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Comprehensive Review on the Anticancer Potential of Thiazolidin-4-One Derivatives

Dalbir Singh[1], Mona Piplani[1], Harsha Kharkwal[2], Sankaranarayanan Murugesan[3], Yogendra Singh[1], Amit Aggarwal[1], Subhash Chander[2]*

[1]School of Pharmacy, Maharaja Agrasen University, Atal Shiksha Kunj, Kalujhanda, Baddi, Solan-174103, Himachal Pradesh, India.
[2]Amity Institute of Phytochemistry & Phytomedicine, Amity University Uttar Pradesh, Noida-201313, India.
[3]Medicinal Chemistry Research Laboratory, Department of Pharmacy, Birla Institute of Technology & Science Pilani, Pilani Campus, Pilani-333031, Rajasthan, India.

***E-mail** ✉ schander1@amity.edu

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ABSTRACT

Thiazolidin-4-ones exhibit a highly adaptable and privileged core structure, consisting of a five-membered heterocyclic ring with a sulfur atom and a cyclic amide bond. Recent research, especially in the last decade, has extensively explored the various biological activities of this scaffold, highlighting its potential therapeutic applications. Several key features, such as drug-likeness, compatibility for diversity-oriented synthesis, and sensitivity to the redox environment of tumors, make it a promising structure for the development of anticancer agents. The thiazolidine-2,4-dione and thiazolidine-4-one are two classical forms of this scaffold, with the former receiving more attention compared to the latter. However, the thiazolidine-4-one core is increasingly attracting research interest, as reflected in numerous studies published in recent years. This comprehensive review primarily focuses on the anticancer potential of thiazolidine-4-one derivatives, exploring the structural variety and substitution patterns of compounds that feature this nucleus. The review explores the various enzymatic targets involved in drug discovery, highlighting their selectivity for cancerous tissues over healthy cells, as well as the structure-activity relationships (SAR). Future research perspectives are also discussed, with an emphasis on advancing translational studies. Further studies on pharmacokinetics and metabolic stability are recommended to move toward potential lead candidates for clinical application.

Keywords: Structure-activity relationship (SAR), Thiazolidin-4-one, Drug discovery, Cytotoxicity, Selectivity, Anti-cancer

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Introduction

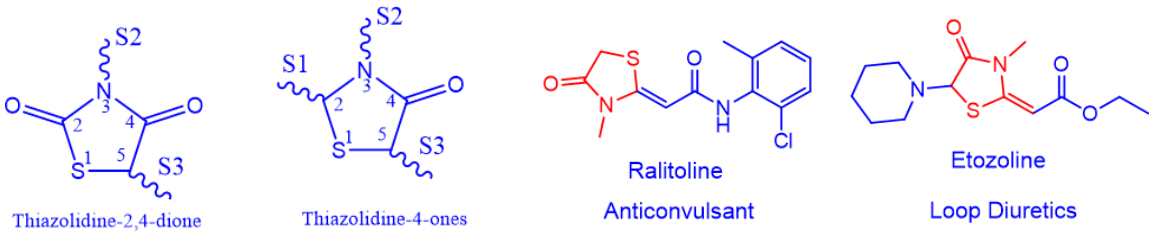
Cancer remains one of the leading causes of death worldwide, accounting for approximately 10 million fatalities in 2020 [1-3]. Among the various types, lung and breast cancers are frequently diagnosed, with lung and colorectal cancers being the most fatal, resulting in 1.80 million and 0.916 million deaths respectively in the same year [4]. Globally, cancer is the second most prevalent cause of death after heart disease [5]. The increasing number of cancer diagnoses, along with challenges such as drug resistance, recurrence, high treatment costs, undesirable side effects, and poor targeting of cancer cells, underscore the pressing need for the development of novel, more affordable, and safer drugs to complement existing chemotherapy treatments [6-10].

Thiazolidine, a crucial and well-regarded structure in medicinal chemistry, consists of a five-membered heterocyclic ring with sulfur and an amide bond [11-13]. Research has highlighted a broad spectrum of biological activities associated with this scaffold, which suggests its potential therapeutic applications [14, 15]. The two

main variants of this scaffold—thiazolidinedione and thiazolidine-4-one—have been subjects of extensive study in the field of medicinal chemistry [16-18].

Thiazolidinedione, which features diketone groups at the 2nd and 4th positions, has been thoroughly investigated for its diverse pharmacological effects, particularly in treating diabetes and cancer [19-21]. Substitutions at the 5th position of 2,4-thiazolidinediones have led to the creation of approved anti-diabetic drugs, such as rosiglitazone and pioglitazone. These compounds function by binding to PPARγ receptors, resulting in hypoglycemic effects [22, 23]. While thiazolidine-2,4-dione has been more extensively studied, thiazolidine-4-one, though less explored, is gaining more attention, as demonstrated by several recent studies [18, 24-27].

The thiazolidine-4-one structure offers more flexibility for modifications because it contains three potential modification sites (S1, S2, S3, **(Figure 1a)**), in contrast to thiazolidine-2,4-dione, which has only two sites (S1, S3, **(Figure 1a)**). This makes thiazolidine-4-one a more favorable scaffold for diversity-oriented synthesis and structural alterations. Additionally, research has investigated thiazolidine-4-one derivatives for their anti-cancer effects, exploring various oxidation states of the sulfur atom in some cases [27].



a) b)

Figure 1. The general structure of thiazolidine-2,4-dione, thiazolidine-4-ones, their available versatile sites for modification a), and clinically approved drugs containing thiazolidine-4-one nucleus b).

Although there have been a few review articles discussing the synthesis and biological properties of thiazolidine-4-one derivatives [24, 25, 28], an in-depth review focusing solely on the anti-cancer potential of this scaffold has not yet been published. This review aims to fill that gap by providing a thorough and structured examination of the anti-cancer properties of compounds featuring this nucleus.

Materials and Methods

We conducted a detailed search of the available literature from multiple sources, including PubMed, Google Scholar, and other well-established publication platforms. The collected studies were then systematically organized, analyzed, and discussed, focusing on key aspects such as substitution patterns, and a wide range of anti-cancer evaluations (including in vitro, in vivo, structure-activity relationship (SAR), computational models, and mechanistic investigations). Moreover, this review highlights the challenges encountered in translating these findings into clinical applications and presents the future directions for research involving this scaffold.

Results and Discussion

Thiazolidine-4-one derivatives with clinical applications

Ralitoline (RLT), a drug based on the thiazolidinedione framework **(Figure 1b)**, has demonstrated significant anticonvulsant properties in both experimental and clinical settings. In comparative studies, ralitoline outperforms conventional antiepileptic medications such as sodium valproate, phenytoin, and diazepam, particularly in terms of rapid onset and superior efficacy in models of electroshock seizures (MES). This drug works by suppressing the rapid firing of sodium action potentials without disrupting glutamate or GABAergic responses [29].

Etozoline, another therapeutic agent incorporating the thiazolidine-4-one structure **(Figure 1b)**, is used as a diuretic for conditions like hypertension and mild to moderate edema. The drug is marketed in Europe under various names such as Etopinil, Diulozin, and Elkapin, though its exact mechanism of action is not fully understood [30].

Diverse substitution patterns of thiazolidine-4-one for cancer research

A detailed examination of 31 research articles on thiazolidine-4-one derivatives as anti-cancer agents has revealed a wide array of modifications to the scaffold, showcasing its adaptability. Researchers have employed mono-substitutions at the 2nd position and various combinations of di- and tri-substitutions at positions 1st, 2nd, 3rd, and 5th. The most frequently encountered modifications include di-substitutions at the 2nd, 3rd, and 2nd, 5th positions, with these patterns appearing in nine and eleven studies, respectively. Tri-substitutions at the 2nd, 3rd, and 5th positions were reported in 8 studies. The highest frequency of substitutions was seen at the 2nd and 5th positions. A comprehensive review of the findings has been organized according to the different substitution patterns.

Anti-cancer properties of tri-substituted thiazolidine-4-one derivatives

Substituted thiazolidine-4-one at 2nd, 3rd, and 5th positions

Panchuk *et al*. [31] designed and synthesized a series of compounds based on the thiazolidine-4-one core, incorporating thio groups at the 3rd and 5th positions and substituting them at the 2nd position **(Figure 2)**. These compounds were tested for their cytotoxic effects and the mechanisms underlying apoptosis were explored using Western blotting for protein expression analysis. The compounds exhibited moderate cytotoxicity against both breast cancer (MCF-7, MDA-MB-231) and leukemia (Jurkat, CCRF-CEM) cell lines. Apoptotic analysis showed that these compounds induced cell death through two distinct pathways: receptor-mediated mitochondrial apoptosis and caspase-independent AIF-mediated apoptosis. The most effective compound, compound 1 **(Figure 2)**, demonstrated an IC50 of 5 μM in the tested cancer cell lines [31, 32].

Holota *et al*. [26] extended the study of the 2-thioxothiazolidin-4-one scaffold by synthesizing and testing a series of compounds against a broad panel of 59 human cancer cell lines, representing nine cancer types, including colon, leukemia, lung, melanoma, breast, ovarian, prostate, renal, and CNS cancers. At an initial screening concentration of 10 μM, compound 2a **(Figure 2)** showed substantial anti-cancer activity. Further evaluation of compound 2a yielded growth inhibition (GI50) values of 2.57 μM, total growth inhibition (TGI) of 57.27 μM, and lethal concentration (LC50) of 94.71 μM [26].

In another investigation, Buzun *et al*. [33] synthesized a new series of 2-thioxothiazolidin-4-one compounds conjugated with ciminalum and tested them against a selection of cancer cell lines from the NCI-60 panel, including human colon cancer (DLD-1), gastric cancer (AGS), and breast cancer (MCF-7, MDA-MB-231). The compounds were tested at various concentrations (ranging from 10−4 to 10−8 M) over 48 hours. Among the series, compound 2b **(Figure 2)** exhibited impressive anti-cancer activity, with GI50 and TGI values of 1.57 μM and 13.3 μM, respectively. In addition, compound 2b demonstrated potent anti-cancer activity against CNS cancer (SF-539), melanoma (SK-MEL-5), colon cancer (SW-620), and leukemia (MOLT-4, SR), with GI50 values below 20 nM. Moreover, compound 2b exhibited minimal toxicity to normal human blood lymphocytes and a selectivity index (SI) greater than 376.14 for leukemia cell lines. SAR studies indicated that the presence of the ciminalum group at the fifth position is crucial for the observed anti-cancer effects [33].

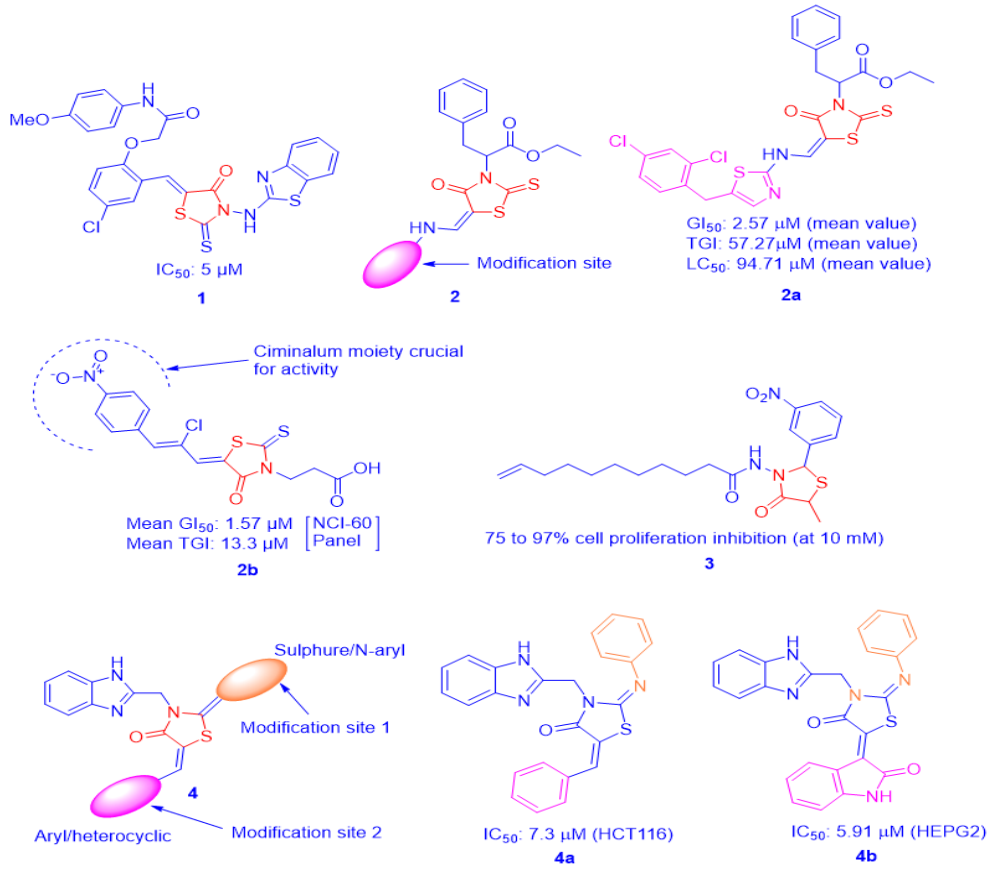


Figure 2. Trisubstituted thiazolidin-4-one-based compounds (1-4b) as anti-cancer agents

Rahman *et al*. [34] focused on synthesizing a series of thiazolidine-4-one derivatives, where long alkyl amide chains were incorporated. These compounds were tested for their anticancer potential against various human cancer cell lines: MCF7 (breast), NCI-H460 (lung), and SF-268 (CNS). Notably, compound 4 demonstrated impressive cytotoxicity across all three cell lines. Further testing revealed that compound 4 also exhibited strong activity against additional cancer types, including lung, melanoma, and renal cancers, reducing cell growth by 75%, 97%, and 84% respectively, when administered at a 10 mM concentration [34].

Arylamine N-acetyltransferase (NAT), an enzyme responsible for acetylating drugs, carcinogens, and other organic substances, has been implicated in the regulation of cancer cell growth [35, 36]. Inhibition of NATs has been proposed as a viable approach in cancer drug development, as several studies suggest its role in cancer progression [37, 38].

Masoud *et al*. [39] synthesized a series of 2-phenylimino-4-thiazolidinone derivatives, fused with a benzimidazole ring, targeting the NAT1 enzyme. The anticancer efficacy of these compounds was evaluated in vitro. Among the synthesized compounds, derivatives 4a and 4b showed significant anti-proliferative effects against human colon carcinoma (HCT 116) and liver cancer (HEPG2) cell lines. A broader screening revealed moderate activity against MCF7 breast cancer cells. Additionally, molecular docking analyses confirmed a strong binding affinity between the active compounds and the NAT1 enzyme, providing a rationale for their anticancer effects [39].

Mahmoodi *et al*. [40] explored the development of 1,3-thiazolidine-4-one derivatives via a solvent-free microwave-assisted cycloaddition method. The synthesized compounds were tested for their cytotoxicity against MKN-45 gastric cancer cells. Among the series, compounds 5a, 5b, 5c, and 5d demonstrated notable anticancer activity, with IC50 values under 10 µM, marking them as promising candidates for further investigation [40].

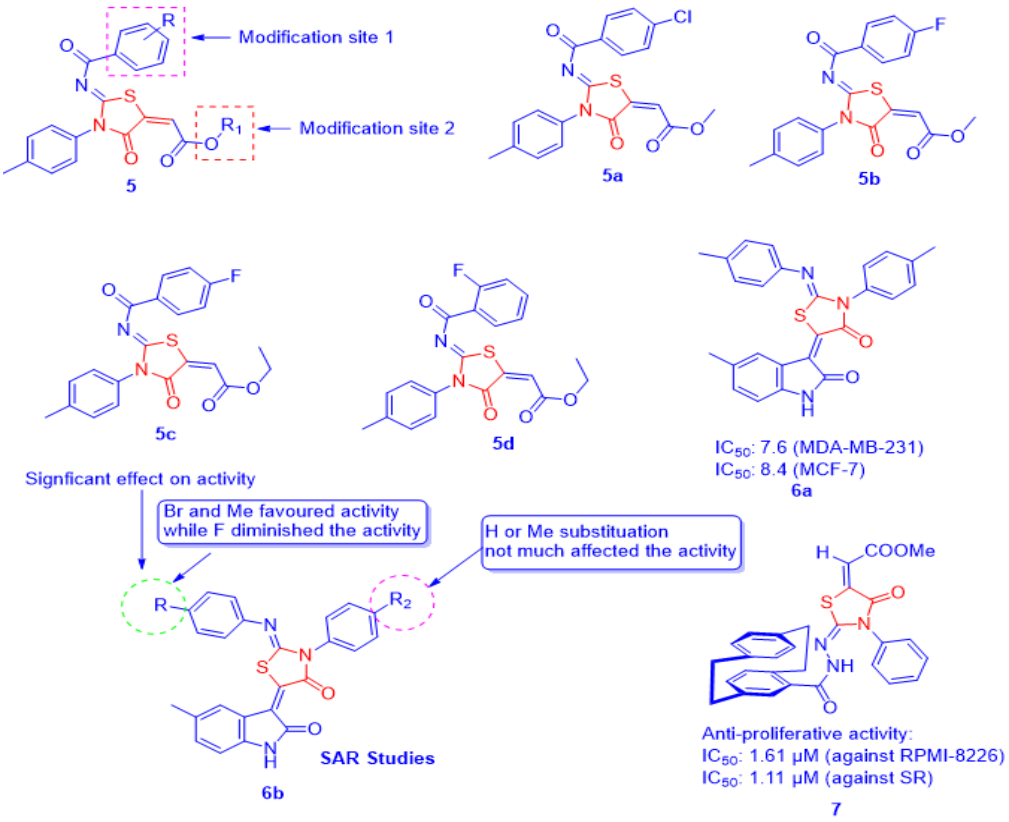


Figure 3. Tri substituted thiazolidine-4-ones derivatives (5-7) as anti-cancer agents.

The oxindole structure, often linked to isatin, is widely regarded as a privileged scaffold in anticancer drug development, leading to several approved therapies as well as promising lead candidates [41-43]. In their work, El-Naggar *et al*. [44] created and synthesized two distinct series of compounds based on thiazolidinone-isatin and thiazolo-[3,2-a]-benzimidazolone-isatin hybrids. These compounds were tested for their ability to inhibit cell growth in two types of breast cancer cell lines: MDA-MB-231 (triple-negative) and MCF-7. The results showed that the compounds had varying levels of efficacy, ranging from moderate (IC50 > 100 µM) to strong (IC50 < 10 µM) anticancer effects. Notably, compound 6a exhibited the most potent activity, with IC50 values of 7.6 µM for MDA-MB-231 and 8.4 µM for MCF-7, which, although effective, was slightly less potent than the reference drug Sunitinib (IC50 of 5.5 µM for MDA-MB-231 and 3.4 µM for MCF-7). Treatment with compound 6a resulted in increased levels of Bax and caspase-3, coupled with a decrease in Bcl-2 expression, suggesting the induction of apoptosis in MDA-MB-231 cells. Additionally, compound 6a promoted a significant shift in the cell cycle, with a fourfold increase in Sub-G1 cells and a 2.5-fold increase in G2-M phase-arrested cells. The apoptotic effect was further confirmed by a sixfold increase in annexin V-FITC-positive cells compared to the control. Importantly, compound 6a demonstrated strong selectivity with a selectivity index (SI) of 9.6 when tested in non-tumorigenic MCF-10A breast cells [44]. The structure-activity relationship of these compounds is shown in **Figure 3**.

Aly *et al*. [45] synthesized six paracyclophanyl thiazolidinone-based compounds and evaluated their activity across a panel of 60 cancer cell lines. Among these, compound 7 **(Figure 3)** was found to exhibit the most promising anticancer effects, particularly against leukemia cell lines RPMI-8226 and SR, with IC50 values of 1.61 µM and 1.11 µM, respectively. The compound was shown to inhibit tubulin with an IC50 of 4.97 µM, closely resembling the activity of colchicine (IC50 of 3.76 µM). Further studies into its apoptotic mechanism revealed significant alterations in the expression of key apoptotic proteins. Caspase-3, a well-established apoptosis marker, was activated, and the balance between the anti-apoptotic Bcl-2 and pro-apoptotic Bax proteins was shifted in favor of apoptosis. Annexin V-FITC staining confirmed a marked increase in apoptotic cells. In silico docking studies indicated that compound 7 binds at a similar site to colchicine, demonstrating overlapping interaction patterns [46].

Anti-cancer potential of thiazolidine-4-ones having a different oxidation state of sulphur with substitution at the third and fifth position

Gududuru *et al*. [27] developed a novel group of thiazolidine-4-one compounds where sulfur was in varied oxidation states, with substituents at the second and third positions (8, **(Figure 4)**). These compounds were assessed for their inhibitory effects on the growth of five different human prostate cancer cell lines: DU-145, PC-3, LNCaP, PPC-1, and TSU, alongside a negative control, RH7777. Of the series tested, 3 compounds (8a, 8b, 8c, **(Figure 4)**) demonstrated potent anti-proliferative effects, with IC50 values in the low micromolar range against the prostate cancer cell lines. Moreover, these compounds showed significantly reduced cytotoxicity against RH7777 cells, with a reduction factor of 2-5 times. The structure-activity relationship (SAR) analysis highlighted that a 2-aryl group at the second position and a long-chain amide at the third position were key for the observed activity. The oxidation state of sulfur had little impact on the efficacy of the compounds. The authors recommended further optimization to enhance the potency and specificity of these compounds for better therapeutic outcomes [27].

Anti-cancer potential of di-substituted thiazolidine-4-ones derivatives

Thiazolidin-4-ones with third and fifth substitutions as anti-cancer agents

In their study, Kamel *et al*. [47] developed a series of thiazolidine-4-one derivatives, incorporating substitutions at the third and fifth positions (9, **(Figure 4)**). These compounds were tested against the MCF7 and HELA cancer cell lines to assess their potential anti-cancer effects. Notably, compounds 9a and 9b, which contained N-(pyridin-2-yl)-benzenesulfonamide substitutions, displayed strong anti-cancer activity, with IC50 values below 3 µg/ml, surpassing the activity of the chemotherapeutic agent doxorubicin (IC50 values: 6.71 and 8.72 µg/ml). Of these, compound 9b, which had an indole group at the first position of the thiazolidine ring, showed slightly superior performance, demonstrating an IC50 of less than 1.95 µg/ml against both cancer lines. Docking simulations suggested that these compounds may interact with protein-tyrosine kinase as their likely molecular target [47].

The involvement of Nuclear factor-κB (NF-κB) in chronic inflammation and its role in cancer progression is well-established [48]. It is known that compounds that inhibit NF-κB can have potent anti-cancer effects by reducing inflammation and slowing tumor growth [49, 50]. Targeting NF-κB, Suthar *et al*. [51] designed a range of quinolone-substituted thiazolidine-4-one derivatives (compound 10, **(Figure 4)**) and performed molecular docking studies to predict their interaction with the NF-κB active site. The top thirty-one compounds were synthesized and tested for their anti-cancer activity on various human cancer cell lines, including COLO-205, BT-549, ACHN, and HeLa. Compounds 10a and 10b exhibited remarkable cytotoxicity, with IC50 values ranging from 31.38-78.86 µg/ml for 10a and 20.73-44.71 µg/ml for 10b against all cell lines. To explore the mechanism of action, RT-PCR was employed to analyze m-RNA expression. The results revealed that compounds 10a and 10b caused an upregulation of the pro-apoptotic protein Bcl-2 and a downregulation of Bax, an anti-apoptotic protein, triggering apoptosis through mitochondrial cytochrome c release. Additionally, the anti-tumor effects of these compounds were confirmed in an in-vivo Ehrlich ascites carcinoma model [51].

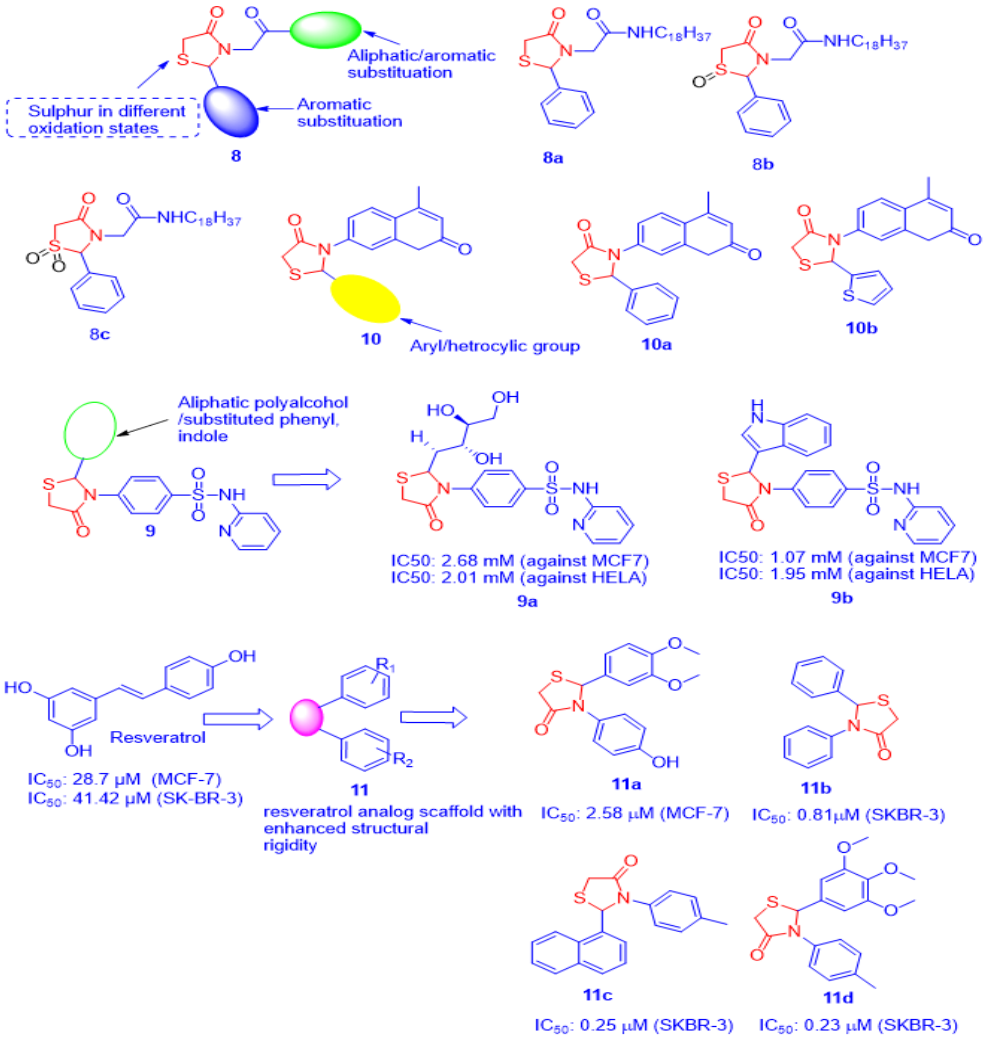


Figure 4. Thiazolidin-4-ones (8-11d) with 3rd and 5th substitution as anti-cancer agents

Resveratrol (RSV) has demonstrated significant potential in cancer prevention and treatment, but its clinical use is often limited due to poor bioavailability and swift elimination from the bloodstream [52-54]. To improve these properties, Sala *et al*. [55] developed a series of thiazolidinone-based compounds that incorporate RSV's structural features to enhance both bioavailability and rigidity. This set of twelve derivatives (compound 11, **(Figure 4)**) included a thiazolidinone ring bonded with two aromatic rings and was tested against MCF-7 and SK-BR-3 (Her2 overexpressing) cell lines. Among them, compound 11a exhibited a low micromolar IC50 value (2.58 µM) against MCF-7, while compounds 11b to 11d demonstrated potent effects against SK-BR-3 with IC50 values under 0.5 µM. These compounds were significantly more potent than resveratrol itself (IC50: 28.7 and 41.42 µM against MCF-7 and SK-BR-3, respectively), suggesting that thiazolidine-4-one derivatives based on RSV could be promising candidates for the treatment of human breast cancer [55].

Wu *et al*. [56] synthesized a set of 2,3-diaryl-4-thiazolidinone derivatives (compound 12, **(Figure 5)**) and evaluated their anti-cancer activity on human lung cancer (A549) and breast cancer (MDA-MB-231) cell lines. The structure-activity relationship (SAR) studies revealed that the derivatives with a 2-(3-(arylalkyl amino carbonyl)-phenyl)-3-(2-methoxy-phenyl)-4-thiazolidinone framework were particularly effective against both cancer cell lines. Migration assays on MDA-MB-231 cells showed significant inhibition, with some compounds achieving IC50 values as low as 0.05 mM. Notably, compounds 12a and 12b exhibited sub-micromolar IC50 values against both A549 and MDA-MB-231 cells, and they demonstrated strong anti-migration activity in both wound healing and trans-well assays (IC50: 0.01-0.05 µM). In vivo tests with compound 12a further confirmed its ability to inhibit tumor growth, reduce metastasis, and improve survival rates compared to controls [56].

A new series of benzoimidazol-thiazolidinone derivatives (scaffold 13, **(Figure 5)**) was developed and tested for antimicrobial and anticancer effects against human colorectal cancer (HCT116) cells. Several compounds in this

series exhibited notable cytotoxicity, with the most potent being compounds 13a and 13b, which showed IC50 values of 0.05 and 0.12 mM/ml, respectively—both of which were more effective than the chemotherapy drug fluorouracil (IC50 = 6.15 mM/ml). Molecular docking studies revealed that these compounds displayed a strong binding affinity for cyclin-dependent kinase-8, supporting their potential as effective therapeutic agents [57].

Glioblastoma multiforme (GBM), a highly aggressive and treatment-resistant brain cancer, presents significant therapeutic challenges [58, 59]. Da Silveira *et al*. [60] synthesized sixteen thiazolidine-4-one derivatives with 2-aryl-3-((piperidin-1-yl)-ethyl)-thiazolidin-4-one structures (compound 14, **(Figure 5)**) and tested them on glioblastoma cells. Thirteen of these compounds reduced glioma cell viability by 30 to 65 percent at a 100 µM concentration. Four compounds (14a, 14b, 14c, and 14d) exhibited significant reductions in viability and were further analyzed at lower concentrations, inducing cell death through necrosis followed by apoptosis. Importantly, these compounds showed selective toxicity, with minimal effects on primary astrocytes. In vivo, these compounds inhibited glioma growth and reduced tumor malignancy in male Wistar rats, without causing mortality or significant damage to peripheral tissues. Additionally, they affected the metabolism of nitric oxide, which may contribute to the observed reduction in tumor progression and malignancy [60].

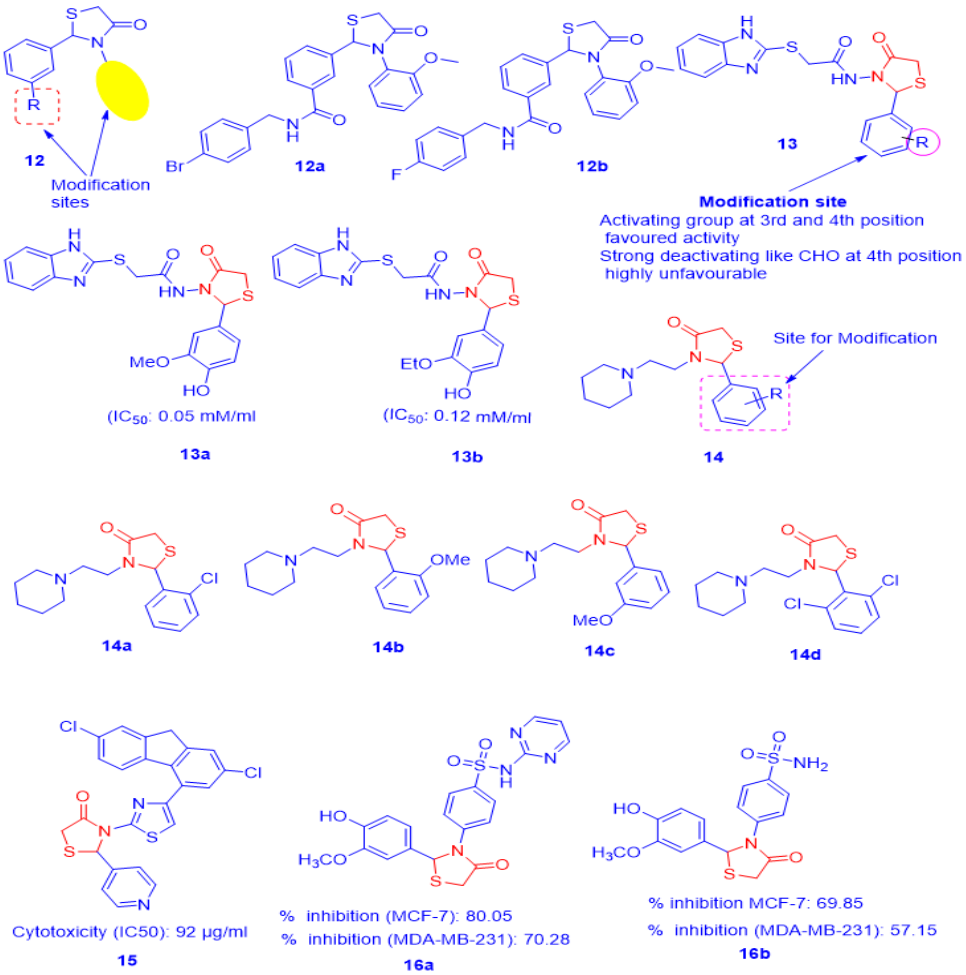


Figure 5. Thiazolidin-4-ones (12-16b) with 3rd and 5th substitution as anti-cancer agents

Dihydrofolate reductase (DHFR) is a well-known therapeutic target, widely explored for its role in treating infections and cancer, with several DHFR inhibitors already in clinical use [61, 62]. Hussein *et al*. [63] developed a new set of compounds, integrating azetidinone and thiazolidinone rings with a thiazole moiety, to target DHFR. These compounds were tested for their anticancer properties on A549 lung carcinoma, WI-38 lung fibroblast, and MDA-MB-231 breast carcinoma cell lines. While most of the compounds demonstrated moderate to weak activity, compound 15 **(Figure 5)** exhibited a stronger cytotoxic effect, especially on lung carcinoma cells, with an IC50 value of 92 µg/ml. Further mechanistic analysis using fluorescence-activated cell sorting (FACS) and docking studies suggested DHFR inhibition as a potential mechanism of action for these compounds [63].

In another study, Kadhim *et al*. [64] synthesized two thiazolidine-4-one derivatives (compounds 16a and 16b, **(Figure 5)**), and evaluated their potential as antimicrobial, anticancer, and hemolytic agents. The anticancer activities were assessed in triple-negative breast cancer (MDA-MB-231) and MCF-7 (ER+, HER2+, ER+) cell lines. The compounds showed strong growth inhibition, with compound 16a reducing MCF-7 cell growth by 80.05 ± 1.72% and compound 16b inhibiting it by 69.85 ± 3.26% after 72 hours at 100 µg/ml. In the MDA-MB-231 cell line, the inhibition was slightly lower, at 70.28% for 16a and 57.15% for 16b. Hemolysis tests revealed minimal RBC damage (less than 4% at 3 mg/ml), suggesting good safety profiles for in vivo applications. Docking studies showed that both compounds had strong binding to ERα, VEGF, and HER2 receptors, aligning with the observed cytotoxic effects. Overall, compound 16a was found to be more effective than compound 16b and even outperformed the reference drug tamoxifen in MCF-7 cells [64].

The PI3K-Akt pathway, a key regulator of cell survival and proliferation, is frequently altered in numerous cancers, including those of the breast, stomach, brain, liver, and lungs, contributing to the pathogenesis of approximately 30% of cancer cases. This makes it an attractive target for novel cancer therapies [65, 66].

In their work, Abdelnaby *et al*. [67] synthesized a series of compounds by fusing coumarin with thiosemicarbazone and thiazolidine-4-one structures **(Figure 6)** and tested them for anticancer effects. Among the nine compounds tested on MCF-7 cells, compound 17a demonstrated the most promising activity, with an IC50 of 1.03 ± 0.05 µM. Further studies confirmed that compound 17a induced cell cycle arrest in the S-phase and significantly increased apoptosis rates, particularly in the late stage. The treatment with 17a also led to an eight-fold increase in caspase-9 levels, indicating caspase-9-dependent apoptosis. Western blot analysis showed that compound 17a reduced levels of p-PI3K, Cyclin D1, and p-Akt, confirming the inhibition of the PI3K-α/Akt-1 pathway. Computational docking further revealed that compound 17a bound tightly to the PI3K binding site, surpassing the reference ligand X6K in binding affinity. Based on these findings, the study proposes compound 17a as a promising candidate for targeting the PI3K/Akt pathway in breast cancer [67].

Thiazolidin-4-ones with 2nd and 5th substitution as anti-cancer agents

Overexpression of P-glycoprotein (P-gp), a member of the ABC transporter family, has been a major factor in the development of drug resistance, particularly in cancer therapies such as paclitaxel [68, 69]. Teraishi *et al*. [70] conducted a screening of various compounds to identify effective anti-cancer agents by targeting two lung cancer cell lines: the paclitaxel-sensitive H460 and the paclitaxel-resistant H460/TaxR. The resistance in the H460/TaxR line is linked to P-glycoprotein overproduction. Among the compounds tested, MMPT (18, **(Figure 6)**) emerged as a potent cytotoxic agent, demonstrating dose-dependent toxicity against both H460 and H460/TaxR cells, with IC50 values of 4.9 to 8.0 µM. Importantly, MMPT did not show any toxic effects in normal fibroblast or mesenchymal stem cells at these concentrations. The compound's anti-proliferative action was found to be unaffected by the levels of p53 or P-glycoprotein. Further investigations showed that MMPT induced apoptosis in cancer cells through activation of caspases 3, 8, and 9, mitochondrial cytochrome c release, and cleavage of poly-(ADP-ribose)-polymerase. In vivo studies using xenograft mice models also revealed that MMPT significantly reduced tumor growth in human H460 cells. This suggests that MMPT could be an effective anti-cancer agent that works against both P-glycoprotein-positive and -negative cancer cells [70].

In a follow-up study, Zhao *et al*. [71] examined MMPT's antineoplastic properties on the H1792 lung cancer cell line at concentrations ranging from 0.1 to 100 µM for 24–72 hours. Results from the MTT assay demonstrated a time- and dose-dependent inhibition of cell growth, which was accompanied by apoptosis, confirmed through assays like Nucleosome ELISA, H33258 staining, and Sub-G1 analysis. Further analysis showed that MMPT activated caspases 3, 6, and 8, but did not affect caspase-9. The apoptosis process was mediated by the Fas/FasL pathway, with increased expression of Fas and Fas ligands. These findings indicate that MMPT inhibits growth in H1792 cells by promoting apoptosis via the Fas/FasL pathway, positioning it as a potential agent to trigger cell death in lung cancer via these molecular mechanisms [71].

The epidermal growth factor receptor (EGFR) tyrosine kinase has been identified as a critical factor in the development of several solid tumors, particularly in breast cancer, including HER2-negative and triple-negative subtypes [72]. EGFR inhibitors such as Gefitinib and Erlotinib work by blocking the ATP-binding site in the kinase domain of EGFR and HER2, making them important therapeutic agents in cancer treatment [73].

In a study targeting EGFR, Fleita *et al*. [74] synthesized and tested a series of triazaspiro-thiazolidin-4-one derivatives (19, **(Figure 6)**) for their ability to inhibit EGFR and inhibit the proliferation of MCF-7 cells. Among the compounds tested, 19a exhibited the strongest EGFR inhibition (IC50: 6.355 µM) and moderate

antiproliferative activity (GI50: 30.6 µM). Other compounds, 19b and 19c, also showed promising antiproliferative effects with GI50 values of 10.8 µM. Structure-activity relationship (SAR) analysis indicated that the sulfur atom in the triazaspiro ring and the electron-withdrawing nitro group at the para position contributed to better EGFR inhibition, while electron-donating groups like methyl and methoxy on the benzylidene ring favored anti-proliferative effects [74].

In a separate study, Abbas and Abd El-Karim [75] examined a new series of 5-aryl-thiazolidin-4-one compounds (20, **(Figure 6)**) for their ability to inhibit EGFR kinase and their anti-cancer effects against HeLa human cervical carcinoma cells using MTT assays. Among the nineteen compounds tested, seven displayed significant activity with IC50 values ranging from 0.60 to 2.99 µM, similar to doxorubicin (IC_{50} = 1.10 µM). Compound 20a, with a 3-chlorobenzylidene moiety, was particularly noteworthy for its EGFR kinase inhibition (IC_{50} = 0.07 µM), surpassing Erlotinib (IC_{50} = 0.08 µM). Additionally, compound 20a showed strong anticancer effects against HeLa cells (IC_{50} = 2.99 µM) while exhibiting minimal toxicity to normal human cervical epithelial cells (HCvEpC) (IC_{50} = 60.12 µM). The compound was found to cause G1/S phase cell cycle arrest and to induce apoptosis in 27.11% of the HeLa cells. Mechanistic studies revealed that compound 20a increased the Bax/Bcl-2 ratio and upregulated the tumor suppressor p53 gene. Molecular docking studies suggested that compound 20a interacts with EGFR kinase-like Erlotinib [75].

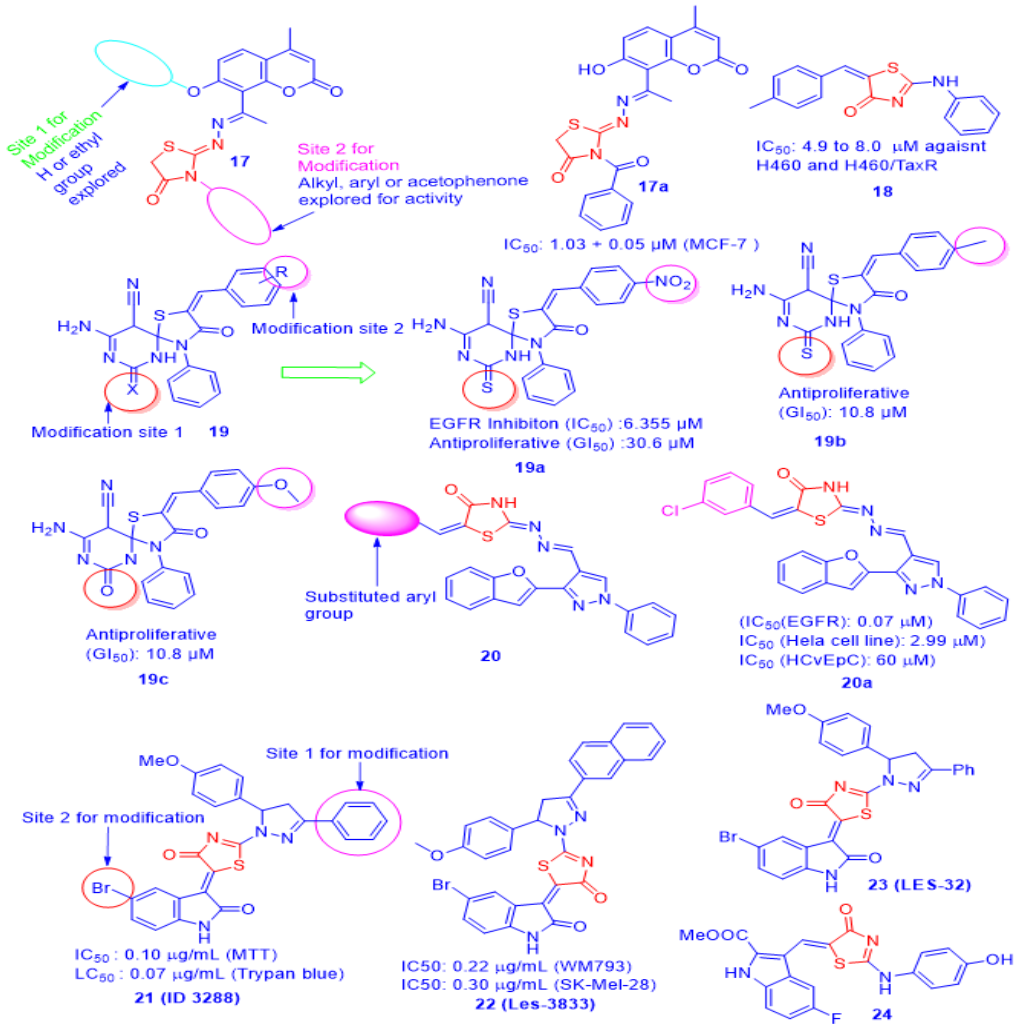


Figure 6. Thiazolidin-4-ones (17-24) with 2nd and 5th substitution as anti-cancer agents

Kobylinska *et al*. [76] investigated the cytotoxic potential of three 4-thiazolidinone derivatives linked to indolin-2-one, testing them against rat glioma C6 cells, with doxorubicin as a reference. The compounds were also evaluated for antioxidant effects and their capacity to generate oxidative stress in rat serum. Of the three tested, ID 3288 (21, **(Figure 6)**) demonstrated the most significant toxicity after 48 hours, with its activity surpassing or

matching that of doxorubicin (IC50: 0.51 µg/mL, LC50: 0.07 µg/mL) in both MTT (IC50: 0.10 µg/mL) and trypan blue assays (LC50: 0.07 µg/mL). Although the compounds caused relatively low ROS activity, their impact on key antioxidants like catalase (Cat), superoxide dismutase (SOD), and glutathione peroxidase (GPO) was weaker than doxorubicin. Consequently, ID 3288 exhibited greater anti-cancer activity in rat glioma cells compared to the control drug, doxorubicin [76].

In an extension of this study, Finiuk *et al*. [77] assessed the cytotoxic properties of compound Les-3833 (22, **(Figure 6)**) against human cancer cell lines, particularly melanoma, while also studying its pro-apoptotic effects. The results from the MTT assay showed that compound 22 was highly effective against melanoma cells (WM793 and SK-Mel-28), with IC50 values ≤ 0.3 µg/mL. Its activity against other cancer cell types such as colon (HCT116), lung (A549), ovarian (SKOV3), and breast (MCF-7) varied, with IC50 values ranging from 2.5 µg/mL to over 5.0 µg/mL. Human embryonic kidney (HEK293) cells were the least sensitive, with IC50 > 5 µg/mL. Apoptotic induction was confirmed by Annexin V/PI staining, alongside activation of caspase 3, MAPK, PARP, and EndoG proteins. Compound 22 also promoted ROS production and arrested the melanoma cell cycle at the G0/G1 phase. Therefore, it showed remarkable potency against melanoma cells, though less effective against carcinoma and leukemia cells [77].

In a related investigation, Kobylinska *et al*. [78] studied the effects of compound 22 and its derivative 23 **(Figure 6)** conjugated with PEG nanoparticles in rat glioma C6 cells. The conjugates were tested for cell cycle alterations, Annexin V expression, DNA damage, and overall cell viability. These conjugates displayed enhanced cytotoxicity at lower concentrations (0.1 and 0.5 µM), outperforming the free drug. At a concentration of 1.0 µM, only LES 3288 exhibited superior toxicity compared to its free form. DNA comet assays revealed DNA strand breaks, confirming the DNA-damaging action of the conjugates [78].

Skora *et al*. [79] synthesized a new series of thiazolidine-4-one derivatives containing indole rings and evaluated their anticancer effects against four cancer cell lines: CACO-2 (colorectal adenocarcinoma), A549 (lung carcinoma), BJ (human fibroblasts), and SH-SY5Y (neuroblastoma). The compounds reduced metabolic activity in BJ, SH-SY5Y, and A549 cells at concentrations ranging from 10 to 100 µM, with compound 24 **(Figure 6)** exhibiting particularly strong cytotoxicity in BJ, A549, and SH-SY5Y cells. This compound also demonstrated pro-oxidant activity that was time-dependent, along with increased caspase-3 activation [79].

Zhang *et al*. [80] conducted a screening of over 100 thiazolidinone-based compound combinations against human non-small cell lung cancer (H460) and its paclitaxel-resistant mutant (H460/TaxR) cells. The combination M4, which included four compounds (25a-25d, **(Figure 7)**) in equal proportions, showed remarkable synergistic effects in inhibiting the growth of both H460 and H460/TaxR cells, as well as tumor growth in xenograft mouse models. M4 demonstrated much higher anti-proliferation activity than the individual compounds and taxol itself (GI50: 0.20 µM and 0.17 µM for M4 vs. 6.2 µM and 252 µM for taxol). This combination was effective irrespective of P-gp receptors and exhibited minimal toxicity to normal fibroblast cells. Further analysis showed that M4 upregulated genes related to microtubule regulation, histone acetylation, apoptosis, and cell cycle arrest. M4-activated proteins are involved in caspase, JNK, and p38 pathways, leading to G2/M arrest and apoptosis. The results suggest that M4 has significant potential for overcoming drug resistance in cancers [80, 81].

Zeng *et al*. [82] focused on developing 4-thiazolidinone derivatives that inhibit human dihydroorotate dehydrogenase (hDHODH), an essential enzyme in pyrimidine biosynthesis. Compound 26 emerged as the most potent inhibitor, with an IC50 of 1.12 µM. Structure-activity relationship (SAR) analysis identified cyano substitutions and ester linkages at the second position of the thiazolidinone scaffold as critical for activity, while hydrophobic N-substituents, such as naphthyl or phenyl rings, further improved inhibition. Docking studies revealed that compound 26 interacts with Tyr38 and Ala55 through hydrogen bonds, suggesting possible directions for optimizing N-substitution to create more potent hDHODH inhibitors [82].

Bhat *et al*. [83] synthesized new 4-thiazolidinone-pyrazole hybrids (27, **(Figure 7)**) and tested their antimicrobial and anticancer activities. These compounds were tested against human dermal fibroblasts, melanoma, and breast cancer cell lines. Several compounds, including 27a, 27b, and 27c, showed moderate activity against human breast cancer and Ehrlich ascites carcinoma cells, with low toxicity towards fibroblasts. SAR studies highlighted halogen substitutions on the N-arylamino ring as beneficial for enhancing anticancer activity. Computational docking of compound 27c with the MDM2 target confirmed strong binding affinity, correlating well with its in-vitro anticancer effects. Molecular dynamics simulations further supported these findings [83].

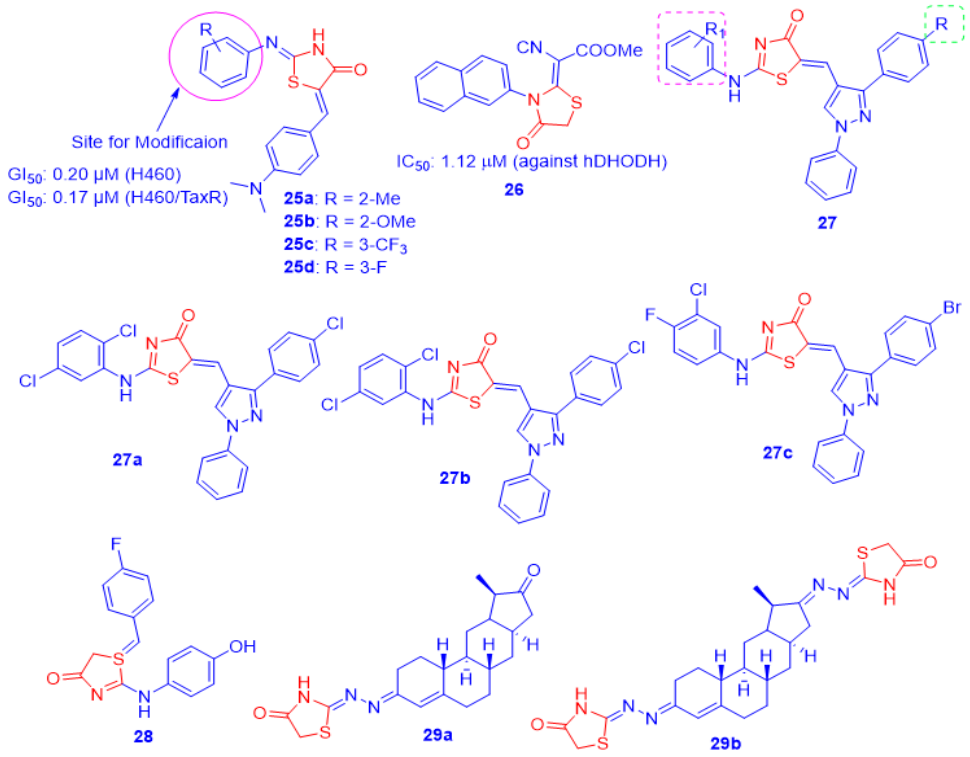


Figure 7. Thiazolidin-4-ones (25-29b) derivatives as anti-cancer agents

Thiazolidin-4-ones with first and fifth substitutions as anti-cancer agents

In a study by Szychowski *et al*. [84], the anticancer effects of 5Z-(4-fluorobenzylidene)-2-(4-hydroxyphenylamino)-thiazol-4-one (28, **(Figure 7)**) were investigated across 4 human cancer cell lines: A549, SCC-15, SH-SY5Y, and CACO-2. The compound was applied at varying concentrations (ranging from one nM to one hundred µM) over periods of 6, 24, and 48 hours. Various cellular processes were analyzed, including reactive oxygen species (ROS) generation, viability, lactate dehydrogenase release, and caspase-3 activation. The compound demonstrated a reduction in ROS levels and a decrease in cellular proliferation across all tested cell lines. Additionally, lactate dehydrogenase release was elevated, and caspase-3 activation occurred in a time-dependent manner. In SH-SY5Y cells, caspase-3 activation was observed after 6 hours of exposure, while the other cell lines showed activation after 48 hours. These findings suggest that the compound may work through PPAR γ-dependent pathways, leading to apoptosis induction in the treated cells [84].

Thiazolidin-4-ones with substitution at the second position as anti-cancer agents

Zivkovic *et al*. [85] investigated another series of thiazolidine-4-one derivatives, this time focusing on substitutions at the second position. They synthesized compounds conjugated with steroidal moieties in stereoisomeric mixtures **(Figure 7)** and assessed their cytotoxic effects. These derivatives showed varying degrees of activity, with several compounds exhibiting potent cytotoxicity against K562, HeLa, and MDA-MB-361 cell lines, and some demonstrating efficacy similar to cisplatin (21.5 µM). Notably, the compounds displayed selective toxicity, sparing normal human fibroblasts (MRC-5) and PBMCs. Two compounds, 29a and 29b **(Figure 7)**, were further examined for their mechanism of action. Both induced apoptosis in HeLa cells via both extrinsic and intrinsic pathways. Additionally, when tested at sub-toxic doses on EA.hy926 endothelial cells, these compounds inhibited angiogenesis, evidenced by their disruption of sprouting and tube formation [85].

Conclusion

The thiazolidin-4-one core structure shows significant promise as a potential anti-cancer agent. Among the various substitution patterns, the di-substituted (2nd & 3rd and 2nd & 5th) and tri-substituted (second, third, & fifth) thiazolidine derivatives are the most commonly studied for their anti-cancer properties. These compounds demonstrate heightened selectivity for cancerous tissues, possibly due to their responsiveness to the redox

environment of tumors compared to normal tissue. Numerous investigations have highlighted the potent activity of thiazolidin-4-one derivatives, often showing superior efficacy compared to standard reference drugs, alongside excellent selectivity. Some compounds have also shown potential in multi-drug resistant (MDR) cancers, especially in cases where P-glycoprotein (P-gp) overexpression confers resistance to treatments like paclitaxel. Additionally, thiazolidin-4-one derivatives have been reported to target several enzymes, including a tyrosine kinase, NF-κB, PI3K-Akt, tubulin, dihydrofolate reductase (DHFR), human dihydroorotate dehydrogenase (hDHODH), and cyclin-dependent kinases (CDKs). This body of work collectively underscores the significant anticancer potential of the thiazolidin-4-one scaffold, with the possibility that further optimization could yield promising candidates for cancer treatment.

Future perspectives

To advance these compounds as viable therapeutic candidates, further research is needed, particularly into their pharmacokinetic profiles and metabolic stability. The reactivity of sulfur in the tumor microenvironment may contribute to the high selectivity of this nucleus, but additional molecular-level investigations are required to confirm this. Furthermore, many studies have yet to identify the precise molecular targets of the compounds, making it crucial to explore these targets in future research. This knowledge would be invaluable in facilitating the identification of appropriate targets and accelerating the optimization of lead compounds.

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