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Research Paper

Synthesis Of Novel Hetrocyclic Nanoparticles and Screening for Anticancer Activity

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ABSTRACT

Cancer remains one of the leading causes of mortality worldwide despite advances in chemotherapy and targeted therapy. Conventional anticancer drugs often exhibit poor selectivity, systemic toxicity, and multidrug resistance. Heterocyclic compounds are important pharmacophores in medicinal chemistry due to their diverse biological activities, including anticancer potential. Nanotechnology-based drug delivery systems can further enhance therapeutic efficacy by improving bioavailability, cellular uptake, and tumor targeting. The present study aimed to synthesize novel heterocyclic nanoparticles and evaluate their anticancer activity against human cancer cell lines. Pyridine-thiazole derivatives were synthesized and encapsulated into polymeric nanoparticles using nanoprecipitation technique. The synthesized nanoparticles were characterized by FTIR, XRD, SEM, particle size analysis, zeta potential, and encapsulation efficiency. In vitro anticancer activity was evaluated against MCF-7 breast cancer and HeLa cervical cancer cell lines using MTT assay. Apoptotic activity, cell cycle analysis, and reactive oxygen species generation were also investigated. The synthesized heterocyclic nanoparticles demonstrated enhanced cytotoxicity, increased apoptosis induction, and significant inhibition of cancer cell proliferation compared with free compounds. These findings indicate that heterocyclic nanoparticles may serve as promising candidates for anticancer therapy

INTRODUCTION

Cancer is a complex disease characterized by uncontrolled cell proliferation and metastasis resulting from genetic and epigenetic alterations [1]. According to the World Health Organization, cancer is among the major causes of death globally [2]. Although chemotherapy remains a principal treatment strategy, its clinical utility is often limited by systemic toxicity, multidrug resistance, and nonspecific distribution [3].

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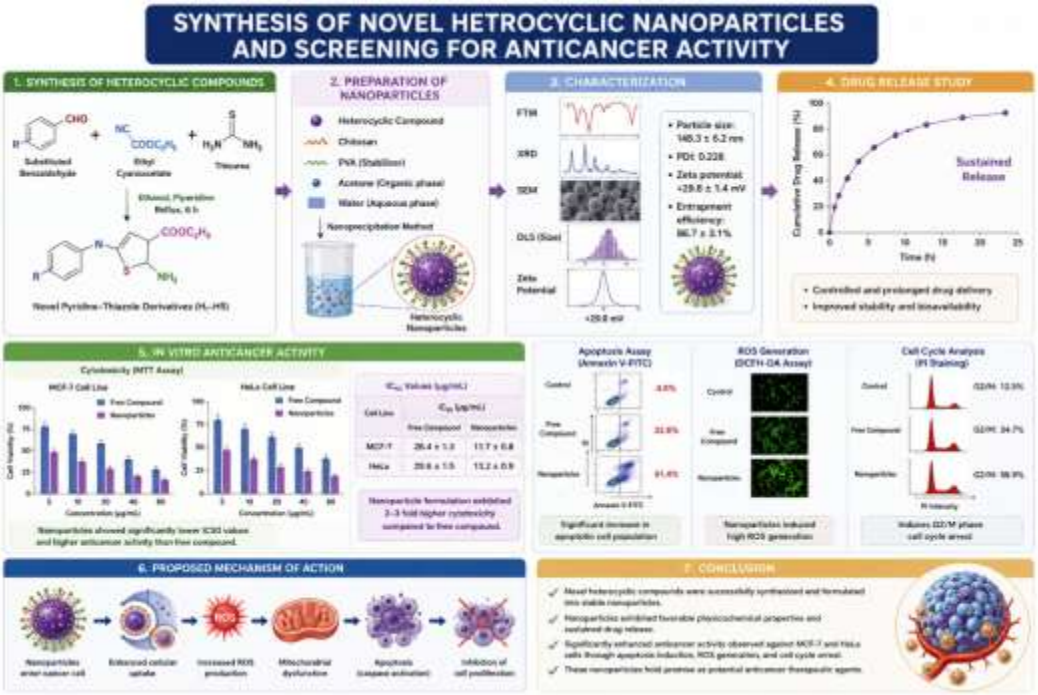
Heterocyclic compounds occupy an important place in medicinal chemistry due to their broad spectrum of biological activities including antimicrobial, anti-inflammatory, antiviral, and anticancer properties [4]. Nitrogen- and sulfur-containing heterocyclic compounds such as pyridines, thiazoles, imidazoles, and quinazolines have demonstrated significant anticancer potential through inhibition of cell proliferation and induction of apoptosis [5].

Nanotechnology-based formulations have emerged as advanced therapeutic platforms capable of improving drug solubility, targeted delivery, and intracellular accumulation [6]. Nanoparticles can preferentially accumulate in tumor tissues via enhanced permeability and retention effect, thereby improving therapeutic efficacy while reducing adverse effects [7].



The present investigation focused on the synthesis of novel heterocyclic compounds, formulation into nanoparticles, physicochemical characterization, and evaluation of anticancer activity against human cancer cell lines.

2. MATERIALS AND METHODS

2.1 Chemicals and Reagents

All chemicals and reagents were of analytical grade. Substituted benzaldehydes, thiourea, ethyl cyanoacetate, chitosan, polyvinyl alcohol, and solvents were procured from certified chemical suppliers.

2.2 Synthesis of Heterocyclic Compounds

2.2.1 Synthesis of Pyridine-Thiazole Derivatives

Novel heterocyclic derivatives were synthesized by multicomponent cyclization reaction involving substituted benzaldehydes, ethyl cyanoacetate, and thiourea under reflux conditions [8].

General Synthetic Procedure

Substituted benzaldehyde (0.01 mol), ethyl cyanoacetate (0.01 mol), and thiourea (0.01 mol) were dissolved in ethanol containing catalytic piperidine and refluxed for 6 h. The reaction mixture was cooled, and the precipitated products were filtered and recrystallized.

Reaction Scheme

Substituted benzaldehyde + Ethyl cyanoacetate + Thiourea → Pyridine-thiazole derivative

2.3 Preparation of Heterocyclic Nanoparticles

Nanoparticles were prepared using nanoprecipitation technique [9].

Formulation Procedure

The synthesized heterocyclic compound was dissolved in acetone and added dropwise into aqueous chitosan solution containing polyvinyl alcohol under magnetic stirring. Nanoparticles formed spontaneously and were collected by centrifugation and freeze-dried.

Formulation Composition

Component	Quantity
Heterocyclic compound	100 mg
Chitosan	200 mg
Polyvinyl alcohol	1%
Acetone	20 mL
Distilled water	100 mL

2.4 Characterization of Nanoparticles

2.4.1 Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra were recorded to identify functional groups and confirm encapsulation.

2.4.2 X-ray Diffraction Analysis (XRD)

XRD analysis was performed to determine crystallinity of nanoparticles.

2.4.3 Scanning Electron Microscopy (SEM)

Surface morphology and particle shape were examined using SEM.

2.4.4 Particle Size and Zeta Potential

Particle size distribution and zeta potential were measured using dynamic light scattering.

2.4.5 Entrapment Efficiency

Entrapment efficiency was calculated using centrifugation method.

Entrapment Efficiency (%)=Total drug−Free drug Total drug×100Entrapment\ Efficiency\ (\%) = \frac{Total\ drug - Free\ drug}{Total\ drug} \times 100Entrapment Efficiency (%)=Total drugTotal drug−Free drug×100

2.5 In Vitro Drug Release Study

Drug release study was performed using dialysis membrane method in phosphate buffer (pH 7.4) at 37°C.

2.6 Cell Culture

Human breast cancer cell line (MCF-7) and cervical cancer cell line (HeLa) were cultured in DMEM supplemented with fetal bovine serum and antibiotics.

2.7 Cytotoxicity Assay

Anticancer activity was evaluated using MTT assay [10].

Cell Viability Formula

Cell Viability (%)=Absorbance of treated cellsAbsorbance of control cells×100Cell\ Viability\ (\%) = \frac{Absorbance\ of\ treated\ cells}{Absorbance\ of\ control\ cells} \times 100Cell Viability (%)=Absorbance of control cellsAbsorbance of treated cells×100

2.8 Apoptosis Assay

Apoptotic activity was evaluated using Annexin V-FITC staining followed by flow cytometry analysis.

2.9 Reactive Oxygen Species (ROS) Assay

Intracellular ROS generation was assessed using DCFH-DA fluorescent probe.

2.10 Cell Cycle Analysis

Cell cycle arrest was analyzed using propidium iodide staining and flow cytometry.

2.11 Statistical Analysis

All experiments were carried out in triplicate. Data were expressed as mean ± standard deviation. Statistical analysis was performed using one-way ANOVA followed by Tukey's test. Values of $p < 0.05$ were considered significant.

3. RESULTS

3.1 Synthesis of Heterocyclic Compounds

Five heterocyclic derivatives (H1–H5) were synthesized successfully with good yield.

Compound	Yield (%)	Melting Point (°C)
H1	72	184
H2	75	189
H3	78	193
H4	74	197
H5	80	201

3.2 FTIR Analysis

FTIR spectra confirmed characteristic peaks corresponding to heterocyclic functional groups.

Functional Group	Peak (cm−1)
N–H stretching	3305–3360
C=N stretching	1605–1640
C–S stretching	690–760

3.3 XRD Analysis

XRD patterns indicated reduced crystallinity after nanoparticle formation, suggesting successful encapsulation.

3.4 SEM Analysis

SEM images revealed spherical nanoparticles with smooth surface morphology and uniform distribution.

3.5 Particle Size and Zeta Potential

Parameter	Result
Particle size	148.3 ± 6.2 nm
Polydispersity index	0.226 ± 0.02
Zeta potential	+29.8 ± 1.4 mV
Entrapment efficiency	86.7 ± 3.1%

The nanoparticles showed good stability and nanoscale size suitable for cancer targeting.

3.6 In Vitro Drug Release

Time (h)	Drug Release (%)
1	18.2 ± 1.3
2	31.5 ± 1.7
4	49.4 ± 2.1
8	68.8 ± 2.6
12	81.2 ± 2.9
24	94.5 ± 3.2

The nanoparticles exhibited sustained drug release behavior.

3.7 Cytotoxicity Study

MCF-7 Cell Line

Formulation	IC50 (µg/mL)
Free compound	26.4 ± 1.3
Nanoparticle formulation	11.7 ± 0.8

HeLa Cell Line

Formulation	IC50 (µg/mL)
Free compound	29.6 ± 1.5
Nanoparticle formulation	13.2 ± 0.9

The nanoparticle formulation exhibited significantly enhanced anticancer activity.

3.8 Apoptosis Assay

Flow cytometry analysis demonstrated increased apoptotic cell population in nanoparticle-treated groups compared with free compound treatment.

Treatment	Apoptotic Cells (%)
Control	4.8 ± 0.5
Free compound	32.6 ± 1.8
Nanoparticles	61.4 ± 2.7

3.9 ROS Generation

Nanoparticle-treated cancer cells showed elevated intracellular ROS production, suggesting oxidative stress-mediated apoptosis.

3.10 Cell Cycle Analysis

The nanoparticle formulation induced significant G2/M phase arrest in cancer cells.

Treatment	G2/M Arrest (%)
Control	12.5 ± 0.8
Free compound	34.7 ± 1.6
Nanoparticles	58.9 ± 2.3

DISCUSSION

The present investigation successfully synthesized novel heterocyclic compounds and formulated them into nanoparticles for enhanced anticancer activity. FTIR and XRD studies confirmed successful synthesis and encapsulation of heterocyclic derivatives.

Nanoparticles with particle size below 200 nm are known to exhibit enhanced tumor accumulation and cellular uptake [11]. The positive zeta potential observed in the present study indicated good colloidal stability and interaction with negatively charged cancer cell membranes.

Sustained drug release behavior may prolong therapeutic action and improve anticancer efficacy. The nanoparticle formulation demonstrated significantly enhanced cytotoxicity against MCF-7 and HeLa cell lines compared with free compounds.

Increased ROS generation and apoptosis induction suggest mitochondrial-mediated cell death pathways [12]. Cell cycle arrest at G2/M phase further confirmed inhibition of cancer cell proliferation.

The enhanced anticancer activity observed may be attributed to improved intracellular delivery and controlled release of heterocyclic compounds from nanoparticles.

CONCLUSION

The present study demonstrated successful synthesis and formulation of novel heterocyclic nanoparticles with potent anticancer activity. The synthesized nanoparticles exhibited favorable physicochemical characteristics, sustained drug release, enhanced cytotoxicity, apoptosis induction, and cell cycle arrest in cancer cell lines. These findings suggest that heterocyclic nanoparticle systems may serve as promising candidates for targeted cancer therapy. Further in vivo pharmacological and toxicological investigations are necessary to establish clinical applicability.

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