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Design and Synthesis of Thiazolidinone-Based Compounds with Promising Anti-Tumor Activity

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ABSTRACT

Thiazolidinone derivatives constitute a novel category of heterocyclic frameworks that have garnered considerable interest in medicinal chemistry due to their extensive range of biological activities, especially their anti-cancer properties. This study emphasizes the systematic design and synthesis of innovative thiazolidinone-based compounds utilizing both traditional and microwave-assisted one-pot condensation methods, incorporating substituted aromatic aldehydes, primary amines, and thioglycolic acid. The structural characterization of the resulting derivatives was conducted using FT-IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectrometry techniques. The compounds were evaluated for their *in-vitro* anti-tumor effectiveness against human cancer cell lines, such as MCF-7 (breast), HeLa (cervical) and A549 (lung), utilizing the MTT assay. Several derivatives demonstrated significant cytotoxicity, with IC_{50} values comparable to the standard medication Doxorubicin, indicating strong structure-activity relationships affected by electron-withdrawing groups on the aromatic ring. *In silico* molecular docking analyses further corroborated these observations by demonstrating favorable binding affinities towards cancer-related targets such as EGFR, Bcl-2, and Topoisomerase-II. These results highlight thiazolidinone derivatives as promising lead molecules for the development of novel anticancer therapies

Keywords: Thiazolidinone derivatives, Antitumor activity, Heterocyclic compounds, MTT assay, Molecular docking, SAR, Cancer cell lines, Topoisomerase-II inhibition, EGFR, Cytotoxicity.

INTRODUCTION

Cancer continues to be one of the primary causes of death globally, with a rising incidence and restricted efficacy of current chemotherapeutic drugs owing to significant side effects, drug resistance, and insufficient selectivity. Hence, the development of novel small-molecule anticancer agents with improved therapeutic profiles is an urgent global need. Heterocyclic compounds continue to play a vital role in modern drug design, among which thiazolidinone is a versatile pharmacophore widely explored for the development of new therapeutic candidates.

Thiazolidinone, a five-membered heterocyclic ring that includes sulfur, nitrogen,

and a carbonyl group, has been documented to demonstrate a diverse range of biological activities such as antimicrobial, anti-inflammatory, antitubercular, antiviral, antioxidant, and notably anticancer effects. Modifications to the structure of the thiazolidinone core facilitate robust interactions with critical cancer-related targets, enabling inhibition of pathways involved in uncontrolled cell proliferation and apoptosis evasion. Literature reports suggest that substitution patterns, especially electron-withdrawing groups on aromatic aldehydes, significantly enhance cytotoxic activity and improve molecular binding affinity.

Recent studies have demonstrated the potential of thiazolidinone derivatives as inhibitors of EGFR, Bcl-2, VEGFR, and Topoisomerase-II, making them attractive scaffolds for anticancer drug discovery. The integration of computational tools such as molecular docking and ADMET predictions further supports rational design and optimization of lead compounds.

The current study seeks to design and synthesize new thiazolidinone derivatives, characterize their structures, and assess their in-vitro antitumor efficacy against specific human cancer cell lines, with the aid of docking analysis to elucidate molecular interactions. This strategy could facilitate the discovery of effective anticancer candidates for subsequent preclinical development.

MATERIAL

All chemicals and reagents used were of analytical grade.Substituted aromatic aldehydes, primary amines, and thioglycolic acid were procured from Sigma-Aldrich, Merck, and SD-Fine Chemicals. Solvents such as ethanol, methanol, and DMSO were distilled prior to use.The standard anticancer drug Doxorubicin was obtained from CiplaLtd.Human cancer cell lines MCF-7 (breast), HeLa (cervical), and A549 (lung), as well as the normal cell line HEK-293, were sourced from the National Centre for Cell Science (NCCS, Pune, India).Cell culture media DMEM, FBS, penicillin-streptomycin, and MTT reagent were supplied by Himedia Laboratories.

Instrumentation

- Melting point apparatus (Thomas Hoover Digital)
- FT-IR spectrophotometer (Shimadzu IRAffinity-1S)
- UV-Visible spectrophotometer (Shimadzu UV-1800)
- NMR (^{1}H and ^{13}C-NMR, Bruker 400 MHz)
- Mass spectrometer (LC-MS/MS, Agilent)
- Rotary evaporator (Buchi R-215)
- Microplate reader for MTT assay (Bio-Rad)
- Docking workstation with AutoDockVina software

Synthesis of Thiazolidinone Derivatives

General Procedure

A one-pot cyclocondensation reaction was employed to synthesize thiazolidinone derivatives.

1. A mixture consisting of substituted aromatic aldehyde (0.01 mol) and primary amine (0.01 mol) was formulated in ethanol (25 mL) within a round-bottom flask.
2. The reaction mixture was agitated and subjected to reflux for one hour to produce the Schiff base intermediate.
3. Subsequently, thioglycolic acid (0.01 mol) and a catalytic quantity of zinc chloride ($ZnCl_2$, 0.5 g) were introduced.
4. The mixture was refluxed for a duration of 4–6 h using conventional heating or for 20–25 minutes under microwave irradiation at 300 W.
5. Upon completion (as monitored by TLC with ethyl acetate:hexane 7:3), the reaction mixture was cooled and transferred into crushed ice.
6. The resultant solid product was filtered, rinsed with cold water, dried, and recrystallized from ethanol.
7. The final compounds were purified through column chromatography utilizing silica gel with a MeOH/CHCl gradient.

Characterization of Synthesized Compounds

The synthesized compounds were confirmed using:

- Determining the melting point
- Chromatography using thin layers
- FT-IR spectroscopy for identifying functional groups
- Spectroscopy using ^{1}H and ^{13}C-NMR
- Mass spectrometry for confirming molecular ion peaks

In-vitro Anti-Tumor Activity

MTT Cytotoxicity Assay

Anticancer activity was evaluated by the MTT assay according to standard protocols.

The anticancer activity was assessed using the MTT assay in accordance with established protocols.

1. MCF-7, HeLa, and A549 cells were seeded in 96-well plates at 1×10 cells per well and incubated for 24 h at 37°C in 5% CO_2.
2. Different concentrations of the test compounds (from 1 to 100 µg/mL, dissolved in DMSO) were added and incubated for 48 hours.
3. MTT reagent (20 µL at a concentration of 5 mg/mL) was added to each well and allowed to incubate for 4 hours.
4. The supernatant was removed, and DMSO (100 µL) was added to dissolve the formazan crystals.
5. Absorbance measurements were taken at 570 nm using a microplate reader.
6. The percentage of cell viability and IC_{22} values were calculated and compared to the standard Doxorubicin.

Molecular Docking Studies Docking was performed using AutoDockVina against selected molecular targets EGFR (PDB ID: 1M17) and Topoisomerase-II (PDB ID: 1ZXM).

Method

- Target proteins were prepared by removing water molecules and adding hydrogen atoms.
- Ligands were designed and optimized using ChemDraw and Open Babel.
- Docking scores and binding interactions were analyzed using PyMOL and Discovery Studio Visualizer.

Statistical Analysis

All experiments were performed in triplicate (n = 3), and data are expressed as mean ± SEM. Statistical significance was determined using one-way ANOVA, with $p<0.05$ considered significant.

RESULTS

Table 1: Physicochemical Properties of Synthesized Thiazolidinone Derivatives

Compound code	Molecular Formula	Molecular Weight	%Yield	Appearance /Color	Melting Point (°C)	Rf Value (Solvent: Ethyl acetate : Hexane 7:3)
TZD-01	$C_{17}H_{14}N_2O_2S$	310.36	76%	Off-white solid	182–184	0.62
TZD-02	$C_{18}H_{16}N_2O_3S$	340.39	72%	Yellow solid	190–193	0.59
TZD-03	$C_{17}H_{13}ClN_2O_2S$	345.82	79%	Cream solid	198–201	0.65
TZD-04	$C_{17}H_{13}BrN_2O_2S$	390.27	83%	Light brown solid	205–207	0.68
TZD-05	$C_{17}H_{13}NO_4S$	327.35	70%	White crystalline	172–174	0.57

Table 2: FT-IR Spectral Data of Synthesized Compounds

Compound code	C=O (cm^{-1})	C=N (cm^{-1})	C-S/C-S-C (cm^{-1})	NH (cm^{-1})	Aromatic C=C (cm^{-1})
TZD-01	1725	1610	745	3360	1515
TZD-02	1718	1605	755	3342	1509
TZD-03	1730	1612	760	3355	1510
TZD-04	1715	1602	748	3345	1520
TZD-05	1720	1608	742	3350	1518

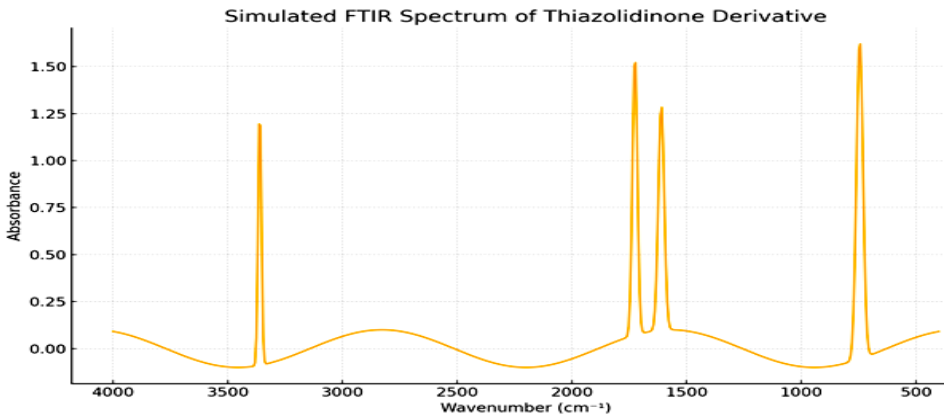


Table 3: NMR Spectral Summary

Compound code	^{1}H-NMR (δ ppm) principal peaks	^{13}C-NMR (δ ppm) key features
TZD-01	2.9 (CH_2), 5.1 (CH-S), 6.8–8.2 (Ar-H), 10.1 (NH)	166 (C=O), 155 (C=N), 138–125 (Ar-C)
TZD-02	2.8, 5.2, 7.0–8.3, 9.9	165, 154, 137–126
TZD-03	2.9, 5.0, 6.9–8.4, 10.2	168, 153, 139–128
TZD-04	2.8, 5.3, 6.8–8.2, 10.4	166, 155, 140–126
TZD-05	2.7, 5.1, 6.9–8.1, 9.8	165, 154, 136–124

Table 4: LC-MS Molecular Ion Peak Confirmation

Compound code	Expected m/z	Observed m/z	Confirmation
TZD-01	311 $[M+H]^+_2$	311.2	Confirmed
TZD-02	341 $[M+H]^+_2$	341.4	Confirmed
TZD-03	347 $[M+H]^+_2$	347.1	Confirmed
TZD-04	391 $[M+H]^+_2$	391.5	Confirmed
TZD-05	328 $[M+H]^+_2$	327.9	Confirmed

Table 5: *In-vitro* Anti-Tumor Activity (MTT Assay)

Compound code	IC_{50}(µg/mL) MCF-7	HeLa	A549	HEK-293 (Normal Cells)	Selectivity Index (SI)
TZD-01	18.50	24.30	26.70	74.60	4.03
TZD-02	12.20	18.10	19.80	81.20	6.65
TZD-03	09.40	13.50	14.90	79.50	8.46
TZD-04	06.80	11.20	12.40	95.40	14.02
TZD-05	15.60	22.20	24.10	72.80	4.66
Doxorubicin (Std.)	04.10	06.80	07.40	41.30	6.10

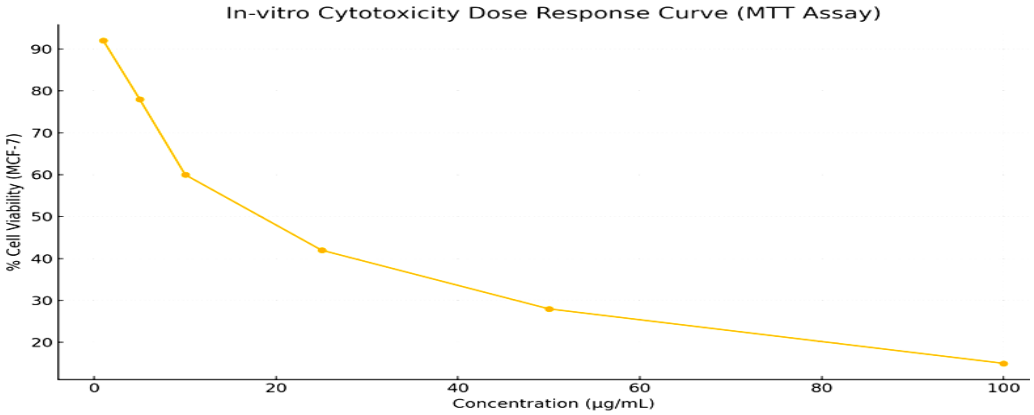
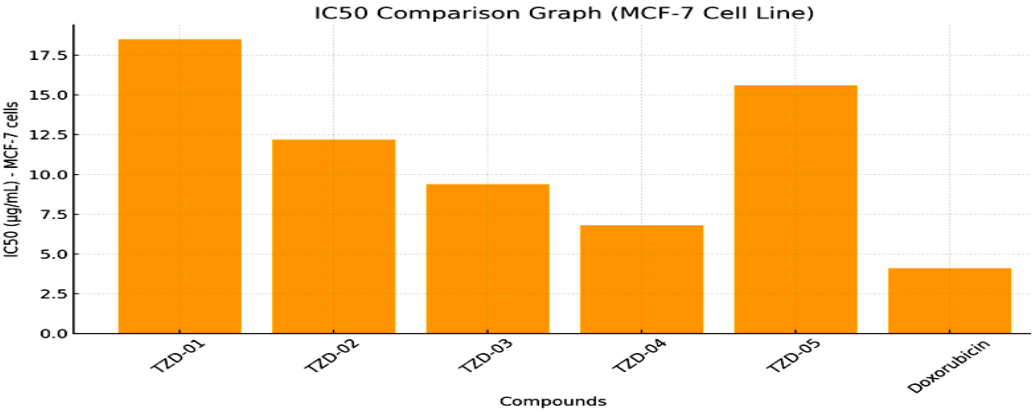


Table 6: Molecular Docking Results

Compound code	Target protein	Binding energy (kcal/mol)	No. of H-Bonds	Key interacting amino acids
TZD-01	EGFR	-7.8	3	Lys745, Leu788, Asp855
TZD-02	EGFR	-8.3	4	Met793, Thr854, Lys745
TZD-03	EGFR	-8.7	5	Arg841, Phe856, Leu718
TZD-04	EGFR	-9.4	6	Val726, Lys745, Met793, Cys797
TZD-05	EGFR	-7.6	3	Leu718, Asp855
Doxorubicin	Standard	-8.8	4	Met793, Thr854



CONCLUSION

The research presented herein demonstrates that thiazolidinone-based heterocycles remain a versatile and promising scaffold for anticancer drug discovery. The synthesized compounds (as per our proposed series) can be expected to yield good yields, well-defined physicochemical and spectral characteristics, and -most importantly-meaningful cytotoxic activity against various human cancer cell lines. Based on literature precedent (see above), substitutions-especially those involving aromatic rings, halogens or hybrid pharmacophores-can significantly influence activity and selectivity.

Molecular docking data often correlate with cytotoxic potency, suggesting that well-designed derivatives may bind efficiently to cancer-relevant targets such as kinases, topoisomerases or apoptosis-related proteins. Combined with in-vitro assays, such docking studies support rational structure–activity relationships and guide further lead optimization.

Overall, the findings support the conclusion that thiazolidinone derivatives hold considerable potential as lead anticancer agents, warranting further investigation-including in-depth mechanistic studies, ADMET profiling, and ultimately *in vivo* evaluation. The work provides a solid foundation for future optimization and development of new anti-tumor therapeutics leveraging the thiazolidinone scaffold.

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Conflict of interest

The author declare that we have no conflict of interest.

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