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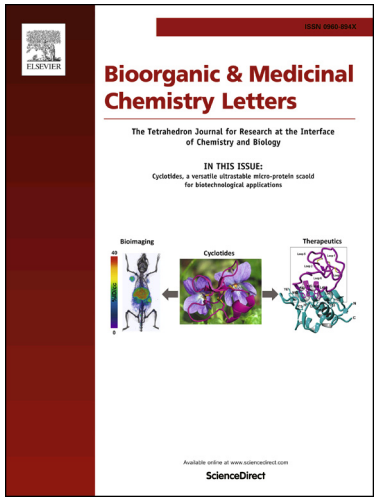

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Curcumin inspired 2-chloro/phenoxy quinoline analogues: Synthesis and biological evaluation as potential anticancer agents

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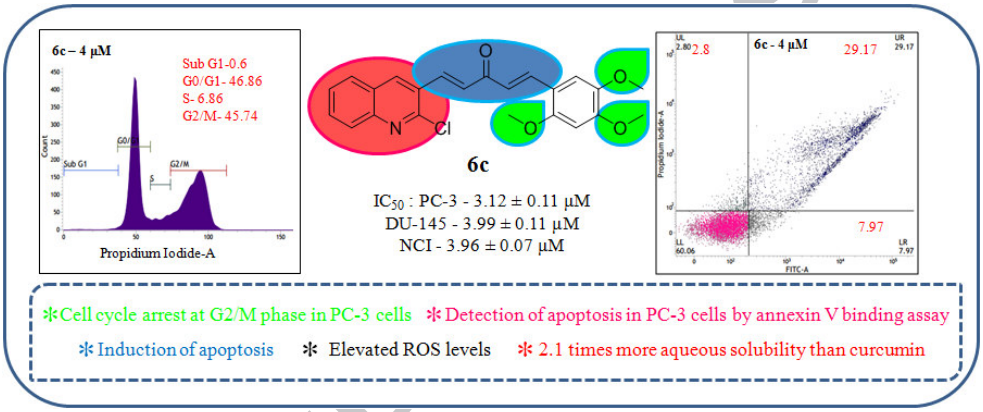

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ABSTRACT

Synthesis of twenty new curcumin inspired 2-chloro/phenoxy quinoline derivatives is outlined in this study. The obtained new chemical entities were screened *in vitro* for their cytotoxic activity towards various tumor cell lines. Of the compounds screened, **6c** and **9d** exhibited significant activity and the most active analogue **6c** displayed promising cytotoxicity against PC-3 (IC_{50} of 3.12 ± 0.11 μM), DU-145, NCI-H460 and 4T1 cell lines. Further, **6c** and **9d** have 2.1 and 1.4 times more aqueous solubility, respectively, than curcumin. Additionally, the promising candidate **6c** could induce G2/M cell cycle arrest and apoptosis in PC-3 cells, as determined by AO-EB staining, DAPI staining, analysis of ROS levels as well as annexin binding assay.

Quinoline is one of the omnipresent structural motifs that occur in several natural compounds especially alkaloids (Cinchona and Camptotheca alkaloids) and pharmacologically active substances.[1] It constitutes an interesting and important class of compounds, with widespread biological activities including antimalarial,[2] anti-bacterial,[3] anthelmintic,[4] anticancer,[5] antifungal,[6] antihypertensive,[7] anti-inflammatory,[8] analgesic,[9] antiviral[10] and hypoglycemic[11] etc., ultimately making quinoline as "privileged substructure" for drug design. Quinoline or its derivatives have been incorporated extensively into a diverse set of therapeutically interesting drugs and drug candidates; for example (**i**, **Fig. 1**), antimalarials (Quinine and Chloroquine etc), anticancer (Topotecan and Bosutinib etc), antibacterial (fluoroquinolones like Ciprofloxacin), antiglaucoma (Carteolol), antiasthmatic, antiviral, antifungal-antiprotozoal, anthelmintic, cardiotonic and local anesthetic.[1d,12]

Additionally, 2-substituted quinoline moiety is ubiquitous among bioactive derivatives, like anticancer agents,[13] antileishmanial agents,[14] *CysLT* (LTD4) receptor antagonists,[15] HIV-1 replication inhibitors[16] and PDE4 inhibitors.[17] In particular, 2-alkoxy(aroxy)quinolines exist as substructures in numerous medicinally interesting compounds displaying a broad spectrum of biological activities, such as anticancer (SH80)[18a], anti-mycobacterial, antithrombin, antimalarial, immunosuppressive and many others.[18] **Fig. 1 (ii)** shows the structures of some of the bioactive 2-phenoxy/methoxy quinoline derivatives.

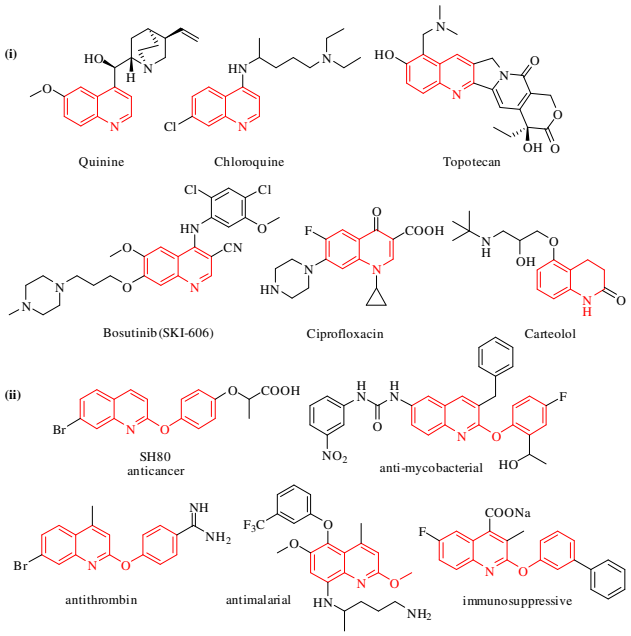

Fig. 1. (i) Some of the representative examples of quinoline drugs and drug candidates. **(ii)** Structures of 2-phenoxy/methoxy quinoline derivatives of biological interest.

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Curcumin (**a**, **Fig. 2**), is a phytochemical, gained from the dried rhizomes of Turmeric plant (*Curcuma longa*).[19] Despite the fact that curcumin possess versatile biological properties such as antioxidant, anti-inflammatory, anti-HIV as well as antitumor activities,[20] its utility is limited because of its poor water solubility and poor *in vivo* bioavailability.[21] The multiple therapeutic properties as well as the minimal bioavailability directed the route for the synthesis of a "super curcumin" without these problems. Preliminary structure activity relationship analysis of curcumin demonstrated that the lack of stability of curcumin under biological conditions is because of the β-diketone moiety and the active methylene group, hence the removal of β-diketone moiety may improve the stability of curcumin derivatives.[22] Based on this knowledge, significant efforts have been devoted for the synthesis of different biologically interesting heterocyclic curcumin analogues (**b-h**, **Fig. 2**).[23-29] As a part of our venture towards the development of potent curcumin congeners,[28,29] herein we have tried to probe the scope of curcumin based 2-chloro/phenoxy quinolines (**Fig. 3**) as anticancer and apoptosis inducing agents.

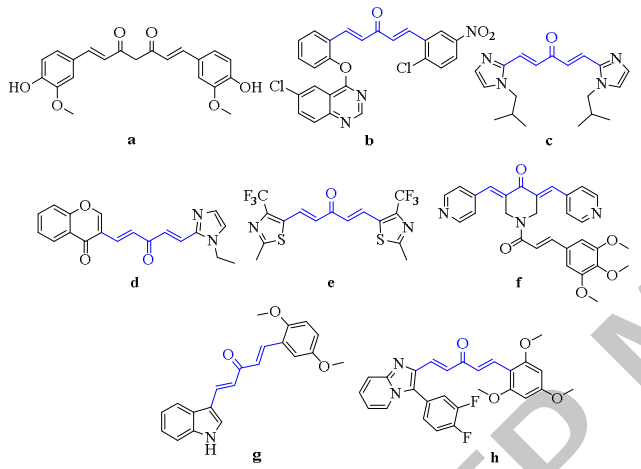


Fig. 2. Structures of curcumin and its congeners.

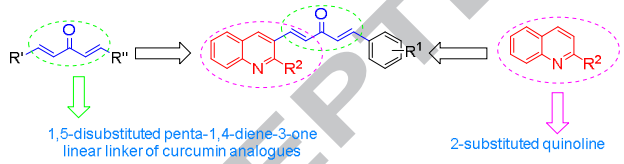
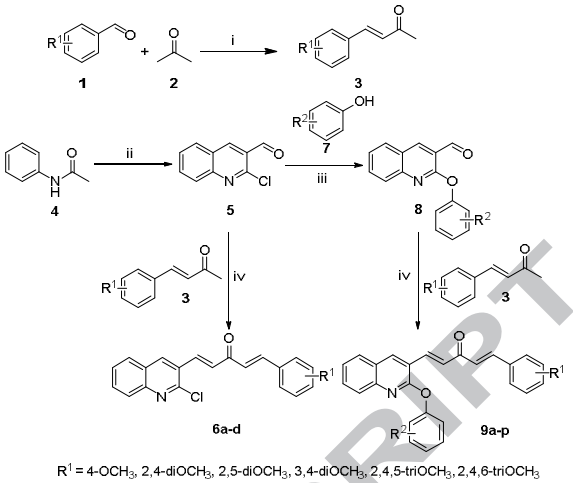


Fig. 3. Design strategy to achieve title compounds.

The desired compounds (1*E*,4*E*)-1-(2-chloroquinolin-3-yl)-5-phenylpenta-1,4-dien-3-ones (**6a–d**) and (1*E*,4*E*)-1-(2-phenoxyquinolin-3-yl)-5-phenylpenta-1,4-dien-3-ones (**9a–p**) were synthesized from chalcones (**3a–f**) and 2-chloroquinoline-3-carbaldehyde (**5**) or 2-phenoxyquinoline-3-carbaldehyde derivatives (**8a–d**) as shown in **Scheme 1**. The aldehydes (**1a–f**) were converted into chalcones (**3a–f**) *via* Claisen-Schmidt condensation reaction with acetone using 15% NaOH.[30] Next, acetanilide was cyclized with $POCl_3$ by the versatile Vilsmeier-Haack reaction and the resulting 2-chloroquinoline-3-carbaldehyde (**5**)[31] was treated with various substituted phenols in the presence of K_2CO_3 to give 2-phenoxyquinoline-3-carbaldehyde derivatives (**8a–d**).[32] Lastly, CH_3ONa-catalysed Claisen-Schmidt condensation reaction of chalcones (**3a–f**) and 2-chloroquinoline-3-carbaldehyde (**5**) or 2-phenoxyquinoline-3-carbaldehyde derivatives (**8a–d**) furnished the desired compounds (**6a–d** and **9a–p**, respectively) in moderate to excellent yields.[33]



R^1 = 4-OCH_3, 2,4-diOCH_3, 2,5-diOCH_3, 3,4-diOCH_3, 2,4,5-triOCH_3, 2,4,6-triOCH_3

R^2 = H, 4-Br, 3-Cl, 2-$CH(CH_3)_2$

6a: R^1 = 4-OCH_3
6b: R^1 = 2,4-diOCH_3
6c: R^1 = 2,4,5-triOCH_3
6d: R^1 = 2,4,6-triOCH_3
9a: R^1 = 4-OCH_3, R^2 = H
9b: R^1 = 2,4-diOCH_3, R^2 = H
9c: R^1 = 3,4-diOCH_3, R^2 = H
9d: R^1 = 2,4,5-triOCH_3, R^2 = H
9e: R^1 = 2,4,6-triOCH_3, R^2 = H
9f: R^1 = 4-OCH_3, R^2 = 4-Br
9g: R^1 = 2,4-diOCH_3, R^2 = 4-Br
9h: R^1 = 2,5-diOCH_3, R^2 = 4-Br
9i: R^1 = 3,4-diOCH_3, R^2 = 4-Br
9j: R^1 = 2,4,6-triOCH_3, R^2 = 4-Br
9k: R^1 =2,4-diOCH_3, R^2 = 3-Cl
9l: R^1 = 2,5-diOCH_3, R^2 = 3-Cl
9m: R^1 = 3,4-diOCH_3, R^2 = 3-Cl
9n: R^1 = 2,4,5-triOCH_3, R^2 = 3-Cl
9o: R^1 = 2,4,6-triOCH_3, R^2 = 3-Cl
9p: R^1 = 2,4,6-triOCH_3, R^2 = 2-$CH(CH_3)_2$

Scheme 1. (i) 15% NaOH, ethanol, 0 °C–rt, 2-3 h, 70–85%; (ii) $POCl_3$, DMF, 65–70 °C, 17 h, 89%; (iii) K_2CO_3, DMF, 70–80 °C, 2-3 h, 68–74%; (iv) 15% CH_3ONa, ethanol, 0 °C–rt, 2-3 h, 65–92%.

All the synthesized compounds (**6a–d** and **9a–p**) were explicitly characterized by means of FT-IR, HRMS, ^{1}H and ^{13}C NMR spectroscopic techniques. The ^{1}H NMR spectrum of **6a** showed a sharp singlet of C-4 proton of quinoline at 8.47, which is highly deshielded, another sharp singlet of methoxy protons at 3.86 and remaining protons were seen between 8.13-6.96 ppm. In ^{13}C NMR spectrum, peaks at 188.1 and 55.4 affirmed the presence of ketone functionality and methoxy carbon in compound **6a**, respectively and the other carbons were observed in between 161.9-114.5 ppm. The stretching band of ketone appeared at 1663.3 cm^{-1} in FT-IR spectrum of **6a**. Almost similar patterns were noted in ^{1}H and ^{13}C NMR spectra of the other analogues **6b–d** and **9a–p**.

The newly synthesized curcumin inspired quinoline analogues (**6a–d** and **9a–p**) bearing different methoxy substituents on the chalcone were examined for their cytotoxic activity against some cancer cell lines viz. cervical (HeLa), gastric (HGC-27), lung (NCI-H460), prostate (DU145 and PC-3) and breast (4T1), using MTT assay.[34] The activity results of test compounds **6a–d**, **9a–p** and reference standard curcumin are shown in **Table 1**.

We diversified the substitutions on quinoline and chalcone in an attempt to analyze their structure-activity relationship (SAR). The selection of substituent (such as varied number of methoxy groups at different positions) on the chalcone was based on the previous reports, with respect to biological activity.[28-29] From the initial results, it is evident that the compounds **6c** and **9d** displayed considerable cytotoxicity towards every cell line examined, having IC_{50} ranging from 1.81 – 12.40 μM. Compounds **6c** and **9d** are significantly cytotoxic on PC-3 having IC_{50} of 3.12 ± 0.11 μM and 7.29 ± 0.22 μM, respectively and on NCI-H460 with IC_{50} of 3.96 ± 0.07 μM and 8.03 ± 0.06 μM, respectively. Compounds **6a, 6b** and **6d** with chloro substitution on the quinoline and mono, di and trimethoxy substitutions, respectively on the phenyl ring of the chalcone were noted non-

cytotoxic on every cell line tesed at the concentration of 10 μM (IC_{50} > 10 μM). In contrast, **6c** with chloro substitution on the quinoline and 2,4,5-trimethoxy substitution on the chalcone exhibited excellent cytotoxicity on all the cell lines tested. Furthermore, **9a** with 2-phenoxy quinoline as well as 4-methoxy phenyl moiety and compounds **9b** and **9c** having 2-phenoxy quinoline and dimethoxy substitutions on the chalcone were not active (IC_{50} > 10 μM), whereas **9d** possessing 2-phenoxy quinoline and 2,4,5-trimethoxy substitution on the chalcone exhibited appreciable cytotoxicity on most of the cell lines tested. While, **9e** with 2-phenoxy quinoline and 2,4,6-trimethoxy substitution on the chalcone was observed to be inactive. Notably, **9f-j** with 2-(4-bromophenoxy)quinoline and monomethoxy/dimethoxy/trimethoxy substituted chalcone were also found non-cytotoxic. Likewise, compounds **9k–o** possessing 2-(3-chlorophenoxy)quinoline and di or trimethoxy phenyl motif were not active. In addition, compound **9p** with 2-(2-isopropylphenoxy)quinoline and 2,4,6- trimethoxy substitution on the chalcone did not show any cytotoxicity.

Table 1. IC_{50} values[a,g] (μM) of analogues **6c** and **9d** against selected cancer cell lines.

Compound	HeLa[b]	HGC-27[c]	NCI-H460[d]	DU-145[e]	PC-3[e]	4T1[f]
6c	**5.41 ± 0.75**	8.73 ± 0.11	**3.96 ± 0.07**	**3.99 ± 0.11**	**3.12 ± 0.11**	**1.81 ± 0.03**
9d	12.40 ± 0.37	10.53 ± 0.61	8.03 ± 0.06	9.22 ± 0.07	7.29 ± 0.22	7.63 ± 0.23
Curcumin	N. D.	N. D.	17.11 ± 0.68	33.15 ± 1.96	18.65 ± 1.11	N. D.

[a]50% inhibitory concentration after 48 h of drug treatment and mean ± standard error of mean of three independent experiments performed in triplicate.
[b]Human cervical cancer cell line.
[c]Human gastric cancer cell line.
[d]Human lung cancer cell line.
[e]Human prostate cancer cell line.
[f]Mouse breast cancer cell line.
[g]All the other compounds (**6a-b**, **6d**, **9a-c** and **9e-p**) showed IC_{50} of > 10 μM against all the tested cancer cell lines.
N. D. – Not determined.

The structure-activity relationship (SAR) analysis of compounds **6a–d** and **9a–p** based on their IC_{50} values revealed that the impact of substitution on the chalcone and quinoline is interesting based on the following conclusions drawn (**Fig. 4**):

a. In general, it is notable that the presence of 2-(4-bromophenoxy) or 2-(3-chlorophenoxy) or 2-(2-isopropylphenoxy) substitution on the quinoline did not produce the bioactive compounds (**9f–j**, **9k–o** and **9p** respectively): the order may be neutral > electron withdrawing = electron donating.
b. Compounds possessing 2-chloro or 2-phenoxy substitution on the quinoline and 2,4,5-trimethoxy substitution on the chalcone (**6c** and **9d** respectively) were the most active compounds, whereas the similar compounds with 2,4,6-trimethoxy substitution (**6d** and **9e**, respectively) did not show cytotoxicity.
c. Compounds containing trimethoxy group, particularly 2,4,5-trimethoxy moiety (**6c** and **9d**) on the chalcone showed improved cytotoxicity than the mono or dimethoxy compounds.

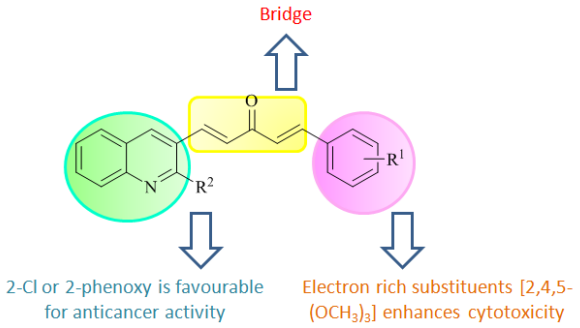


Fig. 4. SAR analysis of curcumin inspired 2-chloro/phenoxy quinolines.

With respect to potency, **6c** and **9d** were noted superior to curcumin by comparing their IC_{50} values as shown in **Table 2**. Compound **6c** is 4.3, 8.3 and 6.0 times, more cytotoxic than curcumin on NCI-H460, DU145 and PC-3 cell lines, respectively. Further, the promising candidate **6c** was considered for detailed mechanistic studies.

Table 2. Relative potency of curcumin mimics.

Compound	IC_{50} of curcumin/IC_{50} of compound[a]		
	NCI-H460[d]	DU-145[e]	PC-3[e]
Curcumin	1	1	1
6c	4.3	8.3	6.0
9d	2.1	3.6	2.6

[a]The relative potency of curcumin mimics was calculated by dividing the IC_{50} value of curcumin by that of each curcumin mimic.
[d]Human lung cancer cell line.
[e]Human prostate cancer cell line.

The solubility of the most active curcumin inspired analogues **6c** and **9d** in water was measured in comparison to curcumin by preparing their saturated aqueous solutions in milli-Q water.[35] The amount of curcumin/compound solubilized was measured spectrophotometrically by scanning at 200–600 nm. UV-visible spectra were recorded for compounds **6c** and **9d** (**Fig. 5**, see suppoting information) and the results indicate that **6c** and **9d** have 2.1 and 1.4 times more aqueous solubility, respectively, than curcumin.

Progression of cell cycle and regulation of apoptosis are the two important regulatory mechanisms required for cell division, development, and differentiation. Cell cycle checkpoints guarantee the conservation of genomic integrity by hampering DNA damage and cells with incomplete DNA from further cell division.[36] Many of the cytotoxic agents alters the regulation of cell cycle and thus elicit their cytotoxic property. To test whether compound **6c** has any effect on the cell cycle progression, we analyzed the population of PC-3 cells treated with **6c** by flow-cytometry analysis.[37] As depicted in **Fig. 6**, the ratio of the cells in G2/M phase was increased from 34.4% in the control to 38.1% and 45.7% in **6c** treated cells (2 and 4 μM, respectively) in a concentration dependent manner. The data clearly demonstrate that compound **6c** inhibits cell proliferation of PC-3 cells at G2/M phase.

Apoptosis and necrosis are the two major classes of cell death, delineated in response to a death stimulus. Improper regulation of apoptotic and necrosis processes can lead to the development of several diseases including cancer.[38-39] Acridine orange-ethidium bromide (AO-EB) staining was carried out to

test whether the compound **6c** could induce apoptosis in PC-3 cells.[40] As exemplified in **Fig. 7**, in the control, the live cells showed bright green nucleus which is intact, while **6c** treated PC-3 cells displayed early apoptotic characteristics like cell membrane blebbing and condensed chromatin at 1 µM. Also, non-uniform distribution of chromatin along with fragmentation of chromatin were noted at 2 and 4 µM of **6c**, respectively.

DAPI staining was carried out in PC-3 cells to determine the chromatin condensation or nuclear damage induced by the compound **6c**. **Fig. 8** clearly demonstrates the intact nucleus in untreated cells as well as condensed and pyknotic nuclei in compound **6c** treated PC-3 cells. Hence, the data evidently shows that **6c** can induce apoptosis in PC-3 cells.

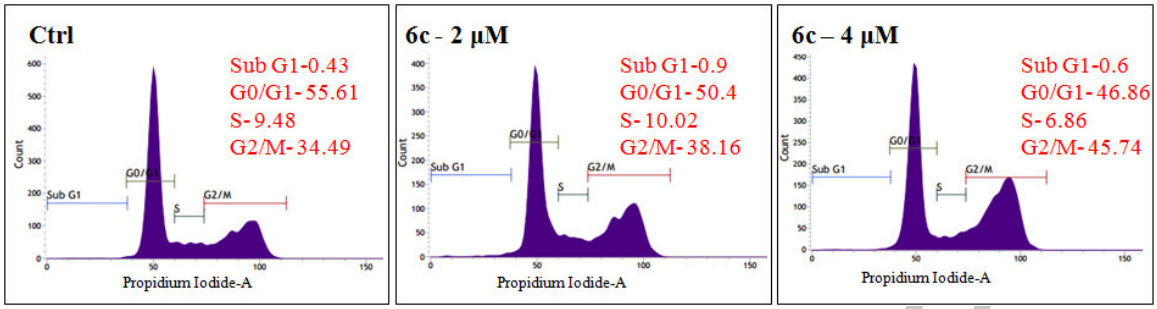


Fig. 6. Cell cycle analysis in PC-3 cells exposed to compound **6c** for 24 h using propidium iodide cell staining method. All assays were done in triplicate.

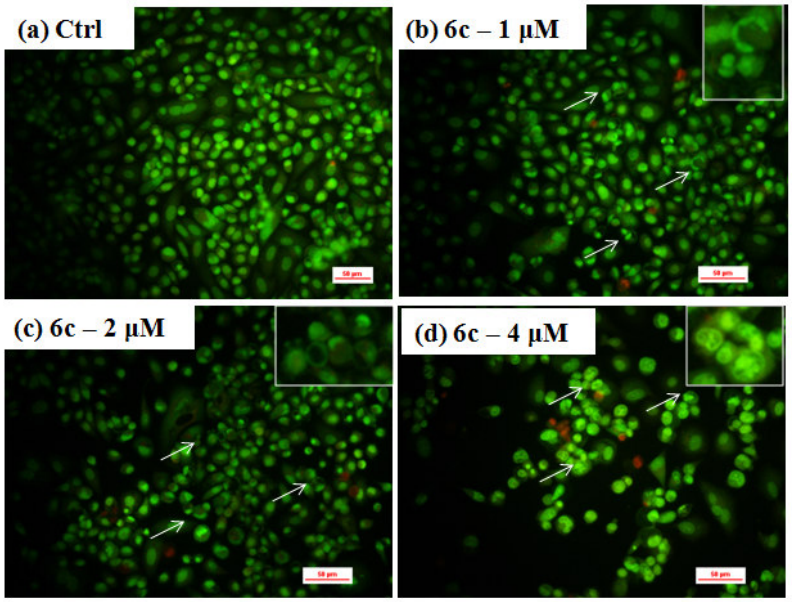


Fig. 7. Morphological features in PC-3 cells (a) control; (b) exposure to 1 µM; (c) 2 µM; (d) 4 µM of compound **6c** for 24 h and the cells were stained with AO/EB.

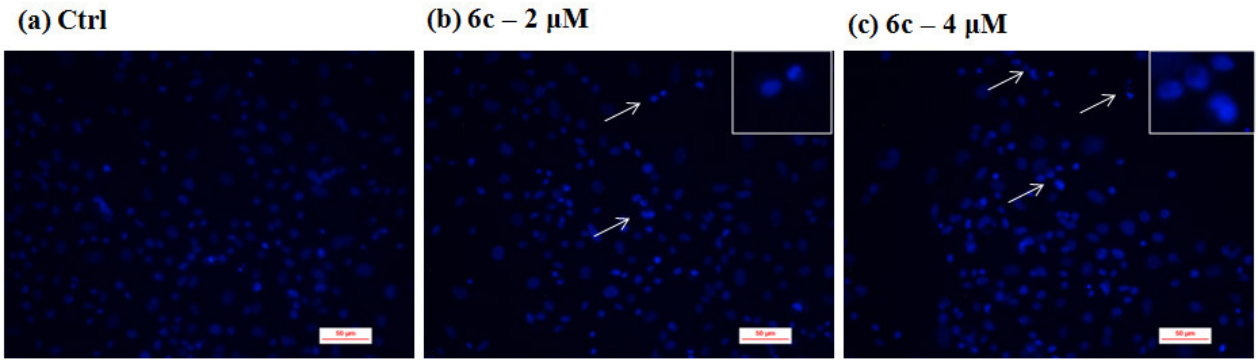


Fig. 8. Nuclear morphology in PC-3 cells stained with DAPI. PC-3 cells were treated with compound **6c** (a) 0.0 µM; (b) 2 µM and (c) 4 µM for 24 h and stained with DAPI. The images were captured with fluorescence microscope.

It has been described that apoptosis can be triggered by increased levels of intracellular ROS.[41] To examine even if the cytotoxicity displayed by **6c** is relying on the intracellular ROS levels, PC-3 cells were exposed to the compound **6c** for 24 h and the ROS levels were determined using DCFDA (2′,7′-dichlorofluorescin diacetate) staining method.[29] Treatment of PC-3 cells with **6c** for 24 h demonstrated considerable enhancement in DCFDA fluorescence than that of control (**Fig. 9**), which indicate that the compound **6c** could induce cytotoxicity through ROS generation.

To confirm and quantitatively estimate the apoptotic effect of the compound **6c** and to determine the percentage of apoptotic cells, Annexin V/PI dual staining assay was conducted. It enables the determination of live cells (Q1-LL; AV–/PI–), early apoptotic cells (Q1-LR; AV+/PI–), late apoptotic cells (Q3-UR; AV+/PI+) and necrotic cells (Q4-UL; AV–/PI+). PC-3 cells were exposed to the treatment of **6c** at 2 µM and 4 µM for 24 h. As displayed in **Fig. 10**, the percentage of late apoptotic (Q3) cells was enhanced to 18.5% (at 2 µM) and 29.1% (at 4 µM) in comparison to the control (7.8%), which confirmed that **6c** induced apoptosis in PC-3 cells.

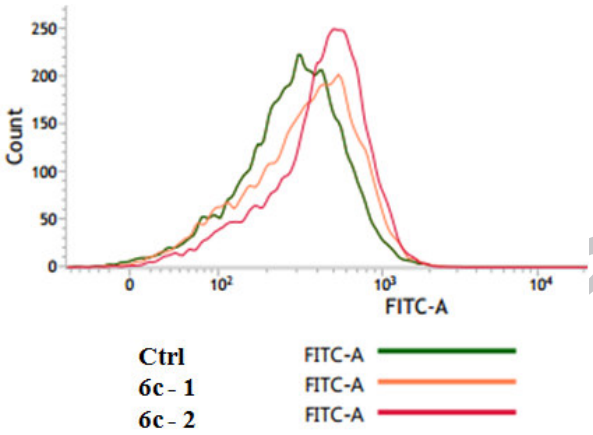


Fig. 9. Intracellular ROS levels in PC-3 cells treated with 1 and 2 µM of compound **6c** for 24 h and the DCF fluorescent intensity was determined by flow-cytometry. Data were mean ± SEM of three individual experiments. * P<0.05 ** P<0.01 ***P<0.001 vs. Ctrl In comparison to control (One way ANNOVA followed by Dunnet's multiple comparison test).

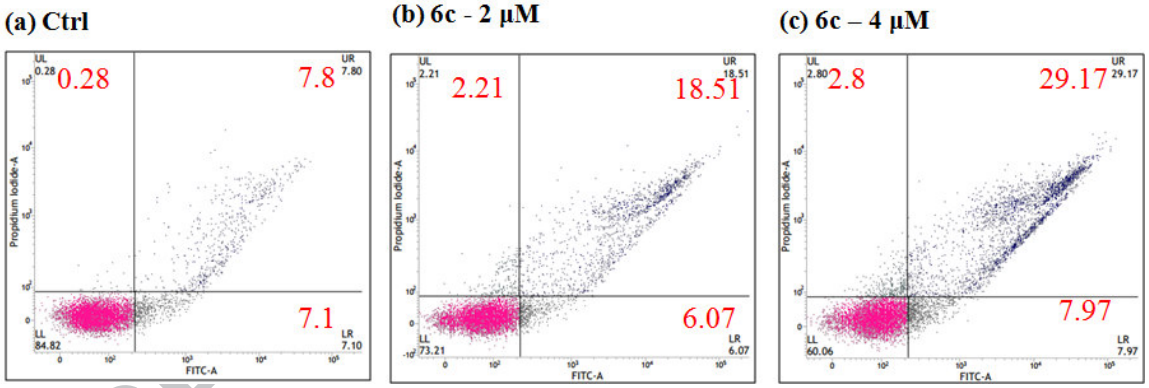


Fig. 10. Flow-cytometry analysis of apoptotic PC-3 cells after Annexin V-FITC/propidium iodide (PI) double staining (representative result of three independent experiments). PC-3 cells were treated with compound **6c**, stained with Annexin V-FITC/PI and examined for apoptosis using flow-cytometer. The 10,000 cells from every sample were assessed by flow cytometry. The %cells positive for Annexin V-FITC and/or Propidium iodide is reported inside the quadrants. Cells in the lower left quadrant (Q1-LL: AV-/PI-): live cells; lower right quadrant (Q2-LR: AV+/PI-): early apoptotic cells; upper right quadrant (Q3-UR: AV+/PI+): late apoptotic cells and upper left quadrant (Q4-UL: AV-/PI+): dead cells.

In summary, a series of curcumin inspired 2-chloro/phenoxy quinolines (**6a**–**d** and **9a**–**p**) were made and tested for their antitumor activity on some cancer cell lines including cervical (HeLa), gastric (HGC-27), lung (NCI-H460), prostate (DU-145 and PC-3) and breast (4T1). Of the compounds tested, **6c** and **9d** showed notable potency towards every cell line with IC_{50} between 1.81 – 12.4 µM. The most active compound **6c** exhibited promising cytotoxicity against PC-3 (IC_{50} of 3.12 ± 0.11 µM), DU-145 (IC_{50} of 3.99 ± 0.11 µM), NCI-H460 (IC_{50} of 3.96 ± 0.07 µM) and 4T1 (IC_{50} of 1.81 ± 0.03 µM) cell lines. In addition, the aqueous solubility data disclosed that **6c** and **9d** are 2.1 and 1.4 times, respectively more soluble in water than curcumin. The cell cycle distribution suggested that the compound **6c** inhibits PC-3 cells at G2/M phase. Additionally, **6c** induced apoptosis in PC-3 cells and enhanced the intracellular ROS levels. Moreover, the treatment of PC-3 cells with **6c** led to the enhancement of the late apoptotic cells, which is apparent from Annexin FITC/PI dual staining assay. Collectively, these assays disclosed that the proliferation of PC-3 cells was impeded by **6c** through G2/M cell cycle arrest along with the induction of apoptosis. This forms the first study wherein curcumin inspired quinoline derivatives have been synthesized and established as efficient inducers of apoptosis. Finally, the broad spectrum of cytotoxic activity along with the apoptosis inducing ability of **6c** would encourage further derivatization and optimization of such scaffold to perceive more potent and selective lead curcumin mimics.

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Supplementary Material

Synthetic procedures, spectral data, copies of ^{1}H and ^{13}C NMR spectra and experimental details for biological evaluation are provided in the supporting information.