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Synthesis, characterization, cytotoxic investigation of curcumin-based 4-phenylchromene derivatives and study of DNA interaction using experimental and computational methods

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Highlights

- 13 curcumin-based derivatives synthesized from curcumin and aryl aldehydes.
- Cytotoxicity tested on A2780 and HeLa cell lines via the MTT assay.
- L3 binds CT-DNA via groove binding with $K_b = 3.98 \times 10^3 \text{ M}^{-1}$.
- FT-IR, UV-vis, fluorescence, and modeling studied ligand-DNA interaction.

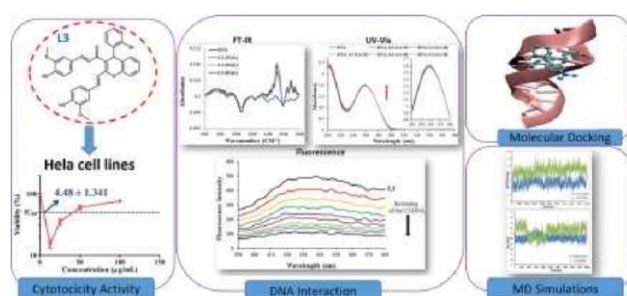
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Abstract

Curcumin exhibits a distinctive anti-proliferative effect on various malignant tumors. However, its limitations, such as low bioavailability and poor aqueous solubility, have led to the development of different curcumin analogs. In this study, thirteen curcumin-based 4-phenylchromene compounds were synthesized as ligands through nucleophilic additions involving curcumin, 3-dimethylaminophenol, and various aryl aldehydes. The structures of these synthesized compounds were verified using FT-IR, ^1H NMR, ^{13}C NMR, and MASS spectral data. Their cytotoxic effects were assessed using the MTT assay on A2780 (ovarian cancer) and Hela (cervical cancer) cell lines. Additionally, FT-IR, fluorescence, UV-vis spectroscopy, and molecular modeling studies were conducted to investigate the interaction between selected ligands and calf-thymus DNA. Among the compounds, L3 emerged as the most toxic ligand, with an IC_{50} ranging from 4 to $4.5\mu\text{g/mL}$, and was found to bind to CT-DNA in a groove-binding mode with a binding constant of $3.98 \times 10^3 \text{M}^{-1}$.

Graphical abstract



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Keywords

Curcumin analogs; Cytotoxicity; MTT assay; DNA interaction; Molecular modeling

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Introduction

Globally, the burden of cancer has been significantly increasing, making its treatment a major concern over the past century [1]. Cervical and ovarian cancers, with their high prevalence and mortality rates, have become a major challenge [2]. Cervical cancer is the second leading cause of death among women, whereas ovarian cancer, despite being less common, is the most fatal of all malignant tumors affecting women [3]. Chemotherapy, radiotherapy, and surgery are the main therapeutic strategies used for treating these types of cancers. However, the limitations and drawbacks of these common therapies cannot be ignored [3]. Undesirable outcomes arise due to insufficient drug concentration at the cancer cell site, significant cytotoxic effects on normal cells, and the development of drug resistance [4], [5]. Hence, access to advanced and efficient formulations leading to the complete elimination of tumors without damaging normal cells has always been an imperative concern and need.

Natural plant compounds have been consistently considered as anti-cancer drugs due to their fewer side effects and greater biocompatibility. Examples include paclitaxel from the plant *Taxus brevifolia*, as well as Vincristine and Vinblastine derived from the plant *Catharanthus roseus* [6]. Curcumin is recognized as the most active polyphenolic substance extracted from *Curcuma longa* [7]. Over the recent decades, extensive research has revealed its incredible bio-functional effects. These include anticancer, antioxidant, antiarthritic, antidiabetic, anti-inflammatory, antimicrobial, and antimutation activities. [8], [9], [10], [11]. It has a special anti-proliferative effect on various malignant tumors, including gastric, carcinoma [8], lung [12], colon [13], ovarian [3], cervical [14], glioblastoma, and breast cancers [15], [16]. β -unsaturated carbonyl moiety, methoxy, diketone, and hydroxyl groups are responsible for these activities (Scheme 1) [17]. Despite all these excellent effects, low bioavailability, low aqueous solubility, oxidation, and hydrolysis of phenolic groups have been counted as limitations of the clinical utility of curcumin [14]. Several strategies have been adopted to eliminate these restrictions. Generally, modifying functional groups of curcumin results in enhanced bioavailability; protection of phenolic groups against ionization and removal of electron-donating groups are the most major related modifications [12], [18], [19]. Hence, the improvement of bioavailability of curcumin with providing synthesis of its structural analogues is been a well-developed task in recent years. In this study, thirteen curcumin derivatives were synthesized based on 4-phenylchromene using a 3-component one-pot synthetic reaction with curcumin,

trimethylaminophenol, and different aldehydes agents in the presence of boric acid (catalyst). Following, the anti-cancer effects of the synthesized derivatives assayed by MTT on A2780 (cell lines of ovarian cancer) and Hela (cervical cancer cell line). Also, the study of compounds' interactions with DNA is performed by FTIR, UV-Visible, fluorescence spectroscopy, molecular docking, and molecular dynamics simulations.

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Section snippets

General information

All starting materials were purchased from Sigma-Aldrich and Merck companies. Double-distilled water was used throughout the experiments. Curcumin derivatives were synthesized using a one-pot reaction with curcumin, trimethylaminophenol, and aldehyde, with boric acid as the catalyst in the presence of ethanol and water solvents. Reactions were monitored using TLC (Merck silica gel 60 F254 plates). Melting points and FTIR spectra were obtained using a calibrated Kofler hot stage apparatus and a ...

Chemistry of synthesis

The combination of three compounds – curcumin, 3-dimethylaminophenol, and various aryl aldehydes – with borax as a catalyst, and using EtOH and distilled water as the reaction solvents, produced products known as (*E*)-1-(4-phenyl)-7-(dimethylamino)-2-((*E*)-4-hydroxy-3-methoxystyryl)-4*H*-chromen-3-yl)-3-(4-hydroxy-3-methoxyphenyl)prop-2-en-1-one L1-L13 (Scheme 2). This method was found to be relatively convenient and effective, allowing for acceptable yields (78–86%) with various electron donating ...

Conclusion

The potential anti-cancer properties of curcumin have been extensively studied. To improve the body's ability to absorb curcumin, researchers have suggested synthesizing a structural analog with 4-phenylchromenes, which also have demonstrated anti-cancer properties. In this study, thirteen curcumin analogs were created and analyzed. The compound L3 showed the highest level of cytotoxicity against A2780 (ovarian cancer) and Hela (cervical cancer) cell lines, with IC₅₀ values of 6.52 and 6.84 μM, ...

CRediT authorship contribution statement

Fereshteh Jalilian: Writing – original draft, Methodology. **Sajad Moradi:** Writing – review & editing, Supervision, Software. **Leila Hosseinzadeh:** Writing – review & editing, Supervision, Conceptualization. **Armin Zarei:** Writing – review & editing, Visualization, Formal analysis. **Pouya Raeisi:** Writing – original draft. **Mohsen Shahlaei:** Software, Methodology. **Komail Sadrjavadi:** Software, Methodology. **Hadi Adibi:** Writing – review & editing, Supervision, Conceptualization. ...

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. ...

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