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# Structure–activity relationship studies of curcumin analogues

James R. Fuchs [a], Bulbul Pandit [a], Deepak Bhasin [a], Jonathan P. Etter [a], Nicholas Regan [a], Dalia Abdelhamid [a], Chenglong Li [a], Jiayuh Lin [b], Pui-Kai Li [a,*]

[a] Division of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, The Ohio State University, 338 Parks Hall, 500 West 12th Avenue, Columbus, OH 43210, USA
[b] Center for Childhood Cancer, Columbus Children's Research Institute, Ohio State University, Columbus, OH 43205, USA

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ABSTRACT

Two series of curcumin analogues, a total of twenty-four compounds, were synthesized and evaluated. The most potent compound, compound **23**, showed potent growth inhibitory activities on both prostate and breast cancer lines with $IC_{50}$ values in sub-micromolar range, fifty times more potent than curcumin. Curcumin analogues might be potential anti-tumor agents for breast and prostate cancers.



Curcumin, 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadien-3,5-dione (Fig. 1), is the primary bioactive compound isolated from turmeric, the dietary spice made from the rhizome of *Curcuma longa*. Turmeric has been a mainstay of traditional Indian folk medicine, and it has been used for the treatment of many diseases such as diabetes, liver disease, rheumatoid arthritis, atherosclerosis, infectious diseases and cancers. The therapeutic effects of curcumin are attributed to its activity on a wide range of molecular targets.

One of the most important aspects of curcumin is its effectiveness against various types of cancer with both chemopreventive and chemotherapeutic properties.[1,2] Unlike most chemotherapeutic agents, curcumin is reported to show little to no toxicity (no dose-limiting toxicity at doses up to 10 g/day in humans).[3] Unfortunately, the potential utility of curcumin is somewhat limited due to poor bioavailability[4] and poor selectivity. The lack of selectivity is due to the numerous molecular targets with which curcumin is known to interact. These include several targets closely associated with cancer cell proliferation such as the transcription factors NF-κB,[5] STATs,[6,7] AP-1[8] and PPAR-g.[9] Other targets include inflammatory enzymes such as COX-2,[10,11] lipoxygenases (LOX)[12] and protein kinases which include EGFR, HER2/neu,[13,14] MAPK[15] and AKT.[16] In addition, proteins regulating the cell cycle and apoptosis are also the targets of curcumin.[17–19]

Numerous analogues of curcumin have been synthesized and tested to investigate their activity against known biological targets and to improve upon the pharmacological profile of the natural product (i.e., improve their selectivity, bioavailability, and stability).[5,20–29] The simple molecular scaffold of curcumin along with the relative density of functional groups provides medicinal chemists with an outstanding target for lead optimization and structure–activity relationship (SAR) studies. Typical strategies dramatically simplify the molecule into two (or three) distinct functional elements: aromatic rings joined via olefin bonds to a β-diketone (Fig. 2). The olefin double bonds, while acknowledged to be important for activity, are generally only considered to be a linker between the two key structural elements and have not been widely modified. Instead, synthetic efforts have primarily been directed at variation of the aromatic rings and their substituents.

In our continuing efforts toward the design of anti-tumor agents for the treatment of both prostate and breast cancers, several series of curcumin analogues (compounds **1**–**24**) were synthesized and evaluated to investigate their structure–activity relationships (Fig. 3). Structurally, the compounds can be divided into two series—(1) a heptadiendione series (compounds **1**–**13**) and (2) a pentadienone series (compounds **14**–**24**).

The synthesis of curcumin, compounds **1**–**4**, **6**, and **10** were carried out using 2,4-pentanedione and commercially available benzaldehydes according to the procedure of Venkateswarlu (Fig. 4).[26]

Compounds **12** and **13** were obtained by treating curcumin with hydrazine and *N*-methylhydrazine in acetic acid, respectively (Fig 5).[23,24,30]

The syntheses of compounds **14**–**19** and **23**–**24** were carried out via condensation of acetone with the appropriately substituted benzaldehydes under standard protic conditions[31] (methods A and B, Fig. 6).

* Corresponding author. Tel.: +1 614 688 0253; fax: +1 614 688 8556.
*E-mail address:* li.27@osu.edu (P.-K. Li).

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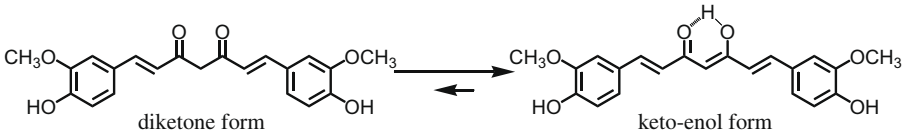



**Figure 1.** The keto–enol tautomerization of curcumin.

For the synthesis of sulfamoylated curcumin analogues (compounds **5**, **8**, **9**, **11**, **20**–**22**), an established procedure[32] was employed, utilizing chlorosulfonamide ($ClSO_2NH_2$) in dimethylacetamide (DMA) at room temperature for 24 h. The synthesis of compound **5** from curcumin is shown in Figure 7.

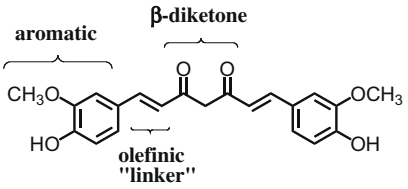



**Figure 2.** Functional regions of curcumin.

Since curcumin and its analogues have been reported to affect multiple molecular targets, the observed effect could be due to the analogues interfering with either a single or multiple targets in the cells. In addition, the effects are also further complicated by the differences in the cancer cells used in the studies. Different cancer cells have significantly different altered signaling pathways. Thus, it is extremely difficult to study the structure–activity relationships of the analogues. Our initial approach is to determine their anticancer activities through measuring the anti-proliferative activities of the compounds. The compounds were examined for their anti-proliferative activities against four cancer cell lines, which included: an androgen-dependent prostate cancer cell line (LNCaP), an androgen-independent prostate cancer cell line (PC-3), an estrogen-dependent (MCF-7) and an estrogen-independent (MDA-MB-231) breast cancer cell line. Cells were treated with test

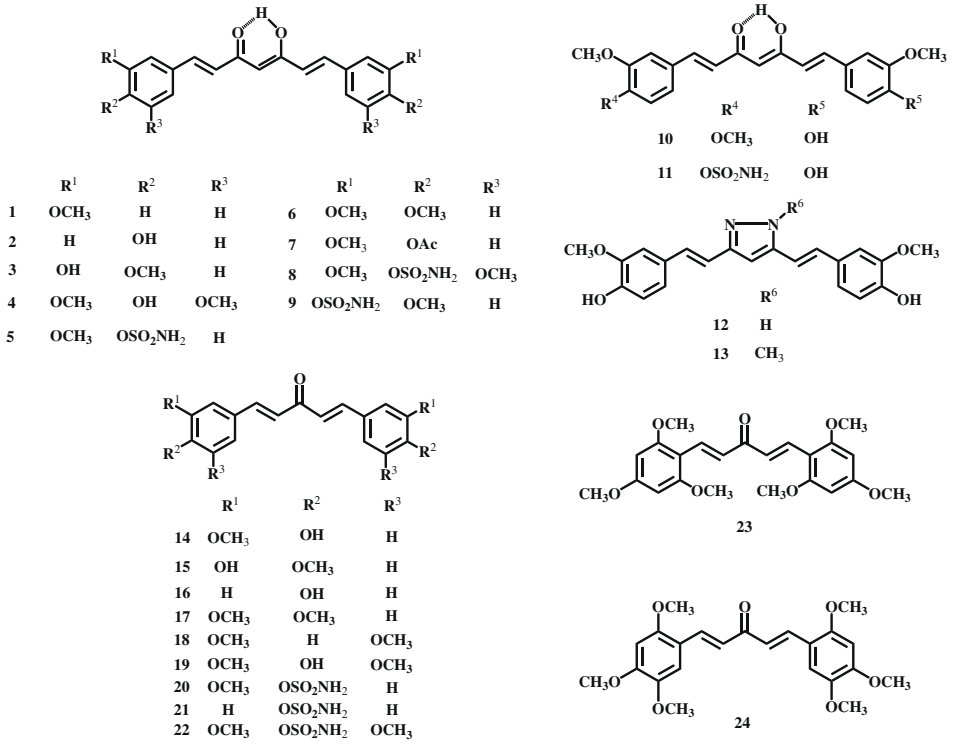



**Figure 3.** Heptadiendione and pentadienone analogues of curcumin.

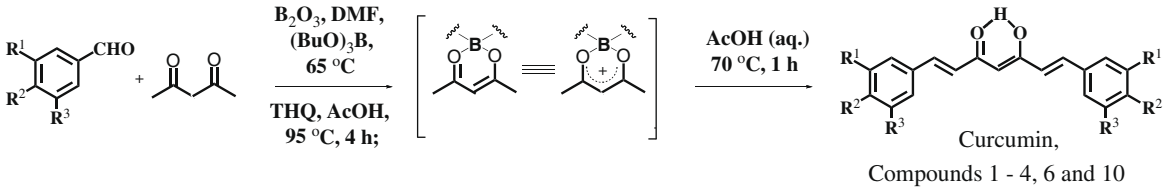



**Figure 4.** Syntheses of compounds **1**–**4**, **6** and **10**.

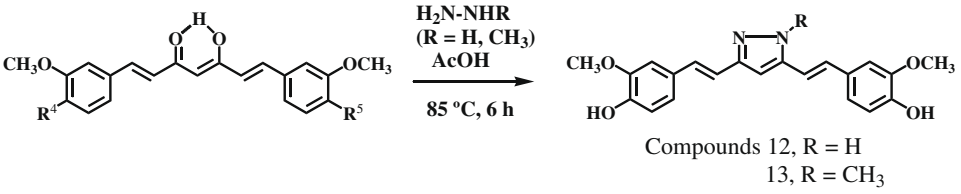



**Figure 5.** Synthesis of compounds **12** and **13**.

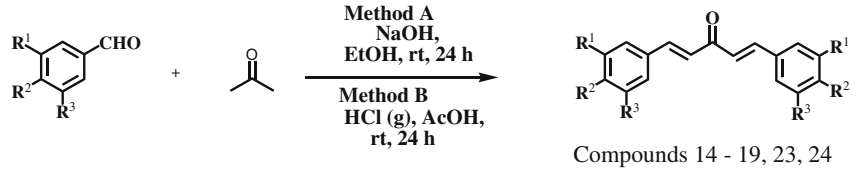



**Figure 6.** Synthesis of compounds **14**–**19**, **23** and **24**.

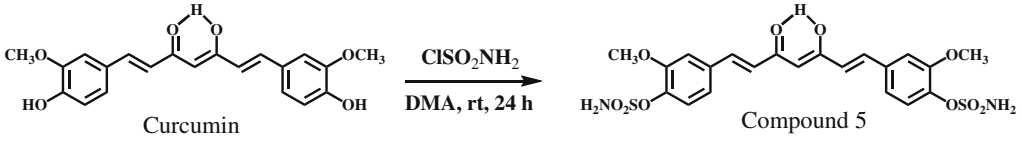
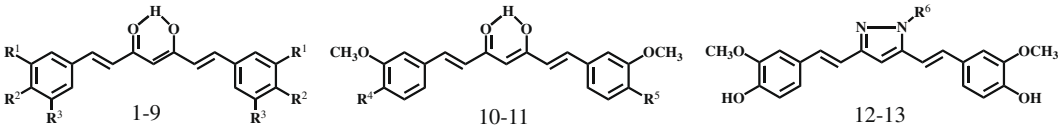



**Figure 7.** Synthesis of compound **5** from curcumin.

**Table 1**
Anti-proliferative activities of curcumin and compounds **1**–**13**




| Compound | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | PC-3 ($IC_{50}$ μM) | LNCap ($IC_{50}$ μM) | MCF-7 ($IC_{50}$ μM) | MDA-MD-231 ($IC_{50}$ μM) |
|---|---|---|---|---|---|---|---|---|---|
| Curcumin | $OCH_3$ | OH | H | — | — | 19.8 ± 2.1 | 19.6 ± 3.7 | 21.5 ± 4.7 | 25.6 ± 4.8 |
| **1** | $OCH_3$ | H | H | — | — | 40 ± 4.9 | 34.7 ± 6.6 | 25.9 ± 9.5 | 31.9 ± 11.1 |
| **2** | H | OH | H | — | — | 27.3 ± 6.6 | 19.7 ± 2.9 | 24.3 ± 1.9 | 21.9 ± 2.0 |
| **3** | OH | $OCH_3$ | H | — | — | >40 | >40 | >40 | >40 |
| **4** | $OCH_3$ | OH | $OCH_3$ | — | — | 37.2 ± 4.1 | 21.1 ± 4.3 | 37.6 ± 6.1 | 41.7 ± 1.2 |
| **5** | $OCH_3$ | $OSO_2NH_2$ | H | — | — | 7.5 ± 1.8 | 5.9 ± 1.7 | 5.5 ± 1.2 | 3.1 ± 1.3 |
| **6** | $OCH_3$ | $OCH_3$ | H | — | — | 5.9 ± 1.3 | 3.9 ± 0.6 | 5.4 ± 0.8 | 4.9 ± 0.9 |
| **7** | OAc | OAc | H | — | — | 12.9 ± 2.3 | 20.2 ± 1.7 | 17.8 ± 5.9 | 12.3 ± 1.0 |
| **8** | $OCH_3$ | $OSO_2NH_2$ | $OCH_3$ | — | — | 13.1 ± 2.1 | 10.4 ± 1.6 | 4.7 ± 0.7 | 5.5 ± 0.1 |
| **9** | $OSO_2NH_2$ | $OCH_3$ | H | — | — | 7.4 ± 1.6 | 7.7 ± 1.5 | 5.5 ± 0.4 | 6.5 ± 0.8 |
| **10** | — | — | — | $OCH_3$ | OH | 20.9 ± 4.8 | 6.8 ± 0.6 | I5.4 ± 1.5 | 7.2 ± 1.1 |
| **11** | — | — | — | $OSO_2NH_2$ | OH | 193 ± 5.4 | 20 ± 1.0 | 15.1 ± 3.5 | 14.3 ± 1.1 |
| **12** | — | — | — | — | — | 5.6 ± 2.0 | 3.4 ± 0.9 | 5.9 ± 0.6 | 6.6 ± 1.9 |
| **13** | — | — | — | — | — | 16.2 ± 1.4 | 12.1 ± 1.3 | I5.8 ± 1.2 | 20.4 ± 3.0 |

compounds for 72 h and cell viability was determined by the MTT assay.

For the heptadienedione series, the modifications focused on the aromatic ring and the β-diketone regions (Fig. 2). The results are summarized in Table 1. Our first structure–activity relationship study was to investigate the substitution pattern of the 3-$OCH_3$ and 4-OH groups on the aromatic ring in curcumin. Elimination of the 4-OH groups (compound **1**) or incorporation of an additional $OCH_3$ group (compound **4**) onto curcumin resulted in a slight decrease in anti-proliferative activities. However, the activities remained the same if the 3-$OCH_3$ groups in curcumin are removed (compound **2**). In addition, it is also interesting to note that when the 3-$OCH_3$ and 4-OH groups exchanged position (compound **3**), this resulted in the elimination of its anti-proliferative activity.

Curcumin exists as a mixture of two tautomeric structures (diketone and keto–enol form) (Fig. 1). Computational chemistry has predicted that, due to (1) the acidic nature of the protons on the central methylene carbon, (2) stabilization of the enol via an intramolecular hydrogen bond, and (3) the establishment of a fully conjugated system, the enol form is 6.7 kcal/mol lower in energy than the diketone tautomer.[33] This prediction has been confirmed through X-ray crystal structures[34] and more recently via NMR analysis of the solution structure of curcumin[35] in which the compound existed solely in the enol form. Thus, compounds **12** and **13**, which mimic the enol form of curcumin, were synthesized to evaluate their anti-proliferative activities. The anti-proliferative activities of compound **12** was similar among all 4 cell lines and was 3–4-fold better than curcumin itself (Table 1). The activities were

similar to those reported by Ishida et al.[21] Interestingly, N-methylation of the pyrazole ring on compound **12** to form compound **13** resulted in the reduction of anti-proliferative activity by 3-fold (Table 1). In addition to its anti-proliferative activity, compound **12** was also reported to have anti-angiogenic and androgen receptor antagonistic activities.[23,36] It is not clear if there is any correlation between the anti-proliferative activity and anti-angiogenic or anti-androgenic activity.

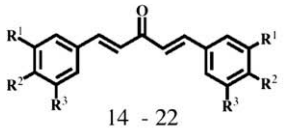
Despite its widely reported biological activities, the potential utility of curcumin is somewhat limited due to poor bioavailability.[4] Part of the reason is the physical and metabolic instability of the molecule. Curcumin decomposes rapidly in neutral and basic conditions. In phosphate buffer solution at pH 7.2, approximately 90% of curcumin decomposes in 30 min.[37] In addition, curcumin has been reported to undergo extensive in vitro and in vivo phase I and phase II metabolism through oxidation, reduction, glucuronidation, and sulfation.[38–41] The glucuronidation and sulfation occurs on the 4-OH groups of curcumin.[39,40] It was reported that protection of the 4-OH groups through methylation (to form 4-$OCH_3$) improved its stability.[42] Thus, compounds **5**–**8** were synthesized with the 4-OH groups converted to methoxy (compound **6**), acetate (compound **7**) and sulfamate (compounds **5** and **8**) derivatives. The rationale for using sulfamate as a protecting group was based on the fact that the sulfamate derivatives of various steroids including estradiol have been shown to increase absorption, leading to increased activity.[43,44] All of the compounds had significantly higher anti-proliferative activity than curcumin. Interestingly, the mono-protected analogues of compounds **5** and **6** (compounds **10** and **11**) were less active than when the OH groups were fully protected (Table 1).

The second series of curcumin analogues contained a pentadienone moiety (compounds **14**–**24**). The results are summarized in Table 2. The compounds exhibited potent anti-proliferative activity with $IC_{50}$ values between 0.4 and 9.5 μM, which is 2–50 times more potent than curcumin (Table 2). Compound **14**, which has the same substitution pattern on the aromatic rings as curcumin, is 5–8 times more potent than curcumin. However, unlike compound **3**, there was no change in anti-proliferative activities when the 3-$OCH_3$ and 4-OH groups exchanged position (compound **15**). In addition, eliminating or adding $OCH_3$ groups to compound **14** (compounds **16** and **19**, respectively) did not result in any change in anti-proliferative activities. In curcumin, the 4-OH groups are metabolically active and protecting the functional groups resulted in an increase in anti-proliferative activity. However, for the pentadienone series, converting the 4-OH groups to methoxy or sulfamate (compounds **17**, **20**–**22**) did not result in any increase in anti-proliferative activity (Table 2) suggesting that a different mechanism of action or a different metabolic pathway of the compounds may be operative.

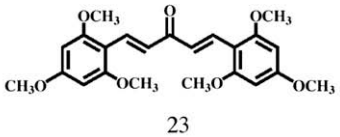
One of the major criteria for cancer drug development is that the agents should be selective against cancer cells. MCF-10A, a spontaneous immortalized but non-malignant mammary epithelial cell line, was used to examine the selectivity of the curcumin analogues on normal versus cancer cells. The anti-proliferative activities of selected compounds on both cancer cells and MCF-10A cells are shown in Table 3. Selectivity ratio was calculated as the ratio of the $IC_{50}$ of the compounds on MCF-10A versus cancer cells with the lowest $IC_{50}$ values. Five compounds (**6**, **12**, **18**, **23**, and **24**) had selectivity ratio of at least 5-fold or higher (Table 3). Interestingly, curcumin did not show any selectivity against cancer cells. Compound **23** is not only the most potent but also the most selective analogue among the 25 compounds tested.

In conclusion, we have examined two series of curcumin analogues with potent anti-proliferative activities in both breast and prostate cancer cell lines. Compound **23** is the most potent analogue with $IC_{50}$ values in sub-micromolar range and a selectivity ratio over 25. This presents the possibility that curcumin analogues might serve as potential anti-tumor agents for breast and prostate cancers.

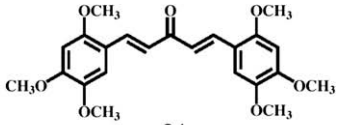
**Table 2**
Anti-proliferative activities of compounds **14**–**24**



14 - 22



23



24

| Compound | $R_1$ | $R_2$ | $R_3$ | PC-3 ($IC_{50}$ μM) | LNCap ($IC_{50}$ μM) | MCF-7 ($IC_{50}$ μM) | MDA-MB-231 ($IC_{50}$ μM) |
|---|---|---|---|---|---|---|---|
| **14** | $OCH_3$ | OH | H | 3.9 ± 1.1 | 2.7 ± 0.4 | 2.4 ± 0.4 | 2.8 ± 1.0 |
| **15** | OH | $OCH_3$ | H | 5.9 ± 0.9 | 2.6 ± 0.4 | 2.9 ± 0.9 | 3.1 ± 0.8 |
| **16** | H | OH | H | 9.5 ± 0.9 | 5.8 ± 0.9 | 6.9 ± 2.1 | 3.9 ± 0.6 |
| **17** | $OCH_3$ | $OCH_3$ | H | 2.9 ± 0.6 | 2.2 ± 0.5 | 2.5 ± 0.4 | 1.6 ± 0.4 |
| **18** | $OCH_3$ | H | $OCH_3$ | 2.5 ± 0.5 | 2.1 ± 0.9 | 2.7 ± 0.5 | 1.5 ± 0.1 |
| **19** | $OCH_3$ | OH | $OCH_3$ | 3.6 ± 1.3 | 2.5 ± 0.3 | 1.7 ± 0.3 | 2.7 ± 1.4 |
| **20** | $OCH_3$ | $OSO_2NH_2$ | H | 6.1 ± 0.3 | 2.4 ± 0.6 | 6.6 ± 1.1 | 1.7 ± 0.1 |
| **21** | H | $OSO_2NH_2$ | H | 5.1 ± 0.8 | 5.1 ± 0.7 | 3.5 ± 0.5 | 4.2 ± 0.6 |
| **22** | $OCH_3$ | $OSO_2NH_2$ | $OCH_3$ | 2.4 ± 0.2 | 1.9 ± 0.4 | 1.5 ± 0.1 | 0.6 ± 0.2 |
| **23** | — | — | — | 2.1 ± 1.1 | 0.5 ± 0.1 | 0.4 ± 0.1 | 0.6 ± 0.1 |
| **24** | — | — | — | 4.6 ± 0.2 | 1.7 ± 0.6 | 2.4 ± 1.0 | 2.4 ± 0.4 |

**Table 3**
Anti-proliferative activities of selected curcumin analogues on cancer and normal cells

| Compound | MCF-10A ($IC_{50}$ μM) | PC-3 ($IC_{50}$ μM) | LNCap ($IC_{50}$ μM) | MCF-7 ($IC_{50}$ μM) | MDA-MB-231 ($IC_{50}$ μM) |
|---|---|---|---|---|---|
| Curcumin | 30.1 ± 3.7 | 19.8 ± 2.1 | 19.6 ± 3.7 | 21.5 ± 4.7 | 25.6 ± 4.8 |
| **6** | 31.5 ± 7.8 | 5.9 ± 1.3 | 3.9 ± 0.6 | 5.4 ± 0.8 | 4.9 ± 0.9 |
| **12** | >50 | 5.6 ± 2.0 | 3.4 ± 0.9 | 5.9 ± 0.6 | 6.6 ± 1.9 |
| **18** | >50 | 2.5 ± 0.5 | 2.1 ± 0.9 | 2.7 ± 0.5 | 1.5 ± 0.1 |
| **23** | >50 | 2.1 ± 1.1 | 0.5 ± 0.1 | 0.4 ± 0.1 | 0.6 ± 0.1 |
| **24** | >50 | 4.6 ± 0.2 | 1.7 ± 0.6 | 2.4 ± 1.0 | 2.4 ± 0.4 |

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