hydroxyl derived 3,4-dihydropyrimidine drivatives of curcumin (**2c**, **2d** and **2k**) demonstrated excellent activity. In this case, hydroxyl in the ortho and para position seems to be required. Structure activity relationship also revealed that para substitution as dimethylamino group (**2e** and **2l**) displayed better activity. It may be strongly

effect of more electrons density (two electron donating $–CH_3$ groups attached at para position) which may be involved in radical scavenging activity. SAR studies showed that when aromatic hydrogen is replaced with electron withdrawing group (**2g**) on meta position and electron releasing groups (rest of compounds) on ortho and para position decreases the scavenging activity. Among all derivatives, five 3,4-dihydropyrimidine derivative of curcumin showed promising effect in nitric oxide scavenging property which follow the order; **2e**>**2k**>**2c**>**2d**>**2l**>**2h**>**2n**>**2b**>**2i**>**2a**>**2m**>**2g**>**2f**>**2j**

Table 3. Antioxidant activity by $NO^{\cdot}$ method

Compound		$NO^{\cdot}$ FRSA%			
	X	50 µM	20 µM	10 µM	2 µM
2a	O	50.2	31.0	20.0	10.5
2b	O	52.2	36.3	23.9	15.5
2c	O	88.0	80.9	71.0	29.9
2d	O	86.2	80.1	72.0	33.3
2e	O	89.2	82.2	69.9	28.2
2f	O	44.2	33.0	20.0	11.2
2g	O	48.0	33.0	19.9	10.2
2h	O	56.0	38.7	23.0	16.6
2i	S	50.4	36.6	22.0	16.6
2j	S	41.0	30.0	19.9	10.2
2k	S	88.5	79.9	70.8	34.0
2l	S	84.0	72.1	59.0	32.3
2m	S	50.0	33.9	20.2	15.0
2n	S	55.6	39.2	21.2	15.5
Curcumin		59.9	36.5	22.2	12.2

All result indicates that, in addition to the phenolic hydroxyl groups (**2c, 2d** and **2k**) is also required for formation of stable phenoxy radical which is believed to play the critical role in radical scavenging activity of the curcuminoids [41-43]. Above, structure activity relationship studies also revealed that substitution on meta potion decreased the activity due to strong nature of nitro as electron withdrawing group and strong releasing group (dimethylamino group) on para position (**2e** and **2l**) enhanced the scavenging activity of 3,4-dihydropyrimidines of

curcumin. Structure-activity relationship presented above indicates that the phenolic hydroxyl group is prerequisite, but alone insufficient for radical scavenging activity effect of the curcuminoids.

2.3 Cytotoxicity

In vitro cytotoxicity of the synthesized curcumin derivatives (2a-2n) were evaluated by MTT assay method [44,45] using three selected human tumor cell lines HeLa, HCT-116 and QG-56. Inhibitory activities (IC_{50}) are being presented in µM concentrations of the synthesized 3,4-dihydropyrimidines of curcumin as shown in Table 4. Structure activity relationship showed good result from molecule design point of view. As we can see among 3,4-dihydropyrimidines (2a-2n), derivatives **2b**, **2c**, **2h**, **2m** and **2n** showed more or less equal cytotoxicity with range of 50-100 µM IC_{50} against HeLa, HCT-116 and Hep-G2. Introduction of dimethylamino substituent at para position (**2e** and **2l**) as electron releasing group showed excellent activity against two cell lines i.e. HCT-116, QG-56 and HeLa, HCT-116 with 12.5 µM IC_{50} which is eight fold than curcumin. It may be due to strong electronic effect of two methyl groups attached on aryl ring which make more activate aryl ring. 3, 4-Dihydropyrimidines **2e** and **2l** also showed better activity against HeLa and QG-56 with 25 µM IC_{50} value which is also four folds of curcumin. Results of cytotoxicity activity have been demonstrated that electron releasing groups (**2b** and **2j**) at para position good cytotoxicity with 12.5 µM IC_{50} against HCT-116 and QG-56, eight folds more active than curcumin. Structure activity relationship also revealed that strong electron releasing groups at para position drastically enhanced the cytotoxicity against all cell lines. As far as rest of 3,4-dihydropyrimidines of curcumin are concerned, their activity were near about curcumin.

Structure activity relationship demonstrated that atomic size of oxygen (**2a**-**2h**) and sulphur (**2i**-**2n**) could not affect the cytotoxicity of all compounds. However, the positive control, adriamycin demonstrated the IC_{50} in the range of <2.5 to 5.0 µM. Interestingly, compound **2e** and **2l** showed potent activity against cancer cell lines, it may be due to involvement of electron in activity. However we have synthesized curcumin derivatives using ortho substitution with electron releasing group (2c, 2d and 2k) but these derivatives didn't show significant cytotoxicity effect against cancer cell lines. Overall structure activity relationship studies demonstrated that electron releasing moiety is significant for cytotoxicity activity.

Table 4. Cytotoxicity of curcumin derivatives/analogues by MTT assay

Compound		Cytotoxicity (IC_{50})		
	X	HeLa	HCT-116	QG-56
2a	O	100	25	50
2b	O	100	12.5	100
2c	O	50	100	100
2d	O	25	100	50
2e	O	25	12.5	12.5
2f	O	25	50	100
2g	O	100	50	25
2h	O	100	50	100
2i	S	25	100	100
2j	S	25	50	12.5
2k	S	25	100	50
2l	S	12.5	12.5	25
2m	S	100	50	100
2n	S	50	100	50
Curcumin[a]		50	50	100
Adriamycin[b]		2.5	5.0	2.5

[a] Isolated from *Curcuma Longa*
[b] Control drug.

2.4 Physico-chemical analyses

The *in silico* physico-chemical properties of synthesized dihydropyrimidones of curcumin has been calculated and showed in table 5. Molecular Polar Surface Area TPSA is calculated based on the methodology previously published [46] as a sum of fragment

contribution, O- and N- centred polar fragments are considered. All the tested compounds displayed TPSA values within the satisfactory range (**100-163** A^o).Results clearly indicated that most of the compounds showed excellent lipophilicity to cross blood–brain barrier. Prediction results of compounds 2a-2n, molecular properties (TPSA, G protein-coupled receptor ligand and ion channel modulator) are valued (Table 5).

Table 5. Physico-chemical properties of curcumin derivatives/analogues

Compd.	MW (g/mole)	Physico-chemical properties[a]					
		TPSA	O/NH	VIOL	ROTB	VOL	CLP
2a	498	117	4	0	8	445	4.31
2b	512	117	4	1	8	462	4.75
2c	514	137	5	1	8	453	4.25
2d	514	137	5	1	8	453	3.83
2e	542	120	4	1	9	490	4.41
2f	567	117	4	2	8	472	5.57
2g	543	163	4	2	9	462	4.24
2h	532	121	3	2	8	453	4.94
2i	515	100	4	1	8	454	4.85
2j	529	100	4	2	8	470	5.30
2k	531	120	5	1	8	462	4.79
2l	558	103	4	1	9	500	5.95
2m	583	100	4	2	8	481	6.11
2n	549	100	4	2	8	467	5.48
Curcumin	368	93	2	0	8	332	2.30

TPSA: Total polar surface area, O/NH: O---HN interraction, VIOL: number of violation; ROTB: Number of rotation; VOL: volume, CLP: cLogP

The in silico physiochemical properties of the target compounds (2a-2n) are listed in Table 5. Synthesized curcumin analogues/derivatives 2a-n showed log P value ranges from 2.30 to 4.94 except compounds 2f, 2l, 2j and 2m. This result clearly indicates that most of the compounds showed excellent lipophilicity to cross blood brain barrier (BBB) easily. TPSA (topological polar surface area) is an important descriptor that was shown to correlate well with

molecular transport through membranes. All the tested compounds (2a-n) displayed TPSA values within satisfactory range (93–163 A °). Moreover, the number of rotatable bonds (n-ROTB), molecular weight, hydrogen bond donor/acceptor were also in acceptable range.

A number of important points emerged concerning the electronic and steric factors which have direct impacts on bioactivity properties. The positive results have recorded, while encouraging for purposes of new drug design confirm that very likely most of these compounds could be used as potential antioxidant agents after major modifications. The future flexible O,O/ O,N-pharmacophore site (s) geometric conformation enables us to prepare molecules for multi-therapeutic materials with high antioxidant activity. The cLog*P* value of a compound, which is the logarithm of its partition coefficient between n-octanol and water, is a well-established measure of the compound's hydrophilicity. Low hydrophilicity and therefore high cLog*P* values may cause poor absorption or permeation. It has been shown for compounds to have a reasonable probability of being well absorb their cLog*P* value must not be greater than 5.0. On this basis, all the series of compounds **2a-2n** is having clog*P* values under the acceptable criteria (except compounds **2f**, **2l**, **2j**, **2m** and **2n**) should be active. The geometrical parameter and the aqueous solubility of a compound significantly affect its absorption, distribution characteristics and bioactivity. Typically, a low solubility goes along with a bad absorption and therefore the general aim is to avoid poorly soluble compounds.

3. Conclusion

In conclusion, we have designed and synthesized a series of 3,4-dihydropyrimidine derivatives/analogues of curcumin (2**a-2n**). Cytotoxicity results exhibited that derivatives **2e** and **2l** (dimethylamino derived) showed much better activity than curcumin. It is due to strong effect of electron donating nature of two methyl group on para position. Our previous and current

finding suggested that hydroxyl substituents is a crucial moiety for antioxidant activity of curcuminoids and might have promising therapeutic potential as antioxidant agents. Results of antioxidant activity demonstrated that hydroxyl substituted 3,4-dihydropyrimide derivatives of curcumin (**2c**, **2d** and **2k**) exhibited significant antioxidant activity due to its involvement in FRSA mechanism. Strong electron donating group (**2e** and **2l**), enhanced the free radical scavenging activity due to involvement of electron in free radical capturing ability of molecules by phenolic hydroxyl group. It is also concluded from virtual and practical screening that the compounds were varied to possess a broad range of lipophilic character, revealed by Log *P* values. These observations may promote further development of our research in this field and activity make these curcumin derivatives/analogues as promising antioxidant and anti-cancer drug candidates.

4. Materials and Methods

4.1 Experimental

The ^{1}H NMR spectra were measured by BRUKER AVANCE II 400 NMR spectrometer with tretramethylsilane as an internal standard at 20-25 ^{o}C; data for ^{1}H-NMR are reported as follow: chemical shift (ppm), integration, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet and br, broad), coupling constant (Hz). IR spectra were recorded by SHIMADZU; IR spectrometer of sample dispersed in KBr pellet or nujol and is reported in terms of frequency of absorption (cm^{-1}). E-Merck pre-coated TLC plates, RANKEM silica gel G for preparative thin-layer chromatography were used. Melting points were determined in open capillaries and are uncorrected. Curcumin, urea, thiourea, and aldehydes were purchased from Hi media Laboratory Ltd., Mumbai, India. All the solvents and reagents used for the synthesis were of analytical

grade. 2,2-Diphenyl-1-picrylhydrazyl (DPPH$^{\cdot}$) was procured from Sigma Chemical Co. (St. Louis, MO, USA).

4.2 Typical procedure for curcumin derivatives (2a-2n)

A mixture of curcumin (5 mmol), substituted aromatic aldehydes (5 mmol) and urea/thiourea (5 mmol) were refluxed at 60-65 ^{o}C in the presence of piperidine as catalysts in methanol solvent. The reaction was monitored by TLC. After completion the reaction, mixture was then poured in cold water and filtered. Product was purified by column chromatography with ethyl acetate and hexane (3:1). The 3,4-dihydropyrimidine derivatives of curcumin were collected as yellow crystals.

4.3 Pharmacological activity

4.3.1 Radical scavenging activity

Radical-scavenging activity of synthesized curcumin derivatives was analyzed by the DPPH$^{\cdot}$ and nitric oxide radical scavenging methods. Individual samples were prepared by dissolving each compound in DMSO. The samples were assayed at different concentrations, making them up to 1 mL with 100 mM Tris–HCl buffer (pH 7.4), followed by addition of 4 mL of 2,2-diphenyl-1-picrylhydrazyl (0.1 mM solution in methanol) and mixing of the contents by vigorous shaking. A control in these experiments was prepared by same protocol except that the compound was not included. The tubes were incubated in the dark at room temperature for 20 min. The absorbance was then recorded at 517 nm using DMSO for baseline correction. The experiments were carried out in triplicates. Free radical scavenging is one of the best known method by which antioxidant inhibit lipid peroxidation. Antioxidant activities viz. DPPH, and nitric oxide radical scavenging activity evaluation are standard assays and offer rapid techniques for screening the radical

scavenging activity (RSA). Radical-scavenging assay (RSA) was evaluated for their antioxidant behavior in comparison with curcumin and the results are shown in the Table 2 and 3.

4.3.2 Cytotoxicity against cell lines

Cytotoxicity was performed by MTT assay method.[44, 45] A 96-well flat bottom tissue culture plate was seeded with 2 x 103 cells in 0.1 mL of MEM medium supplemented with 10% FBS and allowed to attach for 24 h. After 24 hrs of incubation, cells were treated with test compounds to get a concentration of 5, 10, 20, 50 100 and 200 μM/mL incubated for 48 hrs. The cells in the control group received only the medium containing the 0.2% DMSO. Each treatment was performed in duplication. After the treatment, drug containing media was removed and washed with 200 μL of PBS. To each well of the 96 well plate, 100 μL of MTT reagent (Stock: 1 mg/mL in serum free medium) was added and incubated for 4 hour at 37 ºC. After 4 hours of incubation the plate was inverted on tissue paper to remove the MTT reagent. To solubilize formazan crystals in the wells, 100 μL of 100% DMSO was added to each well. The optical density was measured by microtiter plate reader at 590 nm**.** Compound concentration required to reduce the viability of mock-infected cells by 50% as determined by MTT method is summarized in Table 4.

4.3.3 Characterization data

Compound 2a: 4-Phenyl-3,4-dihydropyrimidine-2(1H)-one curcumin

Yellow crystal, mp 206-208 ^{o}C, R_f = 0.65 (DCM / Toluene 3:2); IR (KBr) (υ_{max}, cm^{-1}): 3510 (N-H_{str}), 2922 (C-H_{str}), 2848 (C-H_{str}), 1625 (C=O_{str}), 1500 (C-H_{ben}), 1427 (C-N_{str}), 1382 (C-H_{ben}), 1080-812 (C-H_{def}); ^{1}H NMR (400 MHz, DMSO): δ_H 3.88 (6H, s, OCH_3), 5.90 (2H, s, 2-H), 6.52 (2H, d, 5-H, *J* = 15..64 Hz), 6.87 (2H, d, arom, *J* = 8.16 Hz), 7.04-7.07 (4H, dd, arom), 7.45 (2H, d, arom, *J* = 8.56 Hz), 8.06 (2H, t, arom, *J* = 13.96 Hz), 8.57 (1H, t, arom, *J* = 15.64 Hz), 8.92

(2H, s, NH); ^{13}C NMR (100 MHz, DMSO): 182.75, 148.43, 147.54, 140.24, 129.52, 126.22, 122.52, 120.58, 120.26, 115.68, 115.33, 109.97, 100.70, 55.71; ESI-MS: m/z Calculated for $C_{29}H_{26}N_2O_6$ 498.54 Found $[M+2]^+$ 501.2; C, H and N analyses Calculated for C 69.87, H 5.26, N 5.62, Found C 69.91, H 5.32, N 5.55.

Compound 2b: 4-(4-Methyl phenyl)-3,4-dihydropyrimidine-2(1H)-one curcumin

Yellow crystal, mp 154-158 ^oC, R_f = 0.58 (DCM / Toluene 3:2); IR (KBr) (υ_{max}, cm^{-1}): 3562 (N-H_{str}), 1627 (C=O_{str}), 1508 (C-H_{ben}), 1429 (C-N_{str}), 1280 (C-H_{ben}), 1153 (C-H_{def}), 808-962 (C-H_{def}); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.17 (3H, s, CH_3), 3.96 (6H, s, OCH_3), 5.78 (2H, s, 2-H), 6.48 (2H, d, 5-H, *J* = 3.36 Hz), 6.85-6.95 (2H, m, arom), 7.04 (2H, d, arom, *J* = 1.6 Hz), 7.10-7.13 (2H, dd, arom, *J* = 1.76 Hz), 7.26 (1H, s, -CH), 7.44 (1H, d, arom, *J* = 8.56 Hz), 7.56-7.61 (2H, dd, arom, *J* = 3.92 Hz), 8.08 (1H, d, arom, *J* = 2.0 Hz), 8.36 (2H, s, NH); ^{13}C NMR (100 MHz, DMSO): 182.89, 149.11, 147.74, 140.36, 129.80, 126.22, 122.70, 120.79, 115.77, 115.53, 110.63, 100.79, 98.92, 55.47; ESI-MS: m/z Calculated for $C_{30}H_{28}N_2O_6$ 512.55 Found $[M+NH_4]^+$ 530.5; C, H and N analyses Calculated for C 70.30, H 5.51, N 5.47, Found C 70.41, H 5.49, N 5.60.

Compound 2c: 4-(2-Hydroxy phenyl)-3,4-dihydropyrimidine-2(1H)-one curcumin

Yellow powder, mp >250 ^oC, R_f = 0.67 (DCM / Toluene 3:2); IR (KBr) (υ_{max}, cm^{-1}): 3504 (C-N_{str}), 2941 (C-H_{str}), 1627 (C=O_{str}), 1508 (C-H_{ben}), 1429 (C-N_{str}), 1208 (C-H_{ben}), 813-962 (C-H_{def}); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.92 (6H, s, OCH_3), 5.82 (2H, s, 2-H), 6.45 (2H, d, 5-H, *J* = 15..68 Hz), 6.64-7.58 (10H, arom, m), 8.38 (2H, s, NH), 9.93 (1H, s, OH); ^{13}C NMR (100 MHz, DMSO): 182.82, 149.38, 147.73, 147.57, 146.35, 140.33, 129.29, 128.95, 126.20, 122.67, 120.75, 119.76, 115.75, 115.50, 110.53, 110.53, 108.92, 55.47; ESI-MS: m/z Calculated for

$C_{29}H_{26}N_2O_7$ 514.58 Found $[M]^+$ 514.4; C, H and N analyses Calculated for C 67.70, H 5.09, N 5.44, Found C 67.79, H 5.17, N 5.41.

Compound 2d: 4-(4-Hydroxy phenyl)-3,4-dihydropyrimidine-2(1H)-one curcumin

Yellow powder, mp 148-150 ^oC, R_f = 0.62 (DCM / Toluene 3:2); IR (KBr) (υ_{max}, cm^{-1}): 3321 (OH_{str}), 3043 ($C\text{-}H_{str}$), 2968 ($C\text{-}H_{str}$), 1670 ($C{=}O_{str}$), 1589 ($C\text{-}H_{ben}$), 1516 ($C\text{-}N_{str}$), 1330 ($C\text{-}H_{ben}$), 1244 ($C\text{-}H_{def}$), 744-975 ($C\text{-}H_{def}$); ^1H NMR (400 MHz, $CDCl_3$): δ_H 3.94 (6H, s, OCH_3), 5.80 (2H, s, 2-H), 6.45 (2H, d, 5-H, *J* = 15..68 Hz), 6.85-6.95 (2H, m, arom),7.04 (2H, d, arom, *J* = 1.6 Hz), 7.10-7.13 (2H, dd, arom, *J* = 1.76 Hz), 7.26 (1H, s, -CH), 7.44 (1H, d, arom, *J* = 8.56 Hz), 7.56-7.61 (2H, dd, arom, *J* = 3.92 Hz), 8.08 (1H, d, arom, *J* = 2.0 Hz), 8.38 (2H, s, NH), 10.16 (1H, s, OH); ^{13}C NMR (100 MHz, DMSO): 182.84, 149.34, 147.89, 147.66, 146.63, 140.39, 129.43, 128.27, 127.34, 126.07, 122.77, 120.72, 119.81, 115.58, 115.43, 110.66, 109.02, 98.92, 55.47, 13.97; ESI-MS: m/z Calculated for $C_{29}H_{26}N_2O_7$ 514.58 Found $[M]^+$ 514.5; C, H and N analyses Calculated for C 67.70, H 5.09, N 5.44, Found C 67.68, H 5.11, N 5.41.

Compound 2e: 4-(4-Dimethyamino phenyl)-3,4-dihydropyrimidine-2(1H)-one curcumin

Yellow powder, mp 130-132 ^oC, R_f = 0.52 (DCM / Toluene 3:2); ^1H NMR (400 MHz, $CDCl_3$): δ_H 2.52 (6H, s, $-N(CH_3)_2$), 3.93 (6H, s, OCH_3), 5.79 (2H, s, 2-H), 6.49 (2H, d, 5-H, *J* = 8.0 Hz), 6.83-6.91 (2H, m, arom),7.05 (2H, d, arom, *J* = 1.6 Hz), 7.11-7.16 (2H, dd, arom, *J* = 1.76 Hz), 7.26 (1H, s, -CH), 7.44 (1H, d, arom, *J* = 8.56 Hz), 7.58-7.60 (2H, dd, arom, *J* = 3.92 Hz), 8.09 (1H, d, arom, *J* = 2.0 Hz), 8.48 (2H, s, NH); ^{13}C NMR (100 MHz, DMSO): 181.84, 148.34, 145.89, 145.66, 144.63, 140.30, 128.43, 127.27, 126.34, 125.07, 121.77, 120.72, 118.71, 113.50, 113.40, 109.60, 108.02, 98.92, 55.45, 13.97; ESI-MS: m/z Calculated for $C_{31}H_{31}N_2O_6$ 541.59 Found $[M]^+$ 541.5; C, H and N analyses Calculated for C 68.75, H 5.77, N 7.76, Found C 68.80, H 5.81, N 7.69.

Compound 2f: 4-(2,6-Dichloro phenyl)-3,4-dihydropyrimidine-2(1H)-one curcumin

Yellow powder, mp 106-108 ^{o}C, R_f = 0.62 (DCM / Toluene 3:2); ^{1}H NMR (400 MHz, DMSO): δ_H 3.81 (6H, s, OCH_3), 5.91 (2H, s, 2-H), 6.54 (2H, d, 5-H, *J* = 15..64 Hz), 6.88 (2H, d, arom, *J* = 8.16 Hz), 7.09-7.12 (3H, dd, arom, *J* = 7.4 Hz), 7.49 (2H, d, arom, *J* = 8.56 Hz), 8.06 (2H, t, arom, *J* = 13.96 Hz), 8.57 (1H, t, arom, *J* = 15.64 Hz), 8.90 (2H, s, NH); ^{13}C NMR (100 MHz, DMSO): 182.70, 148.41, 147.44, 140.40, 129.51, 126.00, 121.20, 120.58, 120.16, 115.38, 115.12, 109.80, 100.50, 55.69; ESI-MS: m/z Calculated for $C_{29}H_{24}Cl_2N_2O_6$ 567.42 Found $[M+2]^+$ 570; C, H and N analyses Calculated for C 61.39, H 4.26, N 4.94, Found C 61.44, H 4.31, N 5.02.

Compound 2g: 4-(3-Nitro phenyl)-3,4-dihydropyrimidine-2(1H)-one curcumin

Yellow crystal, mp 160-162 ^{o}C, R_f = 0.69 (DCM / Toluene 3:2); IR (KBr) (υ_{max}, cm^{-1}): ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.87 (6H, s, OCH_3), 5.95 (2H, s, 2-H), 6.40 (2H, d, 5-H, *J* = 15..68 Hz), 6.59-7.89 (11H, m, arom), 9.45 (2H, s, NH); ^{13}C NMR (100 MHz, DMSO): 181.63, 147.91, 146.60, 144.50, 140.42, 139.27, 128.00, 125.90, 121.11, 119.15, 114.70, 114.40, 109.21, 99.70, 54.04, 30.48; ESI-MS: m/z Calculated for $C_{29}H_{25}N_3O_8$ 543.52 Found $[M]^+$ 543.5; C, H and N analyses Calculated for C 64.08, H 4.64, N 7.73, Found C 64.10, H 4.68, N 7.78.

Compound 2h: 4-(2-Chloro phenyl)-3,4-dihydropyrimidine-2(1H)-one curcumin

Yellow powder, mp 144-146 ^{o}C, R_f = 0.64 (DCM / Toluene 3:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.90 (6H, s, OCH_3), 5.88 (2H, s, 2-H), 6.40 (2H, d, 5-H, *J* = 15..68 Hz), 6.82-7.78 (11H, arom, m), 8.38 (2H, s, NH); ^{13}C NMR (100 MHz, DMSO): 182.80, 149.10, 147.10, 147.17, 146.15, 140.03, 129.59, 128.05, 126.00, 122.07, 120.50, 119.15, 115.50, 115.35, 110.33, 110.03, 108.42, 55.17; ESI-MS: m/z Calculated for $C_{29}H_{25}ClN_2O_6$ 532.97 Found $[M]^+$ 533; C, H and N analyses Calculated for C 65.63, H 4.73, N 5.26, Found C 65.57, H 4.79, N 5.31.

Compound 2i: 4-Phenyl-3,4-dihydropyrimidine-2(1H)-thione curcumin

Yellow crystal, mp 215-217 ^{o}C, R_f = 0.67 (DCM / Toluene 3:2); IR (KBr) (υ_{max}, cm^{-1}): 3491 (N-H_{str}), 3007 (C-H_{str}), 1720 (C=O_{str}); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.89 (6H, s, OCH_3), 5.92 (2H, s, 2-H), 6.57-8.00 (10H, m, arom), 9.45 (2H, s, NH); ^{13}C NMR (100 MHz, DMSO): 182.79, 148.99, 147.65, 145.57, 141.42, 140.27, 129.60, 126.96, 122.59, 120.65, 115.73, 115.44, 110.25, 100.72, 55.44, 30.48; ESI-MS: m/z Calculated for $C_{29}H_{26}N_2O_5S$ 514.54 Found $[M+NH_4]^+$ 531.5; C, H and N analyses Calculated for C 67.69, H 5.09, N 5.44, Found C 67.71, H 5.13, N 5.41.

Compound 2j: 4-(4-Methyl phenyl)-3,4-dihydropyrimidine-2(1H)-thione curcumin

Yellow crystal, mp 120-123 ^{o}C, R_f = 0.68 (DCM / Toluene 3:2); IR (KBr) (υ_{max}, cm^{-1}): 3028 (C-H_{str}),1668 (C=O_{str}), 1575 (C-H_{def}), 1519 (C-N_{str}), 1240 (C-H_{def}), 725-1016 (C-H_{def}); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.04 (3H, s, CH_3), 3.96 (6H, s, OCH_3), 5.80 (2H, s, 2-H), 6.54 (2H, d, 5-H, *J* = 15.68 Hz), 6.85-7.61 (10H, s, arom), 9.30 (2H, s, NH); ^{13}C NMR (100 MHz, DMSO): 178.06, 162.38, 148.92, 147.60, 142.66, 141.59, 135.38, 123.61, 122.39, 117.67, 116.46, 109.64, 104.42, 50.71; ESI-MS: m/z Calculated for $C_{30}H_{28}N_2O_5S$ 528.62 Found $[M+NH_4]^+$ 547.1; C, H and N analyses Calculated for C 68.16, H 5.34, N 5.30, Found C 68.20, H 5.30, N 5.26.

Compound 2k: 4-(2-Hydroxy-phenyl)-3,4-dihydropyrimidine-2(1H)-one curcumin

Yellow powder, mp 130-132 ^{o}C, R_f = 0.67 (DCM / Toluene 3:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.89 (6H, s, OCH_3), 5.78 (2H, s, 2-H), 6.55 (2H, d, 5-H, *J* = 15..68 Hz), 6.69-7.67 (10H, arom, m), 8.38 (2H, s, NH), 9.99 (1H, s, OH); ^{13}C NMR (100 MHz, DMSO): 182.83, 149.08, 147.73, 147.07, 146.15, 140.23, 129.39, 128.45, 126.50, 122.60, 120.75, 119.86, 115.95, 115.50, 110.53, 110.53, 108.92, 55.89; ESI-MS: m/z Calculated for $C_{29}H_{26}N_2O_7S$ 530.59 Found $[M]^+$ 531; C, H and N analyses Calculated for C 65.65, H 4.95, N 5.28, Found C 65.76, H 5.02, N 5.31.

Compound 2l: 4-(4-Dimethylamino-phenyl)-3,4-dihydropyrimidine-2(1H)-thione curcumin

Yellow crystal, mp 135-137 ^{o}C, R_f = 0.65 (DCM / Toluene 3:2); IR (KBr) (υ_{max}, cm^{-1}): 3288 (OH_{str}), 2897 ($C\text{-}H_{str}$), 1703 ($C{=}O_{str}$), 1581 ($C\text{-}H_{def}$), 1531 ($C\text{-}N_{str}$), 1377 ($C\text{-}H_{def}$), 1165 ($C\text{-}H_{def}$), 754-977 ($C\text{-}H_{def}$); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.36 (6H, s, $N(CH_3)_2$), 3.40 (6H, s, OCH_3), 5.34 (2H, s, 2-H), 6.99 (2H, s, 5-H), 7.18-7.56 (10H, s, arom), 7.94 (1H, s, arom), 9.64 (2H, s, NH); ^{13}C NMR (100 MHz, DMSO): 182.69, 162.80, 148.96, 146.99, 140.27, 129.80, 126.89, 122.57, 120.64, 115.42, 110.41, 100.22, 55.43; ESI-MS: m/z Calculated for $C_{31}H_{31}N_3O_5S$ 557.54 Found $[M+NH_4]^+$ 575.0; C, H and N analyses Calculated for C 66.77, H 5.60, N 7.54, Found C 66.69, H 5.64, N 7.48.

Compound 2m: 4-(2,6-Dichloro-phenyl)-3,4-dihydropyrimidine-2(1H)-one curcumin

Yellow powder, mp 126-129 ^{o}C, R_f = 0.62 (DCM / Toluene 3:2); ^{1}H NMR (400 MHz, DMSO): δ_H 3.89 (6H, s, OCH_3), 5.85 (2H, s, 2-H), 6.64 (2H, d, 5-H, *J* = 15..64 Hz), 6.84 (2H, d, arom, *J* = 8.16 Hz), 7.11-7.15 (3H, dd, arom, *J* = 7.4 Hz), 7.51 (2H, d, arom, *J* = 8.56 Hz), 8.09 (2H, t, arom, *J* = 13.96 Hz), 8.57 (1H, t, arom, *J* = 15.64 Hz), 8.90 (2H, s, NH); ^{13}C NMR (100 MHz, DMSO): 182.98, 148.53, 147.12, 140.39, 129.11, 126.89, 121.23, 120.40, 120.20, 115.38, 115.25, 109.71, 100.08, 55.49; ESI-MS: m/z Calculated for $C_{29}H_{24}Cl_2N_2O_5S$ 583.48 Found $[M+2]^+$ 585; C, H and N analyses Calculated for C 59.70, H 4.14, N 4.80, Found C 59.68, H 4.21, N 4.89.

Compound 2n: 4-(2-Chloro phenyl)-3,4-dihydropyrimidine-2(1H)-one curcumin

Yellow powder, mp 150-152 ^{o}C, R_f = 0.65 (DCM / Toluene 3:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.87 (6H, s, OCH_3), 5.90 (2H, s, 2-H), 6.46 (2H, d, 5-H, *J* = 15..68 Hz), 6.812-7.79 (11H, arom, m), 8.38 (2H, s, NH); ^{13}C NMR (100 MHz, DMSO): 182.81, 149.10, 147.10, 147.00, 146.21, 140.13, 129.49, 128.25, 126.21, 122.17, 120.20, 119.15, 115.52, 115.35, 110.31, 110.43,

108.42, 55.87; ESI-MS: m/z Calculated for $C_{29}H_{25}ClN_2O_5S$ 549.04 Found $[M]^+$ 549; C, H and N analyses Calculated for C 63.44, H 4.59, N 5.10, Found C 63.49, H 4.69, N 5.11.

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Table Captions

Table 1. Synthesis of dihydropyrimidine derivatives/analogues of curcumin

Table 2. Antioxidant activity by $DPPH^{\cdot}$ method

Table 3. Antioxidant activity by $NO^{\cdot}$ method

Table 4. Cytotoxicity of curcumin derivatives/analogues by MTT assay

Table 5. Physico-chemical properties of curcumin derivatives/analogues

Figure 1. Structure of curcumin

Scheme Captions

Scheme 1. Synthesis of 3,4-dihydropyrimidine derivatives of curcumin (**2a-2n**).

Research highlights

- Antioxidant activity and cytotoxic agents.
- One-pot reaction of curcumin using piperidine.
- Structure activity relationship of curcumin derivatives.
- Good yield and better biological profile.
- In silico and physico-chemical study.