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Design, synthesis, and cytostatic activity of novel cyclic curcumin analogues

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Abstract—A series of novel cyclic analogues of curcumin were synthesized and analyzed for in vitro cytostatic activity. Condensation of 2-acetylcycloalkanones with a variety of aromatic aldehydes resulted in the formation of 2-arylidene-6-(3-arylacryoyl)-cycloalkanone derivatives. A number of these analogues were found to have significant anticancer activity against representative murine and human cancer cell lines during in vitro bioassays. This corroborated with in vitro cytostatic activity against a panel of 60 cell lines studied at the National Cancer Institute (USA).

Curcumin (**1a**,**b**) is a phytochemical obtained from the dried rhizomes of *Curcuma longa* LINN.[1] This yellow pigment is the main constituent of turmeric powder, a widely used spice in Southeast Asia.[1] Curcumin is also used in traditional medicine to treat a wide variety of ailments such as indigestion, urinary tract infections, liver disease, and rheumatoid arthritis (Fig. 1).[2]

This phytochemical has gained interest due to its anti-inflammatory, anti-oxidant, anti-proliferative, anti-angiogenic, and anti-tumorigenic properties.[3–6] In regard of its anticancer properties, curcumin has demonstrated growth inhibition[7] and apoptosis induction[8–10] in a wide variety of cancer cell lines. The anti-angiogenic effects of curcumin include the inhibition of vascular endothelial cell proliferation in vitro and capillary tube formation and growth in vivo.[11,12] Because of its excellent pharmacodynamic profile, curcumin proceeded onto clinical trials;[13,14] however, due to its low potency and poor bioavailability, it has not become a successful drug.[15] Curcumin's significant anti-neoplastic activity, along with its low molecular weight and lack of toxicity, makes this molecule an ideal lead molecule for development of potential chemotherapeutic agents.[16,17]

Curcumin's vast array of biological properties and their molecular mechanisms have been the subject of much scientific investigation. It is widely accepted that curcuminoids are capable of inducing apoptosis by their ability to up-regulate the proapoptotic BAX proteins and their ability to down-regulate the anti-apoptotic Bcl-2 proteins.[8–10] Curcumin has been found to modulate protein function and expression;[8–10] however, its molecular interaction with proteins is not yet fully understood. Since curcumin is essentially an electrophilic molecule, more precisely a Michael acceptor, it is capable of protein thiolation. Such compounds are known to covalently bind with sulfhydryl-rich proteins such as topoisomerase-2 which in turn renders the enzyme inactive.[18] Michael acceptors are not known to conjugate with genetic material due to their reduced affinity for hydroxyl- or amino-functionalities located in nucleic acids.[19] This feature is likely responsible for its reduced mutagenicity and carcinogenicity in comparison to other anticancer drugs.[20]

There are some reports of biological evaluation of curcumin analogues. These studies focused mainly on altering the aryl substitution, 1,3-diketone structure, and simplification of the dicinnamoylmethane pharmaco-

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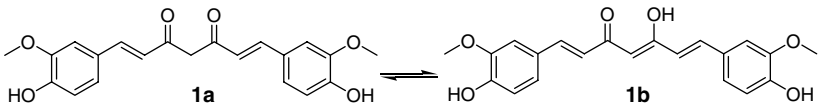
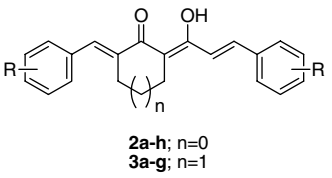


Figure 1. Tautomeric structure of curcumin (**1a**,**b**).

phore.[9,11,21–23] 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 while introducing a ring structure to increase rigidity as well as to create molecules which are more lipophilic. Increased lipophilicity will enable molecules to potentially penetrate through cell membrane more effectively leading to improved absorption. It has previously been reported that curcumin is primarily metabolized by sequential reduction and glucuronidation.[24–27] The rapid metabolism of curcumin by glucuronidation of the phenolic hydroxyl group can be prevented or retarded by O-methylation of the phenolic group or by replacement of the phenolic group with a metabolically resistant functional group such as Cl (obstructive halogenation) or CH_3.[28] Two series of designed curcumin analogues for current investigation are indicated in Figure 2.

Various substitutions on the aromatic ring were introduced in the design in order to evaluate the dependence of biological activity and bioavailability on electronic, steric, and solubility factors due to these substituents as well as to retard first-pass metabolism. Fifteen cyclic curcumin analogues were successfully synthesized using boron trioxide-mediated aldol condensation using conventional heating and microwave irradiation (Scheme 1). The full details of the synthesis and characterization of compounds **2a–h** and **3a–g** have been described previously.[29] Microwave synthesis provided expedited reaction time, increased yield, and simpler purification compared to conventional boron trioxide-mediated procedure previously reported.[30]

X-ray crystallography was undertaken for compound **3c** (R = Me, $n = 1$)[31] to unambiguously establish the double bond geometries which are difficult to ascertain for two of the three alkene bonds one of which is enolic. The crystal structure (Fig. 3) showed the molecule to exist as two enolic tautomers. The stereochemistries at the exocyclic and cinnamoyl double bonds were conclusively established as *E*; the enolic double bond showed expected *Z* geometry owing to the 6-membered cyclic transition state between the two enolic forms involving the H-bond between the carbonyl group and the enolic



a. R=H
b. R=4-Cl
c. R=4-CH_3
d. R=4-OH
e. R=4-OCH_3
f. R=3,4-$(OCH_3)_2$
g. R=3-OCH_3, 4-OH
h. R=4-NO_2

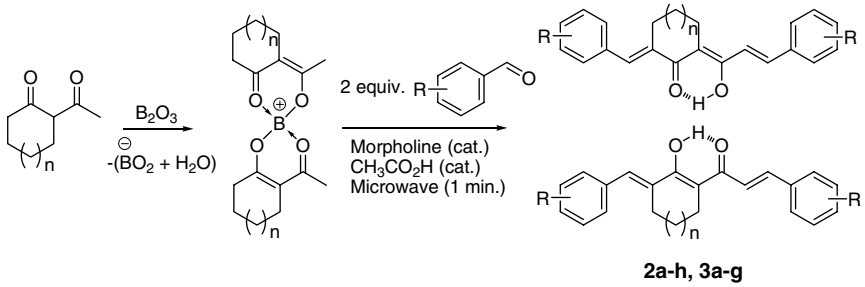
Figure 2. Chemical structures of compounds investigated.

hydroxyl functionality (H-bond distance 1.29–1.36 Å). This corroborates with the ^{1}H NMR results where a peak (~16 ppm downfield to TMS) for the chelated hydroxyl group was observed.[29]

All compounds were assayed in the murine leukemia L1210 and the human lymphoblast Molt 4C/8 and CEM systems using a reported procedure.[32] Murine L1210 cytotoxicity assay is valued as a preliminary predictor of clinical suitability of anticancer drugs.[33] Human Molt 4/C8 and CEM T-lymphocyte cell lines were chosen to evaluate the cytostatic potential of compounds under investigation toward human mutated cells. The IC_{50} values and their standard deviations are reported in Table 1. The clinically used cytoxic drug Alkeran® and curcumin were used as reference drugs.

It becomes obvious from the examination of the data presented in Table 1 that, like curcumin itself, an oxygenated aromatic ring is important for cytostatic activity. With the exception of compound **2e**, all compounds bearing oxygen on aromatic rings in series **2** displayed moderate to pronounced cytostatic activity. Among the two series of compounds tested, compound **2f** displayed best cytostatic profile with potency higher than those for curcumin and Alkeran® against all the cell lines assayed. Interestingly, compound **3f**, the 6-membered cyclic analogue of **2f**, was only weakly cytostatic. This appears unusual but could be due to the ability or lack thereof of the two molecules to interact with the receptor. A 3D comparison of the molecular framework of the two compounds was accomplished by CAChe® molecular modeling software,[34] where they were superimposed through the cinnamoyl enone group. The divergence in the topology of the two is highlighted in Figure 4. Substantial divergence was noted in the position of the arylmethylene groups. Thus it can be argued that owing to cyclic structure and olefinic groups imparting considerable rigidity, the divergence in 3D topology becomes detrimental for compound **3f** to bind favorably with the receptor, which, in turn, leads to weaker cytostatic activity.

Introduction of groups such as –Cl or –CH_3 rather than –OH or –OCH_3 on the aromatic ring to retard metabolism led to loss of cytostatic activity against all three cell lines. It is well documented that phenolic compounds demonstrate anti-oxidant properties owing to their ability to scavenge free radicals.[35] The anti-oxidant activity translates into cancer chemopreventive activity as it obliterates the reactive oxygen and nitrogen species which are involved in the tumorigenesis process. Curcumin possesses superb anti-oxidant activity due to its phenolic and enolic functionalities.[35] This corroborates with our findings in this study that compounds with oxy-



Scheme 1. Synthetic scheme for the production of tautomeric **2a**–**h** ($n = 0$) and **3a**–**g** ($n = 1$). Refer to Figure 2 for R substituents.

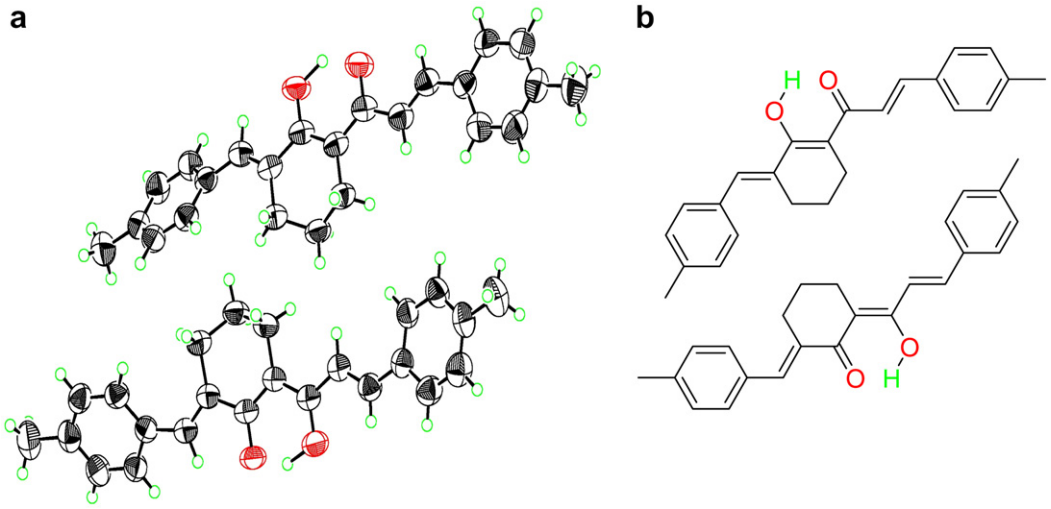


Figure 3. ORTEP diagram of the X-ray crystal structure of compound **3c** (a) and its 2D structural representation (b).

Table 1. Cytostatic activity of curcumin analogues against representative cell lines

Compound	IC_{50} (μM)		
	L1210	Molt4C/8	CEM
2a	65 ± 6	48 ± 9	55 ± 11
2b	436 ± 145	>500	>500
2c	58 ± 14	80 ± 11	74 ± 4
2d	10 ± 1	9.0 ± 1.6	11 ± 0
2e	340 ± 104	462 ± 53	527 ± 35
2f	1.4 ± 0.3	1.2 ± 0.2	1.3 ± 0.3
2g	8.3 ± 0	7.3 ± 0.7	8.3 ± 1.5
2h	71 ± 29	44 ± 5	43 ± 2
3a	50 ± 29	49 ± 0	38 ± 12
3b	304 ± 132	257 ± 21	299 ± 55
3c	300 ± 73	276 ± 32	285 ± 26
3d	9.5 ± 0.6	4.6 ± 0.4	8.9 ± 2.4
3e	120 ± 63	47 ± 8	62 ± 29
3f	55 ± 45	50 ± 4	47 ± 2
3g	8.6 ± 7.3	8.8 ± 0.7	8.1 ± 2.0
—	—	—	—
1[a]	9.0 ± 0.5	9.0 ± 1.9	8.7 ± 1.1
Alkeran®,[b]	2.13 ± 0.03	3.24 ± 0.79	2.47 ± 0.03

[a] Commercial 70% curcumin from Aldrich.
[b] The data for Alkeran® are reproduced from the Eur. J. Med. Chem. 35, 970 (2000).

genated aromatic rings showed cytostatic activity. This was also observed in a related work on curcumin analogues published recently.[36]

In order to verify whether the cytostatic activity correlated with one or more physicochemical properties of the aryl substituents[37] in both series of molecules, linear and semi-logarithmic correlations were obtained[38] between Hammett σ values, the Hansch π values, and molar refractivity (MR) constants (reflecting the electronic, hydrophobic, and steric properties of the aryl group, respectively), and the activity data presented in Table 1. Two other calculated[39] parameters for the whole molecule, viz. $c\mathrm{Log}\,P$ (octanol/water partition coefficient) and dipole (polarity), were also correlated with IC_{50} values. Only the significant correlations obtained for both the series of molecules are presented in Table 2. The value of P in the range 0.05–0.1 indicates a trend toward significance, while values <0.05 suggest significant correlation. The magnitude of coefficient r shows the extent (the closer the values to 1, the better) and the nature (sign positive or negative) of the correlation.

Intriguingly, correlations were established between parameters Hansch π values, $c\mathrm{Log}\,P$, and dipole with cytostatic IC_{50} values (Table 1) for both the series of molecules, albeit to different extents (Table 2). For compounds in series **2**, slight positive linear correlation was established between the π values and cytostatic potential against all three cell lines (P values < 0.18). Calculated partition coefficient $c\mathrm{Log}\,P$ correlated positively and more significantly (P values < 0.07) with the IC_{50} values of compounds in series **2**. For the same series of com-

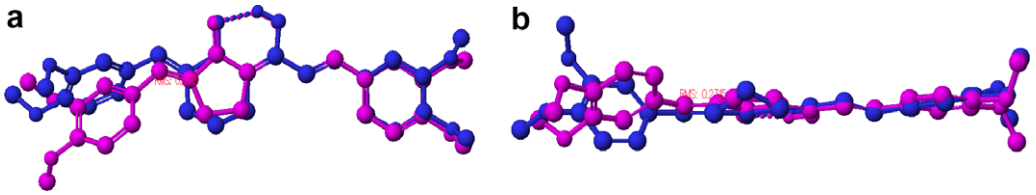


Figure 4. Superimposed structures of compounds **2f** (magenta) and **3f** (blue) in two orientations.

pounds, negative trends toward significant correlations were observed for dipole and IC_{50} values in all the three cell lines studied (P values < 0.1). Similar results were obtained for compounds in series **3** except that the semi-logarithmic correlation of cytostatic potential with parameters Hansch π values and *c*Log *P* was almost perfect ($P \leqslant 10^{-3}$) while dipole correlated less significantly.

Positive correlation of both Hansch π and *c*Log *P* with cytostatic activity infers that when lipophilicity decreases, the IC_{50} decreases leading to improved cytotoxicity. This is clearly evident from the notable cytostatic activity in oxygenated polar compounds presumably because of their ability to act as anti-oxidants. This is further strengthened by the negative correlation between dipole and cytostatic activity values which also means that increase in polarity of the compounds leads to decreased IC_{50} values resulting in increased cytostatic potency. No meaningful correlations were noted between Hammett σ and MR values versus the cytostatic data.

Three representative compounds **2f**, **3d**, and **3g** were also evaluated against 57 human tumor cell lines representing nine different neoplastic conditions, namely leukemia, melanoma, non-small cell lung, colon, central nervous system, ovarian, renal, prostate, and breast cancers. The data generated are summarized in Table 3.

Table 2. Correlation constants between IC_{50} values of curcumin analogues 2 and 3 and certain physicochemical parameters

Series	Independent	Dependent	Type	Correlation coefficient *r*	*P* value
Series **2**	Hansch π	L1210 IC_{50}	Linear	0.599	0.116
		Molt4 IC_{50}	Linear	0.574	0.135
		CEM	Linear	0.535	0.172
	*c*Log *P*	L1210 IC_{50}	Semi-log	0.678	0.064
		Molt4 IC_{50}	Semi-log	0.706	0.050
		CEM IC_{50}	Semi-log	0.684	0.061
	Dipole	L1210 IC_{50}	Semi-log	−0.623	0.099
		Molt4 IC_{50}	Semi-log	−0.679	0.064
		CEM IC_{50}	Semi-log	−0.679	0.064
Series **3**	Hansch π	L1210 IC_{50}	Semi-log	0.973	0.000
		Molt4 IC_{50}	Semi-log	0.985	0.000
		CEM IC_{50}	Semi-log	0.991	0.000
	*c*Log *P*	L1210 IC_{50}	Semi-log	0.950	0.001
		Molt4 IC_{50}	Semi-log	0.947	0.001
		CEM IC_{50}	Semi-log	0.967	0.000
	Dipole	L1210 IC_{50}	Semi-log	−0.623	0.135
		Molt4 IC_{50}	Semi-log	−0.486	0.268
		CEM IC_{50}	Semi-log	−0.582	0.170

Table 3. Evaluation of **2f**, **3d**, **3g** and reference compounds against a panel of human tumor cell lines

Cell lines		**2f**	**3d**	**3g**	Alkeran®[c]
All cell lines	GI_{50} (μM)[a]	2.60	10.26	3.98	16.97
	SI[b]	31.42	79.54	1560	38
Leukemia	GI_{50} (μM)	1.38	1.69	1.52	12.55
Lung cancer	GI_{50} (μM)	3.28	12.01	5.29	19.50
Colon cancer	GI_{50} (μM)	2.31	7.62	2.97	23.36
CNS Cancer	GI_{50} (μM)	2.10	12.33	3.90	13.90
Melanoma	GI_{50} (μM)	3.50	14.06	5.55	15.84
Ovarian cancer	GI_{50} (μM)	2.99	13.02	5.35	17.00
Renal cancer	GI_{50} (μM)	3.88	11.77	5.05	19.30
Prostate cancer	GI_{50} (μM)	1.40	8.60	2.71	Not available
Breast cancer	GI_{50} (μM)	2.56	11.28	3.45	18.67

[a] GI_{50} refers to the compound concentrations required to inhibit the growth of the cells by 50%.
[b] SI refers to the selectivity index. The SI figures for all cell lines were obtained by dividing the GI_{50} values of the least and most sensitive cells.
[c] GI_{50} values for Alkeran® were obtained from online NCI database (COMPARE data vector search, compound ID NSC 8806).

The results summarized in Table 3 demonstrate that when all cell lines are considered, **2f**, **3d**, and **3g** are more cytotoxic than Alkeran®. An important characteristic of a candidate anticancer drug is selective toxicity for certain cells rather than their being indiscriminately cytotoxic. The selectivity index (SI) figures for all cell lines divulge a wide differential sensitivity of the human tumors to **2f**, **3d**, and **3g**; compound **3g** in particular displayed impressive selectivity. A review of the mean graphs[40] revealed that **2f**, **3d**, and **3g** exerted greater toxicity to leukemic cell lines than those representing other neoplastic diseases. Alkeran® is used in combination chemotherapy to treat chronic leukemias.[41] The results in Table 3 reveal that **2f**, **3d**, and **3g** are considerably more potent against leukemic cell lines than Alkeran®. The revelation that the compounds possess significant potencies and preferential cytotoxicity for certain tumor cells suggests that 2-arylidene-5-(-1-hydroxy-3-arylallylidene)cyclopentanone (series **2**) and 2-arylidene-5-(-1-hydroxy-3-arylallylidene)-cyclohexanone (series **3**) are candidate anticancer agents which may display selective toxicity.

In conclusion, 15 curcumin analogues were synthesized under microwave conditions and bio-evaluated for their possible cytostatic activity in pursuit of non-toxic and anti-neoplastic agents. Five products displayed similar or superior activity compared to curcumin. Properties relating to solubility and polarity of the molecule generally correlated very well with the biological activity. Quantitative structure–activity relationship studies indicated that increased polarity with oxygenation in the aromatic ring is vital for cytostatic activity of this type of molecules. This information will be used to further amplify this project.

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