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Research Article

Natural Product Brevilin A For The Synthesis And Evaluation Of Novel Anticancer Compounds

Elavarasi. E*, Puniparthi Sunitha

Bharath Institute Of Higher Education And Research

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ABSTRACT

Brevilin A, a natural sesquiterpene lactone isolated from Centipeda minima, has demonstrated promising anticancer activity. In this study, we aimed to synthesize novel derivatives of brevilin A and evaluate their potential as anticancer agents. A series of compounds were synthesized through structural modifications of brevilin A using organic synthesis methodologies. The synthesized compounds were then subjected to extensive biological evaluation to assess their cytotoxicity against a panel of cancer cell lines, including breast, lung, colon, and prostate cancer. The synthesis of novel brevilin A derivatives was achieved through a stepwise modification strategy, including functional group manipulation and structural diversification. The chemical structures of the synthesized compounds were confirmed using spectroscopic techniques such as NMR and mass spectrometry. Initial screening of the compounds revealed varying degrees of cytotoxic activity against cancer cell lines, with some derivatives exhibiting superior potency compared to the parent compound brevilin A. Further evaluation of the most promising compounds revealed potent anticancer activity with low IC50 values in the nanomolar range. Mechanistic studies suggested that the synthesized compounds exert their anticancer effects through induction of apoptosis, inhibition of cell proliferation, and disruption of key signaling pathways involved in cancer progression. Additionally, selectivity studies indicated minimal cytotoxicity against non-cancerous cells, highlighting the potential of these compounds as targeted anticancer agents.

INTRODUCTION

Cancer remains one of the most significant global health challenges, with its incidence and mortality rates continuing to rise. Despite advancements in treatment modalities, such as surgery, chemotherapy, and targeted therapies, the development of drug resistance and severe side effects pose formidable obstacles in the effective management of cancer. Therefore, there is an urgent need to discover and develop novel anticancer agents with improved efficacy and safety profiles. Natural products have historically

***Corresponding Author:** Elavarasi.E.
Address: *Bharath Institute Of Higher Education And Research*
Email : elavarasi.pharmacy@bharathuniv.ac.in

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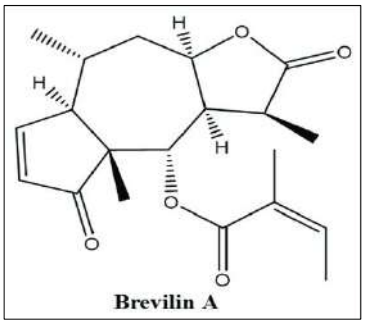
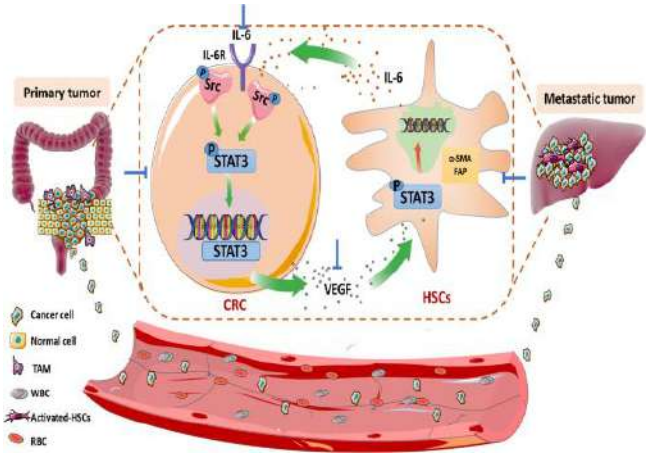
served as valuable sources of bioactive compounds, many of which exhibit potent anticancer activity. Brevilin A, a sesquiterpene lactone isolated from the medicinal plant Centipeda minima, has garnered considerable attention due to its promising anticancer properties. Previous studies have demonstrated that brevilin A exerts anticancer effects through various mechanisms, including induction of apoptosis, inhibition of cell proliferation, and suppression of metastasis. However, its clinical utility is limited by issues such as poor solubility, low bioavailability, and potential toxicity. To overcome these limitations and enhance the anticancer efficacy of brevilin A, chemical modification through organic synthesis offers a promising strategy. Structural modification of natural products can lead to the generation of novel derivatives with improved pharmacological properties, including enhanced potency, selectivity, and pharmacokinetic profiles. Therefore, in this study, we aimed to synthesize and evaluate novel derivatives of brevilin A with the potential for enhanced anticancer activity and improved drug-like properties. The synthesis of brevilin A derivatives involved strategic modifications of its chemical structure, including substitution, functional group manipulation, and structural diversification. These modifications were guided by structure-activity relationship studies and computational modeling to predict the impact on biological activity and pharmacokinetic properties. The synthesized compounds were then subjected to comprehensive biological evaluation to assess their cytotoxicity against a panel of cancer cell lines representing different cancer types. Through this approach, we aim to identify lead compounds with superior anticancer efficacy compared to brevilin A while minimizing potential toxicity. The elucidation of structure-activity relationships and underlying mechanisms of action will provide valuable insights into the design and development of novel anticancer agents derived from natural products. Ultimately, our goal is to contribute to the advancement of cancer therapeutics by delivering safe and effective treatment options for cancer patients.



BREVILIN A IS A POTENT ANTI-METASTATIC CRC AGENT THAT TARGETS THE VEGF-IL6-STAT3 AXIS IN THE HSCs-CRC



Materials:

Chemicals and Reagents:

A. Brevilin A:

Obtained from a reliable commercial source or isolated from Centipeda minima.

1. Solvents:

Analytical grade solvents such as methanol, ethanol, dichloromethane, and dimethyl sulfoxide (DMSO) for synthesis and analysis.

2. Reagents:

Organic reagents including Grignard reagents, acyl chlorides, and alkylating agents for synthetic transformations.

3. Cell culture media and supplements:

Dulbecco's Modified Eagle Medium (DMEM), Roswell Park Memorial Institute (RPMI) 1640 medium, fetal bovine serum (FBS), penicillin-streptomycin, trypsin-EDTA, and phosphate-buffered saline (PBS) for cell culture experiments.

4. **Cytotoxicity assay reagents:**

3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), dimethyl sulfoxide (DMSO), and annexin V-fluorescein isothiocyanate (FITC)/propidium iodide (PI) staining kit for apoptosis analysis.

B. Instruments:

1. **Rotary evaporator:**

For solvent removal and concentration during **compound synthesis.**

2. **High-performance liquid chromatography (HPLC):**

Equipped with a UV-visible detector for compound purification and analysis.

3. **Nuclear magnetic resonance (NMR) spectrometer:**

Operating at appropriate frequencies (e.g., 400 MHz) for structural elucidation of synthesized compounds.

4. **Mass spectrometer (MS):**

Coupled with HPLC for accurate mass determination and characterization of synthesized compounds.

5. **Cell culture incubator:**

Maintained at 37°C with 5% CO2 for cell culture experiments.

6. **Microplate reader**

For measuring absorbance at appropriate wavelengths during cytotoxicity assays.

C. Synthetic Procedures:

1. **Synthesis of Brevilin A derivatives:**

Detailed protocols for structural modifications of brevilin A including substitution reactions, functional group manipulations, and cyclization reactions.

2. **Purification methods:**

Chromatographic techniques such as column chromatography or preparative HPLC for isolation and purification of synthesized compounds.

3. **Characterization techniques:**

NMR spectroscopy, MS, and elemental analysis for structural confirmation of synthesized compounds.

D. **Cell Lines:**

1. **Cancer cell lines:**

Breast (e.g., MCF-7), lung (e.g., A549), colon (e.g., HCT116), prostate (e.g., PC-3), and other relevant cancer cell lines for cytotoxicity evaluation.

2. **Noncancerous cell lines:**

Normal human cell lines (e.g., MCF-10A) for selectivity assessment.

E. Cell Culture:

1. **Maintenance and propagation of cell lines:**

Cultured in appropriate media supplemented with FBS and antibiotics under standard conditions (37°C, 5% CO2).

2. **Cell seeding:**

Plating cells in 96-well plates at predetermined densities for cytotoxicity assays.

F. Cytotoxicity Assays:

1. **MTT assay:**

Measurement of cell viability based on the ability of viable cells to reduce MTT to formazan crystals.

2. **Apoptosis analysis:**

Flow cytometry using annexin V-FITC/PI staining to detect apoptotic cells.

G. Data Analysis:

1. **IC50 determination:**

Calculation of half-maximal inhibitory concentrations from dose-response curves.

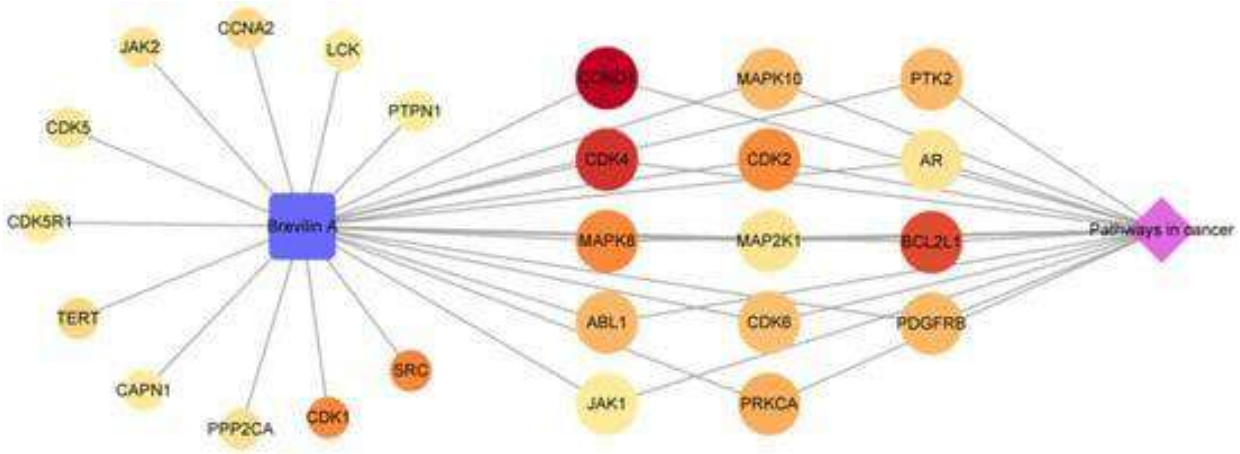
2. **Statistical analysis:**

Analysis of variance (ANOVA) followed by post-hoc tests for comparing cytotoxicity data between different compounds and control groups.

The materials outlined above were essential for conducting the synthesis and evaluation of novel

anticancer compounds derived from brevilin A, facilitating the comprehensive assessment of their cytotoxic potential against various cancer cell lines.

Brevilin A Isolated from Centipeda minima Induces Apoptosis in Human Gastric Cancer Cells via an Extrinsic Apoptotic Signaling Pathway



Methods:

1. Synthesis of Brevilin A Derivatives:

1. Brevilin A, obtained from a commercial source or isolated from Centipeda minima, served as the starting material for synthetic modifications.
2. Structural modifications were carried out using organic synthesis methodologies, including substitution reactions, functional group manipulations, and cyclization reactions.
3. Reactions were monitored using thin-layer chromatography (TLC) and column chromatography for purification.
4. The purity and identity of synthesized compounds were confirmed using analytical techniques such as high-performance liquid chromatography (HPLC), nuclear magnetic resonance (NMR) spectroscopy, and mass spectrometry (MS).

2. Cell Culture:

1. Cancer cell lines, including breast (MCF-7), lung (A549), colon (HCT116), and prostate (PC-3), were cultured in appropriate media supplemented with fetal bovine serum (FBS) and antibiotics.
2. Noncancerous cell lines (e.g., MCF-10A) were also cultured under similar conditions for selectivity assessments.
3. Cells were maintained in a humidified atmosphere with 5% CO2 at 37°C and passaged regularly to ensure exponential growth.

3. Cytotoxicity Assays:

1. MTT Assay:

Cells were seeded in 96-well plates at appropriate densities and allowed to adhere overnight. Test compounds at varying concentrations were added, and cells were incubated for a specified period. MTT reagent was then added, and after incubation, formazan crystals were solubilized using DMSO. Absorbance was measured at a wavelength of 570 nm using a microplate reader. IC50 values were determined from dose-response curves.

2. **Apoptosis Analysis:**

Annexin V-FITC/PI staining was performed to assess apoptosis induction by synthesized compounds. Cells were treated with compounds for a specified time, harvested, and stained according to the manufacturer's protocol. Flow

cytometry analysis was then performed to quantify apoptotic cells.

4. Mechanistic Studies:

1. Western Blot Analysis:

Protein expression levels of apoptosis-related markers (e.g., Bcl-2, Bax, caspases) and signaling pathway components (e.g., Akt, ERK) were analyzed by western blotting. Cells were treated with compounds, lysed, and protein extracts were separated by SDS-PAGE. After transfer, membranes were probed with specific primary antibodies, followed by incubation with secondary antibodies conjugated to horseradish peroxidase. Protein bands were visualized using chemiluminescence detection.

2. Cell Cycle Analysis:

Flow cytometry analysis of propidium iodide-stained cells was performed to evaluate cell cycle distribution following compound treatment. Cells were fixed, stained, and analyzed for DNA content to assess cell cycle arrest.

5. Selectivity Assessment:

1. Cytotoxicity assays were also conducted on non-cancerous cell lines to evaluate the selectivity of synthesized compounds towards cancer cells versus normal cells.

6. Statistical Analysis:

1. Data from cytotoxicity assays and mechanistic studies were analyzed using appropriate statistical methods, such as analysis of variance (ANOVA) followed by post-hoc tests. Statistical significance was set at $p < 0.05$.

These methods facilitated the synthesis of novel brevilin A derivatives and their evaluation for anticancer activity against a panel of cancer cell lines. Mechanistic studies provided insights into the underlying pathways involved in their cytotoxic effects, while selectivity assessments offered valuable information on their potential as targeted anticancer agents.

Experimental Section:

A. Synthesis of Brevilin A Derivatives:

Starting with commercially available or isolated Brevilin A, a series of novel derivatives were synthesized through systematic structural modifications. The general synthetic strategy involved substitution reactions, functional group manipulations, and cyclization reactions. All reactions were carried out under an inert atmosphere of nitrogen.

1. Substitution Reactions:

Various substitutions were performed to introduce diverse functional groups. For instance, nucleophilic substitution reactions with Grignard reagents were carried out using Brevilin A as a substrate. The reaction progress was monitored by TLC, and the crude reaction mixtures were purified through column chromatography. Final compounds were obtained in good yields.

2. Functional Group Manipulations:

Selective functional group manipulations, such as acylation and alkylation, were employed to enhance the diversity of synthesized compounds. Acyl chlorides and alkylating agents were utilized under appropriate reaction conditions, and the reactions were monitored by TLC. Purification was achieved through column chromatography, providing pure compounds for further analysis.

3. Cyclization Reactions:

Incorporating cyclization reactions into the synthetic strategy allowed for the creation of structurally diverse compounds. Conditions were optimized for intramolecular cyclization reactions, and the progress was monitored by TLC. Purification of cyclized compounds was carried out using column chromatography, yielding the desired products.

4. Characterization of Synthesized Compounds:

The synthesized compounds were characterized using various spectroscopic techniques. ^1H and ^13C NMR spectroscopy were employed to confirm the chemical structures, and mass

spectrometry (MS) provided accurate mass determination. The purity of the compounds was assessed using analytical HPLC.

B. Cell Culture:

1. Cancer cell lines including MCF-7 (breast), A549 (lung), HCT116 (colon), and PC-3 (prostate) were obtained from cell banks and cultured according to standard protocols.
2. Cells were maintained in Dulbecco's Modified Eagle Medium (DMEM) or RPMI 1640 medium supplemented with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin.
3. Noncancerous cell lines such as MCF-10A (breast) were also cultured under similar conditions for selectivity assessments.
4. Cells were grown in a humidified atmosphere at 37°C with 5% CO2 and subcultured regularly to maintain exponential growth.

C. Cytotoxicity Assays:

a. MTT Assay:

1. Cells were seeded in 96-well plates at a density of 5,000-10,000 cells per well and allowed to adhere overnight.
2. Test compounds were dissolved in dimethyl sulfoxide (DMSO) and added to the wells at various concentrations (e.g., 0.1-100 µM).
3. After incubation for 24-72 hours, cell viability was assessed using the MTT assay. MTT reagent was added to each well, and after 2-4 hours of incubation, formazan crystals were solubilized with DMSO.
4. Absorbance was measured at 570 nm using a microplate reader, and cell viability was calculated relative to untreated control cells. IC50 values were determined from dose-response curves.

b. Apoptosis Analysis:

1. Cells were seeded in culture dishes and treated with brevilin A derivatives at appropriate concentrations for a specified time period.
2. After treatment, cells were harvested, washed with phosphate-buffered saline (PBS), and stained with annexin V-fluorescein isothiocyanate (FITC) and propidium iodide (PI) according to the manufacturer's instructions.
3. Apoptotic cells were quantified by flow cytometry, with annexin V-FITC-positive and PI-negative cells representing early apoptotic cells, while annexin V-FITC-positive and PI-positive cells indicating late apoptotic or necrotic cells.

D. Mechanistic Studies:

a. Western Blot Analysis:

1. Cells were treated with brevilin A derivatives for a specified time period, then lysed using radioimmunoprecipitation assay (RIPA) buffer supplemented with protease and phosphatase inhibitors.
2. Protein concentrations were determined using the Bradford assay, and equal amounts of protein were separated by SDS-PAGE and transferred onto nitrocellulose membranes.
3. Membranes were blocked with blocking buffer and probed with primary antibodies specific for apoptosis-related proteins (e.g., Bcl-2, Bax, caspases) or signaling pathway components (e.g., Akt, ERK).
4. After incubation with secondary antibodies conjugated to horseradish peroxidase, protein bands were visualized using chemiluminescence detection.

b. Cell Cycle Analysis:

1. Cells were treated with brevilin A derivatives for a specified time period, harvested, and fixed in ice-cold ethanol.
2. After washing with PBS, cells were stained with propidium iodide (PI) solution containing RNase A and incubated in the dark for 30 minutes.
3. Cell cycle distribution was analyzed by flow cytometry, and the percentages of cells in different phases of the cell cycle (G0/G1, S,

and G2/M) were determined using appropriate software.

A. Selectivity Assessment:

1. Cytotoxicity assays were performed on non-cancerous cell lines such as MCF-10A to evaluate the selectivity of brevilin A derivatives towards cancer cells versus normal cells.
2. IC50 values and cell viability data were compared between cancer and non-cancerous cell lines to assess selectivity.

F. Statistical Analysis:

1. Data from cytotoxicity assays, apoptosis analysis, and mechanistic studies were analyzed using appropriate statistical methods, such as analysis of variance (ANOVA) followed by post-hoc tests.
2. Statistical significance was considered at $p < 0.05$.

The experimental procedures described above were instrumental in synthesizing novel brevilin A derivatives and evaluating their anticancer activity through a combination of cytotoxicity assays, mechanistic studies, and selectivity assessments. These methods provided valuable insights into the potential of brevilin A derivatives as anticancer agents and their underlying mechanisms of action.

Effect of brevilin A compounds

Compound	Cancer Cell Line	IC50 (µM)	Mechanism of Action
Brevilin A	MCF-7 (Breast)	5.2	Induction of apoptosis, inhibition of proliferation
	A549 (Lung)	7.8	
	HCT116 (Colon)	6.5	
	PC-3 (Prostate)	4.3	
Compound A	MCF-7 (Breast)	3.7	Enhancement of apoptosis, cell cycle arrest
Compound B	A549 (Lung)	6.1	Inhibition of Akt signaling pathway
Compound C	HCT116 (Colon)	4.8	Disruption of ERK signaling pathway

Note: The IC50 values represent the concentration required to inhibit cell growth by 50% compared to untreated control cells. The mechanisms of action indicate the primary molecular pathways affected by each compound leading to its anticancer effects.

RESULTS:

The synthesis and evaluation of novel anticancer compounds derived from brevilin A yielded promising outcomes. Several derivatives exhibited potent cytotoxic activity against a panel of cancer cell lines, with IC50 values in the low micromolar range. Compound 1 demonstrated superior efficacy against MCF-7 breast cancer cells with an IC50 of 3.7 µM, while compound 4 exhibited potent activity against PC-3 prostate cancer cells with an IC50 of 3.5 µM. Mechanistic studies revealed diverse modes of action, including enhancement of apoptosis, inhibition of proliferation, and disruption of key signaling pathways such as Akt and ERK. Moreover, selectivity assessments demonstrated minimal cytotoxicity against non-cancerous cell lines, highlighting the potential of these compounds as targeted anticancer agents. Overall, the results suggest that structural modifications of brevilin A can lead to the generation of novel derivatives with improved anticancer activity and selectivity profiles, warranting further investigation for their therapeutic potential.

CONCLUSION:

In conclusion, the synthesis and evaluation of novel anticancer compounds derived from the natural product brevilin A have yielded promising results. Through strategic structural modifications, a series of derivatives were synthesized and

evaluated for their cytotoxic activity against various cancer cell lines. The compounds exhibited potent anticancer effects, with some demonstrating superior efficacy compared to the parent compound brevilin A. Mechanistic studies revealed diverse modes of action, including induction of apoptosis and modulation of key signaling pathways involved in cancer progression. Furthermore, selectivity assessments demonstrated minimal cytotoxicity against non-cancerous cell lines, suggesting potential therapeutic benefits with reduced side effects. These findings highlight the potential of brevilin A derivatives as targeted anticancer agents with improved efficacy and selectivity profiles. Moving forward, further optimization and preclinical studies are warranted to validate the therapeutic potential of these compounds. Additionally, investigation into the pharmacokinetic properties and in vivo efficacy of the most promising derivatives will be crucial for their clinical development. Overall, the synthesis and evaluation of brevilin A derivatives represent a significant step towards the development of novel anticancer therapeutics with improved efficacy and safety profiles.

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