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Synthesis, antimalarial activity and cytotoxic potential of new monocarbonyl analogues of curcumin

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ABSTRACT

A series of novel monocarbonyl analogues of curcumin have been designed, synthesized and tested for their activity against Molt4, HeLa, PC3, DU145 and KB cancer cell lines. Six of the analogues showed potent cytotoxicity towards these cell lines with IC_{50} values below 1 μM, which is better than doxorubicin, a US FDA approved drug. Several analogues were also found to be active against both CQ-resistant (W2 clone) and CQ-sensitive (D6) strains of *Plasmodium falciparum* in an in-vitro antimalarial screening. This level of activity warrants further investigation of the compounds for development as anticancer and antimalarial agents.

Natural products have played a vital role in the drug discovery process and approximately 67% of the drugs in the clinical market today are inspired by or derived from natural sources.[1] Curcumin (diferuloylmethane, Fig. 1), isolated from the rhizome of turmeric (Curcuma longa Linn.), is one of such natural compounds, which has been a subject of intense study for many decades.[2] Turmeric has been used since ancient time in South Asian subcontinents particularly in India and China as a dietary pigment, essential spice, and it has also been used in the traditional medicine as an antiseptic, anti-inflammatory and wound-healing agent.[3] Curcumin is also known for its anti-inflammatory, antioxidant, antimicrobial, antiviral, antiangiogenic, chemopreventative, chemotherapeutic and anticancer activities.[4] Recently, curcumin was also explored for its antimalarial activity against both chloroquine (CQ)-sensitive and chloroquine (CQ)-resistance strains of *Plasmodium falciparum*.[5] It has also shown hepato-protective and nephro-protective,[6] thrombosis suppressing,[7] myocardial infarction protective,[8] anti-hypoglycemic,[9] and anti-rheumatic[10] activities, and exhibited decreased tumorigenesis in many organs when tested in vivo.[2,11]

In vitro studies demonstrated that curcumin has potent cytotoxicity towards many cell lines derived from leukemia,[12] cervical cancer,[13] colorectal carcinoma,[14] prostate cancer[15] and human breast cancer cells.[16] However, limited clinical efficacy such as poor solubility, bioavailability and absorption as well as rapid metabolism have been major problems associated with curcumin.[17]

Detailed pharmacological studies conducted on curcumin demonstrates that the β-diketone functionality of curcumin is a substrate for liver aldoketo reductases and this may be one of the reasons for the rapid metabolism of curcumin in vivo.[18] The mono carbonyl analogues of the curcumin have been designed and synthesized in anticipation that the in vivo metabolic stability of these analogues can be improved and some of these compounds have shown very good anticancer activity.[19] Structure–activity relationship studies conducted on these compounds revealed that the heteroaromatic core in these compounds correlated with high anti-proliferative and anti-inflammatory activities.[20] Therefore, as a part of our ongoing programme towards the development of medicinally important molecules,[21] we became interested in modifying the structure of the curcumin by changing the β-diketone structure to mono carbonyl with rigid ring, while retaining

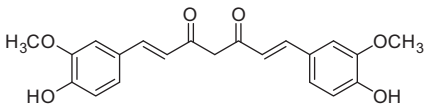

Figure 1. Structure of curcumin.

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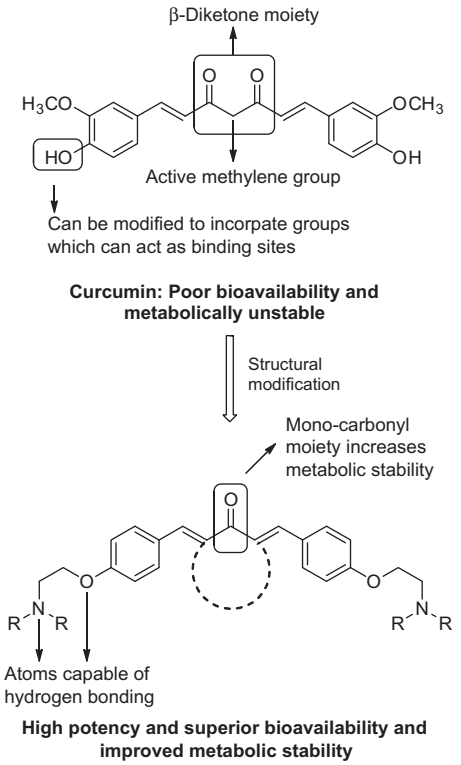


Figure 2. Modification of central β-diketone group and aryl substitution pattern.

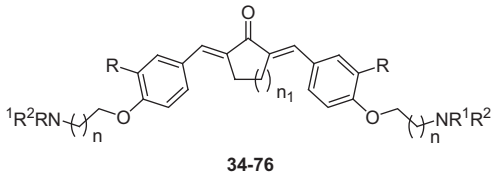


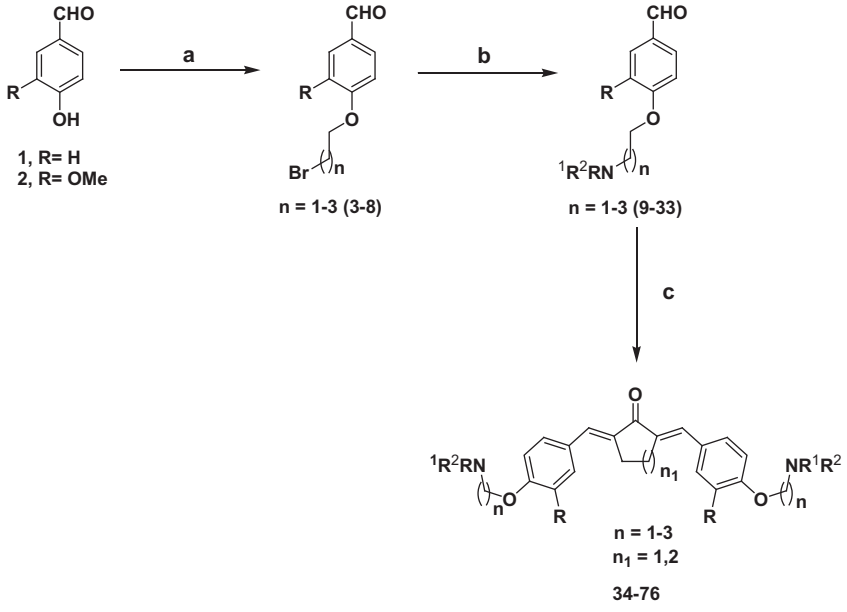
Figure 3. General structure of molecules in the present investigation.

the major skeleton of the structure. In addition, analogues were prepared by adding extra groups at two ends to examine the solubility issue (Fig. 2).

For the mono ketone part, either a five-membered ring or a six-membered ring was incorporated. The impact of rigidity was studied. For the linker on both ends, different lengths of the alkyl chain were applied to study the impact of size. For the substitution group of NR^1R^2, the following groups were used: bromo, morpholino, piperidino, dimethylamino, imidazole, 2-methyl imidazole and azepano group. The impact of the polarity and size of the substitution on two side chains was studied. Overall, a series of 43 analogues having the general structure shown in Figure 3 have been designed and prepared using one synthetic route (Scheme 1).

For the synthesis of desired monocarbonyl analogues of curcumin, commercially available starting materials *p*-hydroxy benzaldehyde (**1**) or vanillin (**2**) were reacted with an excess amount of aliphatic linear dibromoalkanes in the presence of a base (Scheme 1). The resulting aldehydes (**3**–**8**) with free bromo group at terminal position was subjected to nucleophilic substitution by different aromatic or aliphatic secondary amino functionalities to yield the corresponding amino substituted aldehydes (**9**–**33**) in high yield. The resulting compounds (**9**–**33**) were coupled with cyclopentanone or cyclohexanone in an alkaline medium in an aldol type of condensation to yield the desired curcumin analogues in good to excellent yield (70–90%) (**35**–**76**). Synthesis of analogue **34** was achieved by directly coupling cyclopentanone with 4-(2-bromoethoxy)-3-methoxybenzaldehyde (**3**) via aldol condensation.

All the synthesized compounds (Table 1) were screened for their cytotoxicity against the HeLa cancer cell line at three different concentrations. In the first screening, all compounds were tested at a concentration of 50 μM by the MTT assay. The result showed most compounds had cytotoxicity at 50 μM, and hence they were tested for the 2nd round screening at 2.5, 2 or 1 μM. Data showed that 11 compounds displayed comparable or better cytotoxicity than the control compound doxorubicin. All 11 active compounds were tested in the MTT assay with three replicated of every concentration (concentration from10 to 0.25 μM) in HeLa, PC3, DU145, KB or Molt4 cell lines. The MTT data were analyzed by curve-fitting using Sigma plotting to obtain the IC_{50} values (Table 2).



Scheme 1. Reagents and conditions: (a) aliphatic dibromoalkane, K_2CO_3, DMF, 80 °C, 1 h, 50–60%; (b) different secondary amines (HNR^1R^2), K_2CO_3, DMF, 80 °C, 6 h, 80–90%; (c) cyclic ketones, 20% (w/v) NaOH, MeOH, rt, overnight, 70–90%.

Table 1
Synthesized monocarbonyl analogues of curcumin

Compd.	R	*n*	NR^1R^2	n_1
34	OMe	1	Br	1
35	OMe	1	Morpholino	1
36	OMe	1	Piperidino	1
37	OMe	1	Dimethylamino	1
38	OMe	1	Imidazolo	1
39	OMe	1	2-Methyl imidazolo	1
40	OMe	2	Morpholino	1
41	OMe	2	Piperidino	1
42	OMe	2	Piperidino	2
43	OMe	2	Dimethylamino	1
44	OMe	2	Imidazolo	1
45	OMe	2	2-Methyl imidazolo	1
46	OMe	3	Morpholino	1
47	OMe	3	Piperidino	1
48	OMe	3	Azepano	1
49	OMe	3	Imidazolo	1
50	OMe	3	2-Methyl imidazolo	1
51	H	1	Piperidino	1
52	H	1	Piperidino	2
53	H	1	2-Methyl piperidino	1
54	H	1	Morpholino	1
55	H	1	Dimethylamino	1
56	H	1	Imidazolo	1
57	H	1	2-Methyl imidazolo	1
58	H	1	Azepano	1
59	H	2	Piperidino	1
60	H	2	Piperidino	2
61	H	2	Morpholino	1
62	H	2	Morpholino	2
63	H	2	Dimethylamino	1
64	H	2	Imidazolo	1
65	H	2	2-Methyl imidazolo	1
66	H	2	2-Methyl imidazolo	2
67	H	3	Piperidino	1
68	H	3	Piperidino	2
69	H	3	2-Methyl piperidino	1
70	H	3	2-Methyl piperidino	2
71	H	3	Morpholino	1
72	H	3	Morpholino	2
73	H	3	Dimethylamino	1
74	H	3	Azepano	1
75	H	3	Imidazolo	1
76	H	3	2-Methyl imidazolo	1

Table 2
IC_{50} values of screened compounds against HeLa, Molt4, PC3, DU145 and KB cell lines

Compd.	IC_{50} (μM)				
	HeLa	Molt4	KB	PC3	DU145
36	0.4	0.02	4.4	>5	>5
37	0.5	0.03	>5	>5	>5
39	0.9	0.1	3.4	>5	>5
42	1.95	0.55	1.65	6.91	2.05
43	0.64	0.43	0.2	1.5	0.43
45	3.15	0.66	1.99	0.2	3.9
46	0.72	0.36	0.62	0.28	0.67
47	0.49	0.32	0.55	0.5	0.46
48	1.39	0.41	2.25	0.3	1.01
68	3.63	0.73	2.54	1.53	2.11
73	6.8	0.33	1.65	2.9	4.4
DOX.	2.2	0.02	0.33	0.2	0.2

DOX: doxorubicin; HeLa: human cervical cancer cell; Molt4: human acute lymphoblastic leukemia cell; KB: human nasopharyngeal epidermal carcinoma; PC3: human prostatic adenocarcinoma; DU145: human prostate cancer cell.

We were delighted to find some compounds such as **36**, **37**, **39**, **43**, **46** and **47** showing higher potency than doxorubicin (Table 2). From the cytotoxicity data, it is clear that the rigidity didn't play important role to impact the activity. For example, compounds **36**, **42**, **47** and **68** showed very good activity with the IC_{50} in the low micro molar range in HeLa cells though they have different ring sizes at the ketone position. Some other compounds (**40**, **54**, **61** and **62**) didn't show cytotoxicity even at 50 μM although they have the same five- or six-member ring structures. Among all the tested compounds, morpholino substitution on both sides of the compounds showed relatively low cytotoxicity except for compound **46.** The length of the side chain does not seem to have a major effect on the activities. For the most active compounds, a methoxy group on the phenyl ring seems favor the inhibitory effect. For compounds having R = H (**51**–**76**), only compound **68** and **73** showed good activities with a long side chain *n* = 3.

Some symmetrical monocarbonyl analogues of curcumin were tested for their antimalarial activity against CQ-sensitive (D6 clone) and CQ-resistant (W2 clone) strains of *P. falciparum* (Table 3) Out of 20 compounds tested, potent activity were observed with compounds **36**, **37**, **46**, **49**, **56** and **57** (in which the amine probe is attached via ethylene/butylene linker with cyclopentanone ring) against CQ-resistant strain of *P. falciparum* (IC_{50} ranging from 0.37 to 0.63 μM) when compared with standard drug chloroquine (CQ). These compounds (**36**, **37**, **46**, **49**, **56** and **57**) also displayed moderate to good activity against CQ-sensitive strains of *P. falciparum* with IC_{50} ranging from 0.35 to 0.69 μM. All the compounds were found to be non-toxic to Vero cells indicating their safety towards mammalian cells (Table 3).

By observing the dataset of cytotoxicity and antimalarial activity, it was found that the cytotoxicity dataset was not large enough for doing 3D-QSAR. The remaining dataset tested for antimalarial activity against D6 clone was processed for developing a 3D-QSAR model. All the work was done by using PHASE (Schrodinger, Inc., LLC, New York, USA), in Dell precision T3500 work station.

The common pharmacophore is generated and the best pharmacophore AAARR with 3 acceptor features and 2 ring aromatic features is taken based upon the hypothesis scores. 3D-QSAR model generated using training set (12 compounds) was validated using test set (8 compounds). Model generated using partial least sqaure (PLS) analysis showed correlation coefficient R^2 of 0.96, test set

Table 3
In-vitro antimalarial activity of selected symmetrical monocarbonyl analogue of curcumin

Compd.	*P. falciparum* (D6 clone)		*P. falciparum* (W2 clone)		Vero[a]
	IC_{50} (μM)	S.I.	IC_{50} (μM)	S.I.	
34	NA	—	NA	—	NC
35	3.11	>2.6	2.41	>3.4	NC
36	0.50	>16.4	0.53	>15.4	NC
37	0.44	>21.6	0.62	>15.4	NC
38	2.21	>4.0	1.81	>4.9	NC
39	1.28	>6.5	1.38	>6.0	NC
43	1.14	>7.9	1.53	>6.0	NC
44	NA	—	NA	—	NC
45	2.01	>4.0	3.01	>2.6	NC
46	0.69	>10.8	0.63	>11.9	NC
47	1.74	>4.3	2.85	>2.6	NC
48	1.36	>5.3	1.82	>4.0	NC
49	0.53	>14.9	0.56	>14.0	NC
50	4.00	>1.9	4.48	>1.7	NC
56	0.45	>21.6	0.37	>26.4	NC
57	0.35	>26.4	0.43	>21.6	NC
71	NA	—	NA	—	NC
72	NA	—	NA	—	NC
75	2.04	>4.3	3.54	>2.5	NC
76	1.09	>7.7	1.41	>6.0	NC
CQ	0.053	>160	0.43	>20	NC
ART	0.019	>470	0.011	>800	NC

[a] Doxorubicin was taken as positive control; CQ: chloroquine; ART: artemisinin; S.I.: selectivity index (IC_{50} for cytotoxicity to vero cells/IC_{50} for antimalarial activity); NA: not active; NC: not cytotoxic upto 9 μM.

Table 4
Summary of PHASE 3D-QSAR Statistical data

ID	PLS Factors	SD	R^2	*F*	*P*	RMSE	Q^2	Pearson-R
AAARR	*1*	*0.0324*	*0.944*	*118.2*	*1.22 e^{-05}*	*0.243*	*0.61*	*0.742*
	2	0.0375	0.957	126.9	1.31 e^{-08}	0.237	0.62	0.768
	3	*0.0401*	*0.959*	*184.9*	*1.82 e^{-10}*	*0.224*	*0.66*	*0.772*

PLS-partial least squares, SD-standard deviation, R^2-correlation coefficient, *F*-ratio of the model variance to the observed variance, *P*-the significance level of F when treated as a ratio of chi-squared distributions, RMSE-root mean square error, Q^2-test set prediction, Pearson-R-value of correlation between the predicted and observed activity for the test set.

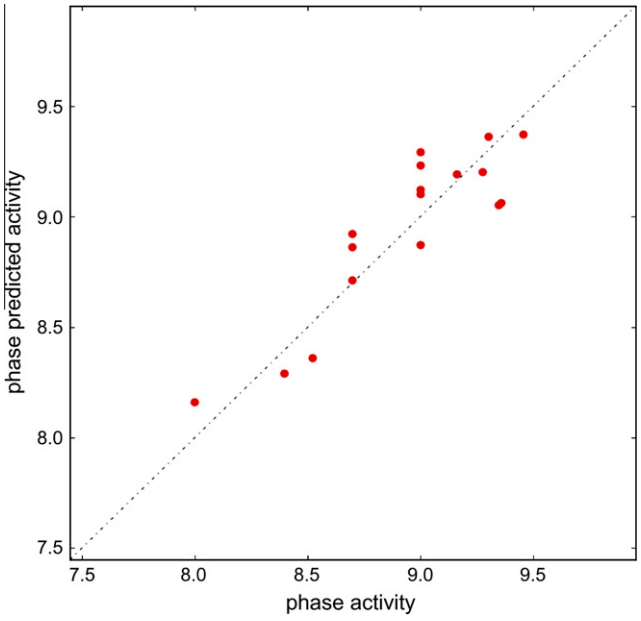


Figure 4. Graph showing correlation between experimental and predicted activities.

prediction Q^2 of 0.66 and Pearson-R of 0.65 (Table 4). The high value of variance ratio (*F*) observed for this model indicates its statistical robustness which is further supported by significant level of variance ratio (*P*). The value of $P < 0.05$ indicates greater degree of confidence which means *F* is significant at the 95% level. The low standard deviation (SD) of 0.04 and RMSE value of 0.22 clearly shows the model nicely predicted the experimental activities. Figure 4 shows the graphical representation of phase predictive pIC_{50} of the compounds against experimental values. Figure 5 showed the visual representation of the QSAR model with point of possible modification for activity improvement. It can be concluded that if these compounds were modified at both ends by adding hydrophobic groups, the activity of these compounds can be enhanced still to a greater extent.

In conclusion, a series of monocarbonyl analogs of curcumin have been synthesized. Among all the active compounds, 6 showed nanomolar activities against the HeLa cell line, which are significantly lower than that of doxorubicin. Some of the analogues also showed comparable activities with doxorubicin in other cell lines. Out of several compounds tested for antimalarial activity, 6 analogues (**36**, **37**, **46**, **49**, **56** and **57)** were found to show excellent activities against both CQ-resistant and CQ-sensitive strains of *P. falciparum*. The results obtained so far should be very useful for the further optimization of the new analogues for further clinical development.

Acknowledgments

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Supplementary data

Supplementary data (experimental details, characterization of compounds, cell culture and MTT assay for anticancer activity,

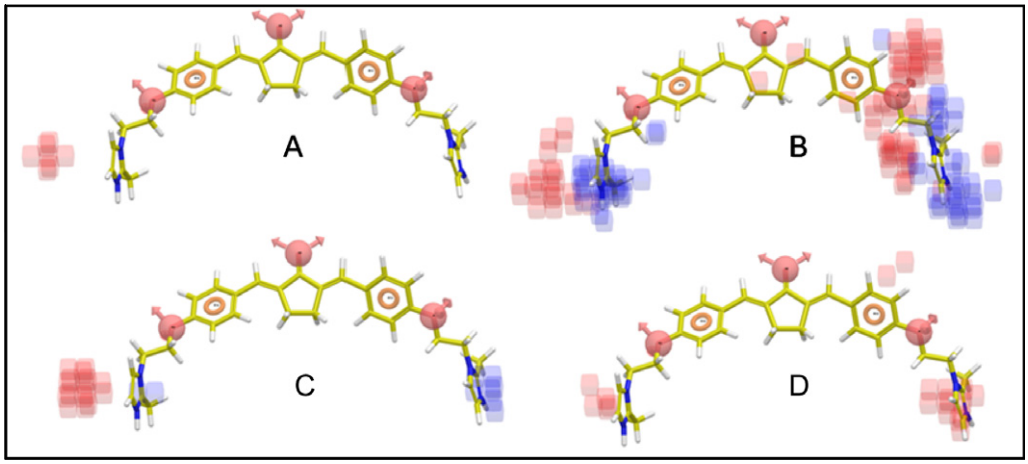

Figure 5. Visual representation of QSAR model and best pharmacophore hypothesis with compound **57**. Blue cube indicates positive coefficient (increase in activity) while red cube indicates negative coefficient (decrease in activity); (A) Hydrogen bond donor regions; (B) Hydrophobic regions; (C) Positive ionic regions; (D) Electron withdrawing regions.

assay for in vitro antimalarial activity, PHASE methodology for molecular modeling and dose–response curves) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.11.004.

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