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Original article

# Design, synthesis, and evaluation of novel heteroaromatic analogs of curcumin as anti-cancer agents

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ABSTRACT

To improve the potential of curcumin to treat advanced hormone-refractory prostate cancer, three series (A–C) of heteroaromatic analogs (thirty two compounds) with different monoketone linkers have been synthesized and evaluated for cytotoxicity against two human androgen-independent prostate cancer cell lines (PC-3 and DU-145). Among them, thirty analogs are more potent than curcumin against PC-3 cells, and twenty one analogs are more cytotoxic towards DU-145 cells relative to curcumin. The most potent compounds (**44**, **45**, **51**, and **52**) also showed impressive cytotoxicity against three other metastatic cancer cell lines (MDA-MB-231, HeLa, and A549), with $IC_{50}$ values ranging from 50 nM to 390 nM. All four most potent analogs exhibited no apparent cytotoxicity towards the MCF-10A normal mammary epithelial cells. Taken together, selective enhancement of cell death in prostate cancer cell lines and other aggressive cancer cell lines suggests that nitrogen-containing heteroaromatic rings are promising bioisosteres of the substituted phenyl ring in curcumin.

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## 1. Introduction

Prostate cancer has the highest incidence and the second highest cancer mortality in American men. The American Cancer Society estimates that 238,590 new cases of prostate cancer will be diagnosed and 29,720 men will die of prostate cancer in the United States in 2013 [1]. Current therapies (radical prostatectomy, chemotherapy, local radiotherapy, or hormonotherapy) are successful in treating localized, androgen-dependent, prostate cancer. However, treatment of hormone-refractory prostate cancer remains hindered by inevitable progression of resistance to first-line treatment with docetaxel. Consequently, novel drugs are needed to treat advanced hormone-resistant prostate cancer [2,3].

Curcumin or diferuloylmethane (**1**, Table 1), a polyphenolic molecule extracted from the rhizome of the plant *Curcuma longa* (turmeric), is a yellow spice used as curry ingredient and has been used for centuries in Ayurvedic, Chinese, and Hindu medicine systems. There is a huge difference in the rate of incidence of prostate cancer between Western (120 per 100,000 in Northern America) and East Asian countries (less than 10 per 100,000 in Asia) [4]. The increased risk of prostate cancer in the first generation of Asian men emigrating to the United States suggests a chemopreventive effect of Asian traditional food. Recent preclinical and clinical studies have demonstrated that curcumin has a number of anticancer properties [5,6]. The potential of curcumin to treat both androgen-dependent and androgen-independent prostate cancer has been demonstrated by the *in vitro* and *in vivo* studies [7,8]. A new philosophy that favors multitargeted drugs has recently gained momentum [9]. Curcumin serves as a good example of a class of compounds that is able to target multiple enzymes with a “magic shotgun” [10]. The anticancer effects of curcumin are associated with its influence on numerous growth factors within the cell [11,12]. The effect of curcumin on any particular growth factor is small, but its aggregate effect is significant. This characteristic is especially valuable for diseases like cancer that are complex, inflammation associated, and often evolve mutations in multiple genes. Because of its potential ability to treat hormone-refractory prostate cancer, its low molecular weight, lack of toxicity, and its mechanism of action against multiple targets, curcumin could be an ideal candidate as an androgen-independent agent against prostate cancer. However, its clinical development has been limited by its suboptimal pharmacokinetics and poor bioavailability caused by poor solubility in water and rapid *in vivo*

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**Table 1**
*In vitro* cytotoxicity ($IC_{50}$, μM)[a] of the compounds against human cell lines.

| Comp. No. | Series | Het | $IC_{50}$ (μM) | | $IC_{50}$ (curcumin)/ $IC_{50}$ (analog) | |
|---|---|---|---|---|---|---|
| | | | DU-145[b] | PC-3[c] | DU-145 | PC-3 |
| Curcumin | – | – | 0.30 | 1.98 | 1 | 1 |
| **21** | **A** | **a** | 0.13 | 0.093 | 2.3 | 21 |
| **22** | **A** | **b** | 0.14 | 0.11 | 2.1 | 18 |
| **23** | **A** | **c** | 0.01 | 6.63 | 30 | 0.3 |
| **24** | **A** | **e** | 1870 | 76 | 0.0002 | 0.03 |
| **25** | **A** | **f** | 1.64 | 1.02 | 0.18 | 1.9 |
| **26** | **A** | **g** | 0.046 | 0.42 | 6.5 | 4.7 |
| **27** | **A** | **h** | 0.43 | 0.80 | 0.7 | 2.5 |
| **28** | **A** | **i** | 0.076 | 0.31 | 3.9 | 6.4 |
| **29** | **A** | **j** | 0.034 | 0.14 | 8.8 | 14 |
| **30** | **A** | **k** | 0.69 | 0.13 | 0.4 | 15 |
| **31** | **B** | **a** | 0.63 | 0.094 | 0.5 | 21 |
| **32** | **B** | **b** | 0.10 | 0.16 | 3 | 12 |
| **33** | **B** | **c** | 0.25 | 0.83 | 1.2 | 2 |
| **34** | **B** | **d** | 0.36 | 0.47 | 0.8 | 4.2 |
| **35** | **B** | **e** | 90 | 130 | 0.003 | 0.015 |
| **36** | **B** | **f** | 0.73 | 0.26 | 0.41 | 7.6 |
| **37** | **B** | **g** | 0.12 | 0.11 | 2.5 | 18 |
| **38** | **B** | **h** | 0.075 | 0.12 | 4 | 16.5 |
| **39** | **B** | **i** | 1.65 | 1.97 | 0.18 | 1 |
| **40** | **B** | **j** | 0.07 | 0.071 | 4.3 | 28 |
| **41** | **B** | **k** | 0.34 | 0.054 | 0.9 | 37 |
| **42** | **C** | **a** | 0.057 | 0.11 | 5.3 | 18 |
| **43** | **C** | **b** | 0.054 | 0.089 | 5.6 | 22 |
| **44** | **C** | **c** | 0.035 | 0.063 | 8.6 | 31 |
| **45** | **C** | **d** | 0.057 | 0.046 | 5.3 | 43 |
| **46** | **C** | **f** | 0.16 | 0.13 | 1.9 | 15 |
| **47** | **C** | **g** | 0.055 | 0.068 | 5.5 | 29 |
| **48** | **C** | **h** | 0.096 | 0.094 | 3 | 21 |
| **49** | **C** | **i** | 0.75 | 0.84 | 0.4 | 2.4 |
| **50** | **C** | **j** | 0.042 | 0.25 | 7.1 | 7.9 |
| **51** | **C** | **k** | 0.016 | 0.041 | 18.8 | 48 |
| **52** | **C** | **l** | 0.020 | 0.033 | 15 | 60 |

[a] $IC_{50}$ is the drug concentration effective in inhibiting 50% of the cell viability measured by the trypan blue exclusion assay after 5 days exposure.
[b] Human androgen-independent prostate cancer cell line.
[c] Human androgen-independent prostate cancer cell line.

metabolism [13]. It has been found that, with oral administration at the dose of 450–3600 mg/day in a phase I trial, the blood concentration of curcumin in plasma and target tissues falls under the detection limit [14].

Curcumin has extensively been used as a lead compound to design and synthesize analogs for the potential treatment of prostate cancer [15–28]. Some analogs, such as JC-9 [22], FLLL11, and FLLL12 (Fig. 1) [19] were found to be more potent than curcumin towards PC-3 prostate cancer cell line. The reported studies focused mainly on changes in the β-diketone structure and aryl substitution pattern of curcumin. It is believed from reported studies that the β-diketone moiety in the structure of curcumin appears to be a specific substrate of a series of aldo-keto reductases and can be decomposed rapidly *in vivo* [29,30]. It has been evidenced that monoketone analogs generally have improved pharmacokinetic profiles over curcumin, and that some monoketone analogs with the acetone or cyclohexanone spacer confer increased cytotoxicity towards PC-3 cell lines [16,19].

To identify new curcumin analogs with improved bioavailability and potential to treat hormone-refractory prostate cancer, we replaced the substituted phenyl rings in curcumin with two identical basic *N*-containing heteroaromatic rings. We focused on basic nitrogen heteroaromatics to take advantage of their ability to exist in both the protonated and neutral form, allowing both solubility in aqueous media and enhanced potential to cross cellular membranes. It has been reported that pyridine analogs had better potency against MDA-MB-231 cancer cells [31], head and neck squamous cell carcinoma [32], and PC-3 prostate cancer cell line [20,33]. To the best of our knowledge, there is no cytotoxic study of *N*-containing five-membered heteroaromatic analogs against prostate cancer cells.

We have synthesized twenty-nine new compounds and three known compounds (Fig. 2), which are classified as three series according to their different linkers: 1-methylpiperidone (series A), cyclohexanone (series B), and acetone (series C). Among them, thirty one are five-membered heteroaromatic analogs and only one is six-membered analog (**52**). In this paper, we describe the synthesis of these curcumin analogs and the *in vitro* evaluation of their anticancer activities.

## 2. Results and discussion

To engineer more effective analogs of curcumin for potential clinical use in treating hormone-refractory prostate cancer, three series of heteroaromatic curcumin analogs with three different monoketone linkers have been designed by replacing the two substituted phenyl rings in curcumin with two identical *N*-containing heteroaromatic rings. All these three series compounds are symmetrical monoketone curcumin analogs with *N*-methylpiperidone, cyclohexanone, or acetone as a linker, respectively (Fig. 2). Twenty nine of them are new, and three analogs (**21**, **31**, and **52**) are known. Analogs **21** and **31** have been synthesized by Yadav and co-workers for the evaluation of their cytotoxicity against ER-negative breast cancer cell line MDA-MB-231 [31]. The cytotoxicity of analog **52** towards colorectal carcinoma HCT 116/p53+/+ cells has been investigated [34]. However, no cytotoxicity of these three known compounds towards prostate cancer cell lines has been reported. Each of them was synthesized through a Claisen–Schmidt condensation of the corresponding aromatic aldehyde with the appropriate ketone. The structures of these analogs have been determined by interpretation of their NMR and HR-MS data. The cytotoxicity of all synthesized analogs has been evaluated against two human androgen-independent prostate cancer cell lines (PC-3 and DU-145). Most of these curcumin analogs exhibited significantly more potent cytotoxicity than curcumin towards PC-3 and DU-145 prostate cancer cell lines.

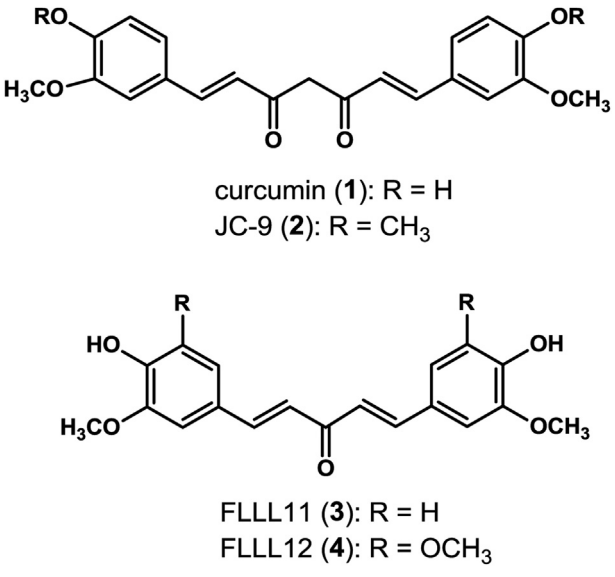


**Fig. 1.** Curcumin and its monoketone analogs.