

## ANTICANCER POTENTIAL OF COMPOUNDS BEARING THIAZOLIDIN-4-ONE SCAFFOLD: COMPREHENSIVE REVIEW

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### ABSTRACT

Thiazolidin-4-ones is a versatile and privileged nucleus comprising of a five five-membered heterocyclic ring system possessing sulphur heteroatom and a cyclic amide bond. Extensive research and review studies mainly published in the last decade explored the diverse types of biological activities of this nucleus with potential therapeutic applications. Various silent features like drug likeness behaviour, suitability for diversity-oriented synthesis, and its sensitivity toward the redox tumour microenvironment makes it an attractive scaffold for anti-cancer drug discovery. Thiazolidine-2,4-dione and thiazolidine-4-ones are the two classical variants of thiazolidine scaffold, the former is more explored in comparison to thiazolidine-4-one. However, thiazolidine-4-one nucleus is also getting the attention of researchers, evident by the various research studies, mainly published in the last few years.

The current comprehensive review focuses on its anti-cancer potential, covering structural diversity and substitution patterns among diverse derivatives containing this nucleus as a core skeleton. This review also gives impetus to the different enzymatic targets, exploited for drug discovery, relative selectivity in cancerous tissue compared to healthy counterpart cells, structure-activity relationship (SAR), and future perspectives for translational research. To generate potential lead candidates with the translational outcome next level studies like pharmacokinetic and metabolic stability are suggested.

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### Introduction

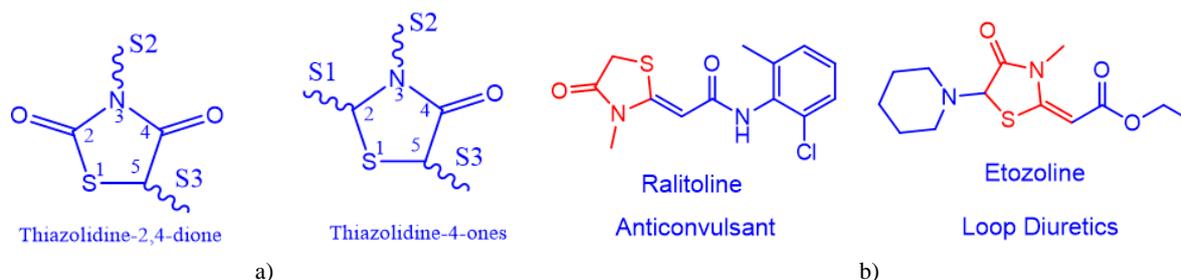
Cancer is a leading cause of death all over the globe, causing around 10 million deaths alone in the year 2020 [1-3]. Among its diverse types, breast and lung cancer are among the most commonly reported forms, while lung and colon-rectum cancer are the top killers with 1.80 and 0.916 million annual deaths, respectively in the year 2020 [4]. Health statistics reported cancer is the second most common cause of death worldwide after cardiovascular diseases [5]. Several factors like continuous rise in the number of cancer cases, emerging incidences of multidrug resistance, relapse cases, high cost of the therapy, associated side effects, poor selectivity, etc., continuously demand the discovery of novel, effective, economic drugs with better safety profile, which can also strengthen our existing chemotherapy pipeline [6-10].

Thiazolidine is an important and privileged scaffold in medicinal chemistry, consisting of a five-membered heterocyclic ring system possessing sulphur and a cyclic amide bond [11-13]. Extensive research studies explored the diverse types of biological activities of this nucleus with potential therapeutic applications [14, 15]. Thiazolidinedione and thiazolidine-4-ones are two classical variants of this nucleus that have been extensively explored in medicinal chemistry [16-18].

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Thiazolidinedione consisting of diketo groups at the 2nd and 4th position has been extensively reported for diverse types of biological activities, particularly for anti-diabetic and anti-cancer activities [19-21]. Bulky substitution at the 5th position of 2,4-thiazolidinediones is an important class of anti-diabetic drugs with approved drug candidates like rosiglitazone and pioglitazone. Mechanistically, these drugs show hypoglycaemic action via agonizing activity at PPAR $\gamma$  receptors [22, 23]. Although, thiazolidine-2,4-diones has been more extensively investigated for pharmacological potential, in comparison to thiazolidine-4-one which is slightly less explored. However, this nucleus is also getting the attention of researchers, evident by the various research and review studies published on this nucleus in the last decade [18, 24-27].

Structurally, thiazolidine-4-ones is more versatile for structural modification, since it possesses three sites (S1, S2, S3, (**Figure 1a**)) compared to thiazolidine-2,4-dione, having only two sites available for modification (S1, S3, (**Figure 1a**)). For the diversity-oriented synthesis and structure modification, the former i.e thiazolidine-4-one is a more suitable candidate compared to the thiazolidine-2,4-dione. Moreover, in a few instances, the thiazolidine-4-one nucleus with different oxidation states of sulphur atom is also explored for anti-cancer activity [27].



**Figure 1.** 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).

Though few review studies are reported on the synthesis and biological spectrum of thiazolidine-4-one nucleus [24, 25, 28], however extensive search of published literature revealed that no review studies have been published exclusively on the anti-cancer potential of this scaffold. In the present review, we systematically and comprehensively cover the anti-cancer activity of compounds constituting this nucleus. We systematically retrieved published research studies on this nucleus from various databases like PubMed, Google Scholar, and all reputed publication houses, subsequently arranged them systematically, analyzed and discussed the key finding pertaining to their substitution pattern, the array of anti-cancer studies, including *in-vitro*, *in-vivo*, SAR, computational and mechanistic studies. In addition to this, we also discussed the key bottlenecks in translational research and future perspectives of this scaffold.

#### Approved Drugs Based Upon Thiazolidine-4-One Scaffold

Ralitoline (RLT) is a thiazolidinedione-based drug (**Figure 1b**) that showed potent anticonvulsant activity in pre-clinical and clinical studies in different seizure models. Compared to other approved antiepileptic drugs such as sodium valproate, phenytoin, and diazepam, ralitoline is a rapid onset of action (within 2 minutes) with better anticonvulsant action in electroshock seizures (MES) models. Mechanistically, the drug blocks the rapid and sustained firing of sodium action potentials without affecting the glutamate and iontophoretic GABA responses [29].

Etozoline is a loop diuretic (**Figure 1b**) that also contains a thiazolidine-4-one nucleus, clinically used to treat hypertension and edema of mild to moderate grade. Etozolin is sold in Europe under different trade names like Etopinil, Diulozin, Elkapin, etc. The exact mechanism of this drug is still not known [30].

#### Substitution Pattern of Thiazolidine-4-One Reported as Anti-Cancer Agents

Upon systematic arrangement of reported thiazolidine-4-one scaffolds as anti-cancer agents from 31 reported research studies (discussed in the present review), revealed diverse substitution patterns and confirmed the versatility of this nucleus. Modifications at different sites, documented mono substitution at a single position (2<sup>nd</sup>), di-substitution at three positions (1<sup>st</sup>, 3<sup>rd</sup>, 2<sup>nd</sup>, 3<sup>rd</sup> and 2<sup>nd</sup>, 5<sup>th</sup>), and tri-substitution pattern at two positions (1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup> and 2<sup>nd</sup>, 3<sup>rd</sup>, 5<sup>th</sup>) among the cited literature. Further analysis reveals a di-substitution pattern at 2<sup>nd</sup>, 3<sup>rd</sup>, and 2<sup>nd</sup>, 5<sup>th</sup> reported in 9 and 11 research studies while tri-substitution (2<sup>nd</sup>, 3<sup>rd</sup>, 5<sup>th</sup>) reported in 8 studies. Overall, thiazolidine-4-one nucleus with substitution at the 2<sup>nd</sup>, and 5<sup>th</sup> positions is reported in the highest number of studies. Key research findings of the thiazolidine-4-one-based scaffolds as an anti-cancer agent are systematically synchronized and discussed based on their substitution pattern.

#### Tri-Substituted Thiazolidine-4-One Derivatives as Anti-Cancer Agents

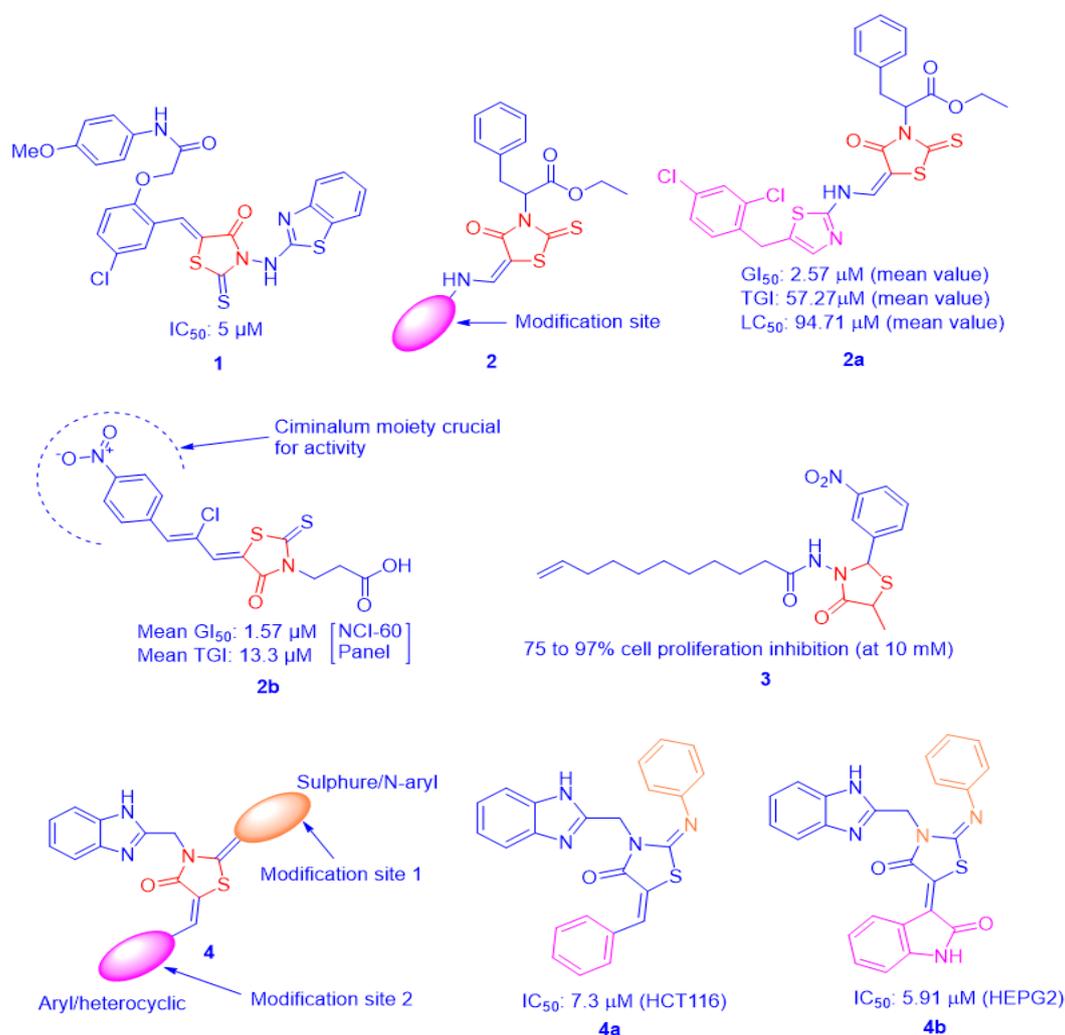
##### Anti-Cancer Potential of Thiazolidine-4-One with Substitution at 2<sup>nd</sup>, 3<sup>rd</sup> and 5<sup>th</sup> Position

Panchuk *et al.* [31], designed and synthesized three heterocyclic compounds constituting thiazolidine-4-one nucleus with substitutions at the 3rd and 5th positions with thio and the 2<sup>nd</sup> position (**Figure 2**). Compounds were screened for cytotoxicity, investigated the underlying mechanism of apoptosis and protein expression using the Western-blot analysis. All three compounds showed almost similar moderate *in-vitro* cytotoxicity potential against breast cancer (MCF-7, MDA-MD-231) and

leukemia (Jurkat, CCRF-CEM) cell lines. Mechanistic studies illustrated that three compounds induced apoptosis via two different mechanisms: receptor-mediated mitochondrial apoptosis and caspase-independent (AIF-mediated apoptosis). The best cytotoxic compound bearing a 4-thiazolidine nucleus (1, (**Figure 2**)) exhibited cytotoxicity with  $IC_{50}$ : 5  $\mu$ M against the tested breast and leukemia cell lines via receptor-mediated mitochondrial apoptosis [31, 32].

Extending work on core scaffold 2-thioxothiazolidin-4-one nucleus 2 (**Figure 2**) Holota *et al.* [26] synthesized and screened two series of compounds against the 59 human cancer lines belonging to nine different types of cancers viz. Colon, Leukemia, NSC lung, Melanoma, CNS, Breast, Ovarian, Prostate, and Renal. Compounds were initially screened at the concentration of 10  $\mu$ M, in which compound 2a (**Figure 2**) displayed significant anti-cancer activity at the tested concentration. Compound 2a was further studied by determination of the growth inhibition ( $GI_{50}$ ), total growth inhibition (TGI), and lethal concentration ( $LC_{50}$ ), mean values were found to be 2.57, 57.27, and 94.71  $\mu$ M, respectively [26].

To discover the potential anticancer agent, Buzun *et al.* [33] synthesized another series of 2-thioxothiazolidin-4-one conjugated with ciminalum and screened them against the selected cell lines of NCI-60 panel, namely, human colon cancer (DLD-1), gastric cancer (AGS), and breast cancer (MCF-7 and MDA-MB-231). Compounds were screened according to the standard protocol at different concentrations ranging from  $10^{-4}$  to  $10^{-8}$  M for 48 h of exposure using SRB protein assay. Among the series, compound 2b (**Figure 2**) was found to be active with mean  $GI_{50}$  1.57  $\mu$ M and mean TGI 13.3  $\mu$ M against the tested cell lines. Moreover, against a few selected cancer cell lines like CNS cancer (SF-539), melanoma (SK-MEL-5) colon cancer (SW-620), and leukemia (MOLT-4, SR), the value of  $GI_{50}$  remained in the low nanomolar range (< 20 nM). Compound 2b showed low toxicity against the normal human blood lymphocyte with an excellent selectivity index (SI) > 376.14 for leukemia panel cell lines. The SAR studies illustrated ciminalum moiety (at the 5<sup>th</sup> position of 4-thiazolidinone) crucial for the activity [33].



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

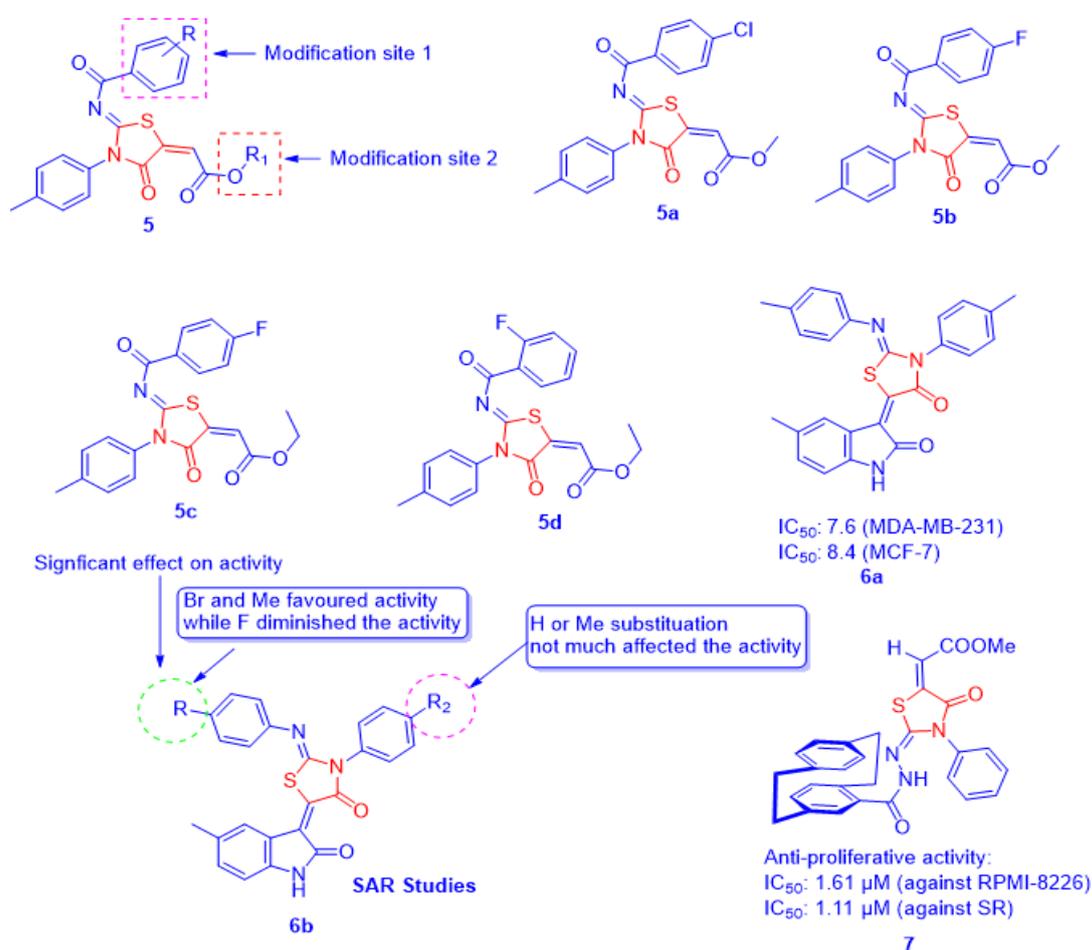
Rahman *et al.* [34] reported the synthesis, stereochemistry, and anticancer activity of thiazolidine-4-one-based series bearing long alkyl amide chain substitution. Some representative compounds were *in-vitro* evaluated for antitumor activity against three types of human cancers; breast (MCF7), lung (NCI-H460), and CNS (SF-268), in which compound 4 showed significant cytotoxic activity against all three cell lines. Further, compound 4 (**Figure 2**) was tested against several other cell lines like leukemia, non-small cell lung cancer, colon cancer, melanoma, ovarian cancer, renal cancer, prostate cancer, and breast cancer,

in which it showed significant activity against lung, melanoma and renal cancer, reducing growth by 75%, 97%, and 84% respectively, at the concentration of 10 mM [34].

Enzyme Arylamine N-acetyltransferase (NAT) has a vital role in the detoxification and metabolism of certain drugs, food components, organic compounds, and carcinogens via acetylation of the free amine group [35, 36]. Several studies illustrated the role of NATs in the growth of cancer cells and proposed its inhibition as the rational approach to cancer drug discovery [37, 38].

Masoud *et al.* [39] synthesized a series of compounds containing iminothiazolidin-4-one conjugated with benzimidazole nucleus varying substitution at the two positions (4, (**Figure 2**), targeting NAT1. Subsequently, compounds were screened for anti-cancer and anti-proliferative activity. Two derivatives of 2-phenylimino-4-thiazolidinone derivatives (4a and 4b) exhibited encouraging *in-vitro* anti-proliferative activity against human colon carcinoma (HCT 116) and human hepatocellular carcinoma (HEPG2) cell lines, respectively, while six compounds showed moderate activity against breast adenocarcinoma (MCF7 cell lines). Molecular docking studies of top active compounds showed significant binding affinity towards human N-acetyl transferase at the NAT1 binding pocket [39].

Mahmoodi *et al.* [40] synthesized a novel series of fourteen compounds containing 1,3-thiazolidine-4-ones via the cycloaddition of *N*-aryl-*N'*-acyl thioureas with acetylenic esters using solvent-free microwave irradiation (5, (**Figure 3**)). Synthesized compounds were evaluated for the anticancer activity against the MKN-45 gastric adenocarcinoma cells using MTT colorimetric assay. Several compounds of the tested series displayed significant anti-cancer activity, particularly compounds 5a, 5b, 5c and 5d displayed IC<sub>50</sub> below 10 μM against the tested cell lines [40].



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

Structural analog of isatin, specially oxindole moiety recognized as privileged for anti-cancer drug discovery, afforded several approved drug candidates as well as lead compounds [41-43]. Naggar *et al.* [44] designed and synthesized two series of compounds based upon thiazolidinone-isatin and thiazolo-[3,2-a]-benzimidazolone-isatin. Compounds were tested for antiproliferative activity against two breast cancer cell lines (triple negative MDA-MB-231 and MCF-7). Compounds of the series exhibited moderate (IC<sub>50</sub> > 100 μM) to good activity (IC<sub>50</sub> < 10 μM) anticancer activity against both the tested cell lines. Compound 6a emerged as the best active compound with IC<sub>50</sub> of 7.6 and 8.4 μM against the MDA-MB-231 and MCF-7 cell lines, slightly weaker compared to reference drug Sunitinib (IC<sub>50</sub> of 5.5 and 3.4 μM, respectively.) Up-regulation level of Bax, caspase-3, while down-regulated Bcl-2 in compound 6a treated MDA-MB-231 cells evident the apoptosis. Cell lines treated

with compound 6a exhibited four times enhancement at Sub-G1 and 2.5 times in G2-M phase arrested cells. Furthermore, annexin V-FITC positive apoptotic was found to be six times higher in compound 6a treated MDA-MB-231 cells compared to the control group. Compound 6a also displayed good selectivity (SI: 9.6) in non-tumorigenic breast MCF-10A cell lines [44]. The structure-activity relationship study of the reported scaffold was depicted in **Figure 3**.

Aly *et al.* [45] synthesized and characterized six paracyclophanyl thiazolidinone-based compounds, subsequently screened against different 60 cancer cell lines. Compound 7 (**Figure 3**) showed comparatively better anti-cancer activity overall compared to the rest of the series, especially against two cell lines of leukemia (RPMI-8226 and SR). All the compounds exhibited anti-proliferative activity against RPMI-8226 and SR with IC<sub>50</sub> values of 1.61  $\mu$ M and 1.11  $\mu$ M, respectively. In mechanistic studies, compound 7 exhibited potent tubulin inhibitory activity (IC<sub>50</sub>: 4.97  $\mu$ M), almost compared to colchicine (IC<sub>50</sub>: 3.76  $\mu$ M). To study the apoptosis, the level of Caspase-3, Bcl-2 and BAX was quantified by the appropriate *in vitro* assay system. Caspase-3 is a well-documented apoptosis effector, and its activation indicates irreversible cell apoptosis. The relative abundance of Bcl-2 and Bax, two well-known anti-apoptotic and apoptotic proteins respectively, decide the cell apoptosis pathways [45]. An assay performed using annexin V-FITC staining to determine the level of Caspase-3, BAX, and Bcl-2 for compound 7, confirmed significant pro-apoptotic activity. Based upon the docking studies, the putative binding site of compound 7 was found to be the same as that of standard colchicine, and also shared several common interaction patterns [46].

#### *Anti-Cancer Potential of Thiazolidine-4-Ones Having a Different Oxidation State of Sulphur with Substitution at the 3<sup>rd</sup> and 5<sup>th</sup> Position*

Gududuru *et al.* [47] reported the synthesis of new series of thiazolidine-4-ones having sulphur in different oxidation states, having substitutions at the 2<sup>nd</sup> and 3<sup>rd</sup> positions (8, (**Figure 4**)). Compounds were subsequently evaluated for the growth inhibitory activity against five human prostate cancer cell lines (DU-145, PC-3, LNCaP, PPC-1, and TSU) and negative control (RH7777) cell lines.

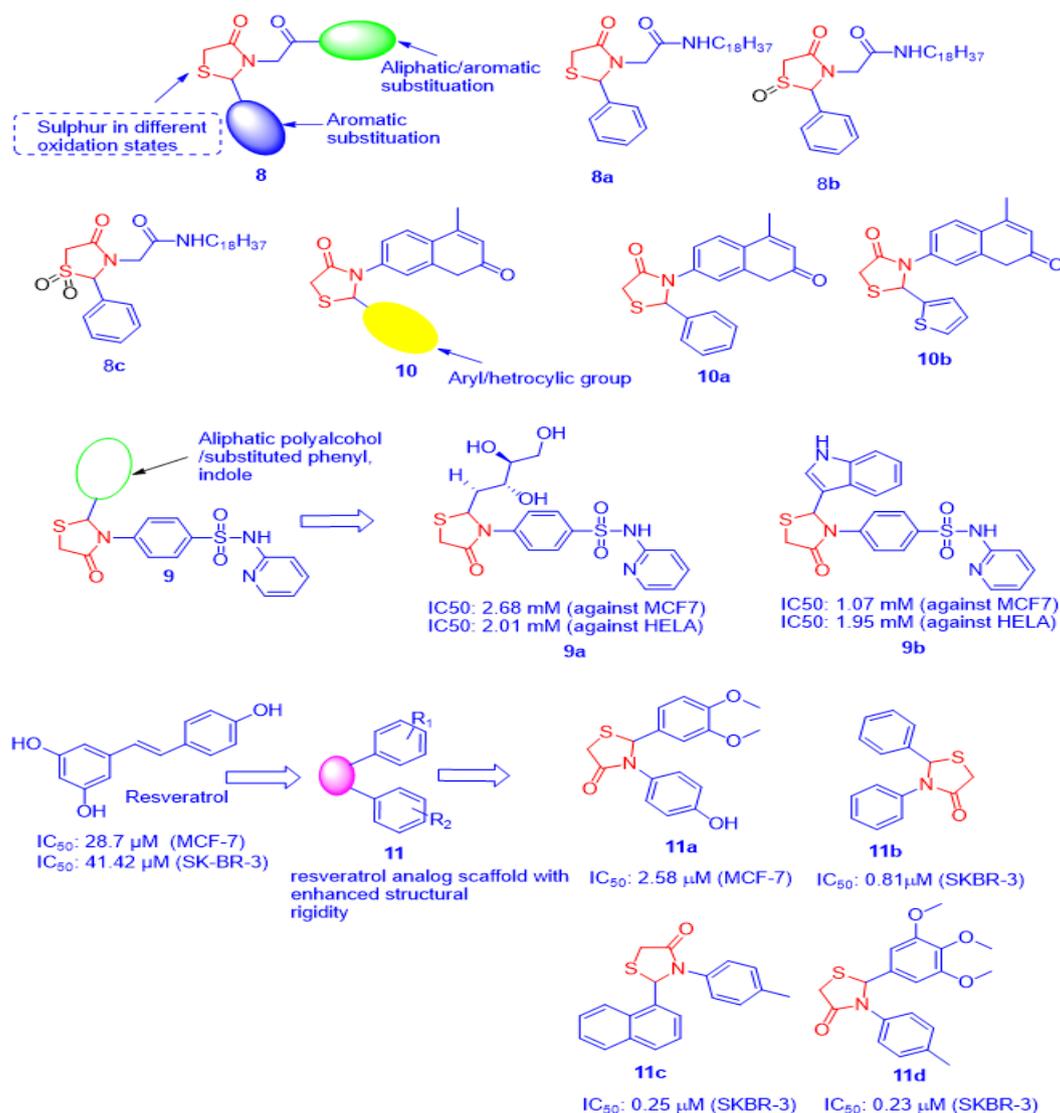
Among the tested series, three compounds (8a, 8b, 8c, (**Figure 4**)), showed significant anti-proliferative activity with IC<sub>50</sub> in low micromolar concentration against the tested cell lines and showed around 2-5 fold lower cytotoxicity towards RH7777 cell line. SAR studies demonstrated that the presence of a 2-aryl ring at the 2<sup>nd</sup> position and a long chain amidic chain at the 3<sup>rd</sup> position is crucial for antiproliferative activity. Oxidation of sulphur to a higher oxidation state did not significantly affect the activity of compounds. Further, the author recommended additional optimization studies to achieve compounds of better potency and selectivity [47].

#### *Anti-Cancer Potential of Di-Substituted Thiazolidine-4-Ones Derivatives*

##### *Thiazolidin-4-Ones with 3<sup>rd</sup> and 5<sup>th</sup> Substitution as Anti-Cancer Agents*

Kamel *et al.* [48] synthesized diverse types of compounds, including two series of compounds comprising of the thiazolidine-4-one nucleus with substitution at the 3<sup>rd</sup> and 5<sup>th</sup> positions (9, (**Figure 4**)). The titled compounds were evaluated for anti-cancer activity against MCF7 and HELA cell lines, in which compounds bearing *N*-(pyridin-2-yl)-benzenesulfonamide substitutions (9a and 9b) showed potent *in-vitro* anti-cancer activity against MCF7 and HELA cell lines with IC<sub>50</sub> < 3  $\mu$ g/ml even superior to the reference drug doxorubicin (IC<sub>50</sub>: 6.71 and 8.72  $\mu$ g/ml, respectively). Particularly, 9b compound bearing indole nucleus at 1<sup>st</sup> position of thiazolidine ring showed slightly better activity with IC<sub>50</sub> < 1.95  $\mu$ g/ml against both tested cell lines compared to compound 9a. Based on the docking studies, authors proposed protein-tyrosine kinase as a probable target of the titled compounds [48].

The role of Nuclear factor- $\kappa$ B, also known as NF- $\kappa$ B has been established in chronic inflammation and increased cancer risk [49]. Drugs inhibiting or suppressing the NF- $\kappa$ B are found to be active against certain cancers and reported to the reduction in inflammation [50, 51]. Targeting the active site of NF- $\kappa$ B, Suthar, *et al.* [52] designed a library of compounds containing quinolone-substituted thiazolidine-4-ones (compound 10, (**Figure 4**)) and *in-silico* screened them against the target via molecular docking analysis. Furthermore, the best-scoring 31 compounds were synthesized and subsequently evaluated for anticancer activity against different human cancer cell lines, namely, COLO- 205, BT-549, ACHN, and HeLa. Compounds 10a and 10b showed significant toxicity with IC<sub>50</sub> values ranging from 31.38-78.86 and 20.73-44.711  $\mu$ g/ml, respectively against all four tested cell lines. To study the mechanistic aspects of cytotoxicity, m-RNA expression studies were performed using RT-PCR, which revealed that both compounds 10a and 10b significantly up-regulated pro-apoptotic protein Bcl-2 and down-regulated Bax which is an anti-apoptotic conductor. Up-regulated Bcl-2 level while down-regulated Bax resulted in cell death via apoptosis mediated by the release of mitochondrial cytochrome c. Antitumor activity of compounds 10a and 10b were also confirmed *in-vivo* by Ehrlich ascites carcinoma studies [52].



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

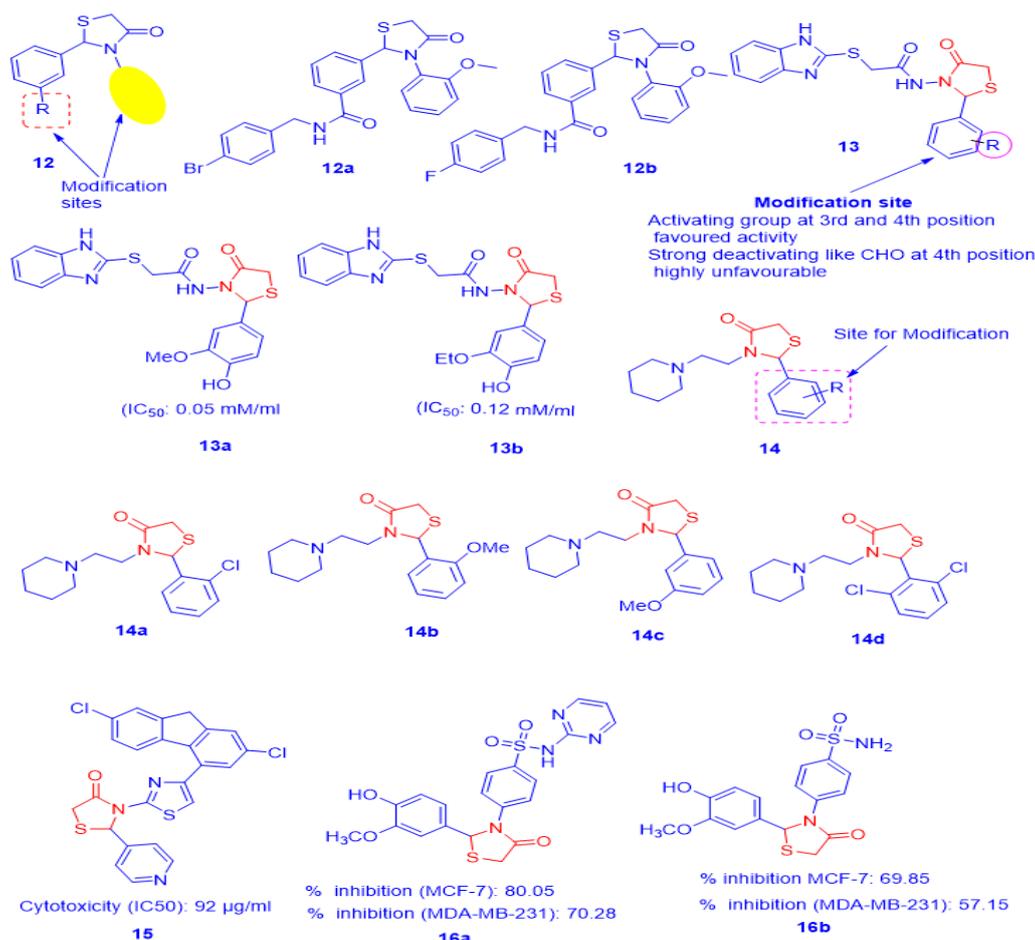
Resveratrol (RSV) has been reported for cancer prevention and its anticancer properties [53, 54] but its clinical application is limited by its low bioavailability and rapid clearance from the circulation [55]. Sala *et al.* [56] designed a series of thiazolidinone-based compounds by taking structural features from RSV, aiming to enhance its bioavailability and structural rigidity. In particular, a library of twelve derivatives in which thiazolidinone nucleus connected with two aromatic rings (compound 11, (Figure 4)) was synthesized, and subsequently evaluated the series against MCF-3 and SK-BR-3 (overexpressing Her2). Compound 11a of the series showed low micromolar potency (IC<sub>50</sub>: 2.58 μM) against the tested MCF-7 while three compounds (11b to 11d) exhibited potent activity against SK-BR-3 cell lines with IC<sub>50</sub> < 0.5 μM). The potency of the four compounds was found to be significantly higher than the reference compound resveratrol (IC<sub>50</sub>: 28.7 and 41.42 μM) against the MCF-7 and SK-BR-3 cell lines, respectively. The study concluded that thiazolidine-4-one-based resveratrol derivatives as newer potent possible drug candidates against human breast cancer which can be explored further [56].

Wu *et al.* [57] synthesized a series of 2,3-diaryl-4-thiazolidinone derivatives (compound 12, (Figure 5)) and tested their antiproliferative activity against human lung cancer (A549) and breast cancer (MDAMB-231) cell lines. SAR studies on the series revealed that 2-(3-(arylalkyl amino carbonyl)-phenyl)-3-(2-methoxy-phenyl)-4-thiazolidinone derivatives were potent inhibitors of both the tested cancer cell lines. Compounds with potent antiproliferative activities were also evaluated for cell migration on MDA-MB-231 cells using two different migration assays, among which a few compounds showed excellent migration inhibition activity with IC<sub>50</sub>: 0.05 mM. Compounds 12a and 12b of the series showed potent anti-proliferative activity with sub-micromolar potency against A549 and MDA-MB-231 cell lines. Both compounds also showed anti-migration activity in the nanomolar range (IC<sub>50</sub>: 0.01-0.05 μM) in wound healing as well as trans-well migration models. Further *in-vivo* studies of compound 12a in two animal models revealed its ability to inhibit tumor growth, and metastasis and enhanced the survival rate as compared to the control group [57].

A series of benzoimidazol-thiazolidinone (scaffold 13, (Figure 5)) was synthesized and *in-vitro* tested for antimicrobial and anticancer activity against human colorectal (HCT116) cell lines. The majority of compounds showed significant cytotoxic

activity against the tested cell lines, particularly, the best active compounds 13a and 13b showed excellent potency ( $IC_{50}$ : 0.05 and 0.12 mM/ml, respectively) even better than the reference drug fluorouracil ( $IC_{50}$  = 6.15 mM/ml). Docking studies reported using the best active compounds against cyclin-dependent kinase-8 showed strong binding affinity [58].

Glioblastoma multiforme (GBM) is a common and aggressive brain tumor that is frequently reported for resistance to radiation as well as chemotherapy [59, 60]. Silveira *et al.* [61] synthesized sixteen compounds containing 2-aryl-3-((piperidin-1-yl)-ethyl)-thiazolidin-4-ones (14, (**Figure 5**)) and tested them against glioblastoma. Among the series, thirteen compounds reduced the viability of glioma cells in the range of 30 to 65% at the tested 100  $\mu$ M concentration compared to the control. Four compounds of the series (14a, 14b, 14c, and 14d) reduced the viability of cells greater than 50% and were further tested at low concentrations, which confirms cell death due to necrosis and later by apoptosis mechanism. Surprisingly, all compounds showed good selectivity without showing significant toxicity against the primary astrocytes used as a non-transformed cell model. Further results demonstrated, the four best active thiazolidine-4-one derivatives (14a, 14b, 14c, and 14d) reduced the *in-vivo* glioma growth as well as malignant characteristics tested in the male Wistar rats without inducing mortality or peripheral damage to animals. Best active compounds also altered the metabolism of nitric oxide which may be associated with reduced growth and malignancy characteristics of gliomas [61].



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

Dihydrofolate reductase (DHFR) inhibition is well documented as a druggable target with approved drugs for treating microbial infections and as anticancer therapeutics [62, 63]. Targeting DHFR, Hussein *et al.* [64] synthesized a series of compounds, comprising azetidinone and thiazolidinone conjugated with thiazole moiety (**Figure 5**), and screened them for anti-cancer activity against human lung carcinoma (A549), lung fibroblast (WI-38) and breast carcinoma (MDA-MB-231) cell lines. The majority of the compounds of the thiazole-based series exhibited weak to moderate activity against all three tested cell lines, except compound (15, (**Figure 5**)), which showed relatively better cytotoxic activity against human lung carcinoma with  $IC_{50}$ : 92  $\mu$ g/ml. Mechanistic studies were also performed using fluorescence-activated cell sorting (FACS) analysis and molecular docking study illustrated dihydrofolate reductase enzyme as the probable target of the titled compounds [64].

Kadhim *et al.* [65] synthesized two thiazolidine-4-one derivatives (compounds 16a, and 16b, (**Figure 5**)), and subsequently screened them for anti-microbial, anti-cancer, and hemolytic activity. Anti-cancer activity of the compounds was tested against triple-negative breast cancer (MDAMB-231) and MCF-7 (ER+, HER2+, and ER+) cell lines.

The outcome of cytotoxicity studies evaluated by the MTT assay revealed that compounds 16a and 16b inhibited  $80.05 \pm 1.72$  and  $69.85 \pm 3.26$  % growth of MCF-7 cell lines, respectively, after 72 h at the tested concentration of 100  $\mu$ g/ml. Under similar

conditions, % growth inhibition of MDA-MB-231 cell lines was found to be slightly less (70.28 and 57.15), respectively, compared to MCF-7 cell lines. RBCs' hemolysis effect of both compounds was found to be less than 4% up to the highest tested concentration of 3 mg/ml, indicating their preliminary estimation of *in-vivo* safety. Results of docking studies confirm the firm binding affinity of both compounds with ER $\alpha$ , VEGF, and HER2 receptors, which complied with *in-vitro* results. Overall, the cytotoxicity of compound 16a was found to be better against MCF-7 cells, than compound 16b and even the reference drug tamoxifen [65].

The phosphoinositide 3-kinase (PI3K)-protein kinase B (Akt) pathway controls various cellular functions and plays a key role in cell proliferation regulation and survival. De-regulation in this pathway due to genetic and epigenetic alteration is approximately associated with 30% of all cancer types, mainly, breast, stomach, brain, colon, liver, and lung cancer. Targeting this pathway for novel anti-cancer drug discovery has been a good rational and well-established approach [66, 67].

Targeting the PI3K-Akt pathway, Abdelnaby *et al.* [68] synthesized two series of compounds by molecular hybridization of coumarin with thiosemicarbazone and thiazolidine-4-one moieties (**Figure 6**). In the *in-vitro* anticancer screening against MCF-7 cells lines (via MTT assay), nine compounds displayed encouraging cytotoxicity, especially, compound 17a displayed promising cytotoxicity with IC<sub>50</sub>: 1.03 + 0.05  $\mu$ M. Further in pro-apoptotic studies, cell cycle arrest in the S-phase was confirmed upon treatment with compound 17a, with increased apoptosis rates up to 5 and 100-fold in early and late stages, respectively. Moreover, 8 times enhancement in caspase-9 level in compound 17a treated cells confirms the caspase-9 induced apoptosis. Mechanistic studies based upon enzyme inhibition revealed the PI3K- $\alpha$ /Akt-1 axis as the target of the tested compounds, further confirmed by Western blot which evident the repressing levels of p-PI3K, Cyclin D1, and p-Akt computational studies illustrated the high binding affinity of compound 17a with PI3K binding site even superior to reference ligands X6K. The overall study proposed compound 17a as a potential anti-cancer against breast cancer by targeting PI3K/Akt axis, which can be further investigated [68].

#### *Thiazolidin-4-Ones with 2<sup>nd</sup> and 5<sup>th</sup> Substitution as Anti-Cancer Agents*

Overexpression of P-glycoprotein (P-gp), a member of ABC transporters, is well-studied drug transporter that confers resistance towards several drugs including the blockbuster anti-cancer drug paclitaxel [69, 70]. Teraishi *et al.* [71] screened a library of compounds to search for potential anti-cancer compounds against two lung cancer cell lines (paclitaxel-sensitive H460 and paclitaxel-resistant cell H460/TaxR). H460/TaxR cell line resistance against the paclitaxel is associated with overexpression of P-glycoprotein. Among the screened library, MMPT (18, (**Figure 6**)) was identified as a potential cytotoxic compound that showed toxicity in a dose-dependent manner against tested H460 and H460/TaxR cell lines with IC<sub>50</sub>: 4.9 to 8.0 micromolar, respectively. Interestingly, no cytotoxic effect of MMPT was observed in normal fibroblast and mesenchymal stem cells at the above concentration range. Interestingly, the anti-proliferative effect of compound 18 in lung cancer cells was not affected by the expression level of p53 and P-glycoprotein. Further study confirmed apoptosis in tested cells upon the exposure of MMPT, induced by the icaspase-3, -8, -9, mitochondrial release of cytochrome c and cleavage of poly-(ADP-ribose)-polymerase. Furthermore, compound 18 upon *in vivo* administration significantly suppressed tumor growth (human H460) in xenograft nude mice. The overall study proposed compound 18 (MMPT) as the selective anti-cancer agent which retained efficacy against the P-glycoprotein-negative as well as positive cancer cells [71].

Continuing a study on MMPT, Zhao *et al.* [72] evaluated its antineoplastic activity against a lung cancer cell line (H1792) at different concentrations (0.1–100  $\mu$ M) for a period of 24-72 h. In the MTT assay, compound MMPT exhibited growth inhibition in a time-dependent as well as dose-dependent manner. This effect was accompanied by apoptosis, evident by Nucleosome ELISA, H33258 stained assay, and Sub-G1 analysis. The study demonstrated that compound MMPT caused the activation of caspase-3, caspase-6, and caspase-8, without affecting caspase-9. MMPT-induced apoptosis in treated cells through a membrane-mediated mechanism was supported by the up-regulated expression of Fas (CD95/APO-1), and Fas ligand. The overall study demonstrated, MMPT-induced growth inhibition of H1792 cells through a Fas-mediated and caspase-dependent apoptosis pathway, which suggested that MMPT might be used as a Fas/FasL and caspases promoter to initiate lung cancer cell apoptosis [72].

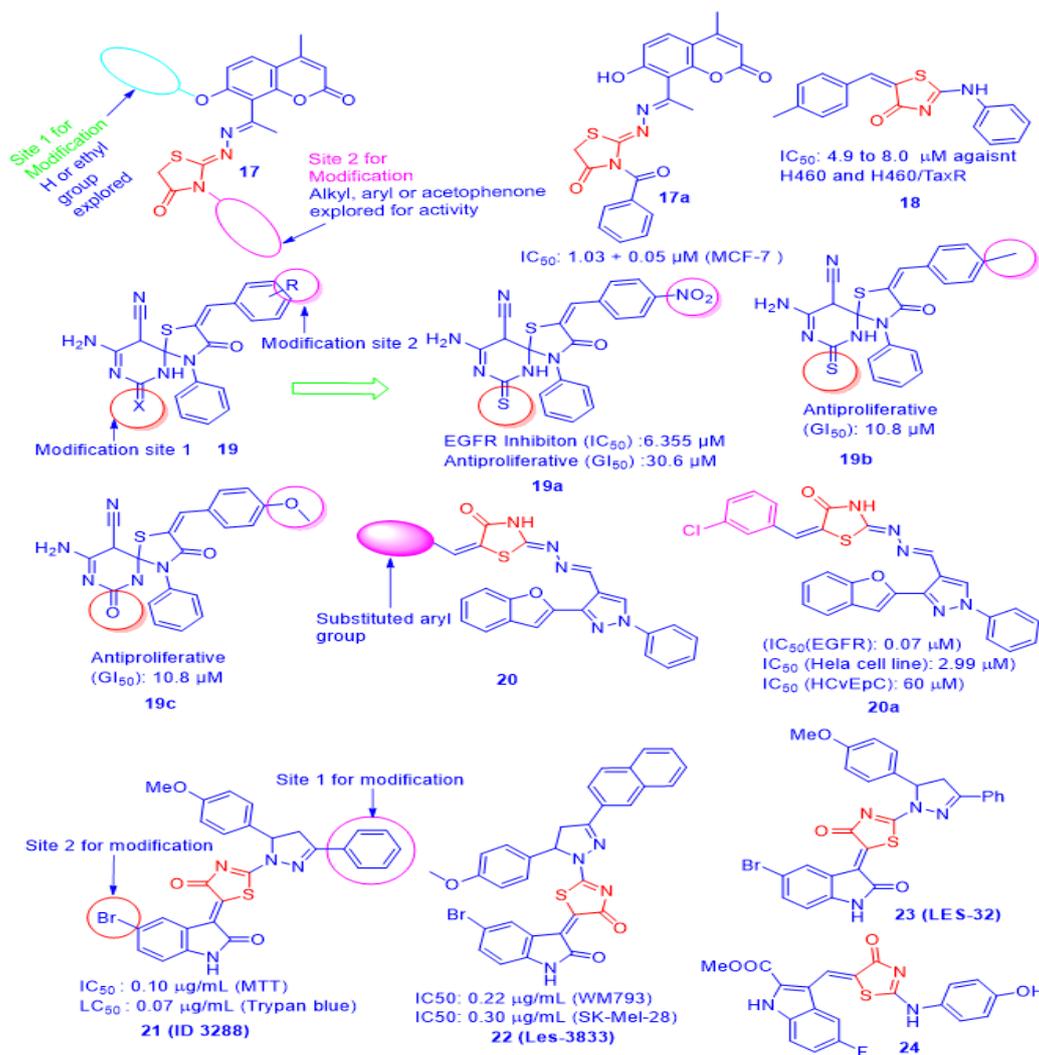
In the development of certain types of solid tumors, EGFR tyrosine kinase is reported to play an important role, particularly because it is an attractive target for breast cancer [73] (Including TNBCs and HER2-negative breast cancer). Clinically approved tyrosine kinase inhibitors like Gefitinib and Erlotinib are important chemotherapeutic agents that act by blocking the ATP binding pocket of the EGFR and HER2 kinase domain [74].

Targeting the EGFR, Fleita *et al.*, [75] designed and synthesized a series of triazaspiro-thiazolidin-4-one-based compounds (19, (**Figure 6**)), subsequently evaluated for *in-vitro* EGFR inhibition and antiproliferative activity against MCF-7 cell lines. Among thirteen compounds, compound 19a showed the best inhibition against EGFR (IC<sub>50</sub>: 6.355  $\mu$ M) with moderate antiproliferative activity (GI<sub>50</sub>: 30.6  $\mu$ M) against MCF-7 cell lines. Compounds 19b and 19c showed superior growth inhibition of MCF-7 cell lines with a GI<sub>50</sub> value of 10.8  $\mu$ M. In SAR studies, sulphur substitution at the triazaspiro ring and strong electron-withdrawing nitro group at the *para* position favored the EGFR inhibition while electron donating groups like methyl and methoxy at the benzylidene ring, favored anti-proliferative activity [75].

Targeting EGFR kinase, Abbas *et al.* [76] screened a new series of compounds containing 5-aryl-thiazolidin-4-one scaffold (20, **Figure 6**) against human cervix carcinoma cells (Hela) using MTT based assay taking doxorubicin as a standard drug. Among the tested nineteen compounds, seven compounds displayed significant activity with IC<sub>50</sub> ranging from 0.60 to 2.99  $\mu$ M, comparable to the reference drug doxorubicin (IC<sub>50</sub> 1.10  $\mu$ M). Above seven derivatives were also tested for EGFR kinase

inhibition potential, in which one compound 20a bearing 3-chlorobenzylidene moiety displayed potent activity ( $IC_{50}$ : 0.07  $\mu$ M) even slightly superior to the reference drug erlotinib ( $IC_{50}$ : 0.08  $\mu$ M). It is worth noting that compound 20a exhibited anti-cancer activity against Hela cell lines with  $IC_{50}$ : 2.99  $\mu$ M, while it showed weak toxicity ( $IC_{50}$ : 60.12  $\mu$ M) towards the normal cell lines of the human cervical epithelium (HCvEpC).

Further studies revealed that compound 20a arrested the cells in the G1/S phase, and it also induced a significant level of apoptosis in the tested cells (27.11%). Studies performed to uncover the mechanistic basis of apoptosis revealed an elevated ratio of Bax/Bcl-2 as well as an increased expression level of tumor suppressor gene p53. The putative binding mode of compound 20a inside EGFR kinase was studied using molecular docking studies which revealed its prominent interaction with key amino acids like reference drug erlotinib [76].



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

Kobylnska *et al.* [77] evaluated the cytotoxicity of three 4-thiazolidinone conjugated with indolin-2-one against rat glioma C6 cells using doxorubicin as a reference control drug. Compounds were also evaluated for their free radical oxidation and antioxidant activity in the rat serum. Among the three tested derivatives, ID 3288 (21, (Figure 6)) exhibited superior toxicity after 48 h exposure against rat glioma C6 cells, in both tested assays i.e. MTT ( $IC_{50}$ : 0.10  $\mu$ g/mL) and trypan blue ( $LC_{50}$ : 0.07  $\mu$ g/mL), which was better ( $IC_{50}$ : 0.51  $\mu$ g/mL) and comparable ( $LC_{50}$ : 0.07  $\mu$ g/mL) to reference drug doxorubicin, respectively. All tested compounds showed reduced ROS-inducing ability, and also showed less activity against catalase (Cat), superoxide dismutase (SOD), and glutathione peroxidase (GPO) compared to doxorubicin. So, overall, ID 3288 showed more potent antineoplastic activity in rat glioma (C6 cell lines) than the reference drug doxorubicin [77].

Extending work on 4-thiazolidinone conjugated with indolin-2-one, Finiuk *et al.* [78] evaluated the cytotoxicity of Les-3833 (22, (Figure 6)) against human cancer cell lines (melanoma and others) and studied pro-apoptotic action against selected cancer cell lines. The result of cytotoxicity studies performed using MTT assay revealed potent activity of compound 22 in melanoma cells (WM793 and SK-Mel-28) with  $IC_{50} \leq 0.3$   $\mu$ g/mL. Against the other cancer cell lines like human colon (HCT116), lung (A549), ovarian (SKOV3), and breast cell lines (MCF-7),  $IC_{50}$  ranges from 2.5 to >5.0  $\mu$ g/mL, while human embryonic kidney cell lines (HEK293) were found to be least sensitive with  $IC_{50} > 5$   $\mu$ g/mL. Based upon the results of Annexin

V/PI staining and activated caspase 3, MAPK, PARP, and EndoG protein, apoptosis was confirmed in compound 22 treated cells. Moreover, treated melanoma cells indicated ROS production and cell cycle arrest in G0/G1 phase. So, overall *in vitro* studies concluded that compound 22 is a highly active compound against human melanoma cells with a less pronounced effect against carcinoma and leukemia cells [78].

Further, extending the above work, Kobylinska *et al.* [79] investigated the pro-apoptotic effect of compound 22 and its other analog 23 (**Figure 6**) conjugated with PEG nanocarrier in the glioma C6 cells of the rat. To study the antineoplastic mechanisms of the conjugate system, studies like cell cycling pattern, Annexin V expression, Cell nativity, and DNA damage were performed. The novel conjugated system possessed excellent aqueous solubility and exhibited apoptosis mechanisms against the glioma C6 cells, which was confirmed by FACS analysis (pre-G1 stage), annexin V positive cells, and higher classes of DNA comets. Conjugates of both drugs showed enhanced toxicity (LES 3288 and LES 3833) at doses of 0.1 and 0.5  $\mu\text{M}$  compared to free drugs, however, at higher concentrations (1.0  $\mu\text{M}$ ) only LES 3288 retained higher toxicity compared to the free drug. Furthermore, DNA comet analysis in glioma C6 cells documented breaks in the nuclear DNA (single strand) without intercalation in the DNA of the tested cells [79].

Skora *et al.* [80] synthesized another series, comprising thiazolidine-4-one conjugated with an indole ring, and subsequently *in-vitro* screened them for their cytotoxic and cytostatic activity against four cancer cell lines, namely epithelial colorectal adenocarcinoma (CACO-2) cells, lung carcinoma (A549), human fibroblasts (BJ), and neuroblastoma (SH-SY5Y). All tested compounds (at a concentration of 10 to 100  $\mu\text{M}$ ) reduced the metabolic activity of three cell lines (BJ, SH-SY5Y, and A549) in comparison to the negative control. Among the four derivatives, compound 24 (**Figure 6**) showed encouraging cytotoxic activity against BJ, A549, and SH-SY5Y with a strong pro-oxidative effect. Moreover, the activity of SK1 was found to be time-dependent, with high caspase-3 activity [80].

Zhang *et al.* [81] *in-vitro* screened around one hundred combinations of different thiazolidinone-based compounds against human non-small cell lung cancer (H460) and its paclitaxel-resistant mutant form (H460/TaxR). Combinations were also tested for tumor growth inhibition effect in H460/TaxR xenograft mice. Finally, an optimized combination (M4) comprising four molecules (25a-25d) in an equimolar ratio (**Figure 7**) synergistically inhibited the cellular growth *in-vitro* (H460 and H460/TaxR) and also tumor growth in xenograft mice models compared to the negative control.

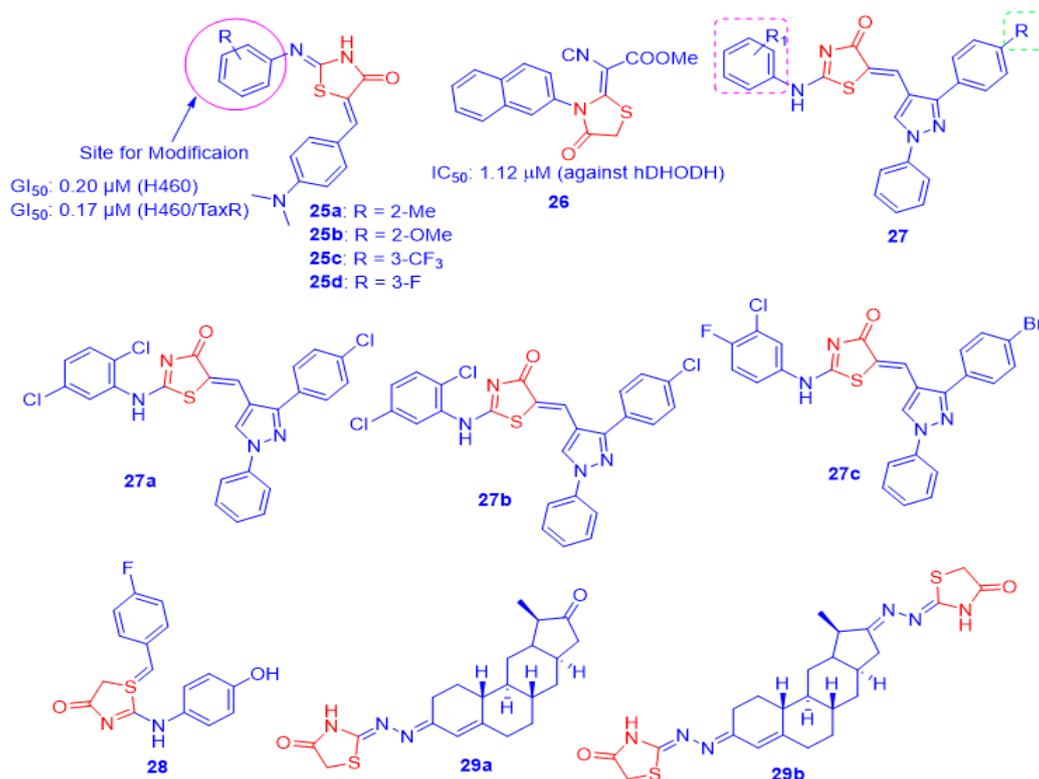
M4 combination showed better anti-proliferation activity than the individual compounds against H460 and H460/TaxR ( $\text{GI}_{50}$ : 0.20  $\mu\text{M}$  and 0.17  $\mu\text{M}$ ), even several folds better than the standard taxol drug ( $\text{GI}_{50}$ : 6.2  $\mu\text{M}$  and 252  $\mu\text{M}$ , respectively). Cytotoxicity of the combination was found to be independent of P-gp receptors and interestingly it showed low toxicity against the normal human fibroblast (NHFB) cells.

Genome microarrays assay evident that certain genes particularly involved in negative regulation of microtubule depolymerization & polymerization, histone acetylation (positive regulation), apoptosis, and cell cycle arrest were found to be upregulated. Compound M4 combination targeted multiple proteins including activation of caspases, JNK, p38 cascades, etc, and resulted in cycle arrest in the G2/M phase and induce cell apoptosis. The study proposed a newer strategy for the search for anticancer agents and their combination, especially against drug-resistant cancers [81]. Human dihydroorotate dehydrogenase (hDHODH) played a central role in pyrimidine de novo biosynthesis, crucial for nucleotide biosynthesis as well as the proliferation of cells. In fast-proliferating tumor cells, it has been documented as one of the validated and attractive targets [82].

Zeng *et al.* [83] synthesized a series of 4-thiazolidinone derivatives and evaluated them for human DHODH inhibition activity. Among the series, the best active compound 26 showed potent activity with  $\text{IC}_{50}$  values of 1.12  $\mu\text{M}$ . The SAR studies revealed that cyano substitution and ester linkage at the 2<sup>nd</sup> position of the 4-thiazolidinone scaffold favored the activity. Furthermore, nitrogen substitution with hydrophobic groups like naphthyl or phenyl ring improved inhibition activity. Docking studies performed using compound 26 showed its hydrogen bonding interactions with Tyr38 and Ala55 (direct and water-mediated, respectively). The author concluded *N*-substitution can be further optimized to search for more potent inhibitors of the hDHODH [83].

Bhat *et al.* [84] synthesized a series of novel fifteen compounds containing a thiazolidinone-pyrazole hybrid nucleus (27, (**Figure 7**), and subsequently evaluated their anticancer and antimicrobial activities. In anticancer studies, compounds were screened against three types of cancer cell lines viz. human dermal fibroblast, human melanoma, and human breast cancer cell lines. Among the tested series, compounds (27a, 27b, and 27c) displayed moderate activity against human breast cancer and Ehrlich ascites carcinoma cells, respectively.

Among the series, except few compounds, the majority of them were found to be less toxic to human dermal fibroblast cells. SAR studies performed on the core scaffold revealed that substitution with halogens at different positions of the *N*-arylamino ring was found to be favorable in enhancing the anticancer potential of compounds compared to other groups. Docking studies performed using the top active compound against the MDM2 target displayed good co-relation between the *in-silico* binding affinity of a compound and its *in-vitro* anti-cancer potential. Molecular dynamics studies were also performed using the top active compound 27c at the active site of MDM2 confirming strong hydrogen bonding and hydrophobic interactions [84].



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

#### Thiazolidin-4-Ones with 1<sup>st</sup> And 5<sup>th</sup> Substitution as Anti-Cancer Agents

Szychowski *et al.* [85] evaluated the anticancer activity of 5Z-(4-fluorophenylidene)-2-(4-hydroxyphenylamino)-thiazol-4-one (28, (**Figure 7**)) in four human cancer cell lines (A549, SCC-15, SH-SY5Y, and CACO-2). The cell lines were exposed to increasing concentrations (1 nM to 100  $\mu$ M) of the studied compound for 6, 24, and 48 h, and parameters like ROS production, cell viability, caspase-3 activity, and cell metabolism were examined. The obtained results showed that the studied compound decreased the production of ROS, increased the release of lactate dehydrogenase, and decreased cell metabolism/proliferation in all five cell lines at low micromolar concentrations. Interestingly, over a wide range of concentrations (from 1 nM to 100  $\mu$ M), compound 28 was able to increase the activity of caspase-3 in SH-SY5Y (after 6 h of exposure), A549, CACO-2, and SCC-15 (after 48 h of exposure) cell lines which could be an effect of the activation of PPAR  $\gamma$ -dependent pathways [85].

#### Thiazolidin-4-Ones with Substitution at 2<sup>nd</sup> Position as Anti-Cancer Agents

Exploring the 2<sup>nd</sup> substituted thiazolidine-4-ones as anti-cancer agents, Zivkovic *et al.* [86] synthesized two series of compounds, containing mono- and bis-(thiazolidine-4-ones) conjugated with steroidal moieties as stereoisomeric mixtures (**Figure 7**) and subsequently evaluated their cytotoxic activities.

Synthesized thiazolidinone derivatives displayed cytotoxic activities in a concentration-dependent manner against the six tested cancer cell lines. The majority of the tested compounds showed significant activity against the tested K562, HeLa cells, and MDA-MB-361 cell lines, while few compounds showed activity comparable to the reference drug cisplatin (21.5  $\mu$ M). Out of the ten tested compounds, eight showed good selectivity when tested on normal human fibroblasts MRC-5 and normal human PBMC. Mechanistic studies were performed using two representative compounds (29a and 29b, (**Figure 7**)) which showed good anti-cancer activity in low micromolar concentration against the majority of tested cell lines with good selectivity. Mechanistic studies revealed, that both compounds induced apoptosis in HeLa cells via extrinsic and intrinsic signaling pathways. When EA.hy926 cells were treated with sub-toxic doses of compounds 29a and 29b, both compounds showed cell growth inhibition via interfering in the sprouting and tube formation [86].

## Conclusion

Thiazolidin-4-one is a very versatile nucleus with potential anti-cancer activity. Among the different substituted series, di-substituted (2<sup>nd</sup> & 3<sup>rd</sup> and 2<sup>nd</sup> & 5<sup>th</sup>) and tri-substituted (2<sup>nd</sup>, 3<sup>rd</sup>, & 5<sup>th</sup>) scaffolds are most frequently reported for anti-cancer activity in different research studies. Compounds sensitivity in a redox environment may be the reason for their higher selective toxicity in the tumor microenvironment compared to the healthy tissue. Several studies illustrated the promising activity of thiazolidine-4-one-based compounds. Moreover, in many instances, it was found to be ever superior to the reference standard drugs with excellent selectivity. Some potential hits retain efficacy in MDR cancers, especially against overexpressing P-gp

efflux which generally confers resistance to multiple drugs including paclitaxel. Compounds of thiazoline-4-one scaffolds are reported for targeting different enzymes like tyrosine kinase, NF-KB, PI3K-Akt, Tubulin protein, dihydrofolate reductase (DHFR), human Dihydroorotate Dehydrogenase (hDHODH) and cyclin-dependent kinases (CDKs). So, the overall study confirms the tremendous anti-cancer potential of this nucleus and potential candidates from this scaffold after systematic optimization studies can afford potential cancer therapeutics.

#### *Future Perspectives*

To generate potential lead candidates with the translational outcome, further studies like pharmacokinetic studies and the metabolic stability of these compounds need to be established. The reducible nature of sulphur in the tumor microenvironment of cancer cells could be the possible reason for the high selectivity of this nucleus, but more molecular-level studies are required in this direction. The exact molecular targets of reported compounds are not explored in several reported research studies, so further research in this direction could be helpful in appropriate target identification and expediting the subsequent hit-to-lead optimization process.

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**Ethics statement:** None

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