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Design, synthesis, synergistic antimicrobial activity and cytotoxicity of 4-aryl substituted 3,4-dihydropyrimidinones of curcumin

Jaggi Lal [a,b,*], S.K. Gupta [a], D. Thavaselvam [c], D.D. Agarwal [a]

[a] School of Studies in Chemistry, Jiwaji University, Gwalior 474 011, India
[b] Department of Industrial Chemistry, Jiwaji University, Gwalior 474 011, India
[c] Microbiology Division, Defense Research & Development Establishment, Jhansi Road, Gwalior 474 002, India

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ABSTRACT

3,4-Dihydropyrimidinones of curcumin were synthesized in excellent yield by multi-component one-pot condensation of curcumin, substituted aromatic aldehydes and urea/thiourea under solvent free conditions using $SnCl_2{\cdot}2H_2O$ catalyst. All the synthesized compounds have been characterized by IR, ^1H NMR, ^{13}C NMR, Mass spectra as well as elemental analyses. The synthesized compounds **4a–n** were evaluated for their synergistic antimicrobial (antibacterial and antifungal) activity against bacteria and fungi. Zone of inhibition was measured by adopting disc diffusion method. In vitro minimum inhibitory concentrations were measured using broth microdilution and food poisoning method. In addition to this in vitro cytotoxicity of synthesized compounds against three human cancer lines Hep-G2, HCT-116 and QG-56 were also evaluated. Most of the compounds showed interesting antimicrobial and cytotoxic activity as compared to curcumin, that is, the compounds derived from 2-hydroxy benzaldehyde, 4-hydroxy benzaldehyde and 4-hydroxy-3-methoxy benzaldehyde showed the highest biological activity as compared to other compounds.

Turmeric (*Curcuma longa* L.) is a herbaceous plant of Zingiberaceae family, originating from India and Southeast Asia. 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)-(1*E*,6*E*) or diferulolylmethane. The ferulolylmethane skeleton of curcumin was confirmed and synthesized by Lampe in 1910. It is insoluble in water and ether whereas soluble in ethanol, methanol, acetone, dimethylsulfoxide, chloroform and dichloromethane. Curcumin exists in enolic and β-diketonic forms.[2] This form is utilized in the synthesis of 3,4-dihydropyrimidinone analogues of curcumin. Curcumin and its derivatives possess a wide variety of pharmacological activity viz., antibacterial,[3] antifungal,[4] antiviral,[5] anti-HIV,[6] anti-inflammatory,[7] anti-Parkinson's,[8] anti-Alzheimer's,[9] anti-angiogenesis,[10] free radical scavenging activity,[11] anti-rheumatic,[12] antimalarial,[13] anticancer,[14] antiprotozoan,[15] anti-mutagenic,[16] wound treatment,[17] hepatoprotective activity,[18] anti-leishmanial activity[19] and amyloid heart disease.[20] In addition to curcumin, resulted 3,4-dihydropyrimidinones also possess various pharmaceutical properties such as antibacterial,[21] antiviral,[22] and antioxidant.[23] Looking into the biological significance of curcumin and resulted dihydropyrimidinone analogues, it was decided to synthesized, characterized and evaluate their biological activity. Curcumin also inhibits bacterial lipopolysaccharide-induced TNF-α over expression and the transcription factor nuclear factor kappa B (NF-κB) activation which are involved in several pathogen-infected diseases.[24] Preclinical and clinical studies showed that, however, curcumin possesses several disadvantages in pharmacokinetics such as poor bioavailability, fast metabolism and requires repetitive oral dosages.[25] However, curcumin is still an excellent lead compound for drug design and development on the basis of explicit bioactivities, non-toxicity and easy synthesis.[26]

In this study, isolation, derivatization and biological assessment of curcumin have been done against standard bacterial strains such as *Escherichia coli, Burkholderia pseudomallei, Pseudomonas aeuriginosa, Salmonella typhi* and *Staphylococcus aureus,* and fungal strains viz., *Aspergillus niger, Aspergillus flavus, Trichoderma viride* and *Curvularia lunata* by adopting disc diffusion, broth micro dilution and food poisoning method. Cytotoxicity of the synthesized derivatives were also evaluated against human cancer lines (hepato carcinoma, colon carcinoma and lung carcinoma) using standard MTT assay. To the best of our knowledge, antibacterial, antifungal and cytotoxicity of 3,4-dihydropyrimidinones of curcumin are not yet reported.

Targeted compounds **4a–n** were synthesized[27] (Table 1) in excellent yield (92–97%) as outlined in Scheme 1 by condensation of aromatic aldehydes (**1**), urea/thiourea (**2**) and curcumin (**3**) in the presence of $SnCl_2{\cdot}2H_2O$ under solvent free conditions using

* Corresponding author. Tel.: +91 9039035228.
E-mail address: jaggitajagra@gmail.com (J. Lal).

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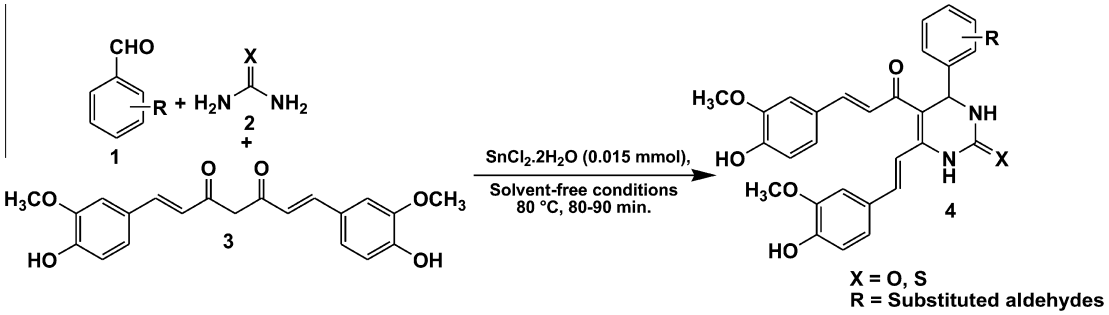
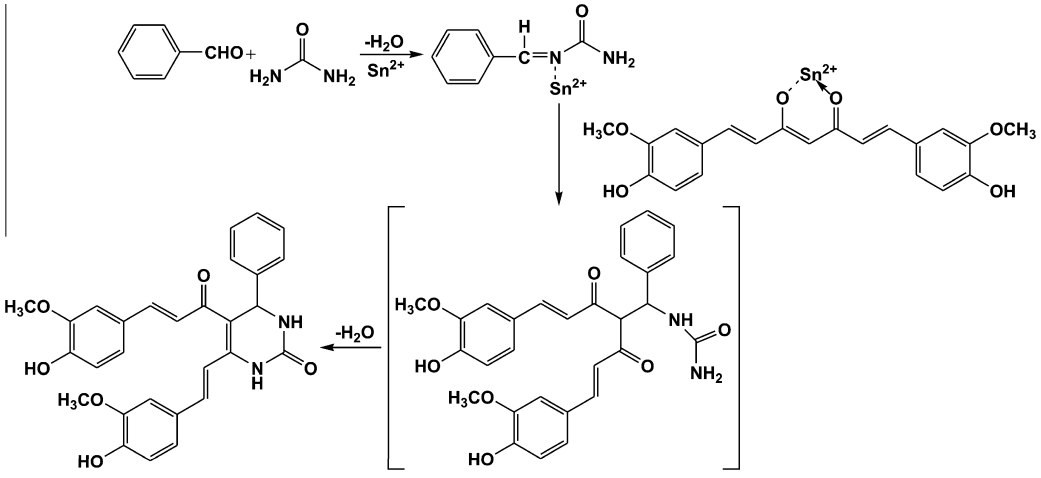
Table 1
Synthesis of 4-aryl substituted 3,4-dihydropyrimidinones of curcumin[a]

Entry	Compound	R	X	Time (min)	Mp[b] (°C)	Yield[c] (%)	Heat of formation[d] (ΔH_f°)
1	**4a**	C_6H_5	O	80	206–208	97	−372.26
2	**4b**	4-Cl–C_6H_4	O	80	201–203	94	−399.47
3	**4c**	4-NO_2–C_6H_4	O	90	198–199	96	−425.65
4	**4d**	4-OCH_3–C_6H_4	O	80	210–212	92	−536.59
5	**4e**	4-OH-3-OCH_3–C_6H_3	O	90	225–226	94	−713.90
6	**4f**	2-OH–C_6H_4	O	90	272–273	96	−549.57
7	**4g**	4-OH–C_6H_4	O	90	151–152	95	−549.57
8	**4h**	4-CH_3–C_6H_4	O	90	158–160	92	−409.37
9	**4i**	C_6H_5	S	80	219–220	95	−368.86
10	**4j**	4-Cl–C_6H_4	S	80	202–204	96	−368.23
11	**4k**	4-NO_2–C_6H_4	S	90	278–279	94	−391.89
12	**4l**	4-OCH_3–C_6H_4	S	80	281–282	92	−582.45
13	**4m**	4-OH-3-OCH_3–C_6H_3	S	90	294–296	93	−656.87
14	**4n**	4-OH–C_6H_4	S	90	261–263	93	−501.21

[a] Reaction conditions: curcumin (2 mmol), aromatic aldehydes (2 mmol), urea/thiourea (2 mmol), (0.02 mmol) $SnCl_2{\cdot}2H_2O$ as catalyst, solvent free conditions for about 80–90 min at 80 °C.
[b] Melting points were uncorrected.
[c] Isolated yield.
[d] Heat of formation was calculated using commercially available semiempirical program package Ampac/Mopac (version 6.0) and measured in kJ/mol.



Scheme 1. Synthesis of 3,4-dihydropyrimidinones of curcumin under solvent free conditions.



Scheme 2. Mechanism of curcumin 3,4-dihydropyrimidinone synthesis.

conventional heating, that is, without microwave irradiations. Banik[28] et al. reported the synthesis of 4-aryl substituted 3,4-dihydropyrimidinones under microwave irradiations using traditional dicarbonyl moieties in place of curcumin. In this reaction in the presence of catalyst, initially urea reacts with substituted aromatic aldehydes to form Schiff's base (Scheme 2), which further reacts with curcumin to form targeted products (**4a**–**n**). In the present reaction curcumin is used as dicarbonyl moiety in place of traditional dicarbonyl moieties such as acetyl acetone and ethyl acetoacetate. Heat of formation (ΔH_f°) for all the reported compounds (**4a**–**n**) has been calculated (Table 1) using commercially available semiempirical program package Ampac/Mopac (version 6.0). Negative values of heat of formation for all the compounds showed exothermic reaction. Compounds derived from 4-hydroxy-3-methoxy benzaldehyde (**4e** & **4m**) in both cases (urea/thiourea) have greater heat of formation than other compounds, heat of formation decreases in case of thiourea derivatives.

The computed molecular structure (ball and stick representation) of curcumin and its 3,4-dihydropyrimidinone derivative, revealing the relative stereochemistry has been represented in Figure 1.

All compounds were spectroscopically characterized and the spectral data agree with the proposed structures.

Theoretical physico-chemical parameter, *C*log*P* values were calculated using commercially available ChemDraw Ultra 8.0.3, for all synthesized compounds (**4a**–**n**) ranged from 2.8 to 5.1. The thumb rule for *C*log*P* values must be lowers than '5' to by-pass the cell barrier.[29] The *C*log*P* values seem to correlate to some extent with lipophilicity. Most of the compounds in the designed series showed *C*log*P* values less than 5 (Table 3).

The newly synthesized curcumin 3,4-dihydropyrimidinones (**4a**–**n**) were evaluated for their in vitro antibacterial activity against five bacteria specially causing secondary infections in human being viz. *Staphylococcus aureus*, *Escherichia coli*, *Burkholderia pseudomallei*, *Salmonella typhi* and *Pseudomonas aeuriginosa*. Zone of inhibition in mm was measured using disc diffusion method (Table 2). Minimum inhibitory concentration (MIC) was measured in μM/ml in Mueller–Hinton broth (Table 2). The antibacterial activity of curcumin dihydropyrimidinone analogues were compared with curcumin isolated from *Curcuma longa* and ampicillin as standard antibiotic reference drug by known micro dilution broth susceptibility test method. The lowest concentration of curcumin dihydropyrimidinones in μM/ml that prevent in vitro growth of microorganism has been represented as MIC (minimum inhibitory concentration) (Tables 2 and 3). In case of *E. coli*, compounds **4b**, **4c**, **4e**–**g, 4i** and **4n** (MIC 20–40) showed antibacterial activity with better zone of inhibition at concentrations (20, 40, 80 and 160 μM/ml) in comparison to curcumin (MIC 40); compound **4k** (MIC 160) does not show any zone of inhibition and was completely inactive. All the remaining compounds were less active comparatively but more active than curcumin. Compounds **4a**, **4d**, **4e**, **4g**, **4i**, **4l**–**n** (MIC 20–40) showed better antibacterial activity against *B. pseudomallei* in comparison to curcumin whereas remaining compounds are moderately active and compound **4b** (MIC 160) was totally inactive. In case of *P. aeuriginosa;* compounds **4e** and **4j** (MIC 160) were totally inactive whereas compounds **4c**, **4d**, **4f**, **4g**, **4i**, **4l** and **4n** (MIC 40) showed much antibacterial

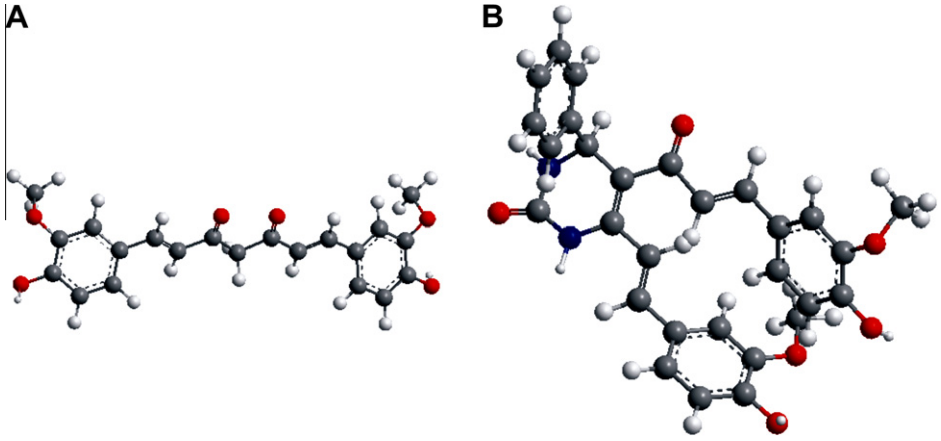


Figure 1. The computed molecular structure (ball and stick representation) of curcumin (A), and 3,4-dihydropyrimidinone derivative (B) of curcumin clearly revealing the relative stereochemistry.

Table 2
Zone of inhibition[a] and MIC[b] correlation diagram of curcumin dihydropyrimidinones against bacterial strains

Compound	Name of bacteria									
	E. coli		*B. pseudomallei*		*P. aeuriginosa*		*S. typhi*		*S. aureus*	
	Zone of Inhibition	MIC	Zone of Inhibition	MIC	Zone of Inhibition	MIC	Zone of Inhibition	MIC	Zone of Inhibition	MIC
4a	17, 9, –, –	40	19, 17, 16, 14	40	14, 12, 9, –	20	11, 8, –, –	80	22, 19, 17, 14	40
4b	19, 16, 11, 9	40	–	160	9, –, –, –	160	11, 9, –, –	80	12, 10, –, –	320
4c	18, 16, 15, 12	40	12, 10, –, –	80	19, 18, 14, 9	40	10, –, –, –	40	11, 10, –, –	80
4d	12, 9, –, –	80	23, 19, 15, 11	40	23, 21, 19, 13	40	–	80	–	80
4e	19, 17, 14, 11	20	16, 16, 14, 10	40	–	160	22, 19, 16, 13	80	–	40
4f	22, 19, 18, 15	20	19, 13, 11, –	40	24, 21, 19, 18	40	–	40	–	160
4g	22, 18, 14, 12	20	19, 15, 11, 9	40	22, 19, 19, 17	40	18, 16, 13, 9	20	24, 22, 19, 16	20
4h	11, 9, –, –	80	10, 9, –, –	40	10, –, –, –	40	11, 9, –, –	40	–	80
4i	21, 18, 14, 12	20	18, 16, 13, 11	40	18, 17, 14, 12	40	–	80	–	80
4j	19, 15, 9, –	80	16, 12, 9, –	80	–	160	22, 19, 17, 13	40	16, 13, 11, 9	40
4k	–	160	11, 9, –, –	80	10, 9, –, –	40	10, –, –, –	40	12, 10, –, –	80
4l	18, 14, 9, –	40	24, 21, 19, 16	20	23, 20, 19, 18	40	–	40	–	80
4m	14, 11, 9, –	40	21, 18, 16, 13	40	14, 11, 9, –	80	14, 12, 9, –	40	11, 9, –, –	40
4n	22, 18, 17, 13	20	19, 17, 16, 14	40	18, 14, 12, 9	40	–	80	12, 10, –, –	80
[c]Curcumin	10, 8, –, –	40	9, 8, –, –	80	11, 9, –, –	80	12, 10, 9, –	80	–	80
[d]Ampicillin	34, 32, 30, 30	20	46, 41, 39, 38	80	39, 36, 34, 31	40	51, 45, 44, 37	20	37, 30, 29, 28	40

(–) Resistant.
[a] Zone of inhibition measured in mm at concentrations 160, 80, 40 and 20 μM/ml.
[b] MIC (minimum inhibitory concentrations) were measured in μM/ml.
[c] Isolated from *Curcuma longa.*
[d] Purchased from HiMedia Pvt. Ltd.

Table 3
Zone of inhibition[a] and MIC[b] correlation diagram of curcumin dihydropyrimidinones against fungal strains

Compound	Name of fungi								*C*log *P*[e]
	Aspergillus niger		*Aspergillus flavus*		*Curvularia lunata*		*Trichoderma viride*		
	Zone of Inhibition	MIC	Zone of Inhibition	MIC	Zone of Inhibition	MIC	Zone of Inhibition	MIC	
4a	9, —, —,—	40	11, 9, —, —	80	18, 12, 9, —	80	14, 11, 9, —	80	4.3
4b	12, —, —, —	160	—	160	22, 18, 12, 9	40	18, 17, 17, 15	40	5.0
4c	—	160	—	80	11, 9, —, —	40	21, 21, 19, 17	40	4.1
4d	11, 9, —, —	80	—	40	17, 16, 14, 11	40	19, 17, 16, 14	40	4.3
4e	—	160	—	80	21, 18, 17, 13	40	21, 18, 16, 15	40	3.5
4f	13, 11, 9, —	80	9, —, —, —	80	23, 21, 20, 17	40	11, 9, —, —	40	3.6
4g	11, 9, —, —	40	13, 11, 9, —	40	21, 20, 20, 18	20	16, 14, 11, 9	20	2.8
4h	12, 9, —, —	20	—	80	22, 18, 16, 12	40	18, 16, 15, 12	40	4.8
4i	16, 14,—,—	20	9, —, —, —	80	26, 23, 21, 18	40	24, 21, 21, 18	40	4.4
4j	11, 9, —,—	80	9, —, —, —	80	15, 13, 12, 9	40	24, 22, 19, 18	40	5.1
4k	13, 11, 9, —	80	11, —, —, —	80	21, 19, 17, 14	40	22, 21, 18, 17	40	4.2
4l	11, 9, —, —	40	9, —, —, —	40	24, 21, 18, 16	40	23, 19, 18, 17	40	4.3
4m	16, 12, 11, 9	40	11, —, —, —	40	24, 22, 21, 19	40	13, 11, 9, —	20	3.6
4n	14, 11, 9, —	40	15, 13, 11, 9	40	24, 22, 21, 20	40	20, 17, 14, 11	80	3.7
Curcumin[c]	—	—	—	—	11, 9, —, —	80	9, —, —, —	80	2.5
Fluconazole[d]	—	—	—	80	31, 28, 27, 24	20	32, 29, 24, 21	20	---

(—) Resistant.
--- *C*log *P* not determined.
[a] Zone of inhibition measured in mm at concentrations 160, 80, 40 and 20 μM/ml.
[b] MIC (minimum inhibitory concentrations) were measured in μM/ml.
[c] Isolated from *Curcuma longa*.
[d] Purchased from HiMedia Pvt. Ltd.
[e] Theoretical values *C*log *P* were calculated using commercially available ChemDraw Ultra 8.0.3.

activity with better zone of inhibition as comparison to remaining compounds, but were more active than curcumin (MIC 80). Compounds **4e**, **4g**, **4j** (MIC 20–40) showed much better activity as compared to curcumin (MIC 80) whereas compounds **4d**, **4f**, **4i**, **4l** and **4n** (MIC 80–160) were completely inactive and remaining compounds showed moderate activity against *S. typhi*. For *S. aureus* compounds **4d**–**f**, **4h**, **4i** and **4l** (MIC 80) do not show any zone of inhibition and were totally inactive and compounds **4a**, **4g**, **4j** (MIC 40–80) were more active than curcumin (MIC 80), whereas remaining compounds showed moderate antibacterial activity. No significant antibacterial activity was observed for electron donating and electron withdrawing moieties.

Antifungal activity of the synthesized products **4a**–**n** was evaluated against four human pathogenic fungal cultures viz. *Aspergillus niger, Aspergillus flavus, Trichoderma viride and Curvularia lunata*. Zone of inhibition was measured in mm by disc diffusion method using potato dextrose agar (PDA) (Table 3) and minimum inhibitory concentration was measured using food poisoning method. In the case of fungi it is clear that synthesized compounds were more effective against *Aspergillus niger* and *Aspergillus flavus,* but the standard antifungal agent fluconazole and curcumin obtained from *Curcuma longa* were ineffective against both these species and no activity was observed. Most of the compounds exhibited significant antifungal activity against *Trichoderma viride* and *Curvularia lunata* (Table 3). When tested against *C. lunata* and *T. viride* compounds **4b**, **4d**–**n** (MIC 40–80) showed better antifungal activity and compounds **4a** & **4c** (MIC 40–80) showed moderate activity, and all compounds tested were more active than curcumin. For *T. viride* compounds **4b**–**e**, **4g**–**l** and **4n** (MIC 20–40) showed better activity with greater zone of inhibition and remaining compounds **4a**, **4f**, **4m** (MIC 40–80) showed moderate activity. Like bacteria there is no significant activity was observed for electron donating and electron withdrawing moieties in case of fungus.

The 3,4-dihydropyrimidinone analogues **4a**–**n** synthesized above were evaluated in vitro cytotoxicity using three selected human tumor cell lines Hep-G2, HCT-116 and QG-56 using the standard MTT assay. Inhibitory activities (IC_{50}) were presented in micro molar per milliliter (μM/ml) concentrations of the synthesized curcumin derivatives as shown in Table 4. Sulfur containing dihydropyrimidinones exhibited higher cytotoxicity than oxygen containing compounds. All the compounds **4a**–**n** exhibited anticancer activity with IC_{50} values ranging from <12.5 to 100 μM/ml, while the positive control, adriamycin demonstrated the IC_{50} in the range of <2.5 to 5.0 μM/ml. The significant anticancer activity showed by the compound derived from 2-hydroxy benzaldehyde **4g** against HCT-116: human colon carcinoma.

In conclusion, the presented work demonstrates the isolation of curcumin. Curcumin thus obtained was utilized in the three component synthesis as a dicarbonyl moiety in place of acetyl acetone

Table 4
Cytotoxicity evaluation of curcumin dihydropyrimidinones against three carcinoma cell lines (IC_{50} μM/ml)[a]

Compound	Cytotoxicity (IC_{50})		
	Hep-G2[b]	HCT-116[c]	QG-56[d]
4a	50	25	50
4b	100	100	100
4c	100	50	100
4d	50	100	50
4e	25	100	50
4f	100	100	100
4g	25	12.5	50
4h	50	50	100
4i	50	100	50
4j	100	50	100
4k	50	100	50
4l	100	50	50
4m	50	100	100
4n	100	50	50
Curcumin[e]	50	50	100
Adriamycin[f]	2.5	5.0	2.5

[a] IC_{50}, concentration of drug that decreases the cell viability by 50% compared to non-treated control cells.
[b] Hep-G2: human hepato carcinoma.
[c] HCT-116: human colon carcinoma.
[d] QG-56: human lung carcinoma.
[e] Isolated from *Curcuma longa*.
[f] Control drug.

and ethyl acetoacetate. Other two components were urea/thiourea and substituted aromatic aldehydes. All the compounds (4-aryl substituted 3,4-dihydropyrimidinones of curcumin) were screened for their biological evaluation against selected human pathogenic bacteria and fungi. Cytotoxicity of the synthesized compounds was also evaluated against selected human cancer cell lines. Among the designed molecules, **4a**–**n**, **4b**, **4e**, **4f**, **4g**, **4i**, **4l**, **4m** and **4n** have showed significant antimicrobial activity against tested bacteria. All the compounds showed better antifungal activity than curcumin and fluconazole, compounds **4b** and **4i** were found to have better antifungal activity. Compound **4g** showed good cytotoxicity against tested human cancer cell lines. In the present Letter synergistic antibacterial and antifungal activity of curcumin has been enhanced using multi-component system.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2012.02.056.

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27. *Selected synthetic procedure* (***4a–n***)**:** A 100 ml round bottom flask was charged with curcumin (2 mmol), substituted aryl aldehyde (2 mmol), urea/thiourea (2 mmol) and (0.02 mmol) $SnCl_2{\cdot}2H_2O$ as catalyst was heated at 80 °C under solvent free conditions for about 80–90 min. The reaction was monitored by TLC using acetone/hexane (4:6) as eluent. After completion the reaction, the contents were dissolved in ethanol and stirred for about 10 min. The product was recrystallized from appropriate solvent. Selected characterization data **(4a):** 97%, dark red powder, soluble in ethanol and methanol, stable at room temperature, R_f (acetone/hexane 7:3) 0.26; IR (ν cm^{-1}, KBr) 3500, 3213, 2937, 1593, 1514, 1435, 1276, 1031, 962; ^{1}H NMR (400 MHz in $CDCl_3$) δ 3.93 (s, 6H, 3′, 3″, OCH_3), 5.79 (s, 2H, 4′,4″, OH), 7.58 (d, J = 15.76 Hz, 2H, H-1,7), 6.47 (d, J = 15.76 Hz, 2H, H-5′, 5″), 6.92 (d, J = 8.61 Hz, 2H, H-2′, 2″), 7.19 (m, 5H, C_6H_5), 5.39 (d, J = 10.44 Hz, 1H, CH), 7.41 (s, 1H, NH), 8.04 (1H, NH); ^{13}C NMR (400 MHz in DMSO d_6) 48.10, 56.02, 115.46, 112.31, 115.46, 124.06, 126.17, 128.68, 143.22, 144.64, 149.03, 151.46, 152.70, 192.11; MS (ESI) (m/z) 498 (M^+); Anal. Calcd for $C_{29}H_{26}O_6N_2$: C, 69.87; H, 5.26; N, 5.62. Found: C, 69.89; H, 5.24; N, 5.59.
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