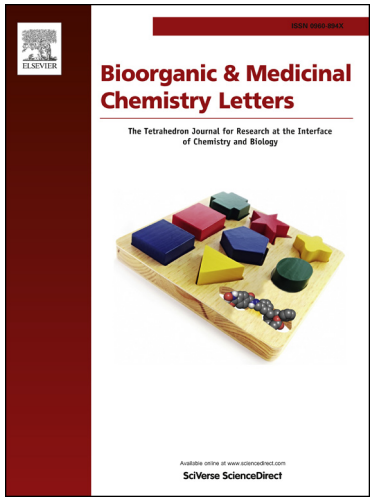

Structure activity relationship, cytotoxicity and evaluation of antioxidant activity of curcumin derivatives

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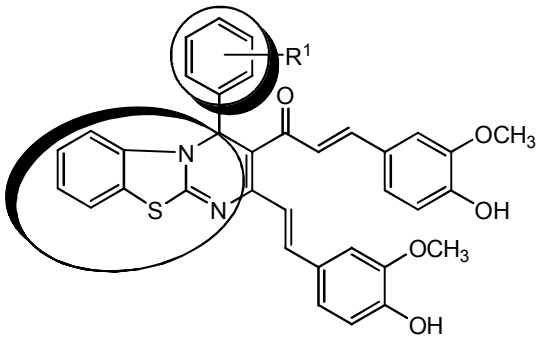
Graphical abstract



(2a-2h)

R^1 = 4-OH

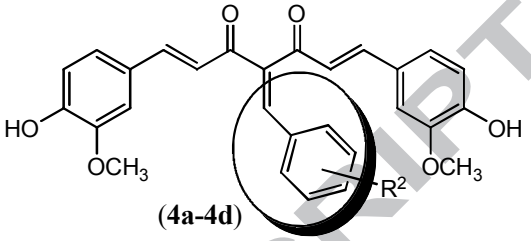
(2f)

Cytotoxicity activity
IC_{50} value **12.5 µM/mL**

R^1 = 4-OH-3-OCH_3, 4-OH,

(2e, 2f)

Antioxidant activity
Activity between
46.6-90.2%



(4a-4d)

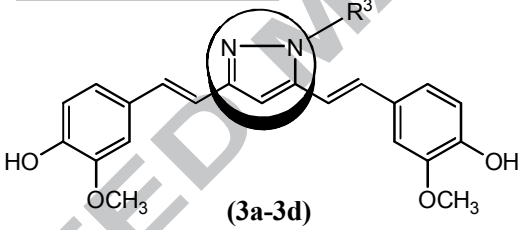
R^2 = 4-OH-3-OCH_3

(4d)

Cytotoxicity activity
IC_{50} value **12.5 µM/mL**

Derivatives (**4a-4d**)

Antioxidant activity
Activity between
50.8-90.2%



(3a-3d)

R^3 = -COC_5H_4N

(3c)

Cytotoxicity activity
IC_{50} value **6.25 µM/mL**

R^3 = -$CSNH_2$, -COC_5H_4N

(3b, 3c)

Antioxidant activity
Activity between
57.7-84.4%

Structure activity relationship, cytotoxicity and evaluation of antioxidant activity of curcumin derivatives

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Abstract

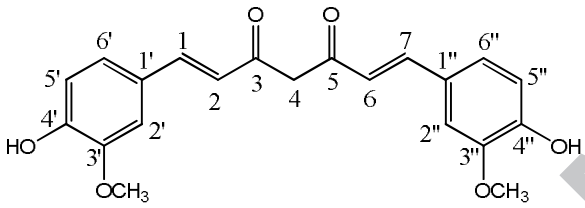
Series of curcumin derivatives/analogues were designed and efficient method for synthesis thereof is described. All the synthesized compounds have been screened for their cytotoxicity and evaluated their antioxidant activity. Cytotoxicity effect has been evaluated against three cell lines Hep-G2, HCT-116 and QG-56 by MTT assay method. Structure activity relationship has revealed that particularly, compound **3c**, (IC_{50} value **6.25** μM) has shown better cytotoxicity effect against three cell lines. According to results of SAR study, it was found that 4H-pyrimido[2,1-b]benzothiazole derivatives (**2e** and **2f**), pyrazoles (**3a**, **3b**, **3c** and **3d**) benzylidenes (**4d**) 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.

Keywords: Antioxidant Activity, Cytotoxicity, Structure-activity Relationship, Curcumin Derivatives/Analogues.

Curcuminoids are the major constituents of turmeric (*Curcuma longa L.*), originated 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)-(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] Curcumin and its derivatives exhibited many interesting biological activity such as antiviral,[4] anti-inflammatory,[5] antimicrobial,[6] antioxidant,[7] anti-HIV,[8] cancer preventive properties,[9, 10] anti-parkinson,[11] anti-Alzheimer's,[12] anti-angiogenesis,[13] free radical scavenging activity,[14] and anticancer.[15]

Figure 1. Structure of curcumin used in experiment

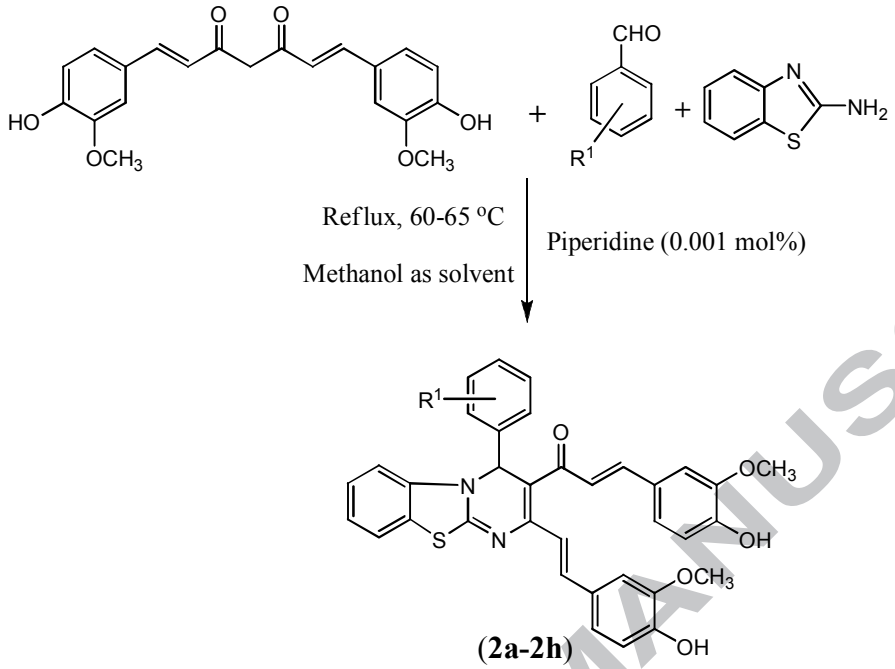


Various curcumin analogs/derivatives have been designed and synthesized in order to enhance metabolic stability and antiproliferative activity against human cancer cells.[16, 17] Recently, many structural modification efforts were carried out by looking at the variations on carbonyl moiety and active methylene group and it was found that some of the active methylene and carbonyl substituted curcumin derivatives/analogues showed better antioxidant activity than curcumin.[18-26] One of the most important aspects of curcumin is its effectiveness against various types of cancer with both chemopreventive and chemotherapeutic properties.[27, 28] Unfortunately, the potential utility of curcumin is somewhat limited due to poor bioavailability[29] and stability in physicological media.[30] 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.[31]

Recently, synthetic modifications on carbonyl and active methylene moiety of curcumin has been studied intensively in order to develop the molecules with enhanced properties and stability.[32, 33] From these studies it has been shown that compounds synthesized using carbonyl and active methylene moiety of curcumin have enhanced activity and stability in biological medium compared to curcumin.[31-33] However, pyrimido[2,1-b]benzothiazole and pyrazole (derived from isoniazide, semicarbazide and thiosemicarbazide) derivatives of curcumin have not been reported so far for their antioxidant activity and cytotoxicity. 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 (hepato carcinoma, colon carcinoma and lung carcinoma) using standard MTT assay method and antioxidant activity by adopting DPPH,[34] superoxide[35] and nitric oxide radical[36] scavenging activity evaluation.

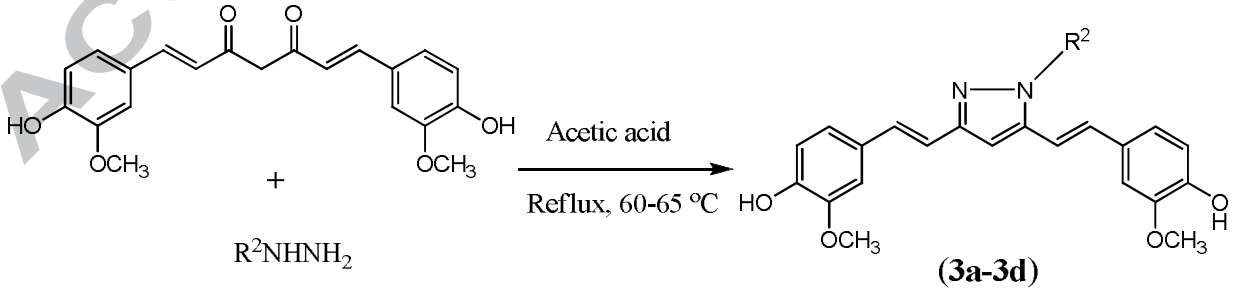
4H-Pyrimido[2,1-b]benzothiazole derivatives of curcumin (**2a-2h**) were synthesized with good yield as outlined in Scheme 1 by condensation of curcumin (5 mmol), aldehydes (5 mmol) and 2-aminobenzothiazole (5 mmol) in the presence of piperidine using conventional heating (Table 1). The structures of 4H-pyrimido[2,1-b]benzothiazole derivatives of curcumin were confirmed by IR, NMR, Mass spectra and elemental analysis.

Scheme 1. Synthesis of 4H-pyrimido[1,2-b]benzothiazole derivatives of curcumin (**2a-2h**).

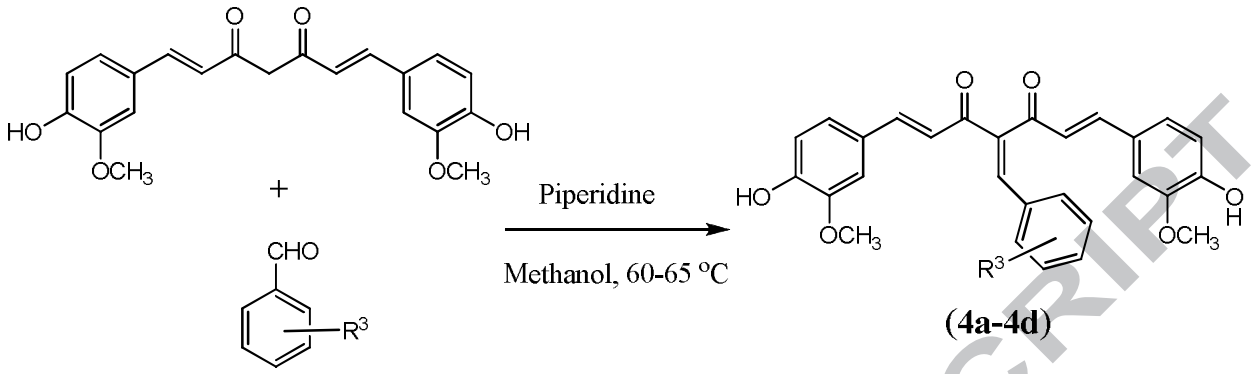


Methodology for the synthesis of pyrazole derivative (**3a-3d**), involves reaction of curcumin (5 mmol), and hydrazines (5 mmol) in acetic acid at 60-65 °C temperature (Scheme 2, see supporting information). Under the above optimized conditions, benzylidene derivatives (**4a-4d**) of curcumin were synthesized (Scheme 3) using curcumin (5 mmol) and substituted aromatic aldehydes (5 mmol); see supporting information.

Scheme 2. Preparation of pyrazoles of curcumin.



Scheme 3. Synthesis of benzylidene derivatives of curcumin.



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.

Table 1. One-pot synthesis of 4H-pyrimido[2,1-b]benzothiazole, pyrazole and benzyliden derivatives of curcumin.

Entry	R^1, R^2, R^3	Product	Time (hrs)/ Yield (%)	M.P.(°C)
1	H	**2a**	16/81	97-98
2	2-OH	**2b**	16/81	155-156
3	4-Cl	**2c**	18/89	112-113
4	4-NO_2	**2d**	18/86	85-86
5	4-OH-3-OCH_3	**2e**	18/81	80-81
6	4-OH	**2f**	20/89	101-102
7	4-CH_3	**2g**	20/84	108-109
8	2,6-Cl_2	**2h**	20/85	90-92
9	-$CONH_2$	**3a**	6/87	204-206
10	-$CSNH_2$	**3b**	7/81	100-101
11	-COC_5H_4N	**3c**	7/83	105-106
12	-$C_6H_3(NO_2)_2$	**3d**	6/86	118-119
13	H	**4a**	12/87	119-120
14	4-$N(CH_3)_2$	**4b**	13/86	104-106
15	2-OH	**4c**	12/89	92-94
16	4-OH-3-OCH_3	**4d**	14/81	98-100

The in vitro cytotoxicity of the synthesized curcumin derivatives (**2a-2h, 3a-3d, 4a-4d**) were evaluated by MTT assay method[37, 38] using three selected human tumor cell lines Hep-G2,

HCT-116 and QG-56. Inhibitory activities (IC_{50}) are being presented in μM concentrations of the synthesized curcumin derivatives as shown in Table 2. As we can see among pyrimido bezohiazole derivatives of curcumin (**2a-2h**), derivatives **2c**, **2d** and **2e** showed good activity with 25 μM IC_{50} against HCT-116, Hep-G2 and QG-56 respectively. Introduction of methyl substituent at para position (**2g**) showed much better activity against two cell lines i.e. HCT-116 and QG-56 with 25 μM IC_{50}. Results of cytotoxicity activity have been demonstrated that electron withdrawing and electron releasing groups at para position enhanced the activity. As far as compounds **3c** (6.25 μM), **3d** (6.25 μM) and **2f** (12.5 μM) are concerned, they showed better activity than curcumin against all of the tested cancer cell lines, indicating a wide anticancer spectrum. Particularly, cytotoxicity of isoniazide moiety containing pyrazole (**3c**), has sharply increased against Hep-G2, HCT-116 (6.25 μM). Anticancer activity of derivatives **3c** might be due to isoniazide moiety because isoniazide itself shown anticancer activity which increased the overall activity by linking with curcumin molecule, because of derivatives **3c** is a hybrid of isoniazide and curcumin.

Compound **3d** showed very potent activity against Hep-G2 (6.25 μM) is over 8-folds higher than curcumin (50 μM), while weak activity towards the other cell lines, indicating selective inhibition effect. However, the positive control, adriamycin demonstrated the IC_{50} in the range of <2.5 to 5.0 μM. In other hand, derivatives **3a** exhibited four folds cytotoxicity against HCT-116 and QG-56 than curcumin. As far as other derivatives are concerned, they showed comparable cytotoxicity activity to curcumin. Interestingly, compound **3c** showed potent activity against both Hep-G2 and HCT-116 cancer cell lines, it may be due to isoniazide moiety in curcumin derivatives.

Table 2. Cytotoxicity of curcumin derivatives against carcinoma cell lines (IC_{50} μM)[a]

Compound	Cytotoxicity (IC_{50})		
	Hep-G2[b]	HCT-116[c]	QG-56[d]
2a	100	50	100
2b	100	50	50
2c	50	25	50
2d	25	50	50
2e	50	100	25
2f	25	12.5	12.5
2g	50	25	25
2h	100	50	100
3a	25	12.5	12.5
3b	12.5	12.5	25
3c	6.25	6.25	12.5
3d	6.25	12.5	12.5
4a	50	100	50
4b	25	100	50
4c	100	50	25
4d	50	50	12.5
Curcumin	50	50	100
Adriamycin[e]	2.5	5.0	2.5

[a] IC50, 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] Control drug.

Structure activity relationship has revealed that pyrazole having isoniazide moiety has showed better influence on cytotoxicity. Isoniazide derived pyrazole derivative of curcumin **3c** showed the potent activity against all tested cancer cell lines, indicating a wide anticancer spectrum while other pyrazole derivatives showed selective cytotoxic activity (4-10 folds better than curcumin). Among benzylidene derivatives of curcumin, only para methoxy derived (**4d**) derivative showed much better activity against QG-56 (12.5 μM) in series. Furthermore, para hydroxyl derivatives (**2f**, 12.5 μM) of 4H-pyrimido[2,1-b]benzothiazole had the 2-8 folds better activity than curcumin while active methylene linked compounds (**4a-4d**, range between 12.5-100 μM) showed weakest activity. It seem to have no influence on the cytotoxicity, as no

significant difference of activity was found in benzylidenes derivatives which have not possess pyrazole moieties in their structure like pyrazole derivatives (**3a-3d**). Overall structure activity relationship studies demonstrated that pyrazole moiety is significant for cytotoxicity activity.

Table 3. Antioxidant activity by DPPH· method of compounds synthesized.

Compound	DPPH· FRSA%			
	50 µM	20 µM	10 µM	2 µM
2a	52.2	42.4	33.0	17.2
2b	47.8	41.2	32.2	19.9
2c	87.2	82.0	71.2	25.5
2d	58.0	52.1	42.2	20.0
2e	86.4	84.2	72.3	35.0
2f	88.2	87.2	72.2	28.6
2g	62.6	60.3	49.0	15.2
2h	60.3	58.1	44.5	18.2
3a	64.1	62.2	49.7	20.0
3b	86.8	82.1	68.2	29.9
3c	89.2	88.1	70.2	31.2
3d	81.2	78.0	61.9	28.3
4a	65.0	62.0	51.2	16.2
4b	83.1	80.8	76.6	22.4
4c	58.2	52.0	39.8	13.3
4d	62.2	60.3	44.2	12.5
Curcumin	50.2	42.2	33.2	6.0

It is believed that curcumin moiety has responsible for antioxidant effect as biological activity. In order to investigate whether target compounds maintain the antioxidant activity, synthesized curcumin derivatives were evaluated for their antioxidant activity by DPPH·, superoxide and nitric oxide radical scavenging activity evaluation methods. The present study identified the structure activity relationship in curcumin derivatives by DPPH method, which underscores the important chemical feature for this class of molecules to increased antioxidant activity. All of the tested compounds showed moderate to strong free radical scavenging activity (FRSA). From structure activity relationship, it can be seen in Table 3 that antioxidant activity of compound **3c** showed the higher FRS activity (89.2%) against DPPH, all other tested compounds

have lower percentage of activity as compared to compound **3c**. However all the compounds have higher FRS activity (between 52.2-88.2%) than curcumin (50.2%). It is obvious from antioxidant activity, thiosemicarbazide (**3b**) and 2,4-dinitro phenyl hydrazine (**3d**) derived pyrazole derivatives also showed better activity with 86.8% and 81.2% respectively.

It may be produced due to combining effect of pyrazole moiety instead of diketone of curcumin. FRSA of 4H-pyrimido[2,1-b]benzothiazole derivatives could be enhanced by the introduction of hydroxyl group (derivatives **2c**, 87.2%; **2e**, 86.4% and **2f**, 88.2%) at ortho and para position. It is due to the involvement of hydroxyl moiety in free radical mechanism. Literature survey also shows that phenolic hydroxyl group is responsible for antioxidant activity.[39]

This result indicates that, in addition to the phenolic hydroxyl group, the adjacent methoxy (**2e**) or hydroxyl groups (**2b** and **2f**) is also required for formation of stable phenoxy radical which is believed to play the critical role in radical scavenging activity of the curcuminoids.[40-42] It is also noticeable that DPPH$^{\cdot}$ scavenging activity of benzylidene derivatives of curcumin is significantly better than curcumin. All the benzylidenes (**4a-4d**, range between 58.2%-83.1%) having two phenolic hydroxy groups, and consequently their FRSA were in magnitude at the same order. There was not most significant effect of aryl moiety of aldehydes used.

In nitric oxide radical scavenging assay, curcumin derivatives with 4-methoxy-3-hydroxy moieties (**2e**, 35-86.4% and **4d**, 80.4%) and hydroxyl derived (**2b** 90.2 % and **2f**, 89.2%) showed better activity due to involvement of electron donating substituents as methoxy and hydroxyl groups in FRSA activity, whereas derivatives have not hydroxyl moiety as substituent failed to reduced the amount of FRSA comparatively. Form table 4 and 5, it is interestingly that curcumin

derivatives (**3a**, **3b** and **3c**) also showed the higher scavenging ability as compare to curcumin due to participation of pyrazole moieties in mechanism of FRSA. Among all derivatives, six derivative showed promising effect in nitric oxide scavenging property which follow the order, **2f>3b>2e>3c>3a>4d.** The structure-activity relationship presented above indicates that the phenolic hydroxyl group is prerequisite, but alone insufficient, for radical-scavenging effect of the curcuminoids.

Table 4. Antioxidant activity of compounds (2a-4d) synthesized and curcumin

Compound	$NO^{\cdot}$ FRSA%			
	50 µM	20 µM	10 µM	2 µM
2a	48.0	38.2	21.2	11.2
2b	90.2	78.8	62.2	25.5
2c	52.2	36.6	29.9	16.8
2d	50.0	33.3	21.0	14.2
2e	86.4	84.2	72.3	35.0
2f	89.2	84.2	70.8	26.6
2g	47.2	35.5	20.2	10.2
2h	55.5	38.3	21.2	17.5
3a	88.8	72.6	49.7	29.9
3b	90.2	76.1	52.5	32.3
3c	82.2	74.2	50.2	31.2
3d	50.8	33.0	20.8	15.5
4a	65.0	49.2	21.2	16.2
4b	57.7	36.6	22.2	12.8
4c	70.2	52.2	38.0	24.2
4d	80.4	72.5	38.2	28.8
Curcumin	59.9	36.5	22.2	12.2

The results clearly revealed that the hydroxyl derivatives and pyrazole moieties enhanced the activity by involvement in the mechanism of scavenging activity. Therefore it could be inferred that 4H-pyrimido[1,2-b]benzothiazole and pyrazole ring structure have considerable role in enhancing the activities. The superoxide scavenging capacity decreases in the order **3c>3b>3a>2f>2e>4c>4a>4d>2c>2b>4b>3d>2a>2d>2g>2h**. The above mentioned structure-activity relationship studies revealed that derivatives possess hydroxyl and electron donating

groups (**3c, 3b, 3a, 2f, 2e a**nd **4c)** demonstrated considerable superoxide radical scavenging and antioxidant capacity. In comparison with curcumin, the FRSA of the derivatives/analogues are much higher. This is probably due to the introduction of the substituent which is an electron donating group and may subsequently enhance the free radical-capturing ability of the phenolic hydroxy group.

Table 5. Antioxidant activity of curcumin derivatives (2a-4d) by superoxide radical method

Compound	FRSA%			
	50 µM	20 µM	10 µM	2 µM
2a	49.8	32.2	20.2	11.2
2b	68.8	48.2	31.2	16.6
2c	65.2	36.6	29.9	17.0
2d	50.0	32.0	21.0	14.8
2e	89.2	76.6	65.5	35.0
2f	88.9	78.0	62.3	33.5
2g	56.6	35.5	21.2	13.2
2h	46.6	32.2	19.9	12.2
3a	62.9	49.0	30.2	20.2
3b	90.0	78.8	48.8	30.2
3c	89.2	76.6	50.2	32.2
3d	58.9	33.0	19.9	14.9
4a	70.8	55.5	30.8	20.8
4b	66.1	52.9	34.2	19.9
4c	84.4	71.9	50.2	34.0
4d	69.9	44.9	31.2	14.9
Curcumin	42.2	30.2	21.2	13.9

Above structure activity relationship studies also revealed that isoniazide derivative **3c** showed the better FRSA over other derivatives in series. Derivatives synthesized using carbonyl (**2a-2h**) moiety of curcumin, hydroxyl derivatives (**2e**) and (**2f**) enhanced the FRSA activity due to involvement of hydroxyl moiety in FRSA mechanism. Curcumin derivative derived using active methylene moiety (**4a-4d**) did not change the nature of radical-scavenging activity. In comparison with curcumin, the FRSA of curcumin derivative/analogues is much higher. This is probably due to introduction of additional moieties as pyrazole and hydroxyl derived pyrimido

benzothiazole in curcumin molecule which may be enhancing the free radical-capturing ability of the phenolic hydroxyl group. Structure-activity relationship presented above indicates that the phenolic hydroxyl group is prerequisite, but alone insufficient for radical scavenging activity effect of the curcuminoids.

Physico-chemical properties of synthesized compounds has been calculated and showed in table 6. The method is very robust and is able to process practically all organic molecules. Molecular Polar Surface Area TPSA is calculated based on the methodology previously published.[43] TPSA has been shown to be a very good descriptor characterizing drug absorption, including intestinal absorption, bioavailability and blood–brain barrier penetration. Prediction results of compounds 2a-2h, 3a-3d and 4a-4d molecular properties (TPSA, GPCR ligand and ICM) are valued (Table 6).

From the data evaluated in Table 6 indicates that, all structures are supposed to be non mutagenic when run through the mutagenicity assessment system and as far as irritating and reproductive effects are concerned, all the compounds are at low risk comparable (except 3d and 4b). 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.

Table 6. Physico-chemical properties and drug score of synthesized curcumin derivatives

Compound	Physico-chemical properties				Drug-score			
	TPSA	O/NH	VIOL	Volume	CLP	S	DL	DS
2a	93	2	2	516	5.89	-7.61	4.85	0.22
2b	113	3	2	524	5.89	-7.31	4.53	0.22
2c	93	2	2	529	6.50	-8.34	6.03	0.18
2d	139	2	2	539	5.76	-8.07	-5.18	0.10
2e	123	3	2	549	5.48	-7.33	4.47	0.22
2f	113	3	2	524	5.59	-7.31	5.15	0.23
2g	93	2	2	532	6.20	-7.95	3.52	0.20
2h	93	2	2	543	7.11	-9.08	5.01	0.16
3a	120	4	0	360	3.09	-4.87	1.13	0.55
3b	103	4	0	369	3.94	-3.25	0.30	0.54
3c	107	2	0	416	4.14	-5.84	1.70	0.41
3d	168	2	3	448	4.32	-6.04	-10.3	0.04
4a	93	2	0	414	4.59	-5.02	1.27	0.43
4b	96	2	0	460	4.59	-5.05	-1.61	0.09
4c	113	3	0	422	4.29	-4.72	2.50	0.50
4d	122	3	1	447	4.19	-4.74	2.21	0.47
Curcumin	93	2	0	332	2.97	-3.62	-3.95	0.39

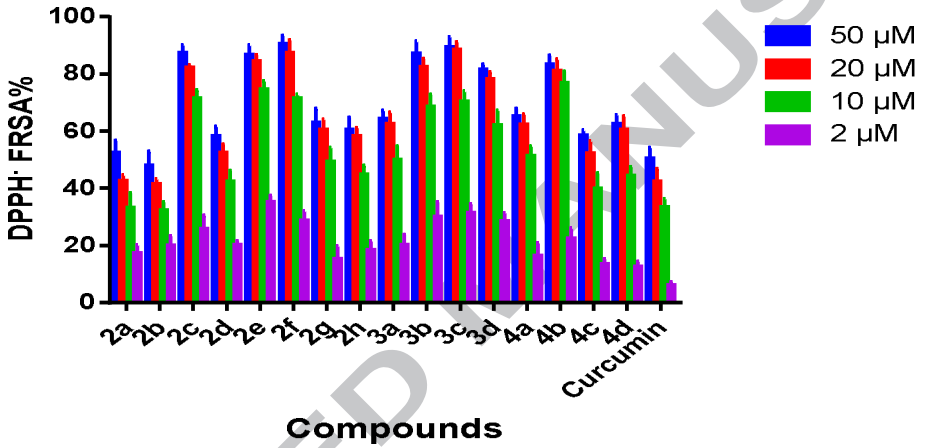
TPSA: Total polar surface area, O/NH: O---HN interraction, VIOL: number of violation;
CLP: *c*Log*P*; Log *P* calculated by Molinspiration, S: Solubility, DL: Drug likness, DS: Drug-Score.

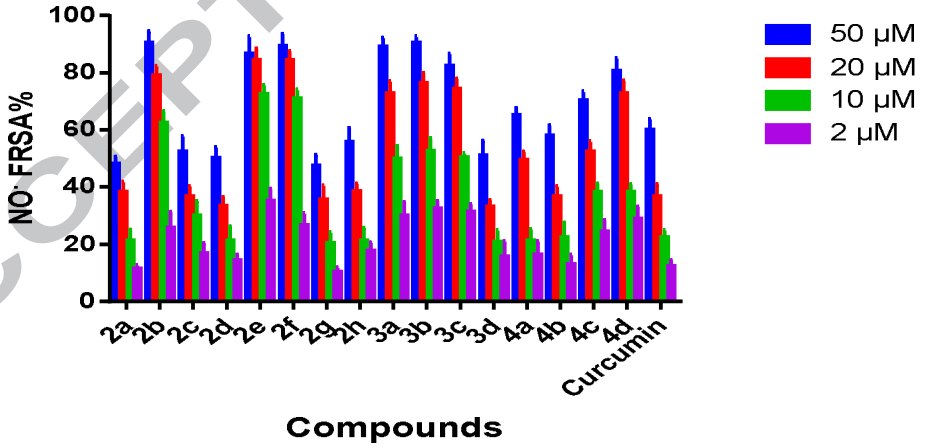
On this basis, all the series of compounds 3a–4d is having clog*P* values under the acceptable criteria should be active. The geometrical parameter and the aqueous solubility of a compound significantly affect its absorption, distribution characteristics and bioactivity. Typically, a low solubility goes along with a bad absorption and therefore the general aim is to avoid poorly soluble compounds. Further, the Table 6 shows drug-likeness of compounds 2a-4d is 0.10-0.23; 0.04-0.55 and 0.09-0.50 respectively for series 2a-2h, 3a-3d and 4a-4d. We have calculated overall drug-score (DS) for the compounds 2a-4d and compared with that of curcumin used. The DS combines drug-likeness and clog*P* in one handy value that may be used to judge the compound's overall potential to qualify for a drug. The reported compounds showed six

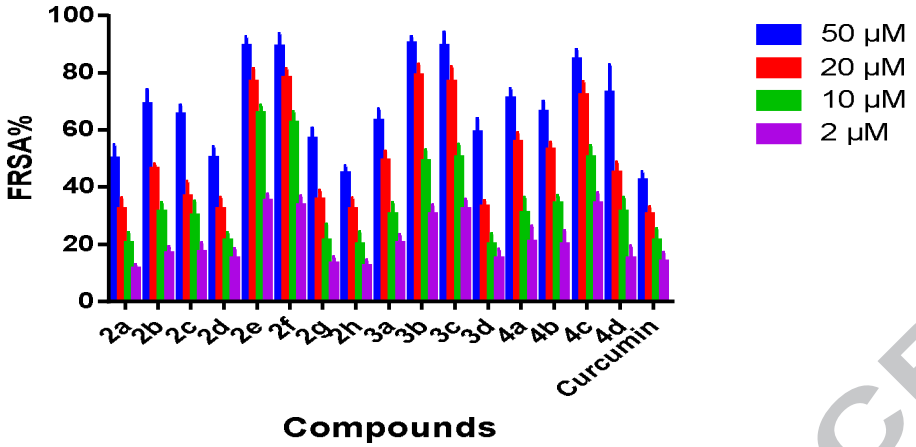
compounds have good DS but the rest of series have low to moderate DS as compared with curcumin.

All statistical analysis was performed using graph pad prism 6.0 version. All the experiments were conducted in triplicates and the results were calculated as mean ± standard deviation (SD) in this study. *P*-values less than 0.05 were considered to be statistically significant (Figure 2).

Figure 2. Data presented are the means ± SD of results from three independent experiments







In conclusion, we have designed and synthesized 4H-pyrimido[2,1-b]benzothiazole (**2a-2h**), pyrazole (**3a-3d**) and benzylidene (**4a-4d**) derivatives of curcumin. The results of cytotoxic activity by MTT assay exhibited that compounds **3c** (**6.25** µM) and **3d** (**6.25** µM) showed much better activity against all tested three human cancer cell lines. In vitro antioxidant activity results revealed all of the target compounds have higher FRSA than curcumin toward DPPH, superoxide and nitric oxide radical. In addition, hydroxyl substituted pyrimido benzothiazole derivatives (**2e**, and **2f**) and pyrazoles (**3b** and **3c**) exhibited significant antioxidant activity due to its involvement in FRSA. Present study showed curcumin derivatives possess electron donating group, enhanced the free radical scavenging activity due to involvement of electron in free radical capturing ability of molecules by phenolic hydroxyl group. The compounds showed suitable drug like properties and are expected to present good bioavailability profile. Thus, from the data obtained from virtual and practical screening, it is concluded 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.

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Supplementary data: Supplementary data associated with this article can be found, in the online version.

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Table Captions

Table 1. One-pot synthesis of 4H-pyrimido[2,1-b]benzothiazole, pyrazoles and benzylidene derivatives of curcumin.

Table 2. Cytotoxicity of curcumin derivatives against carcinoma cell lines (IC_{50} μM).

Table 3. Antioxidant activity by $DPPH^{\cdot}$ method of compounds synthesized.

Table 4. Antioxidant activity of compound (2a-4d) synthesized and curcumin.

Table 5. Antioxidant activity of curcumin derivatives (2a-4d) by superoxide radical method.

Table 6. Physico-chemical properties and drug score of synthesized curcumin derivatives

Figure 1. Structure of curcumin used in experiment

Figure 2. Data presented are the means ± SD of results from three independent experiments

Scheme Captions

Scheme 1. Synthesis of 4H-pyrimido[1,2-b]benzothiazole derivatives of curcumin (**2a-2h**).

Scheme 2. Preparation of pyrazoles of curcumin.

Scheme 3. Synthesis of benzylidene derivatives of curcumin.