Journal of Advances in Medical and Biomedical Research | ISSN:2676-6264

Design and In Vitro Evaluation of Schiff Base-Based Heterocyclic Derivatives as Potential Anticancer Agents Targeting Pancreatic Cancer

Dina Naseer Ali [1*], Ahmed Ahmed [2], Alaa Hussein J. Al-qaisi [2]

1. *Department of Microbial Biotechnology, College of Biotechnology, AL-Nahrain University, Jadriga, Baghdad, Iraq*
2. *Department of chemistry, College of Science, Al-Nahrain University, Baghdad, Iraq*

Article Info

10.30699/jambr.34.2.193

Received: 2025/12/08;
Accepted: 2026/05/11;
Published Online: 2026/05/20;

***Corresponding author:**
Dina Naseer Ali,
Department of Microbial Biotechnology, College of Biotechnology AL-Nahrain University, Jadriga, Baghdad, Iraq
Email:
dina.naseer@nahrainuniv.edu.iq

ABSTRACT

Background & Objective: Pancreatic cancer is a highly aggressive malignancy that necessitates the development of novel chemotherapeutic agents with improved selectivity and efficacy. This study aimed to synthesize and biologically evaluate a series of Schiff base derivatives as potential anticancer agents against pancreatic cancer by assessing their cytotoxicity, selectivity, and ability to induce apoptosis *in vitro*.

Materials & Methods: A different novel heterocyclic derivative, including dihydroquinazoline, oxazepine, tetrazole, and thiazine, were synthesized via a common Schiff base intermediate (Derivative D). The structural characterization of these compounds was performed using FTIR and 1^11H-NMR spectroscopy. To evaluate their therapeutic potential and selectivity, the synthesized derivatives were tested *in vitro* against PANC-1 (pancreatic cancer) and HDFn (normal human dermal fibroblast) cell lines.

Results: MTT assays demonstrated dose-dependent inhibition of cell proliferation by all synthesized compounds. Among them, derivative D4 exhibited greater selectivity toward pancreatic cancer cells, with IC_{50} values of 129.5 µg/mL for PANC-1 cells and 237.4 µg/mL for HDFn cells. In contrast, derivative D5 showed greater overall cytotoxicity but lower selectivity, with IC_{50} values of 68.9 µg/mL for PANC-1 cells and 61.0 µg/mL for HDFn cells. High-content screening revealed that D4 treatment significantly reduced the number of viable cells and decreased mitochondrial membrane potential, accompanied by increased nuclear intensity and cell membrane permeability. Furthermore, D4 significantly activated both caspase-8 and caspase-9 at concentrations of 100 and 200 µg/mL ($P = 0.0019$ and $P < 0.0001$, respectively), indicating activation of both the extrinsic and intrinsic apoptotic pathways.

Conclusion: These findings suggest that the structural optimization of Schiff base-derived heterocycles is a promising strategy for enhancing tumor selectivity and biological safety, potentially offering new avenues for anticancer therapy.

Keywords: Apoptosis; Schiff base; Heterocyclic; Pancreas cancer

How to Cite This Article:

Naseer Ali D, Ahmed A, J. Al-qaisi A H. Design and In Vitro Evaluation of Schiff Base-Based Heterocyclic Derivatives as Potential Anticancer Agents Targeting Pancreatic Cancer. J Adv Med Biomed Res 2026; 34(2):196-202.

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC), commonly referred to as pancreatic cancer, stands as the fourth leading cause of cancer-related mortality in the United States of America (1). In 2008, an estimated 37,700 new cases and approximately 34,300 deaths were attributed to this disease in the USA (2).

The incidence of pancreatic cancer is notably higher in older individuals, and a significant limitation in treatment efficacy stems from the fact that only a small proportion of patients (less than 20%) present with localized tumors amenable to curative therapy (3, 4).

Several risk factors associated with pancreatic cancer have been identified, including a family history of the

disease, personal history of cigarette smoking, chronic pancreatitis, and diabetes mellitus (5). Currently, no established screening procedure exists for identifying high-risk patients (3, 6). This publication aims to provide a comprehensive overview of pancreatic cancer, encompassing its epidemiology, risk factors, pathology, diagnostic approaches, and recent therapeutic advancements (7). The foundational chemistry of Schiff bases (also known as imines or azomethines) was first described by Hugo Schiff in 1864 (8). Schiff bases are characterized by the presence of a carbon-nitrogen double bond functional group (9-10). Their utility spans various applications in organic and inorganic synthesis, including roles as pigments, dyes, catalysts, synthetic intermediates, and polymer stabilizers (11). Furthermore, Schiff bases possess a wide spectrum of biological activities, exhibiting antifungal, antibacterial, antimalarial, antiproliferative, anti-inflammatory, antiviral, and antipyretic properties (12).

Oxazepines are defined as unsaturated heterocyclic compounds containing a seven-membered ring where carbon atoms are replaced by nitrogen and oxygen (13). Derivatives of oxazepine have demonstrated significant medicinal value (14). Recent advancements in tetrazole chemistry have garnered considerable attention due to the manifold biological applications of tetrazole moieties, particularly within medicinal chemistry. The tetrazole ring system serves as a metabolically stable and pharmacokinetically favorable alternative to the carboxylic acid functional group (15, 16). Similarly, 1,3-thiazines, which are heterocyclic compounds, exhibit diverse pharmacological profiles. Various 1,3-thiazine derivatives have been investigated for their antibacterial and fever-relieving properties, and they have also been identified as cholecystokinin antagonists, anti-mycobacterial agents, cannabinoid receptor agonists, and nitric oxide synthase (NOS) inhibitors (17-18).

While Schiff base heterocycles have been explored for their synthetic utility and cytotoxic potential, their specific anticancer effects against pancreatic cancer and their mechanisms of action, particularly concerning apoptotic pathways, remain underexplored. Based on this, we hypothesize that structural modifications of Schiff base heterocycles can modulate both intrinsic and extrinsic apoptotic pathways, thereby promoting selective cytotoxicity against cancer cells.

Despite numerous publications regarding the synthesis and broad cytotoxic assessment of Schiff base-derived heterocyclic compounds, their selective anticancer efficacy against pancreatic ductal adenocarcinoma (PDAC) and the specific apoptotic mechanisms underlying their tumor-targeted action remain poorly understood. Most existing research focuses on broad-spectrum cytotoxic screening, often failing to correlate heterocyclic structural modifications with cancer selectivity or the activation of specific molecular pathways, particularly in the context of apoptosis-resistant PDAC models. The present study introduces a novel approach: the rational design and synthesis of Schiff base-derived heterocycles incorporating dihydroquinazoline, oxazepine, tetrazole, and thiazine scaffolds. We further evaluated these compounds through comprehensive biological profiling, including selectivity assays, high-content screening, and a mechanistic investigation of caspase-mediated apoptotic pathways. We hypothesize that the structural properties and heteroatom composition of these heterocycles can modulate intrinsic and extrinsic apoptotic signaling, thereby enhancing cytotoxicity against pancreatic cancer cells while minimizing toxicity toward normal fibroblasts. To validate this hypothesis, the synthesized compounds were spectroscopically characterized and screened for their anti-proliferative activity against PANC-1 cells. Furthermore, we elucidated the underlying mechanisms by examining mitochondrial dysfunction, membrane permeability, and the activation of caspase-8 and caspase-9.

2. Materials and Methods

All reagents and solvents, including N-(2-hydrazinyl-2-oxoethyl) benzamide, 2-hydroxy-5-nitrobenzaldehyde, 2-aminobenzoic acid, 2-mercaptobenzoic acid, maleic anhydride, sodium azide, sodium bicarbonate, ethanol, dioxane, tetrahydrofuran (THF), benzene, pyridine, and glacial acetic acid, were purchased from Merck (Germany) and used without further purification. Solvents were of analytical grade and freshly distilled before use when necessary. The PANC-1 cell line (human pancreatic ductal adenocarcinoma; ATCC® CRL-1469™) was selected as a representative in vitro model for pancreatic cancer, characterized by its aggressive phenotype, KRAS mutation, and inherent resistance to apoptosis. The HDFn cell line (neonatal human dermal fibroblasts; ATCC® PCS-201-010™) served as the non-cancerous control to evaluate the selectivity and safety profile of the synthesized compounds. Infrared (IR) spectra were recorded on a Shimadzu 8400s spectrophotometer in the range of 4000-400 cm^{-1}. ^{1}H-NMR spectra were acquired in DMSO-d_6 using a Bruker 400 MHz spectrometer. Melting points were determined using an MP90 Melting Point System (Mettler Toledo). In vitro MTT assays were conducted at the Center of Biotechnology Research, Al-Nahrain University. Analyses of cytotoxic parameters, including Caspase-8 and Caspase-9 activity, high-content screening (HCS), and cell cycle analysis, were performed at the Center of Natural Products Research and Drug Discovery, University of Malaya, Kuala Lumpur, Malaysia.

2.1 Synthesis of Schiff Base D (19)

A solution of *N*-(2-hydrazinyl-2-oxoethyl) benzamide (0.02 mol, 4.0 g) and 2-hydroxy-5-nitrobenzaldehyde (0.02 mol, 4.0 g) in 99.9% ethanol (20 mL) was prepared. To this, a catalytic amount of glacial acetic acid was added.

The reaction mixture was stirred and refluxed for 6 h. Upon completion, the mixture was cooled to room temperature, and the resulting precipitate was collected by filtration. The crude product was washed with cold ethanol and purified by recrystallization from ethanol.

2.2 Analytical Data for D (19):

Greenish-yellow powder; yield: 63%; m.p. 300-302 °C. FTIR (KBr, cm^{-1}): 3100-3500 (O-H), 3060 (C-H aromatic), 2939, 2812 (C-H aliphatic), 1664 (C=O), 1633 (C=N), 1500, 1342 (N=O). ^{1}H-NMR (400 MHz, DMSO-d_6, ppm): 9.98 (s, 1H, N-H), 7.03-7.61 (m, 8H, Ar-H), 7.03 (s, 2H, N=CH), 3.47 (s, 2H, N-CH_2-CO).

2.3 Synthesis of N-(2-((2-(2-hydroxy-5-nitrophenyl)-4-oxo-1,2- dihydroquinazolin-3(4H)- Synthesis of Dihydroquinazoline Derivative D3 (20)

A mixture of 2-aminobenzoic acid (0.02 mol) and Schiff base D (0.02 mol) in dioxane (20 mL) was refluxed for 16 h. The solvent was removed under reduced pressure to yield a residue. This crude material was treated with 10% sodium bicarbonate solution, filtered, and the resulting solid was purified by recrystallization from benzene.

2.4 Analytical Data for D3 (20):

Off-white powder; yield: 78%; m.p. 287-289 °C. FTIR (KBr, cm^{-1}): 3373 (O-H), 3089 (C-H aromatic), 2935, 2896 (C-H aliphatic), 1637 (C=C aromatic). ^{1}H-NMR (400 MHz, DMSO-d_6, ppm): 10.25 (s, 1H, N-H, amide), 9.09 (t, 1H, N-H, amine), 8.30 (s, 1H, N=CH), 8.17-7.03 (m, 8H, Ar-H), 3.45 (s, 2H, N-CH_2-C=O).

2.5 Cytotoxic Assay

The cytotoxic effects of the synthesized Schiff base-derived heterocyclic compounds were evaluated using the MTT colorimetric assay. Human pancreatic cancer cells (PANC-1; ATCC® CRL-1469™) and normal human dermal fibroblasts (HDFn; ATCC® PCS-201-010™) were cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum (FBS), 1% penicillin streptomycin, and incubated at 37 °C in a humidified incubator with 5% CO_2.

Cells were seeded into 96-well plates at a density of 5 × 10^3 cells/well in 200 µL of culture medium and allowed to adhere for 24 hours prior to treatment. Stock solutions of the test compounds were prepared in dimethyl sulfoxide (DMSO) and serially diluted in culture medium to achieve final concentrations of 25, 50, 100, 200, and 400 µg/mL. To minimize solvent toxicity, the final DMSO concentration in all wells, including controls, was maintained below 0.1% (v/v).

Following 48 hours of incubation with the compounds, 20 µL of MTT solution (5 mg/mL in phosphate-buffered saline, PBS) was added to each well. The plates were incubated for an additional 4 hours at 37 °C to allow formazan crystal formation. The culture medium was then removed, and the formazan crystals were dissolved by adding 150 µL of DMSO and shaking gently for 10 minutes. Absorbance was measured at 570 nm using a microplate reader. Cell viability was expressed as a percentage relative to untreated control cells, and the half-maximal inhibitory concentration (IC_{50}) values were determined from the dose-response curves. All experiments were performed in duplicate and independently repeated three times to ensure reproducibility.

2.6 Synthesis of Benzo[e] [1,3]thiazin Derivative D4 (21)

Schiff base D (0.02 mol) and 2-mercaptobenzoic acid (0.02 mol) were combined in dry benzene (30 mL) with pyridine (3 drops). The mixture was stirred and refluxed for 3 hours.

Subsequently, the solvent was evaporated under reduced pressure. The residue was filtered, recrystallized from dioxane, and washed with a 10% sodium bicarbonate solution.

2.7 Analytical Data for D4 (21)

Dark yellow powder; yield: 55%; m.p. 349-351 °C. FTIR (KBr, cm^{-1}): 3100-3500 (O-H), 3055 (C-H aromatic), 2943, 2893 (C-H aliphatic), 1684 (C=O), 1645 (C=C aromatic). ^{1}H-NMR (400 MHz, DMSO-d_6, ppm): 9.73 (s, 1H, O-H), 9.09 (s, 1H, N-H), 8.73-7.22 (m, 12H, Ar-H), 6.18 (s, 1H, cyclic C-H).

2.8 Synthesis of Oxazepine Derivative D5 (22)

Schiff base D (0.02 mol) and maleic anhydride (0.02 mol) were dissolved in anhydrous benzene (10 mL). The mixture was refluxed in a water bath for 4 hours. The solvent was evaporated to yield a crystalline solid, which was subsequently purified by recrystallization from dioxane.

White powder; yield: 59%; m.p. 336-338 °C. FTIR (KBr, cm^{-1}): 3100-3500 (O-H), 3089 (C-H aromatic), 2929, 2887 (C-H aliphatic), 1646 (C=O), 1631 (C=C aromatic). ^{1}H-NMR (400 MHz, DMSO-d_6, ppm): 10.22 (s, 1H, O-H), 9.06 (t, 1H, amide N-H), 8.70-7.27 (m, 12H, Ar-H), 4.24 (s, 1H, oxazepine C-H), 4.11 (s, 1H, free O-H), 3.70 (s, 2H, N-CH_2), 3.68-3.51 (t, 4H, CH_2-CH_2 in oxazepane ring).

2.9 Synthesis of Tetrazole Derivative D6 (23)

A solution of Schiff base D (0.0001 mol, 0.5 g) and sodium azide (0.0003 mol, 0.02 g) in a mixture of THF and benzene was refluxed for 8 hours. After evaporation of the solvent, the product was collected and purified by recrystallization from ethanol.

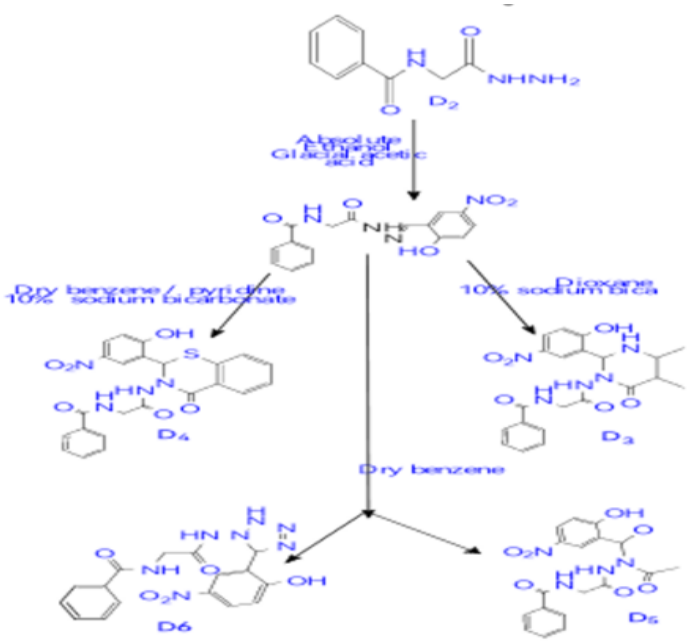
2.10 Analytical Data for D6 (23)

Yellow powder; yield: 67%; m.p. 358-360 °C. FTIR (KBr, cm^{-1}): 3444, 3415 (N-H), 3050 (C-H aromatic), 2931 (C-H aliphatic), 1588 (C=C aromatic). ^{1}H-NMR (400 MHz, DMSO-d_6, ppm): 10.22 (s, 1H, O-H), 9.12 (t, 1H, N-H), 8.74-7.45 (m, 8H, Ar-H), 3.94 (s, 2H, N-CH_2).

3. Result

The condensation reaction between the amine and the aldehyde moiety to form Schiff base D is driven by the nucleophilic attack of the amine nitrogen on the electrophilic carbonyl carbon.

The resulting unstable intermediate undergoes a prototropic shift followed by the elimination of water to establish the C=NC=NC=N double bond. The step-by-step mechanistic pathway is presented in Scheme 1.



Scheme 1. Routes of chalcone (1) and derivatives (D3- D6) (**Prepared by Authors, 2026**).

3.1 Biological Evaluation: Cytotoxic Activity on PANC-1 and HDFn Cell Lines

The cytotoxic potential of the synthesized heterocyclic derivatives was evaluated using the MTT assay against the human pancreatic cancer cell line (PANC-1) and normal human dermal fibroblasts (HDFn). All derivatives demonstrated concentration-dependent reductions in cell viability. IC50 values were calculated to quantify their cytotoxic potency, with data expressed as mean ± SD (n = 3). Statistical significance was assessed via one-way ANOVA followed by Tukey's post-hoc test, using SPSS (version 28.0) and GraphPad Prism. The calculated IC50 values (Table 1) reveal distinct structure-activity relationships. Derivative D5 displayed the most potent, albeit non-selective, cytotoxicity with IC50 values of 68.90 µg/mL (PANC-1) and 61.01 µg/mL (HDFn). In contrast, synthesized derivative D6 exhibited moderate activity as IC50 = 153.7 µg/mL for PANC-1 and 137.0 µg/mL for HDFn. Derivative D3 showed significant antiproliferative effects (IC50 = 210.8 µg/mL for PANC-1) with a relatively higher IC50 in normal cells (178.8 µg/mL) (Table2). Notably, derivative D4 showed the most favorable selectivity profile, with an IC50of 237.4 µg/mL against PANC-1 cells compared to 129.5 µg/mL in the HDFn line (Figure 3).

Table1. Cytotoxic activity and structure–activity relationships of the synthesized Schiff Base derivatives

Inhibitor	Cell line	Viability (mean ± SD)				
		25 (µg/ml)	50 (µg/ml)	100(µg/ml)	200 (µg/ml)	400 (µg/ml)
D	PANC-1	83.29±1.39	74.81±4.49	66.82±0.75	52.82±4.03	41.01±1.09
	HdFn	95.22±0.82	86.07±1.92	84.33±2.66	76.69±2.61	71.95±0.81
D3	PANC-1	94.44±2.81	87.11±2.76	78.74±0.48	60.53±9.25	46.26±5.23
	HdFn	94.64±0.48	93.87±1.10	90.08±1.10	86.07±3.08	74.88±5.00
D4	PANC-1	95.72±0.50	91.20±3.11	76.93±3.07	49.54±2.77	38.93±2.15
	HdFn	96.29±0.87	96.33±0.41	92.28±0.99	84.03±1.25	73.15±1.14
D5	PANC-1	95.22±0.77	91.82±0.93	90.63±0.95	87.89±2.95	75.69±2.01
	HdFn	95.52±0.96	87.35±2.38	76.69±1.94	70.95±2.55	69.56±4.56
D6	PANC-1	96.95±1.24	84.49±0.60	71.88±0.463	53.43±7.96	39.89±2.06
	HdFn	96.18±0.23	94.17±0.77	85.65±3.32	80.21±3.11	72.65±1.96

Table 2. Effects of derivative D4 on cell viability, mitochondrial function, membrane Integrity, and apoptotic markers in PANC-1 cells. VCC, viable cell count; TNI, total nuclear intensity; CMP, cell membrane permeability; MMP, mitochondrial membrane potential; CC, caspase activity.

Conc. (µg/ml)	VCC mean± SD	TNI mean± SD	CMP mean± SD	MMP mean± SD	CC mean± SD
Untreated	3242.5± 188.79	434±8.48	122.5±14.84	562±14.14	399±15.55
200	2017±98.99	734±29.69	284±35.35	369±4.24	664±26.87
100	2122±89.09	579±11.31	147±8.49	410.5±19.09	594±9.89
50	3074.5±75.66	454.5±12.03	132.5±17.67	504.5±23.33	416±26.87
25	3184±73.54	433±28.28	129.5±3.54	535±14.14	402.5±9.19

Given its promising selectivity, synthesized derivative D4 was further investigated using High-Content Screening (HCS) to elucidate its mechanism of action. HCS analysis revealed a significant increase in total nuclear intensity at 100 µg/mL ($P = 0.0024$) and 200 µg/mL ($P < 0.0001$) compared to untreated controls, suggesting potential DNA intercalation and subsequent damage. Furthermore, membrane permeability assays indicated a significant loss of integrity at 200 µg/mL ($P = 0.0012$), whereas lower concentrations (25-100 µg/mL) showed minimal membrane disruption.

While these derivatives exhibit promising antiproliferative activity, the high non-selective toxicity of compounds like D5 highlights the challenges of off-target effects in non-cancerous tissues. Future structural optimizations are required to enhance the therapeutic index and improve the selectivity of these scaffolds for pancreatic cancer cells. (Figure 1,2,3 and 4)

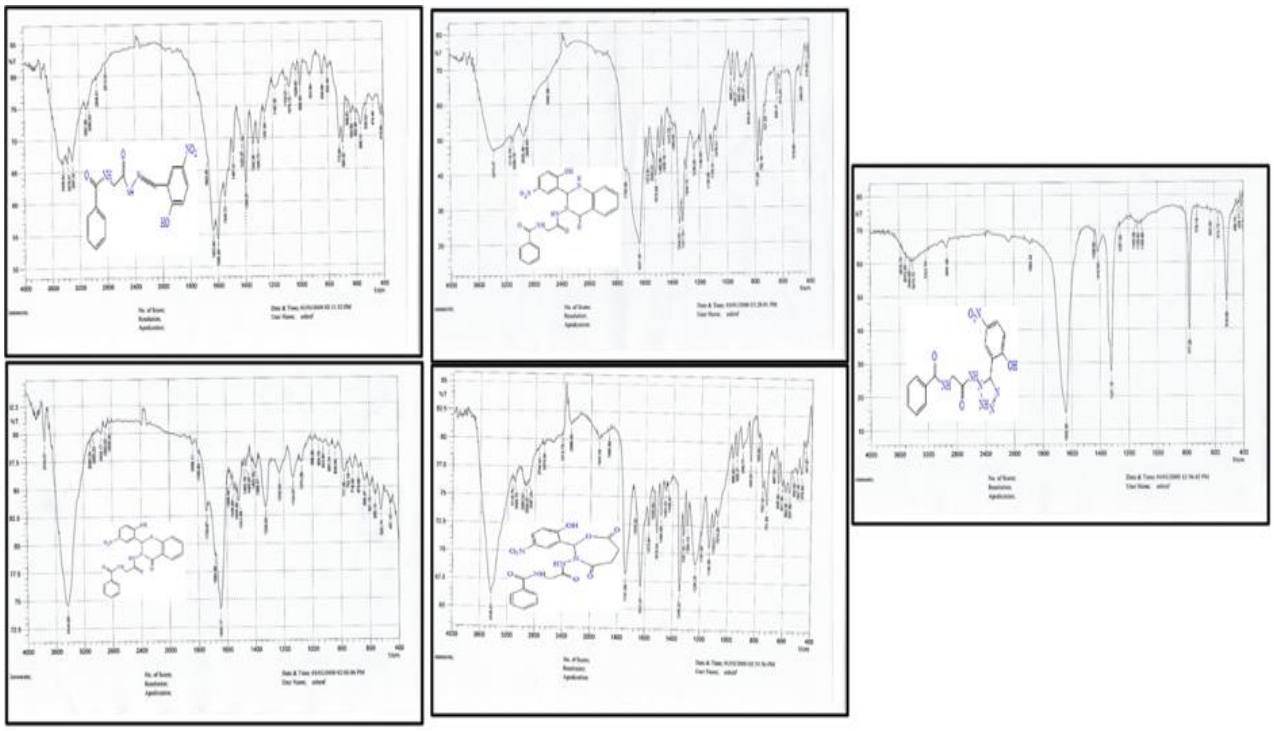


Figure 1. FTIR of synthesized derivatives. (**Prepared by Authors, 2026**).

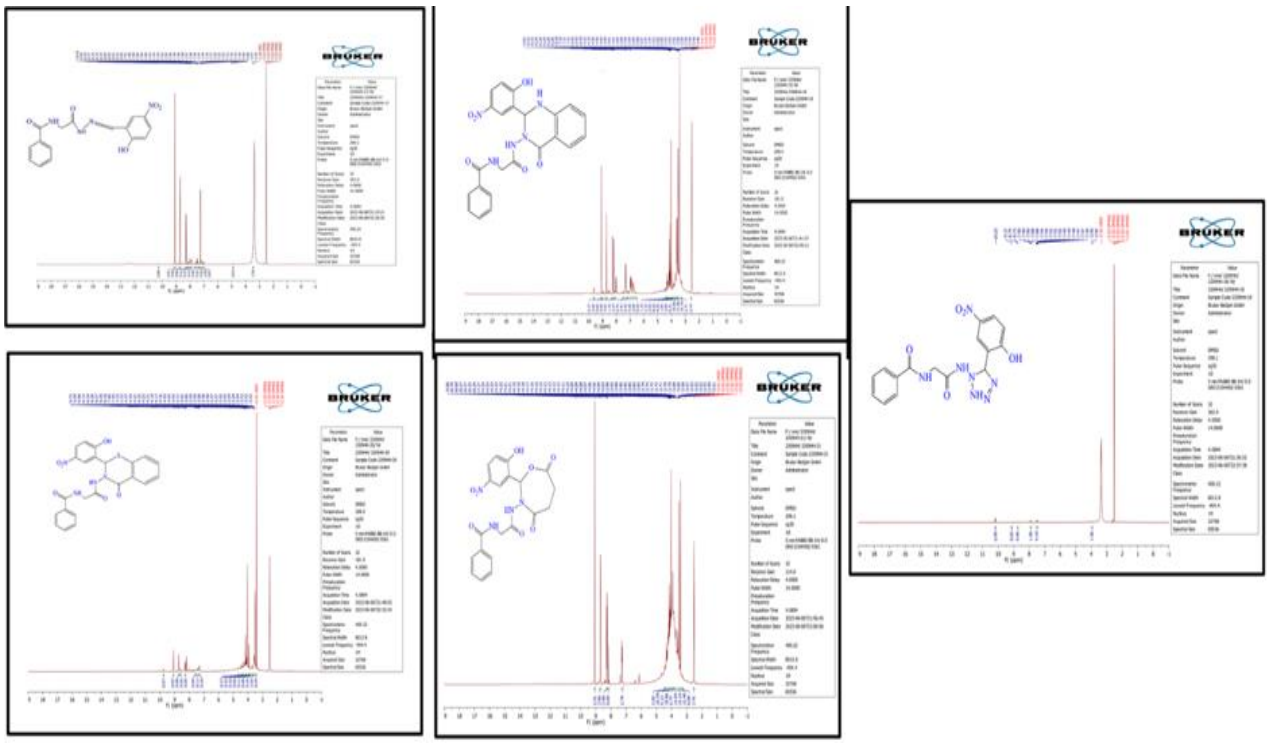


Figure 2. 1HNMR of synthesized derivates. (**Prepared by Authors, 2026**).

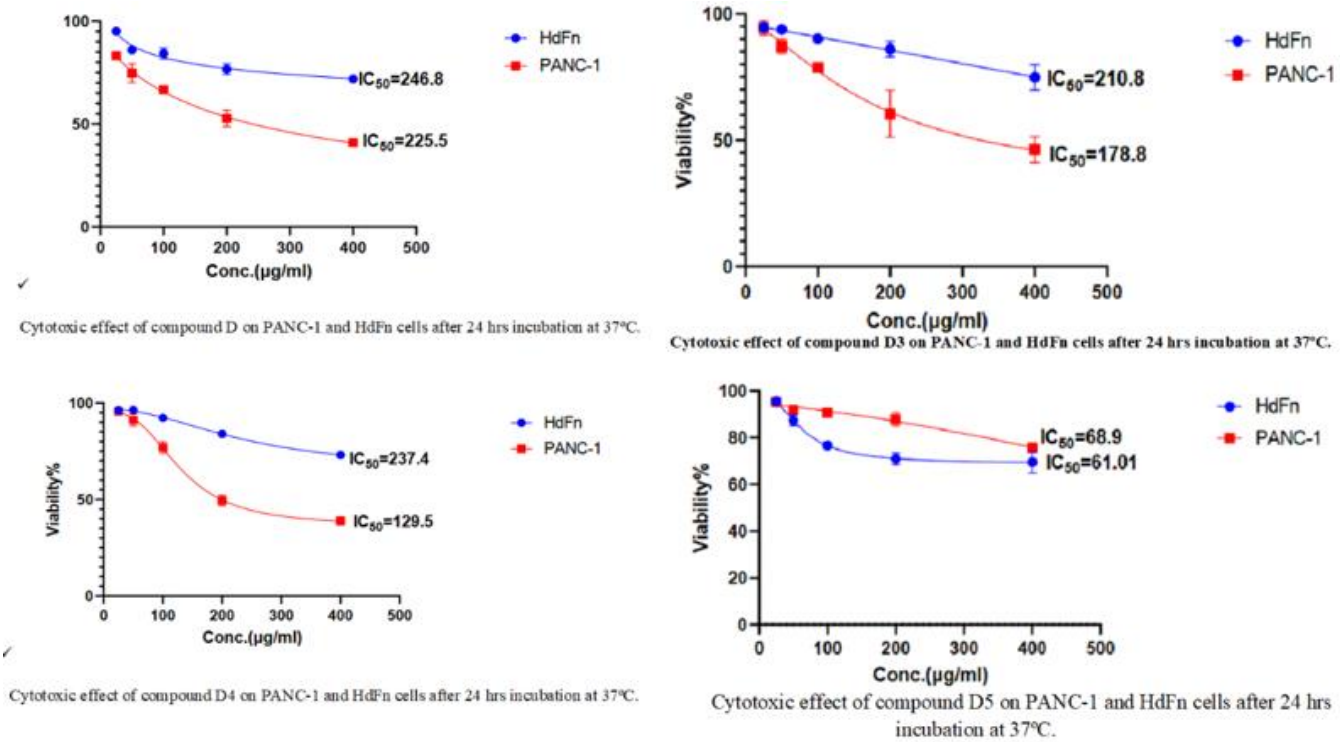
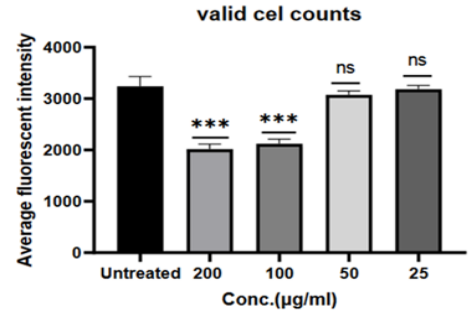
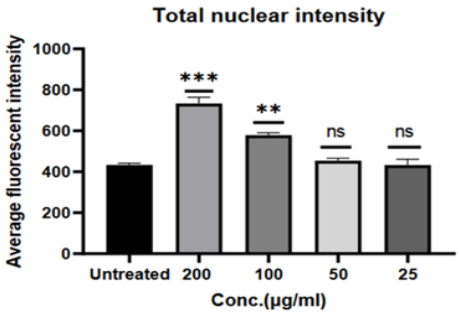


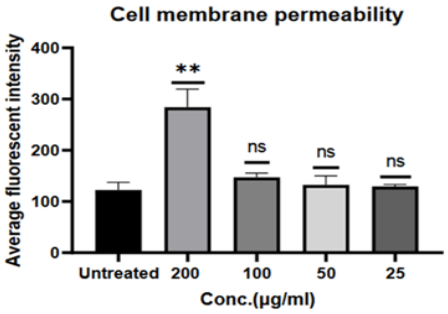
Figure 3. Cytotoxic effect of synthesized derivatives on PANC-1 and HdFn cells after 24 hrs incubation at 37ºC. (**Prepared by Authors, 2026**).



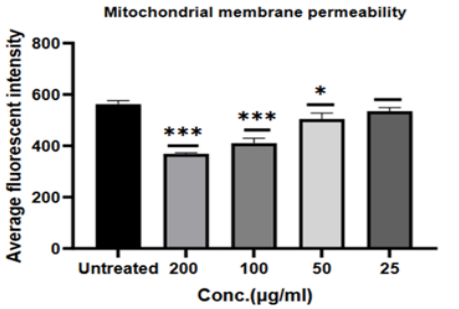
Effect of D4 treatment on viable cell count in PANC-1.



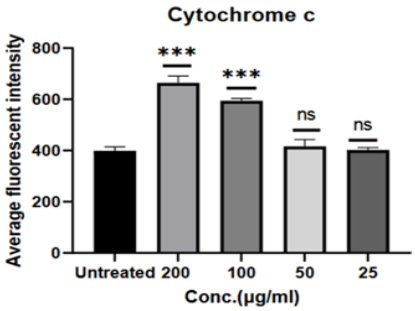
Effect of D4 derivative on total nuclear intensity in PANC-1.



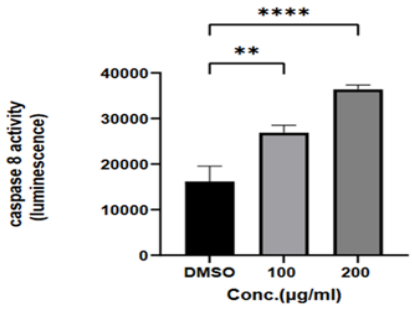
Effect of derivative D4 on cell membrane permeability in PANC-1.



Effect of D4 derivative on Mitochondrial membrane potential in PANC-1.



Effect of D4 derivative on cytochrome C in PANC-1



Cytotoxic effect of compound D6 on PANC-1 and HdFn cells after 24 hrs incubation at 37ºC.

Figure 4. Cytotoxic effect of compound D6 on PANC-1 and HdFn cells after 24 hrs incubation at 37ºC. **(Prepared by Authors, 2026)**.

4. Discussion

This study investigated the cytotoxic selectivity and apoptotic mechanisms of a series of Schiff base-derived heterocyclic compounds against pancreatic cancer cells. The observed structure-activity relationships underscore the profound impact of structural modifications on biological activity. While several derivatives exhibited concentration-dependent antiproliferative effects on PANC-1 cells, synthesized derivative D4 emerged as the most promising candidate due to its favorable safety profile against normal human dermal fibroblasts. In contrast, derivative D5, despite its potent cytotoxicity, displayed indiscriminate activity against both cancerous and normal cell lines, suggesting a generalized cytotoxic mechanism rather than tumor-specific action. This highlights a common challenge with highly reactive heterocyclic systems, which can lead to off-target effects and excessive cytotoxicity due to widespread cellular damage. **(24)**

High-content screening provided valuable insights into the cellular responses induced by synthesized derivative D4. The observed morphological changes, including reduced viable cell counts, nuclear condensation, mitochondrial membrane potential dissipation, and increased membrane permeability, are consistent with apoptosis induction. These findings align with previous reports on Schiff base-containing heterocycles in other cancer models, indicating a conserved apoptotic pathway. While these functional assays provide compelling evidence for apoptosis, they do not pinpoint specific molecular targets or definitively confirm caspase activation. However, based on the observed cellular perturbations and previous literature suggesting that nitrogen- and sulfur-containing heterocycles can modulate apoptotic signaling via mitochondrial dysfunction and death receptor sensitization, we propose that synthesized derivative D4 likely induces apoptosis through both intrinsic (mitochondrial) and extrinsic (death receptor) pathways, potentially involving caspase

cascades. Further studies, such as Western blotting for cleaved caspases and Bcl-2 family members, are warranted to confirm these molecular events at the protein level. (25)

The enhanced selectivity of synthesized derivative D4 is hypothesized to stem from its specific heteroatom composition and ring structure, which may influence its uptake, intracellular distribution, and interaction with apoptosis-sensitive pathways within cancer cells. However, definitive confirmation of these hypotheses requires further investigation, including molecular docking studies, target identification, and proteomic or transcriptomic analyses (26).

This study is subject to certain limitations that necessitate cautious interpretation of the findings. Firstly, the in vitro assessment using a single pancreatic cancer cell line may not fully recapitulate the complex heterogeneity of pancreatic tumors in vivo. Secondly, the determination of apoptosis was primarily based on functional assays, and protein-level validation of apoptotic markers (e.g., caspases, Bcl-2 family proteins) was not performed. Finally, in vivo efficacy, pharmacokinetic profiles, and comprehensive toxicity assessments were beyond the scope of this study. These limitations underscore the need for further research to validate the therapeutic potential of synthesized derivative D4. Future investigations should focus on identifying specific molecular targets, confirming protein-level apoptotic signaling, and evaluating efficacy and safety in preclinical animal models (27).

In conclusion, the structural diversity of Schiff base-derived heterocycles significantly influences their cytotoxic efficacy and selectivity. Derivative D4 demonstrates encouraging preclinical activity and selectivity, warranting further investigation for its potential as a novel therapeutic agent against pancreatic cancer.

5. Conclusion

This research found that Schiff base-derived heterocyclic compounds with dihydroquinazolin, oxazepine, tetrazole, and thiazine frameworks are promising pancreatic cancer research platforms. The synthesized heterocyclic derivatives, incorporating dihydroquinazoline, oxazepine, tetrazole, and benzothiazine scaffolds, represent promising scaffolds for pancreatic cancer research. These compounds exhibited varied concentration-dependent cytotoxicity against PANC-1 cells and HDFn fibroblasts, highlighting the critical role of heteroatom composition and ring fusion in dictating biological selectivity. Derivative D4, in particular, demonstrated a superior therapeutic index-characterized by enhanced anticancer potency and reduced toxicity against normal cells-suggesting that specific structural design is pivotal for achieving tumor-selective effects. Mechanistic investigations indicate that the antiproliferative activity is mediated by both intrinsic and extrinsic apoptotic pathways, evidenced by mitochondrial dysfunction, increased membrane permeability, nuclear condensation, and the activation of caspase-8 and caspase-9. Despite these promising outcomes, the non-selective toxicity observed in several derivatives remains a significant challenge. Consequently, future research should focus on optimizing structure-activity relationships (SAR) to mitigate off-target effects and improve selectivity. Further validation through molecular target identification, in vivo pharmacological assays, and comprehensive ADMET profiling is essential to establish the therapeutic potential of these heterocyclic systems as novel agents for pancreatic cancer therapy.

6. Declarations

6.1 Acknowledgments

We thank Al-Nahrain University.

6.2 Ethical Considerations

None

6.3 Authors' Contributions

Dina Naseer Ali: Conceptualization, Methodology, Data curation, Writing – original draft; Ahmed Ahmed: Formal analysis, Visualization, Validation, Supervision, Project administration; Alaa Hussein J. Al-Qaisi: Supervision, Project administration, Formal analysis, Writing – review & editing.

6.4 Conflict of Interest

The authors declare no conflict of interest.

6.5 Fund or Financial Support

No financial funding available.

6.6 Using Artificial Intelligence Tools (AI Tools)

The authors were not utilized AI Tools.

References

1. van Erning FN, Mackay TM, van der Geest LG, Groot Koerkamp B, van Laarhoven HW, Bonsing BA, et al. Association of the location of pancreatic ductal adenocarcinoma (head, body, tail) with cancer stage, treatment, and survival: a population-based analysis. Acta oncol. 2018;57(12):1655-62. [DOI:10.1080/0284186X.2018.1518593] [PMID]

2. Nakaoka K, Ohno E, Kawabe N, Kuzuya T, Funasaka K, Nakagawa Y, et al. Current status of the diagnosis of early-stage pancreatic ductal adenocarcinoma. Diagnost. 2023;13(2):215. [DOI:10.3390/diagnostics13020215] [PMID] [PMCID]

3. Hu JX, Zhao CF, Chen WB, Liu QC, Li QW, Lin YY, et al. Pancreatic cancer: A review of epidemiology, trend, and risk factors. W J Gastroenterol. 2021;27(27):4298. [DOI:10.3748/wjg.v27.i27.4298] [PMID] [PMCID]

4. Hayashi A, Hong J, Iacobuzio-Donahue CA. The pancreatic cancer genome revisited. Nature reviews Gastroenterol Hepatol. 2021;18(7):469-81. [DOI:10.1038/s41575-021-00463-z] [PMID]

5. Klein AP. Pancreatic cancer epidemiology: understanding the role of lifestyle and inherited risk factors. Nature reviews Gastroenterol Hepatol. 2021;18(7):493-502. [DOI:10.1038/s41575-021-00457-x] [PMID] [PMCID]

6. Cai J, Chen H, Lu M, Zhang Y, Lu B, You L, et al. Advances in the epidemiology of pancreatic cancer: Trends, risk factors, screening, and prognosis. Cancer Lett. 2021;520:1-11. [DOI:10.1016/j.canlet.2021.06.027] [PMID]

7. Wood LD, Canto MI, Jaffee EM, Simeone DM. Pancreatic cancer: pathogenesis, screening, diagnosis, and treatment. Gastroenterol. 2022;163(2):386-402. [DOI:10.1053/j.gastro.2022.03.056] [PMID] [PMCID]

8. Berhanu AL, Mohiuddin I, Malik AK, Aulakh JS, Kumar V, Kim KH. A review of the applications of Schiff bases as optical chemical sensors. TrAC Trends Analyt Chem. 2019;116:74-91. [DOI:10.1016/j.trac.2019.04.025]

9. Raczuk E, Dmochowska B, Samaszko-Fiertek J, Madaj J. Different Schiff bases-structure, importance and classification. Molecules. 2022;27(3):787. [DOI:10.3390/molecules27030787] [PMID] [PMCID]

10. Almashal FA, Mohammed MQ, Hassan QMA, Emshary C, Sultan H, Dhumad AM. Spectroscopic and thermal nonlinearity study of a Schiff base compound. Optic Mater. 2020;100:109703. [DOI:10.1016/j.optmat.2020.109703]

11. Sangle SL. Introduction to Schiff base. Schiff Base in Organic, Inorganic and Physical Chemistry: Intech Open; 2022.

12. Akitsu T. Schiff Base in Organic, Inorganic and Physical Chemistry: BoD-Books on Demand; 2023. [DOI:10.5772/intechopen.104134]

13. Aftan MM, Jabbar MQ, Dalaf AH, Salih HK. Application of biological activity of oxazepine and 2-azetidine compounds and study of their liquid crystalline behaviour. Materials Today: Proceed. 2021;43:2040-50. [DOI:10.1016/j.matpr.2020.11.838]

14. Sodani IJ, Hamid DM, Khalaf RA, Salih TY, Safir NH, Khudair M, et al. Oxazepine derivatives, synthesis and applications.Int J Nat Human Sci.2023;4(2):62-71

15. Gao F, Xiao J, Huang G. Current scenario of tetrazole hybrids for antibacterial activity. Eur J Med Chem. 2019;184:111744. [DOI:10.1016/j.ejmech.2019.111744] [PMID]

16. Myznikov LV, Vorona SV, Zevatskii YE. Biologically active compounds and drugs in the tetrazole series. Chem Heterocycl Compound. 2021;57:224-33. [DOI:10.1007/s10593-021-02897-4]

17. Asif M, Imran M. Antimicrobial activities of various thiazine-based heterocyclic compounds: a mini-review. Mini-Rev Organ Chem. 2022;19(2):166-72. [DOI:10.2174/1570193X18666210629102447]

18. Chaucer P, Sharma PK. Study of thiazines as potential anticancer agents. Plant Arch. 2020;20(2):3199-202.

19. Elangovan N, Thomas R, Sowrirajan S. Synthesis of Schiff base (E)-4-((2-hydroxy-3, 5-diiodobenzylidene) amino)-N-thiazole-2-yl) benzenesulfonamide with antimicrobial potential, structural features, experimental biological screening and quantum mechanical studies. J Molec Struct. 2022;1250:131762. [DOI:10.1016/j.molstruc.2021.131700]

20. Jumaa FH, Shawkat SM. Synthesis of some new bis-2, 3-dihydroquinazolin-4 (1H)-one derivative from dapsone drug and investigating their liquid crystalline properties and antibacterial activities. Iraq J Sci. 2021:3291-306. [DOI:10.24996/ijs.2021.62.9(SI).1]

21. Lemilemu F, Bitew M, Demissie TB, Eswaramoorthy R, Endale M. Synthesis, antibacterial and antioxidant activities of Thiazole-based Schiff base derivatives: a combined experimental and computational study. BMC Chem. 2021;15(1):1-18. [DOI:10.1186/s13065-021-00791-w] [PMID] [PMCID]

22. Dawood AA, Mohammed SR, Mahmoud M. Synthesis, identification and biological activity of new heterocyclic compounds from the reaction of

new Schiff-bases with phthalic anhydride. Sci J Univ Zakho. 2020;8(1):12-8. [DOI:10.25271/sjuoz.2020.8.1.641]

23. Alsahib SA, Dhedan RM. Synthesis and characterization of some tetrazole derivatives and evaluation of their biological activity. Egypt J Chem. 2021;64(6):2925-36.

24. Uddin N, Rashid F, Ali S, Tirmizi SA, Ahmad I, Zaib S, et al. Synthesis, characterization, and anticancer activity of Schiff bases. J Biomolec Struct Dynam. 2020;38(11):3246-59. [DOI:10.1080/07391102.2019.1654924] [PMID]

25. Jaafar MR, Rasool BS, Jawad AA, Abbas AK, Hamid DM, Al-Tabra RH. Synthesis and biological activity of a novel derivatives of Schiff Base. Al-Nahrain J Sci. 2024;27(5): 1-9. [DOI:10.22401/ANJS.27.5.01]

26. Ali ZH, Saleem D, Abbas AK, Rasool BS, Cheyad MS. Synthesis and estimation of the insecticide and antibacterial activities for some new amide derivatives. Indonesia J Chem. 2023;23(6): 1535-1541. [DOI:10.22146/ijc.81972]

27. Ahmed SA, Al-Shanon AF, Al-Saffar AZ, Tawang A, Al-Obaidi JR. Antiproliferative and cell cycle arrest potentials of 3-O-acetyl-11-keto-β-boswellic acid against MCF-7 cells in vitro. J Genet Engin Biotechnol. 2023;21(1):75. [DOI:10.1186/s43141-023-00529-2] [PMID] [PMCID]